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Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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REVIEW

Reappraisal of endoscopic papillary balloon dilation for the management of common bile duct stones

Kwok-Hung Lai, Hoi-Hung Chan, Tzung-Jiun Tsai, Jin-Shiung Cheng, Ping-I Hsu

Kwok-Hung Lai, Hoi-Hung Chan, Tzung-Jiun Tsai, Jin-Shiung Cheng, Ping-I Hsu, Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan
Kwok-Hung Lai, Hoi-Hung Chan, Ping-I Hsu, School of Medicine, National Yang-Ming University, Taipei 112, Taiwan
Author contributions: All the authors solely contributed to this paper.

Correspondence to: Kwok-Hung Lai, Professor, Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung 813, Taiwan. khlai@vghks.gov.tw
Telephone: +886-7-3422121-2074
Fax: +886-7-5574361
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Abstract

Although endoscopic sphincterotomy (EST) is still considered as a gold standard treatment for common bile duct (CBD) stones in western guideline, endoscopic papillary balloon dilation (EPBD) is commonly used by the endoscopists in Asia as the first-line treatment for CBD stones. Besides the advantages of a technical easy procedure, endoscopic papillary large balloon dilation (EPLBD) can facilitate the removal of large CBD stones. The indication of EPBD is now extended from removal of the small stones by using traditional balloon, to removal of large stones and avoidance of lithotripsy by using large balloon alone or after EST. According to the reports of antegrade papillary balloon dilatation, balloon dilation itself is not the cause of pancreatitis. On the contrary, adequate dilation of papillary orifice can reduce the trauma to the papilla and pancreas by the basket or lithotripter during the procedure of stone extraction. EPLBD alone is as effective as EPLBD with limited EST. Longer ballooning time may be beneficial in EPLBD alone to achieve adequate loosening of papillary orifice. The longer ballooning time does not increase the risk of pancreatitis but may reduce the bleeding episodes in patients with coagulopathy. Slowly inflation of the balloon, but not exceed the diameter of bile duct and tolerance of the patients are important to prevent the complication of perforation. EPBLD alone or with EST are not the sphincter preserved procedures, regular follow up is necessary for early detection and management of CBD stones recurrence.

Key words: Common bile duct stones; Complications; Endoscopic balloon dilation; Endoscopic large balloon dilation; Endoscopic sphincterotomy

Core tip: Indication of endoscopic papillary balloon dilation is now extended from removal of small common bile duct stones to large or difficult stones by using large balloon. Balloon dilation itself is not the cause of pancreatitis. Avoidance of unnecessary pancreatic contrast injection, use the suitable balloon and pressure, slowly balloon inflation and adequate ballooning time to achieve a widely opened papillary orifice are the important steps to perform a safe endoscopic papillary large balloon dilation and successful clearance of bile duct.

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INTRODUCTION

In the laparoscopic era, endoscopic retrograde cholangiopancreatography (ERCP) is as efficient as laparoscopic surgery in the treatment of common bile duct (CBD) stones[1]. Since the introduction of endoscopic sphincterotomy (EST) in 1974 by Classen *et al*[2] and Kawai *et al*[3], EST is widespread used for removal of CBD stones in the following 40 years. Although the success rate of EST is high, this procedure may cause pancreatitis, hemorrhage, perforation and other complications. In a prospective cohort study of EST in 2347 patients[4], the overall complications of EST was 9.8%, including pancreatitis 5.4% (severe 0.4% and one patient died), hemorrhage 2% (severe 0.5% and 2 patients died), perforation 0.3% (severe 0.5%, one patient died), cholangitis 1% (severe 0.1% and one patient died), cholecystitis 0.5% (severe 0.1% and one patient died). The risk factors of pancreatitis included dysfunction of sphincter of Oddi, young age, difficulty in cannulating the bile duct, and number of pancreatic contrast injections; whereas the risk factors of hemorrhage included coagulopathy, anticoagulation therapy, cholangitis, mean case volume of endoscopist $\leqslant$ 1/week, and bleeding during the procedure. Thus, the risk of complications was influenced by the technique of endoscopist in the process of bile duct cannulation and cutting the papilla[4].

In 1981, Centola *et al*[5] presented a case with CBD stones who was successfully treated by percutaneous transhepatic balloon dilation of papilla of Vater. Staritz *et al*[6] also reported his experience by using a 15 mm diameter balloon catheter for endoscopic papillary dilation in 10 patients with CBD stones and one patient with benign papillary stenosis in the next year. Six of the ten patients were successfully cleared the bile tract soon after endoscopic papillary balloon dilation (EPBD) and four patients needed mechanical lithotripsy for stone retrieval. There were no complications in this report. For the purpose of preserving the function of sphincter of Oddi and avoidance of late complication, most endoscopists used the smaller balloon catheters (8 mm or less) to dilate the biliary sphincter for removal of the small stones, or combination use of the smaller balloon with lithotripter to treat the larger stones in the following twenty years. The success rate of EPBD was comparable with EST and reduced risk of bleeding was found[7-13]. Higher incidences of pancreatitis after EPBD by using the 8 mm balloon catheter were reported in some studies[14-16]. Although most of the patients with post-EPBD pancreatitis recovered after conservative treatment, a multi-center study from United States and Ireland disclosed two patients with fatal pancreatitis after EPBD[16]. The impact of this report discouraged the use of EPBD as the first line modality for the treatment of CBD stones by some western endoscopists, particularly in United States[17-20]. However, EPBD was still a popular procedure in Asia and parts of Europe[21]. Tsujino *et al*[22] found that 4.8% of their 1000 patients developed pancreatitis after EPBD, but all of them recovered later.

In 2003, Ersoz *et al*[23] reported their retrospective analysis for using the enteric balloon catheter (previously used for esophageal or pyloric dilation) with the diameter 12-20 mm, to treat 58 patients who had received complete endoscopic sphincterotomy but failure to clear the CBD stones. Of the 58 patients, 18 patients had tapered distal bile duct, and another 40 patients had the large, square and barrel shaped stones. Successful stone removal at the first session was 82.8%, and the other 10 patients also achieved clearance of bile duct after second dilation or mechanical lithotripsy. Complications occurred in 15.5%, including moderate bleeding in three patients (5.2%) and mild pancreatitis in two patients (3.4%). In 2004, Lin *et al*[24] from Taiwan reported a randomized controlled study comparing 51 patients receiving EPBD alone by using the enteric balloon catheter (diameter 10-12 mm) with 53 patients receiving EST for removal of CBD stones. The ballooning time was increased to 5 min to avoid the continuous blood oozing after balloon deflation. The successful bile duct clearance rates and the frequencies of mechanical lithotripsy were comparable between two groups. The minor bleeding episodes were more frequent in EST group (2% *vs* 26.4%, $P < 0.001$), but no other adverse effects such as pancreatitis and perforation were reported. Since then, endoscopic papillary large balloon dilation alone (EPLBD) or after sphincterotomy (ESLBD) became popular use for removal the large or difficult CBD stones, the results are satisfactory and even superior to EST in most studies and literatures of meta-analysis[25-61]. Although lethal pancreatitis is rare, life-threatened complications such as perforation and bleeding have been reported after ESLBD or EPLBD[62,63]. In the era of EPLBD/ESLBD, several previous concepts about EPBD, such as the indications, methodology, short-term and long-term complications should be amended.

INDICATIONS OF EPBD/EPLBD

Staritz *et al*[6] firstly reported the good clinical results of EPBD for removal of CBD stones by using the large balloon catheter, but most endoscopists shifted to the smaller balloon catheter (8 mm) for papillary dilation later[9-16,22]. Because of high incidence of post-procedural pancreatitis in a few studies[15,16], the indica-

tions of EPBD was confined to the vulnerable patients (*e.g.*, coagulopathy, cirrhosis), or altered anatomy (*e.g.*, Billroth Ⅱ gastrectomy, Roux-en-y anastomosis, juxtapapillary diverticulum), and the stones were lesser than 1 cm in diameter[19,20]. After ESLBD and EPLBD were widely used to remove the large or difficult stones with good results, the indications extend to the patients with large stones, tapered or stricture of distal bile duct[21,23,25,31,36,41,44,58,61]. As perforation is more likely to occur in those patients with distal bile duct stricture, some studies suggest that the target of EPLBD/ESLBD should include the patients with CBD dilation but without stricture of distal CBD[25,63]. Since stricture of distal bile duct is also a problem after EST, other studies recommend limited EST, gradually inflation of balloon and early use of lithotripter to remove the CBD stones safely[23,63-66].

SUCCESS RATE OF EPBD/EPLBD FOR REMOVAL OF CBD STONES

The overall success rate of EPBD by using the conventional balloon catheter was comparable (94.3% *vs* 96.5%) with EST in a meta-analysis of eight studies[17], another similar analysis of thirteen studies reported that EPBD being less successful overall in regard to stone removal (90.1% *vs* 95.3%)[18]. Both two above studies showed that patients undergoing EPBD were more likely required mechanical lithotripsy for stone extraction (20.9% *vs* 14.8% and 20.0% *vs* 13.3%, respectively)[17,18]. The contradictory results of meta-analyses in clinical trials may be due to diverse nature of the studies in design and methods[67]. Most of the trials excluded the patients with coagulopathy, cirrhosis, distal bile duct stricture, big stones or difficult cases, the detailed methods including the ballooning time and medications were different. The heterogeneity of the trials may interfere the assessment of overall results.

The initial success rate of ESLBD was 91% (75.5%-100%), overall success rate was 98% (88.6%-100%), mechanical lithotripsy was necessary in 9.3% (0-33%)[68]. The overall success rate ESLBD was comparable with EST in most studies, but the need of mechanical lithotripsy was less frequent in ESLBD[25,31,41,44,58]. In patients received EPLBD alone, the overall success rate of CBD stones removal ranged from 92.7%-97.5%, the need for mechanical lithotripsy ranged from 15.8%-21.2%[45,51,69-72]. Minakari *et al*[69] found that there were no significant difference between the success rate of EPLBD alone and EST (97.5% *vs* 96.2%). Hwang et al reported that the overall success rate of CBD stone removal and the needs of mechanical lithotripsy were similar between the patients received EPLBD alone or ESLBD (96.8% *vs* 95.7% and 19.4% *vs* 26.1%, respectively)[57].

METHODS OF EPBD/EPLBD

The diameter of the balloon depends upon the injection pressure inside the balloon according to the manufacturer's instruction[24,45]. A multicenter study demonstrated the efficacy and safety of EPBD by inflating the balloon until its waist disappears, rather than inflating to a prespecified pressure[72,73]. The balloon should be slowly inflated to avoid sudden tearing of the ampullary roof. After EST, the shape of papillary orifice will be triangular and the distal CBD will be narrow in shape. In contrast, the papillary orifice will be shaped as a large round hole with cylindrical configuration without a narrowing at distal bile duct after adequate balloon dilation, the relative stiff accessory instruments such as basket and lithotripter will enter easily into bile duct for stones removal[47]. The traditional balloon catheter (8 mm in diameter, 3 cm in length) was used to remove the small CBD stones and to preserve the integrity of the sphincter[13,74]. The large balloon (≥ 10 mm to 20 mm) is used to remove the big difficult stones without consideration of sphincter preservation[44].

The choice of balloon depends on the size of the largest stones and the CBD diameter[44]. The size of balloon should not exceed the maximal diameter of bile duct. In the patients with a stricture or tapered distal bile duct, gradual dilation with smaller balloon until disappearance of the waist is suggested, and EPBD should be terminated if the patient is intolerant to the dilating procedure.

The ballooning time is heterogeneous in different reports. In several controlled studies, the short ballooning time 20-30 s had the comparable results with the ballooning time 60-120 s[55,72,75]. In the study of Choi *et al*[76] they demonstrated the favorable outcome of immediate balloon deflation method in ESLBD for the extraction of difficult CBD stones. In a randomized trial from Taiwan, Liao *et al*[77] showed that 5-min EPBD improved the efficacy of stone extraction and reduces the risk of pancreatitis in comparison with conventional 1-min EPBD. A meta-analysis also demonstrated the duration of EPBD is inversely associated with pancreatitis risk[60]. Long EPBD can result in adequate loosening of the intact sphincter and less blood oozing, the widely opened papillary orifice may facilitate the insertion of accessary instruments into bile duct, and decrease the injury of pancreas[24,45,77,78]. In the patients who received ESLBD, shorter ballooning time may be enough because the sphincter is partially severed. The longer ballooning time may probably prevent bleeding complication, particularly in the flail patients with bleeding tendency, cirrhosis, uremia or under anti-platelet therapy[37,63,65].

Attasaranya *et al*[38] suggested that EPLBD after EST may result in separation of the pancreatic and biliary orifices and the balloon dilation forces are away

from the pancreatic duct. According to his theory, many endoscopists performed ESLBD to remove the CBD stones recently[26-30,32-35,37,39,40,42-44,46-48,53,54]. Significant bleeding was reported in 2.8% (0-8%) after ESLBD[68]. Hwang *et al*[57] conducted a study of 131 patients to compare the clinical effect of EPLBD alone and ESLBD. The successful stone removal (EPLBD 96.8%, ESLBD 95.7%), need of mechanical lithotripsy (EPLBD 19.4%, ESLBD 26.1%), postprocedural pancreatitis (EPLBD 6.5%, ESLBD 4.3%), perforation (EPLBD 0%, ESBD 1.4%) were no significant differences between two groups[57]. The recent prospective controlled study by Kogure *et al*[77] also demonstrated the similar findings. Another two single-institution retrospective studies reported that the EPLBD alone had the overall success rate 92.7%-97.4%, required the help of mechanical lithotripsy 15.8%-21.1%, postprocedural mild pancreatitis 0-0.8%, and no major bleeding[45,71]. Therefore, EPLBD alone is a simple safe and effective method in patients with large CBD stones, precut sphincterotomy may be unnecessary except in those patients with difficult cannulation of bile duct.

ADVERSE EVENTS AFTER EPBD/EPLBD

Pancreatitis

EPBD is categorized as one of the important causes of pancreatitis since the report of multicenter study from Disario *et al*[16]. From the result of recent studies, pancreatitis is more frequent in the patients using the traditional balloon (8 mm) and short duration (< 3 min) than the patients using the large balloon and long duration[6,12,14-17,24,25,31,36,45,52,58,60,65,71,77,79]. In 2000, Gil *et al*[80] from Spain reported their results by using percutaneous balloon dilation of sphincter of Oddi to clear the bile duct in the 38 patients with CBD stones. The success rate was 94.7% and no patient developed pancreatitis[80]. Another study from Argentina applied similar method in 300 patients, no patients developed pancreatitis after antegrade balloon dilation of biliary sphincter with maximal diameter 20 mm[81]. A Korean retrospective study compared the efficacy and adverse event in 56 patients underwent percutaneous transhepatic papillary dilation (PTPD) with 208 patients underwent retrograde EPBD for removal of CBD stones[82]. Complete bile duct clearance was achieved in 97.1% of EPBD and 98.2% of PTPD. Fourteen (6.7%) of 208 EPBD group *vs* 0% of PTPD developed pancreatitis after the procedure (P = 0.046). Hyperamylasemia occurred in 29.8% of EPBD group and 7.1% of PTPD group (P = 0.0005). These studies disprove the previous concept of balloon dilation being the cause of pancreatitis. The balloon is innocent and the pancreatitis may actually result from the traumatic injury of major papilla or pancreatic duct at the time of selective cannulation of bile duct, or the procedures of stone extraction after balloon dilation. In the patients with difficult cannulation, papillary edema after repeated cannulation, accidental trauma by diagnostic catheter or excessive injection of contrast medium to the pancreatic ducts are not uncommon, particularly in the patients with small papillary orifice or not widely opened orifice after inadequate balloon dilation. The pathogenesis of pancreatitis after EPBD appears multifactorial, only the superfluous injection of contrast medium into pancreatic duct is certainly considered to lead to increasing the risk of pancreatitis[83]. Once the head portion of pancreatic duct filled with contrast, we should stop the contrast medium injection immediately and withdraw the catheter in order to minimize the pancreatic injury. In addition, adequate dilation of papilla to create a large opening of bile duct may facilitate the accessory instruments enter the bile duct easily and to avoid further injury of pancreas[45]. Routine use of pancreatic stent may help for decrease the risk of pancreatitis by experienced endoscopists, but the indication and detailed methodology are not established yet[84].

Bleeding

Less bleeding is believed to be one of the advantages for EPBD in the treatment of CBD stones up to now. In the early meta-analysis from Baron *et al*[17], no patients developed bleeding after EPBD in 8 controlled studies using the traditional balloon for dilation, but 2% of patients had bleeding after EST. In DiSario's study, self-limited or endoscopically controlled bleeding occurred in 27% of the patients undergoing EST and 10.5% of patients undergoing EPBD[16]. Minor oozing after EPBD commonly occurs due to microvascular rupture accompanied by stretching of the mucosa, particularly in the patients receiving EPLBD, but most of them are self-limited and does not considered as a bleeding complication in most studies[44,65]. Park *et al*[85] had conducted a study to compare the results of EPBD using traditional balloon with EST in patients with cirrhosis and coagulopathy. Significant bleeding occurred in six (30%) patients who received EST and three of them died of bleeding related complications. No bleeding episode was reported in patients received EPBD[85]. Unlike the EPBD using a traditional balloon, the bleeding episodes were ranged from 0-16.7% in patients who received the ESLBD for treatment of CBD stones[44], one patient died of bleeding in a multi-center study who received EPLBD after a full EST[63]. Patients who received EPLBD alone had less frequent or less severe bleeding episodes in both prospective and retrospective reports[45,57-71,77]. Lin *et al*[24] prolonged the duration of balloon inflation to 5 min because of continuous oozing after short duration balloon inflation in the initial two cases. Most of published reports excluded the patients with coagulopathy in their protocols, and there is no consensus for the methodology of EPBD or EPLBD in the present

time. To prolong the duration of balloon inflation and the use of EPLBD alone may probably reduce the risk of significant bleeding to the patients with potential coagulopathy[24,65], but it needs further controlled studies to confirm.

Perforation

The incidence of perforation was 0-2% in patients after EPBD, 0-1.7% in patients after ESLBD[17,44], 0-2.5% after EPLBD alone[30,45,57,71,77,86]. Mortalities after EPBD or ESLBD were also reported[7,63,86]. Distal CBD stricture and over-inflation of balloon may be responsible for the fatal perforation[63]. In the patients with stricture or tapered distal bile duct, gradual balloon dilation with a smaller balloon initially and application of lithotripter may help for safely extraction of CBD stones[23,66]. Strong resistance, persistence of notch, and intolerable pain development during balloon inflation indicated stricture of bile duct, additional pressure should not be applied to avoid perforation[63]. In such cases, it should convert to drainage procedure or other stone extraction modalities[63].

Infection

Incidences of infection after endoscopic treatment for CBD stones are heterogeneous in the published reports. They range from 0-8% in EST, 0-10% in EPBD, 0-3.3% in ESLBD and 0-5% in EPLBD alone [30,44,45,57,61,71,77,86,87]. Biliary infection after endoscopic treatment may relate to the concomitant disease and general condition of the patients, contamination during the procedure and incomplete drainage of bile after the procedure. However, even under strict clean and disinfection protocol, biliary infection still occurred in 0.28%[88]. Some endoscopists routinely used the prophylactic antibiotics to the patients who received endoscopic therapy, but Cotton *et al*[88] suggested that prophylactic antibiotics should restrict to patients with predictably undrainable biliary systems or likely to have infected bile (*e.g.*, immunocompromised, prior sphincterotomy, and/or stent). Besides the strict cleaning and disinfection protocol, aspiration of bile from the proximal bile duct above the obstruction level before the contrast injection and to avoid over-filling of intrahepatic ducts during the procedure may reduce disseminating infection[88].

Late complications

The recurrent CBD stones ranged from 0-25% in the patients using traditional EPBD[9,12,22,87,89-91], 4.4%-21% in ESLBD[79,92-95], 4%-14.5% in EPLBD alone[45,70,79]. Tsujino *et al*[22] reported the long term outcome of 1000 patient after traditional EPBD; the recurrence rate was 8.8%. In subgroup analysis, the recurrent rate was highest in the patients with gallbladder left *in situ* with stones (15.6%), followed by cholecystectomy before EPBD (10.8%), gallbladder left *in situ* without stone (5.9%) and elective cholecystectomy after EPBD(2.4%)[22]. Kojima *et al*[92] and Ohashi *et al*[90] reported the highest recurrent rate of CBD stones in patients with cholecystectomy before EPBD (22%, 17.6%). The recurrent rates in other subgroups were gallbladder *in situ* with gallstones 8.9% and 0%, gallbladder *in situ* without stone 4.9% and 4.9%, cholecystectomy after EPBD 4.3% and 7.4%[90,92]. However, the incidences of acute cholecystitis in the patients with intact gallbladder and gallstones were higher than other three groups (4.5%-7.7%)[22,90]. Most of the primary CBD stones and recurrent stones from Asian patients are belonged to loose bilirubinate stone[22,50,86,90,94,96], the small fragments of these stones missed by cholangiography may remain in the bile duct and act as nidi for early recurrent stones[90]. Poor biliary emptying is responsible to the formation of primary and recurrent stones[97]. Gallbladder contraction after meal may flush the bile duct and expel the small stone particles into duodenum. Patients with prior cholecystectomy may lose this flushing function and increase the risk of stone recurrence. In patients with an intact gallbladder and stones, the stone may migrate to cystic duct and CBD resulting to cholecystitis and recurrent CBD stones[22].

In the recent meta-analysis by Zhao *et al*[93], they found that the overall long-term complications were significant lower if patients were treated by EPBD rather than EST. Compared to EST, EPBD markedly decreased the incidence of acute cholecystitis. Although there were no significant difference between EPBD and EST in the incidences of acute cholangitis and recurrent CBD stones, but a study with follow-up for more than one year indicated that the stones recurrence rate decreased significantly in the EPBD group[95]. Tanaka et al found that the recurrent rate of CBD stones within one year was higher in EPBD than EST (25% *vs* 6.3%), but the incidence of recurrent CBD stones was lower in EPBD than EST after follow up for 1-6 years (6.3% *vs* 26.7%)[12]. Similar late complication and stone recurrence rate in patients after ESLBD and EST was reported by Kim *et al*[94]. During a median 22 mo (range, 1-56 mo) follow up, Kogure *et al*[79] found that the incidence of recurrent CBD stones was higher in patients received ESLBD than the patients received EPLBD alone (21% *vs* 11%).

SPHINCTERIC FUNCTION AFTER EPBD/EPLBD

Most endoscopists emphasized the advantage of EPBD in preservation of sphincteric function and the prevention of late complications in the last century, so the traditional balloon (8 mm) was commonly used with this purpose. Sato *et al*[74] had used the microtransducer catheter to check the sphincter of Oddi (SO) function before and after traditional EPBD. The mean SO basal pressure dropped from 13.6 mmHg to

6.3 mmHg at one week after EPBD and increased to 9.3 mmHg after one month[74]. Yasuda *et al*[13] used the same method as Sato *et al*[74] and found that the preservation of SO function was not completed but remained somewhat reduced (SO basal pressure before, one week and one year after EPBD were 9 mmHg, 3.3 mmHg and 4.2 mmHg respectively)[13]. In addition, EPBD caused less pneumobilia than EST (86% *vs* 40%, $P < 0.01$) but the incidences of recurrent CBD stones did not have significant difference between two methods[13]. Both two studies did not include the pharmacological test in manometry[98,99], the incidences of paradoxical response after cholecystokinin or ceruletide in their patients were not known. Failure to relax the sphincter after meal or SO dysfunction may hinder the spontaneous passage of residual stones particles, resulting in recurrent stone formation[12]. In the patients who received EPLBD (> 1 cm), the SO function was not preserved[100]. The Asian patients with CBD stones are male predominant, older age, high percentage of juxtapapillary diverticulum and bilirubinate stones, their characteristics are different from the Western patients[7-10,13-16,30,35,63,83,91]. A recent retrospective study indicates that EPLBD is helpful to prevent re-recurrence of CBD stones after previous EST[101], but further controlled studies are needed to clarify the role of sphincteric function in the Asian patients with CBD stones.

LIMITATION OF EPBD/EPLBD

In patients with papillary stenosis, severe stricture of distal bile duct or impacted stones in papilla, it is difficult to insert the guidewire deeply into bile duct, precut sphincterotomy is necessary to assist EPBD or EPLBD. In patients with non-dilated bile duct or tapered distal bile duct, EPBD should be started with a small balloon and gradual inflation. In the patients with biliary stricture and unsuitable for surgical intervention, EPBD can be tried but the risk of perforation is high[63]. If patient feels intolerable pain during the procedure or the waist of balloon does not disappear after inflating the balloon to 75% of the maximum recommended pressure, balloon pressure should be reduced or change to other modalities[65]. Although EPBD is recommended in the patients with coagulopathy, details of the method for safely handling these high risk patients is not yet established. As non-significant bleeding is common in EPBD/EPLBD, avoid precut sphincterotomy and increased the duration of balloon dilation may be necessary to prevent the lethal bleeding complication. EPBLD alone or with EST are not the sphincter preserved procedures, the patent papillary orifice can facilitate the free drainage of small stone particles into duodenum, but also allows the reflux of duodenal content, regular follow up is necessary for early detection and management of CBD stones recurrence[102].

CONCLUSION

The methods in endoscopic treatment of CBD stones should be individualized. Both EST and EPBD/EPBLD can be safely used in the routine practice to remove the CBD stones by the experienced endoscopists. EPBD/EPLBD is preferred in the patients with difficult CBD stones, altered anatomy, tapered or mild stricture of distal bile duct, and coagulopathy. EST is superior to EPBD in the patients with stones impaction, difficult deep cannulation, and small CBD diameter without stricture. EPLBD is a safe procedure if it is performed according to the following steps: (1) avoidance of unnecessary pancreatic contrast injection; (2) use of suitable balloon and pressure; and (3) slowly balloon inflation and adequate ballooning time to achieve a widely opened papillary orifice. EPLBD alone is as effective as ESLBD but this point needs more controlled studies to confirm. EPLBD as well as EST is not the sphincter preserved procedure, regular follow-up may be necessary for early detection of recurrent CBD stones.

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MINIREVIEWS

Current status of minimally invasive endoscopic management for Zenker diverticulum

Alberto Aiolfi, Federica Scolari, Greta Saino, Luigi Bonavina

Alberto Aiolfi, Federica Scolari, Greta Saino, Luigi Bonavina, Department of Biomedical Sciences for Health, Division of General Surgery, IRCCS Policlinico San Donato, University of Milan, 20097 San Donato Milanese, Milan, Italy
Author contributions: All the authors contributed to this work.
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Correspondence to: Luigi Bonavina, Professor, Department of Biomedical Sciences for Health, Division of General Surgery, IRCCS Policlinico San Donato, University of Milan, Piazza E. Malan 2, 20097 San Donato Milanese, Milan, Italy. luigi.bonavina@unimi.it
Telephone: +39-2-52774621
Fax: +39-2-52774395
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Abstract

Surgical resection has been the mainstay of treatment of pharyngoesophageal (Zenker) diverticula over the past century. Developments in minimally invasive surgery and new endoscopic devices have led to a paradigm change. The concept of dividing the septum between the esophagus and the pouch rather than resecting the pouch itself has been revisited during the last three decades and new technologies have been investigated to make the transoral operation safe and effective. The internal pharyngoesophageal myotomy accomplished through the transoral stapling approach has been shown to effectively relieve outflow obstruction and restore physiological bolus transit in patients with medium size diverticula. Transoral techniques, either through a rigid device or by flexible endoscopy, are gaining popularity over the open surgical approach due the low morbidity, the fast recovery time and the fact that the procedure can be safely repeated. We provide an analysis of the the current status of minimally invasive endoscopic management of Zenker diverticulum.

Key words: Zenker diverticulum; Endoscopic stapling; Cricopharyngeal myotomy; Diverticulectomy; Interventional flexible endoscopy

Core tip: Developments in minimally invasive surgery and interventional endoscopic techniques have led to profound changes in the management of Zenker's diverticula. Transoral techniques, either through a rigid or flexible endoscopic device, have gained popularity due to the low morbidity, fast recovery time and safe repeatability. However, the choice of treatment is still based on phisician's expertise, personal preferences, and area of specialty. Endostapling through rigid endoscopy remains the most frequently performed approach. Interventional flexible endoscopy is an attractive minimally-invasive treatment option. However, due to heterogeneity of data and lack of standardized protocols, a direct comparison of the various techniques is difficult. Prospective clinical studies are required to establish treatment guidelines for Zenker diverticulum.

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INTRODUCTION

The management of Zenker diverticulum is far from being standardized in current clinical practice. Impaired opening of the upper esophageal sphincter due to increased hypopharyngeal bolus pressure and reduced wall compliance[1,2] are the main physiological determinants of this "pulsion" diverticulum which is more frequent in elderly male patients. It s likely that the prevalence of this disorder will increase in the future due to the increased aging population. Common symptoms are dysphagia, weight loss, regurgitation, halitosis, and aspiration with possible episodes of pneumonia. Preoperative workup should include a videofluoroscopic swallowing study and an upper endoscopy to rule out concomitant esophagogastric disease, and treatment should be reserved for symptomatic patients.

Interestingly, the first surgical resection and the first endoscopic approach with punch forceps were performed before World War I; both procedures were soon abandoned because of the high mortality rate. Between 1950 and 1960 both surgical and endoscopic procedures were revisited and restored to favour: surgeons recognized the importance of adding a cricopharyngeal myotomy to resection, whereas endoscopists introduced the CO_2 laser to divide the septum[3].

Nonetheless, more than 50 years later, despite the revolution of minimally invasive surgery and the introduction of disruptive technologies, we are still left in doubt regarding the choice of the ideal therapy. In the real world, a minimally invasive endoscopic operation may sometimes be the only reasonable choice, especially in elderly patients with multiple comorbidities deemed unfit for conventional open surgery. A tailored approach that takes into account the size of the diverticulum and the patient physiological status seems also reasonable, but clinical evidence is still lacking[4,5].

CURRENT THERAPEUTIC OPTIONS

Treatment options for Zenker diverticulum include open surgery through a left cervical incision (cricopharyngeal myotomy with or without resection), and transoral division of the septum through rigid endoscopy (with stapler, CO2-laser, or harmonic scalpel) or interventional flexible endoscopy (free hand or assisted). No controlled trials have been performed to demonstrate the superiority of one technique over another and, as a consequence, there is no accepted guideline for patient management[6].

Open surgical procedures

Surgical repair of Zenker diverticulum is usually performed under general anaesthesia through a left neck access and consists of stapled diverticulectomy with cricopharyngeal myotomy. Myotomy alone may be preferred for small diverticula. The patient is placed supine with a small pillow under the shoulders and the head hyperextended and turned to the right side. The incision is made parallel to the anterior border of sternocleidomastoid muscle. The pharynx and cervical esophagus are exposed by retracting the sternocleidomastoid and carotid sheath laterally, and the larynx and thyroid medially. Cricopharyngeal and proximal esophageal myotomy is performed after dissecting the pouch from the surrounding loose connective tissue. The diverticulum can be surgically excised with a linear stapler (diverticulectomy), uplifted and suspended to the prevertebral fascia (diverticulopexy), or invaginated into the lumen (Table 1). The results of diverticulectomy have been uniformly satisfactory. In the largest series of 888 patients from the Mayo Clinic, the operative mortality was 1.2%. The most frequent complications were recurrent nerve palsy (3.2%), wound infection (3%), and salivary fistula (1.8%). The reported recurrence rate was less than 5%[7]. A similar outcome with no operative mortality, minimal morbidity, and very good to excellent results has been reported in Europe[8]. Reoperation can represent a technical challenge after open diverticulectomy because of the risk of fistula and recurrent nerve injuries[9].

Transoral procedures

Rigid endoscopy: A transoral technique using an endoscopic stapler introduced through a rigid scope was first proposed in 1993[10-12]. The patient is placed supine with the neck hyperextended; the surgeon is sitting behind the patient's head. The operation is performed under general anaesthesia with orotracheal intubation. The Weerda diverticuloscope is introduced into the esophageal inlet in the closed position, under direct 0° telescopic vision, and it is slowly withdrawn to expose the septum between the diverticulum and the esophageal lumen. The two valves of the diverticuloscope are placed inside the esophagus and the diverticulum, respectively. An endoscopic linear stapler with a 35 mm blue cartridge is introduced through the diverticuloscope down to the septum. One or two cartridges are usually necessary to divide the septum depending on the length of the pouch. The stapler allows safe simultaneous cutting and sealing of the septum. By creating this delta-shaped anastomosis the diverticulum and the esophagus become a common cavity.

