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ORIGINAL ARTICLE

Short- and long-term outcomes of minimally invasive esophagectomy in elderly patients with esophageal squamous cell carcinoma

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Summary

Purpose: *In recent years, there has been an increase in the number of elderly patients undergoing surgery for esophageal squamous cell carcinoma (ESCC). However, there are few studies on short- and long-term outcomes of minimally invasive esophagectomy (MIE) in such patients. The purpose of this study was to report both short- and long-term outcomes of MIE in elderly patients with ESCC.*

Methods: *A total of 273 patients with ESCC underwent MIE at our hospital from January 2010 to December 2016. Patients were divided into elderly (≥70 years) and nonelderly (<70 years) groups based on age at the time of surgery. Groups were compared with regard to general preoperative data, intraoperative data, postoperative 30-day complications and their severity, pathological result, recurrence, overall survival (OS), and disease-free survival (DFS) rates.*

Results: *The elderly group was characterized by higher Charlson Comorbidity Index >2 and American Society of Anesthesiologists (ASA) grade. Comparisons of other general preoperative data showed no significant differences. In addition, there were no significant differences in short-term outcomes except for postoperative 30-day complication rate. Although 30-day postoperative complication rate was higher in the elderly group compared with the nonelderly group, the incidence of major complications was similar between groups. Cancer recurrence, 5-year OS, and 5-year DFS rates also were similar between groups.*

Conclusion: *Although elderly patients with ESCC had higher Charlson Comorbidity Index and ASA grade, they could achieve short- and long-term outcomes of MIE similar to those of nonelderly patients.*

Key words: *elderly, esophageal squamous cell carcinoma, minimally invasive esophagectomy, minimally invasive surgery*

Introduction

China's population has been aging over the past 10 years. Occurrence of ESCC is age-related [1-6] and, as a result, there has been an increase in the number of elderly patients with ESCC [7-11]. Surgical resection is the main treatment method for ESCC [12]. However, because of the higher postoperative morbidity and mortality of surgical resection in elderly patients [8], the proportion of elderly patients with ESCC who undergo surgical resection is lower compared with nonelderly patients [8]. With the rise of minimally invasive tumor resections in recent years, MIE also has been progressively carried out at large medical centers [13-16]. Relevant reports have shown that MIE has advantages such as less blood loss, shorter hospital stay, and similar oncologic outcomes compared with open esophagectomy [17]. However, there are only a handful of reports on MIE in elderly patients with ESCC. Furthermore, most reports focus on short-term outcomes, and little attention has been paid on long-term outcomes [18,19]. Therefore, our study aimed to report both short- and long-term outcomes of MIE in elderly patients with ESCC.

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Methods

This research was approved by our local ethics committees. The requirement of informed consent from patients was waived because of the retrospective nature of the research.

A total of 273 patients with ESCC underwent MIE at our hospitals between January 2010 and December 2016 and met the following inclusion criteria: (1) ESCC pathological diagnosis; (2) tumor location in the thoracic esophagus; (3) no preoperative treatment (eg, neoadjuvant therapy, endoscopic mucosal resection); and (4) resection with radical intent. Exclusion criteria were as follows: (1) pathologically non-squamous cell carcinoma (eg, adenocarcinoma, adenosquamous carcinoma); and (2) administration of preoperative neoadjuvant therapy. Patients were divided into elderly (≥70 years) and nonelderly (<70 years) groups based on age at the time of surgery. Surgical indication for MIE was cT1-3N0M0. Preoperatively, patients underwent electronic gastroscopy, endoscopic ultrasonography, neck ultrasonography, and brain, chest and abdominal computed tomography to confirm clinical staging. If necessary, positron emission tomography–computed tomography, bone scan, or other examinations were also performed. Preoperative physical examination, laboratory tests, pulmonary function tests, and electrocardiography were performed to determine whether patients could tolerate surgery. The 2009 TNM staging system, 7th edition, was referenced for tumor staging [19]. Procedures of MIE were as follows: thoracoscopic esophageal mobilization, mediastinal lymphadenectomy, laparoscopic gastric mobilization, gastric tube insertion, abdominal lymphadenectomy, and cervical anastomosis. Specific details of the operation are found in the relevant literature [19].

Postoperatively patients were routinely admitted to the intensive care unit (ICU) for 1 day. If no major complications occurred, they were transferred to the thoracic surgery ward. If major complications occurred, patients remained in the ICU. The severity of postoperative 30-day complications was graded using the Clavien-Dindo classification, which ranks the severity of postoperative complications into 5 grades. Minor complications are classified as grades 1 and 2, while major complications are classified as grades 3, 4, and 5 [20-26].

