



Clinical characteristics and survival of esophageal cancer patients: annual report of the surgical treatment in Shanghai Chest Hospital, 2016

Yuxin Yang^{#^}, Zhichao Liu^{#^}, Yifeng Sun, Xufeng Guo, Bin Li, Rong Hua, Yang Yang, Teng Mao, Hong Zhang, Yuchen Su, Chunguang Li, Zhigang Li[^]

Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Contributions: (I) Conception and design: Yuxin Yang, Z Liu; (II) Administrative support: Z Li; (III) Provision of study materials or patients: Y Sun, X Guo, B Li, H Zhang, Y Su, R Hua, T Mao; (IV) Collection and assembly of data: Yang Yang, C Li; (V) Data analysis and interpretation: Yuxin Yang, Z Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Zhigang Li. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. Email: zhigang.li@shsmu.edu.cn.

Background: Esophageal cancers present a significant burden of disease and remain one of the most lethal of cancers worldwide, particular in China. Surgical treatment remains the cornerstone of esophageal cancers, and a real-world data from a high-volume esophageal cancer center have guiding significance in evaluation of the current clinical practice. This report describes the clinical characteristics, treatment outcomes, and survival of surgical treatment in patients with esophageal cancer in Shanghai Chest Hospital (SCH).

Methods: All patients diagnosed with esophageal cancer who received esophagectomy or endoscopic resection at SCH in 2016 were included in this study. The baseline characteristics, treatment-related outcomes, and follow-up data were collated from the medical records and a prospectively maintained database. The clinicopathological characteristics, surgical complications, and oncologic outcomes were summarized. Kaplan-Meier method was used to estimate their survival and Cox regression model was used to estimate the associated risk factors.

Results: In 2016, a total of 546 patients with esophageal cancer received surgical or endoscopic resection at SCH (including 517 esophagectomies and 29 endoscopic resections). Most patients (52.4%) were between 60–69 years old, 79.5% were male, and for more than half of all patients (51.3%), the tumor was located at the middle thoracic esophagus. Overall, 11.0% (60/546) of patients received neoadjuvant therapy and 45.8% (250/546) of patients were treated with adjuvant therapy. Minimally invasive esophagectomy (including thoracoscopy and robot-assisted) was performed in 58.0% of patients and the R0 resection rate was 90.3%. The postoperative 30- and 90-day mortality was 0.73% and 1.1%, respectively. For the esophagectomy cohort, the 1-, 2-, 3-, 4-, and 5-year overall survival (OS) rates were 86.5%, 67.8%, 59.9%, 54.5%, 51.8%, and for cancer specific survival (CSS), the rates were 91.8%, 74.2%, 66.6%, 61.2%, and 59.1%, respectively.

Conclusions: Through a standardized surgical procedure, the short- and long-term outcomes of patients with esophageal cancer were acceptable with good safety and oncological control in a high-volume center in China. This study reveals important surgical treatment effects of esophageal cancer patients and contributes to improvement of clinical management and future treatment development.

Keywords: Esophageal cancer; esophagectomy; endoscopic resection

[^] ORCID: Yuxin Yang, 0000-0001-7398-7473; Zhichao Liu, 0000-0003-3542-0905; Zhigang Li, 0000-0001-5086-5334.

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Introduction

Esophageal cancer is the sixth leading cause of death resulting from cancer worldwide with esophageal squamous cell carcinoma (ESCC) accounting for over 90% of total esophageal cancer in China (1,2). Most esophageal cancers are locally advanced when diagnosed and the associated extensive lymph node metastasis, especially occult lymph node metastasis, contributes to the complexity of the treatment decisions (3,4). Multidisciplinary treatment including preoperative and postoperative chemoradiotherapy/chemotherapy has been increasingly performed worldwide since it has shown a survival benefit over surgery alone; however, surgery remains the cornerstone of curative treatment of esophageal cancer. Unfortunately, few studies to date have evaluated the real-world data of surgical treatment of esophageal cancer. Analysis of a large volume of homogeneous data may provide meaningful information that is crucial to improve treatment development. Representative database systems of this type include the Japan Esophageal Society (JES) annual report in Japan (5), the National Cancer Database (NCDB) database

in the United States (6), and the European Society of Thoracic Surgeons (ESTS) registry database in Europe (7). In 2016, the first esophageal cancer annual report of JES had published, providing a comprehensive introduction on all aspects of diagnosis and treatment-related outcome of esophageal cancer in Japan, served as a reference parameter in surgical treatment of esophageal cancer. However, except for JES database, annual reports regarding esophageal cancer treatment from the NCDB and ESTS database are also warranted, and China with no exception.

More than 50% of newly diagnosed global esophageal cancers cases being in China (8), yet, the current national data registration system is lacking and incapable to involve all high-volume esophageal cancer centers. There are many single centers with huge volumes of data (more than 500 cases of esophageal cancer operations per year) in China. Although they are not representative of multiple regions, they have unique advantages in terms of therapeutic homogeneity. Notably, many reports have suggested that the future treatment of esophageal cancer should be concentrated in large centers that are able to provide better therapeutic effects (9-12). For this reason, single-center and large-sample data annual reports with standardized treatment will be of great significance in determining treatment strategies for the future treatment development.

Shanghai Chest Hospital (SCH) is a tertiary referral center with more than 800 esophageal cancer surgical operations per year [2019–2021], we have published the first annual report of surgical treatment of esophageal cancer in the Chinese journals in 2015, and plan to provide annual reports in SCH since 2016 to the worlds as reference scientific data. Here, we briefly summarized the comprehensive clinical characteristics and survival of esophageal cancer surgical treatment in SCH, 2016. We present the following article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1672/rc>).

Methods

Clinical data

All patients who had undergone surgical treatments

Highlight box

Key findings

- Surgical treatment conferred acceptable short- and long-term results in a high-volume center in China.

What is known and what is new?

- More than 50% of newly diagnosed global esophageal cancers cases located in China. McKeown and Ivor Lewis surgery of the right thoracic approach had gradually occupied the mainstream of esophageal cancer surgery in China. Surgical safety with less than 1% of operative death within 30 days was becoming the norm in large centers in China.
- The proportion of early-stage patients is a critical factor in determining the ultimate survival outcome.

What is the implication, and what should change now?

- Single-center and large-sample data annual reports with standardized treatment will be of great significance in determining treatment strategies for the future.
- More early-stage patients will be recruited for individualized neoadjuvant therapy with the aim of improving treatment outcomes.

