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Endoscopic treatment of upper gastrointestinal postsurgical leaks

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Título: Tratamento endoscópico de deiscências pós-cirúrgicas do trato digestivo superior

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Abbreviations

AE	Adverse event
APC	Argon plasma coagulation
ASA	American Society of Anesthesiologists
BDS	Biodegradable stents
BMI	Body Mass Index
CT	Computed tomography
EID	Endoscopic internal drainage
ESGE	European Society of Gastrointestinal Endoscopy
EVT	Endoscopic vacuum therapy
FC	Fully covered
OR	Odds Ratio
OTSC	Over-the-scope clip
PC	Partially covered
PSL	Postsurgical leaks
RYGB	Roux-en-Y gastric bypass
SEMS	Self-expandable metal stents
SEPS	Self-expandable plastic stents
SG	Sleeve gastrectomy
TTS	Through-the-scope
UGI	Upper gastrointestinal

Outline of Thesis

In the **Abstract**, a brief description of the Thesis is presented.

In **Chapter I**, the Rational and Motivation of the subject chosen for this Thesis is explained.

In **Chapter II**, an Introduction addressing the major topics of this Thesis is presented, including postsurgical leaks characteristics and specificities, aims of therapy, endoscopic armamentarium and endoscopic outcomes.

In **Chapter III**, the aims of the studies conducted for the present Thesis are presented.

In **Chapter IV**, the publications that build the core for the present Thesis are presented.

In **Chapter V**, an integrated Discussion and Conclusion of all the articles is provided, focusing on the implications of the results in clinical practice.

In **Chapter VI**, potential lines of Future research are discussed.

List of Publications

This Thesis includes studies that were presented in several national and international meetings and articles published in peer-reviewed journals. The full-list of publications and presentations is presented below. The articles for evaluation are marked with (*).

Self-expanding metal stents in postoperative esophageal leaks (*)

Eduardo Rodrigues-Pinto, Pedro Pereira, Armando Ribeiro, Pedro Moutinho-Ribeiro, Susana Lopes, Guilherme Macedo

- Rev Esp Enferm Dig. 2016 Mar;108(3):133-7 (Impact factor 2016: 1.366)

Endoscopic treatment of anastomotic leaks - A tailored approach

Eduardo Rodrigues-Pinto, Rui Morais, Pedro Pereira, Guilherme Macedo

- Dig Liver Dis. 2018 Jul;50(7):728-730 (Impact factor 2018: 3.037)

Choosing the Appropriate Endoscopic Armamentarium for Treatment of Anastomotic Leaks (*)

Eduardo Rodrigues-Pinto, Rui Morais, Guilherme Macedo, Mouen A. Khashab

- Am J Gastroenterol. 2019 Mar;114(3):367-371 (Impact factor 2019: 10.241)

Role of endoscopic vacuum therapy, internal drainage, and stents for post-bariatric leaks

Eduardo Rodrigues-Pinto, Rui Morais, Filipe Vilas-Boas, Pedro Pereira, Guilherme Macedo

- VideoGIE. 2019 Jul 30;4(10):481-485

International multicenter expert survey on endoscopic treatment of upper gastrointestinal anastomotic leaks (*)

Eduardo Rodrigues-Pinto, Alessandro Repici, Gianfranco Donatelli, Guilherme Macedo, Jacques Devière, Jeanin E. van Hooft, Josemberg M. Campos, Manuel Galvão Neto, Marco Silva, Pierre Eisendrath, Vivek Kumbhari, Mouen A. Khashab

- Endosc Int Open. 2019 Dec;7(12):E1671-E1682
- Oral presentation at Digestive Disease Week 2019, San Diego, USA
- Poster presentation at UEG Week 2019, Barcelona
- Oral presentation at Semana Digestiva 2019, Albufeira, USA

Retrospective multicenter study on endoscopic treatment of upper GI post-surgical leaks (*)

Eduardo Rodrigues-Pinto, Pedro Pereira, Bernardo Sousa-Pinto, Hany Shehab, Rolando Pinho, Michael C. Larsen, Shayan Irani, Richard A. Kozarek, Antonio Capogreco, Alessando Repici, Ealaf Shemmeri, Brian E. Louie, Pawel Rogalski, Andrzej Baniukiewicz, Andrzej Dabrowski, João Correia de Sousa, Silvia Barrias, Yervant Ichkhanian, Vivek Kumbhari, Mouen A. Khashab, Nicole Bowers, Allison R. Schulman, Guilherme Macedo

- Gastrointest Endosc. 2021 Jun;93(6):1283-1299.e2 (Impact factor 2021: 9.427]
- Oral presentation at Digestive Disease Week 2020, Online
- Oral presentation at ESGE Days 2020, Online

Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2021 (*)

Manon C.W. Spaander, Ruben D. van der Bogt, Todd H. Baron, David Albers, Daniel Blero, Antonella de Ceglie, Massimo Conio, László Czakó, Simon Everett, Juan-Carlos Garcia-Pagán, Angels Ginès, Manol Jovani, Alessandro Repici, Eduardo Rodrigues-Pinto, Peter D. Siersema, Lorenzo Fuccio, Jeanin E. van Hooft

- Eduardo Rodrigues-Pinto was responsible for the section "Benign disease - Leaks, fistulas, and perforations"
- Endoscopy. 2021 Jul;53(7):751-762 (Impact factor 2021: 10.093)

Stent deployment within a transesophagostomy orifice to treat a postgastrectomy leak

Eduardo Rodrigues-Pinto, Joel Ferreira-Silva, Pedro Pereira, Guilherme Macedo

- VideoGIE. 2021 Jul 10;6(10):454-456

Abstract

Upper gastrointestinal (UGI) postsurgical leaks (PSL) are a life-threatening condition with high mortality rates ranging from 12 to 62%. Their prevalence has increased in recent years, being one of the most feared complications in surgery, as they are the strongest independent risk factor for postoperative mortality.

PSL are challenging to manage and often require radiological, endoscopic, or surgical intervention. Early diagnosis has been reported to improve survival of such leaks, although their management still remains controversial. In fact, several modalities have been used, with surgical treatment being associated with higher morbidity and mortality than endoscopic therapy. Therefore, the latter is often attempted first to avoid additional surgical morbidity.

However, there is a wide diversity of endoscopic options, including stent placement, endoscopic vacuum therapy (EVT), endoscopic internal drainage (EID), over-the-scope clips (OTSCs), suturing, septotomy with or without balloon dilation, and tissue sealants, with no definite consensus on the most appropriate therapeutic approach in the management of PSL. Each of these endoscopic options has different mechanisms of action.

Due to lack of an algorithmic endoscopic approach, the inability to cluster the presentations and varying degrees of collaborative planning among surgical and interventional services, these interventions are often applied in a stepwise manner or an institutional expertise–dependent manner primarily driven by the available technology.

This observation puts the focus on the need to identify patients as earlier as possible, selection of the best therapeutic option for each patient and development of an algorithm for management of PSL taking into consideration predictive factors for successful healing

and resolution. The aims of this Thesis were to define the role of endoscopic therapy in the treatment of UGI PSL, explore their current management, define endoscopic failure and evaluate the effectiveness of endoscopic therapy and associated adverse events (AEs) as well predictive factors for successful closure and AE occurrence.

It was found that endoscopic treatment is safe, effective, and reproducible when a skilled endoscopist is available. Around half of the patients can be treated successfully with 1 endoscopic approach, with approximately 80% of patients eventually having their leak treated with endoscopy without the need for surgery due to endoscopic failure. AEs may occur in almost 40% of the patients, however, only 6% of them may require surgery or lead to death. Clinical success correlates with the duration of treatment, being less likely after 4 months of therapy. Even though no definitive consensus on the definition of endoscopic failure exists, persistent inflammation with clinical sepsis, impossibility to resume oral feeding, inability to close the leak with time should prompt consideration of therapeutic alternatives, namely surgery.

Stents are the technique most widely available and most frequently used in almost every department. Even though OTSCs are also well-represented, they are not a common first option. On the other hand, EID and EVT seem to be increasingly used techniques.

Proper selection of patients is critical for favourable outcomes. Leak location, size, chronicity and associated cavity are probably the most relevant leak characteristics to be considered when deciding treatment. Previous surgery should also influence therapeutic decision. Patients with smaller leak initial diameters, in better clinical condition may respond better, so treatment in these patients should be more aggressive.

Acute and small leaks, without associated collections may be considered for stent placement (up to 3cm), OSTC placement (up to 1cm) or endoscopic suture (up to 2cm). In the setting of associated collections, these techniques can still be considered if

external drainage is also performed; if not, EVT, EID and endoscopic septotomy should be considered, with EVT and EID being an option in acute and chronic leaks, while endoscopic septotomy should only be performed in leaks with more than 4 weeks of duration. While endoscopic septotomy can be considered for all leak sizes, EVT is ideal for leaks larger than 2cm.

The approach to UGI PSL should always be tailored to the single patient, by taking into account the several variables that may at the end influence the outcome. Endoscopic management requires a personalized and multidisciplinary approach, comprising a close collaboration between interventional endoscopist, radiologist and surgeon.

Resumo

As deiscências pós-cirúrgicas (DPC) do trato digestivo superior (TDS) estão associadas a uma elevada taxa de mortalidade, que varia entre 12 e 62%. A sua prevalência tem aumentado nos últimos anos, sendo uma das complicações mais temidas das cirurgias, uma vez que são o fator de risco independente mais importante para mortalidade pós-operatória.

As DPC são difíceis de abordar e muitas vezes requerem intervenção radiológica, endoscópica ou cirúrgica. O diagnóstico precoce das deiscências associa-se a uma melhor sobrevida, embora o seu tratamento ainda seja controverso. De fato, existem várias opções terapêuticas, estando a cirurgia associada a maior morbilidade e mortalidade do que a terapêutica endoscópica. Sendo assim, esta é geralmente a primeira opção terapêutica, para evitar a morbi-mortalidade cirúrgica adicional.

Existe, no entanto, uma grande variedade de opções endoscópicas, desde colocação de próteses luminais, terapêutica endoscópica de vácuo (TEV), drenagem endoscópica interna (DEI), clips over-the-scope (OTSCs), sutura, septostomia com ou sem dilatação com balão, e selantes tecidulares, sem consenso definitivo quanto à abordagem terapêutica mais adequada das DPC. Cada uma destas opções endoscópicas tem o seu mecanismo de ação.

Devido à ausência de um algoritmo de abordagem endoscópica, à incapacidade de agrupar as diferentes situações clínicas e aos diferentes graus de colaboração entre os diferentes serviços, estes procedimentos são frequentemente aplicados de forma gradual, dependente de instituição, com base na experiência da equipa, principalmente impulsionado pela tecnologia disponível.

Estes achados colocam o foco na necessidade de identificar os doentes o mais

precocemente possível, na seleção da melhor opção terapêutica para cada doente e no desenvolvimento de um algoritmo de abordagem às DPC, tendo em consideração os fatores preditivos para sucesso clínico. Os objetivos desta Tese são definir o papel da terapêutica endoscópica no tratamento das DPC, explorar o seu tratamento atual, definir falência endoscópica e avaliar a eficácia da terapêutica e eventos adversos (EAs) associados, bem como fatores preditivos para o sucesso clínico e ocorrência de EAs.

Verificou-se que o tratamento endoscópico é seguro, eficaz e reprodutível quando realizado por um endoscopista experiente. Cerca de metade dos doentes podem ser tratados com sucesso com apenas 1 modalidade endoscópica, sendo que aproximadamente 80% dos doentes alcançam o encerramento da deiscência com o tratamento endoscópico, sem necessidade de cirurgia por falência. Os EAs podem ocorrer em quase 40% dos doentes, no entanto, apenas 6% deles podem requerer cirurgia ou ser fatais. O sucesso clínico correlaciona-se com a duração do tratamento, sendo menos provável após 4 meses de tratamento. Embora não exista um consenso definitivo sobre qual a definição de falência endoscópica, a inflamação persistente com sépsis associada, a impossibilidade de retomar alimentação oral, a incapacidade de encerrar a deiscência com o tempo, devem levar à consideração de alternativas terapêuticas, nomeadamente cirurgia.

As próteses luminais são a técnica endoscópica mais amplamente disponível e utilizada em quase todos os departamentos. Embora os OTSCs também estejam bem representados, não são uma primeira opção habitual. Por outro lado, a DEI e a TEV parecem ser técnicas cada vez mais utilizadas.

A seleção adequada dos doentes é fundamental para se conseguir alcançar resultados favoráveis. A localização da deiscência, o tamanho, a cronicidade, a presença de coleção associada são provavelmente as características mais relevantes a serem

consideradas na decisão terapêutica. O tipo de cirurgia prévia também deve influenciar a decisão terapêutica. Doentes com deiscências de menores dimensões, em condição clínica mais estável poderão responder melhor, sendo que o tratamento deverá ser mais agressivo nesses doentes.

Deiscências agudas e pequenas, sem coleção associada, podem ser consideradas para colocação de prótese luminal (até 3cm), OSTC (até 1cm) ou sutura endoscópica (até 2cm). Se presença de coleção associada, essas técnicas ainda podem ser consideradas se for realizada drenagem externa adicional; caso contrário, deverão ser consideradas a TEV, a DEI ou a septostomia endoscópica, sendo a TEV e a DEI opções em deiscências agudas e crónicas, enquanto a septostomia endoscópica só deve ser considerada em deiscências com mais de 4 semanas de duração. Embora a septostomia endoscópica possa ser considerada para qualquer tamanho de deiscência, a TEV é ideal para deiscências com mais de 2 cm.

A abordagem das DPC do TDS deve ser sempre individualizada, tendo em conta todas as variáveis que podem influenciar o resultado final. O tratamento endoscópico requer uma abordagem personalizada e multidisciplinar, envolvendo uma estreita colaboração entre o endoscopista de intervenção, o radiologista e o cirurgião.

Chapter I - Rational

Upper gastrointestinal (UGI) postsurgical leaks (PSL) are a life-threatening condition with high mortality rates ranging from 12% to 62% (1-5). Their prevalence has increased in recent years, being one of the most feared complications in surgery (5-7), as they are the strongest independent risk factor for postoperative mortality (8).

Even though perforations, leaks and fistulas are terms that are often used interchangeably, in strict terms, they are completely different. Most of the literature so far has evaluated the efficacy of endoscopic therapy encompassing all types of transmural defects. Gastrointestinal leaks are abnormal communications between the intraluminal and extraluminal compartments as a result of a defect in the integrity of the gastrointestinal wall. A fistula is an abnormal connection between the gut and hollow organs, or between the gut and an abscess cavity. They can develop as a result of a prolonged anastomotic leak, especially when the leak results in extraluminal fluid that is managed percutaneously. A perforation is an acute rupture of the gastrointestinal wall, which can occur after endoscopic instrumentation or due to underlying pathology (9).

PSL are challenging to manage and often require radiological, endoscopic, or surgical intervention (10). Historically, they were generally managed either by rescue surgery when the defect was present within the first 7-10 days or a watch-and-wait strategy followed by secondary surgery if symptoms persisted. Nowadays, endoscopy is considered the first line approach for the management of UGI PSL, as it seems to be associated with an improved outcome and better quality of life (11).

Recent publications have demonstrated the safety and efficacy of endoscopic interventions to manage transmural defects as first-line therapy instead of conventional modalities to either avert surgery or optimize patients for definitive future surgery (by

diverting noxious enteric contents, creating enteral access for nutrition, and relieving any obstruction precluding healing) (12). However, there is no definite consensus on the most appropriate therapeutic approach in the management of PSL. Early diagnosis has been reported to improve survival of such leaks. Due to the historically watch-and-wait strategy in clinically stable patients, while waiting for spontaneous closure, these leaks are still referred late for endoscopic treatment, decreasing the chance of successful treatment. Identifying preoperative predictors of outcome can provide important information for early leak diagnosis. Even when leaks are diagnosed early, endoscopic management remains complex, often requiring multiple endoscopic treatments spanning over several months. Due to lack of an algorithmic endoscopic approach, the inability to cluster the presentations and varying degrees of collaborative planning among surgical and interventional services, these interventions are often applied in a stepwise manner or an institutional expertise–dependent manner primarily driven by devices looking for applications.

This observation puts the focus on the need to identify patients as soon as possible, selection of the best therapeutic option for each patient and development of an algorithm for management of PSL taking into consideration predictive factors for successful healing and resolution. Endoscopic failure also needs to be defined, in order to avoid therapeutic futility.

Taking all these considerations in account, in 2016, we decided to conduct an investigational project with the main aim of defining the role of endoscopic therapy in the treatment of UGI PSL. We also intended to explore their current management, define endoscopic failure and evaluate the effectiveness of endoscopic therapy and associated adverse events (AEs) as well predictive factors for successful closure and AE occurrence.

The research questions raised are important for gastroenterology and surgical practice. Our results can contribute to the improvement of knowledge on the best

therapeutic options and their application to different clinical conditions, on the real-life effectiveness of endoscopic therapy on PSL (excluding all other transmural defects), on the identification of predictors of successful endoscopic therapy and AE occurrence, as well as when to stop endoscopic therapy.

Chapter II - Introduction

In this chapter, a review of the literature is presented in five sections, addressing the major topics of this thesis: PSL (A); aims of therapy (B); leak specificities (C), endoscopic armamentarium (D) and endoscopic outcomes (E).

A) Post-surgical leaks

UGI PSL, although rare, are devastating complications as they prolong hospital stay and result in significant mortality. Occurrence of PSL negatively impacts other aspects of postoperative outcomes. They increase the median length of hospital stay, the delay before oral feeding, the risk of anastomotic stricture, and the risk of re-operation up to 60%. (6). Some authors have described a negative association between the occurrence of leaks and recurrence and long-term survival for esophago-gastric cancers (13), negatively impacting quality of life (14).

The frequency of UGI PSL is higher in cervical anastomosis than in intrathoracic anastomosis (13.6% vs 3%) (6, 15). This relates to the need for a longer gastric conduit, more likely positioned in the fundus (where the vascularity is more compromised), and increased risk of tension and/or compression at the junction between thorax and neck (6, 16). It is estimated at 8-26% after esophagectomy (17), 3-12% after total gastrectomy (5), 0.7-5% after Roux-en-Y gastric bypass (RYGB), and 1-2% after sleeve gastrectomy (SG) (18, 19). Leaks may occur immediately post-surgery or more commonly several weeks later. Sleeve leaks are classified as acute (within 7 days), early (within 1–6 weeks), late (6–12 weeks), and chronic (after 12 weeks) (20). Acute leaks are commonly attributed to technical issues, such as anastomotic tension, stapler malfunction, and suture or staple-line seepage. More delayed leaks usually reflect healing insufficiencies, usually due to

ischemia at the staple-line or anastomosis (21-23).

Several risk factors for leaks have been identified, such as age, male gender, emergency surgery, smoking, alcohol abuse, American Society of Anesthesiologists (ASA) score, obesity (BMI > 30 kg/m^2) or underweight patients (BMI < 18.5 kg/m^2), malnutrition (albumin < 3 g/dL), prolonged operative time, anemia, intraoperative blood loss, diabetes, hypertension, renal failure, cardiovascular disease, steroids use or atherosclerotic calcification of the aorta and the arteries supplying the gastric tube (16, 24-29). Identifying preoperative predictors of outcome can provide important information for early leak diagnosis.

The clinical presentation can vary, ranging from asymptomatic leaks, diagnosed on imaging for other reasons, to sepsis-related multiorgan failure. Many factors affect clinical presentation, such as the location of the anastomosis, the size of the defect, the ability to drain the fluid collection, and leakage containment. Common initial clinical signs include fever and intra-thoracic or intra-abdominal abscesses (16). In the early post-operative period, leaks commonly present with chest/abdominal pain, dyspnea, tachycardia, low urine output, elevated C-reactive protein, and leukocytosis. One must have a high degree of suspicion to make an early diagnosis. Tachycardia is the most sensitive indicator of an acute leak; however, chronic leaks have a more inert presentation. Inspection of surgical drains (if present) helps in the early identification of a surgical leak. The presence of digestive fluids, saliva-type fluid, and air discharge into drains are highly suggestive of the presence of a leak. Oral administration of staining solutions such as methylene blue may provide further evidence to the clinical suspicion of anastomotic leak (30).

Fluoroscopy with water-soluble contrast medium and computed tomography (CT) scan with oral contrast are the best imaging modalities for the diagnosis, however they are prone to false-negative test results. The sensitivity of X-ray with oral contrast

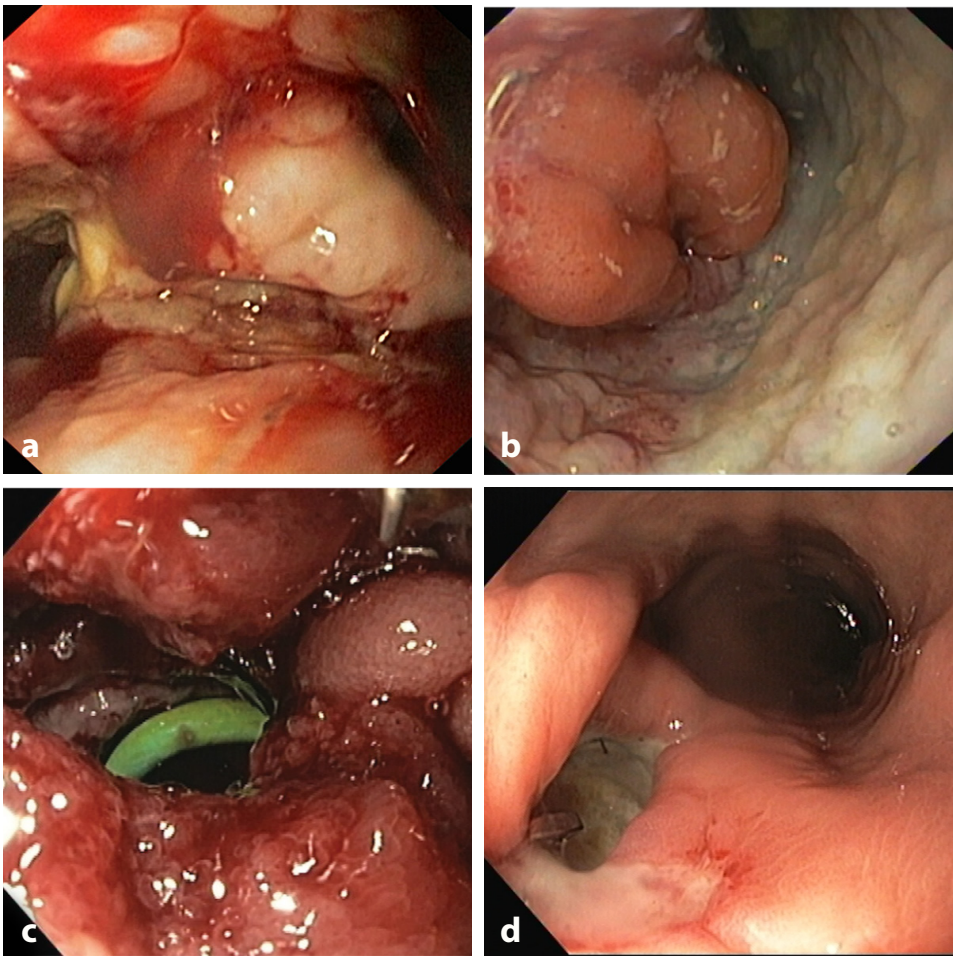

Figure 1. Endoscopic images of post-esophagectomy leak (a), post-gastrectomy leak (b), post-gastric bypass leak (c) and post-sleeve leak (d). *Author own images*

ranges between 33 and 52% (31), with particularly poor results in cervical anastomoses (32). Leakage diagnosis by CT scan is supported by visualization of free or contained extraluminal gas, fluid, and/or contrast material in the mediastinum/abdomen, or by visualization of a transmural defect (33). In addition, CT scan allows inspection of regions beyond the esophago-gastric lumen. Detection of extraluminal manifestations as a

result of leakage may provide important information for initial therapeutic management. Endoscopic examination is crucial to help identifying the leak in cases of uncertainty (34) and to obtain additional information on local damage such as extent of disruption and determine surrounding tissue viability (35). Endoscopy [Figure 1] is a reliable diagnostic modality, since specificity and sensitivity can reach almost 95% (34), although the diagnostic value seems to be lower in cervical anastomosis (sensitivity 56%) (36). The combination of CT scan and endoscopy is emerging as the gold standard to diagnose PSL, as both the mucosal integrity and the perianastomotic conditions can be examined (16). Besides leak diagnosis, it is also important to diagnose downstream strictures that may be perpetuating the leak. On endoscopy, asymmetric staple lines may be seen, as well as twist/rotation of the gastric tube at the incisura angularis and a subtle tortuosity of movement of the scope. The objective determination of a SG leak into low or high-grade is based on fluoroscopic characteristics after injection of contrast immediately below the gastroesophageal junction, with the patient in the supine position. If the antrum fills before the leak, it is a low-grade stenosis. If the leak fills before the antrum with pooling of contrast in the proximal stomach and distal esophagus it is plausibly a high-grade stenosis.

PSL management should be based on several factors, with patient stability and time from surgery being probably the most important (10). The watch-and-wait approach often used by surgeons includes nothing by mouth, broad-spectrum antibiotic therapy (according to infectious parameters), anticholinergic medication (to reduce saliva), proton-pump inhibitors and prokinetics (to decrease leak volume), parenteral nutrition, and imaging directed drainage or diversion of gastrointestinal contents (37). Spontaneous closure rates of medically stable patients with conservative and radiological interventions are highly variable, with reported rates of 16% to 46% (18, 20). The caveat is which

patients will need endoscopic or surgical management selection. Complex and bigger leaks are unlikely to heal spontaneously. Factors that predispose to delay or absence of spontaneous leak closure include older age (>65 years), malnutrition, duodenal leaks, high-output drainage (>500 ml/day), associated malignancy, previous radiation therapy, immunosuppression, sepsis, diabetes, renal failure, and chemotherapy (38-40).

If non-invasive measures fail, patients require surgical or endoscopic intervention, but this is often driven by local expertise, and based on availability of devices and accessories. In patients who undergo rescue or redo surgery, mortality increases to 15-30%, with recurrence occurring in 13% to 33% of the patients with an added mortality of 9% to 30% (41), as well as a 10-fold increase in cost of care of these patients (with an overall health care burden of approximately $10 billion each year). Therefore, endoscopic therapy is often attempted first to avoid additional surgical morbidity.

B) Aims of Therapy

The aims of PSL therapy are to re-establish digestive tract continuity, prevent or treat infections, prevent further contamination, drain collections, and provide nutritional support (14). Determining optimal therapy requires careful examination of patient clinical status, anastomotic defect characteristics (site, length, time, presence of necrosis), and a review of all available options, local expertise, and previous experience.

Surgical treatment

The choice of surgical options for PSL depends mostly on the leakage site and the presence of necrosis. It is usually limited to patients severely septic, with an uncontained leak (allowing irrigation and drainage of intra-abdominal collections), or with defects not amenable to endoscopic closure or who failed endoscopic treatment (6, 14, 42). Outcomes of salvage surgical procedures maybe exaggerated due to selection bias, as patients are generally sicker or have failed multiple previous therapies. Despite the high morbidity and mortality of salvage surgical therapy (43), one must be cognizant of the fact that there are instances where surgical therapy is necessary and should not be ignored if deemed appropriate, for fear of complications or a poor outcome.

For leaks associated with cervical anastomoses, the most common surgery involves wound opening, curettage of infected, necrotic and granulation tissue, and packing. However, external esophagostomy can be an option in the case of advanced local infection. To treat intrathoracic leaks, the surgical options are primarily anastomotic repair, reinforcement of the anastomosis with viable tissue, and esophageal diversion (44).

For intrabdominal leaks, surgical options include peritoneal washout, primary closure and feeding jejunostomy (or gastrostomy if gastric remnant), omentoplasty, fistulojejunostomy, Roux-en-Y gastric bypass (in sleeve patients), or total gastrectomy

with Roux-en-Y esophagojejunostomy (45-47).

Endoscopic treatment

The acceptance of endoscopy as the preferable modality for managing PSL, as well as the awareness of the need for early endoscopic management (11) is reflected by the increase in the number of patients that undergo their first endoscopy for leak management within 30 days of surgery over time (44% vs 75% before and after 2013) (48). Besides, a rise in esophageal stent placement to manage esophageal transmural defects has been observed, from 7% in 2007 to 30% in 2014 (49).

Multiple endoscopic sessions are often unavoidable and one must be capable of adapting the strategy based on the patient's anatomy, physiology, and response to therapy. As demonstrated in clinical model studies, the operating intraluminal pressure due to the endoscopy does not pose risks of anastomosis disruption (35). This way, endoscopy can be performed safely in the early postoperative period under carbon dioxide insufflation, general anesthesia, with fluoroscopic assistance.

Treatment is difficult and complicated by the lack of defined criteria, such as size of the leak, or existence of a wound cavity, for the choice of the best endoscopic treatment strategy. Unfortunately, to date there has been more of an eminence-based rather than an evidence-based therapeutic approach justified by the proclamation of the importance of individualized treatment strategies. The available endoscopic approaches range from primary and secondary closure techniques with the use of endoluminal suturing devices, over-the-scope clips (OTSCs), fibrin glue, and diversion with self-expandable metal stents (SEMS), to endoscopic internal drainage (EID) with the use of nasocystic drains or double-pigtail stents, endoscopic vacuum therapy (EVT), and septotomy with or without pneumatic dilation.

Because not all leaks are created equal and available technical skills vary, we are left with devising a logical management algorithm based on comparative effectiveness and retrospective data but grounded in sound physiologic principles of wound healing and cost effectiveness. The approach to a PSL should focus on clinical presentation and chronicity of the leak, correcting the underlying physiologic defect that predisposed and perpetuated the leak, minimizing the risk of chronic fistula formation, preserving the patient's ability to have enteral nutrition, and minimizing the use of costly, less effective endoscopic accessories and endoscopies.

C) Leaks specificities

Anatomic and physiologic factors, apart from technical errors, are responsible for the development of leaks. Intrinsic esophageal anatomy with the lack of an esophageal serosa and the negative pressure within the thoracic cavity, may contribute to the development of esophagectomy leaks (16). Sufficient blood supply (50, 51) and adequate tension on the anastomosis site (50, 52) are essential for proper healing. Evidence about the effect of the extent and dosage of neoadjuvant chemoradiation or anastomotic techniques with the lowest leakage rates remains controversial (16, 53).

While foreign body material (staples, sutures, percutaneous drains) hamper proper healing, downstream obstruction distal to the surgical anastomosis such as anastomotic strictures (54), narrowing at the incisura angularis or twisted/kinked stomach (54, 55) result in a higher pressure proximally. The consequence is a leak at the area of least resistance. The majority of post-SG leaks (>90%) and RYGB leaks occur at the angle of His where the staple-line meets the gastroesophageal junction (56, 57), an area of intense intragastric pressure, thin gastric wall, susceptibility to ischemia owing to the single blood supply to the gastric pouch, as well as relative dysmotility. However, SG leaks may occur anywhere along the length of the sleeve at the staple line, while RYGB leaks may occur also at the gastrojejunal anastomosis, blind loop, jejunojejunal anastomosis or remnant stomach.

Independently from the surgical approach, technical precautions are commonly considered important aspects to decrease leak risk, as avoidance of excessive traction, compression or twist, incorrect number of sutures, as well as an adequate intraoperative fluid management.

D) Endoscopic armamentarium

Endoscopic techniques for leak closure include close-cover-divert approaches (stents, clip closure, endoscopic suture, tissue sealants) [Figure 2] and active or passive internal drainage approaches (EVT, EID and endoscopic septotomy) [Figure 3]. In recent years, leak management has started to fall in the close-cover-divert approach versus the active or passive internal drainage approach.

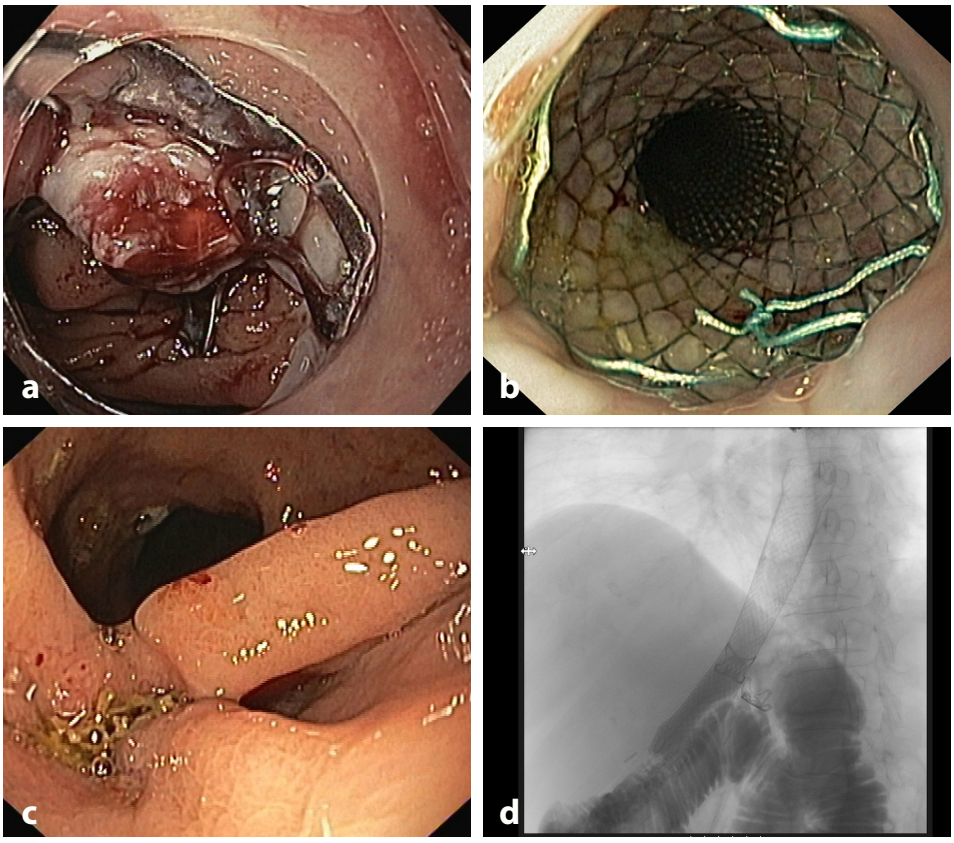

Figure 2. Endoscopic images after OTSC placement (a), stent placement (b) and tissue selant and vicryl mesh placement (c). Fluoroscopic image showing combined therapy with OTSC and stent placement (d). *Author own images*

Stents

Endoscopic stents are cylindrical devices used to preserve or re-establish luminal patency (58). For gastrointestinal defects, the role of a stent is to seal the leak and divert gastrointestinal contents away from the site of leakage. Stents enable restoration of gut continuity, potentially allowing conversion from total parenteral nutrition to oral or enteral feeding (59). This is an off-label use of these devices. The appropriate selection of a particular stent requires an understanding of stent technology, such as stent's type (SEMS, self-expandable plastic stents [SEPS], biodegradable stents [BDS]), dimensions and degree of foreshortening, as well as location and features of the targeted defect.

