

Long-term outcome of concurrent chemoradiotherapy with elective nodal irradiation for inoperable esophageal cancer

Zhao Jing,^{1,4} Tian Chen,^{2,4} Xuebang Zhang³ and Shixiu Wu¹ 

¹Department of Radiation Oncology, Hangzhou Cancer Hospital, Hangzhou; ²Department of Radiation Oncology, Ningbo Medical Treatment Center Lihui Hospital, Ningbo; ³Department of Radiation Oncology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China

Key words

chemoradiotherapy, elective nodal irradiation, Esophageal cancer, salvage treatment, secondary cancer

Correspondence

Shixiu Wu, Department of Radiation Oncology, Hangzhou Cancer Hospital, 34 Yanguan Lane, Hangzhou, China.
Tel: +86 571 56006001; Fax: +86 571 56006088;
E-mail: wushixiu@medmail.com.cn

⁴These authors contributed equally to this work.

Funding Information

No commercial support was provided for this study.

Revised April 18, 2017; Accepted June 25, 2017

Cancer Sci 108 (2017) 1828–1833

doi: 10.1111/cas.13308

Elective nodal irradiation (ENI) might improve overall survival in patients with inoperable esophageal cancer. We conducted a retrospective analysis to assess the long-term survival and toxicity of esophageal cancer patients treated with ENI versus conventional-field irradiation (CFI). All data in the present study were based on our institutional experience from 2000 to 2005 of patients with inoperable esophageal cancer treated with ENI or CFI plus two concurrent cycles of paclitaxel/cisplatin. Based on the inclusion and exclusion criteria, 89 patients were included in the analysis. Of these patients, 51 were treated with ENI, whereas 38 were treated with CFI. For the per-protocol population, the patients in the ENI group significantly improved in terms of their 10-year disease-specific overall survival (43.1% vs 10.5%, $P = 0.019$), 10-year disease-free survival (36.7% vs 10.2%, $P = 0.040$) and 10-year local recurrence-free survival (47.2% vs 17.2%, $P = 0.018$) compared with the CFI group. Aside from radiation esophagitis, the incidence of grade 3 or greater acute toxicities did not differ between the two groups. Multivariate analysis showed that radiation field, tumor length and clinical stage were independent prognostic factors associated with OS. Concurrent chemoradiotherapy with ENI improves both disease-specific overall survival and loco-regional control in patients with inoperable esophageal cancer receiving per-protocol treatment. The regimen has a manageable tolerability profile.

Esophageal cancer is the sixth most common cause of cancer-related death, and 482 300 new cases were diagnosed during 2008.^(1,2) Surgery is the cornerstone in treatment for esophageal cancer, with a median survival time of 13.6–19.3 months and 2-year overall survival (OS) of 34%–45%.^(3,4) However, fewer than 50% of newly diagnosed patients are suitable for curative resection.⁽⁵⁾

The Radiation Therapy Oncology Group (RTOG) 85-01 trial showed that 5-fluorouracil plus cisplatin combined with radiotherapy significantly improved median survival and 5-year OS compared with radiotherapy alone.⁽⁶⁾ Concurrent chemoradiotherapy (CRT) has become the standard treatment for patients with inoperable esophageal cancer, but the incidence of loco-regional recurrence is over 50%.^(7–9)

Further attempts have been made to improve the therapeutic efficacy for esophageal cancer. Paclitaxel has notable activity in esophageal cancer and is a radiation sensitizer. The combination of paclitaxel with cisplatin seems to offer similar response rates and survival but less treatment-related toxicity when concurrently administered with radiotherapy, compared with 5-fluorouracil/cisplatin regimens.^(10,11)

The esophagus contains an extensive submucosal lymphatic plexus; hence, dissemination to regional lymph nodes occurs early in esophageal cancer.⁽¹²⁾ The conventional clinical treatment volume (CTV) is adopted in radiotherapy without prophylactic elective nodal irradiation (ENI) to the draining

lymphatics, which may lead to a high incidence of local-regional recurrence. However, the benefit of ENI in chemoradiotherapy in preventing loco-regional recurrence in esophageal cancer remains uncertain.⁽¹³⁾ A systematic review showed that ENI in chemoradiotherapy for esophageal cancer was feasible with acceptable toxicities.⁽¹⁴⁾ Several retrospective studies have reported that chemoradiotherapy with ENI significantly reduced the loco-regional failure in patients with stage II/III esophageal cancer.^(14,15) We postulated that the addition of ENI to chemoradiotherapy could improve prognosis in patients with inoperable esophageal cancer.

To date, the use of ENI in esophageal cancer is controversial due to a lack of prospective clinical trials. A rigorously designed retrospective study may provide evidence for establishing preferred treatment modality for patients with inoperable esophageal cancer. Therefore, we reviewed our institutional experience to compare the efficiency and safety of ENI with concurrent paclitaxel/cisplatin (TP) versus conventional-field irradiation (CFI) with concurrent TP in patients with inoperable esophageal cancer.

