Diagnosis and therapy of esophageal squamous cell dysplasia and early esophageal squamous cell cancer

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Abstract

Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) comprise the majority of esophageal cancers, and they differ from each other in several aspects. While the incidence of EAC is increasing in the West, ESCC is still the predominant cancer type worldwide. Squamous dysplasia is considered to be a premalignant lesion to ESCC; however, the exact probability and timeline of malignant transformation are not known, hence the lack of guidelines for management of such lesions. ESCC carries a poor prognosis if not detected early, so there has been a trend towards early detection and treatment. Diagnostic modalities include endoscopic ultrasound, white light endoscopy, non-endoscopic methods such as biomarkers, etc. Early diagnosis can identify a subset of patients who could benefit from less invasive endoscopic eradication therapies. This review aims to discuss the different modalities for diagnosis and treatment of early esophageal squamous lesions, including the newer endoscopic therapies, and comparison of different techniques.

Key words: esophageal squamous cell carcinoma; esophageal squamous cell dysplasia; endoscopic resection; radiofrequency ablation

Introduction

Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) comprise the majority of primary esophageal cancers. These two types of cancer differ from each other in several aspects, including but not limited to pathogenesis, risk factors, epidemiology and management. ESCC arises from the stratified squamous epithelium of the esophagus and predominantly involves the middle third, while EAC arises from columnar cells that have replaced the squamous epithelium and is more distal, in the distal third of the esophageal body and the esophago–gastric junction [1].

ESCC is the predominant type of esophageal cancer worldwide. However, in the West, the incidence of EAC has been steadily on the rise. Esophageal cancers occur 20–30 times more commonly in China than in the United States. An esophageal ‘cancer belt’, mainly squamous cell cancer, extends between northeast China and the Middle East [2].

Low-grade intraepithelial neoplasia (LGIN) and high-grade intraepithelial neoplasia (HGIN), collectively referred to as squamous dysplasia, are considered to be the premalignant lesions to ESCC. However, the exact probability and timeline for malignant transformation are not clearly known. When these lesions are diagnosed during routine endoscopic examination, either as part of screening or evaluation of symptomatic patients, a question arises as to whether to opt for the surveillance strategy or treatment.

In China, intraepithelial neoplasia of the esophagus is graded according to the proportion of the epithelial thickness containing neoplasia: 1/3 (low grade), 2/3 (moderate grade) and 3/3 (high grade) [3]. Depending on the depth of invasion,
superficial ESCC is classified into Tis (carcinoma in situ/high-grade dysplasia), T1a (tumor invades the lamina propria or muscularis mucosae) or T1b (tumor invades the submucosa) [4]. Lymph-node metastases occur in 3–6% of T1a cases, while they may occur in 21–24% of T1b cases [5]. Hence, the two stages also differ in the mode of treatment and prognosis. Since, according to 2011 National Comprehensive Cancer Network (NCCN guidelines), squamous cell dysplasia (SCD) and T1a esophageal cancer can be treated endoscopically, accurate staging is important. The clinical path of SCD and ESCC is complex and multifaceted (Figure 1). Tumor staging often requires a combination of endoscopic techniques and imaging (Table 1), while the histologic classification of its various stages is complex and frequently a subject of debate (Table 2).

### Diagnosis

#### Endoscopy

Although white light endoscopy (WLE) is likely the first step of evaluation in many patients, this is usually followed by other advanced techniques to improve detection rates, specifically high-resolution endoscopy (HRE) and electronic chromoendoscopy. Superficial ESCC, especially Tis and T1a ESCC, sometimes lacks any changes in appearance and early detection by conventional WLE is difficult. Disappearance of the vascular network in the mucosa, uneven surface and tiny white coating are indications of the possible presence of superficial ESCC [6]. When identified by WLE, SCD may be flat, erythematous, nodular, plaque-like or erosive-appearing [7].

During endoscopic evaluation, m1 cancer typically shows very slight depressions with a smooth surface and reddening. Sometimes fine granular changes are seen. These changes may also become delineated as unstained lesions by endoscopic Lugol’s solution or toluidine blue-iodine double staining. Dark blue dots, spots or reticular staining are frequently identified in m2 cancers. In cases with m3 or sm1 cancer, coarse granular changes, small nodular elevations or slightly deeper depressed areas in the m1 and m2 lesions suggest sites of deeper invasion [8].

#### Endoscopic ultrasonography (EUS)

Imaging modalities like computed tomography (CT), MRI or Positron emission tomography (PET) scan cannot differentiate between layers of the esophageal wall and cannot distinguish T1a and T1b lesions, but EUS provides accurate information regarding depth of infiltration [5]. In a study comparing CT and EUS in staging of esophageal cancer, CT scan identified lymph-node involvement in only 23% of patients, while EUS detected in 83% of patients, thus restaging the disease in 13 patients and altering the management plan. Two tumors that were not detected by CT due to early disease were also detected by EUS [9].