Recent esophageal SEMS are usually made of nitinol, an alloy of nickel and titanium, allowing flexibility for placement at sharp angles but with less radial force than elgiloy SEMS (60, 61). Esophageal SEMS can be partially (PC) or fully covered (FC). The silicon coating completely covering the FC-SEMS is intended to easily remove the stent but this advantage is overshadowed by the higher trend toward migration (up to 30%). PC-SEMS may be preferable to FC-SEMS as tissue hyperplasia forms at the terminal ends of the stent, creating a watertight seal around the stent as well as decreasing the risk of migration. The major apprehension with the use of PC-SEMS is encountering difficulty during removal (62). However, techniques such as argon plasma coagulation (APC) to fulgurate the hyperplastic tissue (63), grasping the distal end of the stent and inverting it (64) or the stent-in-stent technique where a second FC-SEMS is placed within the initial PC-SEMS to decrease tissue ingrowth and cause pressure necrosis of existing hyperplastic tissue (65, 66) can be utilized to achieve successful stent removal. Stent dell time is highly variable and may range from 2 to 12 weeks (67), even though median stenting time to achieve healing is usually 4 to 8 weeks (68).

Specifically long designed SEMS with large stent diameters, that extend from the

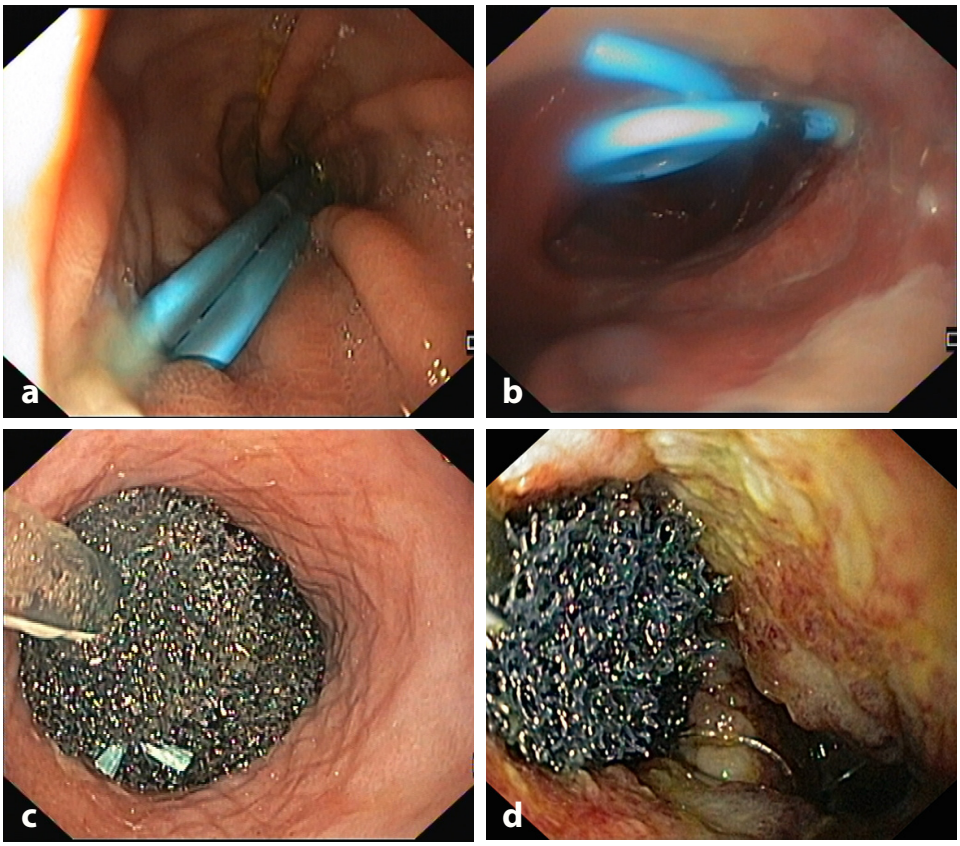

Figure 3. Endoscopic images after endoscopic internal drainage (a & b) and after endoscopic vacuum therapy (c & d). *Author own images*

distal esophagus to the duodenal bulb, may theoretically reduce intragastric pressure by bypassing the pylorus, long narrow gastric conduit and functional stenosis if present, and have a role in the treatment of SG leaks (69).

SEPS consist of a polyester body covered with silicone to prevent tissue ingrowth and polyester braids on the surface to prevent stent migration. Radiopaque markers are positioned at the middle and ends of the stent to allow for visualization of this nonmetallic device during fluoroscopy. SEPS are effective in sealing bowel wall defects, however, they have a propensity for migration (70). In addition, SEPS require mounting on a delivery

system before deployment, making the process complicated compared with SEMS, which are ready for use (60). For these reasons, SEPS use has largely been replaced by SEMS use.

BDS are absorbable stents that degrade in 6 to 24 weeks. Degradation is accelerated by acid exposure. Therefore, acid-suppressive therapy may be warranted in certain situations (71). The radial force of BDS is weaker than that of SEMS (72), being maintained for 6 weeks following deployment before it is degraded. BDS negate the inconvenience of stent removal, however, the severity of tissue hyperplasia cannot be accurately predicted (73) and may result in dysphagia and stenosis that necessitates dilation in approximately 50% of cases (62).

Over-the-scope clips

OTSCs, unlike through-the-scope clips, have a powerful compression force that can result in approximation of even indurated tissue (74). The memory-shape nitinol OTSC is analogous to a "bear claw" in configuration and is loaded onto a transparent cap that is mounted at the tip of the endoscope. The OTSC, therefore, requires either preloading or withdrawal of the endoscope for mounting of the clip, similar to a variceal band ligator. OTSCs are designed to fit on endoscopes of various sizes (OTSC caps of 11, 12, and 14 mm internal diameters) and are also available in 3 types of teeth configuration, which include the blunt or atraumatic type (A type), the traumatic type with short pointed teeth (T type) and the traumatic type with long pointed teeth (GC type), as well as 3 or 6 mm cap depth. The set-up and deployment of the OTSC is similar to a variceal band ligator, as the cap mounted at the tip of the endoscope pulls in the target tissue or defect because of vacuum suction. Tissue or defect entrapment into the cap can be facilitated by a tri-prong anchor retraction device if the tissue is indurated and scarred or by a "twin grasper" forceps whose action enables approximation of the opposite edges of a pliable gaping

defect for efficient pulling of the entire defect into the cap before clip deployment.

Placement of the OTSC may be challenging due to limited access, restricted mobility, and suboptimal alignment with the target lesion. Deployment of an OTSC in a less than optimal manner makes subsequent repair very difficult. A misdeployed clip may be removed with high power APC (with the potential for transmural burn injury and delayed perforation while cutting the clip metal), or with a dedicated device (remOVE system, Ovesco, Tuebingen, Germany) based on a fast and efficient direct current (75). Application of ice-cold normal saline on the clip for one minute, to lower the mechanical resistance of the nitinol frame prior to its extraction by a standard grasping forceps, has also been reported (76).

Closure of large defects that requires more than one OTSC may not be effective as the concave configuration of these clips results in a gap even between two closely placed clips. Another caveat during OTSC placement is inadvertent entrapment of accessories, such as the tri-prong anchor or twin grasper, following clip deployment when these accessories have not been fully retracted into the OTSC cap. OTSC placement requires care, as surrounding healthy and pliable tissue can easily be suctioned inadvertently into the cap and, if passed unrecognized, resulting in complete luminal closure following clip deployment.

In general, OTSCs should be used in situations where the tissue margins are still malleable and the entire target defect can be suctioned or retracted into the cap. They are usually reserved for completion closure of large anastomotic leaks that have been reduced by other measures until the defect size is small enough to be amenable for OTSC closure.

Endoscopic suturing

Presently, most experience is limited to the OverStitch device (Apollo Endosurgery, Austin, Texas), which requires a Olympus double channel therapeutic gastroscope and familiarity with the multistep process associated with activation of the device. Endoscopic suturing with the OverStitch system is restricted to readily accessible areas of the gut owing to instrument configuration and need for a double channel endoscope. In 2018, Apollo released the Overstitch Sx, which can be mounted on more than 20 different types of single-channel gastroscopes manufactured by 4 different endoscope manufacturers. The suturing system enables placement of polypropylene or polydioxanone sutures in an interrupted or continuous fashion without the need to remove the endoscope for suture reloading. Accessories, such as the helix device, can be used to anchor and retract tissue into the suturing arm to facilitate suture placement.

Recently, the X-Tack Endoscopic HeliX Tacking System, which is a through-the-scope suture-based device designed for closure of large, wide, and irregularly shaped defects, was approved by the U.S. Food and Drug Administration for soft tissue approximation (77). The X-Tack device is composed of four, 5mm, surgical steel helix tacks tethered on a single 3-0 polypropylene suture which runs through an eyelet near the mid-point on each tack. Each helix tack is deployed sequentially through a ≥2.8mm working channel of any commercially available gastroscope or colonoscope, without need for instrument withdrawal from the patient. The tacks are screwed into healthy target tissue adjacent to the defect or stent, followed by approximation of the margins by successive gathering of the tacks with applied suture tension and placement of a final cinch to secure the construct (77, 78).

Tissue sealants

Tissue compatible glues are either derivative of proteins involved in coagulation or glue such as cyanoacrylate. Fibrin glue, which consists of human fibrinogen and human thrombin combined with antifibrinolytic agents, is the most commonly used sealant. It is a tissue-compatible adhesive that works in a double manner. It mechanically occludes the wall defect and plays a predominant role in wound healing, inducing cellular response to tissue damage, forming matrix-building strands, which promote neovascularization and fibroblast proliferation (79). Although fibrin glue contains antifibrinolytic agents, accelerated degradation particularly in the setting of gastrointestinal contents or infection remains a concern and, therefore, fibrin glue is considered a poor scaffolding material. Owing to these concerns, recent studies have evaluated infill materials, such as absorbable Vicryl mesh, Surgisis (Biodesign, Cook Medical Inc, Bloomington MA) an acellular matrix extracted from the porcine small intestine submucosa that stimulates proliferation and formation of fibroblasts in the region of wounds and incorporates into the scar without initiating a foreign body inflammatory reaction (80), and BIO-A (W.L. Gore Corporation, Newark, DE) created from synthetic polymers that are approved as anal fistula plugs

Cyanoacrylate, a synthetic glue working as a mechanical sealant, has high adhesive and high antibacterial properties, and thus is suitable for application in infectious sites. It is eliminated by hydrolysis after a significant time period (1–6 months) (81), however, the poor mechanical properties of the film, brittle nature, possible proinflammatory effect as well as the risk of damage of the endoscope because of its rapid polymerization make cyanoacrylate a second-choice method (82).

Endoscopic vacuum therapy

The concept of EVT is that the negative pressure assists wound healing by draining inflammatory exudates and secretions, decreasing bacterial contamination and edema, and by promoting neovascularization and granulation tissue with subsequent epithelialization (16, 83). In EVT, a polyurethane foam sponge tailored into a shape that fits into the wound's dimensions and geometry, as estimated by the endoscopist, is attached at the tip of a polyvinyl chloride suction tube using sutures applied at the proximal and distal ends of the sponge (84-86). It is critical to ensure that the sponge size is smaller than the wound cavity to allow collapse and subsequent closure of the latter. For successful drainage, the side ports of the tube must be in contact with the sponge. At every endoscopic session, the wound size is reassessed and a sponge with appropriate dimensions is fashioned for introduction into the wound cavity.

In all, 2 techniques that are commonly employed in EVT include the back-pack method and the overtube method. The back-pack method involves placement of the sponge drainage system parallel to the endoscope by dragging it to the target site using endoscopic forceps. In the overtube method, the sponge is simply pushed down through the tube (84-88). Endoscopic forceps are typically used to facilitate entry of the sponge into hollow spaces and wound cavities that are anatomically difficult to access. A continuous vacuum pressure of 100-125 mm Hg is applied through the transnasally placed tube. The tube is connected to a vacuum pump externally to maintain continuous pressure (87, 88).

In case the wound cavity has a narrow opening, it is endoscopically dilated to facilitate insertion of the sponge drainage system. However, if the extra-luminal cavity itself is small, the sponge may be placed intra-luminally adjacent to the cavity. For a substantially large cavity, up to 2 sponges can be placed. On subsequent sessions, if the

wound cavity size has significantly reduced in size with no active drainage, the sponge may be placed intra-luminally and subsequently removed once the cavity has completely collapsed. After initial placement of the sponge drainage system, the sponge is changed regularly every 3–4 days for intracavitary sponges (to prevent granulation tissue ingrowth that makes the removal of the sponge difficult) and up to 1-week interval for intraluminal sponges (89), until satisfactory cavity closure is achieved. The endpoint should be to reduce the wound cavity size to a radius < 1cm and depth < 2cm, with formation of a pseudo-diverticulum or a rather small opening that can later be closed using, for example, an OTSC. With the concomitant use of antibiotics and adequate nutritional support through tube feeding, defect closure using the EVT technique can generally be achieved within 15-30 days (90).

There are, however, limitations associated with the use of EVT. First, a transnasal tube must remain in situ for at least 3-4 weeks. Second, multiple endoscopic sessions are required for periodic replacement of the sponge system, increasing the cost of the procedure. Third, an anatomically difficult to access cavity by virtue of its narrow opening necessitates endoscopic dilatation (with potential for AEs), whereas a small cavity warrants placement of the sponge intra-luminally instead of within the cavity itself, which may be less efficient at absorbing secretions and collapsing the cavity (90).

Endoscopic internal drainage

The rationale of EID with deployment of one or more pigtail plastic stents (or nasocystic catheters in cases of large collections requiring lavage to eliminate pus and debris (11)) across the leak orifice is to internally drain fluid collections, so the fluid content can pass from the perigastric collection into the digestive lumen, with progressive reduction in the collection size until it eventually becomes a virtual cavity (91). Meanwhile,

a foreign body reaction in the edges of the leak is triggered by the pigtail stents, promoting re-epithelialization over the stent and leak closure, resulting in an all-in-one procedure without the need of further treatment. A residual small cavity like a pseudodiverticulum is common at the end of the process without any clinical repercussion (92). In some cases, the leak orifice is not clearly identified or the communicating tract between the digestive lumen and the fluid collection is complex, then, internal drainage may be accomplished by endoscopic ultrasound guided drainage, such as for pseudocysts or other postsurgical collections (11, 92-94). In addition to stenting, debridement (endoscopic necrosectomy) may also be needed in cases of infected collections containing necrotic tissue (94-96).

The appropriate time interval for stent exchange or oral diet resumption remains to be defined. While stent exchange may be performed on a regular basis (ex.: every 2 to 6 weeks, until healing of the leak is achieved), to avoid stent obstruction, allow necrosectomy and stimulate tissue granulation (92), others remove the stents 4 months after complete clinical resolution (11), even though in most patients successfully treated, no other endoscopic procedures are required as stents often migrate spontaneously. Oral diet is usually started in the first 24 to 48 hours after confirming biological and clinical improvement with EID (11), or following confirmation of collection reduction in CT scan (92).

Endoscopic septotomy

This procedure derives from the endoscopic treatment for Zencker diverticulum. The principle behind this technique relates to higher intraluminal pressures within the sleeve compared with the perigastric cavity, promoting flow of contents through the leak. To equalize these pressures, the 'septum' between the perigastric cavity and the gastric lumen is cut using APC or a needle knife. This procedure allows internal drainage of the

leak and deviates oral intake. The cut should not exceed the bottom of the perigastric cavity and the eventual downstream stenosis in the gastric lumen (perpetuating the leak) should be treated as well, in order to reduce the intragastric pressure. Multiple endoscopic procedures may be required with more pseudo-septum being incised each time to achieve successful healing (54).

E) Endoscopic outcomes

Stents

Stents are the endoscopic treatment for oncologic and bariatric leaks where most evidence is available. Clinical success ranges from 48 to 100% (65, 97-110). Van Halsema et al.. (111) reported a clinical success of 81.4% (201/247) for PSL. Based on three systematic reviews on the use of PC-SEMS, FC-SEMS, and SEPS in oncologic leaks and perforations (112-114), clinical success was 81 to 87% with no difference among stent types. Repeated endoscopic intervention was needed in 17 to 25% of patients and 7 to 13% required surgical intervention. Treatment failure in oncologic leaks may be higher when longer delays until stent placement (1), persistent leakage after initial stent placement (115), leaks of the proximal esophagus, stents traversing the gastroesophageal junction, leak defects larger than 6cm and leaks associated with distal conduit leaks (116). A pooled analysis of 20 retrospective studies showed a median indwell time of 5 to 7 weeks for FC-SEMS and 7 to 10 weeks for PC-SEMS (111).

Even though SEMS are burdened by an AE rate of 20 to 72% (117), most of them are conservatively managed and not severe. However, severe bleeding and perforation may occur (65, 108, 112-114). Nausea, vomiting and abdominal discomfort are common and usually transient, but severe stent intolerance has been reported, leading to early stent removal. The main drawback is the high rate of migration.

Regarding bariatric leaks, one meta-analysis published in 2011, reported a leak closure of 88%, with stent migration occurring in 17% of cases (118). However, the largest studies have been published after this meta-analysis, with rates of leak closure and AEs ranging from 65 to 100% and 14 to 86%, respectively, with migration being the most frequent complication with rates of 5%-67% (65, 97-108). Multiple endoscopic sessions

using multiple stents as well as other adjunctive therapies may be necessary in order to achieve leak closure (101, 103, 110, 119-121). A recent meta-analysis (122) reported a leak closure of 89%, with stent migration occurring in 23% of the cases, explaining the higher success rate due to more frequent use of stents designed to treat post-bariatric leaks. Nonetheless, recent reports using bariatric stents show similar success rates without statistically significant differences in migration rate when compared with conventional stents (108, 123). Post-bariatric leaks larger than 1cm (124) and longer delays between leak development and stenting also impact endoscopic outcomes (65, 103, 109).

Over-the-scope clips

The effectiveness and safety of OTSCs have been reported in some studies, usually combining all types of transmural defects. Haito-Chavez et al. (125) reported the efficacy of OTSCs for anastomotic leaks in a total of 30 cases, with a success rate of 73%. Clinical success is higher when application of OTSC within one week of diagnosis, minimal inflammation or low level of fibrosis (126, 127). Increasing failure rates for leaks with more than 13mm have been reported (127). Baron et al. (128) and Honegger et al. (129) reported a success rate below 33% for post-esophagectomy leaks, maybe due to the anatomical features of the esophagus (narrow lumen).

A recent systematic review (130), which accounted for 1517 cases, reported OTSC results in 97 anastomotic leaks, with an overall success rate of 66%. Another systematic review considering only anastomotic leaks reported a clinical success of 73% (131). Long-term success might be higher when OTSCs are applied as primary therapy (69.1% vs 46.9%) (125).

OTSCs use in post-bariatric leaks was recently evaluated in a systematic review (122), with a successful closure of 67.1%. Several endoscopic sessions may be needed ranging

from 2 to 7 in one study (132).

Endoscopic suture

The largest study evaluating endoscopic suture included 122 patients, of which 20 had anastomotic leaks, with a clinical success of 27% in leak closure (133). A case series of full-thickness endoscopic suturing of post SG leaks suggested that suturing alone may be sufficient in treating small acute leaks, however, larger leaks may require adjunctive SEMS placement (134).

Tissue sealants

The success rate of tissue sealants is highly variable in the literature, ranging from 55.7 to 96.8% (81, 135-137). The efficacy of glue sealants as the primary treatment of PSL has been questioned (138), as they are frequently used as an adjunct to other treatments, namely stents and clips (81, 82). It might be more suitable for small leaks (<15 mm) or residual small collections after the use of other techniques (82). Complete leak closure might require multiple sealant applications, or the use of vicryl plugs to improve effectiveness (137).

Endoscopic vacuum therapy

The clinical success rate of EVT varies widely, ranging from 66.7 to 100%. Loske et al. (139) and Laukoetter et al. (140) reported leaks closure rates of 95.2% and 92.3% in 21 and 39 patients, with median treatment durations of 11 (range 4–46) and 20 days (range 3 - 104), respectively. Bludau et al. (141) reported a healing rate of 77.9% in 59 patients. In several of these studies additional therapies like OTSCs or stents were performed after EVT therapy.

Recent systematic reviews on oncologic leaks (142) report 79.5% and 90% of clinical

success for esophagectomy and gastrectomy leaks, respectively, with a stenosis rate after treatment of 15.9% and 9.2%, respectively (142). Neoadjuvant treatment, rescue application and intraluminal location have all been associated with a higher risk for EVT failure (143).

In general, EVT is a safe procedure with AEs ranging from 4.1 to 12.0%, the majority being minor events related to minor bleeding upon sponge exchange, sponge dislodgement and discomfort or distress from repeated procedures (144). However, major events like bleeding from sponge erosion into small or major cardiovascular structures, rupture of the descending aorta or bronchoesophageal fistula formation may occur (87, 140, 145). Stricture formation after EVT therapy, due to vigorous formation of granulation tissue, may occur, requiring endoscopic dilation (146).

Endoscopic internal drainage

In the largest series reporting on EID in post-bariatric leaks (92), double pigtails were delivered as a first line approach in 67 patients, with leak closure achieved in 78% of the patients, after a mean of 58 days (range 10-206) and an average of 3.14 sessions (2-16). Among them, 42 had a surgical drain placed close to the leak. Bouchard et al. (11) reported EID outcomes on 33 patients with fluid collections after SG or RYGB (in 19 patients after previous unsuccessful endoscopic treatment), with clinical success in 78.8%, after a mean of 115 days (range 23-773). Gonzalez et al. (91) reported outcomes in 44 patients with SG leaks, either as first-line treatment (n=22) or after prior therapy (n=22). Efficacy was comparable between groups (86% vs 82%, respectively), with a median number of endoscopies of 3±6 vs 4.5 ± 2.4. Excluding follow-up time, healing time at endoscopy was 46 days.

AEs such as discomfort, ulceration, dysphagia, and splenic hematoma are rare (11).

When combined with surgical cleansing in patients presenting with severe sepsis,

EID allows early removal of surgical drainage preventing chronic fistula tract formation (147). Longer delays between diagnosis and treatment, larger leaks, sepsis, presence of gastrobronchial fistula and previous OTSC deployment were all risk factors for treatment failure (48).

Endoscopic septotomy

Endoscopic septotomy may be used as first-line or salvage therapy with clinical success ranging from 70 to 85% (147-149). Baretta et al. (54) reported their experience with endoscopic septotomy in 27 patients with post-bariatric leaks. After 1 to 6 endoscopic sessions, all patients achieved leak resolution, with a mean time to closure of 18 days. More than half of the patients performed additional dilation of stenosis at the angularis incisura. Complications include perforation and bleeding (150).

Chapter III - Aims

The main aim of this thesis was to define the role of endoscopic therapy in the treatment of UGI PSL.

As specific aims, it was intended to:

1.Emphasize the different available endoscopic techniques for the treatment of UGI PSL

2.Explore the current management of UGI PSL

3.Define when to consider endoscopic failure

4.Evaluate the effectiveness of endoscopic therapy and associated AEs

5.Identify factors associated with successful endoscopic therapy and AE occurrence

Chapter IV - Results (Publications)

A) Choosing the Appropriate Endoscopic Armamentarium for Treatment of Anastomotic Leaks

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Choosing the Appropriate Endoscopic Armamentarium for Treatment of Anastomotic Leaks

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INTRODUCTION

Gastrointestinal leaks usually occur following surgery, and are defined as a communication between the intra- and extra-luminal compartments as a result of a defect in the integrity of the gastrointestinal wall [1, 2]. They can be classified as acute (<7 days), early (1–6 weeks), late (6–12 weeks), and chronic (>12 weeks). The aims of therapy are to reestablish digestive tract continuity, prevent/treat infections, prevent further contamination, drain collections, and provide nutritional support [3]. Endoscopic closure can be achieved using a variety of modalities; however, additional percutaneous/surgical drainage of collections is often required, as well as wide-spectrum antibiotics and antifungal therapy, strict fasting, enteral nutrition, pain control, gastric acid suppression, and hemodynamic monitoring and support [4]. The approach chosen is largely institutional and is based on availability of devices and accessories. Consensus regarding the optimal timing of intervention is still lacking; however, shorter periods between diagnosis and beginning of treatment are probably associated with a higher likelihood of successful closure.

CLIPS

In general, through-the-scope (TTS) clips are not large or robust enough to allow closure of leaks [5]. Over-the-scope clips (OTSC) (Ovesco OTSC [Ovesco Endoscopy AG, Tübingen, Germany]) and Padlock Clip™ [Aponos Medical, Kingston, NH, USA] have been developed to overcome TTS clip limitations. The deployment system is similar to that of a variceal band ligator with different features/sizes of applicator caps and clips. A grasping or anchoring device can also be used for better approximation of tissue margins and for retracting more tissue into the cap (Fig. 1). Success might be improved by epithelial ablation/damage prior to OTSC application in order to stimulate tissue regeneration. OTSC are approved for closure of luminal defects up to 20 mm in size. Success rates up to 60–73% have been reported [6]; however, an "en face view" and pliable tissue for successful deployment are needed, as well as defects are relatively small (from10 to 20 mm). However, larger defects can occasionally be closed with placement of multiple OTSCs. It is important to note that recurrent leak may occur after initial success due to OTSC displacement (Fig. 2).

STENTS

Different types of stents are available, including partially covered self-expandable metal stents (PCSEMS), fully covered SEMS (FCSEMS), and biodegradable stents (BDS) [7]. Data regarding the use of BDS are limited, and comparative studies with SEMS are still lacking; however, the radial force of BDS is weaker than that of SEMS. Besides, BDS require mounting on a delivery system before deployment, making the process complicated compared with SEMS, which are preassembled and ready for use. Specifically long-designed metal stents (to allow extension from the esophagus to the antrum) with large stent diameters (in order to achieve optimal adherence to the esophagus), large cell mesh (making the stent softer in order to increase the flexibility and reduce trauma to the mucosa), and antimigration features (outer double layers coated with silicone) may also have a role in the treatment of post-laparoscopic sleeve gastrectomy leaks [8].

Large-diameter SEMS are often desirable in order to provide optimal sealing of leak and divert luminal contents. However, large-diameter SEMS often cause intense chest pain, which usually abates after 48 h, but may persist beyond the early post-procedural period, necessitating stent removal. Sometimes, the leak cannot be effectively covered by the stent; in these cases, stent placement can be combined with closure with clips or sealing of the leak with plugs [9]. The duration of stenting should be individualized (4 to 12 weeks); studies report lower adverse events with shorter dwell times. Clinical success rates (around 80%) are similar between stents; however, migration rates (up to 30%) are higher with self-expandable plastic stents vs SEMS and FCSEMS vs PCSEMS [2]. Although the migration rate may be lower, PCSEMS may be difficult to remove after the leak has resolved; longer dwell times often require additional measures to debride tissue ingrowth at the stent flanges, including argon plasma coagulation or "stent-in-stent"

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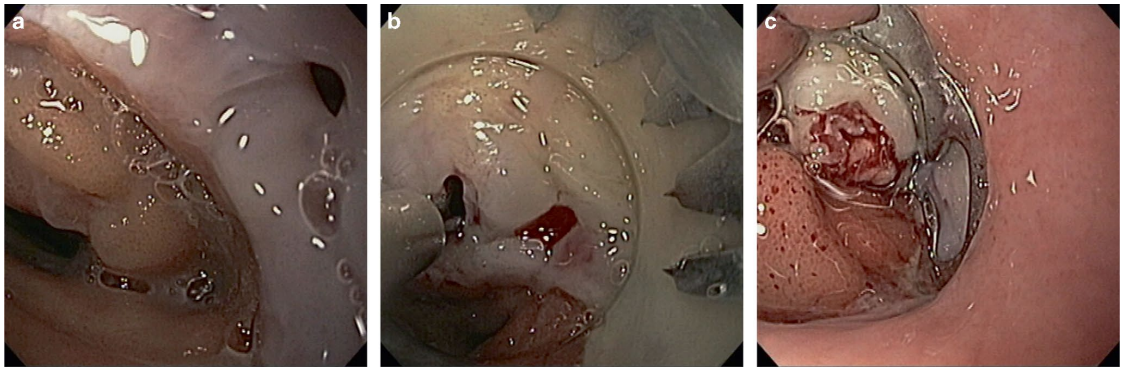

Fig. 1 Upper endoscopy. **a** Leak orifice with 3 mm diameter after total gastrectomy; **b** placement of a 12-mm over-the-scope clip (OTSC) after retracting the tissue margins with an anchoring device and suction of the defect into the applicator cap; **c** OTSC correctly placed

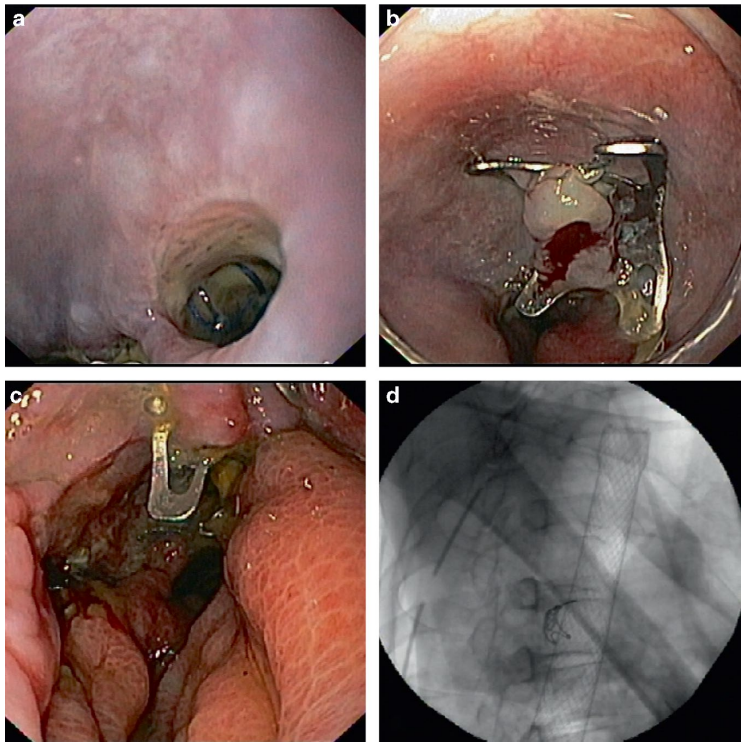

Fig. 2 Upper endoscopy. **a** Anastomotic leak with a diameter of 12 mm after Ivor-Lewis esophagectomy; **b** OTSC correctly placed; **c** leak recurrence 1 week later due to OTSC displacement; **d** fluoroscopic image with self-expandable metal stent (SEMS) covering the leak and the OTSC

technique to free the embedded portions of the stent [10]. Suturing FCSEMS may render a migration rate similar to that of PCSEMS, without the difficulties in removal of PCSEMS [11].

FCSEMS are usually the first option (Fig. 3). Due to the high migration rate, prophylactic suturing [11] or OTSC [12] (to anchor the stent to the esophageal wall) should be performed additionally. PCSEMS should be reserved for patients who have experienced migration despite anchoring maneuvers and in patients with refractory leaks due to incomplete sealing between the stent and esophageal wall, as PCSEMS maximize proximal sealing with tissue ingrowth and overgrowth. Location of the defect at the proximal cervical esophagus, stent traversing the gastroesophageal junction, longer leaks, an anastomotic leak associated with a more distal conduit leak, persistent leakage after initial stent placement, and decreased physical performance preoperatively all predict unsuccessful closure [1].

