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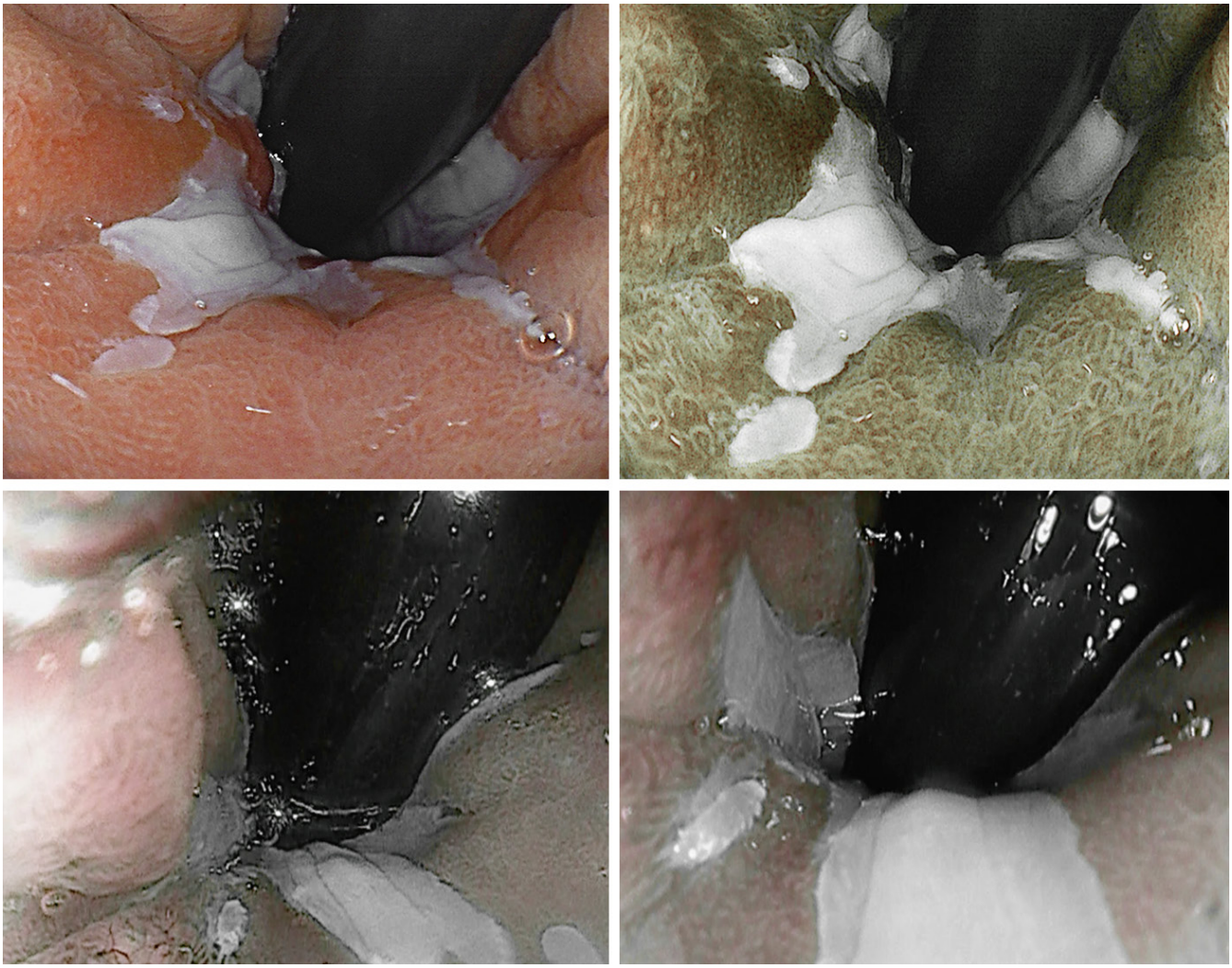

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Review article: Advanced Imaging in Gastrointestinal Endoscopy

Anastomotic leakages after surgery for gastrointestinal cancer – a systematic review and meta-analysis

Palliative care in advanced liver disease

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Aims and Scope

The *GE Portuguese Journal of Gastroenterology* (formerly *Jornal Português de Gastrenterologia*), founded in 1994, is the official publication of Sociedade Portuguesa de Gastrenterologia (Portuguese Society of Gastroenterology), Sociedade Portuguesa de Endoscopia Digestiva (Portuguese Society of Digestive Endoscopy) and Associação Portuguesa para o Estudo do Fígado (Portuguese Association for the Study of the Liver).
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Review Article

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Advanced Imaging in Gastrointestinal Endoscopy: A Literature Review of the Current State of the Art

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Keywords
Advanced imaging · Diagnosis · Endoscopy · Virtual chromoendoscopy

Abstract
Background and Aims: Gastrointestinal (GI) endoscopy has known a great evolution in the last decades. Imaging techniques evolved from imaging with only standard white light endoscopes toward high-definition resolution endoscopes and the use of multiple color enhancement techniques, over to automated endoscopic assessment systems based on artificial intelligence. This narrative literature review aimed to provide a detailed overview on the latest evolutions within the field of advanced GI endoscopy, mainly focusing on the screening, diagnosis, and surveillance of common upper and lower GI pathology. ***Methods:*** This review comprises only literature about screening, diagnosis, and surveillance strategies using advanced endoscopic imaging techniques published in (inter)national peer-reviewed journals and written in English. Studies with only adult patients included were selected. A search was performed using MESH terms: dye-based chromoendoscopy, virtual chromoendoscopy, video enhancement technique, upper GI tract, lower GI tract, Barrett's esophagus, esophageal squamous cell carcinoma, gastric cancer, colorectal polyps, inflammatory bowel disease, artificial intelligence. This review does not elaborate on the therapeutic application or impact of advanced GI endoscopy. ***Conclusions:*** Focusing on current and future applications and evolutions in the field of both upper and lower GI advanced endoscopy, this overview is a practical but detailed projection of the latest developments. Within this review, an active leap toward artificial intelligence and its recent developments in GI endoscopy was made. Additionally, the literature is weighted against the current international guidelines and assessed for its potential positive future impact.

Imagem Avançada Em Endoscopia Gastrointestinal: Uma Revisão Da Literatura

Palavras Chave
Imagem endoscópica avançada · Diagnóstico · Endoscopia · Cromoendoscopia virtual

Resumo
Introdução/objetivos: A endoscopia digestiva conheceu uma grande evolução nas últimas décadas, tendo as técnicas de imagem evoluído de imagens com luz branca

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para endoscópios de alta definição com possibilidade de uso de várias técnicas de melhoramento de cores e até sistemas automatizados apoiados em inteligência artificial. Esta revisão narrativa da literatura visa fornecer uma visão detalhada das últimas evoluções no campo da endoscopia avançada, focando principalmente no rastreio, diagnóstico e vigilância. ***Métodos:*** Pesquisa da literatura sobre estratégias de rastreio, diagnóstico e vigilância utilizando técnicas avançadas de imagem endoscópica publicadas em revistas internacionais revistas por pares e escritas em inglês. Foram selecionados estudos apenas com doentes adultos e foi realizada pesquisa utilizando termos MESH: cromoendoscopia com corante, cromoendoscopia virtual, técnicas de melhoramento de vídeo, tubo digestivo superior, tubo digestivo inferior, esófago de Barrett, carcinoma de células escamosas, cancro gástrico, pólipos colorretais, doença inflamatória intestinal e inteligência artificial. ***Conclusões:*** Esta revisão avaliou de uma forma prática os últimos desenvolvimentos no campo da imagem avançada em endoscopia digestiva, avaliando-se também as perspetivas futuras e o potencial impacto da inteligência artificial.

Introduction

Over the past years, gastrointestinal (GI) endoscopy has pivoted from standard white light endoscopy (WLE) toward a more specified and specialized type of endoscopy using different types of enhancement techniques to optimize optical diagnosis. These advanced endoscopic imaging technologies, denoted as virtual chromoendoscopy (VCE), improve visualization of mucosal abnormalities and enhance subtle structural and microvascular features facilitating decisions for management of GI diseases. Next to (virtual) chromoendoscopy, evolution from using standard white light endoscopes toward high-definition (HD) resolution scopes and magnification endoscopy has also contributed to better detection and characterization of mucosal lesions like colorectal polyps, colorectal cancer, dysplasia, etc. [1, 2]. This review however focuses on the commercially available and emerging VCE technologies. The aim was to provide an overview of the available imaging technologies, their clinical applicability, and added value.

Advanced Endoscopic Imaging Technologies for Detection and Management of Selected GI Diseases

VCE Technologies

Flexible GI endoscopy has known an important evolution in the last decades with the development of a series of so-called push-button VCE technologies to make advanced endoscopic imaging more widely available. These new technologies rely on the use of a narrowed part of the available spectral bandwidth. In contrast to dye-based chromoendoscopy (DCE), currently available VCE uses a combination of optical and digital (pre- or post-processing) filtering to enhance contrast. Next to optimal mucosal visualization, a high-quality bowel preparation, and well-trained experienced operators, HD imaging is a prerequisite for optimal application of these techniques. Nowadays, the commercially available systems are brand-dependent and the most recently available techniques include (1) narrowband imaging (NBI) (Olympus Medical Systems, Japan); (2) blue light imaging (BLI) and linked color imaging (LCI) (Fujifilm, Japan), and (3) i-scan optical enhancement (i-scan OE) (Pentax, Japan). Table 1 provides a summary of the endoscopic imaging methods discussed in this review.

Narrowband Imaging

NBI was the first commercially available type of VCE and relies on the preprocessing technique of the optical filtering of the illumination light. First of all, it discards the standard red, green, and blue filters and second reduces the spectral bandwidth to a concentered wavelength of 415 nm for blue and 540 nm for green light [3]. The narrowed band blue light excites hemoglobin which has an absorption peak of 415 nm and therefore absorbs the blue light, allowing structures containing high levels of hemoglobin (e.g., capillaries, veins) to appear darker, providing a positive contrast to the surrounding mucosa. The 540 nm light corresponds to a secondary hemoglobin absorption peak, enlightening the deeper mucosal and submucosal blood vessels. Hence, the final composite NBI image improves visualization of predominantly mucosal and vascular structures [4].

BLI and LCI

Previously, the Fuji Intelligent Chromo Endoscopy (Fujifilm Corporate, Tokyo, Japan) was a post-processing technology enhancing the visualization of mucosal structures and microcirculation. This has now been replaced by BLI, a preprocessing technology like NBI enhancing the mucosal surface by using blue light that superficially

Table 1. Technical overview of different endoscopic enhancement techniques

Basis	Technique	Technology	Digital image processing	Clinical performance
Dye-based	Chromoendoscopy (CE)	Real-time tissue enhancement using biocompatible dyes	NA	Identification of ESCC, BE, gastric and colorectal cancer, other diseases
Virtual	NBI	Physical spectral filters generate narrow bands of 415 and 540 nm in center wavelength	Pre-image processing	Expose both vascular and mucosal patterns, identification of HG-ESCC, BE, early GC, other precancerous lesions
	BLI	Narrowed spectrum LED light of 410 and 450 nm enabling hemoglobin excitation and a positive mucosal contrast	Pre-image processing	Identification of BE, early GC, colonic precursor lesions, etc.
	LCI	Preprocessing narrowband LED radiation and post-processing color technology that separates imported colors into red, green, and blue what enhances color differences	Pre- and post-image processing	Exposes vascular and mucosal patterns, identification of BE, early GC, colonic precancerous lesions
	i-scan	Enhancement of the image contrast through a real-time post-processing algorithm, basing the different reflective properties of normal and abnormal mucosa	Post-image processing	Identification of nonerosive reflux, HP infection
	i-scan OE	Incorporation of a digital pre-processor optical enhancement to improve visualization of mucosal vascular pattern	Pre- and post-image processing	Identification of BE, early GC, colonic precursor lesions, etc.

NA, not applicable; ESCC, esophageal squamous cell carcinoma; BE, Barrett's esophagus; HG-ESCC, high-grade esophageal squamous cell carcinoma; LED, light-emitting diode; HP, *Helicobacter pylori*.

penetrates the mucosa and excites hemoglobin [5]. BLI is based on an unfiltered emission of short-wavelength blue light generated by adaptation of a four-light-emitting diode (LED) multi-light technology, providing an innovative visualization of the intestinal mucosa. This technology is based on the combination of four types of light as source emitters: blue-violet, blue, green, and red. LCI is a recent development (Fujifilm Corporate) in imaging technology created by a short-wavelength narrowband laser light in combination with a white laser light, enabling a brighter light in distant areas with a higher contrast between white and red spots [6]. BLI and LCI are two of the observation modes of the four-LED multi-light technology that allows enhanced visualization of hemoglobin by, respectively, intensifying the blue or red light spectrum, improving delineation and detection [7–9].

I-Scan Digital Contrast

A third narrow spectrum technology is i-scan. It originally consisted of a post-processing digital contrast technology comprising three enhancement features, involving post-processing algorithms applied on WLE images. The surface enhancement sharpens the image by recognition of edges; contrast enhancement reflects differences between structures and depressed areas (darker spots) via presentation of low-density areas (more blue color); tone enhancement improves individual organ appearance by digital narrowed spectrum imaging [4].

Further developments lead to the i-scan OE system. That, like NBI and BLI, is a preprocessing technique and combines optical and digital enhancement chromoendoscopy [10]. It uses three types of algorithms combining aspects of the original i-scan post-processing system and the new preprocessing filtering technique. The three available modes include surface enhancement (i-scan 1) for the detection of abnormalities in the GI tract; tone enhancement (i-scan 2) for pattern characterization; and optical enhancement (i-scan 3) for characterization of blood vessels, glandular ducts, and mucosa. Each of these algorithms can be selected by pressing a pre-assigned but-

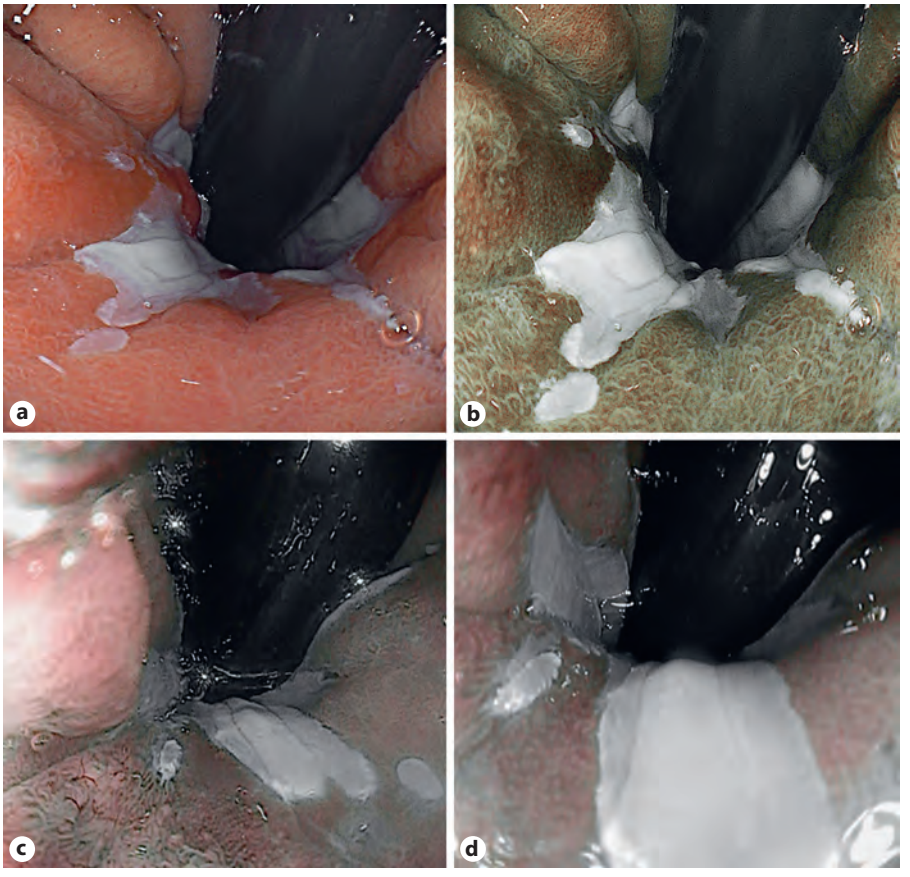

Fig. 1. Virtual chromoendoscopy image of Barrett's esophagus. White light imaging (**a**); blue light imaging (**b**); i-scan 2 imaging (**c**); and i-scan OE imaging (**d**).

ton on the handpiece of the scope. The newly added optical enhancement i-scan 3 function employs band-limited light to achieve higher overall transmittance by connecting the peaks of the hemoglobin absorption spectrum (415, 540, and 570 nm), thus creating a continuous wavelength spectrum, like NBI.

The Clinical Role of Enhanced Endoscopy

The Role of VCE in Detection and Characterization of Upper GI Diseases

Barrett's Esophagus

Barrett's esophagus (BE) is diagnosed when columnar intestinal mucosa replaces the normal stratified squamous mucosa, so the z-line no longer corresponds to the gastroesophageal junction and is histologically confirmed by the presence of intestinal metaplasia (IM). The presence and extent of BE should be described as suggested by the Prague classification, by assessing the circumference and the maximum extent of the endoscopically visualized BE segment proximal of the gastroesophageal junction [11].

Screening and Surveillance. Nowadays, standard of care in BE surveillance remains endoscopic evaluation using the Seattle biopsy protocol. This includes targeted biopsies of visible lesions, but since neoplasia can be patchy, also random biopsies are taken every 1–2 cm in every quadrant over the entire extent of the BE segment [12–14]. Advanced imaging may facilitate lesion detection and improve surveillance accuracy (Fig. 1) [12].

NBI plus targeted biopsies has not proven to be superior to WLE with random biopsies in detection of dysplasia (92% vs. 92%) but is able to detect a larger amount of dysplastic areas (30% vs. 21%, $p < 0.0001$) leading to fewer biopsies per patient (3.6 vs. 7.6, $p < 0.0001$) [15]. Multiple meta-analyses confirm a high sensitivity of 95–96% and high specificity of 94–95% for the detection of high-grade dysplasia (HGD) using NBI [12, 15].

Several VCE-based classification systems have been developed and validated (Table 2) [16–18]. Overall, they all suggest that an irregular mucosal and vascular pattern

Table 2. Different classification systems for BE based on VCE

	Kansas [13]	Amsterdam [14]	Nottingham [15]	BING [17]	BLINC [18]	BING with i-scan classification [22]
Normal	Mucosal pattern: circular Vascular pattern: normal	Mucosal pattern: regular Vascular pattern: regular Abnormal blood vessels: absent	Type A: round/oval pits with regular microvasculature	Mucosal pattern: circular, ridged/villous or tubular Vascular pattern: blood vessels situated regularly along or between mucosal ridges and/or those showing normal, long branching patterns	Mucosal pattern: circular/tubular/gyriform, regular distribution, and normal density Color: no focal darkness Vascular pattern: nondilated, nonbranching, peri-cryptal, and normally distributed	Mucosal pattern: regular circular or villous pits (M1) Vascular pattern: regular and uniform vessels (V1) M1 + V1
IM	Mucosal pattern: ridged/villous Vascular pattern: normal	Mucosal pattern: regular Vascular pattern: regular (villous/gyrus) Abnormal blood vessels: absent	Type B: villous/ridged/linear pits with regular microvasculature Type C: absent pits with regular microvasculature	NA	NA	NA
Dysplasia/ neoplasia	Mucosal pattern: irregular distorted Vascular pattern: abnormal	Mucosal pattern: irregular Vascular pattern: irregular Abnormal blood vessels: present	Type D: distorted pits with irregular microvasculature	Mucosal pattern: absent or irregular patterns Vascular pattern: focally or diffusely distributed vessels not following normal architecture of the mucosa	Mucosal pattern: amorphous circular/tubular/gyriform, irregular distribution, and increased density Color: focal darkness Vascular pattern: dilated, branching, noncryptal, and increased or loss of distribution	Mucosal pattern: M1 or distorted or irregular pits or featureless mucosa (M2) Vascular pattern: V1 or irregular dilated or tortuous vessels (V2) M1 + V2 or M2 + V1/M2 + V2
Diagnostic performance for neoplasia detection	Sensitivity: IM w/out HGD: 93.5% IM w HGD: 100%	Sensitivity: 94% for HGD with NBI and magnification images	Accuracy: non-NBI expert: 84% NBI expert: 89%	Accuracy: 80% 92% in case of high confidence	Accuracy: 86.8% pre-training 88.3% post-training	Accuracy: 69%, without ACA 79% after administration of ACA

NA, not applicable; HGD, high-grade dysplasia; w, with; w/out, without; NBI, narrowband imaging; ACA, acetic acid.

is predictive for dysplasia, and a ridged/villous pattern guides toward a specialized IM (SIM) lesion [4]. When comparing the three commercially available VCE classification systems head-to-head, their diagnostic accuracy for SIM and dysplasia detection was low (SIM: 57% [Nottingham and Kansas] and 63% [Amsterdam]; dysplasia: 75% [irrespective of the classification systems]) [19]. The newer Barrett's International NBI Group (BING) criteria were validated to be used to discriminate between non-neoplastic and neoplastic BE [20]. This classification is also based on simple surface and vascular patterns, and a regular pattern is predictive for non-neoplastic BE and an irregular pattern for neoplastic BE (Table 2) [20].

BLI and i-scan have been studied for characterization of BE lesions and showed comparable performances as NBI when combined with magnification and conventional acetic acid (ACA) application (Fig. 1) [21, 22]. With inter-rater variability remaining a hurdle, LCI improves visibility with 44.4% in a group of 5 expert and 5 trainee endoscopists when compared to WLE resulting in moderate-substantial inter-rater reliability scores [23]. In parallel with the BING criteria, the Blue Light Imaging for Barrett's Neoplasia Classification (BLINC) was validated as a promising tool with high sensitivity for detection [24]. The authors added an easy to identify additional feature, the dark color of neoplastic lesions, that is highlighted by BLI. Furthermore, a multicenter trial validated the

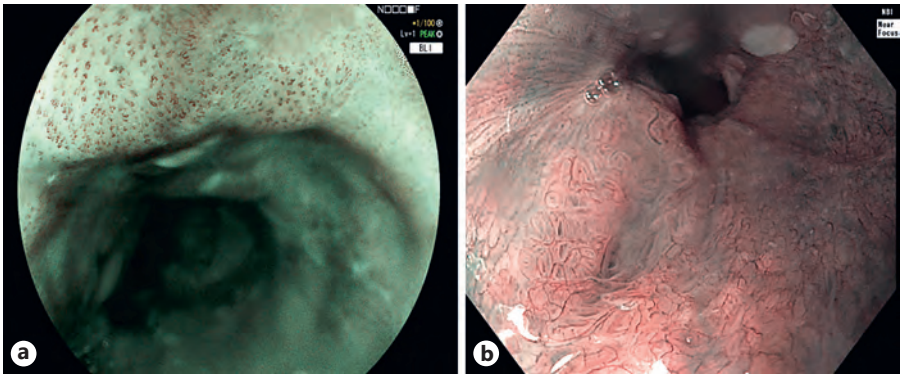

Fig. 2. Different types following the Japanese classification of intrapapillary capillary loops (IPCLs) in esophageal squamous cell carcinoma. IPCL type B1 in flat squamous lesion, visualized with BLI (**a**), IPCL type B2 squamous esophageal lesion, visualized in NBI with near focus (**b**). BLI, blue light imaging; NBI, narrowband imaging.

use of the BING with the i-scan technology using an international group of expert endoscopists viewing videos collected from several European centers. Addition of ACA significantly increased the accuracy of the classification system using i-scan, from 69% to 79% ($p = 0.01$) (Table 2) [22].

Esophageal Squamous Cell Carcinoma

Esophageal squamous cell carcinoma (ESCC) is the most common type of esophageal cancer worldwide and has a poor 5-year prognosis due to late recognition and diagnosis [25]. Timely and accurate diagnosis of early ESCC is crucial to improve patient prognosis and outcome. Lugol staining is currently standard of care but struggles with long procedural time, possible esophageal spasm, and potential allergic complications [26–28]. Compared to Lugol, NBI showed to be as efficient in terms of detection of HGD and ESCC lesions in high-risk patients [29]. When compared to WLE-only, a Japanese multicenter randomized controlled trial (RCT) demonstrated that NBI detected superficial ESCC (SESCC) more frequently (97% v 55%, $p < 0.001$) [30]. A meta-analysis based on 12 studies with expert centers demonstrated NBI to be as adequate as Lugol staining for diagnosis of HGD and ESCC [31]. On a per-lesion level, the sensitivity and specificity for Lugol chromoendoscopy were 92% and 98% versus 88% and 94% for NBI sensitivity and specificity, respectively. Recently, a French group investigated the use of NBI in nonexpert setting on 334 patients with a history of ESCC and demonstrated on a per-patient level a sensitivity of 100% and a specificity of 66% for Lugol staining and a sensitivity of 100% and specificity of 77% for NBI, the latter being significantly superior to Lugol [28]. As previously demonstrated in expert hands, NBI has now proven to be more specific than Lugol staining in normal gastroenterology practice [28]. Hence, the European Society of Gastrointestinal Endoscopy (ESGE) recommends the use of at least HD-WLE in combination with a VCE modality like NBI next to Lugol staining for esophageal cancer screening and lesion assessment [32].

Screening and Surveillance. Intrapapillary capillary loops (IPCLs) are known optical markers for the assessment of SESCC. Several IPCL classifications have been investigated with no superior one. Fan et al. [33] conducted a meta-analysis for the comparison of three IPCL classifications for SESCC staging. This group compared the Inoue, the Arima, and the Japanese Esophageal Society (JES) IPCL classification and assessed impact of IPCL on diagnostic accuracy (Fig. 2). IPCL showed a high diagnostic accuracy for differentiation between epithelial (EP)/lamina propria (LP) and muscularis mucosae (MM) tumors with a pooled sensitivity of 0.91. IPCL showed a rather low sensitivity of 0.72 for diagnosing MM/submucosa stage 1 (<200 μ) (SM1) and submucosa stage 2 (≥200 μ) (SM2) staging. For EP/LP tumors, all three IPCL classifications had high diagnostic accuracy (Inoue 87.2%, Arima 98.7%, and JES 86.7%). When differentiating MM/SM1 staging tumors from EP/LP and ≥SM2 tumors, IPCL scored worse than pathology with 23.1% of the lesions underestimated and 6.3% of the lesions overestimated. When concerned to the different classifications, JES classification outperformed Inoue and Arima but underestimated 17.8% of the MM/SM1 lesions. For ≥SM2 staging with IPCL, an underestimation of 38.9% was shown and Arima classification outperformed the other two (Arima vs. Inoue vs. JES: 84.0% vs. 55.84% vs. 55.0%, $p < 0.005$) (Table 3). Hatta et al. [34] compared the diagnostic ability of magnifying endoscopy with BLI and NBI for the determination of invasion depth of SESCC by application of the JES IPCL classification. The overall accuracies did not significantly differ, and the sensitivity and predictive

Table 3. Relationship between histopathological diagnosis and diagnostic accuracy of IPCL for invasion depth estimation [28]

Histopathological diagnosis	Inoue	Arima	JES
	IPCL diagnosis of invasion depth, diagnostic accuracy, %		
EP/LM	87.2	98.7	86.7
MM/SM1	58.7	68.0	75.5
SM2	55.8	84.0	75.7
	IPCL underdiagnosis of invasion depth, %		
EP/LM	NA	NA	NA
MM/SM1	34.7	28.0	17.8
SM2	44.2	16.0	45.0
	IPCL overdiagnosis of invasion depth, %		
EP/LM	12.8	1.3	13.3
MM/SM1	6.7	4.0	6.7
SM2	NA	NA	NA

IPCLs, intrapapillary capillary loops; JES, Japanese Esophageal Society; EP, epithelial propria; LP, lamina propria; MM, muscularis mucosae; SM1, submucosa stage 1 (<200 μ); SM2, submucosa stage 2 (≥200 μ); NA, not applicable.

values in MM and ≥SM2 tumors were low. Therefore, the authors concluded that diagnosis by magnifying endoscopy alone might be unsatisfactory.

Gastric IM/Dysplasia

Gastric IM (GIM) and dysplasia are precursor lesions of gastric cancer (GC). It can occur both in longstanding atrophic and nonatrophic gastritis. A genetic basis is currently still unknown [35, 36]. High prevalence regions of GC and/or *Helicobacter pylori* infection also tend to have a higher prevalence of GIM [35].

Screening and Surveillance. The mucosal and vascular pattern assessed by NBI is predictive for the presence of GIM and dysplasia (Fig. 3). Ridged or villous patterns suggest the presence of metaplasia, whereas regular patterns suggest the absence of dysplasia [4]. An indicative endoscopic diagnostic sign with a specificity of 93% is the "light blue crest" sign, although its absence does not exclude GIM given its positive predictive value of 91% [37]. A variable density of the vascular pattern is indicative for a *H. pylori* infection [4, 38]. In the same multicenter validation study, the authors showed a high diagnostic accuracy of NBI (>90%) allowing to take only targeted biopsies instead of random biopsies when using NBI [38]. Histological scoring systems like operative link on gastric assessment (OLGA) and operative link on GIM are based on the severity and topographic distribution of gastric atrophy and GIM, respectively. Both systems stratify gastric atrophy/GIM in a four-stage model, and a stage III or IV has shown to be associated with a high risk for GC [39, 40]. The endoscopic grading of GIM (EGGIM) classification using HD VCE with NBI was recently validated [41]. This classification assesses the entire gastric mucosa and rates according to the presence and extent of GIM from 0 to 10. An EGGIM score of ≥5 was found to be the optimal cut-off for the identification of patients with OLGA/operative link on GIM III or IV that are selected for further follow-up surveillance endoscopy. It is the first endoscopic scoring system that showed to be a direct and independent predictor for GC [41]. Therefore, it may replace the histological scoring systems in the future and help to directly select patients that need endoscopic surveillance.

Both BLI and LCI have demonstrated improvement of gastric neoplasia detection. A Japanese group reported that the color difference between GC and the surrounding mucosa using LCI was significantly improved compared to WLE [42–44]. The most pronounced color difference was shown when a GC was surrounded by IM [42–44]. However, detection remains difficult, especially in nonexpert hands. Artificial intelligence (AI) based on LCI images is brought forward as possible solution [45]. Similarly, NBI has been reported to increase neoplasia detection in patients at risk [46]. In patients with previously detected GIM or gastric dysplasia, the overall sensitivity for detection of premalignancy (both GIM or dysplasia) was 71% for NBI versus 51% for WLE [46]. One of the limitations of this first-generation NBI (1G-NBI) is the too dark images, explaining the moderate clinical per-

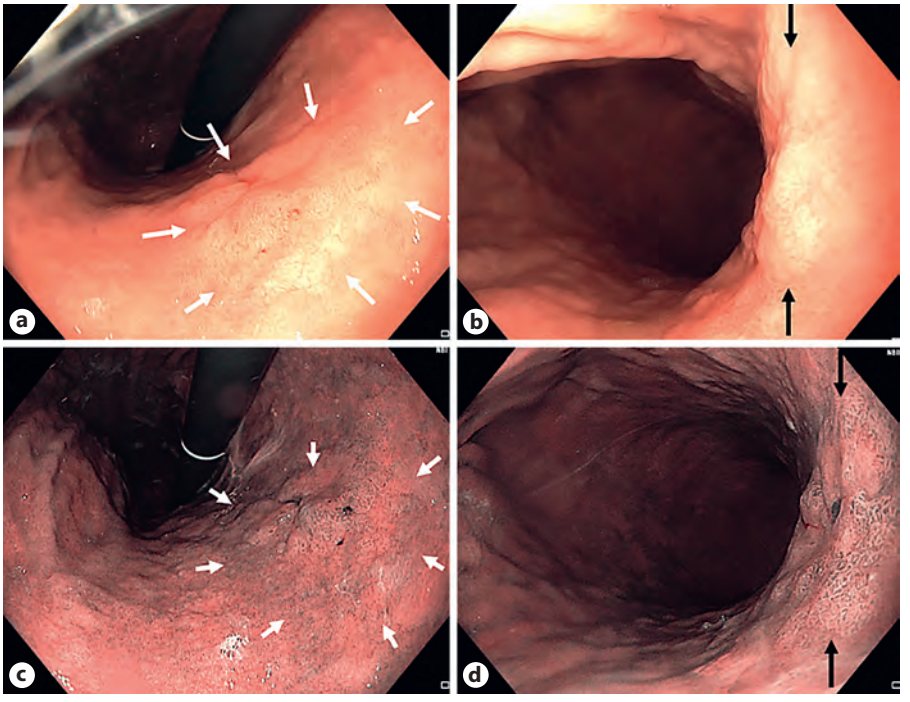

Fig. 3. Zone of gastric intestinal metaplasia (GIM) within gastric atrophy. GIM (white arrows) visualized in WLE (**a**), NBI (**b**). Close-up pictures of zone of GIM (between black arrows) in WLE (**c**) and NBI (**d**).

formances and making 1G-NBI unsuitable for GC screening in high-risk patients. The brightness and resolution obtained using NBI have been improved markedly since the introduction of the Olympus 290 series (EVIS LUCERA ELITE; Olympus, Tokyo, Japan) and 190 series (EVIS EXERA III) endoscopy systems, in comparison with the previous 260 and 180 series, respectively. Recently, a Japanese group investigated the use of second-generation NBI (2G-NBI) for GC screening in high-risk patients, resulting in a sensitivity of 75% for premalignancy detection, comparable to 1G-NBI [47]. Although the positive predictive value was better for 2G-NBI (20.9%) in comparison with WLE (13.5%) ($p = 0.015$), the GC detection rate was not significantly improved over WLE.

