Submucosal Saline Injection Followed by Endoscopic Ultrasound versus Endoscopic Ultrasound Only for Distinguishing between T1a and T1b Esophageal Cancer

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ABSTRACT

Purpose: To examine whether submucosal saline injection (SSI) can improve traditional endoscopic ultrasound (EUS) accuracy in distinguishing between T1a and T1b stage esophageal squamous cell carcinoma (ESCC).

Experimental Design: Patients with T1N0M0 stage ESCC (n = 180) aged 18 to 85 years were enrolled between February 14, 2012 to June 4, 2018 at Sun Yat-sen University Cancer Center (Guangzhou, China). They were randomly assigned (1:1) to receive either EUS examination after 3–5 mL SSI or EUS only examination. All the patients were referred to thoracic surgeons to receive endoscopic resection (ER) or esophagectomy 5 to 10 days after EUS examination. Standard EUS criteria were used to preoperatively stage the ESCC cases, and surgical pathology reports after referral were used to postoperatively stage the cases. The primary endpoint was the diagnostic accuracy of T1b staging [defined as the sum of the true positive (T1b) and true negative (T1a) cases divided by the total number of cases].

Results: Among the per-protocol population, the SSI+EUS group (n = 81) was superior to the EUS-only group (n = 85) in terms of the diagnostic accuracy for T1b staging [93.8% (95% confidence interval (CI), 88.6–99.1) vs. 65.9% (95% CI, 55.8–76.0); P < 0.001]. The positive predictive value of SSI+EUS for diagnosing T1b ESCC reached 90.9% (95% CI, 81.1–100), which was significantly superior to that of EUS only [0.576 (0.450–0.702), P = 0.001].

Conclusions: SSI significantly improves the diagnostic accuracy of EUS in distinguishing between T1a and T1b ESCC, which might help avoid unnecessary esophagectomy and diagnostic ER.

Introduction

Esophageal cancer is one of the most common malignancies in the world, with esophageal squamous cell carcinoma (ESCC) being the predominant histologic subtype in China (1, 2). Treatment and prognosis of ESCC varies greatly across tumor stages. The 7th edition of the American Joint Committee on Cancer (AJCC) divides T1 stage ESCC into T1a and T1b substages according to the depth of tumor invasion. Patients with T1a stage ESCC with lesions confined to the mucosa and lamina propria have low probabilities (3–6%) of metastases in the local lymph nodes and distant organs. However, T1b stage ESCC with lesions invading the submucosal layer have relatively high probabilities (approximately 10–12%) of metastases in the local lymph nodes and distant organs and should be referred to esophagectomy plus lymphadenectomy (3, 5).

Endoscopic ultrasound (EUS) had been the most widely used method for depth evaluation of tumor invasion (T status) for ESCC, as it is the only technique that enables direct visualization of all the layers of the esophageal wall (6, 7). Although EUS was reported to have good performance in overall T staging, previous evidence has shown that EUS is unsatisfactory in distinguishing between T1a and T1b cases due to inadequate differences in echogenicity and the thin boundary between the mucosal and submucosal layers (6, 9). In clinical settings, endoscopists tend to over report T1a stage ESCC as T1b stage ESCC when they are unsure about the stage, which may result in unnecessary esophagectomy and lifelong physical and psychologic sequelae for patients with T1a stage ESCC. Consequently, the current National Comprehensive Cancer Network (NCCN) guidelines recommend ER as a diagnostic tool for distinguishing between T1a and T1b cases. ER is an invasive surgical approach that can adequately identify T1a cases, thus having diagnostic and therapeutic value for these patients; however, a substantial proportion of patients with diagnostic ER–indicated T1b disease would have to be subjected to subsequent esophagectomy, as these patients might not be fully cured by ER (5). Therefore, there is an unmet need to develop reliable and less invasive methods to improve the diagnostic accuracy of T1a and T1b stage ESCC.
**Translational Relevance**