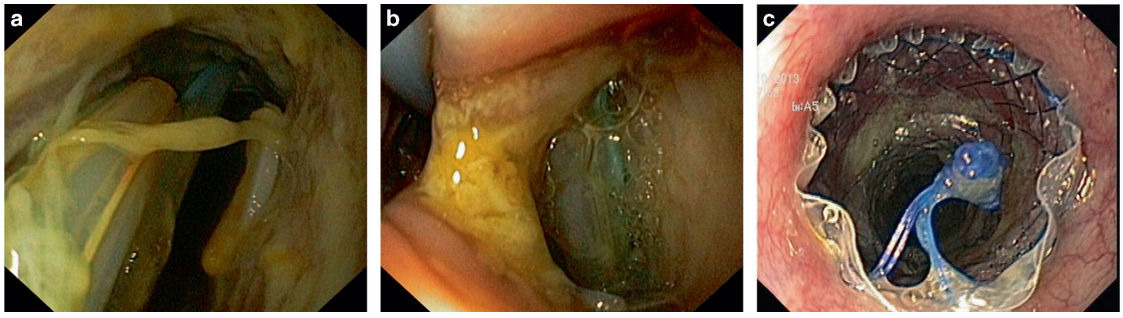

Fig. 3 Upper endoscopy. **a** Anastomotic leak occupying more than 50% of the luminal circumference after total gastrectomy; **b** SEMS system delivery alongside anastomotic leak; **c** immediately after placement of a fully covered SEMSs

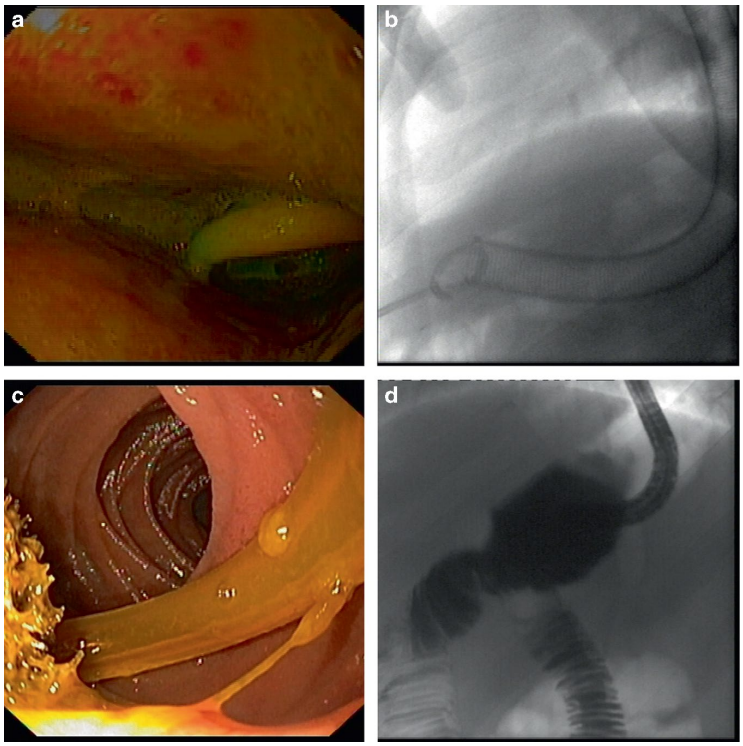

Fig. 4 Upper endoscopy. **a** Anastomotic leak with a diameter of 4 cm after gastric bypass 45 cm from the incisors; **b** use of the longer Esosponge overtube to assist on sponge intracavitary placement; **c** polyurethane sponge inverted upside down in the intraluminal gastric pouch and jejunal efferent limb to optimize apposition between the leak and the sponge; **d** fluoroscopic image with no contrast extravastion at the level of the anastomosis

ENDOSCOPIC VACUUM THERAPY (EVT)

EVT is a promising new approach for management of anastomotic leaks, even with previous failure with stents. By endoscopic insertion of a polyurethane sponge into the defect cavity and transnasal application of external vacuum (100–125 mmHg), defect closure and effective drainage are united. Despite the need for multiple procedures, EVT may result in complete leakage closure [13]. The use of an overtube is recommended to ensure easy passage of the sponge up to the location of interest. Lower-located leaks may be harder to reach. Two encrusted overtubes, one longer overtube (Fig. 4), or an additional suture loop placed at the tip of the sponge (backpack technique) may be used to facilitate placement. Depending on the size of the defect, the sponge may be placed intracavitary or in the lumen of the esophagus, covering the leak. Intraluminal EVT might be easier and safer to place than intracavitary EVT; nevertheless, leak closure might be

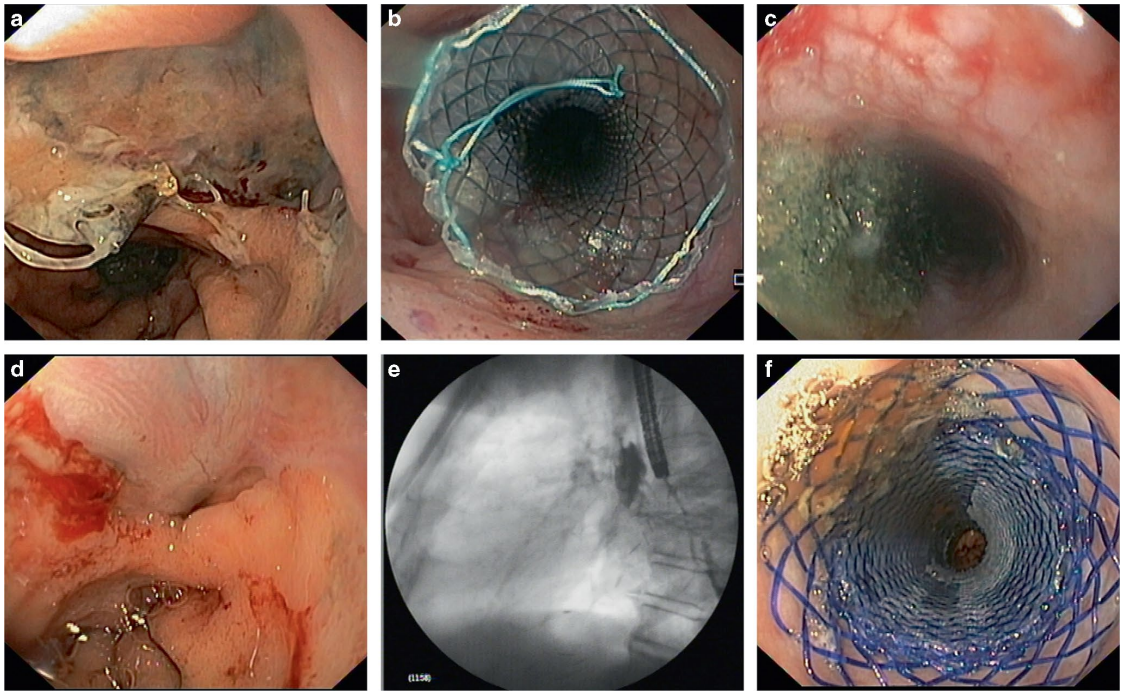

Fig. 5 Upper endoscopy. **a** Anastomotic leak with associated fistula with a diameter of 4 mm after Ivor-Lewis esophagectomy; **b** combined endoscopic vacuum therapy (EVT) with a fully covered SEMS (stent-over-sponge [SOS]) after unsuccessful closure with EVT alone; **c** esophageal lumen after SEMS removal showing sponge displacement to the opposite wall of the leak; **d**, **e** endoscopic and fluoroscopic image showing persistence of the anastomotic leak and associated fistula despite previous SEMS treatment (fully and partially covered), EVT, SOS, combined vycril mesh and fibrin glue placement; **f** immediately after placement of a biodegradable stent

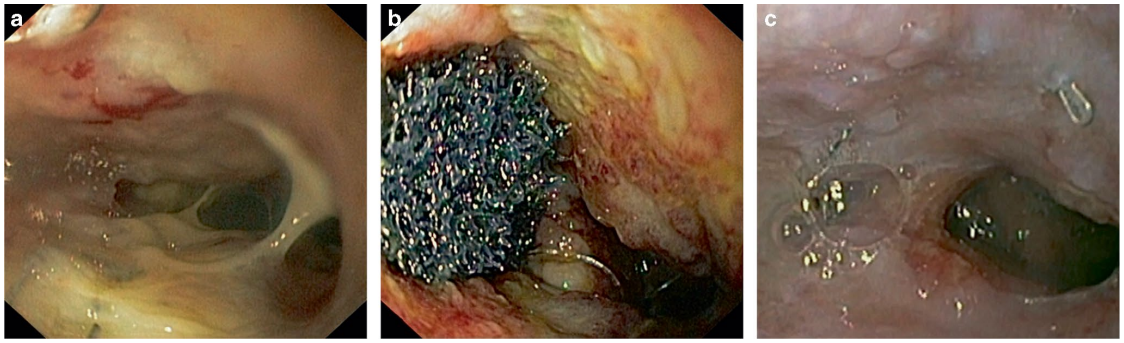

Fig. 6 Upper endoscopy. **a** Anastomotic leakage; **b** placement of the sponge partially in the mediastinal cavity and partially in the esophageal lumen; **c** complete closure of the anastomotic defect

more difficult to achieve with intraluminal EVT alone. Apposition of the sponge to the leak may be suboptimal with intraluminal placement, especially in dilated esophagus. Combined EVT treatment with a SEMS (stent-over-sponge) may be useful by directing the vacuum force toward the cavity by sealing the sponge from the gastrointestinal lumen [14]. However, efforts must be taken that the sponge stays apposed to the leak, since the SEMS may displace it (Fig. 5). In large leakage cavities or in cavities apart from each other, up to two sponges can be placed separately to allow rapid and sufficient drainage. With diminishing defect size, sponge placement could be changed from its initial intracavitary position to an intraluminal position. The sponge should be changed every 3 to 5 days, until complete healing of the esophageal defect is achieved (Fig. 6). Successful closure of 80–100% has

been reported for EVT, with demonstrated superiority to stents in some studies [2].

OTHER ENDOSCOPIC TECHNIQUES

Endoscopic internal drainage (EID)

Similarly to endoscopic drainage of peripancreatic collections (often requiring multiple endoscopic sessions), EID, by temporary placement of trans-gastrointestinal plastic stent(s), has also a place in management of anastomotic leaks; however, it must be integrated into a tailored therapeutic approach based on the anatomical location of the leak, clinical presentation, presence or absence of external drainage, and the timing of treatment after the original insult [15]. EID can be used in acute and chronic leaks with associated collections; better results may be achieved with intra-abdominal leaks and when several pigtail stents can be delivered side-by-side to occlude the leak defect. EVT may be a better approach in mediastinal collections, as they are more difficult to manage.

Endoscopic suturing

Closure of gastrointestinal leaks with sutures has been successfully demonstrated [1], although endoscopic suturing (OverStitch device, Apollo Endosurgery, Austin, TX, USA) is technically more challenging than clip placement and requires additional training and expertise. Endoscopic suturing allows closure of larger defects and permits full-thickness and robust closure.

CONCLUSION

Gastrointestinal leaks are a significant cause of morbidity and mortality. Endoscopic therapies currently available include clipping, stenting, full-thickness suturing, EID, and EVT. Closing the leak with tissue apposition techniques (OTSC/suturing) or diversion therapy (SEMS) may not be the ideal treatment strategy, especially in late or chronic leaks. EVT will probably have a major role in anastomotic leaks. After closure of the leak by stent placement or clips, the drainage of these cavities can be insufficient, accounting for many cases of clinical failure. EVT allows optimal drainage of the cavity, leading to debridement of the cavity with ensuing granulation, utilizing the concept of keeping the fistula open. Even though comparative trials are needed to allow creation of treatment algorithms, multimodality therapy is often required. More important than which technique is better, they should be considered complementary. In several cases, more than one endoscopic approach is used concomitantly, while in other cases therapies are applied sequentially depending on the initial clinical response.

CONFLICT OF INTEREST

Guarantor of the article: Eduardo Rodrigues-Pinto, MD.
Specific author contributions: Eduardo Rodrigues-Pinto: conception of article, drafting of article, critical review and final manuscript approval; Rui Morais: drafting of article; Guilherme Macedo: critical review and final manuscript approval; Mouen Khashab: drafting of article, critical review and final manuscript approval.
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Potential competing interests: Mouen Khashab is on the medical advisory board for Boston Scientific and Olympus, and he is a consultant for Boston Scientific, Olympus, and Medtronic. The remaining authors declare that they have no conflict of interest.

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B) Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2021

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Eduardo Rodrigues-Pinto was responsible for the section "Benign disease - Leaks, fistulas, and perforations"

Guideline

Thieme

Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2021

Authors

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MAIN RECOMMENDATIONS

Malignant disease

1 ESGE recommends placement of partially or fully covered self-expandable metal stents (SEMSs) for palliation of malignant dysphagia over laser therapy, photodynamic therapy, and esophageal bypass.
Strong recommendation, high quality evidence.

2 ESGE recommends brachytherapy as a valid alternative, alone or in addition to stenting, in esophageal cancer patients with malignant dysphagia and expected longer life expectancy.
Strong recommendation, high quality evidence.

3 ESGE recommends esophageal SEMS placement for sealing malignant tracheoesophageal or bronchoesophageal fistulas.
Strong recommendation, low quality evidence.

4 ESGE does not recommend SEMS placement as a bridge to surgery or before preoperative chemoradiotherapy because it is associated with a high incidence of adverse events. Other options such as feeding tube placement are preferable.
Strong recommendation, low quality evidence.

Benign disease

5 ESGE recommends against the use of SEMSs as first-line therapy for the management of benign esophageal strictures because of the potential for adverse events, the availability of alternative therapies, and their cost.
Strong recommendation, low quality evidence.

6 ESGE suggests consideration of temporary placement of self-expandable stents for refractory benign esophageal strictures.
Weak recommendation, moderate quality evidence.

7 ESGE suggests that fully covered SEMSs be preferred over partially covered SEMSs for the treatment of refractory benign esophageal strictures because of their very low risk of embedment and ease of removability.
Weak recommendation, low quality evidence.

8 ESGE recommends the stent-in-stent technique to remove partially covered SEMSs that are embedded in the esophageal wall.
Strong recommendation, low quality evidence.

9 ESGE recommends that temporary stent placement can be considered for the treatment of leaks, fistulas, and perforations. No specific type of stent can be recommended, and the duration of stenting should be individualized.
Strong recommendation, low quality of evidence.

10 ESGE recommends considering placement of a fully covered large-diameter SEMS for the treatment of esophageal variceal bleeding refractory to medical, endoscopic, and/or radiological therapy, or as initial therapy for patients with massive bleeding.
Strong recommendation, moderate quality evidence.

SOURCE AND SCOPE

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It provides guidance on the use of esophageal stents for both malignant and benign conditions. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was adopted to define the strength of recommendations and the quality of evidence.

1 Introduction

Esophageal cancer is the seventh most common cancer type worldwide, with a global incidence of 604 100 new cases in 2020 [1–3]. The main symptoms of esophageal cancer include dysphagia, with concomitant weight loss and odynophagia [4]. Because patients with esophageal cancer are usually asymptomatic in the early stages, more than half of patients are diagnosed at an advanced stage of the disease and are not eligible for treatment with curative intent [5].

One of the main goals of palliative treatment is to relieve dysphagia and improve nutritional intake. A variety of therapeutic options are available, including external beam radiation therapy (EBRT), brachytherapy, and esophageal stent placement. Esophageal stent placement is preferable in patients with an expected short-term survival because of its rapid relief of dysphagia symptoms [6]. Different stent designs are available, varying in stent material (plastic, metal), covering, diameter, and antimigration features. Partially covered self-expandable metal stents (PCSEMSs) and fully covered self-expandable metal stents (FCSEMSs) are most often used in current practice.

In addition to their use for the palliation of dysphagia, esophageal stents can be used for the treatment of benign esophageal diseases. Stents are usually removed after several weeks as this timeframe allows for the resolution of disease and safe stent removal. FCSEMSs have been mostly used for the treatment of benign disorders. In recent years, biodegradable stents (BDSs) have gained increasing attention for obviating the need for stent removal.

This is an update of the clinical guideline on the use of esophageal stents for benign and malignant disease issued in

ABBREVIATIONS

BDS	biodegradable stent
CI	confidence interval
CRP	C-reactive protein
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
ESGE	European Society of Gastrointestinal Endoscopy
ESPEN	European Society of Parenteral and Enteral Nutrition
FCSEMS	fully covered self-expandable metal stent
GRADE	Grading of Recommendations Assessment, Development and Evaluation
LAMS	lumen-apposing metal stent
OD	odds ratio
PCSEMS	partially covered self-expandable metal stent
RBES	refractory benign esophageal stricture
RCT	randomized controlled trial
SEMS	self-expandable metal stent
SEPS	self-expandable plastic stent
TIPS	transjugular intrahepatic portosystemic shunting

2016 by the European Society of Gastrointestinal Endoscopy (ESGE) [7]. In this guideline update, the current evidence will be discussed and recommendations on the use of esophageal stents will be provided.

2 Methods

The ESGE Guidelines Committee (chair, J.v.H.) commissioned this guideline update and appointed a Guideline leader (M.S.). Key questions (**Table 1s**, see online-only Supplementary Material) were prepared by a coordinating team (M.S., R.v.d.B., L.F., T.B., J.v.H.) and were approved by all guideline participants. Each guideline participant was assigned to a research question in one of two areas: malignant disease (taskforce leader, L.F.) and benign disease (taskforce leader, T.B.).

A literature search of MEDLINE and the Cochrane library was conducted in August 2020 using the PICO structure (where P stands for population/patient, I for intervention/indicator, C for comparator/control, and O for outcome). The quality of collected studies was graded according to the Grading Recommendations Assessment, Development and Evaluation (GRADE) system and retrieved study outcomes were translated into evidence tables. Evidence tables and proposed guideline recommendations were collected by the Guideline leader and circulated 2 weeks before the digital face-to-face meeting held on 22 October 2020. During the digital face-to-face meeting, outcomes of the PICOs were discussed and consensus was reached on guideline recommendations.

In November 2020, a draft was prepared by M.S. and R.v.d.B. and sent to the guideline team. The revised draft was reviewed by two independent experts. After adjustment and final approval by the guideline team, the manuscript was submitted for publication by *Endoscopy*.

This Guideline was issued in 2021 and will again be considered for updating in 2025.

3 Malignant disorders

3.1 Efficacy

RECOMMENDATION

ESGE recommends placement of partially or fully covered self-expandable metal stents (SEMSs) for palliation of malignant dysphagia over laser therapy, photodynamic therapy, and esophageal bypass.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends brachytherapy as a valid alternative, alone or in addition to stenting, in esophageal cancer patients with malignant dysphagia and expected longer life expectancy.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends patient characteristics be taken into account when selecting patients for esophageal stent placement as a palliative method.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends against the placement of nonexpandable and expandable plastic stents for the palliation of malignant esophageal strictures.

Strong recommendation, high quality evidence.

Several randomized controlled trials (RCTs) have compared the outcomes of esophageal stent placement with other treatment strategies for the palliation of malignant dysphagia due to esophageal cancer (**Table 2s**). Laser therapy, photodynamic therapy, and esophageal bypass surgery have shown comparable outcomes to esophageal stent placement [8–13].

Based on two RCTs comparing the outcomes of self-expandable metal stent (SEMS) placement versus brachytherapy, brachytherapy may be considered over SEMS placement in patients with expected long-term survival [14, 15]. Even though SEMS placement leads to a more rapid relief of dysphagia, brachytherapy is preferable in these patients for its durable relief of symptoms [15, 16]. Furthermore, the use of brachytherapy is associated with a lower risk of serious adverse events and favorable quality of life outcomes [14, 15]. Despite these benefits, the availability of brachytherapy in daily practice is restricted by the need for local expertise and dedicated logistics

[17]. A short course of EBRT may be a valid alternative to brachytherapy [18]. In patients with a good performance status, chemoradiotherapy can be considered to prolong dysphagia-free survival, but is associated with an increased toxicity compared with radiotherapy alone [19].

Esophageal stent placement is indicated in patients with an expected short-term survival (i.e. less than 3 months) for its rapid relief of symptoms, usually within 1–2 days after stent placement [6]. Several prognostic tools may aid the selection of esophageal stent candidates, but these lack external validation [20–22]. The presence of metastases and poor performance status have repeatedly been shown to be associated with poor survival [21–24]. When esophageal stent placement is considered, SEMSs are recommended over self-expandable plastic stents (SEPSs) owing to a lower rate of symptom recurrence and serious adverse events [6]. To date, there have been no differences shown in the outcomes of FCSEMS and PCSEMS placement, or the placement of SEMSs with or without an anti-reflux mechanism [25–28].

3.2 Safety

In the previous ESGE guideline, a meta-analysis of the available evidence was performed for the occurrence of stent-related adverse events [7]. The major adverse event rate was reported to be 21 % for FCSEMSs and 18 % for PCSEMSs. The most frequent early adverse events were reflux (9.3 %), severe pain (8.7 %), and bleeding (7.6 %). The most frequent late adverse events were reflux (15 %), severe pain (15 %), and ingrowth/overgrowth (14 %).

In recent years, an increase in stent-related adverse events has been reported, which has been attributed to the increased use of chemotherapy and/or radiotherapy before SEMS placement [29]. Other patient characteristics that appear to be associated with an increased risk of adverse events include female sex and dilation before SEMS placement [28, 29].

3.3 Fistula

RECOMMENDATION

ESGE recommends esophageal SEMS placement for sealing malignant tracheoesophageal or bronchoesophageal fistulas.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends the application of double stenting (esophagus and airway) when fistula occlusion is not achieved by esophageal or airway prosthesis placement alone.

Strong recommendation, low quality evidence.

The incidence of esophageal fistulas has increased markedly as a result of advances in palliative therapies for esophageal cancer [30, 31]. Esophageal fistulas usually occur in the context of advanced esophageal cancer, but may also result from other malignancies or prior (palliative) therapy [30–34]. The symptoms of an esophageal fistula include cough, fever, and pneumonia [35]. Because the development of an esophageal fistula is considered to be an indicator of poor survival (weeks to months), treatment strategies should aim to rapidly relieve symptoms and improve the patient's remaining quality of life.

The clinical success rate of SEMS placement for malignant fistulas ranges between 56 % and 100 % [35–44]. Factors associated with treatment failure include proximal fistula location, fistula orifice size >1 cm, and Eastern Cooperative Oncology Group (ECOG) performance status of 3–4 [42, 43]. After the fistula has been successfully sealed, reopening occurs in 0–39 % of patients [39–42]. In most cases, reopening can be managed endoscopically by repositioning the SEMS or by placement of an additional SEMS [41, 42]. Airway stenting may be considered in addition to esophageal SEMS placement to improve the success rate and prevent airway obstruction [44–47].

The outcomes of SEMS placement have been compared with other treatment strategies in two retrospective studies [37, 38]. Chen et al. reported on the outcomes of SEMS placement (n = 30) versus feeding gastrostomy/jejunostomy (n = 35) and found SEMS placement to be associated with an improved overall survival [37]. In a study by Hu et al., the outcomes of SEMS placement (n = 17) were compared with gastrostomy (n = 9) and best supportive care (n = 9) [38]. The median survival was comparable among the treatment arms. Patients who underwent SEMS placement had favorable quality of life outcomes on several subscales, including eating and respiratory problems.

3.4 Bridge to surgery

RECOMMENDATION

ESGE does not recommend SEMS placement as a bridge to surgery or before preoperative chemoradiotherapy because it is associated with a high incidence of adverse events. Other options such as feeding tube placement are preferable.

Strong recommendation, low quality evidence.

Neoadjuvant therapy followed by surgery is the current clinical standard for treatment with curative intent for esophageal cancer [48, 49]. Malnutrition and cachexia – common in esophageal cancer patients – are known risk factors for treatment-related adverse events and poor survival [50–52]. From this perspective, the European Society of Parenteral and Enteral Nutrition (ESPEN) recommends regular assessment of a patient's nutritional status [53]. Initial screening can be performed by assessment of nutritional intake, weight change, and body mass index. Nutritional support is strongly recommended for patients at severe nutritional risk, defined as more than 10 %–15 % weight loss in the previous 6 months [54, 55].

Esophageal stents have been used to improve nutritional status before neoadjuvant therapy and surgery. In a meta-analysis of nine studies (5 SEPS, 3 SEMS, 1 SEPS + SEMS), the outcomes of 180 patients undergoing stent placement prior to or during neoadjuvant therapy were pooled [56]. Stent placement was technically successful in 95 % of patients, with a statistically significant improvement in dysphagia symptoms, but without improvement in weight or serum albumin levels. Stent migration and chest discomfort occurred in 32 % and 51 % of patients, respectively. The relatively high rate of stent migration in this setting has been attributed to neoadjuvant therapy-induced tumor shrinkage, as most of these patients do not require repeated intervention [56, 57]. To overcome the substantial risk of adverse events, van den Berg et al. investigated the outcomes of BDS placement in 10 patients scheduled to undergo neoadjuvant chemoradiotherapy [58]. A statistically significant decrease in dysphagia symptoms occurred without any major adverse events. Nevertheless, 7 of 10 patients required additional nutritional support and median weight loss before surgery was 5.4 kg.

In the past, SEMS placement before surgery has been reported to be associated with a worse oncologic outcome with a lower rate of R0 resections, a higher rate of major adverse events, and decreased overall survival [59, 60]. Contrarily, recent studies have reported no difference in R0 resection rate, overall survival, and postoperative complications [61–63].

Alternatives to esophageal stent placement include oral nutritional supplements, nasogastric tube placement, percutaneous feeding tube placement, and parenteral nutrition. In general, the use of percutaneous feeding tube placement (i. e. percutaneous endoscopic gastrostomy or endoscopic jejunostomy) is recommended when enteral feeding is expected to be continued for at least 4 weeks [64–66]. In surgical candidates, percutaneous endoscopic gastrostomy is considered by some surgical teams to be a contraindication as it may compromise the construction of a gastric conduit created during distal esophageal/proximal stomach reconstruction.

3.5 Combined approach

RECOMMENDATION
ESGE does not recommend the concurrent use of radiotherapy if an esophageal stent is present.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE suggests that SEMS placement with concurrent single-dose brachytherapy is safe and effective for relief of dysphagia.
Weak recommendation, low quality evidence.

To improve the outcome of stent placement, the use of radiotherapy in addition to SEMS placement has been investigated. This combined approach may potentially lead to prolonged dysphagia relief and improved overall survival [67–70]. Nevertheless, a high risk of major adverse events has been reported for the combination of EBRT and stent placement, suggesting stent placement is better reserved for patients who have failed prior radiotherapy [71].

In contrast to EBRT, the combination of single-dose brachytherapy and SEMS placement is safe and effective [67]. The use of irradiated SEMSs has been a topic of interest that potentially provides an advantage of combining the benefits of SEMS placement and brachytherapy. Based on a meta-analysis of six RCTs, the use of irradiated SEMSs led to an increased dysphagia-free time compared with traditional SEMSs, without affecting the rate of adverse events [72]. To date, however, all of these studies have been performed in Chinese populations, thereby warranting (prospective) evaluation in Western populations.

Only one study has investigated the outcomes of single-dose brachytherapy in addition to BDS placement [68]. Although satisfactory relief of symptoms was achieved, an unacceptably high rate of major adverse events was observed, which necessitated premature study termination.

3.6 Prior palliative therapy

In patients with recurrent dysphagia after first-line palliative radiotherapy, SEMS placement is considered the main treatment [73]. However, the association between prior palliative therapy and stent-related adverse events remains controversial. Several studies have reported that prior chemotherapy and/or radiotherapy increase the risk of life-threatening adverse events after SEMS placement, whereas other studies have shown the risk of adverse events to be unaffected [29, 34, 74–82]. Pneumonia, fistula formation, and stent-related pain may be increased in patients with prior therapy who receive stents [29, 34, 80–82].

The increased risk of adverse events has been explained by pulmonary toxicity and radiation-induced changes, which increase the susceptibility to pressure necrosis [29, 79, 81–85]. The potential role of radiotherapy-induced changes is supported by the increase in the rate of adverse events with a corresponding increase in radiation dosage [82, 83]. Regardless, the increased adverse event rate may also be partially explained by advanced disease stage, which is known to be related to an increased risk of life-threatening bleeding and fistula formation [34, 79].

4 Benign disease

4.1 Refractory benign esophageal strictures

RECOMMENDATION
ESGE recommends against the use of SEMSs as first-line therapy for the management of benign esophageal strictures because of the potential for adverse events, the availability of alternative therapies, and their cost.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE suggests consideration of temporary placement of self-expandable stents for refractory benign esophageal strictures.
Weak recommendation, moderate quality evidence.

RECOMMENDATION
ESGE suggests that fully covered SEMS fixation by endoscopic suturing or over-the-scope clips be considered in patients with previous stent migration.
Weak recommendation, low quality evidence.

The use of esophageal stents for the treatment of benign esophageal strictures has mainly been investigated in the context of refractory or recurrent benign esophageal strictures (RBESs; **Table 3s**). As defined by Kochman et al., these patients either fail to reach a target diameter of 14 mm after biweekly dilations over 5 weeks or fail to maintain the target diameter up to 4 weeks after the last dilation [86]. Esophageal stent placement has a potential benefit because of its continuous expansion force, which may lead to stricture remodeling. Although stent placement has not been compared with dilation in treatment-naïve patients, it is generally accepted that esophageal stent placement should only be considered as a second-line approach owing to its relatively high rate of adverse events and its cost.

In a recent meta-analysis, the outcomes of 18 studies with a total of 444 patients were pooled [87]. The clinical success rate after stent placement was 40.5 % (95 % confidence interval [CI] 31.5 %–49.5 %). Stent migration was the most common stent-related adverse event, occurring in 28.6 % (95 %CI 21.9 %–37.1 %). Other adverse events occurred in 20.6 % (95 %CI 15.3 %–28.1 %). Treatment outcomes did not differ among the SEMS, SEPS, and BDS groups.

To reduce the risk of SEMS migration, endoscopic stent fixation by endoscopic suturing or over-the-stent clips has been investigated (**Table 4s**). In general, endoscopic stent fixation is highly successful (96.7 %; 95 %CI 92.3 %–98.6 %) and safe (procedure-related adverse events, 3.7 %; 95 %CI 1.6 %–8.2 %) [88]. In the largest study of RBES patients, endoscopic suturing of the FCSEMS led to a reduction in stent migration rate compared with no suturing (9.4 % vs. 39.5 %; $P = 0.01$) [89]. It remains unclear if there is a benefit of routine stent fixation, and it may be considered in patients with prior stent migration.

Another method to reduce the risk of stent migration is the use of lumen-apposing metal stents (LAMSs). It is believed that the typical wide flanges and short lengths of LAMSs may prevent stent migration. To date, LAMSs have only been investigated in mixed study populations restricted by small sample sizes [90–94]. More studies are needed to evaluate their potential benefit in RBES patients.

4.1.1 Factors predicting successful treatment

RECOMMENDATION
ESGE does not recommend permanent stent placement for refractory benign esophageal stricture; stents should usually be removed at a maximum of 3 months following insertion.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE suggests that fully covered SEMSs be preferred over partially covered SEMSs for the treatment of refractory benign esophageal strictures because of their very low risk of embedment and ease of removability.
Weak recommendation, low quality evidence.

RECOMMENDATION
ESGE does not recommend the use of biodegradable stents over SEMSs in the treatment of benign esophageal strictures.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE recommends the stent-in-stent technique to remove partially covered SEMSs that are embedded in the esophageal wall.
Strong recommendation, low quality evidence.

The current literature provides some evidence that patient characteristics affect outcomes following stent placement in RBES patients. The previously mentioned meta-analysis showed a tendency toward a higher clinical success rate in studies that included a larger proportion of patients with radiotherapy-induced strictures and anastomotic strictures [87]. A similar trend was observed for the risk of stent-related adverse events, with the risk seeming to be lower in anastomotic strictures compared with other etiologies. In addition to stricture etiology, cervical stricture location and increasing stricture length have been reported to be associated with lower clinical success rates [95–97]. Because most studies do not take into account patient characteristics when reporting study outcomes, their specific impact remains unclear.

The optimal stent duration for the management of RBES patients has not been formally tested. It is recommended that stents remain in place for at least 6–8 weeks, but not longer than 10–12 weeks after stent placement. It is believed that this stent duration provides sufficient time to induce stricture remodeling and at the same time prevents stent embedment. One retrospective study investigated the influence of stent duration on the safety of stent removal but found no such association [98]. Stent design was the only independent predictor

of complicated stent removal. Adverse events were more common with PCSEMSs (odds ratio [OR] 8.83; 95 %CI 3.29–23.70) and SEPSs (OR 4.71; 95 %CI 1.39–15.97) when compared with FCSEMSs. The use of BDSs has been suggested to obviate stent removal, but compelling evidence for BDSs over other stent types is lacking [96, 99].

Different methods for endoscopic removal of an embedded PCSEMS have been described [100–106]. Most studies have reported on the use of the stent-in-stent technique, which relies on the placement of an additional FCSEMS fully overlapping the location of the embedded PCSEMS. To induce pressure necrosis, the stent diameter of the additional FCSEMS should be at least that of the embedded PCSEMS. In > 90 % of patients, both SEMSs can be safely removed 10–14 days after placement of the additional FCSEMS [100, 101]. If removal of the embedded PCSEMS is unsuccessful, the stent-in-stent technique can be reattempted.

4.1.2 Combined approach

RECOMMENDATION
ESGE suggests that a combined approach of stent placement with additional techniques (e. g. corticosteroid injection, chemotherapeutic topical application) should not be undertaken in an attempt to improve the long-term benefit of temporary stenting.
Weak recommendation, very low quality evidence.

Concurrent endoscopic incisional therapy, corticosteroid injection, and mitomycin-C application are reported to enhance treatment outcomes of endoscopic dilation therapy. Data on the use of these endoscopic interventions in combination with esophageal stent placement are scarce. Only one study has reported on the outcomes of corticosteroid injection in combination with FCSEMS placement but no clear benefit was found [107].

4.1.3 Options after stent failure

RECOMMENDATION
ESGE suggests alternative treatment strategies such as self-dilation or surgical treatment for patients with refractory benign esophageal strictures that have not satisfactorily improved after two separate treatments with temporary stenting.
Weak recommendation, low quality evidence.

RECOMMENDATION
In poor surgical candidates, ESGE recommends self-dilation with rigid dilators.
Strong recommendation, low quality evidence.

In patients with recurrent dysphagia after stent placement, repeated esophageal stent placement may be considered, but has not been shown to have significant incremental benefit [108, 109]. When repeat esophageal stent placement does not lead to satisfactory results, alternative treatment strategies should be considered. Surgical treatment represents a valid option in selected patients, depending on the stricture location and patient performance status. Furthermore, self-dilation is safe and effective in the majority of patients [110–112]. Treatment success with self-dilation relies on patient compliance, restricting its use to self-motivated patients and poor surgical candidates.

4.2 Leaks, fistulas, and perforations

RECOMMENDATION
ESGE recommends that temporary stent placement can be considered for the treatment of leaks, fistulas, and perforations. No specific type of stent can be recommended, and the duration of stenting should be individualized.
Strong recommendation, low quality of evidence.

