U.PORTO

MESTRADO INTEGRADO EM MEDICINA

GASTRENTEROLOGIA

Endoscopic Submucosal Dissection for the Treatment of Superficial Esophageal Lesions

André da Cunha Pinto

M

2024

Endoscopic Submucosal Dissection for the Treatment of Superficial Esophageal Lesions

ARTIGO ORIGINAL

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Junho 2024

Estudante:

André da Cunha Pinto

Mestrado Integrado em Medicina

Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Endereço eletrónico: andredacunhapinto@hotmail.com

Orientador:

Professor Doutor Ricardo Sigalho Küttner de Magalhães

Assistente Hospitalar. Serviço de Gastrenterologia, Unidade Local de Saúde de Santo António

Professor Associado, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Endereço eletrónico: rkuttner@gmail.com

Coorientadora:

Doutora Sara Rita e Sousa de Oliveira Barreto Archer

Interna de Formação Específica de Gastrenterologia, Unidade Local de Saúde de Santo António

Endereço eletrónico: sararcher@chporto.min-saude.pt

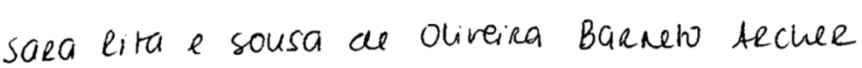
Declaração de Integridade Científica

Eu, André da Cunha Pinto, inscrito no Mestrado Integrado em Medicina do Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, declaro por este meio que, nos termos do disposto na alínea a) do artigo 14.º do Código de Conduta Ética da Universidade do Porto, o conteúdo desta dissertação reflete perspetivas, trabalho de pesquisa e as minhas interpretações no momento da sua submissão. Ao submeter esta dissertação, declaro também que contém os resultados do meu trabalho de pesquisa e contribuições que não foram previamente submetidas a esta ou a qualquer outra instituição. Além disso, declaro que todas as referências a outros autores estão em conformidade com as regras de atribuição e são citadas no texto e identificadas na secção de referências. O projeto não inclui qualquer conteúdo cuja reprodução seja protegida por leis de direitos de autor. Estou ciente de que a prática de plágio constitui uma forma de má conduta académica.

Autor: **André da Cunha Pinto**

Orientador: **Prof. Doutor Ricardo Sigalho Küttner de Magalhães**

Coorientadora: **Dra. Sara Rita e Sousa de Oliveira Barreto Archer**



Porto, Junho de 2024

Agradecimentos

Ao meu orientador, professor Ricardo, pela sua paixão pelo ensino e educação, pelas rápidas respostas e revisão do trabalho e por responder sempre a qualquer dúvida que existisse, e à minha coorientadora Dra. Sara Archer pela revisão ao longo de todo este trabalho.

Ao professor Rui Magalhães pelo apoio na análise e revisão estatística.

Ao meu namorado, Diogo, pelo amor, apoio e paciência durante todos estes anos, que não foram nada fáceis. Concretizamos já muitos sonhos juntos, mal posso esperar para o que o futuro nos reserva!

À minha mãe, Alice, e ao meu pai, Américo, pela motivação e ajuda, estiveram sempre presentes quando eu mais necessitava.

À minha irmã, Magda, por ser a minha companheira para a vida. Quase que acabávamos o Mestrado ao mesmo tempo!! Mal posso esperar por te ver casar em Julho!

À minha madrinha, Sónia, porque sem si não teria conseguido realizar o sonho de ter a minha primeira casa!

Aos meus amigos, à Luana, Sofia, Francisco, João, Mercedes e Bárbara por estarem sempre lá nos momentos mais desafiantes! Foram vocês que muitas vezes me incentivaram a continuar e me ensinaram a não duvidar de mim mesmo! Finalmente chegamos ao fim, juntos!

E aos restantes amigos e família por acreditarem em mim.

Resumo

Enquadramento: Como um dos tipos de cancro mais graves, o cancro do esófago (EC) em estadios avançados apresenta uma mortalidade elevada, havendo assim a necessidade de detetar esta doença nos seus estadios iniciais face às baixas taxas de sobrevivência. O carcinoma epidermoide (SCC) e o adenocarcinoma (AC) são os principais subtipos, que requerem diferentes estratégias de rastreio. A dissecção submucosa endoscópica (ESD) tornou-se recentemente a primeira opção de tratamento para carcinomas esofágicos precoces (EEC), mas apesar de poder ser curativa, complicações graves como a estenose esofágica (ES) podem surgir. Após a ESD, é necessário um seguimento criterioso para maximizar os resultados do paciente.

Objetivos: Avaliar a eficácia e segurança da ESD para lesões esofágicas superficiais, apurar a eficácia das técnicas de prevenção de ES e identificar os fatores preditivos para ES.

Métodos: Foi feita uma análise retrospetiva dos pacientes submetidos a ESD esofágica entre 2018 e 2023. Foram registados dados demográficos, comorbilidades, história de medicação e detalhes do procedimento. A análise estatística foi utilizada para comparar as frequências dos eventos adversos, resseção completa e os fatores de risco para ES pós-ESD.

Resultados: 19 ESDs esofágicas foram realizadas em 18 pacientes em 6 anos. A maioria dos participantes eram homens (88,9 %) com uma média de idade de 66.8 (± 8.6) anos, que apresentavam comorbilidades, especialmente hipertensão (66,7 %) e diabetes mellitus (16,7 %). As lesões eram predominantemente SCC (63,2%) ou AC (21,1%), com um tamanho mediano de 25.0 (13.0-42.0) mm. Em particular, as taxas de resseção em bloco foram elevadas, com 100% para lesões AC e SCC. No entanto, houve uma taxa de resseção curativa inferior de 69,2% para lesões SCC em comparação com as lesões AC (83,33%). Não houve hemorragia ou perfuração, mas foram detetados 8 casos de ES após ESD (42,1%, 6 após ESD circunferencial). 75% dos casos mostraram-se refratários às medidas profiláticas. Houve duas mortes (11,1%) durante o seguimento, não relacionadas com a ESD. A sobrevida total e livre de doença foi de 81,8% aos 2 anos. Um maior risco de ES foi associado ao tamanho da lesão (>30 mm), duração do procedimento (>120 minutos), resseção longitudinal (≥ 5 cm) e ocupação circunferencial (≥ 3/4). Contrariamente, não foi observada uma associação entre fatores relacionados com o paciente e o desenvolvimento de ES.

Conclusões: O estudo destaca a eficácia e segurança da ESD no tratamento de lesões associadas a esófago de Barrett (BE) e SCC, enfatizando altas taxas de sucesso para lesões relacionadas com BE. Apesar dos desafios em alcançar resultados curativos para SCC, as características do paciente e da lesão servem como preditores para a formação de estenose pós-ESD, exigindo estratégias preventivas refinadas. O acompanhamento a longo prazo e estudos colaborativos são necessários.

Palavras-chave: Resseção Endoscópica; Disseção Endoscópica da Submucosa; Neoplasias Esofágicas/Tratamento; Fatores de Risco; Complicações.

Abstract

Background: As one of the most malignant tumors, esophageal cancer (EC) in advanced stages has a high mortality rate, hence the need to detect this disease in its early stages in the face of dismal survival rates. Squamous cell carcinoma (SCC) and adenocarcinoma (AC) are the main subtypes requiring different screening strategies. Endoscopic submucosal dissection (ESD) has recently become the first choice of treatment for early esophageal carcinomas (EEC) with a forewarning that could be curative. However, it may result in esophageal stricture (ES). Following ESD, vigilant management is required to maximize patient outcomes.

Objectives: This study aims to assess ESD efficacy and safety for superficial esophageal lesions, evaluate ES prevention techniques' effectiveness, and identify predictive factors for ES.

Methods: We performed a retrospective analysis of patients who underwent esophageal ESD between 2018 and 2023. Demographics, comorbidities, medication history, and procedural details were recorded. Statistical analysis was used to compare the frequencies of the adverse events, complete resection, and the risk factors for post-ESD esophageal strictures.

