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Endoscopic management of esophageal and gastric lesions with underlying varices

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Abstract

Recent developments in endoscopic techniques have contributed to establishing endoscopy as an essential tool in the management of different types of esophageal and gastric lesions. However, management of these lesions with underlying varices is challenging, considering the technical difficulties and increased risk of bleeding it entails with current endoscopic techniques. Consequently, most endoscopists are hesitant to use this technically challenging procedure. Nevertheless, rare cases of successful endoscopic resection of superficial lesions on or adjacent to varices have been reported. Several endoscopic techniques, including endoscopic mucosal resection, endoscopic submucosal dissection or radiofrequency ablation, have demonstrated safety and feasibility in this setting, sometimes with technical modifications, or in combination with previous variceal eradication procedures that aim to decrease the risk of bleeding. In this review, we summarize the current evidence regarding endoscopic management of gastroesophageal lesions in patients with portal hypertension and underlying varices. It appears that liver cirrhosis, portal hypertension and gastroesophageal varices are not absolute contraindications in selected patients at specialized referral centers. Nevertheless, specific recommendations are lacking and further studies are needed to define the most appropriate endoscopic techniques and to determine which patients may be the best candidates.

Keywords Endoscopic submucosal dissection, radiofrequency ablation, esophageal cancer, esophageal varices, gastric varices

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Introduction

Portal hypertension is a major consequence of liver cirrhosis and may result in the development of esophageal and gastric varices. With optimal medical management, median survival exceeds 12 years in compensated cirrhosis and 1.8 years in decompensated cirrhosis [1]. Therefore, clinical management of dysplasia and early malignancy in esophagus and stomach in cirrhotic patients is relevant, as the neoplasia is often more life-limiting than cirrhosis itself, especially during compensated stages.

Recent developments in endoscopic techniques have contributed to establishing endoscopy as an essential tool in the management of different types of esophageal and gastric lesions [2,3]. While endoscopic submucosal dissection (ESD) has evolved into the preferred option for early esophageal and gastric cancer, given its ability to achieve complete resection with a low recurrence rate, its role in Barrett's esophagus (BE) is limited because of the high efficacy of endoscopic mucosal resection (EMR) [4].

However, the treatment of superficial gastroesophageal lesions with underlying varices is challenging, because of the bleeding risk associated with endoscopic therapy in itself, along with the intrinsic coagulopathy seen in cirrhotic patients and the additional risk of injuring a varix during the procedure and triggering severe bleeding [5]. As a result, most endoscopists are hesitant to use this technically challenging procedure. Nevertheless, rare cases of successful endoscopic resection of superficial lesions on or adjacent to varices have been reported. The aim of this review is to summarize the current evidence regarding endoscopic management of gastroesophageal lesions with underlying varices.

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Endoscopic management of esophageal lesions with underlying varices

Alcohol consumption is an important risk factor for both esophageal squamous cell carcinoma and liver cirrhosis. Consequently, esophageal squamous cell carcinoma and esophageal varices may occasionally coexist [6]. This combination represents a challenging situation, as most endoscopic techniques currently employed are associated with a significant bleeding risk and patients are often also precluded from surgery.

Although current evidence is limited, and is mostly derived from isolated case reports and small case series, a number of endoscopic techniques have been reported to be safe and effective in the management of esophageal lesions adjacent to varices, including EMR, ESD, or radiofrequency ablation (RFA), sometimes with modifications that aim to increase safety in this particular setting (Table 1).

EMR

Endoscopic resection of a superficial lesion (early-stage esophageal carcinoma) with underlying varices was first described in 1991, when the authors performed EMR using a transparent tube after variceal eradication using endoscopic injection sclerotherapy (EIS). This was performed as a 2-stage procedure: in the first stage, a sclerosant (ethanolamine oleate) was injected into the lumen of the varices and, after 1 month, following confirmation that the varices had thrombosed and completely disappeared, EMR of the cancerous lesion was successfully performed without major adverse events (only minor bleeding during the procedure, easily controlled) and allowing histopathological examination and staging [7]. In 2000, resection of early-stage squamous esophageal cancer in a patient with alcoholic cirrhosis and esophageal varices was also performed after EIS with sodium tetradecyl sulfate in 2 sessions: after variceal eradication, EMR was performed with no adverse events or recurrence after 1 year [8].

