

Endoscopic diagnosis and management of early squamous cell carcinoma of esophagus

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Abstract: In recent years, diagnosis of early squamous cell carcinoma (SCC) of the esophagus has been increasingly emphasized. Utilization of image enhanced technology such as narrow band imaging (NBI) and magnification endoscopy allowed detailed examination of the esophageal mucosa. Different patterns of intrapapillary capillary loops (IPCL) have been proven to accurately diagnose and predict the depth of invasion of the tumors. In addition, the application of endoscopic submucosal dissection (ESD) has enabled safe en bloc resection of esophageal lesions. Promising results of ESD have been published and ESD is now the standard of therapy in early SCC of esophagus.

Keywords: Esophageal neoplasms; narrow band imaging (NBI); endoscopic mucosal resection

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Introduction

Squamous cell carcinoma (SCC) remains the most common histological subtype of esophageal cancers in Asia, in particular China and Japan. The disease is associated with poor prognosis and most patients were diagnosed at a late stage when curative treatment is no longer possible. For patients with localized disease, surgery provides a chance of cure but is also associated with significant surgical morbidity and mortality. Much progress has been made in the past decade to improve endoscopic detection of early esophageal cancers. Potential curative endoscopic therapy has also been developed to reduce the morbidity associated with the treatment for esophageal cancers. This article aims to provide an updated review on the latest development of endoscopic diagnosis and treatment of early esophageal SCC.

Endoscopic detection and diagnosis of esophageal SCC

Conventional white light imaging (WLI) endoscopy with endoluminal biopsy has been the gold standard for detection and diagnosis of esophageal cancers. For patients presenting with symptoms such as dysphagia, the tumors are likely of significant size and conventional WLE would be adequate for diagnosis. However, when the endoscopy was performed as a screening or surveillance, the sensitivity of WLE in detecting early lesions would be much lower.

Chromoendoscopy with Lugol's iodine has been utilized as the preferred method of screening in high-risk patients since early 2000s. The agent stains to glycogen in normal squamous epithelium, giving off its brown color under white light endoscopy. In glycogen depleted epithelium such as dysplasia, the mucosa would

appear “unstained”. In one early prospective study of 225 adults from Linxian, China who suffered from esophageal dysplasia or carcinoma, unstained mucosal areas after iodine application had sensitivities of 63%, 93%, 96%, and 100% for identifying mild, moderate, severe dysplasia and early invasive carcinoma, respectively (1). Its use among patients with head and neck cancers had been validated in multiple prospective studies (2-4). However, the use of Lugol’s iodine is associated with a number of problems. First, the solution irritates the esophageal mucosa and can cause chest pain or discomfort. It could also cause hypersensitivity reaction, leading to mucosal damage of the esophagus and stomach (5-8). Second, Lugol chromoendoscopy has low specificity for esophageal neoplasia, leading to a high false positive rate and the need for unnecessary biopsies (1-4). The need for application of the dye also would also potentially increase the procedural time.

Narrow band imaging (NBI) technology was introduced in the early 2000 to facilitate endoscopic diagnosis of gastrointestinal lesions. By using filter of two specific peak wavelengths (415 and 540 nm), the mucosal surface and vascular pattern of the gastrointestinal tract could be enhanced, allowing endoscopists to detect and characterize lesions (9). The system is incorporated now with ordinary endoscopes and could be easily activated by pressing a button. Two different approaches of utilizing NBI technology have been described for screening of esophageal lesions: the non-magnifying endoscopy for detection of lesion and the combination of magnifying endoscopy for characterization of these lesions.

Using non-magnifying NBI endoscopy, normal esophageal mucosa would appear green in color, while in the presence of lesions there would be brownish discoloration. This is an invaluable tool for screening of abnormal lesions in the esophagus as well as the hypopharyngeal area. The NBI mode could be switched on when the endoscope is inserted into the oral cavity. Upon passage of the upper esophageal sphincter examination of the esophagus could be completed without changing of the mode. Conventional white light endoscopic examination of the stomach is currently still the gold standard due to the limitation of the brightness with the NBI technology. After complete examination of the stomach, the esophagus could be examined again using WLI. However, at the level of the cervical esophagus, the NBI mode should be switched on again to avoid missing lesions at this region during scope insertion.

