Original Article
Long-term outcomes following radical esophagectomy for esophageal squamous cell carcinoma in elderly patients

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Abstract: This retrospective study was designed to identify the predictors of long-term survival outcomes after radical esophagectomy for esophageal squamous cell carcinoma patients aged 65 years or older. The clinical and follow-up data of 143 patients aged 65 years or older with esophageal squamous cell carcinoma undergoing radical esophagectomy were analyzed for prognostic factors of long-term survival outcomes. The median age was 71 years (range, 65-76 years). Of the total patient number, 44 had some form of comorbidity diagnosed preoperatively. Thirty-one patients presented with postoperative 30-day complications. The 5-year overall survival rate for this cohort was 46% (Figure 1). The 5-year overall survival rates after radical esophagectomy were 73%, 62%, and 29%, respectively, in pathologic stage I, pathologic stage II, and pathologic stage III. Advanced pathologic stage and medical comorbidities were significant independent predictors of shortened overall survival. Elderly patients with operable esophageal squamous cell carcinoma in this study had a satisfactory long-term outcomes and low mortality rate.

Keywords: Esophageal squamous cell carcinoma, esophagectomy, prognosis, elderly patients

Introduction

The average age of the general population is increasing in China. Esophageal squamous cell carcinoma is the leading cause of cancer-related deaths in Eastern Asia countries, and patients older than 65 years account for about 20% of all esophageal squamous cell carcinoma [1-5]. Thus, the number of elderly esophageal squamous cell carcinoma patients is increasing rapidly in China. The current gold standard treatment of operable esophageal squamous cell carcinoma is radical esophagectomy [6-10]. Radical esophagectomy is feasible and safe in elderly patients with operable esophageal squamous cell carcinoma and guidelines recommend that esophageal squamous cell carcinoma patients should not be denied radical esophagectomy on the grounds of age alone [11-13]. However, elderly patients who undergo radical esophagectomy have a higher incidence of morbidity and mortality than that of younger patients because of the reduced cardiopulmonary function and the increased medical comorbidities [14-17]. In addition, the long-term survival outcomes of radical esophagectomy in elderly patients remain controversial because advanced age is an independent significant predictor of poor overall survival. This study focused on patients aged 65 years and older with operable esophageal squamous cell carcinoma to elucidate predictors of long-term survival outcomes.

Patients and methods

This study complied with the Declaration of Helsinki. This retrospective research was approved by our local ethics committees. The need for informed consent from patients was waived because of retrospective study, not prospective research.

A retrospective review of all patients aged 65 years and older who undergo radical esophagectomy for operable esophageal squamous cell carcinoma from January 2005 to January

Table 1. Patient characteristics

Variable	n
Age (years)	71 (65-76)
Sex	
Male	81
Female	62
ASA score	
I	99
II	33
III	11
Clinical TNM stage (7th AJCC-UICC)	
IB	49
IIA	69
IIB	25
Comorbidity	
None	99
Present	44
Surgery procedure	
Right thoracic-abdominal esophagectomy	69
Left thoracic esophagectomy	74
Pathological TNM stage (7th AJCC-UICC)	
IB	26
IIA	41
IIB	42
IIIA	25
IIIB	9

Table 2. Data of medical comorbidity

Type of medical comorbidity	n
Hypertension	31
Angina pectoris	8
Chronic obstructive pulmonary disease	5
Prior tuberculosis	6
Prior acute coronary syndrome	4
Diabetes mellitus	8
Liver cirrhosis	3
Anemia	4

2015 was performed. Patients were identified from the operating records and all malignancies were confirmed by pathological evaluation.

The clinical data collected included age, gender, American Society of Anesthesiologists (ASA) score, tumor TNM stage and medical comorbidities. Surgical data, pathological data, morbidity, mortality, and length of hospital stay were also reviewed. The tumor stage of esopha-

geal squamous cell carcinoma was based on the 7th edition of the TNM classification of esophageal carcinoma which was proposed by American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) [18-22]. For those of the patients treated before January 2010, their staging was recalculated to match the 7th TNM classification by AJCC and UICC.

Morbidity was defined as postoperative complications occurring within postoperative 30 days. Mortality was defined as death of any cause occurring within postoperative 30 days. Postoperative complication severity was stratified according to the modified Clavien classification. The definition of Clavien-Dindo system was as follows: Grade 1: oral medication or bedside medical care required; Grade 2: intravenous medical therapy required; Grade 3: radiologic, endoscopic, or operative intervention required; Grade 4: chronic deficit or disability associated with the event; and Grade 5: death related to surgical complication. Major complications were defined as grades 3, 4 and 5. Minor complications were classified as 1 and 2. The detail of Clavien-Dindo classification has been reported [23-27].