RECOMMENDATION
ESGE recommends esophageal stents be placed as early as possible for the treatment of leaks, fistulas, and perforations.
Strong recommendation, moderate quality evidence.

RECOMMENDATION
ESGE recommends including stent placement in a multimodality treatment protocol for leaks, fistulas, and perforations to optimize the healing success rate and minimize the risk of adverse events.
Strong recommendation, low quality evidence.

Esophageal stents are increasingly used in the management of esophageal perforations [113]. Based on three systematic reviews on the use of PCSEMSs, FCSEMSs, and SEPSs in anastomotic leaks and perforations, the clinical success rate of esophageal stent placement is 81 %–87 %, with no difference among the stent types [114–116]. Even though the clinical success rates are comparable, SEMSs are reported to perform better than SEPSs in leaks and perforations, with higher technical success (95 % vs. 91 %; $P = 0.03$), and reduced risk of migration (16 % vs. 24 %; $P = 0.001$) and stent repositioning (3 % vs. 11 %; $P < 0.001$), as well as a reduced risk of perforation when considering anastomotic leaks only (0 % vs. 2 %; $P = 0.01$) [116]. Data on the use of BDSs in these patients are restricted to a few small retrospective studies (**Table 5s**) [117–119].

To identify patients who may benefit from esophageal stent placement, van Halsema et al. developed a clinical prediction

rule based on four clinical parameters: etiology (leak, fistula, perforation), location, orifice size, and C-reactive protein (CRP) level [120]. In the validation cohort, the sensitivity and specificity for a 70 % predicted probability of clinical success were 33 % and 89 %, respectively. Multivariable logistic regression showed fistulas and orifice size of > 2 cm to be associated with a lower rate of clinical success. The observed difference between anastomotic leaks and fistulas emphasizes that leaks, fistulas, and perforations are different entities and may require an individual approach. For instance, in fistula patients, SEMS placement is usually performed in combination with other therapies and a longer stent duration may be needed in anastomotic leaks compared with perforations [121, 122]. Nevertheless, the current literature provides insufficient data to formulate separate recommendations.

No study has investigated the optimal stent duration. Stents are usually removed 6–8 weeks after insertion and repeated stent placement is needed in 11 % of patients [114–116]. In patients who are endoscopically treated for benign esophageal perforations, early diagnosis (< 24 hours) has been shown to be associated with a lower need for re-intervention and intensive care admission, and a shorter hospital stay [123].

Recently, the outcomes of SEMS placement have been compared with endoscopic vacuum therapy for the treatment of post-surgical leaks [124]. The use of endoscopic vacuum therapy was associated with a higher leak closure rate, more endoscopic device changes, shorter duration of treatment, and lower in-hospital mortality. Because the management of these patients may be challenging and often requires a multimodality approach, esophageal stent placement may still be considered in addition to other endoscopic techniques to optimize treatment outcomes [119].

4.2.1 Safety

Stent migration is the most common stent-related adverse event and tends to be higher when FCSEMSs (26 %) and SEPSs are used (31 %) compared with PCSEMSs (12 %) [114]. The use of large-diameter SEMSs has been suggested to reduce the risk of stent migration in anastomotic leaks [119]. Furthermore, suturing of FCSEMSs may render migration rates similar to those of PCSEMSs, without the difficulties associated with the removal of PCSEMSs and with a lower risk of adverse events [125]. Other stent-related adverse events include the development of a stricture, stent erosion, perforation, and bleeding [114–116]. Repeated endoscopic intervention is needed in 17 %–25 % of patients and 7 %–13 % require surgical intervention [114–116].

4.3 Acute variceal bleeding

RECOMMENDATION

ESGE recommends considering placement of a fully covered large-diameter SEMS for the treatment of esophageal variceal bleeding refractory to medical, endoscopic, and/or radiological therapy, or as initial therapy for patients with massive bleeding.

Strong recommendation, moderate quality evidence.

Esophageal stent placement for acute variceal bleeding has mainly been investigated in small retrospective studies using a dedicated stent design (SX-ELLA stent DANIS) for the treatment of refractory bleeding (**Table 6s**). Stent duration is reported to range from 1–30 days [126]. Pooled data analysis shows that SEMS placement leads to control of bleeding in > 80 % of patients, without severe stent-related adverse events [126, 127]. In 21 % of patients, bleeding reoccurs within 6 weeks after SEMS placement [128]. Only one RCT has performed a direct comparison of SEMSs and balloon tamponade [129]. In this study of 28 patients, SEMS placement led to a higher rate of control of bleeding during the first 15 days (85 % vs. 47 %; P = 0.04) and a lower rate of adverse events (31 % vs. 73 %; P = 0.02).

Despite its effectiveness, the 30-day mortality rate after SEMS placement may be as high as 36 %, also reflecting the severity of the underlying condition [127]. Accordingly, SEMSs have been proposed as a bridge to transjugular intrahepatic portosystemic shunting (TIPS) or liver transplantation.

Disclaimer

The legal disclaimer for ESGE guidelines [130] applies to this Guideline.

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Competing interests

T.H. Baron has been a speaker and consultant for Boston Scientific and Cook Endoscopy (2014 to present). A. Repici has been on the advisory board and provided consultancy to Boston Scientific and Medtronic, and provided consultancy to ERBE (all 2017 to present). P.D. Siersema receives research support from Pentax, The eNose company, Norgine, Motus GI, and MicroTech; he is Editor-in-Chief of Endoscopy. M.C.W. Spaander has received research support from Boston Scientific (2013 to present). J.E. van Hooft has provided consultancy to Boston Scientific (2014 to 2017) and Olympus (2021), has received lecture fees from Medtronics (2014, 2015, and 2019) and Cook Medical (2019); her department has received research grants from Cook Medical (2014 to 2019) and Abbott (2014 to 2017). D. Albers, D. Blero, M. Conio, L. Czakó, A. de Ceglie, S. Everett, L. Fuccio, J.-C. Garcia-Pagán, A. Ginès, M. Jovani, E. Rodrigues-Pinto, R.D. van der Bogt declare that they have no conflict of interest.

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Supplementary material

Table 1s – Overview of key questions.

Malignant disease section
Taskforce 1: Esophageal stent placement for the treatment of malignant dysphagia
1. Is there new evidence to support/reject/change previous guideline recommendations?
2. Is there sufficient evidence to provide recommendations regarding the use of novel stent types, such as biodegradable stents?
3. Are there any patient characteristics that should be taken into account when selecting the best palliative approach/stent design?
4. Can we reliably identify patients with a longer expectancy? If yes, which factors can be used to predict patient survival?
5. Is there an alternative to brachytherapy if brachytherapy is not available? If yes, are these therapies directly interchangeable?
6. Are there any clinical characteristics related to the risk of stent-related adverse events?
Taskforce 2: Esophageal stent placement for the treatment of fistula and as a bridge to surgery
1. Is there new evidence to support/reject/change previous guideline recommendations?
2. What is the optimal stent design for the management of these patients?
Taskforce 3: Esophageal stent placement in patients undergoing concomitant palliative therapy or with a history of (palliative) therapy
1. Is there new evidence to support/reject/change previous guideline recommendations?
2. Is there sufficient evidence to provide any recommendations on the use of irradiated stents?
3. Does prior palliative therapy affect the outcomes of esophageal stent placement?
Benign disease section
Taskforce 4: Esophageal stent placement for the treatment of (refractory) benign esophageal strictures
1. Is there new evidence to support/reject/change previous guideline recommendations?
2. Is early timing of esophageal stent placement justifiable in patients that are deemed likely to be refractory to other therapies?
3. What is the optimal stent design for the management of these patients?
4. Should stent fixation be routinely performed?
Taskforce 5: Esophageal stent placement in combination with other strategies and options after stent failure in (refractory) benign esophageal strictures
1. Is there new evidence to support/reject/change previous guideline recommendations?
2. Should we use a different stent type after initial failure?
Taskforce 6: Esophageal stent placement for the treatment of leaks, fistulas, perforations, and acute variceal bleeding
1. Is there new evidence to support/reject/change previous guideline recommendations?
2. What is the optimal stent design for the management of these patients?
3. Which clinical characteristics should be taken into account when determining the stent duration in individual patients?

Supplementary material

Table 2s – Overview of randomized controlled trials comparing esophageal stent placement to other treatment strategies for palliation of malignant dysphagia due to esophageal cancer.

First author, year	Interventions	Clinical success	Adverse event	Recurrent dysphagia	Other findings	Level of evidence
Alderson, 1990 [1]	SEMS (n=20) Laser therapy (n=20)	SEMS: 90% Laser therapy: 85%	SEMS: 5% Laser therapy: 25%	SEMS: 10% Laser therapy: 80%	-	Moderate
Carter, 1990 [2]	SEMS (n=20) Laser therapy (n=20)	SEMS: 90% Laser therapy: 90%	SEMS: 20% Laser therapy: 25%	SEMS: 20% Laser therapy: 10%	Patients treated by laser required more readmissions	Moderate
Fuchs, 1991 [3]	SEMS (n=23) Laser therapy (n=17)	SEMS: 83% Laser therapy: 88%	SEMS: 22% Laser therapy: 47%	-	Length of initial hospital stay and rate of readmission were higher in the SEMS group.	Moderate
Adam, 1997 [4]	Covered SEPS(n=23) Uncovered SEPS (n=19) Laser therapy (n=18)	Covered SEPS[a]: 1 Uncovered SEPS[a]: 1 Laser therapy[a]: 2	Covered SEPS: 9% Uncovered SEPS: 5% Laser therapy: 11%	Covered SEPS: 12% Uncovered SEPS: 20% Laser therapy: 12%	-	Moderate
Aoki, 2001 [5]	SEMS (n=13) Bypass surgery (n=10)	SEMS: 77% Bypass surgery: 50%	-	-	SEMS group had a higher duration of possible food intake and lower in-hospital mortality	Moderate
Dallal, 2001 [6]	Photodynamic therapy (n=34) SEMS (n=31)	Photodynamic therapy[b]: 0 SEMS[b]: 0	Photodynamic therapy: 18% SEMS: 26%	Photodynamic therapy: 21% SEMS: 13%	Length of hospital stay and costs were higher in the photodynamic therapy group	Moderate
Homs, 2004 [7]	SEMS (n=108) Brachytherapy (n=101)	SEMS: 76% Brachytherapy: 73%	SEMS: 33% Brachytherapy: 21%	SEMS: 40% Brachytherapy: 43%	Total medical costs and hospital stay were comparable. Brachytherapy was beneficial on most quality of life subscales.	High
Bergquist, 2005 [8]	SEMS (n=34) Brachytherapy (n=31)	No differences were observed in regard to improvement of dysphagia scores.	-	-	SEMS placement led to a more rapid relief of dysphagia based on self-reported outcomes Brachytherapy offers better quality of life in long-term survivors.	High

[a]Median dysphagia score after treatment; a higher score indicates more severe dysphagia symptoms.
[b]Median change in dysphagia score after treatment; a higher change indicates greater effectiveness.
SEMS, self-expandable metallic stent; SEPS, self-expandable plastic stent; -, not reported.

Supplementary material

Table 3s – Outcomes of stent placement in RBES patients.

First author, year	Study design	Participants	Stent type(s)	Clinical success	Migration rate	Adverse event	Level of evidence
Bakken, 2010 [9]	R	25	FCSEMS	56%	45%	-	Low
Repici, 2010 [10]	P	21	BDS	42.9%	9.5%	19%	Low
Eloubeidi, 2011 [11]	R	19	FCSEMS	21%	34%	36.9%	Low
Van Boeckel, 2011 [12]	R	38	BDS (n=18) SEPS (n=20)	BDS: 33% SEPS: 30%	BDS: 22% SEPS: 25%	BDS: 29% SEPS: 15%	Low
Van Hooft, 2011 [13]	P	10	BDS	60%	0%	0%	Low
Canena, 2012 [14]	P	30	BDS (n=10) FCSEMS (n=10) SEPS (n=10)	BDS: 30% FCSEMS: 40% SEPS: 10%	BDS: 20% FCSEMS: 30% SEPS: 60%	BDS: 50% FCSEMS: 60% SEPS: 70%	Low
Hirdes, 2012 [15]	P	28	1st BDS (n=28) 2nd BDS (n=13) 3rd BDS (n=7)	1st: 25% 2nd: 15% 3rd: 0	1st: 11% 2nd: 8% 3rd: 0%	1st: 43% 2nd: 8% 3rd: 29%	Low
Hirdes, 2012 [16]	P	15	FCSEMS	0%	33%	53%	Low
Liu, 2012 [17]	R	24	FCSEMS	75%	3.4%	72.4%	Low
Chaput, 2013 [18]	P	41	FCSEMS	10%	29%	29%	Low
Dan, 2014 [19]	R	25	FCSEMS	26%	40%	-	Low
Dhar, 2014 [20]	RCT	17	BDS (n=10) Dilatation (n=7)	BDS: 1.17[a] Dilatation: 0[a]	-	-	Moderate
Gangloff, 2015 [21]	R	23	PCSEMS (n=17) FCSEMS (n=23)	PCSEMS: 23.5% FCSEMS: 34.7%	PCSEMS: 17.6% FCSEMS: 17.4%	PCSEMS: 35% FCSEMS: 9%	Low
Van Halsema, 2015 [22]	Rev	232 (8 studies)	BDS (n=77) FCSEMS (n=85) SEPS (n=70)	BDS 32.9% FCSEMS 14.1% SEPS 27.1%	BDS: 14.3% FCSEMS: 31.8% SEPS: 27.1%	BDS: 14.3% FCSEMS: 31.8% SEPS: 27.1%	Moderate
Fuccio, 2016 [23]	MA	444 (18 studies)	BDS (n=77) FCSEMS (n=227) SEPS (n=140)	BDS: 32.9% FCSEMS: 40.1% SEPS: 46.2%	BDS: 15.3% FCSEMS: 31.5% SEPS: 33.3%	BDS: 21.9% FCSEMS: 21.9% SEPS: 19.4%	High
Yano, 2017 [24]	P	18	BDS	3 months: 87.5% 6 months: 18.8%	0	-	Moderate
Saeed, 2018 [25]	R	17	BDS (n=5) FCSEMS (n=17)	FCSEMS: 47% BDS: 53%	FCSEMS: 11.8% BDS: 20%	54.6%	Low
Walter, 2018 [26]	RCT	66	BDS (n=32) Dilatation (n=34)	Fewer dilatations at 3 months in BDS group	BDS: 3%	-	Moderate
Kappelle, 2019 [27]	RCT	18	Dilatation (n=9) FCSEMS (n=9)	-	FCSEMS: 22%	-	Moderate

[a]Average dysphagia score during the first six months; a higher score indicates more severe dysphagia symptoms.
BDS, biodegradable stent; FCSEMS, fully covered self-expandable metallic stent; MA, meta-analysis; P, prospective; PCSEMS, partially covered self-expandable metallic stent; R, retrospective; RBES, refractory benign esophageal stricture; RCT, randomized controlled trial; Rev, review SEPS, self-expandable plastic stent; -, not reported.

Supplementary material

Table 4s – Outcomes of endoscopic stent fixation in benign esophageal strictures.

First author, year	Study design	Participants	Intervention(s)	Migration rate	Adverse event	Level of evidence
Vanbiervliet, 2012 [28]	R	44 (18 benign strictures)	FCSEMS (n=21) OTSC-FCSEMS (n=23)	FCSEMS: 57% OTSC FCSEMS: 13%	0%	Low
Irani, 2014 [29]	R	3	OTSC-FCSEMS	67%	0%	Low
Sharaiha, 2015 [30]	R	47 (14 benign esophageal strictures)	ES-SEMS	6.1%%	12.7%	Low
Bick, 2016 [31]	R	101	FCSEMS[a] (n=59) PCSEMS[a] (n=30) ES-FCSEMS[a] (n=25)	FCSEMS: 39.5% PCSEMS: 21.1% ES-FCSEMS: 9.4%	FCSEMS: 14.9% PCSEMS: 15.8% ES-FCSEMS: 3.1%	Low
Ngamruengphong, 2016 [32]	R	125 (56 benign strictures)	ES-FCSEMS (n=44) FCSEMS (n=81)	ES-FCSEMS: 16% FCSEMS: 33%	ES-FCSEMS: 18% FCSEMS: 19%	Low
Law, 2018 [33]	MA	212 (14 studies; 100 benign strictures)	ES-FCSEMS	15.9%	3.7%	Moderate

[a]Some patients underwent placement of multiple stent types
ES, endoscopically sutured; FCSEMS, fully covered self-expandable metallic stent; MA, meta-analysis; OTSC, over-the-scope clipped; PCSEMS, partially covered self-expandable metallic stent; R, retrospective; SEMS, self-expandable metallic stent.

Supplementary material

Table 5s – Outcomes of esophageal stent placement in leaks, fistulas and perforations.

First author, year	Study design	Study population	Intervention(s)	Clinical success	Adverse events	Level of evidence
Cerna, 2012 [34]	R	Leaks and perforations	BDS (n=5)	80%	Migration: 60%	Low
Anikhindi, 2016 [35]	R	Leaks and fistulas	Fixated SEPS (n=12)	75%	Stent migration: 33.3% Esophageal stricture: 25%	Low
Dickinson, 2016 [36]	R	Perforations	ES-FCSEMS (n=6)	100%	-	Low
Persson, 2016 [37]	R	Leaks	FCSEMS (n=46)	63%	All-cause mortality: 26%	Low
Suzuki, 2016 [38]	R	Leaks, fistulas, and perforations	SEMS (n=42)	64.3%	45.2%	Low
Biancari, 2017 [39]	R	Perforations	FCSEMS (n=43)	46.5%[a]	Stent migration: 59.2% In-hospital mortality: 4.6%	Low
Choi, 2017 [40]	R	Leaks	FCSEMS (n=7)	100%	Stent migration: 0% Esophageal stricture: 14.2%	Low
Glatz, 2017 [41]	P	Perforations	PCSEMS + drainage (=16)	50%	Esophageal stenosis: 48% In-hospital mortality: 13%	Low
Persson, 2017 [42]	SR	Leaks, perforations, and ruptures	SEMS (n=371) Surgery (n=368)	SEMS: 88% Surgery: 83%	In-hospital mortality SEMS: 7.5% Surgery: 17%	Low
Silon, 2017 [43]	R	Fistulas (benign + malignant)	FCSEMS (n=16)	56.3%	37.5%	Low
Huh, 2018 [44]	R	Leaks and perforations	FCSEMS (n=29) PCSEMS (n=2)	FCSEMS: 79.3% PCSEMS: 0%	Overall: 12.9% All-cause mortality: 22.6%	Low
Köneş, 2018 [45]	R	Leaks and strictures	BDS (n=13)	85%	Pain: 100%	Low
Oprisanescu, 2018 [46]	R	Fistulas	FCSEMS (n=21)	76%	Stent migration: 42% Pain: 62% Stent-induced ulcer: 19%	Low
van Halsema, 2018 [47]	R	Leaks, fistulas, and perforations	SEMS (n=204)	59%	Mortality: 26.5%	Low
Anderloni, 2019 [48]	R	Leaks	FCSEMS (n=14) PCSEMS (n=35)	FCSEMS: 57.1% PCSEMS: 64.7%	FCSEMS: 50% PCSEMS: 34.4% Overall mortality 13.0%	Low
Berlth, 2019 [49]	R	Leaks	EVT (n=34) FCSEMS (n=77)	EVT: 85.7% FCSEMS: 72.4%	Early adverse events EVT: 15% FCSEMS: 26% Late adverse events EVT: 3.7% FCSEMS: 26%	Low

Supplementary material

Debourdeau, 2019 [50]	R	Fistulas	FCSEMS (n=20) OTSC (n=8)	FCSEMS: 55% OTSC: 75%	Serious adverse events FCSEMS: 45%	Low
Moraveji, 2019 [51]	R	Perforations	SEMS (n=80) Surgery (n=85)	SEMS: 88.7% Surgery: 95.3%	Procedural adverse events SEMS: 3.8% Surgery: 15% Late AE SEMS: 31.2% Surgery: 10.6% Mortality SEMS: 2.5% Surgery: 10.6%	Low
Plum, 2019 [52]	R	Leaks	SEMS (n=70)	70%	28.6%	Low
Azevedo, 2020 [53]	R	Leaks	FCSEMS (n=31) PCSEMS (n=22)	62.3%	Stent migration FCSEMS: 16.1% PCSEMS: 9.1% Stent related morality Overall: 5.6%	Low
Bohle, 2020 [54]	R	Leaks	SEMS (n=34)	76%	Stent migration: 24% Severe adverse events: 14.7%	Low
Kamarajah, 2020 [55]	SR	Leaks and perforations (66 studies)	FCSEMS (n=810) SEPS (n=185)	87%	Stent migration: 12% Stent perforation: 0.7% Bleeding: 0.6% Stent erosion: 4% Overall mortality: 20%	Moderate
Rodrigues-Pinto, 2020 [56]	R	Leaks	BDS (n=8) SEMS (n=178)	BDS: 37.5% FCSEMS: 69.9% PCSEMS: 28.5%	Stent migration BDS: 25% FCSEMS: 25.2% PCSEMS: 12.6%	Low
Scognamiglio, 2020 [57]	MA	Leaks (five studies)	EVT (n=88) SEMS (n=157)	EVT: 81.8% SEMS: 61.1%	Early adverse events EVT: 17.8% SEMS: 22.8% Severe adverse events EVT: 5.6% SEMS: 17.5% In-hospital mortality EVT: 11.2% SEMS: 22.2%	High

[a]Proportion of patients not requiring an additional intervention.
BDS, biodegradable stent; ES, endoscopically sutured; EVT, endoscopic vacuum therapy; FCSEMS, fully covered self-expandable metallic stent; MA, meta-analysis; OTSC, over-the-scope clips; P, prospective; PCSEMS, partially covered self-expandable metallic stent; R, retrospective; SEMS, self-expandable metallic stent; SEPS, self-expandable plastic stent; SR, systematic-review.

Supplementary material

Table 6s – Outcomes of esophageal stent placement in refractory variceal bleeding.

First author, year	Design	Participants	Intervention(s)	Clinical success	Adverse events	Stent migration	Mortality	Level of evidence
Hubmann, 2006 [58]	R	20	FCSEMS	100%	5%	25%	10% (30-day)	Low
Zehetner, 2008 [59]	R	39*	FCSEMS	97%	3%	18%	27% (30-day)	Low
Wright, 2010 [60]	R	10	FCSEMS	70%	10%	10%	50% (6-week)	Low
Dechêne, 2012 [61]	R	8	FCSEMS	88%	12%	0	75% (60-day)	Low
Holster, 2013 [62]	R	5	FCSEMS	80%	40%	20%	40% (in-hospital)	Low
Fierz, 2013 [63]	R	7	FCSEMS	89%	0	22%	71% (6-week)	Low
Marot, 2015 [64]	MA	146	FCSEMS	82%	-	28%	36% (30-day)	High
Zakaria, 2013 [65]	R	16	FCSEMS	88%	15%	38%	25% (in-hospital)	Low
Jain, 2015 [66]	R	3	FCSEMS	100%	0	33%	33% (in-hospital)	Low
Müller, 2015 [67]	R	11	FCSEMS	100%	18%	63.6%	27% (6-week)	Low
Escorsell, 2016 [68]	RCT	13	BT (n=15) FCSEMS (n=13)	BT: 47% FCSEMS: 85%	BT: 73% FCSEMS: 31%	0	BT: 60% (6-week) FCSEMS: 46% (6-week)	Moderate
Goenka, 2017 [69]	R	12	FCSEMS	100%	8.3%	0%	41.7% (30-day)	Low
Maiwall, 2018 [70]	R	35	FCSEMS	89%	-	-	74.3% (6-week)	Low
Pfisterer, 2019 [71]	R	34	FCSEMS	79.4%	11.8%	38.2%	47.1% (6-week)	Low
Rodrigues, 2019 [72]	MA	758 (23 studies)	BT (n=570) FCSEMS (n=188)	BT: 80.2% FCSEMS: 89.7%	-	-	-	Moderate
Mohan, 2020 [73]	MA	574 (21 studies)	FCSEMS (n=176) TIPS (n-398)	FCSEMS: 84.5% TIPS: 97.9%	FCSEMS: 36.9% TIPS: 41.4%	FCSEMS: 31.8% TIPS: n/a	FCSEMS: 43.6% TIPS: 27.9%	Moderate

BT, balloon tamponade; FCSEMS, fully covered self-expandable metallic stent; n/a, not applicable; MA, meta-analysis; R, retrospective; RCT, randomized controlled trial; TIPS, transjugular intrahepatic portosystemic shunting; -, not reported.

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ESGE esophageal stenting guideline update – key questions

I. Esophageal stents in malignant disease – Efficacy **Supervisor Fuccio**	
ESGE recommends placement of partially or fully covered self-expanding metal stents (SEMSs) for palliation of malignant dysphagia over laser therapy, photodynamic therapy, and esophageal bypass (strong recommendation, high quality evidence).	
ESGE recommends against the placement of nonexpendable and expandable plastic stents for the palliation of malignant esophageal strictures (strong recommendation, high quality of evidence).	
Questions	**Experts**
a. Is there new evidence to support/reject/ change these recommendations? b. Are there any clinical characteristics that should be taken into account when selecting the best palliative approach/stent design? c. Is there sufficient evidence to provide recommendations regarding the use of novel stent types, such as biodegradable stents?	Conio, Jovani
II. Esophageal stents in malignant disease – Safety **Supervisor Fuccio**	
For patients with longer life expectancy, ESGE recommends brachytherapy as a valid alternative or in addition to stenting in esophageal cancer patients with malignant dysphagia. Brachytherapy may provide a survival advantage and possibly a better quality of life compared to SEMS placement alone. (Strong recommendation, high quality evidence)	
a. Is there new evidence to support/reject/ change this recommendation? b. Can we reliably identify patients with a longer life expectancy? If yes, which factors can be used to predict patient survival? If no, are there other factors that can guide treatment allocation? c. Is there an alternative to brachytherapy when brachytherapy is not available? If yes, is this alternative therapy directly interchangeable with brachytherapy? d. Are there any clinical characteristics related to the risk of stent-related adverse events? e. Should stent fixation be routinely performed?	Conio, Jovani

III. Esophageal stents in malignant disease – Fistula Supervisor Fuccio	
Esophageal SEMS placement is recommended as the preferred treatment for sealing malignant tracheoesophageal or bronchoesophageal fistula (strong recommendation, low quality of evidence).	
Application of double stenting (esophagus and airways) can be considered when fistula occlusion is not achieved by esophageal or airway prosthesis alone (strong recommendation, low quality evidence)	
a. Is there new evidence to support/reject/ change these recommendations? b. What is the optimal stent design in the management of these patients? c. Should stent fixation be performed when there is no presence of a significant stenosis?	Siersema, Czako
IV. Esophageal stents in malignant disease – Bridge to surgery Supervisor Fuccio	
ESGE does not recommend SEMS placement as a bridge to surgery or prior to preoperative chemoradiotherapy. It is associated with a high incidence of adverse events, and other satisfactory options such as placement of a feeding tube are preferable. (Strong recommendation, low quality evidence.)	
a. Is there new evidence to support/reject/ change this recommendation?	Siersema, Czako
V. Esophageal stents in malignant disease – Concomitant palliative therapy Supervisor Fuccio	
ESGE does not recommend the concurrent use of radiotherapy if an esophageal stent is present (strong recommendation, low quality of evidence)	
ESGE suggest that SEMS placement with concurrent single-dose brachytherapy is safe and effective for relief of dysphagia (weak recommendation, low quality evidence)	
a. Is there new evidence to support/reject/ change these recommendations? b. Is there sufficient evidence to provide any recommendations on the use of radioactive/drug-eluting stents? c. What is the optimal timing of esophageal stent placement when a patient is eligible for palliative chemotherapy?	de Ceglie, Gines
VI. Esophageal stents in malignant disease – Prior palliative therapy Supervisor Fuccio	
a. Is there sufficient evidence to provide any recommendations on the use of esophageal stents in patients who underwent prior palliative therapy? b. Does prior palliative therapy affect the outcomes of esophageal stent placement? If yes, does this affect the role of esophageal stent placement in the management of dysphagia and can we provide any recommendations on the (minimum) time interval between prior therapy and stent placement?	de Ceglie, Gines

VII. Benign disease – Refractory strictures Supervisor Baron	
ESGE recommends against the use of SEMs as first-line therapy for the management of benign esophageal strictures because of the potential for adverse events, the availability of alternative therapies, and costs (strong recommendation, low quality evidence).	
ESGE suggests consideration of temporary placement of self-expandable stents for refractory benign esophageal strictures (weak recommendation, moderate quality evidence).	
ESGE does not recommend a specific type of expandable stent (covered metal, plastic, biodegradable) because none has been shown to be superior to any other for this indication (strong recommendation, moderate quality evidence).	
a. Is there new evidence to support/reject/ change these recommendations? b. Is early timing of esophageal stent placement justifiable in patients that are deemed likely to be refractory to other therapies? c. Should we discourage the use of plastic stents for its higher migration rate?	Repici, Albers
VIII. Benign disease – Factors predicting successful treatment Supervisor Baron	
ESGE does not recommend permanent stent placement for refractory benign esophageal stricture; stents should usually be removed at a maximum of 3 months (strong recommendation, weak quality evidence).	
ESGE suggests that FCSEMSs be preferred over PCSEMSs for the treatment of refractory benign esophageal stricture, because of their lack of embedment and ease of removability (weak recommendation, low quality evidence)	
ESGE recommends the stent-in-stent technique to remove PCSEMS that are embedded in the esophageal wall (strong recommendation, low quality evidence).	
a. Is there new evidence to support/reject/ change these recommendations? b. Should biodegradable stents be preferred over metal stents for obviating the need of stent removal? c. Should stent fixation be routinely performed? d. Is there sufficient evidence to provide any recommendations on the preferred technique of stent removal in case of stent migration?	Repici, Albers
IX. Benign disease – Combined approaches Supervisor Baron	
ESGE suggests that a combined approach of stent placement with additional techniques (e.g., corticosteroid injection, chemotherapeutic topical application) should not be used in an attempt to improve the long-term benefit of temporary stenting (weak recommendation, very low quality of evidence)	
a. Is there new evidence to support/reject/ change this recommendation?	Everett, Blero

X. Benign disease – Options after stent failure Supervisor Baron	
If refractory benign esophageal stricture has not satisfactorily improved after 2 separate treatments with temporary stenting, ESGE suggests alternative treatment strategies such as self-dilatation or surgical treatment (weak recommendation, low quality evidence). In poor surgical candidates, ESGE recommends self-dilatation with rigid dilators (strong recommendation, low quality evidence).	
a. Is there new evidence to support/reject/ change this recommendation? b. Should we use a different stent type after initial failure?	Everett, Blero
XI. Benign disease – Leaks, fistulas, and perforations Supervisor Baron	
ESGE recommends that temporary stent placement can be considered for treatment of leaks, fistulas, and perforations. No specific type of stent can be recommended and the duration of stenting should be individualized. (Strong recommendation, low quality of evidence).	
a. Is there new evidence to support/reject/ change this recommendation? b. Which clinical characteristics should be taken into account when determining the stent duration in individual patients?	Rodrigues-Pinto, Garcia-Pagán
XII. Benign disease – Acute variceal bleeding Supervisor Baron	
ESGE recommends considering placement of a SEMS for the treatment of esophageal variceal bleeding refractory to medical, endoscopic, and/or radiological therapy, or as initial therapy for patients with massive bleeding (strong recommendation, moderate quality evidence).	
a. Is there new evidence to support/reject/ change this recommendation? b. Which stent type should be used?	Rodrigues-Pinto, Garcia-Pagán

C) Self-expanding metal stents in postoperative esophageal leaks

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ORIGINAL PAPERS

Self-expanding metal stents in postoperative esophageal leaks

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ABSTRACT

Background: Postoperative esophageal leaks have a high morbidity and mortality. Self-expanding metal stents (SEMS) have been used as an alternative to re-operation.

Aim: Evaluating predictors of success of SEMS in postoperative esophageal leaks.

Methods: Retrospective study of patients with postoperative esophageal leaks referred for SEMS placement in a reference center during a period of 3 years. Technical success was defined as closure of the leak in barium swallow at 15 days. Clinical success was considered as endoscopic and/or radiographic confirmation of closure after stent removal.

Results: Thirteen patients placed SEMS. Median follow-up was 58 days. Leaks had a median size of 20 mm. Time between surgery and SEMS placement was 20 days. One patient died 2 days after SEMS placement and one had worsening of the fistula after SEMS expansion. Time till stent migration was 9 days. Technical success was achieved in 9 of 11 patients, with clinical success without recurrence in 5 patients. All leaks with less than 20 mm were solved endoscopically. Technical and clinical success was higher when time between surgery and SEMS placement was lower, even though without statistical significance (respectively, p = 0.228 and 0.374). In the 8 patients who died during follow-up, median survival was 59 days.

Conclusions: Technical success of SEMS was higher than 80%; however, due to high morbidity and mortality, only 45% of patients had their stent removed. Lower time from diagnosis to SEMS placement and leak size less than 20 mm may be associated with better results.

Key words: Postoperative esophageal leaks. Self-expanding metal stents. Survival.

INTRODUCTION

Postoperative esophageal leaks can develop after esophagectomy, gastrectomy or mediastinal surgeries with esophageal laceration. Intrathoracic leak rates after esophageal resection occur in 7.9% of the surgeries (1) and after gastrectomy in 4% to 27% (2,3). Endoscopy is useful in diagnosis because the defect, integrity of surrounding tissue, and infection in the adjacent tissue can be assessed. Early diagnosis significantly reduces the rate of complications and mortality (4-7). Clinical manifestations vary depending on the location of the leak and time elapsing from the perforation or rupture. Fever, systemic inflammatory response syndrome, and abnormal C-reactive protein, white blood cell count, and albumin are indicators of postoperative esophageal leak (8,9).

