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Management of Esophageal Squamous Cell Neoplasia

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Abstract

Purpose of review This article reviews the most recent advances regarding the diagnosis and endoscopic treatment of superficial esophageal squamous cell neoplasia.
Recent findings The incidence of superficial esophageal squamous cell carcinoma (ESCC) has increased mainly because of improvement in endoscopic detection. It is estimated that high-definition white light endoscopy has low sensitivity for the detection of ESCC. Lugol's iodine chromoendoscopy significantly improves the diagnosis, but with a low specificity. Recently, magnifying endoscopic assessment of the intrapapillary capillary loops has been shown to accurately predict the depth of invasion and therefore guide the best treatment choice. Consequently, management of neoplasms of the esophagus has changed in recent years as endoscopic resection techniques have gradually become more important.
Summary For superficial ESCC, endoscopic submucosal dissection is considered the preferred approach, enabling accurate *en bloc* resection with a lower recurrence rate and improved survival. Although some studies have shown promising results for endoscopic resection of submucosal tumors, there are limitations and surgery continues to be the standard treatment for more advanced lesions, either alone or in combination with chemoradiotherapy.

Introduction

Esophageal neoplasia ranks seventh in incidence and sixth in mortality among all cancers worldwide [1]. Regarding histopathology, squamous cell carcinoma (SCC) accounts for up to 90% of cases and its distribution varies geographically, with a concentration in areas of greatest risk known as the "esophageal cancer belt," which encompasses the region from northeast Iran, Central Asia, and northeast China [2].

Smoking and alcohol consumption are major risk factors for esophageal squamous cell carcinoma (ESCC). Patients with head and neck squamous cell carcinoma (HNSCC) are at risk to develop a second primary tumor of the esophagus supporting the concept of field cancerization. Results of a screening program in this high-risk group showed that the frequency of a second primary tumor of the esophagus in this population was 8%, with most being superficial lesions amenable to endoscopic curative resection. In a multivariate analysis, SCC of oral cavity and oropharynx and the presence of esophageal low-grade dysplasia (LGD) were found to be predictive factors of ESCC [3]. Survival rates and choice of initial treatment are directly related to invasion depth. According to the Japanese Esophageal Society [4], superficial ESCC is defined as a cancer invading up to the submucosa, regardless of lymphonodal invasion (T1NxMx). Early ESCC, on the other hand is defined as mucosal cancer (T1aNxMx) (Fig. 1). The management of ESCC has been changed over recent years. While esophagectomy was formerly the only treatment choice for superficial esophageal neoplasm endoscopic resection has gradually emerged as the preferred treatment for select early ESCC. In contrast, management of tumors invading deeper than submucosa (T2 or more), still requires a multimodality approach of surgery with or without chemoradiotherapy. As the incidence of ESCC is increasing mainly because of improvement in endoscopic detection, this review will focus on the advances in diagnosis and treatment strategies for superficial ESCC potentially amenable to endoscopic therapy.

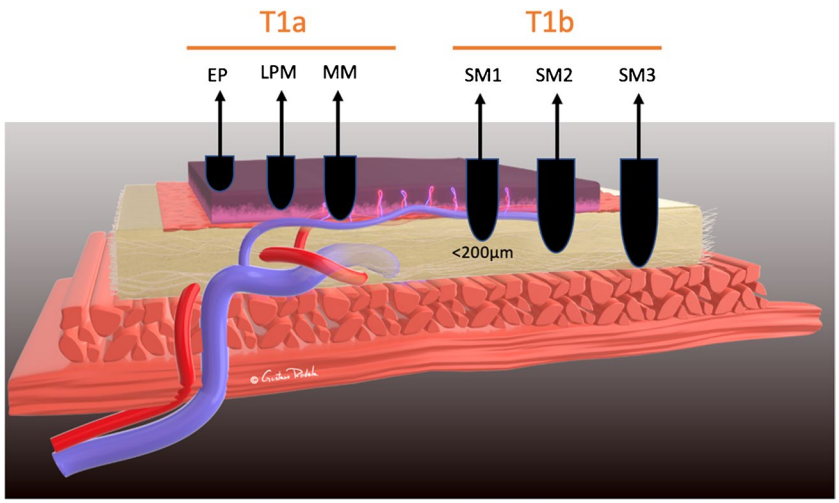


Fig. 1 Subclassification for superficial ESCC

Pretreatment assessment

Most patients with superficial ESCC do not have signs or symptoms caused by the neoplasia. Consequently, the diagnosis of superficial ESCC relies on endoscopy mostly indicated for unrelated gastrointestinal symptoms (e.g., dyspepsia) or in the context of screening programs [5].

