Early Squamous Neoplasia of the Esophagus: The Endoscopic Approach to Diagnosis and Management

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ABSTRACT

Considerable focus has been placed on esophageal adenocarcinoma in the last 10 years because of its rising incidence in the West. However, squamous cell cancer (SCC) continues to be the most common type of esophageal cancer in the rest of the world. The detection of esophageal SCC (ESCC) in its early stages can lead to early endoscopic resection and cure. The increased incidence of ESCC in high-risk groups, such as patients with head and neck squamous cancers, highlights the need for screening programs. Lugol’s iodine chromoendoscopy remains the gold standard technique in detecting early ESCC, however, safer techniques such as electronic enhancement or virtual chromoendoscopy would be ideal. In addition to early detection, these new “push-button” technological advancements can help characterize early ESCC, thereby further aiding the diagnostic accuracy and facilitating resection. Endoscopic resection (ER) of early ESCC with negligible risk of lymph node metastases has been widely accepted as an effective therapeutic strategy because it offers similar success rates when compared to esophagectomy, but carries lesser morbidity and mortality. Endoscopic submucosal dissection (ESD) is the preferred technique of ER in lesions larger than 15 mm because it provides higher rates of en bloc resections and lower local recurrence rates when compared to endoscopic mucosal resection (EMR).

Key Words: Early esophageal squamous cell carcinoma, electronic imaging, endoscopic mucosal resection, endoscopic submucosal dissection, Lugol’s iodine, radio frequency ablation, synchronous head and neck cancer, virtual chromoendoscopy

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Esophageal cancer is the eighth most common cancer in the world, with an estimated incidence of 456,000 cases and 400,000 deaths in 2012.\(^1\) Considerable focus has been placed on esophageal adenocarcinoma in the last ten years due to its rising incidence in the West. However, squamous cell cancer (SCC) continues to be the most common type of esophageal cancer in the rest of the world. The “esophageal cancer belt” extends from the Middle East to northeast China, with the highest-risk of developing esophageal SCC (ESCC).\(^2-4\)

Patients with advanced ESCC, where the carcinoma extends into the submucosal layer (T1b–T4), are often symptomatic on presentation. In contrast, patients with superficial ESCC, where the carcinoma is limited to the mucosa (T1a), are often asymptomatic.\(^5,6\) Patients with advanced ESCC carry a poor 5-year survival rate of 54.9%. On the other hand, early ESCC conveys a higher 5-year survival rate of up to 80%.\(^7,8\) Such patients can be cured by endoscopic resection of the early squamous neoplasia. This highlights the importance of early detection and treatment of ESCC without the need for radical therapies such as chemoradiotherapy or esophagectomy. This review aims to summarise the current evidence for the endoscopic diagnosis and treatment of early squamous neoplasia.

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Risk factors
Adequate awareness of the risk factors leading to the development of ESCC leads to better identification of patients who would be at high risk of developing ESCC. An alcohol intake of more than 12.5 g/day increases the relative risk (RR) of ESCC to 2.62 when compared to abstinence. The RR increases to 5.54 when the daily alcohol intake exceeds 50 g.\(^{10-12}\) Cigarette smoking carries an RR of 2.63 when compared to nonsmokers. The RR of developing ESCC is exponentially increased with the combination of alcohol consumption and cigarette smoking (RR 8.05).\(^{13}\) An increasingly recognized risk factor of ESCC is the concurrent diagnosis of head and neck SCC. The incidence of esophageal squamous cell neoplasia in patients with head and neck cancer in screening studies range between 9.4 and 14%.\(^{14,15}\) This high incidence of synchronous ESCC calls for an urgent need of a screening program in this population.