Endoscopic ultrasound (EUS) is unsatisfactory in distinguishing between T1a and T1b stage esophageal squamous cell carcinoma (ESCC). Consequently, the National Comprehensive Cancer Network guidelines recommend endoscopic resection (ER) as a diagnostic tool for substaging T1 stage ESCC. However, as an invasive approach, diagnostic ER is not an optimal approach especially for T1b cases as most of them might not be fully cured by ER. Therefore, it is necessary to develop reliable and less invasive methods to distinguish between T1a and T1b stage ESCC. In this trial, we found that submucosal saline injection (SSI) significantly improved the diagnostic accuracy of EUS in differentiating between T1a and T1b stage ESCC. It can be used as an alternative to diagnostic ER for preoperative substaging T1 stage ESCC cases in remote regions where few endoscopists are able to perform diagnostic ER. The use of EUS+SSI would help T1b stage patients avoid invasive diagnostic ER.

Submucosal saline injection (SSI) is one of the necessary steps to minimize damage to the surrounding tissues of the esophageal wall during the treatment of esophageal mucosal lesions by ER (10). According to our previous observation, when SSI is performed, a saline cushion forms within the loose connective tissues of the submucosa, this cushion appeared to act as a good medium and echoic contrast-enhancing agent for ultrasound transmission enabling better distinction between the mucosal and submucosal layers (11, 12). In addition, saline can increase the thickness of the digestive tract wall, particularly the thickness of the submucosa. In our previous case series report, there was evidence to suggest SSI improves the performance of EUS in distinguishing between T1a stage ESCC from T1b stage ESCC (12). If our new technique could achieve similar accuracy to that of diagnostic ER, it would help patients avoid invasive diagnostic ER for a substantial proportion of T1b stage cases and might be of great clinical implications for developing countries and remote regions where few endoscopists are able to perform diagnostic ER.

In this randomized controlled trial, we aimed to validate whether SSI can improve the diagnostic accuracy of EUS in distinguishing between T1a and T1b ESCC lesions.

**Materials and Methods**

**Study design and participants**

This study was a single center, randomized controlled clinical trial carried out at Sun Yat-sen University Cancer Center (SYSUCC, Guangzhou, China).

The eligibility criteria were: (i) age between 18–85 years old; (ii) T1 stage lesion indicated by white light endoscopy or EUS at a primary or secondary hospital; (iii) referral for esophageal endoscopic examination at SYSUCC; (iv) normal blood coagulation function; (v) could afford related procedural costs (anesthesia and surgery); (vi) adequate organ function. The exclusion criteria were: (i) T2–T4 diseases; (ii) adenocarcinoma; (iii) lesions in multiple sites of the esophagus; (iv) 75%–100% circumferential lesions; (v) nodal involvement or distant metastasis indicated by prior EUS, CT, or MRE; (vi) received prior radiotherapy or chemotherapy; (vii) severe chronic heart diseases; (viii) pregnancy or lactation or planning pregnancy; and (x) other uncontrolled medical disorders.

This study was approved by the institutional review board of SYSUCC (Guangdong, China). This trial was conducted in accordance with the Declaration of Helsinki, the guidelines for Good Clinical Practice, the European Union Clinical Trial Directive, and local regulations. All participants provided written informed consent. All the authors had access to the study data and reviewed and approved the final manuscript.

**Randomization and masking**

Patients were randomly assigned (1:1) to receive either SSI followed by EUS (SSI+EUS) examination or EUS-only examination. The allocation sequence was computer-generated by a statistician at SYSUCC and carried out using sealed envelopes. No stratification factor was used. Research assistants from SYSUCC’s Department of Endoscopy assigned the enrolled patients into either the SSI+EUS or EUS-only group according to the information inside the sealed envelope. Except for the endoscopists, information regarding the allocation of participants was masked to the participants, research assistants, thoracic surgeons, pathologists, and statisticians. Unmasking was permitted for medical emergencies only.