Duodenal Pathology

NBI combined with magnification, on the one hand, can be helpful in the diagnosis, classification, and determination of remission in patients with gluten enteropathy and on the other hand in the diagnosis of ampullary tumors or mucosal changes in lymphomas [48].

The Role of VCE in Imaging of the Lower GI Tract

Colorectal Polyps and Neoplasia

Initially, 1G-NBI did not show significant differences in colonic polyp detection rate (PDR) and adenoma detection rate (ADR) when compared to both conventional and tandem colonoscopy [49, 50]. After the introduction of the improved 2G-NBI, Horimatsu et al. [51] showed that the mean number of polyps detected per patient was significantly higher in the HD-NBI group than the HD-WLE group (2.01 vs. 1.56; $p = 0.032$). A prospective RCT comparing ADR and PDR between HD-NBI and HD-WLE colonoscopy using the 190 series Olympus endoscopy system found that both rates were significantly higher for NBI than for WL (adenoma: 48.3% vs. 34.4%, $p = 0.01$; polyps: 61.1% vs. 48.3%, $p = 0.02$) [52]. However, in a more recent observational trial in four academic and four community hospitals, 2G-NBI could not improve ADR (43.5% for NBI vs. 44.4% for WLE, $p = 0.71$) nor the mean number of adenomas detected (0.90 ± 1.38 vs. 0.91 ± 1.40, $p = 0.95$) [53]. However, ADR was higher with NBI in the academic group, whereas ADR was higher in the WLE group in community hospitals. NBI did significantly improve the mean number of flat and depressed lesions (0.62 ± 1.34 vs. 0.44 ± 1.01, $p = 0.035$). For sessile serrated polyp (SSP), attracting more and more attention as CRC precursor, the same research group found significantly more SSPs per patient in the HD-NBI group versus the HD-WLE group (0.05 vs. 0.01; $p = 0.036$) [51]. In a more recent RCT (randomization to colon inspection with NBI vs. WLE colonoscopy), the number of sessile serrated lesion (SSL) in the right colon (SSP plus hyperplastic polyps) was higher in the NBI group (204) compared to the

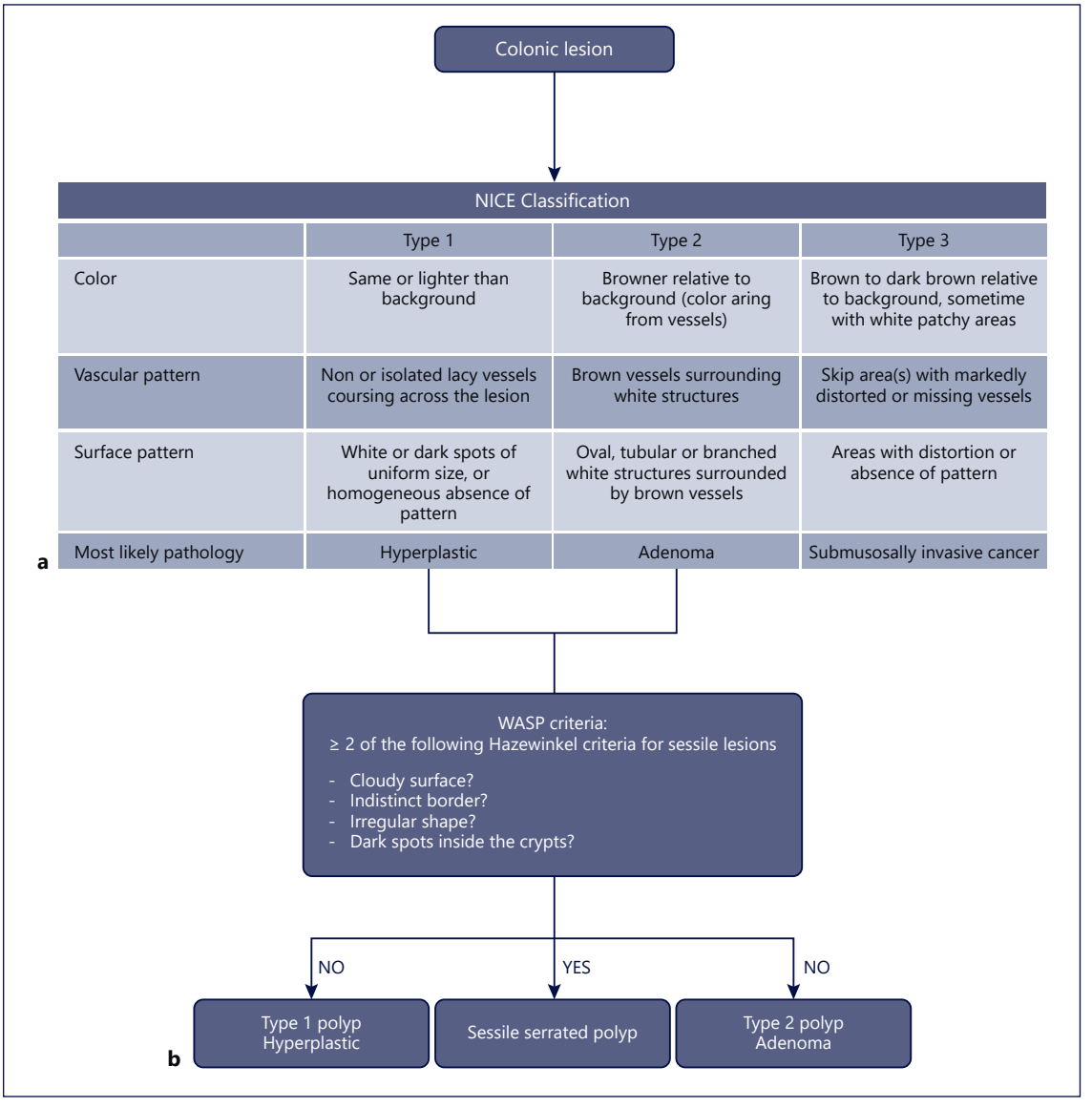

Fig. 4. a The NBI International Colorectal Endoscopic (NICE) classification system. **b** With integration of the Workgroup serrAted polypS and Polyposis' (WASP) classification based on NICE and four Hazewinkel criteria [65, 67, 114].

WLE group (158), without reaching statistical significance ($p = 0.085$) [54]. Similar results were recently shown in a multicenter prospective RCT comparing the SSL detection rate between NBI and HD-WLE in expert hands. SSL detection rate was 7.5% in the NBI group and 8.0% in the WLE group ($p = 0.852$) [55]. Both ADR and PDR were not statistically significantly different between NBI and WLE colonoscopy.

In 2004, NBI visualization of the microvascular pattern was identified as a distinct manner of differentiation between non-neoplastic and neoplastic colonic lesions [56]. Even more, NBI vascular thickness showed to be related to the histological grade and depth of invasion of colonic neoplasms [57]. In addition, NBI microvascular density measurements improve accurate characterization similar to magnified chromoendoscopic assessments based on Kudo pit pattern classification [4, 58–60]. The NICE classification uses color, vessels, and surface pattern criteria for the endoscopic diagnosis of colonic polyps classifying them in three types (Fig. 4a) [3, 4, 61]. This

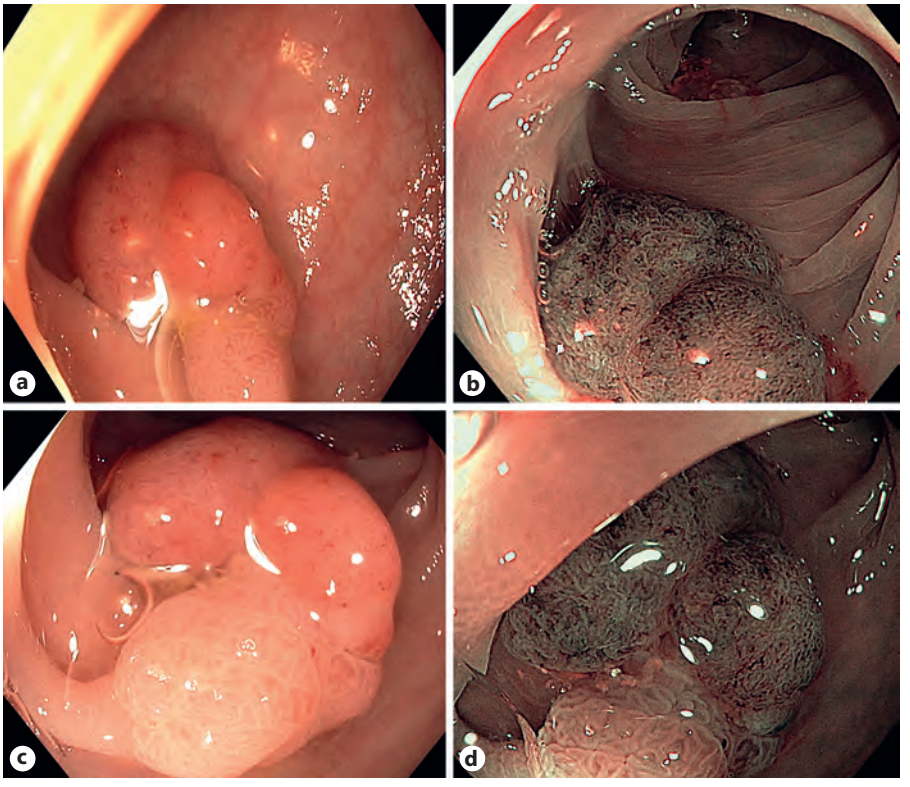

Fig. 5. Visualization of a colorectal polyp with white light versus narrowband imaging with or without magnification endoscopy. White light without near focus (**a**), NBI without near focus (**b**), white light with near focus (**c**), and NBI with near focus (**d**).

new classification system was validated with a real-time sensitivity of 98% and a negative predictive value of 95% [62]. A more specified classification, based on the NICE classification, is the Japanese NBI Expert Team (JNET) classification, subdividing adenomatous lesions (NICE type 2 lesions) in type 2A or low-grade adenomas and type 2B or high-grade adenomas including shallow submucosally invasive carcinomas [63]. Currently, an international multicenter validation trial is ongoing validating the JNET classification in clinical practice and therapeutic decision-making, and results are to be awaited. An important disadvantage of both the NICE and JNET classifications is that SSLs are not incorporated, although they have been identified as important precursor lesions of colonic cancer and thereby cannot be discarded [4, 64]. Ijspeert et al. [65] developed and validated the "Workgroup serrAted polypS and Polyposis" (WASP) classification, combining the NICE criteria and four of the Hazewinkel criteria: (1) clouded surface, (2) indistinct border, (3) irregular shape, and (4) dark spots inside the crypts [4, 64]. A holistic and feasible stepwise approach of endoscopic polyp differentiation has been proposed including hyperplastic polyps, adenoma, and sessile serrated adenoma/SSP (Fig. 4b).

The potential cost saving of optical diagnosis of diminutive polyps is clear. The initial DISCARD trial showed a promising overall accuracy of 93% for optical diagnosis and characterization of polyps <10 mm with NBI and a good prediction of surveillance interval [66]. However, the consecutive multicentric DISCARD 2 trial demonstrated only moderate sensitivities for optical diagnosis (83.9%) far below the 95% the study was powered to detect [67]. On a polyp level, test sensitivity (presence of adenoma, n = 1,620 polyps) was 76.1%. This result could be augmented to 99.4% in a fully adjusted analysis if at least 2 NICE characteristics were present. Hence, NBI-assisted optical diagnosis cannot be routinely recommended and should be preserved for expert hands, as recommended by the ESGE [68]. The optical effect of NBI can be appreciated in Figure 5.

I-scan has also been tested as application for polyp detection and characterization using pit pattern and vascular pattern. Bouwens et al. [69] showed a sensitivity of 79%, a specificity of 86%, and an accuracy of 81% for non-expert endoscopist trained in a single session with i-scan and applying their own developed i-scan classification for endoscopic diagnosis. In terms of adenoma detection, a meta-analysis could not withhold a significant difference

in adenoma detection between i-scan and WLE nor i-scan and HD-WLE [70]. However, a RCT published after this meta-analysis showed a significantly higher ADR in the i-scan group compared to the HD-WLE colonoscopy group (47.2% vs. 37.7%, $p = 0.01$). This outcome could mainly be attributed to an increased detection rate of diminutive, flat, and right-sided adenomas [71]. Recently, the SIMPLE classification, developed as a novel endoscopic optical diagnostic classification system using i-scan, was validated [72]. In a cohort of 399 patients, the investigators assessed the agreement of surveillance intervals determined by optical diagnosis compared with pathology-based results and the diagnostic performances for diminutive polyps. For patients with at least one polyp ≤5 mm, agreement was 93.5% (95% confidence interval [CI] 91.4–95.6), and for polyps ≤10 mm 92.7% (95% CI: 98.7–95.1). The NPV for rectosigmoid adenomas ≤5 mm and ≤10 mm was 86.7% and 85.1%, respectively, too low for clinical implementation.

More recently, the mean number of adenomas per patient was reported to be significantly higher in the BLI group compared with that in the HD-WLE group, but without significantly higher ADR [73]. Furthermore, a BLI classification (BLI Adenoma Serrated International Classification (BASIC)) was developed to enable characterization of colorectal polyps. BASIC significantly improved the pretraining accuracy from 87% to 94% and significantly increased sensitivity and NPV of adenoma [74].

In a multicenter RCT, LCI showed to significantly augment the PDR compared to WLE without prolongation of the procedure time [75]. In terms of miss rate, a recent tandem colonoscopy RCT of the right colon (LCI-WLE vs. WLE-LCI) demonstrated in the LCI-first group a significantly lower adenoma miss rate in the right colon (11.8% vs. 30.6%, $p < 0.001$) [76]. Moreover, when tested for SSP/SSA detection, LCI showed to be superior to WLE and a lower SSA miss rate [77, 78]. In a recent meta-analysis, LCI significantly increased the number of adenomas detected per patient versus WLE (difference 0.22, 95% CI: 0.08–0.36, $p < 0.002$) [7]. The number of flat polyps per patient and the additional PDR were both significantly higher with LCI.

The current ESGE guidelines do not yet recommend VCE for routine practice. VCE can be used in average risk patients to increase ADR. However, the routine use must be balanced against costs and practical considerations. ESGE also suggests as weak recommendation that VCE and DCE can be used, under strictly controlled conditions, for real-time optical diagnosis of diminutive (≤5 mm) colorectal polyps, and can replace histopathological diagnosis [68].

Inflammatory Bowel Disease

Inflammatory bowel diseases, Crohn's disease and ulcerative colitis (UC), result in chronic inflammation of the ileal and/or colonic mucosa and if uncontrolled may lead to intra-epithelial neoplastic (IN) changes and colitis-associated dysplasia or cancer [79]. Colonoscopy surveillance is therefore recommended to detect the IN in curable stages [80, 81].

HD-WLE has shown to improve dysplasia detection when compared to standard WLE with an adjusted prevalence ratio of detecting dysplasia of 2.21 (95% CI 1.09–4.45) [82]. Although the SCENIC guidelines recommend the combination of DCE and targeted biopsies, hard evidence is currently lacking. However, a systematic review including 4 RCTs concluded that DCE is superior (RR: 1.38; 95% CI: 1.02–1.88) [83]. This latter conclusion is supported by more recent research ($n = 305$) showing a significantly better detection of dysplasia in the HD-CE group ($n = 17$) versus the HD-WLE group ($n = 7$) ($p =$ 0,032) [84].

The use of VCE for dysplasia detection has recently been accepted by the ESGE [68, 85]. For NBI, the per-lesion analysis resulted in a significantly inferior false-positive biopsy rate ($p < 0.001$) and a similar true-positive rate as well as more missed IN lesions with NBI, albeit without reaching statistical significance [86]. Additionally, two Dutch groups could not demonstrate a significant improvement of detection of dysplasia when compared to HD-WLE [49, 59]. However, as stated in recent research, NBI in longstanding UC may not be significantly different from DCE for neoplasia detection (21.2% for DCE vs. 21.5% for NBI), but since it significantly shortens the procedural duration and is easier to apply, it could serve as a possible alternative for classical DCE [115].

With the ESGE shifting toward targeted biopsies, the collection of random biopsies during WLE surveillance examination is no longer recommended [85]. For patients with longstanding UC in remission, advanced imaging technologies are useful in identifying areas for targeted biopsies to assess histological disease activity. In UC, colonic mucosal erythema visualized by LCI correlates well with histological inflammation, and the LCI classification can predict relapse rates [87].

Endoscopic assessment of disease activity in both Crohn's disease and UC has shown to be important in terms of patient treatment and prognostication. The Mayo endoscopic subscore (MES) is the most widely used endoscopic scoring system. Despite its simplicity, the MES was never formally validated and is strongly limited by inter- and intra-observer variability. So, more detailed

and specific scoring systems like the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and Ulcerative Colitis Colonoscopic Index of Severity were developed and showed superiority in their operating characteristics over the MES, but remained limited by large observer-dependency [88, 89]. In 2017, a new and more comprehensive VCE score, the Paddington International Virtual Chromoendoscopy (PICaSSO) score, was developed and validated, including details of subtle vascular and mucosal changes reflecting acute or chronic inflammatory changes [90]. Eight assessors were trained with a 60-min training module outlining 3 different i-scan modes of the vascular and mucosal changes in every stage of disease activity in UC. The assessors' performance was evaluated on 20 i-scan videoclips used both before and after the training module. The interobserver agreement for MES was high in both test phases (pre: k = 0 0.85; 95% CI: 0.78–0.90; post: k = 0.85; 95% CI: 0.77–0.90), and the same goes for the UCEIS (pre: k = 0.86; 95% CI: 0.77–0.92; post: k = 0 0.84; 95% CI: 0.75–0.91). The interobserver agreement of the PICaSSO endoscopic score was very high in both the pre- and post-test (k = 0.92; 95% CI: 0.86–0.96 and k = 0.89; 95% CI: 0.84–0.94, respectively), with an accuracy of predicting histological disease activity by the Robarts Histological Index of 72% (95% CI: 64–79%). Hence, the author's conclusion that the PICaSSO score may be used to define the endoscopic findings of mucosal and vascular healing in UC and reflects well the entire spectrum of histological changes.

Prospects and Future Directions

Several enhancement techniques for GI endoscopy have found their way into clinical practice and have proven to be helpful in several situations. All the abovementioned types of VCE increase the detection of neoplasia in both upper and lower GI tracts. Meta-analyses described the positive impact of VCE on the detection and diagnosis of ESCC, GC, and ESCC [31, 91, 92]. Similar meta-analyses have been conducted in the lower GI tract showing comparable positive trends for polyp detection [7, 70]. By improving the characterization of dysplasia in IBD and BE, colorectal polyps, and cancer, VCE has an impact on therapeutic decision-making and patient care. Augmentation of the dysplasia detection rate and less false-positive detections in dysplasia screening in BE and UC has pivoted the current practice toward targeted biopsies rather than random biopsies, what was endorsed by the ESGE for UC [82, 85, 86]. In colorectal cancer prevention, a similar path has been taken with improving characterization and ADR, and a discard strategy has been proposed and approved by the ESGE for diminutive hyperplastic polyps in the rectosigmoid in expert hands [68]. In parallel with the guidelines, novel classifications have been developed and validated, using VCE for both detection and characterization of GI lesions. Classifications like the JNET, WASP, SIMPLE, and BASIC have altered the field of colorectal polyps using VCE, more specific NBI, i-scan, and BLI, respectively [65, 72, 74, 93]. In the field of upper GI endoscopy, the BING/BLINC, the EGGIM score, and the use of JES classification for IPCL for BE, GC, and ESCC, respectively, have been validated [24, 33, 41].

VCE with NBI, BLI, LCI, and i-scan has recently been expanded by Olympus Corporation (Tokyo, Japan) with the introduction of texture and color enhancement imaging (TXI), the extended depth of field technology, and red dichromatic imaging technology, as part of the new EVIS X1 video system. Results are to be awaited, although a recent RCT comparing TXI to WLE, NBI, and DCE with indigo carmine staining for the visualization of serrated colorectal lesions (hyperplastic and SSL) showed that TXI had a significantly superior visibility score to WLE but inferior to NBI and DCE for hyperplastic polyps and SSL detection [94]. On a case-based level, red dichromatic imaging may improve the visualization of cryptogenic gastric bleeds since it improves redness and depth imaging [95]. The same suggestions have been made for the estimation of disease activity in UC and mucosal depth during endoscopic submucosal dissections [96, 97].

The use of VCE requires a certain experience and can reach its optimal impact in expert hands. Both DCE and VCE have their own learning curve and equipment to be controlled [98, 99]. Good training programs in a secured and standardized environment with direct feedback are needed to meet the required skills for optimal results [100]. For example, in case of optical diagnosis with NBI new evidence suggests that by changing the way of introducing this into community-based practice with periodically audited training and immediate feedback, the accuracy is sufficient to avoid post-polypectomy histological examination or to leave hyperplastic lesions in the rectosigmoid [101]. As suggested by the ESGE, before one can perform a qualitative optical diagnosis, the endoscopist should have a personal experience of at least 300 upper and 300 lower GI endoscopies and meeting the ESGE quality measures [102]. In addition, ESGE suggests that every endoscopist should be able and competent to perform UGI/LGI endoscopy with HD white light combined

with VCE and/or DCE before commencing training in optical diagnosis. The required number of DCE and DCE endoscopies is however not specified.

VCE has proven to significantly reduce the procedural duration as a push-on-the-button option. So, one could speculate that this may result in better time management and may increase cost-effectiveness by fewer random biopsies. However, their clinical applicability remains operator dependent and therefore is directly linked to training skills of the performing endoscopist. To overcome human interfering factors, AI has been proposed. Recently developed AI detection tools have shown their positive impact on polyp and adenoma detection [103]. In the field of IBD, Takenaka et al. [104], Bossuyt et al. [105], and Stidham et al. [106] developed an automated AI system for estimation of disease activity and severity in UC patients. The ARGOS project had the first automated system for BE dysplasia detection on WLE images with high accuracy of 92% for detecting and localizing BE dysplasia [107]. Currently, the system is further developed for real-time assessment. Hashimoto et al. [108] developed a similar CADe system which was now trained based on images (dysplastic and nondysplastic) illuminated with WL and NBI, near focus, and non-near focus, resulting in high accuracies for correctly detecting early neoplasia. A real-time deep learning (DL) system for classification and segmentation, differentiating between BE and early adenocarcinoma, has recently been developed. While an expert endoscopist conducts the endoscopic assessment of BE, the DL system captures real-time random images. The diagnostic and classifying accuracy of this DL system was 89.9% on 14 cases with neoplastic BE [109].

Based on the promising results in detection of lesions, there is currently a growing interest for characterization by AI. As well described in a recent systematic review and meta-analysis, most conducted studies are based on retrospective data with still images in WL and NBI [110]. To date, only three research groups used prospectively collected data with NBI. The first compared their computer-based algorithm with experts and nonexperts in terms of classification between neoplastic and non-neoplastic colorectal polyp and achieved a comparable diagnostic performance (expert group: 93.4% sensitivity, 91.8% specificity, and 92.7% accuracy; computer-based algorithm: 95.0% sensitivity, 90.3% specificity, and 93.1% accuracy) [111]. Both are significantly superior to the non-expert group (86.0% sensitivity, 87.8% specificity, and 86.8% accuracy). Second, a Taiwanese group developed a DL computer-aided diagnostic tool for the identification of neoplastic versus hyperplastic diminutive polyps [112]. This system classified polyps with similar clinical performances in a shorter time than the endoscopists. Third, the first single-center open label study was conducted assessing the real-time performance of a support vector machine with endocytoscopes after application of the NBI and methylene blue staining modes, respectively, for classification of diminutive (<5 mm) polyps in neoplastic and non-neoplastic [113]. The system showed performances allowing a resect and discard strategy of diminutive hyperplastic polyps. The CAD NPV was 96.5% (CI: 92.1–98.9%) (best-case scenario) and 95.2% (CI: 90.3–98.0%) (worst-case scenario) with NBI. Hence, the combination of higher detection with a better characterization by VCE and the objectivity and steady reproducibility of an AI system may be golden, based on the preliminary available data. Further investigation of this approach is currently subject of ongoing clinical research.

To conclude, an early endoscopic diagnosis of GI pathology is primordial for high-quality patient management enabling early treatment, a better prognosis, and patient care. WLE is still the first step in the detection of GI diseases, although evidence increases that VCE improves detection. Further characterization by CE, dye-based or virtual, can be applied as an add-on diagnostic tool to yield more details for a definite diagnosis based on targeted biopsies.

With increasing data on the potential of VCE, international guidelines are shifting toward the use of these techniques in specific situations. With the new era of AI in GI endoscopy, a brighter future is probably to be expected since AI can overcome the human limitations of these techniques improving early diagnosis, treatment, prognosis, and overall quality of daily endoscopy.

Conflict of Interest Statement

RB received speaker's fees, consultancy, and research support from Pentax, Fujifilm, and Medtronic. SV has received grants from AbbVie, J&J, Pfizer, Galapagos, and Takeda and has received consulting and/or speaking fees from AbbVie, AbolerIS Pharma, Agomab, Alimentiv, Arena Pharmaceuticals, AstraZeneca, Avaxia, BMS, Boehringer Ingelheim, Celgene, CVasThera, Dr. Falk Pharma, Ferring, Galapagos, Genentech-Roche, Gilead, GSK, Hospira, IMIDomics, Janssen, J&J, Lilly, Materia Prima, MiroBio, Morphic, MRM Health, Mundipharma, MSD, Pfizer, ProDigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Surrozen, Takeda, Theravance, Tillotts Pharma AG, and Zealand Pharma.

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Author Contributions

Pieter Sinonquel and Raf Bisschops are responsible for the concept of this paper and wrote the manuscript. All authors provided valuable feedback, suggestions, and corrections to improve the quality of the manuscript. The manuscript is approved by all authors.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Anastomotic Leakages after Surgery for Gastroesophageal Cancer: A Systematic Review and Meta-Analysis on Endoscopic versus Surgical Management

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Keywords
Anastomotic leak · Gastroesophageal cancer · Surgical treatment · Endoscopic treatment

Abstract
Introduction: With the increase of esophageal and gastric cancer, surgery will be more often performed. Anastomotic leakage (AL) is one of the most feared postoperative complications of gastroesophageal surgery. It can be managed by conservative, endoscopic (such as endoscopic vacuum therapy and stenting), or surgical methods, but optimal treatment remains controversial. The aim of our meta-analysis was to compare (a) endoscopic and surgical interventions and (b) different endoscopic treatments for AL following gastroesophageal cancer surgery. ***Methods:*** Systematic review and meta-analysis, with search in three online databases for studies evaluating surgical and endoscopic treatments for AL following gastroesophageal cancer surgery. ***Results:*** A total of 32 studies comprising 1,080 patients were included. Compared with surgical intervention, endoscopic treatment presented similar clinical success, hospital length of stay, and intensive care unit length of stay, but lower in-hospital mortality (6.4% [95% CI: 3.8–9.6%] vs. 35.8% [95% CI: 23.9–48.5%]. Endoscopic vacuum therapy was associated with a lower rate of complications (OR 0.348 [95% CI: 0.127–0.954]), shorter ICU length of stay (mean difference −14.77 days [95% CI: −26.57 to −2.98]), and time until AL resolution (17.6 days [95% CI: 14.1–21.2] vs. 39.4 days [95% CI: 27.0–51.8]) when compared with stenting, but there were no significant differences in terms of clinical success, mortality, re-interventions, or hospital length of stay. ***Conclusions:*** Endoscopic treatment, in particular endoscopic vacuum therapy, seems safer and more effective when compared with surgery. However, more robust comparative studies are needed, especially for clarifying which is the best treatment in specific situations (according to patient and leak characteristics).

Deiscências anastomóticas após cirurgia para tratamento de cancro gastroesofágico: uma revisão sistemática e meta-análise sobre tratamento endoscópico vs abordagem cirúrgica

Palavras Chave
Deiscência anastomótica · Cancro gastroesofágico · Tratamento cirúrgico · Tratamento endoscópico

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Resumo

Introdução: Com o aumento da incidência de cancro esofágico e gástrico, a cirurgia será mais frequentemente realizada. As deiscências anastomóticas (DA) são uma das complicações pós-operatórias mais temidas da cirurgia gastroesofágica. Podem ser tratadas com métodos conservadores, endoscópicos (como terapêutica endoscópica por vácuo e colocação de próteses) ou cirúrgicos, mas a melhor abordagem ainda é controversa. O objetivo da nossa meta-análise foi a comparação a) entre intervenções endoscópicas e cirúrgicas e b) entre diferentes tratamentos endoscópicos para a DA após cirurgia oncológica gastroesofágica. ***Métodos:*** Revisão sistemática e meta-análise, com pesquisa em 3 bases de dados online de estudos que avaliassem tratamentos cirúrgicos e endoscópicos da DA após cirurgia oncológica gastroesofágica. ***Resultados:*** Um total de 32 estudos englobando 1,080 pacientes foram incluídos. Comparativamente à intervenção cirúrgica, o tratamento endoscópico apresentou sucesso clínico, duração do internamento hospitalar e do internamento na unidade de cuidados intensivos semelhantes, mas menor mortalidade intra-hospitalar (6.4% [95% CI: 3.8–9.6%] vs. 35.8% [95% CI: 23.9–48.5%]). A terapêutica endoscópica por vácuo associou-se a menor taxa de complicações (OR 0.348 [95% CI: 0.127–0.954]), menor duração do internamento na UCI (diferença média −14.77 dias [95% CI: −26.57 to −2.98]) e do tempo até resolução da DA (17.6 dias [95% CI: 14.1–21.2] vs. 39.4 dias [95% CI: 27.0–51.8]) quando comparada com as próteses endoscópicas, mas não houve diferenças significativas em termos de sucesso clínico, mortalidade, reintervenções ou duração do internamento hospitalar. ***Conclusões:*** O tratamento endoscópico, em particular a terapêutica endoscópica por vácuo parece ser mais segura e efetiva em comparação com a cirurgia. Porém, estudos comparativos mais robustos são necessários, especialmente para clarificar qual o melhor tratamento em situações específicas (consoante as caraterísticas do paciente e da deiscência).

Introduction

Surgical treatment of esophagogastric cancer is associated with significant mortality and morbidity rates. Esophagectomy's mortality and morbidity are reported to be as high as 3.8–4.5% and 24.0–44.9%, respectively [1–3]. Gastrectomy for gastric cancer carries a mortality of 4.1–4.7% and a morbidity of 23.6–36.0% [4, 5].

Anastomotic leakage (AL) is one of the most feared postoperative complications of gastroesophageal surgery owing to its association with prolonged hospital stay, increased mortality, and reduced quality of life [6–9]. In recent decades, improving of surgical techniques and better management of postoperative complications led to a decrease of those outcomes [10, 11], although this adverse event is still frequent, with AL incidence rates ranging from 0 to 49% following esophagectomy [12] and from 2.1 to 14.6% after gastrectomy [13].

AL can be managed by conservative (which includes fasting, nutritional support, antibiotic therapy, and wound drainage), endoscopic (clips, stents, tissue adhesives, or endoscopic vacuum therapy [EVT]), or surgical methods (primary closure of the leak, reanastomosis, or resection of the conduit). Currently, treatment decision is usually based on the characteristics of the leakage and the patient's clinical condition, but optimal treatment remains controversial [13–15]. In the past, surgery was the treatment of choice, although it carries a higher mortality rate and nowadays is mostly used in cases of severe sepsis, large defects, or when other treatments failed or are not available/indicated.

Conservative treatment can be an option in clinically stable patients with small leakages [13, 14]. More recently, endoscopic techniques for AL were developed and appear to be safer than surgical reintervention [13, 14]. Recent systematic reviews comparing stenting with EVT found that the latter was associated with higher rate of AL closure and lower mortality [16–19]. Other endoscopic methods have also been reported as safe and effective, but most of this evidence results from small case series [13, 16]. Thus, it is unclear which is the optimal strategy for endoscopic treatment of AL after oncological gastric or esophageal surgery. Moreover, the comparison of endoscopic and surgical treatments for AL is important to confirm if endoscopic treatment should be the first-line strategy. The aims of this meta-analysis were to compare the outcomes of endoscopic and surgical treatments for AL following surgery for both esophageal and gastric cancer and to compare the outcomes of the different endoscopic methods.