Despite aggressive therapy, mortality rate of postoperative esophageal leaks remain as high as 20% (1,10), with treatment delays being associated with increased mortality rates (11). Traditionally, management of leaks with more than 5 mm has been prompt surgery, consisting on surgical drainage and repair, nothing by mouth, parenteral nutrition, and antibiotics; however, up to 30% of repairs demonstrate a persistent leak and may require additional esophageal procedures (12).

Fibrin glue or endoscopic clip placement can be considered for small defects, although patients with dehiscence of 30% to 70% of the esophageal circumference likely warrant stent placement. Self-expanding metal stents (SEMS) placement has become a well-established treatment, by excluding the defect to allow healing and oral feeding. However, SEMS placement can be complicated by inadequate defect closure, stent migration, and difficult removal. Leak of the proximal cervical esophagus, stent traversing the gastro-esophageal junction, esophageal leak with more than 6 cm and anastomotic leak associated with a more distal conduit leak have been associated with failure of leak resolution (13).

The aim of our study was to evaluate the safety, efficacy, and technical and clinical success of SEMS placement in the management of postoperative esophageal leaks.

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Rodrigues-Pinto E, Pereira P, Ribeiro A, Moutinho-Ribeiro P, Lopes S, Macedo G. Self-expanding metal stents in postoperative esophageal leaks. Rev Esp Enferm Dig 2016;108:133-137.

MATERIAL AND METHODS

Retrospective study based on medical records from patients with postoperative esophageal leaks referred for SEMS placement in a reference center between January 2011 and December 2014. Only patients submitted to esophageal, gastric or mediastinal surgeries were included. The diagnosis was made based on clinical symptoms (fever, respiratory distress, hemodynamic shock, and increased output of external drainage) combined with the findings of the computed tomography scan and/or a barium swallow that confirmed the leak. Leak size was measured endoscopically.

Technical success was defined as closure of the leak in barium swallow at 15 days. Clinical success was considered as endoscopic and/or radiographic confirmation of closure after stent removal. Timing for stent removal was individualized by patient according to co-morbidities, nutritional status, size, and location of the esophageal fistula. All the stents were fully covered (Hanarostent M.I. Tech Co., Inc, Seoul, South Korea), with 20 mm diameter, with proximal and distal flares with 26 mm, and were mounted on 18 Fr (6 mm) delivery systems. A .035-inch or .038-inch guidewire was inserted distal to the leak, and stent deployment was performed under direct endoscopic visualization. Clips were not used to anchor the stent to the esophageal mucosa. The length of the stent was chosen to extend each edge of the stent at least 2 cm beyond the proximal and distal extent of the esophageal leak. Nasogastric tubes were not routinely placed after esophageal stent insertion. Barium studies were routinely performed prior to patients' discharge.

Collected data included baseline patient and leak characteristics, type of surgery performed, location of the leak, SEMS extension, time between surgery and SEMS placement, adverse events, technical and clinical success and survival.

Statistics

Descriptive statistics were used to characterize our population. Categorical variables were described through absolute and relative frequencies and continuous variables were described as mean and standard deviation, median, percentiles, minimum and maximum. Hypotheses were tested about the distribution of continuous variables with non-normal distribution, by using the nonparametric Mann-Whitney and Kruskal-Wallis test, depending on the nature of the hypothesis. Pearson Chi-square and Fisher's exact test were used to test hypotheses about independence of categorical variables, as appropriate. Kaplan-Meyer analysis was used to calculate survival. All the reported p values were two-sided, and p values of < 0.05 were considered as statistically significant. All data were arranged, processed and analyzed with SPSS® v.20.0 data (Statistical Package for Social Sciences).

RESULTS

Population

A total of 13 patients (11 males) were analyzed, with a median age of 63 year-old (20-83). Median follow-up was 58 days (IQR: 19-134). Four of the patients were on intensive care units, 3 were on intermediate care units and 6 were on the general ward. Baseline characteristics of patients are present in table I.

Leaks had a median size of 20 mm (8-40), being secondary to Ivor-Lewis esophagectomy in 6 patients, total gastrectomy in 2, thoracic surgery in 2, Nissen fundoplication in 1, after cervical esophagostomy reconstruction in 1 and excision of esophageal diverticulum in 1. Ten of the leaks were located at the level of the anastomosis, with 2 being in the proximal esophagus and 1 in the distal esophagus.

SEMS placement and adverse events

Eight patients placed SEMS longer than 11 cm, with the remaining 5 placing SEMS shorter or with 11 cm.

Time between surgery and SEMS placement was 20 days (8-64). One patient died 2 days after SEMS placement (death not related to stent placement or fistula existence) and one had worsening of the fistula after SEMS expansion. Four patients had migration of the stent, with placement of a second stent in 3 of them and repositioning of the first stent in the other one. Time till stent migration was 9 days (2-23). Migration was not influenced by SEMS extension (25% *vs.* 33%, p = 0.777).

Technical success was achieved in 9 of 11 patients, with clinical success without recurrence in 5 patients (stent removal in median 46 days after placement). All leaks with less than 20 mm were solved endoscopically. Technical and clinical success was higher when time between surgery and SEMS placement was lower, even though without statistical significance (respectively, 10 days [8-27] *vs.* 48 days [10-64], p = 0.228 and 12 days [8-21] *vs.* 20 days [10-64], p = 0.374) (Fig. 1). Clinical success was not influenced by SEMS extension (50% *vs.* 33%, p = 0.599).

In the 8 patients who died during follow-up, median survival was 59 days ($CI_{95\%}$: 45-73). Mortality at the 1st month was 31% (n = 4) and at 3 months was 46% (n = 6).

DISCUSSION

Postoperative esophageal leaks remain the most important complication after upper gastroesophageal surgery. The constant leakage of gastric juices and saliva into the pleural and mediastinal cavities make this a life-threatening condition responsible for 40% of postoperative mortality (14). The incidence of leak with an intrathoracic anastomosis reported in the literature varies between 3% and 25%, even though published guidelines recommend that the incidence of anastomotic leak should not exceed 5% (15). The choice between surgical or alternative (conservative or endoscopic) management remains controversial. The main goals of surgery in this context are closure of the defect by primary repair (eventually reinforced by tissue interposition) and cleaning of the mediastinal or pleural space through

Table I. Baseline characteristic of patients with postoperative esophageal leaks

Age/gender	*Previous surgery*	*Surgery indication*	*Ward*	*Time from surgery to SEMS*	*Leak size*	*Leak location*	*SEMS extension*	*Adverse events other than migration*	*Migration*	*Time until migration*	*Technical success*	*Clinical success*	*Survival*
1-72/Male	Total gastrectomy	Gastric neoplasia	ICU	27 days	25 mm	EI anastomosis	15 cm	NA	No	NA	Yes	No	Death
2-63/M	Ivor-Lewis esophagectomy	Esophageal neoplasia	IMCU	8 days	25 mm	EG anastomosis	15 cm	NA	Yes	2 days	Yes	No	Death
3-63/M	Thoracic surgery	Substernal goiter surgery	ICU	10 days	40 mm	Proximal esophagus	11 cm	NA	No	NA	Yes	No	Death
4-55/M	Ivor-Lewis esophagectomy	Esophageal neoplasia	IMCU	29 days	25 mm	EG anastomosis	11 cm	NA	Yes	7 days	No	No	Death
5-65/M	Total gastrectomy	Gastric neoplasia	ICU	10 days	30 mm	EI anastomosis	14 cm	NA	Yes	23 days	No	No	Death
6-46/M	Ivor-Lewis esophagectomy	Esophageal neoplasia	GW	27 days	10 mm	EG anastomosis	15 cm	NA	No	NA	Yes	No	Death
7-74/M	Excision of esophageal diverticulum	Esophageal diverticulum	GW	9 days	40 mm	EG anastomosis	14 cm	NA	Yes	5 days	Yes	Yes	Alive
8-83/F	Thoracic surgery	Aortic valve substitution	ICU	64 days	20 mm	Proximal esophagus	11 cm	Death 2 days after	No	NA	NA	NA	Death
9-74/F	Nissen fundoplication	GERD and hiatus hernia	IMCU	20 days	20 mm	Distal esophagus	14 cm	Fistula worsening after SEMS expansion	No	NA	NA	NA	Death
10-20/M	Cervical esophagostomy reconstruction	Eosinophilic esophagitis perforation	GW	21 days	8 mm	EI anastomosis	8 cm	NA	No	NA	Yes	Yes	Alive
11-57/M	Ivor-Lewis esophagectomy	Esophageal neoplasia	GW	21 days	15 mm	EG anastomosis	14 cm	NA	No	NA	Yes	Yes	Alive
12-45/M	Mckewon esophagectomy	Esophageal neoplasia	GW	14 days	10 mm	EG anastomosis	14 cm	NA	No	NA	Yes	Yes	Alive
13-60/M	Ivor-Lewis esophagectomy	Esophageal neoplasia	GW	8 days	8 mm	EG anastomosis	11 cm	NA	No	NA	Yes	Yes	Alive

ICU: Intensive care unit; IMCU: Intermediate care unit; GW: General ward; EI: Esophago-intestinal; EG: Esophagogastric; NA: Not applicable.

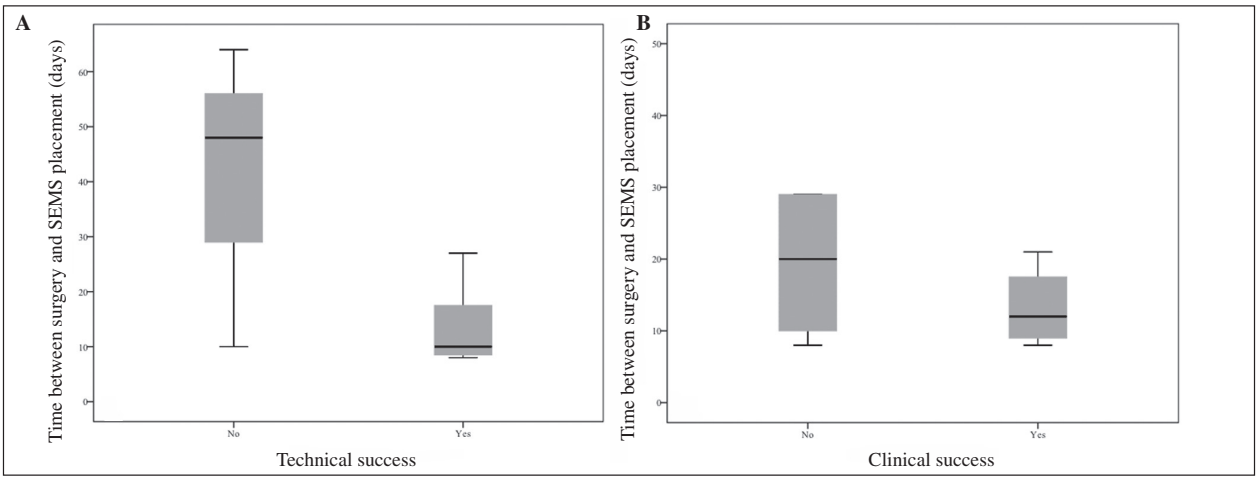

Fig. 1. A. Technical success and B. Clinical success considering time between surgery and SEMS placement. Technical and clinical success was higher when time between surgery and SEMS placement was lower.

surgical debridement and drainage. In more complex or extensive leakage a delayed reconstruction after diversion with a cervical esophagostomy may be required. However, surgical reintervention is associated with high morbidity and mortality (16-18) and prolonged intensive care unit and hospital stays, particularly in patients with a delayed diagnosis and mediastinal and pleural contamination.

Endoscopy can define whether intrathoracic leakage is secondary to gastric conduit necrosis, conduit staple line dehiscence, or esophagogastric anastomosis dehiscence. Insertion of an esophageal stent across the leakage region is the most popular and effective method to seal leaks and avoid surgery, with the use of temporary fully covered SEMS being well documented in various report series (19-21). Migration rate may be explained by the fact that stents used are not designed specifically for the indication of esophageal leakage or fistula. In our study, even though the majority of patients were on intensive or intermediate care units, technical success of SEMS in esophageal leaks was higher than 80%. However, postoperative esophageal leaks were associated with a high morbidity and mortality, partially explained by patients' co-morbidities, as well as surgery adverse events, with mortality rates at 1st month being 31% and at 3 months 46%. Literature suggests that stents should be left in place for 6 to 8 weeks in post-operative esophageal leaks. Considering these, clinical success was low, with only 45% of the patients having their stent removed, once the remaining 4 patients died before removal. However, all the patients who achieved clinical success were alive at the end of follow-up. SEMS seem to be a safe and effective option in the endoscopic sealing of leaks, allowing feeding, nutritional and clinical improvement. Better results seem to be achievable when time from initial diagnosis to SEMS placement is lower and leak size is less than 20 mm. These patients probably benefit the most from SEMS, allowing resolution of leaks and surgery avoidance.

Limitations of our study include its retrospective nature, with results reporting data only from a tertiary and single center, with possible selection bias that may preclude generalizability to community practice, as well as the small number of patients and heterogeneous population of patients. However, it reflects only patients with postoperative esophageal leaks and addresses clinical and endoscopic factors associated with endoscopic resolution of leaks.

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D) International multicenter expert survey on endoscopic treatment of upper gastrointestinal anastomotic leaks.

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International multicenter expert survey on endoscopic treatment of upper gastrointestinal anastomotic leaks

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ABSTRACT

Background and study aims A variety of endoscopic techniques are currently available for treatment of upper gastrointestinal (UGI) anastomotic leaks; however, no definite consensus exists on the most appropriate therapeutic approach. Our aim was to explore current management of UGI anastomotic leaks.

Methods A survey questionnaire was distributed among international expert therapeutic endoscopists regarding management of UGI anastomotic leaks.

Results A total of 44 % of 163 surveys were returned; 69 % were from gastroenterologists and 56 % had >10 years of experience. A third of respondents treat between 10 and 19 patients annually. Fifty-six percent use fully-covered self-expandable metal stents as their usual first option; 80 % use techniques to minimize migration; 4 weeks was the most common reported stent dwell time. Sixty percent perform epithelial ablation prior to over-the-scope-clip placement or suturing. Regarding endoscopic vacuum therapy (EVT), 56 % perform balloon dilation and intracavitary EVT in patients with large cavities but small leak defects. Regarding endoscopic septotomy, 56 % consider a minimal interval of 4 weeks from surgery and 90 % consider the need to perform further sessions. Regarding endoscopic internal drainage (EID), placement of two stents and shorter stents is preferred. Persistent inflammation with clinical sepsis was the definition most commonly reported for endoscopic failure. EVT/stent placement and EVT/EID were the therapeutic options most often chosen in patients with previous oncologic surgery and previous bariatric surgery, respectively.

Conclusions There is a wide variation in the management of patients with UGI anastomotic leaks. Future prospective studies are needed to move from an expert- to evidence- and personalization-based care.

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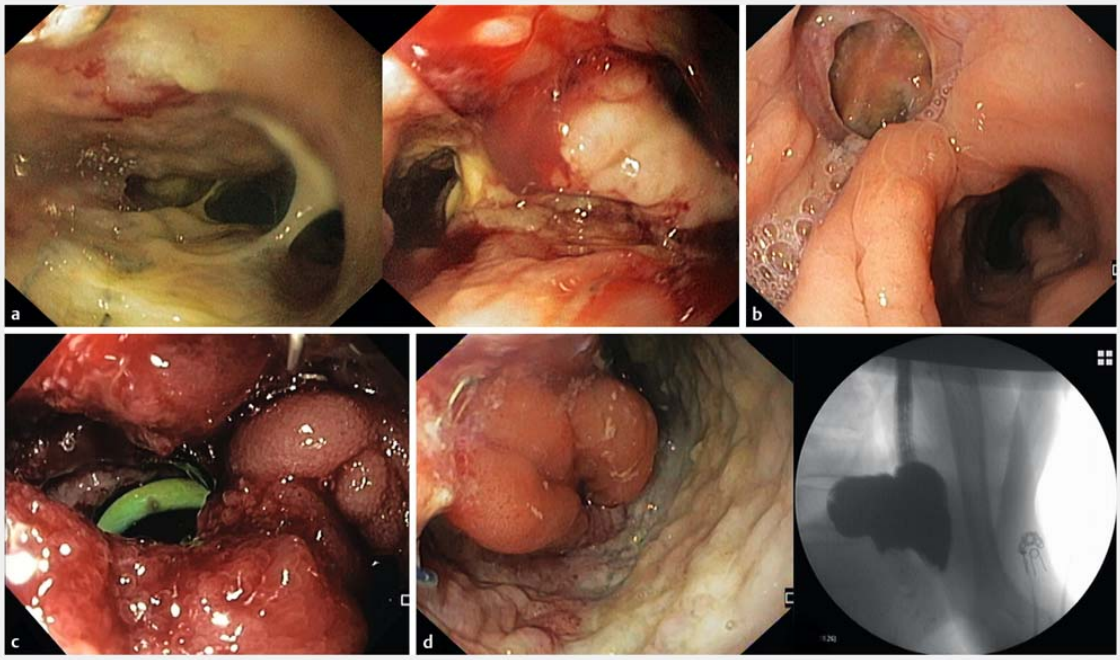
Introduction

Gastrointestinal leaks are abnormal communications between the intraluminal and extraluminal compartments as a result of a defect in the integrity of the gastrointestinal wall [1]. They usually occur due to defects at surgical suture sites, being associated with a high risk of mortality and morbidity. Leaks are responsible for the majority of surgical mortality [2 – 4]. In addition, delayed closure of leaks may result in chronic fistulae formation, which are difficult to manage endoscopically.

Prevalence of upper gastrointestinal (UGI) anastomotic leaks has increased in recent years. Leaks related to oncologic surgery leaks have been reported in 8 % to 26 % after distal esophagectomy and in 3 % to 12 % after total gastrectomy [3, 5]; bariatric surgery leaks have been reported in 2 % to 5 % of patients after Roux-en-Y gastric bypass (RYGB) and in 1 % to 2 % after sleeve gastrectomy [6, 7].

Treatment of UGI anastomotic leaks remains controversial, as indications for surgical, conservative and endoscopic therapy remain non-standardized. Traditionally, surgical therapy has been the mainstay of treatment for anastomotic leaks; however, it tends to be complex and is plagued by high rates of morbidity [8]. Over the last decade, interventional endoscopy has evolved as an effective and less invasive alternative to primary surgery, changing the management paradigm for UGI leaks. A variety of techniques are currently available to reestablish the continuity of the digestive tract, prevent or treat infection related to the leak, prevent further contamination, drain potential collections, and provide nutritional support [9]. Endoscopic options include stent placement (metallic, plastic and biodegradable), endoscopic vacuum therapy (EVT), endoscopic internal drainage (EID), through-the-scope [TTS] and over-the-scope clips [OTSC], endoscopic suturing, endoscopic septotomy plus balloon dilation and tissue sealants [9]. Theoretically, all of these can be used alone or with a multimodality approach, with the approach chosen being tailored to the clinical and morphologic presentation but also largely institutional dependent and based upon availability of devices and accessories.

Even though endoscopic therapy may be associated with an improved outcome and better quality of life, there is no definite



▶ **Fig. 1** **a** Clinical case 1: 52-year-old man with subcutaneous emphysema and respiratory insufficiency after Ivor-Lewis esophagectomy due to esophagus squamous-cell carcinoma; chest CT with oral contrast revealed a 12-cm intrathoracic collection with communication with the gastric tube; upper endoscopy revealed a severe anastomotic leakage 29 cm from the incisors. **b** Clinical case 2: 42-year-old woman, body mass index 38 kg/m^2, who underwent laparoscopic sleeve gastrectomy, without drain placement; 10 days later, she presented with a left pneumonia; chest CT with oral contrast revealed a 4-cm intrathoracic collection with communication with the gastric tube; upper endoscopy revealed a 20-mm anastomotic leakage 35 cm from the incisors; no stricture was present at the level of the incisura angularis. **c** Clinical case 3: 38-year-old man, with a body mass index of 40 kg/m^2, who underwent a Roux-en-Y gastric bypass, and presented 6 days later with fever and leukocytosis; CT with oral contrast revealed an 8 cm intraabdominal collection with communication with the gastric pouch; upper endoscopy revealed an anastomotic leakage 44 cm from the incisors; **d** Clinical case 4: 72-year-old man with recurrent leukocytosis and fever after total gastrectomy; CT with oral contrast revealed contrast extravasation between the gastrointestinal lumen and the intra-abdominal cavity; upper endoscopy revealed a severe anastomotic leakage 41 cm from the incisors.

▶ **Table 1** Techniques rating from the most frequently used to the less frequently used.

	First most used	Second most used	Third most used	Fourth most used	Fifth most used	Sixth most used	Seventh most used	Total	Average ranking
Stent placement	52.1 %	32.4 %	8.5 %	4.2 %	–	1.4 %	–	70	6.3
Endoscopic vacuum therapy	15.5 %	14.1 %	7 %	7 %	8.5 %	15.5 %	11.3 %	56	4.1
Endoscopic suturing	1.4 %	8.5 %	9.9 %	14.1 %	11.3 %	15.5 %	11.3 %	51	3.4
Tissue sealants	7 %	5.6 %	11.3 %	14.1 %	15.5 %	21.1 %	12.7 %	62	3.4
Over-the-scope clips	4.2 %	16.9 %	33.8 %	21.1 %	9.9 %	2.8 %	2.8 %	65	4.6
Endoscopic septotomy plus balloon dilation	2.8 %	11.3 %	4.2 %	8.5 %	15.5 %	8.5 %	16.9 %	48	3.3
Endoscopic internal drainage	16.9 %	9.9 %	21.1 %	16.9 %	14.1 %	–	2.8 %	60	4.7
Not applicable	–	1.4 %	4.2 %	14.1 %	25.4 %	35.2 %	42.3 %		

consensus on the most appropriate therapeutic approach in management of UGI anastomotic leaks. The current study was designed to explore the current practices in the management of UGI anastomotic leaks of a panel comprising international expert therapeutic endoscopists with experience in leaks to help design and inform future prospective studies.

Methods

An online survey was developed to assess the opinion and practice of a panel of international expert therapeutic endoscopists regarding management of UGI anastomotic leaks. The participants were selected based on publications published on PubMed between January 2013 and April 2018 regarding endoscopic treatment of UGI anastomotic leaks. A total of 226 publications were found, corresponding to 182 different authors with available emails (first, last or corresponding authors). The survey was initially distributed, tested and optimized among 12 selected therapeutic endoscopists (ERP, AR, GD, GM, JD, JEvH, JMC, MGN, MS, PE, VK and MAK). Nineteen of the 182 obtained e-mail addresses were inactive. In August 2018, 163 participants were invited via an e-mail link to an online survey programme (http://www.surveymonkey.com), followed by a total of 3-weekly reminders.

The survey consisted of 35 opinion-probing questions (**Appendix 1**) and 4 short clinical cases (▶ **Fig. 1**). With regard to the clinical vignettes, participants were asked to choose one option between the different endoscopic therapies available.

The final percentage in multiple-choice questions may exceed 100 %, as several respondents have chosen more than one answer. Average ranking (AR) in ▶ **Table 1** and **Supplementary Table 1** was calculated to determine which therapeutic choice was most preferred overall. It was calculated as follows, where "w = weight of ranked position" and "x = response count for answer choice"; weights are applied in reverse:

$$\frac{x_1w_1 + x_2w_2 + x_3w_3 \ldots x_nw_n}{Total}$$

Ideal patient characteristics for each endoscopic technique were based on the majority of respondents' answers (▶ **Table 2**).

Data were collected non-anonymously and analyzed using the graphical and analytical features of www.surveymonkey.com and IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, New York, United States). Answers were described as counts and percentages for categorical variables. Continuous variables were summarized as medians and range. Regarding respondents who gave time ranges between treatment sessions, the median value of each range was used to determine the total median value.

This study was conducted according to the Declaration of Helsinki. All authors reviewed and approved the final manuscript.

Results

Participants and endoscopic therapies characterization

A total of 163 surveys were sent and 71 (44 %) were returned. Twenty-five countries on five different continents were represented. Sixty-nine percent of the respondents (n = 49) were gastroenterologists, with the remaining 31 % (n = 22) being surgeons. Eighty-two percent of respondents (n = 58) worked in academic hospitals and 18 % (n = 13) in non-academic teaching hospitals. The number of patients with anastomotic leaks treated within each therapeutic endoscopy unit in 1 year ranged from 1 to 4 at nine centers (13 %) to > 40 at five hospitals (7 %) (▶ **Fig. 2**). Respondents had a median of 10 years [1 – 36] of experience.

Placement of self-expandable metal stents (SEMS) was the technique most available in each department (97 %), followed by OTSC (89 %) and EID (79 %) (▶ **Fig. 3**). Stent placement was

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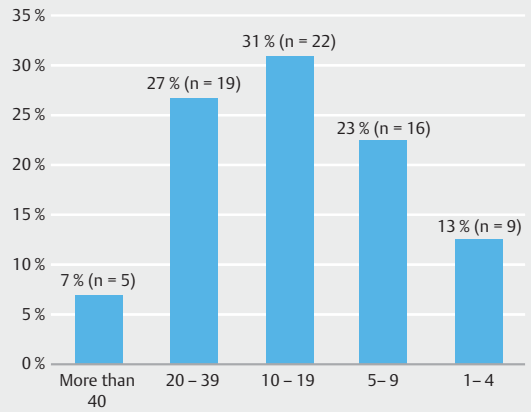
▶ **Table 2** Ideal patient characteristics for each endoscopic technique.

	Ideal patient characteristics[1]					
	Stent	**OTSC**	**EVT**	**Suture**	**Septotomy**	**EID**
Time of leak						
▪ Acute	93.8%	96.8%	48.7%	89.5%	3.2%	54.3%
▪ Chronic	17.2%	19%	71.8%	31.6%	100%	65.2%
▪ NO/NI	n=7	n=8	n=32	n=33	n=40	n=25
Leak size						
▪ 0–1 cm	54.1%	77%	25%	64.7%	51.9%	63.6%
▪ 1–2 cm	63.9%	47.5%	40%	50%	63%	65.9%
▪ 2–3 cm	55.7%	9.8%	67.5%	47.1%	51.9%	45.5%
▪ >3 cm	42.6%	–	77.5%	35.3%	63%	38.6%
▪ NO/NI	n=10	n=10	n=31	n=37	n=44	n=27
Leak location						
▪ Intrathoracic	93.2%	64%	92.5%	58.6%	25%	66%
▪ Intraabdominal	45.8%	92%	60%	96.6%	92.9%	83%
▪ NO/NI	n=12	n=21	n=31	n=42	n=43	n=24
Associated collection						
▪ Yes	11.3%	7%	95.2%	11.1%	90%	97.9%
▪ No	88.7%	93%	4.8%	88 n=35.9%	10%	2.1%
▪ NO/NI	n=9	n=14	n=29		n=41	n=24
Previous surgery						
▪ Bariatric	78.6%	87.8%	81.6%	96.6%	100%	95.5%
▪ Oncologic	75%	71.4%	84.2%	72.4%	25.9%	59.1%
▪ NO/NI	n=15	n=22	n=33	n=42	n=44	n=27

EID, endoscopic internal drainage; EVT, endoscopic vacuum therapy; OTSC, over-the-scope clip; NO/NI, no experience/no information
[1] Final percentage may be higher than 100% as many respondents considered more than one option.



▶ **Fig. 2** Respondents' answers to how many patients with anastomotic leaks does your therapeutic endoscopy unit usually treat in 1 year.

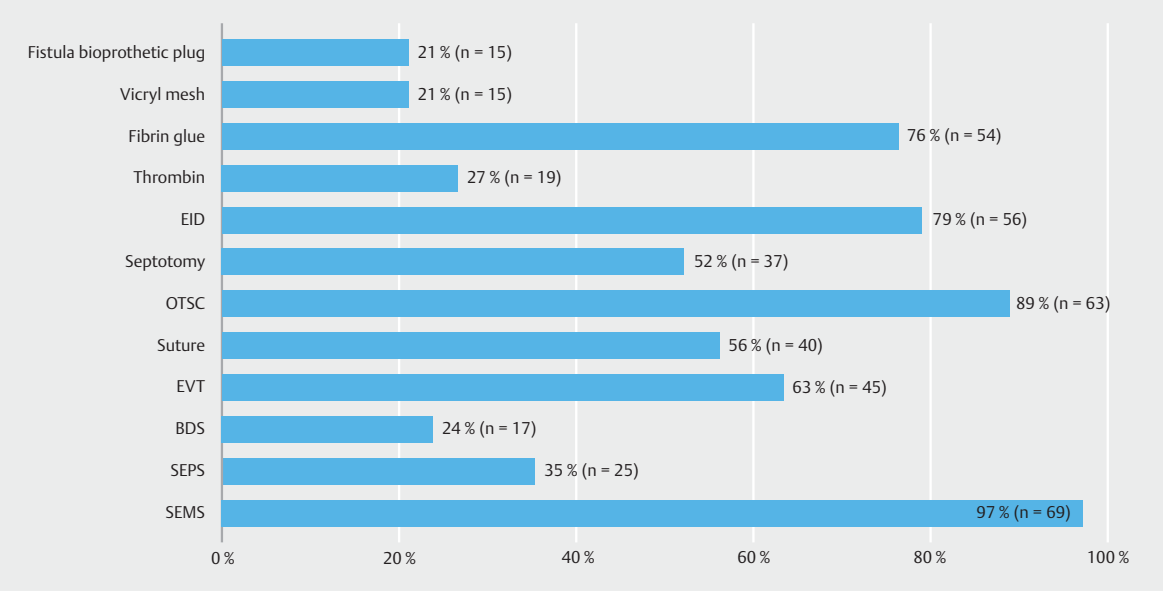
the technique most frequently used (AR: 6.3), followed by EID (AR: 4.7), OTSC (AR: 4.6) and EVT (AR: 4.1) (▶ **Table 1**). AR for each continent, specialty, years of experience and patients treated per year are represented in **Supplementary Table 1.**

Leaks characteristics

Location (94%), size (93%), chronicity (91%) and associated cavity (90%) were the most relevant characteristics considered by respondents to impact choice of treatment. Sixty-five percent of the respondents treat bariatric leaks differently from oncologic surgery leaks. Collections not reachable by endoscopy (69%) and insufficient internal drainage (66%) were the most common indications for need for additional percutaneous/surgical drainage (**Supplementary Table 2**).

Self-expandable stents

Fifty-six percent of the 69 respondents with stent experience reported fully-covered SEMS (FC-SEMS) to be their usual first option, while 42% preferred partially-covered SEMS (PC-



▶ **Fig. 3** Respondents' answers to techniques available in endoscopic departments.

SEMS). The majority (80 %) used techniques to minimize stent migration, with 38 % (n = 21) of them using combined therapies; placement of PC-SEMS is usually the preferred technique (45 %), followed by suture of the stent to the mucosa (33 %) and anchoring the stent with TTS clips (25 %) or OTSC (16 %).

Additional techniques to minimize stent migration are considered in patients with previous stent migration (52 %), if incomplete sealing between stent and esophageal wall (34 %) and when stents placed across jejunal anastomoses (19 %) (▶ **Table 3**).

The most common stent dwell time reported was 4 weeks (49 %) (range: 2 – 10 weeks) (▶ **Table 3**).

Patients with acute leaks (94 %), without associated collections (89 %), with intra-thoracic location (93 %) and less than 3 cm in diameter were considered ideal for stent placement; the majority of respondents considered both previous surgeries (bariatric or oncologic) suitable for stent placement (▶ **Table 2**).

Over-the-scope clips

Sixty-six percent and 37 % of the 64 participants with OTSC experience reported placing them in acute and early leaks, respectively; 17 % reported always performing epithelial ablation/damage prior to OTSC application, with 62 % performing it at least in half of procedures (▶ **Table 3**).

Patients without associated collections (93 %), with intra-abdominal location (92 %), up to 1 cm in diameter (77 %) and resulting from previous bariatric surgery (88 %) were considered ideal patients for OTSC placement (▶ **Table 2**).

Endoscopic vacuum therapy

Seventy-five percent of the 40 respondents with EVT experience reported changing the polyurethane sponge every 3 to 5 days; 72 % applied similar negative pressure for intra-thoracic and intra-abdominal leaks. Most commonly, negative pressures from 70 to 100 mm Hg (41 %) and 100 to 125 mm Hg (~35 %) were used (▶ **Table 4**).

Regarding patients with large cavities but small leak defects, 56 % performed balloon dilation and intracavitary EVT, while 28 % placed the sponge intraluminally; 37 % considered stent-over-sponge if difficulties in directing the vacuum force towards the leak, while 37 % considered it to seal the sponge from the gastrointestinal lumen (▶ **Table 4**).

Patients with chronic leaks (72 %), with associated collections (95 %), with intra-thoracic location (92 %) and with more than 2 cm in diameter were considered ideal for EVT therapy; the majority of respondents considered both previous surgeries suitable for EVT (▶ **Table 2**).

Endoscopic suture

Thirty-six percent of 36 respondents with suturing experience reported always performing epithelial ablation/damage prior to suturing, while 61 % performed it in at least half of procedures (▶ **Table 3**).

Patients with acute leaks (89 %), without associated collections (89 %), up to 2 cm in diameter, with intra-abdominal location (97 %) and resulting from previous bariatric surgery (97 %) were considered ideal for endoscopic suturing (▶ **Table 2**).

▶ **Table 3** Respondents' answers to opinion probing questions regarding primary closure techniques.