**Procedures**

Recruited patients started their allocated examinations within one week after randomization. All the patients were sedated intramuscularly with 2 mg of diazepam 30 minutes before the EUS procedure, thus the patients were awake during the whole examination. Carrying out the procedure this way helped to avoid the aspiration of water. The detailed EUS examination procedure can be found elsewhere (13). Experienced endoscopists performed EUS with a 20-MHz miniature ultrasonic probe (Olympus GF-UM2000 Endoscopic System, Olympus Co. Ltd) following the sterile deaerated water immersion method as described below. After confirming the site of the lesion, the endoscopist positioned a balloon under the cardia using the guidance of the endoscope. Next, they injected approximately 30 mL of water into the balloon to inflate it. Then, the inflated balloon acted as a dam between the esophagus and cardia that could efficiently block the cardia and prevent the deaerated water from leaking into the stomach. The endoscopist stopped injecting the water when the lesion had been completely submerged. The balloon method efficiently prevents the deaerated water from leaking and reducing the total volume of injected water and risk of water aspiration. We defined T1a (tumor invading the lamina propria or muscularis mucosa but not the submucosa) and T1b (tumor invading the submucosa) cases according to the 7th AJCC staging scheme for ESCC (14). The ultrasound characteristics of T1a lesions with the 20-MHz probe included low echogenicity in the lamina propria and muscularis mucosal layers and normal echogenicity in the submucosal layer of the esophageal wall. For T1b lesions, the ultrasound characteristics included low echogenicity in the lamina propria, muscularis mucosal, and submucosal layers and normal echogenicity in the muscularis propria layer of the esophageal wall. EUS examination and staging were simultaneously performed by two endoscopists. One endoscopist performed the EUS examination and tentatively staged the depth of the lesion, while the other endoscopist served as a second blind examiner and independently staged the EUS images again. We recorded the final consensus between the two endoscopists as well as the result of each endoscopist in the Case Report Form.

Patients in the SSI+EUS group received EUS examination immediately after SSI. Two endoscopists staged the depth of the lesion by regular and iodine dye–enhanced endoscopy before performing SSI. Then one of the endoscopists injected 3–5 mL of saline into the submucosa within 10 minutes using a single-use 22G mucosal needle (Endo-Flex Co.). The puncture point was located 0.5 cm from the edge.
of the lesion, and the saline injection was stopped when the esophageal mucosa was elevated by approximately 1 cm. Supplementary Figure S1 shows the schematic diagram for SSI. After SSI, the two endoscopists independently determined the stage of the lesion.

The EUS only and SSI+EUS procedures were performed by the same group of endoscopists. Patients in the SSI+EUS and EUS-only groups were referred to thoracic surgeons to receive either ER or esophagectomy 5–10 days after the initial EUS examination. The technicians in the Department of Pathology made the slides by cutting in 2–3 mm intervals for both the ESD and surgical specimens. Experienced pathologists independently reviewed the resected tissues and staged the lesions using the 7th AJCC staging scheme for ESCC.

Outcomes

The primary endpoint of the study was diagnostic accuracy for T1b staging [defined as the sum of the true positive (T1a) and true negative (T1b) cases divided by the total number of cases]. Secondary endpoints included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for T1b stage cases, and interobserver reliability for T1 substaging. All adverse events during the SSI+EUS or EUS-only examinations were recorded and graded according to the National Cancer Institute Common Terminology Criteria (version 4.0.3).

Statistical analyses

On the basis of published reports and our experience at the time of the study, the diagnostic accuracy rate for EUS in distinguishing between T1a and T1b disease was estimated at 65% (9). We hypothesized that the diagnostic accuracy rate could be increased to 85% with the introduction of the SSI strategy. With the two-sided Fisher exact test at a significance level of 0.05, 81 participants were needed in each group to ensure a power of 80% to detect the positive improvement in diagnostic accuracy.

