

Demarcation of early esophageal squamous cell carcinoma during endoscopic submucosal dissection

A comparison study between Lugol's iodine staining and narrow-band imaging

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Abstract

Lugol's iodine staining (LIS) and narrow-band imaging (NBI) are currently the most common methods applied in demarcating early esophageal squamous cell carcinoma (EESCCs) during endoscopic submucosal dissection. The purpose of the present study was to investigate the effects on clinical outcomes in comparison between LIS and NBI for the demarcation of EESCCs during endoscopic submucosal dissection.

This was a single-center, retrospective, cohort study. A total of 172 patients were involved. 109 patients received demarcation of the lesion by LIS and 63 patients by NBI. Data on baseline characteristics, clinical outcomes and follow-up information were collected for analyses.

The mean diameter of the lesions was 3.9 ± 1.5 cm. R0 resection rate was 89.5%. The rate of total and in-hospital adverse events was 25.6% and 9.3%. The cumulative recurrence rate was 2.9% and 3-year disease-specific survival rate was 98.3%. Compared to patients of the LIS group, patients of the NBI group showed significantly shorter procedure time (44.8 ± 32.2 v.s. 57.0 ± 40.6 , $P = .044$), lower rate of using of scopolamine butylbromide (19.0% vs 35.8%, $P = 0.021$), reduced number of clips used (1.3 ± 1.2 vs 1.8 ± 1.5 , $P = .017$) and alleviated discomfort evaluated by visual analog system score after operation (4.7 ± 0.8 vs 5.5 ± 1.0 , $P < .001$). There was no significant difference of R0 resection rate, margin status, adverse events, cumulative recurrence rate and 3-year disease-specific survival rate between the two groups.

Demarcation of EESCCs by NBI could achieve comparable accuracy and clinical outcomes with more convenience and safety compared with demarcation by LIS.

Abbreviations: CT = computed tomography, EESCCs = early esophageal squamous cell carcinoma, ESD = endoscopic submucosal dissection, LIS = Lugol's iodine staining, NBI = narrow-band imaging, VAS = visual analog system.

Keywords: demarcation, endoscopic submucosal dissection, esophageal squamous cell carcinoma, Lugol's iodine staining, narrow-band imaging

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1. Introduction

Nowadays, the endoscopic resection of early esophageal squamous cell carcinoma (EESCCs) has been well recognized as the first-line treatment because of its minimally invasiveness with conserved organ function and quality of life.^[1,2] Among a series of endoscopic resection approaches, endoscopic submucosal dissection (ESD) has gradually become the standard treatment according to current guidelines.^[3,4] It allows *en bloc* resection of the lesions regardless of the diameter and extent. Studies regarding both short-term and long-term outcomes have reported favorable results.^[5–7] Compared with conventional endoscopic multi-band mucosectomy or endoscopic mucosal resection, ESD involves a first and pivotal step of margin determination and marking around the lesions. The marking procedure rendering the advantages of ESD by contributing to an adequate tumor-free margin to minimize residual and recurrence. Lugol's iodine staining (LIS) and narrow-band imaging (NBI) are currently the two most common methods applied in the demarcation of EESCCs. Although the diagnostic accuracy of LIS and NBI in pre-operative screening and detection of EESCCs have been substantially studied,^[8–10] there have been rare reports about comparison of their applications in the intra-operative demarcation of the lesions. It remains unclear whether the two different demarcation approaches would exert influences on procedure-related adverse events and margin status, and ultimately result in different long-term outcomes.

The present study is aimed to investigate the effects on clinical outcomes between LIS and NBI in the demarcation of EESCCs during esophageal ESD and provide evidences to direct future clinical practice.

2. Materials and methods

2.1. Study population

A total of 172 patients were retrospectively selected from consecutive patients with EESCCs that underwent ESD in Changhai hospital from January 2014 to December 2015. Preoperative computed tomography (CT) and endoscopic ultrasonography were conducted to exclude patients with regional lymph node or distant metastasis. Patients with histopathologically demonstrated EESCCs were included in the study. Patients with chronic esophagitis or low-grade intraepithelial neoplasia, undergoing previous treatments such as chemoradiotherapy prior to ESD, or aged over 80 years old were excluded in the present study. Among the 172 patients, 109 patients received margin determination of the lesion by LIS and 63 patients by NBI (Fig. 1). The study was approved by the ethics committee of Changhai hospital and written informed consents were obtained from all subjects.