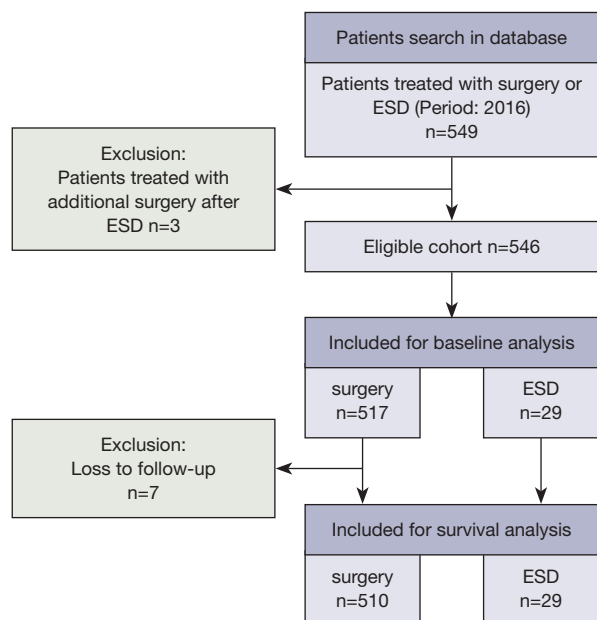


Figure 1 A flowchart of the analysis procedure. ESD, endoscopic submucosal dissection.

including esophagectomy and endoscopic resection with esophageal cancer at SCH in 2016 were enrolled in this study. Data were extracted from the esophageal cancer single disease database in our center for analysis. A total of 546 eligible patients with esophageal cancer who underwent primarily esophagectomy, as well as minor endoscopic submucosal dissection (ESD) at SCH in 2016 were included. All operations had more than 10 attending thoracic surgeons, but were mainly performed by 3 attending surgeons affiliated to the Section of Esophageal Surgery (Z Li, Y Sun, and T Mao). Although more than 87% of the pathologic types were squamous cell carcinomas, we also included the rare histology of gastroesophageal junction adenocarcinoma, small cell neuroendocrine tumors, etc. Endoscopic resections were performed by esophageal surgeons and gastrointestinal physicians (Z Li, H Zhang, and Y Su) and were therefore also included. Clinicopathological characteristics was analyzed in all 546 patients, but a total of 7 patients who were lost to follow-up in the first 2 years after the operation were excluded from the long-term survival analysis (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of the Shanghai Chest Hospital (No. IS21111). Individual consent for this retrospective analysis was waived.

Evaluation

All patients underwent preoperative esophagogastroduodenoscopy (EGD) to locate the lesion and biopsy for histological diagnosis. Endoscopic ultrasonography (EUS) was only used for the diagnosis of T staging in early stage patients, but was not routinely used for T staging and EUS/fine needle aspiration (FNA) biopsy for advanced tumors. T and metastatic lymph node staging were performed for each patient using contrast-enhanced computed tomography (CT) scan of the chest and abdomen. Cervical paraesophageal and supraclavicular lymph node staging was routinely performed using neck ultrasound. For tumors or bulking metastatic lymph nodes in the upper thoracic mediastinum, a bronchoscopy was routinely performed. Endobronchial ultrasonography (EBUS) was not commonly used. Positron emission tomography (PET)/CT was routinely used after 2020, but was not mandatory during this current study period [2016]. For suspected liver metastases, brain metastases, or bone metastases, additional enhanced liver magnetic resonance imaging (MRI), enhanced brain MRI, and bone radionuclide scans were performed. The staging was based on the 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging criteria for esophageal cancer (13).

To assess the patient's general condition, echocardiography, treadmill exercise testing, pulmonary function, and arterial blood gas assessments were conducted. Nutritional assessment was mandatory for admission.

Multidisciplinary treatment

Multidisciplinary therapy was used in patients with advanced tumors. The indication and strategy varied depending on the physician or patient preference. Neoadjuvant therapy was mainly used for patients with extensive lymph node metastasis (≥ 2 fields) or T3 to T4a tumor invasion. In neoadjuvant chemotherapy, fluorouracil (5-Fu), paclitaxel, or docetaxel supplemented with cisplatin or carboplatin was used commonly, mostly with two cycles. Neoadjuvant chemoradiotherapy was largely based on the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery (CROSS) regimen. Postoperative adjuvant therapy was more commonly used than preoperative adjuvant therapy. For patients with tumors in the upper thoracic esophagus or lymph node metastases at the upper mediastinum or neck, or patients with R2 resection, postoperative adjuvant radiotherapy

was routinely recommended. For other patients with pN+/ypN+, an additional three cycles of platinum-containing chemotherapy were administered, otherwise only active surveillance was recommended.

Esophagectomy or endoscopic resection

In our center, the right thoracic approach of McKeown or Ivor-Lewis procedure and thoracoabdominal two-field or selective three-field lymph node dissection were routinely used to complete radical esophagectomy. Very few patients with esophageal squamous cell carcinoma used the left thoracic approach (Sweet procedure). Gastroesophageal junction adenocarcinomas were mostly operated by the transhiatal or left thoracic approach. Thoracoscopic and robotic assisted minimally invasive esophagectomy were routinely performed in 2016, but some cases of open approach were still performed by some doctors.

Endoscopic resection was used in patients with clinically intramucosal invasion and no lymph node metastasis (cT1aN0). The procedure was performed under general anesthesia and endotracheal intubation. ESD-*en bloc* resection was the preferred method, and circumferential resection was avoided as much as possible to prevent intractable stenosis after the operation. Standard pathological evaluations were performed postoperatively.

Data collection

A prospectively single-disease database regarding esophageal cancer was established in SCH. The following baseline patient characteristics were collated: age, gender, height and weight at admission, diagnosis, tumor related information (such as location of tumor, pathological type, differentiation status, residual tumor status, and pathological stage), treatment relevant outcomes (including surgical technique, route, substitute organ, fields of lymph node dissection, radiotherapy, chemotherapy, or chemoradiotherapy), and perioperative results (including postoperative morbidity, 30- and 90-day mortality, length of in-hospital stay, length of intensive care unit (ICU) stay, and numbers of lymph node dissection). For pathological results, resected tumor specimens were recoded with proximal and distal margins. R0 resection was defined as non-positive discovery in both resection margins; R1 was defined as microscopical residual tumor; and R2 was defined as a macroscopical tumor. Postoperative complications were classified using the Esophagectomy Complications Consensus Group (ECCG)

system and Clavien-Dindo grading system (14,15). These data were extracted from patient's medical records under permission. After smooth discharge from the SCH, the follow-up strategy was initiated by telephone or out-patient clinics until June 2022. The routine follow-up was conducted every 3 months in first year, and then every 6 months in the subsequent years. Through follow-up, linkage was established between the patients' medical records and the data of the esophageal cancer registry database which could provide patients' survival status. Overall survival (OS) was calculated from the day of esophageal relevant operation (day 0) to the day of death or the day of last follow-up. Similarly, cancer specific survival (CSS) was calculated from the intervals of day 0 to the day of cancer specific death or the last day of follow-up, as was the recurrence free survival (RFS), which measured the interval between day 0 and any recurrence or progression in cancer.

Statistical analysis

All analyses were performed using the SPSS software version 26.0 (IBM Corporation, Armonk, NY, USA). Categorical data was documented as numbers and percentages. Continuous data was recorded as median [interquartile range (IQR)] or mean \pm standard deviation (SD). Multivariate Cox analysis was conducted to clarify prognostic factors affecting long-term outcome. To determine the effect of neoadjuvant therapy on survival, a propensity-score matched (PSM) analysis was performed to draw an unbiased marginal estimate of the exposure effect. Propensity score was calculated for each patient and matching was performed using a 1:1 matching protocol without replacement (greedy-matching algorithm) and a caliper width of 0.02. In this model, the included variable was clinical stage, which was used to compare the survival outcome between patients with neoadjuvant therapy and without neoadjuvant therapy. Survival data were analyzed and graphed using the Kaplan-Meier method and compared using Log-rank tests using the GraphPad Prism 8 software (GraphPad Software, San Diego, CA, USA). A P value less than 0.05 two-sided was considered statistically significant.