The procedure is generally not indicated in small diverticula (< 3 cm)[3]. In case of borderline diverticulum size, traction sutures applied at the apex of the septum with a laparoscopic endostitching device can help to engage the septum between the stapler jaws and allow a more complete septal division[13,14]. Transoral septum stapling is the preferred initial treatment for Zenker diverticulum in many centers and it has been shown to be a safe and effective proce-

Table 1 Outcome of open surgical procedures for Zenker diverticulum

Ref.	No. pts	Technique	Satisfactory outcome (%)	Overall morbidity (%)	Salivary fistula (%)
Orringer[46]	12	M, DM	85	25	8
Ellis *et al*[47]	10	DM	100	0	0
Konowitz *et al*[48]	20	DM	100	20	5
Barthlen *et al*[49]	43	M, DM	82	7	0
Payne *et al*[7]	888	D	93	30	1
Morton *et al*[50]	15	DM	100	40	13
Bonafede *et al*[51]	87	D, DM, DpM	78	24	NA
Fraczek *et al*[52]	37	DM, DpM	93	23	5
Van Eeden *et al*[53]	17	M, DM, DpM	59	6	14
Zbären *et al*[54]	66	DM	77	15	12
Busaba *et al*[55]	9	DM	100	0	0
Leporrier *et al*[56]	40	DM, DpM	92	10	3
Sydow *et al*[57]	13	M, DM, DpM	NA	27	23
Gutschow *et al*[58]	101	M, D, DM, DpM	98	13	13
Zaninotto *et al*[59]	34	DM, M	100	12	6
Colombo-Benkmann *et al*[60]	79	D, DM	99	4	4
Bonavina *et al*[3]	116	DM	94	0.8	0.8
Rizzetto *et al*[4]	77	DM, DpM, M	95	13	4

M: Myotomy; DM: Diverticulectomy/myotomy; D: Diverticulectomy; DpM: Diverticulopexy/myotomy; NA: Not available.

dure[15-17].

The harmonic scalpel (Ultracision, Ethicon Endo-Surgery, Cincinnati, Ohio), operated through the Weerda diverticuloscope, has been used to divide the septum as an alternative to stapling[18-20]. The device is able to cut and simultaneously coagulate tissue with minimal lateral thermal spreading and optimal haemostasis. The small diameter of the scalpel allows an easy maneauverability and the cutting surface extends to its distal tip allowing a distally extended miotomy in small diverticula that could not be suitable for endoscopic stapling.

CO2-laser division of the septum, first introduced in 1981 by van Overbeek[21], represents another alternative or a complementary technique to endoscopic stapling. The operation is generally performed under narcosis with endotracheal intubation. An operating microscope with a 400-mm lens and attached CO_2 laser micromanipulator is introduced and focused on. Using the laser on continuous mode the septum is transected on the midline down to the bottom[22,23]. The CO_2 laser technique is precise but strictly operator-dependent, and the risk of perforation and mediastinitis should not be underestimated. Table 2 shows the results of the transoral procedures through rigid endoscopy.

Interventional flexible endoscopy: Flexible endoscopy was proposed in 1995 for the treatment of Zenker diverticulum[24,25]. Some centers offer this option to all patients, although most authors recommend the endoscopic flexible approach for a selected subset of highly morbid patients who are unfit for surgery or for rigid endoscopy under narcosis[26,27].

Patients are placed in a left lateral decubitus position. The operation is performed either in conscious sedation or under narcosis. The technique can be "freehand" or a variety of different accessories (capo, hood, overtube) can be used to improve septum exposure, stabilize its position, and protect the esophagus and the pouch from thermal injury[28,29]. A novel device for improving the operative field and fixing the septum is the soft diverticuloscope (Zenker overtube; Cook Endoscopy, Winston-Salem, North Carolina, United States)[30,31]. Similar to the Weerda diverticuloscope, this transparent soft-rubber overtube has two distal flaps that protect the esophagus anteriorly and the diverticulum posteriorly. The overtube is advanced over the endoscope and the septum is properly displayed under direct endoscopic vision. Different cutting devices can be used (needle-knife, monopolar forceps, hook-knife, argon plasma coagulation)[32]. Hondo *et al*[33] have recently described the use of the harmonic scalpel introduced through a soft diverticuloscope.

With the needle-knife, the septum is generally divided through a midline incision directed distally towards the bottom of the pouch. The wound edges of the septum separate immediately after the incision. The risk of mediastinal perforation associated with the procedure has led some operators authors to use a clip-assisted (clip and cut) technique where, prior to dissection, two endoclips are placed on either side of the septum[34,35]. Other operators place one or more metal endoclips at the bottom of the incision to secure the margins and prevent microperforations[31].

An incomplete cricopharyngeal myotomy may account for the high recurrence rates associated with single session flexible endoscopy diverticulotomy. A step-wise approach with a limited initial incision followed by multiple repeat procedures could improve the overall clinical outcome and further reduce the risk of perforation[26]. Table 3 shows the results of the transoral procedures through interventional flexible endoscopy.

CLINICAL OUTCOME AND FUTURE PERSPECTIVES OF TRANSORAL PROCEDURES

The obvious advantages of endoscopic stapling over the conventional open surgical approach are the absence of cutaneous incision, shorter operative time, reduced postoperative discomfort, faster return to oral feeding, and shorter length of hospital stay. An additional advantage is expected in patients who had

Table 2 Outcome of transoral rigid procedures for Zenker diverticulum

Ref.	No. pts	Technique	Satisfactory outcome	Overall morbidity	Salivary fistula	Conversion rate
Fremling *et al*[61]	6	Stapling	100%	0%	0%	0%
Peracchia *et al*[36]	95	Stapling	93%	1%	0%	3%
Narne *et al*[62]	102	Stapling	100%	0%	0%	4%
Philippsen *et al*[15]	14	Stapling	100%	0%	0%	21%
Cook *et al*[16]	74	Stapling	97%	3%	2%	8%
Lüscher *et al*[63]	23	Stapling	96%	1%	4%	0%
Jaramillo *et al*[64]	32	Stapling	80%	4%	0%	16%
Thaler *et al*[65]	23	Stapling	87%	0%	0%	30%
Counter *et al*[66]	31	Stapling	95%	10%	10%	0%
Chang *et al*[22]	24	CO_2 laser	90%	8%	0%	0%
Fama *et al*[18]	25	Harmonic Scalpel	96%	12%	0%	0%
Sharp *et al*[19]	48	Stapling/Harmonic Scalpel	88%	12%	2%	0%
Helmstaedter *et al*[23]	40	CO_2 laser	NA	10%	NA	NA
Wasserzug *et al*[67]	55	Stapling	90%	4%	2%	7%
Peretti *et al*[68]	28	CO_2 laser	85%	7%	4%	4%
Nicholas *et al*[13]	7	Stapling	100%	14%	0%	0%
May *et al*[20]	7	Harmonic Scalpel	100%	0%	0%	0%
Bonavina *et al*[14]	91	Stapling	80.8%	5%	1%	13.2%
Adam *et al*[69]	128	Stapling/CO_2 laser	NA	4.6%	0%	NA

NA: Not available.

previous surgical procedures on the left side of the neck in whom the recurrent laryngeal nerve is more likely to be injured at conventional reoperation[36].

Despite all these features and the proof of safety and efficacy, transoral stapling has not been widely accepted as first-line treatment for Zenker diverticulum for a number of reasons: (1) lack of long-term audit; (2) lack of controlled clinical studies; (3) lack of technical expertise and dedicated equipment in many hospitals; (4) lack of confidence or proper training with the transoral access by surgical specialists other than otolaryngologists; and (5) fear of carcinoma arising within the non resected pouch.

Collective data from retrospective or prospectively recorded case series consistently show that a satisfactory outcome with endoscopic stapling is obtained in more than 90% of patients, with a 6% recurrence or persistence rate[37]. A recent article by Leong *et al*[38] reviewed the experience with transoral stapling in England where this technique is performed by the majority of otolaryngologists and is endorsed by the National Institute for Clinical Excellence (NICE). Out of 585 patients reviewed, 540 (92.3%) successfully underwent transoral stapling with an intraoperative conversion rate of 7.7%, an overall complication rate of 9.6%, and an overall recurrence rate of 12.8%. Most of the patients in whom the procedure failed underwent repeat endoscopic stapling.

Small diverticula (< 3 cm) have indeed represented a major cause of long-term failure of transoral stapling[3]. This is due to the difficulties in accommodating of the 30-35 mm anvil. However, in most patients with borderline diverticulum size, the application of traction sutures the apex of the common septum can improve the engagement of the spur in the stapler jaws with a net gain of about 1 cm of stapled tissue[14]. In case of recurrent symptoms, the procedure can be successfully repeated through a transoral approach (rigid or flexible). CO_2 laser or ultrasonic cutting techniques may have a complementary role in some circumstances[39].

Interventional flexible endoscopy is an attractive therapeutic alternative, especially in elderly patients unfit for surgery, and may overcome some of the physical limitations of rigid endoscopy. Flexible endoscopy can be performed in the endoscopic suite, under conscious sedation with midazolam. The procedure allows quick resumption of oral feeding and fast hospital discharge. In patients with persistent or recurrent symptoms the procedure is easily repeatable, and appears to be safe even after failure of endostapling. A recent study has reported similar outcomes for flexible and rigid endoscopy regarding hospital stay, dysphagia score improvement and complication rates[40]. Several case series have shown the safety and efficacy of interventional flexible endoscopy with clinical success rates ranging from 56% to 100%. Perforations and bleeding have been reported in up to 27% and 10% of cases, respectively[27].

Interventional flexible endoscopy for Zenker diverticulum is not standardized, and different cutting techniques can be combined with different accessories depending physicians' personal experience and preferences. The needle-knife is the most frequently used device, often in combination with a transparent cap, hood or soft diverticuloscope. No significant differences in clinical outcomes have emerged by using of one or the other accessory[41,42]. An overall clinical recurrence rate of 25% has been reported in the literature[43]. It is generally recommended that the incision should be carefully balanced in order not to cause mediastinal perforation; on the other hand, a too

Table 3 Outcome of transoral flexible procedures for Zenker diverticulum

Ref.	No. pts	Incision device	Accessories	Satisfactory outcome	Overall morbidity	Salivary fistula
Mulder *et al*[25]	20	Coagulation	Forceps	NA	0%	0%
Ishioka *et al*[24]	42	Needle Knife	Mix	93%	1%	2%
Hashiba *et al*[70]	47	Needle Knife	Mix	96%	2%	13%
Mulder[71]	125	Argon Plasma	None	100%	2%	15%
Sakai *et al*[28]	10	Needle Knife	Hood	100%	1%	0%
Costamagna *et al*[31]	28	Needle Knife	Cap	43%	14%	18%
Rabenstein *et al*[72]	41	Argon Plasma	Cap	95%	0%	3%
Christiaens *et al*[32]	21	Monopolar forceps	Hood	100%	0%	5%
Vogelsang *et al*[34]	31	Needle Knife	Cap	84%	3%	23%
Tang *et al*[35]	6	Needle Knife	Hood/Endoclips	100%	0%	0%
Case *et al*[73]	22	Needle Knife	Cap	100%	32%	27%
Repici *et al*[29]	32	Hook knife	None	88%	6%	3%
Al-Kadi *et al*[74]	18	Needle Knife	None	78%	12%	6%
Hondo *et al*[33]	6	Harmonic scalpel	Soft diverticuloscope	100%	0%	0%

short transection may lead to incomplete myotomy and higher clinical recurrence rates. Unfortunately, when the incision is made in a proximal to distal direction it may be difficult to identify secure landmarks other than the muscular fibres. This has prompted some investigators to assess the safety and efficacy of the hook-knife by directing the incision from bottom to top. The more controlled and precise cut appears to reduce the risk of perforations[29]. More recently, an insulated-tip needle (IT-Knife 2), originally developed for endoscopic submucosal dissection has been tested in a series of 19 patients. The authors noted a more controlled septum incision and no adverse events. Over a median follow-up of 27 mo, dysphagia relapsed in two patients[44]. Finally, a diverticulum cap prototype with a swinging needleknife that is similar in principle to the device used for biliary sphincterotomy has been described and may provide in the future more precise and efficient septum dissection[45].

CONCLUSION

Treatment of Zenker diverticulum has evolved thanks to a better appraisal of the pathophysiology of the disease and the implementation of new techniques in the field of minimally invasive surgery and interventional flexible endoscopy. Over the past three decades the transoral approach has been revisited and, once again, the emphasis of research has shifted from diverticulectomy to myotomy. However, heterogeneity of data and lack of standardized protocols preclude a direct and meaningful comparison of the techniques. No randomized trials nor retrospective case series have demonstrated the superiority of single treatment modalities and, therefore, the choice still depends on physician's expertise and personal preferences. Interventional flexible endoscopy is indeed an attractive treatment option, but at present transoral stapling has a longer follow-up and has been associated with significantly improved quality of life[75]. Further investigation and prospective clinical studies are eagerly awaited to define treatment guidelines for Zenker diverticulum.

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Colonoscopy appropriateness: Really needed or a waste of time?

Antonio Z Gimeno-García, Enrique Quintero

Antonio Z Gimeno-García, Enrique Quintero, Servicio de Gastroenterología, Hospital Universitario de Canarias, 38320 Tenerife, Spain
Antonio Z Gimeno-García, Enrique Quintero, Instituto Universitario de Tecnologías Biomédicas (ITB) and Centro de Investigación Biomédica de Canarias (CIBICAN), Departamento de Medicina Interna, Universidad de La Laguna, 38320 Tenerife, Spain
Author contributions: Gimeno-García AZ and Quintero E contributed to this paper; all authors have participated sufficiently in the conception of this review, as well as the writing, drafting and revising it critically for important intellectual content and final approval of the version to be published.

Correspondence to: Antonio Z Gimeno-García, MD, PhD, Servicio de Gastroenterología, Hospital Universitario de Canarias, Ofra s/n, La Laguna, 38320 Tenerife, Spain. antozeben@gmail.com
Telephone: +34-92-2678554
Fax: +34-92-2678554
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Abstract

Technical and quality improvements in colonoscopy along with the widespread implementation of population screening programs and the development of open-access units have resulted in an exponential increase in colonoscopy demands, forcing endoscopy units to bear an excessive burden of work. The American Society for Gastrointestinal Endoscopy appropriateness guideline and the European panel appropriateness of gastrointestinal endoscopy guideline have appeared as potential solutions to tackle this problem and to increase detection rates of relevant lesions. Inappropriate indications based on either guideline are as high as 30%. Strategies based on these clinical criteria or other systems may be used to reduce inappropriate indications, thus decreasing waiting lists for outpatient colonoscopy, saving costs, prioritizing colonoscopy referrals and subsequently decreasing interval times from diagnosis to treatment. Despite the potential role of appropriateness guidelines, they have not been widely adopted partly due to fear of missing significant lesions detected in inappropriate indications. We review the main appropriateness and prioritising systems, their usefulness for detecting relevant lesions, as well as interventions based on those systems and cost-effectiveness.

Key words: Colonoscopy appropriateness; European panel appropriateness of gastrointestinal endoscopy Ⅱ; National Institute for Health and Clinical Excellence; Colonoscopy prioritisation; Open access endoscopy unit

Core tip: There is increasing worldwide demand for colonoscopy referrals, overburdening endoscopy units. Controlling the appropriateness of colonoscopy referrals has been proposed to decrease the increased workload. The American Society for Gastrointestinal Endoscopy appropriateness and the European panel appropriateness of gastrointestinal endoscopy guidelines, and prioritisation criteria such as those of the National Institute for Health and Clinical Excellence and the Scottish Intercollegiate Guidelines network are good candidates for this task. We review the available systems and interventions designed to rationalize colonoscopy demand.

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INTRODUCTION

During the last decade we have witnessed a gradual increase of endoscopic procedures and a reduction of radiological techniques to examine the gastrointestinal tract such as esophagus-gastro-duodenal transit or barium enema. Some significant quality improvements have contributed to the widespread diffusion of endoscopic techniques, including conscious sedation[1], safety[2] and technological developments.

Furthermore, the implementation of screening programs for the early detection of colorectal cancer (CRC) and the development of open-access endoscopy units may further increase the demand for outpatient colonoscopy and the overall workload of endoscopy units. These factors are particularly worrisome in universal insurance health care systems.

In this setting, rationalization of the demand is mandatory to prevent overburdening endoscopy units, to improve efficiency in colonoscopy and to reduce costs and potential risks arising from inadequate colonoscopy referrals.

This review analyses, firstly, the causes of increasing workload of endoscopy units, with greater emphasis on especially focusing on population screening programs and open-access endoscopy units; secondly, strategies developed to control colonoscopy appropriateness and their results, including appropriateness criteria and adherence to guidelines, and finally criteria for prioritising referrals with higher risk of advanced colorectal neoplasms. Table 1 shows the highlights of this review.

Table 1 Summary box

Appropriateness guidelines and prioritising criteria have been developed to lessen colonoscopy workload in endoscopy units
The sensitivity of EPAGE Ⅱ criteria is higher than that of EPAGE Ⅰ criteria for detecting significant colorectal lesions (especially CRC); however, specificity should be further improved. Since these criteria are not perfect, in clinical practice, they should be used to assist the clinician before requesting a colonoscopy but they should not be the sole criteria for the decision
Although EPAGE Ⅱ criteria might be used to cancel inappropriate colonoscopy referrals, in clinical practice they should be used with caution, because some life-threatening lesions are missed, even in inappropriate requests
NICE criteria used for prioritising colonoscopy are not accurate enough for detecting advanced colorectal neoplasms, but may be improved in combination with other markers (*i.e.*, immunochemical fecal occult blood tests)
Adherence to guidelines required to decrease inappropriate indications and colonoscopy waiting lists

EPAGE: European panel appropriateness of gastrointestinal endoscopy; CRC: Colorectal cancer; NICE: National Institute for Health and Clinical Excellence.

INCREASING WORKLOAD OF ENDOSCOPY UNITS: SCREENING COLONOSCOPY AND OPEN ACCESS ENDOSCOPY UNITS

A recent survey carried out in the United States found that the number of colonoscopies performed had risen three to four times between 1998 and 2004[3], with colonoscopy being the most demanded endoscopic procedure. Similar patterns have been found in Europe[4]. Furthermore, the European Commission has recommended the implementation of programs for the detection of CRC in all countries of the Union[5]. A recent report assessed the amount of colonoscopies generated by a population screening program, depending on the screening strategy and uptake. Assuming a participation rate of 60%, screening might double the annual workload of endoscopy units[6]. Another source of additional referrals arising from screening programs are subsequent surveillance colonoscopies required after the resection of colorectal adenomas and CRC. Notably, surveillance colonoscopy after resection of colorectal adenomas is the most frequent indication in patients aged over 74 years in the United States, accounting for 28.9% in women and 37.9% in men[7]. Furthermore, according to a recent meta-analysis, more than 30% of the average-risk population may have colorectal adenomas[8]. Similar data have been reported in European studies[9-11]. Such a volume of colonoscopies represents a substantial burden.

A potential source of inappropriate referrals is open-access endoscopy units, increasingly frequent in both the United States and Europe. In open-access endoscopy units, any physician (not only a gastroenterologist) may request an endoscopic procedure[12]. These units emerged in an effort to save costs, preventing unnecessary office consultations with the gastroenterologist. Open-access endoscopy units may also be useful as a "shortcut", decreasing waiting times between consultation and colonoscopy. In fact, time off work for appointments is a problem for patients and open-access endoscopy units may expedite the diagnosis of severe diseases, and decrease empirical treatments[13]. However, one wonders whether the ease of access would not also increase the workload of endoscopy units resulting from a higher rate of inappropriate referrals, further increasing waiting lists and total costs. Thus, rationalization of the indication is considered essential.

Open access endoscopy units can be roughly classified as simple or censored. While no control system is applied in the former, in the latter, referral appropriateness is continuously checked by trained staff[14].

Table 2 Main indications for colonoscopy according to European panel appropriateness of gastrointestinal endoscopy Ⅱ (www.epage.ch)

Iron deficiency anemia
Hematochezia
Discomfort or pain in the lower abdomen persisting ⩾ 3 mo
Uncomplicated chronic diarrhea
Assessment of ulcerative colitis
Assessment of Crohn disease
Colorectal cancer screening
Colorectal cancer screening in patients with inflammatory bowel disease
Surveillance colonoscopy after polypectomy
Surveillance colonoscopy after colorectal cancer resection
Miscellaneous

APPROPRIATENESS CRITERIA FOR IMPROVING COLONOSCOPY INDICATION

A procedure is deemed appropriate as long as health advantages outweigh the theoretical risks by a wide margin of safety[15]. As resources are limited, adherence to the appropriate indications for colonoscopy is necessary. Appropriateness guidelines may be useful not only to prevent unnecessary colonoscopies and potential risks resulting from them, but also to prioritize colonoscopy[10,16].

American Society for Gastrointestinal Endoscopy and European panel appropriateness of gastrointestinal endoscopy Ⅰ criteria

The first guideline was developed by the American Society for Gastrointestinal Endoscopy (ASGE)[17]. It consists of 27 general indications for colonoscopy. This guideline has been adopted with some modifications by the Italian Society of Gastrointestinal Endoscopy which uses wider criteria and includes some indications unlisted by the original guideline, such as significant weight loss and changes of bowel habit[18]. The application of these modified criteria slightly increases the rates of appropriateness and detection of significant lesions, especially CRC[19]. In 1999, European experts, including gastroenterologists, surgeons and family physicians, designed the criteria of the European panel appropriateness of gastrointestinal endoscopy (EPAGE-Ⅰ)[20]. These criteria are based on a detailed review of the literature. The European panel established 12 main indications for colonoscopy, including 309 different clinical scenarios. Each clinical situation is scored from 1 to 9 (appropriate 7-9; 1-3 inappropriate; 4-6 uncertain). Colorectal cancer, adenomas, inflammatory bowel disease, stenosis and angiectasia are usually considered "significant lesions". Compared with ASGE criteria, EPAGE-Ⅰ criteria are more specific and detailed. With regard to the prediction of appropriateness, the two systems have been shown to be similar[19,21-28]. The rate of inappropriate referrals ranged from 20%-30% for both guidelines[21-24,26,27,29]; however, they have never been compared for colonoscopy referrals. One factor that might influence appropriateness is the role of physician specialty. In this regard, results are controversial; in some studies no differences between gastroenterologists and other specialists were found[21,23], in others, the data were favourable to gastroenterologists[28].

It must be said that neither set of criteria is perfect. First, significant lesions are detected in about 30% of inappropriate colonoscopies[22]. This has been attributed to incidental findings of asymptomatic lesions. In fact, one meta-analysis showed the suboptimal sensitivity of alarm symptoms for CRC detection, ranging from 5%-64% across the studies[30]. Second, it is well-known that some alarm signs and symptoms are also frequent in other diseases, leading to poor specificity. A recent meta-analysis assessed the performance of ASGE and EPAGE-Ⅰ criteria for the detection of significant lesions (as defined in each manuscript)[31]. Sensitivity, specificity, positive and negative likelihood ratios were: 89% (95%CI: 82%-93%), 26% (95%CI: 21%-31%), 1.16 (95%CI: 1-1.3), 0.44 (95%CI: 0.25-0.8), respectively. These data were similar to those reported for CRC. The authors concluded that a more effective strategy is needed and that both sets of criteria need further refinement to increase sensitivity (especially for CRC) and positive predictive value, and to minimize the number of colonoscopies in patients without significant lesions.

The most frequent cause of inappropriateness identified by both sets of criteria is surveillance colonoscopies after polypectomy or CRC surgery that are performed too early[25,27,28]. In a study involving more than 3000 colonoscopies, the most frequent causes of inappropriate indication were surveillance colonoscopies performed by general practitioners (GPs), surgeons and internists, and by gastroenterologists in the context of inflammatory bowel disease[26].

EPAGE Ⅱ criteria

EPAGE-Ⅰ and ASGE appropriateness guidelines are not sufficiently widespread. As mentioned, there are some concerns regarding safety when using these criteria, as a significant percentage of relevant lesions are detected in improperly requested colonoscopies.

More recently, an updated version of the EPAGE-Ⅰ criteria for colonoscopy has been published (EPAGE-Ⅱ criteria), after a comprehensive review of the literature from 1998 to February 2008 (Table 2)[32]. To date, four studies have assessed the benefit of EPAGE-Ⅱ criteria for predicting appropriateness and diagnostic yield of significant lesions (Table 3)[9-10,16,33]. Only in the largest study was the design fully prospective[10]. Three studies were carried out in Spain[9-10,33] and one in Norway[16]. Although statistical performance with confidence intervals of EPAGE-Ⅱ studies were described in only two of the studies[10,16], enough information was available in the other two for

Table 3 European panel appropriateness of gastrointestinal endoscopy Ⅱ studies addressing appropriateness and diagnostic yield

Ref.	Design[1] (referrals)	EPAGE Ⅱ[2] (% appropriate)	S[3] (95%CI)	Sp (95%CI)	PPV (95%CI)[4]	NPV (95%CI)
Carrión *et al*[33] (2010)	R 655	82.0	80.3 (74.0-84.3)	16.8 (14.9-18.5)	24.8 (23.1-26.4)	71.3 (63.1-78.6)
Arguello *et al*[9] (2012)	R 619	82.6	78.3 (73.8-82.4)	34.4 (31.3-37.3)	45.2 (42.6-47.6)	69.6 (63.4-75.4)
Gimeno García *et al*[10] (2012)	P 968	89.5	93.1 (90.0-96.3)	12.7 (10.0-15.0)	38.8 (36.0-42.0)	75.5 (67.0-84.0)
Eskeland *et al*[16] (2014)	R 295	91.0	92.6 (84.8-96.6)	22.9 (17.8-29.0)	31.3 (25.3-37.3)	89.1 (80.7-97.5)

[1]Study design: R (retrospective); *P* (prospective); [2]Appropriate and uncertain referrals jointly analysed; [3]S (sensitivity); Sp (specificity); [4]PPV (positive predictive value); NPV (negative predictive value).

calculation[9,33]. Taking into account the pooled results of the four studies, 75.4% of colonoscopy referrals were deemed appropriate, 13.9% inappropriate and 10.7% uncertain.

A validation study of these criteria showed that significant lesions were more prevalent in appropriate colonoscopies than in those considered inappropriate (38.8% *vs* 24.5%; OR = 1.95, 95%CI: 1.22-3.13; $P < 0.005$)[10]. This study also reported the performance for significant neoplastic lesions (advanced adenoma and CRC), showing sensitivity, specificity, positive and negative predictive values of 98% (95%CI: 95-100), 11.5% (95%CI: 9-14), 11.2 (95%CI: 9-13) and 98% (95%CI: 95-100) respectively. In accordance with other studies, an appropriate indication was more frequent in patients over 50 years compared with younger individuals (92.9% *vs* 76.7%; OR = 3.98, 95%CI: 2.60-6.09, $P < 0.001$). In fact, 50% of inappropriate referrals were found in patients younger than 50 years, despite constituting only 20% of referrals. In studies carried out in Spain, the indication with the highest rate of inappropriateness was surveillance colonoscopy, ranging from 41% to 76%[9-10,33], whilst in the Scandinavian study, this was lower abdominal symptoms (49%)[16]. In one study, inappropriateness in subjects younger than 50 years was separately analyzed. CRC screening at a younger age than usually recommended (33.3%) followed by surveillance colonoscopy at shorter intervals than recommended (20.8%) were the most frequent causes of colonoscopy overuse[10].

Recent evidence has shown that the application of EPAGE-Ⅱ criteria decreases rates of inappropriateness compared with EPAGE-Ⅰ criteria and, more importantly, decreases the rate of missed significant lesions[9,16]. In both studies, the specificity of EPAGE-Ⅱ criteria was lower than that of the first version, theoretically decreasing the impact of EPAGE-Ⅱ criteria on saving colonoscopies. Nevertheless, EPAGE-Ⅱ might be considered safer than EPAGE-I with respect to missed significant lesions. Some authors have suggested jointly calculating uncertain and inappropriate colonoscopies, as opposed to what is usually done (combining appropriate and uncertain together)[16]. In fact, no significant differences in diagnostic yield were found in two studies that compared different combinations[9,16]. However, some CRC might be missed with this approach. Of 109 CRC diagnosed in the 4 series, 2 were diagnosed in inappropriate referrals (1.83%) and 3 more in uncertain ones (2.75%). Therefore, it seems safer to consider uncertain and appropriate referrals together to prevent missing significant lesions. Recently, the combination of EPAGE criteria with blood or fecal biological markers was tested with the purpose of increasing appropriateness and improving diagnostic yield of significant lesions[34]. In one study, fecal calprotectin[34], which has shown its capacity to distinguish organic diseases (*i.e.,* inflammatory bowel disease) from functional disorders, was tested with EPAGE criteria in 224 consecutive patients with abdominal discomfort. Diagnostic yield for significant lesions was significantly higher when the combined strategy was used (70.2%) compared with either EPAGE or calprotectin alone (diagnostic yield 23.6% and 57.4% respectively). The combined strategy also improved re-classification of patients with a higher rate of appropriateness.

In summary, the refined EPAGE Ⅱ criteria are more sensitive than the old EPAGE Ⅰ, and may be an effective strategy to assist the clinician to decide whether a colonoscopy should be requested or not. They may also be a useful tool for decreasing colonoscopy overuse, as well as increasing diagnostic yield.

INTERVENTIONS BASED ON APPROPRIATENESS CRITERIA

Several studies have suggested that the medical specialty of the referring physician may influence colonoscopy appropriateness[9,10,21,28], with surveillance after polypectomy at shorter intervals than recommended being the most inappropriate indication. Therefore interventions based on audits and training of referring physicians are warranted to increase appropriateness.

Using EPAGE Ⅱ criteria[10], 91% of the inappropriate referrals corresponded to CRC screening, surveillance of neoplastic lesions (adenomas or CRC) or to subjects younger than 50 years. Subjects with any of these conditions had a lower rate of significant lesions and advanced neoplastic lesions than those who did not meet these conditions (31.2% *vs* 46.6%, $P < 0.001$; OR = 1.9, 95%CI: 1.47 to 2.51 and 5.1% *vs* 18.1%, $P < 0.001$; OR = 4.1, 95%CI: 2.60 to 6.41, respectively). In an interventional prospective study[35], 451 patients with high probability for inap-

propriateness (age < 50 years, surveillance colonoscopy or screening colonoscopy) were attended in an appropriateness outpatient clinic. EPAGE Ⅱ criteria along with current Spanish Association of Gastroenterology guidelines[36-38] were applied and colonoscopy was finally requested when deemed appropriate. In patients with an inappropriate indication, a different approach was carried out; a more suitable examination was requested, (*i.e.,* biochemical tests, abdominal ultrasonography) or treatment was prescribed when a functional disorder (intestinal bowel syndrome or functional dyspepsia) was suspected. Appropriateness was compared with a historical cohort of 968 patients who underwent colonoscopy and to whom EPAGE-Ⅱ criteria were applied. The intervention achieved a significant reduction of inappropriateness (5.2% *vs* 10.5%, OR = 0.46, 95%CI: 0.27-0.81) and, furthermore, increased the diagnostic yield of significant lesions (50.7% *vs* 37.3%, OR = 1.73; 95%CI: 1.33-2.25). However, these encouraging results of a censored open access unit should be taken with caution as the cost-effectiveness of this strategy has not been evaluated yet.

In another interventional study[19], involving 133 GPs, a tailored educational program was assessed using ASGE/SIED appropriateness guidelines. Fifty GPs finally attended the course and completed a multiple choice test to assess the level of learning. The rest received a brief summary of the ASGE/SIED appropriateness criteria by regular mail. Colonoscopy appropriateness was compared before and after the intervention. In this study, appropriate referrals significantly increased from the first to the second period, resulting in a mere 7% of inappropriateness (23% *vs* 7% respectively; $P < 0.001$). Although the effect was more striking among attendants, appropriateness also increased in those GPs who did not attend the course but received the ASGE/SIED criteria by mail. Furthermore, the authors also reported long-term efficacy of the intervention, with the benefit being maintained 1 year later. Therefore, this study encourages greater diffusion of the current guidelines on the main colonoscopy indications and the usefulness of periodic educational programs in an open access unit setting.

ADHERENCE TO GUIDELINES

Several studies have addressed the impact of compliance with the current surveillance guidelines after adenoma or CRC resection on colonoscopy waiting lists[39,40]. One study evaluated the effect of good compliance with the guidelines proposed by the American Gastroenterology Association (AGA) for surveillance after resection of colorectal adenomas on improving appropriateness and decreasing the waiting list[40]. Compliance with guidelines not only improved appropriateness in this indication but also increased the interval between surveillance colonoscopies by 0.73 years, with a 14% reduction of annual colonoscopies for this indication. Another work assessed the impact of compliance with the guidelines of the British Society of Gastroenterology and the Association of Coloproctology of the United Kingdom and Ireland for screening and surveillance after endoscopic polypectomy[39]. In this multicenter study, researchers from a tertiary care referral center applied these guidelines to the waiting list of several hospitals, recommending the exclusion of patients with an inappropriate referral. Overall, in 78% of cases the indication was inappropriate. The appointment was delayed in 27% on them, whilst the indication was deemed inappropriate in the remaining 51% and were cancelled. The authors therefore concluded that adherence to the guidelines could reduce waiting times for diagnostic colonoscopy, but might trigger ethical and moral debate.

