Clinical Outcomes of Radiotherapy in Elderly and Younger Patients with T4 Esophageal Cancer: A Retrospective Single-Center Analysis

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Abstract

Background/Aim

The standard of treatment for esophageal cancer with adjacent organ invasion (T4) has not been established. Radiotherapy (RT) is a treatment option, but its efficacy and safety in elderly patients remains unclear. We retrospectively analyzed the clinical outcomes of RT in elderly and younger patients with T4 esophageal cancer.

Materials and Methods

Sixty-nine patients with T4 esophageal cancer who underwent RT at the Kanagawa Cancer Center between January 2014 and November 2020 were included in this study. Patients aged ≥ 70 years were defined as the elderly group and those aged < 70 years were defined as the younger group. The total dose of RT was set at 60 Gy in 30 fractions. Chemotherapy combined with 5-fluorouracil and cisplatin was administered concurrently with RT. The overall survival (OS) rate was estimated using the Kaplan–Meier method. Adverse events were assessed using the CTCAE v4.0. Clinical outcomes were compared between the elderly and younger groups.

Results

The median survival time (MST) of the elderly group was 21.5 months, and the OS rates at 1, 3, and 5 years were 63.7%, 31.3%, and 15.6%, respectively. The MST of the younger group was 12.5 months, and the OS rates at 1, 3, and 5 years were 52.2%, 29.4%, and 29.4%, respectively. A significant difference in OS was not observed between the two groups ($p = 0.767$). The multivariate analysis revealed that the complete response (CR) of the primary tumor and adjuvant chemotherapy (ACTx) were significant predictors of OS ($p < 0.001$ and < 0.001 , respectively). Regarding toxicity, the frequency of thrombocytopenia was significantly higher in the elderly group, whereas the frequency of esophageal fistula was significantly higher in the younger group ($p = 0.012$ and 0.022 , respectively). Other toxicities were not significantly different between the two groups.

Conclusions

OS was not significantly different between the elderly and younger groups. ACTx and CR were predictors of OS. The frequency of thrombocytopenia was higher in the elderly group and that of esophageal fistula was higher in the younger group. However, other toxicities were not significantly different between the two groups.

Introduction

Esophageal cancer is the 6th most common cause of death from malignancies worldwide, accounting for 5.3% of all deaths [1]. In Japan, esophageal cancer constitutes 3.1% of all malignant deaths [2]. Because the esophagus lacks a serous membrane and is located in a very narrow mediastinum, it tends to invade

surrounding organs such as the trachea and aorta [3, 4]. According to the Comprehensive Registry of Esophageal Cancer in Japan, approximately 15% of esophageal cancers exhibited direct invasion of adjacent organs (T4) [5].

Unresectable esophageal cancer with direct invasion of adjacent organs is a devastating disease [6]. There are two treatment strategies for T4 esophageal cancer: definitive chemoradiation (CRT) and preoperative chemotherapy (CTx) or preoperative CRT followed by conversion surgery [7]. However, the treatment strategy for T4 esophageal cancer has not been established yet. The combination of cisplatin and 5-fluorouracil (5-FU) (CF) is the standard chemotherapy regimen for definitive concurrent CRT for esophageal cancer [8]. In previous reports, CRT with CF has been shown to be effective in treating esophageal cancer, including T4 lesions [3, 7, 9].

According to the Cancer Statistics in Japan 2007, 46.5% of new patients with esophageal cancer in Japan were older than 70 years [10]. In general, elderly patients are characterized by the presence of multiple comorbidities and impaired organ and bone marrow function [11]. Moreover, because elderly patients are often excluded from randomized controlled trials, the results of such trials cannot be directly applied to this population [12]. Several studies have reported clinical outcomes of CRT for resectable esophageal cancer in inoperable patients [13–15]. However, there have been no reports of radiotherapy (RT) for T4 esophageal cancer in elderly patients, and its safety and usefulness remain unclear.

Therefore, we retrospectively investigated and analyzed cases of RT for T4 esophageal cancer at our hospital. The patients were divided into two groups: elderly and younger, and the clinical outcomes of both groups were compared.