More recently, EMR after endoscopic variceal ligation (EVL) was performed in a total of 6 patients with early-stage esophageal carcinoma [9-11]. All lesions were successfully resected piecemeal, using the cap-assisted technique during a single EMR session [10,11], except for 1 patient who needed a second EMR after 3 months due to recurrence [9]. In most patients, a 2-stage approach was performed, with EVL preceding EMR, apart from 1 case where EVL was done at the same time as EMR [10]. There were no significant complications and no cases of recurrence were detected after long-term follow up [10,11]. Interestingly, a case series of 4 patients suggests that EMR after previous EVL is also safe and feasible in patients with BE and high-grade dysplasia (HGD) or adenocarcinoma in the setting of portal hypertension [12].

EMR of a polypoid adenocarcinoma (Paris 0-Ip) on a long Barrett's segment without previous variceal eradication was also described. The lesion was snared with a band ligator cap mounted on the endoscope as a precautionary measure that would enable direct variceal ligation in case of bleeding. The resection was uneventful and EVL was not necessary. However, a residual lesion was detected after 2 months, perhaps because of a very superficial resection related to fear of inducing massive hemorrhage [11]. Considering this significant risk of bleeding, EMR without previous variceal eradication cannot be recommended.

In conclusion, EMR preceded by variceal eradication with EIS or EVL appears to be feasible for early-stage esophageal cancer with underlying varices. EIS has the potential advantages of inducing less fibrosis and leaving the lesion intact, which may facilitate subsequent resection, although further studies are needed to assess whether it is associated with better outcomes than EVL.

Endoscopic band ligation

An alternative strategy for small lesions on esophageal varices is to "ligate and let go": after ligation of the varix with the overlying early neoplasm, the lesion will become necrotic and fall off spontaneously. This method has been described as successful for diminutive cancers in the distal esophagus overlying varices, without adverse events or recurrence after long-term follow up [11,13]. Although associated with less risk of bleeding, this technique has limitations, as it does not allow complete excision of large lesions and does not provide a full specimen for histological examination and evaluation of the lesion's extent and infiltration depth.

In contrast to resection of focal lesions, banding alone did not demonstrate significant efficacy for BE-HGD in a retrospective study that compared 8 BE-HGD patients and concomitant esophageal varices, managed initially with endoscopic banding ligation, to a group of 52 BE-HGD patients without esophageal varices managed with other techniques. This study revealed that banding alone rarely resulted in resolution of Barrett's epithelium [14].

ESD

The safety and effectiveness of esophageal ESD in patients with liver cirrhosis has been demonstrated in a retrospective study where *en bloc* and R0 resection rates were similar between cirrhotic and non-cirrhotic patients. However, the rate of intraprocedural bleeding was significantly higher in cirrhotic (18.2%) than non-cirrhotic (0%) patients and mostly related to the presence of large varices [15].

Therefore, the presence of underlying varices is a relevant factor that must be kept in mind when planning esophageal ESD. As with EMR, the risk of bleeding is significant, perhaps even higher considering the increased depth of invasiveness of ESD into the submucosal level where the varicose veins are located. Nevertheless, several case reports demonstrated the feasibility of ESD for superficial esophageal cancer in patients

Table 1 Summary of cases of successful endoscopic treatment of esophageal lesions adjacent to esophageal varices

