Clinical outcomes of elderly patients (≥70 years) with resectable esophageal squamous cell carcinoma who underwent esophagectomy or chemoradiotherapy

A retrospective analysis from a single cancer institute

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Abstract

A retrospective analysis was conducted to investigate outcomes of elderly patients with resectable esophageal squamous cell carcinoma (ESCC) who underwent surgery or chemoradiotherapy (CRT).

We performed a retrospective review of the records of elderly patients (≥70 years) with resectable ESCC who underwent esophagectomy or CRT between January 2009 and March 2013. According to the main treatment strategy, patients were allocated into either surgery group or CRT group. Overall survival (OS), cancer-specific survival and progression-free survival were calculated by the Kaplan–Meier method. Univariate and multivariate survival analyses were performed by the Kaplan–Meier method and Cox proportional hazards model, respectively.

A total of 188 patients were enrolled. Eighty-eight patients underwent esophagectomy, and 100 patients underwent CRT. The median age of the patients was 73 years (range, 70–81 years) in the surgery group and 76 years (range, 70–88 years) in the CRT group. The median survival time (MST) for the whole cohort was 25.6 months, and 1-, 3-, and 5-year survival rates were 69.2%, 36.1%, and 21.9%, respectively. The MST in the surgery group and the CRT group was 36 months and 15 months, respectively. The 1-, 3-, and 5-year survival rates in the CRT group were 58.0%, 24.1%, and 7.8% in the CRT group ($P<0.0001$). Multivariate analysis revealed that lymph node status (hazard ratio [HR] = 0.598, $P = 0.011$) and treatment strategies (HR = 0.538, $P = 0.001$) were independent and significant prognostic factors for OS in elderly patients.

Surgery was the main treatment strategy for elderly patients with ESCC. Advanced age and comorbidities should not be the cause for elderly patients to avoid aggressive regimens. Delivered therapeutic approaches should be individualized on the basis of carefully evaluating the balance of benefits, risks, and life expectancy.

Abbreviations: CRT = chemoradiotherapy, CSS = cancer-specific survival, CTV = clinical targeted volume, EC = esophageal cancer, ESCC = esophageal squamous cell carcinoma, GTV = gross tumor volume, IFI = involved-field irradiation, LN = lymph node, OS = overall survival, PFS = progression-free survival.

Keywords: chemoradiotherapy, elderly, esophageal cancer, prognosis factor, surgery, survival

1. Introduction

Cancer has become the leading cause of death in the elderly aged from 60 to 79 years in the United States; approximately 70% of all cancers will be diagnosed in the elderly aged ≥65 years by 2030.[1,2] Esophageal cancer (EC), which the incidence projected increased from 35% in 2020 to 68% in 2030, has become the fifth in male and eighth in female cause of cancer death worldwide; approximately 482,300 new cases and 406,800 deaths from EC occurred in 2008 worldwide.[2,3] As actuarial life expectancy increases, it is extremely urgent to pay more attention to choose optimal anticancer strategy in the elderly. In addition, with the establishment of evidence-based medicine, especially the advent of precision medicine, the decision of treatment options is based on evidence and paid more attention on individual.

Unfortunately, the elderly was often underrepresented in clinical trials considering advanced age and comorbidities. As a result, high levels of evidences are shortage to guide the choice of treatment for elderly cancer patients. To date, there is no standardized treatment strategy for elderly patients with EC.

Surgery remains the main approach to treat patients with EC. However, high rates of postoperative morbidity and mortality occurred in patients aged ≥70 years who treated with...
esophagectomy. Furthermore, considering high risk factors of surgery, such as advanced age and comorbidities, the approach of surgery was not being chosen or refused by patients themselves and their families. Hence, for patients with high risk of postoperative morbidity, concurrent chemoradiotherapy (CRT) was the standard treatment regimen. Regardless of similar response rate and overall survival (OS) compared with younger populations treated with CRT, the survival rate remains poor with approximately 25% to 64% of 2-year OS rate in the elderly. Thus, for elderly patients with potentially resectable thoracic EC, comparison of outcomes between surgery and CRT is very necessary.

The modality of treatment that elderly patients could benefit from remains unknown. Hence, we conducted a retrospective study to analyze the prognostic factors of elderly patients with non-metastatic EC, who treated with different treatment strategies (surgery, CRT, and combination therapies), and attempted to afford new evidences of choosing optimal approaches in such patients.

