Objective: The aim of this study was to review the treatment outcomes of surgery and definitive chemoradiotherapy (CRT) in elderly patients with squamous cell carcinoma of the thoracic esophagus.

Methods: A total of 64 patients aged 75 or older were retrospectively reviewed; 40 were treated with surgery and 24 with CRT. The CRT group included eight patients with unresectable disease and four patients medically unfit for surgery. Surgery included esophagectomy with lymphadenectomy and CRT consisted of 60–70 Gy of radiation concurrent with 5-fluorouracil alone or combined with cisplatin. Short- and long-term outcomes and survival of each modality were assessed.

Results: In the surgery group, 33 patients (82.5%) had co-morbid conditions. Complete resection rate was 90.0%. An overall post-operative complication rate was 65.0% and in-hospital mortality was seen in three patients (7.5%). In the CRT group, complete response rate was 41.7%. Leukopenia was most common Grade 3 hematological toxicity. Treatment-related deaths caused by acute toxicities occurred in three patients (12.5%), whereas those caused by late toxicities in four (16.7%). For cStage I disease in the surgery group, the overall 1-, 3- and 5-year survival rate were 90.9%, 63.6% and 54.5%, respectively, with a median survival time of 78.7 months. For cStages II–IV, the median survival time of the surgery and the CRT group was 18.7 and 12.8 months, respectively.

Conclusions: The short- and long-term outcomes of surgery for the elderly seemed acceptable; however, definitive CRT may be a promising treatment modality. Further investigation may alter the sphere of influence in the field of esophageal cancer treatment in the elderly.

Key words: aged 75 years or older – chemoradiotherapy – esophagectomy – retrospective study – squamous cell carcinoma of the thoracic esophagus

INTRODUCTION

Esophageal carcinoma is a disease that mainly develops in elderly patients. As the general population is aging, we often encounter elderly patients with esophageal carcinoma for whom it is difficult to decide the best treatment of choice. Because the average life expectancy of a 75-year-old Japanese man and woman is 11.07 and 14.83 years, respectively (1), the life-limiting event may be their cancer and not their remaining lifespan. Although the poor prognosis of carcinoma of the esophagus combined with the shorter life expectancy of the elderly tended to favor palliation in the past, aggressive treatment including radical surgery and definitive chemoradiotherapy (CRT) has been demonstrated to cure the disease recently.

Although surgical resection has been widely accepted as the standard treatment for esophageal carcinoma, definitive CRT also has a curative potential for locally advanced...
disease. It is uncertain whether definitive CRT achieves comparable treatment outcomes to those of surgery because a randomized controlled trial has not yet been conducted. Such a trial would be quite difficult to perform due to the differing treatment characteristics. In addition, most randomized studies have excluded patients aged 75 years or older, which results in the lack of decision-making information to be offered to both physician and the elderly.

We therefore conducted this retrospective review in a single institution to clarify the patient and treatment characteristics of each modality and to assess the short- and long-term outcomes of each modality, with special reference to the patients aged 75 years or older.

PATIENTS AND METHODS

PATIENTS

A total of 322 patients with primary squamous cell carcinoma of the thoracic esophagus underwent esophagectomy in Niigata University Medical and Dental Hospital between January 1992 and December 2003. Of these patients, 282 patients were under 75 years of age and excluded from this study. The remaining 40 consecutive patients (12.4%) aged 75 years or older were all recruited and retrospectively reviewed from the medical records. Pre-operative risks were assessed based on history, symptoms of chronic lung or heart disease, chest X-ray, electrocardiogram (ECG), arterial blood gas analysis and pulmonary function test, as well as biochemical and hematological tests. Definitions of risk assessments were as follows: (i) pulmonary dysfunction including symptomatic chronic pulmonary disease or abnormal lung function (forced expiratory volume at 1 s is <70% of predicted normal or arterial oxygen tension <70 mmHg); (ii) cardiovascular disease including past history or current symptoms and signs of ischemic heart disease, heart failure, valvular disease, hypertension or abnormal ECG requiring medical intervention; (iii) renal dysfunction including past history or current symptoms and signs of chronic renal disease or renal function impairment (24 h creatinine clearance <70 ml/min); (iv) established diagnosis of diabetes mellitus requiring medical intervention; and (v) cerebrovascular disease including past history or current symptoms and signs of cerebrovascular events. Patients with co-morbid conditions were referred to the experts of each disease, if indicated. We used the American Society of Anesthesiologists (ASA) physical status classification system to evaluate the pre-operative general risk.