Methods

This meta-analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses checklist [20]. Since we performed a systematic review, no institutional board review approval or written consent was obtained.

Search Strategy

To identify published literature, a systematic search strategy was performed using 3 electronic databases (MEDLINE through PubMed, ISI Web of Knowledge, and Scopus), with last search performed on 2nd September 2020. No language or publication date restrictions were imposed. The search query for PubMed was ("anastomotic leak" OR "anastomotic dehiscence" OR "anastomosis dehiscence" OR "anastomotic fistula") AND (gastric OR stomach OR esophag* OR oesophag* OR gastroesophageal OR "upper gastrointestinal tract") AND (endoscopy OR "endoscopic management" OR "OTSC" OR stent OR sponge OR esophagectomy OR gastrectomy).

In addition, reference lists of review articles on the topic were searched to identify additional studies. We contacted all authors of studies that did not present the data as per inclusion criteria. Studies from authors that did not answer were not included in the quantitative analysis.

Study Selection

Studies were reviewed initially based on title and abstract by two independent investigators (I.A. and R.O). The full text of the included studies was then independently screened by the same two investigators according to the criteria below. A third author (D.L.) intervened in case of disagreement. The reasons for excluding studies were recorded. This phase was performed with Rayyan online platform. We included (1) randomized controlled trials, case-control or cohort studies (prospective or retrospective), and case series; (2) including patients who underwent endoscopic or surgical interventions as the first treatment for an AL following a gastroesophageal cancer surgery; (3) and evaluating the success of the endoscopic and surgical interventions in terms of at least one of the primary or secondary outcomes mentioned below. Studies were excluded if they were (1) review articles, editorials, comments, letters, and surveys; (2) case reports; (3) animal studies; (4) if they included fewer than 10 patients who met the eligibility criteria; or (5) if there was population overlap between studies. In this last case, only the study with the largest sample or study period was included.

Outcomes

The primary outcomes were (a) clinical success (defined as a complete closure of the AL, confirmed by upper endoscopy or imaging exam, with no need for reintervention and no death occurring as a consequence of the AL or its treatment, during follow-up); (b) in-hospital mortality (overall and treatment-related mortality). Secondary outcomes were rate of technical success (defined as a successful application of the chosen therapy), rate of endoscopic and surgical reintervention, rate of complications, hospital, and intensive care unit (ICU) length of stay, time until AL resolution and time until oral intake.

Data Collection

Data were extracted and recorded on an electronic data extraction sheet by two independent investigators (I.A. and R.O). Disagreements were solved by consensus. We retrieved information about: (1) study (title, first author, year of publication, country of origin, study period, study design, number of participants, number of patients with AL, and risk of bias); (2) participants (age, gender, and comorbidities); (3) tumor characteristics (location, staging, neoadjuvant therapy and type of resection, and reconstruction); (4) AL characteristics (time between surgery and AL diagnosis, modality of diagnosis, location, and dimensions of AL); (5) interventions (number of patients treated with each endoscopic and surgical method, time between cancer surgery or AL diagnosis and treatment, characteristics of each treatment), and (6) the aforementioned outcomes.

Assessment of Methodological Quality

The risk of bias within studies was evaluated by I.A. using the Newcastle-Ottawa Scale for cohort studies and independently checked by R.O. Disagreements were solved by consensus. We also assessed the existence of publication bias by visual inspection of funnel plots and using the Egger's test for primary outcomes.

Statistical Analysis

We performed a meta-analysis including all studies (single-arm or double-arm) presenting data allowing the calculation of pooled prevalence (for categorical variables) and weighted mean (for continuous variables), using random-effects model with MetaXL 5.3. Double-arm comparative studies were analyzed through calculation of odds ratio (OR) and weighted mean differences (WMD). Heterogeneity between studies was tested using I^2 statistic and Cochran's Q test. Significant heterogeneity was defined as I^2 >40% and/or $p < 0.05$. Subgroup analysis was conducted to explore potential sources of heterogeneity according to (a) tumor location (esophageal vs. gastric) and (b) mortality definition (overall mortality vs. treatment-related mortality). Sensitivity analyses were also conducted in case of important definition and/or technical differences between studies and presence of outliers.

Results

Study Selection, Study Characteristics, and Quality Evaluation

After removing 2,382 duplicates, 2,733 titles and abstracts were screened, and 126 articles underwent full-text assessment, of which 32 were included in the systematic review (Fig. 1) [21–52]. We also checked the reference list of previous systematic reviews on the topic but found no further relevant studies.

General characteristics of the included studies (29 retrospective and 3 prospective) are shown in Table 1. Details regarding demographic and clinical characteristics of the patients are presented in online supplementary Table 1 (see www.karger.com/doi/10.1159/000527769 for all online suppl. material). Twenty-one of the included studies (65.6%) evaluated endoscopic treatment [21–25, 28–30, 32–36, 41–44, 46, 49, 50, 52], 3 (9.4%) focused on surgical intervention [37, 38, 47], and 8 (25.0%) evaluated both types of intervention [26, 27, 31, 39, 40, 45, 48, 51].

Overall, 936 patients were treated with endoscopic methods, including 533 with stent placement (22 studies) [21–23, 25–31, 33, 34, 36, 40–43, 45, 48, 50–52], 133 with

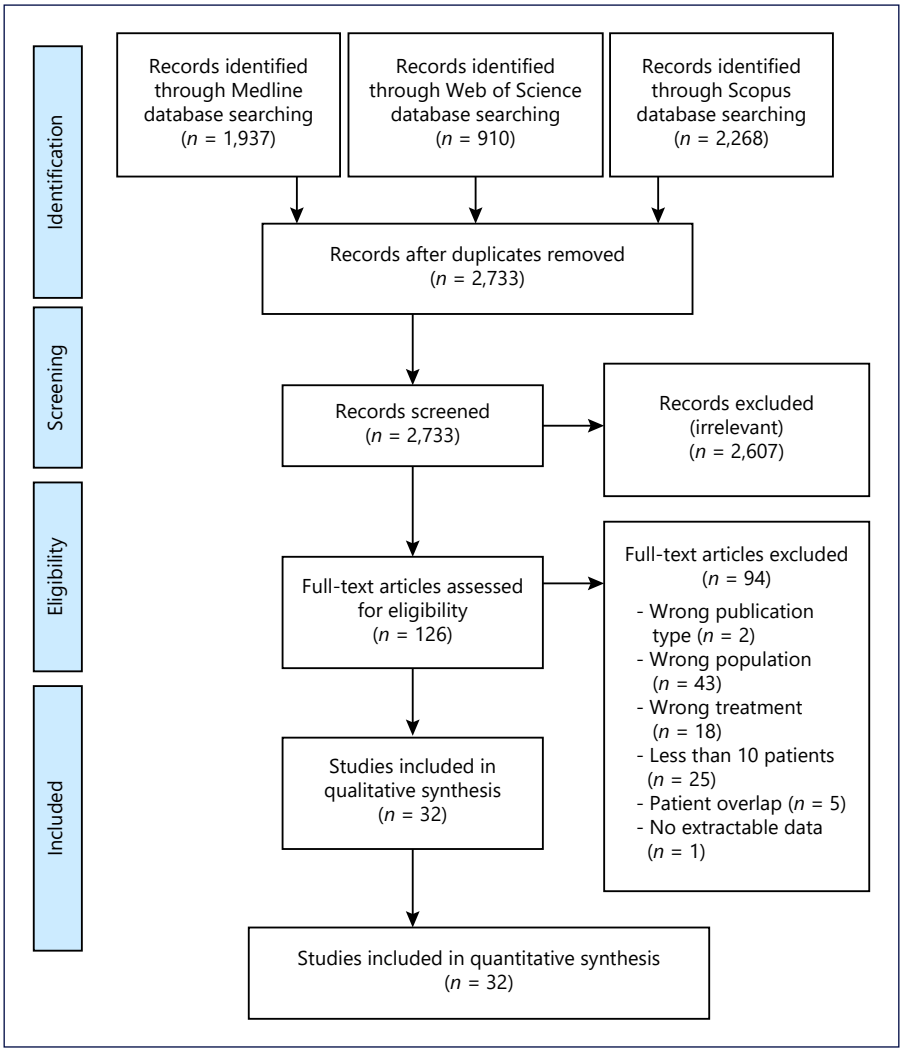

Fig. 1. Flow diagram of study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses.

EVT (6 studies) [22, 33, 44, 46, 48, 49], 70 with clips (3 studies) [21, 43, 45, 50], 14 with fibrin glue (2 studies) [34, 50], 86 with argon plasma coagulation (1 study) [43], and 45 with multimodal interventions (3 studies) [24, 39, 41]. In 75 patients across 4 studies, the outcomes of different endoscopic treatments were evaluated together [31, 32, 35, 50]. Regarding stent placement, most studies used self-expanded metal stents, which were fully covered in the majority of the patients. Meta-analysis comparing partially and fully covered metal stents was not performed due to the low number of studies evaluating outcomes separately. Details about the endoscopic treatment are summarized in online supplementary Table 2.

A total of 144 patients were treated with surgical interventions, including 13 with anastomosis disassembly and ostomy (3 studies) [27, 31, 47], 17 with suture of anastomosis (3 studies) [37, 38, 40], 20 with reanastomosis (3 studies) [31, 45, 47], and 19 with other surgical interventions (3 studies) [31, 38, 47]. In 75 patients across 4 studies, the outcomes of different surgical treatments were evaluated together [26, 39, 48, 51].

Methodological quality of the included studies is described in Table 1. The median Newcastle-Ottawa score was 6 (IQR 5–6). Funnel plots and Egger's test did not show evidence of publication bias when evaluating in-hospital mortality after endoscopic ($p = 0.410$) and surgical treatment ($p = 0.169$) and clinical success after endoscopic treatment ($p = 0.053$).

Surgical versus Endoscopic Treatment

Technical success was presented in 6 endoscopic studies, with 5 of them reporting a technical success of 100%

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Table 1. General characteristics and quality evaluation of the included studies

Author, year	Country	Study period	Tumor location	Esophagectomy, *n* (%)	Neoadjuvant therapy, *n* (%)	AL, *n* (%)	Time until AL diagnosis[a], mean ± SD	Quality[b]	M-A
Prospective studies									
Endoscopic treatment									
Feith et al. [28], 2011	DE	2003–2009	E	87 (75.7)	89 (77.4)	–	8.4±3.5	6	Yes
Kucukay et al. [36], 2013	TR	–	G	0 (0)	–	–	5.4±1.8	4	Yes
Fernandez et al. [29], 2015	ES	2011–2013	E, G	4 (28.6)	–	–	–	6	Yes
Retrospective studies									
Endoscopic treatment									
Freeman et al. [30], 2015	USA	7-year period	E	45 (100)	38 (84.4)	–	–	5	Yes
Gonzalez et al. [32], 2016	FR	2010–2014	E	34 (97.1)	25 (71.4)	–	8.2±5.6	4	Yes
Kauer et al. [34], 2007	DE	1998–2005	E	12 (100)	–	12 (4.5)	–	4	Yes
Leenders et al. [41], 2013	NL	2007–2010	E	15 (100)	–	19 (16.0)	–	6	Yes
Mennigen et al. [44], 2015	DE	2009–2015	E	15 (100)	11 (73.3)	–	11.8±11.5	6	Yes
Min et al. [46], 2019	KR	2015–2017	E	20 (100)	10 (50.0)	–	14.7±8.0	6	Yes
Wu et al. [52], 2017	CN	–	E	27 (100)	–	–	–	5	Yes
Kim, et al. [35], 2013	KR	2003–2011	G	0 (0)	–	66 (12.6)	8.6±5.4	6	Yes
Al-issa et al. [21], 2014	DK	2007–2010	E, G	–	–	20 (9.6)	–	6	Yes
Berlth et al. [22], 2018	DE	2007–2016	E, G	93 (83.8)	68 (61.3)	–	10.2±11.4	6	Yes
EVT					18 (52.9)		12.6±13.7		
SEMS					50 (64.9)		8.5±4.6		
Bohle et al. [23], 2020	DE	2009–2015	E, G	27 (79.4)	22 (64.7)	–	9.3±6.5	6	Yes
Böhm et al. [24], 2010	DE	2000–2007	E, G	–	–	81 (25.9)	11±8	6	Yes
Dai et al. [25], 2009	DE	2001–2007	E, G	17 (77.3)	–	–	6.5±NA	6	Yes
Hwang et al. [33], 2016	KR	2008–2014	E, G	9 (50.0)	–	–	–	6	Yes
Licht et al. [42], 2015	USA	2003–2012	E, G	–	–	–	8.9±5.8	4	Yes
Ma et al. [43], 2018	CN	2008–2016	E, G	–	–	263 (10.1)	–	6	Yes
Schorsch et al. [49], 2014	DE	2006–2013	E, G	9 (45.0)	10 (50.0)	–	9.9±5.4	6	Yes
Schubert et al. [50], 2006	DE	2000–2004	E, G	19 (73.1)	–	–	6.7±2.8	6	Yes
Surgical treatment									
Lee et al. [38], 2012	KR	2000–2010	E	10 (100)	–	23 (3.5)	12.0±8.6	5	Yes
Page et al. [47], 2004	UK	9-year period	E	17 (100)	–	–	9.3±5.6	6	Yes
Lang et al. [37], 2000	DE	1968–1998	G	0 (0)	–	83 (7.5)	–	4	Yes
Endoscopic and surgical treatment									
Angulo et al. [26], 2018	ES	2011–2016	E	10 (100)	6 (60.0)	10 (11.8)	–	6	Yes
Etxaniz et al. [27], 2013	ES	2003–2011	E	10 (100)	–	18 (23.4)	–	6	Yes
Fumagali et al. [31], 2018	IT	2014–2017	E	40 (100)	–	59 (11.8)	–	4	Yes
Schniewind et al. [48], 2013	DE	1995–2012	E	47 (100)	–	62 (16.9)	–	8	Yes
Schweigert et al. [51], 2014	DE	2004–2013	E	49 (100)	14 (28.6)	49 (13.8)	–	6	Yes
Lee et al. [39], 2015	KR	2000–2013	G	0 (0)	–	133 (0.7)		7	Yes
Endoscopy							9.8±5.5		
Surgery							17.9±24.0		
Lee et al. [40], 2018	KR	2002–2016	G	0 (0)	–	13 (3.1)	3.9±1.7	6	Yes
Milek et al. [45], 2016	PL	1996–2014	G	0 (0)	–	23 (4.7)	7±NA	6	Yes

NA, not available; DE, Germany; TR, Turkey; ES, Spain; DK, Denmark; USA, United States of America; IT, Italy; FR, France; KR, South Korea; NL, The Netherlands; CN, China; PL, Poland; UK, United Kingdom; E, esophageal and/or esophagogastric junction; G, gastric; M-A, included in meta-analysis. [a] Defined as time between cancer surgery and AL detection. [b] Quality evaluation using Newcastle-Ottawa Quality Assessment Scale for cohort studies.

Table 2. Primary outcomes according to treatment and tumor location

Mortality	Pooled mortality (95% CI)	I^2, %
Endoscopic studies		
Overall	6.4 (3.8–9.6) [21–32, 34–36, 39–41, 44–46, 48–52]	57
AL after esophageal tumor	6.2 (2.2–11.3) [26–28, 30–32, 34, 41, 44, 46, 48, 51, 52]	66
AL after gastric tumor	6.3 (0.3–0.14.8) [35, 36, 39, 40, 45]	53
EVT	6.0 (1.8–11.4) [22, 44, 46, 48, 49]	10
Stent placement	8.6 (4.6–13.4) [21–23, 25–31, 34, 36, 40, 41, 45, 48, 50–52]	61
Surgical studies		
Overall	35.8 (23.9–48.5) [26, 27, 31, 37–40, 45, 47, 48, 51]	52
AL after esophageal tumor	33.3 (18.3–49.6) [26, 27, 31, 38, 47, 48, 51]	55
AL after gastric tumor	42.3 (17.4–68.6) [37, 39, 40, 45]	61
Clinical success	**Pooled clinical success rate (95% CI)**	**I^2, %**
Endoscopic studies		
Overall	83.2 (77.0–88.6) [21–30, 33–36, 39–42, 44–46, 49, 50, 52]	72
AL after esophageal tumor	86.6 (76.4–95.0) [26–28, 30, 34, 41, 42, 44, 46, 52]	78
AL after gastric tumor	80.0 (61.3–95.5) [35, 36, 39, 40, 45]	76
EVT	91.3 (79.2–99.6) [22, 33, 44, 46, 49]	77
Stent placement	81.5 (73.6–88.3) [21–23, 25–30, 33, 34, 37, 40–42, 45, 50, 52]	72
Surgical studies with >5 patients		
Overall	82.2 (67.7–93.3) [38, 39, 45, 47]	41
AL after esophageal tumor	75.8 (45.4–98.7) [38, 47]	61
AL after gastric tumor	87.8 (64.8–100) [39, 45]	53

[25, 27, 28, 32, 52] and the other presenting a rate of 92.9% [29]. Clinical success (leak closure rate) was similar in endoscopic and surgical studies (83.2% [95% CI: 77.0–88.6%] vs. 82.2% [95% CI: 67.7–93.3%]) (online suppl. Fig. 1; Table 2). However, overall in-hospital mortality was significantly higher in surgical studies than in endoscopic studies (35.8% [95% CI: 23.9–48.5%) vs. 6.4% [95% CI: 3.8–9.6%]) (Fig. 2; Table 2). Death directly due to adverse events of endoscopic treatment was described in 8 endoscopic studies, and the pooled treatment-related mortality was 1.4% (95% CI: 0.0–3.8%). Clinical success and mortality were similar when stratifying by lesion location (Table 2).

After surgical treatment, there were no surgical reinterventions (0% [95% CI: 0–4.8%]) [26, 27, 31, 38–40, 45, 47]. After endoscopic treatment, the rate of surgical reintervention was 4.9% (95% CI: 2.7–7.6%) (online suppl. Fig. 2) [21–36, 39–42, 44–46, 49, 50, 52].

Surgical complications were presented in 3 studies, which reported development of stenosis, fistulae, and severe bleeding in 17.6% [47], 30.0% [38], and 2.9% [39] of the patients, respectively. Overall adverse events occurred in 26.6% of the patients treated with EVT or stenting (95% CI: 20.7–33.0%; detailed below).

There were no significant differences in terms of hospital or ICU length of stay (Table 3). Most studies defined hospital length of stay as time between cancer surgery and discharge. Sensitivity analysis excluding two studies with slightly different definitions of this outcome [30, 39] did not significantly affect the estimates.

Time until AL resolution was only presented in 1 surgical study (50.1 ± 60.0 days) [38]. In endoscopic studies, mean time until AL resolution ranged from 12.0 to 63.4 days [22–26, 29, 30, 32, 33, 41, 42, 44, 46, 49, 50, 52].

EVT versus Stent

Single-Arm Meta-Analysis

EVT, in comparison to stent, was associated with a nonsignificantly higher clinical success rate (91.3% [95% CI: 79.2–99.6%] vs. 81.5% [95% CI: 73.6–88.3%]) (Table 2) and a nonsignificantly lower in-hospital mortality rate (6.0% [95% CI: 1.8–11.4%] vs. 8.6% [95% CI: 4.6–13.4%]) (Table 2).

EVT was associated with a nonsignificantly lower rate of surgical reinterventions (1.8% [95% CI: 0–5.2.0%] vs. 5.7% [95% CI: 2.6–9.6%]), but a nonsignificantly higher rate of endoscopic reinterventions (8.3% [95% CI: 0–21.4%] vs. 4.0% [95% CI: 2.2–6.4%]) [21–23, 25–30, 33,

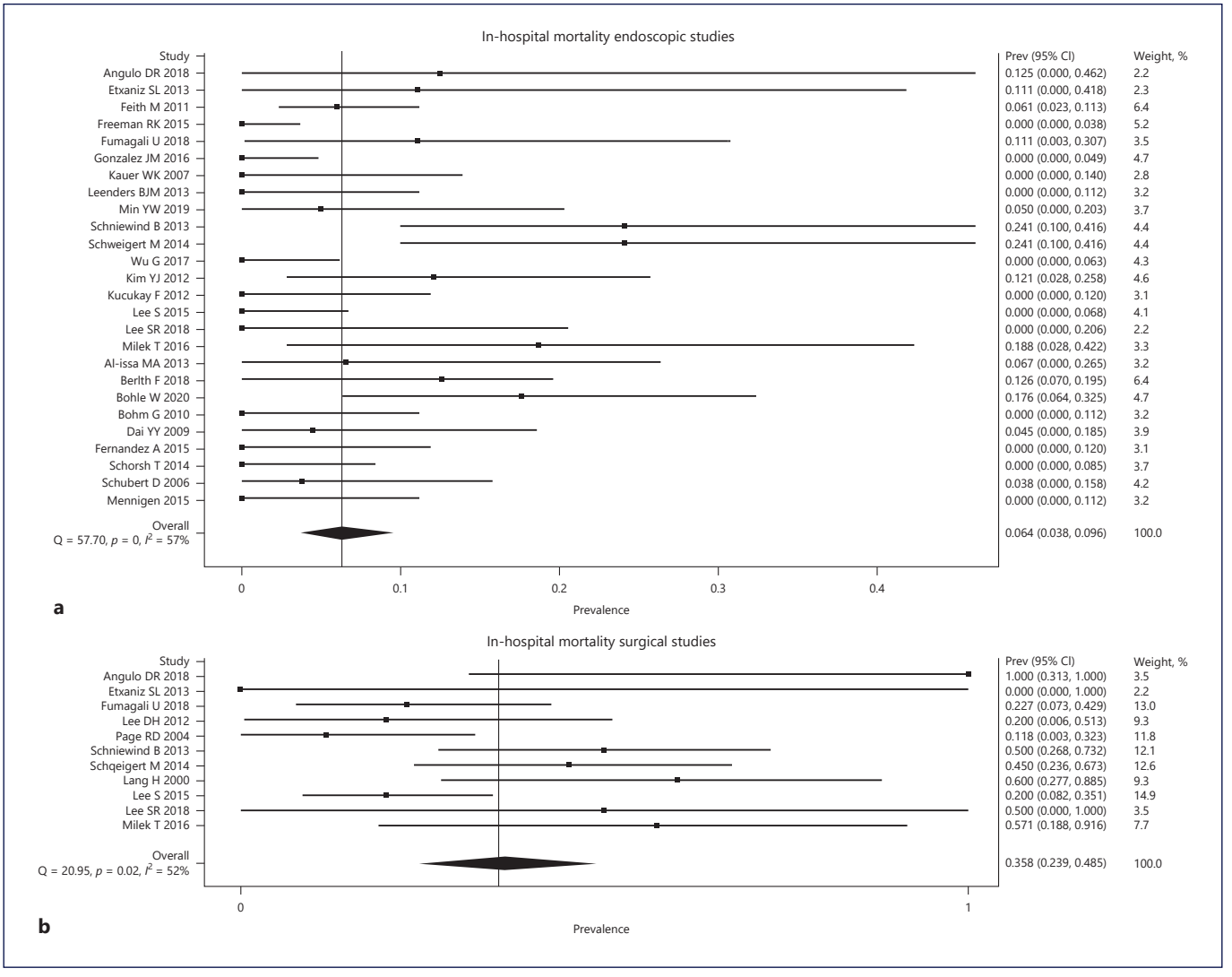

Fig. 2. Forest plot of in-hospital mortality according to treatment: (**a**) endoscopic treatment; (**b**) surgical treatment.

34, 36, 40–42, 44–46, 49, 50, 52]. Moreover, EVT required 1 to 18 sponges, while the number of stents ranged from 1 to 7 (online suppl. Table 2).

EVT and stenting complications are shown in Table 4. The overall complications rate, considering the occurrence of migration of endoscopic device, stenosis, severe bleeding, perforation, or fistulization, was nonsignificantly lower in the EVT group (14.0% [95% CI: 3.2–27.7%] vs. 32.6% [95% CI: 24.0–41.9%]) [21–23, 25, 26, 28–30, 33, 34, 36, 40–46, 49–52]. Sensitivity analysis, excluding an outlier (Feith et al. [28], 67.0% of overall complications after stenting), did not significantly affect the estimates. EVT was associated with a nonsignificantly lower migration rate compared to stenting. Sensitivity analysis excluding an outlier (Feith et al. [28], 53% migration after stent placement) did not significantly affect the estimates. Stenosis rate was nonsignificantly higher in the EVT group. Sensitivity analysis excluding two outliers (Min et al. [46], 35% stenosis after EVT; Ma et al. [43], 43% stenosis after stent placement) found that stenosis rate was similar in EVT and stent studies. Other adverse events (severe bleeding, perforation, and fistulization) were infrequent (<3.5%) and were similar in EVT and stent groups.

There were no significant differences in terms of hospital or ICU length of stay (Table 3). Freeman et al. [30], which included patients who underwent stent placement before being transferred from other facilities, reported a

Table 3. Hospital and ICU length of stay according to treatment

	Weighted mean (95% CI)	I^2, %
Hospital length of stay, days		
Endoscopic treatment	45.9 (35.9–55.9) [22, 26, 30, 33, 35, 39–41, 43, 44, 46, 48, 51]	97
EVT	51.4 (45.1–57.7) [22, 33, 44, 46, 48]	32
Stent placement	44.6 (31.8–57.4) [22, 26, 30, 33, 40, 41, 43, 48, 51]	97
Surgical treatment	41.9 (30.9–52.9) [39, 47, 48, 51]	72
ICU length of stay, days		
Endoscopic treatment	19.5 (13.0–26.0) [22, 48, 50]	69
EVT	18.1 (3.8–32.5) [22, 48]	87
Stent placement	21.1 (12.7–29.5) [22, 48, 50]	41
Surgical treatment	21.7 (3.4–40.1) [47, 48]	86

Table 4. Complications according to treatment

	Pooled prevalence (95% CI)	I^2, %
Overall complications		
EVT	14.0 (3.2–27.7) [22, 33, 44, 46, 49]	65
Stent placement	32.6 (24.0–41.9) [21-23, 25, 26, 28-30, 33, 34, 37, 40-43, 45, 50-52]	75
Migration		
EVT	6.1 (0.8–13.9) [22, 33, 44, 46, 49]	80
Stent placement	21.5 (13.5–30.8) [21–23, 25, 26, 28–30, 33, 34, 36, 40–43, 45, 50–52]	41
Stenosis		
EVT	8.1 (0–20.2) [22, 33, 44, 46, 49]	32
Stent placement	4.9 (2.6–7.7) [21–23, 25, 26, 28–30, 33, 34, 36, 40–43, 45, 50–52]	69
Severe bleeding		
EVT	1.1 (0–3.8) [22, 33, 44, 46, 49]	0
Stent placement	2.0 (0.8–3.6) [21–23, 25, 26, 28–30, 33, 34, 36, 40–43, 45, 50–52]	10
Perforation		
EVT	1.1 (0–3.8) [22, 33, 44, 46, 49]	0
Stent placement	1.7 (0.7–3.0) [21–23, 25, 26, 28–30, 33, 34, 36, 40–43, 45, 50–52]	0
Fistulization		
EVT	1.1 (0–3.8) [22, 33, 44, 46, 49]	0
Stent placement	3.2 (1.9–5.0) [21–23, 25, 26, 28–30, 33, 34, 36, 40–43, 45, 50–52]	0

shorter hospital length of stay (9.0 days [95% CI: 7.2–10.8]); sensitivity analysis excluding this study did not significantly affect the estimates.

EVT was associated with a significantly shorter time until AL resolution compared with stenting (17.6 days [95% CI: 14.1–21.2] vs. 39.4 days [95% CI: 27.0–51.8]) (online suppl. Fig. 3) [22, 23, 28, 29, 33, 41, 42, 44, 46, 49, 50, 52]. Sensitivity analysis excluding an outlier (Freeman et al. [30], 12 days until AL resolution after stent placement) did not significantly affect the estimates. Mean time until oral intake, only reported in 4 stent studies, ranged between 1.7 and 28.8 days [25, 36, 40, 43].

Double-Arm Meta-Analysis

Meta-analysis of the studies directly comparing EVT with stent placement revealed that EVT was associated with nonsignificantly higher clinical success (OR 1.91 [95% CI: 0.47–7.79]) [22, 33], lower in-hospital mortality (OR 0.39 [95% CI: 0.13–1.18]) [22, 48], and lower endoscopic (OR 0.21 [95% CI: 0.02–1.88]) (online suppl. Fig. 4) and surgical (OR 0.45 [95% CI: 0.04–5.61]) reintervention rates [22, 33]. There were also nonsignificantly lower rates of migration of endoscopic device (OR 0.51 [95% CI: 0.17–1.55]) and stenosis (OR 0.58 [95% CI: 0.09–3.97]), but a significantly lower rate of overall complications in the EVT group (OR 0.35 [95% CI: 0.13–0.95]) (online suppl. Fig. 5) [22, 33].

EVT was associated with nonsignificantly shorter time until AL resolution (WMD –8.67 days [95% CI: –22.54 to 5.20]) [22, 33] and shorter hospital length of stay (WMD –12.98 days [–31.27 to 7.98]) (online suppl. Fig. 6) [22, 33, 48]. There was a significantly shorter ICU length of stay in the EVT group compared to the stent group

(WMD −14.77 days [95% CI: −26.57 to −2.98]) (online suppl. Fig. 7) [22, 48].

Other Endoscopic Treatments

Some of the included studies focused on other endoscopic treatments besides stents and EVT, namely clips, fibrin glue, argon plasma coagulation, and multimodal modalities that were not included in meta-analysis due to the reduced number of studies on these treatments. There were no deaths directly related to any of these treatments. Clipping and fibrin glue had clinical success in 66.7% and 78.6% of the patients, respectively. Multimodal modalities had higher rates of clinical success ranging from 80.0% to 96.0%. Details on the outcomes of these treatments are shown in online supplementary Table 3.

Discussion

This systematic review and meta-analysis evaluated the efficacy of endoscopic and surgical interventions in the management of AL after gastroesophageal cancer surgery. Even though there have been some reviews regarding the treatment of AL, to our knowledge, this is the first meta-analysis simultaneously comparing (1) endoscopic versus surgical interventions and (2) EVT versus stent placement in this specific context.

Our results demonstrated that endoscopic treatment, in comparison to surgical intervention, was associated with a significantly lower in-hospital mortality rate. However, no significant differences were found between these treatments in terms of clinical success, surgical reinterventions, hospital length of stay, and ICU length of stay. The decreased mortality found in the endoscopic therapy group may be related with the lesser invasiveness of these therapies, although it is also possible that there are differences in the clinical status and/or dehiscence characteristics of the patients between the two groups that may contribute to this difference in mortality. For instance, Schweigert et al. [51] found that patients in the surgical group were generally in worse condition, being more frequently septic. A recent cohort study also concluded that AL with a more severe initial presentation (i.e., requiring operative management) was associated with a lower rate of primary management success [53]. In our meta-analysis, however, most studies did not present data on AL size or clinical status at presentation.

The use of stents for the treatment of postoperative esophagogastric AL has already been established [54]. However, recent systematic reviews have shown that EVT is associated with improved rates of AL closure, lower mortality, and lower rates of adverse events, when compared to stenting [16–19]. The differences we found, even though not always statistically significant, are consistent with the aforementioned previous literature.

We found a nonsignificantly higher clinical success rate and a nonsignificantly lower in-hospital mortality rate for EVT compared to stent placement. As EVT is a relatively new technique, it is possible that the first studies evaluating this method included patients in which a favorable outcome was expected (selection bias), thus influencing the results [16].

Our single-arm meta-analysis revealed no significant differences between EVT and stent placement in terms of reinterventions or complications. However, there was a significantly lower rate of overall complications in the EVT group, although this difference is mainly explained by a single study, which had a weight of 89.6% [22].

We found that EVT was associated with a significantly shorter time until AL resolution compared with stent placement. This might be due to the fact that, in EVT, sponges were changed frequently, usually every 72–120 h, until successful healing of the AL [22, 33, 44, 46, 49]. In contrast, the stents usually remain in place for 4–8 weeks until follow-up endoscopy with stent change or stent removal [27, 28]. Therefore, we cannot exactly ascertain the moment when AL closure was achieved in the case of stent placement. As pointed out by Scognamiglio et al. [16], a more adequate outcome parameter to measure the success of therapy would be the time until resolution of AL-associated symptoms or the time until start of oral nutrition. However, none of the studies reported time until resolution of AL-associated symptoms, but 4 stent studies presented the mean time until oral intake, which ranged from 1.7 to 28.8 days (lower than the reported time until to AL resolution).