2. Patients and methods

2.1. Patients

We retrospectively reviewed the records of patients with EC who underwent surgery or CRT in our cancer department between January 2009 and March 2013. The criteria of enrollment were treatment-naïve patients with histologically proven thoracic esophageal squamous cell carcinoma (ESCC); aged ≥70 years; KPS ≥70; clinical stage T1-3; complete resection (R0); without any other site of carcinoma or with metastatic disease. Complete records showed that patients were suitable for surgery without serious cardiopulmonary comorbidities after cautious assessment. Comorbidities were evaluated by the Charlson criteria system. Clinical tumor stage and status of lymph node (LN) were evaluated by computed tomography (CT) scan, according to the criteria of Union for International Cancer Control Tumor-Node-Metastasis cancer staging, 7th edition (2010). Tumor length was measured by esophagography before treatment. All data were analyzed anonymously. This study was approved by the institutional ethics committee of Shandong Cancer Hospital Affiliated to Shandong University.

2.2. Procedures

In our department, standard surgical procedures consisted of 2 types: for upper and middle sites, esophagectomy with mediastinal lymphadenectomy via left thoracotomy, upper abdominal lymphadenectomy, reconstruction of the gastric tube, and anastomosis above the aortic arch or in the cervical incision were recommended; for lower sites, laparotomy with mediastinal and abdominal lymphadenectomy, and anastomosis under the aortic arch were recommended. Whether cervical lymphadenectomy or not was based on the location of the primary tumor and invasion of regional LNs.

Radiotherapy was administered by 3-dimensional conformal radiotherapy or intensity modulated radiation therapy. For involved-field irradiation (IFI), the gross tumor volume (GTV) was defined any visible esophageal lesions measured by any available imaging examinations, including CT, barium esophagogram, positron emission tomography (PET)/CT and localizable CT, and any involved regional LNs. Clinical targeted volume (CTV) was defined as the GTV plus at least 3-cm margin superior and inferior to the primary tumor and a lateral margin 0.8 to 1.0 cm (for LN at least 0.5 cm). For elective nodal irradiation, GTV and CTV of primary tumor was defined similar with that of IFI, CTV of LN include involved LNs and related lymphatic drainage areas. Elective treatment of nodal regions depended upon the location of the primary tumor. Planning targeted volume was defined as the CTV plus a 0.5 to 1.0 cm radial margin. A single daily fraction of 1.8 to 2.0 Gy was administered, for a total dose of 50.4 to 66 Gy to the primary lesions and involved LNs, and 40 to 50.4 Gy for elective node irradiation.

Chemotherapy consisted of adjuvant chemotherapy and concurrent chemotherapy. Cisplatin (25mg/m², on days 1–3) and 5-fluorouracil (1000mg/m², on days 1–5)/docetaxel (75mg/m², on days 1) were administered every 3 weeks up to 2 to 4 cycles.

2.3. Mortality and complications

Short-term mortality is defined as death occurred during hospital admission or within 30 days of surgery. Complications consists of any grade postoperative complications, which was assessed using the criteria of modified Clavien-Dindo classification, and grade 3 or greater CRT adverse events, which was accessed using the CTCAE version 3.0. Infection included pyothorax or chylothorax, abdominal abscess, or incision infection. Pulmonary complications were defined as pneumonia, or hypoxia requiring intervention. Cardiac complications were defined as heart failure, myocardial infarction, or arrhythmia requiring intervention.

2.4. Follow-up

Cervical ultrasonography, chest and abdominal CT, and/or esophagography were performed to monitor the course of disease. For patients with surgery, CT scan was performed every 3 months up to 2 years, every 6 months up to 3 years, and annually thereafter. For patients with CRT, CT scan was performed every 3 months for the first year, and then every 6 months for the next 3 years, and annually thereafter. Other necessary follow-up evaluation included history, physical examination, complete blood count, and serum biochemistry. Another unscheduled evaluation was conducted according to the clinical situation.

2.5. Statistical analysis

Chi-square test was performed to compare the difference of patients’ characteristics. OS was measured from the date of diagnosis to the date of death from any cause or the last known follow-up date. Cause-specific survival (CSS) was defined as the interval from the date of treatment to death from any cause or the last follow-up. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of disease progression or death from any cause, or to the date of censor. OS, CSS, and PFS were calculated using the Kaplan–Meier method, and the log-rank test was used to evaluate the difference in survival curves between different arms. Univariate survival analysis was performed by the Kaplan–Meier method. Multivariate analysis for OS was performed using Cox regression and a backward–forward stepwise method was selected. All variables with P values <0.10 in the univariate analysis were included in the multivariate analysis. All statistical tests were 2-tailed, and P<0.05 was considered statistically significant.