CLINICAL IMPACT AND COST-EFFECTIVENESS OF APPROPRIATENESS GUIDELINES

The educational-based intervention study reported by Grassini *et al*[19], noted above, estimated a saving of 19500 euros per year in a low-volume endoscopy unit (1700 colonoscopies per year) and a 15% reduction on the waiting list for outpatient colonoscopy. A recent systematic review assessed the impact of ASGE and EPAGE-Ⅰ criteria on the cost-effectiveness of colonoscopy based on the appropriateness of an indication in selecting patients who were referred ~~to~~ for colonoscopy[41]. Appropriateness studies reported until 2007 were considered for inclusion. In a decision-analysis model, a relatively high prevalence of CRC was found in inappropriate referrals (1.1%; 95%CI: 0.7%-1.4% *vs* 5.6%; 95%CI: 5.1%-6%) along with a significant reduction in survival because of CRC diagnostic delay. Therefore, the authors recommended refining the current criteria before using them in routine clinical practice. However, only the first version of EPAGE criteria was used in the studies included, but not the more recent EPAGE Ⅱ criteria, which as previously mentioned are significantly more sensitive, especially for CRC.

STRATEGIES FOR PRIORITIZING PATIENTS

Some systems have been developed to prioritise patients with alarm signs or symptoms. The most well-known is the one developed in the United Kingdom by the National Institute for Health and Clinical Excellence (NICE), implemented in 2000 (Table 4)[42]. Based on this system, patients meeting certain clinical criteria are referred for consultation with the gastroenterologist within two weeks in order to decrease waiting times for CRC diagnosis[43]. This guideline was updated in 2005, with the goal of reducing death

Table 4 Clinical criteria for prompt colonoscopy referral (2 wk) according to the National Institute for Health and Clinical Excellence in the United Kingdom[44]

Patients ⩾ 40 yr with rectal bleeding and change of bowel habit persisting ⩾ 6 wk
Patients ⩾ 60 yr with rectal bleeding persisting ⩾ 6 wk without a change in bowel habit and without anal symptoms
Patients ⩾ 60 yr with a change of bowel habit persisting ⩾ 6 wk without rectal bleeding
Patients with right lower abdominal mass
Patients with palpable rectal mass
Patients with unexplained iron deficiency anemia (⩽ 11 g/100 mL in men and ⩽ 10 g/100 mL in women)

rates by 20% in people under 75 years in 2010[42]. The United Kingdom National Health Service later developed the "straight to test" approach for suspected CRC, in order to delete time-wasting visits and therefore delays in the diagnosis phase[44]. The Scottish Intercollegiate Guidelines network (SIGN) has also developed referral criteria which are less strict than NICE criteria. They are also based on alarm signs and symptoms of CRC[45] (Table 5).

Beggs *et al*[46], compared the effect of the two week-referral pathway for colonoscopy with the traditional pathway (referring the patient firstly to the gastroenterologist) on colonoscopy waiting lists and direct costs (only consultation and colonoscopy). The former strategy was less costly (saving more than £ 26.000), and also significantly reduced colonoscopy waiting list numbers compared with the usual care process (by 166.6 d, $P < 0.01$). Another study assessed the time intervals between referral for colonoscopy, diagnosis and treatment in a fast referral group compared with the usual care process[47]. As expected, delay to endoscopic and histological diagnosis was significantly lower for the fast referral group ($P < 0.0001$), but also to treatment ($P = 0.048$). One study showed that the "straight to test" strategy was also an effective strategy for CRC detection at early stages compared with the standard of care[48].

A recent Spanish multicenter study highlighted the limited accuracy of NICE criteria in a prospective cohort of 787 symptomatic patients referred for colonoscopy[49]. NICE and SIGN criteria were compared with the immunochemical fecal occult blood test (FIT) at 100 ng/ml threshold for CRC detection. FIT was significantly more sensitive than NICE criteria (87.6% *vs* 61.9% respectively; $P < 0.001$) but similar to SIGN criteria (82.5%, $P = 0.4$). However, the specificity of FIT was significantly higher than either NICE or SIGN criteria (77.4%, 65.2% and 42.7% respectively; $P < 0.001$). These data support the idea that, in isolation, NICE criteria lack sufficient diagnostic accuracy and should be used in combination with other markers. Studies using a combination of clinical, blood and fecal markers are currently ongoing in order to improve the accuracy of the clinical criteria[50].

Recently, risk scores based on demographic and clinical information have been developed for either symptomatic or asymptomatic patients in order to prioritise outpatient colonoscopy[51,52]. Law *et al*[52], with 1013 symptomatic Asian subjects, showed that a score higher than 17 predicted CRC with a specificity of 96%. The area under the curve of the risk score was 0.83, proving that the model had a good discrimination, leading the authors to conclude that this model might be useful to prioritise colonoscopy. Another recent study, carried out in asymptomatic Caucasian patients[51], validated a model for detecting advanced colorectal neoplasia based on demographics and family history of CRC. The authors suggested that this model might help health care providers to make decisions about screening.

Table 5 Scottish Intercollegiate Guidelines network referral criteria[45]

1 Persistent rectal bleeding without anal symptoms
2 Persistent change in bowel habit (> 6 wk)
3 Significant family history
4 Right-side abdominal mass
5 Palpable rectal mass
6 Unexplained iron deficiency anemia
7 Persistent diarrhea

CONCLUSION

Although appropriateness criteria (ASGE and EPAGE Ⅱ criteria) enable a better selection of colonoscopy referrals and increase the rate of significant lesions detected, further refinement is required since some relevant lesions are still missed even when the more sensitive EPAGE Ⅱ criteria are used. Prioritising systems such NICE criteria seem to accelerate CRC diagnosis and treatment, without increasing the waiting list for outpatient colonoscopy, but they might not be sensitive enough for selecting patients with CRC. Educational programs on surveillance colonoscopy and adherence to the current guidelines are warranted to reduce inappropriate referrals. Finally, the combination of clinical criteria (appropriateness or prioritising criteria) with blood or fecal markers might be a better approach than isolated clinical criteria to increase the diagnostic yield of significant lesions.

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Sedation in gastrointestinal endoscopy: Where are we at in 2014?

Alexandre Oliveira Ferreira, Marília Cravo

Alexandre Oliveira Ferreira, Serviço de Gastrenterologia, Centro Hospitalar do Algarve, Unidade Hospitalar de Portimão, 8500 Portimão, Portugal
Marília Cravo, Serviço de Gastrenterologia, Hospital Beatriz Ângelo, 2674-514 Loures, Portugal
Author contributions: Ferreira AO and Cravo M contributed equally to this manuscript.

Correspondence to: Alexandre Oliveira Ferreira, MD, Serviço de Gastrenterologia, Centro Hospitalar do Algarve, Unidade Hospitalar de Portimão, Sítio do Poço Seco, 8500 Portimão, Portugal. alex.gastrohep@gmail.com
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Abstract

Gastrointestinal endoscopies are invasive and unpleasant procedures that are increasingly being used worldwide. The importance of high quality procedures (especially in colorectal cancer screening), the increasing patient awareness and the expectation of painless examination, increase the need for procedural sedation. The best single sedation agent for endoscopy is propofol which, due to its' pharmacokinetic/dynamic profile allows for a higher patient satisfaction and procedural quality and lower induction and recovery times, while maintaining the safety of traditional sedation. Propofol is an anesthetic agent when used in higher doses than those needed for endoscopy. Because of this important feature it may lead to cardiovascular and respiratory depression and, ultimately, to cardiac arrest and death. Fueled by this argument, concern over the safety of its administration by personnel without general anesthesia training has arisen. Propofol usage seems to be increasing but it's still underused. It is a safe alternative for simple endoscopic procedures in low risk patients even if administered by non-anesthesiologists. Evidence on propofol safety in complex procedures and high risk patients is less robust and in these cases, the presence of an anesthetist should be considered. We review the existing evidence on the topic and evaluate the regional differences on sedation practices.

Key words: Hypnotics and sedatives; Propofol; Conscious sedation; Endoscopy; Gastrointestinal

Core tip: Sedation in endoscopy is a hot topic. There is a wide range of practices depending on the countries and even regionally at a national level. These differences range from no sedation to traditional sedation or propofol based sedation (with or without an anesthetist) and are the result of several factors which include cultural aspects, medical training, legal responsibility and societal lobbying. Herein we review the most important evidence regarding the sedation aspects in the endoscopy suite and compare practices which vary among several countries.

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INTRODUCTION

Sedation is a fundamental aspect of gastrointestinal (GI) endoscopy. Although some patients can perform diagnostic esophagogastroduodenoscopy (EGD) and colonoscopy without sedation, the use of sedation is associated with a higher patient satisfaction[1,2] and procedural quality[3]. There is also an increasing demand for sedation by the patients and all endoscopists should be in position to comply with such demand.

There are several options for sedation which range from light sedation (anxiolysis) to general anesthesia depending on the procedure being performed, the center expertise and the individual patient. Still, the most commonly used sedation is moderate-deep sedation achieved by midazolam with or without an opioid (meperidine/pethidine, fentanyl or alfentanyl), which is commonly designated as "traditional sedation", with the other option being propofol which can also be used alone or in combination with analgesic opioids or midazolam. This review revolves around the value of sedation, the most common options and the similarities and differences between them. We also aim to discuss the role of anesthesia providers in the equation.

SEDATION AND PHARMACOLOGY

Midazolam is a short acting, water soluble, highly lipophilic benzodiazepine that was approved in the 80's. The agents of this class act by binding to the type A γ-aminobutyric acid (GABA) receptor and enhancing its' inhibitory actions on the central nervous system. Midazolam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant and antegrade amnestic properties[4]. It's 1.5-3.5 times more potent than diazepam and it has a shorter onset (1-2 min) and duration of action (15-80 min) when compared to other benzodiazepines[5,6]. Midazolam is metabolized by the liver and its' metabolites are excreted by the kidney.

Intravenous midazolam allows for moderate (conscious) sedation with commonly used doses in endoscopy ranging from 2 mg to 6 mg[7] but frequently a state of deep sedation is inadvertently achieved, at least when used in combination with an opioid[8].

The major side effect is respiratory depression but it may also cause cardiovascular effects (hypotension and dysrhythmias) and occasionally "paradoxical" reactions occur with hostility and aggression occurring after administration. This reaction has been described to have an incidence of 1.4% and while it usually doesn't preclude completion of the procedure it renders it more difficult. The combination of pethidine has been suggested, in an observational study, to lower the risk for such reactions[9].

Midazolam action can be reversed by the administration of flumazenil (a benzodiazepine antagonist) which has an onset of action of 1-2 min with a duration of 60 min, a little shorter than midazolam explaining why the sedation level may deepen again after some time.

Propofol (2, 6-diisopropofol) is a hypnotic drug with minimal analgesic properties. Propofol also exerts its effect through potentiation of the GABA by reducing the rate of GABA-receptor dissociation[10].

It is highly lipophilic which enables it to have a quick onset, corresponding to one arm-brain circulation time (30-45 s) and a short, predictable duration of action (4-8 min)[11]. Propofol is metabolized in the liver and excreted by the kidney. Several factors significantly alter its' pharmacokinetic profile and clinical effects with the major ones being age, weight and sex, with the elderly being significantly more sensitive to low doses.

Propofol formulations vary but usually they contain soybean oil and purified egg phosphatide and it should be avoided in patients with known allergies/hypersensitivity to egg and soy products.

Propofol induces respiratory depression in a dose-response fashion and it has a negative cardiac inotropic effect causing a decrease in cardiac output, systemic vascular resistance and arterial pressure[7]. Transient pain on injection site is common, affecting up to 50% of patients[12]. Apart from these clinically non-significant effects, serious adverse events leading to death are very rare and the risk is estimated to be even slimmer in low risk patients (ASA Ⅰ-Ⅱ), ranging from 1:10000 to 1:300000[13].

The most common agents used for sedation and their pharmacologic profile are shown in Table 1.

HISTORICAL AND GLOBAL PERSPECTIVE

GI endoscopies are invasive, unpleasant and sometimes painful experiences. To overcome such unpleasantness, we have been searching for ways to minimize it since the introduction of the fiberscope in the 50's.

The technological advances in endoscopy have improved the diagnostic and therapeutic capabilities throughout the GI tract but they have also allowed for faster and less painful examinations. Advances like the utilization of thinner endoscopes[14], variable stiffness colonoscopes[15], CO_2 insufflation[16] and water immersion techniques (in colonoscopy)[17] allow for less painful procedures. Although helpful, these options are probably not as effective as medical sedation has been shown to be.

There has been a continuous evolution on sedation practices for endoscopy since the early 60's when pentobarbital use was described in conjunction with a transtracheal xylocaine injection[18]. The use of meperidine as an analgesic was an initial strategy and it was followed by the widespread adoption of the combination with diazepam, which was shown to improve the rate of "satisfactory examinations" by 20% comparing to meperidine alone[19]. This set the *rationale*

Table 1 Pharmacologic profile of commonly used drugs for procedural sedation

Drugs	Onset of action (min)	Duration of action (min)	Usual doses	FDA pregnancy category	Adverse effects
Pethidine	3-6	60-180	25-100 mg	C	Respiratory depression, vomiting
Fentanyl	1-2	30-60	50-200 μg	C	Respiratory depression, vomiting
Alfentanyl	< 1	30-60	0.250-2 mg	C	Respiratory and cardiovascular depression
Midazolam	1-2	15-80	1-6 mg	D	Respiratory depression, disinhibition
Propofol	< 1	4-8	40-400 mg	B	Respiratory and cardiovascular depression
Flumazenil	1-2	60	0.1-1 mg	C	Agitation, withdrawal symptoms
Naloxone	1-2	30-45	0.2-1 mg	B	Narcotic withdrawal

for the so called traditional sedation.

After almost two decades there was the advent of midazolam[6]. Midazolam had a very good acceptance in the endoscopy community in virtue of its faster induction time, higher effectiveness and shorter duration of action comparing to diazepam while keeping the safety feeling provided by the existence of a reversal agent. However, there were several (71) death reports in the 80's with midazolam based sedation and the Food and Drug Administration (FDA) issued a warning on this topic. Later, a more systematic epidemiological approach, led by a joint effort from the FDA and the American Society of Gastrointestinal Endoscopy (ASGE), failed to show an increased risk of death with midazolam compared with diazepam[20]. At the present time, midazolam is considered a safe agent and is commonly used as a sedative in gastrointestinal endoscopy.

Propofol, an ultra-short acting hypnotic agent, entered the arena a few years after midazolam[12] but it had a much slower uptake due to its use mostly as an anesthetic agent and as a sedative for critically ill patients and its' product label states that it "should be administered by persons with training in general anesthesia" in the United States and by anesthetists and intensive care physicians in some European countries. Because of this, most endoscopists feel untrained to administer propofol. Still, from a pharmacokinetic/pharmacodynamic point of view, propofol is superior to midazolam as it has a faster onset and a shorter predictable duration of action[11]. Propofol has since been proved to be a better sedative for endoscopy when compared to traditional sedation, improving both patient and endoscopist satisfaction, procedural quality indicators (such as cecal intubation time), induction, wake up and psychomotor recovery times[1,2,21-23]. These improvements are achieved without an increased risk for adverse events as shown in several meta-analyses of randomized controlled trials (RCT)[1,2,24]. These characteristics may have significant impact in procedural quality, patients' acceptance (especially for screening procedures) and endoscopic unit productivity.

One important concern regarding sedation in colonoscopy is the theoretical increase in perforation risk. In two observational but robust population based studies in the United States it has been shown that propofol sedation is not associated with an increased perforation risk[25,26]. It may, however, be associated with a slightly higher risk for aspiration pneumonia[26]. Another recent observation study showed an increased risk for perforation but only in therapeutic colonoscopy and when adjusted for confounders the odds ratio was 1.34 with a *P* value of 0.04[27]. Obviously, it is hard to detect small effect sizes for rare outcomes such as colonic perforation, but so far, the available evidence suggest that sedation doesn't play a significant role in perforation rates.

Despite the advantages of propofol and the endorsement of propofol sedation by several national and international societies[28-32], it is still underused in most settings, because of medico-legal aspects, namely the requirement of an anesthesiologist and, consequently, increased costs[33].

The non-availability of NAAP seems to be a limiting step for the availability of propofol sedation and it significantly increases costs in a non-reasonable tradeoff. This has been shown in a recent cost-effectiveness analysis by Cesare Hassan, with a calculated cost of 1.5 million USD/life year gained[34].

There is wide variability in sedation practice worldwide. In the United States the number of endoscopic procedures in increasing[35], as a result of the increased uptake of colorectal cancer screening colonoscopy. The participation of an anesthesiologist in endoscopy has doubled from 14% in 2003 to 30% in 2009[36] and it's expected to pass the 50% mark by 2015[37]. On the other hand, non-anesthesiologist administration of propofol (NAAP) is becoming less common, as a result of Medicare reimbursement change in 2009[38], although this policy has been rejected by several states.

In Europe the variability is even bigger. In most countries routine diagnostic EGDs are performed without sedation[39] with colonoscopies being more likely to receive some form of sedation[33]. The countries with highest rates of propofol sedation are probably Switzerland[40] and Germany[41] with high rates of NAAP. In the latter, over 90% of the colonoscopies are performed with sedation, 97% of them with propofol and only 2% of those with support of an anesthesiologist. These data were acquired from a German national survey in 2011 with 732 respondents and showed an increase in sedation and propofol rates

comparing to the first survey, 4 years earlier.

NAAP is also a common practice in Denmark, Austria, Spain, Italy, Greece, the Netherlands and Sweden[32,42-45].

In other countries, like France and Portugal, virtually all endoscopic sedation with propofol is performed with an anesthesiologist. Unpublished data from our group regarding a national survey performed in Portugal in 2014, showed less than 3% of endoscopists perform NAAP and that propofol is used in less than half of the colonoscopies.

SEDATION IN SPECIAL POPULATIONS

There are populations that require specific considerations[46], especially the elderly, the obese, patients with cirrhosis, pregnant women, patients with pulmonary disease and acutely ill patients.

In the elderly one must be aware of the slower onset of sedation and the higher sensitivity to sedatives. These patients are at an increased risk for cardiopulmonary events and aspiration syndrome. The recovery times are also increased due to slower hepatic and renal clearance and a higher fat body mass. Sedatives should be titrated at a slower pace and smaller doses should be generally used[47].

Obesity is a growing pandemic, especially in the United States. Obesity is frequently associated with other comorbidities and is considered an independent risk factor hypoxemia and the need for airway permeabilization maneuvers[48]. Still, even though these patients are at a higher risk for minor events, it's considered safe to perform sedation for endoscopic procedures by trained personnel[46].

Cirrhosis is a comorbid condition with significant impact on a patient's health status. Cirrhotic patients are supposed to undergo surveillance EGDs for esophageal varices and frequently undergo endoscopic procedures for indications such as anemia, bleeding, liver transplant evaluation or adenoma surveillance. Sedation in these patients pose some concerns due to hepatic dysfunction, decreased drug clearance and risk for hepatic encephalopathy. Several studies looked into this effect. Riphaus *et al*[49] performed a RCT that showed that propofol sedation was superior to midazolam in terms of recovery times and cognitive impairment after EGD[49]. A larger RCT comprising 211 patients confirmed these findings[50]. In a more recent RCT, in South Korea, propofol was shown to be safe in cirrhotic patients comparing to healthy controls[51]. Propofol is, therefore, considered the best option for sedation in patients with cirrhosis.

Pregnant women seldom need endoscopic procedures and common sense dictates that elective procedures should be postponed if possible. However, in some instances endoscopy has to be performed. While sedation is considered safe for the woman, there isn't high quality evidence to confirm it and some considerations have to made because of the possible risks to the fetus and are discussed in a ASGE guideline[52]. Among narcotics, meperidine is the favored agent. Benzodiazepines are classified as FDA pregnancy class D and are best avoided. Propofol is class B and may be used during pregnancy and preferably by an anesthesiologist. All agents are best avoided during the first trimester due to higher theoretical risks to the fetus. During lactation propofol and fentanyl are considered safe options with no need to withhold breastfeeding.

Acutely ill or decompensated patients are best managed by an anesthesiologist and most guidelines recommend considering anesthesiologist support for ASA $\geqslant$ Ⅲ patients, since most evidence on NAAP is on low risk patients and death have been reported only in ASA $\geqslant$ Ⅲ patients[44].

EVIDENCE

There is high quality evidence comparing propofol to traditional sedation, which includes several RCTs and five systematic reviews (4 of them with meta-analysis - Table 2)[1,2,21,23,24]. The results are very consistent in showing a similar rate of adverse events with propofol versus traditional sedation. The advantages of propofol are shorter recovery and discharge periods, higher post-anesthesia recovery scores, better sedation, and greater patient cooperation. One limitation of the majority of the RCTs included in the meta-analysis is the lack of anesthesiologist participation. This may limit the generalizability of the data but it's unlikely that there would be a decrease in the safety or quality of this sedation when performed by an anesthesiologist.

The big question is therefore who should be responsible for the administration of propofol[53].

To address this issue there is only one RCT[54]. This study by Poincloux *et al*[54] randomized 90 low risk patients undergoing colonoscopy for sedation by anesthesiologist using a target control infusion (TCI) or by the endoscopist using a modified patient controlled sedation pedal. In this study patients who were sedated by anesthesiologists had more frequent side events (16% *vs* 3%; P = 0.008), had higher doses of propofol (94 mg *vs* 260 mg), less pain but similar satisfaction levels.

Currently, we are performing a non-inferiority randomized trial addressing the safety of NAAP by comparing it no anesthesiologist sedation in low risk patients (ClinicalTrials.gov - NCT02067065). The interim analysis (100 patients) did not show a significant difference in the incidence of adverse events (primary endpoint) between the two groups (ref).

Apart from randomized controlled trials, there's significant experience with NAAP and extensive prospective evaluation on the safety and effectiveness of this type of sedation, especially for low risk patients. Rex *et al*[38] published in 2009 a sum of all published evidence on NAAP and collected unpublished prospective and retrospective records from several centers all

Table 2 Meta-analysis of randomized controlled trials of propofol *vs* traditional sedation in endoscopy

Ref.	Procedures	Sedation compared	No. of studies (cases)	OR (95%CI) for adverse events
Qadeer *et al*[23], 2005	EGD/colonoscopy/ERCP/EUS	Propofol *vs* traditional sedation	12 (1161)	0.74 (0.44-1.24)
Singh *et al*[2], 2008	Colonoscopy	Propofol *vs* traditional sedation	22	Hypoxia: 0.69 (0.25-1.89); Hypotension: 1.03 (0.28-3.83)
Bo *et al*[21], 2011	ERCP	Propofol *vs* traditional sedation	6 (663)	1.69 (0.82-3.50)
Garewal *et al*[24], 2012	ERCP	Propofol *vs* traditional sedation	4 (510)	Narrative
Wang *et al*[1], 2013	EGD/colonoscopy/ERCP	Propofol *vs* traditional sedation	22 (1798)	0.90 (0.70-1.17)

EGD: Esophagogastroduodenoscopy.

Table 3 Existing societal guidelines for non-anesthesiologist administration of propofol

Scientific society	Limitations	Consider anethesiologist
Sociedad Española de Endoscopia Digestiva, 2014	Complex procedure; ASA Ⅲ	ASA ≥ Ⅲ; long/complex procedure; difficult airway
Austrian Society of Gastroenterology and Hepatology (OGGH), 2007	NA	NA
Canadian Association of Gastroenterology, 2008	NA	ASA ≥ Ⅲ; long/complex procedure; difficult airway
German S3 guidelines - DGVS/DGAI, 2008	ASA ≥ Ⅲ; long/complex procedure; difficult airway	ASA ≥ Ⅳ; long/complex procedure; difficult airway
European Society of Gastrointestinal Endoscopy (ESGE/ESGENA), 2010/2013	NA	ASA ≥ Ⅲ; long/complex procedure; difficult airway
American multisociety guideline - AGA/ACG/ASGE/AASLD, 2009/2012	NA	ASA ≥ Ⅲ; long/complex procedure; difficult airway

ASGE: American Society of Gastrointestinal Endoscopy; NA: Not available.

around the world, totaling 646080 cases out of which 4 patients died and 11 were intubated. These numbers are not very different from published mortality rates for general anesthesia which is 1:13322 (overall) and 1:200200 in ASA Ⅰ-Ⅱ[13]. Recently, a large German experience of 24 441 cases on propofol and propofol with midazolam has been published[55]. The data was collected prospectively and severe adverse events were reported in only 4 patients, with no severe outcomes (death or permanent neurologic damage).

With such a track record it will be very difficult to design a RCT powered to detect a difference in mortality or even in the need for endotracheal intubation (EOT). If we consider a probability of 1:20000 for EOT (3 times higher than published by Rex), then we would need a sample size of 17 133802 patients to exclude a 20% difference (of the expected incidence) between the groups with a confidence of 90% and a one-sided confidence interval of 95%.

COST-EFFECTIVENESS

In the study by Hassan *et al*[34], the authors calculated the costs of training of nurses for EDP and assuming the published mortality rate of 0.0008% for EDP-colonoscopy and 0% for anesthesiologist sedation they concluded that the incremental cost-effectiveness ratio was 1.5 million USD/life year gained in the United States, 31 times above the accepted value of $50000 USD. This means that to make it cost effective a reduction in anesthesiologist reimbursement (for Medicare) from $95 to $6 would have to take place.

This study is based on the assumption that the presence of an anesthesiologist is 100% effective in avoiding death in these procedures.

GUIDELINES

As a consequence of the advantages provided by propofol sedation and the difficulty in adopting its use due to logistical, financial and medico-legal issues, several national and international guidelines have been published in the last decade and are shown in Table 3[28-32,45,56,57]. These guidelines help to provide the framework to allow endoscopists to perform NAAP in their countries.

Of note, the German guidelines were the result of a collaboration between the GI endoscopy and anesthesia national societies and are therefore a valuable evidence based consensus document made by the country that has the highest level of propofol sedation in endoscopy in the world.

An interesting aspect is what occurred with the ESGE/ESGENA guideline. This one was also a joint effort with the European Society of Anesthesia (ESA) and was published in the November 2010 with the ESA support in both Endoscopy[29] and the European Journal of Anesthesiology[58]. Following this guideline, several national Anesthesiology societies declared to be against such endorsement and that position as was made public in a "Special Article" in the *ESA* journal in June 2011 by Perel[59] and undersigned by 21 national societies. The argument used was the concern for patient safety based on the manufacturer's package insert that states that "DIPRIVAN Injectable

Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure". As a consequence of this pressure there was a vote at the ESA General Assembly to retract the support of the ESA for the guideline that had been previously evaluated and approved by the ESA guidelines committee and Board of Directors. As of April 2012, without significant new evidence to support the change, or any kind of review of the same evidence, the ESA retracted the support[60].

CONCLUSION

Propofol is currently considered the best candidate drug for sedation in endoscopic procedures. Still, we are in need for well-designed randomized clinical trials (with meaningful primary endpoints) to provide the definite proof of safety comparing to traditional sedation when used by non-anesthesiologists.

This kind of high quality evidence will help the different professional societies to overcome their differences and determine a robust, evidence-based, approach for safe and cost-effective sedation and monitoring in endoscopy.

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MINIREVIEWS

Narrow-band imaging with magnifying endoscopy for the evaluation of gastrointestinal lesions

Alina Boeriu, Cristian Boeriu, Silvia Drasovean, Ofelia Pascarenco, Simona Mocan, Mircea Stoian, Daniela Dobru

Alina Boeriu, Silvia Drasovean, Ofelia Pascarenco, Daniela Dobru, Department of Gastroenterology, University of Medicine and Pharmacy Tirgu Mures, 540139 Tirgu Mures, Romania
Cristian Boeriu, University of Medicine and Pharmacy Tirgu Mures, Tirgu Mures County Emergency Hospital, 540136 Tirgu Mures, Romania
Simona Mocan, Department of Pathology, Tirgu Mures County Emergency Hospital, 540136 Tirgu Mures, Romania
Mircea Stoian, Department of Anesthesia and Intensive Care, Mures County Hospital, 540000 Tirgu Mures, Romania
Author contributions: Boeriu A, Boeriu C, Pascarenco O and Dobru D contributed equally to this work; Boeriu A, Pascarenco O and Dobru D performed the endoscopies; Boeriu A and Boeriu C performed the literature search; Mocan S performed the histopathological examinations; Stoian M performed the anesthesia for endoscopies; Boeriu A and Drasovean S analyzed the data; Boeriu A and Boeriu C wrote the manuscript.
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Correspondence to: Cristian Boeriu, MD, PhD, Department of Anesthesia Intensive Care and Emergency Medicine, University of Medicine and Pharmacy Tirgu Mures, Tirgu Mures County Emergency Hospital, No.50 Gheorghe Marinescu St., 540136 Tirgu Mures, Romania. cboeriu@gmail.com
Telephone: +40-723-388810
Fax: +40-265-219102
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Abstract

Narrow band imaging (NBI) endoscopy is an optical image enhancing technology that allows a detailed inspection of vascular and mucosal patterns, providing the ability to predict histology during real-time endoscopy. By combining NBI with magnification endoscopy (NBI-ME), the accurate assessment of lesions in the gastrointestinal tract can be achieved, as well as the early detection of neoplasia by emphasizing neovascularization. Promising results of the method in the diagnosis of premalignant and malignant lesions of gastrointestinal tract have been reported in clinical studies. The usefulness of NBI-ME as an adjunct to endoscopic therapy in clinical practice, the potential to improve diagnostic accuracy, surveillance strategies and cost-saving strategies based on this method are summarized in this review. Various classification systems of mucosal and vascular patterns used to differentiate preneoplastic and neoplastic lesions have been reviewed. We concluded that the clinical applicability of NBI-ME has increased, but standardization of endoscopic criteria and classification systems, validation in randomized multicenter trials and training programs to improve the diagnostic performance are all needed before the widespread acceptance of the method in routine practice. However, published data regarding the usefulness of NBI endoscopy are relevant in order to recommend the method as a reliable tool in diagnostic and therapy, even for less experienced endoscopists.

Key words: Narrow band imaging magnifying endoscopy; Premalignant; Early cancer; Mucosal patterns; Vascular patterns

Core tip: The article summarizes recent data regarding the potentials of one of the most advanced endoscopic technique used in clinical practice. There are many classification systems of mucosal and vascular patterns already reported in literature, therefore a review could be useful for a better systematization of data. Strategies and challenges in the application of the method in routine practice represent another issue of interest in this article. The picture selection actually reflects the work in the endoscopy department and could serve as a tool in the learning process.

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INTRODUCTION

Narrow band imaging (NBI) represents an advanced endoscopic technique consistings in the assessment of surface patterns and microvascular architecture by utilization of a narrowed spectrum light. Blue and green wavelengths are selected by optical filters, with the elimination of red light[1]. These lights with narrowed bandwidths penetrate the superficial mucosal structures and are better absorbed by hemoglobin, providing an enhancement of mucosal features and blood vessels (capillaries from superficial mucosal layer, deeper mucosal and submucosal vessels)[2,3].

Clinical studies have shown the ability of NBI method to evaluate lesions and to estimate their histology in real time. The combination between NBI and magnification endoscopy (NBI-ME) enables an accurate assessment of lesions in the gastrointestinal (GI) tract, the differentiation between premalignant and malignant lesions, and the detection of early neoplasia by emphasizing neovascularization. The visualization of vascular details by magnification allows the early detection of changes associated with malignant transformation. Different classification systems including mucosal and vascular patterns were proposed to differentiate preneoplastic and neoplastic lesions and also to predict the depth of invasion in superficial cancer.

APPLICATIONS OF NBI-ME IN ESOPHAGEAL LESIONS

Magnifying endoscopy with NBI of normal esophagus enables visualization of capillary vessels of mucosa (intra-epithelial papillary capillary loop, IPCL) and submucosal vascularity (branching vessels) (Figure 1A). In reflux esophagitis, dilated, elongated IPCLs have been detected on NBI endoscopy[4]. The examination of the gastroesophageal (GE) junction and lower esophagus using NBI and magnification in patients with symptomatic GERD has allowed the detection of modified mucosa and vascularity: microerosions, an increased vascularity at the GE junction, an increased number, and dilatation and tortuosity of IPCLs[5].

Five different IPCL patterns have been described in association with different esophageal features, from normal mucosa to modified mucosa due to inflammation, dysplasia or cancer: type Ⅰ corresponds to normal mucosa (Figure 1A), type Ⅱ to inflammation, type Ⅲ corresponds to borderline lesions, often related to low-grade intraepithelial neoplasia, type Ⅳ (Figure 2A) and Ⅴ corresponds to high-grade intraepithelial neoplasia (HGIN) or carcinoma[6]. Dilation, tortuosity, irregularity in vessels caliber and form, destruction of IPCLs and replacement with tumor vessels are vascular features associated with esophageal carcinoma. The assessment of IPCLs and submucosal vascularity allows the detection of superficial squamous carcinoma and also the prediction of the depth of invasion[7]. The utility of the estimation of submucosal invasion in clinical practice influences the decision of performing endoscopic therapy.