During the same period, 24 consecutive patients with primary squamous cell carcinoma of the thoracic esophagus aged 75 years or older received definitive CRT in our institution and three affiliated hospitals and all enrolled in this study. The reasons for selecting the treatment were as follows: cancer inoperable due to far advanced disease (bulky T3, T4 and/or unresectable nodes) in eight patients, cancer medically inoperable in four, refusal of surgery in five, physician’s decision considering patient’s general condition in four and unknown reason in three.

STAGING

The tumor stages were classified according to the TNM classification of the International Union Against Cancer (UICC) (2). Clinical staging was based on chest radiography, esophagography, esophagoscopy and computed tomography (CT) of the neck, chest and abdomen. Endoscopic ultrasonography (EUS), magnetic resonance imaging, bronchoscopy or bone scintigraphy was additionally performed if indicated for the determination of individual staging.

SURGERY

A total of 12 patients underwent transthoracic esophagectomy with three-field lymphadenectomy (n = 1), or with two-field lymphadenectomy (n = 11), and 28 underwent transhiatal esophagectomy with lower mediastinal and abdominal lymphadenectomy (n = 19), or with abdominal lymphadenectomy alone (n = 9). Twenty-five patients underwent gastric pull-up for reconstruction via the posterior mediastinal route and nine via the retrosternal route; four underwent colon interposition via the posterior mediastinal route and two via the retrosternal route. All anastomoses were performed in the neck through a cervical incision. Esophagastrectomy was completed with two-layer hand-sewn suture (n = 8) or circular stapling device (n = 34); esophagogastrostomy with hand-sewn technique (n = 2) or circular stapler (n = 4). The quality of tumor clearance was determined using the residual tumor (R) classification of the UICC-TNM classification (2).

Post-operative adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE) guidelines (3). We defined post-operative complications as Grade 2 (moderate) or more adverse events, which are generally symptomatic and for which medical or operative intervention is indicated. Vocal cord function was assessed by laryngofiberscopy in all patients, regardless of the presence or absence of hoarseness.

CHEMORADIOThERAPY

Treatment details were described previously (4). Radiotherapy was performed using 6 or 10 MV linear accelerators with standard fractionation (1.8–2.0 Gy/fraction, 5 days/week), with the total prescribed dose of 60–70 Gy. Initial anterior–posterior opposed radiation field for carcinoma of the upper thoracic esophagus encompassed the primary tumor, and the bilateral supraclavicular and upper-to-middle mediastinal lymph nodes. The initial field for carcinoma of the middle or lower thoracic esophagus encompassed the primary tumor, and all of the mediastinal, perigastric and celiac lymph nodes. After a dose of 45–46 Gy to the initial field, the radiation field was reduced.
to a booster field limited to gross tumor volume with an adequate margin, using an oblique-opposed technique to exclude the spinal cord from the field.

Concurrent chemotherapy consisted of a 24 h continuous infusion of 5-fluorouracil (5-FU) alone or in combination with 1 h bolus infusion of cisplatin (CDDP) before and after irradiation. Low-dose protracted infusion of 5-FU at a dose of 250 mg/m² was used until 1993; however, CDDP at a dose of 3 mg/m² was added from 1994. Minor modifications of chemotherapy dose were allowed according to the physician’s decision considering patient conditions.

The initial response was evaluated 1 month after completion of the CRT, by esophagography for the primary tumor and by CT scanning for lymph node metastasis, in accordance with the criteria of the Japanese Society for Esophageal Diseases (5). In brief, the responses were classified as follows: complete response (CR), the disappearance of all known disease; partial response (PR), 50% or more decrease in total tumor load of the lesions and no appearance of new lesions or progression of any lesions. Acute toxicities were assessed according to CTCAE guidelines (3). Late toxicity was defined as that occurring more than 90 days after the initiation of treatment.

Follow-up and Statistical Analysis

Patients received follow-up care at regular intervals at our institution or at affiliated hospitals; all patients included in this study underwent routine physical and laboratory examinations after discharge. Chest radiography, ultrasonography or CT scanning was performed at least every 6 months to detect possible recurrent disease. Esophagography and esophagoscopy were additionally performed to detect local recurrence for patients in whom CR was achieved by CRT. The median follow-up period of surviving patients was 94.1 months (range, 32.5–138.9 months).