Cancer recurrence was diagnosed after radiological and/or pathological assess. Our institution's routine follow-up protocol for any patient with radical resection of esophageal squamous cell carcinoma included 3-monthly review with abdominal and chest computed tomography scan and ultrasonography of neck for the first 2 years followed by 6-monthly review for the subsequent 3 years. Surveillance gastrointestinal endoscopy would be performed 1 year after radical resection of esophageal squamous cell carcinoma. Recurrence was classified as locoregional recurrence, distant metastasis and mixed. Locoregional disease was defined as recurrence within the esophagus bed, the regional lymph nodes, or the anastomosis. Distant disease included metastasis at distant organ sites (brain, lung, liver, bone, adrenal, distant lymph nodes or other organs) [28-33]. The overall survival was assessed from the date of radical esophagectomy until the last follow up or death of any cause. The disease-free survival was calculated from the date of radical esophagectomy until the date of cancer recurrence or death from any cause.

Table 3. Surgical data and postoperative course

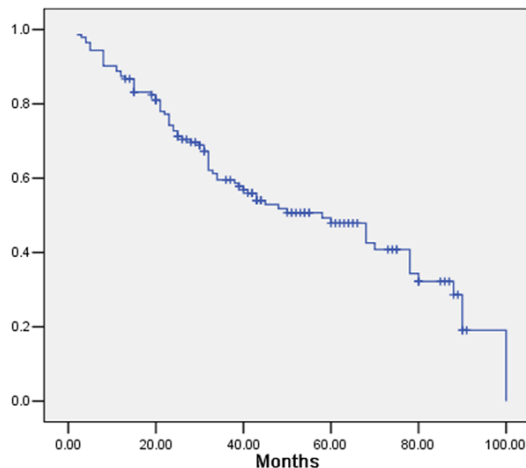|	
Operative time (min)	180 (160-250)
Blood loss (ml)	240 (170-600)
Postoperative stay (days)	15 (12-38)
Complications	
Pneumonia	13
Anastomosis leakage	7
Recurrent laryngeal nerve injury	4
Arrhythmia	4
Atelectasis	3
Heart failure	3
Acute coronary syndrome	1
Atrial fibrillation	1
Adult respiratory distress syndrome	1
Major complications	6
Minor complications	31

Figure 1. Postoperative overall survival curves of the whole cohort.

Table 4. Summary of Causes of Death during follow-up period

Cause of Death	n
Esophageal cancer-related death	67
Other cancer-related death	4
Died of nonmalignant diseases	6

SPSS (Solutions Statistical Package for the Social Sciences) 13.0 for Windows version (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The variables were analyzed to the various outcomes using the Fisher's exact test, and their odds ratio (OR) and 95% confidence interval (95% CI) were also reported. For the multivariate analysis, the logistic regression model was applied. The survival outcome was estimated according to the Kaplan-Meier method, and the Cox multivariate analysis would be performed to identify independent factors for overall survival and disease-free survival outcomes. $P < 0.05$ was considered statistically significant.

Results

As shown in **Table 1**, the median age was 71.0 years (range, 65 years - 76 years). A total of 69 right thoracic-abdominal esophagectomies and 74 left thoracic esophagectomies were performed. Cervical-right thoracic-abdominal esophagectomies, were not performed in this cohort. After pathologic diagnosis of the surgical specimens undergoing radical esophagectomy, 26 patients were classified as pathologic stage I, whereas 117 patients were diagnosed with a more advanced disease including 83 pathologic stage II patients and 34 pathologic stage III patients. Eleven patients had ASA score more than II, and 44 patients were diagnosed with some type of medical comorbidity (**Table 2**) before radical esophagectomy. Eighteen patients had two medical comorbidities and three patients had three medical comorbidities. The most common medical comorbidity was hypertension.

A total of 31 patients presented with postoperative 30-day complications. Two complications occurred in six patients. The most common complications in order of frequency were pneumonia followed by anastomosis leakage (**Table 3**). According to the Clavien-Dindo classification, most complications were classified as minor complication. No postoperative 30-day death was occurred in our series.

The 5-year overall survival rate for this cohort was 46% (**Figure 1**). The 5-year overall survival rates after radical esophagectomy were 73%, 62%, and 29%, respectively, in pathologic stage I, pathologic stage II, and pathologic stage III. Seventy-seven patients died of causes listed in **Table 4**. Six patients died of nonmalignant diseases, such as heart failure and pneumonia, during the follow-up period. A univariate analysis was used to evaluate the prognostic factors for overall survival. Good differentiation grade, pathological stage I disease and absence of medical comorbidity were significant prognos-

Table 5. Multivariate analysis of overall survival: Cox proportional hazard model

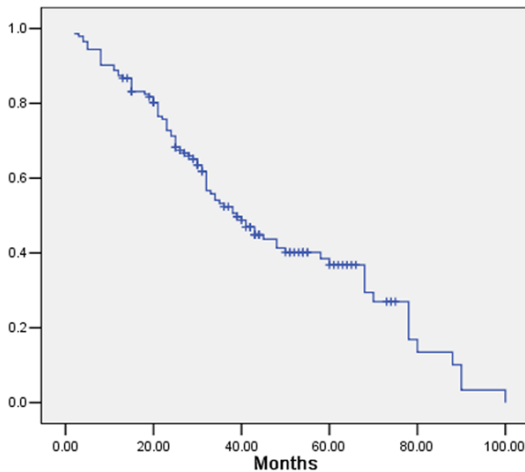| Variable	Reference	HR	95% CI	P value
Pathological stage (stage II or III)	Stage I	2.100	1.361-5.807	0.003
Comorbidity (Yes)	No	1.986	1.258-3.502	0.020
Differentiation grade (Poor)	Good	1.200	0.875-1.658	0.085

Figure 2. Postoperative disease-free survival curves of the whole cohort.

tic factors for longer overall survival. A multivariate analysis showed that pathological stage I disease and absence of medical comorbidity were independent significant beneficial factors for overall survival (**Table 5**).