Materials And Methods

Patients

The clinical stage was determined according to the TNM Classification of Malignant Tumors, 7th Edition, published by the Union for International Cancer Control [16]. The clinical stage was determined by physicians, surgeons, and radiation oncologists. The study candidates were patients with T4 esophageal cancer who started definitive RT at our hospital from January 2014 to November 2020. The eligibility criteria were as follows: (i) T4a or T4b, (ii) histopathologically diagnosed squamous cell carcinoma or adenocarcinoma, (iii) no distant metastasis, (iv) performance status (PS) of 0–2, (v) irradiated with a total dose of at least 50 Gy, and (vi) no prior esophageal cancer treatment. Patients aged ≥ 70 years were defined as the elderly group and those aged < 70 years were defined as the younger group. Clinical data were collected in June 2021. The hospital institutional review board approved this study (approval number: 2021-55).

RT

Computed tomography (CT) was performed using 2.5–5-mm-thick slices, under free breathing and inspiration and expiration phases. Primary gross tumor volume (GTV) (i.e., GTV of the primary tumor) and node GTV (i.e., GTV of the node) were identified based on CT findings, gastrointestinal endoscopy, and F-fluorine deoxyglucose-positron emission tomography (FDG-PET)/CT. The primary tumor size was measured as the largest diameter in the axial plane of the primary GTV. The primary clinical target volume (CTV) (i.e., CTV of the primary tumor) was expanded from the primary GTV by 2–3 cm along the long esophageal axis. Subclinical CTV included the following lymph node areas, depending on the location of the primary tumor site: cervical to superior mediastinal lymph node regions in the cervical esophagus, supraclavicular and superior mediastinal lymph node regions in the upper thoracic esophagus, superior and inferior mediastinal and intraperitoneal lymph node regions in the mid-thoracic esophagus, and inferior mediastinal and intraperitoneal lymph node regions in the lower thoracic and abdominal esophagus. Planning target volume (PTV) 1 was 0.5 cm from the primary CTV and subclinical CTV in the circumferential direction, with a 1–2-cm margin in the caudal direction, including respiratory movement. PTV 2 was primary CTV and node GTV plus 0.5–1 cm. In principle, the total dose of RT was set at 60 Gy in 30 fractions, with 40 Gy in 20 fractions for PTV 1 and 20 Gy in 10 fractions for PTV 2. Since 2016, intensity-modulated RT has been used as needed in cases in which it is difficult to meet the dose constraints for normal organs. The dose constraints for normal organs were as follows: the maximum dose for the spinal cord was 50 Gy, and percentage of the lungs volume receiving at least 20 Gy was < 30%

CTx

During RT, cisplatin (70 mg/m² on days 1 and 29) and 5-FU (700 mg/m², days 1–4 and 29–32) were administered concurrently [17]. After the completion of concurrent CRT, additional CF was administered as adjuvant CTx (ACTx). After 2020, a leucovorin–fluorouracil–oxaliplatin (FOLFOX) regimen was administered to patients in whom CF was not indicated owing to renal or cardiac dysfunction. During RT, three cycles of FOLFOX were administered every 2 weeks. One cycle of FOLFOX comprised oxaliplatin (85 mg/m² on day 1), fluorouracil (400 mg/m² on day 1, followed by continuous intravenous infusion of 800 mg/m² on day 1), and leucovorin (200 mg/m² on day 1) [18]. Additional FOLFOX was administered after CRT as ACTx.

Follow-up

CT, gastrointestinal endoscopy, and blood examinations were performed every 1–3 months after treatment. If necessary, FDG-PET/CT was performed to evaluate recurrence. Complete response (CR) was defined as no gross tumor on gastrointestinal endoscopy and no malignant cells on biopsy. The observation period and time to event were calculated from the date of the first RT. Toxicity was assessed using the Common Terminology Criteria for Adverse Events version 4.0. The worst toxicity grade was considered the final grade of toxicity.