Results

Patient background

A total of 546 cases were included (*Figure 1*). The majority

Table 1 Baseline characteristics of the patients

Variables	Cases (%)
Age (years)	
<30	0 (0.0)
30–39	0 (0.0)
40–49	16 (2.9)
50–59	121 (22.2)
60–69	286 (52.4)
70–79	106 (19.4)
≥80	17 (3.1)
Gender	
Male	434 (79.5)
Female	112 (20.5)
BMI (kg/m ²)*	
<18.5	43 (7.9)
18.5–23.0	247 (45.2)
>23.0	256 (46.9)
Location	
Cervical	3 (0.5)
Upper thoracic	67 (12.3)
Middle thoracic	280 (51.3)
Lower thoracic	146 (26.7)
EGJ	50 (9.2)
Diagnosis	
Esophageal cancer	538 (98.5)
Esophageal concurrent cancers	8 (1.5)

*, BMI in accordance with the Asia-Pacific standards. BMI, body mass index; EGJ, esophagogastric junction.

of patients (52.4%) were aged 60–69 years, with 79.5% of patients being male (Table S1). There were 43 (7.9%) malnourished patients whose body mass index (BMI) was less than 18.5. The tumor was mainly located at the middle thoracic esophagus (51.3%) (Table 1). There were 125 cases (22.9%) of superficial carcinomas (Tis, T1a, T1b). Neoadjuvant therapy was administered in 60 cases (11.0%). Cure-intended esophagectomy and endoscopic resection was conducted in 517 cases (94.7%) and 29 cases (5.3%), respectively (Tables 2,3).

Table 2 Therapeutic approaches

Approaches	Cases (%)
ESD	29 (5.3)
Esophagectomy	517 (94.7)
McKeown	369 (67.6)
Ivor-Lewis	77 (14.1)
Sweet	52 (9.5)
Transhiatal	16 (2.9)
TPLE	2 (0.4)
Cervical esophagectomy	1 (0.2)
Total	546

ESD, endoscopic submucosal dissection; TPLE, total pharyngo-laryngo-esophagectomy.

Table 3 Predominant esophageal treatments

Treatments	Cases (%)
Endoscopic resection*	29 (5.3)
Esophagectomy alone**	457 (83.7)
Perioperative multidisciplinary treatment	283 (51.8)
Preoperative therapy + esophagectomy	60 (11.0)
Chemotherapy	28 (5.1)
Radiotherapy	1 (0.2)
Chemoradiotherapy	31 (5.7)
Endoscopic resection + adjuvant	2 (0.4)
Esophagectomy + adjuvant***	248 (45.4)

*, due to dissatisfied endoscopic resection, 3 cases received additional surgery; **, 1 case received esophagectomy as well as endoscopic resection at the same time; ***, 27 cases which received preoperative therapy were included simultaneously.

Resection-esophagectomy

Surgery

Of all esophagectomies performed (n=517), the McKeown approach accounted for 67.6%, Ivor-Lewis 14.1%, Sweet 9.5%, and transhiatal 2.9% (Table 2). Minimally invasive techniques were used in 58% of patients, including robotic assisted esophagectomy in 114 patients (22.1%) (Table 4). Complete resection (R0) was achieved in 90.3% of patients (Table 5). Among conduit selection, the stomach was used

Table 4 Surgical outcomes

Outcomes	Cases (%)
Surgical technique (n=517)	
RAE	114 (22.1)
MIE	186 (36.0)
OPEN	217 (42.0)
Organs (n=517)	
Gastric tube	510 (98.6)
Colon	7 (1.4)
Reconstruction route (n=517)	
None	2 (0.3)
Posterior mediastinal	327 (63.3)
Retrosternal	187 (36.2)
Subcutaneous	1 (0.2)
Fields of lymph node dissection (n=517)	
None	1 (0.2)
One field-thoracic	12 (2.3)
One field-abdominal	24 (4.6)
Two fields-thoracic + abdominal	436 (84.3)
Three fields-cervical + thoracic + abdominal	44 (8.5)

RAE, robotic assisted esophagectomy; MIE, minimally invasive esophagectomy; OPEN, open approach esophagectomy.

Table 5 Residual tumor (esophagectomy)

Residual tumor (R)	Cases (%)
R0	467 (90.3)
R1	18 (3.5)
R2	32 (6.2)
Total	517

in 98.6% of patients and the posterior mediastinum was used in 59.4% of patients as the reconstruction route. In the remaining patients, 36.2% were retrosternal and 0.2% were subcutaneous. The method of 3-field lymph node dissection was used in 15.7% of all patients.

Multidisciplinary treatment

In the esophagectomy cohort, 281 patients received perioperative multidisciplinary treatment. The composition

ratio was as follows: 28 patients (10.0%) received neoadjuvant chemotherapy, and the clinical staging ranged from cII to cIVA; 31 patients (11.0%) received neoadjuvant chemoradiotherapy, with the clinical staging ranging from cII to cIVA (the corresponding clinical stage distribution of patients is provided in Table S2); and the last 1 patient who received radiotherapy was in stage cIVA. Postoperative adjuvant therapy was performed in 248 patients (88.3%), and 11 patients were postoperative pathological stage I, 54 patients were stage II, 142 patients were stage III, and 41 patients were stage IV. A total of 27 patients (9.6%) received both preoperative and postoperative treatments.

Safety-complications

A total of 214 patients satisfied the complications definition of ECCCG. Total complications occurred in 41.4% of patients and Clavien-Dindo stage III–IV morbidity was evident in 11.2%. Postoperative pneumonia was one of the most common morbidities observed in 2016, with an incidence of 15.9%, followed by recurrent laryngeal nerve injury (13.9%). Other in-hospital complications were listed in Table 6.

Resection-endoscopic therapy

Among the 29 cases that underwent ESD therapy, all were staged as cT1aN0M0. The *en bloc* resection rate was 96.6% and the margin-negative resection (R0) rate was 79.3% (22/29). There were 7 patients who underwent non-radical resection, including 5 patients with positive horizontal margin and 2 patients with positive vertical margin. In post-resection pathology, the tumor invaded to the mucous epithelium in 15 cases, the lamina propria in 4 cases, the muscularis mucosa in 4 cases, and the submucosa in 6 cases. Lymphovascular invasion (LVI) only occurred in 1 patient who presented with submucosal invasion. The median length of the lesions was 2 cm. No severe perioperative complications occurred, except for 4 strictures. Adjuvant therapy was conducted in 2 patients and salvage esophagectomy was performed in 3 patients to prevent recurrence (Table 3).

Pathology profile

Postoperative pathology analysis showed that squamous cell carcinoma was the most common pathology type in our center, with 453 cases out of 517 patients (87.6%). In the endoscopic resection cohort, 14 out of 29 patients (48.3%) presented with squamous cell carcinoma, and 15 cases were high grade dysplasia (HGD). The pathological

Table 6 Total complications (esophagectomy)

Complications	Cases (%)
Total complications (ECCG)	214 (41.4)
Clavien-Dindo complications \geq III	58 (11.2)
Pulmonary	
Pneumonia	82 (15.9)
Pleural effusion	50 (9.7)
Pneumothorax	4 (0.8)
Respiratory failure	7 (1.4)
ARDS	30 (5.8)
Cardiovascular	
Cardiac arrhythmia	3 (0.6)
Gastrointestinal	
Anastomotic leakage	39 (7.5)
Gastrointestinal bleeding	1 (0.2)
Liver dysfunction	1 (0.2)
Thromboembolic	
Deep venous thrombosis	2 (0.4)
Neurologic/psychiatric	
Recurrent laryngeal nerve injury	72 (13.9)
Delirium	2 (0.4)
Infection	
Wound infection	13 (2.5)
Chyle leak	10 (1.9)
Total	517

ECCG, Esophagectomy Complications Consensus Group; ARDS, acute respiratory distress syndrome.