Statistical analysis was performed using the χ² or Fisher’s exact probability test for two-proportion comparisons. Survival rates were calculated from the date of surgery or that of the initiation of treatment until death or the last follow-up for surviving patients using the Kaplan–Meier method. Differences between the survival curves were assessed using the log-rank test. A P value of <0.05 was considered significant. All analyses were performed with StatView for Windows version 5.0 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient Characteristics

Table 1 summarizes the baseline characteristics of the patients in this study. There was no significant difference in gender, age or histology between patients in the surgery and CRT groups. The tumor location was significantly lower in patients who underwent esophagectomy. Pre-treatment nodal status was comparable. cT1 tumor and cStage I disease were more frequent in the surgery group than in the CRT group. Of 11 patients with cT1 tumors in the surgery group, 5 cT1 tumors were diagnosed by esophagoscopy alone and 6 were in combination with EUS (54.5%). A total of 13 patients were found to have pT1 tumors by pathological examination of the resected specimen; accuracy to distinguish T1 tumor pre-operatively was 95.0% (38/40), with a sensitivity of 84.6% (11/13) and a specificity of 100% (27/27). pStage distribution of patients in the surgery group was as follow: pStage 0 and I in 11 patients (27.5%), pStage II in 7 (17.5%), pStage III in 17 (42.5%) and pStage IV in 5 (12.5%).

In the surgery group, 33 patients (82.5%) had co-morbid conditions and 16 patients (40.0%) had two or more diseases. Chronic pulmonary disease including abnormal lung function and cardiovascular disease including abnormal ECG were frequent, followed by chronic renal disease (Table 2). An ASA risk score ≥3 was observed in 14 patients (35.0%).

The Short- and Long-Term Outcomes of Surgical Resection

Complete resection (R0) was achieved in 36 patients (90.0%). In one patient, resection was microscopically
incomplete (R1) because positive involvement of the external surface was proven histologically. In the remaining three patients, resection was macroscopically incomplete (R2) because of extensive lymph node metastasis. A total of 26 patients had one or more post-operative complications, which accounted for an overall post-operative complication rate of 65.0% (Table 3). Vocal cord palsy (42.5%) and anastomotic leakage (40.0%) were major complications followed by pulmonary complications (35.0%) (Table 2). There was no correlation between pulmonary complications and vocal cord palsy or anastomotic leakage. The 30-day mortality rate and the in-hospital mortality rate were 5% (2/40) and 7.5% (3/40), respectively. Sudden death probably due to cardiopulmonary accident occurred in two patients on the 15th and 25th post-operative day (POD), respectively, and an 81-year-old male succumbed to pneumonia on the 87th POD.

At the median follow-up time of 108.2 months for survivors (range, 32.5–138.9 months), 6 patients were alive with no evidence of disease, 16 died of the disease, 15 died of the other diseases and 3 died of unknown causes. The other diseases included were as follows: pneumonia in five, second primary cancer in four, cardiopulmonary accidents in four and cerebrovascular accident in one. One patient died of strangulation ileus at 29.4 months after surgery, which was regarded as treatment-related death. The overall 1-, 3- and 5-year survival rates were 77.5%, 37.3% and 24.0%, respectively, with a median survival time of 22.3 months. In 11 patients with cStage I disease, the corresponding survival rates were 90.9%, 63.6% and 54.5%, respectively, with a median survival time of 78.7 months. A total of three patients were alive with no evidence of disease and seven died of the other diseases. In 29 patients with cStages II–IV disease, the corresponding survival rates were 72.4%, 27.2% and 11.6%, respectively, with a median survival time of 18.7 months. A total of three patients were alive with no evidence of disease, 16 died of the disease and 8 died of the other diseases (Fig. 1).

**Table 2.** Pre-operative co-morbidities

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Pulmonary dysfunction</td>
<td>16 (40.0)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>ASA score ≥ 3</td>
<td>14 (35.0)</td>
</tr>
<tr>
<td>Total</td>
<td>33 (82.5)</td>
</tr>
</tbody>
</table>

ASA, the American Society of Anesthesiologists.

**Table 3.** Post-operative complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocal cord palsy</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>16 (40.0)</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>14 (35.0)</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Anastomotic stenosis</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Total</td>
<td>26 (65.0)</td>
</tr>
</tbody>
</table>

**Figure 1.** Overall survival rates for patients with cStage I disease (solid line) and cStages II–IV disease (dotted line) in the surgery group.

**The Efficacy and Toxicity of CRT**

The median radiation dose administered was 67 Gy (range, 56–71 Gy). All patients completed radiotherapy at the standard fractionation that was initially planned. A total of 11 patients received concurrent combined chemotheraphy of 5-FU and CDDP, whereas 14 were given 5-FU alone. Acute toxicities of CRT are summarized in Table 4.