Multiple prospective studies have shown that non-

magnified NBI examination is superior to WLI in detection of early esophageal lesions for screening of high-risk patients (10-13). The performance of non-magnified NBI and Lugol chromoendoscopy were similar in these studies. With the addition of magnified endoscopy, characterization of surface vascular pattern by observing the intrapapillary capillary loops (IPCL) would help to increase the accuracy of NBI endoscopy. In a multicenter randomized study by Muto et al, NBI with magnification was compared with WLI as screening modality for patients with head and neck SCC (14). Among 320 enrolled patients, 212 esophageal superficial cancers were detected. NBI with magnifying endoscopy achieved a significantly higher sensitivity (97.2% vs. 55.2%), accuracy (88.9% vs. 56.5%), and NPV (72.8% vs. 20.3%) than WLI endoscopy. A recent meta-analysis including 11 cross sectional studies and 1 randomized study with a total of 1,911 patients, found no difference in sensitivity between NBI and Lugol chromoendoscopy for diagnosing early esophageal cancer (15). In addition, NBI endoscopy also had a higher specificity comparing to Lugol chromoendoscopy (per lesion analysis 82% vs. 37%). Although Lugol chromoendoscopy is still considered as the gold standard, NBI endoscopy should be regarded as a reliable alternative option for screening of early esophageal cancers, with potential additional benefit of less patient discomfort and shorter procedural time.

Evaluation of IPCL

Inoue *et al.* first reported his observation of esophageal mucosal microvascular pattern utilizing magnifying WLI endoscopy (16,17). A progressive change in the IPCL was also noted with increasing destruction of the mucosa by neoplastic transformation of the esophagus. Characterization of IPCL using WLI is particularly challenging due to poor contrast of the vessels comparing with background pinkish mucosa. The use of NBI greatly facilitates observation of changes in the microvascular pattern of the esophagus by selectively enhancing the brown colored IPCL. According to the original classification, a total of 5 subtypes of IPCL were identified (18,19).

IPCL I & II—normal esophagus or esophagitis

Using NBI endoscopy with magnification, IPCL can be visualized readily as brown colored loops. Occasionally flow of individual red blood cells within the IPCL could be

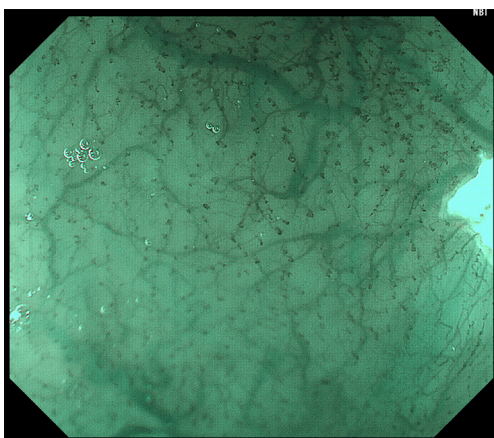


Figure 1 Normal intrapapillary capillary loops (IPCL); Inoue type 1, JES type A.

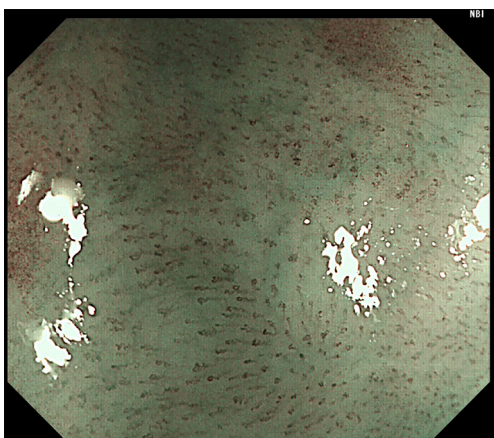


Figure 2 Some brownish discoloration but minimum change in microvascular pattern. IPCL Inoue type III, JES type A.



Figure 3 Presence of brownish discoloration with associated dilatation of IPCL. Inoue type IV, JES type B1.

observed as well. In normal esophageal mucosa, there would not be any color change of the mucosa on NBI, i.e., absence of brownish discolored area. The IPCL would appear as small open coiled loops with a diameter of ~7–10 nm (IPCL-I) (Figure 1). With inflammatory change of the esophagus, there would typically be dilatation and elongation of IPCL over the margin of the lesion (IPCL-II).

