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Involved-field irradiation in definitive chemoradiotherapy for T4 squamous cell carcinoma of the esophagus

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ABSTRACT

Objectives Definitive concurrent chemoradiotherapy (CCRT) is currently a therapeutic option for locally advanced esophageal cancer. However, clinical practice differs with respect to the target volume for irradiation. The purpose of the present study was to analyze failure patterns and survival, and to determine the feasibility of using involved-field irradiation (IFI) with concurrent chemotherapy for T4 squamous cell carcinoma (SCC) of the esophagus.

Methods Between January 2003 and January 2013, 56 patients with clinical T4M0 SCC of the esophagus received CCRT using IFI. The radiation field included the primary tumour and clinically involved lymph nodes. Target volumes and sites of failure were analyzed, as were treatment-related toxicity and survival time.

Results In this 56-patient cohort, 13 patients (23.2%) achieved a complete response, and 21 (37.5%) achieved a partial response, for a total response rate of 60.7%. The major toxicities experienced were leucocytopenia and esophagitis, with 14 patients (25.0%) experiencing grade 3 toxicities. At a median follow-up of 34 months, 48 patients (85.7%) had experienced failure: 39 (69.6%) in-field, 7 (12.5%) elective nodal, and 19 (33.9%) distant. Only 1 patient (1.8%) experienced isolated elective nodal failure. The 1-, 2-, and 3-year survival rates were 39.3%, 21.4%, and 12.5% respectively.

Conclusions For patients with T4M0 SCC of the esophagus, definitive CCRT using IFI resulted in an acceptable rate of isolated elective nodal failure and an overall survival comparable to that achieved with elective nodal irradiation. A limited radiation therapy target volume, including only clinically involved lesions, would therefore be a feasible choice for this patient subgroup.

Key Words Esophageal cancer, T4 disease, chemoradiotherapy, involved-field irradiation, patterns of failure

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INTRODUCTION

Esophageal cancer (ECA) is a highly lethal disease. Of the two predominant histologic types, adenocarcinoma and squamous cell carcinoma (SCC), SCC accounts for 95% of all Chinese ECA patients, and more than 50% of ECAs are at a locally advanced stage when diagnosed[1]. The lack of a serosal layer in the esophagus and the location of this conduit in a very narrow mediastinal space allows for tumour invasion into the local structures, which represents disease stage T4[2]. Despite advances in surgical techniques, T4 disease is usually considered inoperable. The current therapeutic options for locally advanced disease of this kind are chemoradiotherapy followed by surgery and definitive concurrent chemoradiotherapy (CCRT)[3].

The current radiotherapy standard is external-beam radiation using the 3-dimensional conformal technique, based on 3-dimensional computed tomography (CT) planning. However, clinical practice for determining the clinical target volume (CTV)—especially the lymph node volume—varies. Elective nodal irradiation (ENI), in which the lymph nodes to optimally include in the radiation field are determined according to the primary site in the esophagus, is one method. However, serious toxicities occurred in at

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least 50% of a patient group with locally advanced ECA who received CCRT using ENI[4–6]. Theoretically, treatment-related toxicities should decline with smaller irradiated volumes. Involved-field irradiation (IFI)—that is, a nodal target volume that includes only the metastatic nodes—is a selective way of decreasing the irradiated volume.

Involved-field irradiation might be feasible for a subgroup of patients with ECA. For instance, Kawaguchi *et al.*[7] found that IFI did not result in a significant incidence of regional lymph node failure in patients with clinical stage I thoracic ECA. In some studies, 3-dimensional conformal radiotherapy without ENI was used in locally advanced patients, for whom the rate of isolated out-of-field nodal failure was only 2%–8%[8,9].

In the present study, we retrospectively analyzed failure patterns, treatment toxicity, and survival to observe the feasibility of CCRT using IFI for clinical stage T4M0 SCC of the esophagus.

METHODS

The use of IFI with concurrent chemotherapy has been routine for ECA at our institution since 2003. We reviewed clinical records to identify patients with clinical T4 SCC ECA treated from January 2003 to January 2013. Disease had been confirmed by biopsy or brush samples and had not previously been treated. In every case, staging examinations included esophagography, endoscopic ultrasonography, and CT; some patients also underwent positron-emission tomography (PET) as part of PET–CT fusion imaging. Patients were excluded if they had distant metastasis, a history of any other malignant tumour, or fistulae before treatment. The institutional review board of the Shandong Cancer Hospital and Institute approved the study.