In a systemic review and meta-analysis evaluating the diagnostic accuracy of EUS in differentiating T1a and T1b lesions, the pooled sensitivity, specificity, and positive and negative likelihood ratios of EUS for T1a staging were 0.85 (95% confidence interval (CI), 0.82–0.88), 0.87 (95% CI, 0.84–0.90), 6.62 (95% CI, 3.61–12.12) and 0.20 (95% CI, 0.14–0.30), respectively. For T1b staging, these results were 0.86 (95% CI, 0.82–0.89), 0.86 (95% CI, 0.83–0.89), 5.13 (95% CI, 3.36–7.82) and 0.17 (95% CI, 0.09–0.30), respectively, thereby concluding that EUS has good accuracy in staging superficial esophageal cancers [10].

In a retrospective analysis involving 72 patients with pathologically confirmed T1a and T1b lesions, the accuracy of EUS for diagnosing T1 lesions was 93.2%. However, the accuracy of diagnosing T1a vs T1b lesions was approximately 65%, thus concluding that EUS—as a technique—needs to be improved in order to be more accurate in this regard. This study also showed that the accuracy of diagnosis varied according to the tumor site and length, and that accuracy was lower for lesions in the middle portion compared to the upper and lower portions of the esophagus [5].

Another prospectively collected EUS database of patients undergoing esophagectomy showed similar results for EUS for patients with early cancer. The sensitivity and specificity of EUS for determining the true pathologic staging were poor for early-

| Table 1. Staging of esophageal squamous dysplasia/cancer |
|--------------------------------------------------------|
| Patients undergo high-resolution endoscopy with Lugol’s staining (1–3%) and electronic chromoendoscopy |
| Targeted biopsies are obtained of all visible lesions and Lugol voiding lesions |
| The macroscopic type of lesions is classified according to the Paris classification |
| Endoscopic ultrasound is performed to exclude deep tumor infiltration and regional lymph-node involvement; suspicious lymph nodes are sampled by fine needle aspiration |
| Patients with esophageal squamous cell cancer undergo a CT scan of the chest and abdomen |

| Table 2. Histologic classification of esophageal squamous dysplasia/cancer |
|---------------------------------------------------------------|
| No intraepithelial neoplasia |
| Indefinite for intraepithelial neoplasia |
| Low-grade intraepithelial neoplasia |
| High-grade intraepithelial neoplasia (high-grade intraepithelial neoplasia; T1m1) |
| Esophageal squamous cell carcinoma |
| Infiltrating into lamina propria (T1m2) |
| Infiltrating into the muscularis mucosae (T1m3) |
| Infiltrating the superficial third of the submucosa (T1sm1) |
| Infiltrating the middle third of the submucosa (T1m2) |
| Infiltrating the deep third of the submucosa (T1m3) |
| Resection specimens are assessed for: |
| Infiltration depth |
| Radical resection (vertical resection margin) |
| Grade/Tumor differentiation |
| Lymphatic/vascular invasive tumor growth |

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Figure 1. The clinical path of esophageal squamous dysplasia and cancer. ER, endoscopic resection; ESD, endoscopic submucosal dissection; XRT, external radiation therapy.
stage esophageal cancers. Of the EUS-staged N0 lesions, there were pathologically positive lymph nodes in 15% (2/13) of T1a lamina propria lesions and 18% (5 of 28) of T1a muscularis mucosa lesions [11]. All these studies indicate a need for more accurate diagnostic methods and advancements in the current techniques.

The combination of submucosal saline injection with EUS has been shown to improve accuracy rates [5]. In one study, the accuracy of submucosal saline injection combined with EUS for staging T1a or T1b was 86.7%—better than that using EUS alone (60.0%) [12].

**Chromoendoscopy**

One of the reasons esophageal squamous cell lesions are not detected early is the tendency to evaluate esophagus using only WLE, which may not detect subtle dysplastic lesions [13]. Biologic endoscopy refers to techniques that provide deeper insight into the target lesion or allow visualization of lesions that are not otherwise visible [14]. Iodine staining of squamous epithelium was first described in 1933 for the detection of early squamous cell carcinoma [15]. Lugol’s iodine is a glycophilic substance that binds the normal glycogen-containing cells of squamous epithelium, staining it mahogany brown. Precancerous and neoplastic tissues with reduction of cytoplasmic glycogen granules appear as mustard-yellow or saffron-colored after Lugol’s iodine staining [14]. The accuracy of the ‘pink color sign’ for diagnosing early ESCC has been verified by a quantitative analysis, and the sensitivity and specificity were 88% and 95%, respectively [16]. The value of Lugol chromoendoscopy to detect dysplastic lesions in high-risk patients has been evaluated in several studies, particularly in cohorts of patients with squamous cell carcinoma of head and neck who are prone to a secondary esophageal carcinoma.

In a study assessing the risk of developing secondary esophageal cancer in patients with squamous cell carcinoma of the head and neck based on the presence of Lugol voiding lesions (LVLs) on chromoendoscopy, 55% of the patients with many irregular-shaped multifluid LVLs had synchronous second primary ESCC [17]. In another prospective observational study of 326 patients with primary head and neck cancer, a standard endoscopy was performed, followed by Lugol’s chromoendoscopy. While chromoendoscopy and standard WLE were equivalent in the diagnosis of advanced and invasive esophageal cancer, standard endoscopy diagnosed 55% of HGIN, in comparison to chromoendoscopy that detected 100% [18].