Magnifying NBI endoscopic diagnosis of Barrett's esophagus

The surveillance of Barrett's esophagus (BE) for early detection of adenocarcinoma continues to represent a challenge in clinical practice due to the large number of random biopsies required and to sampling errors. New endoscopic techniques improve the visualization of Barrett mucosa and improve the detection of dysplasia and early cancer by targeting biopsies from areas with modified pattern. Numerous reports have described mucosal and vascular features displayed in BE.

Chromoendoscopy and magnifying endoscopy has been used for better detection of specialized intestinal metaplasia (SIM) and early neoplasia in BE[8-10]. However, the dye application alters the visualization of vascular patterns. Additional time is required for better fixation of the dye on the tissue surface, followed by repeated water rinses and suctions to remove excess dye. NBI technique has the advantage of identification of both vascular and mucosal patterns without dye application, is easier to perform, and adds useful information about the mucosal morphology.

Different mucosal patterns have been described that can be detected at the GE junction during magnifying NBI endoscopy: rounded, circular (Figure 1C) or oval crypts (columnar mucosa), flat (Figure 1D), villous (Figure 1E), and gyrus-shaped patterns [intestinal metaplasia (IM)][11]. Apart from these regular

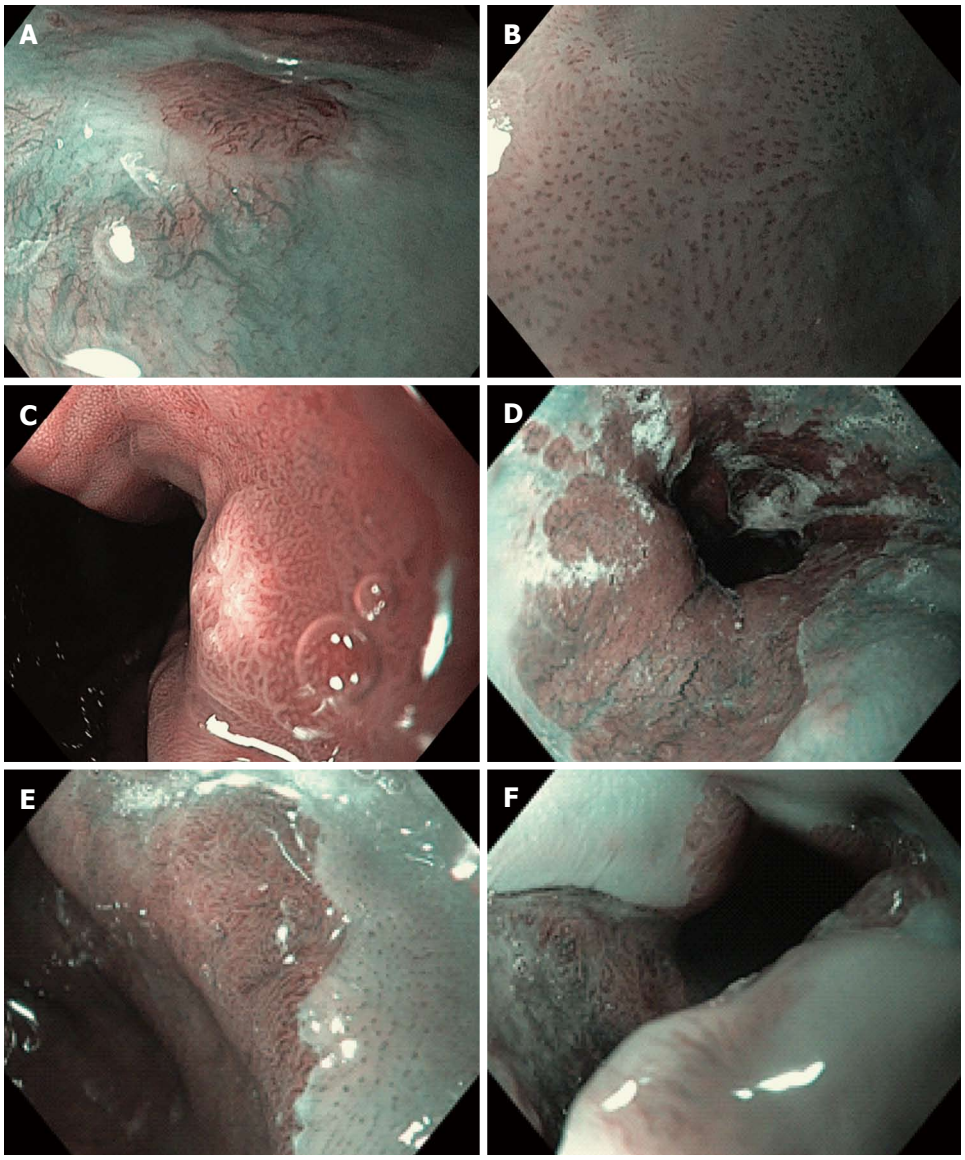

Figure 1 Narrow band imaging with magnification endoscopy images of the esophagus. A: Normal esophageal mucosa: branching vessel network and intra-epithelial papillary capillary loop (IPCL) surrounding an island of Barrett's esophagus (BE); B: IPCL type V1: dilatation of intra-epithelial papillary capillary loop, irregular caliber, and form variation; C: Round pits with regular microvasculature corresponding with columnar mucosa; D: Non-dysplastic BE: flat-type mucosa with regular long branching vessels; E: Non-dysplastic BE: regular villous/ridge mucosal pattern; F: Dysplastic BE: distorsion of mucosal pattern and irregular vascular pattern.

patterns, the identification of an irregular, disrupted mucosal pattern raises the suspicion of a dysplastic/cancerous lesion. The second element that should be evaluated is the vascular pattern: the presence of a regular pattern with normal-appearing vessels or an irregular pattern with abnormal blood vessels. In non-dysplastic BE a regular vascular pattern is associated with the regular villous/gyrus-like pattern or with flat-type mucosa (Figure 1D, E). Areas presenting an irregular mucosal pattern or abnormal blood vessels (irregular, dilated, corkscrew type vessels) are suspicious for the presence of high-grade dysplasia (HGD) or cancer (Figure 1F).

The significance of the detection of irregular mucosal and vascular patterns and abnormal blood vessels for the diagnosis of HGIN by using NBI-ME was previous outlined by Kara *et al*[12] (94% sensitivity, 76% specificity, 64% PPV and 98% NPV for HGIN). Other studies have reported the sensitivity, specificity and positive predictive value (PPV) of ridge/villous pattern for diagnosis of IM (93.5%, 86.7% and 94.7% respectively) and the sensitivity, specificity and PPV of irregular/distorted pattern for HGD (100%, 98.7% and 95.3% respectively), but also have emphasized the inability to differentiate areas of IM from areas with low-grade dysplasia[13].

The reproducibility and repeatability of a simplified classification of mucosal and vascular patterns visualized in BE by experts and non-NBI-experts endoscopists was reported by Singh *et al*[14]. They have

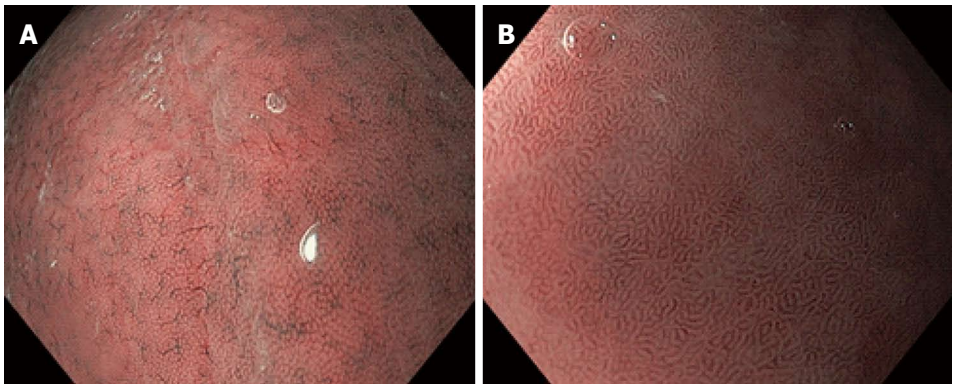

Figure 2 Narrow band imaging with magnification endoscopy images of normal gastric mucosa. A: Round pits surrounded by the subepithelial capillary network (SECN) and collecting venules (CVs) in normal corporeal mucosa; B: Coil-shaped appearance of SECN, without the visualization of the CVs in normal antral mucosa.

described four different patterns on NBI-ME: type A-round pits with regular microvasculature (Figure 1C) corresponded with columnar mucosa without IM (PPV and NPV were 100% and 97% respectively); type B-villous/ridge pits with regular microvasculature and type C-absent pits with regular microvasculature (Figure 1D, E) corresponded with IM (PPV and NPV were 88% and 91% respectively); type D-distorted pits with irregular microvasculature (Figure 1F) was associated with HGD (PPV and NPV were 81% and 99% respectively)[14].

Due to the multiplicity of classification systems, the clinical utility of NBI-ME in the assessment of BE is still under evaluation. In a study performed by Alvarez Herrero *et al*[15], a simplified classification of mucosal and vascular patterns (regular patterns in nondysplastic BE, irregular patterns in dysplastic BE) has shown a moderate interobserver agreement and a disappointing rate for correctly identifying HGIN/early cancer (67% and 71% of the images with HGIN/early cancer were correctly identified). The limitations of the available classification systems concerning accuracy in identification of SIM and dysplasia, as well as limited interobserver agreement, are arguments that the surveillance protocol of BE based on random 4-quadrant biopsies and biopsies from suspicious areas, cannot be yet replaced[16]. A targeted NBI-ME examination of suspicious areas previously identified on white light endoscopy (WLE), such as mucosal irregularities, depressed areas, ulcerations, or nodules, is useful for the delineation of modified mucosal or vascular patterns and for the guidance of directed biopsies.

NBI-ME has also successfully been used as an adjunct for therapeutic procedures. The method has proved to be helpful in targeting and delineating areas with early Barrett's neoplasia, previously identified by high-resolution endoscopy and autofluorescence imaging, for endoscopic mucosal resection[17]. The trimodal imaging evaluation, which combines high-resolution WLE, autofluorescence, and NBI could be an alternative to dye-spraying techniques for the detection and the lateral spread assessment of early cancer before endoscopic therapy.

Applications of NBI-ME in gastric lesions

The normal gastric mucosa displays particular features in the corpus and antrum on NBI-ME. A regular arrangement of small, round pits surrounded by the subepithelial capillary network (SECN) with a honeycomb appearance and the collecting venules (CVs) are detected in the gastric body (Figure 2A). A coil-shaped appearance of SECN, without the detection of the CVs are specific features associated with normal antral mucosa (Figure 2B). Modified patterns should be evaluated by comparison with these normal mucosal and vascular features. The detection of modified patterns due to inflammatory and atrophic changes of the corporeal mucosa and the interpretation of such endoscopic features could represent a challenge in clinical practice: the enlargement of pits with irregular SECNs in *Helicobacter pylori* gastritis (Figure 3A), or the detection of oval or tubulovillous pits with coiled or wavy vessels in IM (Figure 3B) and atrophic gastritis (AG)[18]. Targeted biopsies from areas with modified patterns are mandatory for a proper evaluation of the lesions.

The detection of blue whitish slightly raised areas, described as the "light blue crest sign" (Figure 3C) was reported to have a good sensitivity (89%), specificity (93%) and accuracy (91%) for the diagnosis of IM[19]. This sign could represent a marker for global gastric atrophy[20]. The detection of extensive and severe atrophy and IM and the detection of dysplasia are important steps in the identification of patients at risk for gastric neoplasia. According to European guidelines, these patients should be included in a surveillance program[21]. Targeted surveillance and directed biopsies guided by NBI-ME for IM and AG mapping could represent a better alternative to a surveillance protocol based on randomly taken biopsies.

Different mucosal and vascular patterns have been

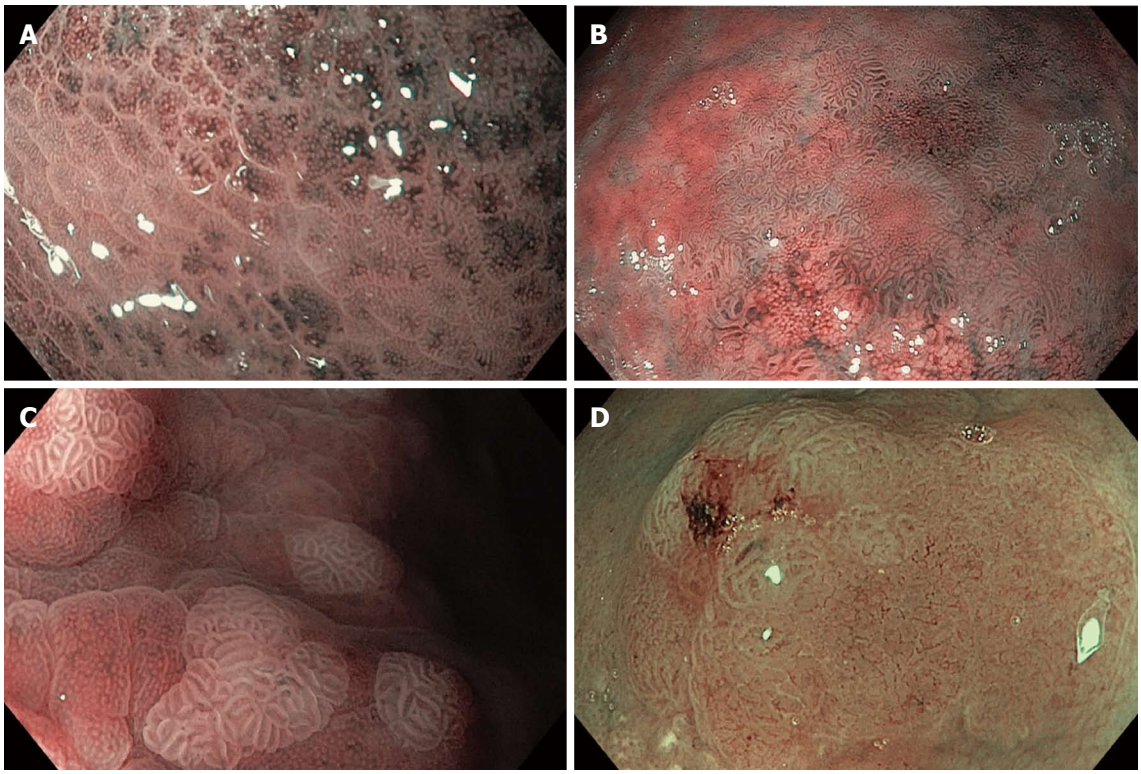

Figure 3 Narrow band imaging with magnification endoscopy images of gastric lesions. A: *Helicobacter pylori* gastritis: enlargement of pits, variable vascular density (alternation of lighter and darker areas); B: Extensive areas of intestinal metaplasia (tubulovillous mucosal pattern) and remnant normal gastric body mucosa (small regular and circular pits); C: Areas of intestinal metaplasia: blue whitish slightly raised areas (the light blue crest sign) with regular, tubulovillous mucosal pattern; D: Dysplasia: area with architectural loss of mucosal pattern and irregular vascular pattern.

reported in association with normal gastric mucosa, preneoplastic and neoplastic gastric lesions. Pimentel-Nunes *et al* have proposed a classification system for the diagnosis of gastric preneoplastic lesions: pattern A (regular and circular mucosal patterns with regular vascular patterns - Figure 2A) corresponds with normal mucosa (accuracy 83%; 95%CI: 75%-90%), pattern B (regular, ridge or tubulovillous mucosal patterns with regular vessels - Figure 3C) corresponds with IM (accuracy 84%; 95%CI: 77%-91%), and pattern C (absent or irregular mucosal patterns with irregular vascular patterns - Figure 3D) corresponds with dysplasia (accuracy 95%; 95%CI: 90%-99%)[22].

Magnifying NBI endoscopic diagnosis of early gastric cancer

Diagnostic accuracy for early gastric cancer was improved by the development of NBI-ME, which allows the detection of subtle mucosal changes. The estimation of the histology and the delineation of the lateral spread of gastric cancer are possible during endoscopic examination[23-25]. An estimation of the deep of invasion of early gastric cancer was also achieved by NBI endoscopy. The superiority of NBI-ME over WLE for the diagnosis of superficial gastric lesions in a population at high risk of gastric cancer was demonstrated in clinical studies[26].

Three criteria have been use by Kaise *et al*[27] for the detection of superficial gastric cancer: the disappearance of fine mucosal structure, microvascular dilation and heterogeneity in shape of vessels. The sensitivity of these criteria for the diagnosis of cancer was 92.9%, with 94.7% specificity[26]. Yao *et al*[28] have used a "VS classification", based on the assessment of microvascular pattern (V) and microsurface pattern (S). They have identified the irregular microvascular pattern and/or the irregular microsurface pattern and the demarcation line as hallmarks of early gastric cancer (Figure 4). The delineation of the lateral margins of differentiated carcinoma prior to endoscopic resection has been performed using NBI-ME[28].

Yamada *et al*[29] have recently reported that the demarcation (DL) line and an irregular microvascular pattern (IMVP) on NBI-ME represent reliable criteria for the diagnosis of small, depressed, early gastric cancer. An irregular margin and a spiny depressed area on conventional WLE represent diagnostic criteria for depressed cancer. The diagnostic accuracy increases by using both methods: the initial detection of a depressed lesion on conventional WLE, followed by magnifying NBI assessment for the presence of DL and IMVP[29]. The combination of conventional WLE with NBI-ME in clinical practice has proved to enhance diagnosis accuracy of small, depressed gastric mucosal cancer (96.6% accuracy, 95.0% sensitivity, and

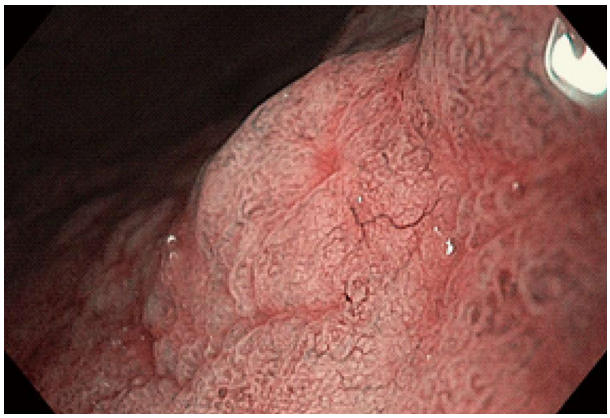

Figure 4 Superficial gastric cancer: Disappearance of microsurface pattern, irregular microvascular pattern with a demarcation line.

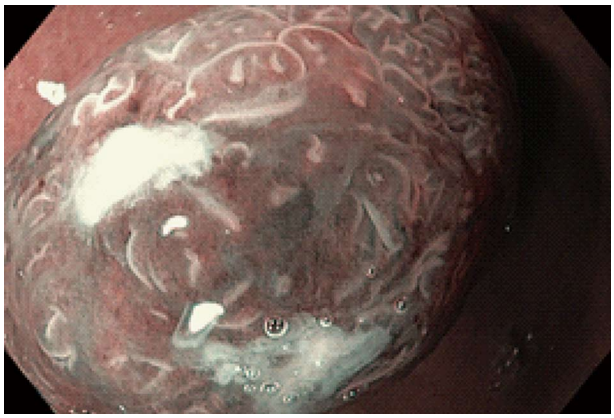

Figure 5 Gastric adenoma: White opaque substance with regular distribution obscures the subepithelial microvascular pattern.

96.8% specificity)[30].

Regarding the application of NBI-ME in the assessment of elevated gastric lesions, a regular microsurface and microvasculature was detected in adenomas, while the microvascular changes (irregular caliber, meandering, heterogeneity) and the line of demarcation were associated with carcinoma[31]. There are situations when an estimation of the microvascular pattern is difficult, due to a white opaque substance (WOS) within the neoplastic epithelium, which obscures the microvessels (Figure 5). Yao *et al*[32] have identified the WOS in 0-Ⅱa type neoplasms, and more frequently in adenomas (78%) than in carcinomas (43%). A regular distribution of WOS was detected within adenomas, whereas an irregular distribution was found in carcinomas. Besides the assessment of the microvascular pattern, morphologic analysis of the WOS could represent a valuable optical sign discriminating between adenoma and carcinoma[32].

The demarcation line could also be identified in focal gastritis, but in this situation the regular mucosal and vascular patterns differentiate the lesion from early cancer. Doubtful lesions are better sent for pathologic assessment after endoscopic submucosal dissection.

Distinct vascular patterns are related to different histologic types of cancer. The fine network pattern, appearing as mesh microvessels, correlates with well-differentiated adenocarcinoma, whereas the corkscrew pattern, with isolated and tortuous microvessels, corresponds with undifferentiated adenocarcinoma[33]. Li *et al*[34] have reported a good sensitivity, specificity, and accuracy of NBI-ME in distinguishing between differentiated from undifferentiated adenocarcinoma (92.3%, 89.7%, and 90.4%, respectively) and in differentiation between cancerous and noncancerous lesions (97.3%, 84.4% and 90.2% respectively). The authors have described three distinct patterns associated with different type of gastric lesions and with the depth of cancer invasion. A regular surface and microvascular pattern (type A pattern) corresponds with noncancerous lesions. The type B pattern, consisting of thickened, dilated, irregular vessels, with an asymmetrical distribution, and an irregular surface pattern, corresponds with differentiated adenocarcinoma and intramucosal/superficially invasive cancers. The type C pattern, consisting of the disappearance of the surface pattern, with markedly distorted, sparse, isolated microvessels, or with avascular areas, is indicative of undifferentiated adenocarcinoma or differentiated cancer with deep submucosal invasion[34].

In a recent report, Yagi *et al*[35] have also emphasized the usefulness of NBI-ME in the evaluation of the depth of submucosal invasion of the carcinoma. They have described the blurry mucosal pattern (BMP) and the irregular mesh vascular pattern (IMP) as endoscopic features suggestive of submucosal invasion of gastric differentiated adenocarcinoma (Figure 6). A mucosal cancer could be estimated by correlating the absence of these NBI-ME criteria (BMP, IMP) with the absence of conventional endoscopic criteria for invasion (extremely uneven or depression, nodularity at the verge, obvious hardening of the wall and unusual elevated non-cancerous mucosa on the verge)[35]. When the margins of early gastric cancer are difficult to identify using chromoendoscopy, NBI-ME represents a reliable alternative to delineate the horizontal extent of the differentiated carcinoma. The difficulty in determining the real extent of undifferentiated cancer still remains a problem, and a proper evaluation by biopsies from the apparently normal mucosa around the lesion is recommended in these situations[36].

Applications of NBI-ME in colonic lesions

The ability of NBI for the prediction of a polyp's histology has been reported in different studies. Kudo's classification system of mucosal pit pattern detected on magnification has included 5 different types: type Ⅰ - round pits, type Ⅱ - stellar or papillary pits, type Ⅲ L- large tubular or roundish pits, type Ⅲ s-

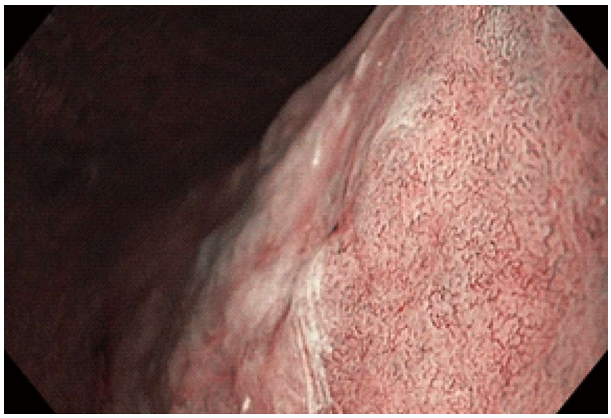

Figure 6 Gastric cancer with submucosal invasion: Blurry mucosal pattern and irregular mesh vascular pattern.

small tubular or roundish pits, type Ⅳ- branch-like or gyrus-like pits and type Ⅴ- non-structural pits[37]. A proper evaluation of a colonic lesion consists in the assessment of mucosal pattern and also of vascular pattern. Sano *et al*[38] have proposed an evaluation of "capillary pattern" by using NBI colonoscopy with magnification for the differential diagnosis of colorectal lesions: type Ⅰ - absent meshed brown capillary network (MBCN) in hyperplastic polyps (Figure 7A), type Ⅱ - regular pattern in adenomatous polyps (Figure 7B), and type Ⅲ- irregular pattern in cancerous lesions (Figure 7C).

According to these diagnostic criteria for mucosal and vascular patterns, specific features on NBI-ME have been described, corresponding with different colonic lesions: type Ⅰ or Ⅱ mucosal pattern (round, stellar or papillary pits) and type Ⅰ vascular pattern (absence of vascular structure) in hyperplastic polyps (Figure 7A); type Ⅲ or type Ⅳ mucosal pattern (tubular or branching pits) and type Ⅱ vascular pattern (regular vessels) in adenoma (Figure 7B); type Ⅴ mucosal pattern (disappeared pits) and type Ⅲ vascular pattern (irregular vessels) in adenocarcinoma (Figure 7C). This combined classification system, based on mucosal and vascular patterns assessment, was used for the prediction of polyp histology. The accuracy of the NBI-ME method has proven to be superior to high-resolution WLE for the prediction of polyp histology[39].

The NBI International Colorectal Endoscopic (NICE) classification has been proposed by an international expert group for the diagnosis of colonic lesions[40]. The classification is based upon the evaluation of lesion color, microvascular architecture, and surface pattern, and can be applied for NBI observation either with or without use of magnification. The similar or lighter color of the polyp compared with the background mucosa, with no vessels or isolated vessels coursing across the polyp surface, the homogenous lack of mucosal pattern, the detection of dark or white spots of uniform size, are features corresponding with hyperplastic polyps (Figure 7A). A browner color of the polyp relative to the background mucosa, the visualization of brown vessels surrounding oval, tubular or branched white structures are features mainly associated with colonic adenomas (Figure 7B). A brown color of the lesion relative to background, sometimes with patchy whiter areas, an absent or amorphous mucosal pattern, and a vascular pattern with disrupted or missing vessels, all represent endoscopic criteria for the diagnosis of deep submucosal invasive colorectal carcinomas according to NICE classification (Figure 7D)[41].

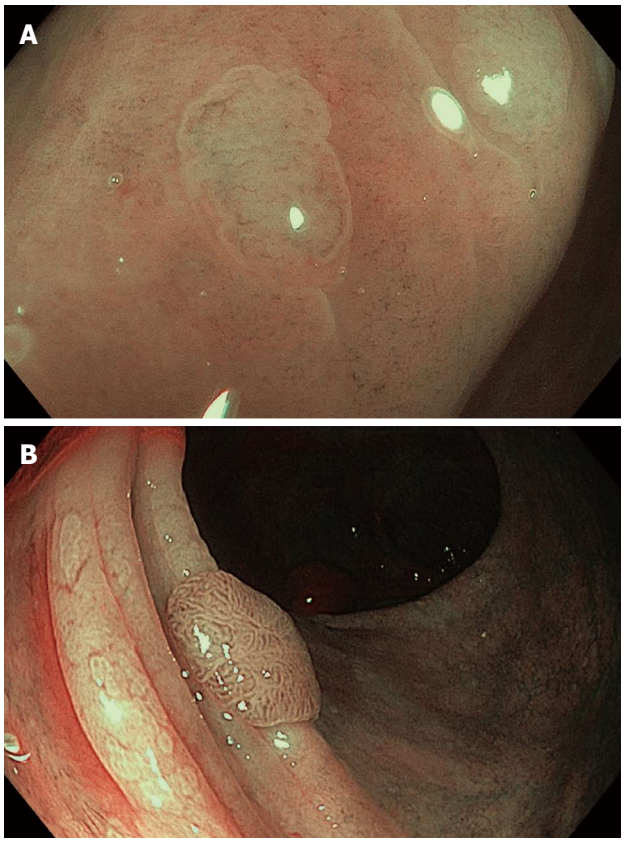

Figure 7 Assessment of colonic lesions by narrow band imaging with magnification endoscopy according to different classification systems. A: Hyperplastic polyp: absent mesh brown capillary network (Type Ⅰ MBCN) (Sano classification); a lighter color of the polyp than the background, isolated vessels coursing across the lesion (NICE criteria); B: Adenomatous polyp: regular mesh brown capillary network (Type Ⅱ MBCN) and Kudo's Type Ⅳ mucosal pattern; the brown color relative to background, thick brown vessels surrounding white structures (NICE criteria); C: Cancerous colonic lesion: irregular mucosal and vascular patterns (Type Ⅲ MBCN); D: Deep submucosal invasive colorectal cancer: amorphous surface pattern and disrupted vessels (NICE criteria).

The real time estimation of polyp histology could play an important role in clinical decisions regarding the therapeutic strategy for polyps ≤ 5 mm in size and for the duration of post-polypectomy surveillance intervals. Different cost-saving strategies were previously proposed in this setting. A "resect-and discard" policy was proposed for polyps ≤ 5 mm, which consists in a real-time estimation of polyp histology by NBI, followed by resection without pathologic as-

sessment[42]. The "resect and discard" strategy for diminutive adenomatous polyps could decrease the cost of colonoscopy. The post-polypectomy surveillance intervals could be recommended on the basis of the estimation of polyp histology by NBI and of the pathologic assessment of the larger polyps submitted to histology[43].

The accurate estimation of the histology of the polyps (real-time optical biopsy) could prevent unnecessary polypectomies in cases of diminutive rectosigmoid hyperplastic polyps ("do-not-resect" strategy). On the basis of the evaluation of polyp histology by NBI criteria (color, vessels, pit pattern), experts have demonstrated that leaving diminutive distal hyperplastic polyps in place without pathologic assessment could be a reliable approach in clinical practice[44].

According to the Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) statement, developed by The American Society for Gastrointestinal Endoscopy (ASGE), the thresholds of endoscopic technology for the assessment of polyps histology are: optical diagnosis for diminutive colorectal polyps combined with pathologic assessment of all other polyps should provide $\geqslant$ 90% agreement in determining post-polipectomy surveillance intervals when compared with decisions based on pathology assessment of all polyps, and the recommended NPV for adenomatous histology in diminutive rectosigmoid polyps should be $\geqslant$ 90%. After the achievement of PIVI thresholds, the NBI technology could be used to guide the "characterize, resect and discard" strategy in clinical practice[45]. Recent studies have focused on the ability of NBI diagnosis to meet these ASGE thresholds[46,47]. The incorporation of real-time histology in clinical practice still represents a matter of debate[48].

Regarding the widespread use of the aforementioned strategies in clinical practice, the lack of accurate criteria for the differentiation between sessile serrated adenomas (SSAs) and hyperplastic polyps on NBI could represent a real challenge. A type Ⅱ open-pit pattern (Type Ⅱ-O), characterized by wider and rounded pits, was identified on magnification to be specific to SSAs[49]. Recent reports from community gastroenterologists have showed that endoscopic features of SSAs under NBI according to NICE classification were intermediate to the patterns observed in hyperplastic polyps and adenomas[50]. The misclassification of SSAs could affect clinical decisions regarding therapeutic strategy and surveillance intervals. The approach to serrated polyps in clinical practice should take into account their malignant potential[51].

Another problem regarding the global use of optical biopsy in practice is related to the level of training and expertise. A high performance level of the optical diagnosis of the polyps using NBI-ME was reported by the experts[47], but these studies were mainly performed in academic centers. Recent studies investigating optical biopsy performance in community practice have shown that the results are not as good as those obtained in the academic setting: only 25% of gastroenterologists assessed polyps with $\geqslant$ 90% accuracy. The thresholds for optical biopsy recommended by ASGE were achieved for identification of adenoma (NPV $\geqslant$ 90%), but not for the surveillance interval agreement[46]. The level of performance in clinical practice might be improved by training programs including the evaluation of frozen images or videos, real-time optical diagnosis during NBI colonoscopy, as well as creation of computer-aided diagnostic tools[52].

CONCLUSION

A tremendous development in the applications of NBI endoscopy with magnification has been reported in recent years. The method has made significant contributions to diagnostic accuracy, screening, surveillance, and cost-saving strategies. The method is used for better characterization of GI tract lesions by focusing the endoscopic examination on modified areas in which to perform targeted biopsies from suspicious lesions. The distinction between neoplastic and non-neoplastic lesions *in vivo* represents an important tool in clinical decisions regarding surveillance or therapy. Looking for the best therapeutic strategy in early cancer, the estimation of the depth of invasion and the delineation of the horizontal extent of carcinoma are mandatory before a therapeutic procedure such endoscopic therapy or surgical resection can be recommended. NBI-ME has been successfully applied in practice to select the optimum therapy and to guide endoscopic resections.