Results: 19 esophageal ESDs were performed in 18 patients over 6 years. Most of the participants were men (88.9 %) with a mean age of 66.8 (± 8.6) years having comorbidities especially hypertension (66.7 %) and diabetes mellitus (16.7 %). The lesions were predominantly SCC (63.2%) or AC (21.1%), with a median size of 25.0 (13.0-42.0) mm. In particular, en bloc resection rates were high, with 100% for AC and SCC lesions. However, there was a lower curative resection rate of 69.2% for SCC lesions than that in the AC lesions which was 83.33%. There were no delayed bleeding or perforation cases, but 8 instances of ES after ESD were detected (42.1%, 6 after a circumferential ESD). 75% of cases proved refractory to even prophylactic steroid measures. There were two deaths (11.1%) during follow-up that were not related to ESD events. The total and disease-free survival rate at 2 years was 81.8%. Higher risk of ES was associated with lesion size (>30 mm), duration of the procedure (>120 minutes), longitudinal resection (≥ 5 cm), and circumference occupation (≥ 3/4). On the contrary, no significant association was observed between patient-related factors and ES development.

Conclusions: The study highlights ESD's efficacy and safety for managing BE (Barrett's Esophagus) associated lesions and SCC, emphasizing high success rates for BE-related lesions. Despite challenges in achieving curative outcomes for SCC, patient and lesion characteristics serve as predictors for post-ESD stricture formation, necessitating refined preventive strategies. Long-term follow-up and collaborative studies are warranted.

Keywords: Endoscopic Resection; Endoscopic Submucosal Dissection; Esophageal Neoplasms/therapy; Risk Factors; Adverse Events.

List of Abbreviations

AC - Adenocarcinoma

AT - Antithrombotic Therapy

BE - Barrett's Esophagus

CRT - Chemoradiotherapy

DOACs - Direct Oral Anticoagulants

EC - Esophageal Cancer

EEC - Early Esophageal Carcinomas

EMR - Endoscopic Mucosal Resection

ES - Esophageal Stricture

ESD - Endoscopic Submucosal Dissection

ESGE - European Society of Gastroenterology

GERD - Gastroesophageal Reflux Disease

HGD - High-Grade Dysplasia

IQR - Interquartilrange

JES - Japan Esophageal Society

LNM - Lymph Node Metastasis

MMC - Mitomycin C

OR - Odds Ratio

SCC - Squamous Cell Carcinoma

SD - Standard Deviation

TA - Triamcinolone Acetonide

ULSdSA - Unidade Local de Saúde de Santo António

Index

List of Tables

Introduction

Esophageal cancer (EC) is a significant global health concern, ranking eighth in cancer incidence and sixth in cancer-related deaths as of 2020. The main reason for this is that it is often diagnosed at advanced stages when curative surgery is not a viable option. The 5-year survival rate is only around 10-25%, so an early diagnosis is critical, as the best results are associated with detecting early esophageal carcinomas (EEC) which typically occur before patients develop obvious symptoms. Therefore, identifying EEC is essential to improve mortality outcomes significantly. [1–3]

There are 2 primary neoplasias in the esophagus: squamous cell carcinoma (SCC) and adenocarcinoma (AC). SCC predominates globally, particularly in East Asia, whereas AC is more prevalent in developed nations. While SCC incidence has declined in many regions, AC cases are rising rapidly in high-income countries, and it's soon projected that AC will become the most common form of EC. [1,3] SCC affects squamous cells of the esophagus mucosa, mainly in the cervical esophagus or upper and middle thoracic esophagus. Conversely, AC can potentially develop in Barrett's esophagus (BE), which is typically found in the lower esophagus. BE is characterized by a transformation to a columnar-lined mucosa, known as intestinal metaplasia, which appears salmon-colored during high-definition endoscopy. When BE is suspected, biopsies should be performed, and a careful evaluation should be conducted to determine if dysplasia is present, considering that histological progression is thought to be related to the length of Barrett's segment. [1,3–5]

EC is more common in middle-aged and elderly people, as the risk ultimately increases with age. [1] White people are at greater risk of developing this type of cancer than other groups, and men are more likely to develop SCC and AC in most countries. [2] Alcohol increases the risk of SCC while smoking increases the risk of both AC and SCC. Gastroesophageal reflux disease (GERD), obesity, and a poor diet are also major risk factors for AC. Genetics also play a significant role, as verified by tylosis, a genetic disorder associated with SCC development. In populations with high rates of EC (>30 cases/100000 inhabitants per year), such as in northern China, there is also a familial link. [3]

Divergent screening methods are employed for AC and SCC. In most countries, patients with BE are managed with endoscopic surveillance at regular intervals, because the consequences of a diagnosis of invasive adenocarcinoma are severe with high lethality and treatment-associated morbidity. Ideally, screening for AC involves using high-resolution endoscopes, virtual chromoendoscopy, and acetic acid chromoendoscopy wherein random biopsies should be taken from all four quadrants and every 2 cm of columnar epithelium. Moreover, biopsies of suspicious areas should also be performed. On the other hand, screening for SCC remains controversial, resulting in the absence of a standardized global screening program. However, its cost-effectiveness

has been demonstrated in regions with a high incidence. Screening protocols typically incorporate high-resolution endoscopy and virtual chromoendoscopy, with lugol staining for enhanced visualization. In Europe, the comparatively low incidence of SCC and the high prevalence of public health systems may represent key factors contributing to the absence of screening initiatives for this condition. These screening protocols aim to identify precursor lesions and EEC, encompassing T1 EC with the involvement of the lamina propria (T1a m2), muscularis mucosae (T1a m3), or superficial submucosa (T1b sm1), characterized by less than 200 µm invasion from the muscularis mucosae for SCC and less than 500 µm for AC. [3,4,6,7]

The current approach to managing EEC typically avoids immediate surgical intervention. Instead, most patients undergo endoscopic resection techniques. Endoscopic resection serves curative, staging, and preventive purposes for these lesions, intending to eliminate them and prevent their progression to advanced stages. [3,4]

Endoscopic submucosal dissection (ESD) was developed in Japan during the 1990s as a response to the limitations of endoscopic mucosal resection (EMR) in removing large superficial gastric malignancies. This technique entails a systematic process, beginning with the evaluation of the lesion, marking, injection of fluid into the submucosa to elevate the mucosal lesion, incision to access the submucosal space, followed by dissection of the submucosal connective tissue beneath the lesion. This meticulous procedure intends to do a complete *en bloc* resection of the lesion. [8–10] EMR consists also of submucosal injection of a liquid to project the lesion, but then a snaring of the protruded area is performed, so it might not be whole, and it is typically reserved for smaller lesions.[11] ESD is more challenging than EMR, taking longer procedural times, and leading to a higher rate of complications. However, the *en bloc* resection enables accurate histopathological assessment of lesion margins and depth of invasion, which are critical criteria for **curative resection**. ESD in the esophagus is more challenging because of its narrow lumen and challenging workspace, circular configuration, decreased thickness of the muscle wall, and the influence of both respiratory and cardiac movements. This minimally invasive procedure represents a significant breakthrough, especially given the morbidity and mortality normally associated with conventional esophageal surgery, particularly strenuous for elderly patients. [12–15]

Esophageal lesions should be categorized morphologically using the Paris classification, which divides them into three types: protruding (0-I), flat (0-II), and excavated (0-III). This classification is essential for endoscopists as it aids in assessing resectability and predicting the likelihood of lymph node metastasis (LNM). [4] Posteriorly, for SCC, the European Society of Gastrointestinal Endoscopy (ESGE) proposes to estimate the depth of invasion according to the Japan Esophageal Society (JES) classification that categorizes the lesions according to the type of microvessels, where type A, microvessels without severe irregularity correspond to

noncancerous/low-grade dysplastic lesions whereas type B microvessels with severe irregularity, divided into 3 groups (B1, B2, and B3) are suggestive of cancerous lesions. The overall accuracy of type B microvessels for predicting a tumor's depth of invasion was 90.5%. For AC-related lesions BING or PREDICT classifications, that core themselves in chromoendoscopy techniques, should be applied. [16–18]