Methods and Materials

Patients. Eligible patients were required to have histologically confirmed esophageal cancer (either squamous cell carcinoma or adenocarcinoma) by biopsy. Additional inclusion

criteria were as follows: age between 18 and 70 years; surgically or medically unresectable disease (stage T1–T4, N0/1, M0–1a according to the 2002 International Union Against Cancer TNM stage criteria) excluding patients with tracheoesophageal fistula or complete esophageal obstruction; Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; and normal hemogram and adequate function of major organs (including cardiac, hepatic and renal function).

Ineligibility criteria included active uncontrolled infection; clinically significant cardiovascular disease; history of other malignancies; and previous treatment with radiotherapy, chemotherapy or immunotherapy.

The study was approved by the independent ethics committee of Wenzhou Medical University. The research protocol followed the Declaration of Helsinki. Informed consent was obtained from all patients before treatment initiation.

Pretreatment evaluation. Pretreatment evaluation included barium swallowing, endoscopic ultrasound of the esophagus, and enhanced computed tomography (CT) of the neck, chest and abdomen. ¹⁸F-fluorodeoxyglucose CT-PET scan was optional.

Radiotherapy planning and target volume definition. Radiotherapy (CFI and ENI) was delivered with megavoltage equipment (≥ 6 MV) using 3-D conformal radiotherapy or intensity-modulated radiation therapy, beginning on the first day of chemotherapy. The gross tumor volume (GTV) was defined as the primary tumor and any enlarged regional lymph nodes indicated by the transesophageal ultrasound, esophagram, CT scan and PET/CT (when available). The clinical target volume (CTV) consisted of CTV1 and CTV2. For patients receiving ENI, the initial clinical target volume (CTV1) included whole esophagus plus regional lymph nodes. According to the location of the tumor, the regional lymph nodes were prophylactic irradiated. For the cervical esophageal tumor, the level II/III lymph nodes in the neck, supraclavicular, paratracheal, posterior mediastinal, aortopulmonary, subcarinal, paraesophageal, pulmonary ligament, diaphragmatic and paracardial lymph nodes were included. For the upper and middle thoracic tumor, supraclavicular, paratracheal, posterior mediastinal, aortopulmonary, subcarinal, paraesophageal, pulmonary ligament, diaphragmatic, paracardial and left gastric lymph nodes were included. For the lower thoracic tumor, paratracheal, posterior mediastinal, aortopulmonary, subcarinal, paraesophageal, pulmonary ligament, diaphragmatic, paracardial, left gastric and celiac lymph nodes were included. For patients receiving CFI, CTV1 was defined as GTV plus superior–inferior 4-cm margin and radial 1-cm margin. After 40 Gy of radiotherapy, CTV2 (boost CTV) was defined as GTV plus the superior–inferior 2-cm and radial 1-cm margin. In patients receiving CFI, CTV1 was defined as GTV plus the superior–inferior 4-cm margin and radial 1-cm margin. After 40 Gy of radiotherapy, CTV2 (boost CTV) was defined as GTV plus the superior–inferior 2-cm and radial 1-cm margin. A total of 60 Gy of radiation doses was delivered over 30 fractions in 6 weeks. Initially, 40 Gy was given to CTV1, and a boost dose of 20 Gy was then delivered to CTV2. The maximum dose to the spinal cord was limited to 45 Gy and the lung V20 was less than 35%. Patients' radiotherapy was postponed when grade 4 hematological toxicity or grade 3/4 toxicities related to radiation (esophagitis and gastrointestinal reactions) developed at the clinician's discretion. The radiation therapy resumed until the toxicity improved to grade 2 or less, with no reduction in prescribed radiation dose.

Chemotherapy regimen and dose modification. All patients received chemotherapy comprising intravenous paclitaxel (135 mg/m², day 1) and cisplatin (20 mg/m², days 1–3) or oxaliplatin (130 mg/m², day 2) every 4 weeks for two cycles. Doses used in the second cycle were adjusted according to toxicities in the first cycle.