The good results already reported regarding clinical applicability of NBI represent arguments that the method could become an increasingly reliable tool in diagnostic and therapy, even for inexperienced endoscopists. Whether or not NBI will become a standard in endoscopy practice, it entirely depends on the widespread use of the technique in current practice by endoscopists with varying levels of experience, after a proper training.

Despite all these advances, there are still challenges in application in clinical practice, particularly regarding the standardization of endoscopic criteria in order to achieve a simplified and accurate descriptive system of mucosal and vascular patterns. The validity of the different classification systems is still under evaluation and further randomized multicenter studies are needed to confirm their clinical utility. The adoption of real-time optical diagnosis in routine practice requires training and expertise in the recognition of endoscopic features on the basis of standardized NBI-ME criteria.

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Circumstance of endoscopic and laparoscopic treatments for gastric cancer in Japan: A review of epidemiological studies using a national administrative database

Atsuhiko Murata, Shinya Matsuda

Atsuhiko Murata, Shinya Matsuda, Department of Preventive Medicine and Community Health, School of Medicine, University of Occupational and Environmental Health, Yahatanishi-ku, Kitakyushu 807-8555, Japan
Author contributions: Murata A and Matsuda S contributed to this paper.
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Correspondence to: Atsuhiko Murata, MD, PhD, Department of Preventive Medicine and Community Health, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan. amurata@med.uoeh-u.ac.jp
Telephone: +81-93-6917244
Fax: +81-93-6034307
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Abstract

Currently, endoscopic submucosal dissection (ESD) and laparoscopic gastrectomy (LG) have become widely accepted and increasingly play important roles in the treatment of gastric cancer. Data from an administrative database associated with the diagnosis procedure combination (DPC) system have revealed some circumstances of ESD and LG in Japan. Some studies demonstrated that medical costs or length of stay of patients receiving ESD for gastric cancer had become significantly reduced while length of hospitalization and costs were significantly increased in older patients. With respect to LG, some recent reports have shown that this has been a cost-beneficial treatment for patients compared with open gastrectomy while simultaneous LG and cholecystectomy is a safe procedure for patients with both gastric cancer and gallbladder stones. These epidemiological studies using the administrative database in the DPC system closely reflect clinical circumstances of endoscopic and surgical treatment for gastric cancer in Japan. However, DPC database does not contain detailed clinical data such as histological types and lesion size of gastric cancer. The link between the DPC database and another detailed clinical database may be vital for future research into endoscopic and laparoscopic treatments for gastric cancer.

Key words: Gastric cancer; Endoscopic submucosal dissection; Laparoscopic gastrectomy; Diagnosis Procedure Combination; Administrative database; Epidemiological studies

Core tip: Currently, endoscopic submucosal dissection (ESD) and laparoscopic gastrectomy (LG) have become accepted for treatment of gastric cancer and increasingly played important roles on the treatments of gastric cancer in Japan. Using the database on national administrative database associated with the diagnosis procedure combination (DPC) system, the various studies with regards to ESD and LG for gastric cancer have been revealed. We herein describe the circumstance of ESD and LG for gastric cancer in Japan based on reports using Japanese administrative database associated in the DPC system in this review.

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INTRODUCTION

Gastric cancer is one of the most frequent cancers and causes of cancer-related deaths[1,2]. Although a trend of declining incidence has been observed, gastric cancer still causes a great health care burden[3]. According to the report by the Ministry of Health, Labour and Welfare of Japan (MHLW), roughly 50000 Japanese people die due to gastric cancer annually, representing 15% of cancer-related deaths[2]. Therefore, health care policies for gastric cancer are increasingly focused on detection and treatment in the early stage because the 5-year cancer survival in the early stage of gastric cancer has been reported to be greater than 90%[4,5]. Almost half of gastric cancers have been discovered at an early stage because of early detection measures[6].

Regarding the endoscopic treatments for early gastric cancer, endoscopic mucosal resection (EMR) was standard practice[6]. However, significant progress in endoscopic treatment has contributed to more effective resection of early gastric cancer. Endoscopic submucosal dissection (ESD) has achieved a high rate of histologically curative en bloc resection for early gastric cancer regardless of size, permitting the resection of previously non-resectable tumors. The ESD technique has spread rapidly owing to its excellent eradication rate compared with EMR[6-8]. ESD is recognized as an established endoscopic therapy for the treatment of early gastric cancer[8-10].

Although almost early gastric cancers can be treated by ESD, the number of surgical operation for gastric cancer still remains high. Also in the field of surgical treatments, recent advances have allowed more effective and safe procedure for gastric cancer. Laparoscopic gastrectomy (LG) is significantly less invasive than open gastrectomy (OG), with lower mortality and morbidity rates[11-13]. Furthermore, LG is now performed not only as distal gastrectomy but also as proximal and total gastrectomy[11-13]. Currently, LG has been accepted for the treatment of gastric cancer, with the number of patients requiring this surgical procedure increasing in Japan, as well as other developed countries[13-15].

Currently, endoscopic and laparoscopic treatments such as ESD and LG are increasingly playing important roles for the treatment of gastric cancer. In this review, we report the circumstances of ESD and LG for gastric cancer in Japan, based on reports using Japanese administrative database associated with the diagnosis procedure combination (DPC) system.

ADMINISTRATIVE DATABASE ASSOCIATED WITH THE DPC SYSTEM

History of the DPC system

The health care system of Japan has severe problems owing to the expense of new medical technology and extended hospitalizations of patients[16]. To solve these problems, the MHLW started to investigate whether the case-mix classification system can be adopted to standardize medical profiling and payment[16-20]. In 2003, Japanese case-mix projects based on the DPC system were introduced to 80 university and 2 national hospitals.

DPC participating hospitals have adopted a unique reimbursement system, whereby the paid medical treatment fees become proportionally higher as the length of stay (LOS) becomes shorter. Therefore, a shorter hospitalization leads to an increase in income for the hospitals. Furthermore, payment per hospitalization is strictly determined by the DPC payment system. Currently, the number of DPC-participating hospitals has been increasing. Enormous amounts of data on hospitalization of patients have been collected annually, covering roughly 55% of the total hospitalizations, according to the report from the MHLW in 2014[21].

Component of data in the DPC system

This system collects important data during hospitalization in addition to the characteristics of the unique reimbursement system. Each patient's background information or discharge summary, which includes principal diagnosis, complications, comorbidities, and outcomes are recorded in the administrative database associated with the DPC system. These patient data are coded using the International Classification of Diseases and Injuries 10th Revision (ICD-10th) code. Also, this database includes the hospital information, number and date of clinical procedures, such as operations or drug therapies that are indexed in the original code determined by the MHLW[16-20]. Detailed contents of data in the database of the DPC system are shown in Table 1[22].

Collection and use of DPC data

Comprehensive surveys of DPC-participating hospitals are conducted by the DPC research group that has worked on the DPC data utilization project for research purposes, independently of the MHLW. DPC-participating hospitals sent the anonymized and provided detailed data to the DPC research group, which then sent to the server in the DPC research group. Using the sent data from DPC-participating hospitals, many studies have been reported in the various fields of medical research[16-20,23-26].

Table 1 Contents of data in the national administrative database[22]

Hospital information
Location of hospital
Number of beds
Patient background information
Age
Sex
Zip code
Diagnoses
Main diagnoses (coded with International Classification of Diseases and Injuries 10th Revision (ICD-10th) code)
Main diagnoses (coded with the ICD-10th codes)
Complications after admission (coded with the ICD-10th codes)
Procedures for patients
Surgery, anesthesia and other procedures (coded with the Japanese original codes)
Drugs and devices (coded with the Japanese original codes)
Dates of each procedure
Dates of use for each drug and device
Admission and discharge data
Urgent or elective admission
Ambulance service use
Dates of admission and discharge; length of stay
Discharge status (discharge to home, rehabilitation hospital or other facility, or death)
Claim data
Total charge
Itemized charges for hospitalization, medication, examination, surgery and others
Other clinical data
Height/body weight
Smoking index
Pregnancy
Japan Coma Scale at admission
TNM classification of malignant tumors
Activity of Daily Living scale
Modified Rankin scale
Hugh-Jones classification of respiratory status
New York Heart Association classification of heart failure symptoms
Canadian Cardiovascular Society classification of angina pectoris
Killip classification of acute myocardial infarction
Severity classification of community-acquired pneumonia
Child-Pugh classification of liver cirrhosis
Severity classification of acute pancreatitis
Burn index
Global Assessment of Functioning scale

EPIDEMIOLOGICAL STUDIES ON ESD FOR GASTRIC CANCER USING DPC DATABASE

ESD for gastric cancer (Table 2)

Time trend of outcomes of ESD in Japan: According to the report about the time trend of outcomes of ESD in Japan, the rate of ESD-related complications was stable (3.2% in 2009 *vs* 3.5% in 2010 *vs* 3.3% in 2011, $P = 0.496$) between 2009 and 2011[27]. In the early 2000s, some clinical studies in single centers reported that the complication rate of ESD was from 5% to 8%[28,29]. However, the complication rate of ESD based on an administrative database was approximately 3% between 2009 and 2011, which indicated that complications of ESD remained low. Therefore, the decrease in complication rates may suggest that the number of experienced endoscopists has been increasing between the early and late 2000s, and their technical skill level in ESD has been favorably stable from 2009 to 2011. In addition, the LOS and medical costs of patients had become significantly reduced in Japan (10.5 d in 2009 *vs* 9.8 d in 2010 *vs* 9.5 d in 2011 and 6768.4 US dollars in 2009 *vs* 6507.7 US dollars in 2010 *vs* 6427.6 US dollars in 2011; $P < 0.001$, respectively)[27]. The efficiency of ESD for gastric cancer as well as stable technical skills has been progressing in Japan.

Outcomes of ESD in high-volume hospitals: With respect to the report about hospital characteristics such as hospital volume, ESD-related complications were significantly lower in higher-volume hospitals (> 100 cases between 2009 and 2011) than lower- (< 50 cases) or medium-volume hospitals (50-100 cases) in upper gastric cancer (6.5% in lower-volume hospitals *vs* 5.2% in medium-volume hospitals *vs* 3.4% in higher-volume hospitals; $P = 0.017$)[30]. Multivariate logistic regression analysis also revealed that high-volume hospitals were significantly associated with a decrease of relative risk of ESD-related complications in upper gastric cancer [odds ratio (OR) for higher-volume hospitals 0.51; 95% confidence interval (CI), 0.32-0.81, $P = 0.005$]. Meanwhile, no significant differences for ESD-related complications were seen for middle and lower gastric cancers among the different hospital volume categories ($P > 0.05$)[30]. Some previous studies also pointed out that a higher skill level with ESD is required for upper gastric cancers than for middle or lower gastric cancers[31-33]. Higher volume hospitals were more likely to have experienced endoscopists can provide sufficient treatment, which significantly contributed to fewer complications or shorter LOS[34,35]. Thus, it is reasonable that the decreases in ESD-related complications and in LOS of patients with upper gastric cancer were observed at higher-volume hospitals.

Comparison between non-elderly and elderly patients treated by ESD: A comparison between elderly (80 years or more) and non-elderly patients (less than 80 years) regarding outcome of ESD was also reported[36]. A recent study revealed that there was no statistically difference with regard to ESD-related complications (3.9% *vs* 4.3%, $P = 0.152$)[36]. The findings about complications of ESD has been consistent with those of some previous studies in Japan[37,38]. Kakushima *et al*[37] showed that the complication rate of ESD in elderly patients was not significantly different from that in non-elderly patients, while Tokioka *et al*[38] also reported that the occurrences of perforations during ESD were similar in non-elderly and elderly patients. However, length of hospitalization and direct costs during hospitalization

Table 2 Reports of endoscopic and laparoscopic treatments for gastric cancer using national administrative database

	No. of patients	No. of hospitals	Study period	Investigated outcomes
Endoscopic submucosal dissection				
Murata *et al*[27]	32943	907	2009-2011	Complications, length of stay, and medical costs
Murata *et al*[30]	27385	867	2009-2011	Complications and length of stay
Murata *et al*[36]	27385	867	2009-2011	Complications, length of stay, and medical costs
Laparoscopic gastrectomy				
Yasunaga *et al*[40]	9388	805	2010	Complications, length of stay, medical costs, in-hospital mortality and 30-d readmission rates
Kuwabara *et al*[41]	17761	258	2006-2008	Length of hospital stay, medical costs and operative time
Murata *et al*[42]	14006	744	2009-2011	Complications, length of stay, medical costs and in-hospital mortality
Kuwabara *et al*[46]	3054	420	2007	Complications and operative time
Kuwabara *et al*[47]	3914	258	2006-2008	Complications, length of stay, medical costs, in-hospital mortality and blood transfusions
Ryu *et al*[48]	209	5	2007-2008	Length of hospital stay (pre and post operative) and duration of antibiotic administration and post operative fasting

were significantly increased in elderly patients requiring ESD for gastric cancer, compared with non-elderly patients (12.2 d *vs* 9.3 d and 7346.3 US dollars *vs* 6295.6 US dollars; $P < 0.001$, respectively). The growing life expectancy and an aging population will unavoidably lead to an increasing number of elderly patients in Japan[39]. Therefore, providing appropriate care in endoscopic treatments for elderly patients is becoming significantly important in Japan. More efficient medical implementation for elderly patients with gastric cancer treated with ESD will be required in the future.

LG for gastric cancer

Comparison between LG and OG for gastric cancer: Using the data in 2010, Yasunaga *et al*[40] reported that patients treated by LG had shorter LOS compared with those with OG (13 d *vs* 15 d, $P < 0.001$) while no significant difference was observed in mortality and occurrence of postoperative complications (LG *vs* OG, 0.36% *vs* 0.28%, $P = 0.80$ and 12.9% *vs* 12.6%, $P = 0.73$, respectively). Kuwabara *et al*[41] also reported that LG offered a significant economic advantage over OG (14405 US dollars *vs* 17260 US dollars, $P < 0.001$). These results show that LG has been a beneficial treatment for patients who require surgical resection for gastric cancer.

Influence of additional laparoscopic cho-lecystectomy on outcomes of LG for gastric cancer: A recent report revealed that adding laparoscopic cholecystectomy did not influence to outcomes of patients undergoing LG for gastric cancer (OR for laparoscopy-related complications 1.02, 95%CI: 0.84-1.24, $P = 0.788$ and OR for in-hospital mortality 1.16, 95%CI: 0.49-2.76, $P = 0.727$)[42]. These results have been consistent with previous studies in other developed countries[43,44]. The greater surgeon's experience and continuing technical progress for laparoscopic resection has resulted in expanded indications in Japan[42]. Besides, there has been an increase in the types of surgical operations together with laparoscopic procedure, and the number of surgeons interested in simultaneous laparoscopic procedures has increased[45]. Thus these results indicate that the combined LG and cholecystectomy is safe procedure for patients with both gastric cancer and gallbladder stones.

Impact of hospitals and regional differences for outcomes of LG for gastric cancer in Japan: With regard to hospital characteristics in LG for gastric cancer, several studies reported that higher-volume hospitals had shorter operation times and postoperative LOS of patients compared with low case-volume hospitals[46,47]. In an analysis of regional differences in LG for gastric cancer, Ryu *et al*[48] reported that there were significant differences with respect to rate of laparoscopic resection or duration of antibiotic administration between cancer centers of different regions. In addition, their report revealed that significant variation in pre- or postoperative LOS was observed between hospitals. Such reports could contribute to the quality of medical care for patients, which could have significant implications for decision making of health care policy in Japan.

ADVANTAGE OF EPIDEMIOLOGICAL STUDIES USING DPC DATABASE

Unlike the single center study, these studies have been conducted based on a nationally representative sample of patients in a community setting. One of the advantages of the clinical epidemiological studies using DPC data is that they facilitated evaluation of a large sample of patients in unbiased manner[16-20]. Usually, ESD and LG are performed in hospitals that have more experienced endoscopists or surgeons as well as more resources or availa-ble facilities. The DPC participating hospitals play important roles in providing advanced care or me-dical studies, as well as educating students and medical residents[16-20]. Furthermore, medical data with regards to proce-

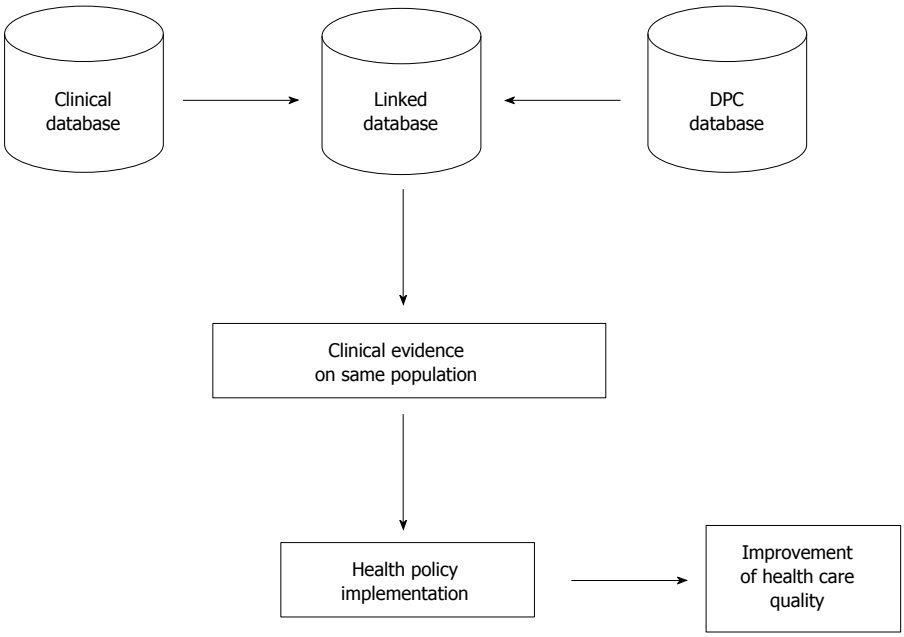

Figure 1 Framework for future clinical epidemiological studies. DPC: Diagnosis procedure combination.

dures or medications have been extensively indexed with original codes[16-20]. These data are recorded on a daily basis for each patient[16-20]. Therefore, this administrative database also enables to evaluate the clinical outcomes with detailed medical treatments, in particular for medical economic outcomes. The epidemiological studies using the DPC database directly reflect the present circumstances of endoscopic or surgical treatment for gastric cancer in Japan.

LIMITATIONS OF EPIDEMIOLOGICAL STUDIES USING DPC DATABASE

Some potential limitations of clinical epidemiological studies using DPC data also should be acknowledged. This database does not contain patient data such as lesion size, histological type and staging of gastric cancer. It is reasonable that the lack of these data may influence the results of the studies using the DPC database. In addition, the types of devices for ESD or the kinds of stapling devices used for laparoscopic resection have not been included in the DPC database. Therefore, DPC data may be currently unsuitable to the detailed clinical investigation of ESD and LG for gastric cancer.

FUTURE IMPLEMENTATION

To resolve the lack of detailed clinical data, a link between our database and the other database may be vital for future research about ESD and LG for gastric cancer in Japan. The Japanese Gastric Cancer Association (JGCA) began a project to register patients who were treated by ESD since 2011[49]. In addition, some studies has been reported using the data of the National Clinical Database (NCD)[50,51]. The results from the database of this project will be useful information for the quality of ESD and LG for gastric cancer in the near future. However, we consider that more valuable information can be produced by a link between our administrative database and the database in this project. For example, the Surveillance, Epidemiology and End Results program of cancer registries, which is a cancer registry database in the United States, has been linked to the Medicare Claim Database, a payment system for medical services. As a result, many clinical studies have reported using these linked databases[52]. Therefore, we believe that a link between our database and the database of the JGCA or NCD may be vital for future research for ESD and LG for gastric cancer in Japan. If this is carried out, more valuable information showing the favorable quality of ESD for gastric cancer can be expected in patients who undergo ESD and LG for gastric cancer (Figure 1).

CONCLUSION

From recent studies using the national administrat-ive database, the various circumstances of endosco-pic and laparoscopic treatments for gastric cancer are revealed. These findings are useful for future studies of the treatments of gastric cancer, which could in turn have important implications for care of patients with gastric cancer in Japan. However, this administrative database is still lacking detailed clinical data of gastric cancer. The link between the administrative database and the other detailed clinical database may be vital for future research into endoscopic and laparoscopic treatments for gastric cancer in Japan.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis: From guidelines to clinical practice

Joana Magalhães, Bruno Rosa, José Cotter

Joana Magalhães, Bruno Rosa, José Cotter, Gastroenterology Department, Centro Hospitalar do Alto Ave, 4835-044 Guimarães, Portugal
José Cotter, Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, 4710-057 Braga, Guimarães, Portugal
José Cotter, ICVS/3B's, PT Government Associate Laboratory, 4710-057 Braga, Guimarães, Portugal
Author contributions: Magalhães J participated in the design of the study, performed data analysis and literature research and drafted the manuscript; Rosa B performed literature research and critically revised the manuscript; Cotter J critically revised the manuscript and approved the final version to be submitted; all the authors read and approved the final manuscript.
Ethics approval: This study was approved by the institutional review board of Centro Hospitalar do Alto Ave, Guimarães, Portugal.
Informed consent: All patients provided written consent to undergo endoscopic retrograde cholangiopancreatography and were informed of the risks and potential benefits of the procedure.
Conflict-of-interest: The authors declare that there is no conflict of interests regarding the publication of this paper.
Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at jmagalhaes@chaa.min-saude.pt. The consent of the participants was not obtained but the presented data are anonymized and risk of identification is low.

Correspondence to: Joana Magalhães, MD, Gastroenterology Department, Centro Hospitalar do Alto Ave, Rua dos Cutileiros, Creixomil, 4835-044 Guimarães,
Portugal. jmagalhaes@chaa.min-saude.pt
Telephone: +351-253-540330
Fax: +351-253-421308

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Abstract

AIM: To study the practical applicability of the American Society for Gastrointestinal Endoscopy guidelines in suspected cases of choledocholithiasis.

METHODS: This was a retrospective single center study, covering a 4-year period, from January 2010 to December 2013. All patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) for suspected choledocholithiasis were included. Based on the presence or absence of predictors of choledocholithiasis (clinical ascending cholangitis, common bile duct (CBD) stones on ultrasonography (US), total bilirubin > 4 mg/dL, dilated CBD on US, total bilirubin 1.8-4 mg/dL, abnormal liver function test, age > 55 years and gallstone pancreatitis), patients were stratified in low, intermediate or high risk for choledocholithiasis. For each predictor and risk group we used the χ^2 to evaluate the statistical associations with the presence of choledocolithiasis at ERCP. Statistical analysis was performed using SPSS version 21.0. A P value of less than 0.05 was considered statistically significant.

RESULTS: A total of 268 ERCPs were performed for suspected choledocholithiasis. Except for gallstone pancreatitis (P = 0.063), all other predictors of cho-

ledocholitiasis (clinical ascending cholangitis, $P = 0.001$; CBD stones on US, $P \leqslant 0.001$; total bilirubin > 4 mg/dL, $P = 0.035$; total bilirubin 1.8-4 mg/dL, $P = 0.001$; dilated CBD on US, $P \leqslant 0.001$; abnormal liver function test, $P = 0.012$; age > 55 years, $P = 0.002$) showed a statistically significant association with the presence of choledocholithiasis at ERCP. Approximately four fifths of patients in the high risk group (79.8%, 154/193 patients) had confirmed choledocholithiasis on ERCP, *vs* 34.2% (25/73 patients) and 0 (0/2 patients) in the intermediate and low risk groups, respectively. The definition of "high risk group" had a sensitivity of 86%, positive predictive value 79.8% and specificity 56.2% for the presence of choledocholithiasis at ERCP.

CONCLUSION: The guidelines should be considered to optimize patients' selection for ERCP. For high risk patients specificity is still low, meaning that some patients perform ERCP unnecessarily.

Key words: Choledocholithiasis; Endoscopic retrograde cholangiopancreatography; Cholangitis; Common bile duct stones; Dilated common bile duct

Core tip: The American Society for Gastrointestinal Endoscopy (ASGE) proposes a stratification of patients according to the risk for choledocholithiasis, influencing subsequent management. Our study shown that the risk stratification, according to ASGE guidelines, may improve risk estimation of choledocholithiasis and should be considered to optimize patients' selection for endoscopic retrograde cholangiopancreatography (ERCP). However, even in the "high risk group" the specificity was low. Thus, at this point, it seems advisable that also "high risk" patients undergo further testing before being submitted to ERCP, similarly to those patients with "intermediate risk", while for patients with "low-risk" of choledocholithiasis a watchful waiting strategy seems adequate.

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INTRODUCTION

Choledocholithiasis is the most common cause of biliary obstruction. Approximately 5% to 22% of the Western population has gallstones[1] and common bile duct stones occur in 8%-20%[2,3] of those patients. Patients suspected of having choledocholithiasis are diagnosed with a combination of laboratory tests and imaging studies[4]. The first imaging study obtained is typically a transabdominal ultrasonography (US). When the ultrasound findings are not enough for a diagnosis a magnetic resonance cholangiopancreatography (MRCP) or an endoscopic ultrasound (EUS) should be considered.

The diagnosis of choledocholithiasis usually should be followed by some therapeutic intervention to remove the stones[4-7]. Endoscopic retrograde cholangiopancreatography (ERCP) is the standard method for the diagnosis and therapy of bile duct stones, however it is an invasive procedure not free of complications[8-11].

According to the results of laboratory tests and US, the American Society for Gastrointestinal Endoscopy (ASGE) proposes to stratify a patient in low, intermediate or high risk for choledocholithiasis. Subsequent management will vary depending on the patient's level of risk[12]. The purpose of this study was to evaluate the practical applicability of the American Society for Gastrointestinal Endoscopy guidelines in a population of patients undergoing ERCP for suspected choledocholithiasis.

MATERIALS AND METHODS

Patients

We performed a retrospective single center study, covering a 4-year period, from January 2010 to December 2013. Patients referred for ERCP for suspected bile duct lithiasis were consecutively included. Patients presenting for stent exchange or follow-up of known and incompletely removed stones on previous ERCP were excluded.

Clinical data recorded from disease onset (age, gender, symptoms at presentation, laboratorial values) to the time of the ERCP (therapeutic procedures and related complications) were collected.

Predictors of choledocholithiasis

According to ASGE guidelines[12], cholangitis, total bilirubin > 4 mg/dL and common bile duct (CBD) stone on US were considered very strong predictors. Total bilirubin 1.8-4 mg/dL and dilated CBD on US were considered strong predictors and abnormal liver biochemical tests, age > 55 years and gallstone pancreatitis were considered moderate predictors. Patients with strong predictors or any very strong predictor were considered at high risk for choledocholithiasis. Patients without any predictor and all other patients were considered low and intermediate risk for choledocholithiasis, respectively. The diagnosis of cholangitis was established by the presence of Charcot's triad (fever, abdominal pain and jaundice). The diagnosis of CBD stone on US was considered when an intraductal echogenic focus with distal acoustic

Table 1 Baseline characteristics of the study population *n* (%)

Variable	Total (*n* = 268)
Gender, female	161 (60.1)
Age, mean ± SD	66.8 ± 16.8
Very strong predictors	
Clinical ascending cholangitis	36 (13.4)
Common bile duct stone on US	109 (40.7)
Total bilirubin > 4 mg/dL	102 (38.1)
Strong predictors	
Total bilirubin 1.8-4 mg/dL	84 (31.3)
Dilated common bile duct on US	195 (72.8)
Moderate predictors	
Abnormal liver function test	231 (86.2)
Age > 55 yr	197 (73.5)
Gallstone pancreatitis	63 (23.5)

US: Ultrasonography.

shadow was identified. Dilated CBD on US was considered when bile duct diameter was > 6 mm in a patient without cholecystectomy. Abnormal liver biochemical tests were considered when aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (AP) presented elevated laboratory values, considering the reference lab values in our institution. Gallstone pancreatitis was considered when patients presented with abdominal pain (epigastric pain often radiating to the back), lipase (or amylase activity) at least 3 times higher than the upper limit of normal, stones or biliary sludge within gallbladder and no history of alcohol abuse.

Endoscopic retrograde cholangiopancreatography procedure

Every ERCP was performed using Olympus® TJF 160 VR or TJF 145 side-viewing endoscopes. All patients provided written consent to undergo ERCP and were informed of the risks and benefits of the procedure. Patients were under propofol sedation assisted by an anaesthesiologist. Stone size and number were documented on the initial diagnostic cholangiogram at ERCP. Endoscopic sphincterotomy was performed over a guide wire. Some patients underwent papillary balloon dilation using a through-the-scope balloon catheter for oesophageal/pyloric dilation, gradually inflated to 12-18 mm according to the size of the largest stone and the maximal diameter of the distal bile duct on the cholangiogram. Stones were removed using a retrieval balloon catheter and/or a Dormia basket. When necessary, mechanical lithotripsy was performed to fragment the stones prior to removal. Complete clearance of the bile duct was documented with a balloon catheter cholangiogram at the end of the procedure. In the case of residual lithiasis, a biliary 7 Fr double pigtail plastic stent was placed and a second ERCP was planned within 10-12 wk. At the end of each ERCP, 100 mg rectal indomethacin was routinely given, to prevent post-ERCP pancreatitis. Prophylactic antibiotics were not routinely administered.

Statistical analysis

Statistical analysis was performed using SPSS version 21.0 (SPSS® Inc., Chicago, IL, United States).

Quantitative data were described as mean ± SD and qualitative data as proportions. For each predictor and risk group the χ^2 was used to access differences between presence *vs* absence of choledocolithiasis on ERCP. A P value < 0.05 was considered statistically significant.

For each risk group and their predictors the sensitivity, specificity, positive predictive values (PPV) and negative predictive value (NPV) were assessed.

RESULTS

From January 2010 to December 2013, a total of 268 patients were referred for ERCP for suspected choledocholithiasis. Patients included in our study were predominantly female (60.1%), with a mean age of 66.8 ± 16.8 years. Choledocholithiasis was present in 179 ERCPs (66.8%). The predictors more often seen in our patients were the presence of abnormal liver biochemical tests (86.2%), age > 55 years (73.5%) and dilated CBD on US (72.8%). Main clinical features of the study population are shown in Table 1.

Predictors of choledocholithiasis

Except for gallstone pancreatitis (P = 0.063), all other predictors showed a statistically significant difference between presence *vs* absence of choledocholithiasis on ERCP (cholangitis, P = 0.001; CBD stone on US, P < 0.001; total bilirubin > 4 mg/dL, P = 0.035; total bilirubin 1.8-4 mg/dL, P = 0.001; dilated CBD on US, P < 0.001; abnormal liver function test, P = 0.012; age > 55 years, P = 0.002) (Table 2).

The risk of choledocholithiasis, as shown by *odds ratio*, was increased for patients who presented with cholangitis (OR: 6.48, 95%CI: 1.93-21.80), common bile duct stone on US (OR: 11.25, 95%CI: 5.32-23.81), total bilirubin > 4 mg/dL (OR: 1.79, 95%CI: 1.04-3.08), total bilirubin 1.8-4 mg/dL (OR:3.15, 95%CI: 1.63-6.08), dilated common bile duct on US (OR:5.06, 95%CI: 2.85-8.99), abnormal liver function test (OR:2.43, 95%CI: 1.20-4.90) and age > 55 years (OR:2.37, 95%CI: 1.36-4.15) (Table 2).

Risk group for choledocholithiasis

Of the 268 patients included in this study, 72% were stratified into the high risk group. Of the remaining patients, 27.2% e 0.8% were stratified into the intermediate and low risk groups, respectively. Approximately four fifths of patients in the high risk group (79.8%, 154/193 patients) had confirmed choledocholithiasis on ERCP. The presence of choledocholithiasis was identified in 34.2% (25/73) of intermediate risk patients. Any patient into the low risk group had choledocholithiasis on ERCP. There was a statistically significant association between

Table 2 Predictors of choledocholithiasis - univariate analysis *n* (%)

Variable	Choledocholithiasis on ERCP	No Choledocholithiasis on ERCP	OR	95%CI	*P* value
Very strong predictors					
Clinical ascending cholangitis	33 (91.7)	3 (8.3)	6.48	1.93-21.80	0.001
Common bile duct stone on US	100 (91.7)	9 (8.3)	11.25	5.32-23.81	< 0.001
Total bilirubin > 4 mg/dL	76 (74.5)	26 (25.5)	1.79	1.04-3.08	0.035
Strong predictors					
Total bilirubin 1.8-4 mg/dL	63 (75.0)	21 (25.0)	3.15	1.63-6.08	0.001
Dilated common bile duct on US	150 (76.9)	45 (23.1)	5.06	2.85-8.99	< 0.001
Moderate predictors					
Abnormal liver function test	161 (69.7)	70 (30.3)	2.43	1.20-4.90	0.012
Age > 55 yr	142 (72.1)	55 (27.9)	2.37	1.36-4.15	0.002
Gallstone pancreatitis	36 (57.2)	27 (42.8)	0.58	0.32-1.03	0.063

ERCP: Endoscopic retrograde cholangiopancreatography; US: Ultrasonography.