2.2. Marking method selection

Generally, for all patients treated by NBI or LIS, the decision was made before ESD by the operator according to his judgments based on images of preoperative endoscopy. The operators were all skilled endoscopists (CX, JC, XS, and FL) with over ten-year experiences in analyzing images of NBI and LIS and experiences of more than 200 ESDs for lesions of the esophagus.

2.3. Endoscopic procedure

The ESD procedures were regularly performed with a single-channel endoscope (GIF-Q260J; Olympus Optical, Tokyo, Japan)

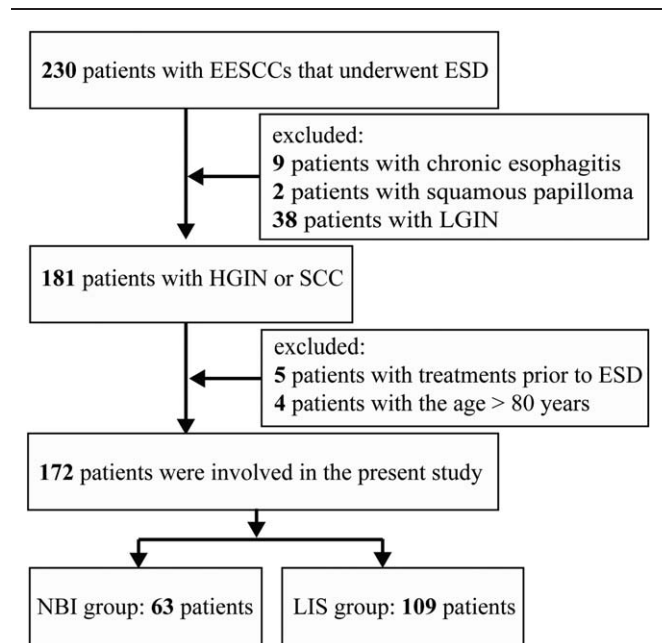


Figure 1. Flow diagram for patient selection.

with a transparent cap attachment. A high-resolution magnifying endoscope (GIF-H260Z; Olympus) was used for patients of NBI group in the marking if necessary. The ESD procedures were performed as follows: (1) The lesions were identified under white light and NBI; (2) For patients of LIS group, 10 to 20 ml of 2.5% Lugol's solution was sprayed onto the lesion area with a spraying catheter (PW-5L; Olympus). Multiple dots were marked around the unstained area at about 2–3 mm lateral to the margin. For patients of NBI group, the margin of the lesions was determined by the distinctive brownish color and irregular capillary microvasculature under NBI inspection with or without magnification, and the marking dots were made at about 2–3 mm lateral to the margin as well. Figure 2 showed two typical cases of marking by the two methods respectively. A water-jet Hybrid knife (Erbe Elektromedizin GmbH, Tübingen, Germany) was regularly used for the marking. (3) The sterile normal saline premixed with 1% indigo carmine and 0.01% epinephrine was injected into the submucosal layer at multiple sites lateral to the marked points with Hybrid knife; (4) Circumferential incision of the mucosa closely outside the marking dots and submucosal dissection were performed using Hybrid knife, until the lesion was completely removed. For patients with esophageal peristalsis disturbing the dissection, 20 mg of scopolamine butylbromide was injected intravenously. A coagrasper hemostatic forceps (FD-410LR; Olympus) was used for haemostasis of oozing or pulsating bleeding or for preventive coagulation of large vessels as judged by the endoscopists. Any suspected perforations or obvious injury of the muscularis propria were carefully closed up with metal clips (ROCC-D-26-195; Micro-Tech, Nanjing, China). All ESDs were performed with tracheal intubation and general anesthesia. Carbon dioxide insufflations were applied throughout all ESD procedures.