Another study involving 190 asymptomatic high-risk subjects with history of alcohol abuse revealed that the esophagus of those with LVLs had an eight-fold higher chance of revealing dysplasia than those with uniform staining. The authors concluded that Lugol’s iodine endoscopy should be added to conventional upper gastrointestinal endoscopy in patients at risk for ESCC [19]. However, iodine is an irritant and may cause a choking sensation or chest pain in sensitive individuals. Further, even if the pink color sign is used, it is difficult to differentiate between LGIN and HGIN without histology [20].

**Confocal laser endomicroscopy (CLE)**

CLE is a recently introduced imaging technique that combines confocal laser microscopy and endoscopy. Once a suspicious area of the mucosa is identified by WLE/HRE, a contrast agent (i.e. fluorescein) is given intravenously and in vivo confocal endomicroscopic examination is then performed by placing the probe against the targeted area of the mucosa [21]. CLE enables clear visualization of the vascular mucosal networks. Normal squamous epithelium has regular intraepithelial papillary capillary loops (IPCLs) directed towards the luminal surface. In superficial ESCC, dilated IPCLs are visible at the upper layer of the squamous mucosa [22].

In a single-center prospective trial, the use of CLE for ESCC had a sensitivity, specificity and accuracy of 94.6%, 90.7%, and 92.3%, respectively [23]. While Lugol’s iodine chromoendoscopy requires biopsy to improve its diagnostic accuracy, combining this method with CLE was shown to be successful in some studies. In one such study, CLE scanning when used in LVLs could easily find typical lesions, thus reducing the procedure time and the false-positive and false-negative rate. Thus, directly progressing to endoscopic resection without further biopsy procedures may become the standard after further research into CLE in the future [24]. However, differentiation between grades of intraepithelial neoplasms by CLE is not yet possible with the currently available staining techniques [21].

**Electronic chromoendoscopy**

Narrow-band imaging (NBI) is an optical technique that applies narrow-band spectrum filters to enhance the visualization of mucosal and submucosal microvascular patterns. The filtered wavelengths penetrate the superficial layers of the mucosa, thus highlighting the capillary network, and deeper levels, enhancing the sub-mucosal vessels [25]. Superficial squamous neoplasms in the esophagus are frequently enhanced as ‘brownish areas’ by non-magnified NBI endoscopy without the need for either magnification or Lugol’s staining procedure [26]. In a multi-center prospective randomized controlled study, NBI endoscopy was found to be better than WLE in the detection and diagnostic accuracy of ESCC [27]. Morphological change of the IPCLs observed by magnified NBI endoscopy is a useful marker for identifying superficial squamous neoplasms. HGIN or invasive squamous cell carcinoma of the esophagus can be identified by severe morphological change of the IPCLs [28]. In a study that assessed the potential of NBI imaging in differentiating between mucosal high- and low-grade neoplasia, or non-neoplastic lesions, the sensitivity and specificity of NBI for differentiating mucosal high-grade from low-grade neoplasia were 85% and 79%, respectively [29]. However, there have also been studies demonstrating no added benefit to this technique. A multi-center prospective trial compared WLE alone vs WLE followed by magnifying endoscopy (ME) with NBI and found that ME-NBI showed no additional benefit to WLE for diagnosis of invasion depth of superficial ESCC [30]. Another interesting study put forth the suggestion that it would be better to evaluate depth of invasion of ESCC with both ME-NBI and EUS before deciding on a management strategy [31].

A post-hoc analysis of randomized controlled trials proposed an ‘ideal’ endoscopic technique as two steps: first is the assessment for the presence of elevated or depressed lesions and brownish areas using NBI non-ME; second is the evaluation of all suspicious lesions for the presence of various shapes and proliferation under NBI-ME. This way, endoscopists can detect and discriminate ESCC from inflammation from LGIN easily, quickly and accurately [32].

One study compared probe-based CLE and dual-focus NBI in LVLs and found that probe-based CLE tended to provide higher specificity, positive predictive value and accuracy than dual-focus NBI for the diagnosis of ESCC. Perhaps the trend of lower specificity of dual-focus NBI in this study was possibly because
of the interference from Lugol’s staining on the interpretation of IPCLs [33].

Autofluorescence imaging (AFI)

AFI produces real-time pseudo-color endoscopic images based on natural tissue reflectivity. This method may identify lesions, including malignancies, by detecting differences in tissue natural fluorescence, thus revealing early carcinomas, not yet detectable by conventional WLE [34]. However, in a study comparing NBI and AFI, the former was found to be superior [35]. While this technique—combined with NBI and HRE, called tri-modal imaging—has been studied well in Barrett’s esophagus and early EAC, further studies are required for its use in SCD and early cancer.

Other techniques

A study that screened freshly resected specimens from patients with a series of aminopeptidase-activatable fluorescence probes indicated that dipeptidylpeptidase IV (DPP-IV) is specifically activated in ESCC and would be a suitable molecular target for detection of esophageal cancer. Therefore, these authors designed, synthesized and characterized a series of DPP-IV-activatable fluorescence probes. When the selected probe was topically sprayed onto endoscopic submucosal dissection or surgical specimens, tumors were visualized within 5 min and, when the probe was sprayed on biopsy samples, the sensitivity, specificity and accuracy reached 96.9%, 85.7% and 90.5%, respectively [36].