3. Results

3.1. Patients characteristics

A total of 214 patients with ESCC who underwent esophagectomy or CRT in our cancer center were collected between January
2009 and March 2013. The median follow-up period for the whole cohort was 28.5 months (range, 0–81 months). At the end of the follow-up, 26 (12.1%) patients were lost, and 58 patients remained alive. Finally, 188 patients were enrolled in this study, including 88 patients in the surgery group and 100 patients in the CRT group, while the median age were 73.0 years (range, 70–81 years) and 76.0 years (range, 70–88 years), respectively. Of 88 patients treated with surgery, 63 patients underwent surgery alone, and the remaining 25 patients, including 10 patients of surgery in combination with chemotherapy, 11 patients of surgery in combination with radiotherapy, and 4 patients of surgery in combination with CRT. All characteristics of patients are listed in Table 1. Although the baseline data on LNs status showed a significant difference between the CRT group and the surgery group, the clinical stage before treatment were similar (data not show).

### 3.2. Survival

Figure 1A shows OS and PFS curve for entire group who underwent surgery and CRT. For the whole patients’ cohort, the median PFS was 18 months; 3- and 5-year PFS rates were 31.0% and 19.5%, respectively. The median survival time (MST) was 25.6 months, and 1-, 3-, and 5-year survival rates were 69.2%, 36.1%, and 21.9%, respectively.

Figure 1B shows PFS of patients between the surgery group and the CRT group. The median PFS for surgery group and CRT group were 27 months and 12 months, respectively. And, 1-, 2-, and 3-year PFS rates were 71.8%, 52.8%, and 41.5% in the surgery group, which were significant higher than that of 47.3%, 29.2%, and 19.1% in the CRT group ($P < 0.0001$).

Figure 1C shows the survival of patients who underwent surgery or CRT. For the surgery group, 1-, 3-, and 5-year survival rates were 84.4%, 67.5%, and 52.7%, and 63.0%, 39.9%, and 26.5%, respectively. The difference was significant with less than 0.0001 of $P$ value. The MST in the surgery group was 36 months, whereas 18 months in the CRT group.

Figure 1D shows CSS of patients who underwent surgery or CRT. For the surgery group and CRT group, 1-, 3-, and 5-year survival rates were 84.4%, 67.5%, and 52.7%, and 63.0%, 39.9%, and 26.5%, respectively. The difference was significant with less than 0.0001 of $P$ value. The MST in the surgery group was 38 months, whereas 15 months in the CRT group.

### 3.3. Prognostic factors

The patient characteristics evaluated to determine their prognostic value for OS are summarized in Table 2. Univariate analysis revealed that sex, age, tumor stage, location, tumor length, smoking status, and drinking status were not associated with

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**Table 1**

| Characteristic | N    | S (%) | CRT (%) | P       |
|---------------|------|-------|---------|---------|
| Sex           |      |       |         |         |
| Male          | 120  | 65 (73.9) | 55 (55) | 0.007   |
| Female        | 68   | 23 (26.1) | 45 (45) |         |
| Age, y        |      |       |         |         |
| Median        |      | 73    | 76      |         |
| Range         |      | 70–81 | 70–88   |         |
| ≤75           | 115  | 65 (73.9) | 50 (50) | <0.001  |
| >75           | 73   | 23 (26.1) | 50 (50) |         |
| KPS score     |      |       |         |         |
| ≥80           | 172  | 84 (95.5) | 88 (88) | 0.07    |
| <80           | 16   | 4 (4.5)  | 12 (12) |         |
| Tumor stage   |      |       |         |         |
| T1–2          | 52   | 23 (26.1) | 29 (29) | 0.66    |
| T3            | 136  | 65 (73.9) | 71 (71) |         |
| LN status     |      |       |         |         |
| N0            | 73   | 47 (53.4) | 26 (26) | <0.001  |
| N+            | 115  | 41 (46.6) | 74 (74) |         |
| Location      |      |       |         |         |
| Upper         | 28   | 6 (6.8)   | 22 (22) | 0.01    |
| Middle        | 106  | 52 (52.1) | 54 (54) |         |
| Distant       | 54   | 30 (54.1) | 24 (24) |         |
| Comorbidities |      |       |         |         |
| Negative      | 87   | 40 (45.5) | 47 (47) | 0.83    |
| Positive      | 101  | 48 (54.5) | 53 (53) |         |
| Tumor length, cm |    |       |         |         |
| ≤5            | 115  | 55 (62.5) | 60 (60) | 0.73    |
| >5            | 73   | 33 (43.5) | 40 (40) |         |
| Smoking status|      |       |         |         |
| Yes           | 92   | 45 (51.1) | 47 (47) | 0.57    |
| No            | 96   | 43 (47.9) | 53 (53) |         |
| Drinking status |     |       |         |         |
| Yes           | 109  | 55 (62.5) | 54 (54) | 0.24    |
| No            | 79   | 33 (37.5) | 46 (46) |         |

