Multicenter, prospective trial of white-light imaging alone versus white-light imaging followed by magnifying endoscopy with narrow-band imaging for the real-time imaging and diagnosis of invasion depth in superficial esophageal squamous cell carcinoma CME

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Background: Magnifying endoscopy with narrow-band imaging (ME-NBI) has been used to estimate the invasion depth of superficial esophageal squamous cell carcinoma (SESCC), but the real diagnostic power of ME-NBI remains unclear because of few prospective studies.

Objectives: To evaluate whether ME-NBI adds additional information to white-light imaging (WLI) for the diagnosis of invasion depth of SESCC.

Design: Multicenter, prospective trial using real-time imaging and diagnosis.

Setting: Seven Japanese institutions.

Patients: Fifty-five patients with SESCC were enrolled from June 2011 to October 2013, and the results for 49 lesions were analyzed.

Interventions: Patients underwent primary WLI followed by ME-NBI, and reports of primary WLI (WLI alone) were completed before secondary ME-NBI (WLI followed by ME-NBI). To standardize diagnosis among examiners, this trial was started after achievement of a mean κ value $\geq$ .6 among 11 participating endoscopists.

Main Outcome Measurements: Diagnosis of invasion depth by each tool was divided into cancer limited to the epithelium and the lamina propria mucosa and cancer invading beyond the muscularis mucosae ($\geq$T1a-MM) and then collated with the final pathologic diagnosis by an independent pathologist blinded to the clinical data.

Results: The accuracy of invasion depth in WLI alone and WLI followed by ME-NBI was 71.4% and 65.3% (P = .375), respectively. Sensitivity for $\geq$T1a-MM was 61.1% for both groups (P = 1.000), and specificity for $\geq$T1a-MM was 77.4% for WLI alone and 67.7% for WLI followed by ME-NBI (P = .375).

Limitation: Open-label trial.

Conclusions: ME-NBI showed no additional benefit to WLI for diagnosis of invasion depth of SESCC. (University Hospital Network Clinical Trials Registry number: UMIN000005632.) (Gastrointest Endosc 2015;81:1355-61.)

Abbreviations: CI, confidence interval; ESD, endoscopic submucosal dissection; IPCL, intraepithelial papillary capillary loop; ME-NBI, magnifying endoscopy with narrow-band imaging; NBI, narrow-band imaging; SESCC, superficial esophageal squamous cell carcinoma; T1a-EP/LPM, cancer limited to the epithelium and the lamina propria mucosa; $\geq$T1a-MM, cancer invading beyond the muscularis mucosae; T1a-MM/T1b-SM1, cancer with muscularis mucosae to slight submucosal invasion $\leq$ 200 μm; >T1b-SM2, cancer with deep submucosal invasion > 200 μm; WLI, white-light imaging.

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Superficial esophageal squamous cell carcinoma (SESCC) is defined as carcinoma invading within the mucosa or submucosa. For SESCC, endoscopic resection is currently indicated for cancer limited to the epithelium and the lamina propria mucosa (T1a-EP/LPM) because previous studies showed the absence of lymph node metastasis in T1a-EP/LPM.[1-3] On the other hand, surgical resection with lymph node dissection or chemoradiotherapy is recommended for cancer invading beyond the muscularis mucosae (≥T1a-MM) because the incidence of lymph node metastasis was 0% to 26.5% in cancer with muscularis mucosae to slight submucosal invasion ≤ 200 μm (T1a-MM/T1b-SM1) and 30.4% to 41.9% in cancer with deep submucosal invasion > 200 μm (>T1b-SM2).[3-5] However, esophagectomy is invasive, with high morbidity and mortality.[6] Endoscopic submucosal dissection (ESD) enables en bloc resection of a wide lesion,[7-9] thereby contributing to high quality of life for patients with SESCC. Hence, accurate diagnosis before treatment is very important for SESCC to avoid unnecessary invasiveness.