The 5-year disease-free survival rate after radical eso phagectomy was 37%. The 5-year overall survival rates after radical esophagectomy ere 65%, 48%, and 15%, respectively, in pathologic stage I, pathologic stage II, and pathologic stage III (**Figure 2**). A univariate analysis was used to evaluate the prognostic factors for disease-free survival. No angiolymphatic invasion, no smoker, pathological stage I disease and absence of medical comorbidity were significant prognostic factors for longer disease-free. A multivariate analysis showed that only pathological stage I disease was independent significant beneficial factors for disease-free survival (**Table 6**).

Discussion

Radical esophagectomy offers the highest probability of cure in all patients with operable esophageal squamous cell carcinoma [34-36]. However, thoracic surgeons often hesitate to recommend radical esophagectomy for elderly patients with esophageal squamous cell carcinoma because these patients have higher morbidity, mortality and the uncertainty of long-term survival outcomes [11-19]. More information regarding the short-term surgical and long-term survival outcomes would help thoracic surgeons to select a subgroup of elderly patients suitable for radical esophagectomy [37-42]. This study analyzed 143 patients aged from 65 to 75 years with operable esophageal squamous cell carcinoma.

The long-term survival outcomes in this study were acceptable. The 5-year survival rate was similar to those reported recently in literatures of elderly patients undergoing radical esophagectomy [39, 40, 42-46]. Multivariate analysis identified pathological TNM stage and medical comorbidities as significant factors influencing long-term survival outcomes. Although pathological TNM stage is a well-known prognostic factor for long-term survival outcomes [11-19], the role of medical comorbidities in prognosis is less studies. Medical comorbidities might influence the risk for death from causes other than esophageal squamous cell carcinoma in elderly patients, as previously studied [39, 40, 42-46]. Thoracic surgeons should consider medical comorbidities and clinical TNM staging in selecting those elderly patients most likely to achieve long-term benefit from radical esophagectomy.

The postoperative 30-day complication rate in our series was lower than those cited in recent studies with large cohort of patients that described postoperative 30-day complication rate ranging from 23% to 45% [39, 40, 42-46]. The postoperative 30-day complication rate in our series is comparable with the morbidity rate of esophagectomy in the general population as previous reported [39, 40, 42-46]. Possible reasons for this comparable morbidity rate may be the lower rate of patients with medical comorbidities and the higher proportion of patients undergoing less invasive surgery in this study.

Nonsurgical therapies, such as chemotherapy and radiotherapy, are currently used in the

Table 6. Multivariate analysis of disease-free survival: Cox proportional hazard model

Variable	Reference	HR	95% CI	P value
Pathological stage (stage II or III)	Stage I	1.897	1.102-3.205	0.015
Comorbidity (Yes)	No	1.258	0.758-1.895	0.085
Angiolymphatic invasion (Yes)	No	1.584	0.850-2.021	0.070
Smoker (Yes)	No	1.320	0.458-1.580	0.103

treatment of esophageal squamous cell carcinoma [47]. In most literatures, these nonsurgical therapies are indicated for high-risk patients unfit for radical esophagectomy [2-5]. However, there is little data on comparison of these nonsurgical therapies with radical surgery with respect to overall survival outcome and disease-free survival outcomes. Randomized clinical trials comparing the efficiency of these different modalities would reliably help future surgical decision making with regard to treatment of esophageal squamous cell carcinoma in the elderly [2-5]. Until such randomized clinical trials are performed, the experiences in this series may constitute a basis on which to compare results.

Although minimally invasive esophagectomy has been shown to be safe and beneficial in elderly patients with operable esophageal squamous cell carcinoma [48], the routine adoption of minimally invasive esophagectomy in our institution only began over the past few years. Some of its reported benefits included less blood loss, fewer postoperative 30-day complication rates, better cosmetic results, reduced pain, and shorter length of postoperative hospital stay [48].

Limitations of this study were that the study was retrospective, not prospective study. Quality of life after radical esophagectomy was not assessed in this study, which is very important for considering radical esophagectomy.

In summary, the long-term results of esophageal squamous cell carcinoma in elderly patients were acceptable, with a 5-year overall survival rate of 46%. Pathologic TNM stage II or higher TNM stage and the presence of medical comorbidity were significantly independent factors predicting short survival.

Acknowledgements

Discourse of conflict of interest

None.

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