Patient follow-up was conducted at the outpatient clinic, via telephone, and by contact with local community health service centers. Patients were examined once every 3 months in the first year, every 4 months in the second year, and once annually thereafter. Upper gastrointestinal endoscopy was suggested once annually after esophagectomy. The final follow-up was April 1, 2017. Tumor recurrence was diagnosed by history, physical examination, endoscopic evaluation, radiologic investigation, and/or pathologic result, when available. Recurrence was classified as locoregional recurrence, distant metastasis, or mixed [27]. Locoregional disease was defined as recurrence within the esophageal bed, regional lymph nodes, or anastomotic site [27]. Distant disease included metastasis at distant organ sites [27].

Statistics

Data were presented as means and standard deviations for variables with normal distribution. For data with non-normal distribution, results were expressed as medians and ranges. Survival rates were analyzed

Table 1. Baseline characteristics of the two groups

Characteristics	*Elderly group (n= 94) n (%)*	*Nonelderly group (n=179) n (%)*	*p value*
Age, years, median (range)	74 (70-77)	59 (48-69)	0.000
Sex			0.417
Male	65 (69.1)	115 (64.2)	
Female	29 (30.9)	64 (35.8)	
Charlson comorbidity index> 2	29 (30.9)	12 (6.7)	0.000
Tumor location			0.879
Upper	6 (6.4)	13 (7.3)	
Middle	57 (60.6)	103 (57.5)	
Lower	31 (33.0)	63 (35.2)	
Clinical TNM stage (7th AJCC-UICC)			0.617
IB	11 (11.7)	25 (14.0)	
IIA	39 (41.5)	61 (34.1)	
IIB	44 (47.8)	93 (52.0)	
ASA score			0.004
I	45 (47.9)	108 (60.3)	
II	28 (29.8)	62 (34.6)	
III	21 (22.3)	9 (5.0)	

ASA: American Society of Anesthesiologists using the Kaplan-Meier method with log-rank test. Univariate analyses were performed to identify prognostic variables related to OS and DFS. Univariate analyses were also performed to identify the prognostic variables related to conversion. Univariate variables with probability values <0.05 were selected for inclusion in the multivariate Cox proportional hazard regression model. A p value < 0.05 was considered statistically significant. SPSS 14.0 (SPSS Inc., Chicago, IL, USA) Windows version was used for all statistical analyses.

Results

There were 94 and 179 patients in the elderly and nonelderly groups, respectively. Comparison of general preoperative data between groups revealed that the elderly group had higher Charlson Comorbidity Index >2 (p=0.000) and American Society of Anesthesiologists (ASA) grade (p=0.004). Other general preoperative data (sex, tumor location, tumor staging) showed no significant differences (Table 1).

Intra- and postoperative data of both groups are shown in Table 2. There were no significant differences between groups in terms of operating time, intraoperative blood loss, intra- and postoperative blood transfusion rate, days in the ICU and days of hospitalization. There was no intraoperative or 30-day postoperative mortality in either group (Table 2). Although postoperative 30-day complication rate was higher in the elderly group than in the nonelderly group (p=0.040), the incidence of major complications was similar between groups. The higher postoperative 30-day complication rate in the elderly group was due to higher incidence of pulmonary infection (p=0.017). There were no significant differences between groups in terms of pathological staging or tumor differentiation (Table 3).

Median follow-up was 35 months for all patients (34 months in the elderly group, 37 months in the nonelderly group). During the follow-up period, 33 and 54 patients died in the elderly and nonelderly groups, respectively and 37 and 62 patients had disease recurrence in the elderly and nonelderly groups, respectively. There were no significant differences in recurrence rate or location of recurrence between groups (Table 4).

Five-year OS rate of the elderly and nonelderly groups was 47% and 53%, respectively, which was not significantly different (Figure 1, p=0.131). Multivariate analysis showed that T stage, N stage, and tumor differentiation status were independent predictors of OS (Table 5). Five-year DFS rate of the elderly and nonelderly groups was 33% and 46%, respectively, which was not significantly different (Figure 2, p=0.139). Multivariate analysis showed that T stage and N stage were independent predictors of DFS (Table 6).