Staging

The T4 lesions were diagnosed by CT criteria[2], which included loss of fat planes between the tumour and adjacent structures in the mediastinum, and displacement or indentation of other mediastinal structures. Aortic invasion was suggested if 90 degrees or more of the aorta was in contact with the tumour or if obliteration of the triangular fat space between the esophagus, aorta, and spine adjacent to the primary tumour was evident. Bronchoscopy was performed in some cases when tracheobronchial involvement was suspected.

The regional lymph nodes included any paraesophageal lymph nodes extending from the cervical lymph nodes to the celiac lymph nodes. The primary criterion for nodal involvement was size (nodes >1.0 cm in the short axis or >1.5 cm in the long axis on CT imaging); nodes with a high uptake of fluorodeoxyglucose on PET images (high maximum standardized uptake value) were also considered to be metastatic. Other criteria to determine the presence of nodal metastasis included an enhancement pattern and the presence of extranodal tumour extension.

Radiotherapy

All radiation treatments were delivered using the 3-dimensional conformal or intensity-modulated techniques with standard fractionation (1.8-Gy or 2.0-Gy fractions administered once daily, 5 days per week). Treatment plans were generated using a 3-dimensional planning system (ADAC Pinnacle 3, version 5.0: Philips Medical Systems, Madison, WI, U.S.A.). The gross tumour volume (GTV) was defined as any visible esophageal lesion (GTV_e), plus clinically involved nodes (GTV_n). The CTV_e was defined as the GTV_e plus a 3.0-cm margin superior and inferior to the primary tumour and a 0.8-cm to 1.0-cm radial margin. The CTV_n was defined as the GTV_n plus a 0.5-cm to 1.0-cm radial margin. The planning target volume was defined as the CTV plus a 0.5-cm to 1.0-cm margin. All organs at risk were outlined. Radiation was delivered by high-energy (6 MV or 15 MV) linear accelerators. Patients were treated to a total dose of 54–64 Gy given in 27–32 fractions.

Chemotherapy

Chemotherapy was administered concurrently with the start of radiation treatment. The chemotherapeutic regimens included 5-fluorouracil–cisplatin in 35 patients, docetaxel–cisplatin in 13 patients, paclitaxel–carboplatin in 5 patients, and single-agent 5-fluorouracil in 3 patients.

Treatment-Related Acute Toxicity

Treatment-related acute toxicity throughout the treatment period was scored using the Radiation Therapy Oncology Group criteria. Major treatment toxicities included myelosuppression, esophagitis, and nausea or vomiting.

Result Assessment and Follow-Up

Response was evaluated by esophagography, esophagoscopy, and CT imaging. For esophageal lesions, complete remission (CR) was defined as no dysphagia, a normal esophagogram, and disappearance of all visible tumours, including ulceration, for at least 4 weeks, confirmed by normal endoscopic biopsy samples. Partial remission (PR) was defined as an improvement in dysphagia, a greater than 50% reduction in intra-esophageal tumour extension as assessed by esophagography, and a greater than 50% reduction in the area of the primary tumour as observed on esophagography. Progressive disease was considered to be an increase in the area of the tumour of more than 25%. Lymph node response was evaluated and classified according to the RECIST (Response Evaluation Criteria in Solid Tumors) system[10], and the final results were recorded in the follow-up data.

Failures were assessed by esophagography, CT, or PET–CT imaging and were compared with the original CT-based radiation treatment plans. Suspected esophageal recurrences were confirmed by histologic or cytologic testing. Lymph node recurrences were diagnosed when nodes reappeared after having completely disappeared; when nodes became enlarged after having remained stable; and when new nodes appeared in regions where no enlarged nodes had been identified before irradiation. Suspected supraclavicular node recurrences were confirmed by fine-needle aspiration. "In-field recurrences" included the primary lesion and the involved nodes before treatment. "Elective nodal failure" was defined as recurrence in initially uninvolved regional nodes. Nodal metastases outside the regional level were considered to

be distant failures. All failure patterns were included in the analysis regardless of the timing of previous failures. The overall survival (OS) and progression-free survival (PFS) durations were calculated from the first day of radiation delivery.

Statistical Analyses

Continuous variables are summarized by descriptive statistics such as mean with standard deviation or median and range. Categorical variables are tabulated as frequencies and percentages. The Kaplan–Meier method and log-rank tests were applied to estimate survival probabilities. Model variables were chosen by backward selection. The SPSS Statistics software application (version 17.0: SPSS, Chicago, IL, U.S.A.) was used for data analysis. The level of significance was set at $p < 0.05$.

