Radical esophagectomy in elderly patients with esophageal cancer

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Abstract  Background: The increasing lifespan of the aging population has resulted in an increased number of elderly patients with esophageal cancer.  Purpose: This study was conducted to determine the effects of age on outcomes following surgery in elderly patients with esophageal cancer.  Methods: Patients with esophageal cancer who received curative esophagectomy between January 2001 and December 2012 were enrolled in this study. The patients were divided into two groups according to their age at diagnosis: Group 1 comprised patients aged ≥70 years and Group 2 comprised patients aged <70 years. Perioperative variables, the length of hospital stay, rates of surgery-related morbidity and mortality, and survival outcomes were analyzed and compared between the two groups.  Results: The study comprised 185 patients, with 39 patients in Group 1 and 146 patients in Group 2. Perioperative variables, namely pulmonary function, chemoradiotherapy, length of intensive care unit stay (4.5 days vs. 3.1 days), and hospital stay (30.2 days vs. 21.6 days), were significantly different between the two groups. The patients in Group 1 showed higher mortality (7.7% vs. 3.4%) and morbidity (46.1% vs. 29.5%) compared with those in Group 2, with no statistical significance. Cardiopulmonary-related complications (30.8%) following esophagectomy were most frequently observed in elderly patients. With less intensive chemotherapy and/or radiotherapy, the overall survival of the patients in Group 1 was prolonged compared with that of the patients in Group 2 (15.8 months vs. 13.7 months, \( p = 0.44 \)). Esophagectomy followed by chemoradiotherapy did not yield more positive outcomes than those of esophagectomy alone in patients in Group 1.

Conflicts of interest: The authors have no conflicts of interest.

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1. Introduction

Esophageal cancer is a highly fatal disease.1,2 Esophagectomy is commonly accepted as a local curative treatment for esophageal cancer and offers an opportunity for long-term survival.1,3,4 Because of the globally increasing life expectancy and size of the aged population,5-9 a growing number of elderly patients are becoming potential candidates for esophagectomy for esophageal cancer.7,8 However, esophagectomy, being a major operative surgery, has previously shown high mortality and poor long-term survival in elderly patients.10-12 Despite advanced surgical technologies and perioperative care techniques, the adequacy of esophagectomy in elderly patients with esophageal cancer remains controversial.5,10 Data on the effects of surgery and the survival outcome following esophagectomy in elderly patients remain scant.5,6,9 The short-term surgical risk and potential loss in quality of life must be analyzed against the long-term benefit of the surgery.

No standard cutoff age for identifying patients as elderly in relation to esophagectomy has been defined. Along with a gradual decline in physiological function and functional reserve, aging slows the process of recovery from major stress conditions such as surgery.13 A study reported that an age >70 years was associated with a significantly increased risk from surgery for esophageal cancer.14 The stress-buffering properties of physiological support following esophagectomy were more evident in patients aged >70 years than in those aged <70 years. Thus, the age of 70 years was considered a critical cutoff point for identifying patients who received esophagectomy as elderly. In the current study, we retrospectively enrolled patients with esophageal cancer and compared their surgical and long-term survival outcomes by assigning them to two groups.

2. Methods

Patients who received curative esophagectomy for esophageal cancer between January 2001 and December 2012 were enrolled and assigned to two groups according to their age at diagnosis: Group 1 comprised patients aged >70 years and Group 2 comprised patients aged <70 years. Esophagectomy and reconstruction of the esophagus were conducted using the Orringer transhiatal technique for lower esophageal tumors and the two-stage Ivor–Lewis or three-stage McKeown procedure for tumors of the mid and upper third of the esophagus. Clinical data of the patients were retrospectively collected and analyzed. The definitions of tumors, metastatic descriptors, and staging classification used in the current study were based on the definitions described in the seventh edition of the American Joint Committee on Cancer staging manual.15 Thus, the stages of patients who were treated before 2009 were revised according to the new staging system. Because a standard definition of celiac and cervical lymph nodes related to lower thoracic and upper thoracic esophageal cancer is not described in the manual, the stage of these cases in both groups was considered as the M1 stage.