All the analyses were based on the per-protocol population, which excluded patients in a major violation of the inclusion or exclusion criteria, patients who withdrew consent or did not receive the planned protocol managements. In addition to diagnostic accuracy [defined as the sum of the true positive (T1a) and true negative (T1b) cases divided by the total number of cases], sensitivity (defined as the proportion of the pathologic T1b cases that were correctly identified as T1b in preoperative examination), specificity (defined as the proportion of the pathologic T1a cases that were correctly identified as T1a in preoperative examination), PPV (defined as the proportion of preoperatively reported T1b cases that were pathologic T1b cases), and NPV (defined as the proportion of preoperatively reported T1a cases that were pathologic T1a cases), we also used the receiver operating characteristic (ROC) curve and AUCs to compare the diagnostic performance between the SSI+EUS and EUS-only groups. The larger the area under the ROC curve indicated better diagnostic performance. Kappa concordance index was used to test the interobserver reliability of EUS and SSI+EUS, respectively, for substaging T1a and T1b cases. Considering that some of the cases might be diagnosed as high-grade dysplasia (HGD) or T2/T3/T4 disease in postoperative.
pathology, we had preplanned to classify the former into T1a and the latter into T1b in the analyses. We also performed subgroup analysis after excluding patients with HGD or T2/T3/T4 to test the robustness of results.

Data analyses were performed by SAS version 9.3 (SAS Institute Inc.). All statistical tests were two-sided with a significance level of 0.05. The study is registered at ClinicalTrials.gov, number NCT01555801.

**Data sharing**

The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.com). It is available upon reasonable request.

**Results**

Between February 14, 2012 and June 4, 2018, 180 patients were enrolled and randomly assigned to receive SSI+EUS examination (n = 90) or EUS-only examination (n = 90) (Fig. 1). Because of patient withdrawals (Fig. 1), 81 patients who received SSI+EUS examinations and 85 patients who received EUS-only examinations were included into the per-protocol analysis. The two groups were balanced with respect to age, sex, and body mass index (Table 1). In postoperative pathology, the SSI+EUS group had a slightly higher proportion of HGD cases (34.6% vs. 29.4%) and lower proportion of T1b cases (39.5% vs. 44.7%) than the EUS-only group (Table 1). No patients were diagnosed with T2–T4 disease postoperatively. All the patients were found node negative after EUS with or without SSI and subsequent surgery.

Figure 2 shows the EUS images and associated schematic diagrams of the lesions for T1a and T1b cases. In the EUS-only group, the echogenicity contrast of the mucosa and submucosa was inadequate for both T1a (Fig. 2A) and T1b (Fig. 2B) lesions. It was difficult to determine whether the lesion had invaded the submucosal layer or not due to the dim boundary between the edge of the lesion and submucosa (Fig. 2A and B). However, after SSI, the mucosa had relatively enhanced echogenicity compared with the submucosa that was filled with saline (Fig. 2C and D). The boundary between the edge of the lesion and submucosa was obvious after SSI due to the saline formed cushion in the submucosa (Fig. 2C and D). As such, it was much easier to determine whether the lesion had invaded the lamina propria or muscularis mucosa but not the submucosa (Fig. 2C), or whether it had invaded the submucosa (Fig. 2D) after SSI. Figure 3 shows the endoscopic (Fig. 3A, B, E, F) and pathologic images (Fig. 3C, D, G, H) of T1a and T1b lesions, respectively.