Technique	Question	Answer	%
Stents[1]	Self-expandable stent – first option	Fully-covered	56.5 %
		Partially-covered	42 %
		Plastic	1.4 %
	Techniques to minimize stent migration (in patients without previous stent migration)	TTS clips/OTSC	36.2 %
		Suture	33.3 %
		PC-SEMS	44.9 %
		None	20.3 %
	When to use additional techniques to minimize stent migration?	Patients with previous stent migration	52.2 %
		Incomplete sealing between stent and esophageal wall	34.3 %
		Jejunal anastomoses	19.4 %
		Never	11.9 %
		Always	25.4 %
	Common stent dwell time	2 weeks	6 %
		4 weeks	49.3 %
		6 weeks	28.4 %
		≥ 8 weeks	16.4 %
Over-the-scope clips[2]	Time limit between leak and OTSC placement	< 7 days (acute leaks)	65.6 %
		1 to 6 weeks (early leaks)	37.5 %
		6 to 12 weeks (late leaks)	6.3 %
		> 12 weeks (chronic leaks)	9.4 %
		Not relevant	20.3 %
	Epithelial ablation prior to OTSC placement	Always	17 %
		> 90 % of the cases	20.8 %
		75 % to 90 % of the cases	13.2 %
		50 % to 75 % of the cases	11.3 %
		< 50 % of the cases	20.8 %
		Never	17 %
Endoscopic suture[3]	Epithelial ablation prior to suture	Always	36.1 %
		> 90 % of the cases	16.7 %
		75 % to 90 % of the cases	5.6 %
		50 % to 75 % of the cases	2.8 %
		< 50 % of the cases	25 %
		Never	13.9 %

OTSC, over-the-scope clip; PC-SEMS,partially covered self-expandable metal stent; TTS, through-the-scope
[1] Two to four endoscopists reported no experience with stents placement.
[2] Seven to 18 respondents reported no experience with OTSC placement.
[3] Thirty-five respondents reported no experience with endoscopic suture.

Endoscopic septotomy

Fifty-six percent of the 32 respondents with septotomy experience reported that the minimal time interval from surgery should be 4 weeks; 53 % considered that limits of septotomy should be defined on a case-by-case basis. Regarding patients with previous sleeve gastrectomy, 13 % always performed additional balloon dilation, while 81 % only performed it if associated transgastric hyper-pressure. Ninety percent considered the need to perform further septotomy sessions, with presence of residual septum (50 %) and incomplete drainage (30 %) being the main indications; a median of 11 days (6 – 35) between treatments was reported (▶ **Table 4**).

Patients with chronic leaks (100 %), with associated collections (90 %), with intra-abdominal location (93 %) and resulting from previous bariatric surgery (100 %) were considered the ideal patients for endoscopic septotomy; all leak sizes were considered amenable to endoscopic septotomy (▶ **Table 2**).

Endoscopic internal drainage

The majority of respondents with EID experience reported preferring placement of two plastic stents (82 % of 45) and shorter stents (62 % of 21) for drainage; 30 % of 56 respondents referred to never performing necrosectomy. A median of 14 days (1 – 90) between stents exchange was reported. A median of 4.5 days (0 – 42) until oral diet resumption was reported, with 21 % of respondents (n = 9) starting the day of procedure or day after (▶ **Table 4**).

Patients with chronic leaks (65 %), with associated collections (97 %), with intra-abdominal location (83 %), up to 2 cm in diameter and resulting from previous bariatric surgery (95 %) were considered ideal for endoscopic internal drainage (▶ **Table 2**).

Endoscopic failure

Persistent inflammation with clinical sepsis (55 %) was the definition most commonly reported for endoscopic failure, followed by inability to resume oral feeding (42 %), duration of treatment (39 %), chronic reepithelized fistula (37 %), number of endoscopic sessions (30 %) and closure not achieved after 1 month of treatment with one single technique (28 %).

Clinical cases

EVT was the therapeutic option most often chosen (27 %) in post Ivor-Lewis esophagectomy with an intra-thoracic associated collection (clinical case 1), followed by stent placement plus drainage (23 %) and stent placement (14 %) (▶ **Fig. 4a**); EVT and EID were the therapeutic options most often chosen in post-sleeve gastrectomy 2 cm in diameter (clinical case 2) and post RYGB with an intraabdominal associated collection (clinical case 3) (21 % and 20 %, respectively), followed by stent placement plus drainage (17 % and 14 %) (▶ **Fig. 4b**, ▶ **Fig. 4c**); surgery was the therapeutic option most often chosen in post total gastrectomy (clinical case 4) (24 %), followed by stent placement with or without drainage (19 %) (▶ **Fig. 4d**).

Discussion

Therapeutic endoscopy plays a major role in management of UGI anastomotic leaks, offering an effective treatment alternative to repeat surgery [10]. The available endoscopic approaches range from primary to secondary closure techniques, with varying degrees of technical and clinical success and adverse events, generating a lack of consensus regarding the most appropriate endoscopic management [11].

This survey shows that placement of stents, specifically SEMS, is the technique most available and most frequently used in almost every department. Even though OTSC are also well-represented, they are not a common first option, as represented in the clinical cases section. This is probably related to the need for pliable tissue for successful placement, as well as risk of leak recurrence due to OTSC displacement [8, 12]. Other reasons for failed closure may be related to poor integrity of the tissue surrounding the leak as a result of ischemia and inflammation as well as poor/partial placement over often large defects. On the other hand, EID and EVT seem to be increasingly used techniques; this is probably related to the fact that closing leaks with tissue apposition techniques or diversion therapy does not seem to be the ideal treatment strategy in some cases, especially in late or chronic leaks. EVT and EID allow optimal drainage of the cavity, ensuring granulation, utilizing the concept of keeping the leak open [12].

The majority of participants considered that bariatric leaks should be treated differently from oncologic leaks, with location, size, chronicity, and associated cavity being the most relevant leak characteristics. Need for additional percutaneous/surgical drainage is almost always considered when closure techniques (tissue apposition or diversion techniques) are chosen, as internal drainage is not achieved, either by the collection not being reachable (69 %) or sealed (66 %). All of these is reflected in clinical cases choices. EVT and stent placement, with or without percutaneous/surgical drainage, were the therapeutic options most often chosen in patients with previous oncologic surgery, while EVT and EID were the therapeutic options most often chosen in patients with previous bariatric surgery. Interestingly, surgery was the first option in post-total gastrectomy case (24 % of respondents), despite no previous endoscopic treatment failure nor presence of uncontained leak. This might be explained by the almost complete leak of the anastomosis.

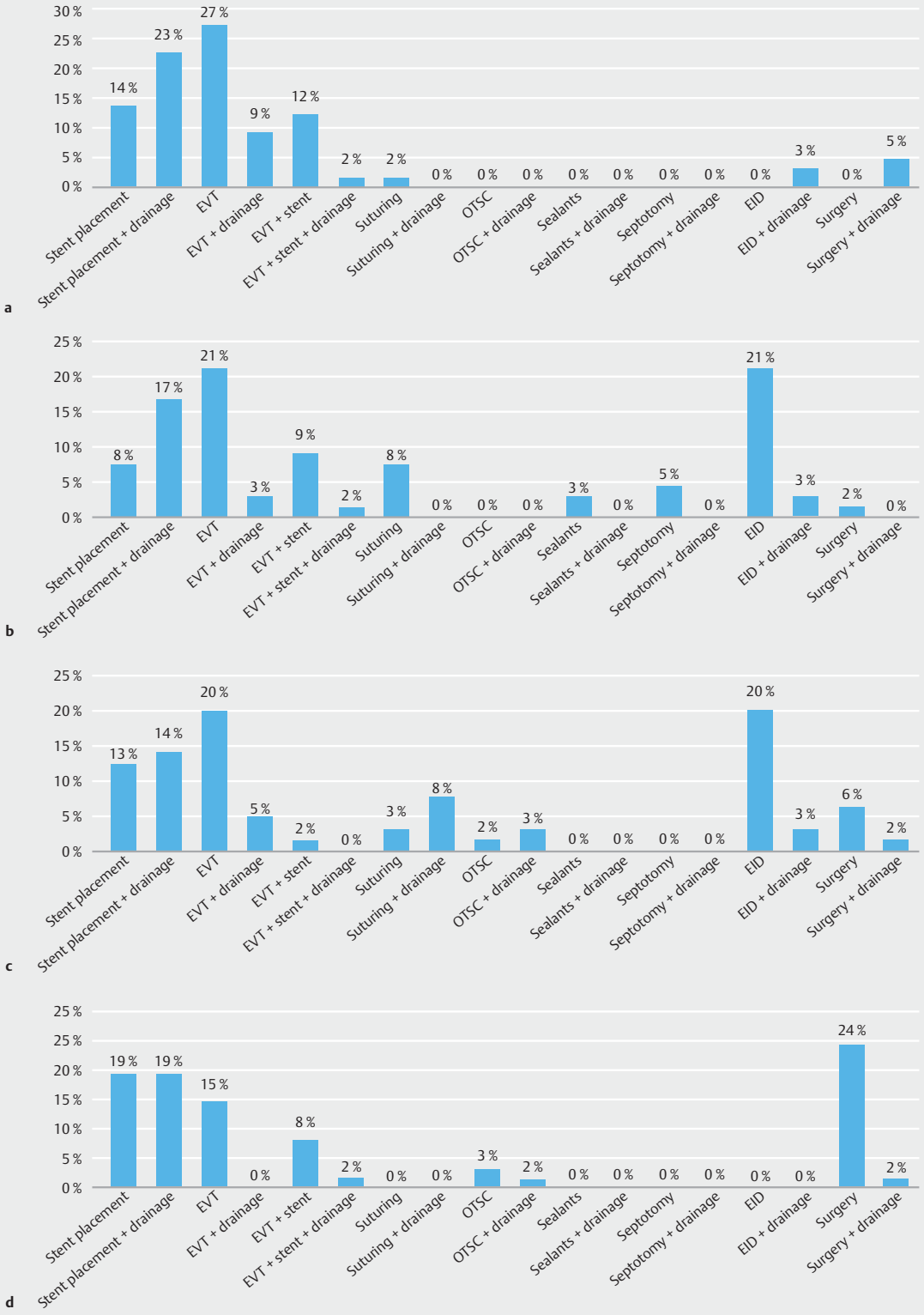
Regarding self-expandable stents, both FC (56 %) and PC-SEMS (42 %) were similarly selected as first options, even in patients without previous stent migration; besides PC-SEMS, 35 % of respondents used other additional techniques to minimize stent migration (in patients without previous stent migration), with endoscopic suturing of FC-SEMS being the preferred technique, as it seems to lower rates of stent migration [13]. Optimal duration of stent dwell is unknown and is likely related to leak classification and size as well as patient-related factors [14]. Stent dwell time ranged from 4 to 6 weeks in 77 % of respondents.

Regarding endoscopic suturing, respondents believed it provides the ability to close larger defects than OSTC (2 cm versus

▶ **Table 4** Respondents' answers to opinion probing questions regarding secondary closure techniques.

Technique	Question	Answer		%
Endoscopic vacuum therapy[1]	Approach in patients with large cavities but small leak defects	Intraluminal EVT		28.2 %
		Balloon dilation and intracavitary EVT		56.4 %
		EVT plus stent		15.4 %
	How often change sponge in EVT	< 3 days		5 %
		Every 3 to 5 days		75 %
		Every 5 to 7 days		15 %
		Case by case		5 %
	Negative pressure for intra-thoracic/intra-abdominal leaks	< 70 mm Hg		16.2 %
		70 mm to 100 mm Hg		40.5 %
		100 mm to 125 mm Hg		35.9 %/35.1 %
		> 125 mm Hg		7.7 %/8.1 %
	When stent-over-sponge	If difficulties in directing vacuum force towards the leak		36.7 %
		To seal the sponge from the gastrointestinal lumen		36.7 %
		Never		43.3 %
Endoscopic septotomy[2]	When perform additional balloon dilation	If associated transgastric hyper-pressure (stricture/twist)		80.6 %
		Always		12.9 %
		Never		6.5 %
	Minimal time interval since surgery	2 weeks		15.6 %
		4 weeks		56.3 %
		> 6 weeks		28.1 %
	Limits of septotomy	Cavity length behind septum		47.1 %
		Case-by-case		52.9 %
	Need for further sessions	Yes		90 %
		No		10 %
	When further situations	Leak clearance		30 %
		Residual septum		50 %
		If cavity is not healing		5 %
		Larger collections		15 %
	Time between sessions	Median, range (n = 20)		11 days (6 – 35)
Endoscopic internal drainage[3]	When to perform necrosectomy	Always		5.4 %
		If presence of necrosis		64.3 %
		Never		30.4 %
	Which stents	Number	Single	11.1 %
			Double	82.2 %
			One or the other	6.7 %
		Length	Shorter	61.9 %
			Longer	33.3 %
			One or the other	4.8 %
	Time between sessions	Median, range (n = 47)		14 days (1 – 90)
	Time until oral diet resumption	Median, range (n = 42)		4.5 days (0 – 42)
		End of treatment		12.5 %

EVT, endoscopic vacuum therapy
[1] Thirty-one to 41 endoscopists reported no experience with EVT.
[2] Seven to 41 endoscopists reported no experience with endoscopic septotomy.
[3] Five to 29 endoscopists reported no experience with endoscopic internal drainage.



▶ **Fig. 4** Respondents' answers to clinical cases section.

1 cm). Both require robust mucosa to hold the sutures when tissue is pulled in apposition [8]; epithelial ablation/damage to the defect edges before OTSC or suturing may increase procedure success and result in a more durable seal, with ~60 % of respondents performing it in more than half of procedures.

Regarding EVT, sponges can be placed intracavitary and/or intraluminal, depending on the defect size and presence of an extraluminal cavity [1]. Even though intraluminal EVT might be easier and safer than intracavitary EVT [12], the majority (56 %) of respondents preferred to perform balloon dilation and intracavitary EVT, as leak closure might be better [12]. One of the great disadvantages of EVT is the need for repeat endoscopic procedures, as the majority of respondents (90 %) changed the polyurethane sponge every 3 to 5 days or 5 to 7 days.

Similar to peripancreatic collections drainage, an organized walled-off collection must be established for endoscopic septotomy to be safe and effective. This was reflected by the majority of respondents (56 %), who only consider it at least 4 weeks after surgery. Management of the downstream stenosis within the sleeve that creates an unfavorable pressure gradient was also considered critical to enhance drainage and correction of one of the underlying physiologic defects that predisposed and perpetuated the leak. Need for repeated septotomy (90 %) was mostly based on presence of residual septum (50 %) or incomplete clearance of the cavity (30 %).

Although EID with transgastric stents appears to be effective, controversies exist regarding optimal technique [15]. Even though necrosectomy may expedite clinical improvement, 30 % of respondents reported never doing it. A median of 4.5 days until oral diet resumption was reported, with 21 % starting it the day of or after procedure, as it is believed oral contents do not enter the perigastric cavity. Regarding stent exchange, while some saw no value in routine stent exchange unless necrosectomy was also performed [15], performance of multiple procedures may allow to evaluate treatment progression to adapt internal drainage, as well as promote healing by inducing trauma in the pseudocavity with exchange of the pigtail stents [16].

As there are no comparative studies between the different endoscopic techniques, it is difficult to establish a therapeutic algorithm in these patients. Determining optimal therapy for such patients requires careful examination of patient clinical status, anastomotic defect, and a review of all available options, local expertise, and previous experience. The approach to UGI anastomotic leaks should always be individualized and multidisciplinary. Considering the majority of respondents' answers, acute and small leaks without associated collections may be considered for stent placement (up to 3 cm), OSTC placement (up to 1 cm) or endoscopic suture (up to 2 cm). In the setting of associated collection, these techniques can still be considered if external drainage is also performed; if not, EVT, EID and endoscopic septotomy should be considered, with EVT and EID being an option in acute and chronic leaks, while endoscopic septotomy should only be performed in leaks with more than 4 weeks' duration. While endoscopic septotomy can be considered for all leak sizes, EID is ideal for leaks up to 2 cm and EVT for leaks larger than 2 cm. Intrathoracic leaks may be better served with stents or EVT, and intraabdominal leaks with OTSC, suturing, septotomy or EID. Leaks resulting from previous bariatric surgery should ideally be treated with OTSC, suture, septotomy or EID, while stents and EVT can be considered for leaks related to bariatric and oncologic surgeries.

Conclusion

In conclusion, this study provides an overview of the techniques used for endoscopic management of UGI leaks and shows that there is wide variation in management of patients with UGI anastomotic leaks, even among the most expert in the field, particularly concerning difficult-to-treat patients, possibly reflecting the poor quality of evidence available at the moment. Limitations of our study include a survey response rate of only 44 % which may subject the study to bias, making interpretation of results more challenging. However, this study presents information which to date has not been available, with inclusion of experts from various countries, different opinion questions regarding each technique, and different clinical scenarios. Even though there is no consensus on the definition of endoscopic failure, persistent inflammation with clinical sepsis and impossibility to resume oral feeding should be strongly considered. Future prospective studies should address these issues, and for which transnational collaborations are urgently needed, so that we move from an expert- to an evidence- and personalization-based care in endoscopic treatment of upper anastomotic leaks.

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Competing interests

Alessandro Repici is a consultant for Boston Scientific. Jacques Devière is a consultant for Boston Scientific and Olympus. Jeanin E. van Hooft is a consultant for Medtronic and Boston Scientific and has a research grant from Cook Medical and Abbott. Manoel Galvao Neto is a consultant for Olympus, Ethicon Endosurgery, Apollo Endosurgery, Meditronics, Fractyl Laboratories, GI Dynamics, GI Windows, Alacer Biomedica, CMS/Sci-Tech, M.I.Tech and NitiNotes. Pierre Eisendrath received a research grant from Endo Tools Therapeutics. Vivek Kumbhari is a consultant for Apollo Endosurgery, Boston Scientific, Medtronic, Pentax Medial, ReShape Lifesciences and receives research support from ERBE and Apollo Endosurgery. Mouen A. Khashab is a consultant for Boston Scientific, Olympus and Medtronic. None of the authors disclosed personal conflicts of interest or financial relationships relevant to this publication.

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E) Retrospective multicenter study on endoscopic treatment of upper GI postsurgical leaks

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ORIGINAL ARTICLE: Clinical Endoscopy

Retrospective multicenter study on endoscopic treatment of upper GI postsurgical leaks

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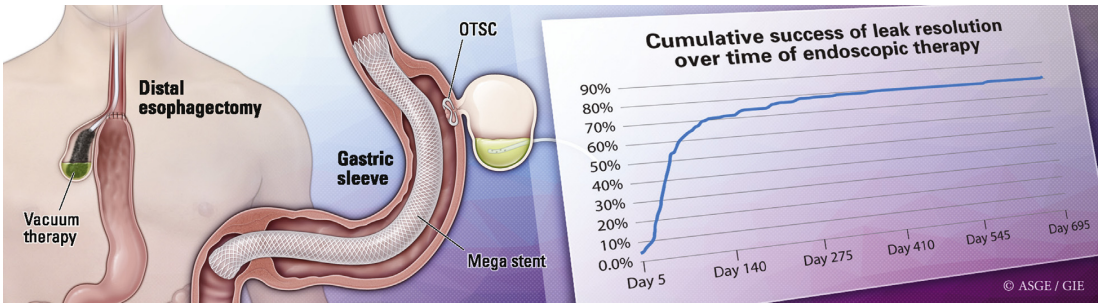
GRAPHICAL ABSTRACT



Background and Aims: Therapeutic endoscopy plays a critical role in the management of upper GI (UGI) postsurgical leaks. Data are scarce regarding clinical success and safety. Our aim was to evaluate the effectiveness of endoscopic therapy for UGI postsurgical leaks and associated adverse events (AEs) and to identify factors associated with successful endoscopic therapy and AE occurrence.

Methods: This was a retrospective, multicenter, international study of all patients who underwent endoscopic therapy for UGI postsurgical leaks between 2014 and 2019.

Results: Two hundred six patients were included. Index surgery most often performed was sleeve gastrectomy (39.3%), followed by gastrectomy (23.8%) and esophagectomy (22.8%). The median time between index surgery and commencement of endoscopic therapy was 16 days. Endoscopic closure was achieved in 80.1% of patients after a median follow-up of 52 days (interquartile range, 33-81.3). Seven hundred seventy-five therapeutic endoscopies were performed. Multimodal therapy was needed in 40.8% of patients. The cumulative success of leak resolution reached a plateau between the third and fourth techniques (approximately 70%-80%); this was achieved after 125 days of endoscopic therapy. Smaller leak initial diameters, hospitalization in a general ward, hemodynamic stability, absence of respiratory failure, previous gastrectomy, fewer numbers of therapeutic endoscopies performed, shorter length of stay, and shorter times to leak closure were associated with better outcomes. Overall, 102 endoscopic therapy–related AEs occurred in 81 patients (39.3%), with most managed conservatively or endoscopically. Leak-related mortality rate was 12.4%.

Conclusions: Multimodal therapeutic endoscopy, despite being time-consuming and requiring multiple procedures, allows leak closure in a significant proportion of patients with a low rate of severe AEs. (Gastrointest Endosc 2021;93:1283-99.)

(footnotes appear on last page of article)

Upper GI (UGI) postsurgical leaks are a life-threatening condition with high mortality rates ranging from 12% to 50%.[1-3] The frequency of UGI postsurgical leaks has been estimated at 8% to 26% after distal esophagectomy,[4] 3% to 12% after total gastrectomy,[5] .7% to 5% after Roux-en-Y gastric bypass (RYGB), and 1% to 2% after sleeve gastrectomy.[6,7]

Early diagnosis has been reported to improve survival of such leaks,[8] although their management still remains controversial.[9,10] In fact, several modalities have been used in managing postsurgical leaks, with surgical treatment apparently associated with higher morbidity and mortality than endoscopic therapy. Therefore, the latter is often attempted first to avoid additional surgical morbidity. However, there is a wide diversity of endoscopic options, including stent placement, endoscopic vacuum therapy (EVT), endoscopic internal drainage (EID), through-the-scope and over-the-scope clips (OTSCs), suturing, septotomy with or without balloon dilation, and tissue sealants. Theoretically, all these options can be used alone or with a multimodality approach.[11]

Currently, no consensus exists on the preferred endoscopic modality. Information on the clinical effectiveness of each modality is limited because of the diversity of therapeutic modalities but also by nonuniformity of leak definition, heterogeneity of leak characteristics, small sample sizes, or analysis of treatment of several transmural defects together. Therefore, in this study we aimed to assess the effectiveness of endoscopic therapy for UGI postsurgical leaks and associated adverse events (AEs) and to identify factors associated with successful endoscopic therapy and AE occurrence.

METHODS

We conducted a multicenter, international, retrospective study of all patients who underwent endoscopic therapy for UGI postsurgical leaks between January 2014 and August 2019. Data were collected from 10 tertiary care centers, all with experience and expertise in the endoscopic management of surgery AEs. Leaks were defined as a dehiscence of the surgical site. Their diagnosis was made by the presence of contrast extravasation on fluoroscopy, CT, and/or dynamic oral contrast radiography or by identification of a defect at the surgical site in the upper endoscopy with leakage of contrast agent identified at fluoroscopy. Patients with incomplete follow-up, with ongoing treatment, or whose endoscopic therapy was started before referral to the study institution were excluded.

We reviewed electronic medical records of included participants, retrieving information on their gender, age, index surgery, need for additional surgeries, associated collections, additional percutaneous/surgical drainage, place of hospitalization (ie, general ward or intensive care unit), associated shock, and leak characteristics. All endoscopic therapeutic sessions were analyzed, with information retrieved on the specifics of each procedure, therapeutic modality used at each procedure (self-expandable metal stent [SEMS], OTSC, EVT, EID, septotomy, suture, biodegradable stents, tissue sealant placement), total number of therapeutic sessions, need for multimodal treatment, total number of different therapeutic modalities, AE occurrence and its characterization, technical and clinical success, leak resolution, global leak closure, total number of days hospitalized, patient final status, and leak-related mortality. All dates of surgeries and endoscopic procedures were recorded.

No algorithmic protocol was followed regarding endoscopic management. Treatment was tailored to clinical and morphologic presentation, in addition to institutional availability of devices and accessories. Similarly, each center used its own clinical decision-making in assessing the need for repeat endoscopic therapy. Regarding endoscopic technique principles, stent placement diverts enteric contents past the leak while maintaining GI continuity. Clips and sutures are used to close luminal defects. EVT works by intraluminal and intracavitary apposition of wound edges, providing internal drainage by placement of a polyurethane sponge into the defect cavity and transnasal application of an external vacuum. EID consists of the temporary placement of a trans-GI plastic stent(s), similarly to peripancreatic collections, to adapt internal drainage and to promote healing by inducing trauma in the pseudocavity with the exchange of the pigtail stents. Endoscopic septotomy facilitates internal drainage of refractory leaks by incision and enlargement of the fistulous tract to equalize the pressures between the gastric lumen and perigastric collection. Sealants are used to obliterate the leak, by injection in the leak or in the submucosal tract. All of these techniques may require multiple endoscopic procedures.

Technical success was defined as successful completion of the endoscopic procedure as planned. Clinical success was defined as closure of the leak (lack of extraluminal air or extravasation of contrast on fluoroscopy, CT, and/or dynamic oral contrast radiography); in patients who received a SEMS, clinical success could only be assessed after stent removal. Because some oncologic patients—because of a higher performance status, more advanced cancer staging, or residual disease—did not have their stents removed, we defined leak resolution as clinical success or having stents left in place without contrast extravasation. The definition of clinical success applies to endoscopic, radiologic, or surgical closure. Cessation of percutaneous/surgical drain output was not considered as an outcome. Multimodal treatment was considered when different endoscopic therapies were used. However, it was not considered in patients who had more than 1

TABLE 1. Baseline patient and leak characteristics

Characteristic	Value
Hospital	
Centro Hospitalar Universitário São João, Porto, Portugal	33 (16)
Cairo University Hospital, Cairo, Egypt	30 (14.6)
Hospital de Vila Nova de Gaia, Porto, Portugal	28 (13.6)
Virginia Mason Medical Center, Seattle, Washington, USA	24 (11.7)
Humanitas Research Hospital, Milan, Italy	21 (10.2)
Swedish Cancer Institute, Seattle, Washington,USA	21 (10.2)
Medical University Bialystok, Bialystok, Poland	16 (7.8)
Hospital Geral de Santo António, Porto, Portugal	15 (7.3)
Johns Hopkins Medical Institution, Baltimore, Maryland, USA	12 (5.8)
University of Michigan, Ann Arbor, Michigan, USA	6 (2.9)
Male gender	105 (51)
Age at beginning of treatment, y, mean ± standard deviation	53.8 ± 14.5
Previous surgery	
Esophagectomy*	47 (22.8)
Gastrectomy†	49 (23.8)
Sleeve gastrectomy‡	81 (39.3)
Gastric bypass§	23 (11.2)
Other¶	6 (2.9)
Associated collection‖	133 (64.6)
Collection size, mm	61 (41.75-99.5)
Need for additional surgery	86 (41.7)
Additional percutaneous/surgical drainagell	144 (69.9)
Hospitalization	
General ward	107 (51.9)
Intermediate care	30 (14.6)
Intensive care	56 (27.2)
No hospitalization	11 (5.3)
Unknown	2 (1)
Shock	44 (21.4)
Leukocytes at beginning of therapy, $\times 10^9$	11.1 (8.5-16.2)
C-reactive protein at beginning of therapy, mg/L	148.7 (65.5-277.5)
Time between index surgery and beginning of endoscopic therapy, days	16 (9-30)
Leak chronicity	
Acute (<7 days)	23 (11.2)
Early (1-6 wk)	145 (70.4)
Late (7-12 wk)	19 (9.2)
Chronic (>12 wk)	15 (7.3)
Unknown	4 (1.9)
Leak location	
Esophagogastric anastomosis	54 (26.2)
Esophagojejunal anastomosis	45 (21.8)
Gastrojejunal anastomosis	5 (2.4)
Distal esophageal anastomosis	5 (2.4)
Sleeve, staple line	3 (1.5)

(*continued on the next page*)

TABLE 1. Continued

Characteristic	Value
Sleeve, upper portion of remnant tube gastric	63 (30.6)
Sleeve, lower portion of remnant tube gastric	9 (4.4)
RYGB, gastric pouch	15 (7.3)
RYGB, gastrojejunal anastomosis	7 (3.4)
Leak initial size, mm	10 (5.3-20)
<10 mm	67 (32.57)
10-19 mm	56 (27.2)
20-39 mm	40 (19.4)
≥40 mm	5 (2.4)
Unknown	38 (18.4)
Number of hospitalizations	1 (1-2)
Total hospitalization days	26 (11-51)
Follow-up, days	303 (87.5-775)

Values are n (%) or median (interquartile range) unless otherwise defined.
RYGB, Roux-en-Y gastric bypass.
*This group includes 31 Ivor-Lewis esophagectomies, 14 Mckeown esophagectomies, and 2 Akiyama esophagectomies.
†This group includes 45 total gastrectomies and 4 distal gastrectomies.
‡This group includes 80 gastric sleeves and 1 sleeve gastroplasty/stapled partitioning.
§This group includes 22 gastric bypasses and 1 minigastric bypass.
¶Other: Nissen fundoplication (n = 1), epiphrenic diverticulum excision (n = 4), surgery for Boerhave (n = 1).
‖No information for 5 patients.

SEMS placed at different endoscopic attempts if SEMS placement was the only therapy used; it was also not considered when additional percutaneous or surgical drainage was performed or when endoscopic procedures were performed to manage AEs. AEs were defined as any unplanned event related to the procedure that required the patient to be medicated pharmacologically, admitted to the hospital, required to stay in the hospital longer than expected, or required to undergo other unplanned interventions; because of a lack of information on the length of hospitalization related to each AE, AEs were classified according to their management (conservative, need for repeat endoscopy, surgery, or death). Ten cases from 2 centers were previously published as original articles or case reports.[12-15] This study was approved by the institutional review board of each participating center.

Statistical analysis

Categorical variables were described using absolute and relative frequencies, whereas continuous variables were described using means and standard deviations or medians and interquartile ranges (IQRs). We built conditional logistic models to assess the association between each outcome variable (such as clinical success, leak resolution, AE occurrence) and each independent variable, clustering observations by hospital and adjusting for the time between surgery and endoscopy. Exponentials of regression coefficients were interpreted as odds ratio (OR). To further assess whether the number of performed therapeutic endoscopies were associated with success of the first technique, we built a classification tree based on recursive partitioning to allow the nonsupervised identification of different endoscopic success classes based on the number of performed endoscopic procedures.

Significance level was defined at $P < .05$. Statistical analysis was performed using software R (version 3.5.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients and leak characteristics

Demographics and leak characteristics of the 206 patients who underwent endoscopic therapy for postsurgical leaks are summarized in Table 1. Mean patient age at the beginning of endoscopic therapy was 53.8 ± 14.5 years, and 51% were men. Most leaks were related to sleeve gastrectomy (39.3%; n = 81), followed by gastrectomy (23.8%; n = 49), esophagectomy (22.8%; n = 47), and RYGB (11.2%; n = 23).

Sixty-five percent of patients (n = 133) had associated collections to the leak. Forty-two percent of patients (n = 86) underwent additional surgery for washout, drainage, attempts of leak repair, or jejunostomy tube placement; 69.9% of patients (n = 144) had a surgical or percutaneous drain placed. Forty-two percent of patients (n = 86) were hospitalized in step-up or intensive care units.

The median time between index surgery and commencement of endoscopic therapy was 16 days (IQR, 9-30) with

TABLE 2. Characterization of number of therapeutic endoscopies, different endoscopic therapies, leak outcome, adverse event occurrence, and patient and leak mortality according to previous surgery performed

	Global (n = 206)	Esophagectomy* (n = 47)	Gastrectomy† (n = 49)	Roux-en-Y gastric bypass/minigastric bypass‡ (n = 23)	Sleeve gastrectomy/ sleeve gastroplasty§ (n = 81)	Other¶ (n = 6)
No. of therapeutic endoscopies	3 (2-4)	3 (2-5)	2 (1.5-3)	3 (2-4)	4 (2-5)	2 (2-5.5)
Multimodal treatment	84 (40.8)	17 (36.2)	5 (10.2)	11 (47.8)	50 (61.7)	1 (16.7)
No. of different endoscopic treatments						
1	122 (59.2)	30 (63.8)	44 (89.8)	12 (52.2)	31 (38.3)	5 (83)
2	58 (28.2)	9 (19.1)	4 (8.2)	9 (39.1)	36 (44.4)	0 (0)
3	18 (8.7)	3 (6.4)	1 (2)	2 (8.7)	11 (13.6)	1 (16.7)
4	6 (2.9)	4 (8.5)	0 (0)	0 (0)	2 (2.5)	0 (0)
5	2 (1)	1 (2.1)	0 (0)	0 (0)	1 (1.2)	0 (0)
Technical success	187 (90.8)	40 (85.1)	46 (93.9)	20 (87)	76 (93.8)	5 (83.3)
Leak outcome						
Endoscopic closure	165 (80.1)	38 (80.9)	38 (77.6)	15 (65.2)	70 (86.4)	4 (66.7)
Stent left in place (no leak)	7 (3.4)	0 (0)	6 (12.2)	0 (0)	1 (1.2)	0 (0)
Radiologic closure	1 (.5)	0 (0)	0 (0)	0 (0)	1 (1.2)	0 (0)
Spontaneous closure	1 (.5)	0 (0)	0 (0)	1 (4.3)	0 (0)	0 (0)
Surgical closure	12 (5.8)	0 (0)	0 (0)	3 (13)	8 (9.9)	1 (16.7)
Surgery without leak closure	2 (1)	0 (0)	1 (2)	1 (4.3)	0 (0)	0 (0)
Closure not achieved	18 (8.7)	9 (19.1)	4 (8.2)	3 (13)	1 (1.2)	1 (16.7)
Time until endoscopic leak closure, days	52 (33-81.3)	45.5 (29.7-74.2)	49 (36.7-63)	74 (42-103.3)	58 (32.5-111.7)	73.5 (49-110)
Global adverse events	81 (39.3)	20 (42.6)	10 (20.4)	9 (39.1)	39 (48.1)	3 (50)
No. of adverse events						
0	125 (60.7)	27 (57.4)	39 (79.6)	14 (60.9)	42 (51.9)	3 (50)
1	60 (29.1)	15 (31.9)	9 (18.4)	6 (26.1)	29 (35.8)	1 (16.7)
2	21 (10.2)	5 (10.6)	1 (2)	3 (13)	10 (12.3)	2 (33.3)
Death during follow-up	53 (26.6)	23 (48.9)	23 (47.9)	2 (9.1)	3 (3.9)	2 (33.3)
Leak-related mortality	25 (12.4)	9 (19.1)	10 (20.4)	2 (8.7)	2 (2.6)	2 (33.3)

Values are median (interquartile range) or n (%).
*This group includes 31 Ivor-Lewis esophagectomies, 14 Mckeown esophagectomies, and 2 Akiyama esophagectomies.
†This group includes 22 gastric bypasses and 1 minigastric bypass.
‡This group includes 45 total gastrectomies and 4 distal gastrectomies.
§This group includes 80 gastric sleeves and 1 sleeve gastroplasty/stapled partitioning.
¶Other: Nissen fundoplication (n = 1), epiphrenic diverticulum excision (n = 4), surgery for Boerhave (n = 1).

most leaks being acute (11.2%) or early (70.4%). The median leak initial diameter was 10 mm (IQR, 5.3-20), with most leaks of known size less than 20 mm in diameter (73%). Median hospitalization and follow-up periods were 26 days (IQR, 11-51) and 303 days (IQR, 87.5-775), respectively.