A suspension of chemotherapy dosing was required if patients developed grade 3 leucocytopenia with fever or grade 4 leucocytopenia, and the chemotherapy restarted when the toxicity improved to grade 2 and with a 20% dose reduction of cisplatin and paclitaxel. Prophylaxis use of granulocyte colony-stimulating factors was permitted according to

Table 1. Patient and tumor characteristics

Characteristics	ENI (N = 51)		CFI (N = 38)		P-value
	No.	%	No.	%	
Age(years)					
<65	27	52.9	19	50.0	0.784
≥ 65	24	47.1	19	50.0	
Gender					
Male	49	96.1	36	94.7	1.000
Female	2	3.9	2	5.3	
ECOG PS					
0–1	37	72.5	31	81.6	0.321
2	14	27.5	7	18.4	
Tumor Length (cm)					
<5	6	11.8	8	21.1	0.301
5–8	28	54.9	22	57.9	
>8	17	33.3	8	21.1	
Pathology					
Squamous carcinoma	49	96.1	38	100.0	
Adenocarcinoma carcinoma	1	2	0		
Adenosquamous carcinoma	1	2	0		
Tumor differentiation					
Well	3	5.9	5	13.2	0.128
Moderately	18	35.3	20	52.6	
Poorly	16	31.4	5	13.2	
Unknown	14	27.5	8	21.1	
Location of primary tumor					
Cervical	1	2.0	4	10.5	0.159
Upper thoracic	17	33.3	9	23.7	
Middle thoracic	26	51.0	16	42.1	
Lower thoracic	7	13.7	9	23.7	
Stage grouping (AJCC 2002)					
Stage II	24	47.1	20	52.6	0.167
Stage III	12	23.5	13	34.2	
Stage IV	15	29.4	5	13.2	
Response rate					
Complete and/or partial response	37	72.5	25	65.8	0.493
Stable and/or progressive disease	14	27.5	13	34.2	
Endoscopic biopsy at completion of treatment					
Negative	36	70.6	28	73.7	0.758
Positive	15	29.4	10	26.3	
Length of spinal irradiation when 40 Gy (cm)					
Mean	32.14		18.78		0.000
Standard deviation	3.10		3.57		

ECOG PS, Eastern Cooperative Oncology Group performance status; AJCC, American Joint Committee on Cancer; RECIST, Response Evaluation Criteria in Solid Tumors; ENI, elective nodal irradiation; CFI, conventional-field irradiation.

physician's decisions. In addition, cisplatin was given at a 20% dose reduction to patients with a glomerular filtration rate (GFR) of less than 50 mL/min.

Response and toxicity assessment. Toxicity assessment was performed weekly during the treatment. Acute toxicity of the treatment was evaluated according to the Common Toxicity Criteria for Adverse Events Version 3.0 (CTCAE v3.0). Clinical response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) 4–6 weeks after completion of the treatment regimen. Late toxicity was evaluated based on the RTOG/European Organization for Research and Treatment of Cancer (EORTC) criteria 6 months after the completion of the treatment regimen. Per-protocol population in this study was defined as receiving at least one cycle of chemotherapy and a radiation dose of 60 Gy, or two cycles of chemotherapy and a radiation dose of more than 50 Gy.

Follow-up. Follow-up visits occurred every 3 months during the first 2 years, then every 6 months until 5 years and yearly thereafter. At each visit, a physical examination was performed, and a barium swallow, chest CT, and abdominal ultrasound were obtained. 18F-fluorodeoxyglucose PET-CT scan was optional. Additional tests were performed as clinically indicated.

Statistical analysis. The primary endpoint was overall survival (OS). The second endpoints included disease-free survival (DFS), local recurrence-free survival (LRFS), and treatment toxicity. All time-related endpoints were measured from when treatment was initiated. We assessed the time-to-event endpoint using the Kaplan–Meier method and applied the log-rank test for comparison. The χ^2 -test and Student's *t*-test were used to evaluate differences in groups' characteristics and treatment toxicities. Independent prognostic factors were identified by multivariate analyses using the Cox proportional hazards model. All of the statistical analyses were performed using the SPSS 17.0 statistical software (SPSS, Chicago, IL, USA). A two-sided *P*-value <0.05 was considered statistically significant.

Results

Patient characteristic. Between October 2000 and December 2005, a total of 89 patients (51 in the ENI group and 38 in the CFI group) with inoperable esophageal cancer were enrolled. There were no significant differences in baseline characteristics between the two groups (Table 1). The median age was 65 years (range, 47–75 years). The tumor histology was squamous cell cancer in 87 patients (97.8%). In the present study, 50.6% of the patients had stage III/IV cancer. The location of the primary tumors included cervical/upper/middle/lower thoracic portions, with the following distribution: 5/26/42/16 (5.6%/29.2%/47.2%/18.0%). After CRT, 62 patients (69.7%) achieved CR/PR with the following distribution in ENI/CFI groups: 37/25 (72.5%/65.8%).

Treatment compliance. Four patients (3 in the ENI group and 1 in the CFI group) with stage IVB disease received two cycles of consolidation chemotherapy. The per-protocol rate was 85.39% (76/89) for all patients, with 90.20% (46/51) in the ENI group and 78.95% (30/38) in the CFI group. Four patients received 38–40 Gy of radiation in the ENI group and 7 patients received 36–40 Gy of radiation in the CFI group. Sixteen patients declined to receive the second cycle of chemotherapy (10 in the ENI group and 6 in the CFI group). Five patients received a reduced dose of chemotherapy in the second cycle (2 in the ENI group and 3 in the CFI group).