2.4. Postoperative managements

All patients were fasted at least 24 hours and given intravenous fluids with broad-spectrum antibiotics and proton pump inhibitors for

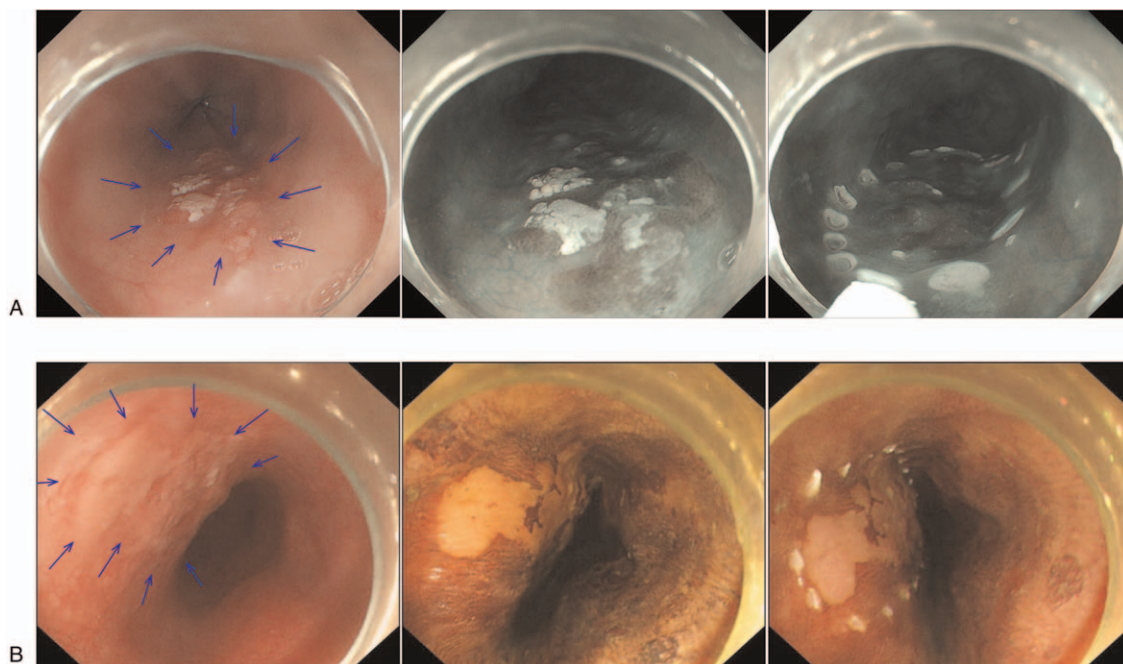


Figure 2. Margin marking of early esophageal squamous cell carcinoma during endoscopic submucosal dissection. A, marking by narrow-band imaging; B, marking by Lugol's iodine staining. Blue arrow indicated the margin of the lesion under white light.

48 hours after the operation. Clear fluids and subsequent soft diets were allowed gradually. The visual analog system (VAS) was applied to evaluate the pain feeling after operation and daily thereafter. The score ranged from 0 (no pain) to 10 (severe pain). If the VAS score was above 5 and there were symptoms such as chest distress, dyspnea, abdominal distension or signs of peritonitis, a thoracoabdominal CT would be performed to rule out perforation. Using of painkillers such as meperidine hydrochloride was allowed afterwards. Repeated endoscopy would be performed at occurrence of hematemesis or melena and endoscopic hemostasis would be carried out if necessary.

2.5. Histopathological assessments

The specimens were attached onto a small plastic board with full stretch and fixed by 10% formalin for histopathological assessments. The slices were cut at intervals not more than 2 mm. The histopathological assessments were performed by experienced pathologists.

2.6. Adverse events and additional therapies

All adverse events were reported and evaluated as previously described.^[11,12] For patients with high risks of esophageal stenosis, oral prednisone was prescribed for prophylaxis according to previous reports.^[13] Endoscopic balloon dilation was performed to relieve dysphagia and repeated to maintain a relatively normal swallowing if necessary. Additional therapies were recommended for patients with non-curative resection according to the guidelines by Japanese Classification of Esophageal Carcinoma.^[3]

2.7. Follow-ups

Surveillance endoscopy was requested to be repeated to observe wound healing or detect any residual or recurrent lesion at the

3rd, 6th and 12th month and annually thereafter. Lymph node or distant metastasis was evaluated by contrast-enhanced CT/MRI every 6 to 12 months.

2.8. Definitions

The procedure time was measured as the time between marking of the first dot and the last withdraw of the endoscope. En bloc resection was defined as an intact excision of the tumor in one piece without fragmentation. R0 resection was defined as en bloc resection achieving tumor-free lateral and vertical margins. The disease-specific survival was defined as the months from the date of ESD to the date of death associated with ESCCs or the last follow-up.