**Table 4.** Acute toxicities of chemoradiotherapy

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Leukocyte</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1</td>
</tr>
<tr>
<td>Platelets</td>
<td>3</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>8</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>14</td>
</tr>
</tbody>
</table>

Figures represent the number of patients. AST, aspartate aminotransferase; ALT, alanine aminotransferase.
review of the medical record was available in 21 patients (87.5%). Grade 3 or worse leukopenia and anemia were observed in four (19.0%) and one (4.8%) patient, respectively. Grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation and anorexia were seen in four (19.0%) and three (14.3%) patients, respectively, and Grade 3 esophagitis and nausea/vomiting in one (4.8%). One patient died of pneumonia at 2.4 months after the initiation of treatment and one patient succumbed to small bowel necrosis at 2.5 months. Treatment-related death caused by late toxicities occurred in five patients. The causes of death and the time after the initiation of treatment were as follows: pneumonia at 4.5 months, pulmonary embolism at 14.5 months, cardiac infarction at 32.2 months, uncontrolled pleural effusion at 33.7 months and congestive heart failure at 57.6 months. There were no patients in whom secondary cancer developed after receiving CRT.

Initial responses of the 24 patients who received CRT were as follows: CR was achieved in 10 patients, PR was achieved in 10 and one patient died of pneumonia before the initial response evaluation, with the overall response rate of 83.3% (20/24). There was no salvage treatment including esophagectomy or endoscopic resection for locoregional failure.

At the median follow-up time of 72.5 months for survivors (range, 12.4–95.3 months), 3 patients were alive with no evidence of disease, 20 died of cancer- and treatment-related conditions and 1 died of unrelated medical conditions. One patient with cStage I died of recurrent disease at 34.2 months after the initiation of treatment. In the remaining 23 patients with cStages II–IV, the overall 1-, 3- and 5-year survival rates were 60.9%, 17.4% and 11.6%, respectively, with a median survival time of 12.8 months (Fig. 2).

**Figure 2.** Overall survival rates for patients with cStages II–IV disease in the chemoradiotherapy group. One patient with cStage I disease was excluded.

**DISCUSSION**

Our population of elderly patients who underwent surgery was quite unique in terms of tumor location and clinical stage distribution. We prefer the transhiatal to the transthoracic approach, for carcinoma located in the lower thoracic esophagus without a clinically positive node in the mediastinum. Because the transhiatal approach is regarded as less invasive surgery, especially for elderly patients with cardio-pulmonary co-morbidity, we select this procedure if permitted oncologically. On the other hand, surgery for elderly patients with carcinoma of the upper thoracic esophagus tends to be avoided because of the negative impact on impaired cardiopulmonary function. In addition, esophagectomy with less radical lymphadenectomy for elderly patients with early esophageal carcinoma seems easy to perform. The imbalance of tumor location and clinical stage distribution seen in this study was probably due to selection bias.

Evaluating a patient’s co-morbid condition at presentation is of great importance when determining the operability, especially in highly invasive surgery such as transthoracic en bloc esophagectomy for elderly patients. Patients with mild systemic disease or abnormal laboratory finding alone were regarded as having co-morbid conditions in this study, which accounts for the relatively high co-morbidity rate of 82.5%. Despite the high co-morbidity rate, the proportion of patients with an ASA score ≥3 was 35.0%, which was comparable to the proportion listed in previous reports (6,7). Of these co-morbid conditions, cardiovascular and respiratory diseases were the most common, as reported previously (7–14). Therefore, there is no difference in prevalence of elderly patients with pre-operative risk, compared with the previous studies.

Pulmonary complications developed in 14 of 40 elderly patients (35%), which was comparable to the complications rate described in previous reports (6,11–15). Although the reason was obscure why anastomotic leakage developed frequently in this population, the grade of leakage was generally moderate and was not life threatening. In this period, four surgeons performed all resections alternately; in the following period from 2004 to 2008, single surgeon did almost all esophagectomy. Anastomotic leakage developed in 3 of 11 elderly patients and the incidence decreased to 27.3%, which was probably due to skilled and stabilized surgical technique by a fixed surgeon. Laryngofiberscopy was not usually used to assess the vocal cord palsy in the previous study; however, only clinical presentation such as hoarseness may lead underestimation of the actual incidence of the disease. Direct observation can detect more subclinical or incomplete palsy than expected, from which patients usually recover spontaneously during the follow-up period. Long-term outcomes of esophagectomy for the elderly differ among the previous studies, with 1-, 3- and 5-year survival rates of 50.6–65.6%, 23–40.7% and 13.3–40.9%, respectively, and median survival time of 13.6–28 months (6–13,15–20). In the present series, the patient selection and
short- and long-term outcomes of surgery for the elderly seemed acceptable, which was similar to the results reported in previous studies. Recent advances in minimally invasive esophagectomy potentially have the advantage of reducing post-operative morbidity and mortality, especially in the elderly patients (21). In addition, considering the favorable outcomes of less radical esophagectomy, surgical resection is still the first treatment of choice for elderly patients with cStage I disease because treatment outcomes of CRT are lacking. Randomized control trial comparing between surgery and CRT for this stage is now ongoing in Japan.