Currently, ESGE suggests that ESD might be considered for en bloc resection of noncircumferential clinically staged T1a-m3/T1b-sm1 or for circumferential clinically staged T1a-m1/m2 esophageal SCC. On the other hand, for BE-associated lesions, ESGE suggests using ESD for lesions suspicious of submucosal invasion, for malignant lesions > 20mm, and for lesions in scarred/fibrotic areas. EMR is restricted to ≤ 20mm visible lesions with a low probability of submucosal invasion and for larger or multifocal dysplastic lesions. After endoscopic resection, it is recommended to do an ablation of all the BE mucosa. As previously mentioned, ESD is prioritized over surgery or chemoradiotherapy (CRT) in these patients due to its enhanced safety profile, minimally invasive nature, and superior cost-effectiveness. [4,17,19]

In terms of post-endoscopic resection management, a **very low risk (curative) resection**, in accordance with ESGE, is met when an *en bloc* R0 resection is achieved with histology no more advanced than m2 cancer, for SCC, or m3 cancer, for AC, with well to moderately differentiation, and with no lymphovascular invasion. In these cases, no further staging procedure or treatment is recommended. Conversely, *en bloc* R0 resection of an esophageal m3 or sm1 SCC, ideally less than 2 cm, or sm1 AC with the same previous histological characteristics, should be categorized as a **low risk (curative) resection**, and likewise, no further treatment is generally recommended. However, in these instances, there is a real (albeit low) risk of LNM, particularly if SCC > 20 mm in size, and complete staging is recommended, with the risk from further therapy, surgery, or CRT, being balanced against the risk of LNM, in a multidisciplinary discussion. SCC has a more limited scope for potentially curative endoscopic therapy due to its earlier invasion of submucosa and LNM. [4,17]

As previously stated ESD leads to more complications in comparison to EMR, such as pain post-procedure, perforation, bleeding, and, most importantly, esophageal stricture (ES). In the case of intraoperative perforation during esophageal ESD, endoscopic management should be initially attempted. [12,13,20–22] ES, the most common adverse event of esophageal ESD, vastly affects the quality of life of the patients and has been proven to have various risk factors. Studies have shown that its occurrence after ESD is related to the infiltration of postoperative inflammatory cells and vascular proliferation, and it mostly occurs in 2 to 4 weeks after ESD. [23–25] The most significant risk factor is linked to the extent of resection of the circumference of the esophageal lumen, with resections exceeding three-quarters substantially escalating the risk. The other factors are histological depth (depth of invasion above m1), cervical or upper thoracic location (upper third of

the esophagus), longitudinal length of the resection, Paris IIa/IIc lesions, muscular injury, longer procedure time and CRT history. [20,26–35] Refractory ES is commonly defined as an inability to successfully maintain stricture to a diameter of 14 mm over 5 sessions at 2-week intervals. [36–39]

In contemporary practice, addressing post-ESD strictures typically commences with dilation techniques, aimed at alleviating dysphagic symptoms in patients. Two primary types of dilators are employed: balloon-type dilators and push-type dilators such as Savary-Guilliard dilators. However, it is important to note that perforation is a potential complication associated with the use of these methods. [22,40–42] There's unanimity that there should be a focus on the prevention of ES, and a lot of methods were and are being created that are valid in different situations, being that habitually prevention therapy is recommended for lesions >1/2 of the esophageal circumference. Some of them are steroid therapy, such as steroid injection therapy (triamcinolone acetonide (TA)) or oral steroid administration (prednisone). Combined steroid therapy, both oral and injection steroid, is the standard nowadays, but it is mostly recommended when the lesions are circumferential. Lastly, we can recur to temporary auto-expandable metal stent placement, which is usually used in refractory cases after ESD. [22,24,41,43–45]

In Portugal, there is limited data available regarding the utilization of ESD for managing superficial esophageal lesions, primarily due to the relatively low incidence of this type of cancer in its early stages, henceforth the need for this article to shed light on the efficacy and safety of this procedure.

Objectives

The current study's primary objective is to assess the efficacy and safety of ESD for superficial esophageal lesions, and our secondary aims are to evaluate the efficiency of ES prevention techniques and to determine the principal predictive factors of ES and refractory ES.

Methods

The following research was carried out at the Gastroenterology Department of Unidade Local de Saúde de Santo António (ULSdSA). The study involved a retrospective analysis of the medical records of the patients who underwent esophageal ESD between January 2018 and December 2023 with a prospectively maintained database of all these patients. The evaluation of the lesions was made using high-resolution endoscopies, virtual chromoendoscopy, and acetic acid staining for BE-associated lesions or lugol staining for SCC-related lesions and classified according to the Paris classification. [37] The research gathered a comprehensive set of information about patients including their demographics, comorbidities, medication history (including antithrombotic therapy (AT) such as aspirin, P2Y12 antagonists, and dual antiplatelet therapy, as well as anticoagulant agents like warfarin, acenocoumarol, and direct oral anticoagulants (DOACs)), past medical records, surgical history, results of complementary diagnostic exams, and treatments. This data was obtained from the SClínico® and RSE® databases. To ensure patients' confidentiality, all data was coded and anonymized, and therefore, informed consent was not required. The study was approved by the *Conselho de Administração*, *Comissão de Ética para a Saúde*, *Gabinete Coordenador de Investigação* and *Direção de Departamento do Ensino, Formação e Investigação da ULSdSA* (REF. 2023.229(189-DEFI/181-CE)).

A single endoscopist performed all the esophageal ESDs according to a standardized procedure for all patients in a single center. Various aspects of the lesion and procedure were assessed, such as lesion size, circumferential range, fibrosis level, longitudinal length of resection, the type of knife used, the technique employed, procedure time, traction assistance, and adverse events. The gross morphology of the lesions was classified in compliance with the Paris Classification in type 0-I, type 0-II, type 0-III, and complex morphology when there was a combination of multiple forms. In addition, the study evaluates the occupation of the lesion's lumen circumference, the TA injection on the scar, the intake of oral prednisolone, or the combination of both, if required.

To assess the efficacy of these procedures, we used the percentage of ***en bloc*** **resection,** which is defined as a complete and intact endoscopic resection of the lesion. With the parameters on the histopathological evaluation, we observed the percentage of **R0 resection**, which is defined as negative, lesion-free, horizontal and vertical margins, and the proportion of **curative resection**, which depends not only on the margins, but also the degree of differentiation, depth of invasion (intramucosal vs. submucosal), and the presence of vascular, lymphatic, or perineural permeation. The criteria utilized to deem the procedure curative were based on the guidelines established by the ESGE. [46–48]

The safety of esophageal ESD was assessed by examining potential adverse events. Post-procedural bleeding was identified based on classic clinical symptoms such as melena, hematochezia, hematemesis, or a drop of ≥ 2 g/dL in hemoglobin levels compared to the patient's baseline that happened up to 30 days post-ESD. [49] Perforation of the esophagus was described as a transmural hole or tear between the esophageal lumen and the mediastinum, which can lead to mediastinitis, pericarditis, and possibly sepsis or shock. [50,51] ES post-ESD was established when a patient experienced dysphagia and a high-definition endoscopy was performed to confirm the presence of ES. Treatment included dilation techniques or stent placement, with prophylaxis comprising TA injection and/or oral prednisolone, which is taken on the 3rd day after ESD, with an initial dose of 30 mg/d, and then decreased gradually (30, 30, 25, 25, 20, 15, 10, and 5 mg for 1 week each) according to the method developed by Yamaguchi et al in 2011. [43,52] Refractory ES was defined as ≥5 dilations or requiring stent placement. [36–38] Another important factor we considered was thrombosis, which we defined as the occurrence of thrombotic events such as stroke, pulmonary embolism, transient ischemic attack, or deep vein thrombosis within the seven days before the procedure and up to thirty days after it.

To identify risk factors associated with ES following esophageal ESD, the study compared various patient-related factors including gender, age, and comorbidities; lesion-related factors such as size, depth of invasion, and circumference occupation; and procedure-related parameters such as operating time and longitudinal resection length. For the analysis of lesion and procedure-related factors, each lesion was considered an independent procedure, and all esophageal lesions were included.

Statistical analysis

All the patients were recorded in a database with anonymized information that included demographic, clinical, histopathological, and procedural characteristics.