Author [ref.]	Case	Sex	Age	Etiology of cirrhosis	Child -Pugh	Type of lesion	Varices size	Endoscopic technique	Adverse events	Outcome
Inoue *et al* [7]	#1	Male	71	-	B	SCC	F1	EMR (after EIS)	Minor bleeding	No recurrence after 6 months
Iwase *et al* [8]	#2	Male	58	Alcohol	-	SCC	-	EMR (after EIS)	None	No recurrence after 1 year
Endlicher *et al* [9]	#3	Female	71	Alcohol	-	SCC	-	EMR (after EVL)	None	Recurrence after 3 months; after 2nd EMR no recurrence after 18 months
Ciocirlan *et al* [10]	#4	Male	64 (mean)	Alcohol	A	SCC	F1	EMR (after EVL)	Minor bleeding	Died after 1 week from mesenteric infarction
	#5	Male		Alcohol	A	SCC	F1	EMR (after EVL)	None	No recurrence after a median follow-up of 7 months (range 5-17)
	#6	Male		Alcohol	B	SCC	F2	EMR (after EVL)	None	
	#7	Male		Alcohol	B	SCC	F2	EMR (at the same time that EVL)	Minor bleeding	
Kunzli *et al* [11]	#8	Male	66	-	-	BE-associated adenocarcinoma	F2-F3	EMR	None	Recurrence after 2 months; after 2nd EMR no recurrence after 4.5 years
	#9	Male	50	-	-	BE-associated adenocarcinoma	F2	Band ligation alone	None	No recurrence after 16 months
	#10	Male	66	-	-	SCC	F2	EMR (after EVL)	None	Positive tumor margins → RT No recurrence after 4 months
Prasad *et al* [12]	#11	Male	82	NAFLD	B	BE-HGD	F1	EMR (after EVL)	None	No recurrence after 4 months
	#12	Male	58	NAFLD	B	BE-HGD	F2	EMR (after EVL)	None	No recurrence after 6 weeks; at this time underwent PDT to treat the remaining dysplastic mucosa
	#13	Male	78	Alcohol	A	BE-associated adenocarcinoma	F1	EMR (after EVL)	Minor bleeding	Incomplete resection; a 2nd EMR was performed with no recurrence after 3 months
	#14	Male	60	Alcohol	A	BE-HGD	F1	EMR (after EVL)	Minor bleeding	No recurrence after 3 months
Akiyama *et al* [13]	#15	Male	77	Alcohol	-	Minute adenocarcinoma	F2	Band ligation alone	None	No recurrence after 2 years
Jovani *et al* [16]	#16	Male	47	Alcohol	-	SCC	F2	ESD (after EVL)	None	Positive tumor margins . esophageal resection
Shiratori *et al* [17]	#17	Male	70	Alcohol	-	SCC	F1	ESD (after EVL)	None	R0 resection
Wang *et al* [18]	#18	Male	54	Alcohol	-	BE-HGD	F1	ESD (direct varices coagulation)	None	R0 resection No recurrence after 6 months

(Contd...)

Table 1 *(Continued)*

Author [ref.]	Case	Sex	Age	Etiology of cirrhosis	Child -Pugh	Type of lesion	Varices size	Endoscopic technique	Adverse events	Outcome
Mohapatra *et al* [19]	#19	Female	65	Alcohol	B	BE-associated adenocarcinoma	F2	ESD (direct varices coagulation)	None	R0 resection
Ueda *et al* [20]	#20	Male	67	Alcohol	A	BE-associated adenocarcinoma	F1	ESD (direct varices coagulation)	None	No recurrence after 2 months
Kolb *et al* [21]	#21	Male	62	-	-	BE-associated adenocarcinoma	F2	ESD (direct varices coagulation)	None	R0 resection
Dhaliwal *et al* [22]	#22	Male	65	Alcohol	-	Adenocarcinoma	F1	Water-pocket ESD (direct varices coagulation)	None	R0 resection
Miyazaki *et al* [23]	#23	Male	72	Alcohol	-	SCC	F1	RDI-assisted ESD	Minor bleeding	R0 resection
NeSmith *et al* [24]	#24	Male	66	Hepatitis C	A	BE-HGD	F1	EMR (after TIPS)	Minor bleeding	Negative margins No recurrence after 15 months
Probst *et al* [25]	#25	Male	56	Alcohol	A	BE-associated adenocarcinoma	F2	ESD (after TIPS)	Minor bleeding	R0 resection
Xu *et al* [26]	#26	Male	66	Hepatitis B	A	SCC	F1	ESD (direct varices coagulation)	None	R0 resection
	#27	Male	56	Hepatitis B	B	SCC	F1	ESD (direct varices coagulation)	None	R0 resection
	#28	Male	48	Alcohol	B	SCC	F2	ESD (after EVL)	Major bleeding	No R0 resection
	#29	Male	66	Alcohol	C	SCC	F1	ESD (after EVL)	Major bleeding	R0 resection
	#30	Male	53	Alcohol	A	SCC	F2	ESD (after TIPS)	Minor bleeding	R0 resection
	#31	Male	52	Alcohol	B	SCC	F2	ESD (after TIPS)	Minor bleeding	-
Wang *et al* [27]	#32	Male	53	Alcohol	A	SCC	-	RFA	Intramural hematoma	A 2nd session of RFA was required Complete response at 12 months
	#33	Male	42	Alcohol+ Hepatitis B	A	SCC	-	RFA	Mucosal laceration	A 2nd session of RFA was required Complete response at 12 months
	#34	Male	52	Alcohol	A	HGD	-	RFA	None	Complete response after primary RFA
	#35	Male	76	Alcohol	A	HGD	-	RFA	None	Complete response after primary RFA