Table 2 shows the preoperative and postoperative stages for ESCC cases in the SSI+EUS and EUS-only groups. As preplanned, HGD cases were combined with T1a cases for further analyses. Overall, SSI+EUS significantly improved the accuracy rate of T1b staging compared with EUS-only [93.8% (95% confidence interval (CI), 88.6–99.1) vs. 65.9% (95% CI, 55.8–76.0); Fisher exact test P < 0.001]. The interobserver reliability (Kappa) in subtyping T1 ESCC was high for both the SSI+EUS and EUS-only [0.845 (95% CI, 0.726–0.964) and 0.831 (95% CI, 0.742–0.919), respectively]. The percentage of T1b cases misclassified as T1a was similar for the SSI+EUS [2 of 32; sensitivity, 93.8% (95% CI, 85.4–100)] and EUS-only groups [4 of 38; sensitivity, 89.5% (95% CI, 79.7–99.2)]; Fisher exact test P = 0.681]. SSI+EUS identified 46 out of 49 patients with pathologic T1a disease, achieving a specificity of 93.9% (95% CI, 87.2–100.0). In contrast, 25 of 47 T1a cases were misclassified as T1b with EUS-only, resulting in a significantly inferior specificity (46.8%; 95% CI, 32.5–61.1; Fisher exact test P < 0.001) to SSI+EUS. In addition, as measured by the AUC, the discrimination between T1a and T1b diseases was significantly better with SSI+EUS than with EUS-only [0.938 (95% CI, 0.884–0.993) vs. 0.681 (95% CI, 0.594–0.769); Z test P < 0.001; Supplementary Fig. S2]. The PPV was significantly better with EUS+EUS than with EUS-only [0.909 (95% CI, 0.811–1.000) vs. 0.576 (95% CI, 0.450–0.702); P = 0.001; Supplementary Table S1], whereas NPV was 0.958 (95% CI, 0.902–1.000) for EUS+EUS and 0.846 (95% CI, 0.702–0.985; P = 0.176). Subgroup analyses showed that the percentage of HGD and non-HGD T1a cases misclassified as T1b was significantly lower in the EUS+EUS group than in the EUS-only group [HGD: 0 of 28 (0.0%) vs. 10 of 25 (40.0%); T1a: 3 of 21 (14.3%) vs. 15 of 22 (68.2%); Fisher exact test P < 0.001 and P = 0.001, respectively]. After excluding patients with HGD, similar findings were yielded regarding diagnostic accuracy, sensitivity, specificity, PPV, and NPV (Supplementary Table S2).

Adverse events during examination were recorded in one patient in the SSI+EUS group and one in the EUS-only group, both were a grade 1 esophageal hemorrhage.

**Discussion**

In this randomized study, SSI+EUS over EUS-only clearly improved the diagnostic accuracy in differentiating between T1a and T1b stage ESCC. The introduction of SSI to EUS did not increase the risk of complications during examination, indicating the safety of this technique. The reasons why SSI significantly improves the diagnostic accuracy of EUS in differentiating between T1a and T1b cases may be explained by the following. First, saline injected into the submucosa may serve as a contrasting agent for ultrasound examination, markedly increasing the acoustic impedance difference as well as accentuating the boundary between the edge of the lesion and the submucosa.