2.9. Statistical analysis

The SPSS software (version 17.0; SPSS Inc., Chicago, IL) was used for statistical analyses. Data were expressed as mean \pm standard deviation and the statistical significance between groups was examined by unpaired Student *t* test. Comparison of categorical variables was performed using χ^2 tests or Fisher exact tests. Survival analysis was computed using Kaplan-Meier method and comparison of survival rates was conducted using the log-rank test. A two-sided $P \leq .05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics

The study population consisted of 113 (65.7%) males and 59 (34.3%) females with a mean age of 56.8 ± 9.3 (range 35 – 79) years. A total of 172 esophageal lesions were successfully removed by ESD. The mean diameter of the lesions was 3.9 ± 1.5

Table 1**Clinical characteristics of all patients (n = 172).**

Age, n (%)		
mean ± s.d (yr)	56.8 ± 9.3 (range 35–79)	
< 57 yr	88 (51.2)	
≥ 57 yr	84 (48.8)	
Gender, n (%)		
Male	113 (65.7)	
Female	59 (34.3)	
Lesion location, n (%)		
Upper thoracic	27 (15.7)	
Middle thoracic	83 (48.3)	
Lower thoracic	62 (36.0)	
Macroscopic morphology, n (%)		
0-I	1 (0.6)	
0-IIa	29 (16.9)	
0-IIb	135 (78.5)	
0-IIc	7 (4.1)	
Lesion diameter, n (%)		
mean ± s.d (cm)	3.9 ± 1.5 (range 0.8–10.0)	
< 4 cm	91 (52.9)	
≥ 4 cm	81 (47.1)	
Circumferential extent, n (%)		
< 1/2	84 (48.8)	
≥ 1/2 and < 3/4	56 (32.6)	
≥ 3/4	32 (18.6)	
Follow-up period, n (%)		
mean ± s.d (mo)	42.2 ± 7.2 (range 11–55)	
< 36 mo	34 (19.8)	
≥ 36 mo	138 (80.2)	

cm (range 0.8 – 10.0 cm). The baseline clinical characteristics of all patients were listed in Table 1. The comparisons of these baseline clinical characteristics between patients of the two groups revealed no statistical significance as shown in Table 2.

Table 2**Comparisons of baseline clinical characteristics between patients of the NBI group (n = 63) and the Lugol's iodine group (n = 109).**

Variables	NBI group (n = 63)	Lugol's iodine group (n = 109)	P value
Gender (M/F)	40/23	73/36	.643
Age, yr	57.5 ± 9.2	56.4 ± 9.3	.445
Lesion diameter, cm	3.6 ± 1.6	4.0 ± 1.4	.112
Lesion location, n (%)			
Upper thoracic	10 (15.9)	17 (15.6)	.962
Middle thoracic	32 (50.8)	51 (46.8)	.613
Lower thoracic	21 (33.3)	41 (37.6)	.573
Macroscopic morphology, n (%)			
0-I	1 (1.6)	0 (0)	.366
0-IIa	12 (19.0)	17 (15.6)	.560
0-IIb	47 (74.6)	88 (80.7)	.346
0-IIc	3 (4.8)	4 (3.7)	.727
Circumferential extent, n (%)			
< 1/2	34 (54.0)	50 (45.9)	.306
≥ 1/2 and < 3/4	19 (30.2)	37 (33.9)	.610
≥ 3/4	10 (15.9)	22 (20.2)	.484
Follow-up period, mo	42.3 ± 7.9	42.1 ± 6.8	.844

cm = centimeter, F = female, M = male, NBI = narrow-band imaging.

Table 3**Comparisons of clinical outcomes after endoscopic submucosal dissection between patients of the NBI group (n = 63) and the Lugol's iodine group (n = 109).**