Biomarkers

Immunohistochemistry

Increased p53 expression in the pathogenesis of ESCC indicates that p53 overexpression is involved in the initial stages of carcinogenesis and contributes to the development of precancerous lesions [37]. One study reported positively stained p53 in 87% of ESCC, 80% of dysplasia and not in normal individuals [38]. Another study found that positive protein expression of p53, Carcinoembryonic antigen (CEA) and CA19-9 was associated with esophageal carcinogenesis and reported a moderate association between these three biomarkers; when combined, the specificity for diagnosis of esophageal lesions was 88.8%, which was the target level for screening high-risk individuals, and the sensitivities markedly increased with the severity of the esophageal lesions. Based on these results, these authors proposed that an endoscopic screening program that detects these three biomarkers would be beneficial in identifying high-risk individuals with esophageal diseases [39].

In another comparative study between high-risk and low-risk populations in China, the number of p53 positive cells/mm2 in ESCC from a high-incidence area was almost five-fold higher than ESCC from a low-incidence area (p < 0.01), indicating that p53 protein accumulation is an important early biomarker for identifying high-risk subjects for ESCC [40]. Other immunohistochemical markers related to vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), E-cadherin, etc. are also being studied.

Autoantibodies

Carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1) and squamous cell carcinoma antigen (SCCA) are the most commonly used non-invasive detection biomarkers in ESCC detection [41], but their accuracies have not been satisfactory. Many studies have shown that serum autoantibodies against tumor-associated antigens (TAAs) could be used as potential biomarkers in the detection of several types of cancer, such as hepatocellular carcinoma, lung cancer and colorectal cancer. Compared to other biomarkers, including TAAs themselves, autoantibodies have many appealing features, including high stability and persistence in serum samples, that make them ideal non-invasive biomarkers. However, the frequency of autoantibodies against single TAA is relatively low in cancer patients. Using a customized TAAs array can significantly improve diagnostic performance. Zhang et al. studied a panel of nine TAAs and found that an optimized model with four TAAs has a high diagnostic performance for ESCC detection, especially for early-stage ESCC [42].

MicroRNA-based markers

MicroRNAs are a group of single chain non-coding Ribonucleic acids (RNAs) that participate in cell differentiation, proliferation, metabolism and apoptosis. Circulating plasma and serum microRNAs are potential markers for non-invasive cancer diagnosis [43]. A favorable role for miR129 in esophageal cancer was noted by Kang et al., making it a promising biomarker [44]. Another study found that levels of plasma miR-16, miR-21, miR-185 and miR-375 correlated with patients who presented with ESCC. The plasma level of miR-16 has the potential to support tumor staging, while a higher level of plasma miR-16 and miR-21 suggests a poor prognosis in ESCC patients who have received radiotherapy [45]. Overall, this is an evolving diagnostic tool and several mRNA markers have been studied, including miR-373, miR-1297, miR-613, etc., to name a few [46-48].

Recently, long coding RNAs have also been studied as a biomarker and as a potential target for therapy for ESCC [49].

Cancer screening

Unlike colorectal cancer, there are no current guidelines and no approved method for ESCC screening in the West. However, in many countries in the East, where prevalence is high, there has been a trend towards cancer-screening programs. A national esophageal cancer-screening and early treatment program has been initiated since 2005 in rural areas in China with a high esophageal cancer incidence [50]. A population-based cancer registry had been established in Linzhou, China, for decades; therefore, Linzhou city was selected as a pilot area to conduct a population-based screening program. Endoscopy with Lugol’s staining and indicative biopsies for residents aged 40-69 years old was used to identify precursor lesions and early cancer. A recent population-based case-control study found that endoscopic screening was of benefit to individuals 50 years or older, with no differences between men and women. The study did not find screening to be of value in the 40- to 49-year-old group [51]. A recent study, based on economic parameters and management, made a comparison between 12 different existing screening methods in high-risk/high incidence of ESCC in China.

The two key strategies to be followed in order to ensure cost-effective programs taking into account the acceptance of the population and the distribution of wealth in different regions were: (i) screening once throughout life and starting at the age of 50, following up after 5 years of detecting low-grade dysplasia and 3 years after intermediate-grade dysplasia, for areas with...
limited access to healthcare, impoverished and with a difficult track the target population economy; and (ii) screening three times throughout life, starting at the age of 40, and monitoring low-grade dysplasia and intermediate-grade dysplasia as above, for areas with appropriate access to health care, and economies that are more advanced and a good monitoring program by the target population [52].

In a study of 1345 subjects in Japan who underwent routine endoscopy, dysplasia was found in 3%. Due to lack of prospective studies, the relationship between dysplasia and cancer in this region is still unknown [53,54]. In an Italian study where 1906 participants were invited for screening endoscopy, only 302 showed up, and the prevalence of dysplasia was 6%. It was concluded that developing non-endoscopic screening methods and screening individuals with one or more risk factors might improve these rates [55].

With the discovery of several biomarkers, non-endoscopic screening methods for ESCC are being studied. Although, as of now, no approved method has been developed, the ideal method of screening may very well be a combination of invasive and non-invasive techniques, suited to a particular population and based on risk factors [56].