Preoperative evaluation included a detailed risk assessment based on the history of cardiopulmonary, cerebrovascular, hepatic, and renal diseases. All patients were subjected to endoscopy, barium esophagography, abdominal sonography, computed tomography, cell and biochemistry profiling, electrocardiography, pulmonary functional tests, and arterial blood-gas analysis before surgery. Patients with a clinical stage ≤ Stage III and having a performance status ≤ 2 were evaluated by a multidisciplinary team and were considered surgical candidates. Following esophagectomy of locally advanced or recurrent esophageal cancer, eligible patients received concurrent or sequential chemotherapy and/or radiotherapy, according to their performance and tumor status. The adjuvant chemotherapy involved first-line treatment using a cisplatin-based doublet combination with fluorouracil and advanced-line treatments (for 13 patients) with cetuximab (for six patients), taxanes (for four patients), doxorubicin (for two patients), and bevacizumab (for one patient).

Patients were regularly followed up for 1–2 months and systemically examined every 3 months for the first 2 years, and 6 months thereafter. The postoperative analysis included chest roentgenography, computed tomography, abdominal sonography, measurement of serum levels of carcinoembryonal antigen (for adenocarcinoma) and squamous cell carcinoma (for squamous cell carcinoma), and a Tc-m99 whole body bone scan, and brain scan or whole body positron emission tomography. Patients were immediately examined if symptoms and signs specific to the progression of a suspicious disease were observed. Tumor progression or recurrence was defined using biopsy or at least two positive clinical examinations.

Several variables, namely sex, nutritional status, performance status, pulmonary function (functional vital capacity and first-second forced expiratory volume), tumor location (upper third, middle third, and lower third), tumor size, tumor grade (I, II, III, IV), histology, and chemoradiotherapy, were compared between the two groups to determine the major effects of age on the surgical and survival outcomes. The surgical outcomes were compared using six variables, namely blood loss during surgery, completeness of resection (R0: resection with negative
margins; R1: resection with microscopic positive margins; and R2: resection with grossly positive residual margins), lengths of postoperative intensive care unit (ICU) and hospital stays, morbidity, and mortality.

Patients who preoperatively received neoadjuvant therapy were excluded. Survival was calculated as the period from the date of surgery to the date of the most recent follow-up or the date of death. Statistical analyses were performed using the independent Student t test and the Chi-square test or Fisher’s exact test for continuous and categorical variables, respectively. Data were collected by referring to medical records and by personally interviewing the patients. The survival outcomes were calculated using the Kaplan–Meier method and compared using the log-rank test. The analyses were performed using the SPSS/PC+ Advanced Statistics software package (Version 12.0, SPSS Inc., Chicago, Illinois, USA). Results were considered statistically significant when the p value was <0.05.

3. Results

Data on 895 patients diagnosed with and treated for esophageal cancer were collected. The types of treatment received by these patients are shown in Table 1. Of the patients, 185 (20.7%) were enrolled in the current study. Group 1 comprised of 39 patients and Group 2 comprised of 146 patients. Characteristics of these patients are shown in Table 2. More than 95% of esophagectomies in both groups were of the R0 resection type. Most patients (76.9%) with pathologically advanced disease or tumor relapse had received chemotherapy and/or radiotherapy. Compared with the elderly patients in Group 1, a significantly higher number of the younger patients in Group 2 had received chemotherapy and/or radiotherapy.

The perioperative variables and surgical results of the patients in both groups are shown in Table 3. Although blood loss during surgery and the completeness of the resection were comparable, the patients in Group 1 had longer ICU and hospital stays compared with the patients in Group 2. The patients in Group 1 showed higher rates of morbidity and mortality following esophagectomy compared with the patients in Group 2; although no statistical difference was observed. Among various comorbidities, cardiopulmonary complications (30.8% and 6.8%) affected the highest number of patients in both groups. Three patients (7.7%) in Group 1 died following surgery.