(Contd...)

Table 1 *(Continued)*

Author [ref.]	Case	Sex	Age	Etiology of cirrhosis	Child -Pugh	Type of lesion	Varices size	Endoscopic technique	Adverse events	Outcome
	#36	Male	57	Alcohol	A	HGD	-	RFA	None	Complete response after primary RFA
	#37	Male	61	Alcohol	A	HGD	-	RFA	None	Complete response after primary RFA; additional APC for LGD
	#38	Male	47	Alcohol+ Hepatitis C	A	SCC	-	RFA	None	Complete response after primary RFA
	#39	Male	59	Alcohol	A	HGD	-	RFA	Intramural hematoma	Complete response after primary RFA
Uchima *et al* [28]	#40	Male	51	Alcohol+Hepatitis C	A	BE-HGD	F2	EVL+EMR+RFA	No	Complete eradication of dysplasia and intestinal metaplasia No recurrence after 13 months
	#41	Male	52	Alcohol	B	BE-associated adenocarcinoma	F2	EVL+EMR+RFA	Post-EMR bleeding	Complete eradication of dysplasia and intestinal metaplasia No recurrence after 24 months
	#42	Male	63	Alcohol	A	BE-associated adenocarcinoma	F2	EVL+EMR+RFA	No	Complete eradication of dysplasia and intestinal metaplasia No recurrence after 36 months
Dias *et al* [29]	#43	Male	49	Alcohol	A	BE+angiectasias	F1	RFA	No	No recurrence of gastrointestinal bleeding and stable hemoglobin after 4 months
Coyle *et al* [30]	#44	Female	71	Hepatitis C	-	BE-associated adenocarcinoma	F1	Endoscopic spray cryotherapy	No	No recurrence after 24 months
	#45	Male	64	Hepatitis C	-	BE-associated adenocarcinoma	F1	Endoscopic spray cryotherapy	No	No recurrence after 12 months

APC, argon plasma coagulation; BE, Barrett's esophagus; EIS, endoscopic injection sclerotherapy; EMR, endoscopic mucosal resection; EVL, endoscopic variceal ligation; ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NAFLD, nonalcoholic fatty liver disease; PDT, photodynamic therapy; RFA, radiofrequency ablation; RT, radiation therapy; RDI, red dichromatic imaging; SCC, squamous cell carcinoma; TIPS, transjugular intrahepatic portosystemic shunt

with cirrhosis and esophageal varices, whence we can infer strategies that may help decrease the bleeding risk.