### Endoscopic eradication therapy

Treatment options for SCD and early-stage ESCC include endoscopic therapies (such as resection and/or ablation) and surgery and the decision to choose one over the other depends on accurate staging. According to NCCN guidelines, in the absence of lymph-node metastasis, lymph-vascular invasion or poor differentiation grade, T1a disease can be treated with full endoscopic resection. Lesions beyond T1b disease should be treated with esophagectomy. In cases of T1a disease with unfavorable characteristics, the choice between endoscopic resection plus ablation vs esophagectomy should be made on an individual basis [57].

Because of their risk for invasive disease, MGIN and HGIN are considered clinically significant lesions, and justify therapy in order to prevent progression to cancer. However, fewer studies are available regarding approach to LGIN lesions. One randomized study divided patients with LGIN into treatment (endoscopic resection) and observation groups. Concerning the percentages of esophageal lesions that changed from serious conditions into slight conditions (namely from high-grade to low-grade intraepithelial dysplasia, basal cell hyperplasia, esophagitis and normal mucosa), there was a significantly linear trend relationship between the treatment group and control group. In down-staging of dysplasia grade, the total percentage for the 52 cases (82.5%) in the treatment group was significantly higher than that for the 32 cases (49.2%) in the control group. Further, in patients who remained at the LGIN grade or had upstaging of their dysplasia, the proportions of the change were significantly different between the two groups [58]. Because the study did not report any malignant transformation, longer follow-up will likely be necessary to determine this. High-grade dysplasia and early cancer have traditionally been treated with esophagectomy but, with the recent advent of improved endoscopic resection and ablation techniques as well as earlier recognition, minimally invasive strategies are being increasingly preferred. In one study, 80% of surgeries performed for HGIN were deemed unnecessary [59]. A proposed approach to endoscopic eradication therapy is presented in Table 3.

| Table 3. Steps in multimodality endoscopic eradication therapy for early ESCC |
|---|
| Use high-resolution endoscope (HRE, preferably with digital chromoendoscopy) |
| Record esophageal landmarks with still endoscopic images (at 1-cm intervals) or video |
| EMR or ESD of non-flat USL (type 0-IIa or 0-IIc) in order to render the mucosa flat and enable histology; for lesions suspicious for submucosal invasion, ESD is preferred |
| At 2 months after resection, perform HRE with Lugol’s staining and biopsies to determine eligibility for ablation, such as: |
| ≥1 unstained lesion (LVL) upon HRE with Lugol’s staining |
| Squamous HGIN or mucosal ESCC upon biopsy of ≥1 LVL |
| Completely flat (Paris type 0-IIb), slightly elevated (type 0-IIa) or slightly depressed (type 0-IIc) USLs |
| Endoscopic resection specimens demonstrating ≤T1m3, negative deep resection margins, G1-G2 tumor differentiation, no lymphatic/vascular invasive growth |
| ≤T1m2 immediately prior to ablation |
| Negative EUS and CT scanning of chest and abdomen |

ESCC, early esophageal squamous cancer; HRE, high-resolution endoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; USL, unstained lesion; LVL, Lugol voiding lesion; HGIN, high-grade intraepithelial neoplasia; EUS, endoscopic ultrasound.

### Endoscopic resection

Studies on ESCC show that it is reasonable to consider endoscopic therapy for lesions invading the mucosa (m1) and lamina propria (m2). In one series, mucosal carcinomas of the m1 and m2 layer showed no lymph-node metastasis. When the tumor infiltrated the m3 layer, the lymph-node metastasis varied from 0 to 5.3%. When carcinoma infiltrated the submucosa, the probability of lymph-node metastasis increased from 8.7% in the sm1 layer to 37.5% in the sm3 layer. Hence it was concluded that m1 and m2 infiltration are ‘absolute’ indications of endoscopic treatment and m3 infiltration and sm1 infiltration are ‘relative’ indications, but they need to be followed up closely; surgical treatment is needed when the infiltration reaches sm2 or sm3 [60]. The Japanese Esophageal Society guidelines indicate that endoscopic resection is recommended in patients with ESCC limited to the intraepithelial (m1) and lamina propria layer (m2) without vascular invasion or lymph-node metastasis [61]. However, there have been studies that extended these indications to include m3 or sm1, with favorable outcomes.

### Endoscopic mucosal resection (EMR)

Staging and therapeutic EMR of early ESCC is a widely used technique that involves a submucosal injection of the suspected lesion creating a fluid cushion, thereby a safety margin for cauterity and cutting. In a similar technique, the ligation-assisted EMR, which is the most commonly used technique in the US, a cap with single- or multiple-band ligators is first attached to tip of the endoscope; after application of suction to the lesion, creation of a pseudopolyp that can then be removed using a specimen of 2 cm in diameter corresponding to one-third to one-half of the circumference of the esophageal wall is obtained for both staging and therapy purposes [63]. Earlier studies after EMR have reported 5-year survival rates up to 95%. In a study of 142 patients with early esophageal cancer,
there was no local or distant metastasis in a follow-up of 9 years [64].

