

Outcomes of super minimally invasive surgery vs. esophagectomy for superficial esophageal squamous cell carcinoma: a single-center study based on propensity score matching

Jiancong Feng^{1,2}, Ningli Chai², Enqiang Linghu², Xiuxue Feng², Longsong Li², Chen Du², Wengang Zhang², Qingzhen Wu²

¹Medical School of Chinese People's Liberation Army, Beijing 100853, China;

²Department of Gastroenterology and Hepatology, The First Medical Center of Chinese People's Liberation Army General Hospital, Beijing 100853, China.

Super minimally invasive surgery (SMIS) is a new concept proposed in 2016, which is defined as “curing the disease while preserving the integrity of human organ anatomy.”^[1] Its concept has been accepted by the World Endoscopy Organization and Chinese Society of Digestive Endoscopy. The obvious advantage of SMIS is to cure diseases without damaging the structure and function of organs. For cancer patients, it can ensure a normal survival time and postoperative quality of life (QoL).^[1] Nevertheless, high-quality comparative studies between SMIS and esophagectomy in the treatment of superficial esophageal squamous cell carcinoma (SESCC) are lacking. Hence, the present study mainly aimed to compare the outcomes of SMIS and esophagectomy directly, especially in terms of QoL and lifestyle.

We reviewed patients who were hospitalized in Chinese People's Liberation Army (PLA) General Hospital with SESCO from January 2018 to June 2020 and received SMIS or esophagectomy. The diagnosis of SESCO is based on postoperative pathological results. The following exclusion criteria were employed: (1) tumor–node–metastasis (TNM) staging does not satisfy T1N0M0; (2) other previous treatments for the current disease (such as chemotherapy or radiotherapy); (3) second primary malignancy or previous other malignancy treatments. In the SMIS group, patients who underwent rescue esophagectomy immediately were excluded from the intention-to-treat analysis because this procedure goes beyond the scope of SMIS. As shown in Supplementary Figure 1, <http://links.lww.com/CM9/B250>, 120 patients were included in the SMIS group and 62 patients were included in the esophagectomy group. The present study was approved by the Ethics Committee of PLA General

Hospital (No. S2017-010-02) and informed consent was received from each patient.

Before the procedure, all patients underwent gastroscopy and were evaluated by magnifying endoscopy/blue light laser/chromoendoscopy with Lugol solution/narrow-band imaging. In addition, endoscopic ultrasound, computed tomography (CT), and/or positron emission tomography–CT were used to determine the tumor boundary, depth of invasion, and lymph node metastasis. Based on the size of the tumor and the condition around the lesion, endoscopic submucosal dissection or endoscopic submucosal tunnel dissection can be used in SMIS, and the specific steps were carried out as described previously.^[2] Esophagectomy can be divided into open esophagectomy and minimally invasive esophagectomy according to whether thoracotomy was performed, and the procedures have been described in detail in the previous study.^[3]

The primary outcomes were QoL and lifestyle changes during postoperative follow-up. The secondary outcomes included overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS). QoL was evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire.^[4] And the degree of dysphagia and the change of sleep position were also highlighted during the follow-up. Dysphagia was divided into five levels according to the Mellow–Pinkas score.^[5] The change of sleep position was evaluated by whether the patient could sleep supine or not. The patients were scheduled for follow-up at 3, 6, and 12 months after the operation, including tumor marker assessments, gastroscopy, and CT. Patients were also

Jiancong Feng and Ningli Chai contributed equally to this work.

Correspondence to: Enqiang Linghu, Department of Gastroenterology and Hepatology, The First Medical Center of Chinese People's Liberation Army General Hospital, 28 Fuxing Road, Haidian District, Beijing 100853, China
E-Mail: linghuenqiang@vip.sina.com

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contacted to obtain the QLQ-C30 scores and lifestyle via interview at the clinic or via telephone.

Statistical analyses were processed using the SPSS (IBM Statistics 25.0, USA). A comparison of categorical variables was performed using the χ^2 test or Fisher's exact test. Continuous variables were compared using Student's *t*-test or Mann-Whitney *U* test. The survival analysis was used for the Kaplan-Meier method. And *P* values <0.05 (two-sided) were indicated statistical significance. To minimize selection bias, we used propensity score matching (PSM) to compare the outcomes between the SMIS and esophagectomy groups. PSM included ten factors that may influence treatment choice and treatment prognosis, including age, sex, Charlson comorbidity index, tumor diameter, tumor location, differentiation grade, invasion depth, lymphovascular invasion, margin positivity, and follow-up period. The SMIS group and the esophagectomy group were matched at a ratio of 1:1, and the PSM caliper value was set to 0.01.