Statistical analysis

Continuous variables in the two groups were compared using the Mann–Whitney U test. Binary variables in the two groups were compared using the Fisher’s exact test. Overall survival (OS) and progression-free survival (PFS) rates were assessed using the Kaplan–Meier method, and differences in survival rates between the two groups were compared using the log-rank test. The correlation of clinical variables with OS was assessed via Cox regression analyses. Prognostic factors, for which *p* values were calculated as < 0.10, were evaluated using the multivariate stepwise Cox regression model [19]. A *p* value of < 0.05 was considered significant. Statistical analyses were performed using STATA software (version 13.1, TX, USA).

Results

Patient characteristics

Table 1 presents the patient characteristics. In total, 69 patients were analyzed in this study. Of these, 35 patients were in the elderly group with a median age of 74 (range, 70–84). The younger group consisted of 34 patients with a median age of 63 (range, 44–69). There was no significant difference in PS between the two groups (*p* = 0.054). Esophageal stricture was the most common symptom, found in 21 (60.0%) patients in the elderly group and 21 (61.7%) patients in the younger group (*p* = 1.000). Most of the lesions in both groups were T4b, with tracheal or bronchial invasion in 28 (80.0%) patients in the elderly group and 27 (79.4%) patients in the younger group (*p* = 0.766). The median total dose of RT was 60 Gy in both groups (*p* = 0.572). A significant difference was not observed in the irradiation delivery between the two groups (*p* = 0.195). CTx was administered concurrently with RT in 82.9% of patients in the elderly group and 94.1% of patients in the younger group (*p* = 0.477). Of the patients who did not receive CTx in the elderly group, five patients were not indicated due to complications, and one patient refused the CTx. In the younger group, there was one case of off-label treatment due to complications and one case of refusal. In the elderly group, 26 (89.7%) patients received CF and 3 (10.3%) patients received FOLFOX out of 29 CTx treatments. A median of 2 (range, 1–8) cycles of CF (*n* = 16) and a median of 3 (range, 1–3) cycles of FOLFOX (*n* = 3) were administered as ACTx in the elderly group. In the elderly group, all patients received CF. A median of 2 (range, 1–10) cycles of CF were administered as ACTx in the younger group. Of the patients who did not receive ACTx in the elderly group, six patients received RT alone in the initial treatment, four received off-label treatment due to their general condition, two refused ACTx, two had early recurrence, and one died early. In the younger group, two received RT alone in the initial treatment, one received off-label treatment due to general condition, one refused ACTx, three had early recurrence, one died early, and one underwent salvage surgery.

Survivals

Figure 1 shows the OS of the elderly and younger groups. At the time of analysis, 48 patients had died. Overall mortality in the elderly and younger groups was 24 and 24, respectively, with 17 and 24 deaths from the primary disease (*p* = 0.087), respectively. The median survival time (MST) of the elderly group was 21.5 months, and the 1-, 3-, and 5-year OS rates were 63.7%, 31.3%, and 15.6%, respectively. The MST

of the younger group was 12.5 months, and the 1-, 3-, and 5-year OS rates were 52.2%, 29.4%, and 29.4%, respectively. Significant differences were not observed in OS between the two groups ($p = 0.767$).

Figure 2 shows the PFS of the elderly and younger groups. The median PFS time of the elderly group was 17.5 months, and the 1-, 3-, and 5-year PFS rates were 61.3%, 19.4%, and 9.7%, respectively. The median PFS time in the younger group was 12.1 months, and the 1-, 3-, and 5-year PFS rates were 52.2%, 24.6%, and 20.5%, respectively. Significant differences were not observed in PFS between the two groups ($p = 0.926$). The first recurrence in the elderly group was local recurrence of the primary tumor in 2 cases, regional lymph node recurrence in 3 cases, primary tumor and regional lymph node in 1 case, and distant metastasis in 14 cases. In the younger group, there were 7 cases of local recurrence of the primary tumor, 2 cases of regional lymph node recurrence, 2 cases of primary tumor and regional lymph node recurrence, 8 cases of distant metastasis, and 1 case of primary tumor and distant metastasis.