As sponge changes are much more frequent than stent replacement, EVT requires a higher number of endoscopic devices and procedures. This offers the possibility to assess the wound regularly, which might help in detecting complications before their progression, which might contribute to the lower rate of overall complications in EVT studies. In addition, it allows endoscopic lavage and debridement at each sponge exchange, which has been shown to reduce pleural inflammation and leakage-associated mortality [55]. However, the higher number of endoscopic procedures and devices increases the cost of EVT, which has been shown to be twice the cost of stent placement [56]. Regarding hospital and ICU length of stay, there were no significant differences between EVT

and stent placement in single-arm studies, although in comparative studies EVT was associated with a significantly shorter ICU length of stay compared to stenting.

Our study has some limitations. Included studies are mostly retrospective, single-arm, and/or include a small sample size. In addition, one problem that led to limited comparability of several outcomes was the fact that their definitions were heterogenous or absent in many studies. Another limitation was the heterogeneity found on most analyses that did not decrease when stratifying by tumor location. Variables such as presence of comorbidities, dimensions and location of AL, time until diagnosis, or time until treatment have differences between studies and may also contribute for heterogeneity. Moreover, whereas stent placement is quite standardized and reproducible, EVT procedure may differ between institutions in terms of the magnitude of negative pressure, interval between sponge changes and placement of the sponge (extra- or intraluminal). A fourth limitation refers to the relatively low number of EVT studies and patients, which may have led to underpowerment to detect existent differences.

In conclusion, we found that endoscopic treatment was associated with a lower in-hospital mortality compared to surgical intervention. EVT is associated with a lower rate of overall complications and a shorter ICU length of stay compared to stenting. Other differences, although not statistically significant, seemed to point to a greater suggest similar efficacy and better safety profile of endoscopic treatment when compared to surgical intervention and of EVT compared to stenting. These findings can help in the definition of standardized treatment algorithms.

Although EVT seems like a promising treatment, the lack of comparative studies and standardization of clinical conditions poses a challenge in making definite conclusions. Therefore, it is essential to develop more robust prospective randomized comparative studies with standardized interventions and outcomes in order to compare EVT with other modalities and define which is the best treatment in specific situations (according to patient and leak characteristics).

Statement of Ethics

Not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

Drs. Isabel Azevedo, Raquel Ortigão, Pedro Pimentel-Nunes, Pedro Bastos, and Diogo Libânio have no conflicts of interest or financial ties to disclose. Dr. Rui Silva has ties with Boston Scientific and Cook Medical. Dr. Mário Dinis-Ribeiro has ties with Medtronic, Boston, and Fujifilm.

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Author Contributions

Dr. Isabel Azevedo was responsible for the conception of study design, study selection, data extraction, and writing of the manuscript. Dr. Raquel Ortigão contributed to the conception of study design, study selection, data extraction, and revision of the manuscript. Dr. Diogo Libânio contributed to the conception of study design, selection of studies, meta-analysis, and revision of the manuscript. Drs. Rui Silva and Mário Dinis-Ribeiro were involved in the conception of study design and revision of the manuscript. Drs. Pedro Pimentel-Nunes and Pedro Bastos were also involved in the revision of the manuscript.

Data Availability Statement

The data and forest plots generated during this study are included in this article and its supplementary material files or can be requested to the corresponding author on reasonable request.

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Palliative Care in Advanced Liver Disease: Similar or Different Palliative Care Needs in Patients with a Prospect of Transplantation? Prospective Study from a Portuguese University Hospital and Transplantation Center

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Keywords
Palliative care · End-stage liver disease · Liver transplantation

Abstract

Background and Aims: End-stage liver disease (ESLD) is an important cause of morbidity and mortality, comparable to a large extent to other organ insufficiencies. The need for palliative care (PC) in patients with ESLD is high. In Portugal, in the only identified study, more than 80% of patients hospitalized with ESLD had criteria for PC. No results specified which needs they identified or their transplantation prospect status. ***Methods:*** Prospective observational study including 54 ESLD patients who presented to a university hospital and transplantation center, between November 2019 and September 2020. Assessment of their PC needs through the application of NECPAL CCOMS-ICO© and IPOS, considering their transplantation perspective status. ***Results:*** Of the 54 patients, 5 (9.3%) were on active waiting list for transplantation and 8 (14.8%) under evaluation. NECPAL CCOMS-ICO© identified 23 patients (n = 42.6%) that would benefit from PC. Assessment of PC needs by clinicians, functional markers and significant comorbidities were the most frequent criteria (47.8%, n = 11). IPOS also revealed a different sort of needs: on average, each patient identified about 9 needs (8.9 ±2.8). Among the symptoms identified, weakness (77.8%), reduced mobility (70.3%), and pain (48.1%) stood out, as well as the psychoemotional symptoms of depression (66.7%) and anxiety (77.8%). There were no significant differences between the subgroups of patients analyzed. Only 4 patients (7.4%) were followed by the PC team. ***Conclusion:*** All the ESLD patients included, independently of the group they belonged to, presented with PC needs. No significant differences between the subgroups of patients were identified, confirming that even patients with a transplantation prospect have important needs for PC.

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Cuidados paliativos na doença hepática avançada – necessidades paliativas diferentes ou semelhantes no doente com perspetiva de transplante? Estudo prospetivo a partir de um hospital universitário português e centro de transplantação

Palavras Chave
Cuidados paliativos · Doença hepática avançada · Transplante hepático

Resumo
Introdução e objetivos: A doença hepática avançada (DHA) é uma causa importante de morbilidade e mortalidade, comparável em grande medida a outras insuficiências de órgão. A necessidade de cuidados paliativos (CP) em doentes com DHA é elevada. Em Portugal, no único estudo identificado até ao momento, mais de 80% dos doentes hospitalizados com DHA apresentavam critérios para CP. Não foram especificadas que necessidades de CP nem a perspetiva de transplante dos referidos doentes, que com o presente estudo se pretende ajudar a esclarecer. ***Métodos:*** Estudo prospectivo observacional incluindo 54 doentes com DHA assistidos num hospital universitário e centro de transplante, entre novembro de 2019 e setembro de 2020. Avaliação das necessidades de CP por meio da aplicação do NECPAL CCOMS-ICO© e IPOS, considerando a sua perspectiva de transplante. ***Resultados:*** Dos 54 doentes, cinco (9,3%) estavam em lista de espera ativa para transplante e oito (14,8%) em avaliação. O NECPAL CCOMS-ICO© identificou 23 doentes (n = 42,6%) que beneficiariam de CP. A avaliação das necessidades de CP por médicos, os marcadores funcionais e as comorbidades significativas foram os critérios mais frequentes (47,8%, n = 11). O IPOS também revelou diversas necessidades de CP: em média, cada doente identificou cerca de 9 necessidades (8,9 + -2,8). Entre os sintomas identificados, destacaram-se a fraqueza (77,8%), a mobilidade reduzida (70,3%) e a dor (48,1%), bem como os sintomas psicoemocionais de depressão (66,7%) e ansiedade (77,8%). Não houve diferenças significativas entre os subgrupos de doentes analisados. Apenas 4 doentes (7,4%) foram acompanhados pela equipa intra-hospitalar de CP. ***Conclusão:*** Todos os doentes com DHA incluídos, independentemente do grupo a que pertenciam, apresentaram necessidades de CP. Não foram identificadas diferenças significativas entre os subgrupos de doentes, confirmando que mesmo os doentes com perspectiva de transplante têm importantes necessidades de CP.

Introduction

End-stage liver disease (ESLD) is associated with high mortality [1], with compensated cirrhosis survival estimated to be 10–13 years and about 2 years in decompensated patients [1]. This mortality is comparable to other organ insufficiencies such as heart failure [2] and chronic obstructive pulmonary disease [3]. The need for palliative care (PC) in patients with ESLD is presumed to be very relevant – a high prevalence of symptoms has been described, with about 80% of ESLD patients with at least one symptom of moderate to severe intensity and an average of 4.1 severe symptoms/patient [4]. These needs are also in line with similar symptom prevalence in other organ insufficiencies in advanced stages, namely for pain and dyspnea. In addition to physical needs, other needs – such as psychological, social, and even spiritual – may arise in patients with ESLD. These are often associated with chronic consumption of alcohol or other drugs, in a population that often is in full active life, and specific guidance would be beneficial for the patient, family, and caregivers [5].

Previous studies suggested benefits of PC in patients with ESLD, such as reduced hospital readmissions [6–8], less invasive treatments, shorter hospital length of stay [9, 10], and higher rates of advanced care planning [11]. In Portugal, in the only identified study [12], more than 80% of patients hospitalized with ESLD due to a decompensation episode had NECPAL CCOMS-ICO© [13] criteria for PC. The needs they referred and their transplantation perspective status were not specified.

PC referral rates in these patients remain very low, and the available data are scarce in this regard [9]. Very few studies addressed PC in ESLD patients with transplantation prospect, none including Portuguese population. In one of the few known studies, only 10% of patients excluded from the transplant list were referred to PC [14]. Low rates of advance care planning discussions persist among liver transplant candidates [15], and the current growing trend, of older age and with more comorbidities, poses greater complexity of their needs and care [16]. This subgroup of patients is also frequently the target of more aggressive treatment proposals and, consequently, at risk of greater complications and greater needs. Transplant candidates should not be excluded from PC studies [17].

The purpose of this study was to evaluate what are the specific PC needs of ESLD patients, including those with transplantation perspective, and to investigate whether there are significant differences in this subgroup. Given

the coexistence of cancer may have an impact, hepatocellular carcinoma (HCC) as a comorbidity was also considered.

Materials and Methods

Patient Selection

This is a single-center prospective study that included all consecutive adult patients (>18 years) diagnosed with ESLD who underwent hospital admission related to their liver disease (for acute decompensation or HCC treatment) at Centro Hospitalar e Universitário do Porto (Porto, Portugal), between November 2019 and September 2020. Patient identification was carried out twice a week by systematic search of the list of patients admitted to the Departments of Gastroenterology, Medicine, Hepato-Bilio-Pancreatic Transplant and Medical-Surgical Intermediate Care Units. Patients aged <18 years, with previous liver transplantation, or with isolated acute liver failure or with another terminal disease (except HCC) were excluded.

Data Collection

Demographic, functional (through the Palliative Performance Scale (PPS) [18]) and clinical characteristics were registered. Patients were screened for PC criteria using NECPAL CCOMS-ICO© [13]. It is an instrument capable of both identifying patients in need of PC and accurately predicting mortality, thus facilitating planning for end-of-life care [19]. NECPAL CCOMS-ICO© is a validated physician screening tool which combines the Surprise Question with additional indicators (request or need for PC, general clinical indicators of severity and progression, including comorbidity and resource use, and disease specific indicators, including ESLD). Patients with positive Surprise Question (if physician would not be surprised if the patient were to die in the next 12 months) were also considered NECPAL positive when they presented at least one additional parameter from the NECPAL tool. The questionnaire was answered by an internal medicine resident and reviewed by an internal medicine specialist with PC competence. Specific PC needs were assessed through the IPOS questionnaire [20]. This is also a validated instrument widely used globally and specifically developed for use among patients with advanced diseases including ESLD. IPOS questionnaire is a concise but comprehensive instrument, assessing not only symptoms (pain, shortness of breath, weakness or lack of energy, nausea, vomiting, poor appetite, constipation, sore or dry mouth, drowsiness, and poor mobility), but also extending to communication needs, practical concerns, anxiety or low mood, family anxieties and overall feeling of being at peace. IPOS has ten questions (17 items), for the majority of these, five response options are provided. The overall IPOS score is the sum of the scores from each question, ranging from zero to 68. It has two versions, to be completed by healthcare professional or patient, the last one was considered in the present study. When patients presented with encephalopathy (with West Haven grade II or more [21]), IPOS questionnaires were answered by the caregiver considered to be his/her legal representative. Subgroup comparative analysis was performed between ESLD patients with and without HCC and patients with a transplantation perspective (under evaluation or already awaiting liver transplantation) and patients without transplantation perspective (without evaluation or already excluded for transplantation). The local ethics committee considered this study favorably and written informed consent was collected for all patients included, prior to data collection.

Data Analysis

Statistical significance was set at $p < 0.05$. Statistical analysis was performed using IBM SPSS Statistics 26. Baseline characteristics, PC criteria, and specific PC needs were compared between subgroups by the Mann-Whitney test.

Results

Study Population

From initial 73 patients considered, 54 were included (Table 1), with a mean age of 60.5 years. Nineteen patients were excluded because of previous liver transplantation (n=7), isolated acute liver failure (n=2), another terminal disease (n=7) or impossibility of completing the assessment (n=3). Alcohol was the most frequent etiology of ESLD patients (79.6%, n=43), nine of these in association with another etiology. Twenty-two patients were consuming alcohol (40.7%). Twenty-four patients (44.4%) presented at least with one current or previous ESLD complication, most frequently ascites (14.8%, n=8), followed by gastrointestinal bleeding (13.0%, n=7) and encephalopathy (11.1%, n=6). Three patients presented encephalopathy West Haven [20] grade II or more, and their IPOS questionnaires were answered by their legal representative. Twenty-one patients (38.9%) had at least one emergency department visit in the past 12 months, and 27.7% (n = 15) had at least one hospitalization in the same period. About 2/3 of the patients (68.5%, n = 37) were admitted with acute decompensation episode of ESLD. Regarding prognosis scores, 81.5% (n = 44) were admitted on Child-Pugh B or C, with a mean of 9.0 ± 2.4 points and with a Model for ESLD (MELD) of 15, 9 ± 6.4 points, and MELD-Na of 18.6 ± 6.5 points, respectively. Eleven patients (20.4%) had HCC, almost 2/3 in Barcelona Clinic Liver Cancer (BCLC) stages C-D (n = 7). As to comorbidities, 11 patients (20.4%) presented with another associated organ failure (cardiac, renal, or respiratory). Most patients (51.9%, n = 28) presented PPS >70, even though 18.5% (n = 10) presented with significant level of dependence (PPS <50). Length of stay was on average 22.1 ± 19.3 days (minimum of 2 and maximum of 99 days).

Table 1. Baseline main demographic and clinical characteristics of the study population (n=54)

Features	*N* (%)	Features	*N* (%)
Age (mean), years	60.5 (±10.9)	MELD (mean at admission)	15.9 (±6.4)
Sex, male	39 (72.2)	MELD-Na (mean at admission)	18.6 (±6.5)
Etiology		Acute ESLD decompensation	37 (68.5)
Alcohol	34 (63.0)	HCC	
Viral	3 (5.6)	BCLC A	3 (27.3)
Autoimmune	2 (3.7)	BCLC B	1 (9.1)
Alcohol+viral	7 (13.0)	BCLC C	6 (54.5)
Alcohol+autoimmune	2 (3.7)	BCLC D	1 (9.1)
NASH	2 (3.7)	Comorbidities	
Others	4 (7.4)	Other organ failure	11 (20.4)
Past alcohol consumption	23 (42.6)	Dementia	1 (1.9)
Current alcohol consumption	22 (40.7)	HIV	1 (1.9)
ESLD complication (acute or previous)		PPS	
Ascites	8 (14.8)	>70	28 (51.9)
Encephalopathy	6 (11.1)	50–70	16 (29.6)
Digestive hemorrhage	7 (13.0)	30–50	8 (14.8)
SBP	2 (3.7)	0–30	2 (3.7)
Hydrothorax	1 (1.9)	Length of stay	
None	30 (55.6)	Minimum	2
Emergency department visits (in past 12 months)	21 (38.9)	Maximum	99
Hospitalizations (in the past 12 months)	15 (27.8)	Mean	22.1 (±19.3)
Child-Pugh (admission)		Evaluation for transplantation	
A	10 (18.5)	No or excluded	41 (75.9)
B	21 (38.9)	Under evaluation	5 (9.3)
C	23 (42.6)	On active waiting list	8 (14.8)

NASH, nonalcoholic steatohepatitis; ESLD, end-stage liver disease; SBP, spontaneous bacterial peritonitis; MELD model for end-stage liver disease; HCC, hepatocellular carcinoma; BCLC Barcelona Clinic Liver Cancer; PPS Palliative Performance Scale.

Evaluation for Transplantation

Of the 54 patients, more than 3/4 had no evaluation for transplantation or had been already excluded from this proposal (n = 41, 75.9%), five (9.3%) were on active waiting list for transplantation and 8 (14.8%) under evaluation. One patient had been withdrawn from the list due to the development of multifocal HCC.

PC Needs Assessment

Regarding the Surprise Question "Would I be surprised if the patient died in the next 12 months?", in almost half of the patients (48.1%, n = 26), the clinician would not be surprised (Table 2). NECPAL CCOMS-ICO© questionnaire identified 23 patients (n = 42.6%) as benefiting from PC. In those patients, the assessment of PC needs by clinicians, functional markers, and significant comorbidities were the most frequent criteria (47.8%, n = 11). PC recognition by patient versus by clinician was significantly higher in the latter ($p<0.05$), particularly in patients without transplantation perspective (0% vs. 58.8%).

The IPOS questionnaire also revealed a different sort of needs (Table 3). On average, each patient identified about 9 needs (8.9 ± 2.8). Psychoemotional symptoms, as a group, were the most prevalent, firstly due to patient's anxiety (77.8%, n = 42), followed by family/friends' anxiety (72.2%, n = 39) and depression (66.7%, n = 36). Concerning physical symptoms, weakness was the most prevalent (77.8%, n = 42), followed by reduced mobility (70.3%, n = 38), somnolence (61.1%, n=33), pain (48.1%, n = 26) and poor appetite (37.0%, n = 20). Regarding other needs, emphasis was placed on the lack of peace (74.1%, n = 40) and the difficulty in communicating with family/friends (57.4%, n = 31). In contrast, the difficulty in communicating with the medical team (25.9%, n = 14), assessed by access to medical information, was one of the least prevalent needs. Intensity evaluation of needs revealed that 43 (79.6%) patients had at least one severe

Table 2. NECPAL results ($N = 54$)

	All ESLD patients ($n = 54$)	ESLD patients with transplantation perspective ($n = 13$)	ESLD patients without transplantation perspective ($n = 41$)	*p* value*	ESLD patients with HCC ($n = 11$)	ESLD patients without HCC ($n = 43$)	*p* value*
NECPAL+	23 (42.6%)	6 (46.2%)	17 (41.5%)	>0.05	4 (36.4%)	19 (44.2%)	>0.05
Surprise question	26 (48.1%)	8 (61.5%)	18 (43.9%)	>0.05	5 (45.4%)	19 (35.2%)	>0.05
Self or caregiver's request of palliative care	1 (4.3%)	1 (16.7%)	0 (0%)	>0.05	0 (0%)	1 (5.3%)	>0.05
Health professional assessment need for palliative care	11 (47.8%)	1 (16.7%)	10 (58.8%)	>0.05	0 (0%)	11 (57.8%)	>0.05
Nutritional markers	8 (4.8%)	4 (66.7%)	5 (29.4%)	>0.05	0 (0%)	9 (47.4%)	>0.05
Functional markers	11 (47.8%)	3 (50.0%)	8 (47.1%)	>0.05	1 (25.0%)	10 (52.6%)	>0.05
Other disease markers of severe frailty	0 (0%)	0 (0%)	0 (0%)	>0.05	0 (0%)	0 (0%)	>0.05
Psychological suffering	5 (21.7%)	3 (50.0%)	2 (11.8%)	>0.05	0 (0%)	5 (26.3%)	>0.05
Additional Factors in Resource Usage	8 (34.8%)	5 (83.3%)	3 (17.6%)	<0.05	0 (0%)	8 (42.1%)	>0.05
Comorbidities	11 (47.8%)	0 (0%)	13 (64.7%)	<0.05	3 (75.0%)	8 (42.1%)	>0.05
Advanced cirrhosis	7 (40.4%)	4 (66.7%)	3 (17.6%)	<0.05	0 (0%)	7 (36.8%)	>0.05
HCC stage C or D (BCLC)	4 (17.4%)	1 (16.7%)	3 (17.6%)	>0.05	4 (100%)	0 (0%)	<0.05

* *p* value - statistical significance was set at $p < 0.05$ ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; BCLC, Barcelona clinic liver cancer.

need (intensity 3), and 19 (35.2%) at least one very severe (intensity 4). Finally, given that both questionnaires, NECPAL CCOMS-ICO© and IPOS, are based on different methodologies, it was found that patients with positive NECPAL CCOMS-ICO© had an average IPOS of 19.7 ± 8.5 (minimum of 7 and maximum of 41), while those with a negative NECPAL CCOMS-ICO© presented an average IPOS of 13.5 ± 6.2 (minimum of 1 and maximum of 26).

ESLD with and without Transplantation Perspective

Global PC needs assessed by NECPAL CCOMS-ICO© and IPOS revealed no significant differences between ESLD patients with and without transplantation prospect (Tables 2 and 3). However, regarding specific PC needs applying NECPAL CCOMS-ICO© questionnaire, the presence of comorbidities, advanced cirrhosis, and emergency department visit in the last 12 months were significantly more frequent ($p<0.05$) in patients without transplantation prospect. The IPOS questionnaire revealed a total score marginally higher in patients with transplantation prospect (16.9 ± 11.0 vs. 15.9 ± 6.6). Prevalence of specific needs according to this questionnaire came out as globally similar between groups, with weakness or lack of energy being the only ones significantly higher in patients without prospect for transplantation ($p <0.05$).

ESLD with and without HCC

ESLD patients with HCC were less frequently identified with PC needs ($p>0.05$) by NECPAL CCOMS-ICO© (Table 2). None of these patients identified psychological distress as other groups did. Presence of HCC was the only PC need that stood out. Regarding IPOS, ESLD patients with and without HCC showed no difference on the total IPOS score (14.5 ± 7.8 vs. 16.6 ± 7.8, respectively, with vs. without HCC patients) or on the mean number of PC needs (7.6 ± 3.3 vs. 9.2 ± 2.6, respectively, with vs. without HCC patients) (Table 3). Depression was the only PC need significantly more prevalent in patients without HCC ($p<0.05$).

Subsequent Health Resource Use and Mortality

Hospital mortality was 11.1% (n = 6), higher in the group of patients without transplantation prospect versus with (12.2 vs. 7.7%) and in patients without HCC versus with (14.0% vs. 0), but in both cases $p> 0.05$ (Table 4). Follow-up by the PC team occurred only in 4 patients, all of whom died during hospitalization. Six months after discharge, mortality increased to 33.3% (n = 18), particularly in the group of HCC patients (54.5%, n = 6). In the

Table 3. IPOS results (*N* = 54)

	All ESLD patients (*n* = 54)	ESLD patients with transplantation perspective (*n* = 13)	ESLD patients without transplantation perspective (*n* = 41)	*p* value*	ESLD patients with HCC (*n* = 11)	ESLD patients without HCC (*n* = 43)	*p* value*
Total IPOS score	16.1±7.8	16.9±11.0	15.9±6.6	>0.05	14.5±7.8	16.6±7.8	>0.05
Number of identified needs	8.9±2.8	7.8±3.6	9.2±2.4	>0.05	7.6±3.3	9.2±2.6	>0.05
Pain	26 (48.1%)	7	19	>0.05	4	22	>0.05
Dyspnea	15 (27.8%)	3	32	>0.05	3	12	>0.05
Weakness	42 (77.8%)	6	36	<0.05	7	35	>0.05
Nausea	18 (33.3%)	3	15	>0.05	4	14	>0.05
Vomiting	8 (14.8%)	3	5	>0.05	3	5	>0.05
Poor appetite	20 (37.0%)	3	17	>0.05	3	17	>0.05
Constipation	19 (35.2%	5	14	>0.05	5	14	>0.05
Sores or dry mouth	21(38.9%)	4	17	>0.05	4	17	>0.05
Somnolence	33 (61.1%)	6	27	>0.05	15	28	>0.05
Poor mobility	38 (70.4%)	7	31	>0.05	8	30	>0.05
Anxiety	42 (77.8%)	10	32	>0.05	8	34	>0.05
Family and friends anxiety	39 (72.2%)	10	36	>0.05	9	38	>0.05
Depression	36 (66.7%)	5	31	>0.05	5	31	<0.05
Lack of peace	40 (74.1%)	10	30	>0.05	5	35	>0.05
Difficulties in sharing with family and friends	31 (57.4%)	7	24	>0.05	5	26	>0.05
Difficulties in medical information	14 (25.9%)	3	11	>0.05	1	13	>0.05
Difficulties in solving practical problems	21 (38.9%	7	14	>0.05	3	18	>0.05

**p* value - statistical significance was set at $p < 0.05$. ESLD, end-stage liver disease; HCC, hepatocellular carcinoma.

same period, 21 (43.8%) of the patients that were discharged alive went to the emergency department at least once and 27.0% (n = 13) required at least one subsequent hospitalization.

Discussion

All the ESLD patients included in this study, including ESLD patients with transplantation prospect, presented with PC needs, assessed either by the NECPAL CCOMS-ICO© or the IPOS questionnaires. The NECPAL CCOMS-ICO© questionnaire, which refers to information provided by the healthcare professional, reassured this through the Surprise Question, in which almost half of the patients (48.1%, n = 26) scored, and by 42.6% (n = 23) of patients that also had a positive final score. Regarding the criteria identified by this questionnaire, the recognition of PC needs by the clinician (47.8%, n = 11) stands out, as opposed to the recognition by the patients themselves (4.3%, n = 1) ($p < 0.05$). This difference might be a consequence of a lack of information about their prognosis or PC, insufficient communication with the health care team, or of limitations of the questionnaire itself to assess this dimension. Of the remaining criteria, the most frequently identified were the functional ones, followed by the presence of comorbidities and Child-Pugh C stage. IPOS questionnaire, which directly assesses PC needs by the patient or caregiver, identified psychoemotional needs as the most prevalent, namely patient's anxiety (77.8%, n = 42). Of the remaining needs, the spiritual dimension assessed through the feeling of peace was also relevant for 74.1% (n = 40). In contrast, communication with the health care team was a problem pointed out by only 25.9% (n = 14) of the patients.

This study broadens the knowledge about the PC needs of patients with ESLD, in different contexts, including patients with transplantation prospect as suggested by few other studies [9, 22]. Similar to the study published by Carvalho et al. [12], this study reassures, through the NECPAL CCOMS-ICO© questionnaire, a high prevalence of PC needs in the hospitalized ESLD patients. To our knowledge, no previous studies have suggested that patients with ESLD themselves fail to identify their need for PC, so these findings must be further researched. Through the IPOS questionnaire, this study also suggests the notion that more often several needs are dealt with simultaneously (average of 8.9 ± 2.8): more than ¾ of the patients (79.6%, n = 43) had at least one severe need and about 1/3 (35.2%, n = 19) of the patients had a very severe one.

Table 4. Subsequent health resource use and mortality ($N = 54$)

	All ESLD patients ($n = 54$)	ESLD patients with transplantation perspective ($n = 13$)	ESLD patients without transplantation perspective ($n = 41$)	*p* value*	ESLD patients with HCC ($n = 11$)	ESLD patients without HCC ($n = 43$)	*p* value*
Mortality during hospitalization	6 (11.1%)	1 (7.7%)	5 (12.2%)	>0.05	0	6 (14.0%)	>0.05
Mortality 6 months after discharge	12 (25.0%)	3 (25.0%)	9 (25%)	>0.05	6 (54.5%)	6 (16.2%)	>0.05
Total mortality	18 (33.3%)	4 (30.8%)	14 (34.1%)	>0.05	6 (54.5%)	12 (27.9%)	>0.05
Patients with 1 or more emergency department resources 6 months after discharge	21 (43.8%)	4 (33.3%)	17 (47.2%)	>0.05	3 (27.3%)	18 (48.6%)	>0.05
Patients with 1 or more hospitalizations 6 months after discharge	13 (27.0%)	5 (41.7%)	7 (19.4%)	>0.05	3 (27.3%)	10 (27.0%)	>0.05

* *p* value - statistical significance was set at $p < 0.05$. ESLD, end-stage liver disease; HCC, hepatocellular carcinoma.

The symptoms identified more frequently – weakness (77.8%), reduced mobility (70.3%), somnolence (61.1%), and pain (48.1%) – are in line with those described by Peng et al. [4]. Similarly, the psychoemotional symptoms of depression (66.7%) and anxiety (77.8%) were very common, the latter more frequent than previously described by Peng et al. [4]. This result, combined with the needs identified in the spiritual domain, relevant in 74.1% (n = 40) of the patients, suggests an important psychoemotional and existential suffering in this population, an aspect that deserves to be better clarified and supported. Contrary to what was described by Low et al. [23], who identified the existence of significant communication difficulties among patients with ESLD, their families, and healthcare professionals, this was not observed in the present study, being pointed out by only 25.9% (n = 14) of the patients. However, this result must be carefully analyzed, namely if we consider the aforementioned psychoemotional and existential suffering described that can denounce communication deficiencies. A more careful assessment of communication needs may be justified. Comparing the results obtained by the two questionnaires, in addition to the fact that all patients with positive NECPAL CCOMS-ICO© scored in the IPOS questionnaire, it was also found that even patients with negative NECPAL CCOMS-ICO©, also scored at least one in the IPOS questionnaire, revealing that they had at least one need/problem that fits in the palliative scope. This result is not surprising given the different methodologies associated with each questionnaire, as well as the diversity of needs/problems identified, and their high prevalence also reported by Peng et al. [4]. The use of both these instruments might complement each other and suggests that frequently patients with still negative NECPAL CCOMS-ICO© might already present some PC needs, identified by IPOS.

Analysis by groups showed no statistically significant difference in the total scores of the NECPAL CCOMS-ICO© and IPOS questionnaires. These results suggest that even patients with ESLD with transplantation prospect also have important PC needs, as described by Baumann et al. [22], who showed the benefit of an early PC intervention in these patients. In the present study, there was a lower tendency for positive NECPAL CCOMS-ICO© and IPOS scores in the group of patients with HCC versus without. These results are probably because most of the patients with HCC have been admitted for elective procedures, without criteria for acute liver decompensation. Regarding specific criteria, the use of health care services in the 12 months prior to hospitalization, the pres-

ence of comorbidities, advanced cirrhosis, and symptoms like weakness and depression, were significantly higher in ESLD patients without perspective for transplantation. This is probably in agreement with greater clinical deterioration of these patients compared to patients with transplantation perspective. When comparing specific criteria of PC needs in patients with HCC versus without HCC, depression came out as the only significantly more prevalent symptom in patients without HCC, probably for the reason mentioned previously. Yet, these results suggest that ESLD itself poses no less need for PC than HCC associated to ESLD, as is sometimes supposed.

Limitations

This study presents some limitations. The sample consisted of patients admitted to a single hospital, even though it includes patients with some geographical diversity, as it is a liver transplantation center. The recruitment of patients was conditioned in terms of time and access to patients because it occurred in overlap with the SARS-CoV-2 pandemic, resulting in a prolonged recruitment period and in a sample of 54 patients. This sample also presented with a heterogeneous distribution among the subgroups considered, and this may also introduce some analysis bias. Finally, PC needs assessment, as it is evaluated in a single moment, does not allow to reflect their dynamical nature.

Issues for the Future

For future research, it will be relevant to evaluate methodologies that allow for the access of different groups of patients with ESLD to PC, including patients with transplantation prospect, identifying the main needs and barriers to its implementation and allowing this access to occur as early as desirable [24].

Conclusion

The present study affirms important PC needs in patients with ESLD. It amplifies the knowledge about these, suggesting that most patients present several needs simultaneously, often of severe or very severe intensity and with wide diversity. Of the identified symptoms, psychoemotional ones stand out, as they are no less frequent than weakness, reduced mobility, and pain, which seem to be the most frequent physical symptoms. This study also found no relevant difference between the different subgroups of patients considered and, therefore, points out that PC is relevant in most patients with ESLD, including those with transplantation prospect.