depth of tumor invasion was dominated by pT3 (48.4%) in esophagectomy. Lymph node metastasis was detected in 50.7% of patients. A total of 194 cases (37.5%) were predominately pStage III in esophagectomy. There were 214 (41.4%) cases of moderately differentiated specimens of esophagectomy, 208 cases (40.2%) of poorly differentiated or undifferentiated specimens, and 65 cases (12.6%) of well differentiated specimens. LVI was detected in 69 patients (13.3%) in the esophagectomy cohort, and 1 patient (3.4%) in the ESD cohort (Tables 7-14). The total number of lymph node dissection in surgery was 17.1 ± 9.4 (mean \pm SD). The average postoperative stay of all 546 patients was 17.7 ± 15.9 days (mean \pm SD), and the ICU length of stay was 3.3 ± 4.6 days (mean \pm

Table 7 Histological classification of esophagectomy

Histological classification	Cases (%)
Squamous cell carcinoma	453 (87.6)
Adenocarcinoma	47 (9.1)
Absolute adenocarcinoma	44 (8.5)
Signet-ring cell carcinoma	1 (0.2)
Adenocarcinoma mixed with others	2 (0.4)
Neuroendocrine carcinoma	10 (1.9)
Big cell carcinoma	1 (0.2)
Small cell carcinoma	8 (1.5)
Neuroendocrine carcinoma (undefined)	1 (0.2)
Mixed neuroendocrine/non-neuroendocrine carcinoma	1 (0.2)
Combined small cell-squamous cell carcinoma	1 (0.2)
Adenosquamous carcinoma	2 (0.4)
Multiple carcinoma	4 (0.8)
Squamous cell carcinoma+ adenocarcinoma	4 (0.8)
Total	517

Table 8 Histological classification of endoscopic treatment

Histological classification	Cases (%)
High grade dysplasia	15 (51.7)
Squamous cell carcinoma	14 (48.3)
Total	29

SD) (Table 15), it seemed that pT3 patients encountered the most cases of ICU readmission (Table 16). The postoperative 30- and 90-day mortality was 0.73% and 1.1%, respectively.

OS and subtype analysis

The routine postoperative follow-up lasted to June 2022, with a median (IQR) of 60 [19–61] months. A total of 7 cases lacked postoperative follow-up data and finally, 539 cases were included in the survival analysis. As for the endoscopic treatment cohort, the postoperative 1-, 2-, 3-, 4-, and 5-year OS were 100.0%, 96.4%, 96.4%, 96.4%, and 96.4%, respectively (Figure S1). For the surgery cohort, the relevant 1-, 2-, 3-, 4-, and 5-year OS were 86.5%, 67.8%, 59.9%, 54.5%, and 51.8%, respectively (Figure 2) and the CSS rates were 91.8%, 74.2%, 66.6%, 61.2%, and 59.1%,

Table 9 Pathological depth of tumor invasion of esophagectomy, pT (AJCC TNM 8th)

Pathological depth of tumor invasion	Cases (%)
pT0*	18 (3.5)
pTis	6 (1.2)
pT1a	17 (3.3)
pT1b	73 (14.1)
pT2	100 (19.3)
pT3	250 (48.4)
pT4a	21 (4.1)
pT4b	32 (6.2)
Total	517

*, including 16 patients who received neoadjuvant therapy and 2 patients who had undergone ESD previously (in another medical center). AJCC, American Joint Committee on Cancer; TNM, tumor-node-metastasis; ESD, endoscopic submucosal dissection.

Table 10 Pathological depth of tumor invasion of endoscopic specimens

Pathological depth of tumor invasion	Cases (%)
pTis-M1	15 (51.7)
pT1a-M2	4 (13.8)
pT1a-M3	4 (13.8)
pT1b-SM1	1 (3.4)
pT1b-SM2	1 (3.4)
pT1b-undefined	4 (13.8)
Total	29

Table 11 Pathological grading of lymph node metastasis (esophagectomy), pN (AJCC TNM 8th)

Lymph node metastasis	Cases (%)
pN0	255 (49.3)
pN1	150 (29.0)
pN2	82 (15.9)
pN3	30 (5.8)
Total	517

AJCC, American Joint Committee on Cancer; TNM, tumor-node-metastasis.

Table 12 Pathological stage (AJCC TNM 8th)

pTNM stage	Cases (%)	
	Esophagectomy	Endoscopy
0	7 (1.4)	15 (51.7)
I	93 (18.0)	14 (48.3)
II	151 (29.2)	–
III	201 (38.9)	–
IV	65 (12.6)	–
Total	517	29

AJCC, American Joint Committee on Cancer; TNM, tumor-node-metastasis.

Table 13 Differentiation of all pathological samples

Differentiation	Cases (%)	
	Esophagectomy	Endoscopy
G1-well	65 (12.6)	3 (10.3)
G2-moderately	214 (41.4)	4 (13.8)
G3-poorly/undifferentiated	208 (40.2)	2 (6.9)
GX	30 (5.8)	20 (69.0)
Total	517	29

Table 14 Lymphovascular invasion

Lymphovascular invasion	Cases (%)	
	Esophagectomy	Endoscopy
Negative	448 (86.7)	28 (96.6)
Positive	69 (13.3)	1 (3.4)
Total	517	29

Table 15 Length of in-hospital stay and number of lymph node dissections

Variables	Mean ± SD
Length of postoperative stay (days)	17.7±15.9
Length of ICU stay (days)	3.3±4.6
Number of lymph node examined (n=517)	17.1±9.4

ICU, intensive care unit; SD, standard deviation.

Table 16 The correlation between pT and ICU readmission

Pathological depth of tumor invasion	ICU cases (%)
pT0/Tis	0 (0.0)
pT1a	1 (4.3)
pT1b	4 (17.4)
pT2	4 (17.4)
pT3	11 (47.8)
pT4a	1 (4.3)
pT4b	2 (8.7)
Total	23

ICU, intensive care unit.

respectively. Regarding the stratification of pT, pN, and pTNM stage, the OS, RFS, and CSS in each subgroup were analyzed (Figures 3-8, Figure S2). The Kaplan-Meier survival curves diverged in nodal-staging (pN) for both OS and CSS. In pT analysis, the survival of pT4a was better than pT4b in OS, however, the survival curves were almost identical between pT4a and pT4b in CSS. The survival curves showed a good discriminatory ability in the pathological stage for both OS and CSS. The residual tumor (R0/R1/R2) exhibited a satisfying discrimination in OS ($P < 0.001$). However, there was no significant difference in the CSS subtype analysis ($P = 0.063$). To determine why radical resection could not be applied, the location of tumor invasion in R2 resection patients was analyzed (Table 17). For post pathologically verified ESCC patients after esophagectomy, the postoperative 1-, 2-, 3-, 4-, and 5-year OS were 85.9%, 67.8%, 60.7%, 55.0%, and 52.4%, respectively (Figure 9). A total of 250 deaths during follow-up was documented and 193 cases of them (77.2%) were due to recurrence (Table 18).

In multivariate Cox regression analysis, male gender, deeper tumor invasion layers, positive lymph nodes metastasis, and induction of neoadjuvant therapy were prognostic factors associated with poor OS and CSS both in esophagectomy cohort and ESCC cohort (Tables S3,S4).

In the subtype analysis for the ESCC cohort (Figure 10), after matching according to clinical stage using the PSM method, a total of 55 pairs of patients with neoadjuvant therapy or not under a similar clinical staging background were analyzed. There was no divergence in OS between patients who accepted neoadjuvant therapy and patients who did not ($P = 0.170$), however, as for CSS, patients who

underwent esophagectomy without neoadjuvant therapy showed a better survival rate over patients who underwent preoperative inducement plus surgery ($P = 0.049$).