Table 2 shows the results of the analysis of OS predictors in all patients. In the univariate analysis, ACTx and CR of the primary tumor were significant predictors ($p < 0.001$ and < 0.001 , respectively). In multivariate analysis, ACTx and CR were also significant predictors, with hazard ratios (HR) of 0.20 [95% confidence interval (CI) 0.09–0.42] ($p < 0.001$) and 0.20 (95% CI 0.08–0.44) ($p < 0.001$), respectively. Figure 3(a) shows the OS of all patients with and without ACTx. The MST in the ACTx group ($n = 47$) was 22.8 months, and the 1-, 3-, and 5-year OS rates were 71.3%, 42.6%, and 37.8%, respectively. The MST in the non-ACTx group ($n = 22$) was 6.4 months, and the 1-, 3-, and 5-year OS rates were 29.2%, 5.8%, and 0%, respectively. The OS was significantly better in the ACT group ($p < 0.001$). Figure 3(b) shows the OS of all patients with and without CR of the primary tumor. The MST in the CR group was 63.8 months, and the 1-, 3-, and 5-year OS rates were 89.4%, 68.9%, and 51.6%, respectively. The MST in the non-CR group was 9.3 months, and the 1-, 3-, and 5-year OS rates were 45.2%, 17.1%, and 14.3%, respectively. The OS was significantly better in the ACT group ($p < 0.001$).

Table 3 shows the results of the analysis of OS predictors in elderly patients. In the univariate analysis, ACTx was a significant OS predictor ($p = 0.001$). In multivariate analysis, ACTx and CR were significant predictors, with HRs of 0.14 (95% CI 0.37–0.53) ($p = 0.004$) and 0.22 (95% CI 0.06–0.78) ($p = 0.019$), respectively. Figure 4(a) shows the OS of elderly patients with and without ACTx. The MST in the ACTx group was 25.7 months, and the 1-, 3-, and 5-year OS rates were 85.5%, 47.0%, and 31.3%, respectively. The MST in the non-ACTx group was 9.0 months, and the 1-, 3-, and 5-year OS rates were 31.4%, 7.9%, and 0%, respectively. OS was significantly better in the ACTx group ($p < 0.001$). Figure 4(b) shows the OS of elderly patients with and without CR of the primary tumor. The MST in the CR group was 38.5 months, and the 1-, 3-, and 5-year OS rates were 92.3%, 57.0%, and 0%, respectively. The MST in the non-CR group was 10.7 months, and the 1-, 3-, and 5-year OS rates were 47.1%, 17.9%, and 12.0%, respectively. Significant differences in OS were not observed between the CR and non-CR groups ($p = 0.051$).

Toxicities

Table 4 summarizes the toxicities. In the elderly group, grade 3 or more hematologic toxicities of leukopenia, neutropenia, lymphopenia, hemoglobinopenia, and thrombocytopenia were observed in 11 (31.4%), 11 (31.4%), 1 (2.9%), 3 (8.6%), and 3 (8.6%) patients, respectively. In the younger group, grade 3 or more leukopenia, neutropenia, lymphopenia, hemoglobinopenia, and thrombocytopenia were observed in 8 (22.9%), 4 (11.4%), 4 (11.4%), 5 (14.3%), and 1 (2.9%) patients, respectively. The frequency of thrombocytopenia was significantly higher in the elderly group ($p = 0.012$). In terms of nonhematologic toxicities, in the elderly group, grade 3 or more hyponatremia, hypokalemia, esophagitis, esophageal fistula, and congestive heart failure were observed in 5 (14.3%), 5 (14.3%), 3 (8.6%), 1 (2.9%), and 1 (2.9%) patients, respectively. In the younger group, grade 3 or more hyponatremia, hypokalemia, esophagitis, dermatitis, nausea, esophageal stricture, and esophageal fistula were observed in 3 (8.8%), 2 (5.9%), 1 (2.9%), 1 (2.9%), 1 (2.9%), 2 (5.9%), and 7 (20.6%) patients, respectively. The frequency of esophageal fistula was significantly higher in the younger group ($p = 0.022$). Esophageal fistula was not associated with pretreatment stricture symptoms and tracheal/bronchial invasion ($p = 0.136$ and 1.000 , respectively). Other nonhematologic toxicities were not significantly different between the two groups. There were 2 (5.7%) and 5 (14.7%) deaths due to massive hematemesis after initiation of treatment in the elderly and younger groups, respectively ($p = 0.259$).