Survival of all enrolled patients. Median follow-up was 102.2 months (range 2.4–142.2) for the overall cohort: 123.1 months (range 3.17–142.2) in the ENI group and 91.2 months (Range 2.4–131.7) in the CFI group. There were 75 deaths among the 89 patients (84.27%) during the follow-up period. Most (*n* = 56; 74.67%) died from recurrent cancer (28 in the ENI group and 28 in the CFI group). Nine patients died from intercurrent disease (3 in the ENI group and 6 in the CFI group) and 10 died from unknown causes (3 in ENI group and 7 in CFI group).

The median OS was 20.13 months (range, 2.4–131.7) in the ENI group and 17.30 months (range, 3.17–142.2) in the CFI group. The 5-year and 10-year OS were 33.8% vs 23.7% and 16.0% vs 13.2% for patients treated with ENI or CFI, respectively. There was no significant difference between the ENI group and the CFI group (hazard ratio [HR] = 0.87; 95% confidence interval [CI] 0.55–1.39; *P* = 0.561, Fig. 1a). The 5-year and 10-year disease-specific OS were 43.0% vs 30.2% and 39.4% vs 16.8% for patients treated with ENI or CFI, respectively (HR = 1.21; 95% CI 0.74–1.97; *P* = 0.239, Fig. 1b). The 5-year and 10-year DFS were 33.1% vs 21.1% and 33.1% vs 14.1% for patients treated with ENI or with CFI, respectively (HR = 0.68; 95% CI 0.41–1.11; *P* = 0.120, Fig. 1c). The 5-year and 10-year LRFS were 43.8% vs 37.6% and 43.8% and 31.9% for patients treated with ENI or CFI, respectively (HR = 0.57; 95% CI 0.33–0.98; *P* = 0.039, Fig. 1d).

Survival of per-protocol population. There were 24 deaths among the 76 patients with per-protocol treatment (46 in ENI group and 30 in CFI group). Table 2 shows the characteristics of per-protocol patients. The 5-year OS (31.7% vs 22.9%) and 10-year OS (13.6% vs 3.6%) were not significantly different between the ENI group and the CFI group (HR = 1.65, 95% CI 0.98–2.77; *P* = 0.056, Fig. 2a). The 5-year and 10-year disease-specific OS were 47.0% vs 26.2% and 43.1% vs 10.5% for patients treated with ENI or with CFI, respectively (HR = 2.01, 95% CI 1.11–3.62; *P* = 0.019, Fig. 2b). The 5-year and 10-year DFS were 36.7% vs 15.3% and 36.7% vs

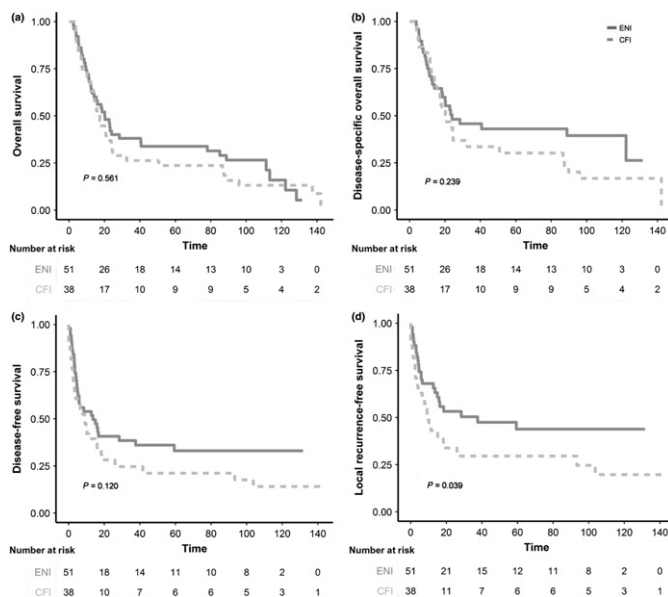


Fig. 1. Kaplan–Meier curves of overall survival (a), disease-specific overall survival (b), disease-free survival (c) and local recurrence-free survival (d) for elective nodal irradiation (ENI) versus conventional-field irradiation (CFI) (entire cohort).

10.2% for patients treated with ENI or with CFI, respectively (HR = 1.78, 95% CI 1.02–3.13; $P = 0.040$, Fig. 2c). The 5-year and 10-year LRFS were 47.2% vs 25.8% and 47.2% vs 17.2% for patients treated with ENI or with CFI, respectively (HR = 2.09; 95% CI 1.12–3.93; $P = 0.018$, Fig. 2d).