A few reports about CRT for elderly patients with esophageal carcinoma have been published, some of which demonstrated that CRT was tolerable for the elderly and concluded that patients with adequate functional status should not be excluded from potentially curative treatment based on age alone (22–24). In this study, the CR rate of 41.7% (10/24) was lower than that of a Japanese retrospective comparison between elderly and non-elderly patients with Stage II–III (non-T4) squamous cell carcinoma of the esophagus, in which 63.6% of the elderly patients achieved CR (25). The elderly patients in the study received standard-dose CRT; however, the recurrence after CR, discontinuations at the end of CRT and over Grade 3 hematological adverse events were more frequent (25). Grade 3 or worse leukopenia occurred in 19.0% (4/21) of our patients, which is a lower incidence than that reported in patients receiving standard-dose CRT (25–29). Esophagitis was a major non-hematological toxicity seen in 14 patients (66.7%), including 1 (4.8%) with Grade 3. Following AST/ALT elevation was not common as a non-hematological toxicity, which should be kept in mind for the elderly whose liver function may be impaired. The median survival time of 14.7 months was reported in the above-mentioned study, which was almost identical with that of the present study (25). Low-dose protracted infusion of concurrent chemotherapy with radiotherapy in this study seems tolerable even for medically compromised elderly patients, with less acute hematological toxicity and almost identical impact on survival.

Late toxicity including cardiopulmonary complications after definitive CRT is a critical issue to be resolved. The causes of death in patients who survived more than 2 years were as follows: treatment-related death caused by late toxicities in three patients and the disease progression in two. On the other hand, those after surgery were as follows: eight died of the other diseases and five died of the disease. The other diseases included pneumonia in three patients, second primary cancer in three, cardiopulmonary accidents in one and strangulation ileus in one as treatment-related death. One patient who suffered from pneumonia had vocal cord palsy; however, it is difficult to distinguish whether the other diseases such as pneumonia or cardiopulmonary accidents were truly unrelated to surgery. Nevertheless, treatment-related death caused by late toxicities was quite characteristic of long-term survivors in CRT group. To prevent these toxicities, Ishikura et al. (29) concluded that three-dimensional conformal radiotherapy, intensity-modulated radiotherapy and proton therapy have potential advantages over traditional radiotherapy (RT) in reducing the dose to the heart and lung, and their incorporation may be beneficial. In addition, all five patients who died of late cardiopulmonary toxicity in this study had a primary tumor in the middle thoracic esophagus. To reduce late toxicity, not only an improvement in RT techniques but also considering tumor location may be mandatory.

Major criticisms of this study are that patient baseline characteristics were quite different and there is little sense in comparing treatment outcomes between the two modalities. Despite these substantial biases, the overall 5-year survival rates of patients with cStages II–IV disease were equivalent. This phenomenon was consistent with our clinical impression, which made us to conduct this study. Cause-specific survival of the surgery group was superior to that of the CRT group because patients in the former died of the other diseases more than the latter during the long-term period (data not shown); however, we believe that death from the other diseases should not be excluded because it is not a negligible issue especially for the elderly and not clearly distinguishable from cancer- or treatment-related death just as mentioned above. Although elderly patients with esophageal carcinoma represent a growing proportion in everyday clinical practice, it is difficult to conduct a randomized control trial with this population because of the variety and specialty of patient characteristics. A multi-institutional prospective study unifying patient baseline characteristics is needed to compare the two modalities, even if randomization is impossible.

In conclusion, the short- and long-term outcomes of surgery for the elderly seemed acceptable; however, definitive CRT may be a promising treatment modality, given that more than half of the patients in this group were surgically or medically inoperable. Further investigation, including application of definitive CRT for cStage I disease, minimally invasive esophagectomy and conformal RT technique may alter the sphere of influence in the field of esophageal cancer treatment for the elderly.

Conflict of interest statement
None declared.

References