Continuous variables were tested for normality using Shapiro-Wilk test and were then described using the mean± standard deviation (SD), or median and interquartile range (IQR), when its distribution was normal and non-normal, respectively. They were recoded into categorical variables to be compared.

Categorical variables were presented as absolute frequencies and relative frequencies, n (%), and were compared with the outcome of developing ES using either the Pearson Chi-square test or Fisher's Exact test, depending on the appropriateness of each method.

Statistical analyses were performed using IBM SPSS Statistics version 29.0.1.1 (IBM Corp. Armonk, New York, USA). P-values of < 0.05 were considered statistically significant.

Results

There was a total of 19 esophageal ESDs performed in 18 patients, during the 6-year evaluation of this study. These patients had a mean follow-up of 30.9 (±20.6) months.

Most patients were male (n=16, 88.9%), and the mean age was 66.8 (± 8.6) years. Many patients had comorbidities, such as hypertension (n=12, 66.7%), diabetes mellitus (n=3, 16.7%), ischemic heart disease (n=1, 5.6%), cerebrovascular disease (n=2, 11.1%), lung disease (n=2, 11.1%), and liver cirrhosis (n=1, 5.6%). Approximately one-fourth of the patients were under AT (n=5, 27.8%). Among the antiplatelet agents, 22.2% of patients were taking aspirin (n=4), and 5.6% were taking clopidogrel (n=1). None of the patients were under dual antiplatelet therapy. Regarding anticoagulant agents, 5.6% (n=1) of the patients were taking DOACs.

A total of 19 esophageal lesions were submitted to esophageal ESD, as previously stated. The median size of the lesions was 25.0 (IQR 13.0-42.0) mm. A total of 5.3% (n=1) of the lesions were in the upper esophagus, 26.3% (n=5) were in the middle esophagus and 68.4% (n=13) were in the distal esophagus. The morphology of the lesions was categorized according to Paris Classification: 0-II (n=10, 52.6%), complex morphology (n=8, 42.1%), and 0-I (n=1, 5.3%). The mean procedure time was 122.3 (± 73.4) min, and the mean longitudinal length of the resection was 6.9 (± 3.3) cm. Regarding the circumference occupation, 68.42% (n=13) lesions occupied ≥3/4, and 31.6% (n=6) were circumferential lesions. Traction assistance was employed in 47.4% (n=9) of cases. Regarding histopathology, 5.3 % (n=1) were SCC-HGD, 10.5% (n=2) were BE-HGD, 21.0% (n=4) were AC and 63.2% (n=12) were SCCs. Ulceration was present in 57.89% (n=11) of the lesions. Concerning the depth of invasion, m1 was reported in 31.58% (n=6) of the cases, m2 was also described in 31.58% (n=6), m3 existed in 15.79% (n=3), and lastly, invasion further than sm1 was stated in 21.05% (n=4).

The baseline characteristics of the patients are shown in Table I, and the baseline characteristics of lesions and procedures are displayed in Table II.

In terms of efficacy, out of the 19 esophageal lesions, 6 were related to BE. All 6 lesions were in the distal esophagus, and 4 of them were ACs, while the other 2 were lesions with HGD. The *en bloc* rate for AC-related lesions was 100%, while the R0 rate was 83.3% (5/6). Likewise, the curative resection rate for these lesions was 83.3%. In contrast, 13 squamous cell neoplasias were resected in the esophagus, with 1 lesion in the upper, 5 lesions in the middle, and 7 lesions in the distal esophagus. The histopathologic assessment showed that 12 of these lesions were SCC, while the other one had HGD. The *en bloc* R0 rate for these lesions was 100%. However, the curative resection

rate was 69.2% (9/13). The most common reason for noncurative resection was deep submucosal invasion (n=4, 100%), preceded by lymphovascular permeation (n=2, 50%).

The results showing the efficacy of esophageal ESD, independently for SCC-related lesions and BE-related lesions are shown in Table III.

In what concerns safety, there were no cases of delayed bleeding and perforation. However, there was a case of a cardiovascular event, more specifically a thromboembolism, on the 13th day of hospitalization treated initially with enoxaparin.

Regarding ES, eight cases were reported (42.1%). All these eight cases occurred after ESD of at least three-fourths of the circumference being that 6/8 cases (75%) occurred after circumferential ESD. A total of 12.5% (n=1) of the lesions were in the cervical esophagus, and 87.5% (n=7) were in the thoracic and distal esophagus. Refractory ES occurred in 6/8 cases (75%), and both dilation techniques and stent placement were performed individually in 5/8 cases (62.5%). This happened despite the use of combined prophylactic steroid measures in 6 of the patients (75%) and individual oral prednisolone intake post-ESD in 1 patient (12.5%).

Two patients died (11.1%) throughout the follow-up of this study, but not because of an ESD-related adverse event. One patient died because of advanced-stage EC, and the other patient died of metastasized lung cancer. Overall and disease-free survival rates at 2 years for patients having a follow-up of at least 2 years were 81.8% (9/11).

The outcomes presenting the safety and overall survival of esophageal ESD, independently for SCC-related lesions and BE-related lesions, are shown in Table III. The analysis of Refractory ES in our patients is displayed in Table IV.

We determined that there was a positive association between ES after esophageal ESD and lesion size (>30 mm) (p=0.024), time of the procedure (>120 minutes) (p=0.024), longitudinal resection length (≥ 5 cm) (p=0.045), lesion's occupation of at least three-fourths of the circumference (p=0.018), and, consequently, circumferential lesion (p=0.021).

The lesion-related and procedure-related risk factors are shown in Table II.

We assessed that there was no statistically significant association between ES after ESD and any of the patient-related factors we evaluated in our study. The patient-related risk factors are exhibited in Table I.

Discussion

A registry for ESD procedures was established at the ULSdSA to evaluate curative resection rates and long-term outcomes. In this article, the results from the ULSdSA ESD registry are presented, incorporating data from 19 procedures. Although the sample size is small, this is an important step in assessing the effectiveness of ESD for treating EC on a national level. The results include information on en bloc resection, R0 resection, curative resection rates, as well as complication and survival rates. [46,47]

Concerning patient characteristics and risk factors, it was observed that the majority of patients were male, with a mean age of 66.8 years. Approximately one-fourth of the patients were under AT, but there were no cases of delayed bleeding which might imply that AT in the perioperative period isn't as important in terms of outcomes in esophageal ESD as it is in gastric ESD, where bleeding rates post-ESD are usually higher. [53]

This study demonstrates the high efficacy of ESD in treating BE-related lesions, though the *en bloc* resection rate was 100%, and the R0 and curative resection rates were lower at 83.3%. The only case where positive margins were encountered was an RX, which demonstrates the difficulty of delineating BE-related lesions, but in this case, salvage therapy with EMR was performed. To better our results at complete resection with clear margins, which is essential for preventing recurrence, possibly we can modify the ESD technique from conventional resection (marking is performed up to 5mm from the tumor margins) to wide-field ESD, where marking is performed approximately 10mm from the tumor margins, as suggested by a study, which leads to high en bloc resection rates, that provide a more precise histologic assessment, and favorable lateral R0, associated with reduced local recurrence. Additionally, it enables dissection with a high safety profile. These findings align with previous studies showing high en bloc resection rates and low recurrence after curative resection, affirming ESD as a valuable tool for managing BE neoplasia. Additionally, ESD is validated as a salvage therapy for BE-associated lesions previously treated with EMR or ablation therapy, proving feasible and safe while achieving high en bloc and R0 resection rates. EMR remains an alternative for certain BE lesions. However, the six lesions treated with ESD in this study did not meet the ESGE selection criteria for EMR. Therefore, it is challenging to directly compare the two techniques, as ESD was appropriately performed on selected lesions. [54–56]

On the other hand, concerning SCC, while the *en bloc* R0 resection rates were 100%, the curative resection rate was notably lower at 69.2%. This discrepancy highlights the challenges in achieving curative outcomes, but it aligns with previous studies and guidelines, where approximately 70% of cases of SCC lesions have a curative outcome. Thus, this suggests the need

for improved pre-procedure assessment to identify lesions with a higher risk of noncurative resection. [18,57] While not all patients receive adjuvant therapies (such as surgery and/or chemoradiotherapy) following a high-risk (noncurative) resection, it is strongly recommended for esophageal SCC. In these instances, thorough staging is imperative. The primary risk factor for LNM is lymphovascular invasion, which was observed in two cases. This factor is also the strongest indicator for adjuvant therapy, ensuring appropriate treatment for these patients. However, submucosal (sm2) invasion was the sole high-risk criterion in two other patients. For elderly or otherwise unfit patients, as in these cases, the risk of additional therapy might outweigh the benefits compared to surveillance alone. Such decisions should be made during a multidisciplinary team meeting, which is recommended for all patients with noncurative resection. [17] An interesting occurrence was that most SCC lesions were present in the distal esophagus, which is unusual because SCC presents itself mainly in the upper or middle third of the esophagus. This may go against the paradigm nowadays accepted, but as we have a small sample, we would have to evaluate patients on a much larger scale.