RESULTS

Patient Characteristics

From January 2003 to January 2013, complete data were available for 56 patients. Median age in the cohort was 60 years (range: 42–72 years). Most of the patients had a good performance status. All 56 patients had histologically proven SCC. In 11 patients, the delivered radiation dose was less than 60 Gy; in 45 patients, it was 60 Gy or more. In 3 patients, treatment was not completed because of treatment-related toxicities and perforation of the esophagus during treatment. Additional courses of chemotherapy were delivered after definitive chemoradiation in 31 patients. Table I shows clinical and treatment characteristics for the cohort.

TABLE I Patient characteristics

Characteristic	Value
Patients (*n*)	56
Sex [*n* (%)]	
Men	48 (85.7)
Women	8 (14.3)
Age (years)	
Median	60
Range	42–72
Tumour category [*n* (%)]	
T4N0	13 (23.2)
T4N+	43 (76.8)
Tumour location [*n* (%)]	
Cervical	2 (3.6)
Upper thoracic	11 (19.6)
Mid-thoracic	25 (44.6)
Lower thoracic	18 (32.1)
Tumour length (cm)	
Median	6.0
Range	4–12
Radiation dose (Gy)	
Median	60
Range	50–64
Radiation dose category [*n* (%)]	
<60 Gy	11 (19.6)
≥60 Gy	45 (80.4)
Adjuvant chemotherapy [*n* (%)]	
Yes	31 (55.4)
No	25 (44.6)
Chemotherapy cycles (*n*)	
Median	2
Range	0–5

Acute Toxicities from Chemoradiotherapy

The most commonly reported toxicities during CCRT were myelosuppression and esophagitis. Grade 3 leucocytopenia, anemia, thrombocytopenia, esophagitis, and nausea or vomiting occurred in 32.1%, 8.9%, 5.4%, 0%, and 3.6% of patients respectively. Table II details the toxicities documented in the cohort.

Perforation

Perforation of the esophageal wall developed in 6 patients (10.7%; 3 during and 3 immediately after radiation). The diagnosis of perforation was made after CT imaging and iodine examination identified esophagobronchial fistula ($n = 2$), esophagovascular fistula ($n = 1$), and esophagomediastinal fistula ($n = 3$). Of the 6 patients, 3 died of massive bleeding (2 during and 1 after radiation), 2 died of infection after chemoradiation, and 1 recovered from an esophagomediastinal fistula.

Response

Of the 56 patients, 13 (23.2%) achieved a CR, and 21 (37.5%), a PR, for a total response rate of 60.7%. In 19 patients (33.9%), disease persisted ("stable disease"), and 1 patient (1.8%) experienced progressive disease from distant non-regional lymph node metastasis. Of the 6 patients experiencing perforation, 4 achieved a PR according to RECIST, and 2 died of massive bleeding during chemoradiation, with no response evaluation.

Patterns of Failure

At the time of the last follow-up contact in December 2013, 48 patients had experienced treatment failure (excludes the 5 patients who died during and after radiation). Disease persistence and in-field recurrence were the most frequent causes of in-field failure in this group of patients ($n = 39$, 69.6%). In-field recurrence only, with death from ECA, occurred in 26 patients (46.4%). Distant recurrence affected 19 patients (33.9%), with 7 of them experiencing a distant-only recurrence (12.5%). Elective nodal failure occurred in 7 patients (12.5%), of whom only 1 experienced an isolated failure (1.8%). The remaining 6 patients (10.7%) also experienced in-field or distant recurrences. Among the 13 patients with a CR, 10 experienced recurrence, with the pattern of first failure being in-field only (n = 3), distant only (n = 5), elective nodal only (n = 1), and both in-field and distant (n = 1). Table III summarizes the failure patterns.