In a prospective evaluation of long-term outcomes in patients undergoing EMR for ESCC involving muscularis mucosa or submucosa carrying an increased risk of lymph-node metastasis, the overall 5-year survival rates in the extended EMR group surgical resection groups were, respectively, 77% and 84%, and there was no significant difference between survival distributions. Cause-specific survival rates at 5 years in extended EMR and surgical resection groups were, respectively, 95% and 93.5%. Survival curves for the groups were similar [65]. In patients with m3 or sm1 ESCC, tumors that have lymphatic invasion, larger superficial size and wider lamina muscularis mucosa invasion are associated with a high risk for lymph-node metastasis. EMR might be indicated for the treatment of patients with m3 or sm1 ESCC without these characteristics [66].

Another study followed 219 patients who underwent EMR and found local recurrence in 8.3%. All patients with recurrence had received piecemeal resection and 67% of them were detected by endoscopic surveillance within 1 year. All recurrences were treated again using EMR and their pathology revealed mucosal cancer. Metachronous esophageal cancer was found in 11% of all EMR cases; 65% of those were detected 1–3 years after resection. Metachronous esophageal cancer after EMR was frequently found among cases with esophageal mucosa, which has many small-unstained areas. Malignant lesions were found in 33 cases (15%) of all patients treated by EMR synchronously and 37 (17%) metachronously [67].

Endoscopic submucosal dissection (ESD)

ESD involves dissection of the submucosal layer after a circumferential incision around the lesion. This allows en bloc resection of the lesion, irrespective of its size or shape. Glyceroil or diluted sodium hyaluronate solution is used to separate mucosa from the muscle layer as an injection solution, since they remain in situ for longer time periods to allow resection. A carbon dioxide insufflation system is useful to prevent mediastinal emphysema [68].

In one of the earliest studies of ESD in ESCC, the en bloc resection rate in 58 patients was 100%, and tumor-free lateral and basal margins (R0 resection) was 78% (45/58). Of 40 lesions in 31 patients with node-negative tumors, one lesion reoccurred after 6 months, and it was treated by a second ESD procedure [69]. Since then, larger studies with longer duration of follow-up have been conducted. In a systematic review and meta-analysis of 21 studies, involving 1152 patients who underwent ESD for early ESCC, the pooled en bloc resection rate was 99% (95% CI, 99–100%). Stratified by tumor size, en bloc resection rates did not show any difference. The pooled en bloc resection rate was 99% (95% CI, 98–100%) for large tumors (diameter > 25 mm) and 100% (95% CI, 99–100%) for small tumors. The pooled R0 resection rate was 90% (95% CI 87–93%); 85% (95% CI, 80–90%) for large tumors and 92% (95% CI, 87–93%) for small tumors (p < 0.001). The authors concluded that ESD was effective for early ESCC and that tumor size affected the R0 rate. Park et al. published their 10-year experience of ESD for ESCC in a single center in which endoscopic and oncologic outcomes were evaluated. The overall en bloc resection (resection of a targeted lesion in one piece), complete resection (tumor-free lateral margins > 2 mm and tumor-free vertical margins > 0.5 mm on histologic examination) and curative resection (absence of a poorly differentiated component, lymphovascular invasion, perineural invasion or submucosal invasion in en bloc resected case) rates were 93.9%, 89.7% and 77.0%, respectively. Adverse events occurred in 33 patients (12.6%) and included bleeding (1.5%), perforation (4.6%) and stricture (6.5%). The 5-year overall and disease-specific survival rates were 89.7% and 100%, respectively. The overall recurrence rate was 13.0%, including 15 synchronous and 11 metachronous squamous epithelial neoplastic lesions during a median follow-up period of 37 months. Most recurrences occurred within 16 months of the initial ESD. Although there is no established guideline for the follow-up schedule after resection, endoscopic surveillance during the first 2 years after endoscopic resection is essential for the early detection of local recurrence as well as synchronous or metachronous lesions [70].

Similar results were obtained in a multi-center retrospective study where the en bloc resection and complete resection rates were 96.7% (95% CI, 94.4–98.1%) and 84.5% (95% CI, 80.5–87.8%), respectively. Follow-up data (median 35 months) showed significant differences in overall survival (p = 0.03) and recurrence-free survival (p < 0.01) rates between patients with curative and non-curative resections [71]. However, in another large cohort study of ESD in ESCC patients, although the en bloc resection rate was 93%, the complete resection rate was 78%—lower than other studies. One of the reasons given for this was that the definition of complete response in the study was stricter compared to others [72].

Comparison between ESD and EMR

Several studies have compared ESD with mucosal resection for early ESCC, and many concluded that ESD, although technically more difficult, is more effective than EMR. In a meta-analysis that included eight studies, en bloc resection rate for ESD was significantly higher at 97%, compared to 49% in the EMR group; curative resection rates were 92% and 52%, respectively. While the rates of stricture and bleeding were comparable in both groups, perforation rates were higher in ESD [73]. However, in another meta-analysis, ESD had better resection rates, but was found to be more time-consuming and with higher bleeding and perforation rates than EMR [74]. ESD also allows resection of larger lesions, indicated by longer endoscope length, larger specimen size and more lesions extending for more than half the circumference of esophagus when compared with EMR [75].

ESD was also compared to EMR using a transparent cap and two-channel EMR separately, and similar results with higher curative resection rates were found for ESD [76]. As compared to EMR, ESD also carries a better disease-free survival (Figure 2) [77].