Prognostic factors of per-protocol population. As shown in Table 3, univariate analysis revealed the radiation field (HR 0.52, 95% CI 0.30–0.92; $P = 0.025$), tumor length (HR 1.60, 95% CI 1.01–2.53; $P = 0.044$) and clinical stage (HR 2.46, 95% CI 1.24–4.90; $P = 0.010$) as potentially influential factors for OS. The variables that were significantly associated with the LRFS were radiation field (HR 0.48, 95% CI 0.26–0.88; $P = 0.018$) and tumor length (HR 2.04, 95% CI 1.25–3.33; $P = 0.005$).

The significant variables associated with OS or LRFS in the multivariable Cox model were: radiation field (OS: HR 0.39, 95% CI 0.21–0.72, $P = 0.003$; LRFS: HR 0.33, 95% CI 0.18–0.64, $P = 0.001$), tumor length (OS: HR 1.85, 95% CI 1.16–2.97, $P = 0.010$; LRFS: HR 2.63, 95% CI 1.55–4.47, $P = 0.000$) and clinical stage (OS: HR 2.57, 95% CI 1.28–5.14; $P = 0.008$) (Table 4).

Table 2. Characteristics of per-protocol patients

Characteristics	ENI (N = 46)		CFI (N = 30)		P-value
	No.	%	No.	%	
	Age(years)				
<65	25	54.3	14	46.7	0.561
≥65	21	45.7	16	53.3	
Gender					
Male	44	95.7	28	93.3	0.656
Female	2	4.3	2	6.7	
ECOG PS					
0–1	35	76.1	24	80.0	
2	11	23.9	6	20.0	
Tumor Length (cm)					
<5	6	13.0	5	16.7	0.586
5–8	25	54.3	19	63.3	
>8	15	32.7	6	20.0	
Pathology					
Squamous carcinoma	44	95.6	30	100.0	0.512
Adenocarcinoma carcinoma	1	2.2	0		
Adenosquamous carcinoma	1	2.2	0		
Tumor differentiation					
Well	3	6.5	2	6.7	0.085
Moderately	16	34.8	18	60.0	
Poorly	14	30.4	4	13.3	
Unknown	13	28.3	6	20.0	
Location of primary tumor					
Cervical	1	2.2	4	13.3	0.181
Upper thoracic	15	32.6	8	26.7	
Middle thoracic	24	52.2	12	40.0	
Lower thoracic	6	13.0	6	20.0	
Stage grouping (AJCC 2002)					
Stage II	22	47.8	16	53.3	0.281
Stage III	11	23.9	9	30.0	
Stage IV	13	28.3	5	16.7	
Response rate					
Complete and/or partial response	35	76.1	20	66.7	0.169
Stable and/or progressive disease	11	23.9	10	33.3	

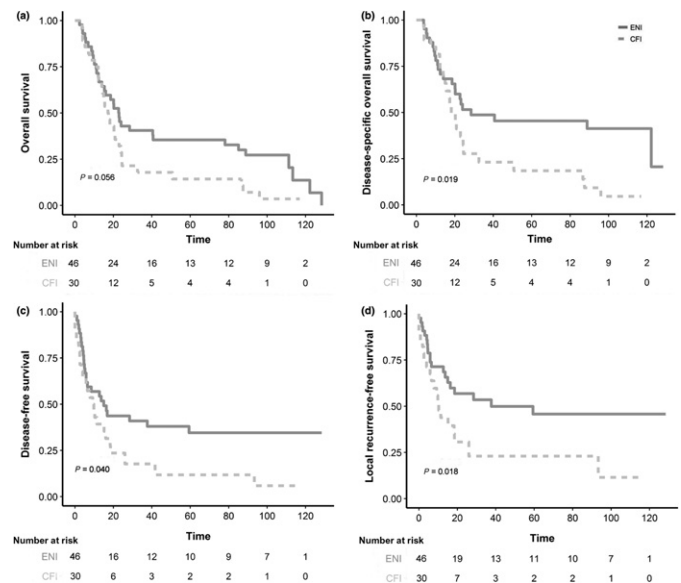


Fig. 2. Kaplan–Meier curves of overall survival (a), disease-specific overall survival (b), disease-free survival (c), and local recurrence-free survival (d) for elective nodal irradiation (ENI) versus conventional-field irradiation (CFI) (per-protocol population).

Adverse effects. For all 89 patients, no protocol-related deaths were observed during treatment. Table 5 shows the most frequently acute toxicities. In the present study, 13 (31.4%) of 51 patients in the ENI group had severe (grade ≥3) radiation esophagitis vs 5 (13.2%) of 38 patients in the CFI group ($P = 0.035$). Other severe acute toxicities were similar between the ENI group and the CFI group.