Statement of Ethics

This study protocol was reviewed and approved by Comissão de Ética do Centro Hospitalar Universitário do Porto, approval number 194-19 (160-DEFI/166-CE). Written informed consent was obtained from participants or their legal representatives.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.V.S. contributed to the conception of the work, the acquisition analysis, interpretation of data, drafting the work and final approval of the version to be published. P.B. contributed to the acquisition analysis, interpretation of data, drafting the work and final approval of the version to be published. I.F. contributed to the acquisition analysis, interpretation of data, drafting the work and final approval of the version to be published. E.F. contributed to the interpretation of data, revising the work critically and final approval of the version to be published. H.P.M. contributed to the interpretation of data, revising the work critically and final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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Treating Advanced Hepatocellular Carcinoma with Sorafenib: A 10-Year Single Center Experience

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Keywords
Sorafenib · Hepatocellular carcinoma · Overall survival · Time to progression

Abstract

Introduction: Sorafenib was the first therapy used for systemic treatment of unresectable hepatocellular carcinoma (HCC). Multiple prognosis factors associated with sorafenib therapy have been described. ***Objectives:*** The aim of this work was to evaluate survival and time to progression (TTP) on HCC patients treated with sorafenib, and check for predictive factors of sorafenib benefit. ***Materials and Methods:*** Retrospectively, data from all HCC patients treated with sorafenib in a Liver Unit from 2008 to 2018 were collected and analyzed. ***Results:*** Sixty-eight patients were included; 80.9% were male, the median age was 64.5 years, 57.4% had Child-Pugh A cirrhosis and 77.9% were BCLC stage C. Macrovascular invasion (MVI) was present in 25% of the patients and 25% of the subjects had other extrahepatic metastasis. The median survival was 10 months (IQR 6.0–14.8) and median TTP was 5 months (IQR 2.0–7.0). Survival and TTP were similar between Child-Pugh A and B patients: 11.0 months (IQR 6.0–18.0) for Child-Pugh A and 9.0 months (IQR 5.0–14.0) for Child-Pugh B ($p = 0.336$). In univariate analysis, larger lesion size (LS >5 cm), higher alpha-fetoprotein (AFP >50 ng/mL), and no history of locoregional therapy were statistically associated with mortality (HR 2.17, 95% CI 1.24–3.81; HR 3.49, 95% CI 1.90–6.42; HR 0.54, 95% CI 0.32–0.93, respectively), but only LS and AFP were independent predictive factors, as shown in multivariate analysis (LS: HR 2.08, 95% CI 1.10–3.96; AFP: HR 3.13, 95% CI 1.59–6.16). MVI and LS >5 cm were associated with TTP shorter than 5 months in univariate analysis (MVI: HR 2.80, 95% CI 1.47–5.35; LS: HR 2.1, 95% CI 1.08–4.11), but only MVI was an independent predictive factor of TTP shorter than 5 months (HR 3.42, 95% CI 1.72–6.81). Regarding safety data, 76.5% of patients reported at least one side effect (any grade), and 19.1% presented grade III–IV adverse effects leading to treatment discontinuation. ***Conclusions:*** We observed no significant difference in survival or TTP in Child-Pugh A or Child-Pugh B patients treated with sorafenib, as compared to more recent real-life studies. Lower primary LS and AFP were associated with a better outcome, and lower AFP was the main predictor of survival. The reality of systemic treatment for advanced HCC has recently changed and continues to evolve, but sorafenib remains a viable therapeutic option.

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Tratamento de carcinoma hepatocelular avançado com sorafenib: dez anos de uma experiência unicêntrica

Palavras Chave
Sorafenib · Carcinoma hepatocelular · Sobrevivência · Tempo até progressão

Resumo
Introdução: O sorafenib foi o primeiro fármaco usado em primeira linha na terapêutica sistémica do carcinoma hepatocelular (CHC) em estadio avançado. Têm sido descritos múltiplos factores modificadores de prognóstico associados à sua utilização. ***Objectivos:*** Caracterizar um grupo de doentes com CHC que realizaram terapêutica com sorafenib, estudar a sobrevivência e o tempo até progressão (TAP), e avaliar os factores preditores de benefício. ***Material e Métodos:*** Estudo retrospectivo com recolha e análise dos dados relativos a todos os doentes com CHC tratados com sorafenib numa Unidade de Hepatologia, entre 2008 e 2018. ***Resultados:*** Foram incluídos no estudo sessenta e oito doentes; 80.9% do sexo masculino, com mediana de idades de 64.5 anos, 57.4% tinham cirrose em estadio A de Child-Pugh e 77.9% apresentavam CHC em estadio C do Barcelona Clínic Liver Cancer (BCLC). A invasão macrovascular (IMV) estava presente em 25% dos doentes, e também 25% dos doentes tinha metastização extra-hepática (que não a IMV). A mediana de sobrevivência foi de 10 meses (IQR 6.0-14.8) e a mediana de TAP foi de 5 meses (IQR 2.0–7.0). A sobrevivência e o TAP foram similares nos doentes Child-Pugh A e B: 11.0 meses (IQR 6.0–18.0) para Child-Pugh A e 9.0 meses (IQR 5.0–14.0) para Child-Pugh B ($p = 0.336$). Na análise univariada, o tamanho da lesão >5 cm (TL), alfa-fetoproteína > 50 ng/mL (AFP) e a ausência de terapêuticas locorregionais prévias (TLP) tiveram relação estatisticamente significativa com a mortalidade (TL: HR 2.17, 95% CI 1.24–3.81; AFP: HR 3.49, 95% CI 1.90–6.42; TLP: HR 0.54, 95% CI 0.32–0.93), mas apenas o TL e AFP foram fatores preditores independentes, como mostrou a análise multivariada (TL: HR 2.08, 95% CI 1.10–3.96; AFP: HR 3.13, 95% CI 1.59–6.16). A IMV e o TL >5 cm estiveram associados com o TAP <5 meses na análise univariada (IMV: HR 2.80, 95% CI 1.47–5.35; TL: HR 2.1, 95% CI 1.08–4.11), mas apenas a IMV foi um fator preditor independente de TAP <5 meses (HR 3.42, 95% CI 1.72–6.81). Relativamente aos dados de segurança, 76.5% dos doentes relataram pelo menos um efeito lateral (qualquer grau), e 19.1% apresentaram efeitos adversos de grau III-IV, que levaram à suspensão do fármaco. ***Conclusões:*** Não foi observada diferença significativa na sobrevivência ou no tempo até progressão nos doentes Child-Pugh A ou Child-Pugh B tratados com sorafenib, quando comparado com estudos real-life recentes. Menor TL e AFP estiveram associados a melhor outcome e um valor de AFP baixo mostrou-se o principal preditor de sobrevivência. A realidade da terapêutica sistémica para o CHC avançado alterou-se recentemente e continua em mudança, mas o sorafenib permanece uma alternativa terapêutica viável.

Introduction

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death, globally. Hepatocellular carcinoma (HCC) is the most common form of liver cancer [1]. In Portugal, the number of hospital admissions for HCC has steadily increased in the last 20 years [2, 3] and the reported death rate is 4.3/100,000, which represents an increase of 66% between 2006 and 2012 [4].

Curative treatments such as radiofrequency ablation, surgical resection, and liver transplantation are recommended for early-stage HCC. Despite the active surveillance programs to detect early-stage HCC in patients with liver cirrhosis, a significant amount of them are still diagnosed in advanced stages. For these patients, treatment recommendations are transarterial chemoembolization and systemic therapy [1]. Sorafenib, an oral multikinase inhibitor, was the first effective systemic treatment in HCC and continues to be one of the standards of care for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumors [5, 6]. There is no clear recommendation in Child-Pugh B patients, although cohort studies have reported a similar safety profile in patients of this class with no decompensation. Still, the reported outcome for Child-Pugh B patients from the non-interventional GIDEON trial was poor [1, 7].

In order to identify predictive factors of response to sorafenib treatment, a pre-planned subgroup analysis was carried out in the SHARP and AP trials [5, 6]. Similar results across subgroups (based on ECOG performance status, tumor burden, age, and hepatitis B virus infection) were observed in these studies, with sorafenib providing treatment survival benefit in all subgroups (although in the SHARP trial the benefit was less prominent in pa-

tients with extrahepatic spread; EHS). An exploratory analysis of the two studies showed that, although sorafenib benefit was observed in all subgroups, hepatitis C-positive patients, those without EHS, and those with a lower neutrophil-to-lymphocyte ratio (NLR) derived the most significant survival benefit [8]. Other studies have also described predictors of sorafenib benefit in observational studies of routine clinical practice [9–12], acknowledging the need to strengthen real-life evidence.

This study aimed to evaluate the survival and time to progression (TTP) with sorafenib therapy, as well as to identify associated factors for better survival and TTP, in a consecutive cohort of patients, in a single center, since the introduction of sorafenib in 2008.

Materials and Methods

Design, Setting, and Participants

We performed a retrospective cohort study including all adult patients (≥18 years) treated with sorafenib for HCC in a Liver Unit at Centro Hospitalar Trás-os-Montes Alto Douro (CHTMAD, Vila Real, Portugal) between January 2008 and December 2018.

All our patients who presented unresectable HCC, not eligible to locoregional therapies, and who had preserved liver function were treated with sorafenib. During the study period this was the only available systemic therapy. In our unit, the protocol for starting sorafenib consists of an initial dose of 200 mg twice daily, followed by a close monitoring of tolerance and a careful increase in dose up to a maximum 400 mg twice daily.

The inclusion criteria were the following: age ≥18 years, diagnosis of cirrhosis and HCC, initiation of treatment with sorafenib during the study period, follow-up in the CHTMAD Liver Unit (follow-up period until December 2018). The minimum follow-up considered for inclusion in the study was 6 months. The exclusion criteria were liver transplant and treatment duration inferior to 31 days (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000522572).

We made a sub-population analysis of the long-term survivors: patients surviving more than 12 months after initiating sorafenib were considered long-term survivors, since the estimated overall survival (OS) for patients undergoing sorafenib is around 10 months [5].

All therapeutical decisions related to HCC were discussed in a multidisciplinary meeting with several medical specialties (Hepatology, General Surgery, Medical Oncology, Interventional Radiology, and Radio-Oncology). Patients were followed with triphasic CT scan every 3 months (local protocol).

The current retrospective study was performed according to the requirements of the local ethics committee and complied with the Declaration of Helsinki principles [13]. Patient informed consent was not required for the current study, according to the guidelines of the local ethics committee.

Data Collection and Endpoints

The patient selection was performed using the hospital pharmacy database. Data from patients prescribed with sorafenib for HCC in our Liver Unit from January 2008 to December 2018 were collected by reviewing their clinical records. The following data were collected at the start of treatment: demographics (birth date and gender); dates of diagnosis of HCC and start of treatment with sorafenib; the presence of diabetes mellitus; baseline liver disease (presence and etiology of cirrhosis, Child-Pugh score); laboratory results (alpha-fetoprotein, albumin, bilirubin, neutrophils and lymphocytes count); HCC characteristics (BCLC staging, size of hepatic lesions, extrahepatic metastasis, and macrovascular invasion; MVI), and previous treatment with surgery, chemoembolization, thermal or radiofrequency ablation. During the follow-up, the following data were collected: date and motive of sorafenib suspension, adverse effects, date of death, maximal tolerated dose, and TTP, evaluated by an experienced liver-related radiologist, using mRECIST [14]. Follow-up data were collected until July 31, 2019.

Patients were divided into two groups according to the Child-Pugh score (Child-Pugh A and B). The primary outcomes were survival and TTP of sorafenib-treated patients. The secondary aim was the identification of predictive factors of better survival and higher TTP.

Statistical Analysis

Baseline characteristics are described as number (%) for categorical variables and the median (interquartile range; IQR) for continuous variables (normal distribution was excluded by Kolmogorov-Smirnov test). Associations of baseline characteristics with the primary and secondary endpoint were assessed using survival analysis with univariate and multivariate Cox regressions. Covariates in the multivariate models were selected if associated with a $p < 0.05$ in the univariate analysis. Survival of Child-Pugh groups was represented by a Kaplan-Meier survival plot. Statistical significance was set at $p < 0.05$. The statistical analysis was performed using SPSS Statistics® version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' Baseline Characteristics

Sixty-eight patients were enrolled; 9 patients were excluded because of a treatment duration inferior to 31 days. The characteristics of the patients are reported in Table 1. Treatment was given in first-line therapy in 44.1% of the patients. The patients had a median age of 64.5 years and were mostly men. The etiology of cirrhosis was predominantly alcohol related (67.7%). Thirty-nine patients (57.4%) were classified as Child-Pugh A and 29 (42.6%) as Child-Pugh B. Among these Child-Pugh B patients, 14 had a score of 7; 9 had a score of 8, and 6 had a score of 9. There were no significant differences in BCLC staging and in the prevalence of previous locoregional therapy (LRT) between Child-Pugh A and B groups (Table 1). MVI was present in 25% of patients and 25% of subjects had other extrahepatic metastasis.

Table 1. Baseline characteristics of patients treated with sorafenib and comparison between groups according to Child-Pugh score status: univariate analysis

	Overall (*n* = 68)	Child-Pugh A (*n* = 39)	Child-Pugh B (*n* = 29)	*p* value
Age, years	64.5 (57.0–72.0)	67.0 (59.0–72.0)	61.0 (55.0–72.0)	0.128[c]
Male gender	55 (80.9)	32 (82.1)	23 (79.3)	1.000[a]
Diabetes mellitus	23 (33.8)	14 (35.9)	9 (31.0)	0.796[a]
Etiology				
HBV	10 (14.7)	6 (15.4)	4 (13.8)	0.820[b]
HCV	6 (8.8)	1 (2.6)	5 (17.2)	0.038[b]
Alcohol	46 (67.7)	26 (66.6)	20 (69.0)	0.605[a]
Others	6 (8.8)	6 (15.4)	0	0.027[b]
BCLC stage				
A	0	0	0	–
B	15 (22.1)	10 (25.6)	5 (17.2)	0.557[a]
C	53 (77.9)	29 (74.4)	24 (82.8)	0.989[a]
LRT	38 (55.9)	22 (56.4)	16 (55.2)	1.000[a]
EHS	17 (25.0)	11 (28.2)	6 (20.7)	0.577[a]
MVI	17.0 (25.0)	9 (23.1)	8 (27.6)	0.779[a]
AFP, ng/mL	45.9 (12.0–445.5)	33.2 (10.3–284.4)	72.0 (22.6–985.0)	0.159[c]
OS, months	10.0 (6.0–14.8)	11.0 (6.0–18.0)	9.0 (5.0–14.0)	0.336[a]
TTP, months	5.0 (2.0–7.0)	4.5 (2.0–6.8)	5.0 (2.5–10)	0.528[c]
F/U, months	13.0 (8.0–27.0)	13.0 (8.0–30.0)	12.0 (6.5–24.0)	0.159[c]
Treatment duration, months	6.0 (3.0–10.0)	7.0 (3.0–11.0)	5.0 (2.0–10.0)	0.374[c]

Data are given as the median (IQR) or *n* (%). AFP, alpha-fetoprotein; EHS, extrahepatic spread; F/U, time of follow-up since diagnosis of HCC; HBV, hepatitis B virus; HCV, hepatitis C virus; LRT, locoregional therapy; MVI, macrovascular invasion; OS, overall survival; TTP, time to progression (mRECIST). [a] *p* values of bivariate analysis of CP A vs. B/C patients. [b] Cramer's V test. [c] Mann-Whitney U test.

Table 2. Predictors of mortality in patients treated with sorafenib (*n* = 68): univariate and multivariate Cox regression analysis

	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (per 1-year increase)	0.99 (0.97–1.01)	0.398		
Male sex	1.83 (0.62–2.25)	0.607		
Diabetes mellitus	0.87 (0.50–1.53)	0.634		
Child-Pugh A	0.81 (0.48–1.36)	0.419		
Etiology of cirrhosis				
HVB	1.68 (0.82–3.46)	0.154		
HVC	1.04 (0.44–2.45)	0.930		
Alcohol	0.78 (0.44–1.37)	0.389		
BCLC C	1.38 (0.71–2.67)	0.339		
MVI	1.56 (0.86–2.84)	0.141		
LS (≥5 cm)	2.17 (1.24–3.81)	0.007	2.08 (1.10–3.96)	0.025
EHS	0.98 (0.54–1.80)	0.957		
LRT	0.54 (0.32–0.93)	0.025	0.56 (0.29–1.08)	0.085
AFP >50 ng/mL	3.49 (1.90–6.42)	<0.001	3.13 (1.59–6.16)	<0.001
Number of lesions (per 1 lesion increase)	0.96 (0.89–1.04)	0.301		
NLR (per 1 point increase)	0.98 (0.88–1.09)	0.702		
ABG (per 1 point increase)	1.00 (0.99–1.01)	0.960		
SRF dose >400 mg/day	0.82 (0.49–1.39)	0.710		

AFP, alpha-fetoprotein; EHS, extrahepatic spread; LRT, locoregional therapy; LS, lesion size; MVI, macrovascular invasion; NLR, neutrophil-to-lymphocyte ratio; ABG, albumin-bilirubin grade; SRF, sorafenib.

Table 3. Predictors of TTP shorter than 5 months in patients treated with sorafenib (n = 68): univariate and multivariate Cox regression analysis

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Age (per 1-year increase)	0.98 (0.95–1.01)	0.224		
Male sex	0.81 (0.36–1.83)	0.566		
Diabetes mellitus	1.22 (0.64–2.33)	0.556		
Child-Pugh A	1.03 (0.55–1.93)	0.592		
Etiology of cirrhosis				
HBV	1.62 (0.72–3.68)	0.078		
HCV	1.34 (0.53–3.44)	0.924		
Alcohol	0.58 (0.30–1.10)	0.102		
BCLC C	2.05 (0.86–4.90)	0.053		
MVI	2.80 (1.47–5.35)	<0.001	3.42 (1.72–6.81)	<0.001
LS (≥5 cm)	2.10 (1.08–4.11)	0.042	1.69 (0.90–3.2)	0.105
EHS	1.37 (0.68–2.74)	0.235		
LRT	0.54 (0.29–1.01)	0.162		
AFP >50 ng/mL	1.62 (0.85–3.08)	0.407		
Number of lesions (per 1 lesion increase)	0.95 (0.87–1.04)	0.700		
NLR (per 1 point increase)	1.00 (0.88–1.14)	0.482		
ABG (per 1 point increase)	1.24 (0.77–1.99)	0.789		
SRF dose >400 mg/day	0.69 (0.37–1.32)	0.352		

AFP, alpha-fetoprotein; EHS, extrahepatic spread; LRT, locoregional therapy; LS, lesion size; MVI, macrovascular invasion; NLR, neutrophil-to-lymphocyte ratio; ABG, albumin-bilirubin grade; SRF, sorafenib.

Twenty-three patients (35.4% of the total population) were considered long-term survivors. Among these, the median age was 67 years, 73.9% of patients were male, 78.3% had an alcohol-related cirrhosis, 56.5% were classified as Child-Pugh A, 73.9% were staged at BCLC C, 73.9% did not present extrahepatic spread, and 13.0% had portal vein thrombosis. Seven patients (30.4%) had a tumor size ≥5 cm. Only 4 patients (17.4%) presented an AFP >50 ng/mL. Ten patients (43.5%) tolerated 400 mg of sorafenib daily, against 21.7% that tolerated the maximum recommended dose of 800 mg daily. The median survival amongst this subgroup was 20 months (13–42). For the radiological response, evaluated by the modified RECIST criteria, none of the patients reached complete response, 13.6% presented a partial response, 46.2% had stable disease, and 40.2% underwent disease progression.

Survival

At the time of analysis (July 2019), 59 patients were dead (86.8%). The median duration of treatment of the alive patients was 15 months (IQR 10.0–20.5). The overall median survival was 10 months (IQR 6.0–14.8). The median survival of Child-Pugh A patients was 11 months (IQR 6.0–18.0) versus 9 months (IQR 5.0–14.0) in Child-Pugh B patients.

In univariate analysis, a larger lesion size (LS >5 cm), higher alpha-fetoprotein (AFP >50ng/mL), and no history of prior LRT were statistically associated with mortality (HR 2.17, 95% CI 1.24–3.81; HR 3.49, 95% CI 1.90–6.42; HR 0.54, 95% CI 0.32–0.93, respectively). EHS, NLR, albumin-bilirubin grade (ABG), sorafenib dose, and etiology of cirrhosis were not statistically associated with mortality, as presented in Table 2.

Multivariate analysis adjusted for age, gender, diabetes mellitus, Child-Pugh, and BCLC scores was performed. LS and AFP were shown to be independently associated with survival (LS: HR 2.08, 95% CI 1.10–3.96; AFP: HR 3.13, 95% CI 1.59–6.16).

Time to Progression

The overall median TTP was 5 months (IQR 2–7). The median TTP of Child-Pugh A patients was 4.5 months (IQR 4.5–6.8) and 5.0 (IQR 2.5–10.0) for Child-Pugh B patients.

In univariate analysis, MVI and LS were statistically associated with TTP greater than 5 months (HR 2.80, 95%

CI 1.47–5.35; HR 2.10, 95% CI 1.08–4.11, respectively). Multivariate analysis adjusted for age, gender, diabetes mellitus, Child-Pugh, and BCLC scores confirmed an independent predictive association of MVI with TTP shorter than 5 months (MVI: HR 3.42, 95% CI 1.72–6.81). LRT, EHS, AFP, NLR, ABG, sorafenib dose, BCLC stage, Child-Pugh score, and etiology of cirrhosis were not statistically associated with TTP, as presented in Table 3.

Safety Data

Of the total patients treated with sorafenib, 52 patients (76.5%) reported at least one side effect (any grade). The most frequent adverse reactions were diarrhea (38.2%), anorexia (30.9%), fatigue (29.4%), skin reactions including hand-foot syndrome (17.6%), nausea (13.2%), vomiting (11.8%), arterial hypertension (2.9%) and dysphonia (1.5%). Among the total of patients with adverse events, 57.7% were Child-Pugh A patients and 42.3% were Child-Pugh B ($p = 0.087$).

Almost a third of the patients (27.9%) tolerated the maximum daily dose of 800 mg, while the remainder required dose adjustment due to any form of intolerance: 19.1% tolerated 600 mg daily and 47.1% tolerated 400 mg daily. Thirteen patients (19.1%) presented grade III–IV adverse effects leading to treatment discontinuation. Of the patients that tolerated the daily maximum dose of 800 mg, 77.8% were Child-Pugh A patients, and 22.2% were Child-Pugh B patients ($p = 0.041$).

Discussion

Sorafenib has been proven to be beneficial in selected patients with advanced HCC. However, few data are available on the use of sorafenib in a non-selected cirrhotic population, namely on Child-Pugh B patients.

Hollebecque et al. [15] prospectively evaluated patients with advanced HCC treated with sorafenib and observed a higher survival among Child-Pugh A patients (11.1 months) compared with Child-Pugh B patients (4.5 months). Pressiani et al. [16] reported survival of 10 months in Child-Pugh A versus 3.8 months in Child-Pugh B patients, with similar adverse events in the two groups. Cardoso et al. [17] reported a very low OS of 6.8 months, with a median survival of 3.2 months for Child-Pugh B. Reis et al. [18], analyzing a subgroup of long survivors (>24 months under sorafenib), found that Child-Pugh A was an independent predictor of long-term survival, although also recognizing that sorafenib offers benefit regardless of baseline conditions or prognostic survival factors. The GIDEON trial, a global, non-interventional study, was conducted to evaluate sorafenib's safety for HCC treatment under real-life practice conditions, particularly in Child-Pugh B patients. Shorter median survival was also observed in this group (4.8 months in Child-Pugh B vs. 10.3 months in Child-Pugh A patients), despite the safety profile favoring the use of sorafenib in Child-Pugh B patients [7]. The poor outcome of Child-Pugh B patients has also been demonstrated in other studies and has been attributed to the development of clinical features of liver insufficiency or tumor spread rather than safety profile issues [7, 8, 15].

In our sample, survival was not statistically different between the Child-Pugh groups, contrary to the previously described studies [5, 7, 15, 16]. TTP was also similar between the Child-Pugh groups. More recent real-life studies share similar results, showing no difference in survival between Child-Pugh A and B patients treated with sorafenib, but with significant heterogeneity amongst the population and OS [19, 20]. The incidence of adverse reactions in our population was similar to other studies, namely to what was reported in the SHARP study. The Child-Pugh class did not influence the incidence of adverse reactions, but Child-Pugh B patients seemed to tolerate less often the maximum sorafenib daily dose.

Alcohol-related cirrhosis was more prevalent in our population than in the previously described trials, although etiology was not associated with OS [7, 17, 20]. Since abstinence status was not confirmed, alcohol consumption could explain the worse liver function at enrolment in our study. Further experience and improvement in the management of sorafenib side effects have been associated with a longer treatment duration and better OS [21]. Of notice, treatment discontinuation was similar between Child-Pugh groups in our sample, which differs from other studies, such as in the GIDEON trial where Child-Pugh B patients had higher discontinuation rates (not drug related), and this might explain the similar survival between groups. Data related to liver function evolution and cirrhosis complications during the treatment period were not collected and so further rationale for these differences could not be enlightened.

Baseline characteristics and staging systems, including ECOG PS, Child-Pugh score, and BCLC stage, appeared to be prognostic factors for GIDEON survival, as were albumin, bilirubin, and ascites. Besides, measures of the extent of disease, including EHS, larger tumor size, a higher number of lesions, and AFP, were prognostic factors of shorter survival time [7]. Similarly, in a SHARP and AP trial subgroup analysis ECOG PS, albumin, bili-

rubin, larger target LS, a higher number of target lesions, and extent of disease factors (BCLC stage C, MVI, tumor burden, AFP, and high NLR) were identified as prognostic factors for poorer survival in patients receiving sorafenib [12]. In our analyses, primary LS larger than 5 cm, AFP higher than 50 ng/mL, and no history of LRT were significantly associated with higher mortality. However, only LS and AFP were independent predictors of mortality. MVI predicted a shorter TTP (5 months or less) in our sample.

Even though real-life observational studies provide an opportunity to assess treatment patterns in clinical practice in less selected patients, as an observational study, it is inherently limited by the lack of a randomized, controlled population and the potential for selection bias. Other limitations to our study include the size and heterogeneity of the cohort. Nevertheless, our analyzed prognostic factors are consistent with data from several studies about prognosis in HCC patients.

In the last few years, the reality of systemic treatment for advanced HCC is shifting, with new treatment modalities apporting more options, defying sorafenib as the standard of care.

Another first line option actually available is lenvatinib, a multikinase inhibitor that showed no inferiority when compared to sorafenib. Lastly, the recently approved combinations of bevacizumab with atezolizumab, or tremelimumab with durvalumab, showed superiority when compared to sorafenib, concerning OS and progression-free survival. However, a significant percentage of patients with advanced HCC may not be appropriate candidates for these options and still be considered for sorafenib or lenvatinib because of lower risk of serious bleeding, and also because of financial barriers [22].

Conclusion

In a northern Portuguese cohort of advanced HCC patients treated with sorafenib, there was no significant difference in survival or TTP in Child-Pugh A or Child-Pugh B patients treated with sorafenib as compared to more recent real-life studies. Lower primary LS and AFP were associated with a better outcome, and lower AFP was the main predictor of survival. It is important to mention that at the time of the analysis there was no other choice of treatment, after failure of LRT. Nowadays the reality is changing and new players are apporting more choices and results, but sorafenib remains a viable therapeutic option.

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Statement of Ethics

This study was performed according to the local ethics committee requirements and complied with the principles of the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to report.

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Author Contributions

S.T. performed data collection, statistical analysis, bibliographic research, and drafted the manuscript. A.B. and J.L.P. helped to collect data. I.P., S.C., and P.C. reviewed the manuscript. J.P.R. developed the idea. S.T., I.P., and J.P.R. finalized the manuscript.

Data Availability Statement

No additional data are available.

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Outcomes and Learning Curve in Endoscopic Submucosal Dissection of Rectal Neoplasms with Severe Fibrosis: Experience of a Western Center

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Gastrointestinal endoscopy · Endoscopic mucosal resection · Rectal neoplasms

Abstract

Introduction: Endoscopic submucosal dissection (ESD) of lesions with severe submucosal fibrosis has been associated with worse outcomes, such as lower curative resection rate and higher incidence of adverse events. This study aims to investigate its true impact on rectal ESD performed in the West and to assess predictive factors of severe fibrosis. ***Methods:*** We conducted a retrospective study including all rectal ESDs performed at our tertiary center from January 2013 to January 2021. Lesions were grouped as nonsevere fibrosis or severe fibrosis. ESD outcomes, predictors of severe fibrosis, and the learning curve were evaluated. ***Results:*** ESD was performed in 195 lesions, 45 with severe fibrosis. Three resections were interrupted (one due to severe fibrosis). The presence of severe fibrosis was related to a significantly lower resection speed (16.93 mm^2/min vs. 24.66 mm^2/min, p = 0.007), en bloc (86.4% vs. 96.6%, p = 0.019), R0 (61.4% vs. 79.7%, p = 0.013), and curative (54.5% vs. 78.4%, p = 0.003) resection rates and a higher rate of hybrid ESD required to complete resection (13.6% vs. 2.0%, p = 0.005). No significant difference was noted regarding adverse events rate (18.2% vs. 8.1%, p = 0.09). Male sex, ulcerative colitis, pelvic radiotherapy, a lesion on the anastomotic site, previous manipulation, and deep submucosal invasion were independent predictors for severe fibrosis. En bloc resection rate improved during time (60.0% vs. 94.1%, p = 0.018). ***Conclusions:*** Severe submucosal fibrosis is an important factor related to noncurative resections and challenging rectal ESD. Factors predicting its severity are extremely important and could allow more experienced endoscopists to be assigned to more difficult cases, allowing safer procedures.

Resultados e curva de aprendizagem da disseção endoscópica da submucosa de lesões retais com fibrose severa: experiência de um centro ocidental

Palavras Chave
Endoscopia gastrointestinal · Mucosectomia endoscópica · Neoplasia do reto

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Resumo

Introdução: A disseção endoscópica da submucosa (DES) de lesões com fibrose severa tem sido associada a piores resultados, nomeadamente uma menor taxa de ressecção curativa e maior taxa de complicações. Este estudo tem como objetivo investigar o impacto da fibrose severa na DES de lesões do reto realizada no ocidente e avaliar fatores preditivos de fibrose severa. ***Métodos:*** Foi realizado um estudo retrospetivo incluindo todas as DES de lesões do reto realizadas no nosso centro entre janeiro de 2013 e janeiro de 2021. As lesões foram agrupadas em lesões sem fibrose severa ou com fibrose severa. Foram analisados os resultados da DES, preditores de fibrose severa e a curva de aprendizagem. ***Resultados:*** Foi realizada DES em 195 lesões: 45 com fibrose severa. Três resseções foram interrompidas (uma devido a fibrose severa). A presença de fibrose severa associou-se a uma significativa menor velocidade de resseção (16.93 mm^2/min vs. 24.66 mm^2/min, $p = 0.007$) e significativas menores taxas de excisão em bloco (86.4% vs. 96.6%, $p = 0.019$), R0 (61.4% vs. 79.7%, $p = 0.013$) e curativa (54.5% vs. 78.4%, $p = 0.003$), bem como uma maior taxa de resseção híbrida necessária para completar a excisão (13.6% vs. 2.0%, $p = 0.005$). Não se verificou uma diferença estatisticamente significativa em relação aos efeitos adversos nos dois grupos (18.2% vs. 8.1%, $p = 0.09$). O sexo masculino, a presença de colite ulcerosa, radioterapia pélvica prévia, localização em anastomose, manipulação prévia ou invasão profunda da submucosa foram identificados como fatores preditores de fibrose severa. A taxa de excisão em bloco aumentou ao longo do tempo (60.0% vs. 94.1%, $p = 0.018$). ***Conclusão:*** A fibrose severa é um importante fator relacionado com excisões não curativas e mais complexas. A identificação de fatores proditores da sua gravidade é de extrema importância e pode permitir a alocação de endoscopistas mais experientes para casos mais difíceis, permitindo procedimentos mais seguros.

Introduction

Endoscopic submucosal dissection (ESD) is a well-established treatment for colorectal lesions, enabling en bloc resection regardless of a lesion's size and morphology and allowing precise assessment of histological curability [1, 2]. However, its implementation in Western countries has been slow and challenging, mainly due to the long learning curve required, higher risk of associated adverse events, lack of structured training programs, few suitable starting cases in the stomach, and lack of experts [3, 4]. As a result, only a handful of centers in Europe have established comprehensive and proficient ESD programs.

When compared to the stomach, colorectal ESD remains technically challenging due to anatomical features of the colon, including thin walls, narrow lumen, and the presence of peristalsis, which are associated with difficulties on the endoscopic maneuverability.

Besides these anatomical features, several studies have shown that submucosal fibrosis, tumor size and location, and paradoxical movements of the endoscope were also related to procedure difficulty during colorectal ESD [5–7]. Severe submucosal fibrosis can complicate the identification of the appropriate submucosal layer and its separation from the muscular layer and has been linked to incomplete resection, lengthy procedure time, and higher rate of perforation [7–12]. It has been related to prior biopsy or tattooing, residual or recurrent lesions, chronic inflammation (such as ulcerative colitis), and tumor invasion of the submucosal layer [12–19]. Simultaneously, large tumor size, lesions across the fold, protruding morphology, nodular-mixed granular lateral spreading tumors (LST G-M), and non-granular pseudo-depressed type LST (LST NG-PD) have inconsistently been identified as preoperative predictors of severe fibrosis [8, 14, 19, 20].

These observations have been obtained from expert centers in Asia, and data on the effect of severe fibrosis on the results of rectal ESD performed in the West, where endoscopic mucosal resection (EMR) is widely performed (predictably resulting in lesions with profound submucosa fibrosis), are lacking.

Therefore, we conducted a retrospective study to compare outcomes of rectal ESD between lesions with severe fibrosis and lesions without severe fibrosis in a European center and examined the learning curve in lesions with severe fibrosis.