Discussion

This annual report summarized the baseline characteristics, tumor pathological results, and surgery-related outcomes of esophageal cancer patients in SCH. The results demonstrated that following standard surgical quality control in a large-scale esophageal surgery center, relatively satisfactory tumor treatment results can be obtained, including good surgical risk control and long-term survival.

In recent years, the basic biological characteristics of esophageal cancer patients in China has changed, including a later age of onset and better nutritional conditions (16,17). This is closely related to the improvement of medical living conditions in China. However, other parameters have changed little, such as the increasing number of squamous cell carcinoma patients, more tumors located in the middle esophagus, and the advanced stage at primary diagnosis.

In our limited number of endoscopically treated patients, the R0 resection rate was only 79%. Although our previous study showed that positive lateral margins did not affect long-term prognosis (18), for patients with deep invasion to the submucosa, or those patients with muscularis mucosae invasion and positive LVI, adjuvant therapy is still necessary. The Japan Clinical Oncology Group Study (JCOG0508) clinical trial provided adequate salvage therapy recommendations for patients with low-risk submucosal invasion (19), but it remains unknown whether patients with more generalized submucosal invasion will necessarily achieve satisfactory long-term tumor control with nonsurgical management. Our previous study has shown that reoperation is safe for patients who have failed endoscopic therapy (20), however, a further study named Ad-ESD trial is warranted to verify these results (21).

In China, the left thoracic operation (Sweet approach) has dominated esophageal surgery for decades (22). In many town hospitals, surgeons can complete a Sweet operation for esophageal squamous cell carcinoma in 2 hours. However, with the pursuit of total mediastinal lymph node dissection, especially the rise of minimally invasive surgery (23,24), the McKeown and Ivor Lewis surgery of the right thoracic approach has gradually occupied the mainstream of esophageal cancer surgery in China. This study demonstrated that in 2016, the proportion of minimally invasive surgery in SCH exceeded 50%, and the

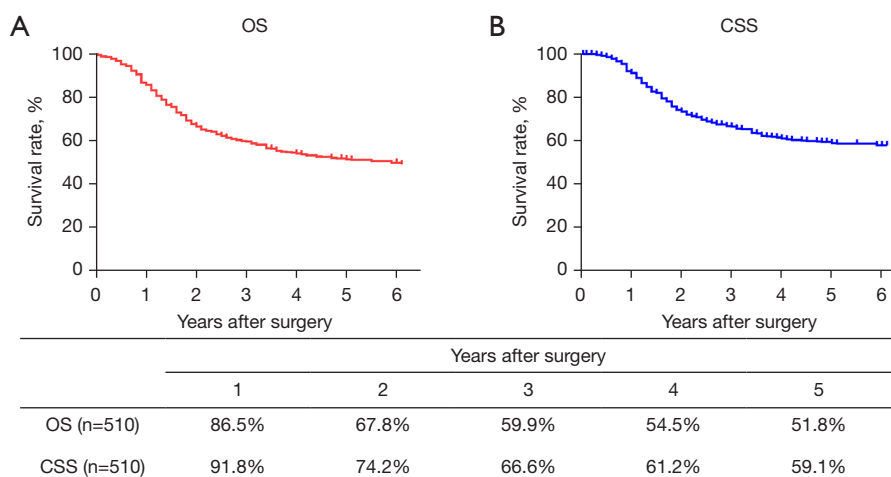


Figure 2 The OS and CSS of patients who underwent esophagectomy. OS, overall survival; CSS, cancer specific survival.

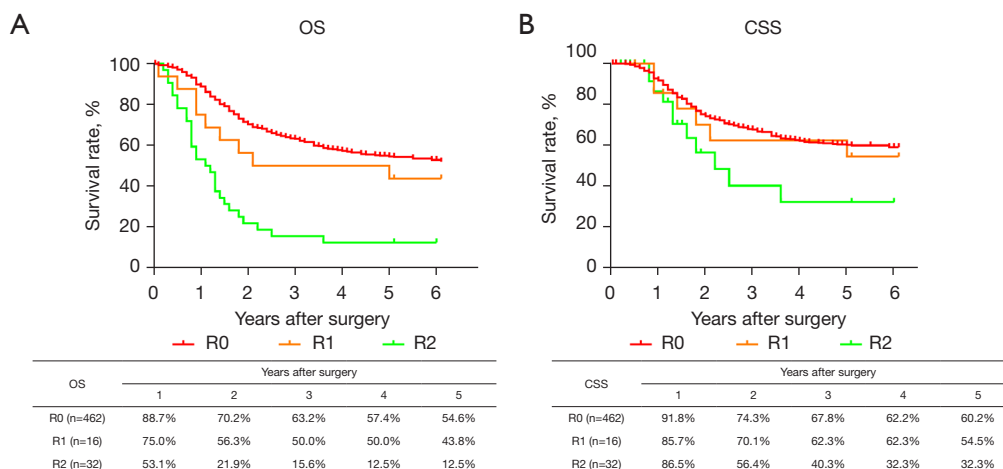


Figure 3 The OS and CSS of patients who underwent esophagectomy according to R statistical software. OS, overall survival; CSS, cancer specific survival.

right thoracic surgery approach exceeded 80%. The adoption of new surgical approaches, especially minimally invasive surgery, may increase surgical risks and reoperation rates (25). However, this report demonstrated that the surgical safety of the entire cohort was very stable, with less than 1% of operative death within 30 days being the norm in large centers in China.

The 5-year survival rate of patients undergoing R0 resection was 54.6% in our center. This result is similar to that of another surgical treatment retrospective report from a Chinese multicenter (17). However, compared with Japan’s 2013 annual report, in which the 5-year survival

of surgically treated patients was 59.5% (26), our long-term survival results were not very satisfactory (Table 19). To explain this disparity, we conducted a comparative analysis of the two groups of people. There are two main differences in the basic composition of the populations and the intervention methods. First, the proportion of pT1 in Japanese patients reached 39%, while in our group of patients, it was only 17.6%. Furthermore, there were more early-stage patients in the Japanese group. The second difference is the proportion of patients receiving neoadjuvant therapy, which was 37.5% in the Japanese cohort compared to 11% in the SCH cohort, meaning that

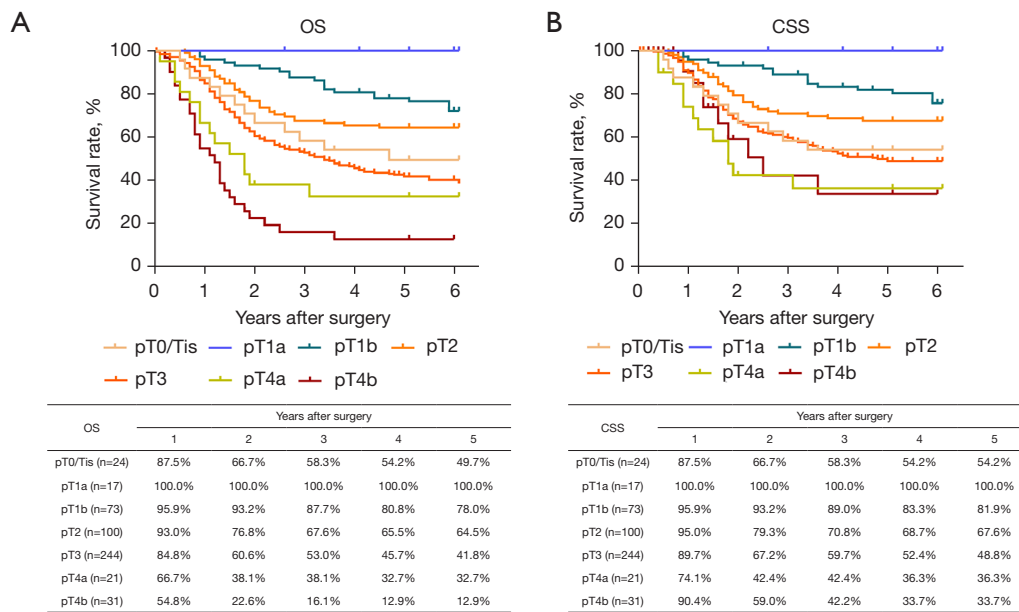


Figure 4 The OS and CSS of patients who underwent esophagectomy according to the depth of tumor invasion (AJCC 8th edition). OS, overall survival; CSS, cancer specific survival; AJCC, American Joint Committee on Cancer.