Endoscopy

The accurate evaluation of disease extent is crucial for the selection of the appropriate treatment strategy and endoscopic assessment of tumor depth is indispensable. Nevertheless, mucosal changes associated with early cancers may be subtle and missed. Therefore, appropriate preparation for an endoscopic examination is mandatory. The first step is to remove mucus and bubbles from the mucosal surface with mucolytics and/or defoaming agents. Adequate conscious sedation is indicated to ensure adequate time examining the esophagus is spent to avoid missing a lesion.

It is estimated that high-definition white light endoscopy (HD-WLE) has a 50% sensitivity for the detection of ESCC. The macroscopic assessment by the Paris classification [6] may help determine the depth of invasion into submucosa. Polypoid and excavated lesions, classified as Paris 0-Ip and 0-III respectively, are easy to recognize but account for only 20% of superficial cancer and contain invasive submucosal cancer in more than 80% cases. By contrast, most early esophageal cancer has a flat appearance (Paris 0-II) with small changes on the mucosal surface and is thus more difficult to identify.

Given the challenges of endoscopic identification of early esophageal cancer, Lugol chromo endoscopy was developed to improve diagnostic accuracy. This relies on the principle that iodine ties to glycogen. In the normal esophageal squamous mucosa, glycogen is abundant and therefore gives a positive iodine reaction and turns into brown. In contrast tissue with immature or quickly dividing cells, like those present in inflammation, dysplasia, or neoplasia, have less abundant glycogen and are consequently not stained by the dye. Lugol's chromoendoscopy is cheap, widely available and easy to perform. Compared with WLE, Lugol's iodine chromoendoscopy significantly improves

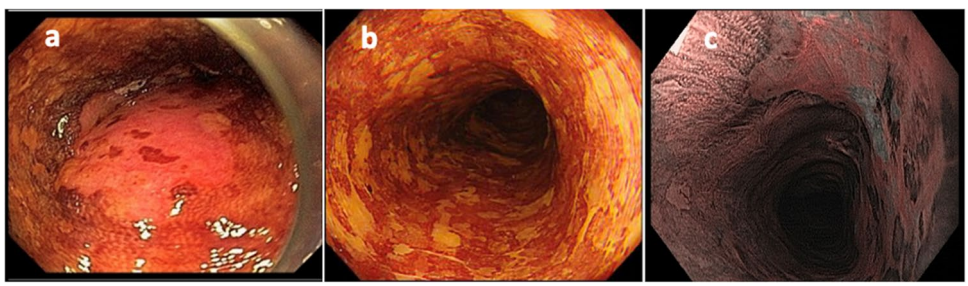


Fig. 2 **A** Lugol pink color sign. **b** Leopard print pattern. **c** Metallic silver sign

the sensitivity of endoscopic diagnosis of superficial ESCC. However, this method has some drawbacks: (1) specificity is low due to poor differentiation between inflammatory and neoplastic changes and (2) side effects such as chest pain, although this can be reducedby using less concentrated iodine and antidotes solutions [5, 7–9].

The pink-color sign represents a color change from brownish yellow to pink 2 to 3 min after iodine staining and is another potential important indicator of esophageal squamous cell carcinoma. Several studies have described significantly improved specificity of this finding compared to Lugol staining for diagnosing high-grade intraepitelial dysplasia (HGIN) and invasive cancer [10, 11]. The presence of multiple small Lugol-void lesions (the so-called leopard print pattern) can denote a high-risk factor for the development of metachronous high-grade dysplasia and cancer. This is significantly associated with a history of smoking and alcohol use, especially in those with modification of the aldehyde dehydrogenase type 2 gene [12]. In this scenario, the presence of the pink-color sign can guide the correct site for adequate biopsies. Sometimes, particularly when using low concentration iodine solutions, the pink color sign may be difficult to recognize. With narrow band image (NBI), highly suspicious lesions appear with a metallic silver color. Its presence can also accurately predict the presence of a dysplastic or neoplastic lesion, regardless of macroscopic and histopathologic features [13] (Fig. 2).