### Table 1. Demographic and clinical characteristics of the submucosal saline injection followed by EUS (SSI+EUS) and endoscopic ultrasound (EUS)-only groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>SSI+EUS (N = 81)</th>
<th>EUS (N = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>60.7 (7.6)</td>
<td>61.1 (8.0)</td>
</tr>
<tr>
<td>Age group, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>38 (46.9)</td>
<td>38 (44.7)</td>
</tr>
<tr>
<td>≥60 years</td>
<td>42 (52.1)</td>
<td>47 (55.3)</td>
</tr>
<tr>
<td>BMI in kg/m², mean (SD)</td>
<td>23.3 (3.8)</td>
<td>23.1 (2.7)</td>
</tr>
<tr>
<td>BMI groups, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5 kg/m²</td>
<td>10 (12.4)</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td>≥18.5 and &lt;24 kg/m²</td>
<td>39 (48.2)</td>
<td>52 (61.2)</td>
</tr>
<tr>
<td>≥24 kg/m²</td>
<td>31 (38.3)</td>
<td>26 (29.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1.2)</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61 (75.3)</td>
<td>64 (75.3)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (24.7)</td>
<td>21 (24.7)</td>
</tr>
<tr>
<td>Site of the lesion, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper third</td>
<td>10 (12.4)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Middle third</td>
<td>44 (55.3)</td>
<td>53 (62.4)</td>
</tr>
<tr>
<td>Lower third</td>
<td>27 (33.3)</td>
<td>29 (34.3)</td>
</tr>
<tr>
<td>Preoperative stage based on EUS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>48 (59.3)</td>
<td>26 (30.6)</td>
</tr>
<tr>
<td>T1b</td>
<td>33 (40.7)</td>
<td>59 (69.4)</td>
</tr>
<tr>
<td>Postoperative stage based on pathology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HGD</td>
<td>26 (34.6)</td>
<td>25 (29.4)</td>
</tr>
<tr>
<td>T1a</td>
<td>21 (25.9)</td>
<td>22 (25.9)</td>
</tr>
<tr>
<td>T1b</td>
<td>32 (39.5)</td>
<td>38 (44.7)</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index.
Second, the saline cushion can increase the thickness of the esophageal wall, especially the thickness of the submucosa, thus facilitating improved visualization of the depth of tumor invasion (12).

The accuracy of EUS for T1 substaging varies greatly among the literature (8, 15, 16). Despite that, a sensitivity of >89% with EUS-only for T1b staging was achieved in our institute (i.e., a tertiary hospital). But a diagnostic accuracy of 65.9% with EUS-only for T1a staging was at the lower end of the range of reported accuracies in previous literature (9, 17), primarily owing to the unsatisfactory performance of EUS-only in terms of specificity (as low as 46.8%). One possible

Figure 2. Ultrasound images and associated schematic diagrams of T1a and T1b esophageal squamous cell carcinoma cases before (A and B) and after (C and D) saline injection. With the use of SSI only, the acoustic impedance difference between the lesion and the submucosa was inadequate and the boundary of them was dim. The distance between the mucosa and submucosa was short. With the use of SSI+EUS, the acoustic impedance difference between the lesion and the submucosa was increased and the boundary of them was more obvious. It was much easier to determine whether the lesion had invaded the submucosa or not due to the echoic contrast effect of the saline cushion and the increased thickness of the esophageal wall.
explanation is that endoscopists tend to over-stage T1a disease as T1b when there is uncertainty. This over-staging might result in unnecessary esophagectomy and lifelong physical and psychologic sequelae such as an esophagogastric anastomotic leak, dysphagia, and increased mortality for patients with T1a stage ESCC (18). The proposed EUS+SSI technique, which significantly improved the diagnostic accuracy of EUS in this study (over 90%), might facilitate the use of less aggressive treatment methods (i.e., ER) and reduce esophagectomy associated physical and psychologic sequelae (19).

Because of the inadequate accuracy of traditional EUS in sub-staging T1 cases, current NCCN guidelines recommend ER as a diagnostic technique for substaging T1 stage ESCC. With the introduction of SSI, the sensitivity and PPV of EUS+SSI both exceed 90% for T1b staging, which indicates that EUS+SSI can successfully identify the vast majority of pathologic T1b cases and that almost all the EUS+SSI-suggested T1b cases are true T1b cases. Considering that esophagectomy is the mainstay treatment option for T1b ESCC, the proposed low-risk and cost-effective EUS+SSI approach has the potential to avoid diagnostic ER for some of these patients. This has great clinical implications for developing countries and remote regions where few endoscopists are able to perform diagnostic ER. The SSI+EUS procedure was not designed to replace but to provide an alternative to diagnostic ER. Endoscopists should balance the pros and cons in the decision-making process regarding diagnostic ER versus SSI+EUS. Specifically, the use of SSI+EUS could avoid diagnostic ER for the vast majority (93.8%) of T1b stage cases, at the cost of a small proportion (6.1%) of T1a cases receiving unnecessary esophagectomy.