Variables	NBI group (n = 63)	Lugol's iodine group (n = 109)	P value
Histological type (HGIN/SCC)	34/29	60/49	.891
Invasion depth, n (%)			
m1 (HGIN)	34 (54.0)	60 (55.0)	.891
m2	4 (6.3)	5 (4.6)	.617
m3	13 (20.6)	24 (22.0)	.832
sm	12 (19.0)	20 (18.3)	.910
En bloc resection, n (%)	63 (100)	109 (100)	NA
R0 resection, n (%)	57 (90.5)	97 (89.0)	.759
Lateral margin (P/N)	4/59	7/102	.985
Vertical margin (P/N)	3/60	7/102	.654
Vascular invasion (P/N)	0/63	3/106	.300
Lymphatic invasion (P/N)	0/63	0/109	NA
Procedure time, min	44.8 ± 32.2	57.0 ± 40.6	.044
Postoperative hospital stay, d	4.1 ± 4.5	4.0 ± 2.3	.934
Using of SB, n (%)	12 (19.0)	39 (35.8)	.021
Using of hemostatic forceps, n (%)	18 (28.6)	45 (41.3)	.095
Using of clips	1.3 ± 1.2	1.8 ± 1.5	.017
VAS score after operation	4.7 ± 0.8	5.5 ± 1.0	< .001
VAS score after 24 h	3.2 ± 0.6	3.3 ± 0.7	.153
Adverse events, n (%)			
Total adverse events	14 (22.2)	30 (27.5)	.443
Esophageal stenosis	13 (20.6)	26 (23.9)	.627
In-hospital adverse events	4 (6.3)	12 (11.0)	.311
Fever (> 38°C)	2 (3.2)	9 (10.1)	.189
Bleeding	2 (3.2)	4 (3.7)	.865
Perforation	1 (1.6)	2 (1.8)	.905
Mediastinal emphysema	1 (1.6)	4 (3.7)	.434
Subcutaneous emphysema	1 (1.6)	4 (3.7)	.434
Pleural effusion	1 (1.6)	5 (4.6)	.302
Pneumothorax	1 (1.6)	2 (1.8)	.905
Esophageal fistula	1 (1.6)	0 (0)	.187
Cumulative recurrence rate, n (%)	3 (4.8)	2 (1.8)	.271

°C = centigrade, d = day, HGIN = high-grade intraepithelial neoplasia, min = minute, N = negative, NBI = narrow-band imaging, P = positive, SB = scopolamine butylbromide, SCC = squamous cell carcinoma, VAS = visual analog system.

3.2. Histopathological and therapeutical outcomes

All patients underwent ESD successfully with a mean procedure time of 52.5 ± 38.1 minutes. The procedure time of patients of NBI group was significantly shorter than that of patients of LIS group (44.8 ± 32.2 vs 57.0 ± 40.6, $P = .044$) (Table 3). Patients of LIS group showed intensified peristaltic movements of the esophagus after spraying of Lugol's solution. The rate of intra-operative using of antispasmodic scopolamine butylbromide was significantly higher in patients of LIS group compared to those of NBI group (35.8% vs 19.0%, $P = .021$) (Table 3). *En bloc* resection was achieved in all patients and R0 resection was achieved in 89.5% (154/172) patients. Histopathological assessments indicated that there was no significant difference of histological type, invasion depth, R0 resection rate, margin positivity and lymphovascular invasion between patients of the two groups (Table 3).

3.3. Adverse events

A total of 44 (25.6%) patients suffered adverse events, including 16 (9.3%) patients with in-hospital adverse events and 39 (22.7%) with esophageal stenosis. All in-hospital adverse events