Some macroscopic features of mucosal ESCC by HD-WLE are flat areas with a smooth surface, slightly elevated lesion with granular or uneven surface, reddish flat lesions and slightly depressed lesion ≤ 2 cm. Submucosal ESCC may appear as irregular, protruded, and ulcerated lesions [14••] (Fig. 3). Compared with HD-WLE, electronic, and optic chromoendoscopy (NBI, BLI, FICE, i-scan) have a higher sensitivity for the diagnosis of ESCC although the sensitivity is still lower than Lugol chromoendoscopy.

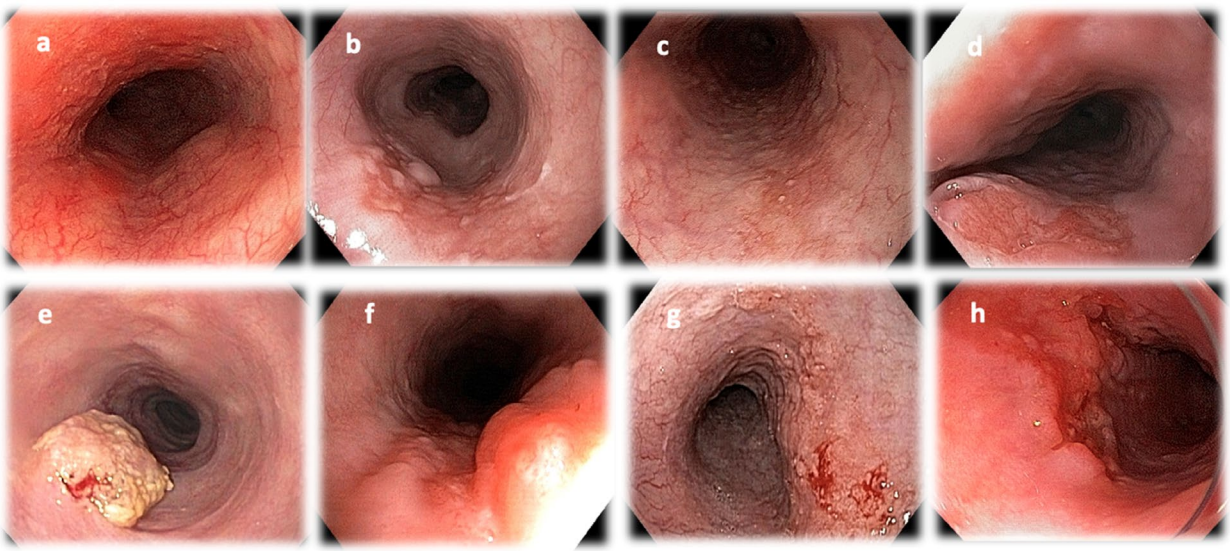


Fig. 3 Macroscopic features under HD-WLE of mucosal ESCC (**a**, **b**, **c**, and **d**) and submucosal ESCC (**e**, **f**, **g**, and **h**)