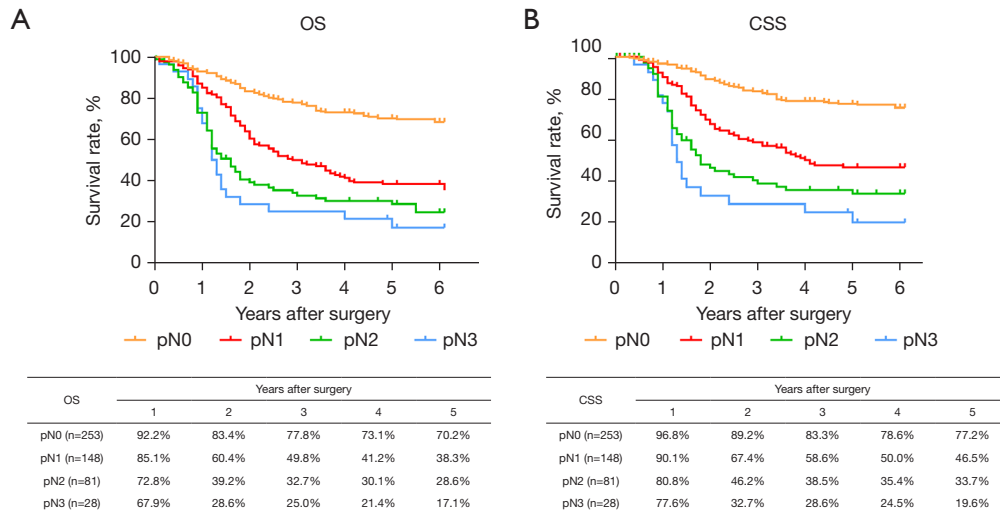


Figure 5 The OS and CSS of patients who underwent esophagectomy according to lymph node metastasis (AJCC 8th edition). OS, overall survival; CSS, cancer specific survival; AJCC, American Joint Committee on Cancer.

almost all Japanese patients above T3 received preoperative treatment. Despite the proportion of patients above pT3 in our group being close to 60%, the current use of neoadjuvant was only 11%. We suggest that earlier staging confers better survival compared to neoadjuvant therapy. A similar conclusion can be drawn among pT2 patients,

where neoadjuvant therapy was rarely used in both groups, and the surgical results in our cohort was superior to that observed in the Japanese group. For pT3 and pT4a, the two most common local progression for tumors, preoperative neoadjuvant therapy was commonly used in Japan, while it was less frequently administered by the Shanghai team. Our

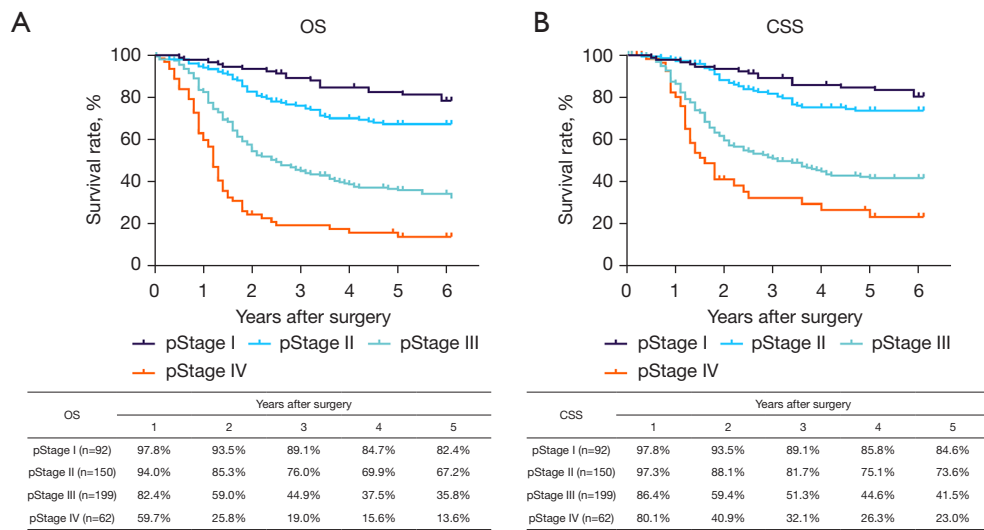


Figure 6 The OS and CSS of patients who underwent esophagectomy according to pathological stage (AJCC 8th edition). OS, overall survival; CSS, cancer specific survival; AJCC, American Joint Committee on Cancer.

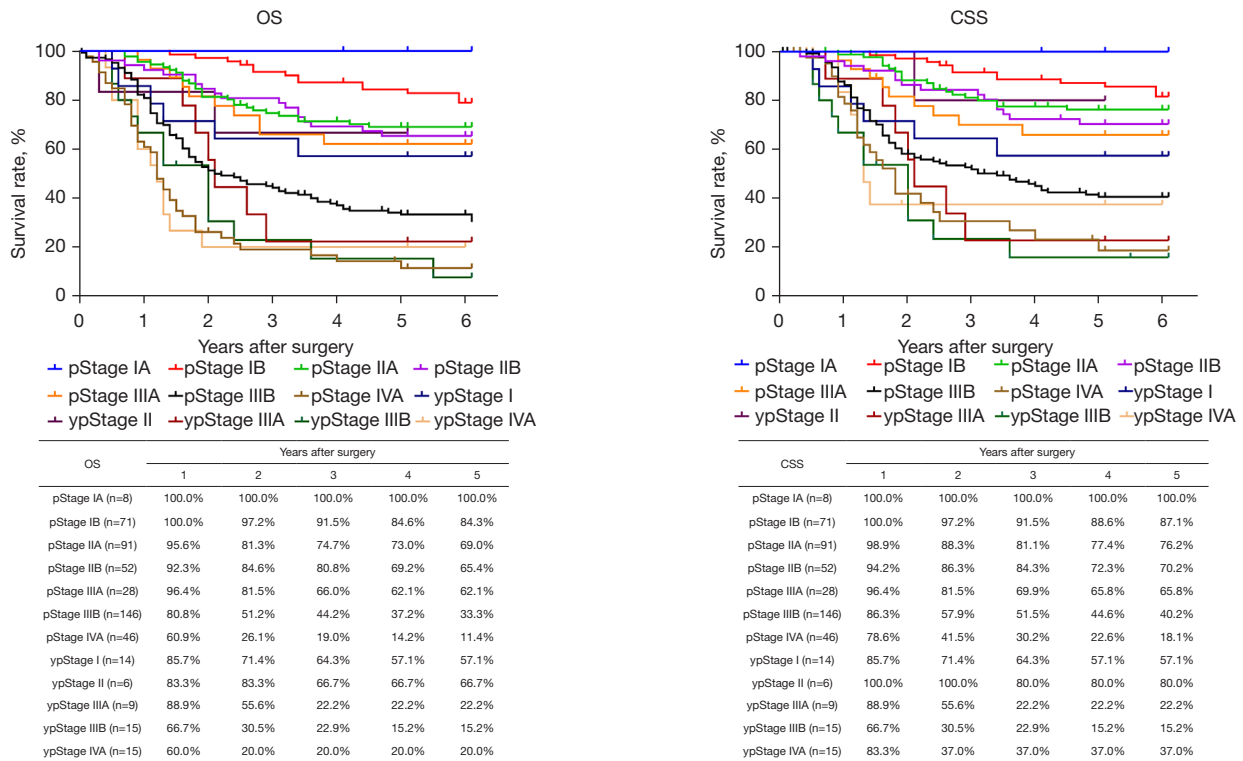


Figure 7 The OS of patients who underwent esophagectomy according to pathological and neoadjuvant stage (AJCC 8th edition). OS, overall survival; AJCC, American Joint Committee on Cancer.