Patients and Methods

Patients and Lesions

We reviewed the records of 195 lesions in 192 consecutive patients with rectal neoplasms referred to ESD at our tertiary center at Centro Hospitalar de Lisboa Ocidental between January 2013 and January 2021. All patients had been informed about the risks and benefits of ESD and provided written informed consent.

All ESDs were performed by the same expert endoscopist (P.B.), and lesions were investigated by white light and narrow-band imaging to detect signs of invasive cancer and to assess the most optimal endoscopic resection technique.

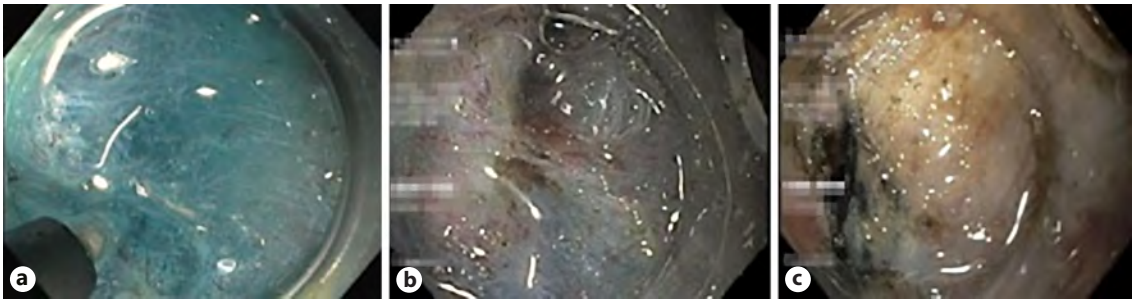

Fig. 1. Degree of fibrosis of the submucosal layers according to appearance of the layers during submucosa injection. **a** F0. **b** F1. **c** F2.

The endoscopic appearance of the lesions was classified according to the Paris endoscopic classification, and tumors were macroscopically classified as protruding tumors (0-Is) or 1 of the 4 subtypes of LST: LST granular homogeneous (LST G-H), LST G-M, LST non-granular flat-elevated (LST NG-F), and LST NG-PD [21, 22].

Indications for rectal ESD were described in a previous study of our center and were adapted from those proposed by the Colorectal ESD Standardization Implementation Working Group and in accordance with the European Society of Gastrointestinal Endoscopy (ESGE) [23–25]. Those included LST NG ≥20 mm, LST G (mixed type) ≥40 mm, depressed tumors ≥20 mm, lesions with type 2B classification of the Japan Narrow Band Imaging Expert Team (JNET) Classification, and lesions that otherwise cannot be optimally and radically removed by snare-based techniques (i.e., lesions located near or at the dentate line, those with nonlifting sign, prior failed EMR, sporadic localized tumors in chronic inflammation) [26]. Neuroendocrine tumors and subepithelial lesions were excluded.

ESD Procedure

According to the expected procedure time and difficulty, procedures were performed by using conscious sedation (with midazolam and fentanyl), deep sedation, or general anesthesia with endotracheal intubation, at the discretion of the endoscopist and anesthesiologist (if involved). Patients were monitored with continuous electrocardiographic registration, pulse oximetry, and noninvasive blood pressure measurement.

With slight variations, rectal ESD was performed in accordance with our previous report [23]. A single-channel gastroscope (GIF-HQ190; Olympus America, Inc., Center Valley, PA, USA) with a disposable distal attachment (D-201; Olympus, Tokyo, Japan) on the tip and carbon dioxide insufflation were used. DualKnife (KD-650L; Olympus) was routinely used in combination with ITknife nano (KD-612L; Olympus) until the end of June 2017, while from July 2017, the endoscopist mostly used a FlushKnife BT (1.5 mm) (Fujinon-Toshiba ES System Co., Omiya, Japan). The electrosurgical ERBE ICC 200 generator unit (ERBE Elektromedizin, Tubingen, Germany) was set at "Endocut" (effect 3, 60 W) for mucosal incision, "Forced Coag" (45–55 W) for submucosal dissection, and "Soft Coagulation" for hemostasis (45–55 W). During submucosal dissection of areas with severe fibrosis, "Endocut" was used at the discretion of the endoscopist. Submucosal injection was performed using a mixture of 4% gelatin solution (Gelofundin 4%, B. Braun Melsungen AG, Germany), indigo carmine and adrenaline (1:250,000). Hemostatic forceps (Coagrasper, FD-411UR, Olympus) were used if hemostasis by the knife in use was ineffective.

When the presence of severe submucosal fibrosis was predicted, the tunneling technique was performed ad initium. Whenever submucosal fibrosis was not predicted and was encountered during the procedure, different strategies were used, including tunneling technique, pocket-creation method, or rarely clip with line to assist traction, which have been described elsewhere [27–29]. In cases where ESD had to be abandoned, a conversion to EMR (Hybrid ESD) was considered.

Classification of Fibrosis

Submucosal fibrosis was evaluated based on findings obtained at the time of submucosal injection and dissection. The degree of submucosal fibrosis was classified into 3 types (F0–2): F0 – no fibrosis, which is demonstrated as a blue transparent layer; F1 – mild fibrosis, which appeared as a white web-like structure in the blue submucosal layer; and F2 – severe fibrosis, which appeared as a white muscular-like structure without a blue transparent layer in the submucosal layer (Fig. 1) [8].

Patients were divided into F0/F1 (nonsevere fibrosis) and F2 (severe fibrosis) groups.

Histopathology Assessment

The resected tissue specimens were pinned on cork after removal and fixed using 4% neutral buffered formalin, before being sent to the pathology department. In cases of piecemeal resections, if possible, the specimen was reconstructed by appropriate fixation onto cork. Histological evaluation was performed in accordance with ESGE guidelines [25, 30].

Outcome Measures and Definitions

Procedure time was defined as the time from mucosal incision to complete removal of the lesion. Resection speed was defined as square millimeter resected per minute (mm^2/min), calculated from the surface area (specimen diameter in long axis × specimen diameter in short axis × π × 0.25) divided by the procedure time [3].

En bloc resection was considered when the tumor was resected as a single piece with macroscopic evidence of complete lesion removal. Resection was considered complete (defined as R0) when

the tumor was removed en bloc with horizontal (at least 1 mm tumor free) and vertical margins tumor free. Resection was considered incomplete when tumors were removed in fragments (piecemeal), horizontal margins were positive (less than 1 mm tumor free), or margins could not be evaluated due to artificial burn effect (RX). When the vertical margin was positive for carcinoma, resection was defined as R1 [25].

Resection was considered curative when an en bloc R0 resection of a superficial lesion with histology no more advanced than a well-differentiated adenocarcinoma (G1/G2), <1 mm submucosal invasion, and with no lymphovascular invasion was achieved [25].

Learning Curve

For an analysis of the learning curve in lesions with severe fibrosis, the study time was divided into 2 periods: first period with resections 1–10 and second period with resections 11–44.

Adverse Events and Post-ESD Management

Perforation was diagnosed either when the muscle layer was injured, and the peritoneal cavity was observed endoscopically, or when free air was found on a plain abdominal radiograph or computed tomography image. Intraoperative bleeding was considered a *major* adverse event when it required special measures, such as emergency surgery, intraoperative blood transfusion, or vasopressor therapy, or when it led to the premature termination of the procedure. Intraoperative bleeding was considered a *minor* adverse event when it changed the procedure plan (e.g., use of hemoclips) or took ≥5 min to be controlled by endoscopy (without meeting criteria for *major* bleeding). Delayed bleeding was defined when clinical bleeding signs were observed (rectal bleeding or hemoglobin drop >2 g/L) until 30 days after ESD.

Noncurative resections were discussed in a multidisciplinary team and decision regarding subsequent management was made on a case-by-case basis and according to the patient's preferences. In curative resections, initially, all patients underwent surveillance endoscopy at 3–6 months after the index treatment, and 12 months after that surveillance if no recurrence was found [25]. However, as new evidence appeared, when a curative resection was observed, patients underwent surveillance endoscopy at 12 months after the index treatment [31]. After piecemeal resection or with presence of positive lateral margins without indication for surgery, colonoscopy was performed at 3–6 months [25]. In endoscopic surveillance, a residual disease was defined as the presence of a lesion at the same place where ESD was performed following a non-R0 resection, found in the first or second endoscopic control; after this period or if resection was R0, it was considered local recurrence.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or median and interquartile ranges for skewed distributions. Continuous parameters were analyzed using Student's *t* test or the Mann-Whitney U test, whereas categorical variables were compared using the χ^2 test and Fisher's exact test, as appropriate. Multivariable logistic regression analysis was performed to assess factors predicting severe fibrosis. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for each variable. Variables were included on the multivariable model and retained in the final model if the *p* value was <0.1 on univariate analysis.

All reported *p* values are two-tailed, with a *p* value of 0.05 indicating statistical significance. Analyses were performed with the use of SPSS software, version 23 (IBM Corp.; Armonk, NY, USA).

Results

Patients and Lesion Characteristics

A total of 195 lesions from 192 patients were evaluated (mean age 68.0 ± 11.0 years; 63.6% male). Median tumor size was 40 mm(IQR 27), and lesions were mainly located on the distal rectum (*n* = 99, 50.8%). Granular-type LST was the most common macroscopic type (*n* = 140, 71.8%; nodular mixed granular type *n* = 103, homogeneous granular type *n* = 37), followed by protruding type (*n* = 34, 17.4%) and nongranular type (*n* = 21, 10.8%; flat type *n* = 13, pseudodepressed *n* = 8). Three patients had 2 lesions that were simultaneously resected by ESD and 1 patient with noncurative ESD resection had a recurrence treated by ESD. Among the 195 lesions, 150 (76.9%) had no fibrosis or mild fibrosis (F0/F1 group), and 45 (23.1%) had severe fibrosis (F2 group). Resection could not be completed in 3 patients, 2 due to deep submucosal invasion diagnosed during ESD, and 1 due to severe fibrosis, and these were not included in the outcomes analysis. Baseline characteristics are shown in Table 1.

Table 2 shows ESD outcomes of the 192 lesions included (148 in the F0/F1 group and 44 in the F2 group). The median procedure time was 75 min (IQR 85). The overall en bloc, R0, and curative resection rates were 94.3%, 75.5%, and 72.9%, respectively. For tumors considered to have noncurative resections (*n* = 52), most comprised adenomatous lesions with a positive or no evaluable horizontal margin (*n* = 34) and 18 had deep submucosal invasion, 5 of which had a positive vertical margin. Hybrid ESD was necessary in 9 (4.7%) resections. Adverse events were observed in 20 patients (10.4%) and included intraoperative *minor* bleeding in 9 procedures (4.6%), delayed bleeding in 7 procedures (3.6%), and perforation in 3 procedures (1.6%); 1 patient had the procedure complicated by both intraoperative *minor* bleeding and perforation (0.5%). No adverse event required surgery or discontinuation of the ESD procedure. Additional surgery with lymphadenectomy was performed in 3 patients who underwent noncurative resections; none of these patients had lymph node metastasis.

Table 1. Baseline characteristics of included patients and lesions and multivariable analysis of predictive factors for severe submucosal fibrosis

Baseline	All (*n* = 195)	F0/F1 (*n* = 150)	F2 (*n* = 45)	*p* value	Adjusted OR (95% CI)*
Age, mean (SD), years	68.0 (11.0)	67.6 (11.1)	69.5 (10.6)	0.308	
Male sex, *n* (%)	124 (63.6)	87 (58.0)	37 (82.2)	0.003	12.275 (1.410–106.829)
Conditions (ulcerative colitis, pelvic radiotherapy, lesion on anastomotic site), *n* (%)	11 (5.6)	4 (2.7)	7 (15.6)	0.004	13.357 (2.215–80.568)
Size, median (IQR), mm	40.0 (27)	44.5 (30)	36.0 (26)	0.044	0.993 (0.973–1.013)
Diameter >40 mm, *n* (%)	103 (52.8)	83 (55.3)	20 (44.4)	0.199	
Location, *n* (%)				0.557	
Distal rectum	99 (50.8)	73 (48.7)	26 (57.8)		
Medium rectum	52 (26.7)	42 (28.0)	10 (22.2)		
Proximal rectum	44 (22.6)	35 (23.3)	9 (20.0)		
Paris classification, *n* (%)				0.301	
Is	33 (16.9)	22 (14.7)	11 (24.4)		
IIa	83 (42.6)	62 (41.3)	21 (46.7)		
Is + IIa	23 (11.8)	18 (12.0)	5 (11.1)		
IIa + Is	46 (23.6)	40 (26.7)	6 (13.3)		
IIa + IIc	10 (5.1)	8 (5.3)	2 (4.4)		
Morphology, *n* (%)				0.039	
LST G-M	103 (52.8)	86 (57.3)	17 (37.8)		1
LST G-H	37 (19.0)	25 (16.7)	12 (26.7)		0.340 (0.057–2.009)
LST NG-F	13 (6.7)	8 (5.3)	5 (11.1)		0.781 (0.080–7.616)
LST NG-PD	8 (4.1)	8 (5.3)	0 (0)		0
Protruded	34 (17.4)	23 (15.3)	11 (24.4)		0.713 (0.149–3.405)
Previous manipulation (EMR attempt/residual or recurrent lesion), *n* (%)	30 (15.4)	2 (1.3)	28 (62.2)	<0.001	663.320 (57.162–7,697.335)
Previous tattoo, *n* (%)	5 (2.6)	2 (1.3)	3 (6.7)	0.082	0.772 (0.003–189.494)
Previous biopsies, *n* (%)	45 (23.1)	35 (23.3)	10 (22.2)	0.877	
Histology, *n* (%)				–	
Adenoma	171 (87.7)	136 (90.7)	35 (77.8)		
Superficial SM carcinoma	4 (2.0)	4 (2.6)	0 (0)		
Deep SM carcinoma	20 (10.3)	10 (6.7)	10 (22.2)		
Deep SM invasion, *n* (%)	20 (10.3)	10 (6.7)	10 (22.2)	0.003	11.558 (2.865–46.627)
Interrupted, *n* (%)	3 (1.5)	2 (1.3)	1 (2.2)	0.547	

SD, standard deviation; IQR, interquartile range; LST G-M, lateral spreading tumor granular nodular-mixed; LST G-H, LST granular homogeneous; LST NG-F, LST non-granular flat-elevated; LST NG-PD, LST non-granular pseudodepressed; EMR, endoscopic mucosal resection; SM, submucosal. * Variables with *p* value <0.1 on univariable analysis were included in the model.

Severity of Submucosal Fibrosis, Lesion Characteristics, and Procedure Results

Compared to lesions with nonsevere fibrosis, lesions with severe fibrosis were significantly smaller (F2 group: mean size 36 mm, IQR 26; F0/F1 group: mean size 44.5 mm, IQR 30; $p = 0.044$) and were more frequently associated with deep submucosal invasion (22.2% vs. 6.7%, $p = 0.003$) (Table 1). There was a significant difference between groups concerning a predisposition for severe fibrosis in the presence of previous conditions (ulcerative colitis, pelvic radiotherapy, or a lesion on an anastomotic site) (15.6% vs. 2.7%, $p = 0.004$) and previous manipulation, such as a previous EMR attempt or a residual or recurrent lesion (62.2% vs. 1.3%, $p < 0.001$). Regarding morphology, most lesions in the F2 group were LST G-M (37.8%), followed by LST G-H (26.7%) and protruded lesions (24.4%). No significant difference was found between the two groups regarding patient age, tumor location, previous tattooing, or pretreatment biopsies. The discontinuation rate was 2.2% in the F2 group and 1.3% in the F0/F1 group ($p = 0.547$).

No difference was observed regarding total procedure time between the F0/F1 and F2 groups (75 vs. 75 min, $p = 0.474$); however, for lesions in the F2 group, resection speed was lower (16.93 mm^2/min vs. 24.66 mm^2/min, $p = 0.007$) (Table 2). Severe fibrosis was associated with significantly lower rates of en bloc (86.4% vs. 96.6%, $p = 0.019$), R0 (61.4% vs. 79.7%, $p = 0.013$), and curative (54.5% vs. 78.4%, $p = 0.003$) resection. A significantly higher rate of hybrid ESD was required to complete resec-

Table 2. Outcome of rectal ESD according to degree of fibrosis

Baseline	All (*n* = 192)	F0/F1 (*n* = 148)	F2 (*n* = 44)	*p* value
Procedure time, median (IQR), min	75 (85)	75 (85)	75 (85)	0.474
Resection speed, median (IQR), mm^2/min	23.25 (26.63)	24.66 (28.17)	16.93 (21.21)	0.007
En bloc resection, *n* (%)	181 (94.3)	143 (96.6)	38 (86.4)	0.019
R0 resection, *n* (%)	145 (75.5)	118 (79.7)	27 (61.4)	0.013
R1 resection, *n* (%)	5 (2.6)	2 (1.4)	3 (6.8)	0.081
RX resection, *n* (%)	42 (21.9)	28 (18.9)	14 (31.8)	0.069
Curative resection, *n* (%)	140 (72.9)	116 (78.4)	24 (54.5)	0.003
Hybrid method, *n* (%)	9 (4.7)	3 (2.0)	6 (13.6)	0.005
Adverse events, *n* (%)	20 (10.4)	12 (8.1)	8 (18.2)	0.087
Perforation	4 (2.1)	3 (2.0)	1 (2.3)	1

IQR, interquartile range.

Table 3. Learning curve of lesions with severe fibrosis

Baseline	First period (1–10)	Second period (11–44)	*p* value
Procedure time, median (IQR), min	117.5 (69)	70 (83)	0.11
Resection speed, median (IQR), mm^2/min	5.94 (5.64)	21.99 (20.31)	0.007
En bloc resection rate, *n* (%)	6 (60.0)	32 (94.1)	0.018
R0 resection rate, *n* (%)	7 (70.0)	20 (58.8)	0.716
Curative resection rate, *n* (%)	6 (60.0)	18 (52.9)	0.734
Hybrid method, *n* (%)	5 (50.0)	1 (2.9)	0.001
Adverse events, *n* (%)	2 (20)	6 (17.6)	1
Perforation	0 (0)	1 (2.9)	1

IQR, interquartile range.

tion in the F2 group (13.6% vs. 2.0%, $p = 0.005$). Adverse events were more commonly observed in the F2 group (18.2% vs. 8.1%, $p = 0.087$), but this did not reach statistical significance.

Predictive Factors of Severe Fibrosis

Multiple logistic regression analysis was performed to identify independent factors predictive of severe fibrosis. Male sex (OR 12.275; 95% CI 1.410–106.829), the presence of previous conditions (ulcerative colitis, pelvic radiotherapy, or a lesion on the anastomotic site) (OR 13.357; 95% CI 2.215–80.568), previous EMR attempt or residual/recurrent lesions (OR 663.320; 95% CI 57.162–7,697.335), and deep submucosal invasion (OR 11.558; 95% CI 2.865–46.627) were identified as independent predictors of severe fibrosis (Table 1).

Learning Curve of Lesions with Severe Fibrosis

Based on the analysis according to earlier and later periods (10 and 34 lesions, respectively), procedure time improved (earlier period, median 117.5 min; later period, median 70 min; $p = 0.11$) and resection speed improved significantly (earlier period, median 5.94 mm^2/min; later period, median 21.99 mm^2/min; $p = 0.007$). En bloc resection rate was significantly higher in the later period (earlier vs. later, 60.0% vs. 94.1%, $p = 0.018$), and R0 and curative resection rates were nonsignificantly lower in the later period (earlier vs. later, 70.0% vs. 58.8%, $p = 0.716$, and 60.0% vs. 52.9%, $p = 0.734$, respectively). A significantly lower rate of hybrid ESD was required to complete resection in the later period (earlier vs. later, 50.0% vs. 2.9%, $p = 0.001$). Adverse events were reduced nonsignificantly over time (earlier vs. later, 20.0% vs. 17.6%, $p = 1$) (Table 3).

Long-Term Prognosis after Noncurative ESD

No residual disease nor local recurrence was found in patients with curative resections. Among the 52 patients with noncurative resections, 34 comprised adenomatous lesions with a positive or no evaluable horizontal margin,

and during a mean follow-up of 27.3 months, 2 local recurrences were observed and treated endoscopically. The remaining 18 patients had lesions with deep submucosal invasion, and 3 were submitted to salvage surgery with lymphadenopathy (specimen analysis revealed no residual tumor and no lymph node metastasis), 6 were submitted to adjuvant therapy with radiotherapy (with or without chemotherapy), and 9 patients were kept on surveillance; during a mean follow-up of 20.8 months, 1 recurrence was diagnosed and endoscopically treated.

Discussion

In this retrospective study, we aimed to determine whether the presence of severe fibrosis would interfere with the clinical outcomes of rectal ESD. Results of our study demonstrated that the presence of severe fibrosis in submucosa is associated with a lower resection speed (16.93 mm^2/min vs. 24.66 mm^2/min), lower rates of en bloc (86.4% vs. 96.6%), R0 (61.4% vs. 79.7%), and curative resections (54.5% vs. 78.4%), and higher rate of hybrid ESD required to complete resection (13.6% vs. 2.0%). In our study, no difference was observed in procedure time (75 min), probably because lesions with severe fibrosis were smaller than those without severe fibrosis. Overall, our R0 and curative resection rates were low (75.5% and 72.9%, respectively), especially when compared to our high en bloc resection rate (94.3%). This may be explained by our conservative definition of R0 resection, in which we only considered R0 in the presence of a horizontal margin of at least 1 mm tumor free, contrarily to definitions presented in other studies where only a lateral margin free of tumor was needed to be considered a complete resection [2]. Consequently, despite our low R0 and curative resection rates in lesions with severe fibrosis, only 1 patient developed local recurrence in the nonmalignant group, which was manageable endoscopically; simultaneously, in the noncurative group, due to deep submucosal invasion, only 1 patient presented with local recurrence, which was once again treated endoscopically. We observed a higher rate of adverse events in the excision of lesions with severe fibrosis (18.2% vs. 8.1%); however, all adverse events were *minor* and were solved conservatively or endoscopically.

Our results reinforce the necessity of accurately predicting fibrosis prior to rectal ESD, as this would allow a more experienced endoscopist to be assigned to more difficult cases, allowing safer procedures. Simultaneously, it would allow some considerations to be taken during the procedure, such as the performance of the initial mucosal incision further away from the lesion than usual, the exposure in advance of the fibrotic areas by thoroughly dissecting the surrounding nonfibrotic submucosa, the utilization of different settings on the electrosurgical generator unit, and the use of traction methods or alternative strategies to assist the dissection. In a retrospective study, Yoshida et al. [32] described the utilization of the pocket-creation method as an aid for lesions with severe fibrosis, allowing a safer and accurate dissection of the fibrosis and resulting in higher en bloc resection rates, shortened procedure time, and reduced discontinuation rate. Several studies have tried to preoperatively predict fibrosis, mainly based on the morphology of the lesion; however, their results are inconsistent. Matsumoto et al. [8] reported an incidence of F2 fibrosis in LST G-M that was significantly higher than that in LST G-H, Chiba et al. [14] found LST NG-PD to be an independent predictor of fibrosis, and Kaosombatwattana et al. [20] observed that tumors with protruding morphology carried a higher possibility of severe fibrosis. In our study, no morphological aspects were associated with the presence of severe fibrosis, possibly related to the small number of cases. Some studies have reported the influence of preoperative biopsy for rectal lesions on ESD. Fukunaga et al. [13] reported that preoperative biopsies tended to cause F2 fibrosis in the submucosal layer. In our study, no difference was found between the two groups (F0/F1 and F2) regarding preoperative biopsies. However, it should be mentioned that most lesions were referred from other institutions to ESD in our center, hampering the correct assessment of previous biopsies. Makino et al. [33] tried to propose endoscopic ultrasonography as a means to preoperatively assess submucosal fibrosis; however, endoscopic ultrasonography in LST showed only moderate sensitivity and low specificity (77.8% and 57.1%, respectively) for the prediction of fibrosis; as a result, its relevance is still undefined. In our study, severe submucosal fibrosis was independently associated with male sex, the presence of previous conditions, such as ulcerative colitis, pelvic radiotherapy, or a lesion located on an anastomotic site, previous manipulation (EMR attempt and residual or recurrent lesion), and deep submucosal invasion. Nevertheless, our confidence interval was large, due to the small sample size of our study, and caution should be taken when interpreting the results.

We analyzed our learning curve during ESD performed in lesions with severe fibrosis. As expected, procedure time and hybrid ESD decreased, and procedure speed and en bloc resection rate increased over time.

Contrary to our predictions, a nonsignificant reduction in R0 and curative resection rates over time was noted. This may be explained by an increase in the complexity of lesions removed by ESD in our center over time. As our experience increased, more complex cases were referred. As an example, we performed ESD for coalescent polyps located in the anal transitional zone after restorative proctocolectomy and ileal-pouch anal anastomosis in a patient with familiar adenomatous polyposis [34].

Our study has several limitations. First, it is a single-center retrospective study and is limited by a small sample size, especially for subgroup analysis. Second, we evaluated the degree of fibrosis based on endoscopic findings during the procedure. Histopathological assessment may be more objective than clinical assessment, which depends on the judgment of the operator; however, many studies reported clinical evaluation of the degree of fibrosis by the endoscopist during the procedure [8, 10–13, 19]. Histological assessment may be influenced by the dissection procedure, the depth of the dissection, or thermal injury by electrocoagulation [13]. Therefore, histologic severity of fibrosis does not necessarily reflect endoscopic severity, and subsequently its clinical relevance. Third, we have a mean follow-up of about 2 years, which might limit the evaluation of recurrence, particularly metastatic disease. A main strength of our study was the performance of all the procedures by the same endoscopist, circumventing performance variation between different endoscopists. However, caution should be taken when extrapolating the results.

In conclusion, ESD is a safe and effective treatment for complete resection of lesions with severe fibrosis, despite being associated with lower en bloc, R0, and curative resection rates, even with expert endoscopists. The presence of ulcerative colitis, pelvic radiotherapy, a lesion located on an anastomotic site, or previous manipulation can preoperatively help to predict cases with severe fibrosis. To the best of our knowledge, this is the first European study to assess the relevance of severe fibrosis on the ESD outcomes and the learning curve of lesions with severe fibrosis.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki for Medical Research Involving Human Subjects, and all patients provided written informed consent. Due to the retrospective design, it was waived by the ethical committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Catarina Félix and Pedro Barreiro were involved in the conception and design of the study, analysis and interpretation of the data; Catarina Félix wrote the article; all authors critically revised the article and approved its final version.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Critical Analysis of the Applicability of Small Bowel Capsule Endoscopy Performance Measures among 2 Portuguese Centers with Different Capsule Endoscopy Platforms

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Keywords
Performance measures · Small bowel capsule endoscopy · Endoscopic units

Abstract
Introduction: The European Society of Gastrointestinal Endoscopy (ESGE) identified the need to benchmark the quality of small bowel capsule endoscopy (SBCE) and produced a set of performance measures (PM). The aim of this study is to critically evaluate the accordance of the PM for SBCE in two Portuguese centers with different SBCE platforms. ***Methods:*** The authors conducted a cross-sectional analysis of consecutive SBCE performed in an 18-month period in 2 Portuguese centers that used two different SBCE platforms Mirocam® (IntroMedic, Seoul, South Korea) and PillCam® (Medtronic, Yokneam, Israel). A total of 10 PM (6 key, 4 minor) were evaluated and compared between the 2 centers. ***Results:*** A total of 493 SBCE were included. The minimum standard established by ESGE was reached in 3/6 key PM (complete visualization, lesion detection rate, and capsule retention rate), and none of the 4 minor PM. PM compliance significantly differed between the 2 centers: complete small bowel visualization 95.9 and 90% ($p = 0.01$), diagnostic yield 50.6 and 63% ($p = 0.005$), adequate small bowel cleansing level according to Brotz scale 69.54 and 84.6% ($p \leq 0.001$), patients with high risk of capsule retention offered a patency capsule 4.2 and 73% ($p \leq 0.001$), respectively. ***Conclusion:*** This study highlights and critically discusses technical and organizational issues that should be considered in defining more realistic PM thresholds, aiming to improve SBCE quality.

Análise crítica da aplicabilidade das medidas de desempenho na enteroscopia por cápsula em 2 centros portugueses com diferentes plataformas de cápsula endoscópica

Palavras Chave
Medidas de desempenho · Enteroscopia por cápsula · Unidades de Endoscopia

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Resumo

Introdução: A Sociedade Europeia de Endoscopia Digestiva (ESGE) identificou a necessidade de avaliar a qualidade da enteroscopia por videocápsula (EVC) e produziu um conjunto de medidas de desempenho (MD). O objetivo deste estudo é avaliar criticamente a concordância das medidas de desempenho de EVC em dois centros portugueses com diferentes plataformas de EVC. ***Métodos:*** Análise transversal de EVC consecutivas realizadas em 2 centros portugueses, com diferentes plataformas de EVC Mirocam® (IntroMedic, Seul, Coreia) e PillCam® (Medtronic, Yokneam, Israel), respetivamente. Um total de 10 medidas de desempenho (6 principais, 4 minor) foram avaliadas e comparadas entre os 2 centros. ***Resultados:*** Foram incluídas 493 EVC. O standard mínimo estabelecido pela ESGE foi alcançado em 3/6 MD principais (visualização completa, taxa de detecção de lesões e taxa de cápsula retida), e nenhum nas quatro MD minor. O cumprimento das MD diferiu significativamente entre os 2 centros: visualização completa do intestino delgado 95,9 e 90% (p = 0,01), taxa de deteção de lesões 50,6% e 63% (p = 0,005), adequada preparação do intestino delgado de acordo com a escala de Brotz 69,54 e 84,6% ($p \leq 0{,}001$), doentes com alto risco de retenção da cápsula a quem foi oferecida cápsula de patência 4,2 e 73% ($p \leq 0{,}001$), respetivamente. ***Discussão/Conclusões:*** Este estudo destaca e discute criticamente questões técnicas e organizacionais que devem ser consideradas na definição de limiares de MD mais realistas, com o objetivo de melhorar a qualidade da EVC.

Introduction

Ensuring the quality of gastrointestinal endoscopy is nowadays a priority for endoscopy units, endoscopists, and patients. In order to provide high-quality practice in gastrointestinal endoscopy, the European Society of Gastrointestinal Endoscopy (ESGE) has established the ESGE Quality Improvement Committee to analyze and define a list of performance measures (PM) in the different endoscopic areas [1–5].

Recently, the ESGE Quality Improvement Committee developed a working group dedicated to the study of the small bowel (ESGE Quality Improvement Committee ESBWG) that identified 10 quality PM (6 key and 4 minor), and for which a minimum and a target standard were established by consensus.

Rondonotti et al. [6] have conducted a survey for Italian endoscopic small bowel capsule endoscopy (SBCE) services that compared SBCE PM in their centers with ESGE standards [5]. The main goals were to provide a snapshot of the current clinical practice with SBCE and to identify areas that might be targeted in future programs. They concluded that only 4/10 (40%) SBCE procedural minimum standards were met by a relevant proportion of the centers (≥80%).

Likewise, quality in SBCE is still an issue to scrutinize. The authors aimed to evaluate and critically review the SBCE PM in 2 Portuguese centers with different SBCE platforms in an individual and global perspective. Moreover, the authors aimed to explore if different SBCE platforms, Mirocam® (IntroMedic, Seoul, South Korea) or PillCam® (Medtronic, Yokneam, Israel), could impact some of SBCE PM results.

Materials and Methods

The authors conducted a cross-sectional analysis of consecutive SBCE performed from January 2018 to July 2019 in Centro Hospitalar Vila Nova de Gaia/Espinho (CHVNG/E), and from January 2017 to June 2019 in Centro Hospitalar Lisboa Ocidental (CHLO). The time period was selected to include approximately a similar number of SBCE procedures. The SBCE procedures were analyzed before the implementation of the ESGE PM for SBCE at the service level [5].

In both CHVNG/E and CHLO, SBCE were read or supervised by gastroenterology experts who have completed and reported more than 300 procedures. In CHVNG/E there was a mean of 7 operators (4 residents and 3 assistants) and in CHLO a mean of 3 operators (3 assistants). In CHVNG/E and CHLO, a medium of 3 SBCE and 2 SBCE were performed every week, respectively. In both centers, the patient's medical history, indications, and contraindications were previously assessed by a SBCE-dedicated gastroenterologist before the SBCE procedure.

According to previous statements [5, 7], patients considered to be at high risk of capsule retention were those with: known Crohn's disease, symptoms of obstruction, long-term non-steroidal anti-inflammatory drugs (NSAIDs), abdominopelvic radiation and previous small bowel resection. ESGE recommends that a patency capsule should be offered to these patients before undergoing SBCE in order to reduce retention. As defined by ESGE technical review [7], SBCE retention was the identification of SBCE on abdominal radiological imaging over 14 days after ingestion. A "watch and wait" policy was instituted, as spontaneous passage of the capsule has been reported in the literature [8], and only 1 patient from CHLO required endoscopic removal by device-assisted enteroscopy (DAE).

