Review

Endoscopic diagnostic strategy of superficial esophageal squamous cell carcinoma

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The prognosis of the esophageal squamous cell carcinoma is still poor. Early detection is ideal to improve patient survival. In particular, superficial cancer limited within the mucosal layer is a good candidate for minimally invasive treatment by endoscopic resection with curative intent. However, an effective endoscopic diagnostic strategy is not established worldwide. Herein, we review the published papers on this subject.

Key words: endoscopic ultrasonography (EUS), esophagus, image-enhanced endoscopy (IEE), Lugol chromoendoscopy, narrow-band imaging (NBI), esophageal squamous cell carcinoma (ESCC)

INTRODUCTION

SQUAMOUS CELL CARCINOMA (SCC) is the predominant histological type of esophageal cancer worldwide.1 Asia (China, Kazakhstan, Taiwan and Japan) and Eastern Africa are the areas with the highest incidence. Smoking, ethanol in alcoholic beverages and acetaldehyde associated with alcoholic beverages are definite risk factors for esophageal SCC (ESCC).2 Because these definite risk factors are recognized, early detection of ESCC can be expected for those at risk.

Endoscopy plays an important role in the early detection of cancer in the gastrointestinal tract, which includes the esophagus. However, detection is not always easy for endoscopists, because endoscopic findings of superficial esophageal cancers are slight and minimal. Therefore, an ideal strategy for the early detection of ESCC is required.

According to the depth of the 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) by the International Union Against Cancer Classification of Malignant Tumours (7th edition) (Fig. 1).3 Because more than half of the patients with superficial ESCC have no symptoms associated with cancer, effective screening is important for early detection. Early detection enables us to use minimally invasive treatment, such as endoscopic resection (EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection), and those with superficial ESCC can expect to be cured.

IDEAL DIAGNOSTIC STRATEGY

(i) Identification of subject at risk:
1. drinkers;
2. smokers;
3. aldehyde dehydrogenase type 2 (ALDH2) deficiency;
4. inadequate intake of green-yellow vegetables and fruits.

(ii) Detection:
1. conventional white light imaging (WLI);
2. Lugol chromoendoscopy;
3. equipment-based image-enhanced endoscopy (IEE).

(iii) Differential diagnosis:
1. conventional WLI;
2. Lugol chromoendoscopy;
3. equipment-based IEE.

(iv) Estimation of the depth of invasion:
1. conventional WLI;
2. equipment-based IEE;
3. endoscopic ultrasound (EUS).

(v) Histological confirmation by biopsy.

WHITE LIGHT IMAGING

SUPERFICIAL ESCC, ESPECIALLY Tis and T1a ESCC, sometimes lacks any changes in appearance. In these cases, early detection of superficial ESCC by...
conventional WLI is difficult. Disappearance of the vascular
network in the mucosa (Fig. 2), uneven surface and tiny
white coating are indications of the possible presence of
superficial ESCC (Fig. 3).

LUGOL CHROMOENDOSCOPY

LUGOL CHROMOENDOSCOPY IS the standard
method for detecting and identifying the margin of the
lateral extension of ESCC. However, it causes unpleasant
reactions, such as chest pain and discomfort, in those who
undergo endoscopic examination, and occasionally causes
allergic reactions including flushing, asthma and iodine
shock. Sodium thiosulfate solution is useful in reducing these
adverse symptoms. Giving i.v. steroids before examination is
sometimes effective in preventing allergic reactions.

After staining with Lugol solution, a pink color change
indicates ESCC (Fig. 4). The pink color change is clearly
revealed after 2–3 min after Lugol staining. Shimizu et al.
reported that when used as a diagnostic index for high-grade
intraepithelial squamous neoplasia and SCC, the pink
color sign shows sensitivity and specificity of 91.9% and
94.0%, respectively. Ishihara et al. also reported that sen-
sitivity and specificity of diagnosis of high-grade intraepi-
thelial neoplasia or invasive cancer were 88% and 95%,
respectively.

The so-called ‘Tatami-no-me’ sign is a useful indicator
of the depth of invasion of ESCC (Fig. 5). ‘Tatami’ means
traditional Japanese-style flooring and the endoscopic
appearance of the ‘Tatami-no-me’ sign is similar to the
surface pattern of Tatami (Japanese traditional floor). If
the Tatami-no-me sign is not seen in a cancerous lesion, the
neoplasia might have invaded the deep layer of the lamina
propria. If the Tatami-no-me sign is seen, the lesion will not
have invaded the deep layer of the lamina propria.