Figure 8 The CSS of patients who underwent esophagectomy according to pathological and neoadjuvant stage (AJCC 8th edition). CSS, cancer specific survival; AJCC, American Joint Committee on Cancer.

Table 17 Causes of R2 resection

Invasion spot of R2 resection	Cases (%)
Trachea	15 (42.9)
Aorta	10 (28.6)
Recurrent laryngeal nerve	2 (5.7)
Atrium	1 (2.9)
Pancreas	1 (2.9)
Lung	1 (2.9)
Thyroid	1 (2.9)
Missing data	4 (11.4)
Total spots	35

results were comparable to those in Japan. Therefore, for the entire population, the proportion of early-stage patients is a more critical factor in determining the ultimate survival outcome.

Both the CROSS and NEROTEC5010 studies clearly showed that preoperative neoadjuvant improved OS in the intervention group (27,28), but neither group of patients were routinely given postoperative adjuvant therapy, establishing a highly unbalanced setting in terms of full perioperative care. Although the JCOG9907 trial clearly confirmed that preoperative neoadjuvant chemotherapy is superior to postoperative adjuvant therapy (29), the control group only received two cycles of chemotherapy after surgery. Obviously, the course and dose of chemotherapy were very weak. Moreover, in the postoperative adjuvant therapy group of patients in the JCOG9907 trial, none of the pN0 patients received adjuvant therapy, and all the neoadjuvant group received neoadjuvant chemotherapy. From this point of view, there was obvious selection bias in the study. In our patients, the postoperative adjuvant therapy was mainly radiotherapy and chemoradiotherapy, with the intensity being significantly higher than that of the postoperative adjuvant group in the JCOG9907 trial. In our study, we found that OS in the neoadjuvant treatment group was even worse than that in the primary surgery population, which may reflect a very narrow window of benefit from neoadjuvant treatment. Furthermore, the JCOG9907 trial concluded that neoadjuvant treatment was more effective in patients in clinical stage II, or cases involving the upper and the middle third of the esophagus, or cases which do

not invade the deeper layers. The development of novel neoadjuvant treatment regimens with high intensity is warranted and immunotherapy may be an important future direction for preoperative treatment (30,31).

This report summarized the real-world data of esophageal cancer surgical treatment in a high-volume single center of China. The use of standardized surgical treatment and minimally invasive surgery has helped patients obtain acceptable early and long-term postoperative outcomes. However, there were some limitations in this study. First, the present study was a real-world observational-retrospective study, and bias might exist in the reporting and collection of patient information. Second, the included operations were performed by more than 10 different surgeons. Although a few surgeons accounted for the vast majority of operations, some bias in medical treatment by different surgeons may have influenced the estimate in the overall therapeutic outcomes. Third, the proportion of patients receiving neoadjuvant therapy was low at SCH in 2016, since the NEOCRTEC5010 trial comparing neoadjuvant chemoradiotherapy plus surgery versus surgery alone was not published until 2018 (32) and included in the Chinese guidelines; in other words, neoadjuvant therapy was not recommended in China during our study period [2016]; for this reason, most patients in our study with locally advanced stage esophageal cancer usually received postoperative adjuvant therapy. This situation has changed dramatically since 2020, and the current proportion of neoadjuvant patients has exceeded 40%. Our future work will recruit more early-stage patients for individualized neoadjuvant therapy, with the aim of improving treatment outcomes.

Conclusions

Through a standardized surgical procedure, surgical treatment conferred acceptable short- and long-term results in a high-volume reference center in China. The 5-year OS and CSS rate were 51.8% and 59.1%, respectively. The efficacy of neoadjuvant therapy was not tested in this cohort for limited number of patients, as the surgery plus adjuvant therapy was the preferred treatment regimen for locally advanced stage patients in 2016. This report reveals important surgical treatment effects of esophageal cancer patients and provides helpful data for their clinical management and future treatment development.

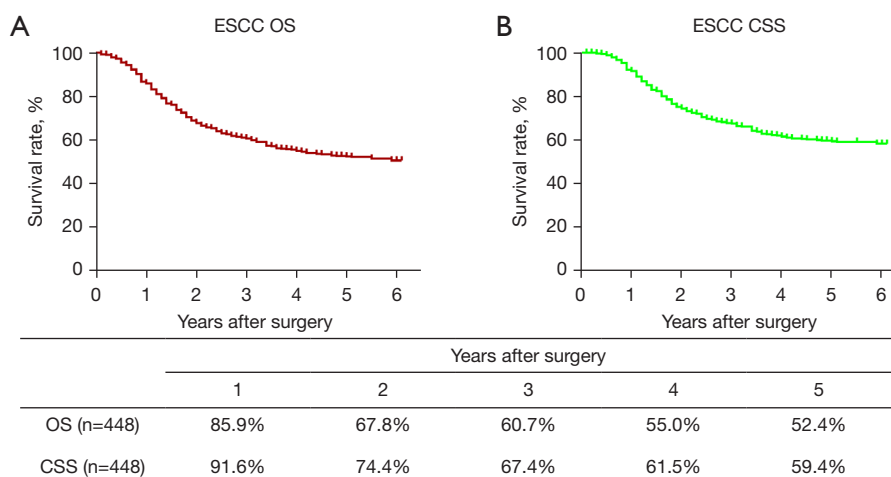


Figure 9 The OS and CSS of the ESCC cohort. OS, overall survival; CSS, cancer specific survival; ESCC, esophageal squamous-cell carcinoma.

Table 18 Causes of death

Cause of death	Cases (%)
Death due to recurrence	193 (77.2)
Death due to other cancer	1 (0.4)
Death due to other disease (recurrence+)	2 (0.8)
Death due to other disease (recurrence-)	54 (21.6)
Death due to other disease (recurrence?)	0 (0.0)
Operative death*	4 (1.6)
Postoperative hospital death**	0 (0.0)
Total of death cases	250

*, operative death refers to death within 30 days after operation in or out of hospital. The operative mortality rate was 0.73%; **, postoperative hospital death is defined as death during the same hospitalization, regardless of department at time of death. The hospital death rate in our center was 0.