Procedure data

Seven hundred seventy-five therapeutic endoscopies were performed, with a median of 3 endoscopies per patient (IQR, 2-4) (Table 2). Multimodal therapy was needed in 40.8% of patients (n = 84), with patients with previous bariatric surgery needing it more often ($P < .001$). Only patients with previous esophagectomy and sleeve gastrectomy needed to undergo a fourth and fifth different technique.

SEMSs (68.4% and 28.2%), EID (9.2% and 7.3%), OTSCs (6.8% and 5.3%), and EVT (4.9% and 2.4%) were the most-used options (in that order) both for first and second endoscopic techniques, with SEMS placement maintaining this preference for third (11.2%) and fourth (2.4%) endoscopic techniques (Supplementary Table 1, available online at www.giejournal.org). Characterization of endoscopic techniques used is summarized in Tables 3 and 4. AE characterization and their management are summarized in Table 5.

Self-expandable metal stents

Two hundred forty-nine procedures for SEMS placement were performed in 178 patients over 3 different

TABLE 3. Characterization of endoscopic techniques regarding primary closure options

Technique	Question	Answer		No. of cases (%)
Self-expandable metal stents (249 stents placed in 178 patients)	Clinical success after stent technique (n = 249)	Leak closure		103 (41.4)
		Leak persistence		138 (55.4)
		Stent left in place without leak persistence		8 (3.2)
	SEMS placement endoscopic attempts (178 patients)*	One attempt		107 (60.1)
		Two attempts		61 (34.3)
		Three attempts		10 (5.6)
		Patients with previous stents placed (n = 71)	Stent placed after previous stent removal	54 (76)
			Stent in stent (previous stent still in place)	17 (24)
	No. of stents placed simultaneously (n = 249)	Only 1 stent*		243 (97.6)
		Two overlapping stents*		6 (2.4)
	Stent manufacturer (n = 249)	MI Tech	Hanarostent (EPW [n = 29] + NES [n = 3])	32 (12.8)
			Gastroseal	7 (2.7)
			Diabolo-shape	1 (.4)
		Boston Scientific	Wallflex (n = 83) or Ultraflex (n = 6)	89 (35.7)
		Taewoong	Megastent	40 (16.1)
			Niti-S-Beta (n = 14) or unknown (n = 3)	17 (6.8)
		Merit	Endomaxx (n = 23) or Alimaxx (n = 3)	26 (10.4)
		ELLA-CS	SX-ELLA Stent Danis	2 (.8)
		No information		5 (2)
	Stent cover (n = 249)	Fully covered		174 (69.9)
		Partially covered		71 (28.5)
		Fully and partially covered		2 (.8)
		Unknown		2 (.8)
	Stent body diameter (n = 249)	<17 mm		3 (1.2)
		18-21 mm		78 (32.4)
		22-24 mm		110 (45.6)
		25-28 mm		50 (20.1)
		Unknown		3.2 (8)
	Stent extension (n = 249)	Mean ± standard deviation, mm		147.15 ± 43.58
	Techniques to minimize stent migration (n = 249)	None		194 (77.9)
		Through-the-scope clips		23 (9.2)
		OTSC		19 (7.6)
		Suture		13 (5.2)
	Stent repositioned (n = 249)			26 (10.4)
	Techniques needed for stent removal (n = 249)	No additional technique needed		188 (75.5)
		Stent-in-stent		26 (10.4)

(*continued on the next page*)

TABLE 3. Continued

Technique	Question	Answer	No. of cases (%)
		APC	11 (4.4)
		Stent-in-stent plus APC	3 (1.2)
		Surgical removal	1 (.4)
		Removal not tried	20 (8)
	Stent dwell time (n = 249)	Median days (interquartile range)	35 (21-50)
		≤2 wk	45 (18.1)
		2-4 wk	61 (24.5)
		4-6 wk	56 (22.5)
		6-8 wk	38 (15.3)
		8-10 wk	19 (7.6)
		>10 wk	30 (12)
	No. of therapeutic endoscopies (n = 249)	Median (min-max)	2 (1-7)
		1	20 (8)
		2	174 (69.9)
		3	40 (16.1)
		≥4	15 (6)
OTSC (n = 39)	Clinical success after OTSC technique	Leak closure	26 (66.7)
		Leak improvement	8 (20.5)
		Leak persistence	5 (12.8)
	No. of clips placed in the same procedure	1	36 (92.3)
		2	2 (5.1)
		3	1 (2.6)
	Epithelial ablation before OTSC placement	APC	21 (53.8)
		No	18 (46.2)
	OTSC placement technique	Aspiration	26 (66.7)
		Anchor device	5 (12.8)
		Twin grasper	7 (17.9)
		Unknown	1 (2.6)
	OTSC diameter	12 mm	37 (94.9)
		14 mm	1 (2.6)
		Unknown	1 (2.6)
Suture (n = 13)	Clinical success after suture technique	Leak closure	5 (38.5)
		Leak improvement	5 (38.5)
		Leak persistence	3 (23.1)
	Epithelial ablation before suture	APC	7 (53.8)
		No	6 (46.2)
Tissue sealants (n = 9)	Clinical success after sealant technique	Leak closure	2 (22.2)
		Leak persistence	7 (77.8)
	Which tissue sealant	Thrombin	3 (33.3)
		Fibrin glue	3 (33.3)

(*continued on the next page*)

TABLE 3. Continued

Technique	Question	Answer	No. of cases (%)
		Histoacryl	2 (22.2)
		Platelet rich plasma	1 (11.1)
	Placement of mesh		5 (55.6)
	Location of sealant injection	Leak/fistula tract	8 (88.9)
		Submucosal injection	1 (11.1)
	No. of procedures	1	6 (66.7)
		2	3 (33.3)
	Time between procedures	Median, days (min-max)	4 (1-10)
Biodegradable stent (n = 8)	Clinical success after biodegradable stent placement	Leak closure	3 (37.5)
		Leak improvement	4 (50)
		Leak persistence	1 (12.5)
	Biodegradable stent covering	Fully covered	2 (25)
		Partially covered	6 (75)
	Biodegradable stent body diameter	23 mm	2 (25)
		25 mm	6 (75)
	Biodegradable stent extension	80 mm	4 (50)
		100 mm	3 (37.5)
		135 mm	1 (12.5)
	Techniques to minimize stent migration	Clip	4 (50)
		None	4 (50)

APC, Argon plasma coagulation; *OTSC,* over-the-scope clip.
*Percentages calculated in function of the number of patients.

endoscopic attempts. In 6 of these procedures, 2 overlapping stents were placed. Thirty-four percent of patients (n = 61) underwent 2 different endoscopic attempts for SEMS placement and 5.6% (n = 10) underwent 3 different endoscopic attempts (Tables 3 and 4). Fully covered SEMSs (FC-SEMSs) and partially covered SEMSs were used in 69.9% (n = 174) and 28.5% (n = 71) of procedures, respectively. The median stent dwell time was 35 days (IQR, 21-50), with almost half (47%) placing them for 2 to 6 weeks. Sixteen percent of patients needed an additional technique for stent removal. Two perforations and 3 fistulas occurred in 2% of procedures.

In addition to placement of partially covered SEMSs, additional techniques to minimize stent migration were used in 20% of procedures (n = 55); however, migration still occurred in 12 procedures (21.7%). In the univariable regression model (Supplementary Table 2, available online at www.giejournal.org), SEMS migration was lower when larger diameter SEMSs were used (OR, .90; 95% confidence interval [CI], .82-1.00; $P = .049$) and higher when FC-SEMSs were used (OR, 2.44; 95% CI, 1.13-5.31; $P = .024$) or through-the-scope clips were used as an additional technique to minimize migration (OR, 2.59, 95% CI, 1.05-6.35; $P = .038$).

Effectiveness of endoscopic therapy and AEs

Technical success was achieved in 90.8% of patients (n = 187) (Table 2). Individual endoscopic leak closure was 41.4% for SEMSs (44.6% if we consider leak resolution), 66.7% for OTSCs, 38.5% for suture, 22.2% for tissue sealants, 37.5% for biodegradable stents, 23.8% for EVT, 52.6% for EID, and 66.7% for endoscopic septotomy (Tables 3 and 4). Overall endoscopic clinical success was achieved in 80.1% of patients (n = 161) and was lower in patients who had undergone RYGB (65.2%), although without statistical significance ($P = .159$). The median time to leak closure was 52 days (IQR, 33-81.3). In 7 patients (3.4%), a stent was left in place permanently, without evidence of leak persistence during follow-up (6 were oncologic patients with advanced disease and residual margins and 1 patient had a sleeve gastrectomy and died before stent removal).

When considering endoscopic leak resolution, success increased to 83.5%. Despite similarities in the percentage of leak resolution for each technique (43.7% [90/206] for the first endoscopic technique, 45.3% [48/106] for the second technique, 37.8% [17/45] for the third technique, and 59.1% [13/22] for the fourth technique), cumulative success of endoscopic leak resolution reached a plateau

TABLE 4. Characterization of endoscopic techniques regarding secondary closure options

Technique	Question	Answer		No. of cases (%)
Endoscopic vacuum therapy (n = 21)	Clinical success after endoscopic vacuum therapy	Leak closure		5 (23.8)
		Leak improvement		11 (52.4)
		Leak persistence		5 (23.8)
	Sponge initial location	Intracavitary		9 (42.9)
		Intraluminal		12 (57.1)
	Placement technique	Overtube (endosponge [n = 7], esosponge [n = 1])		8 (38.1)
		Over-the-wire		2 (9.5)
		Dragged with endoscope		11 (52.4)
	Time between sponge exchanges	Median, days (min-max)		4 (3-7)
	Negative pressure	100-125 mm Hg		11 (52.4)
		125 mm Hg		6 (28.6)
		175 mm Hg		4 (19)
	Stent-over-sponge	Performed		4 (19)
		Clinical success after stent-over-sponge	Leak improvement	3 (75)
			Leak persistence	1 (25)
		No. of days with stent-over-sponge	6	1 (25)
			15	1 (25)
			17	2 (50)
		Only 1 stent		2 (50)
		Stent-over-sponge changed every 4 days		2 (50)
	No. of procedures	Median (min-max)		4 (1-19)
Endoscopic internal drainage (n = 38)	Clinical success after endoscopic internal drainage	Leak closure		20 (52.6)
		Leak improvement		8 (21.1)
		Leak persistence		10 (26.3)
	No. of plastic stents placed simultaneously	1		15 (39.5)
		2		17 (44.7)
		3		2 (5.3)
		4		4 (10.5)
	Stent length	Short		37 (97.4)
		Long		1 (2.6)
	Stent format	Double-pigtail		37 (97.4)
		Straight		1 (2.6)
	Associated necrosectomy			3 (7.9)
	Additional flushing catheter			15 (39.5)
	Stents dwell time	Median, days (IQR)		30 (15.7-53.2)
	Time until oral resumption	Median, days (IQR)		3 (2-21)
		Oral diet not started		7 (18.4)
	No. of procedures	Median (min-max)		1 (1-4)
Endoscopic septotomy (n = 9)	Clinical success after endoscopic septotomy	Leak closure		6 (66.7)
		Leak improvement		2 (22.2)
		Leak persistence		1 (11.1)
	Septotomy limits	End of cavity		7 (77.8)

(*continued on the next page*)

TABLE 4. Continued

Technique	Question	Answer		No. of cases (%)
		Partial		1 (11.1)
		Unknown		1 (11.1)
	Additional balloon dilation	Yes		8 (88.9)
		Balloon diameter	18 mm	1 (12.5)
			30 mm	3 (37.5)
			35 mm	2 (25)
			Unknown	2 (25)
	Need for further sessions	Yes		3 (33.3)
		Reason	Residual septum	2 (66.7)
			Incomplete drainage	1 (33.3)
	No. of procedures	Median (min-max)		1 (1-7)
	Time between procedures	Median, days (min-max)		7 (6-14)
	Time until oral resumption	Median, days (IQR)		2 (1-75)
		Oral diet not started		2 (22.2)

IQR, Interquartile range.

between the third and fourth techniques (around 70%-80%); this was achieved after 125 days of endoscopic therapy (Fig. 1). Two percent of patients (n = 4) still achieved leak resolution with the fifth technique, with the only patient who underwent 6 techniques not achieving leak resolution. Although patients who had undergone previous sleeve surgery had an initial lower leak resolution with the first technique, similar endoscopic leak resolutions were achieved at the end of endoscopic treatment. Regarding the number of endoscopic procedures, higher chances of leak resolution were achieved in patients who had undergone between 2 and 9 procedures (Fig. 2). Leak resolution within each center is presented in Supplementary Figure 1 (available online at www.giejournal.org).

Fourteen patients (6.8%) underwent surgery after endoscopic treatment failure, with surgical leak closure possible in 12 of them. One patient underwent radiologic leak closure, and 1 patient had spontaneous closure. Global leak closure was observed in 186 patients (90.3%).

Overall, 102 endoscopic therapy–related AEs occurred in 81 patients (39.3%; 1 AE, n = 60; 2 AEs, n = 21) (Tables 2 and 5); SEMSs were responsible for 89 of 102 AEs observed (including patients who had 2 AEs), with only 13 of the remaining AEs associated with other endoscopic techniques. Most AEs were managed conservatively or endoscopically, with 6 AEs requiring surgery (n = 5) or leading to death (n = 2, 1 of which underwent surgery). During follow-up, 26.6% of patients (n = 53) died, most of whom were oncologic patients; leak-related mortality was 12.4% (n = 25).

Predictive factors for clinical success, leak resolution, and AEs

Logistic regression analyses were performed to evaluate predictive factors for clinical success and leak resolution at the first endoscopic technique, at the end of 3 endoscopic techniques, and at the end of treatment (Table 6). Smaller leak initial diameters were found to be associated with clinical success at the first endoscopic technique (OR, .96; 95% CI, .92-1.00; $P = .047$), and hospitalization in a general ward was associated with clinical success at the end of 3 endoscopic techniques (OR, 2.11; 95% CI, 1.00-4.44; $P = .049$) and at the end of treatment (OR, 4.01; 95% CI, 1.69-9.52; $P = .002$). Hemodynamic stability was associated with clinical success at the end of treatment (OR, 4.25; 95% CI, 1.89-9.52; $P < .001$), and absence of respiratory failure was associated with leak resolution at the end of 3 endoscopic techniques (OR, 3.02; 95% CI, 1.33-6.85; $P = .008$) and clinical success at the end of treatment (OR, 6.71; 95% CI, 2.67-16.95; $P < .001$). Previous gastrectomy predicted leak resolution at the first endoscopic technique (OR, 3.27; 95% CI, 1.38-7.74; $P = .007$) and at the end of 3 endoscopic techniques (OR, 3.82; 95% CI, 1.31-11.15; $P = .014$). Fewer numbers of therapeutic endoscopies performed, shorter length of stay, and shorter times to leak closure were associated with clinical success and leak resolution at all time points. There was a trend for an earlier start to treatment being associated with clinical success (OR, .99; 95% CI, .98-1.00; $P = .082$) and leak resolution (OR, .99; 95% CI, .98-1.000; $P = .069$) at the first endoscopic technique, with previous RYGB associated with lower rates of

TABLE 5. Adverse events characterization and severity

		Adverse event management			
	Adverse events n (%)	Conservative treatment	Repeat endoscopy	Surgery	Fatal
SEMS (n = 249)					
Migration	54 (21.7)	9	45 (stent repositioning/ removal/new stent)	—	—
Stricture on stent-induced ulcers	13 (5.2)	6	7 (balloon dilation)	—	—
Pain	9 (3.6)	3	6 (early stent removal)	—	—
Bleeding	4 (1.6)	4	—	—	—
Nausea and vomiting	3 (1.2)	2	1 (early stent removal)	—	—
Perforation	2 (.8)	—	1 (placement of 2 overlapping stents)	1 (duodenal perforation with surgical repair)	—
Tracheoesophageal fistula	1 (.4)	—	—	1 (surgical repair)	—
Aortoesophageal fistula	1 (.4)	—	—	—	1 (sepsis)
Gastrocolic fistula	1 (.4)	—	1 (over-the-scope clip closure)	—	—
Cholangitis	1 (.4)	1	—	—	—
Over-the-scope clip (n = 39)					
Leak worsening	2 (5.1)	—	2 (SEMS placement)	—	—
Accidental release in the esophagus	1 (2.6)	1	—	—	—
Endoscopic internal drainage (n = 38)					
Stent migration with ileal perforation	1 (2.6)	—	—	—	1 (sepsis despite surgery)
Stent migration with spleen injury	1 (2.6)	—	1 (stent removal)		—
Stent migration into lumen	1 (2.6)	—	1 (stent removal)		—
Leak collection perforation by stent	1 (2.6)	—	—	1 (surgical irrigation and drainage)	—
Gastrobronchial fistula formation	1 (2.6)	—	—	1 (surgical closure)	—
Endoscopic vacuum therapy (n = 21)					
Tension pneumothorax	1 (4.8)	—	—	1 (chest tube placement)	—
Endoscopic suture (n = 13)					
Bleeding	1 (7.7)	1	—	—	—
Tissue sealants (n = 9)					
Aspiration into left bronchus fistula	1 (11.1)	1	—	—	—
Endoscopic septotomy (n = 9)	—	—	—	—	—
Biodegradable stents (n = 8)					
Migration	2 (25)	2	—	—	—

SEMS, Self-expandable metal stent; —, not applicable.

clinical success at the end of treatment (OR, .39; 95% CI, .14-1.11; $P = .079$).

Bigger leak initial diameters (OR, 1.05; 95% CI, 1.00-1.09; $P = .016$), higher numbers of therapeutic endoscopies performed (OR, 1.20; 95% CI, 1.06-1.37; $P = .005$), use of FC-SEMSs individually (OR, 2.12; 95% CI, 1.06-4.26; $P = .035$) or combined with other techniques (OR, 2.51; 95% CI, 1.22-5.16; $P = .012$), and longer length of stays (OR, 1.01; 95% CI, 1.00-1.02; $P = .016$) were associated with overall AE occurrence. However, previous gastrectomy was protective for its occurrence (OR, .20; 95% CI, .07-.53; $P = .001$).

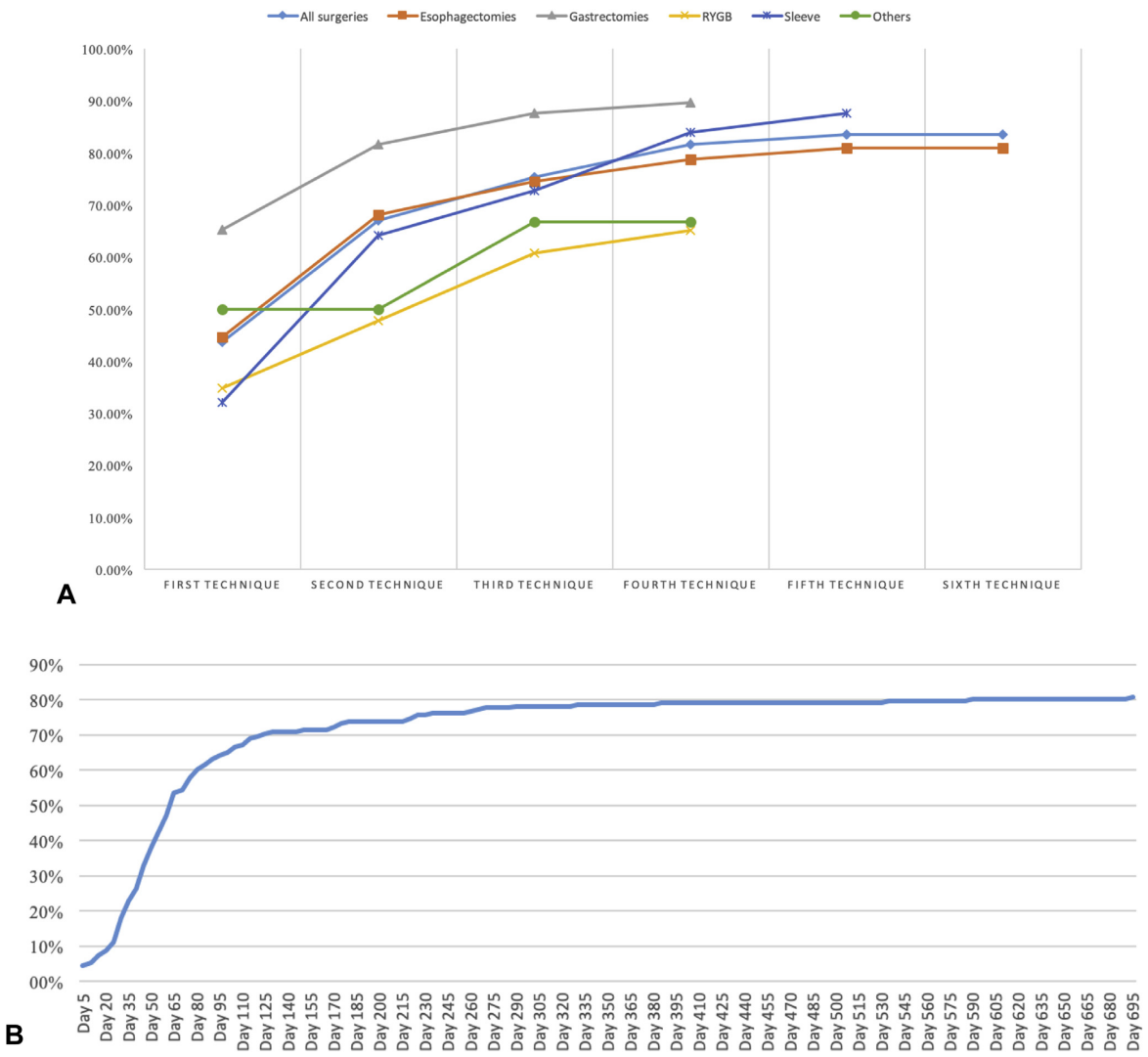


Figure 1. A, Cumulative success of leak resolution with different endoscopic therapies according to surgery responsible for the leak. **B,** Cumulative success of leak resolution over time of endoscopic therapy. *RYGB*, Roux-en-Y gastric bypass.

DISCUSSION

The variety of endoscopic approaches and devices, including closing, covering, and drainage methods, has transformed endoscopy into a first-line approach for the treatment of UGI postsurgical leaks. Despite this, there is wide variation in the management of these patients, even among experts in the field, particularly concerning difficult-to-treat patients, possibly reflecting the poor quality of evidence available at the moment.[11] The literature is limited to case reports, case series, and only a few retrospective observational cohort studies, which assess different transmural defects together or mainly based on a given center's experience.

To the best of our knowledge, this is the largest multicenter study including only patients with UGI postsurgical leaks. Clinical success and leak resolution were achieved in 80.1% and 83.5% of the 206 patients, respectively. This is consistent with the literature, with clinical success rates of 60% to 100% for various endoscopic modalities.[12,16-19] During endoscopic treatment, often more than 1 endoscopic approach is used concomitantly,[12] whereas in other cases, therapies are applied sequentially depending on the initial clinical response. For this reason, individual leak closure of each endoscopic technique should be interpreted with caution. Because many patients have already undergone different endoscopic techniques, clinical success may decrease with time, and these leaks

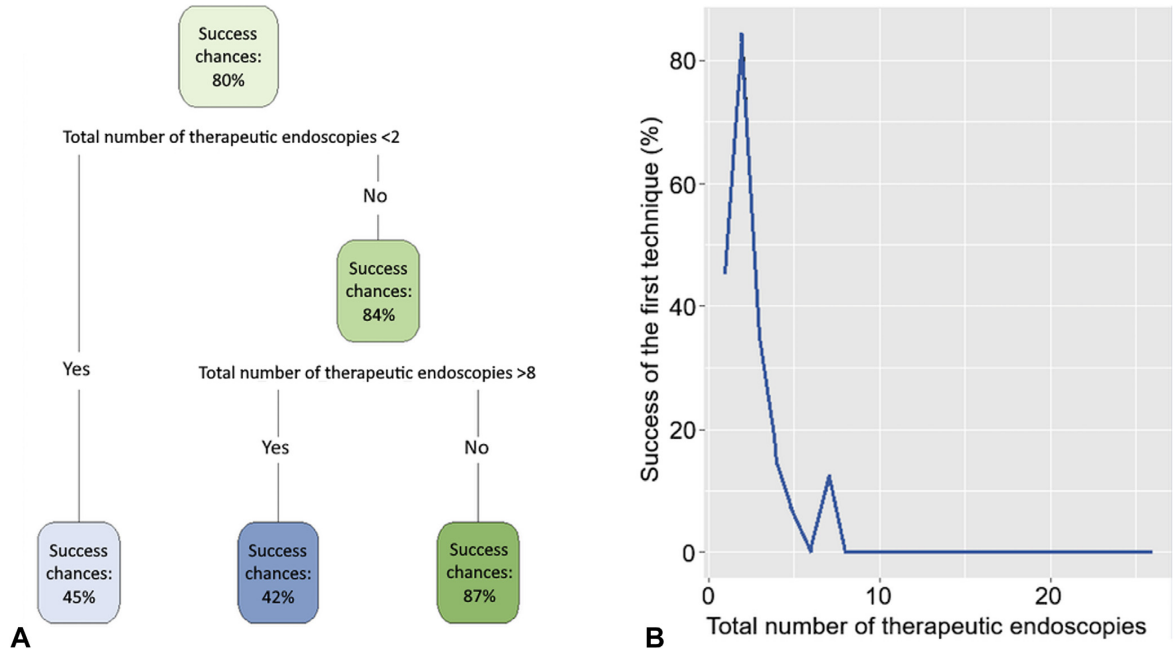


Figure 2. Probability of leak resolution at first endoscopic technique according to the number of therapeutic endoscopies performed: (**A**) classification tree; (**B**) line graph.

(by having already failed previous endoscopic techniques) may be more difficult to treat. Although it would be important to identify the most effective technique, our data suggest that this may be particularly difficult, especially in complex leaks, where several endoscopic techniques are used; in these cases, the endoscopic techniques should be considered complementary.

In a prospective study that evaluated an entirely endoscopic approach for management of 27 bariatric leaks, the first procedure was successful in 41%, with all patients eventually achieving resolution after a mean of 4.4 endoscopies at a mean of 86 days.[20] In our study, multimodal therapy was required in 40.8% of patients, with patients with previous bariatric surgery needing it more often. Around 44% of leaks were successfully treated with 1 endoscopic technique. Although the percentage of leak resolution with each technique was relatively similar, cumulative success of endoscopic leak resolution reached a plateau between the third and fourth techniques (around 70%-80%). The median time to leak closure was 52 days with a median of 3 endoscopies performed per patient.

Even though multiple endoscopic procedures should be considered before endoscopic failure,[21] the success rates of endoscopic treatment correlate with the duration of treatment. In one multicenter retrospective study,[16] the probability of successful endoscopic therapy in sleeve gastrectomy leaks decreased markedly with time, from 76.4% at 1 month to 48.5% at 6 months. In our study, only 10% of leaks were successfully closed after 125 days of treatment.

It is important to highlight that surgery still has a key role while addressing postsurgical leaks, both at initial stages (allowing irrigation and drainage of intra-abdominal collections) and at later stages if endoscopic treatment is not successful; 42% of our cohort needed repeat surgery at earlier stages, whereas 7% of patients (n = 14) underwent surgery after endoscopic treatment failure, with leak closure achieved in 12 of them. Final leak closure was achieved in 90.3% of patients.

Several endoscopic techniques can be used to obtain leak closure. A recent survey showed that placement of stents, specifically SEMSs, is the most available technique and most frequently used in almost every department.[11] Our study confirmed this, because SEMS placement was the technique most frequently used until the fourth endoscopic approach. Thirty-four percent and 5.6% of our patients underwent 2 and 3 different attempts of SEMS placement, respectively. It should be noted, however, that persistent of leakage after positioning of the first stent has been associated with higher chances of therapeutic failure.[17,22] EID, OTSCs, and EVT were also common options, but always at percentages lower than 10%. Perhaps the fact that almost 70% of patients had a surgical or percutaneous drain placed before index endoscopy could explain a lower use of therapeutic

TABLE 6. Clinical success, leak resolution, and adverse event occurrence predictors

	Clinical success predictors at first technique*		Leak resolution predictors at first technique*		Clinical success predictors at first 3 techniques*	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Time between surgery and endoscopy	.993 (.985 - 1.001)	.082	.993 (.985 - 1.001)	.069	.999 (.998 - 1.001)	.447
Female gender	1.034 (.529 - 2.023)	.921	.859 (.442 - 1.668)	.653	.719 (.278 - 1.864)	.497
Age	1.005 (.982 - 1.030)	.656	1.010 (.986 - 1.034)	.407	.996 (.971 - 1.021)	.731
Previous surgery						
Esophagectomy	.977 (.395 - 2.418)	.961	.692 (.283 - 1.692)	.419	1.075 (.421 - 2.744)	.879
Roux-en-Y gastric bypass/minigastric bypass	.924 (.338 - 2.527)	.878	.833 (.304 - 2.278)	.722	.571 (.220 - 1.484)	.250
Sleeve gastrectomy/gastroplasty	.541 (.245 - 1.193)	.128	.539 (.247 - 1.176)	.121	1.091 (.495 - 2.408)	.829
Gastrectomy	2.076 (.898 - 4.800)	.088	3.270 (1.382 - 7.737)	.007	1.499 (.620 - 3.63)	.369
Other	1.186 (.223 - 6.301)	.841	.937 (.179 - 4.911)	.938	.670 (.143 - 3.132)	.611
Leak initial size	.961 (.923 - .999)	.047	.966 (.929 - 1.004)	.078	.997 (.964 - 1.032)	.883
Leak-associated collection	1.062 (.537 - 2.101)	.862	1.090 (.555 - 2.141)	.802	1.214 (.590 -2.499)	.598
C-reactive protein at beginning of therapy	.998 (.994 - 1.001)	.251	.998 (.995 - 1.002)	.329	1.001 (.996 - 1.006)	.756
Leukocytes at beginning of therapy	.998 (.952 - 1.055)	.933	.996 (.947 - 1.049)	.890	1.004 (.925 - 1.090)	.925
Hemodynamic stability	1.228 (.581 - 2.597)	.590	.861 (.416 - 1.782)	.687	1.504 (.523 - 4.310)	.449
Absence of respiratory failure	1.718 (.797 - 3.704)	.168	1.201 (.573 - 2.525)	.626	2.778 (.965 - 8.000)	.058
Hospitalization						
General ward	1.151 (.577 - 2.295)	.689	.923 (.466 - 1.830)	.820	2.11 (1.004 - 4.435)	.049
Intermediate/intensive care unit	.760 (.374 - 1.543)	.447	.968 (.481 - 1.948)	.927	.380 (.177 - .816)	.013
Intensive care unit	.616 (.299 - 1.268)	.188	.757 (.374 - 1.530)	.437	1.009 (.941 - 1.083)	.799
No. of therapeutic endoscopies	.340 (.285 - .561)	<.001	.323 (.219 - .477)	<.001	.721 (.613 - .849)	<.001
Endoscopic technique						
partially covered SEMS (only)	.516 (.214 - 1.243)	.140	.573 (.244 - 1.346)	.201	.861 (.369 - 2.008)	.728
FC-SEMS (only)	1.618 (.805 - 3.256)	.177	1.875 (.934 - 3.764)	.077	1.482 (.727 - 3.022)	.279
Partially covered SEMS (any including it)	.515 (.218 - 1.220)	.131	.570 (.247 - 1.317)	.188	.943 (.407 - 2.188)	.892
FC-SEMS (any including it)	1.686 (.831 - 3.422)	.148	1.958 (.968 - 3.962)	.062	1.510 (.740 - 3.077)	.257
Over-the-scope clip (any including it)	1.825 (.676 - 4.928)	.235	1.543 (.572 - 4.164)	.392	1.524 (.513 - 4.530)	.448
Endoscopic internal drainage	2.270 (.650 - 7.931)	.199	2.158 (.622 - 7.483)	.225	.646 (.195 - 2.136)	.474
Endoscopic vacuum therapy	.192 (.022 - 1.650)	.132	.161 (.019 - 1.359)	.093	.280 (.071 - 1.109)	.070
Hospitalization length of stay	.981 (.969 - .993)	.002	.976 (.964 - .989)	.002	.984 (.975 - .993)	<.001
Time until leak closure	.986 (.978 - .994)	.001	.986 (.978 - .994)	.001	1.006 (1.001 - 1.011)	.033