TABLE II Acute toxicities of chemoradiotherapy

Toxicity	Grade [*n* (%)]				
	0	1	2	3	4
Leucocytopenia	7 (12.5)	5 (8.9)	30 (53.6)	14 (25.0)	0
Anemia	22 (39.3)	12 (21.4)	16 (28.6)	5 (8.9)	0
Thrombocytopenia	40 (71.4)	7 (12.5)	6 (10.7)	3 (5.4)	0
Esophagitis	20 (35.7)	23 (41.1)	13 (23.2)	0	0
Nausea or vomiting	7 (12.5)	27 (48.2)	20 (35.7)	2 (3.6)	0

TABLE III Patterns of failure after treatment[a]

Location of failure	Value [*n* (%)]
No evidence of disease	3 (5.4)
Treatment-related death	5 (8.9)
Any site	48 (85.7)
In-field	39 (69.6)
In-field alone	26 (46.4)
Elective field	7 (12.5)
Elective nodal alone	1 (1.8)
Distant	19 (33.9)
Distant alone	7 (12.5)
In-field, elective field, and distant	3 (5.4)
In-field and elective field	2 (3.6)
Elective field and distant	1 (1.8)
In-field and distant	8 (14.3)

[a] All failure patterns were included, regardless of the timing of earlier failures.

Survival

The median follow-up period was 34 months (range: 7–50 months), and median survival duration for the 56 patients was 8 months (95% confidence interval: 5.8 to 10.2 months; Figure 1). At the time of writing, 5 patients (8.9%) were still alive, including 3 with no evidence of disease. Of the 51 patients who died (91.1%), 48 died from their cancer (including the 5 who experienced perforation); 3 died from other diseases. The 1-, 2-, and 3-year survival rates were 39.3%, 21.4%, and 12.5% respectively.

No significant difference in median os was observed for the patients with and without regional lymph node metastasis (8 months vs. 7 months; 95% confidence interval: 5.1 to 10.8 months vs. 3.6 to 10.3 months; $p = 0.898$, Figure 2). The median os for patients experiencing CR, PR, and other responses was 38 months, 11 months, and 5 months respectively (log-rank chi-square: 61.17; $p < 0.0001$, Figure 3). The median time to disease progression in the 56 patients overall was 5 months. The PFS duration differed significantly for the patients who experienced a CR ($n = 13$), a PR ($n = 21$), and other responses (log-rank chi-square: 61.29; $p < 0.0001$). Median PFS for patients experiencing no response was just 2 months; it was 34 months for patients experiencing a CR and 6 months for patients experiencing a PR.

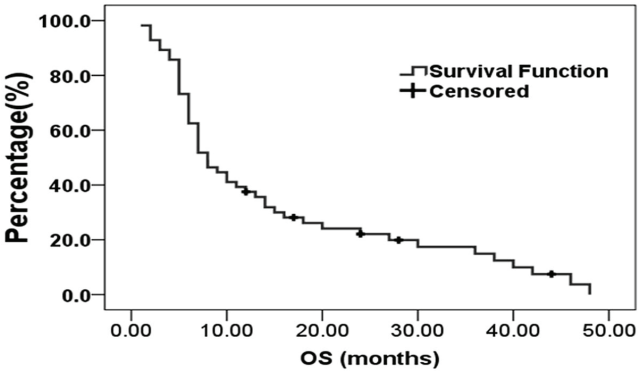

FIGURE 1 Overall survival (OS) rates after chemoradiation using involved-field irradiation for patients with T4 esophageal squamous cell carcinoma. Median survival for the 56 patients was 8 months (95% confidence interval: 5.8 to 10.2 months), and the OS rates at 1, 2, and 3 years were 39.3%, 21.4%, and 12.5% respectively.

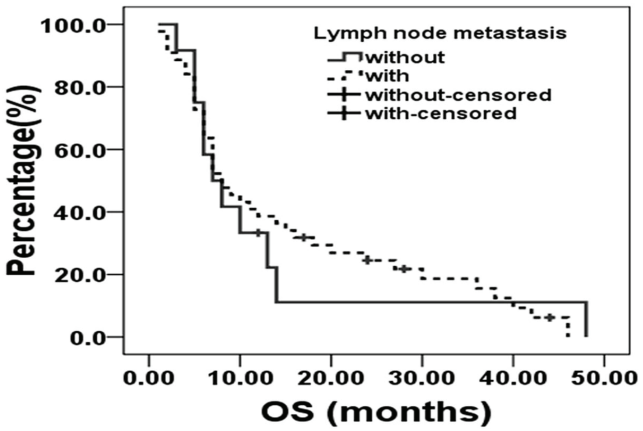

FIGURE 2 Overall survival (OS) for patients having T4 esophageal squamous cell carcinoma, with and without regional lymph node metastasis. Kaplan–Meier curves and log-rank tests showed no significant differences between patients with and without such metastases ($p = 0.898$).