Table 3 Risk group for choledocholithiasis - univariate analysis *n* (%)

Variable	Total	Choledocholithiasis on ERCP	No Choledocholithiasis on ERCP	*P* value
High risk group	193 (72.0)	154 (79.8)	39 (20.2)	< 0.001
Intermediate risk group	73 (27.2)	25 (34.2)	48 (65.8)	
Low risk group	2 (0.8)	0 (0)	2 (100)	
Very strong predictors				
None	97 (36.2)	39 (40.2)	58 (59.8)	< 0.001
One	104 (38.8)	80 (76.9)	24 (23.1)	
Two	58 (21.6)	51 (87.9)	7 (12.1)	
Three	9 (3.4)	9 (100)	0 (0)	
Strong predictors				
None	27 (16.4)	3 (11.1)	24 (88.9)	< 0.001
One	78 (47.3)	50 (64.1)	28 (35.9)	
Two	60 (36.4)	50 (83.3)	10 (16.7)	

ERCP: Endoscopic retrograde cholangiopancreatography.

the presence of choledocholithiasis on ERCP and the risk group ($P < 0.001$) (Table 3). The odds ratio (OR) for choledocholithiasis in high risk patients was 7.89 (95%CI: 4.36-14.32). The combination of any two or all very strong predictors elevated the probability of choledocholithiasis for 87.9% (51/58) and 100% (9/9), respectively. The combination of both strong predictors presented 83.3% (50/60) of probability of choledocolithiasis.

Sensitivity, specificity, positive predictive values and negative predictive values for choledocolithiasis

Cholangitis was the parameter that had the higher specificity (96.6%), however for the same parameter the sensitivity was low. Total bilirubin > 4 mg/dL or the presence of CBD stones on US also presented a good specificity (89.9% and 70.8%, respectively). The PPV was high for very strong predictors, mainly clinical ascending cholangitis (PPV 91.7%) and CBD stones on US (PPV 91.7%). The high risk group had a high sensitivity (86%) and PPV (79.8%), but low specificity (56.2%) for the presence of CBD stones (Table 4).

DISCUSSION

According to ASGE guidelines, a patient stratified as high risk has > 50% of probability of choledocholithiasis[12]. In our study, patients stratified as high risk following ASGE criteria had 79.8% probability of choledocholithiasis. These results are consistent with those presented in the study by Rubin *et al*[13]. All the very strong predictors (clinical ascending cholangitis, CBD stones on US or total bilirubin > 4 mg/dL) presented a statistically significant association with the presence of choledocholithiasis. The combination of any of two or three very strong predictors increased the probability of choledocholithiasis for 87.9% and 100%, respectively.

Transabdominal ultrasound is the most commonly used initial imaging modality for suspected biliary stones. In our study, the presence of CBD stones detected during the US evaluation presented an OR of 11.25 for choledocholithisis. The diagnosis of choledocholithiasis is often difficult, with the sensitivity for the detection of CBD stones by US ranging from 20% to 80%[14]. The diagnostic accuracy of US is operator dependent but it is also influenced by some clinical features of patients (shadowing from bowel gas, overweight and stone size)[14].

In our study, the combination of strong predictors (dilated CBD on US, total bilirubin 1.8-4 mg/dL) presented 83.3% of probability of choledocholithiasis confirmed at ERCP. Strong predictors presented a sta-

Table 4 Sensitivity, specificity, positive predictive values and negative predictive values for choledocolithiasis

Variable	Sensitivity	Specificity	PPV	NPV
Very strong predictors				
Clinical ascending cholangitis	18.4	96.6	91.7	37.0
Common bile duct stone on US	55.9	89.9	91.7	50.3
Total bilirubin > 4 mg/dL	42.5	70.8	74.5	37.8
Strong predictors				
Total bilirubin 1.8-4 mg/dL	61.1	66.6	75	51.2
Dilated common bile duct on US	83.8	49.4	76.9	60.3
Moderate predictors				
Abnormal liver function test	89.9	21.3	69.7	51.3
Age > 55 yr	79.3	38.2	72.1	47.9
Gallstone pancreatitis	20.1	69.7	57.1	30.2
High risk group	86	56.2	79.8	66.7
Intermediate risk group	13.9	46	34,2	21

PPV: Positive predictive values; NPV: Negative predictive values; US: Ultrasonography.

tistically significant association with the presence of choledocholithiasis, which is in line with other previously published data[15-18]. The OR for choledocholithiasis in a patient with a CBD dilation was 5.06. However, the CBD dilation should always be interpreted according to patient characteristics, particularly previous cholecystectomy and age[19-21]. Previous studies[15-17,22,23] have reported some utility of serum bilirubin levels as a predictor of CBD stones. In this study, a bilirubin value between 1.8-4 g/dL had an OR of 3.15 and a specificity of 66.6% for choledocolithiasis. The specificity increased to 70% when the bilirrubin value was > 4 mg/dL. These results are in agreement with those previously reported by ASGE guidelines[12].

Individually, moderate predictors, such as abnormal liver function test and age > 55 years, presented a statistically significant association with the presence of choledocholithiasis in our series and a sensitivity of 89.9% and 79.3% for the prediction of choledocholithiasis on ERCP. In a study by Barkun *et al*[16], abnormal liver function tests, such as alkaline phosphatase > 300 units/L and AST > 120 units/L present a sensitivity of 79% and 81% to predict choledocholithiasis, respectively. At the same study, age > 55 years, only presented a sensitivity of 57%, however, when combined with other predictors (elevated bilirubin and CBD dilation on US) the model predicted with 94% of probability the presence of choledocholithiasis.

As previously reported by other authors[13,24], also in our results the diagnosis of gallstone pancreatitis was not related with the presence of choledocholithiasis at ERCP ($P > 0.05$). Stone size may be an explanation, as larger stones are less likely to migrate[24] and the small gallstones, that most commonly are the source of pancreatitis[25], frequently pass spontaneously. Some studies have reported that in the absence of cholangitis, patients with gallstone pancreatitis do not benefit from early ERCP[26,27].

In patients stratified into the intermediate and low risk group, the probability of choledocholithiasis is 10%-50% and < 10%, respectively[12]. In this study, the probability of choledocholithiasis was 34.2% (25/73) and 0 (0/2) for intermediate and low risk groups, respectively. For these risk groups the sensitivity, specificity, PPV and NPV did not show values with clinical interest. In the intermediate risk group, ASGE guidelines[12] recommended less invasive options for detecting choledocholithiasis, such as MRCP or EUS. The two techniques showed a good sensitivity and specificity for choledocholithiasis[28,29], so deciding which test should be performed first depends on various factors such as availability, cost, patient-related factors and the suspicion for a small stone. Because it is noninvasive, MRCP is the first test performed to look for CBD stones. However, for small CBD stones (< 5 mm) the sensitivity of MRCP is lower[30], so, if the MRCP is negative, but the suspicion for a common bile duct stone remains moderate to high, EUS is an appropriate next step.

In conclusion, our study confirms that the combination of choledocolithiasis predictors, according to ASGE guidelines[12], enables risk stratification of patients based on the likelihood for the presence of choledocholithiasis. However, for high risk patients the specificity was still low (56.2%), with 39 patients (20%) false positive, meaning that a significant proportion of patients will be submitted to ERCP unnecessarily. In the future, the inclusion of new predictors or different combinations of previous predictors will be essential to improve the classification of patients as high risk, obviating the need of other imaging tests (MRCP/EUS) before ERCP. However, at this point, it seems advisable that also "high risk" patients undergo further testing with MRCP and/or EUS before being submitted to ERCP, similarly to those patients with "intermediate risk", while for patients with "low-risk" of choledocholithiasis a watchful waiting strategy seems adequate.

COMMENTS

Background

Patients suspected of having choledocholithiasis are diagnosed with a combination of laboratory tests and/or imaging studies. Endoscopic retrograde cholangiopancreatography (ERCP) has been established as the standard method for the management of bile duct stones, but it may be associated with substantial morbidity and mortality. In the evaluation of suspected choledocolithiasis, the American Society for Gastrointestinal Endoscopy (ASGE) proposes to stratify a patient as high risk, intermediate risk or low risk for having choledocholithiasis. Subsequent management will vary depending on the patient's level of risk.

Research frontiers

In this study, the authors aimed to assess the practical applicability and to validate the current ASGE guidelines in a population of patients undergoing ERCP for suspected choledocholithiasis.

Innovations and breakthroughs

The study confirms that the combination of choledocolithiasis predictors, according to ASGE guidelines may improve risk estimation of choledocholithiasis and should be considered to optimize patients' selection for ERCP. However, even in the "high risk group" the specificity was low (56.2%), meaning that a significant proportion of patients will still perform ERCP unnecessarily.

Applications

The results of this study suggest that the inclusion of new predictors of choledocholithisis or different combinations of previous predictors will be essential to improve the classification of patients as high risk, obviating the need of other imaging tests before endoscopic retrograde cholangiopancreatography. Thus, at this point, it seems advisable that also "high risk" patients undergo further testing before being submitted to ERCP, similarly to those patients with "intermediate risk", while for patients with "low-risk" of choledocholithiasis a watchful waiting strategy seems adequate.

Terminology

Choledocholithiasis is defined as the occurrence of stones in the bile duct and has a propensity for life-threatening complications such as cholangitis and acute pancreatitis. Endoscopic retrograde cholangiopancreatography is a technique that combines the use of endoscopy and fluoroscopy to diagnose and treat problems of the biliary or pancreatic ductal systems. It has evolved from a diagnostic procedure to an almost exclusively therapeutic technique.

Peer-review

Title and running title accurately reflects the topic and contents of the paper key words.

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SYSTEMATIC REVIEWS

Clinical outcomes of self-expandable stent placement for benign esophageal diseases: A pooled analysis of the literature

Emo E van Halsema, Jeanin E van Hooft

Emo E van Halsema, Jeanin E van Hooft, Department of Gastroenterology and Hepatology, Academic Medical Center, 1105 AZ Amsterdam, The Netherlands

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Data sharing: All data in this systematic review were extracted from the original articles and are presented in the literature Tables 1 and 4. No additional data are available.

Correspondence to: Jeanin E van Hooft, MD, PhD, Department of Gastroenterology and Hepatology, C2-116, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. j.e.vanhooft@amc.uva.nl
Telephone: +31-20-5667918
Fax: +31-20-6917033

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Abstract

AIM: To analyze the outcomes of self-expandable stent placement for benign esophageal strictures and benign esophageal leaks in the literature.

METHODS: The PubMed, Embase and Cochrane databases were searched for relevant articles published between January 2000 and July 2014. Eight prospective studies were identified that analyzed the outcomes of stent placement for refractory benign esophageal strictures. The outcomes of stent placement for benign esophageal leaks, perforations and fistulae were extracted from 20 retrospective studies that were published after the inclusion period of a recent systematic review. Data were pooled and analyzed using descriptive statistics.

RESULTS: Fully covered self-expandable metal stents (FC SEMS) (n = 85), biodegradable (BD) stents (n = 77) and self-expandable plastic stents (SEPS) (n = 70) were inserted in 232 patients with refractory benign esophageal strictures. The overall clinical success rate was 24.2% and according to stent type 14.1% for FC SEMS, 32.9% for BD stents and 27.1% for SEPS. Stent migration occurred in 24.6% of cases. The overall complication rate was 31.0%, including major (17.7%) and minor (13.4%) complications. A total of 643 patients were treated with self-expandable stents mainly for postsurgical leaks (64.5%), iatrogenic perforations (19.6%), Boerhaave's syndrome (7.8%) and fistulae (3.7%). FC SEMS and partially covered SEMS were used in the majority of patients. Successful closure of the defect was achieved in 76.8% of patients and according to etiology in 81.4% for postsurgical leaks, 86.0% for perforations and 64.7% for fistulae. The pooled stent migration rate was 16.5%. Stent-related complications occurred in 13.4% of patients, including major (7.8%) and minor (5.5%) complications.

CONCLUSION: The outcomes of stent placement for refractory benign esophageal strictures were poor. However, randomized trials are needed to put this into perspective. The evidence on successful stent placement for benign esophageal leaks, perforations

and fistulae is promising.

Key words: Self-expandable stents; Benign esophageal strictures; Esophageal perforation; Esophageal fistula; Anastomotic leak; Systematic review

Core tip: After a systematic search of the literature, we performed a pooled analysis on the clinical outcomes of self-expandable stent placement for benign esophageal diseases. We analyzed the clinical success, adverse events and removal outcome of stent placement in 232 patients with refractory benign esophageal strictures and 643 patients with benign esophageal leaks, perforations and fistulae. Additional analyses were performed for clinical outcomes according to stent type and etiology.

van Halsema EE, van Hooft JE. Clinical outcomes of self-expandable stent placement for benign esophageal diseases: A pooled analysis of the literature. *World J Gastrointest Endosc* 2015; 7(2): 135-153 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i2/135.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i2.135

INTRODUCTION

Esophageal self-expandable stent placement is a well-established, evidence-based treatment for the palliation of malignant dysphagia. By the end of the 90's self-expandable metal stents have replaced the traditional rigid plastic tubes, because of their superiority in safety and cost-effectiveness[1-6]. Ever since the stent designs have evolved in order to improve their efficacy, durability and safety, and to expand their use for different clinical indications.

Besides malignant indications, esophageal self-expandable stents are nowadays used for refractory benign strictures, benign perforations, postoperative anastomotic leaks and benign fistulae[1,7]. To define the heterogeneous group of patients with refractory benign esophageal strictures Kochman *et al*[8] have proposed a uniform definition that has been widely accepted. According to Kochman's criteria an esophageal stricture is refractory or recurrent when it cannot be remediated to a diameter of 14 mm over 5 dilatation sessions at 2-wk intervals, or when a satisfactory luminal diameter cannot be maintained for 4 wk once the target diameter of 14 mm has been achieved[8]. The definition only applies in the absence of active inflammation and neuromuscular dysfunction. In this subgroup of patients with refractory strictures self-expandable stent placement is performed to extend the dysphagia-free period and to reduce the number of dilatations (Figure 1A and B).

There is a varied offer of esophageal self-expandable stents, that can be divided into four main groups: (1) removable fully covered metal stents (FC SEMS); (2) removable partially covered metal stents (PC SEMS); (3) removable covered plastic stents (SEPS); and (4) biodegradable stents (BD stents). In this literature review we aim to provide an overview of the clinical outcomes of self-expandable stent placement for benign esophageal diseases including a by clinical indication and by stent design breakdown.

MATERIALS AND METHODS

The PubMed, Embase and Cochrane databases were searched for publications from January 2000 to July 2014. Key words that were used included esophagus, stent and benign. Articles were screened by title and abstract for their relevance. Studies were considered for inclusion when they reported on the clinical outcomes of esophageal self-expandable stent placement for benign strictures, benign perforations, anastomotic leaks and/or benign fistulae. The exclusion criteria and search results are shown in Figure 2. The primary endpoint was clinical success, which was defined as the absence of dysphagia at end of follow-up after single stent placement in case of esophageal strictures and successful closure of the defect after single or multiple stent placements in case of an esophageal leak, perforation or fistula. Clinical failures were defined as recurrent dysphagia in case of esophageal strictures and persistent leak or death during stent therapy in case of esophageal leaks, perforations and fistulae. Secondary endpoints were the technical success rates of esophageal stent placement, morbidity rates, mortality rates and stent removal outcome. Technical success was defined as stent placement across the lesion at the end of the procedure, including successful stent repositioning after immediate migration. Successful stent removal was defined as uneventful endoscopic stent extraction without the need for additional interventions or procedures. So stent removal by the stent-in-stent procedure, which is used to induce pressure-necrosis of granulation tissue to facilitate the removal of an embedded stent, was considered an adverse event.

Statistical analysis

This manuscript contains descriptive statistics. Data were pooled and presented as frequency and percentage, so no biostatistical tests were used.

RESULTS

Refractory benign esophageal strictures

After searching the literature no randomized controlled trials (RCTs) were found that studied the outcomes of stent placement for refractory benign esophageal strictures. Twelve prospective, nonrandomized studies were identified that reported on the outcomes of esophageal stent placement for benign strictures

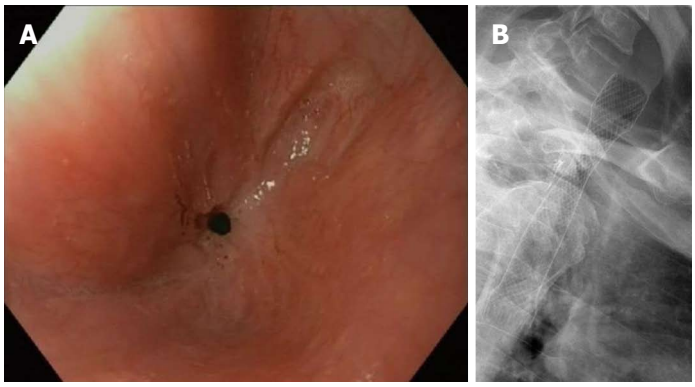

Figure 1 Refractory benign anastomotic stricture after esophagectomy (A) and fully covered self-expandable metal stent placement for a refractory benign esophageal anastomotic stricture (B).

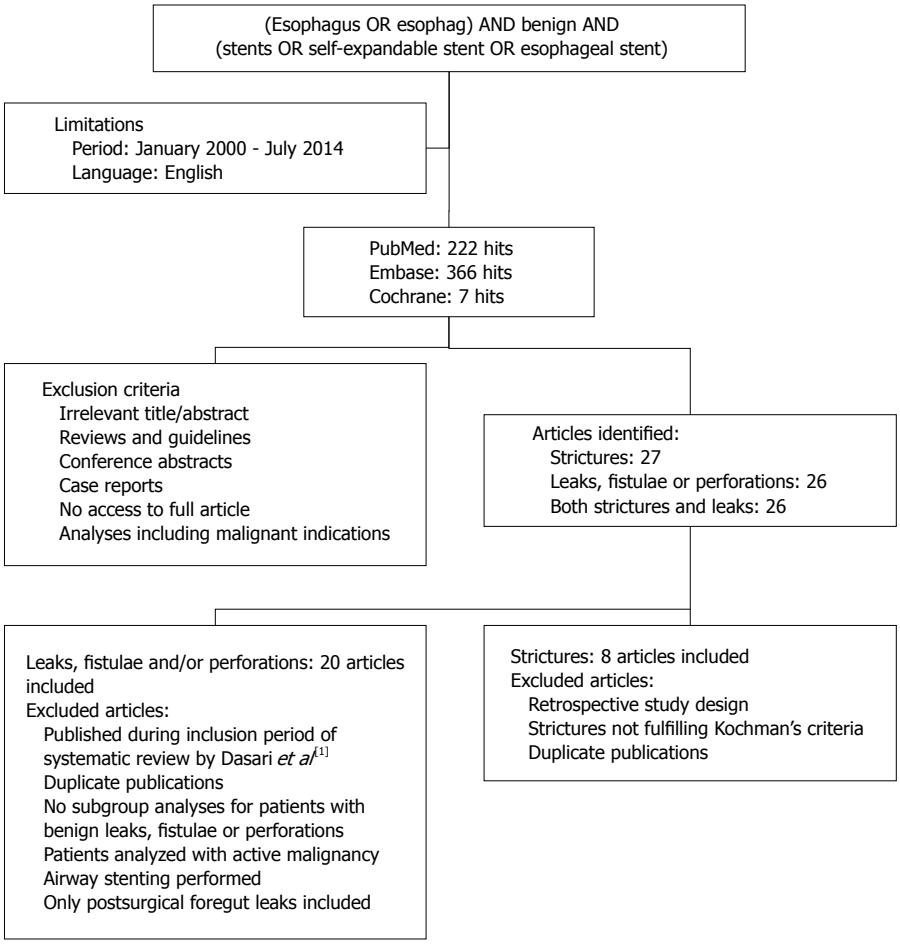

Figure 2 Literature search.

(Table 1)[9-20]. One was excluded because of a duplicate publication[20]. To create a homogeneous population only the studies were analyzed that included patients with refractory benign esophageal strictures according to Kochman's criteria[8]. A total of eight prospective cohort series were included that reported on 232 patients with refractory benign esophageal strictures[9-16]. In 85 patients a FC SEMS was placed, 77 patients received a BD stent and a SEPS was inserted in 70 patients. No PC SEMS were used in any of the included articles. The overall pooled technical success rate of esophageal stent placement was 98.7%. Details on stricture etiology, stent type and clinical outcomes are summarized in Table 2. Analyses by stricture etiology were not possible due to lacking data.

Clinical success: The overall clinical success rate after single stent placement was 24.2%. The clinical success rates per type of stent are presented in Table 2. The time to recurrence of dysphagia after failed stent therapy varied widely. Stricture recurrence after FC SEMS removal was reported by three studies after median periods ranging from 15 d to 1.7 mo[9,10,12]. Recurrence of dysphagia after SEPS removal was re-

Table 1 Literature on self-expandable stent placement for refractory benign esophageal strictures

Ref.	Study design	Patients, indications	Stent type, technical success rate, scheduled removal	Follow-up median (range)	Complications	Successful stent removal	Clinical success (dysphagia-free)
Prospective cohort studies including patients with RBES according to Kochman's criteria							
Chaput *et al*[9] 2013	Prospect	Patients with recurrent benign strictures after more than 3 dilatations to more than 15 mm during the previous 12 mo: *n* = 41 1 Anastomotic stricture: 29% (12/41) 2 Peptic stricture: 39% (16/41) 3 Caustic stricture: 7% (3/41) 4 Radiation stricture: 20% (8/41) 5 Others: 5% (2/41)	Standard FC SEMS: 100% (24/24) - 4 wk Multilayer silicone FC SEMS: 100% (17/17) - 3 mo	24 mo	Overall complications: Stent migration: 29.3% (12/41) Chest pain requiring stent removal or repositioning: 9.8% (4/41) Chest pain resolved with conservative management: 2.4% (1/41) Vomiting: 2.4% (1/41) Pneumonia: 2.4% (1/41)	FC SEMS: 100% (41/41)	Overall clinical success: 9.8% (4/41)
Canena *et al*[10] 2012	Prospect	Patients with RBES according to Kochman criteria: *n* = 30 1 Anastomotic stricture: 43% (13/30) 2 Peptic stricture: 23% (7/30) 3 Caustic stricture: 10% (3/10) 4 Radiation stricture: 7% (2/30) 5 Idiopathic stricture: 17% (5/30)	BD stent: 100% (10/10) SEPS: 100% (10/10) - 12 wk FC SEMS: 100% (10/10) - 12 wk	23.4 (8-66) mo	Patients with complications (P = 0.38): BD stent 50%, SEPS 70%, FC SEMS 60% Stent migration (P = 0.16): BD stent 20%, SEPS 60%, FC SEMS 30% Tissue hyperplasia (P = 0.09): BD stent 30%, SEPS 0%, FC SEMS 0% Associated with one major bleeding and recurrent dysphagia in two patients Minor complications in 17% (5/30) of patients: 1 Globus sensation: BD stent 0%, SEPS 0%, FC SEMS 10% 2 Moderate chest pain: BD stent 0%, SEPS 20%, FC SEMS 10% 3 Reflux: BD stent 0%, SEPS 10%, FC SEMS 10% Major complications in 7% (2/30) of patients: 1 Major bleeding: BD stent 10%, SEPS 0%, FC SEMS 0% 2 Severe chest pain: BD stent 10%, SEPS 0%, FC SEMS 0%	SEPS: 100% (10/10) FC SEMS: 100% (10/10)	Overall: 27% (8/30) Stent type (P = 0.27): 1 BD stent: 30% (3/10) 2 SEPS: 10% (1/10) 3 FC SEMS: 40% (4/10)
Hirdes *et al*[11] 2012	Prospect	Patients with RBES according to Kochman criteria: *n* = 28 1 Peptic stricture: 32% (9/28) 2 Anastomotic stricture: 25% (7/28) 3 Radiation stricture: 11% (3/28) 4 Caustic stricture: 7% (2/28) 5 Others: 11% (3/28) 6 Unknown origin: 14% (4/28)	Single BD stent: *n* = 15 Sequential BD stent: *n* = 13 Technical success: 100% (28/28) In total 59 BD stent placed	630 (21-1121) d	Stent migration: 10.7% (3/28) Food impaction: 10.7% (3/28) Major complications of 59 stent placements in 28 patients: 29% (8/28) of patients 1 Retrosternal pain and vomiting: 7.1% (2/28) 2 Retrosternal pain: 7.1% (2/28) 3 Bleeding: 7.1% (2/28) 4 Fever and vomiting: 3.6% (1/28) 5 Aspiration pneumonia: 3.6% (1/28) Minor complications of 59 stent placements in 28 patients: 14% (4/28) of patients 1 Retrosternal pain: 7.1% (2/28) 2 Reflux: 3.6% (1/28) 3 Vomiting: 3.6% (1/28) One patient (3.6%) died of aspiration pneumonia, relation to stent unclear	Not applicable	At 6 mo after: First stent: 25% (7/28) Second stent: 15% (2/13) Third stent: 0% (0/7)

Hirdes *et al*[12] 2012	Prospect	Patients with RBES according to Kochman criteria: *n* = 15 1 Peptic stricture: 40% (6/15) 2 Caustic stricture: 20% (3/15) 3 Radiation stricture: 13% (2/15) 4 Other: 7% (1/15) 5 Unknown cause: 20% (3/15)	FC SEMS: 100% (15/15) 109 d (87-222)	After stent removal: 86 (14-330) d	Stent migration: 33% (5/15) Tissue overgrowth: 20% (3/15) Major complications in 20% (3/15) of patients: 1 Severe pain requiring stent removal: 7% (1/15) 2 Severe persistent odynophagia: 7% (1/15) 3 Nausea/vomiting: 13% (2/15) 4 Aspiration pneumonia: 7% (1/15) Minor complications: 1 Pain: 20% (3/15)	93% (14/15) Stent-in-stent: 7%	0% (0/15)
Eloubeidi *et al*[13] 2011	Pro- and retrospect	Patients with benign esophageal lesions treated with Alimaxx-E stent: *n* = 35 Leaks/fistulae: *n* = 12 Perforations: *n* = 4 RBES: *n* = 19 1 Anastomotic stricture: 37% (7/19) 2 Peptic stricture: 21% (4/19) 3 Caustic stricture: 11% (2/19) 4 Radiation stricture: 11% (2/19) 5 Others: 21% (4/19)	FC SEMS: 100% (19/19) In situ for: 64 ± 74 d (range 6-300)	161 ± 111 (range 24-360) d	Stent migration: 36.8% (7/19) Minor complications in patients with RBES: 1 Stent infolding/invagination: 16% (3/19) 2 Chest pain: 5% (1/19) 3 Abdominal pain: 11% (2/19) 4 Globus sensation: 5% (1/19) 5 Fever: 5% (1/19) Major complications in patients with RBES: 1 Arrhythmia: 5% (1/19)	97% (34/35) Stent fracture: 3%	21% (4/19)
Van Boeckel *et al*[14] 2011	Prospect	Patients with RBES according to Kochman criteria: *n* = 38 1 Anastomotic stricture: 34% (13/38) 2 Peptic stricture: 18% (7/38) 3 Radiation stricture: 18% (7/38) 4 Caustic stricture: 16% (6/38) 5 Others: 11% (4/38) 6 Unknown etiology: 3% (1/38)	BD stent: 100% (18/18) SEPS: 95% (19/20) - 6 wk	BD stent: 166 (21-559) d SEPS: 385 (77-924) d	Major complications: 15.8% (6/38) 1 Hemorrhage: SEPS 5%, BD stent 11% 2 Perforation: SEPS 5%, BD stent 0% 3 Severe pain requiring opiates: SEPS 0%, BD stent 11% Minor complications: 10.5% (4/38) 1 Reflux: SEPS 0%, BD stent 6% 2 Nausea/vomiting: SEPS 5%, BD stent 11% Stent migration: SEPS 25% (5/20), BD stent 22% (4/18) Food impaction: SEPS 0%, BD stent 11% (2/18) Tissue in-/overgrowth: SEPS 0%, BD stent 11% (2/18) A FC SEMS was placed in both patients	SEPS: 100% (16/16)	Stent type (*P* = 0.83): 1 SEPS: 30% (6/20) 2 BD stent: 33% (6/18)
Repici *et al*[15] 2010	Prospect	Patients with RBES according to Kochman criteria: *n* = 21 1 Peptic stricture: 33% (7/21) 2 Anastomotic stricture: 24% (5/21) 3 Radiation stricture: 24% (5/21) 4 Caustic stricture: 10% (2/21) 5 Other: 5% (1/21) 6 Idiopathic stricture: 5% (1/21)	BD stent: 100% (21/21)	53 (25-88) wk	Stent migration: 9.5% (2/21) Severe thoracic pain requiring analgesics: 14.3% (3/21) Minor bleeding: 4.8% (1/21) Dysphagia caused by hyperplastic tissue: 4.8% (1/21)	Not applicable	45% (9/20)
Dua *et al*[16] 2008	Prospect	Patients with RBES according to Kochman criteria: *n* = 40 1 Anastomotic stricture: 30% (12/40) 2 Caustic stricture: 20% (8/40) 3 Radiation stricture: 18% (7/40) 4 Peptic stricture: 5% (2/40) 5 Others: 28% (11/40)	SEPS: 95% (38/40) 4 wk	53 (11-156) wk	Stent migration: 22.2% (8/36) Severe chest pain requiring medication: 11.1% (4/36) Fistula: 2.8% (1/36) Perforation: 5.6% (2/36) Gastroesophageal reflux: 5.6% (2/36) Bleeding: 8.3% (3/36) Stent-related mortality: 2.8% (1/36) Massive bleeding probably due to stent eroding into major vessel	94% (31/33) Inability to remove stent: 6% (2/33)	30% (12/40)
Remaining prospective cohort studies							

Van Hooft *et al*[17] 2011	Prospect	Patients with an esophagogastric anastomotic stricture who did not have had any endoscopic treatment: n = 10	BD stent: 100% (10/10)	6 mo	Food impaction: 10% (1/10) Hyperplasia-induced obstruction: 20% (2/10)	Not applicable	60% (6/10)
Evrard *et al*[18] 2004	Prospect	SEMS-induced stricture: n = 5 Esophagocolonic anastomotic stricture: n = 4 Refractory benign strictures after a median of 6 (range 1-12) dilation sessions per year: n = 8 Anastomotic leak: n = 4	SEPS: 100% (21/21) Range 2 d–18 mo	After stent removal: 21 (8-39) mo	Stent migration: 57.1% (12/21) Stridor due to tracheal compression: 4.8% (1/21) Inflammatory epiglottic stenosis: 4.8% (1/21)	100% (21/21)	76% (13/17)
Repici *et al*[19] 2004	Prospect	Patients with persisting benign esophageal strictures after at least 6 dilation sessions: n = 15 1 Caustic stricture: 33% 2 Anastomotic stricture: 27% 3 Radiation stricture: 27%	SEPS: 100% (15/15) 6 wk	Mean: 22.7 (19-27) mo	Severe chest pain requiring analgesics: 33% (5/15) Mild/moderate mucosal hyperproliferation: 27% (4/15) Stent migration: 7% (1/15)	100% (15/15)	80% (12/15)

RBES: Refractory benign esophageal strictures; SEPS: Self-expandable plastic stent; BD stent: Biodegradable stent; FC SEMS: Fully covered self-expandable metal stent.

ported by one study after a mean of 4 (range 2-9) wk[10]. After BD stent placement dysphagia recurred after mean periods ranging from 4 wk to 19 wk[10,15].

Stent migration, reactive tissue formation and food impaction: The overall pooled stent migration rate was 24.6% (57/232). By stent type migration rates were 31.8% (27/85) for FC SEMS, 14.3% (11/77) for BD stents and 27.1% (19/70) for SEPS.

Tissue hyperplasia was reported in 4.3% (10/232) of patients, causing recurrent dysphagia in 5 patients (2.2%) who all had received a BD stent. Hyperplastic tissue growth according to stent type was 3.5% (3/85) for FC SEMS, 7.8% (6/77) for BD stents and 1.4% (1/70) for SEPS. Food impaction was reported in 2.2% (5/232) of patients and occurred only in patients with a BD stent (6.5%, 5/77).

Adverse events: Excluding stent migration, reactive tissue formation and food impaction which were analyzed separately, 72 (31.0%) patients suffered a total of 77 complications due to stent placement. Major complications were reported in 17.7% of patients and minor complications in 13.4%. Major and minor complication rates per stent design are presented in Table 3. There was one (0.4%) stent-related death from a massive bleeding probably due to SEPS erosion into a major vessel[16]. Another patient with a BD stent died of aspiration pneumonia, which may have been caused by stricture recurrence[11].