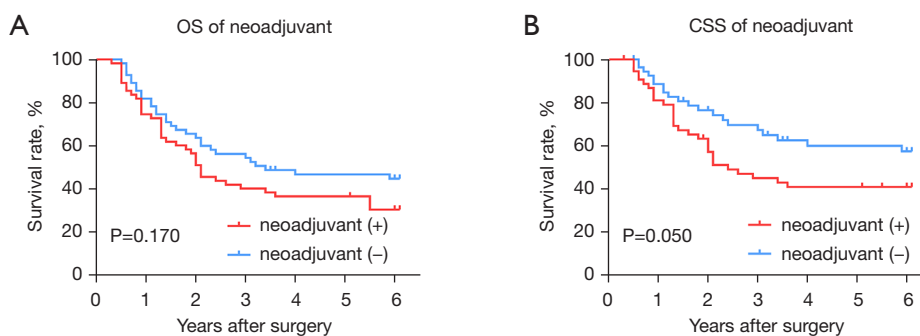


Figure 10 Survival analysis of neoadjuvant therapy in the ESCC cohort (propensity score matching, n=55). OS, overall survival; CSS, cancer specific survival; ESCC, esophageal squamous-cell carcinoma.

Table 19 A comparison between the 2013 Japanese annual report and the SCH 2016 annual report

pT	2013 Japanese annual report		2016 SCH annual report	
	Proportions	Survival rate	Proportions	Survival rate
pT0/Tis	3.3%	81.1%	4.7%	49.7%
pT1a	12%	81.6%	3.3%	100%
pT1b	27%	76%	14.3%	78%
pT2	12.4%	56.4%	19.6%	64.5%
pT3	38.7%	43.4%	47.8%	41.8%
pT4a	0.8%	24.5%	4.1%	32.7%
pT4b	2.2%	15.2%	6.1%	12.9%

SCH, Shanghai Chest Hospital.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1672/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1672/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of the Shanghai Chest Hospital (No. IS21111). Individual consent for this retrospective analysis was waived.

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References

1. Arnold M, Soerjomataram I, Ferlay J, et al. Global incidence of oesophageal cancer by histological subtype in 2012. *Gut* 2015;64:381-7.
2. Arnold M, Abnet CC, Neale RE, et al. Global Burden of 5 Major Types of Gastrointestinal Cancer. *Gastroenterology* 2020;159:335-349.e15.
3. McGill MJ, Byrne P, Ravi N, et al. The prognostic impact of occult lymph node metastasis in cancer of the esophagus or esophago-gastric junction: systematic review and meta-analysis. *Dis Esophagus* 2008;21:236-40.
4. Liu YP, Ma L, Wang SJ, et al. Prognostic value of lymph node metastases and lymph node ratio in esophageal squamous cell carcinoma. *Eur J Surg Oncol* 2010;36:155-9.
5. Watanabe M, Toh Y, Ishihara R, et al. Comprehensive registry of esophageal cancer in Japan, 2014. *Esophagus* 2022;19:1-26.
6. Boffa DJ, Rosen JE, Mallin K, et al. Using the National Cancer Database for Outcomes Research: A Review. *JAMA Oncol* 2017;3:1722-8.
7. Falcoz PE, Brunelli A. The European general thoracic surgery database project. *J Thorac Dis* 2014;6 Suppl 2:S272-5.
8. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115-32.

9. He Y, Liang D, Du L, et al. Clinical characteristics and survival of 5283 esophageal cancer patients: A multicenter study from eighteen hospitals across six regions in China. *Cancer Commun (Lond)* 2020;40:531-44.
10. Wouters MW, Wijnhoven BP, Karim-Kos HE, et al. High-volume versus low-volume for esophageal resections for cancer: the essential role of case-mix adjustments based on clinical data. *Ann Surg Oncol* 2008;15:80-7.
11. Voeten DM, Gisbertz SS, Ruurda JP, et al. Overall Volume Trends in Esophageal Cancer Surgery Results From the Dutch Upper Gastrointestinal Cancer Audit. *Ann Surg* 2021;274:449-58.
12. Speicher PJ, Englum BR, Ganapathi AM, et al. Traveling to a High-volume Center is Associated With Improved Survival for Patients With Esophageal Cancer. *Ann Surg* 2017;265:743-9.
13. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017;67:93-9.
14. Low DE, Alderson D, Ceconello I, et al. International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg* 2015;262:286-94.
15. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250:187-96.
16. Wu Y, Li Y, Giovannucci E. Potential Impact of Time Trend of Lifestyle Risk Factors on Burden of Major Gastrointestinal Cancers in China. *Gastroenterology* 2021;161:1830-1841.e8.
17. Mao YS, Gao SG, Wang Q, et al. Analysis of a registry database for esophageal cancer from high-volume centers in China. *Dis Esophagus* 2020;33:doz091.
18. Liu Z, Li Z. Letter to the Editor: Comparison of Outcomes Between Additional Esophagectomy After Noncurative Endoscopic Resection and Upfront Esophagectomy for T1N0 Esophageal Squamous Cell Carcinoma. *Ann Surg Oncol* 2021;28:837-8.
19. Kurokawa Y, Muto M, Minashi K, et al. A phase II trial of combined treatment of endoscopic mucosal resection and chemoradiotherapy for clinical stage I esophageal carcinoma: Japan Clinical Oncology Group Study JCOG0508. *Jpn J Clin Oncol* 2009;39:686-9.
20. Liu Z, Zhang J, Su Y, et al. Additional Esophagectomy Following Noncurative Endoscopic Resection for Early Esophageal Squamous Cell Carcinoma: A Multicenter Retrospective Study. *Ann Surg Oncol* 2021;28:7149-59.
21. Yang Y, Su Y, Zhang X, et al. Esophagectomy versus definitive chemoradiotherapy for patients with clinical stage N0 and pathological stage T1b esophageal squamous cell carcinoma after endoscopic submucosal dissection: study protocol for a multicenter randomized controlled trial (Ad-ESD Trial). *Trials* 2020;21:603.
22. Mao YS, He J, Cheng GY. Current status of surgical management of esophageal cancer in China and the future strategy. *Zhonghua Zhong Liu Za Zhi* 2010;32:401-4.
23. Zhu C, Jin K. Minimally invasive esophagectomy for esophageal cancer in the People's Republic of China: an overview. *Onco Targets Ther* 2013;6:119-24.
24. Mu JW, Gao SG, Xue Q, et al. Updated experiences with minimally invasive McKeown esophagectomy for esophageal cancer. *World J Gastroenterol* 2015;21:12873-81.
25. Oshikiri T, Takiguchi G, Miura S, et al. Current status of minimally invasive esophagectomy for esophageal cancer: Is it truly less invasive? *Ann Gastroenterol Surg* 2019;3:138-45.
26. Watanabe M, Tachimori Y, Oyama T, et al. Comprehensive registry of esophageal cancer in Japan, 2013. *Esophagus* 2021;18:1-24.
27. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015;16:1090-8.
28. Yang H, Liu H, Chen Y, et al. Long-term Efficacy of Neoadjuvant Chemoradiotherapy Plus Surgery for the Treatment of Locally Advanced Esophageal Squamous Cell Carcinoma: The NEOCRTEC5010 Randomized Clinical Trial. *JAMA Surg* 2021;156:721-9.
29. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol* 2012;19:68-74.
30. Yang Y, Zhu L, Cheng Y, et al. Three-arm phase II trial comparing camrelizumab plus chemotherapy versus camrelizumab plus chemoradiation versus chemoradiation as preoperative treatment for locally advanced esophageal squamous cell carcinoma (NICE-2 Study). *BMC Cancer* 2022;22:506.
31. de Castro Junior G, Segalla JG, de Azevedo SJ, et al. A randomised phase II study of chemoradiotherapy with or

- without nimotuzumab in locally advanced oesophageal cancer: NICE trial. *Eur J Cancer* 2018;88:21-30.
32. Yang H, Liu H, Chen Y, et al. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma

of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. *J Clin Oncol* 2018;36:2796-803.

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