Regarding the safety of ESD in the esophagus, remarkably, there were no cases of delayed bleeding or perforation. In Japan, where the procedure is best established, the complication rates (including perforation, peritonitis, and bleeding) are 3.3% for esophageal ESD. [12] Normally, the rates of perforation are 1.4%-4.6% and in our center, it is 0%. The outcomes may be attributed to the use of traction-assisted ESD in the procedures where an optimal endoscopic view wasn't possible, which has been shown to reduce the incidence of perforation. Additionally, the use of endoscopic clips in areas of greater fragility as a preventive measure diminishes inflammation following esophageal ESD and positively influences the clinical course post-ESD. [22,58,59] There was also one case of thromboembolism observed in a specific patient in whom the procedure exceeded five hours, although the appropriate prophylactic measures were put into practice.

However, the study reports an ES rate of 42.1%, indicating a significant incidence of ES formation. This is noteworthy because the incidence of post-ESD stricture in superficial esophageal neoplasms is predicted to be 5% to 17%, although the exact incidence remains unknown. It is crucial to note that all cases of ES formation occurred when at least three-fourths of the circumference was occupied, which is considered one of the most critical risk factors. [60] This underscores the importance of implementing strategies to mitigate this complication, given its adverse impact on patient quality of life and the necessity for repeated interventions. Aside from the fact that all the lesions occupied more than three-fourths of the circumference, more proven risk factors were present, which shows that even with preventative stricture measures the patients were still at a very high risk of developing an ES.

Our study also notes the positive association between ES and various factors such as lesion size ≥30 mm, procedure time ≥120 minutes, longitudinal resection length ≥5 cm, circumference occupation ≥3/4, and circumferential lesions suggesting that these characteristics play a significant role in predicting the risk of stricture formation post-ESD, corroborating previous published studies in this area. [20,26–31] Clinicians can use these factors to identify patients at higher risk and implement preventive measures accordingly. As we only had one case of cervical esophagus cancer, it is difficult to conclude anything about the location of lesions and stenosis. Still, many studies have stated that these two have a strong correlation. We likewise didn't note a statistical relation between ES and the depth of invasion, but, as well, many previous articles have reported this as an important predictive factor. [48,61]

Numerous studies have aimed to develop and validate scoring models capable of effectively identifying patients at risk of developing ES, with some achieving success. An ideal model can be selected and implemented on a broader scale to assess its applicability across different countries, patient demographics, and diseases. These models are designed to accurately predict the risk of ES following ESD, which is crucial for guiding clinical interventions and reducing stricture incidence. One such model ranges from 0 to 16 points, corresponding to a probability of ES from 0% to 100%. This study validated a scoring model comprising six independent predictors identified in multivariate analysis: operating time (≥1 h), age (≥65 years), lesion location (upper thoracic due to smaller diameter), lesion circumference (≥2/3), longitudinal resection length, and depth of infiltration (≥m3-sm1). This simplified model with fewer risk factors is easier to apply, although further optimization is needed to enhance accuracy. Additionally, the model should be updated to incorporate novel risk factors identified in prospective studies in the future. [28,62]

Many measures can be implemented during the procedure or after as already indicated to prevent the formation of ES. There is steroid therapy, such as intraprocedural TA injection or oral prednisolone administration, and some centers combine both techniques, as was done in this study. Previous research has yielded conflicting results, and in our case, nearly 90% of the patients who developed ES underwent these preventative treatments. This raises questions about the effectiveness of prophylactic steroid treatment, as it is nowadays implemented. A study hypothesized increasing the dose of oral prednisone acetate (50 mg/d) and prolonging the treatment time (13 weeks) in 14 patients with SCC-associated lesions occupying ≥3/4 circumference after ESD. Meticulous attention was paid to avoid the injury of the muscularis propria, a known risk factor for ES, and patients with additional CRT treatment or surgery were excluded. During these weeks, a proton pump inhibitor, oral calcium, and vitamin D3 were taken simultaneously, to prevent systemic steroids associated adverse events. The outcome was remarkable, since every single

patient remained free from ES, or any negative effects related to glucocorticoid treatment. Henceforth, this could serve as a hypothesis warranting further consideration. [23,43,45]

Other prophylactic techniques are being studied like the self-assembling peptide gel that has been shown to promote tissue healing and re-epithelialization and a study has demonstrated that its application is easy, quick, and associated with a relatively low stricture rate compared to other prophylactic methods. [63] Moreover, surprisingly, statin drugs are being studied in preventing post-ESD ES, exhibiting a substantial decrease in the incidence of ES as well as in the proportion of individuals developing refractory ES compared to non-treatment and other prophylactic options. This could likewise be a favorable option for patients who require statin drugs for combined cardiovascular and cerebrovascular diseases. [44] Esophageal mucosal autograft might also prove to be an efficient approach to promoting local esophageal re-epithelization, which can form a barrier against gastric acid and prevent ES after wide-spread ESD, at least 5 mm margins. [64] Further investigation, as the ones previously detailed, is warranted to elucidate the underlying mechanisms and optimize preventive strategies, being that new approaches to prevent ES are now primarily focused on anti-fibrotic strategies. [44] Lastly, mitomycin C (MMC) injections have recently been introduced as an isolated treatment or in combination with dilation techniques and have astonishing results, but most of the investigation is done in children with ES post-caustic ingestion. MMC is an antineoplastic agent that inhibits fibroblast proliferation and decreases fibroblastic collagen synthesis, and its application consists of 4 quadrant injections of 0.4 mg/mL MMC. Studies in adults post esophageal ESD are needed before MMC injection can be broadly implemented to prevent ES. [39,65,66]

Regarding survival rates, the 2-year disease-free survival rate observed in this study was notably high at 81.8%. This goes in agreement with the WESTEROS study, which has a similar rate, but contrasts with other studies, although they have 5-year survival rates instead of 2-year, which report substantially lower survival rates, 62%, likely attributable to the comorbidities present in their selected patient populations.[57]

This study has key positive aspects since it was the first study to our knowledge to evaluate the efficacy and safety of esophageal ESD in Portugal, and it corroborated previously identified risk factors for the development of ES after esophageal ESD. Also, the procedures were done by a single experienced operator with a high volume of practice during a long period (8 years). There was likewise a clear definition of ES post-ESD and its management.

Nevertheless, our study had some **limitations**. The study's sample size is relatively small, limiting the generalizability of the findings. It was a retrospective analysis, single-centered, but possible bias was avoided. The follow-up time was insufficient for some lesions, mainly affecting our survival rates in SCC lesions, and we could not comprehensively evaluate the refractory ES in some

patients. Due to these limitations, prospective randomized controlled studies should be established to validate the efficacy and safety of this procedure, but that is difficult at a hospital level.

Future studies with larger cohorts are needed to validate the results. While the study reports promising short-term outcomes, long-term follow-up data are essential to assess the durability of ESD in preventing disease recurrence and improving overall survival. Advances in endoscopic imaging and therapeutic techniques may further enhance the safety and efficacy of ESD. Future studies should explore the role of novel technologies in optimizing patient outcomes and reducing procedural complications, so it is critical to investigate more efficient ways of preventing ES because it is a severe complication that takes a toll on the patient's life.