One possible strategy is to perform previous EVL until complete variceal eradication is obtained. Although several cases support its effectiveness in preventing major bleeding [16,17], the number of EVL sessions and the optimal timing to perform variceal banding before ESD have not been clearly established. Previous reports of bleeding associated with a single ligation, and incomplete eradication before proceeding to ESD [15], suggest that it might be prudent to achieve complete variceal eradication before ESD, even if multiple sessions are required. The risk of bleeding from ESD performed too soon after EVL needs to be balanced against the technical difficulties associated with fibrosis development from banding if there is an excessive delay.

However, depending on the location of the lesion, such as the gastroesophageal junction, it may be difficult to perform preventive variceal eradication before ESD. An alternative is to perform direct variceal coagulation during the procedure by grasping bared varices with hemostatic forceps and cauterizing them with soft coagulation. Several cases support the safety and effectiveness of this approach for early esophageal cancer with underlying varices [18-21]. Remarkably, it allowed extensive, even circumferential, esophageal ESD without significant bleeding [21]. At the same time, it also causes disappearance of the varices, probably related to shutting off their feeding vessels [20]. However, it is only feasible for small varices (F1); if large esophageal varices (F2-F3) are present, direct variceal coagulation may have a higher risk of bleeding, and preventive treatments such as EVL should be addressed.

Water-pocket ESD, where dissection is carried out in the submucosa beneath the target lesion within a locally created water pool to create a submucosal tunnel, also appears to be an interesting technique refinement for resection of early esophageal cancer with underlying varices. Its advantages include elimination of electrosurgical smoke, magnification of the field of view, and stretching and thinning of submucosal vessels, which improves their identification and coagulation with the dissection knife [22].

Red dichromatic imaging (RDI)-assisted ESD may also be useful for resection of lesions adjacent to varices. RDI is a technology that enables visualization of blood vessels in deep submucosa using 3 different relatively long-wavelength lights (green, amber, and red). In 1 case, ESD was performed using RDI during injection for high-risk superficial esophageal cancer located on post-EVL scars and adjacent to residual esophageal varices. RDI allowed the incision to avoid submucosal vessels and during the procedure there was only minor bleeding [23].

Another important point is proper medical preoperative optimization. These patients often present coagulopathy and hypersplenism, so correction of platelet count and coagulation studies may be important. Nevertheless, although most reported cases were performed with a platelet count >50,000/μL, in one case ESD was performed in a decompensated stage with severe thrombocytopenia (45,000/μL); there were no adverse events, suggesting that platelet count is not an absolute contraindication [19]. Another possible precautionary measure is to perform ESD under vasoactive therapy, which acts on the splanchnic circulation to decrease portal hypertension and alleviate collateral circulation, minimizing risk of bleeding [18].

Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS implantation followed by endoscopic resection also appears to be a promising strategy in the treatment of early esophageal neoplasia in patients with esophageal varices. This approach was described in 2 patients who had BE-associated lesions with HGD [24] or early adenocarcinoma [25] and underlying large varices, where TIPS resulted in rapid regression of the esophageal varices, allowing safe ESD of the overlying lesions. In both cases, minimal bleeding was successfully controlled during the procedure and the patients evolved favorably.

One study compared EVL and TIPS preceding resection of early esophageal cancer, demonstrating that TIPS is associated with less intraprocedural bleeding and a shorter procedure time compared with EVL [26]. An additional advantage is that it does not induce local scarring and the accuracy of staging is maintained. Although the technique seems promising, further studies are needed to evaluate the efficacy and safety of this strategy.

RFA

Endoscopic RFA is a rapidly evolving therapeutic modality for early esophageal squamous cell neoplasia. Its feasibility in the setting of esophageal varices has been evaluated in a retrospective study where 8 consecutive patients with well-compensated cirrhosis and early flat-type early esophageal squamous neoplasia, on or adjacent to esophageal varices, underwent circumferential RFA. Three adverse events were recorded (2 intramucosal hematomas and 1 mucosal laceration), all of which spontaneously resolved without further management. No major adverse events were reported. A complete response was achieved in 6/8 patients after a single treatment and, after the addition of focal-type RFA treatment for residual neoplasia, all the remainder achieved a complete response at 12 months. These results suggest that RFA is an effective therapeutic modality with an acceptable adverse event profile for early esophageal squamous neoplasia in patients with esophageal varices [27].