As already discussed, the endoscopic determination of the depth of invasion based on the macroscopic appearance of a lesion is limited. It is therefore essential to aggregate a more accurate staging method utilizing several methods beyond traditional endoscopy. The development of techniques employing magnifying endoscopic evaluation of the intrapapillary capillary loops (IPCL) has been shown to predict the extent of invasion [15, 16]. Furthermore, in ESCC, IPCL arrangement alterations present as dilatation, weaving, change in caliber, and variety in shape, the so-called "four characteristic markers of cancer." The role of magnifying endoscopy was further delineated by the Japanese Esophageal Society classification [17••]. Microvessels are classified as type A if they have three or fewer characteristics markers and type B if they have all of them. Accordingly, type A vessels represents non-cancerous epithelium, including normal mucosa, inflammation, and low-grade dysplasia. Type B vessels, on the other hand, characterize cancerous epithelium (high-grade dysplasia and invasive cancer) and are further subclassified into three categories: B1, B2, and B3. Type B1 express a type B vessel that contain a loop-like formation and commonly have the appearance of small dots in a target area. When a lesion has only type B1 vessels, the predictable invasion depth is epithelium (M1) or lamina propria (M2). Type B2 indicates vessels that have lost the loop-like appearance and shows elongated and stretched modifications. The B2 vessels often show a multilayered arrangement or irregularly branched/running pattern. This pattern is related to lesions invading the muscularis mucosa (M3) and superficial submucosa (SM1, up to 200 micra). B3 is defined as highly dilated abnormal vessels whose caliber appears to be more than 3 times that of the usual B2 vessels and often appear green in color. This finding predicts invasion depth into the deep submucosa (> 200 micra) (Fig. 4).

Endoscopic ultrasound (EUS)

For locoregional staging of ESCC, EUS has been extensively studied and can be adopted for tumor (T) and node (N) staging. In general, EUS sensitivity, and specificity rates for the correct evaluation of T stage are 81 to 92%, and 94 to 97%, respectively [18]. The overall accuracy for N staging is 74% when used alone [19].

The utility of EUS in superficial cancer is, however, controversial. A meta-analysis of 19 studies and 1019 patients with superficial ESCC, demonstrated an overall accuracy of 93% of EUS for T staging. However, the heterogeneity of this meta-analysis was high due to multiple factors including the location and type of lesion, method and frequency of EUS probe and the experience of the endosonographer [20]. In our experience, the EUS accuracy to differentiate T1a from T1b lesions is suboptimal and we give preference to magnifying endoscopy. We utilize EUS in superficial ESCC when the findings of magnifying endoscopy are unclear, aiming at a more accurate T and N staging. This occurs mainly in lesions with type B2 vessels, when magnifying endoscopy accuracy to predict the invasion of muscularis mucosa and SM1 has been found to be only 55.7% [21••]. Furthermore, in stenotic advanced tumors EUS evaluation may not be technically possible.

In a multicenter study involving 100 patients with stenotic esophageal neoplasms, the EUS scope could not traverse the stricture in 70, with all such patients ultimately staged with T3Nx or T4Nx disease. This fact has reduced the enthusiasm for tumor dilation to facilitate complete EUS staging [22].

Cross-sectional studies

The evaluation for distant metastasis includes commonly computed tomography (CT) and/or positron emission tomography (PET-CT). These methods can also provide complementary information for T and N staging.

As most superficial ESCC are not detected on CT or PET-CT, these modalities should not be routinely performed. [23]. In cases that a submucosal invasion depth is suspected, it is crucial to have an accurately stage to select the best approach. Therefore, in this scenario, the evaluation of locoregional involvement and the presence of metastasis by cross-sectional studies is mandatory,

Treatment strategy

The initial treatment strategy should take into consideration a multidisciplinary assessment of the patient's condition and preferences, disease extension, presence of metastasis, tumor size, location, depth of invasion, and circumferential extent.