Narrow band imaging (NBI) with magnifying endoscopy is another commonly used method for substaging early-stage ESCC (20). SSI+EUS compared favorably with NBI with magnifying endoscopy in terms of diagnostic accuracy for T1a staging (21). Although the NBI system is effective and easy to operate, it has several drawbacks. First, patients with ESCC are prone to bleeding during NBI examination, as the NBI camera has to be placed tightly on the esophageal mucosa to enable clear visualization of the intraepithelial papillary capillary loop. Once bleeding occurs, NBI examination becomes difficult and staging accuracy is likely compromised. The SSI+EUS approach, which uses a miniature ultrasonic probe to identify early-stage ESCC, is not influenced by the state of the esophageal mucosa. Second, the NBI system may be unavailable in less developed areas. SSI+EUS is a simple and cost-effective procedure that could be used as an alternative in hospitals that do not have access to the NBI system or for patients unsuitable for NBI examination. Another limitation of NBI in staging of ESCC is that it is unable to visualize the whole lesion especially when the lesion is large or occurs in different sites of the esophagus.

This study has some limitations. One, SSI+EUS requires a longer period of examination than EUS-only, which might increase patients’ discomfort and thus impact its acceptability. However, no participants withdrew from this study due to intolerable discomfort. Two, all the patients in this study cohort had ESCC.

**Table 2.** Preoperative and postoperative stages for ESCC in the SSI+EUS and EUS-only groups.

<table>
<thead>
<tr>
<th>Preoperative EUS reported stage</th>
<th>Postoperative pathologic stage</th>
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<tbody>
<tr>
<td>T1a</td>
<td>46 (93.9) 2 (6.2)</td>
</tr>
<tr>
<td>T1b</td>
<td>3 (6.1) 30 (93.8)</td>
</tr>
<tr>
<td>EUS, n (%)</td>
<td>22 (46.8) 4 (10.5)</td>
</tr>
<tr>
<td>T1a</td>
<td>25 (53.2) 34 (89.5)</td>
</tr>
</tbody>
</table>

*As preplanned, cases with high-grade dysplasia were classified into T1a.
Further studies are needed to verify the robustness of our findings in patients with other histologic types of esophageal cancer such as adenocarcinoma. Three, as we mentioned before a small proportion (6.1%) patients with T1a were judged to be T1b using SSI+EUS. These patients would need to receive aggressive esophagectomy instead of expected ER, and their surgeons would need to balance the pros and cons of using our new technique in guiding clinical decisions. Four, our study was a single center based clinical trial and the findings might be subject to insufficient generalizability. A multicenter study is planned to test the generalizability of our findings among broader population. Five, SSI might cause esophageal fibrosis and make ESD difficult to perform. Yet, according to our experience, the formation fibrosis takes approximately 10 days. We suggest eligible patients accept an ESD procedure within 10 days after SSI.

SSII significantly improves the diagnostic accuracy of EUS in distinguishing between T1a and T1b stage ESCC. It can be used for patients with preoperative substage T1 stage ESCC and substantially reduce the proportion of diagnostic ER for T1b stage ESCC cases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: J.-J. Li
Development of methodology: L.-J. He, C. Xie, J.-J. Li
Writing, review, and/or revision of the manuscript: L.-J. He, C. Xie, Z.-X. Wang, L.-N. Luo, J.-J. Li

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.-J. He, C. Xie, L.-N. Luo, J.-J. Li

Study supervision: G.-L. Xu, J.-J. Li

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References


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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis) L.-J. He, C. Xie, Z.-X. Wang, J.-J. Li

Writing, review, and/or revision of the manuscript L.-J. He, C. Xie, Z.-X. Wang, L.-N. Luo, J.-J. Li

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