Conclusion

The study provides significant insights into the efficacy and safety of ESD for managing BE-associated lesions and SCC.

It demonstrates impressive success rates, particularly evident in BE-related lesions, where R0 and curative resection were encouraging at 83%, which entails that ESGE's indications for ESD treatment of BE lesions should be obeyed. While challenges persist in achieving curative outcomes for SCC lesions, the findings align with previous research, emphasizing the necessity for enhanced preoperative assessment to identify high-risk lesions.

Despite encountering a relatively high rate of ES formation, this rate was expected considering the circumferential involvement. Strategies such as adjusting the prophylactic steroid therapy regimen for ES may be contemplated. Patient characteristics and lesion features, including size, procedure time, longitudinal resection length, and circumferential involvement, emerge as useful predictors of post-ESD stricture formation, facilitating risk stratification and tailored preventive interventions. Implementing a predictive scoring model may be a valuable consideration.

While the study provides significant short-term outcomes, long-term follow-up data are imperative to evaluate the durability of ESD in preventing disease recurrence and improving overall survival. Collaboration across institutions and prospective studies is warranted to validate these findings.

In conclusion, ESD represents a substantial advancement in the management of esophageal neoplasms, offering high rates of complete resection and curative outcomes with a favorable safety profile. Further refinement of preventive strategies for ES post-ESD is necessary.

Appendix

Table I - Baseline characteristics of patients (analysis of patient-related predictive factors for ES after ESD)

Variable	Total	Esophageal Stricture		p value
		Absent	Present	
Number of Patients, n (%)	18	10 (55.6)	8 (44.4)	
Gender, n (%)				
Male	16 (88.9)	10 (62.5)	6 (37.5)	0.183
Female	2 (11.1)	0 (0.0)	2 (100.0)	
Age, years (mean ± SD)	66.8 ± 8.6			
<65 years, n (%)	8 (44.4)	4 (50.0)	4 (50.0)	1.000
≥65 years, n (%)	10 (55.6)	6 (60.0)	4 (40.00)	
Comorbidities, n (%)				
Hipertension	12 (66.7)	7 (58.3)	5 (41.7)	1.000
Diabetes mellitus	3 (16.7)	2 (66.7)	1 (33.3)	1.000
Ischemic heart disease	1 (5.6)	1 (100.0)	0 (0.0)	1.000
Cerebrovascular disease	2 (11.1)	1 (50.0)	1 (50.0)	1.000
Lung disease	2 (11.1)	1 (50.0)	1 (50.0)	1.000
Liver cirrhosis	1 (5.6)	1 (100.0)	0 (0.0)	1.000
ASA, n (%)				
II	10 (55.6)	4 (40.0)	6 (60.0)	0.188
III	8 (44.4)	6 (75.0)	2 (25.0)	
Antithrombotic therapy, n (%)	6 (33.3)	3 (50.0)	3 (50.0)	1.000
Antiplatelet agents				
Aspirin	4 (22.2)	2 (50.0)	2 (50.0)	
Clopidogrel	1 (5.6)	1 (100.0)	0 (0.0)	
Anticoagulant agents				
DOAC	1 (5.6)	0 (0.0)	1 (100.0)	

Table II – Baseline characteristics of esophageal lesions and esophageal ESD (lesion-related and procedure-related predictive factors for ES after ESD)

Variable	Total	Esophageal Stricture		p value
		Absent	Present	
Number of Lesions, n (%)	19	11 (57.9)	8 (42.1)	
Lesion Size, mm (Median [P25-P75])	25.0 (13.0-42.0)			
≥30 mm	8 (42.1)	2 (25.0)	6 (75.0)	**0.024**
Location, n (%)				
Cervical	1 (5.3)	0 (0.0)	1 (100.0)	
Thoracic	5 (26.3)	4 (80.0)	1 (20.0)	
Distal	13 (68.4)	7 (53.8)	6 (46.2)	
Paris Classification, n (%)				
0-I	1 (5.3)	1 (100.0)	0 (0.0)	
0-II	10 (52.6)	7 (70.0)	3 (30.0)	
Complex	8 (42.1)	3 (37.5)	5 (62.5)	
Procedure Time, min (mean ± SD)	122.3 ± 73.4			
≥120 min	8 (42.1)	2 (25.0)	6 (75.0)	**0.024**
Longitudinal Length, cm (mean ± SD)	6.9 ± 3.3			
≥5 cm	14 (73.7)	6 (42.9)	8 (57.1)	**0.045**
Circumference Occupation				
≥3/4	13 (68.4)	5 (38.5)	8 (61.5)	**0.018**
Circumferential	6 (31.6)	0 (0.0)	6 (100.0)	**0.021**
Histology, n (%)				
SCC - HGD	1 (5.3)	1 (100.0)	0 (0.0)	
BE - HGD	2 (10.5)	1 (50.0)	1 (50.0)	
Adenocarcinoma	4 (21.0)	2 (50.0)	2 (50.0)	
Squamous cell carcinoma	12 (63.2)	7 (58.3)	5 (41.7)	
Ulceration	11 (57.9)	5 (45.5)	6 (54.5)	0.352
Depth of Invasion				
HGD/M1	6 (31.6)	5 (83.3)	1 (16.7)	0.351
M2	6 (31.6)	2 (33.3)	4 (66.7)	
M3	3 (15.8)	2 (66.7)	1 (33.3)	
>SM1	4 (21.0)	2 (50.0)	2 (50.0)	

Table III – Efficacy and Safety of ESD for superficial esophageal lesions

Variable	Total	BE lesions		SCC lesions	
		HGD	AC	HGD	SCC
Number of Lesions, n (%)	19	2 (10.5)	4 (21.0)	1 (5.3)	12 (63.2)
Efficacy					
Resectability, n (%)					
En bloc resection	19 (100.0)				
R0 resection	18 (94.7)	2	3	1	12
		5 (83.3)		13 (100.0)	
Curative resection	14 (73.7)	2	3	1	8
		5 (83.3)		9 (69.2)	
Depth of Invasion, n (%)					
>SM1	4 (21.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (33.3)
Lymphovascular Permeation, n (%)	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)
Safety					
Adverse Events, n (%)	8 (42.1)	1 (12.5)	2 (25.0)	0 (0.0)	5 (62.5)
Bleeding	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Perforation	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Esophageal Stricture	8 (42.1)	1 (12.5)	2 (25.0)	0 (0.0)	5 (62.5)
Cardiovascular Events	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Follow-up, months (Mean ± SD)	30.9 ± 20.6				
Follow-up ≥ 24 months, n (%)	11 (57.9)				
Survival Rate, n (%)	9 (81.8)	1 (11.2)	4 (44.4)	0 (0.00)	4 (44.4)
Deaths, n (%)	2 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
Lesion-related	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Non ESD- related	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)

Table IV – Refractory ES and Prophylactic Techniques

Variable	Total	Refractory ES	
		Absent	Present
Strictures, n (%)	8	2 (25.0)	6 (75.0)
EBD ≥5	5 (62.5)		
Stent	5 (62.5)		
Prophylatic measures, n (%)	7 (87.5)		
TA injection	6 (75.0)	0 (0.0)	6 (100.0)
Prednisolone Administration	7 (87.5)	1 (14.3)	6 (85.7)