### Table 1. Characteristics of patients according to treatment group.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean ± SD</td>
<td>71.5 ± 3.6</td>
<td>71.8 ± 3.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male: 31 (79.5)</td>
<td>139 (92.5)</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>Female: 8 (20.5)</td>
<td>11 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>0: 33 (84.6)</td>
<td>135 (92.5)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>1: 4 (10.3)</td>
<td>10 (6.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2: 2 (5.1)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Nutrition status</td>
<td>Body mass index</td>
<td>16.0 ± 2.4</td>
<td>15.8 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>Serum albumin</td>
<td>3.24 ± 1.87</td>
<td>3.15 ± 2.12</td>
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</tbody>
</table>

### Table 2. Treatments by age group.

<table>
<thead>
<tr>
<th>Groups/treatments</th>
<th>Surgical resection (%)</th>
<th>Nonsurgical treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients &lt;70 y (n = 631)</td>
<td>188 (29.8%)</td>
<td>443 (70.2%)</td>
</tr>
<tr>
<td>Patients ≥70 y (n = 264)</td>
<td>48 (18.2%)</td>
<td>216 (81.8%)</td>
</tr>
<tr>
<td>Total (n = 895)</td>
<td>236 (26.4%)</td>
<td>659 (73.6%)</td>
</tr>
</tbody>
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Treatments include surgery alone, surgery plus adjuvant chemoradiotherapy, and induction chemoradiotherapy plus surgery, which was excluded in the study as described in the text. *p < 0.001.
Multiple complex complications were observed in several patients. By contrast, five deaths (3.4%) occurred in Group 2 because of postoperative pneumonia with adult respiratory distress syndrome (three patients) and anastomotic leakage with sepsis (two patients, one receiving intrathoracic anastomosis and one receiving intra-abdominal anastomosis).

The mean follow-up period of all patients was 20.8 months (range, 0.5–129.9 months). The long-term survival outcomes of patients with tumors of different grades are shown in Figure 1. The tumor grade significantly influenced the survival outcomes. Figure 2 shows the overall survival outcomes of patients in both groups. With less intensive chemotherapy and/or radiotherapy, the patients in Group 1 [median survival time (MST) = 15.8 months; 95% confidence interval (CI) = 7.3–24.3 months] had longer survival compared with the patients in Group 2 (MST = 13.7 months; 95% CI = 12.1–15.3 months); however, the difference was not statistically significant ($p = 0.44$). No patient who received chemotherapy and/or radiotherapy following esophagectomy showed significantly longer survival than that of patients who received esophagectomy alone ($p = 0.19$ and 0.08).

### 4. Discussion

The most effective treatment for primary esophageal cancer is curative esophagectomy. However, esophagectomy is reported to have high morbidity and mortality. Physicians, caregivers, and elderly patients must consider esophagectomy, because age can offset oncologic advantages. In the current study, age significantly influenced the rate of surgical resection. Compared with the patients in Group 2 (29.8%), a lower number of patients in Group 1 (18.2%) received surgical resection. By contrast, the elderly patients who received less intensive chemotherapy and/or radiotherapy following surgery showed longer survival compared with the younger patients; although no significant difference was observed. Several factors besides esophagectomy are likely to have influenced this result and require further discussion and evaluation in elderly patients.

In the current study, preoperative pulmonary functions in the elderly patients were significantly poorer than those in the younger patients. The poor physiological conditions adversely affected the postoperative outcomes: rates of mortality and morbidity were higher in the elderly patients than in the younger patients (Table 3). Elderly patients typically have limited functional reserve and a poor performance status. Esophagectomy and anesthesia affect elderly patients, prolonging the period for recovery and hospital stay. Old age delays recovery from functional loss of physiological stress loads. However, in the current study, the compared data did not differ significantly, probably because of advanced perioperative care techniques and surgical technologies. Functional changes caused by aging adversely affect recovery following esophagectomy in elderly patients, particularly by prolonging the postoperative ICU and hospital stay.