OR, Odds ratio; *CI*, confidence interval; *SEMS*, self-expandable metal stent; *FC*, fully covered; —, not applicable.
*Results were clustered on the hospital and adjusted for the time between surgery and endoscopy.

options like EID and EVT, although emerging data suggest that secondary closure, using the concept of keeping the leak open,[23] may be superior to closure.[18,24]

Only a limited number of studies have compared the efficacy of different endoscopic modalities for management of leaks. Farnik et al[25] retrospectively compared FC-SEMSs and OTSCs, with leak closure in 69% and 31%, respectively; clinical success after primary intervention was 40% for FC-SEMSs and 70% for OTSCs. However, defects treated with FC-SEMSs were larger than those treated with an OTSC (12.6 mm vs 7.1 mm). Manta et al's[19] primarily approach for upper postsurgical leaks was OTSCs and OTSCs plus SEMSs, with leak closure achieved in as many as 81% to 85% of cases treated with these approaches. However, similar success rates have been reported for EVT, with demonstrated superiority to stents in some studies[26-29] and lower mortality rates and shorter median treatment duration (23 vs 33 days).[28]

Proper selection of patients is critical for favorable outcomes. A precise diagnosis of the leak site and leak duration; understanding of the surgical anatomy, septic state, and associated collections; and an appropriate endoscopic approach to the leak are essential in the effective management of this condition.[2,11] In our study, smaller leak initial diameters, hospitalization in a general ward, hemodynamic stability, absence of respiratory failure, previous

TABLE 6. Continued

Leak resolution predictors at first 3 techniques*		Clinical success predictors at end of treatment*		Adverse event occurrence predictors *	
OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
.999 (.998 - 1.001)	.416	1 (.998 - 1.003)	.773	1 (.998 - 1.001)	.639
.935 (.448 - 1.952)	.858	1.862 (.833 - 4.162)	.130	1.041 (.525 - 2.063)	.909
1.005 (.979 - 1.032)	.695	.982 (.953 - 1.011)	.212	.983 (.959 - 1.007)	.166
.628 (.238 - 1.656)	.347	.958 (.338 - 2.711)	.935	2.303 (.891 - 5.953)	.085
.489 (.188 - 1.269)	.141	.394 (.139 - 1.114)	.079	.804 (.306 - 2.116)	.659
1.069 (.466 - 2.454)	.875	2.292 (.877 - 5.988)	.090	2.134 (.972 - 4.688)	.059
3.817 (1.307 - 11.146)	.014	1.203 (.474 - 3.054)	.697	.196 (.073 - .527)	.001
.490 (.104 - 2.300)	.366	.422 (.088 - 2.014)	.279	.965 (.193 - 4.817)	.966
1.014 (.971 - 1.058)	.540	.996 (.954 - 1.040)	.859	1.049 (1.001 - 1.090)	.016
1.160 (.541 -2.488)	.703	1.131 (.494 - 2.587)	.771	.926 (.459 - 1.868)	.831
.999 (.995 - 1.002)	.412	.997 (.994 - 1.001)	.126	.999 (.995 - 1.002)	.445
.966 (.915 - 1.019)	.204	.977 (.924 - 1.033)	.408	1.009 (.953 - 1.068)	.763
2.028 (.938-4.386)	.072	4.255 (1.893 - 9.524)	<.001	.904 (.428 - 1.908)	.791
3.021 (1.331-6.849)	.008	6.711 (2.667 - 16.949)	<.001	.747 (.341 - 1.634)	.465
1.449 (.676 - 3.108)	.340	4.006 (1.686 - 9.521)	.002	1.266 (.628 - 2.553)	.509
.570 (.260 - 1.248)	.160	.221 (.090 - .541)	<.001	.869 (.426 - 1.774)	.700
.347 (.157 - .765)	.008	.185 (.078 - .438)	<.001	.693 (.333 - 1.443)	.327
.649 (.537 - .784)	<.001	.854 (.757 - .963)	.010	1.203 (1.057 - 1.369)	.005
.933 (.383 - 2.274)	.879	.606 (.231 - 1.590)	.309	.735 (.325 - 1.661)	.459
1.835 (.856 - 3.935)	.119	1.070 (.484 - 2.378)	.862	2.120 (1.056 - 4.259)	.035
1.030 (.425 - 2.496)	.948	.606 (.231 - 1.590)	.309	.661 (.295 - 1.482)	.315
2.086 (.961 - 4.528)	.063	1.228 (.544 - 2.769)	.621	2.509 (1.219 - 5.162)	.012
1.207 (.406 - 3.594)	.735	1.872 (.489 - 7.164)	.360	.636 (.228 - 1.771)	.386
.599 (.181 - 1.983)	.401	6.070 (.700 - 52.63)	.102	.311 (.085 - 1.133)	.077
.207 (.053 - .815)	.024	.377 (.094 - 1.521)	.171	.746 (.184 - 3.023)	.682
.979 (.969 - .989)	<.001	.984 (.974 - .993)	<.001	1.011 (1.002 - 1.020)	.016
.991 (.985 - .998)	.008	—	—	1.001 (.997 - 1.007)	.453

gastrectomy, lower numbers of therapeutic endoscopies performed, shorter length of stays, and shorter times to leak closure were associated with better outcomes. Outcomes regarding hospitalization in a general ward and shorter length of stays are probably explained by patients being in better clinical condition (hemodynamically stable and without respiratory failure). There was also a trend for an earlier start to treatment being associated with better outcomes. Christophorou et al[16] and El Hajj et al[1] also reported better outcomes with a shorter time between diagnosis and treatment and smaller luminal openings[1,16] and interval between surgery and leak $\leq$3 days.[16] The heterogeneity of treatment management and the frequent combination of several different endoscopic techniques in the same patient meant that comparison of efficacy between the different techniques was not possible.

Leaks are associated with a high risk of morbidity and mortality.[5,30,31] In our study, the overall rate of AEs was 39.3% (102 AEs in 81/206 patients); however, only 6 AEs required surgery or led to death. Even though SEMSs were responsible for most AEs observed (89/102 AEs, occurring in 249 SEMS procedures), they were typically managed endoscopically, with only 2 requiring surgery and 1 leading to death. Migration was the main AE in SEMS placement, occurring in 21.7% of procedures,

although antimigration measures, such as partially covered SEMS placement and anchoring techniques, were used in 28.5% and 20% of our cohort, respectively, which is similar to previous reports.[32,33] In a regression analysis, migration rates were higher when smaller SEMSs or FC-SEMSs were used. On the other hand, EID was associated with a 13.2% AE rate (5 AEs in 38 patients), of which 2 required surgery and 1 led to death. Other techniques were fraught by AE rates of 5% to 10%. Previous reports of exsanguinating hemorrhage after intracavitary sponge placement also highlight the potential for serious AEs related to EVT.[26] Bigger leak initial diameters, use of FC-SEMSs, higher numbers of therapeutic endoscopies performed, and longer length of stays predicted AE occurrence, whereas previous gastrectomy was protective for its occurrence. Although 26.6% of our cohort died during follow-up, more evident in oncologic patients, leak-related mortality was 12.4%, with previous reports of 13% to 14%.[17,34] In our study, it was slightly higher in oncologic patients.

This study is the largest multicenter series evaluating the efficacy of interventional endoscopy in the treatment of UGI postsurgical leaks. However, there are some limitations to the study. First, we included several surgery types responsible for the leaks, which prevented analysis and regression from being adjusted for a greater number of variables. Second, despite exhaustive data collection, the retrospective design of the study may have resulted in information bias, because patients were heterogeneously distributed between the different centers. Third, this is a multicenter retrospective cohort. The centers used a wide array of treatment modalities, and there was no single protocol or algorithm in place for the endoscopic management of leaks and no a priori definitions of failure or when to proceed with another endoscopic approach. We tried to address this limitation by analyzing data as "clustered by center" with conditional logistic regression models. Nevertheless, all included centers had experience and expertise in the endoscopic management of surgical AEs (with the exception of 1 center, all the others had leak resolution around 80%). The fact that all involved centers were tertiary hospitals with high endoscopic experience and dealing with complex patients could limit study generalizability. The heterogeneity of treatment management and the frequent combination of several different endoscopic techniques in the same patient prevented head to head comparisons between the different endoscopic techniques. Our study covers a recent time period (2014-2019), and we were able to include more recent endoscopic modalities such as EVT and EID. However, even considering this, the number of procedures performed with these newer techniques was significantly fewer than those with SEMSs.

Currently, complex endoscopic surgical treatment or combined treatment with simultaneous or sequential use of several endoscopic methods seems optimal in management of UGI postsurgical leaks. We present data focusing on the effectiveness of complex therapies rather than individual endoscopic methods. Our study shows endoscopic treatment is safe, effective, and reproducible when a skilled endoscopist is available. Around half of the patients were treated successfully with 1 endoscopic approach, with approximately 80% of patients eventually having their leak treated with endoscopy without the need for surgery. Clinical success correlated with the duration of treatment, with only 10% of leaks successfully closed after 125 days of treatment. Leak resolution reached a plateau between the third and fourth endoscopic techniques, with little benefit in adding more techniques. Because an earlier start to treatment seems to be associated with improved clinical outcomes, these patients should be referred sooner rather than later. Patients with smaller leak initial diameters, in better clinical condition, and with previous gastrectomy respond better, so we should be more aggressive when treating these patients. A high index of suspicion is key to early diagnosis. Knowing what is available in our own institutions and the available skill sets will guide treatment decisions.

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Abbreviations: AE, adverse event; EID, endoscopic internal drainage; EVT, endoscopic vacuum therapy; FC-SEMS, fully covered self-expandable metal stent; IQR, interquartile range; OR, odds ratio; OTSC, over-the-scope clip; RYGB, Roux-en-Y gastric bypass; SEMS, self-expandable metal stent; UGI, upper GI.

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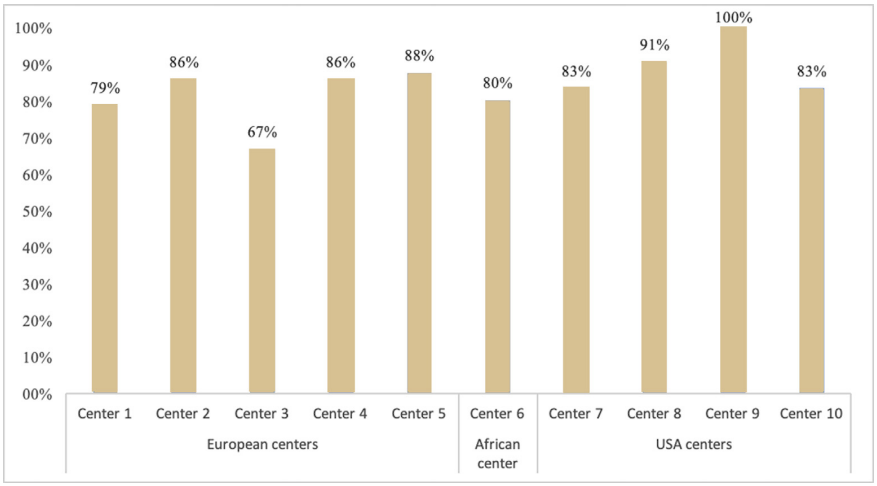

Supplementary Figure 1. Leak resolution within each center.

SUPPLEMENTARY TABLE 1. Techniques rating from the most frequent option to the less frequent option

	First option	Second option	Third option	Fourth option	Fifth option	Sixth option
SEMS (partially covered and fully covered)*	141 (68.4)	58 (28.2)	23 (11.2)	5 (2.4)	—	—
Endoscopic internal drainage	19 (9.2)	15 (7.3)	3 (1.5)	4 (1.9)	2 (1)	—
Over-the-scope clip	14 (6.8)	11 (5.3)	1 (.5)	1 (.5)	1 (.5)	—
Endoscopic vacuum therapy	10 (4.9)	5 (2.4)	4 (1.9)	2 (1)	—	—
Over-the-scope clip on leak plus SEMS	7 (3.4)	5 (2.4)	1 (.5)	—	—	—
Biodegradable stent	6 (2.9)	—	2 (1)	—	—	1 (.5)
Leak suture plus SEMS	4 (1.9)	2 (1)	2 (1)	—	—	—
Other†	3 (1.5)	3 (1.5)	3 (1.5)	1 (.5)	—	—
Endoscopic suturing	2 (1)	2 (1)	—	1 (.5)	—	—
Endoscopic vacuum therapy plus SEMS (stent-over-sponge)	—	3 (1.5)	—	1 (.5)	—	—
Septotomy plus balloon dilation	—	1 (.5)	4 (1.9)	4 (1.9)	1 (.5)	—
Tissue sealant	—	1 (.5)	2 (1)	3 (1.5)	1 (.5)	—
Not applicable‡	—	100 (48.5)	161 (78.2)	184 (89.3)	201 (97.6)	205 (99.5)

Values are n (%).
SEMS, Self-expandable metal stent; —, not applicable.
*Includes bariatric stents.
†Other: through-the-scope clips (n = 2), through-the-scope clips plus detachable loop (n = 1), pneumatic dilation (n = 4), diabolo stent between pouch and gastric remnant (n = 1), septotomy plus endoscopic internal drainage (n = 1), tissue sealant on leak plus SEMS (n = 1).
‡Number of patients who did not undergo additional endoscopic options.

SUPPLEMENTARY TABLE 2. Predictors of SEMS migration

	SEMS migration (n = 54)	No SEMS migration (n = 195)	Odds ratio (95% confidence interval)	*P* value
SEMS body diameter	—	—	.902 (.815-.999)	.049
SEMS length	—	—	.995 (.988-1.003)	.230
SEMS covering				
Partially covered	9 (16.7)	62 (31.8)	.476 (.225-1.007)	.052
Fully covered	44 (81.5)	130 (66.7)	2.443 (1.125-5.305)	.024
Antimigration technique				
Any technique	16 (29.6)	39 (20)	1.684 (.852-3.329)	.134
Through-the-scope clip	9 (16.7)	14 (7.2)	2.586 (1.053-6.352)	.038
Over-the-scope clip	6 (11.1)	13 (6.7)	1.750 (.632-4.845)	.281
Suture	1 (1.9)	12 (6.2)	.288 (.037-2.264)	.237
Placement technique				
First SEMS placed	43 (79.6)	135 (69.2)	1.737 (.838-3.601)	.137
SEMS placed after previous stent removal	8 (14.8)	46 (23.6)	.563 (.248-1.279)	.170
Stent-in-stent (previous stent still in place)	3 (5.6)	14 (7.2)	.761 (.210-2.749)	.676
Previous surgery				
Esophagectomy	16 (29.6)	46 (23.6)	1.364 (.697-2.668)	.365
Gastrectomy	9 (17.3)	47 (24.1)	.630 (.287-1.384)	.250
Gastric bypass	6 (11.5)	20 (10.3)	1.094 (.416-2.875)	.856
Sleeve gastrectomy	18 (34.6)	78 (40)	.750 (.398-1.414)	.374

Values are n (%).
SEMS, Self-expandable metal stent; —, not applicable.

Chapter V - Discussion and Conclusions

Discussion

In the Results section we have included the articles relevant for this thesis. In the Discussion section, the main results of our work will be further discussed.

Therapeutic endoscopy plays a major role in the management of PSL, offering an effective treatment alternative to repeat surgery (151). Despite this, there is wide variation in the management of these patients, even among experts in the field, particularly concerning difficult-to-treat patients.

It is important to highlight that surgery still has a key role in addressing PSL, both at the initial stages (allowing irrigation and drainage of intra-thoracic or intra-abdominal collections) and at later stages if endoscopic treatment is not successful. Forty two percent of the patients of one of our cohorts (152) needed repeat surgery at earlier stages, while 7% of patients underwent surgery after endoscopic treatment failure.

Our multicenter retrospective study (152), the largest one including only patients with UGI PSL, demonstrated high clinical success (80.1%) and leak resolution (83.5%). Multimodal therapy was required in 40.8% of the patients, with the first endoscopic technique being successful in only 44% of the leaks. Clinical success correlated with the duration of treatment, with leak resolution reaching a plateau between third and fourth endoscopic techniques (around 70-80%), with a median time to leak closure of 52 days, with only 10% of leaks being successfully closed after 125 days of treatment. A different study (153) also demonstrated a decrease in the endoscopic resolution rate of SG leaks with time, from 76.4% at 1 month to 48.5% at 6 months. This reflects the need to define when to consider endoscopic failure. In our survey study (154), even though there was no definitive consensus on the definition of endoscopic failure, persistent inflammation

with clinical sepsis, and impossibility to resume oral feeding were suggested. Inability to close the leak with time, especially after 4 months of treatment, should also prompt consideration of therapeutic alternatives, namely surgery. A recent study suggested endoscopic treatment with stents should not be performed for leaks extending more than 30% of the luminal circumference (6).

There are a limited number of studies comparing efficacy of different endoscopic modalities for management of leaks. Farnik et al. (155) retrospectively compared FC-SEMS and OTSCs, with leak closure in 69% and 31%, respectively; clinical success after primary intervention was 40% for the FC-SEMS and 70% for the OTSCs, however, defects treated with FC-SEMS were larger than those treated with an OTSC (12.6mm vs 7.1mm). In our unicenter retrospective study (156) all leaks with less than 20mm achieved endoscopic resolution with SEMS only. On the other hand, one of the reasons for the poor performance of the SEMS (41%) in our multicenter study (152) could relate to the fact that 22% of the patients had leaks larger than 20mm. Manta et al. (157) primarily approach for UGI PSL was OTSCs and OTSCs plus SEMS, with leak closure being achieved in as many as 81 to 85% of the cases treated with these approaches. Lorenzo et al. (48) reported better outcomes of EID compared with stents/tissue sealants/OTSCs (86% vs 64%, p=0.55) in 100 patients with post-SG leaks. Recently, the outcomes of SEMS placement have been compared to EVT for the treatment of PSL in several meta-analyses, as stated in our review for the European Society of Gastrointestinal Endoscopy (ESGE) guidelines (158). EVT seems to be associated with a higher leak closure rate (16 to 21% higher), lower mortality (10 to 12% lower) (142, 159, 160), fewer AEs (160) and shorter treatment duration (159, 160), with no differences regarding the length of hospital stay (142, 160). These results have not been replicated in all studies. Berlth et al. (161) reported on a large cohort of 111 patients, including only patients with post-esophagectomy leaks, in which a closure rate of 85.7%

for EVT vs 72.4% for SEMS was not found to be statistically significant. In our multicenter study (152), the heterogeneity of treatment management and the frequent combination of several different endoscopic techniques in the same patient prevented head to head comparisons between the different endoscopic techniques. Besides, technique-specific results should be interpreted with caution as the individual techniques reported were not always the first or the index approach during the multimodal management. This is particularly important as clinical success decreases with time.

Our survey study (154) showed that placement of stents, specifically SEMS, is the technique most widely available and most frequently used in practically every endoscopic department. Our multicenter study (152) also confirmed this, as SEMS was the technique most frequently used until the fourth endoscopic approach. In Christophorou et al. (153) study, most common endoscopic techniques were stenting, clip placement and sealants application, with the key role of endoscopic treatment relying on stenting. Despite higher chances of therapeutic failure after persistence of leakage with first stent positioning (115, 162), in our multicenter study (152), a significant percentage of patients still underwent 2 and 3 different attempts of SEMS placement (34% and 5.6%, respectively). OTSCs were not a common first therapeutic option, either in the survey (154) or multicenter study (152), probably related to poor integrity of the tissue surrounding the leak as a result of ischemia and inflammation. On the other hand, EID and EVT seem to be increasingly used/considered techniques, probably related to the fact that closing leaks with tissue apposition techniques or diversion therapy may not be the ideal treatment strategy, especially in late or chronic leaks. However, in our multicenter study (152), EID and EVT were still used at percentages lower than 10%. These might be explained by the presence of a surgical/percutaneous drain before the index endoscopy in 70% of the patients, however, a lower familiarity with these newer techniques even in experienced centers, or

difficulties in embracing new therapies might also be responsible for it.

The selection of the right self-expandable stent design also remains a challenge. Even though clinical success rates are comparable, in our review for the ESGE guidelines (158), SEMS perform better than SEPS in leaks and perforations, with higher technical success (95% vs 91%, p=0.032), reduced risk of migration (16% vs 24%, p=0.001) and need for stent repositioning (3% vs 11%, p<0.001), as well as lower risk of perforation when considering anastomotic leaks only (0% vs 2%, p=0.013) (114). Migration rates are higher with FC-SEMS vs PC-SEMS (OR 2.44, 95%CI 1.13–5.31) (152), however, suturing FC-SEMS may render migration rates similar to PC-SEMS (adjusted OR 0.56, 95%CI 0.15-2.00), without the difficulties in removal of PC-SEMS and a lower risk of AEs (21% vs 46%, p=0.37) (163). Shim technique (164) as well as stents with wider diameters (152, 165) may also result in lower migration rates. Data regarding the use of BDS are limited (152, 166, 167), and comparative studies with SEMS are still lacking (168). While in the survey study (154), both FC and PC-SEMS were similarly reported as first options (even in patients without previous stent migration), in the muticenter study FC and PC-SEMS were used in 69.9% and 28.5% of the procedures, respectively. Despite the lower risk of migration with PC-SEMS, the higher difficulties in removal may explain these differences in real life situations. No study has investigated the optimal stent duration (158). Although animal studies suggest that a stent dwell time of 30 days is sufficient to guarantee healing (169), stents are usually removed 6-8 weeks after insertion, and repeated stent placement is needed in 11% of patients [112-114]. In our survey study, it ranged from 4 to 6 weeks in the majority of respondents (154). In our multicenter study (152), median stent dwell time was 35 days, with almost half being placed for 2 to 6 weeks, while in our unicenter study was 45 days (156). In our review for the ESGE guidelines (158), while there's a tendency to remove or replace stents at shorter interval times (154), to reduce stent-related AEs,

median stent dwell time ranged from 22 to 83.5 days, with patients placing a median of 1.19 to 2 stents (range: 1-13).

In the survey study (154), respondents considered endoscopic suture provides the ability to close larger defects than OSTCs (2cm vs 1cm), however, both require robust mucosa to hold the sutures when tissue is pulled in apposition (170). Regarding EVT, even though intraluminal EVT might be easier and safer than intracavitary EVT, the majority of respondents prefer to perform balloon dilation and intracavitary EVT, as leak closure might be better (143). Endoscopic septotomy was usually only considered in patients with SG, at least 4 weeks after surgery, with management of the downstream stenosis being considered critical to enhance endoscopic closure. Regarding EID with transgastric stents, a median of 4.5 days until oral diet resumption was reported, with 21% starting it in the day of procedure or following day. This relates to the fact that oral contents likely do not enter the cavity by virtue of the negative pressure gradient (11). However, Donatelli et al (171), differently from other authors, advise enteral nutrition by means of a feeding tube placed in the third part of the duodenum for the first 4 weeks in order to allow hyper-alimentation. Regarding stent exchange, while some see no value in routine stent exchange unless necrosectomy is also performed (172), the performance of multiple procedures may allow to evaluate treatment progression in order to adapt internal drainage (173).

Proper selection of patients is critical for favourable outcomes. Precise diagnosis of the leak site, leak duration, understanding the surgical anatomy, septic state, associated collections, and an appropriate endoscopic approach to the leak is essential in the effective management of this condition (2). According to experts opinion in our study (154), leak location, size, chronicity and associated cavity are the most relevant leak characteristics to be considered when deciding treatment. Previous surgery (bariatric

or oncologic) should also influence therapeutic decision. In the clinical case section of our survey study (154), EVT and stent placement, with or without percutaneous/surgical drainage, were the therapeutic options most often chosen in patients with previous oncologic surgery, while EVT and EID were the therapeutic options most often chosen in patients with previous bariatric surgery. Due to anatomical reasons, lower rates of leak closure with stents are expected in post-bariatric leaks as the area to cover is larger, it is more difficult to obtain close apposition between the stent and the wall defect and tissue hyperplasia increasing the water tightness is less common (97). In our multicenter study (152), smaller leak initial diameters, hospitalization in general ward, hemodynamic stability, absence of respiratory failure, previous gastrectomy, lower numbers of therapeutic endoscopies performed, shorter length of stay and shorter times to leak closure were associated with better outcomes. Outcomes regarding hospitalization in general ward and shorter length of stays are probably explained by patients being in better clinical condition (hemodynamically stable and without respiratory failure). In Christophorou et al. interventional multimodal endoscopy study (153), time between SG and leak diagnosis lower than 3 days, time between leak diagnosis and first endoscopy earlier than 21 days, and smaller diameter leaks were also associated with clinical success. Either in our unicenter (156) and multicenter (152) retrospective studies, there was a trend for earlier beginning of treatment being associated with better outcomes. El Hajj et al. (1) and van Halsema et al. (174) also reported better outcomes when shorter times between diagnosis and treatment or smaller luminal openings.

Regarding AEs, in our multicenter study (152) the overall rate was 39.3% (102 AEs in 81 patients, out of 206 patients), however, only 6 AEs required surgery or led to death. Even though SEMS were responsible for the vast majority of AEs observed (89 of the 102, occurring in 249 SEMS procedures), they were typically managed endoscopically,

with only 2 requiring surgery and 1 leading to death. Migration was the main SEMS AE, occurring in 21.7% and 30.7% of the procedures of our multicenter and unicenter studies, similarly to previous reports (118, 175). In the regression analysis of our multicenter cohort (152), migration rates were higher when smaller-SEMS or FC-SEMS were used. On the other hand, EID was associated with a 13.2% AE rate (5 in 38 patients), of which 2 required surgery and 1 led to death. Other techniques were fraught by AE rates of 5 to 10%. Previous reports of exsanguinating hemorrhage after intracavitary sponge placement also highlight the potential for serious AEs related to EVT (141). Bigger leak initial diameters, use of FC-SEMS, higher numbers of therapeutic endoscopies performed, and longer length of stays predicted AEs occurrence, while previous gastrectomy was protective for its occurrence. Leak-related mortality was 12.4%, with previous reports of 13 to 14% (162, 176).

Considering the majority of respondents' answers to our survey (154), acute and small leaks, without associated collections may be considered for stent placement (up to 3cm), OSTC placement (up to 1cm) or endoscopic suture (up to 2cm). In the setting of associated collection, these techniques can still be considered if external drainage is also performed; if not, EVT, EID and endoscopic septotomy should be considered, with EVT and EID being an option in acute and chronic leaks, while endoscopic septotomy should only be performed in leaks with more than 4 weeks of duration. While endoscopic septotomy can be considered for all leak sizes, EVT is ideal for leaks larger than 2cm. Intra-thoracic leaks may be better served with stents or EVT, and intra-abdominal leaks with OTSC, suturing, septotomy or EID. Leaks resulting from previous bariatric surgery should ideally be treated with OTSC, suture, septotomy or EID, while stents and EVT can be considered for leaks related to bariatric and oncologic surgeries. As earlier beginning of treatment seems to be associated with improved clinical outcomes (152), patients should

be referred sooner rather than later. Patients with smaller leak initial diameters, in better clinical condition, and with previous gastrectomy respond better, so we should be more aggressive when treating these patients.

Conclusions

Endoscopy is emerging as first line approach over surgery for the management of UGI PSL. The steadfast advancements of interventional endoscopy in the last decades allowed for new endoscopic devices and techniques, which provide a minimally invasive and more effective therapeutic option than surgery. A single therapy, or a combination of different techniques, can integrate the use of different endoscopic options.

The following principles should be followed [Figure 4]:

- Referral of leaks for endoscopic treatment should be as soon as possible;

- In patients whose condition is unstable, with acute leaks and systemic inflammatory response syndrome, mediastinitis or peritonitis, surgical washout with or without drain placement is mandatory and should not be delayed. Concurrent endoscopic management with stent placement is effective in this setting before the formation of an organized collection. PC-SEMS may be preferable due to higher changes of watertight seal and lower risk of migration, even though stent fixation of FC-SEMS may render similar migration rates;

- Combined treatment with simultaneous or sequential use of several endoscopic methods seems optimal in management of UGI PSL;

- Symptomatic and small (<10 mm) acute lesions, with healthy margins of the leak defect, may be considered for stenting, OTSC or suture. Stenting may be a better option for intra-thoracic leaks, while OTSC and suture may be better suitable for intra-abdominal

leaks;

- For acute lesions with nonviable margins or size > 10-15 mm, stenting or EVT can be considered. EVT might be a superior tool for the management of cervical leaks, larger leaks (> 3cm) and chronic leaks;

- EID may be considered for the management of subacute or chronic post-bariatric leaks with an organized walled-off collection. If this fails, more aggressive management with EVT might be needed;

- Endoscopic septotomy may be performed in late or chronic sleeve leaks with organized walled-off collections, especially if clinical failure with other techniques;

- In patients with post-SG leaks with high-grade downstream stenosis, additional pneumatic dilation with a balloon is required;

- In the setting of associated collections, if closure techniques are used, external drainage is required. EID and EVT allow early removal of external drainage preventing chronic fistula tract formation;

- OTSCs and tissue sealants may be considered for closure of residual small collections after the use of other techniques;

- Have a high index of suspicion for situations in which endoscopic closure will probably not be effective. These situations include persistent inflammation with clinical sepsis, impossibility to resume oral feeding, inability to close the leak (especially after 4 months of treatment) and formation of enterocutaneous or enteropleural fistulas.

Our research shows endoscopic treatment is safe, effective, and reproducible when a skilled endoscopist is available. The approach to UGI PSL should always be tailored to the single patient, by taking into account the several variables that may at the end influence the outcome. Endoscopic management requires a personalized and multidisciplinary

approach, comprising a close collaboration between interventional endoscopist, radiologist and surgeon, allowing PSL management with high clinical success rate and low rate of morbidity and mortality.

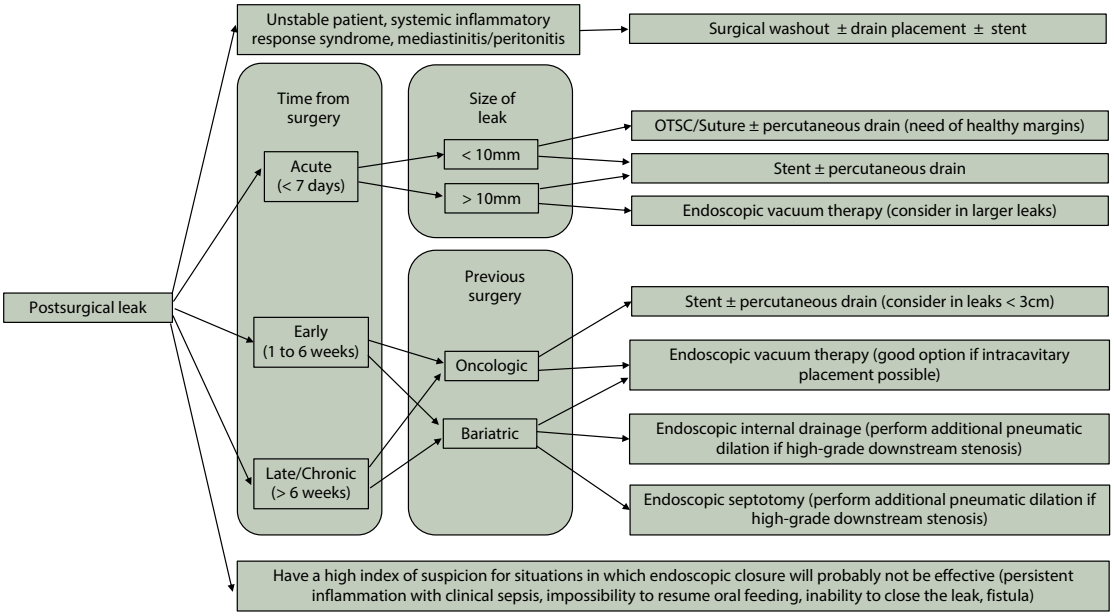

Figure 4. Endoscopic algorithm for management of postsurgical leaks. Combined treatment with simultaneous or sequential use of several endoscopic methods should always be considered.

Chapter VI - Future Research

Comparison between different approaches is difficult due to heterogeneous populations, prevalence of retrospective studies, lack of uniform definitions and lack of comparative studies. Therefore, it is difficult to establish a standardized therapeutic algorithm. Combined treatment with simultaneous or sequential use of several endoscopic methods seems optimal in management of UGI PSL. Therefore, future research (ideally randomized controlled trials) should focus on assessing the effectiveness of combined therapies rather than individual endoscopic methods. Consensus on endoscopic failure definition needs to be achieved.

In the technical aspect, improving or specifically designing devices to divert contents and to repair mucosal disruptions will probably improve endoscopic outcomes. Developing biodegradable agents (importing concepts from cardiovascular, pulmonary or interventional radiology) that could conform to the shape of the leak, with anti-septic or antibacterial properties, as well as promote angiogenesis and fibrogenesis, may also have great potential. Stem cell therapy (emulsified adipose tissue stromal vascular fraction) should be explored in the treatment of refractory leaks.

Exploring novel avenues of current endoscopic therapies, like the pre-emptive use of EVT at the site of anastomosis following different gastroesophageal surgeries may also have a role in identifying anastomotic ischemia as a precursor to the onset of anastomotic leak, allowing mucosal recovery after EVT.

Studies evaluating the economic consequences in patients with PSL (cost of healthcare interventions, to treat AEs and their cost effectiveness) are needed, as healthcare systems are operating under significant resource constraint.

Other PhD related outputs

Invited oral presentations

Técnicas Gastroenterológicas na abordagem da deiscência

Eduardo Rodrigues-Pinto

Masterclass Bariátrica SPCO, Maio 2021

Endoscopic treatment of surgical complications

Eduardo Rodrigues-Pinto

Semana Digestiva Digital 2020, Novembro 2020

Esophago-gastric stenting: guidelines and how I deal with difficult cases

Eduardo Rodrigues-Pinto

Live SPED 2019, Março 2019

Complications, a new paradigm:

stents and endo-sponge... a surgeon's saver?

Eduardo Rodrigues-Pinto

Sky Meeting 2018, Outubro 2018

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