Stent removal: Removal of SEPS or FC SEMS was scheduled after 4 to 12 wk and BD stents were left in place to dissolve. Stent removal was attempted in 92.9% (144/155) of patients with a SEPS or FC SEMS. Successful stent removal was achieved in 97.2% (140/144) of patients; FC SEMS (97.6%, 83/85) and SEPS (96.6%, 57/59). Two SEPS were removed during surgery, because one migrated SEPS could not be pulled through the ileocecal valve in a patient with a colon – ileocecal valve – terminal ileum interposition, and one was partially embedded by granulation tissue above the stent[16]. One FC SEMS had to be removed by a stent-in-stent procedure due to severe reactive tissue growth through the disrupted cover of the stent[12]. Another FC SEMS fractured during removal and was retrieved in two pieces[13].

Benign esophageal leaks, perforations and fistulae

The literature search revealed a recently published systematic review that analyzed the clinical outcomes of self-expandable stent placement for benign esophageal leaks and perforations in the literature published from 1990 to 2012[1]. Therefore, the studies published after the systematic review of Dasari *et al*[1] were considered for analysis. No RCTs that focused on the outcomes of stent placement for benign esophageal leaks, perforations or fistulae were identified. A total of 28 studies were selected from the literature, but after more careful reading of the articles eight more studies were excluded because they analyzed patients with active malig-

Table 2 Pooled analysis of 232 patients with refractory benign esophageal strictures according to Kochman's criteria treated with self-expandable stent placement *n* (%)

Stricture etiology	
Anastomotic strictures	69 (29.7)
Peptic strictures	58 (25.0)
Radiation strictures	36 (15.5)
Caustic strictures	29 (12.5)
Others	26 (11.2)
Unknown	14 (6.0)
Stent type	
FC SEMS	85 (36.6)
BD stent	77 (33.2)
SEPS	70 (30.2)
PC SEMS	0 (0)
Technical success	
Overall	229 (98.7)
FC SEMS	85 (100)
BD stent	77 (100)
SEPS	67 (95.7)
Clinical success	
Overall (*n* = 231)	56 (24.2)
FC SEMS (*n* = 85)	12 (14.1)
BD stent (*n* = 76)	25 (32.9)
SEPS (*n* = 70)	19 (27.1)

FC SEMS: Fully covered self-expandable metal stent; BD stent: Biodegradable stent; SEPS: Self-expandable plastic stent; PC SEMS: Partially covered self-expandable metal stent.

nancy[21], performed a double stent strategy including airway stenting[22-24], included only postsurgical foregut leaks[25], did not perform subgroup analyses for patients with benign esophageal leaks, perforations or fistulae[26,27], or because of duplicate publication[28]. Ultimately, 20 studies were included for analysis, all with a retrospective study design (Table 4)[13,29-47]. A total of 643 patients with benign esophageal leaks, perforations and fistulae were considered for analysis. A total of 852 stents were inserted in 573 patients. In the remaining 70 patients the number of stents used was not reported. The main indications for self-expandable stent placement were postsurgical leaks (64.5%), iatrogenic perforations (19.6%), Boerhaave's syndrome (7.8%) and fistulae (3.7%). The majority of inserted stents were FC SEMS (41.0%) and PC SEMS (37.7%). Stent placement was technically successful in 99.9% of cases. Further details are summarized in Table 5. Data on concurrent drainage of fluid collections were available for 425 patients, of whom 57.4% (244/425) underwent drainage procedures.

Clinical success: The overall clinical success rate of esophageal stent placement for benign leaks, perforations and fistulae was 76.8% (480/625). Subgroup analysis according to etiology was possible for 358 patients. The highest clinical success rate was achieved in patients with perforations (86.0%), followed by postsurgical leaks (81.4%) and fistulae (64.7%) (Table 5). When solely FC SEMS were used, clinical success was achieved in 73.0% (135/185) of patients. Solely PC SEMS were used in two studies with a pooled clinical success rate of 78.2% (68/87). Only one study focused on the outcomes of SEPS placement and reported clinical success in 90% (27/30) of patients with anastomotic leaks.

Table 3 Pooled analysis of adverse events in patients with refractory benign esophageal strictures *n* (%)

Overall complications	72 (31.0)
Overall major complications	41 (17.7)
FC SEMS (*n* = 85)	9 (10.6)[1]
Severe retrosternal pain	5 (5.9)
Severe nausea and vomiting	2 (2.4)
Aspiration pneumonia	2 (2.4)
Arrhythmia	1 (1.2)
Percutaneous endoscopic gastrostomy because of impaired intake caused by severe, persistent odynophagia	1 (1.2)
BD stents (*n* = 77)	22 (28.6)[1]
Severe retrosternal pain	10 (13.0)
Hyperplasia-induced stenosis	5 (6.5)
Bleeding, hematemesis	5 (6.5)
Severe nausea and vomiting	3 (3.9)
Aspiration pneumonia	1 (1.3)
SEPS (*n* = 70)	10 (14.3)
Severe retrosternal pain	4 (5.7)
Perforation	3 (4.3)
Bleeding, hematemesis[2]	2 (2.9)
Stent-induced fistula	1 (1.4)
Overall minor complications	31 (13.4)
FC SEMS (*n* = 85)	15 (17.6)[1]
Retrosternal pain	6 (7.1)
Stent infolding/invagination	3 (3.5)
Abdominal pain	2 (2.4)
Globus sensation	2 (2.4)
Reflux symptoms	1 (1.2)
Vomiting	1 (1.2)
Fever	1 (1.2)
BD stents (*n* = 77)	8 (10.4)
Nausea and vomiting	3 (3.9)
Retrosternal pain	2 (2.6)
Reflux symptoms	2 (2.6)
Minor bleeding	1 (1.3)
SEPS (*n* = 70)	8 (11.4)
Reflux symptoms	3 (4.3)
Retrosternal pain	2 (2.9)
Minor bleeding	2 (2.9)
Nausea and vomiting	1 (1.4)

[1]Patients can have more than one complication; [2]Including one stent-related death from massive bleeding. FC SEMS: Fully covered self-expandable metal stent; BD stent: Biodegradable stent; SEPS: Self-expandable plastic stent; PC SEMS: Partially covered self-expandable metal stent.

Stent migration, reactive tissue formation and food impaction: Stent migration could be analyzed in 320 patients who received a total of 468 self-expandable stents. The overall pooled stent migration rate was 16.5% (77/468). By stent type migration rates were 21.8% (53/243) for FC SEMS and 10.6% (23/218) for PC SEMS. Data were insufficient to analyze the stent migration rate of SEPS.

Pooled analysis of tissue hyperplasia was possible for 384 patients in whom 530 stents were inserted.

Table 4 Literature on self-expandable stent placement for benign esophageal leaks, perforations and fistulae

Ref.	Study design	Patients	Stent type, technical success (%) and time to removal	Additional sepsis-related procedures, follow-up	Complications and mortality	Successful stent removal	Clinical success
Dua *et al*[29] 2014	Pro- and retrospect	Patients treated with a non-foreshortening FC SEMS for benign esophageal leaks: *n* = 6 1 Postsurgical leaks: *n* = 5 2 Esophagopericardial fistula: *n* = 1 Single stent: 83% (5/6) Multiple stents: 17% (1/6)	FC SEMS: 100% (7/7) Median time to removal: 50 (49-56) d	Unknown FU: unknown	Minor complications: Pneumoperitoneum during endoscopy secondary to air insufflation: 17% (1/6) Stent migration: 17% (1/7) Mortality rate: 33.3% (2/6) - cerebral embolism: 16.7% (1/6) - sepsis-related: 16.7% (1/6)	FC SEMS: 100% (4/4)	Overall: 67% (4/6) -Postsurgical leaks: 80% (4/5) -Fistula: 0% (0/1)
El Hajj *et al*[30] 2014	Retrospect	Patients with attempted stent placement for esophageal leaks, fistulae and perforations: 1 Postsurgical leaks: *n* = 29 Single stent: 72% (21/29) Multiple stents: 28% (8/29) Excluded from analysis because patients were included with active malignancy: 1 Perforations: *n* = 10 2 Fistulae: *n* = 15	PC SEMS: 100% (19/19) - 4 to 6 wk FC SEMS: 100% (30/30) - 6 to 8 wk SEPS: 100% (15/15) - 6 to 8 wk	Not analyzed for subgroup of patients with anastomotic leaks ≥ 3 mo FU: 100%	No subgroup analysis for patients with esophageal leaks 1 Chest pain 2 GI Bleed 3 Pneumothorax 4 Increase size of leak during deployment 5 Breakage of stent 6 Dysphagia 7 Aspiration pneumonia Stent migration not analyzed for subgroup of patients with esophageal leaks Mortality rate: 0% (0/29)	No subgroup analysis for patients with postsurgical leaks -Stent-in-stent procedure: 2 -Breakage of stent: 1	Overall: 82.8% (24/29) -Primary closure rate: 72% (21/29) -Secondary closure rate: 38% (3/8)
Freeman *et al*[31] 2014	Retrospect	Patients with intrathoracic leak after surgical repair of an acute iatrogenic esophageal perforation: *n* = 29 Single stent: 100% (29/29)	SEPS: 100% (24/24) FC SEMS: 100% (5/5) Mean time to removal: 22 (13-41) d	PEG: 10.3% (3/29) Thoracoscopic decortication: 10.3% (3/29) Jejunostomy: 3.4% (1/29) Median FU: 6 wk	No stent-related complications. Stent migration: 17.2% (5/29) - not analyzed according to stent type Mortality rate: 0% (0/29)	100% (25/25) Not analyzed according to stent type	86.2% (25/29)
Gubler *et al*[32] 2014	Retrospect	Patients with benign (gastro)esophageal leaks, fistulae or perforations: *n* = 85 1 Iatrogenic perforations: *n* = 32 2 Anastomotic leaks: *n* = 31 3 Fistulae: *n* = 7 4 Boerhaave: *n* = 7 5 Other perforations: *n* = 8 Single stent: 78% (66/85) Multiple stents: 22% (19/85)	Total SEMS: *n* = 113 PC SEMS: *n* = 72 FC SEMS: *n* = 28 Unknown: *n* = 13 Technical success: 100% Average time to removal: 15 (1-111) d	Percutaneous/ thoracoscopic drainage: 55.3% (47/85) OTSC: 2.4% (2/85) Vacuum-therapy: 2.4% (2/85) FU: at least 4 wk after stent removal	Stent migration: 8.8% (10/113) - not analyzed according to stent type Food bolus obstruction: 0.9% (1/113) - not analyzed according to stent type Mortality rate: 9.4% (8/85) 1 Unrelated to in situ stent: 3.5% (3/85) 2 Multi-organ failure: 2.4% (2/85) 3 Acute respiratory distress syndrome: 1.2% (1/85) 4 Heart insufficiency: 1.2% (1/85) 5 Aortic dissection: 1.2% (1/85)	98.2% (107/109) - Irremovable: 2 - Spontaneous passage after migration: 1 Not analyzed according to stent type	Overall: 79% (67/85) -Postsurgical leaks: 74% (23/31) -Fistulae: 43% (3/7) -Iatrogenic: 94% (30/32) -Boerhaave: 71% (5/7) -Others: 75% (6/8) PC SEMS: 68% (49/72) FC SEMS: 54% (15/28)

Orive-Calzada *et al*[33] 2014	Pro- and retrospect	Patients treated with FC SEMS for benign upper gastrointestinal fistulae and perforations: *n* = 56 1 Postsurgical leaks: *n* = 44 2 Iatrogenic perforations: *n* = 6 3 Boerhaave syndrome: *n* = 4 4 Other perforations: *n* = 2 Single stent: 59% (33/56) Multiple stents: 41% (23/56)	FC SEMS: 100% (87/87) PC SEMS: 100% (1/1) Median time to removal: 42 (9-1460) d	Surgical drainage: 30% (17/56) Percutaneous drainage: 41% (23/56) FU: unknown	Minor complications: Atrial fibrillation: 1.8% (1/56) Major complications: Stent-related perforation: 5.4% (3/56) Stent migration: 20.5% (18/88) - FC SEMS: 20.7 (18/87) - PC SEMS: 0% (0/1) Mortality rate: 16% (9/56) - cerebrovascular accident: 1.8% (1/56) - nosocomial pneumonia: 1.8% (1/56) - neoplasia: 1.8% (1/56) - secondary to sepsis: 10.7% (6/56)	FC SEMS: 100% (87/87) PC SEMS: 0/1 -Stent-in-stent procedure: 1	Overall: 79% (44/56) -Postsurgical leaks: 78% (36/46) -Perforations: 80% (8/10)
Persson *et al*[34] 2014	Retrospect	Patients with benign spontaneous, iatrogenic or traumatic esophageal perforations: *n* = 40 1 Iatrogenic perforation: *n* = 16 2 Boerhaave syndrome: *n* = 23 3 Other perforations: *n* = 1 Single stent: missing Multiple stents: missing	Total No. of stents missing Stent type missing Time to removal: 4-6 wk	Unknown FU: unknown	No stent-related complications Stent migration not analyzed according to stent type Mortality rate: 7.5% (3/40) 1 Multi-organ failure: 5% (2/40) 2 Respiratory insufficiency without sepsis: 2.5% (1/40)	Stent type and no. of stents removed missing -Removal during second procedure: 1	82.5% (33/40) No subgroup analysis according to etiology
Sharaiha *et al*[35] 2014	Retrospect	Patients treated with stent placement for benign upper GI leaks: *n* = 18 1 Postsurgical leaks: *n* = 12 2 Iatrogenic perforation: *n* = 1 3Other fistulae: *n* = 5 Single stent: 28% (5/18) Multiple stents: 72% (13/18)	Total stents: *n* = 47 1 FC SEMS 2 PC SEMS 3 SEPS 4 Uncovered Technical success: 100% Mean time to removal: 54 (18-118) d	Clip/endoloop: 27.8% (5/18) Dilation: 33.3% (6/18) Surgery: 16.7% (3/18) FU: median 283 d (IQR 38-762)	Overall 9 complications in 5 patients 5 minor complications in 4 patients: - reflux/esophagitis: 16.7% (3/18) - abdominal pain: 5.6% (1/18) - collapsed stent: 5.6% (1/18) 4 Major complications in 3 patients: - aspiration pneumonia: 11.1% (2/18) - perforation: 5.6% (1/18) - stricture: 5.6% (1/18) Tissue hyperplasia: 5.6% (1/47) - stent type unknown Food impaction/bezoar: 11.1% (2/47) - stent type unknown Stent migration not analyzed for subgroup of patients with esophageal leaks Overall mortality rate: 5.6% (1/18) Not specified	No subgroup analysis for patients with benign leaks -Stent-in-stent procedure: 7 -Irremovable uncovered stent: 1	Overall: 47% (7/15) -Postsurgical leaks: (5/11) -Fistula: 67% (2/3) -Iatrogenic: 0% (0/1)
Shim *et al*[36] 2014	Retrospect	Patients who underwent endoscopic treatment for anastomotic leakage after total gastrectomy: *n* = 27 1 FC SEMS: *n* = 13 2 Non stent therapy: *n* = 14 Single stent: 85% (11/13) Multiple stents: 15% (2/13)	FC SEMS: 100% (15/15) PC SEMS: 100% (1/1) Median time to removal: 38 (0-69) d	Concurrent fluid drainage: 61.5% (8/13) FU: unknown	Minor complication: Stent malposition: 6.3% (1/13) Stent migration: 25% (4/16) - FC SEMS: 26.7% (4/15) - PC SEMS: 0% (0/1) Tissue in- or overgrowth: 6.3% (1/16) - FC SEMS: 6.7% (1/15) Mortality rate: 15.4% (2/13) - sepsis related: 7.7% (1/13) - non-stent related bleeding: 7.7% (1/13)	FC SEMS: 100% (11/11) PC SEMS: 100% (1/1)	Overall: 67% (8/12) -Primary closure rate: 67% (8/12) -Secondary closure rate: 0% (0/4)

Brangewitz *et al*[37] 2013	Retrospect	Patients with esophageal defects treated with stent placement: *n* = 39 1 Postsurgical leaks: *n* = 31 2 Iatrogenic perforations: *n* = 6 3 Boerhaave syndrome: *n* = 2 Single stent: 100% (39/39)	FC SEMS: 100% (39/39) Median time to removal: 33 (9-132) d	Unknown FU: unknown	Minor complications: - stent-related ulcers: 12.8% (5/39) Major complications: - severe bleed at upper end of stent: 2.6% (1/39) - death due to esophageal necrosis at proximal end of stent: 2.6% (1/39) Stent migration: 15.4% (6/39) Mortality rate: 25.6% (10/39) - esophageal necrosis at proximal stent end: 2.6% (1/39) - not specified: 23.1% (9/39)	FC SEMS: 90.3% (28/31) -Self-limiting bleed: 2 -Migrated stent requiring surgical removal: 1	53.8% (21/39) No subgroup analysis according to etiology
Leenders *et al*[38] 2013	Retrospect	Patients with anastomotic leakage after esophageal resection or bariatric surgery: *n* = 26 Single stent: 81% (21/26) Multiple stents: 19% (5/26)	FC SEMS: 100% (31/31) PC SEMS: 100% (2/2) Mean time to removal: 11 (1-63) wk	Unknown FU: range 2-144 wk	Minor complications: - stent disintegration all with FC SEMS: 11.5% (3/26) Major complications: - stent-related perforation with FC SEMS: 3.8% (1/26) Stent migration: 24.2% (8/33) - FC SEMS: 25.8% (8/31) Tissue ingrowth: 6.1% (2/33) - PC SEMS: 100% (2/2) Mortality rate: 19.2% (5/26) - sepsis-related: 19.2% (5/26)	FC SEMS: 100% (26/26) PC SEMS: 0% (0/2) -Traumatic removal due to tissue ingrowth: 2	80.8% (21/26)
Wilson *et al*[39] 2013	Retrospect	Patients treated with FC SEMS placement for benign esophagogastric diseases: *n* = 33 1 Perforation: *n* = 7 2 Anastomotic leak: *n* = 14 3 Sleeve gastrectomy leak: *n* = 6 4 Fistula: *n* = 6 Single stent: missing Multiple stents: missing	FC SEMS: 100% (40/40) Average time to removal: 47 d	Drainage procedure: 66.7% (22/33) VATS/open: 36.4% (12/33) Tube thoracostomy: 21.2% (7/33) Percutaneous: 9.1% (3/33) FU: unknown	Major complications: - severe hemorrhage from aorta-esophageal fistula: 3.0% (1/33) No subgroup analysis for patients with esophageal leaks, fistulae and perforations: - stent migration - food impaction Mortality rate: 0% (0/33)	No subgroup analysis for patients with esophageal leaks, fistulae and perforations -Stent fracture: 2	94% (31/33) avoided open repair -Postsurgical leaks: 95% (19/20) -Perforations: 86% (6/7) -Fistulae: 100% (6/6)
Van Boeckel *et al*[40] 2012	Retrospect	Patients treated with a SEMS or SEPS for sealing a benign esophageal rupture or anastomotic leak: *n* = 52 1 Anastomotic leak: *n* = 32 2 Iatrogenic perforation: *n* = 13 3 Boerhaave syndrome: *n* = 4 4 Others: *n* = 3 Single stent: missing Multiple stents: missing	PC SEMS: 98% (60/61) FC SEMS: 100% (15/15) SEPS: 100% (7/7) Median time to removal: 25 (1-197) d	Concurrent fluid drainage: 46.2% (24/52) Median FU: 470 (25-1200) d	Major complications: Severe retrosternal pain: 3.8% (2/52) - all PC SEMS Hemorrhage: 3.8% (2/52) - FC SEMS: stent-related death 1.9% (1/52) - PC SEMS: required adrenaline injections: 1.9% (1/52) Ruptured stent cover: 7.2% (6/83) - PC SEMS: 9.8% (6/61) Tissue in-/overgrowth: 9.6% (8/83) - PC SEMS: 13.1% (8/61) Stent migration: 12.0% (10/83) - FC SEMS: 20% (3/15) - PC SEMS: 10% (6/61)	88.7% (63/71) Tissue in- and/or overgrowth at removal of 8 PC SEMS -Stent-in-stent procedure: 4 -Esophageal rupture: 2 -Second endoscopic procedure: 1 -Esophagectomy: 1 Not analyzed according to stent type	65.4% (34/52) *No subgroup analysis according to etiology* PC SEMS: 69% FC SEMS: 56% SEPS: 71%

					- SEPS: 14% (1/7) Food obstruction: 3.6% (3/83) - PC SEMS: 4.9% (3/61) Mortality rate: 13.5% (7/52) - severe stent-related hemorrhage: 1.9% (1/52) - sepsis related: 7.7% (4/52) - malignancy: 1.9% (1/52) - active euthanasia: 1.9% (1/52)		
Buscaglia *et al*[41] 2011	Retrospect	Patients treated for benign esophageal conditions by FC SEMS placement: - fistula or leak: *n* = 15 Single stent: 67% (10/15) Multiple stents: 33% (5/15)	FC SEMS: 100% (24/24) Median time to removal: 42.5 (3-122) d	Unknown FU: unknown	Stent migration: 33.3% (8/24) Further complications not analyzed for subgroup of patients with fistulae and leaks - chest pain - globus sensation Mortality rate: 6.7% (1/15) - paraspinal abscess related to persistent fistula	No subgroup analysis for patients with esophageal leaks and fistulae -Removal during surgery: 1 -Stent-in-stent procedure: 1	79% (11/14) No subgroup analysis according to etiology
Dai *et al*[42] 2011	Retrospect	Patients treated with SEPS for: - postoperative esophageal anastomotic leaks: *n* = 30 Single stent: missing Multiple stents: missing Excluded from analysis because patients were included with active malignancy: - esophageal perforations: *n* = 6 - fistulae: *n* = 5	Total no. of SEPS missing Technical success: 100% Mean time to stent removal: 30 (7-62) d	Interventional drainage: 40% (12/30) Tracheotomy: 43% (13/30) Mean FU: 12.8 (1-61) mo	Major complications: - stent dislocation and inability to place new stent requiring rethoracotomy: 3.3% (1/30) Stent migration not analyzed for subgroup of patients with esophageal leaks Mortality rate: (2/30) - persistent sepsis and multi-organ failure: 6.7% (2/30)	No. of removed stents missing One migrated stent in a patient with an esophago-colonic anastomotic leak could not be removed	90% (27/30)
David *et al*[43] 2011	Pro- and retrospect	Patients treated with SEMS for esophageal or gastric perforation and intrathoracic contamination: *n* = 30 - postsurgical leak: *n* = 13 - boerhaave syndrome: *n* = 6 - iatrogenic perforation: *n* = 6 - fistulae: *n* = 4 - other perforation: *n* = 1 Single stent: 50% (15/30) Multiple stents: 50% (15/30)	At least 62 stents - FC SEMS - PC SEMS Technical success: 100% Average duration of stenting: 29 d	Chest tube thoracostomy: - Alone: 23.3% (7/30) - Additional intervention: 76.7% (23/30) Pleural decortication: 56.7% (17/30) Muscle-flap reinforcement: 36.7% (11/30) Average FU: 8.1 mo	Minor complications: - pain: 6.7% (2/30) - hiccups: 3.3% (1/30) - nausea: 3.3% (1/30) Major complications: - bowel obstruction: 6.7% (2/30) - erosion: 3.3% (1/30) - left atrial compression: 3.3% (1/30) Stent migration: 6.7% (2/30) - not analyzed according to stent type Mortality rate: 10% (3/30) - multi-organ failure: 3.3% (1/30) - multiple emboli caused by esophago-atrial fistula: 3.3% (1/30) - aspiration during contrast study: 3.3% (1/30)	No. of removed stents missing Not analyzed according to stent type	76.7% (23/30) No subgroup analysis according to etiology

Eloubeidi *et al*[13] 2011	Pro- and retrospect	Patients with benign esophageal lesions treated with Alimaxx-E stent: *n* = 16 - postsurgical leaks: *n* = 11 - fistula: *n* = 1 - iatrogenic perforations: *n* = 3 - other: *n* = 1 Single stent: 81% (13/16) Multiple stents: 19% (3/16)	FC SEMS: 100% (16/16) In situ for: 51 ± 45 d (range 9-163)	Dilation: 6.3% (1/16) PEG placement: 6.3% (1/16) FU: unknown	Minor complications: 1 Stent infolding/invagination: 6.3% (1/16) 2 Chest pain: 6.3% (1/16) 3 Dysphagia: 6.3% (1/16) 4 Globus sensation: 6.3% (1/16) Major complications: 1 Respiratory compromise: 6.3% (1/16) 2 Aspiration pneumonia: 12.5% (2/16) Stent migration: 31.3% (5/16) Mortality rate: 0% (0/16)	FC SEMS: 100% (16/16) One stent was retrieved in two pieces	43.8% (7/16) *No subgroup analysis according to etiology*
Freeman *et al*[44] 2011	Unknown	Hospitalized patients with an anastomotic leak after esophagectomy: *n* = 17 Single stent: 100% (17/17)	SEPS: 100% (14/14) FC SEMS: 100% (3/3) Mean time to removal: 17 (12-27) d	VATS pleural drainage: 29.4% (5/17) Pharyngostomy: 5.9% (1/17) Tube jenunostomy: 5.9% (1/17) FU: at least 3 mo after stent removal	No complications associated with stent placement or removal Stent migration: 17.6% (3/17) - not analyzed according to stent type Mortality rate: 0% (0/17)	SEPS: 100% (14/14) FC SEMS: 100% (3/3)	94% (16/17)
Nguyen *et al*[45] 2011	Retrospect	Patients who developed postoperative leaks after minimally invasive esophagectomy: *n* = 18 - conventional treatment: *n* = 9 - FC SEMS placement: *n* = 9 Single stent: 100% (9/9)	FC SEMS: 100% (9/9) Removal after 6 wk	Percutaneous drainage: 22% (2/9) Tracheostomy: 11% (1/9) FU: unknown	No stent-related complications Mortality rate: 0% (0/9)	FC SEMS: 100% (9/9)	100% (9/9)
Schweigert *et al*[46] 2011	Retrospect	Patients treated with stent placement for intrathoracic leak after esophagectomy: *n* = 12 Single stent: 100% (12/12)	PC SEMS: 100% (12/12) Median time to removal: 48 (16-99) d	Tube thoracostomy: 100% (12/12) FU: unknown	Major complications: 1 Death by hemorrhage from stent-related erosion into the aorta: 8.3% (1/12) 2 Stent-related fistula after removal: 8.3% (1/12) Stent migration: *n* = missing Mucosal hyperproliferation: *n* = missing Mortality rate: 16.7% (2/12) 1 Stent-related death by hemorrhage: 8.3% (1/12) 2 Pulmonary aspiration after stent removal and successful healing of the leak: 8.3% (1/12)	PC SEMS: 100% (10/10)	81.8% (9/11)
Swinnen *et al*[47] 2011	Retrospect	Patient treated with PC SEMS placement for benign upper GI leaks or perforations: *n* = 88 - postsurgical leaks: *n* = 65 - boerhaave syndrome: *n* = 4 - iatrogenic perforation: *n* = 14 - other perforations: *n* = 5	PC SEMS: 100% (153/153) Median time to removal for 33 PC SEMS: 23 d Median time to removal for 99 PC SEMS: 69 d	Drainage of collections: 47.7% (42/88) - Surgical: 26.1% (23/88) - Percutaneous: 15.9% (14/88) - Endoscopic: 5.7% (5/88)	Minor complications: - transient stent-related dysphagia: 11.4% (10/88) Major complications: - bleeding requiring intervention: 5.7% (5/88) - stent-related perforation: 1.1% (1/88)	PC SEMS: 24.4% (33/135) Stent-in-stent procedure: 73.3% (99/135) Removal during surgery: 2.2% (3/135)	77.6% (59/76) No subgroup analysis according to etiology

Single stent: 58% (51/88) Multiple stents: 42% (37/88)	Follow-up after removal: 3 mo: 83% 7 mo: 81% 1 yr: 72%	- tracheal compression: 1.1% (1/88) - dysphagia due to tissue hyperplasia: 18.2% (16/88); PC SEMS: 10.5% (16/153) Stent migration: 11.1% (17/153) of PC SEMS mortality rate: 10.2% (9/88) 1 Sepsis related: 3.4% (3/88) 2 Pulmonary embolism: 1.1% (1/88) 3 Full-blown AIDS: 1.1% (1/88) 4 Cardiac disease: 1.1% (1/88) Three additional deaths during first 3 mo after treatment: 1 Sepsis after surgery: 1.1% (1/88) 2 Tension pneumothorax: 1.1% (1/88) 3 Pneumonia: 1.1% (1/88)

FC SEMS: Fully covered self-expandable metal stent; FU: Follow-up; PC SEMS: Partially covered self-expandable metal stent; SEPS: Self-expandable plastic stent; VATS: Video-assisted thoracic surgery; PEG: Percutaneous endoscopic gastrostomy; OTSC: Over-the-scope-clips; IQR: Interquartile range.

Tissue hyperplasia was directly reported or deduced out of context (*e.g.*, stent-in-stent procedure for removal) in 111 cases (28.9% of patients and 20.9% of stents). The rate of reactive tissue formation according to stent type was 0.4% (1/267) for FC SEMS, 50.5% (110/218) for PC SEMS and 0% (0/45) for SEPS.

Of the 812 stents that were inserted in 540 patients, food impaction was reported in 6 cases (1.1% of patients and 0.7% of stents). Data were insufficient to analyze food impaction according to type of stent.

Adverse events and mortality: Two studies including 44 patients and 88 stent placements could not be analyzed because of missing subgroup analyses for patients with benign esophageal leaks[30,41]. So adverse events were evaluated for 599 patients. Excluding stent migration, reactive tissue formation and food impaction, which were analyzed separately, 80 (13.4%) patients suffered a total of 82 complications due to stent placement. The overall pooled major and minor complication rate were 7.8% and 5.5%, respectively. Complication rates according to stent type are presented in Table 6.

Mortality during the course of stent therapy was reported in 10.0% of all patients with benign leaks, perforations and fistulae. Stent-related mortality was reported in three cases (0.5%). One was caused by severe bleeding in a patient treated with a FC SEMS who refused further interventions[40]. In another case esophageal necrosis at the proximal end of a FC SEMS resulted in a fatal outcome[37]. The third stent-related death was due to massive hemorrhage caused by erosion of a PC SEMS into the aorta[46]. Other non-stent-related causes for mortality are summarized in Table 7.

Stent removal: The outcome of stent removal could be analyzed in 13 studies in which 555 of the 615 inserted stents were subsequently removed. The overall pooled successful removal rate was 78.7% (437/555). Causes of failure were stent embedding by granulation tissue requiring stent-in-stent procedures for removal (n = 104, 18.7%), surgical removal (n = 5, 0.9%), esophageal ruptures (n = 2, 0.4%), irremovable stent (n = 2, 0.4%), self-limiting bleedings (n = 2, 0.4%), traumatic removal due to tissue ingrowth (n = 2, 0.4%) and additional endoscopic procedures (n = 1, 0.2%). When uneventful stent-in-stent procedures were considered as successful removals, the overall successful stent removal rate increased up to 97.5% (541/555). Stent removal outcome could be analyzed for 187 FC SEMS of which 84% (158/187) were removed after a median period of 5 to 7 wk. FC SEMS removal was successful in 98.4% (184/187) of procedures, including one fractured stent that was retrieved in two pieces. There were two cases of a self-limiting bleeding and one migrated FC SEMS required surgical removal. The majority of PC SEMS (73%, 109/149) were removed after a median period of 7 to 10 wk. One study accounted for 91% (135/149) of the PC SEMS removals[47]. Successful endoscopic removal of PC SEMS was achieved in 29.5% (44/149) of cases and in 96.6% (144/149) after stent-in-stent procedures. Three PC SEMS were removed during surgery and two removals were traumatic due to tissue ingrowth. The two cases of esophageal rupture also occurred during the removal of PC SEMS, but could not be included

Table 5 Pooled analysis of 643 patients with benign esophageal leaks, perforations and fistulae treated with self-expandable stent placement

Etiology	
Postsurgical leaks	415 (64.5)
Iatrogenic perforations	126 (19.6)
Boerhaave's syndrome	50 (7.8)
Fistulae	24 (3.7)
Others/not specified	28 (4.4)
Stent type of 852 stents used in 573 patients[1]	
FC SEMS	349 (41.0)
PC SEMS	321 (37.7)
SEPS	60 (7.0)
Stent type unknown	122 (14.3)
Technical success	
Overall	851 (99.9)
FC SEMS	349 (100)
PC SEMS	320 (99.7)
SEPS	60 (100)
Stent type unknown	122 (100)
No. of stents per patient	
Single stent placement	357 (55.5)
Multiple stents inserted	131 (20.4)
Unknown	155 (24.1)
Clinical success	
Overall (n = 625)	480 (76.8)
According to etiology (n = 358)	
Postsurgical leaks (n = 247)	201 (81.4)
Perforations[2] (n = 86)	74 (86.0)
Fistulae (n = 17)	11 (64.7)
Others/not specified (n = 8)	6 (75.0)

[1]In two studies including 70 patients the total number of stents used was not reported; [2]Including iatrogenic and spontaneous perforations. FC SEMS: Fully covered self-expandable metal stent; PC SEMS: Partially covered self-expandable metal stent; SEPS: Self-expandable plastic stent.

in the pooled analysis because the overall number of removed PC SEMS was not reported[40]. The ruptures were successfully treated with another stent. The outcome of SEPS removal could be extracted from one study and was successful in 100% (14/14) of cases after a mean stent time of 17 d[44].