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IMAGE-ENHANCED ENDOSCOPY

Image-enhanced endoscopy is expected to accurately diagnose high-grade intraepithelial neoplasia and SCC with minimal invasion of the esophagus. IEE combined with magnification is a powerful tool to characterize the lesion.

Among the IEE types, narrow-band imaging (NBI) has been found to provide a highly accurate diagnosis of superficial ESCC. The NBI endoscopy system uses two narrow-band illuminations of 415 nm and 540 nm by the NBI filter, corresponding to the peaks of absorption of hemoglobin. Therefore, thin blood vessels, such as capillaries, in the epithelium or mucosal layer can be seen more distinctly than in conventional WLI. Under NBI observation, most of the
superficial cancer is seen as a brownish area (Fig. 6).\textsuperscript{15,16} With magnification, irregularity of the intraepithelial papillary capillary loop (IPCL) is also seen (Fig. 6).\textsuperscript{17}

In a prospective multicenter randomized controlled study, Muto et al. reported that NBI detected superficial ESCC more frequently than did WLI (97\% vs 55\%, $P < 0.001$).\textsuperscript{18} The sensitivity and accuracy of NBI for the diagnosis of superficial ESCC were 97.2\% and 88.9\%, respectively. Furthermore, even small lesions (<10 mm) were more effectively detected by NBI with magnification than with WLI (94\% vs 39\%, $P = 0.03$).

The screening of second primary ESCC in patients with head and neck cancer is important, and Lugol chromoendoscopy has been used for its detection.\textsuperscript{19} In a study reported by Takenaka et al.,\textsuperscript{20} the specificity of NBI was significantly superior to conventional WLI (95.4\% vs 84.7\%, $P < 0.001$), whereas the sensitivity of NBI and Lugol chromoendoscopy was equivalent (90.9\% vs 100\%, not significant). Further-
more, most of the Lugol-voiding lesions overlooked by NBI were low-grade intraepithelial neoplasia or lesions with atypical findings. These results indicate that NBI is a useful and less invasive screening method for ESCC.

In contrast, when NBI is used without magnification, the false-positive rate is high. Therefore, NBI is recommended for use with magnification to provide both higher sensitivity and higher specificity.

**ENDOSCOPIC ULTRASONOGRAPHY**

The depth of ESCC invasion into the esophageal wall is closely associated with metastasis to lymph nodes. The frequency of metastasis in the lymph nodes in ESCC that is confined to the mucosa is 3%. The risk increases to 12% for cancer invading the muscularis mucosae, and increases markedly to 26–46% in those with submucosal invasion. Because ESCC confined to the mucosal layer is correlated with a low frequency of metastasis, and because surgery confers a high risk of morbidity and mortality, these patients are considered to be appropriate candidates for minimally invasive treatment by EMR or ESD. ESCC invading the muscularis mucosae is indicated for surgical resection, but may still be treated by ESD. ESCC with submucosal invasion necessitates surgical resection and/or chemoradiotherapy.

To estimate the depth of ESCC invasion for superficial ESCC, standard endoscopy with image enhancement and EUS are currently considered the best methods. Other methods, such as the barium meal, computed tomography (CT) and positron emission tomography (PET), are considered less appropriate for superficial ESCC because of their resolution limitations.

**Figure 7** Endoscopic ultrasonography (EUS) image of the normal esophageal wall by 20 MHz miniprobe demonstrates a nine-layered structure (arrow). The first five layers correspond to the echogenic luminal surface (high echo), mucosa (low echo), lamina propria (high echo), muscularis mucosae (low echo), submucosa (high echo). Next are inner circular (low echo) and outer longitudinal layers (low echo) of muscularis propria. They are separated by a thin hyperechoic layer of the connective tissue (high echo).

**Figure 8** Endoscopic ultrasonography (EUS) image demonstrates a low echoic mass located in the submucosal layer (arrow).

To estimate the depth of invasion, the distinct tissue layers of the esophageal wall should be identified. To visualize them, 20 MHz or 30 MHz miniature probes should be used. These high-resolution probes provide nine-layered echostructures (Fig. 7). Generally, a tumor can be seen as a low echoic mass by EUS (Fig. 8). If the cancerous lesion invades the submucosal layer, EUS delivers a low-echo mass in the high-echo layer and corresponding submucosal layer. A balloon should be attached to the tip of the endoscope to keep deaerated water in the esophageal lumen and prevent...
regurgitation to the pharynx. An endoscope with a water jet function is desirable to keep the esophageal lumen wider and to obtain clear images.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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