IPCL III & IV—tissue atypia or early neoplastic change

Lesions with brownish discoloration on NBI should be further evaluated with magnifying endoscopy. Those with minimal microvascular proliferation can be categorized as IPCL type III (Figure 2). These lesions are most likely regional atrophic mucosa or low-grade intraepithelial neoplasia, and regular endoscopic surveillance should be performed. IPCL type IV is characterized by dilatation and elongation of the vessels, representing high-grade intraepithelial neoplasia (Figure 3).

IPCL V1–3 and V_N—from carcinoma in-situ to submucosal invasive carcinoma

In carcinoma in situ, four characteristic changes of IPCL in the esophageal brown discolored areas have been observed (IPCL V1): dilatation, meandering, caliber change and non-uniformity in the appearance (Figure 4). Progressive destruction of the IPCL would occur in deeper extension of the esophageal carcinoma. In IPCL V2 corresponding to M2 invasive carcinoma, the morphology of IPCL demonstrated additional elongation of the vessels in the vertical plane (Figure 5). IPCL V3 is characterized by loss of the loop configuration of the vessels (Figure 6). On histology, these usually represent M3 to SM1 invasive carcinoma. When large new abnormal vessels are observed (usually >3 times of V3 IPCL), they likely correspond to deep submucosal invasive carcinoma and are classified as IPCL type V_N.

Using the above classification, Sato *et al.* analyzed 446 lesions from 358 patients with esophageal neoplasia (20). The sensitivity and specificity for IPCL type V1–2 for M1–2 disease was 89.5% and 79.6% respectively. This is an important finding as M1–2 carcinomas are lesions amenable for endoscopic resection, which would be discussed further in this review. A substantial interobserver and intraobserver agreement for the IPCL classification was reported as well, but only three reviewers were involved in the calculation of the kappa value in their study.

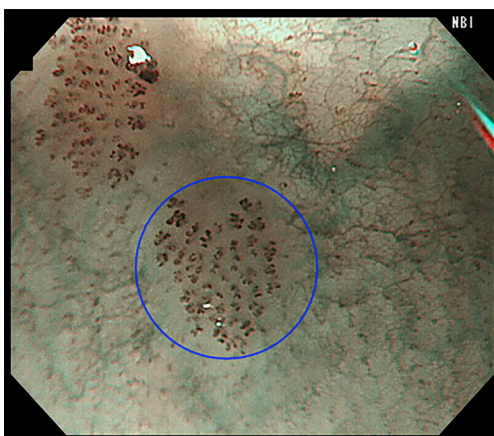


Figure 4 Demonstration of dilatation, meandering, caliber change and non-uniformity of the IPCL. Inoue type V1, JES type B1.

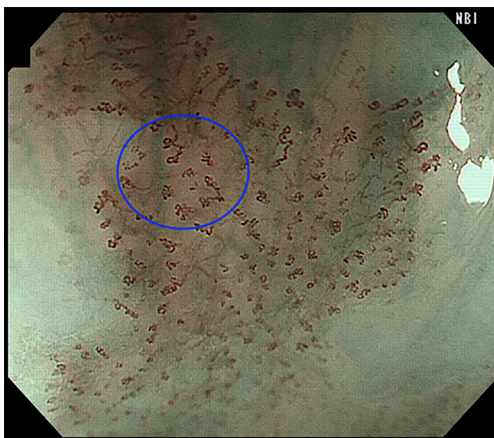


Figure 5 Further destruction of IPCL with elongation of microvessels in vertical plan. Inoue type V2, JES type B1.

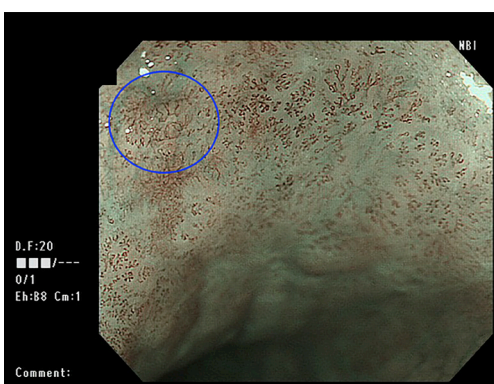


Figure 6 Loss of loop like appearance in the advanced IPCL. Inoue type V3, JES type B2.