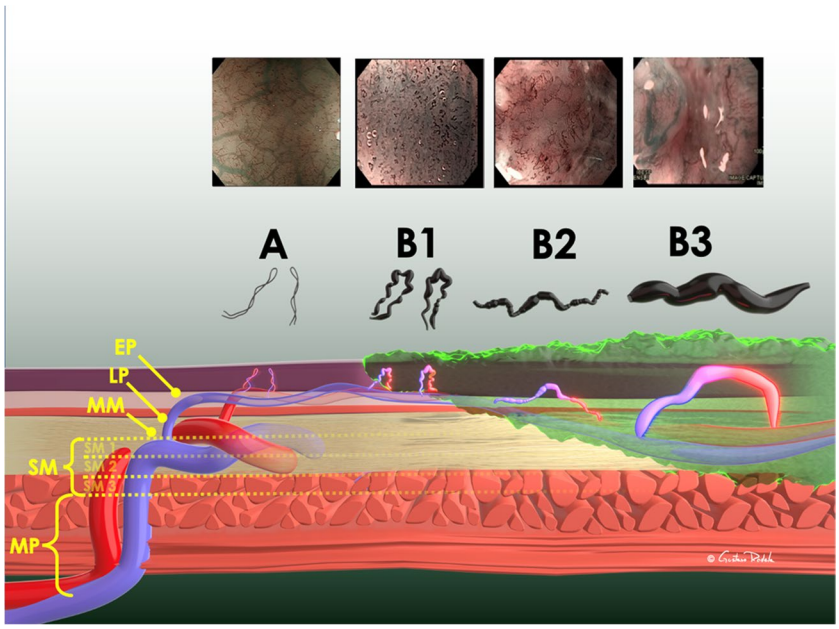


Fig. 4 JES classification

Among these factors, cancer invasion depth is the most important factor which shows a correspondence between risk of metastasis and curability.

Indications of endoscopic resection

As described above, T1 (superficial) lesions are defined as those invading the mucosa (T1a) and submucosa (T1b). These lesions have been further categorized into six subtypes (M1, M2, M3 and SM1, SM2, SM3, respectively) according to the profundity.

Esophageal lesions classified as M1 (intraepithelial) or M2 (invades the lamina propria) have virtually no risk of lymph node involvement. This risk increases to 8 to 18% in lesions that invade the muscularis mucosa (M3), to 11–53% in lesions that invade the submucosa up to 200 μm (SM1), and 30–54% in deeper lesions (SM2) [17••]. Additional features implicated in the risk of lymph node metastasis are vascular invasion, size of the lesion and histological differentiation degree.

Due to the negligible risk of lymph node involvement, mucosal lesions classified as M1 and M2 (IPCL type B1) are absolute indications for endoscopic resection (ER). Lesions clinically classified as invading muscularis mucosa (M3) or superficial submucosa (SM1) can be also treated by endoscopic resection. However, considering the real risk of lymphonodal metastasis, they are considered relative indication. Lesions with endoscopic features of deep submucosa invasion (more than 200 μm or≥SM2) are correlated with a risk of lymph node metastasis at a frequency of about 50% and should be managed a priori, similarly to advanced carcinomas [24••, 25••, 21••, 26]. Endoscopic resection of submucosal carcinomas is discussed below.

It is important to again highlight that the endoscopic diagnosis of the invasion depth has some limitations, mostly on extensive lesions and lesions with IPCL Type B2, where the JES classification accuracy is only 55.7% [21••]. Accordingly, the assessment of the histological diagnosis of resected specimens is crucial considering the potential inconsistencies between endoscopic and pathologic diagnosis. In patients with tumors histologically categorized as M1 or M2 after resection, close follow-up is mandatory. Meanwhile, subjects with lesions reaching the muscularis mucosa (M3) or superficial submucosa (SM1) and positive vascular invasion, an additional treatment (surgical or chemoradiotherapy) is usually required, as stated by most of the guidelines. Lesions showing deep submucosal invasion, regardless lymphovascular metastasis, require additional treatment with esophagectomy or chemoradiotherapy [26]. The decision between surgery and chemoradiotherapy should be made according to the patient's clinical status (Table 1).

Endoscopic resection techniques

Endoscopic mucosa resection (EMR) and endoscopic submucosal dissection (ESD) are established as less invasive techniques for curative resection of superficial neoplasms of the esophagus (Fig. 5). Currently, ESD is assumed

to be the best choice to treat superficial ESCC, given that it enables higher rates of *en bloc* resection with a lower recurrence rate and improved survival [27–30]. In a multicenter retrospective study that included 148 tumors (80 treated by EMR and 68 by ESD), the recurrence rate was significantly higher in the EMR group (23.7 versus 2.9%) and 5-year recurrence-free survival rates were worse (73.4 versus 95.2%) [31] compared to the ESD group. While no randomized trials are available, available evidence shows that the long-terms outcomes of ESD and surgery are comparable. In a retrospective study, 116 T1a ESCC larger than 2 cm treated either surgically ($n = 47$) or endoscopically ($n = 69$) were compared. The overall survival rate was similar (97.1% vs 91.5%, $p = 0.18$), but procedure-related complication occurred more often in the surgical group (8.5% vs. 0, $p < 0.05$) [32].