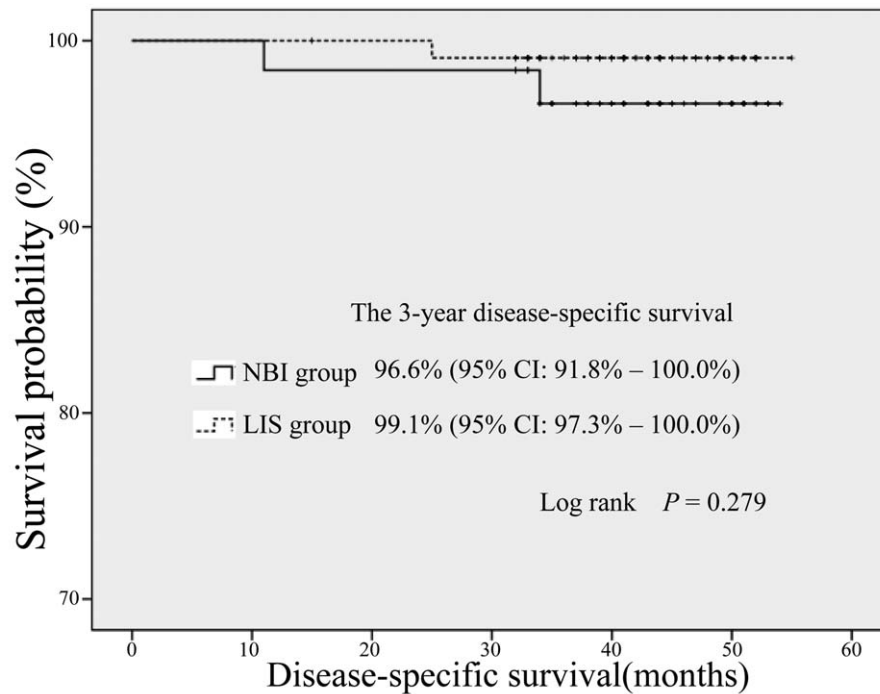


Figure 3. Comparisons of survival after endoscopic submucosal dissection between patients of the NBI group (n=63) and the Lugol's iodine group (n=109).

were managed by endoscopic methods and conservative treatments. Patients with esophageal stenosis received relief of symptoms after an average of 3.0 ± 3.3 (range 1 – 15) endoscopic balloon dilation sessions. Comparison analysis of the adverse events between patients of the two groups showed no significant difference (Table 3). However, patients of LIS group seemingly suffered higher risks of injury to the muscularis propria with significantly elevated number of clips used during the procedure to prevent delayed perforation as compared to patients of NBI group (1.8 ± 1.5 vs 1.3 ± 1.2 , $P = .017$). The VAS score of pain evaluation after operation was significantly higher in patients of LIS group than that in patients of NBI group (5.5 ± 1.0 vs 4.7 ± 0.8 , $P < .001$) (Table 3).

3.4. Follow-ups and survival analysis

After a mean follow-up period of 42.2 ± 7.2 months (range 11–55), a total of 5 (2.9%) patients developed recurrences, including 2 local recurrences and 3 lymph node or distant metastases. One patient with local recurrence belonged to the NBI group and the other belonged to the LIS group. The rates of local recurrences between the two groups showed no significant difference (1/63, 1.6% vs 1/109, 0.9%, $P > .05$). The three patients with lymph node or distant metastases consisted of 2 from the NBI group (2/63, 3.2%) and 1 from the LIS group (1/109, 0.9%) ($P > .05$). The cumulative recurrence rate showed no significant difference between patients of the two groups (Table 3). The two patients with local recurrence were re-treated by ESD successfully. A total of 5 deaths were observed, among which 3 were disease-specific. The estimated overall and disease-specific survival rates at 3 years were 97.7% and 98.3%, respectively. No significant difference of survival was observed between patients of the two groups (Fig. 3).

4. Discussion

An accurate demarcation of EESCCs is very important for esophageal ESD. Lesions should be resected with ideally tumor-free margin and unnecessary adverse events. For a long period of time, even up to date, LIS has almost served as the gold standard in margin determination during esophageal ESD.^[14] Lugol's solution is an absorbent dye based on iodine affinity to intracellular glycogen in normal squamous epithelium cells. Since glycogen is over-consumed and reduced in dysplastic and cancerous epithelium cells, the iodine staining of such cells is slighter or completely absent, manifesting as Lugol-voiding areas.^[15] LIS enables revelation of flat and invisible lesions by routine endoscopy and can produce clearer border of visible lesions, facilitating targeted biopsy and endoscopic resection.^[16] However, there remain a series of issues related to the limitations of LIS. It involves extra medical expenses of the Lugol's solution and the spraying catheter. The use of Lugol's solution often causes mucosal irritation leading to severe thoracoabdominal discomforts after operation and possesses potential risks of allergic reaction.^[14] Moreover, LIS may give rise to intensified peristaltic movements of the esophagus which would possibly disturb the dissection, prolong the total procedure time and increase the risks of undesired injury to the deep muscularis propria layer. It is notable that intra-operative demarcation by LIS may be complicated by widely-used iodine staining during preoperative endoscopy examination.^[17] There have been many reports about toxic mucosal damages induced by preoperative iodine staining such as esophagitis, erosions and ulcers.^[18–20] These lesions may also display as Lugol-voiding areas by intra-operative LIS, which may lead to expanded resection extents and unnecessary stricture as well.^[15] Whether mucosal damages by repeated iodine staining would exert influences on post-operative

histopathological evaluation is also questionable and worth paying attention to.

