Concurrent liposomal paclitaxel and cisplatin chemotherapy improved outcomes for locally advanced esophageal squamous cell carcinoma treated with intensity-modulated radiotherapy

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Background: To ascertain whether concurrent chemotherapy using liposomal paclitaxel and cisplatin could improve the outcomes of patients with locally advanced esophageal squamous cell carcinoma receiving intensity-modulated radiotherapy (IMRT).

Methods: A total of 72 patients with locally advanced esophageal squamous cell carcinoma, which were admitted to our hospital from October 2011 to December 2013, were retrospectively analyzed in this study.

Results: Thirty-six patients (50%) were treated with IMRT alone, while the other 36 patients (50%) were treated by IMRT combined with chemotherapy containing liposomal paclitaxel and cisplatin. Patients treated with chemoradiotherapy showed significantly superior overall survival (OS) and progression-free survival (PFS) compared to patients treated with IMRT alone (median OS: respectively, 29.7 *vs.* 12.9 months, P=0.0287; median PFS: respectively, 14.0 *vs.* 6.5 months, P=0.0186). Multivariate Cox analysis confirmed the inclusion of chemotherapy as an independent predictor of favorable OS and PFS. Both chemoradiotherapy and IMRT were well-tolerated in our cohort.

Conclusions: Chemotherapy improved the prognosis of locally advanced esophageal squamous cell carcinoma treated with IMRT. Large prospective studies are needed to confirm the therapeutic value of IMRT combined with chemotherapy in locally advanced esophageal squamous cell carcinoma.

Keywords: Esophageal cancer (EC); esophageal squamous cell carcinoma; intensity-modulated radiotherapy; chemoradiotherapy, paclitaxel

Introduction

Esophageal cancer (EC) is one of the most common cancers worldwide. Each year, there are 480,000 new cases of EC and 400,000 patients who die of this disease (1). Surgical resection remains the main method of curing the disease; however,

over two-thirds of patients with EC cannot receive surgical resection because of the presence of advanced disease or remote metastasis (2). Definite chemoradiotherapy (CRT) is an alternative treatment for patients who are not candidates for surgical resection. In the Radiation Therapy Oncology

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Group (RTOG) 85-01 trial, the 5-year survival rate was 26% in patients who received combined CRT compared with 0% in patients receiving radiotherapy alone (3).

Recently, new radiotherapy modality or novel regimens of chemotherapy have been investigated to improve local control and long-term survival (4-6). Intensity-modulated radiotherapy (IMRT), which has been employed in the clinic in recent years, uses computer-controlled linear accelerators to deliver precise radiation doses to the planning target volume (PTV) (6,7). Therefore, IMRT can increase the radiation dose to the tumor to improve the local control rate while sparing normal tissues, which provides advantages over conventional radiotherapy (8). Although IMRT combined concurrent paclitaxel plus cisplatin to treat EC has been previously reported on by Tu *et al.*, it was a single-arm study (9). To the best of our knowledge, there has been no study comparing IMRT alone versus IMRT with concurrent paclitaxel plus cisplatin in treating locally advanced ESCC. From October 2011 to December 2013, 72 patients with locally advanced esophageal squamous cell carcinoma (ESCC) received IMRT or IMRT combined with chemotherapy in our institute. In this study, we aimed to determine whether chemotherapy consisting of liposomal paclitaxel and cisplatin improved the prognosis of locally advanced ESCC receiving intensity-modulated radiotherapy. Safety profiles were also compared between these two types of treatments.

Methods

Patients

Patients were included in this study if they had locally advanced ESCC. All of the patients had an upper endoscopic examination with tumor biopsy, barium esophagography, and chest and abdominal computed tomography (CT) scans to determine their clinical stages. Patients were staged based on the 6th edition of the American Joint Committee on Cancer (AJCC) staging system. Patients were excluded from this study if they had esophageal perforation or prior surgery. From October 2011 to December 2013, 72 patients with newly-diagnosed ESCC were retrospectively included in this study. The median age was 69 (range: 50–84), and 51 patients were male (70.8%). All the patients had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1. In the 72 patients, 36 patients received IMRT combined with chemotherapy, while 36 patients received IMRT alone.