In addition to the depth of invasion, circumferential extent of the lesion should be taken into consideration because of the high risk of stenosis of lesions involving more than 75% of the circumference after ESD. Nevertheless, more effective prophylaxis with oral and/or intravenous corticosteroids have recently been developed with promising results [33, 34]. Furthermore, dilatation is another effective method to prevent stenosis following post ESD stenosis. In terms of outcomes, complete resection rates following circumferential esophageal ESD is reported to be as high as 100% and curative resection rate, 70% [35–37].

Submucosal tumors

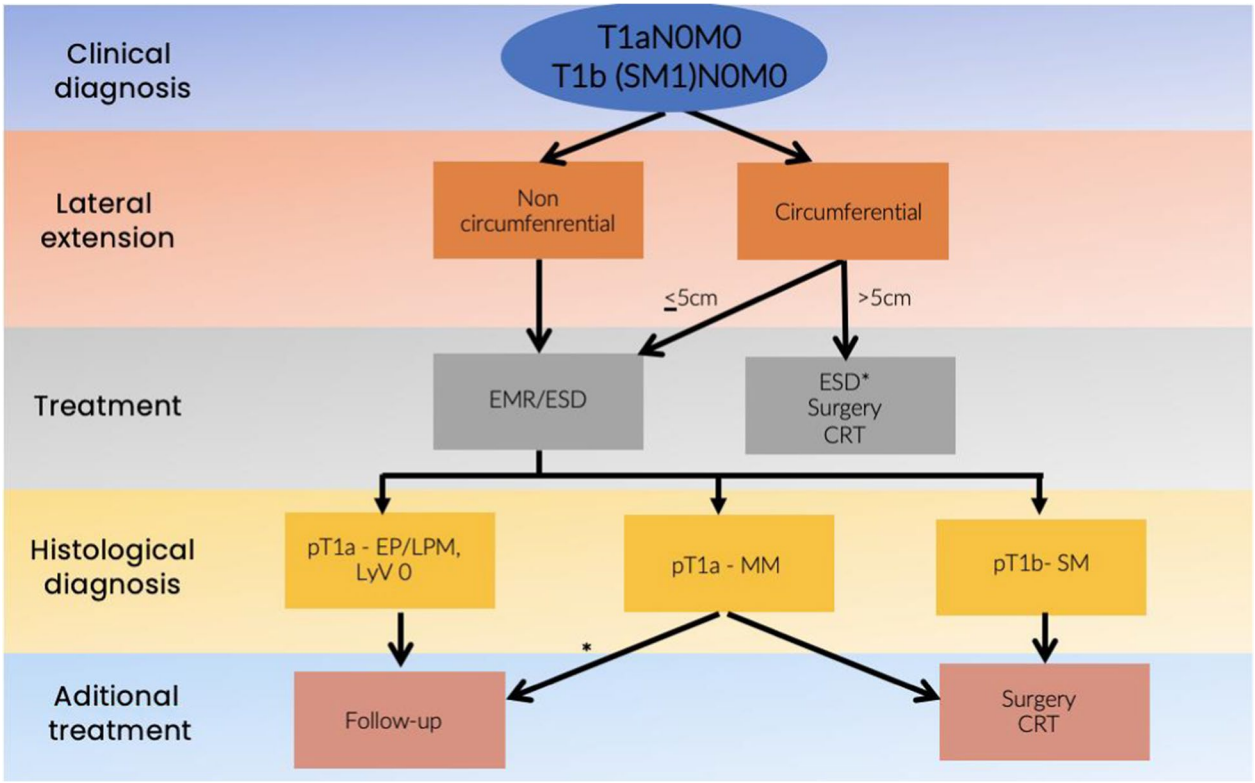
New approaches for the treatment of submucosal tumors are gaining interest and recently research has been conducted to evaluate the outcomes of endoscopic resection and surgery for pT1 ESCC.