On the other hand, Arima *et al.* proposed another classification based on magnifying endoscopy (21). The vascular patterns were divided into four subtypes. In addition, the concept of avascular areas (AVA) was also introduced, with the larger size AVA representing deeper invasion of the esophageal carcinoma.

In an attempt to avoid multiplicity of classification systems and complicated criteria, the Japanese Esophageal Society (JES) proposed a new classification in 2012 (22). In this new system, morphology of IPCL is classified into type A and B based on the presence of abnormality including weaving, dilatation, irregular caliber, and difference in shape (Figures 1,2). Type B vessels are further subclassified into B1–B3 based on the size of the abnormal IPCL and whether a loop-like appearance is preserved. AVA were also classified into small (<0.5 mm), medium 0.5–3 mm), large size (>3 mm), and further incorporated with the IPCL morphological classification in predicting the depth of invasion (Figures 3–6). A prospective multicenter study was reported using this classification (23). The overall accuracy of the system was 90.5%. The sensitivity and positive predictive value of B1 vessels for M1–M2 tumors were 97.5% and 92.4% respectively, reflecting optimal diagnostic accuracy in deciding for endoscopic resection.

Endoscopic treatment of esophageal SCC

Two prerequisites are required for successful endoscopic treatment of esophageal SCC: complete removal of the primary tumor in the absence of regional lymph node metastasis. In order to achieve that, reliable method of endoscopic resection is mandatory, ideally with en bloc removal of the tumor, as well as an accurate prediction of the risk of lymph node metastasis. In Japan, endoscopists have been performing endoscopic mucosal resection (EMR) for early esophageal cancers for disease confined to the mucosa since the 1990s. In a large nationwide study of 2,418 patients with early esophageal cancers, the risks of lymph node metastasis were 0% and 3.3% for M1 (disease confined to epithelium) and M2 (disease confined to lamina propria mucosa) respectively (24). Tumors invading to muscularis mucosae (M3) or superficial third of submucosa (SM1) had a much higher risk of lymph node metastasis at 10.2% and 26.5%. In another study of 240 surgically resected early carcinomas, tumors that invade beyond lamina propria (M3 & SM1) had no lymph node metastasis if there was absence of lymphovascular permeation, vertical tumor invasion <200 μ m and tumor grading of 1 or 2 (25).

As a result, endoscopic resection has been recommended only for SCC confined to M1 or M2 level (absolute indication). M3 or SM1 tumors <200 μm are considered relative indications if there is no clinical evidence of lymph node metastasis (26).

EMR involves the use of endoscopic snare for resection of a lesion usually after artificially raising the lesion with submucosal injection of a mixed solution. Various techniques have been used to facilitate the EMR procedure, such as the band assisted or cap assisted techniques. The major limitation of EMR lies in the difficulty in achieving en bloc resection for larger size lesions. In the aforementioned nationwide study, piecemeal resection was required in 94% of the cases if the tumor diameter is larger than 2 cm (24). Pathological assessment of the resected tumor becomes inaccurate if tumors are resected in piecemeal manner, in particular determination of margin clearance and the depth of invasion. Moreover, residual tumor could be left at the edge of each snare application during piecemeal EMR and led to an increased risk of local recurrence (27).

Endoscopic submucosal dissection (ESD)

ESD is an endoscopic technique initially developed for resection of gastric neoplasms (28-30). Compared with EMR where lesion size is the main factor in determining the need for piecemeal resection, ESD could achieve en bloc resection regardless of the lesion size and is also less affected by fibrosis in the submucosal layer. The technique of ESD has now been extended to the rest of the gastrointestinal tract including early esophageal neoplasia. Compared to gastric ESD, esophageal ESD is more difficult to perform due to narrow space in the lumen as well as a higher risk of perforation owing to a thin muscular layer. Favorable outcomes have been reported and will be elaborated further below.