The baseline characteristics of the patients are shown in Supplementary Table 1, <http://links.lww.com/CM9/B250>. And the baseline characteristics of the 34 matched patient pairs were comparable after PSM. The mean follow-up period was 23.1 ± 8.8 months in the SMIS group and 23.8 ± 8.2 months in the esophagectomy group. No significant differences in overall mortality, disease-specific mortality, or recurrence and/or metastasis rates between the SMIS and esophagectomy groups were noted at the end of follow-up before and after PSM. In the matched cohort, the rate of additional therapy in the esophagectomy group was slightly lower (11.8%, 4/34), but no statistically significant difference was noted between the two groups ($P = 0.072$) [Supplementary Table 2, <http://links.lww.com/CM9/B250>]. Moreover, the SMIS group still belonged to the mode of organ preservation after additional therapy. As shown in Supplementary Figure 2, <http://links.lww.com/CM9/B250>, the 3-year DSS rates of the two groups before and after matching were 93.0% vs. 92.4% ($P = 0.472$) and 100% vs. 97.1% ($P = 0.429$), respectively. The 3-year RFS rates of the two groups before and after matching were 80.1% vs. 81.7% ($P = 0.649$) and 80.6% vs. 85.5% ($P = 0.575$), respectively.

The matched cohort QoL scores are shown in Supplementary Table 3, <http://links.lww.com/CM9/B250>. In propensity score-matched analysis with two groups, the global health status score and physical and social function scores of the functional scale in the SMIS group were significantly better than those in the esophagectomy group, with statistically significant differences ($P = 0.002$; $P = 0.048$; $P = 0.005$). The scores of fatigue, pain, sleep disturbance, and economic impact in the esophagectomy group were significantly higher than those in the SMIS group, and the differences were statistically significant ($P = 0.024$; $P = 0.022$; $P = 0.030$; $P = 0.001$). During the follow-up, we also asked the patients about lifestyle changes such as diet and sleep position. The median of Mellow-Pinkas score in the SMIS group and esophagectomy group were 0 (0, 0) and 0 (0, 2), respectively, with the statistical difference between the two groups ($P < 0.05$). In the SMIS group, only one patient (1/34,

2.9%) could not be supine at night. In the esophagectomy group, 19 patients (55.9%) were unable to lie flat and needed to sleep by increasing the height of pillows or raising the head of the bed [Supplementary Table 4, <http://links.lww.com/CM9/B250>].

To date, there are few comparative studies on endoscopic resection and esophagectomy in the treatment of SESCC. Although PSM was used, previous studies focused more on survival analysis. The SMIS ushered in a new stage of surgical treatment.^[1] It is of great importance to compare the two modes, especially when the focus is no longer limited to the survival rate.

In the present study, we established strict inclusion and exclusion criteria and matched patients to ensure that there was no statistically difference in demographic characteristics and tumor characteristics among all patients. Under this premise, the outcomes of SMIS and esophagectomy in the treatment of SESCC were compared. The postoperative QoL at a mean follow-up of two years in the SMIS group was superior to that in the esophagectomy group according to retrospectively collected EORTC QLQ-C30 questionnaire, especially in the aspects of social function, global health status, and financial impact. The huge trauma of esophagectomy leads to fatigue and impairment of physical function. Higher pain and sleep disturbance scores may be associated with a higher incidence of reflux. In the field of dysphagia, the severity of the esophagectomy group was higher than the SMIS group. Due to the small sample size, this result needs to be carefully interpreted. The mechanism may be that the integrity of the organ is preserved after SMIS, and only the elasticity of the esophageal wall is affected. Dysphagia is more caused by the decline in compliance. In the esophagectomy group, due to the reconstruction of anatomical integrity through the anastomosis of organs, dysphagia was mainly due to "obstructive" stenosis caused by fibrosis. In terms of sleep position, most patients in the esophagectomy group complained that they could not sleep supine at night, which caused great annoyance to the patients. In the SMIS group, the majority of patients could sleep supine. From the perspective of lifestyle, the effect of esophagectomy on diet and sleep was significantly better than that of SMIS. In conclusion, the QoL and lifestyle of patients in the SMIS group were significantly better than in the esophagectomy group. In addition, no significant differences in OS, DSS, or RFS were noted between the SMIS group and the esophagectomy group. It should be noted that this study is not only a comparison of specific surgical methods, but also a comparison of two surgical concepts.

There are several limitations of this study. The main limitation is the potential selection bias in the retrospective design of a single center; however, a prospective trial design is difficult to achieve due to ethical and other reasons. Second, it was difficult to obtain the precise depth of tumor in the esophagectomy group, especially for submucosal invasion. However, we used PSM to control bias. Third, the follow-up was relatively short and the size of cohort was relatively small. Next, we will also carry out esophageal manometry on the patients.

To conclude, the survival rates of SMIS and esophagectomy were comparable at the mid-term follow-up, whereas SMIS showed great advantages in terms of QoL and lifestyle. Further studies with longer follow-up time and larger samples are needed.

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Conflicts of interest

None.

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