A Japanese trial [38••] evaluated the efficacy of ER followed by chemoradiotherapy. Patients with histologically M3 lesions, positive vascular invasion and negative resection margins or histologically SM invasion and negative resection margin underwent prophylactic chemoradiotherapy; patients with SM invasion and positive resection margin underwent definitive chemoradiotherapy. Favorable results were obtained in the prophylactic chemoradiotherapy group, with a 3-year overall survival rate of 90.7% (90% CI: 84.0–94.7%). This study showed that even when ER is not curative, a good prognosis can be expected if additional chemoradiotherapy is administered. A multicenter study involving 7 western centers reported a 25% residual/recurrence rate of esophageal cancer (both adenocarcinoma and ESCC) after ESD for T1b lesions (hazard ratio, 6.25; 95% confidence interval, 1.29–30.36; $p = 0.023$). Those findings corroborate the limitation of ER for esophageal cancer with submucosa invasion [39•].

Advanced tumors (T2 or more)

For patients with locally advanced disease, endoscopic therapy does not play any role in management and esophagectomy with or without chemoradiation

Table 1. Therapeutic strategy for superficial ESCC. Adapted from Ishiara et al. Dig Endosc, 2020.



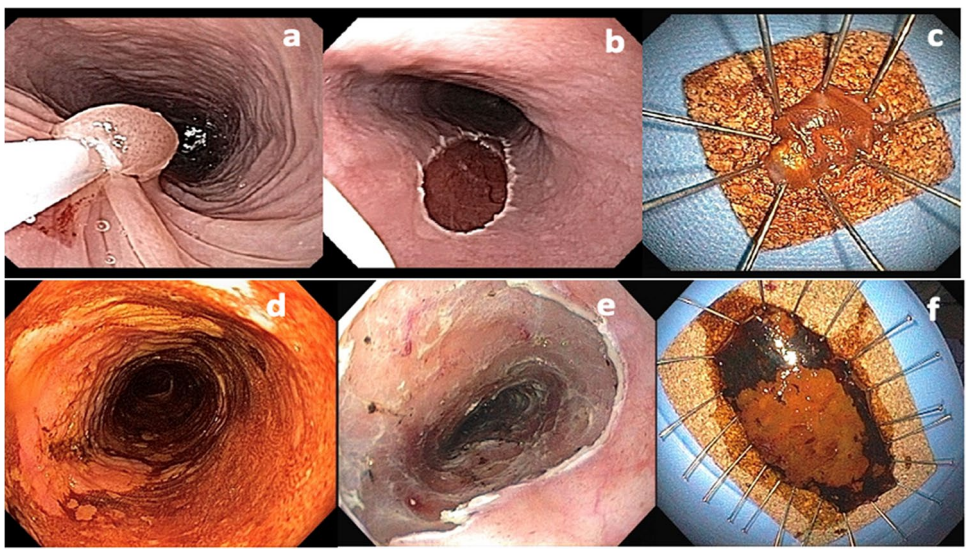


Fig. 5 Esophageal endoscopic mucosal resection/EMR (**a**, **b**, and **c**) and submucosal dissection/ESD (**c**, **d,** and **e**)

remains the standard therapy. For non-surgical subjects or T4b tumors, chemoradiation should be offered as a definitive treatment after a multidisciplinary discussion.

Conclusion

The diagnosis of superficial ESCC diagnosis continues to increase worldwide. The endoscopic prediction of the depth of tumor invasion is the most important factor in selecting the treatment strategy and optimizing outcomes. The endoscopic resection techniques of EMR and ESD have become the most important treatment of superifical ESCC and provide high curative rates and organ preservation. Outcomes of endoscopic resection for submucosal tumors show promise and may be similar to surgery, but significant limitations still exist and it is role is currently limited to very select cases.

Author Contribution

All authors contributed to the study conception and design. The first draft of the manuscript was written by Renata Nobre and Fauze Maluf-Filho commented on previous versions, read and approved the final manuscript.

Declarations

Competing Interests
Renata Nobre declares that she has no conflict of interest.
Fauze Maluf-Filho declares that he has no conflict of interest.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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