Table 2. Short-term outcomes of the two groups

Outcomes	*Elderly group (n= 94) n (%)*	*Nonelderly group (n=179) n (%)*	*p value*
Operative time, min, median (range)	220 (180-300)	240 (160-320)	0.320
Estimated blood loss (ml)	240 (180-440)	230 (170-500)	0.285
Conversion to thoracotomy	6 (6.4)	9 (5.0)	0.641
Conversion to laparotomy	2 (2.1)	2 (1.1)	0.896
Blood transfusion	11 (11.7)	15 (8.3)	0.374
Patients with postoperative 30-day complications	28 (29.8)	37 (20.7)	0.040
Pneumonia	14 (14.9)	11 (6.1)	0.017
Pulmonary dysfunction	7 (7.4)	10 (5.6)	0.546
ARDS*	2 (2.1)	1 (0.6)	0.568
Pulmonary embolism	1 (1.1)	2 (1.1)	1.000
Atrial fibrillation	6 (6.4)	12 (6.7)	0.919
Heart failure	3 (3.2)	7 (3.9)	1.000
Anastomotic leak	7 (7.4)	12 (6.7)	0.819
Delayed gastric emptying	3 (3.2)	4 (2.2)	0.942
Recurrent laryngeal nerve injury	1 (1.1)	1 (0.6)	1.000
Chylothorax	2 (2.1)	1 (0.6)	0.568
Patients with major complications	9 (9.6)	16 (8.9)	0.863
Thirty-day mortality	0 (0.0)	0 (0.0)	-
Postoperative hospital stay, days, median (range)	10 (8-29)	11 (9-25)	0.358

* Acute respiratory distress syndrome

Table 3. Short-term oncological data of the two groups

Data	*Elderly group (n= 94) n (%)*	*Nonelderly group (n=179) n (%)*	*p value*
Retrieved lymph nodes, median (range)	18 (16-22)	21 (17-28)	0.128
Residual tumor (R0/R1/R2)	94/0/0	179/0/0	1.000
Histologic grade			0.113
G1	22 (22.4)	61 (34.1)	
G2	48 (51.1)	79 (44.1)	
G3	24 (25.5)	39 (21.8)	
Pathological TNM stage (7th AJCC-UICC)			0.569
IB	8 (8.5)	14 (7.8)	
IIA	24 (25.5)	38 (21.2)	
IIB	21 (22.3)	43 (24.0)	
IIIA	18 (19.1)	32 (17.9)	
IIIB	22 (23.4)	41 (22.9)	
IIIC	4 (4.3)	11 (6.1)	

Table 4. Follow-up data of the two groups

Outcomes	*Elderly group (n= 94) n (%)*	*Nonelderly group (n=179) n (%)*	*p value*
Tumor recurrence	39 (41.5)	64 (35.8)	0.353
Locoregional	23 (24.5)	36 (20.1)	0.406
Distant	12 (12.8)	19 (10.6)	0.594
Mixed	4 (4.3)	9 (5.0)	1.000
Time to recurrence, median, months (range)	17 (2-34)	21 (6-53)	0.210
Mortality	33 (35.1)	54 (30.2)	0.405
Died of cancer	30 (31.9)	52 (29.1)	0.624
Died of non-cancer-related diseases	3 (3.2)	2 (1.1)	0.460

Table 5. Multivariate analysis of overall survival

Regression variables	*Adjusted hazard ratio*	*95% CI*	*p value*
Pathological T stage			
T_1-T_2	1.00		
T_3-T_4	2.35	1.55-2.88	0.038
Pathological N stage			
N_0-N_1	1.00		
N_2-N_3	2.80	1.48-3.61	0.028
Histological grade			
G1-G2	1.00		
G3	2.58	1.57-3.10	0.015

Table 6. Multivariate analysis of disease-free survival

Regression variables	*Adjusted hazard ratio*	*95% CI*	*p value*
Pathological T stage			
T_1-T_2	1.00		
T_3-T_4	1.97	1.41-2.59	0.040
Pathological N stage			
N_0-N_1	1.00		
N_2-N_3	2.38	1.69-2.74	0.036

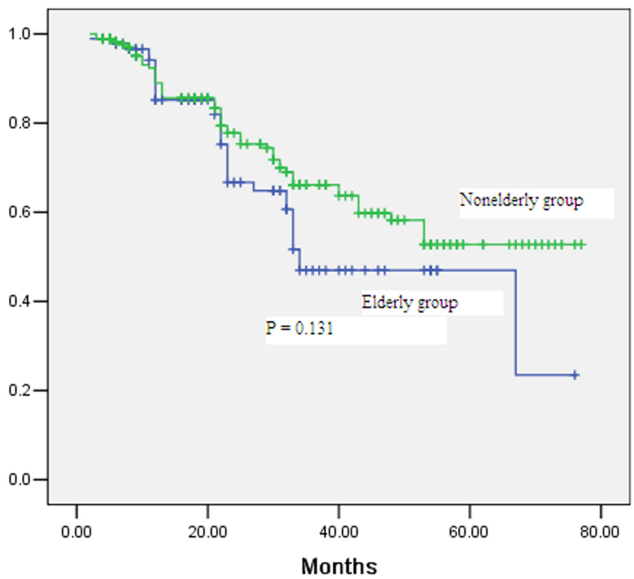

Figure 1. Comparison of overall survival rate between elderly and non-elderly group. There was no significant difference between the two groups (p=0.131).