Endoscopic detection and characterization of early esophageal squamous cell cancer
On standard non-magnified endoscopy, intra-mucosal cancer commonly appears flat with little impact on the contour of the mucosal surface (Paris classification 0-IIa, IIb, IIc) making it difficult to detect [Figure 1]. On the other hand, advanced cancer is easily seen as elevated (0-I) or excavated (III) or a combination of the two.\(^{16}\)

Lugol’s iodine chromoendoscopy
The detection of early ESCC is augmented by the use of Lugol’s iodine staining. Lugol is a vital stain that contains iodine and is actively taken up by glycogen found in normal esophageal squamous cells. The cells in areas of esophageal neoplasia are glycogen poor, resulting in a reduced uptake of the iodine in Lugol dye, appearing as Lugol voiding areas, otherwise known as the ”pink-color sign” [Figure 2].\(^{17,18}\) The sensitivity and specificity of Lugol chromoendoscopy in detecting early ESCC ranges from 96 to 100% and 57 to 64%, respectively, making it the gold standard detection test.\(^{14,19}\) Lugol dye spray in the esophagus can lead to minor adverse events such as hypersensitivity to iodine, laryngitis, pneumonitis, chest discomfort and nausea. Spraying the esophagus with sodium thiosulphate following the administration of Lugol dye has been shown to reduce chest discomfort usually experienced with Lugol chromoendoscopy.\(^{20}\)

**ELECTRONIC ENHANCEMENT TECHNIQUES**

**Narrow band imaging**
Narrow band imaging (NBI) is an optical image enhancing technique that provides a detailed assessment of the mucosal surface and microvasculature within the mucosa of the gastrointestinal tract.\(^{21}\) The mucosal vessel pattern in squamous mucosa was described by Inoue et al. as intrapapillary capillary loops (IPCL). They described five different IPCL patterns corresponding to normal squamous mucosa to various grades of squamous neoplasia [Table 1].\(^{22-24}\) NBI with magnification has been shown to diagnose the depth of invasion with an accuracy of 76.8 to 85.2%.\(^{25-27}\) However, a well-powered multicenter prospective study carried out by Ebi et al. was not able to demonstrate an improved accuracy in diagnosing the depth of invasion of ESCC using NBI with magnification when compared with high definition white light alone.\(^{28}\)

Blue Laser Imaging is a new optical image enhancement technology by Fujinon that uses laser light to transmit light with wavelengths of 410 and 450 nm. This provides for narrow band observation of mucosal vascular and surface patterns similar to NBI [Figure 3].

![Figure 1: Early esophageal squamous cell neoplasia seen on standard white light endoscopy](image1)

![Figure 2: (a) 0-Ia esophageal squamous cell neoplastic lesion is clearly seen on white light endoscopy. (b) The addition of Lugol dye reveals multiple Lugol voiding areas indicating further areas of squamous neoplasia](image2)

![Figure 3: (a) NBI with DualFocus demonstrating type V2 intrapapillary capillary loop pattern. (b) BLI with zoom demonstrating Type V3 intrapapillary capillary loop pattern](image3)
Endoscopic diagnosis and management of early ESCC

Fujinon intelligent color enhancement

FICE is a post-acquisition based image enhancement technique.\(^{(29)}\) It is used to delineate tumor margins and degree of invasion by examining IPCLs.\(^{(10)}\) Li et al. performed a prospective study comparing FICE and magnified FICE against Lugol chromoendoscopy and magnified Lugol chromoendoscopy. They found that the positive rates of early ESCC detection for FICE

### Table 1: Intrapapillary Capillary Loop (IPCL) pattern classification

| IPCL   | Schematic drawing | Pattern description                                      | Pathology       |
|--------|-------------------|----------------------------------------------------------|-----------------|
| Type I | ![Type I Schematic](image1) | Smooth running, small diameter capillaries                | Normal          |
| Type II| ![Type II Schematic](image2) | Dilatation and elongation of Type I capillaries           | Inflammation    |
| Type III| ![Type III Schematic](image3) | Normal IPCL within a brownish lesion                      | Inflammation/LGN|
| Type IV| ![Type IV Schematic](image4) | Increased vessel caliber and elongation of IPCL toward the epithelial surface | LGN/HGN         |
| Type V1| ![Type V1 Schematic](image5) | Non-uniform, irregularly dilated IPCL                     | m1              |
| Type V2| ![Type V2 Schematic](image6) | Elongation of Type V1 capillaries                         | m2              |
| Type V3| ![Type V3 Schematic](image7) | Loss of loop configuration and spread to horizontal plane | m3/SM1          |
| Type Vn| ![Type Vn Schematic](image8) | Vessel caliber 3x larger than V3 – new tumour vessels     | SM2             |