At the end of follow up, 65 patients (37 in the ENI group and 28 in the CFI group) were eligible for evaluating the late toxicities. The late toxicities were similar between the ENI group and the CFI group ($P > 0.05$). No radioactive myelitis was seen in either group. There were 4 late toxicity-related deaths, with 2 patients in each group. The ENI did not exacerbate the acute and late toxicities associated with chemotherapy in patients with esophageal cancer.

Patterns of failure and salvage treatment. For all enrolled patients, 63 patients experienced treatment failure, with local–regional recurrences only in 38 patients (60.3%), distant metastasis only in 20 patients (31.7%), and both local–regional and distant metastasis in 5 patients (8.0%). For the per-protocol population, 31 patients experienced treatment failure, which was local–regional only in 17 patients (54.8%), distant only in 10 patients (32.3%), and both local–regional and distant in 4 patients (12.9%). A total of 13 patients with loco–regional recurrence without distant metastasis received salvage therapy including surgery (2 in the ENI group and 4 in the CFI group) or radiotherapy (4 in the ENI group and 3 in the CFI group). There were no deaths related to salvage treatment.

Discussion

The CFI has been used as a standard treatment for esophageal patients with reduced incidence of radiation toxicities. However, approximately 85% of patients failed locoregionally inside the radiation fields. The local–regional failure rate was decreased in RTOG 85-01 (44.3%), which used ENI rather than the standard-dose arm in 94-05 (55%), which omitted

Table 3. Univariate analysis (OS and LRFS)

Factors	OS			LRFS		
	HR	95% CI	P	HR	95% CI	P
Radiation field (ENI versus CFI)	0.52	0.30–0.92	0.025	0.48	0.26–0.88	0.018
Age (<65 vs >65)	0.95	0.53–1.69	0.862	0.88	0.48–1.62	0.682
Gender (male versus female)	0.65	0.16–2.67	0.545	0.35	0.05–2.56	0.301
ECOG PS (0–1 vs 2)	0.76	0.38–1.54	0.450	0.82	0.38–1.78	0.624
Tumor length (cm) (<5 vs 5–8 vs >8)	1.60	1.01–2.53	0.044	2.04	1.25–3.33	0.005
Tumor differentiation (Well, moderately versus poorly)	1.06	0.51–2.20	0.884	1.25	0.60–2.60	0.552
Clinical stage (II vs III vs IV)	2.46	1.24–4.90	0.010	1.63	0.79–3.36	0.183

OS, overall survival; LRFS, local recurrence-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; ENI, elective nodal irradiation; CFI, conventional-field irradiation; HR, hazard ratio; CI, confidence interval; bold: significant *P*-values.

Table 4. Multivariate analysis (OS and LRFS)

Factors	OS			LRFS		
	HR	95% CI	P	HR	95% CI	P
Radiation field (ENI versus CFI)	0.39	0.21–0.72	0.003	0.33	0.18–0.64	0.001
Tumor length (cm) (<5 vs 5–8 vs >8)	1.85	1.16–2.97	0.010	2.63	1.55–4.47	0.000
Clinical stage (II vs III vs IV)	2.57	1.28–5.14	0.008			

OS, overall survival; LRFS, local recurrence-free survival; ENI, elective nodal irradiation; CFI, conventional-field irradiation; HR, hazard ratio; CI, confidence interval.

Table 5. Acute Toxicities

Acute toxicities	ENI group (N = 51)		CFI group (N = 38)	
	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Haematological				
Leucopenia	36 (70.6%)	10 (19.6%)	28 (73.7%)	7 (18.4%)
Neutropenia	34 (66.7%)	17 (27.5%)	24 (63.2%)	9 (29.0%)
Thrombocytopenia	11 (21.6%)	4 (7.8%)	8 (21.1%)	4 (10.5%)
Anaemia	15 (29.4%)	2 (3.9%)	11 (28.9%)	2 (5.3%)
Non-haematological				
Nausea	16 (31.4%)	3 (5.9%)	11 (28.9%)	3 (7.9%)
Vomiting	8 (15.7%)	4 (7.8%)	5 (13.2%)	2 (5.3%)
Diarrhea	5 (9.8%)	2 (3.9%)	4 (10.5%)	3 (7.9%)
Fatigue	16 (31.4%)	9 (17.6%)	12 (31.6%)	8 (21.1%)
Renal insufficiency	2 (3.9%)	0	1 (2.6%)	0
Cardiac disorders	1 (2.0%)	0	1 (2.6%)	0
Radiation esophagitis	33 (64.7%)	16 (31.4%)	25 (65.8%)	5 (13.2%)

ENI, elective nodal irradiation; CFI, conventional-field irradiation.

ENI.⁽⁸⁾ Furthermore, it has been reported that 71% of lymph nodes classified as tumor-free by routine histopathology showed lymphatic micro-metastases with immunohistochemistry.⁽¹⁶⁾ ENI is currently a standard treatment for esophageal cancer patients in Japan.