Discussion

The clinical outcomes of RT for T4 esophageal cancer in elderly patients were investigated and compared with those in the younger group. The clinical outcomes in the elderly group were generally similar to those in the younger group. To the best of our knowledge, no study has been reported on the clinical outcomes of RT for T4 esophageal cancer in the elderly patients.

Despite the development of multidisciplinary treatment, the prognosis of T4 esophageal cancer is still poor. A systematic review of T4 esophageal cancer reported that the 1-, 3-, and 5-year OS rates of CRT for T4 esophageal cancer were 26–79%, 0–44%, and 0–14%, respectively [7]. In Japan, there are two reports of clinical trials for T4/M1 lymph node metastasis esophageal cancer. One was a phase II trial in which two cycles of CF were combined with RT. The MST was 10.0 months and the 2-year OS rate was 31.5% [17]. The other was a randomized trial comparing low-dose and standard-dose CTx with CRT combined with CF [6]. In that study, no significant differences were observed between the two groups: MST was 14.4 months and the 3-year OS rate was 25.7% in the low-volume CTx group. MST was 13.1 months and the 3-year OS rate was 25.9% in the standard group. In a review comparing the results of CRT and CRT followed by surgery for T4 esophageal cancer, the 1-, 3-, and 5-year OS rates for the CRT group were 26–44%, 0–23%, and 0–14%, and the 1-, 3-, and 5-year OS rates for the CRT followed by surgery group were 24–73%, 5–45%, and 0–38%, respectively [3]. Our results were generally similar to those previously reported, but relatively better results were observed in CR and ACTx patients.

There have been several reports on prognostic factors in esophageal cancer. In a study of esophageal cancer with adjacent organ invasion, serum albumin level was a prognostic factor (20). In other studies of RT for esophageal cancer, serum albumin level was also reported as a prognostic factor (21, 22). In

addition, in a study of CRT for T4/M1 lymph node esophageal cancer, serum hemoglobin level was a predictor of OS (23). Response to treatment was also reportedly a prognostic factor in CRT for esophageal cancer, and several studies have shown that CR is associated with OS (24, 25). In a study of CRT for stage II/III esophageal cancer in elderly patients, CR was also a predictor of OS (11). Recently, the relationship between lymphopenia and esophageal cancer outcomes has been reported. Baseline or treatment-induced lymphopenia has been shown to reduce survival in various cancers, including esophageal cancer (26, 27). In the present study, among these factors, CR was a predictor of OS, whereas other factors were not associated with OS.

In definitive CRT for esophageal cancer, two cycles of CF are administered concurrently with RT and two additional cycles are administered after RT [28]. In a Japanese clinical trial of stage II/III esophageal cancer, definitive CRT was performed with a similar regimen [29]. However, Chen M *et al.* reported that ACTx after CRT for esophageal cancer did not contribute to the prognosis [30]. In the present study, ACTx was found to be a significant predictor of OS in T4 esophageal cancer. To date, there have been no clinical trials to date examining the benefit of ACTx after CRT for esophageal cancer. Hence, further research on ACTx after CRT for esophageal cancer is warranted.