(Modified from reference 24,25). IPCL pattern classification from IPCL type I to type V-1 is used for the tissue characterization of flat lesions (red outline). IPCL pattern classification from IPCL type V-1 to type VN reflects cancer infiltration depth
and Lugol chromoendoscopy were similar, 92.6% vs. 88.9% ($P = 0.642$). The addition of magnification endoscopy did not significantly improve the detection rates of 96.3% vs. 92.6%, respectively ($P = 0.556$).[31]

**i-scan**

i-Scan is a post-acquisition image enhancement technology designed to enhance surface and vascular patterns. There is limited published data on the use of i-Scan in the detection and assessment of ESCC. However, in a single-center prospective non-inferiority sequential trial, the detection rate of early ESCC was 10.4% when compared to 12.9% detection rate with Lugol chromoendoscopy.[32]

Most studies highlight the difficulties in the detection of early ESCC with white light alone. However, enhancement techniques described above significantly improve the detection rate of early ESCC. We highly recommend the use of these techniques for the detection and characterization of early ESCC. Lugol chromoendoscopy remains the gold standard, but there is an urgent need of head-to-head studies comparing the detection rates of early ESCC using Lugol’s versus virtual chromoendoscopy. This will help to decide if Lugol’s can be replaced by virtual chromoendoscopy, which has a better safety profile.

**Endoscopic management of early esophageal squamous cell cancer**

Neoplasia restricted to the mucosa or with limited invasion into the superficial part of the submucosa is defined as early, irrespective of the risk of lymph node involvement. However, clinicians managing ESCC need to have a very clear understanding of the different stages of this cancer and the risk of lymph node metastasis [Table 2].[33‑37]

**Endoscopic resection vs. surgery/radical chemoradiotherapy**

Endoscopic resection (ER) of early ESCC with negligible risk of lymph node metastases has been widely accepted as an effective therapeutic strategy because it offers similar success rates when compared to esophagectomy but carries lesser morbidity and mortality.[38,39] Historically, surgery has been viewed as the gold standard treatment for patients with esophageal carcinoma. However, esophagectomy is associated with a high risk of complications with a morbidity of 20–50% and a mortality rate of 3–11%, depending on volume of procedures.[40‑42] Moreover, it has been shown that patients with early ESCC have a much greater mortality rate post-esophagectomy than those with early esophageal adenocarcinoma, 11% vs. 5%.[41]

Because of the significant risk of lymph node metastases in lesions extending to m1 and beyond, curative endoscopic resection should only be offered to those patients with early ESCC, extending as far as the m2 layer.

**Endoscopic mucosal resection vs. endoscopic submucosal dissection**

Experience of endoscopic resection for early ESCC began in the early 1990s in Asia; since then, techniques have significantly developed. Initial experience came from the strip biopsy technique, which was further refined with the suck-and-cut technique.[44] A randomized control trial comparing cap-assisted versus multi-band endoscopic mucosal resection (EMR) found that both methods are equally safe and efficacious; with multi-band EMR being significantly more cost-efficient and faster technique.[45] However, the en-bloc resection rates are low with large lesions requiring piecemeal resection making adequate histological assessment difficult. EMR has been demonstrated to have recurrence rates of 4–26%.[46‑48]

Endoscopic submucosal dissection (ESD) has the advantage of being able to provide an en-bloc resection regardless of lesion size or submucosal fibrosis, allowing accurate histological staging at the expense of procedure duration, steep learning curve, and greater risks.[49] Ono et al.[50] treated 107 early ESCC in 84 patients, achieving a 100% en-bloc resection rate, with only 1 patient suffering from recurrence, and a perforation rate of 4%. They were able to achieve a 100% 5-year survival rate in patients whose lesions were limited to the m2 layer.