References

1. Liu CQ, Ma YL, Qin Q, et al. Epidemiology of esophageal cancer in 2020 and projections to 2030 and 2040. *Thorac Cancer*. 2023;14(1):3. doi:10.1111/1759-7714.14745
2. Huang FL, Yu SJ. Esophageal cancer: Risk factors, genetic association, and treatment. *Asian J Surg*. 2018;41(3):210-215. doi:10.1016/J.ASJSUR.2016.10.005
3. José M, Arnal D, Ferrández Arenas Á, et al. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. *World J Gastroenterol*. 2015;21(26):7933-7943. doi:10.3748/wjg.v21.i26.7933
4. Zeki SS, Bergman JJ, Dunn JM. Endoscopic management of dysplasia and early oesophageal cancer. *Best Pract Res Clin Gastroenterol*. 2018;36-37:27-36. doi:10.1016/j.bpg.2018.11.003
5. Bujanda DE, Hachem C. Barrett's Esophagus. *Mo Med*. 2018;115(3):211. doi:10.1097/pas.0000000000000598
6. Barret M, Prat F. Diagnosis and treatment of superficial esophageal cancer. *Ann Gastroenterol*. 2018;31(3):256. doi:10.20524/AOG.2018.0252
7. Manner H, Pech O. Measurement of the tumor invasion depth into the submucosa in early adenocarcinoma of the esophagus (PT1b): Can microns be the new standard for the endoscopist? *United European Gastroenterol J*. 2015;3(6):501-504. doi:10.1177/2050640615617724
8. Bhatt A, Abe S, Kumaravel A, Vargo J, Saito Y. Indications and techniques for endoscopic submucosal dissection. *American Journal of Gastroenterology*. 2015;110(6):784-791. doi:10.1038/ajg.2014.425
9. Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol*. 2006;41(10):929-942. doi:10.1007/s00535-006-1954-3
10. Fujishiro M. Endoscopic submucosal dissection for stomach neoplasms. *World Journal of Gastroenterology : WJG*. 2006;12(32):5108. doi:10.3748/WJG.V12.I32.5108
11. Nishizawa T, Yahagi N. Endoscopic mucosal resection and endoscopic submucosal dissection: Technique and new directions. *Curr Opin Gastroenterol*. 2017;33(5):315-319. doi:10.1097/MOG.0000000000000388
12. Harlow C, Sivananthan A, Ayaru L, Patel K, Darzi A, Patel N. Endoscopic submucosal dissection: an update on tools and accessories. *Ther Adv Gastrointest Endosc*. 2020;13. doi:10.1177/2631774520957220
13. Fukuzawa M, Gotoda T. History of endoscopic submucosal dissection and role for colorectal endoscopic submucosal dissection: A Japanese perspective. *Gastrointestinal Intervention*. 2012;1(1):30-35. doi:10.1016/J.GII.2012.09.001
14. Song BG, Min YW, Lee JH, et al. Efficacy and safety of endoscopic submucosal dissection in elderly patients with esophageal squamous cell carcinoma. *Surg Endosc*. 2017;31(10):3905-3911. doi:10.1007/S00464-017-5421-4
15. SPED - SPED. Accessed May 16, 2024. https://www.sped.pt/index.php/component/content/article/28-novidades/destaques/1594-caso-mes-maio-de-2024?Itemid=101
16. Oyama T, Inoue H, Arima M, et al. Prediction of the invasion depth of superficial squamous cell carcinoma based on microvessel morphology: magnifying endoscopic classification of the Japan Esophageal Society. *Esophagus*. 2017;14(2):105-112. doi:10.1007/s10388-016-0527-7
17. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2022. *Endoscopy*. 2022;54(6):591-622. doi:10.1055/A-1811-7025
18. Ishihara R, Arima M, Iizuka T, et al. Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. *Digestive Endoscopy*. 2020;32(4):452-493. doi:10.1111/DEN.13654
19. Al-Haddad MA, Elhanafi SE, Forbes N, et al. American Society for Gastrointestinal Endoscopy guideline on endoscopic submucosal dissection for the management of early esophageal and gastric cancers: methodology and review of evidence. *Gastrointest Endosc*. 2023;98(3):285-305.e38. doi:10.1016/J.GIE.2023.03.030
20. Isomoto H, Yamaguchi N, Minami H, Nakao K. Management of complications associated with endoscopic submucosal dissection/ endoscopic mucosal resection for esophageal cancer. *Dig Endosc*. 2013;25 Suppl 1(SUPPL.1):29-38. doi:10.1111/J.1443-1661.2012.01388.X
21. Fujishiro M, Yahagi N, Kakushima N, et al. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. *Clin Gastroenterol Hepatol*. 2006;4(6):688-694. doi:10.1016/J.CGH.2006.03.024
22. Hatta W, Koike T, Abe H, et al. Recent approach for preventing complications in upper gastrointestinal endoscopic submucosal dissection. *DEN open*. 2021;2(1). doi:10.1002/DEO2.60
23. Zhan SG, Wu BH, Li DF, et al. Oral higher dose prednisolone to prevent stenosis after endoscopic submucosal dissection for early esophageal cancer. *World J Clin Cases*. 2022;10(36):13264. doi:10.12998/WJCC.V10.I36.13264
24. Jain D, Singhal S. Esophageal Stricture Prevention after Endoscopic Submucosal Dissection. *Clin Endosc*. 2016;49(3):241-256. doi:10.5946/CE.2015.099
25. Yang F, Hu Y, Shi Z, et al. The occurrence and development mechanisms of esophageal stricture: state of the art review. *J Transl Med*. 2024;22(1). doi:10.1186/S12967-024-04932-2
26. Lin N, Lin J, Gong J. Risk factors of postoperative stricture after endoscopic submucosal dissection for superficial esophageal neoplasms: A meta-analysis. *Medicine*. 2021;100(51):E28396. doi:10.1097/MD.0000000000028396
27. Xu Y, Lin Z, Zhong S, Liang W. Muscular injury was identified the risk factor of post-operative stenosis after large area but non-circumferential esophageal endoscopic submucosal dissection. *Scand J Gastroenterol*. 2022;57(6):740-747. doi:10.1080/00365521.2022.2034939