In CHVNG/E, DAE is conducted in the same center. In CHLO, patients are referred to other centers to undergo DAE, since the procedure is not available in this center.

Table 1. Minimum and target standards for the PM

PM		Minimum, %	Target, %
Key	Indication for SBCE	≥95	≥95
	Complete cecal or stomal visualization	≥80	≥95
	Lesion detection rate	≥50	≥50
	Timing for SBCE in overt bleeding	≥90	≥90
	Appropriate referral to DAE	≥75	≥90
	Capsule retention	<2	<2
Minor	Adequate bowel preparation	≥95	≥95
	Patient selection	≥95	≥95
	Use of standard terminology	≥90	≥90
	Reading speed	≥90	≥95

PM, performance measures; CHVNG/E, Centro Hospitalar Vila Nova de Gaia e Espinho; CHLO, Centro Hospitalar Lisboa Ocidental; SBCE, small bowel capsule endoscopy; DAE, device assisted enteroscopy. [1] According to Spada et al. [5].

CHVNG/E: SBCE Protocol

SBCE were performed using the Mirocam® system following a protocol which consists of a clear liquid diet on the day before and an overnight fast with prior bowel preparation with 2 L of polyethylene glycol 12 h before the procedure. Real-time view 1 h after SBCE ingestion was performed to confirm SBCE presence in the small bowel, if the capsule remained in the stomach a prokinetic was administered, and if not effective after 30 min, endoscopic placement of SBCE in the duodenum was achieved. After confirming pylorus passage, patients resumed normal daily activities on an outpatient basis (except for hospitalized patients), ingested a light diet 4 h after, and the recorder was removed 12 h after SBCE ingestion or earlier if real-time viewing confirmed that the device has already reached the colon.

CHLO: SBCE protocol

SBCE were performed using the PillCam® system following a protocol which consists of a clear liquid diet on the day before with prior bowel preparation with a 2 L split-dose polyethylene glycol (PEG) regimen (1 L of PEG in the evening before and 1 L of PEG in the morning). The capsule was ingested with water and 40 mg of simethicone. Real-time view was performed 1 h after SBCE ingestion, ingestion of clear liquids 2 h after and a light diet 4 h after SBCE ingestion, and removal of the recorder at the end of the battery or once the capsule had been eliminated. If at real-time view capsule was still in the stomach, a similar protocol to CHVNG was followed to achieve capsule passage to the small bowel.

Data Collection

Data collection was performed by investigators from each center, in CHVNG/E this was executed by C.G. and in CHLO this was executed by C.O., A.R.F. and A.M. Data for each PM was collected and analyzed according to the description and the criteria suggested in the ESGE document [5]. The authors reported whether the ESGE standard (minimum and target) was met in each center (Table 1). The PM were also compared between the 2 centers, in order to evaluate if SBCE software or the center methodology could impact the results.

For the assessment of the rate of adequate bowel preparation, the authors considered an appropriate evaluation when reports described at least one of the Brotz scales (quantitative index, QI; qualitative evaluation, QE; or overall adequacy assessment, OAA) [9].

Statistical Analysis

Categorical variables were presented as frequencies and percentages, and continuous variables as mean and standard-deviation for parametric data and median and interquartile range (IQR) for non-parametric data. χ^2 test or Fisher test, Student t test and Mann-Whitney U test were used to compare non-continuous and continuous data, respectively. For all comparisons, a $p < 0.05$ (2-sided statistical hypothesis test) was considered statistically significant. The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) program version 20 (IBM Corporation, Armonk, NY, USA).

Results

A total of 493 SBCE reports were audited (241 Mirocam® SBCE from CHVNG/E, and 252 PillCam® SBCE from CHLO), 53.3% were female and the mean age was 61 ± 18.4 years. The minimum standard was obtained in 3 out of 6 key PM (complete visualization, lesion detection rate, and capsule retention rate), and none of the 4 minor PM (Table 2).

Key Performance Measures

Indication for SBCE

The use of a drop-down menu for indication has facilitated data acquisition for this PM. When evaluating the percentage of patients undergoing SBCE in accordance with the ESGE clinical guideline for SBCE [7, 10], 93.9% (92.5% CHVNG/E and 94.8% CHLO, $p = 0.29$) complied with this PM (Table 2). The characterization of SBCE performed at each center according to ESGE indications is stated in Table 3.

Complete Cecal or Stomal Visualization

The rate of SBCE reaching the cecum or stoma was 93.1% ($n = 458$, 231 CHVNG/E and 227 CHLO). This measure was documented in a written report including photo documentation. When comparing this rate between centers, it was higher in CHVNG/E (CHVNG/E = 95.9% vs. CHLO = 90%, $p = 0.01$; Table 2).

Lesion Detection Rate

The ESGE document [5] specifies significant findings related to the indication as: P2 and P1 lesions according

Table 2. PM evaluation in CHVNG/E and CHLO

PM		Global, %	CHVNG/E, %	CHLO, %	*p* value
Key	Indication for SBCE	93.9	92.5	94.8	0.29
	Complete cecal or stomal visualization	**93.1**	95.9	90	0.01
	Lesion detection rate	**57.1**	50.6	63	0.005
	Timing for SBCE in overt bleeding	78.9	79	69	0.56
	Appropriate referral to DAE	37.2	36.6	37.9	0.87
	Capsule retention	**0.6**	0.42	0.79	1
Minor	Adequate bowel preparation	77.2	69.4	84.6	<0.001
	Patient selection	45.9	4.2	73	<0.001
	Use of standard terminology	77.2	63.9	89.7	<0.001
	Reading speed	0.2	NA	0.4	NA

Bold values state the PM where the minimum target was reached. PM, performance measures; CHVNG/E, Centro Hospitalar Vila Nova de Gaia e Espinho; CHLO, Centro Hospitalar Lisboa Ocidental; SBCE, small bowel capsule endoscopy; DAE, device-assisted enteroscopy.

Table 3. SBCE characterization in CHVNG/E and CHLO

SBCE characterization	Global, %	CHVNG/E, % (*n*/*d*)	CHLO, % (*n*/*d*)	*p* value
Indication for SBCE				
Iron deficiency anemia	52.9	58.9 (142/241)	46.4 (117/252)	0.006
Overt obscure GI bleeding	15.9	7.9 (19/241)	23.4 (59/252)	<0.001
Known Crohn's disease	8.1	7.9 (19/241)	8.3 (21/252)	0.85
Suspected Crohn's disease	14.4	15.4 (37/241)	13.5 (34/252)	0.55
Suspected small bowel tumors	0.6	0 (0/241)	1.2 (3/252)	0.25
Abnormal radiological imaging	0.6	0.8 (2/241)	0.4 (1/252)	0.62
Complicated and/or refractory celiac disease	1.6	1.6 (4/241)	1.6 (4/252)	1
Other	6.3	7.4 (18/241)	5.2 (13/252)	0.18
Lesion detection rate according to indication				
Iron deficiency anemia	54.1	42.2 (60/142)	68.4 (80/117)	<0.001
Overt obscure GI bleeding	76.9	73.7 (14/19)	78.0 (46/59)	0.76
Known Crohn's disease	85	78.9 (15/19)	90.5 (19/21)	0.40
Suspected Crohn's disease	47.9	70.3 (26/37)	23.5 (8/34)	<0.001
Suspected small bowel tumors	33.3	0 (0/0)	33 (1/3)	1
Abnormal radiological imaging	33.3	0 (0/2)	100 (1/1)	1
Complicated and/or refractory celiac disease	75	100 (4/4)	50 (2/4)	0.43
Other	16.1	16.7 (3/18)	15.4 (2/13)	1

n, numerator; *d*, denominator; CHVNG/E, Centro Hospitalar Vila Nova de Gaia e Espinho; CHLO, Centro Hospitalar Lisboa Ocidental; GI, gastrointestinal; SBCE, small bowel capsule endoscopy.

to the Saurin classification [11] for intestinal bleeding; ulceration, erosions, or strictures in the context of suspected/established Crohn's disease; small bowel tumors and small bowel polyps. In our analysis, the global diagnostic yield (DY) was 57.1%. Although the DY was higher in CHLO (CHVNG/E = 50.6% vs. CHLO = 63%, p = 0.0056; Table 2), this was not reproducible within all indications, as in suspected Crohn's disease the DY was higher in CHVNG/E (Table 3).

Timing of SBCE for Overt Bleeding

According to the ESGE working group [10], a SBCE should be performed within 14 days of the overt bleeding episode. The proportion of SBCE that complied with

these recommendations was 78.9% (15/19 CHVNG/E and 41/59 CHLO, $p = 0.56$; Table 2). The medium time was 5 days (IQR 1.5–23; CHVNG/E: 2, IQR 1–9, and CHLO: 7, IQR 2–33.2, $p = 0.09$).

Appropriate Referral for DAE

The ESGE technical review [7] recommended that a DAE is indicated in patients with: significant findings at capsule endoscopy (P1 and P2 lesions according to the Saurin classification [11] for GI bleeding), suspicion of Crohn's disease on SBCE (for biopsy), suspicion of a small bowel tumor (for biopsy and/or tattooing), when a submucosal mass is detected by SBCE and inherited polyposis syndromes when polypectomy is indicated. In line with these recommendations, 148 SBCE revealed pathological findings which may warrant further investigations. In this analysis, appropriate referral for DAE occurred in 37.2% ($n = 55$) [36.6% (30/82) CHVNG/E and 39% (25/66) CHLO, $p = 0.87$; Table 2]. Furthermore, 1 patient from CHLO was referred for DAE for management of SBCE retention ($n = 1$, 1 CHLO). Patients with indication for DAE who were not referred were: P1 or P2 lesions with controlled anemia and without persistent bleeding, or with a diffuse pattern ($n = 47$, 15 CHVNG/E and 32 CHLO), small bowel erosions or ulcerations without other significant lesions in patients with an uncertain diagnosis ($n = 29$, 27 CHVNG/E and 2 CHLO), non-ulcerated subepithelial lesions ($n = 10$, 6 CHVNG/E and 4 CHLO – in which 5 were suggested a CT enterography, 3 CHVNG/E and 2 CHLO), refractory celiac disease without malignancy suspicion ($n = 3$, 3 CHVNG/E), blue rubber bleb nevus syndrome ($n = 1$, 1 CHLO), suspicion of small bowel polyp referred for magnetic resonance imaging ($n = 1$, 1 CHLO), and suspicion of Meckel diverticulum referred for scintigraphy ($n = 2$, 1 CHVNG/E and 1 CHLO).

Capsule Retention Rate

Only 0.6% ($n = 3$, 1 CHVNG/E and 2 CHLO, $p = 1$; Table 2) of the patients had a SBCE retention.

Minor Performance Measures

Rate of Adequate Bowel Preparation

The rate of patients with an adequately prepared small bowel in SBCE according to a validated cleansing scale was 77.2% (370/479; CHVNG/E 69.4%, 161/232, and CHLO 84.6%, 209/247, $p < 0.001$; Table 2). For this measure, emergency SBCE or patients with active bleeding were excluded from the analysis (9 CHVNG/E and 4 CHLO).

Patient Selection

In total, 61 patients (24 CHVNG/E and 37 CHLO) were considered at high risk of capsule retention. From those, 45.9% ($n = 28$, CHVNG/E 4.2%, 1/24, and CHLO 73%, 27/37, $p < 0.001$) were offered a patency capsule (Table 2).

Use of Standard Terminology

The authors identified which SBCE reports followed the capsule endoscopy structured terminology (CEST) [12]. Overall, 77.2% ($n = 380$, 63.9% CHVNG/E and 89.7% CHLO, $p < 0.001$) complied with these recommendations (Table 2).

Reading Speed of SBCE

Only 1 SBCE report from CHLO stated an adequate reading speed of 10 frames per second.

Discussion

Our analysis of SBCE PM in 2 Portuguese centers revealed that the minimum standard was reached in 3 out of 6 key PM (complete visualization, lesion detection rate, and capsule retention rate), and none of the 4 minor PM. These data are similar to what was demonstrated by Rondonotti et al. [6], where 80% of the inquired centers reached 4 out of 6 key PM (adequate indication, complete visualization, lesion detection rate, and capsule retention rate) and none of the minor PM.

Adherence to appropriate indications for SBCE may optimize the use of limited resources (considering the high costs and time-consuming reading of SBCE) and protect patients from potential harms of unnecessary procedures [7, 10]. In our study, the minimum standard for this PM (indication for SBCE) was close to the target (93.9%). According to the study of Rondonotti et al. [6], 80.3% of the participant centers have achieved the minimum proposed standard (≥95%), mainly low-volume centers (<35 SBCE per year) when compared with medium- to high-volume centers (90.2 vs. 72.1%; $p = 0.05$). This may be due to less restriction on performing SBCE in centers with higher availability of this method, as our centers.

Complete small bowel visualization is a prerequisite for an adequate inspection of the mucosa, and incomplete examinations result in further costs due to the SBCE repetition and/or the need for an alternative investigation [5]. In this study, although the target standard was not reached, the minimum standard for completion rate was

achieved (93.1%). The completion rate was higher in CHVNG/E (95.9% vs. 90%, $p = 0.01$), and this could be due to what was previously recognized by Choi et al. [13], stating that the longer reading time of the Mirocam® system may result in higher rates of complete small bowel examination (Mirocam® battery life 11–12 h and SB-3 ≥8 h). CHLO used a split-dose regimen and this did not appear to influence small bowel transit time [14]. It is uncertain if this split-dose regimen could impact the completion rate.

Lesion detection reflects adequate inspection of the small bowel mucosa, and both standards for this measure were accomplished (57.1%). Variations from expected rates raise the possibility of inadequate patient selection, procedure quality, reading, and/or reporting. In our study, we confirmed a suboptimal DY, around 16%, for indications apart from published recommendations which could ultimately compromise DY, as previously demonstrated in other studies (DY 7–23%) [15, 16]. Moreover, our DYs by indication were not inferior compared to previous literature [5], with rates that ranged between 31 and 68% for suspected GI bleeding, 6 and 38% for suspected Crohn's disease, and 39% for active disease in known Crohn's disease. In CHVNG/E, the overall DY was significantly lower compared to the DY of CHLO (50.6 vs. 63%, $p = 0.006$), although this was not seen in the DY for suspected Crohn's disease, which was higher in CHVNG/E. According to society guidelines [17], the presence of at least 3 small bowel ulcers is highly suggestive of a diagnosis of Crohn's disease, provided the patient has not been using NSAIDs for at least 1 month before the test. However, the results of SBCE have to be interpreted regarding other clinical biomarkers and imagiological parameters, to be able to be diagnostic. Apart from this subjective evaluation by the SBCE reader, the appreciation between small erosions and mucosal denudation may be difficult. As recognized by the small bowel working group [5], the DY could be affected by the reader interpretation of a relevant finding. Moreover, it is questionable if the difference in the DY could be associated to the SBCE platform, although previous data regarding the influence of SBCE platforms in the DY is somewhat contradictory [18, 19].

In the context of overt obscure GI bleeding, a timely SBCE was shown to increase the DY in various observational series [20–24], although a meta-regression model in a recent meta-analysis [25] revealed that timing of endoscopy was only significantly associated with the therapeutic yield. In our analysis, the PM regarding the timing of SBCE in overt bleeding was not achieved, being 78.9%. Rondonotti et al. [7] also found that only around 30% of the Italian centers have reached the minimum standard. Nonetheless, this did not impact our DY for overt bleeding (76.9%), as this was superior to the most recent data (65.2%) [25]. Variations from expected targets may suggest suboptimal timing of procedures and different strategic approaches facing overt bleeding [5]. Rondonotti et al. [6] argued that patients with overt bleeding may be evaluated in clinical settings where the gastroenterologist is not immediately or routinely involved, and patients could only be referred to a gastroenterologist consultation once the acute event has resolved.

DAE is most often performed following a less invasive and simple procedure as SBCE. As stated by Rondonotti et al. [6], less than one third of the centers (32.2%) have reached the minimum standard of ≥75%, corroborating the difficulty to attain the referral target to DAE. In our study, the majority of lesions which did not motivate a subsequent DAE were P1 or P2 lesions with controlled anemia or without persistent bleeding ($n = 47$), small bowel erosions or ulcerations in patients with an uncertain diagnosis ($n = 29$) and non-ulcerated subepithelial lesions ($n = 10$). The authors consider that some SBCE-positive findings do not need a subsequent DAE, an invasive procedure, since some patients could be better managed with other treatment/diagnostic strategies, i.e., iron replacement therapy for some P1 or P2 lesions, or radiological methods for subepithelial lesions. The authors believe that the PM threshold concerning referral for DAE should be revised, as a significant proportion of patients can be managed by other treatment modalities (conservative, medical, surgical) as demonstrated by our series and Rondonotti's study [6], as well as other published evidence [26, 27]. The referral rate from SBCE to DAE was similar between centers, and this was not affected by the DAE availability in CHVNG/E in relation to CHLO.

The optimal approach and timing of bowel preparation to enhance mucosal visibility in SBCE remains debatable, mainly its impact on completion rate and DY [7, 28, 29]. Although high performance standards are desirable, some PM for the rate of adequate small bowel cleansing do not appear to be attainable in clinical practice or even in clinical trials evaluating purgative solutions for small bowel cleansing [28–31]. In fact, it was neither attained in our study (77.2%) nor in Rondonotti's study [6] (only 15.5% of participant centers reached ≥95%). CHLO have more often stated an adequate bowel preparation, and we hypothesized that this could be associated to the split-dose regimen as this was proved to impact the overall and the distal assessment of small bowel cleansing [32]. Equally, the presence of multiple grading scales with dif-

ferent technical characteristics makes the classification with a validated scale more demanding and time consuming, which may explain why it was not stated in some of our reports.

As previously described, SBCE is generally a safe method with a low rate of capsule retention; however, certain underlying conditions and symptoms could predispose to capsule retention [32]. In our analysis, although only 45.9% of high-risk patients had performed a patency capsule, the capsule retention rate was low (0.6%), which implies appropriate patient selection in real-life scenarios. Likewise, in the Italian survey [6], only 10.9% of centers complied with this measure (≥95%). The use of a patency capsule is not consensual, as we found between our two centers (4.2% in CHVNG/E and 73% in CHLO, $p < 0.001$). The different adoption of patency capsule may be due to a lack of a standard protocol to detect patency capsule retention and to a non-negligible rate of false positives in abdominal radiography when identifying patency capsule location [33]. Moreover, it implies additional cost, it is not a risk-free procedure [34], and there are reported cases of SBCE retention after a negative patency capsule [35]. In contrast to previous data, a recent meta-analysis by Pasha et al. [36] showed that the retention rate in known Crohn's disease was 4.6%, predominantly in patients with obstructive symptoms. In our sample, almost all Crohn's disease patients did not present those symptoms, which may not have warranted a patency capsule. Furthermore, some patients with previous dedicated imaging modalities excluding signs of obstructive disease did not undergo a patency capsule.

There are no evidence-based recommendations regarding optimal frame rate for reading SBCE recordings. ESGE technical review [7] recommends a maximum speed of 10 frames per second in single view, considering that the reading rate should be slowed within the proximal small bowel where the risk of missing lesions appears to be higher. The reading speed is obviously platform dependent and the threshold of 10 frames per second is probably based on studies using the PillCam® SBCE platform and is certainly not equivalent to 10 frames per second in other platforms, such as Mirocam®. This could explain why this PM was not stated in our center's reports.

The authors acknowledge some limitations of the study. Firstly, although data were collected on consecutively performed SBCE, the study has an observational design and retrospective data collection and analysis. Related to data collection, some parameters were difficult to check and may lack precision, such as ascertaining the factors associated with retention risk, evaluating the exact time between an overt bleeding episode and SBCE, some of which were not systematically included in the report and implied extensive searching of hospital databases. Secondly, parameters such as reading speed were not included in the report and could not be evaluated. Additionally, due to the descriptive nature of the study it could not provide an objective explanation for the observed variations between centers. Finally, the clinical outcomes were not evaluated and it was not possible to verify if accordance with the proposed SBCE PM impacts on relevant patients' outcomes. In the author's perspective this issue is of greatest importance and should be addressed in future studies.

Conclusion

Auditing PM is of utmost importance to improve quality of care. This study evaluates, compares between centers, and critically discusses the applicability in clinical practice of the expert consensus-based criteria and thresholds for SBCE PM. It may contribute to future revision of proposed PM, which should ideally be based on demonstrable patient's clinical outcomes. It highlights some technical and organizational issues that could be addressed for further quality improvement in SBCE but also raises questions on its applicability to different SBCE platforms. Furthermore, the platform-dependent particularities should also be addressed in the construction of performance standards.

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Statement of Ethics

The study was conducted in accordance with the declaration of Helsinki. Due to its retrospective design involving analysis of existing data and since subjects cannot be identified, this study was granted an exemption from requiring ethics approval by our local ethics committees. All patients gave informed consent for the SBCE procedures.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.G. and C.O. design the work, acquired, analyzed, and interpreted data, and drafted the manuscript. R.P. and R.B. contributed to the conception of the work, interpretation of data, and revised the manuscript critically for important intellectual content. A.P., P.M.-C., A.R., C.C., and J.C. revised the manuscript critically for important intellectual content. All authors approved the final version.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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A Rare Case of Ectopic Adrenocorticotropic Hormone Secretion from Pancreatic Neuroendocrine Tumour Presenting with Cushing Syndrome

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Keywords
Adrenocorticotropic hormone · Pancreatic neuroendocrine tumour · Cushing syndrome

Abstract
Ectopic adrenocorticotropic hormone secretion (EAS) from the pancreatic neuroendocrine tumour (PNET) is rare, aggressive, and challenging to treat. We hereby present a rare case of EAS from PNET presenting with Cushing syndrome diagnosed with endoscopic ultrasound-guided fine-needle aspiration cytology. This case highlights the advanced presentation of EAS from PNET with poor clinical correlation of hypercortisolism and the grade of PNET.

Um caso raro de secreção ectópica de hormona adrenocorticotrópica por tumor neuroendócrino pancreático apresentando-se com síndroma de Cushing

Palavras Chave
Hormona adrenocorticotrópica · Tumor neuroendócrino pancreático · Síndroma de Cushing

Resumo
A secreção ectópica de hormona adrenocorticotrópica (SEA) por tumores neuroendócrinos pancreáticos (TNE-P) é rara, agressiva e difícil de tratar. Apresentamos um caso raro de SEA por TNE-P apresentando-se com síndroma de Cushing, diagnosticado através de ecoendoscopia com punção aspirativa com agulha fina. Este caso enfatiza a apresentação avançada dos TNE-P com SEA e a correlação baixa com o grau de hipercortisolismo e o grau do TNE-P.

Introduction

Pancreatic neuroendocrine tumours (PNETs) are neoplasms that arise from the islet cells of the pancreas, and these tumours account for 1–3 % of pancreatic neoplasms. PNETs are categorised as functioning or non-functioning tumours based on their ability to secrete specific hormones resulting in clinical symptoms [1]. The non-functional PNETs are commonly detected incidentally on imaging or from symptoms due to the mass effect of the tumour. Insulinoma, glucagonoma, gastrinoma, somatostatinoma are the few common examples of functioning PNETs with variable presentation depending on the overproduced hor-

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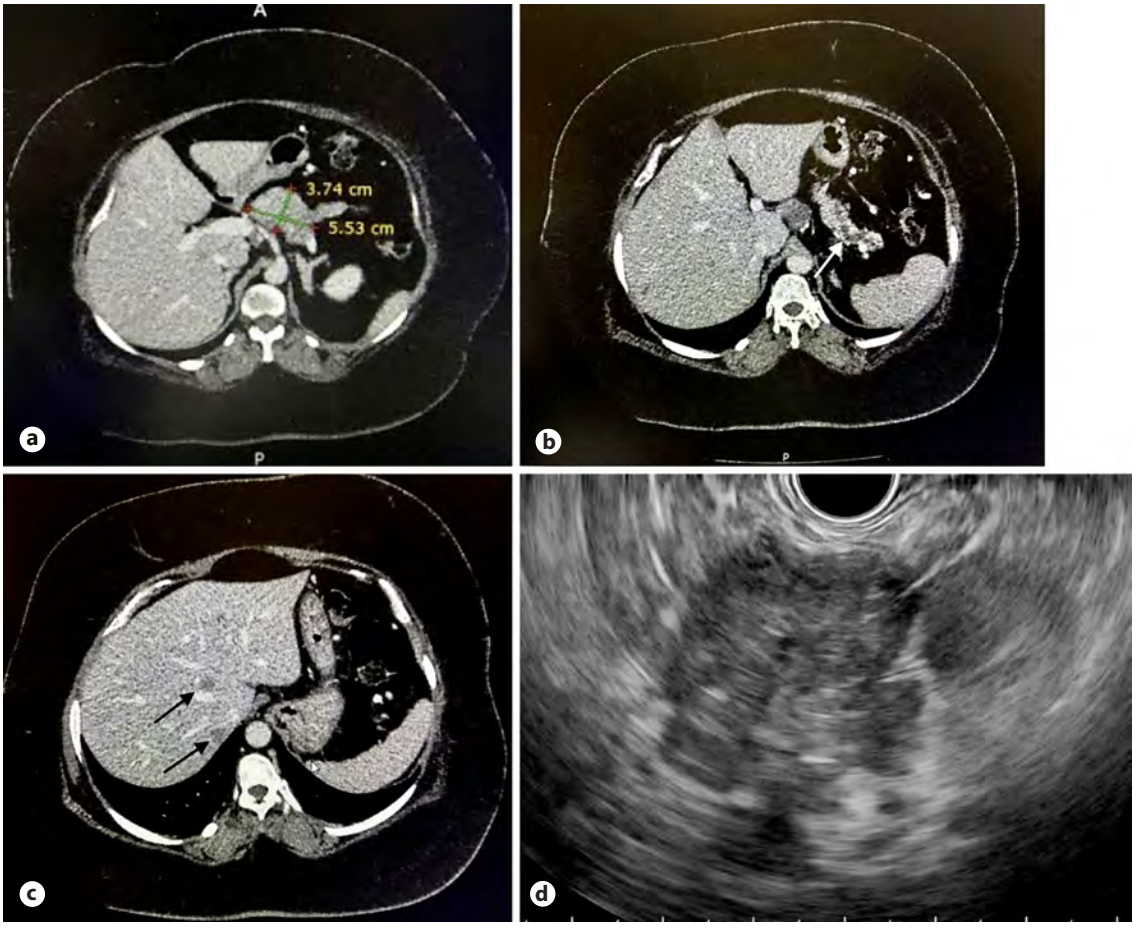

Fig. 1. CT showed an ill-defined hypodense lesion at the body of pancreas (**a**) causing main pancreatic duct dilatation with pancreatic tail atrophy (white arrow, **b**) and small hypodense liver lesions suggestive of metastases (black arrows, **c**). An ill-defined hypoechoic lesion at the body of pancreas was visualised on EUS (**d**).

mones [2]. However, ectopic secretion of adrenocorticotropic hormone (ACTH) from PNET causing Cushing syndrome is rare, with only a few cases reported worldwide [1].

Case Report/Case Presentation

A 29-year-old lady presented with excessive weight gain, proximal muscle weakness, facial acne, and amenorrhea for 6 months. She has no family history of endocrine-related malignancy. Clinical examination revealed cushingoid appearance, central obesity, purplish striae at the abdomen and both arms. Her blood pressure was 155/99 mm Hg, and her body mass index was 54. She was diagnosed of having hypertension and diabetes mellitus on her admission. 24-hour urinary cortisol was 1,649.9 nmol/L and serum cortisol was 656.8 nmol/L on an overnight dexamethasone suppression test. A diagnosis of Cushing syndrome was made after magnetic resonance imaging of the brain excluded pituitary disease. Computed tomography of the adrenal found an ill-defined hypodense lesion at the body of pancreas measuring 3.7 × 5.5 cm (Fig. 1a) with atrophic pancreatic tail and dilated distal pancreatic duct (Fig. 1b). In addition, there were ill-defined hypodense lesions in the liver suggestive of metastases (Fig. 1c) with normal adrenal glands bilaterally. Gallium-68 dotatate scan revealed heterogeneous uptake at the pancreatic body lesion suggesting somatostatin receptor avid primary disease. Endoscopic ultrasonography (EUS) showed an ill-defined hypoechoic lesion at the body of pancreas (Fig. 1d). Fine-needle aspiration cytology performed on the lesion yielded well-differentiated tumour cells on cell block (Fig. 2a, H&E staining, ×400). Immunohistochemistry study showed these cells were positive for chromogranin (Fig. 2b) and synaptophysin (Fig. 2c), CKAE1/AE3 (Fig. 2d) as well as ACTH (Fig. 2e, ×200) confirming ACTH-secreting pancreatic neuroendocrine tumour. Ki-67 proliferative index was 5% with no mitotic figure seen (Fig. 2f), indicating PanNET G2 on World Health Organisation (WHO) 2017 classification and grading of pancreatic neuroendocrine neoplasm with T2N0M1 based on TNM staging. She was commenced on oral ketoconazole to suppress her hypercortisolism. A multidisciplinary meeting had agreed on the consensus that distal pancreatectomy

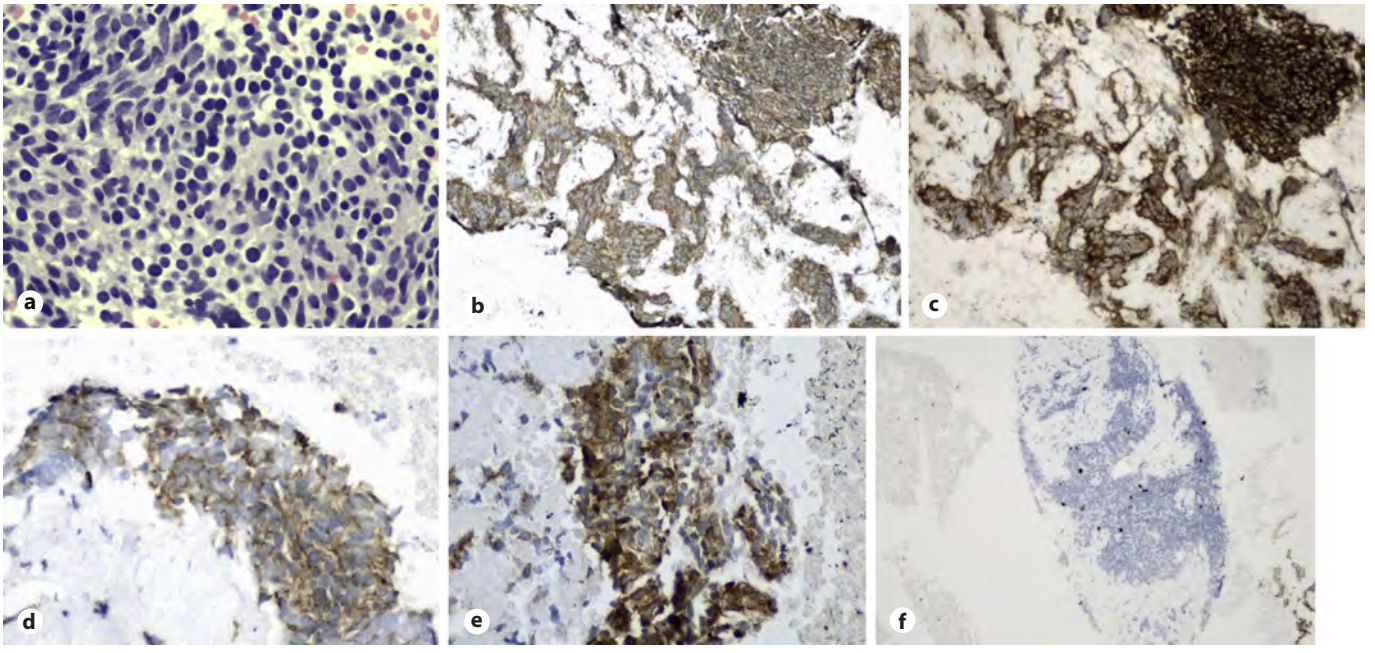

Fig. 2. Well-differentiated tumour cells were seen on cell block (**a**, H&E staining, ×400). These cells were positive for chromogranin (**b**) and synaptophysin (**c**), CKAE1/ AE3 (**d**) as well as ACTH (**e**, ×200) confirming ACTH-secreting pancreatic neuroendocrine tumour. Ki-67 proliferative index was 5% with no mitotic figure seen (**f**).

would be the most suitable option to control her disease. Unfortunately, she refused surgical resection and defaulted her follow-up and medications before succumbing to sepsis a few months later.