Figure 2. Local recurrence rates with en bloc resection during ESD vs EMR in piecemeal fashion. Adapted from Ishihara et al., Gastroint Endosc 2008;67:799-804.
Follow-up and treatment after endoscopic resection

The NCCN guidelines for follow-up after endoscopic resection in patients with Tis or T1a cancer recommend that, after endoscopic resection for Tis lesion, upper endoscopy should be carried out at 6-month intervals for 1–2 years, and then annually thereafter for 3 years. For T1a lesions, the recommendation is for endoscopy every 3 months during the first year, every 4–6 months for the second year, then annually for 3 years [78]. However, these recommendations are not supported by clinical trials and mainly apply to Barrett’s esophagus and EAC. The clinical practice guidelines for esophageal cancer proposed by the European Society for Medical Oncology (ESMO) recommend that appropriate action should be taken only upon the development of symptoms or other abnormalities because evidence showing that regular follow-up can improve outcomes is lacking [79].

Esophagectomy with lymph-node dissection is the mainstay treatment after incomplete endoscopic resection or invasive tumor depth because of the risk of local recurrence and lymph-node metastasis. However, esophagectomy is associated with increased mortality, high surgical risk and reduces the patient’s quality of life. Patient’s age, performance status and various concomitant diseases should be considered prior to offering additional surgical therapy. Radiotherapy and/or chemotherapy are possibly valid alternative options with similar oncologic outcomes to surgical resection, with fewer complications than surgical resection [80].

Complications of endoscopic resection

Perforation is rare with EMR, but is slightly more common in ESD. Perforations during endoscopic closure may be treated by complete endoscopic closure with endoclips. Delayed perforations, however, may require surgical treatment [81]. Post-ESD stricture/stenosis occurs more often after entire circumferential esophageal ESD with muscle-layer damage and ≥5 cm of longitudinal mucosal defect length [82]. Esophageal strictures can cause dysphagia, decreased quality of life and may contribute to aspiration pneumonia; they are usually treated by endoscopic balloon dilation, with repeated sessions if needed. For strictures resistant to dilation, therapies like intra-lesional steroid injection, temporary esophageal stenting and systemic steroid use have been tried with some success. The dose and duration of oral prednisone are not clearly defined, but up to 30 mg daily for 8 weeks have been used [83]. Technical advancements with tissue-engineered cell sheets for prevention and treatment of strictures are also under study [84,85].

Mucosal ablation

Radiofrequency ablation (RFA)

RFA makes use of the radiofrequency energy waveform that is delivered upon contact with the target epithelium, resulting in water vaporization, coagulation of proteins and tissue necrosis. The instrument (HALO) consists of a radiofrequency generator and either a balloon catheter or several focal ablation catheters. RFA has been studied extensively in the treatment of Barrett’s esophagus with or without dysplasia and early EAC, with excellent results, but it has also been used in early flat-type HGIN and early ESCC [86]. In a prospective case series, patients with at least one esophageal LVL using Lugol’s chemoendoscopy and squamous HGIN/ESCC upon biopsy were included. In the case of non-flat LVLs, endoscopic resection was performed for staging and in order to render the mucosa flat. After endoscopic resection and subsequent circumferential RFA, chromoendoscopy was repeated every 3 months with focal RFA of residual LVLs. All 13 patients achieved a complete response after a median of two RFA sessions (interquartile range, one to three sessions). RFA-related complications included two mucosal lacerations (at the endoscopic resection scar) and one intramural hematoma, none requiring therapy. Endoscopic resection-/RFA-related complications were three stenoses. There were no recurrences during a median follow-up of 17 months [87].

In another prospective cohort study, 29 patients with early ESCC (MGIN, HGIN and early flat-type esophageal carcinoma) underwent circumferential RFA creating a continuous treatment area including all LVLs. At 3 months after one RFA session, 86% of patients (25/29) had a complete response. At 12 months, 97% of patients (28/29) had a complete response. There was no neoplastic progression. There were four strictures, all dilated to resolution [88]. However, in a study examining outcomes from the UK RFA registry, the results were not as promising. Complete reversal dysplasia was 50% at protocol completion, although dysplasia was later reversed in two further patients following more RFA sessions; 20% of patients progressed to invasive disease after only one session of RFA and were then offered chemo-radiotherapy. Two additional patients who were treated with an initial circumferential RFA followed by an EMR at follow-up endoscopy progressed to invasive cancer at protocol end. This suggests that a single RFA treatment might even be considered as a staging procedure. Early failure would identify patients who should be treated with more conventional modalities. The failure rate may also indicate that these patients may have been understaged and may in some cases harbor more aggressive neoplasia at baseline. Also, the median number of ablations in this study was one compared to other studies [89]. Of note, Lugol’s chemoendoscopy (1–2% solution) is required in all cases of Esophageal squamous cell neoplasia (ESCN). Given the caustic effect of this solution, RFA should not be performed within 2 weeks after Lugol’s chemoendoscopy, since the Lugol’s solution has been shown to make the epithelium vulnerable to superficial bleeding, which hampers visibility and the proper application of RFA [90].