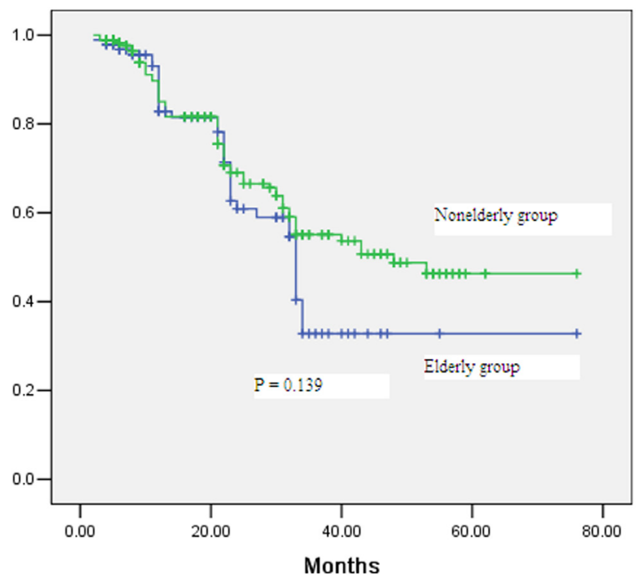

Figure 2. Comparison of disease-free rate between elderly and non-elderly group. There was no significant difference between the two groups (p=0.139).

Discussion

Owing to cumulative experience, continuous improvement of surgical instruments and publication of related reports, MIE is gradually being performed at large medical centers. However, the vast majority of MIE-related studies have focused on nonelderly patients, and only few geriatric cases have been reported [18,19,28]. According to our search of Medline, Embase, Scopus, and Web of Science, our study is the first to report short- and long-term outcomes of MIE in elderly and nonelderly patients with ESCC. Our results showed that although patients in the elderly group had higher Charlson Comorbidity Index and ASA grade compared with those in the nonelderly group, the rate of major complications was similar between groups. The rate of complications was slightly higher in the elderly group due to increased incidence of pulmonary infection and all cases were cured with intravenous antibiotics. Recurrence, OS and DFS rates were similar between groups during the follow-up period; age was not an independent predictor of prognosis.

In this study, the incidence of pulmonary infection was higher in the elderly group, and the cause was age-related. Studies have shown that age is a risk factor for pulmonary infection after esophagectomy [3-7]. Elderly patients have declined function of their organ reserve, and their degree of tolerance to surgery is decreased compared with nonelderly patients [3-7]. Moreover, nonspecific immunity of elderly patients is also decreased, ultimately causing higher rate of pulmonary infection [8-11]. Fortunately, in terms of severity, all pulmonary infections were relatively mild and cured by antibiotics.

In this study, approximately 30% of patients had Charlson Comorbidity Index >2. Open esophagectomy is often contraindicated in such patients. Without radical resection, the 5-year overall survival rate is nearly 0% in patients with ESCC [16]. Therefore, MIE can be used for radical resection in the abovementioned patients, who are deemed to have poor tolerance for open esophagectomy in preoperative assessment, to improve their survival [18,19,28].

Oncology does not have a specific age limit for elderly cancer patients. In previous publications, the age limit for elderly patients was generally 65 to 75 years [29-32]. For malignancies with better overall prognosis, such as colon and rectal cancer, elderly age is generally defined as ≥75 years [30], whereas for malignancies with worse prognosis, such as anaplastic astrocytoma and glioblastoma [31,32], elderly age is generally defined as ≥65 years. ESCC is a highly malignant tumor [33,34], and in previous reports of ESCC [18,19,28], elderly age was defined as ≥70 years. Therefore, the cutoff age for elderly patients in this study was defined as ≥70 years.

In this study, long-term outcomes of both groups, specifically recurrence, OS, and DFS rates were similar. Only a few studies have reported the effect of MIE on long-term outcomes of elderly patients with esophageal cancer [18,19]. Previous reports have shown that 5-year OS rate of elderly patients with esophageal cancer who underwent MIE was 30-55% [18,19]. The results of this study are similar to those of previous studies.

There are several limitations of this study, primarily due to its retrospective, single-center design and small sample size. However, to our knowledge, this study currently has the largest sample size regarding elderly patients with ESCC who have undergone MIE. Therefore, our study can serve as a foundation for future multicenter, large-sample studies.

Conclusion

In conclusion, the results of this study show that MIE does not increase postoperative complications or mortality in elderly patients with ESCC. Additionally, elderly patients with ESCC can achieve long-term outcomes with MIE, similar to those of nonelderly patients. Thus, for elderly patients with ESCC, age is no longer a contraindication for MIE.

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Conflict of interests

None of the authors have any financial interest relevant to the work presented in this manuscript.

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