A modified EMR technique with previous band ligation and subsequent RFA has also been assessed for eradication of neoplastic BE with esophageal varices and has shown promising results. After identifying and marking the target lesion, the distal-to-proximal variceal flow was blocked by endoscopic band ligation distal to the lesion. Conventional band ligation-assisted EMR of the target lesion was then performed in the

same session, followed by another EMR session if needed. After complete removal of the lesions, RFA was performed in further sessions to achieve complete eradication of BE. A case series of 3 patients supported the safety and efficacy of this method [28].

RFA has also been used for the treatment of an unusual combination of esophageal angiectasias and BE with underlying varices. In this case, RFA had a double therapeutic effect for both angiectasias and BE, and its maximal ablation depth only reaches the *muscularis mucosae*, sparing the varices in the submucosa, and therefore would be theoretically safer than argon-plasma coagulation. RFA was performed with no adverse events and clinical improvement was noted, supporting its effectiveness and safety for the treatment of superficial esophageal lesions without previous variceal eradication [29].

Endoscopic spray cryotherapy

The use of endoscopic spray cryotherapy to manage pathological conditions of the esophagus has become increasingly common. Liquid nitrogen cryosprays, delivered through a specialized cryocatheter in brief repeated cycles, can ablate dysplastic or cancerous tissue by causing rapid freezing, gradual thawing, and subsequent necrosis of cells. It is believed to carry a lower risk of bleeding than other modalities, because of the mechanism by which it induces necrosis, which involves significant vascular thrombosis and circulatory stasis [30].

Its efficacy in the setting of portal hypertension and varices is supported by a recent case series including 2 patients with invasive esophageal adenocarcinoma with underlying varices and severe thrombocytopenia: both underwent mucosal ablation using liquid nitrogen cryosprays with no adverse events, complete oncologic resolution and no recurrence during a 2-year follow up [30].

Endoscopic management of early gastric cancer (EGC) with underlying varices

ESD of EGC has been increasingly performed as an alternative to surgery because of its excellent clinical outcomes, especially in high-risk patients such as those with underlying liver cirrhosis. In fact, ESD has been demonstrated to be less expensive, less invasive, less time-consuming and associated with a better patient-reported quality of life compared to surgery [31], while also being associated with higher rate of complete resection and lower rate of local recurrence than EMR [32].

However, the presence of underlying gastric varices may pose significant challenges to the endoscopic treatment of EGC, as there is an associated risk of severe bleeding if the submucosal varices are injured during the procedure. Current evidence in the literature is scarce and there are no specific recommendations for the management of gastric lesions with underlying varices. There are 4 case reports suggesting that ESD can be safely performed for neoplastic lesions on varicose veins if the underlying varices are treated in advance, and illustrating several methods to accomplish their prior eradication (Table 2).

One possible approach involves EIS of the varices with ethanolamine oleate or cyanoacrylate. This method was described in 2 patients with EGC and underlying fundic varices where previous EIS was performed and complete variceal regression was documented with endoscopic ultrasound after 1-2 weeks. ESD was then safely performed with only minor intraprocedural bleeding easily controlled with hot biopsy forceps [33,34]. Although effective, EIS may result in fibrosis and scarring in the submucosal layer, leading to poor or no lifting of tissues and making *en bloc* resection difficult. EIS should therefore be performed in fewer injection sites and at distant varices from the site of ESD.

Balloon retrograde transvenous obliteration (BRTO) has also been reported as a useful method for eradicating gastric varices prior to ESD, allowing safe resection of the overlying lesion with the advantage of inducing less fibrosis than EIS. However, it may aggravate esophageal varices if present, and the time interval between BRTO and ESD may be longer than for EIS (in the reported case regression of gastric varices was documented 1 month after BRTO), which may be a limiting factor for resection of EGC. Another limitation is that its effectiveness implies the existence of a spleno–gastro–renal shunt and therefore the selection of the method for inducing previous variceal regression must be selected case by case, considering each individual's hemodynamics and local relationships [35].