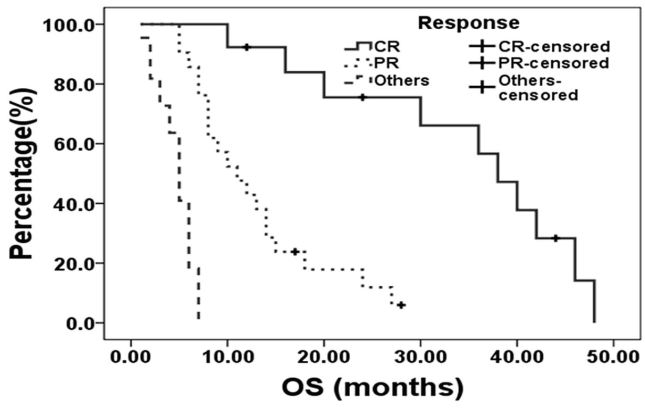

FIGURE 3 Kaplan–Meier curves for overall survival (OS) in patients with T4 esophageal squamous cell carcinoma, by response status. The median OS durations for patients with a complete (CR), partial (PR), or other response were 38, 11, and 5 months respectively ($p < 0.0001$).

DISCUSSION

Our study identified a clinical CR rate of 23.2% and a total response rate of 60.7%, highlighting the effectiveness of CCRT as a therapy for T4 SCC of the esophagus. During a median follow-up of 34 months, median survival was 8 months. The 1-, 2-, and 3-year OS rates were 39.3%, 21.4%, and 12.5% respectively. Those results are comparable to results in a similar population receiving CCRT using ENI, which demonstrated a CR rate of 15%–33% and a median survival duration of 9–10 months in patients with T4 or M1a disease[11,12].

In the cohort considered in the present study, we also observed no significant difference in survival between patients with and without regional node metastasis. That finding indicates that T4 stage had a greater effect on outcome than did the presence of affected regional lymph nodes. It is possible that, to some extent, a lower CR rate for the primary tumour resulted in shorter patient survival. Median duration of PFS in patients with no response to treatment was just 2 months, and median OS was 5 months. Seto *et al.*[13] similarly examined prognosis according to the response to chemoradiotherapy in T4 patients and reported 1-, 3-, and 5-year survival rates of 83%, 33%, and 33% respectively for patients experiencing a CR, compared with 23%, 0%, and 0% for patients not experiencing a CR.

In our study, in-field failure was observed in 69.6% of patients (39 of 56), indicating that in-field failure was the predominant pattern after definitive CCRT using IFI for T4 ECA. Among those 39 patients, 67% (n = 26) experienced recurrence without any other site of failure—a rate higher than that reported for resectable (T1–3N0–1M0) disease. In the randomized Radiation Therapy Oncology Group 85-01 trial, the incidence of local or regional failure and local or regional persistence of disease was 47% in patients receiving combined-modality therapy; moreover, advanced T stage was found to be a negative factor for locoregional control[14–16]. Welsh *et al.*[14] reported that, among patients with locally advanced ECA undergoing CCRT using ENI, 119 (50%) experienced local recurrence (most occurring in the GTV). Specific T stage was also associated with a risk of GTV (in-field) failure, in which the local control rate was 77% for T1 or T2 tumours compared with 46% for T3 or T4 tumours.

Distant failure is another important issue in patients with advanced ECA, occurring in 33.9% of the patients analyzed in the present study—a rate that was lower than the rate in the resectable population just mentioned. According to Welsh *et al.*[14], 48% of patients experienced distant failure (defined as being outside the radiation field). In a study by Versteijne *et al.*[17], 76 of 184 patients (41%) experienced distant metastasis, of whom 37 (20%) also experienced locoregional recurrence. Another study demonstrated that the proportion of residual carcinomas after preoperative chemoradiotherapy was significantly correlated with patterns of locoregional and distant failure[18]. In our study, the high local recurrence rate could have masked distant failures, because many of the locally advanced patients died before detection of any distant metastases. New regimens must be developed to improve both local and distant control in patients with advanced ECA.