28. Xia S yuan, Lu Q, Wang Z jing, Gan T, Yang J lin, Wang Z. Development and validation of a model to determine the risk of esophageal strictures after endoscopic submucosal dissection for esophageal neoplasms. *Surg Endosc*. 2023;37(3):2163-2172. doi:10.1007/S00464-022-09729-2
29. Li X, Xing J, Li P, et al. A nomogram and risk classification system predicting esophageal stricture after endoscopic submucosal dissection of a large area for early esophageal cancer. *J Surg Oncol*. 2023;127(4):568-577. doi:10.1002/jso.27172
30. Zhou B, Zhao Z, Wang XW, et al. Prediction of Esophageal Stricture after Endoscopic Submucosal Dissection in Patients with Early Esophageal Cancer. *J Gastrointest Surg*. 2022;26(12):2434-2443. doi:10.1007/S11605-022-05467-X
31. Miyake M, Ishihara R, Matsuura N, et al. Predictors of stricture after non-circumferential endoscopic submucosal dissection of the esophagus and single-dose triamcinolone injection immediately after the procedure. *Gastrointest Endosc*. 2023;98(2):170-177. doi:10.1016/J.GIE.2023.03.017
32. Tang J, Kong F, Li J, Liu F, Kong X, Li Z. Independent risk factors for esophageal refractory stricture after extensive endoscopic submucosal dissection. *Surg Endosc*. 2021;35(7):3618-3627. doi:10.1007/S00464-020-07840-W
33. Geng ZH, Zhu Y, Li QL, et al. Muscular injury as an independent risk factor for esophageal stenosis after endoscopic submucosal dissection of esophageal squamous cell cancer. *Gastrointest Endosc*. 2023;98(4):534-542.e7. doi:10.1016/J.GIE.2023.05.046
34. Chen M, Dang Y, Ding C, Yang J, Si X, Zhang G. Lesion size and circumferential range identified as independent risk factors for esophageal stricture after endoscopic submucosal dissection. *Surg Endosc*. 2020;34(9):4065-4071. doi:10.1007/S00464-020-07368-Z
35. Iizuka T, Kikuchi D, Hoteya S, Kajiyama Y, Kaise M. Efficacy and safety of endoscopic submucosal dissection for superficial cancer of the cervical esophagus. *Endosc Int Open*. 2017;5(8):E736-E741. doi:10.1055/S-0043-112493
36. Miwata T, Oka S, Tanaka S, et al. Risk factors for esophageal stenosis after entire circumferential endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *Surg Endosc*. 2016;30(9):4049-4056. doi:10.1007/S00464-015-4719-3
37. Mizuno J, Urabe Y, Oka S, et al. Predictive factors for esophageal stenosis in patients receiving prophylactic steroid therapy after endoscopic submucosal dissection for esophageal squamous cell carcinoma. *BMC Gastroenterol*. 2024;24(1):1-8. doi:10.1186/S12876-024-03135-9/FIGURES/2
38. Pérez-Cuadrado Robles E, Moreels TG, Piessevaux H, Yeung R, Aouattah T, Deprez PH. Risk factors of refractory post-endoscopic submucosal dissection esophageal strictures. *Revista espanola de enfermedades digestivas*. 2021;113(12):813-819. doi:10.17235/REED.2021.8061/2021
39. Siersema PD. How to Approach a Patient With Refractory or Recurrent Benign Esophageal Stricture. *Gastroenterology*. 2019;156:7-10. doi:10.1053/j.gastro.2018.11.040
40. Yoda Y, Yano T, Kaneko K, et al. Endoscopic balloon dilatation for benign fibrotic strictures after curative nonsurgical treatment for esophageal cancer. *Surg Endosc*. 2012;26(10):2877-2883. doi:10.1007/S00464-012-2273-9
41. Yamamoto Y, Kikuchi D, Nagami Y, et al. Management of adverse events related to endoscopic resection of upper gastrointestinal neoplasms: Review of the literature and recommendations from experts. *Dig Endosc*. 2019;31 Suppl 1(S1):4-20. doi:10.1111/DEN.13388
42. Ahmad M, Janjua I, Ayub M, Zaman M, Gilani N. Comparing the Safety & Efficacy of Savary-Gilliard and Balloon Dilatators in Corrosive Esophageal Strictures. 13(2).
43. Hikichi T, Nakamura J, Takasumi M, et al. Prevention of Stricture after Endoscopic Submucosal Dissection for Superficial Esophageal Cancer: A Review of the Literature. *J Clin Med*. 2021;10(1):1-17. doi:10.3390/JCM10010020
44. Duan Y, Jia W, Liang Y, Zhang X, Yang Z, Yang Q. Progress in the treatment and prevention of esophageal stenosis after endoscopic submucosal dissection. *Clin Res Hepatol Gastroenterol*. 2024;48(3). doi:10.1016/J.CLINRE.2024.102290
45. Jia Y, Guo B, Zhang W, Li E, Zhang Q. Efficacy and safety of triamcinolone acetonide in the prevention of esophageal stricture after endoscopic submucosal dissection: a meta-analysis. *Dis Esophagus*. 2022;35(12). doi:10.1093/DOTE/DOAC039
46. Fleischmann C, Probst A, Ebigbo A, et al. Endoscopic Submucosal Dissection in Europe: Results of 1000 Neoplastic Lesions From the German Endoscopic Submucosal Dissection Registry. *Gastroenterology*. 2021;161(4):1168-1178. doi:10.1053/j.gastro.2021.06.049
47. Rodríguez de Santiago E, Herreros-de-Tejada A, Albéniz E, et al. Implementation of esophageal endoscopic submucosal dissection in Spain: Results from the nationwide registry. *Gastroenterol Hepatol*. 2024;47(2):119-129. doi:10.1016/J.GASTROHEP.2023.02.008
48. Rodríguez de Santiago E, van Tilburg L, Deprez PH, et al. Western outcomes of circumferential endoscopic submucosal dissection for early esophageal squamous cell carcinoma. *Gastrointest Endosc*. 2024;99(4):511-524.e6. doi:10.1016/J.GIE.2023.10.042
49. Choi J, Cho SJ, Na SH, et al. Use of direct oral anticoagulants does not significantly increase delayed bleeding after endoscopic submucosal dissection for early gastric neoplasms. *Sci Rep*. 2021;11(1):9399. doi:10.1038/S41598-021-88656-Z

50. Adams JG. *Emergency Medicine: Clinical Essentials, SECOND EDITION*. Elsevier; 2012. Accessed May 29, 2024. http://www.sciencedirect.com:5070/book/9781437735482/emergency-medicine
51. Zaheer A, Raman SP. *Diagnostic Imaging: Gastrointestinal*. Elsevier; 2015. doi:10.1016/B978-0-323-37755-3.50001-5
52. Yamaguchi N, Isomoto H, Nakayama T, et al. Usefulness of oral prednisolone in the treatment of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *Gastrointest Endosc*. 2011;73(6):1115-1121. doi:10.1016/J.GIE.2011.02.005
53. Kim TS, Min BH, Baek SY, et al. Antithrombotic Therapy Increases the Risk of Bleeding after Endoscopic Submucosal Dissection for Early Gastric Cancer: A Propensity Score-Matched Analysis. *Cancers (Basel)*. 2023;15(10). doi:10.3390/CANCERS15102844
54. Yang D, Zou F, Xiong S, Forde JJ, Wang Y, Draganov P V. Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. *Gastrointest Endosc*. 2018;87(6):1383-1393. doi:10.1016/J.GIE.2017.09.038
55. Tomizawa Y, Friedland S, Hwang JH. Endoscopic submucosal dissection (ESD) for Barrett's esophagus (BE)-related early neoplasia after standard endoscopic management is feasible and safe. *Endosc Int Open*. 2020;8(4):E498-E505. doi:10.1055/A-0905-2465
56. Omae M, Hagström H, Ndegwa N, et al. Wide-field endoscopic submucosal dissection for the treatment of Barrett's esophagus neoplasia. *Endosc Int Open*. 2021;9(5):E727-E734. doi:10.1055/A-1386-3668
57. Beaufort IN, Frederiks CN, Overwater A, et al. Endoscopic submucosal dissection for early esophageal squamous cell carcinoma: long-term results from a Western cohort. *Endoscopy*. 2024;56(5). doi:10.1055/A-2245-7235
58. Yamaguchi H, Fukuzawa M, Kawai T, et al. Efficacy of endoscopic clip closure for nonperforated muscle layer exposure during esophageal endoscopic submucosal dissection. *Dis Esophagus*. 2022;35(10). doi:10.1093/DOTE/DOAC009
59. Nagata M. Optimal traction direction in traction-assisted gastric endoscopic submucosal dissection. *World J Gastrointest Endosc*. 2022;14(11):667. doi:10.4253/WJGE.V14.I11.667
60. Ha Kim G, Jee SR, Jang JY, et al. Stricture Occurring after Endoscopic Submucosal Dissection for Esophageal and Gastric Tumors. *Clin Endosc*. 2014;47(6):516. doi:10.5946/CE.2014.47.6.516
61. Muroi K, Kakushima N, Furukawa K, et al. Effects of steroid use for stenosis prevention after endoscopic submucosal dissection for cervical esophageal cancer. *Int J Clin Oncol*. 2022;27(5):940-947. doi:10.1007/S10147-022-02139-3
62. Yan J, Yang Z, Gao L, et al. A novel risk score model of esophageal stricture for patients undergoing endoscopic submucosal dissection. *Eur J Gastroenterol Hepatol*. 2023;35(12):1362-1369. doi:10.1097/MEG.0000000000002664
63. Yang D, Hasan MK, Xiao Y, et al. The Use of a Self-Assembling Peptide Gel for Stricture Prevention in the Esophagus after Endoscopic Submucosal Dissection: A U.S. Multicenter Prospective Study. *Gastrointest Endosc*. Published online March 2024. doi:10.1016/J.GIE.2024.03.012
64. Zhang Y, Mao XL, Zhu W, et al. Esophageal Mucosal Autograft for Preventing Stricture After Widespread Endoscopic Submucosal Dissection of Superficial Esophageal Lesions. *The Turkish Journal of Gastroenterology*. 2022;33(4):312. doi:10.5152/TJG.2021.201032
65. Méndez-Nieto CM, Zarate-Mondragón F, Ramírez-Mayans J, Flores-Flores M. Topical mitomycin C versus intralesional triamcinolone in the management of esophageal stricture due to caustic ingestion. *Rev Gastroenterol Mex*. 2015;80(4):248-254. doi:10.1016/J.RGMX.2015.07.006
66. Bartel MJ, Seeger K, Jeffers K, et al. Topical Mitomycin C application in the treatment of refractory benign esophageal strictures in adults and comprehensive literature review. *Dig Liver Dis*. 2016;48(9):1058-1065. doi:10.1016/J.DLD.2016.06.024

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**