Table 2 Summary of cases of successful endoscopic treatment of gastric lesions adjacent to gastric varices

Author [ref.]	Case	Sex	Age	Etiology of cirrhosis	Child -Pugh	Type of lesion	Varices type	Endoscopic technique employed	Adverse events	Outcome
Uno *et al* [33]	#1	Male	77	-	B	EGC	IGV1	ESD (after EIS)	Minor bleeding	No recurrence
Kim *et al* [34]	#2	Male	52	Alcohol	A	EGC	IGV1	ESD (after EIS)	None	No recurrence
Masui *et al* [35]	#3	Male	80	Alcohol	A	EGC	GOV2	ESD (after BRTO)	None	No recurrence
Namikawa *et al* [36]	#4	Female	75	Hepatitis B	-	EGC	GOV2	LECS	None	No recurrence after 13 months

BRTO, balloon retrograde transvenous obliteration; EGC, early gastric cancer; EIS, endoscopic injection sclerotherapy; ESD, endoscopic submucosal dissection; GOV2, gastroesophageal varices type 2; IGV1, isolated gastric varices type 1; LECS, laparoscopic-endoscopic cooperative surgery

Alternatively, laparoscopic-surgery cooperative surgery (LECS) has also been described as an effective modality to achieve safe and complete resection of EGC with underlying varices. LECS is a suitable option for precise dissection of gastrointestinal tumors that involves endoscopic dissection from the mucosal layer to the submucosal layer and then laparoscopic seromuscular resection; it may be appropriate for select patients in whom ESD would be difficult, such as those with underlying varices [36].

Global analysis

A total of 49 patients undergoing endoscopic treatment of gastroesophageal lesions with underlying varices were described in the literature and their general characteristics are described in Table 3. Forty-five were male (91.8%) and mean age was 62.0 years. The most common underlying etiology for liver disease was alcohol (65.3%) followed by hepatitis C (6.1%), hepatitis B (6.1%), and nonalcoholic fatty liver disease (4.1%). Most patients were classified as Child-Pugh class A (64.5%), followed by class B (32.3%), whereas only one was Child C, possibly related to the higher bleeding risk and low benefit-to-risk ratio in these patients.

The lesions were most commonly located in the esophagus (45 patients, 91.8%) and were most commonly superficial squamous cell carcinoma (44.4%), followed by HGD/adenocarcinoma associated with BE (37.7%), dysplastic flat lesions (11.1%), adenocarcinoma (4.4%), and angiectasias (2.2%). In 17 patients (37.8%) the lesions were resected by EMR, preceded by variceal eradication with EVL (n=13), EIS (n=2), or TIPS (n=1), or without previous eradication (n=1). Adverse events included minor bleeding in 5 patients, with a higher rate after EIS (1/2) than after EVL (4/13). ESD was used in 15 patients (33.3%), most commonly with direct variceal coagulation during the procedure (n=8); other approaches included previous variceal eradication with EVL (n=4) or TIPS (n=3). Interestingly, the incidence of bleeding was higher after previous variceal eradication (5/7) than when direct coagulation of varices was performed without previous eradication (1/8). Further studies involving a larger number of individuals are needed to confirm these differences between techniques.

Table 3 General characteristics of all patients reported in the literature who underwent endoscopic treatment for gastroesophageal lesions with underlying varices. For a more detailed description of each case, please see Tables 1 and 2