To date, there are no prospective randomized trials to compare the efficacy between ENI and CFI in esophageal cancer. However, several retrospective studies have demonstrated that ENI is effective for preventing loco-regional failure with

manageable toxicities.^(17–19) In a retrospective study, ENI improved survival compared with a normal radiation field.⁽¹⁸⁾ Yamashita *et al.*⁽¹⁹⁾ report that ENI including the gross tumor volume and elective lymph nodes significantly decreased the elective nodal failure for patients with thoracic esophageal squamous cell cancer.

To our knowledge, there has been no long-term follow-up study of patients with esophageal cancer receiving ENI in combination with concurrent chemotherapy. Our results showed that no significant differences between ENI and CFI groups were found for OS, disease-specific OS and DFS. However, the ENI group had a significantly higher LRFS than the CFI group. For the per-protocol population, the ENI group significantly improved in regards to 5-year and 10-year disease-specific OS, DFS and LRFS compared with the CFI group. These results suggest that ENI improved both disease-specific OS and local-regional control in patients with inoperable esophageal cancer receiving per-protocol treatment.

The superiority of the ENI radiation with chemotherapy cannot be attributed to underperformance in the CFI group. The median survival of 17.30 months and 5-year OS were 29.3% for the CFI group, which was similar to that observed in RTOG 85-01.⁽⁶⁾

A radiation dose of 60 Gy was administered in the present study. In our systemic review and pooled analysis, ≥60 Gy concurrent chemoradiotherapy improved the response rate, local-regional control, distant failure and OS without a significant increase in radiation-related toxicities.⁽²⁰⁾ A recent population-based propensity-score-matched analysis also showed that a high dose (≥60 Gy) may lead to better survival for non-operated localized esophageal squamous cell cancer patients undergoing concurrent chemoradiotherapy.⁽²¹⁾ It is reasonable to believe that delivering a prescribed dose of 60 Gy at 2.0 Gy/fraction is an appropriate radiation regimen in the definitive concurrent chemoradiotherapy for Chinese patients with esophageal cancer.⁽²²⁾

The acute and late toxicities were relatively high in the ENI group and presumably caused by the extended radiation field. A wider radiation field may increase the esophagitis. In our study, ENI was associated with a higher rate of ≥ grade 3 radiation-induced esophagitis compared with CFI. Other radiation-related toxicities and treatment compliance were similar between the two groups. Although the incidence was relatively high, acute toxicity was manageable with sufficient support. The ENI could be safely added to concurrent chemotherapy. Grade ≥2 late toxicities were observed in 38.5% of patients, mainly with radiation pneumonitis (21.5%) and esophageal

stenosis (24.6%), which was comparable to that reported by previous studies.^(23,24) In addition, in the present study, 5 patients developed second malignancies, 2 patients had lung cancer, 2 patients had gastric cancer and 1 patient had a laryngocarcinoma. Two patients received surgical treatment.

For loco-regional recurrence patients, salvage treatment including surgery or radiotherapy is a possible therapeutic option. It has been reported that 13%–30% of patients undergo salvage surgery after definitive CRT.^(25,26) Although the post-operative mortality remains high (10%–33%), some patients achieve long-term survival with a 5-year survival rate of 25%–35%.^(27,28) The patients with pretreatment T1–2 tumors and those with relapse after CR are eligible for salvage esophagectomy.⁽²⁹⁾ In the present study, 13 patients underwent salvage treatment and there were no deaths related to salvage treatment. The optimal timing and procedure of salvage therapy is evaluated in JCOG 0909, a phase II trial of CRT for resectable esophageal squamous cell cancer followed by salvage surgery for residual or recurrent disease. Salvage therapeutic strategy after chemoradiotherapy should be considered at the time that treatment is initiated.