CRT = chemoradiotherapy, KPS = Karnofsky performance status, LN = local-regional nodes, N+ = regional lymph node positive, N- = regional lymph node negative, S = surgery.
survival; however, LN status ($P=0.000$), comorbidities ($P=0.03$), and treatment strategies ($P=0.000$) were significant prognostic factors for survival. Multivariate analysis revealed that LN status (hazard ratio [HR]=0.598, $P=0.011$) and treatment strategies (HR=0.538, $P=0.001$) were independent and significant prognostic factors for OS in elderly patients.

### 3.4. Morbidity and mortality

Treatment-induced toxicities are detailed in Table 3. As detailed in the surgery group, infection (12.5%) and anastomotic leakage (6.8%) were the main complications, whereas leukopenia (21%), esophagitis (12%), and pneumonia (10%) were in the CRT group.

Table 4 shows mortality of patients treated with surgery and CRT. A total of 130 patients (54 in the surgery group and 76 in the CRT group) died of primary tumor or other causes. Of 54 deaths in the surgery group, 5 (9.3%) patients died of perioperative complications; 29 (53.7%) and 6 (11.1%) patients died of primary tumor and hemorrhage in long-term follow-up analysis, respectively. Only 4 patients died of nontumor-related cause, including 2 of secondary primary tumor, each case of cardiovascular complication and accident. For the CRT group, primary tumor (61.8%), radiation pneumonia (13.2%), and hemorrhage (9.2%) were the main causes of death. Of 7 patients with nontumor-related death, 4 patients died of pulmonary complications ($n=2$) and cardiac complications ($n=2$), and each case died of accident, cerebral hemorrhage, and miscellaneous complication.

#### Table 2

Univariate and multivariate analyses of the effect of prognostic factors on OS in patients with EC.

| Factors         | Univariate analysis | Multivariate analysis |
|-----------------|---------------------|----------------------|
|                 | 1-y OS (%) | 3-y OS (%) | 5-y OS (%) | $X^2$ | $P$ | HR   | 95% CI     | $P$ |
| Sex             |            |            |            |       |     |      |            |     |
| Male            | 65.8       | 37.7       | 24.1       | 0.017 | 0.895 |
| Female          | 72.1       | 42.0       | 15.6       |       |     |
| Age, y          |            |            |            |       |     |      |            |     |
| $<75$           | 67.0       | 36.7       | 26.3       | 0.432 | 0.511 |
| $>75$           | 69.9       | 33.2       | 13.8       |       |     |
| Tumor stage     |            |            |            |       |     |      |            |     |
| T1–T2           | 67.3       | 42.0       | 30.6       | 2.30  | 0.129 |
| T3              | 68.4       | 33.0       | 17.4       |       |     |
| LN status       |            |            |            |       |     |      |            |     |
| N0              | 74.0       | 51.3       | 33.6       | 14.3  | 0.000 | 0.598 | 0.402–0.889 | 0.011 |
| N+              | 64.3       | 24.7       | 12.3       |       |     |
| Location        |            |            |            |       |     |      |            |     |
| Upper           | 82.1       | 38.8       | 19.4       | 1.205 | 0.547 |
| Middle          | 62.3       | 35.4       | 23.5       |       |     |
| Distant         | 72.2       | 34.4       | 17.5       |       |     |
| Comorbidities   |            |            |            |       |     |      |            |     |
| Negative        | 73.6       | 44.1       | 26.4       | 7.023 | 0.03  | 0.777 | 0.485–1.246 | 0.295 |
| 1               | 69.2       | 35.8       | 19.7       |       |     |
| $\geq$2         | 52.8       | 14.2       | 14.2       |       |     |
| Tumor length, cm|            |            |            |       |     |      |            |     |
| $\leq$5         | 71.3       | 41.7       | 22.9       | 3.8   | 0.051 | 0.812 | 0.569–1.159 | 0.251 |
| $>5$            | 63.0       | 26.4       | 19.0       |       |     |
| Smoking status  |            |            |            |       |     |      |            |     |
| Yes             | 59.8       | 33.4       | 21.5       | 0.998 | 0.318 |
| No              | 76.0       | 41.5       | 21.5       |       |     |
| Drinking status |            |            |            |       |     |      |            |     |
| Yes             | 60.8       | 33.5       | 19.0       | 0.651 | 0.42  |
| No              | 73.4       | 36.7       | 22.7       |       |     |
| Treatment strategies |       |            |            |       |     |      |            |     |
| Surgery         | 79.5       | 52.6       | 32.2       | 18.9  | 0.000 | 0.538 | 0.369–0.786 | 0.001 |
| CRT             | 58.0       | 24.1       | 7.8        |       |     |