DISCUSSION

This pooled analysis of the literature showed that the overall clinical success rate of self-expandable stent placement was 24.2% for refractory benign esophageal strictures and 76.8% for benign esophageal leaks, perforations and fistulae. With regard to refractory benign strictures, the meta-analysis by Thomas *et al*[7] found sustained improvement of dysphagia in 46.2% of patients treated with self-expandable stents, which is almost twice as high as the clinical success rate (24.2%) in this pooled analysis. Also the systematic review by Repici *et al*[48] reported a much higher clinical success rate of 52% after SEPS placement for benign esophageal strictures. The difference in clinical success between our pooled analysis and the aforementioned systematic reviews may be explained by the etiology and the severity of the strictures. The study population of Thomas *et al*[7] mainly included corrosive (43%), postsurgical (25%) and radiation (11%) strictures. The etiologies of the patients in the systematic review on SEPS treatment mainly included postsurgical (38%), corrosive (25%) and radiation (15%) strictures[48]. In our analysis, peptic strictures accounted for 25.0% of patients, while corrosive strictures represented only 12.5%. However, the literature data were insufficient to analyze the clinical outcomes of stent placement according to stricture etiology. With regard to the severity of the strictures, Thomas *et al*[7] included three studies, that accounted for 50% of weight in the meta-analysis, in which patients had a history of two or less dilatations before stent placement. The review by Repici *et al*[48] did not provide details on the number of previous dilatations, but included mainly retrospective studies with heterogeneous definitions of refractory or recurrent strictures. We think that the more homogeneous population included in this analysis of prospective studies, that fulfilled Kochman's criteria[8], had more severe strictures and therefore a poorer outcome of stent therapy. Thomas *et al*[7] reported a significantly higher clinical success rate for Polyflex stents (55.3%) compared with nitinol stents (36.7%). Our results also showed a lower clinical success rate with the use of FC SEMS (14.1%) compared with SEPS (27.1%) and BD stents (32.9%). We do not have a good explanation for this finding. Complication, stent migration and tissue response rates were not significantly higher with the use of FC SEMS.

Safety analyses in patients treated with self-expandable stents for refractory benign strictures showed an overall complication rate of 31.0%, including a major complication rate of 17.7%. That complications are frequent during the course of stent therapy has also been demonstrated by several retrospective studies that were not included in our analyses[49-53]. The major complication rate of BD stents (28.6%) was twice as high as those of SEPS (14.3%) and FC SEMS (10.6%), because they caused more retrosternal pain, hyperplasia-induced stenoses and bleedings. Severe retrosternal pain occurred in 13.0% of patients who received a BD stent. Pain after stent placement has been postulated to be caused by the radial force of the stent against the tight stricture and is mainly reported within the first week after stent placement[9,11,15,49,53]. However, *in vitro* analysis of the radial and axial forces of 23 esophageal stent models showed that BD stents had a relatively low radial force and high axial force[54]. Therefore, it is more likely that because of the rigid stent design BD stents interact less well with the peristalsis of the esophagus causing more spasm and pain. In this analysis clinically relevant hyperplastic tissue growth was reported in 7.8% of BD stents. Two case series not included in this review also showed that reactive tissue formation is common after BD stent placement (Figure 3)[17,55]. The occurrence of tissue growth may be explained as a reaction to the chemical processes of degradation,

Table 6 Pooled analysis of adverse events in patients with benign esophageal leaks, perforations and fistulae

Total number of patients analyzed: *n* = 599	No. of patients (*n* = 599)	No. of FC SEMS (*n* = 295)	No. of PC SEMS (*n* = 302)	No. of SEPS (*n* = 75)[1]	Stent type unknown (*n* = 162)[2]
Overall complications	80[3] (13.4)	26 (8.8)	38 (12.6)	1 (1.3)	17 (10.5)
Overall major complications	47[3] (7.8)	11 (3.7)	28 (9.3)	1 (1.3)	8 (4.9)
Hyperplasia-induced stenosis	16 (2.7)	0	16	0	0
Hemorrhage[4]	8 (1.3)	2[4]	6	0	0
Stent-related perforation	6 (1.0)	4	1	0	1
Aspiration pneumonia	4 (0.7)	2	0	0	2
Respiratory compromise/ tracheal compression	2 (0.3)	1	1	0	0
Severe retrosternal pain	2 (0.3)	0	2	0	0
Bowel obstruction	2 (0.3)	0	0	0	2
Erosion[4]	2 (0.3)	0	1[4]	0	1
Hemorrhage from aorta-esophageal fistula	1 (0.2)	1	0	0	0
Stricture formation	1 (0.2)	0	0	0	1
Stent-related fistula	1 (0.2)	0	1	0	0
Stent dislocation and inability to place new stent requiring rethoracotomy	1 (0.2)	0	0	1	0
Left atrial compression	1 (0.2)	0	0	0	1
Death due to esophageal necrosis at proximal stent end	1 (0.2)	1	0	0	0
Overall minor complications	33[3] (5.5)	15 (5.1)	10 (3.3)	0 (0)	9 (5.6)
Transient stent-related dysphagia	11 (1.8)	1	10	0	0
Stent-related ulcers	5 (0.8)	5	0	0	0
Reflux/esophagitis	3 (0.5)	0	0	0	3
Chest pain	3 (0.5)	1	0	0	2
Stent disintegration	3 (0.5)	3	0	0	0
Stent collapse/invagination	2 (0.3)	1	0	0	1
Pneumoperitoneum during endoscopy secondary to air insufflation	1 (0.2)	1	0	0	0
Atrial fibrillation related to sedation	1 (0.2)	1	0	0	0
Stent malposition	1 (0.2)	1	0	0	0
Abdominal pain	1 (0.2)	0	0	0	1
Nausea	1 (0.2)	0	0	0	1
Globus sensation	1 (0.2)	1	0	0	0
Hiccups	1 (0.2)	0	0	0	1

[1]Including 30 patients in whom the number of SEPS used was not reported; [2]Including 40 patients in whom the number of stents used was not reported; [3]Patients can have more than one complication; [4]Including one stent-related death. FC SEMS: Fully covered self-expandable metal stent; PC SEMS: Partially covered self-expandable metal stent; SEPS: Self-expandable plastic stent.

Table 7 Overall mortality in 643 patients treated with self-expandable stents for benign esophageal leaks, perforations and fistulae *n* (%)

Overall mortality	64 (10.0)
Stent-related	3 (0.5)
Sepsis-related	23 (3.6)
Multi-organ failure	5 (0.8)
Cerebral embolism/cerebrovascular accident	2 (0.3)
Heart insufficiency/cardiac disease	2 (0.3)
Pneumonia	2 (0.3)
Malignancy	2 (0.3)
Non stent-related bleeding	1 (0.2)
Respiratory insufficiency without sepsis	1 (0.2)
Pulmonary embolism	1 (0.2)
Acute respiratory distress syndrome	1 (0.2)
Pulmonary aspiration after healing of leak	1 (0.2)
Aortic dissection	1 (0.2)
Tension pneumothorax	1 (0.2)
Paraspinal abscess related to persistent fistula	1 (0.2)
Full-blown AIDS	1 (0.2)
Aspiration during contrast study	1 (0.2)
Multiple emboli caused by esophago-atrial fistula	1 (0.2)
Active euthanasia	1 (0.2)
Not specified	13 (2.0)

which may also trigger bleedings from the affected esophageal mucosa. So one should be aware that the higher efficacy of BD stent placement is attended by an increased risk of complications.

The clinical success rate (76.8%) of self-expandable stent placement for benign esophageal leaks, perforations and fistulae found in this pooled analysis is comparable with the 81% of the systematic review by Dasari *et al*[1] (Figure 4A and B). In contrast to our analysis, the latter review excluded patients with leaks from the gastric staple line after sleeve gastrectomy and did not analyze patients with fistulae. In our study clinical success according to etiology was 81.4% for postsurgical leaks, 86.0% for perforations and 64.7% for fistulae. Though derived from retrospective series, these results seem promising. Patients with esophageal leaks or ruptures are usually in poor condition with elevated septic parameters and require invasive management, like drainage procedures, surgery and ICU care. This is reflected by the increased mortality rate of 7.2%-25.8% after postsurgical esophageal leakage[56-58]. Several treatment strategies have been described for the management

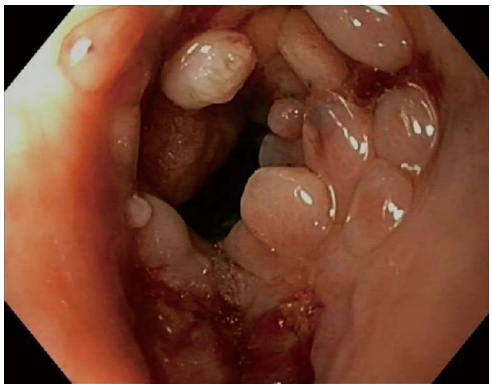

Figure 3 Endoscopic image of granulation tissue growth 4 mo after biodegradable stent placement for a refractory benign esophageal anastomotic stricture.

of esophageal leaks, such as endoscopic vacuum therapy, nose fistula tube drainage, surgical repair and conservative management[59-61]. Retrospective comparison of 41 patients with an anastomotic leak after esophagectomy who were matched by clinical status, showed that endoscopic vacuum therapy resulted in a lower mortality rate (12%, 2/17) compared with surgical treatment (50%, 9/18) and stent placement (83%, 5/6) in systemically ill patients[58]. Another retrospective study reported a significantly higher closure rate after endoscopic vacuum therapy (84%) compared with stent therapy (53.8%) in 71 patients with esophageal defects[37]. However, one should keep in mind that success of stent placement depends on the size of the esophageal lesion, the delay between diagnosis and stent placement and if the patient has elevated septic parameters[30,33,34,47]. Stent placement is most likely to fail in a large lesion (> 15 mm), that exists for several weeks in a septic patient. Therefore, patients with an esophageal leak should receive a multidisciplinary patient-tailored approach.

The removability of self-expandable stents was safe and feasible with an overall successful removal rate of 97.2% in patients with refractory strictures and 78.7% in patients with esophageal leaks. The fact that PC SEMS were used in 38% of patients with esophageal leaks resulted in a lower overall successful removal rate. PC SEMS removal was often complicated by stent embedding requiring stent-in-stent procedures to induce pressure-necrosis of the granulation tissue to facilitate the removal procedure. The vast majority of stent-in-stent procedures were reported in the study by Swinnen *et al*[47]. The removal of FC SEMS and SEPS removal was much safer with successful removal rates of 96.6% up to 98.4%. The relation between the use of PC SEMS and complicated stent removal has also been demonstrated by several large retrospective series[62,63].

This pooled analysis of the literature has several limitations. The prospective data on the outcomes of stent placement for refractory benign esophageal strictures reflect a patient population with various

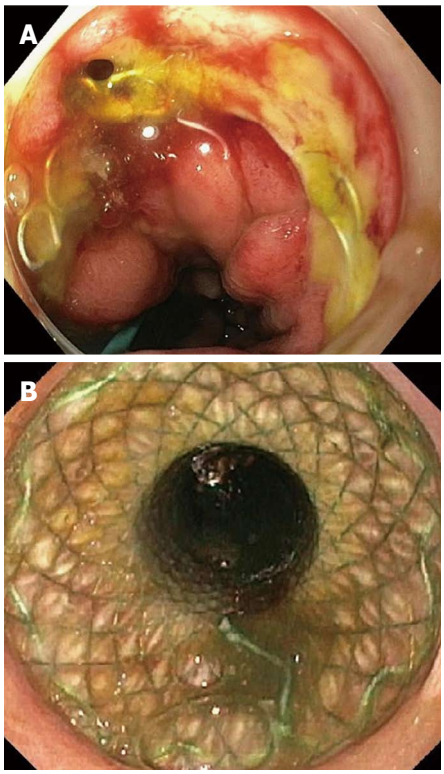

Figure 4 A small leak at the anastomosis of the esophagus and the gastric tube 5 d after esophagectomy (A) and esophageal fully covered self-expandable metal stent placement for a small anastomotic leak (B).

causes for stricture formation. Data were insufficient to provide analyses according to stricture etiology. The studies that were analyzed on the outcomes of esophageal stent placement for benign leaks, perforations and fistulae were all retrospective, causing heterogeneity and underreporting of adverse outcomes.

In conclusion, the outcomes of self-expandable stent placement for refractory benign esophageal strictures were poor with a clinical success rate of 24.4% and a major complication rate of 17.7%. However, randomized trials are needed to put these outcomes into perspective. Although derived from retrospective series, the evidence on stent placement for benign esophageal leaks, perforations and fistulae is promising with an overall clinical success rate of 76.8%.

COMMENTS

Background

Self-expandable stents in various types are increasingly being used for the treatment of refractory benign esophageal strictures and benign esophageal leaks, perforations and fistulae.

Research frontiers

It is hypothesized that esophageal stent placement for benign refractory strictures prolongs the dysphagia-free period compared with conventional dilatation therapy. Besides application for the treatment of strictures, esophageal stents are also used to seal leaks, perforations and fistulae.

Innovations and breakthroughs

The literature on esophageal stent placement for benign indications is heterogeneous and usually includes small samples. In this systematic review

we performed a pooled analysis on the treatment outcomes of 232 patients with refractory strictures and 643 patients with leaks, perforations and fistulae.

Applications

This pooled analysis may be helpful for the endoscopist in the decision-making on the indication for esophageal stent placement and also to inform the patient on the risks and benefits of stent therapy.

Terminology

Biodegradable stents are only used for strictures, because they have the property to dissolve. Nitinol metal stents (SEMS) have an outer membrane of silicone or polytetrafluoroethylene to prevent hyperplastic tissue ingrowth. Because they are covered, they are removable and can also be used to seal leaks. Partially covered SEMS usually become partially embedded by granulation tissue, which prevents stent migration, but makes them harder to remove. Self-expandable plastic stents consist of plastic instead of metal and are fully covered.

Peer-review

This review is well-written and comprehensive review about this subject.

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CASE REPORT

Rare case of dysphagia, skin blistering, missing nails in a young boy

Jasbir Makker, Bharat Bajantri, Prospere Remy

Jasbir Makker, Bharat Bajantri, Prospere Remy, Division of Gastroenterology, Department of Medicine, Bronx Lebanon Hospital Center, Albert Einstein College of Medicine of Yeshiva University, New York, NY 10457, United States

Author contributions: Makker J and Bajantri B contributed equally in writing the manuscript; Remy P edited and approved the final version of manuscript.

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Correspondence to: Jasbir Makker, Gastroenterology Fellow, Division of Gastroenterology, Department of Medicine, Bronx Lebanon Hospital Center, Albert Einstein College of Medicine of Yeshiva University, 1650 Grand Concourse Bronx, New York, NY 10457, United States. makkerjs@gmail.com
Telephone: +1-347-3228242
Fax: +1-718-5185111

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Abstract

Epidermolysis bullosa is a group of genetic disorders with an autosomal dominant or an autosomal recessive mode of inheritance and more than 300 mutations. The disorder is characterized by blistering mucocutaneous lesions and has several varying phenotypes due to anchoring defect between the epidermis and dermis. The variation in phenotypic expression depends on the involved structural protein that mediates cell adherence between different layers of the skin. Epidermolysis bullosa can also involve extra-cutaneous sites including eye, nose, ear, upper airway, genitourinary tract and gastrointestinal tract. The most prominent feature of the gastrointestinal tract involvement is development of esophageal stricture. The stricture results from recurrent esophageal mucosal blistering with consequent scarring and most commonly involves the upper esophagus. Here we present a case of a young boy with dominant subtype of dystrophic epidermolysis bullosa who presented with dysphagia, extensive skin blistering and missing nails. Management of an esophageal stricture eventually requires dilatation of the stricture or placement of a gastrostomy tube to keep up with the nutritional requirements. Gastrostomy tube also provides access for esophageal stricture dilatation in cases where antegrade approach through the mouth has failed.

Key words: Epidermolysis bullosa; Dysphagia; Esophageal stenosis; Gastrostomy; Blistering

Core tip: Epidermolysis bullosa is a genetic disorder with four main types. The most prominent feature of the disease is extensive skin blisters. Extra-cutaneous manifestations like dysphagia vary among different subtypes. Recessive type of dystrophic epidermolysis bullosa is the subtype most commonly associated with esophageal strictures. Treatment of dysphagia secondary to esophageal stricture involves changing diet texture, dilatation of the stricture and placement of a gastrostomy tube.

Makker J, Bajantri B, Remy P. Rare case of dysphagia, skin blistering, missing nails in a young boy. *World J Gastrointest Endosc* 2015; 7(2): 154-158 Available from: URL: http://www.

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INTRODUCTION

Epidermolysis bullosa is a multisystem inherited disorder with extensive skin blistering as the most prominent feature. Four distinct types of epidermolysis bullosa recognized are epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB) and kindler syndrome. Severity and extent of cutaneous and extra-cutaneous features can vary among different subtypes and depends on the type of skin structural protein affected.

CASE REPORT

A 15-year-old boy with blistering skin disease since birth presented to this hospital complaining of worsening dysphagia for 3 d. He had been generally well till the age of 9 years when he started experiencing dysphagia. He described his symptoms as gradually worsening difficulty in swallowing solids for past 6 years. He mostly consumed liquids and soft consistency meals during these years. He reported an episode of worsening swallowing difficulty with inability to swallow liquids as well about 6 mo prior to presentation. At that time, he was admitted to another hospital and a barium esophagogram was obtained which showed upper esophageal stenosis. He also reported a failed endoscopic attempt at that time. Subsequently, he improved spontaneously in 2-3 d and resumed his liquid diet until 3 d ago when he again experienced difficulty swallowing liquids and solids both. He described his symptoms as inability to swallow and the food being stuck in his throat. He also claimed to have a choking sensation when he tried to drink milk. He denied chest pain, shortness of breath, fever and drooling of saliva. He denied any worsening of his skin condition.

He had an extensive skin blistering disease since birth and was advised by his pediatric dermatologist to use a moisturizing cream on the raw skin areas exposed by ruptured blisters. Review of his skin lesion biopsy done previously revealed the diagnosis of dystrophic epidermolysis bullosa dominant type. He denied any prior surgeries. He did not smoke, use alcohol or any illicit drug. He lived with his mother who was apparently healthy without any chronic skin disease. His mother was separated from his father and did not have any details about his father's medical conditions.

On examination, he appeared comfortable, afebrile with pulse 93 beats per minute, blood pressure 111/68 mmHg, respiratory rate 18 per minute and body mass index (BMI) was 16.1 kg per square meter. He had extensive erosions and crust formation with whitish papules involving face, neck, trunk, and extremities (Figure 1). On examination of his extremities, many of his finger and toenails were missing (Figure 1). His oral cavity examination and the systemic examination including chest, cardiac, abdomen and neurological examination were unremarkable.

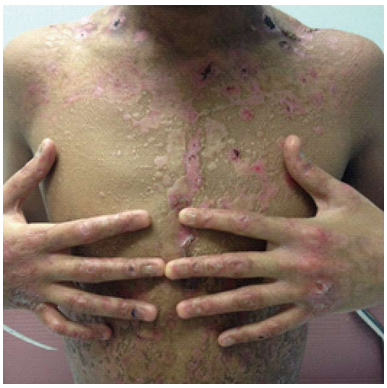

Figure 1 Extensive erosions, crusts, scars on the skin and missing nails.

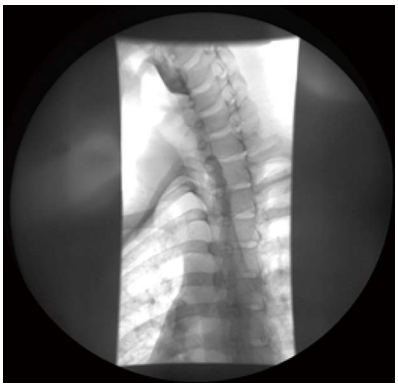

Figure 2 Upper esophageal stenosis as seen on an esophagogram.

During his hospital stay, an esophagogram was done which showed tight stenosis at the level of cervical esophagus (Figure 2). An upper gastrointestinal endoscopy was performed which showed a tight stenosis involving the upper esophagus (Figure 3). Stenosed region of the upper esophagus could not be traversed even with the use of an extra slim 5.5 mm diameter endoscope. Patient eventually underwent a percutaneous gastrostomy tube placement.

DISCUSSION

A German dermatologist Heinrich Koebner coined the term epidermolysis bullosa in 1886[1]. Epidermolysis bullosa comprises a group of hereditary disorders characterized by recurrent mucocutaneous blisters that result from minor trauma. Due to several genotypic and phenotypic variants of epidermolysis bullosa, classifying this group of disorder was challenging. In 1962, Epidermolysis bullosa was first classified by Pearson based on the detailed structures of dermo-

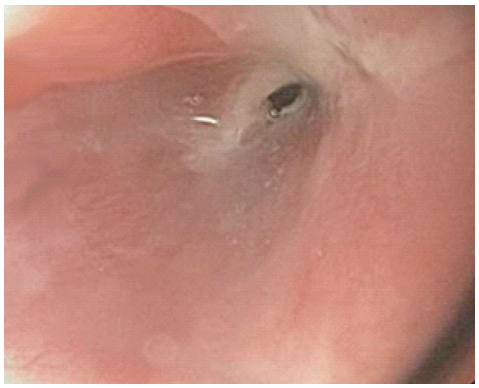

Figure 3 Upper esophageal stenosis as seen on an esophagogastroduodenoscopy.

epidermal junction as seen on the electron microscope[2]. Since then the group of experts have had four international consensus meetings on diagnosis and classification of epidermolysis bullosa to include all the subclasses under one classification system.

The last international consensus meeting results were released in 2014 and the expert group continues to recognize epidermolysis bullosa into four major types based on the level of cleavage in the skin layers[1]. Skin is composed of an outer epidermis, inner dermis and an intermediate layer called basement membrane zone, which lies between the epidermis and dermis. Basement membrane zone has been further divided into four layers - hemidesmosome, lamina lucida, lamina densa and sub-lamina densa[3]. Four major types (Figure 4) of epidermolysis bullosa with their level of cleavage are – EBS (intra-epidermal cleavage), JEB (intra-lamina lucida cleavage), DEB (intra sub-lamina densa cleavage) and kindler syndrome (multiple levels of cleavage)[1].

Epidemiology

Epidermolysis bullosa has a variable worldwide prevalence. The variability is likely due to genetic differences between different populations but the differences in recognizing and reporting of the disease are also contributory. In countries where epidermolysis bullosa registries have been established, epidemiological data is slowly emerging but is still underestimated. Prevalence of 10 per million in Australia[4], 49 per million in Scotland[5], 32 per million in Ireland[6] and 10.1 per million in Italy[7] has been reported. In United States, National Epidermolysis Bullosa Registry (NEBR) was founded in 1986 and since then it has emerged as the largest registry of epidermolysis bullosa in the world. According to 1990 estimates of NEBR, the prevalence of epidermolysis bullosa was 8 per million in United States[8].

Etiopathogenesis

Epidermolysis bullosa is inherited as an autosomal dominant or an autosomal recessive disease. Mutations in genes encoding for structural proteins of epidermis, dermis and basement membrane zone are responsible for the fragility of the skin. Phenotypic heterogeneity of epidermolysis bullosa depends on the structural protein involved. Various proteins implicated in different subtypes of epidermolysis bullosa are shown in Figure 4[9].

Clinical features

Cutaneous manifestations: Skin blisters are the most prominent manifestations of epidermolysis bullosa. Blisters may involve oral mucosa as well. Besides skin blisters, other skin lesions described in literature are erosions, milia (small white papules), deformity or absence of finger and toenails, scarring and extensive granulation tissue. Skin lesions vary in severity and extent among different subtypes.

EBS is the predominant type prevalent in western countries and in general has milder skin lesions as compared to JEB or DEB. The herlitz subtype of JEB is less prevalent than the non-herlitz JEB, but both can have characteristic enamel hypoplasia. Skin scarring is a predominant feature of herlitz subtype JEB. In addition, involvement of the mucosal surfaces of esophagus, upper airway and cornea with subsequent scarring can also be seen with herlitz subtype JEB. The non-herlitz JEB has fewer tendencies to develop extracutaneous manifestations. Dominant form of DEB develops skin blisters at birth. Recurrent involvement of esophagus with subsequent scarring and stenosis can be seen among these patients. Recessive form of DEB is the most severe form of epidermolysis bullosa and leads to disfiguring skin scars, hand and foot deformities, growth retardation and failure to thrive. Kindler syndrome is characterized by photosensitivity and skin pigmentation besides skin blistering[8].

Extra-cutaneous manifestations

Epidermolysis bullosa, in addition to skin involvement, may involve extra-cutaneous sites leading to significant morbidity and mortality. It can involve eye, oral cavity, nose, gastrointestinal tract, genitourinary tract, respiratory tract and heart. Involvement of eye may manifest as conjunctival edema, keratitis, corneal erosions, corneal ulcerations and scarring. Genitourinary involvement may manifest as scarring of glans penis or vaginal vestibule, urethral strictures leading to hydroureter and hydronephrosis. Repeated blisters involving nose, oral cavity and ear may lead to scarring and occlusion of external nares, oropharynx and external auditory canal. Blisters may involve larynx and upper respiratory tract epithelium leading to scarring and respiratory compromise[10]. Musculoskeletal involvement in recessive DEB is characterized by extensive blistering and scarring that eventually leads to fusion of fingers and toes (mitten deformity). Other features of musculoskeletal involvement are contractures involving multiple

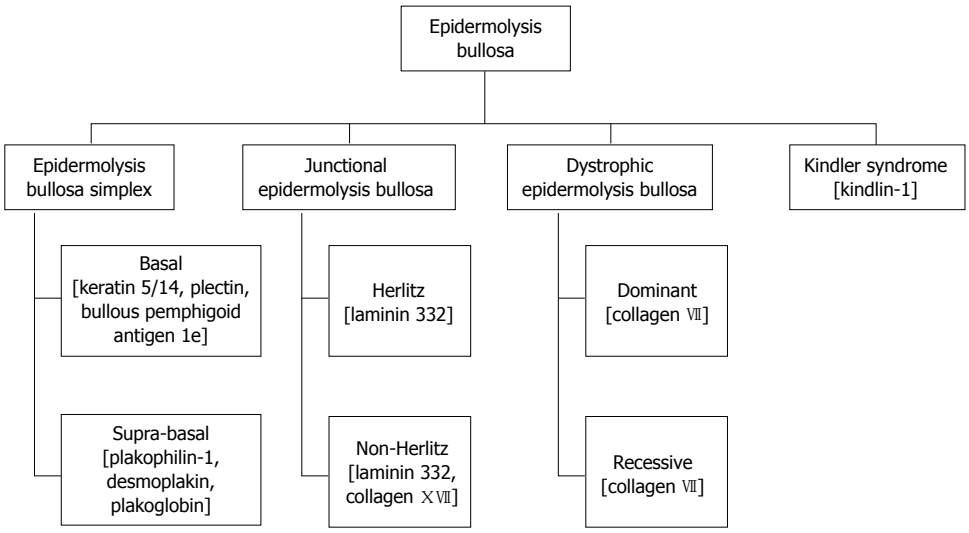

Figure 4 Major types and subtypes of epidermolysis bullosa with affected structural skin proteins in parenthesis.

joints, muscular dystrophy and osteoporosis.

Anemia is commonly seen in patients with JEB and recessive DEB. Cardiomyopathy secondary to micronutrient deficiencies, anemia and transfusion related iron overload has been uncommonly seen in recessive DEB. Skin cancers like squamous cell carcinoma, basal cell carcinoma and melanoma are also known to occur in patients with epidermolysis bullosa[11]. Squamous cell carcinoma is the leading cause of mortality in several subtypes of epidermolysis bullosa. It most commonly affects recessive form of epidermolysis bullosa and the cumulative risk increases with age[12].

Gastrointestinal manifestations

The gastrointestinal tract is commonly involved in different subtypes of epidermolysis bullosa. Repeated blistering of the esophageal mucosal surface most commonly leads to scarring and stenosis of the upper esophagus. The resulting strictures can vary in length and may involve multiple sites. Recessive type of DEB is the subtype most commonly associated with esophageal strictures, however other types including dominant DEB, JEB and EBS may also show similar findings[13]. Analysis of 3280 epidermolysis bullosa patients enrolled in National Epidermolysis Bullosa Registry showed the highest cumulative risk of esophageal strictures in the recessive subtype of DEB. Cumulative risk of about 95% and 35% were seen respectively in patients with recessive DEB and herlitz JEB[14].

Patients usually present with symptoms of dysphagia, odynophagia and malnutrition. Strictures, though commonly affect the upper esophagus, may involve mid and lower esophagus as well. Lower esophageal strictures can be precipitated by gastroesophageal reflux disease (GERD) besides blistering of the mucosa. The other common gastrointestinal problems affecting epidermolysis bullosa patients are constipation and fecal impactions, which result from painful perianal blistering or anal canal stenosis. Pyloric atresia that mostly involves JEB patients is another serious gastrointestinal problem that manifests early in life[11].

Treatment

Currently there is no effective therapy available for curing epidermolysis bullosa. However, over the last decade several potential future therapies including protein replacement and gene therapies have been explored. Model systems using these approaches show promise for significant advances in future. Gene therapy for non-Herlitz junctional epidermolysis bullosa has been performed and shown to be efficacious[15]. In the absence of a definite therapeutic modality to cure or modify epidermolysis bullosa disease course, management is largely symptomatic. Management of skin lesions focuses on avoiding further skin trauma and secondary bacterial infections[8].

Dietary modification with fiber supplementation is an effective initial approach to manage constipation. Osmotic laxatives can also be tried if dietary measures fail. GERD symptoms usually respond to histamine type 2 receptor antagonists or proton pump inhibitors.

Treatment of an esophageal stricture begins with modification of diet texture to soft, puree and liquids. Supplementation of multivitamins and minerals is an additional important measure. Despite these measures, patients may not be able to keep up with the required caloric intake resulting in malnutrition and growth retardation. Severe strictures eventually may require esophageal dilatation that can be done either with the use of a balloon catheter or a bougie. Both the methods have comparable efficacy, however balloon catheters are preferred due to their relative safety over bougies. Single or multiple sessions of esophageal dilatations may be needed. Usually an antegrade approach is used where a balloon catheter

is inserted from the mouth under endoscopic or fluoroscopic guidance. In cases with microstomia due to oropharyngeal scarring, a retrograde approach from the gastrostomy tube may also be tried. With each dilatation small but definite risk of esophageal perforation exists[16]. Rarely, colonic interposition or transposition has also been used. Management of most of these complications of epidermolysis bullosa requires a multi-modality approach with multi-disciplinary coordination.

COMMENTS

Case characteristics

A 15-year-old boy with blistering skin disease since birth, dysphagia since age nine presented with worsening dysphagia for 3 d.

Clinical diagnosis

He had extensive skin erosions and crust formation involving face, neck, trunk, and extremities and many of his finger and toenails were missing.

Differential diagnosis

Four main types of epidermolysis bullosa: epidermolysis bullosa simplex, junctional epidermolysis bullosa, dystrophic epidermolysis bullosa and kindler syndrome.

Laboratory diagnosis

Skin lesion biopsy showed dominant type dystrophic epidermolysis bullosa.

Imaging diagnosis

Esophagogram showed tight stenosis at the level of cervical esophagus and an upper gastrointestinal endoscopy showed a tight stenosis involving the upper esophagus.

Pathological diagnosis

Gene mutation affecting collagen VII leads to skin blisters involving uppermost part of dermis.

Treatment

Management of skin lesions is largely symptomatic but protein and gene replacement therapies are emerging. Worsening dysphagia may require esophageal stricture dilatation or gastrostomy tube placement.

Related reports

Recessive type of dystrophic epidermolysis bullosa (DEB) is the subtype most commonly associated with esophageal strictures, however other types including dominant DEB, junctional epidermolysis bullosa and epidermolysis bullosa simplex may also show similar findings.

Term explanation

Epidermolysis bullosa comprises a group of hereditary disorders characterized by recurrent mucocutaneous blisters that result from minor trauma.

Experiences and lessons

This case report highlights the association of skin blisters, missing nails and dysphagia in patients with epidermolysis bullosa.

Peer-review

This is a very nice case report.

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