Discussion/Conclusion

PNET is a heterogeneous neoplasm group with unique tumour biology, natural history, and prognosis compared to exocrine pancreatic tumours. Most PNETs are malignant in behaviour, with 60 % of them having metastases on presentation [3]. These tumours are reported to have a dismal prognosis with 2-year and 5-year survival rates of 40 % and 16%, respectively [4]. Ectopic ACTH syndrome (EAS) is found in 5% to 10% of all cases of Cushing syndrome, and EAS caused by PNETs is considered rare yet aggressive [5]. This was evident in our case as the patient had liver metastases when she presented to us. One possible explanation for such phenomenon is that the metastatic lesions could have been the predominant source of ACTH secretion instead of the pancreatic lesion, leading to delayed clinical presentation [5]. However, there was no gallium uptake by the liver lesions in our case, but false-negative metastases have been reported in biopsy-proven NET, although gallium-68 scan is still an overall sensitive test in detecting small tumours with somatostatin receptor [6]. The ACTH-secreting PNET in this case was categorised as well-differentiated Pan NET G2 but had the florid presentation of hypercortisolism. This was attributed to the fact that there may be a dissociation between the severity of hypercortisolism and the tumour grades [7]. In addition, a clinicopathological study on ACTH-secreting PNET by Maragliano et al. found that most of the PNETs were of G1 and G2, although limited by small sample size [8].

Our literature review revealed female preponderance of EAS from PNETs as shown in this case and previous reports, although more studies are needed to confirm this possible association [1, 4, 5, 8, 9]. ACTH-secreting PNETs are more commonly found in the tail of the pancreas and the liver is the most frequent site of metastases. Clinical features of EAS from PNET include hypokalaemia, diabetes, lethargy, hypertension, and cushingoid facial appearance. Wu et al. reported a mean survival time of 23 months in patients with ACTH-secreting PNET [9]. The two treatment targets that need to be addressed in the management of EAS from PNET are control of symptomatic hormone oversecretion and prolonging survival by limiting tumour growth and burden. In general, hypercortisolism in EAS is considered as an endocrine emergency as mortality risk increases if left untreated, as illustrated in this

case. The intensity of hypercortisolism should be aggressively reduced with pharmacological approaches or resection of the functioning tumour, and the decision rests on multidisciplinary team discussion tailored to the patient's condition. Pharmacotherapies that inhibit steroidogenesis such as metyrapone and ketoconazole are the first-line treatment of hypercortisolism, and its efficacy is measured by normalisation of glycaemic control, hypertension, and hypokalaemia. Somatostatin analogues such as octreotide and lanreotide could be considered in EAS treatment, but their partial and transient effect in suppressing ACTH secretion has limited their use as monotherapy. Surgical excision of locoregional NET without distant metastases offers a cure for EAS [7]. In metastatic PNETs, especially those with liver involvement, cytoreductive surgery has a role in well-differentiated grade 1 or 2 NET, less than 50 percent hepatic replacement, surgically favourable anatomy, and normal liver function test. Radiofrequency ablation and hepatic artery embolization are the localised antitumor therapy directed to the liver metastases from PNETs. Bilateral adrenalectomy is the rescue treatment for severe EAS when inhibition of steroidogenesis with drugs has failed in unresectable PNET [7]. Systemic antineoplastic treatments for metastatic PNETs include everolimus, sunitinib, peptide receptor radionuclide therapy, capecitabine and temozolomide (CAPTEM) [3].

In conclusion, ACTH-secreting PNET is an aggressive disease that typically presents at an advanced stage with distant metastases. EAS from PNET is potentially fatal if left untreated, and a multidisciplinary approach should be adopted to manage these challenging cases. There seems to be a dissociation between the intensity of the hypercortisolism and the grade of NET in ACTH-secreting PNET. EUS-guided fine-needle aspiration or fine-needle biopsy should be considered in tissue acquisition to establish diagnosis of PNET and guide further therapies. Owing to the scarcity of cases reported and lack of consensus in management of EAS from PNET, more prospective data are needed to establish its best treatment strategy and recommendations.

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Statement of Ethics

Informed consent for publication of case details was obtained from the next of kin.

Conflict of Interest Statement

None to disclose.

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Author Contributions

Conceptualization: S.L. Lee. Data curation: S.L. Lee, C.Y. Ng, A. Awang. Formal analysis: S.L. Lee, C.Y. Ng, J. Sidhu. Investigation: S.L. Lee, J. Sidhu, A. Awang. Methodology: S.L. Lee, C.Y. Ng. Project administration: S.L. Lee. Resources and software: S.L. Lee, A. Awang. Supervision: J. Sidhu Visualization: S.L. Lee. Writing original draft: S.L. Lee. Writing review and editing: S.L. Lee, C.Y. Ng, J. Sidhu, A. Awang.

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Endoscopic Snapshot

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Hepaticoduodenostomy (Right Intrahepatic Biliary Duct) Using a Lumen-Apposing Metal Stent

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Keywords
Hepaticoduodenostomy · Lumen-apposing metal stent · Endoscopic ultrasound-guided biliary drainage

Hepatoduodenostomia (ducto biliar intrahepático direito) com prótese lumen-apposing

Palavras Chave
Hepatoduodenostomia · Prótese de aposição luminal · Drenagem biliar · Ecoendoscopia

Biliary decompression in cases of hilar obstruction is challenging, and the intrahepatic approach is often necessary [1]. We describe a case of endoscopic ultrasound-guided biliary drainage (EUS-BD) for unresectable hilar malignant obstruction, using lumen-apposing metal stent (LAMS).

A 85-year-old woman was admitted due to abdominal pain, jaundice, and choluria. From the personal history, it is worth noting a rectovaginal septum gastrointestinal stromal tumor (GIST), treated surgically in 2002 and with imatinib for 2 years. She was also being followed for pulmonary nodules, suspected of malignancy. Abdominal computed tomography showed a 76 × 57 × 61 mm mass on the left hepatic lobe, with irregular borders, and central necrosis, suggestive of metastasis. This mass compressed the biliary tree at the hilar plaque and led to intrahepatic biliary dilatation (Fig. 1). She had portal vein invasion, pulmonary and peritoneal metastasis. Biochemical workup showed a cytocholestase pattern and total bilirubin of 26 mg/dL. The patient refused liver biopsy. After multidisciplinary discussion it was decided for an endoscopic palliative treatment. Transpapillary access through endoscopic retrograde cholangiopancreatography (ERCP) was attempted but failed due to impossibility of biliary cannulation.

The procedure was performed under deep sedation. A linear echoendoscope (GF-UCT260; Olympus Medical Systems, Tokyo, Japan) was used. There was a significant intrahepatic biliary dilation (12.8 mm), and the right intrahepatic biliary duct was close enough to the duodenal bulb (5 mm), without intervening vessels (as confirmed by color doppler). As so, we performed an hepaticoduodenostomy using a 6 × 8 mm LAMS (HotAxios™, Boston Scientific®, Marlborough, MA, USA): under ultrasound control, the right intrahepatic biliary duct was punctured

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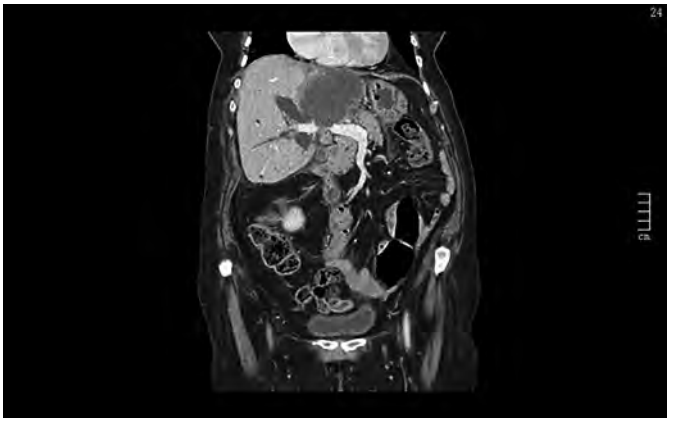

Fig. 1. Abdominal CT before the procedure.

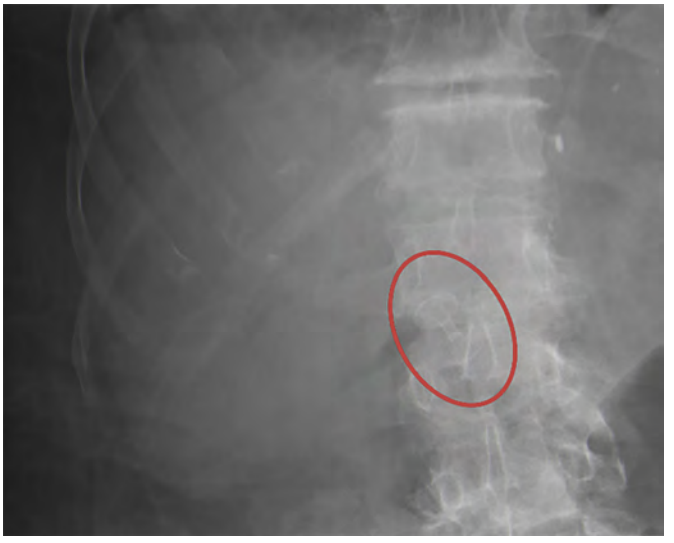

Fig. 2. Hepaticoduodenostomy at the end of the procedure on fluoroscopy.

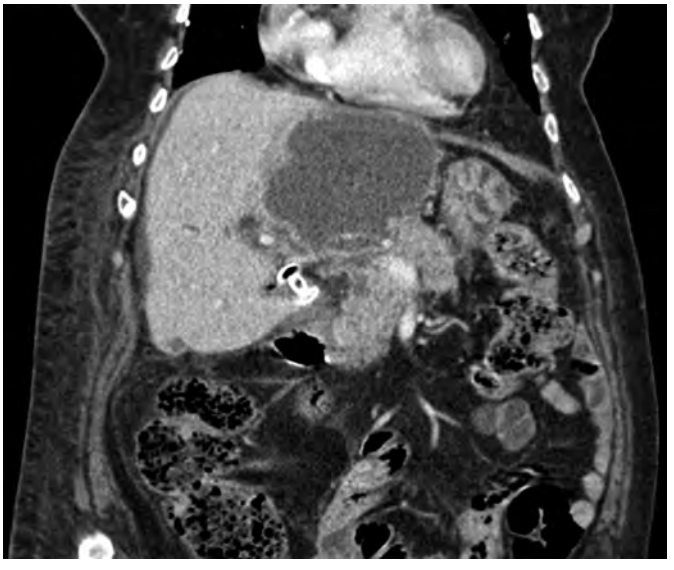

Fig. 3. Hepaticoduodenostomy on abdominal CT.

through the duodenal bulb. After deployment of the stent, we assisted to an abundant drainage of bile (online supplementary video, available at www.karger.com/doi/10.1159/000522578). Position of the stent was confirmed at the end of the procedure by fluoroscopy (Fig. 2).

The patient showed a clinical and laboratory improvement, with a total bilirubin of 7.37 mg/dL 72 h after the procedure. Control abdominal CT showed an improvement in intrahepatic biliary dilatation (Fig. 3). She was followed in palliative care, remained asymptomatic and without complications related to the LAMS. She died 33 days after the procedure, due to disease progression.

The ease of deployment, lumen apposition configuration, and wider diameter of LAMS led to its use in an expanding variety of clinical scenarios, with a good safety profile [2]. Nevertheless, there are risks associated with its use, most commonly misdeployment of the distal or proximal flange and massive bleeding during fistulotomy [3]. Long-term complications described with the use of LAMS are stent migration or obstruction due to tumor progression or food impaction [4].

Although EUS-BD with LAMS has been extensively reported at the extrahepatic duct, LAMS may be an option to intrahepatic EUS-BD when there is enough intrahepatic duct dilation, no intervening vessels, and a stable access route [5]. We describe one of the first cases of hepaticoduodenostomy using LAMS.

Statement of Ethics

The subject's family gave their written informed consent to publish this case and images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

None.

Author Contributions

Carolina Chálim Rebelo was responsible for writing the clinical case, review of literature, editing the video, and script of the manuscript. Nuno Nunes performed the procedure, gave important scientific input, and reviewed the manuscript. Margarida Flor de Lima and Diogo Bernardo Moura contributed with review of the literature and figure selection. José Renato Pereira and Maria Antónia Duarte guaranteed the accuracy of the content and did the final review before submitting.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author.

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Images in Gastroenterology and Hepatology

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Not Everything That Ulcerates Is Crohn's Disease

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Keywords
Erosive enteritis · Crohn's disease · MALT lymphoma · Non-gastric MALT lymphoma

Nem tudo o que ulcera é Crohn

Palavras-chave
enterite erosive · Doença de Crohn · Linfoma MALT · Linfoma MALT não-gástrico

A 41-year-old male with a history of Crohn's disease (CD) with penetrating phenotype (A2L2B3p, Montreal Classification), who was diagnosed aged 17 years and had started treatment with infliximab monotherapy at 30 years old, had been on clinical, imagiological, and endoscopic remission for the previous 2 years. On follow-up ileocolonoscopy with the purpose of considering stopping biological treatment (per the patient's wishes), only 2 superficial ulcers in the sigmoid colon and 3 small erosions in the terminal ileum (shown in Fig. 1) were detected. Histological examination of the ileum erosions demonstrated an infiltrate of atypical lymphoepithelial cells, CD20 positive and CD5, CD23, CD10, and cyclinD1 negative, compatible with a marginal zone B-cell lymphoma of the mucosal-associated lymphoid tissue (MALT; shown in Fig. 2). Immunoglobulin deposition was not identified in this tissue. Cervico-thoraco-abdominopelvic computed tomography and magnetic resonance bowel enterography were unremarkable. The histological specimens were analyzed by two different pathologists with expertise in hematopathology. Serum lactate dehydrogenase, β2-microglobulin, and immunoglobulin levels were normal. Hepatitis C virus antibodies and DNA of *Campylobacter jejuni* on ileum tissue were negative. Staging was complete as a MALT-lymphoma Galian stage A and Lugano stage I. A 6-month course of antibiotic therapy with combined metronidazole and ampicillin was proposed after consultation with Hematology. As the patient was in clinical remission and the endoscopic activity was residual, biologic therapy was suspended due to an unfavorable risk/benefit. Unfortunately, CD recurred clinically and endoscopically so vedolizumab was started after endoscopic and histologic documentation of MALT remission (1 year after diagnosis, 6 months after antibiotics). Due to a primary non-response, the patient was swapped to ustekinumab and is currently in clinical remission, with a further endoscopic evaluation at 6–9 months.

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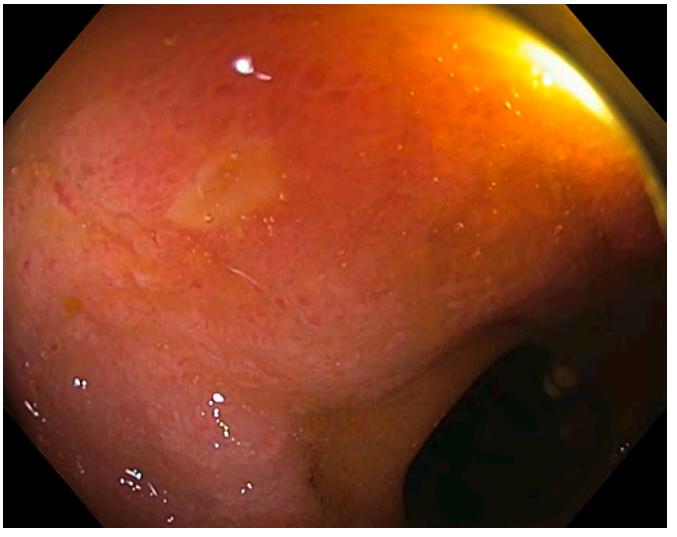

Fig. 1. Small erosion in the terminal ileum on ileocolonoscopy.

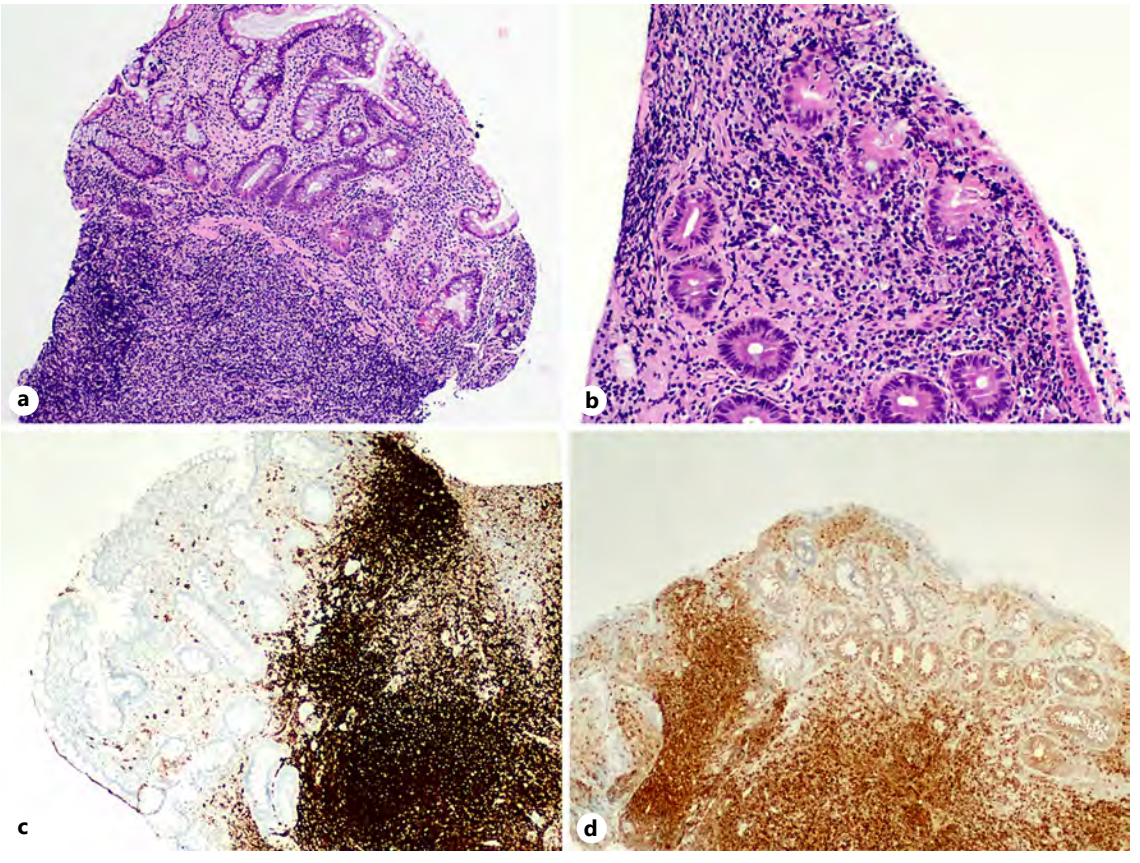

Fig. 2. Histopathological findings of small bowel biopsy. **a** Villous atrophy and focal decrease of mucus secretion. HE. Original magnification ×20. **b** Atypical and prominent lymphoplasmocytic infiltrate within the lamina propria, exhibiting a roughly nodular architecture, predominantly comprised by small lymphocytes with centrocytoid and monocytoid morphology. There were occasional immunoblasts and lymphoepithelial lesions. HE. Original magnification ×40. The small lymphocytes expressed both CD20 (**c**) and Bcl-2 (**d**).

Immunoproliferative small intestinal disease (IPSID) is a subtype of MALT lymphoma, with only sporadic cases in Western countries. IPSID may result from chronic immune stimulation by either autoimmune disorders (such as CD) or infectious agents (such as *C. jejuni*) [1, 2]. B-symptoms are rare in this disorder, creating another barrier to the final diagnosis [3]. While there is a slightly elevated risk of lymphoma development with thiopurine/combination therapy, there is little convincing evidence to date associating anti-TNF monotherapy and lymphoma development in IBD patients and the benefits of CD control clearly outweigh the risk of malignancy [4]. MALT lymphoma generally shows an indolent course, but non-gastric MALT lymphomas have a poorer prognosis compared to the gastric type [5]. Despite controversy, in a localized early-stage disease, IPSID could be treated with antibiotics, since it is associated with durable remissions in the majority of patients [6]. Although current evidence is still lacking, vedolizumab/ustekinumab appears to have an acceptable safety profile in this setting, while anti-TNF and thiopurines probably should not be used unless strictly necessary [7]. In conclusion, this case represents the difficulties in managing IBD patients and immunosuppressive medications, requiring constant risk/benefit analysis and careful follow-up.

Statement of Ethics

Informed consent was obtained from the patient for publication of text and images. Approval for publication was obtained from the local ethical board.

Conflict of Interest Statement

The authors report no conflicts of interest

Funding Sources

No funding was obtained.

Author Contributions

E.A. and C.G. devised and wrote the manuscript; A.P., J.P.C., and M.E. critically reviewed the manuscript; A.R. analyzed the histology.

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Direct Mucosal-Side Fibrosis Cutting for Salvage Endoscopic Submucosal Dissection of Secondary Barrett's Neoplasia Adjacent Multiband Resection Scars

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Keywords
Barrett´s esophagus · Early cancer · Endoscopic submucosal dissection · Perforation · Fibrosis · Multiband resection

Incisão mucosa directa de fibrose para ESD de resgate de neoplasia em Barrett adjacente a cicatrizes de ressecção multibanda

Palavras Chave
Esófago de Barrett · Neoplasia precoce · Disseção endoscópica da submucosa · Perfuração · Fibrose · Ressecção multibandas

A 54-year-old male patient with long-standing Barrett's esophagus underwent multiband ligation endoscopic mucosal resection (MBL-EMR) 1 year previously due to low-risk early cancer (pT1m2, L0, V0, G2, R0). Of note, a nodular-type small Barrett's neoplasia was resected en bloc in one EMR specimen, while the remaining specimens contained areas of low-grade dysplasia without circumscribed lesions. Radiofrequency ablation of the remaining non-dysplastic Barrett's mucosa with preserved acetic acid whitening was scheduled; however, the patient missed several follow-up appointments. At repeat EGD, a secondary Paris 0-IIa lesion estimated at 15 mm and representing a second Barrett's neoplasia emerged adjacent to MBL-EMR scars at oral (towards the mouth) and anterior (towards the sternum) aspects (Fig. 1a, linked color imaging). Acetic acid staining was only abrogated within the lesion itself and endoscopic biopsies confirmed well-differentiated adenocarcinoma. The patient presented for endoscopic submucosal dissection (ESD) after adequate counselling, including alternative surgery. First, an uncomplicated C-shaped incision from the anal side around the posterior (towards the back, or towards 6 o'clock) parts was performed. Unlike the conventional ESD approach to high-grade fibrosis (distant mucosal incision, submucosal approach to fibrosis with or without tunnel technique), direct cutting into the scar area was tried using an articulating ESD knife (3.5-mm ClutchCutter, Fuji, Düsseldorf, Germany). An initial injection of indigo carmine-saline mixture likewise failed to reasonably lift the mucosa. Special attention was paid to first cut in an ultra-superficial fashion as indicated by a crepe paper-like appearance (electrosurgical settings as for mucosal incision: endo cut 1, effect 2, duration 4, interval 1; hemostasis: soft coagulation, effect 4, 100 W; Fig. 1b). Of note, a hard and longer Inoue-type cap was used to adequately grasp the tissue in a superficial fashion. With the incised mucosa continuously pushed aside by the opened scissors, deeper cuts through dense high-

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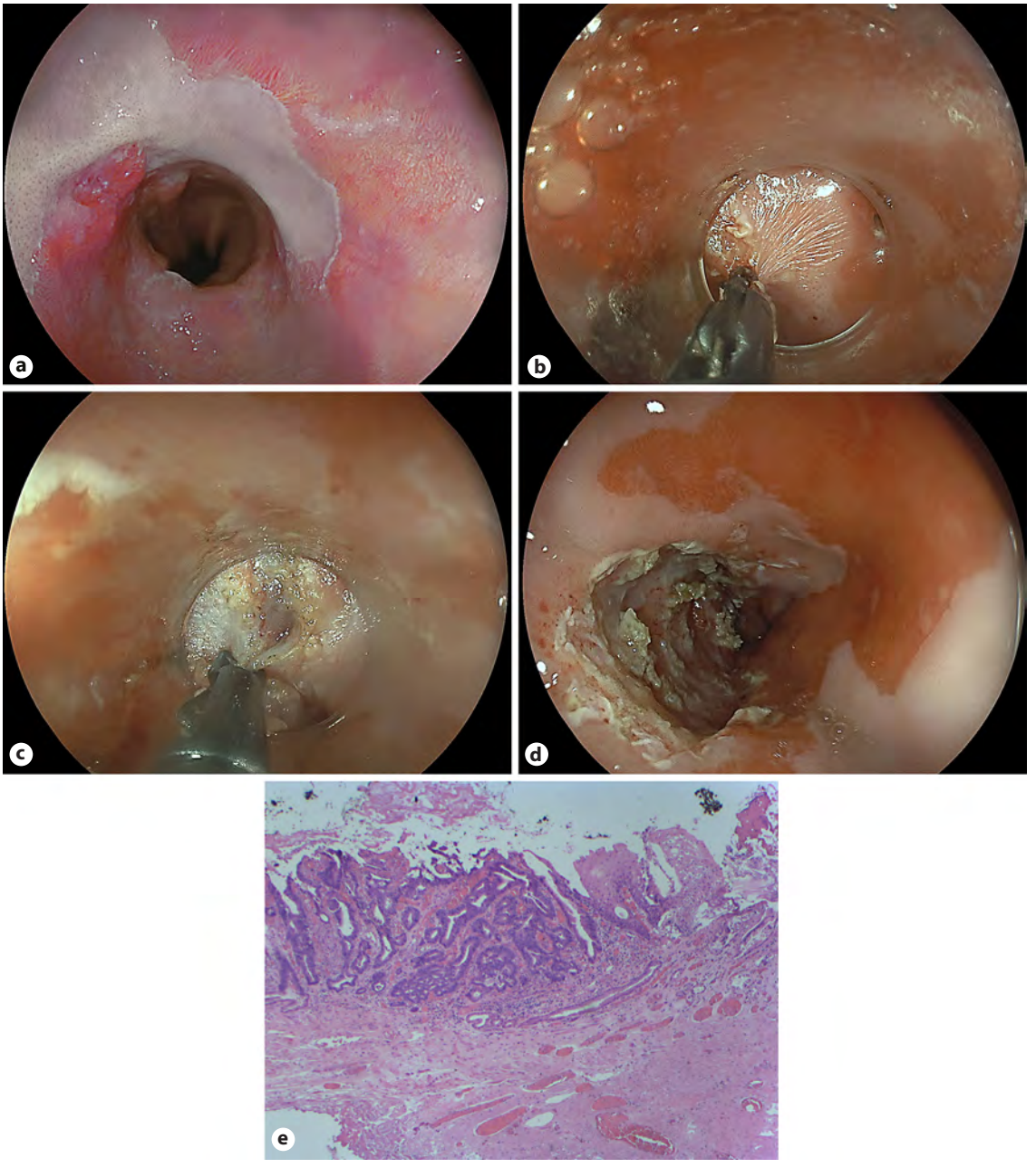

Fig. 1. a Linked color imaging illustrating an estimated 15-mm, Paris 0-IIa neoplastic lesion adjacent multiband resection scars. **b** Ultra-superficial direct mucosal-side fibrosis cutting using an articulating knife (ClutchCutter, Fuji). **c** Transection of exuberant submucosal F2 fibrosis at later stages. **d** Final operative situs indicating en bloc R0 resection as confirmed by final pathology: pT1m2, L0, V0, G1, R0. **e** Representative histopathology of the Barrett carcinoma. HE stain, ×10.

grade F2 fibrosis were performed, and this appeared to indicate the correct resection plane (Fig. 1c). The final histopathology confirmed en bloc resection: pT1m2, L0, V0, G1, R0 (Fig. 1d, e).

Salvage ESD for secondary Barrett's cancer after MBL-EMR has rarely been reported and may pose significant challenges due to marked fibrosis [1]. While high-grade fibrosis in ESD is conventionally tackled by distant mu-

cosal incision with a submucosal approach to fibrotic areas, in this approach the fibrotic area is directly approached from the mucosal side by ultra-superficial cuts using an articulating knife followed by pushing aside the fibrotic mucosa followed by deeper cuts into the fibrotic area [2]. While risk of perforation is real, potential benefits may be in the reduction of the overall resection area, thus potentially translating into reduced risk of ESD-related strictures. Albeit such an approach clearly warrants systematic studies in terms of efficacy and safety, as of now the endoscopic treatment in such complex situations equally clearly needs to be individualized [3].

Statement of Ethics

The patient has given written informed consent for publication (including the publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

V.Z. – clinical care, drafting, and finalization of the manuscript; B.B. – pathology care, critical revision, and final approval.

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INFORMAÇÕES ESSENCIAIS COMPATIVEIS COM O RESUMO DAS CARACTERISTICAS DO MEDICAMENTO. DENOMINAÇÃO DO MEDICAMENTO: Dioralyte, pó para solução oral. **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA: Substâncias activas** g/saqueta: Glicose 3,56; Cloreto de sódio 0,47; Cloreto de potássio 0,30; Citrato dissódico 0,53. **INDICAÇÕES TERAPÊUTICAS:** Correcção da perda de líquidos e electrólitos nos lactentes, crianças e adultos. Tratamento da diarreia aquosa de várias etiologias, incluindo as gastrenterites, em todos os grupos etários. **POSOLOGIA E MODO DE ADMINISTRAÇÃO:** Cada saqueta deve ser sempre dissolvida em 200 ml de água. O volume de Dioralyte reconstituído a tomar deve ser decidido pelo médico assistente, tendo em consideração o peso do doente e o estado e gravidade da situação. Um princípio básico no tratamento da diarreia é a substituição da perda de líquidos e a manutenção de uma ingestão de líquidos suficiente para repor a sua perda nas fezes. A ingestão diária deve ser baseada num volume de 150 ml/Kg de peso nos lactentes e 20–40 ml/Kg de peso nos adultos e crianças. Uma aproximação razoável é a seguinte: -lactentes – 1 a 1,5 vezes o volume alimentar habitual, - crianças – 1 ou 2 saquetas após cada dejecção diarreica, - adultos – 1 ou 2 saquetas após cada dejecção diarreica. Inicialmente, podem ser necessárias maiores quantidades de Dioralyte para assegurar uma reposição precoce do equilíbrio hidro-electrolítico. Nos estadios iniciais do tratamento da diarreia, todos os alimentos, incluindo o leite de vaca e o leite artificial, devem ser interrompidos. Não se deve no entanto interromper o aleitamento materno. Nas crianças amamentadas sugere-se que se dê à criança o mesmo volume de Dioralyte do que o da alimentação normal, seguindo-se o aleitamento. Pode ser necessário, durante este período, a expressão do leite residual da mama. Após 24-48 horas, quando os sintomas desaparecerem, a dieta normal deve ser retomada gradualmente para evitar o agravamento da situação. O regime sugerido para o tratamento da diarreia infantil grave baseado no peso corporal em Kg é apresentado no quadro anterior. Quando a diarreia é acompanhada de vómitos, sugere-se ingestão frequente de pequenas quantidades de Dioralyte. No entanto, é importante que seja tomado o volume total necessário de Dioralyte. Quando o funcionamento dos rins é normal torna-se difícil superhidratar por via oral e quando existem dúvidas acerca da dosagem correcta, mais vale tomar a mais do que a menos. **CONTRA-INDICAÇÕES:** Não se conhecem contra-indicações ao Dioralyte. No entanto, existem algumas situações em que o tratamento com Dioralyte é inapropriado, tais como por exemplo, situações de oclusão intestinal requerendo intervenção cirúrgica, ou em caso de vomitos persistentes e desidratação grave ou diarreia infantil grave em que será necessária uma terapêutica por via intravenosa. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO:** O Dioralyte só deve ser reconstituído com água. Cada saqueta deve ser sempre reconstituída em 200 ml de água. Uma solução mais fraca do que a recomendada não contem a concentração óptima de glicose e electrólitos e uma solução mais forte do que a recomendada pode provocar desequilíbrio electrolítico. Se a diarreia não melhorar rapidamente, os doentes deverão ser reavaliados. Nos idosos, a administração de soluções contendo glucose e electrólitos deve ser cuidadosa em caso de alterações renais ou hepáticas graves ou em outras situações em que o balanço electrolítico normal se encontre alterado. Nos lactentes, deve interromper-se durante 24 horas a alimentação com leite de vaca ou leite artificial, que deverão ser reintroduzidos gradualmente quando a diarreia tiver diminuído. Não se deve interromper o aleitamento materno. **EFEITOS INDESEJÁVEIS:** Podem ocorrer náuseas ou vómitos após a administração da solução, em particular quando esta é ingerida com demasiada rapidez. Estão também descritos casos isolados de desconforto abdominal e de obstipação.Data da revisão do texto: Janeiro de 2004. **TITULAR DA AUTORIZAÇÃO DE INTRODUÇÃO NO MERCADO:** KORANGI - Produtos Farmacêuticos, Lda. Medicamento não sujeito a receita médica. **Para mais informações contactar o Titular da Autorização de Introdução no Mercado**

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