Esophageal ESD could be performed under conscious sedation or general anaesthesia. Generally, we prefer procedure under general anaesthesia especially for cases with expected long duration and lesions locating in the proximal esophagus as the risk of perforation significantly increase if the patient could not cooperate well during conscious sedation. Special endoscopic electrosurgical knives are required during the ESD procedures. These are specially designed devices for precise tissue cutting and hemostasis. Two types of knives have been developed: the non-insulated and the insulated tip knives. In our ESD procedures we usually use the Dual Knife J (KD655Q, Olympus Medical

Systems, Tokyo, Japan), a type of non-insulated knife with a knob-shaped tip and injection port. A high definition endoscope with water-jet function and a transparent hood mounted at the tip is preferred. Esophageal ESD involves four steps: Marking, lifting, incision and dissection. Precise marking of the margin of the lesion is imperative as once the lesion is lifted the margins would become indistinct. Next, lifting of the lesion is performed by submucosal injection of a mixed solution. Normal saline, hyaluronic acid or glycerin solution have all been used for injection, with the addition of adrenaline and indigo carmine as a dye to highlight the submucosal plane. Circumferential mucosal incision would then be performed, usually from the anal side of the lesion. Particular attention has to be made with regard to the effect of gravity, as pooling of fluid in the dependent area could significantly obscure the endoscopic view. After mucosal incision, complete submucosal dissection could be performed by clearly visualizing the submucosal plane between the mucosa and the muscularis propria. Various retraction methods have been reported to facilitate dissection. The “clip traction” method is one of the easiest techniques reported (31,32). It involves the use of a long thread of suture tied to an endoscopic clip, which is applied on the oral side of the lesion after mucosal incision and the suture retrieved in the mouth. Upon pulling of the suture externally, countertraction could be achieved for better exposure of the submucosal plane. A shorter duration of procedure using the “clip traction” method was required compared to conventional ESD (33). Careful hemostasis is needed to avoid reactionary and delayed hemorrhage. Large submucosal vessels encountered during dissection could be coagulated with the electrosurgical knives or hemostatic forceps (Coagrasper, FD-410LR, Olympus Medical Systems, Tokyo, Japan). Resected specimen should be pinned on a block fixed in formalin for dedicated pathological assessment.

Outcomes of endoscopic resection of early esophageal cancers

Early reports on clinical outcomes of esophageal ESD have been promising with a high en bloc resection rate of 95–100% and a low complication rate (Bleeding 0%, perforation 3–6%) (34-36). In a recent meta-analysis of 8 comparative studies between esophageal ESD and EMR, ESD achieved a significant higher rate of en bloc resection (odds ratio =52.8, 95% CI: 25.6–108.8) but at a higher risk of perforation (odds ratio =2.19, 95% CI: 1.08–4.47) (37).

A longer procedural time was required with ESD. Risk of local recurrence was significantly lower with ESD when compared to EMR (0.3% versus 11.5%; odds ratio =0.08, 95% CI: 0.03–0.23). Ono *et al.* reported the long-term outcomes of esophageal ESD of 84 patients with early squamous cell cancers (36). The 5-year cause-specific survival was 100% for M1–M2 carcinomas and 85% for M3/SM1 invasive carcinomas. A comparable cause specific survival at 5 years was also reported in an earlier study between conventional EMR and surgery for M3/SM1 carcinomas (95% and 93.5%) (38).

In recent years, post-procedural strictures have become one of the major concerns for esophageal ESD. Studies with multivariate analysis have identified dissection of >3/4 circumference of the lumen as the most important risk factor for occurrence of such complication (39–41). Risk of stricture after near circumferential ESD could be as high as 100%. Numerous preventive strategies have been proposed, including the use of topical or systemic anti-inflammatory agents, prophylactic endoscopic balloon dilation and tissue engineering approaches (42–46). Unfortunately, the efficacy of these strategies is not well established, and there is currently a lack of standardized approach in prevention of this potentially debilitating complication.

Conclusions

In the recent decade, numerous advances have been made in accurate endoscopic diagnosis of early esophageal SCC, as well as the advent of novel endoscopic approach in curative resection of such lesions. With increased in detection and endoscopic resection of early esophageal carcinoma, patients suffering from this traditionally lethal disease could hopefully enjoy an extended survival with improved quality of life.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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