In our study, 12.5% of patients experienced elective regional lymph node failure (7 of 56), but isolated elective nodal failure occurred in only 1 patient (1.8%). Morota *et al.*[19]. reported a 7% regional failure rate in patients with thoracic ECA undergoing CCRT using ENI. In an analysis of recurrence patterns after definitive CCRT not using ENI, Button *et al.*[20] reported that 3 patients (2%) developed isolated regional recurrence. In a study of IFI in patients with locally advanced ECA, the rate of in-field recurrence was 44% (compared with the 64.3% reported here), but 8% of patients experienced isolated regional nodal recurrence (compared with 1.8% in the present study)[8]. Thus, regardless of whether radiation was administered using ENI or IFI, regional lymph node failure was not the main pattern of recurrence in advanced-stage ECA patients. On the other hand, the rationale for use of ENI is to prevent regional nodal relapse rather than to improve survival. In a prospective randomized trial, Ma *et al.*[21] compared ENI with IFI in patients with cervical and upper thoracic ECA, observing no significant difference in the 3-year OS or locoregional control rate between the IFI and ENI groups (32.0% and 80.1% vs. 41.3% and 85.7% respectively). Liu *et al.*[22] noted that out-of-field regional cervical node metastasis occurred in 8% of the IFI group and 10% of the ENI group in patients with cervical and upper thoracic ECA. Use of ENI did not result in better OS or long-term control in cervical lymph nodes.

Locoregional control after definitive CCRT remains an important issue in locally advanced ECA. The lower response rate suggests that more-intensive local treatment is needed for this type of bulky unresectable disease. However, high-dose radiation therapy can increase the risks for esophageal stricture and perforation, and in the Radiation Therapy Oncology Group 94-05 trial[5], high-dose radiation failed to improve local control and survival in a population with clinical stage T1–3N0–1 disease.

Perforation of the esophageal wall is an unavoidable but significant toxic side effect of treatment administered to patients with T4 disease. Our study reports a perforation rate of 10.8% (6 of 56) during and after CCRT. Fistulae form in 9%–18% of patients with T4 disease receiving chemoradiation, and of complicated cases, most end in early death after a median duration of 2 months[23,24]. Perforation and hemorrhage could have been related to antitumour treatment, the tumour itself, the response, or even poor general condition of the patients. Although CCRT is not contraindicated for T4 tumours, the high incidence of esophageal perforation must be kept in mind, especially in the presence of invasion of the trachea, great vessels, or heart.

The toxicities most commonly reported during CCRT are myelosuppression and esophagitis. In our study, no grade 4 acute toxicities were observed, and grade 3 leucocytopenia, anemia, thrombocytopenia, and esophagitis occurred in 25%, 8.9%, 5.4%, and 0% of patients respectively. Zhao *et al.*[8] reported rates of grade 3 acute and late toxicities of 9% and 6% respectively after IFI, and no patients experienced acute or late grade 4 or 5 toxicities. Ma *et al.*[21] reported significant differences between IFI and ENI groups with respect to hematologic toxicity, infection, and vomiting. Those results appear promising, because treatment-related toxicities were less severe

than those observed in trials using an extended field. Studies of ENI reported that 25%–60% and 23%–29% of patients experienced grade 3 or greater acute and late toxicities respectively[4–6]. In the 85-01 trial, 8% of patients receiving combined-modality therapy experienced acute life-threatening toxic side effects, and an additional 2% died as a direct consequence of treatment. In the study by Kaneko *et al.*[25], which used extended-field irradiation and concurrent chemotherapy for patients with malignant strictures from esophageal carcinoma, grade 3 and greater leucocytopenia, anemia, thrombocytopenia, and esophagitis occurred in 30%, 33%, 14%, and 25% of patients respectively. Thus, IFI can result in reduced incidences of treatment toxicities, enabling more patients to tolerate CCRT.

Our study has some limitations. First, as a retrospective analysis, the treatment offered to patients differed for each patient in terms of radiation dose and chemotherapy regime. Second, the patient sample was small and might therefore have influenced the statistical analysis. Third, tumour staging was performed mainly by CT, and although CT has been the mainstay for ECA staging, the increased use of endoscopic ultrasonography and PET has improved the staging algorithm for newly diagnosed ECA. When IFI is used, the more accurate pre-therapeutic staging modalities should be used to avoid overlooking any metastatic nodes.

CONCLUSIONS

In patients with T4 SCC of the esophagus undergoing CCRT using IFI, survival was comparable to that for patients receiving ENI; the incidence of isolated regional lymph node recurrences was also acceptable. A limited target volume including only clinically involved lesions can therefore be a reasonable choice. Further observations from prospective and randomized clinical trials are needed to verify the feasibility of IFI for locally advanced SCC of the esophagus.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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