Comparison between RFA and ESD

Although in many countries RFA is the treatment of choice for Barrett’s esophagus, its use in squamous dysplasia and early cancer would require a more conservative approach. In a study comparing RFA and ESD for early flat large ESCC, although both were found to be equally effective for short-term treatment, RFA did not allow pathology to evaluate curability after ablation, and this might be a concern in ESCC, due to unpredictability of invasiveness. In the same cohort, 14 out of 47 patients had histological upgrading in the final resected specimens compared with pre-ESD biopsies. Further, four of them were found to have lymphovascular invasion and additional treatment was suggested. These results highlight the limitations of relying on endoscopic biopsies to stage patients and determine who benefits from RFA [91].

Argon plasma coagulation (APC)

APC is a non-contact method of thermal ablation, in which argon gas is ionized and used to conduct electrical current to the target tissue. The power settings are much higher than for typical use, with settings between 60–90 W at 1–2L/min [92]. In 17 patients with T1a and T1b lesions who could not undergo surgery or endoscopic resection due to comorbidities, APC showed reasonable success, with only two recurrences, which were again treated by APC [93]. Similar success rates were obtained in
a study involving 19 patients (5 LGIN, 12 HGIN, early ESCC): 95% had complete response at 12-month follow-up [94]. In a 5-year follow-up of 160 patients with precancerous lesions and 11 patients with early cancer, APC was found to be more effective in the former group, with a low survival rate in the latter [95].

Photodynamic therapy (PDT)

PDT is a laser treatment involving a photosensitizer such as porphyrin and light of a specific wavelength. The photosensitizer is administrated orally or intravenously and is localized to a target neoplasia. Treatment occurs when the photosensitizer is activated by endoscopically applied laser directly to the target lesion. Damage to tissue occurs through cell necrosis, apoptosis and ischemia [96,97]. PDT has been mainly used for palliative therapy in advanced esophageal cancers, or salvage therapy after failure of chemotherapy; however, there have been few studies on treatment for early cancer. In an early study, Savary et al. treated 24 patients with Tis or T1a ESCC, and the cure rate was 84% over a mean follow-up period of 2 years [98]. In another study of 38 patients with median follow-up of 64 months, complete remission was achieved in 87% patients. All patients had large unifocal lesion or multifocal lesions that were too large to be resected endoscopically [99]. PDT is known to have significant side effects. In a randomized multi-center study, 94% of patients treated with PDT for Barrett’s high-grade dysplasia developed photosensitivity (69%) and stricture formation (35%) [100,101].

Cryotherapy

Cryotherapy is designed to deliver a high rate of thermal energy transfer via a catheter in a non-contact manner. There is rapid delivery of thermal energy by using liquid nitrogen at ~196 °C effectively snap-freezing the tissue, resulting in immediate cell death. Spray cryotherapy preserves the underlying tissue architecture and extracellular matrix, producing a favorable wound response with little evidence of long-term scarring [102]. Greenwald et al. described 17 patients with dysplasia and early cancer who underwent cryotherapy showing complete elimination of HGIN in 94% patients. Impressive response was also seen in three patients with stage I cancer and four with intramucosal carcinoma who were not candidates for traditional therapies, with all seven patients showing complete regression of cancer and six showing complete regression of dysplasia [103]. In another study evaluating 79 cryotherapy patients, endoscopic complete response was achieved in 61.2% overall and 75% of mucosal cancers with a mean follow-up of almost 1 year in the T1 group [102].

Focal Cryoballoon Ablation therapy (FCBA) comprises a through-the-scope (TTS) catheter with a conformable balloon that obviates the need for sizing, a handle and a small disposable cryogen cartridge. The balloon is simultaneously inflated with nitrous oxide from the cartridge, resulting in an oblong cryo-penetrative area of 3 cm². FCBA is easy to use and requires no capital equipment. FCBA of Barrett’s esophagus is also quite effective. In a recent study with 30 patients, complete eradication of intestinal metaplasia and dysplasia was observed in 100% of the completely ablated areas without stricture formation [104]. Another study of nine patients with esophageal squamous neoplasia (seven with focal disease and two with circumferential) reported squamous regeneration in 100% with no LVLs on at least one follow-up biopsy (pathological complete response 100%) at a mean follow-up of 165 days and without serious adverse events. Five patients had self-limited pain not requiring narcotics and two developed inflammatory strictures requiring dilation [105].

Multimodality approach

In patients with multifocal ESCC, a combination of endoscopic resection and ablation may increase the success rate. In a series of six consecutive patients with multifocal ESCC, the treatment comprised EMR using the cap technique or ESD, in combination with RFA. The main outcome measure was complete tumor eradication after therapy and during the follow-up period. Using such an approach, complete eradication of cancer was achieved in all patients during follow-up. No major adverse events occurred [106].

Conclusions

If not detected earlier, ESCC carries a very poor prognosis. Hence, newer and more efficient diagnostic methods would help in early diagnosis and accurate staging is key, since endoscopic eradication therapy can be considered for intraepithelial (m1) and lamina propria layer (m2) without vascular invasion or lymph-node metastasis. The field of endoscopic therapy for ESCC is still evolving and, with several new methods in practice, there is scope for combination treatment too, although more randomized controlled trials are needed.

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