References

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69–90.
- Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1893–907.
- Burmeister BH, Smithers BM, GebSKI V *et al.* Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005; **6**: 659–68.
- Bedenne L, Michel P, Bouche O *et al.* Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFD 9102. *J Clin Oncol* 2007; **25**: 1160–8.
- Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003; **349**: 2241–52.
- Cooper JS, Guo MD, Herskovic A *et al.* Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01) Radiation Therapy Oncology Group. *JAMA* 1999; **281**: 1623–7.
- Teoh AY, Chiu PW, Yeung WK, Liu SY, Wong SK, Ng EK. Long-term survival outcomes after definitive chemoradiation versus surgery in patients with resectable squamous carcinoma of the esophagus: results from a randomized controlled trial. *Ann Oncol* 2013; **24**: 165–71.
- Minsky BD, Pajak TF, Ginsberg RJ *et al.* INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002; **20**: 1167–74.
- Versteijne E, van Laarhoven HW, van Hooft JE *et al.* Definitive chemoradiation for patients with inoperable and/or unresectable esophageal cancer: locoregional recurrence pattern. *Dis Esophagus* 2015; **28**: 453–9.
- Song T, Zhang X, Fang M, Wu S. Concurrent chemoradiotherapy using paclitaxel plus cisplatin in the treatment of elderly patients with esophageal cancer. *Oncol Targets Ther* 2015; **8**: 3087–94.
- Kim DW, Blanke CD, Wu H *et al.* Phase II study of preoperative paclitaxel/cisplatin with radiotherapy in locally advanced esophageal cancer. *Int J Radiat Oncol Biol Phys* 2007; **67**: 397–404.
- Akiyama H, Tsurumaru M, Udagawa H *et al.* Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg* 1994; **220**: 364–72.
- Jiang L, Zhao X, Meng X *et al.* Involved field irradiation for the treatment of esophageal cancer: is it better than elective nodal irradiation? *Cancer Lett* 2015; **357**: 69–74.
- Du D, Song T, Liang X *et al.* Concurrent chemoradiotherapy with elective lymph node irradiation for esophageal cancer: a systemic review and pooled analysis of the literature. *Dis Esophagus* 2016; <https://doi.org/10.1111/dote.12471>.
- Hsu FM, Lee JM, Huang PM *et al.* Retrospective analysis of outcome differences in preoperative concurrent chemoradiation with or without elective nodal irradiation for esophageal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2011; **81**: e593–9.
- Hosch SB, Stoecklein NH, Pichlmeier U *et al.* Esophageal cancer: the mode of lymphatic tumor cell spread and its prognostic significance. *J Clin Oncol* 2001; **19**: 1970–5.
- Kato K, Nakajima TE, Ito Y *et al.* Phase II study of concurrent chemoradiotherapy at the dose of 50.4 Gy with elective nodal irradiation for Stage II-III esophageal carcinoma. *Jpn J Clin Oncol* 2013; **43**: 608–15.
- Onozawa M, Nihei K, Ishikura S *et al.* Elective nodal irradiation (ENI) in definitive chemoradiotherapy (CRT) for squamous cell carcinoma of the thoracic esophagus. *Radiother Oncol* 2009; **92**: 266–9.
- Yamashita H, Okuma K, Wakui R, Kobayashi-Shibata S, Ohtomo K, Nakagawa K. Details of recurrence sites after elective nodal irradiation (ENI) using 3D-conformal radiotherapy (3D-CRT) combined with chemotherapy for thoracic esophageal squamous cell carcinoma—A retrospective analysis. *Radiother Oncol* 2011; **98**: 255–60.
- Song T, Liang X, Fang M, Wu S. High-dose versus conventional-dose irradiation in cisplatin-based definitive concurrent chemoradiotherapy for esophageal cancer: a systematic review and pooled analysis. *Expert Rev Anticancer Ther* 2015; **15**: 1157–69.
- Chen CY, Li CC, Chien CR. Does higher radiation dose lead to better outcome for non-operated localized esophageal squamous cell carcinoma patients who received concurrent chemoradiotherapy? A population based propensity-score matched analysis. *Radiother Oncol* 2016; **120**: 136–9.
- Chen Y, Wu X, Bu S *et al.* Promising outcomes of definitive chemoradiation and cetuximab for patients with esophageal squamous cell carcinoma. *Cancer Sci* 2012; **103**: 1979–84.
- Morota M, Gomi K, Kozuka T *et al.* Late toxicity after definitive concurrent chemoradiotherapy for thoracic esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 2009; **75**: 122–8.
- Ishikura S, Nihei K, Ohtsu A *et al.* Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. *J Clin Oncol* 2003; **21**: 2697–702.
- Marks JL, Hofstetter W, Correa AM *et al.* Salvage esophagectomy after failed definitive chemoradiation for esophageal adenocarcinoma. *Ann Thorac Surg* 2012; **94**: 1126–32.
- Tachimori Y, Kanamori N, Uemura N, Hokamura N, Igaki H, Kato H. Salvage esophagectomy after high-dose chemoradiotherapy for esophageal squamous cell carcinoma. *J Thorac Cardiovasc Surg* 2009; **137**: 49–54.
- Swisher SG, Wynn P, Putnam JB *et al.* Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. *J Thorac Cardiovasc Surg* 2002; **123**: 175–83.
- Oki E, Morita M, Kakeji Y *et al.* Salvage esophagectomy after definitive chemoradiotherapy for esophageal cancer. *Dis Esophagus* 2007; **20**: 301–4.
- Watanabe M, Mine S, Nishida K *et al.* Salvage esophagectomy after definitive chemoradiotherapy for patients with esophageal squamous cell carcinoma: who really benefits from this high-risk surgery? *Ann Surg Oncol* 2015; **22**: 4438–44.