In the current study, longer survival was observed in the elderly patients than in younger patients, with no statistical significance. The association between esophagectomy and the survival outcome in elderly patients has been controversial. Differences in inclusion criteria, the lack of a standard definition of an elderly age, and variation in study designs may have caused variable discrepancies. From the viewpoint of treatment, the advantages of esophagectomy with lymph node dissection depend upon accurate tumor grading, which provides data valuable in determining whether adjuvant therapy is necessary. Moreover, surgery can resolve functional obstruction by a tumor, potentially preventing tumor-related complications and improving quality of life and nutritional support. Thus, the role of esophagectomy cannot be evaluated according to the result of survival outcomes. In the current study, patients with preoperative neoadjuvant therapy were excluded to avoid confounding factors attributable to unclear staging, which may crucially affect the outcome of surgery. Thus, the results of the current study are likely to accurately reflect the effects of age on the outcomes of esophagectomy.

Cancer is an immunogenic disease, and the immune system protects the body against tumorigenesis. The
elderly population, with decreased immune function, has an increased risk of cancer, but age may change tumor behavior. In the current study, elderly patients who received less intensive chemotherapy and radiotherapy following esophagectomy showed a longer survival time (MST = 15.8 months) compared with the younger patients (MST = 13.7 months). Such a survival benefit in elderly patients seems to contradict the effects of a poor immune system in old age. This result supports the suggestion of Weksler et al\textsuperscript{19} that aging slows tumor growth, reduces metastasis, and increases survival. Age has diverse effects on both tumor growth and tissue aging.\textsuperscript{20} Cellular senescence seems to activate a potent mechanism of tumor suppression and protection,\textsuperscript{21} resulting in slow growth of cancer in elderly patients. However, various factors, including exposure to carcinogens and changes in the host defense during aging, may affect the outcomes of treatment for esophageal cancer. The current study could not determine the complex association between cancer and aging, but the effect of age on the treatment of elderly patients with esophageal cancer should not be neglected. Additional studies are necessary to understand the relationship between carcinogenesis and aging in detail.

Considering the efficacy and benefits of esophagectomy in the elderly patients, the procedure must be used in combination with alternative nonsurgical treatments, such as chemotherapy and radiotherapy. Several studies have shown that in an advanced stage of cancer or a tumor relapse, when adjuvant or salvage therapy is used as a treatment option, elderly patients show a greater response to less intensive chemotherapy and/or radiotherapy than younger patients do.\textsuperscript{5,22} Reluctance to treat elderly patients and fear of toxicity are likely causes of the small number of elderly patients who receive chemotherapy and/or radiotherapy.\textsuperscript{13} Moreover, several randomized trials have shown no benefits of chemoradiotherapy.\textsuperscript{23,24} Furthermore, previous studies based on target therapy for esophageal cancer could not prove that it benefits treatment-related survival.\textsuperscript{25,26} Thus, considering these unsatisfactory results, esophagectomy alone yields more benefits in elderly patients than in younger patients.

Finally, elderly patients are likely to die from various age-related diseases, such as cardiopulmonary disorders. Additional studies are required to determine whether the superior overall survival outcomes with no statistical significance support the benefit of esophagectomy in elderly patients with esophageal cancer. A previous report by Yang et al\textsuperscript{1} suggested that only a few patients with esophageal cancer died from conditions other than cancer. Thus, conditions other than cancer should have a limited effect on the survival analysis of elderly patients with esophageal cancer.

This study has limitations such as a retrospective design, mixed therapies, and mismatched comparisons between the two groups. However, the survival benefit of esophagectomy in elderly patients with esophageal cancer
cannot be denied, because the surgical procedure is the main evidence-based effective treatment for esophageal cancer and has positive long-term survival outcomes. In addition, frequency-matching between the two groups with different ages in an age-based study is difficult. If surgery is an appropriate treatment modality, elderly patients should not be denied this option because of their age.

The results of the current study suggest that esophagectomy followed by less intensive chemotherapy and/or radiotherapy in elderly patients has a superior survival outcome compared with that in younger patients; although perioperative courses in elderly patients may be more complicated. Considering that surgery remains the most effective modality for treating solid tumors, age alone should not affect treatment-related decisions and should not be included in exclusion criteria. In elderly patients with esophageal cancer, esophagectomy yields a superior outcome.

**References**