NBI is a revolutionary technology of virtual chromoendoscopy.^[21] Studies on superficial squamous neoplasms have shown that NBI could reveal subtle lesions as a well-demarcated brownish area without iodine staining.^[22,23] In addition, NBI combined with magnifying endoscopy is able to visualize the capillary microvasculature of the mucosal surface and has proven to be useful in predicting the histology of the lesions and assessing the invasion depth.^[22,24,25] Comparison studies between LIS and NBI in the detection of EESCCs have revealed that NBI could provide comparable or even better diagnostic accuracy with greater convenience while avoiding the limitations inherent to the use of Lugol's solution as mentioned above.^[8–10,26] Especially, the specificity of NBI with or without magnifying endoscopy was higher than that of LIS.^[9,10]

Despite many studies comparing NBI versus LIS in the screening, detection or diagnosis of EESCCs, only two studies have been reported to focus on the effectiveness of NBI versus LIS in delineating EESCCs margin during endoscopic resection.^[27,28] Costa et al reported the first study comparing NBI with LIS for endoscopic resection of esophageal squamous cell lesions and showed that mucosal inspection with LIS before endoscopic resection was not associated with increased complete lateral resection rate when compared with NBI.^[27] This study involved a relatively small number of 102 patients, including cases of low-grade dysplasia and cases treated by endoscopic mucosal resection. Some baseline characteristics, the scope models and follow-up time varied significantly between NBI group and LIS group. These limitations may exert influences on the interpretation of the results. What's more, the clinical outcomes regarding adverse events and long-term survival outcomes between patients of the two groups were not investigated in this study. The other study by Cono et al involved a large number of 223 patients with 304 lesions.^[28] However, this was a tandem but not a parallel study. The authors included only lesions that are difficult to delineate with LIS and marking with NBI followed by LIS was performed in each individual patient. Lesions clearly delineated using LIS alone were excluded from this study. Also, this study design made it inapplicable to investigate whether use or not use of LIS would affect the therapeutical short-term or long-term outcomes of ESD for EESCCs.

In the present study, we performed so far the largest parallel study comparing short-term and long-term outcomes of NBI versus LIS in the demarcation of EESCCs during ESD. Our results revealed that the use of NBI without Lugol's solution in the demarcation significantly correlated with a shorter procedure time and lower rates of antispasmodic drug injection. Although the rate of adverse events showed no significant difference between the two methods, patients with demarcation by NBI may suffer lower risks of injury to the deep muscularis propria as indicated by a reduced number of clips used during the procedure. They also displayed significantly alleviated discomforts after operation. On the contrary, there was no significant difference concerning the margin status, *R0* resection rates, recurrences and long-term survivals. Our study demonstrated that use of NBI in the demarcation of EESCCs during ESD could achieve comparable accuracy and clinical outcomes as compared with demarcation of LIS. Since NBI was more convenient, with lower costs and without the risks raised by Lugol's solution, a recommendation of NBI over LIS as the first-choice in the demarcation of EESCCs during ESD is more preferable.

Considering that LIS is based on the chemical reaction, the concentration of Lugol's solution may be an important factor correlated with the side-effects. The concentration of the solution in previous studies ranged from 0.5% to 5%. It has been reported that higher concentration (3% to 5%) of Lugol's solution might be associated with higher risk of adverse events.^[20] In our study, Lugol's solution was used at a concentration of 2.5%. Although the rate of adverse events showed no significant difference, there was still obvious irritation to the esophagus and the patients also suffered enhanced discomforts. Whether lower concentrations such as 1.25% or 0.75% would provide amelioration with consistent efficacy needs further investigation. On the other hand, it is recommended to carefully aspirate Lugol's solution from the stomach once the marking is completed, which would be helpful to minimize the side-effects.

There were limitations of the present study. It was a retrospective study conducted at a single tertiary hospital. These limitations may be related to a confined wide-spread applicability of the results. Although the retrospective nature of the study may be related to an unequal distribution of the subjects, the baseline characteristics showed no significant difference between the two groups of patients. A multi-center and prospectively randomized controlled study is warranted for further investigations in the future.

Author contributions

Conceptualization: Can Xu.

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