Takahashi et al. published a retrospective review of 300 consecutive patients undergoing ER for early ESCC. One hundred and eighty four patients underwent EMR and 116 underwent ESD.[51] They demonstrated that the en-bloc resection rates (53.5% vs. 100%) and local recurrence rates (9.8% vs. 0.9%) were significantly better in the ESD group when compared with the EMR group. However, they also demonstrated that when EMR is performed for lesions <15 mm, no local recurrence was seen, further supporting the report from Ishihara et al.[52] The overall efficacy of ESD in the management of early ESCC was demonstrated in a meta-analysis of 15 studies encompassing

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**Table 2: Risk of lymph node metastases according to depth of invasion of SCC**

| Depth          | Lymph node risk % |
|----------------|-------------------|
| Low/high grade dysplasia | 0                 |
| m1             | 0                 |
| m2             | 0                 |
| m3             | 8-18.2            |
| sm1            | 17-24             |
| sm2            | 21-28             |
| sm3            | 37-44             |
776 ESD-treated lesions.\[53\] In this study, the pooled estimate of en-bloc resection rate was above 95% and the complete resection rate was 89%.

Careful selection of cases is key for an optimum outcome following endoscopic resection. In both their studies, Mizuta and Ono et al. found that lesions with a greater depth of invasion (>pT1m2) led to higher stricture rates. Lesions and resection margins extending over 59% and 71% of the esophageal circumference, respectively, were also found to be strong predictors of post-ESD esophageal stricturing.\[54,55\] However, post-ESD esophageal stricturing can be successfully managed by endoscopic dilatation with or without the use of locally injected or orally administered steroids.\[56,57\]

We would, therefore, suggest that ER is performed with curative intent in patients with ESCC limited to m2 layer. Lesions <15 mm can be effectively treated with either cap-assisted EMR or ESD, but lesions >15 mm should be treated by ESD where the expertise is available.

ER offers a real potential of cure in patients with low grade dysplasia, high grade dysplasia, m1 and m2 cancer with well differentiation and without lymphovascular invasion. In cases of M3 or SM1 cancer, ESD could be considered as an alternative to radical therapy (surgery or chemoradiotherapy) when histology shows R0, well-differentiated cancers without lymphovascular invasion, especially in elderly patients or in patients with significant comorbidities.\[58\]

Radio frequency ablation for esophageal squamous cell cancer
Radiofrequency ablation (RFA) for esophageal neoplasia involves the application of heat generated by an energy waveform. The heat is delivered to a depth of 800 μm via a bipolar electrode array to the esophageal mucosa. The electrode is located either on the outside of a balloon, on an articulating platform attached to the distal end of an endoscope, or on the end of a through-the-scope catheter. The role of endoscopic RFA in the management of Barrett’s dysplasia is well established. However, similar success has not been demonstrated with RFA in the management of early ESCC.

Several studies have demonstrated variable success of RFA in treating early ESCC. In a prospective single-center cohort study of Chinese patients, 96 patients with early flat (type 0-IIb) neoplasia (maximum depth of T1m2) underwent RFA.\[59\] In a 12-month follow-up, 81% of patients had complete response having had a mean number of 1.9 ± 0.8 RFA procedures. In contrast, a prospective cohort study from eight tertiary centers in the United Kingdom found that, in a 12-month follow-up period, only 50% of patients achieved complete eradication of early ESCC. Furthermore, 30% of patients progressed to invasive cancer at 1 year.\[60\]

There are several drawbacks in treating early ESCC with RFA. This technique does not allow for tissue acquisition and post-treatment analysis. Therefore, the histological examination for depth of invasion and lymphovascular involvement cannot be made. Unlike Barrett’s, ESCC is more aggressive, and therefore, under treatment of inappropriately selected patients can be catastrophic.\[55\] We feel that the role of RFA in the management of ESCC is questionable and should only be performed under special circumstances.

CONCLUSION
ESCC is the major type of esophageal cancer worldwide; it can be readily treated provided it is detected early. Several high-risk groups have been recognized but patients with SCC of the head and neck are at a very high risk of developing ESCC. We highly recommend a screening program where one does not exist. White light endoscopy alone is insufficient to detect early ESCC and this is best done using Lugol’s chromoendoscopy, which remains the gold standard technique. Safer techniques, such as virtual chromoendoscopy, on the other hand would be ideal, but studies comparing the sensitivity and specificity of the two techniques are sorely lacking. Early diagnosis of ESCC leads to early endoscopic curative therapy. Here, EMR can be carried out for lesions <15 mm and ESD for lesions >15mm.

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Conflicts of interest
There are no conflicts of interest.

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