Characteristics	N=49 (%)
Age, mean (years)	62.0
Sex	
Male	45 (91.8%)
Female	5 (8.2%)
Etiology for chronic liver disease	
Alcohol	32 (65.3%)
Hepatitis C	3 (6.1%)
Hepatitis B	3 (6.1%)
Nonalcoholic fatty liver disease	2 (4.1%)
Alcohol+hepatitis C	2 (4.1%)
Alcohol+hepatitis B	1 (2.0%)
Not reported	6 (12.2%)
Child-Pugh score	
A	22 (44.9%)
B	11 (22.4%)
C	1 (2.0%)
Not reported	15 (30.6%)
Lesion location	
Esophagus	45 (91.8%)
Squamous cell carcinoma	20 (44.4%)
HGD/adenocarcinoma in Barrett	17 (37.7%)
Dysplastic flat lesion	5 (11.1%)
Adenocarcinoma	2 (4.4%)
Angiectasia	1 (2.2%)
Gastric	4 (8.2%)
Early gastric cancer	4 (100%)
Endoscopic resection technique (esophagus)	N=45
Endoscopic mucosal resection	17 (37.8%)
After band ligation	13
After sclerotherapy	2
After TIPS	1
Without previous therapy	1
Endoscopic submucosal dissection	15 (33.3%)
Direct varices coagulation	8
After band ligation	4
After TIPS	3
Radiofrequency ablation	9 (20.0%)
Band ligation alone	2 (4.4%)
Endoscopic spray cryotherapy	2 (4.4%)
Endoscopic resection technique (stomach)	N=4
Endoscopic submucosal dissection	4 (100%)
After sclerotherapy	2
After BRTO	1
After TIPS	1

BRTO, balloon retrograde transvenous obliteration; HGD, high-grade dysplasia; TIPS, transjugular intrahepatic portosystemic shunt

Concluding remarks

The presence of superficial esophageal or gastric lesions with underlying varices represents a challenging situation associated with increased technical difficulties and bleeding risk. However, several cases have demonstrated the feasibility of a variety of endoscopic techniques in this setting, including EMR, ESD or RFA, with particular technical adaptations that increase safety and effectiveness (Table 4). Therefore, liver cirrhosis, portal hypertension and gastroesophageal varices are not absolute contraindications for the endoscopic management of superficial esophageal or gastric lesions in selected patients at specialized referral centers. We hope this review may inspire further studies that can provide more insight into the endoscopic management of superficial lesions with underlying varices. Future directions for research in this field should focus on determining which endoscopic techniques and specific technical refinements may increase safety and effectiveness and define subgroups of patients that may be candidates for endoscopic resection, or when these procedures are contraindicated.

Table 4 Summary of all endoscopic techniques and technical modifications used for resection of gastroesophageal lesions with underlying varices

Endoscopic technique	Comments
	Esophagus
Endoscopic mucosal resection	Feasible for early-stage esophageal cancer after variceal eradication by sclerotherapy or band ligation Sclerotherapy has potential advantages of inducing less fibrosis and leaving the lesion intact Due to safety concerns cannot be recommended without previous variceal eradication
Endoscopic submucosal dissection	May be performed after variceal eradication by band ligation or after TIPS or with direct varices coagulation during the procedure for small varices (F1) Technical modifications, such as water-pocket or RDI-assisted endoscopic submucosal dissection, may be useful Proper medical preoptimization (platelet count, coagulation parameters) is essential Performing the procedure under vasoactive therapy may also reduce bleeding risk
Band ligation alone	Successfully described for diminutive cancers in distal esophagus overlying varices Lower bleeding risk Does not allow complete excision of large lesions and does not provide a full specimen for histological examination and accurate staging
Endoscopic spray cryotherapy	Apparently associated with a low rate of adverse events, complete oncologic resolution and low recurrence rate
Radiofrequency ablation	Theoretically safe without previous variceal eradication, considering that maximal ablation depth only reaches muscularis mucosae and does not reach submucosal varices Feasible for esophageal superficial lesions and angiectasias. Also useful for eradication of associated Barrett's esophagus
	Stomach
Endoscopic submucosal dissection	Feasible for resection of early gastric cancer after variceal eradication by sclerotherapy or balloon-retrograde transvenous obliteration Sclerotherapy should be performed in fewer injection sites and at distant varices from the site of endoscopic submucosal dissection to avoid fibrosis
Laparoscopic-endoscopic cooperative surgery	Described as an effective modality to achieve complete and safe resection of early gastric cancer with underlying varices

RDI, red dichromatic imaging; TIPS, transjugular intrahepatic portosystemic shunt

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