CRT = chemoradiotherapy, HR = hazard ratio, LN = local-regional nodes, N+ = regional lymph node positive, N0 = regional lymph node negative, OS = overall survival.
EC is one of the most common causes of cancer deaths worldwide, and the incidence has been rising in recent years. Squamous cell carcinoma is the most common histology of EC in Asia. With quickening the population aging, newly diagnosed EC in elderly patients increased dramatically. However, the optimal strategy for the elderly was still inconsistent. Hence, we conducted a retrospective study to compare survival and adverse events in elderly patients with ESCC who underwent surgery or CRT. Clinical features but not LN status and tumor location in the surgery and CRT group were well balanced. More positive LNs distributed in the CRT group, and multivariate analysis demonstrated positive LNs was a negative prognostic factor on survival. For patients with surgery, 5-year survival rate was significant higher than that of patients with CRT (33.3% vs 7.8%, )

 CRT = chemoradiotherapy.

4. Discussion

EC is one of the most common causes of cancer deaths worldwide, and the incidence has been rising in recent years.

Table 3

| Side effects of patients who underwent surgery or CRT. |
|---------------------------------|
| No. of cases (%)               |
| Surgical complications n=88 |
| Infection                      3 (3.4) |
| Anastomotic leakage            6 (6.8) |
| Pulmonary complications        9 (1.0) |
| Cardiac complications          1 (1.1) |
| CRT complications n=100        |
| hematologic toxicity ≥3        |
| Leukopenia                     21 (21)  |
| Anemia                         11 (11) |
| Thrombocytopenia               9 (9)  |
| Esophagitis ≥3                 12 (12) |
| Pneumonitis                    10 (10) |

Emerging data from clinical studies indicated that the 5-year CSS rate was approximately 41.5% to 61.7% in elderly patients aged 70 years treated with surgery.

Table 4

| Mortality of patients who underwent surgery or CRT. |
|---------------------------------|
| Surgery (%) (n=54)               |
| CRT (%) (n=76)                   |
| Primary tumor                   52 (53.7) |
| Perioperative complications     5 (9.3)  |
| Hemorrhage                      6 (11.1) |
| Anastomatic leakage             4 (7.4)  |
| Infection                       2 (3.7)  |
| Radiation pneumonia             1 (1.9)  |
| Others                          2 (3.7)  |
| Non-tumor-related death         4 (7.4)  |
| Total                           54     |

CRT = chemoradiotherapy.
may be attributed to the improvement of surgical technique and postoperative nursing management. Moreover, the CRT-induced toxicities were also acceptable. Comorbidities were likely to increase the risk of treatment toxicities and even treatment-induced death for patients. A large-scale observation study including 17,712 patients showed worse survival in patients with more severe levels of comorbidity. Another large-scale retrospective study demonstrated that comorbidity was an independent prognostic factor for patients with cancer. However, multivariate analysis in present study revealed that comorbidities were not the prognostic factor on survival. However, more comorbidities were likely to contribute to the lower performance status that might increase the risk of postoperative complications. Considering inconsistent evidences of complications and comorbidities on survival, comorbidities and the risk of postoperative complications should be evaluated carefully to perform the individualized treatment.

A notable issue in present study is that the status of LNs was not well balanced between the 2 groups. Previous studies indicated the nodal status, particularly the number of involved LNs, influenced the survival of patients with EC. Patients with negative LNs have the best prognosis, whereas patients with more involved LNs, in particular the number of involved LNs, is an independent prognostic factor for patients with cancer. Another large-scaled observation study including 17,712 patients showed worse survival in patients with more severe levels of comorbidity. Another large-scaled retrospective study demonstrated that comorbidity was an independent prognostic factor for patients with cancer. However, multivariate analysis in present study revealed that comorbidities were not the prognostic factor on survival. However, more comorbidities were likely to contribute to the lower performance status that might increase the risk of postoperative complications. Considering inconsistent evidences of complications and comorbidities on survival, comorbidities and the risk of postoperative complications should be evaluated carefully to perform the individualized treatment.

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