Several studies have reported RT outcomes for esophageal cancer in elderly patients. A study of CRT with CF for stage II/III esophageal cancer without T4 lesions reported higher hematologic toxicity, poorer compliance, and significantly poorer OS in patients older than 70 years compared to the younger group [31]. Other studies have also reported higher toxicity in CRT for patients older than 70 years [12]. In contrast, a Japanese phase II trial of CRT with docetaxel for stage II/III esophageal cancer in patients older than 70 years reported an MST of 27.7 months and a 2-year OS rate of 62.5% [32]. That study concluded that although grade 3 esophagitis was present in >30% of patients, CRT was a definitive treatment option in elderly patients. Additionally, a study on CRT of esophageal cancer in very elderly patients aged >80 years reported that there were no significant differences in MST and 5-year OS rates between the very elderly group, the intermediate group (65–79 years), and the younger group (<65 years) [11]. That study showed that the frequency of grade 3 pneumonitis was higher in the very elderly group. In the present study, the OS in the elderly group was not significantly different from that in the younger group. Additionally, the frequency of thrombocytopenia as a hematologic toxicity was significantly higher, however, grade 3 thrombocytopenia occurred in less than 10% of elderly patients, and it was considered tolerable. Conversely, esophageal fistulas were significantly more frequent in the younger group than they were in the elderly group. Several studies have pointed out T4 and esophageal stricture as risk factors for esophageal fistula after CRT for esophageal cancer [33–35]. In addition, bronchial invasion was a risk factor for esophageal fistula in a study of T4b esophageal cancer [36]. However, in the present study, esophageal stricture and bronchial invasion were not associated with the appearance of esophageal fistula. Because the studies comparing the clinical outcomes of esophageal cancer in the elderly and younger groups are still limited, further studies are warranted to reveal the efficacy and toxicities of RT for elderly patients.

This study has several limitations; these include the study being a single-center, retrospective study with heterogeneous treatment methods. Regarding histopathological types, only one case of adenocarcinoma was found. Further, because of the limited number of long-term survival cases, late toxicity in the heart, lungs, and esophagus may not have been completely evaluated. Large randomized controlled trials are warranted to define a standard treatment strategy for T4 esophageal cancer.

Conclusion

The clinical outcomes of RT for T4 esophageal cancer were compared between the elderly and younger groups. OS and PFS were not significantly different between both groups. ACTx and CR were predictors of OS. The frequency of thrombocytopenia was higher in the elderly group and that of esophageal fistula was higher in the younger group, but other toxicities were not significantly different between the groups.

Abbreviations

CRT: radiotherapy; CTx: chemotherapy; 5-FU: 5-fluorouracil; CF: cisplatin and 5-FU; RT: radiotherapy; PS: performance status; CT: computed tomography; GTV: gross tumor volume; FDG-PET: 18F-fluorine deoxyglucose-positron emission tomography; CTV: clinical target volume; PTV: planning target volume; ACTx: adjuvant CTx; FOLFOX: leucovorin–fluorouracil–oxaliplatin; CR: complete response; OS: overall survival; PFS: progression-free survival; MST: median survival time; HR: hazard ratio; CI: confidence interval

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of Kanagawa Cancer Center (approval number: 2021-55)

Consent for publication

Written informed consent was obtained from all patients.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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There is no funding to declare.

Authors' contributions

YT collected and analyzed the data and drafted the manuscript. HK, DY, and TK analyzed the data and contributed to the final draft of the manuscript. KK, S Shima, RT, MI, TA, and S Saito collected and analyzed the clinical data. KT, NM, and IS aided in writing the manuscript and contributed to the final draft of the manuscript. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, Tables are only available as a download in the Supplemental Files section.

Figures

Figure 1

Overall survival (OS) in the elderly and younger groups. Significant differences were not observed in OS between the elderly and younger groups ($p = 0.767$).

Figure 2

Progression-free survival (PFS) in the elderly and younger groups. Significant differences were not observed in PFS between the elderly and younger groups ($p = 0.926$).

Figure 3

Overall survival (OS) in all patients. (a) OS with and without adjuvant chemotherapy (ACTx). OS was significantly better in the ACTx group ($p < 0.001$). (b) OS with and without complete response (CR). OS was significantly better in the ACT group ($p < 0.001$).

Figure 4

Overall survival (OS) in elderly patients. (a) OS with and without adjuvant chemotherapy (ACTx). OS was significantly better in the ACTx group ($p < 0.001$). (b) OS with and without complete response (CR). Significant differences in OS were not observed between the CR and non-CR groups ($p = 0.051$)

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