Diagnosis of invasion depth for SESCC had been generally performed by standard endoscopic observation with white-light imaging (WLI) and EUS. Previous studies have reported the accuracy rates of invasion depth as 74% to 86.7% with esophagography or standard endoscopy with WLI[3] and 76% to 92.0% with EUS.[10,11] It has also been reported that esophageal neoplasms can be distinguished from normal mucosa by the shape of the intraepithelial papillary capillary loop (IPCL) and that distortion of the IPCL depends on cancer progression.[12] Advanced narrow-band imaging (NBI) with wavelengths of 415 and 540 nm that are absorbed by hemoglobin has been used, and combination magnifying endoscopy with NBI (ME-NBI) achieved detailed observation of the IPCL.[13,14] Indeed, NBI was more useful for detection of SESCC than WLI in a prospective, randomized, controlled trial.[15] Meanwhile, ME-NBI also contributes to diagnosing the invasion depth of SESCC; the accuracy rate of invasion depth was 77.8% to 85.2% in a retrospective study.[14] The latest prospective study of ESD for SESCC reported that the preoperative accuracy of invasion depth using WLI and/or ME-NBI was 76.8% in the subset analysis.[16] One prospective study for invasion depth of SESCC comparing ME-NBI with EUS and WLI showed no significant differences for any parameters among the 3 tools.[17] However, the evidence level of this prospective trial was not high because of problems of study design and criteria.

Hence, the real diagnostic power of ME-NBI for invasion depth of SESCC remains unclear. Therefore, using real-time imaging and diagnosis, this prospective study of ME-NBI was conducted to evaluate whether ME-NBI provides additional information to WLI on invasion depth.

METHODS

Patients

All patients who met all of the following inclusion criteria were prospectively enrolled in this study: (1) histologically confirmed high-grade intraepithelial neoplasia or squamous cell carcinoma by biopsy sampling, (2) SESCC diagnosed as flat type according to the Paris Workshop guidelines (type 0-IIa, IIb, IIc),[18] (3) 20 ≤ age ≤ 85 years, and (4) Eastern Cooperative Oncology Group performance status of 0 to 2.

Patients with the following criteria were excluded from study enrollment: (1) patients with previous history of any esophageal treatment; (2) patients on potent anticoagulant therapy; (3) patients with severe heart, lung, and renal dysfunction; (4) patients who could not undergo endoscopic and surgical resection because of their physical condition or other therapy, such as radiotherapy and chemotherapy; and (5) patients with cervical esophageal cancer. Patients without complete resection of primary tumor were excluded from the final analysis.

Seven Japanese institutions participated in the present trial, and the study protocol was approved by the ethics committee at each institution. The trial was carried out according to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008), and all patients provided their written, informed consent before study entry. This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry before the trial was started (UMIN000005632).

Study design

This multicenter, prospective trial was intended to assess the additional efficacy of ME-NBI to WLI in SESCC. The written report of primary WLI alone was completed before the start of ME-NBI by an assistant, after which the lesions were observed by secondary ME-NBI and the report of ME-NBI was completed. Once the written report of the results was completed, no changes were permitted. The reports of both WLI alone and WLI followed by ME-NBI were collected for each patient, and the comparison between the 2 groups was performed.

Observation by WLI was performed in standard white-light mode, and ME-NBI was done in NBI mode, using a commercially available magnifying endoscope (GIF-Q260Z; Olympus Optical Co, Tokyo, Japan) with a transparent cap. All procedures were carried out by experienced endoscopists, and all diagnoses of invasion depth were performed according to the diagnostic criteria of WLI and ME-NBI described below. This trial was started after achievement of a mean κ value ≥ .6 among all endoscopists, as previously described[19] (Supplemental File, available online at giejournal.org). To ensure the accuracy and completeness of reporting of studies of diagnostic accuracy, the present study complied with the Standards