Treatments

IMRT

All patients received IMRT (*Figure 1*) (10). Generally, the gross target volume (GTV) consisted of the primary tumor and involved lymph nodes that were determined by contrast-enhanced CT. A margin of 0.5–0.8 cm was added in axial and 3 cm in a longitudinal direction to the primary tumor to define the clinical target volume (CTV). All the lymphatic drainage regions were radiated prophylactically according to the site of the primary tumor. Based on the CTV, a 0.3 cm margin was added in all directions to construct the PTV. The prescription dose to cover at least 95% of the PTV was 50 Gy. The dose for the primary tumor and involved lymph nodes was increased to 60–66 Gy. The radiation was delivered at 2.0 Gy per fraction and 5 fractions per week. The V20 for the lungs and the V30 for the heart was within 28% and 30%, respectively. The maximum tolerated dose for the spinal cord was 45 Gy.

Chemotherapy

For patients who received chemotherapy (1), the regimen was administered as follows (*Figure 1*): liposomal paclitaxel (35 mg/m^2, d1) plus cisplatin (25 mg/m^2, d2–d4) administered weekly, for 6 weeks.

Evaluation of response and follow-up

At one month after the completion of therapy, the response to IMRT or IMRT combined with chemotherapy was assessed using Response Evaluation Criteria in Solid Tumors (RECIST 1. 1) (11). Chemotherapy-associated adverse events were evaluated according to National Cancer Institute Common Toxicity Criteria Version 3.0 (12). Toxicities caused by radiation including radiation esophagitis and radiation pneumonitis were evaluated according to the toxicity criteria of RTOG and the European Organization for Research and Treatment of Cancer (EORTC) grading (13). Regular follow-up was carried out at least once three months to within 2 years after the completion of therapy and every 6 months thereafter. Routine follow-up included at least physical examination, endoscopy, or barium esophagography and contrast-enhanced CT.

Statistics

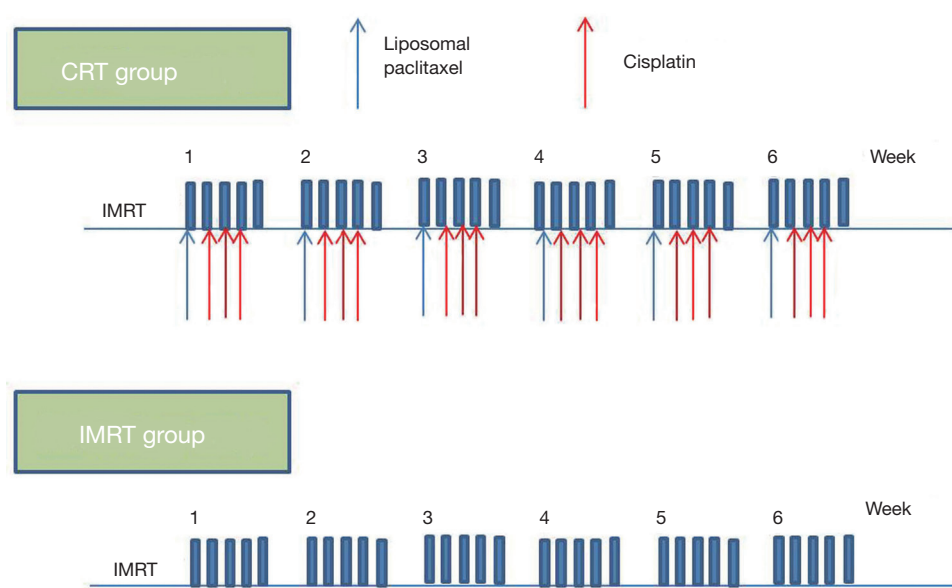The Student's t-test or Mann-Whitney U test was used

Figure 1 Treatment protocols in two arms.

to compare continuous variables between two groups. D'Agostino-Pearson omnibus normality test was used to examine if the values came from Gaussian distribution. Student's t-test was used if the values passed normality test, or we used Mann–Whitney U-test. Categorical variables were compared by means of Fisher's exact test. Overall survival (OS) was defined as the time from the initiation of therapy until death or last follow-up. Progression-free survival (PFS) was calculated from the time of therapy initiation to the time of local failure, metastasis, or last follow-up. Survival curves were plotted by Kaplan-Meier method, and the log-rank test was utilized for comparison, and variables consisting of gender, age, size of the tumor (T), lymph node involvement, and treatment were included in this analysis. Multivariate analysis was done by multivariate Cox model. All statistical analyses were performed using GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA), SPSS (version 19.0) software (IBM Corporation, Armonk, NY, USA). Statistical significance was defined as a P value less than 0.05.

Results

Baseline characteristics of the two arms are summarized in *Table 1*. The patients treated by IMRT plus chemotherapy were significantly younger than those treated by IMRT alone (median: 63 *vs.* 76.5, P=0.0002). There were no

significant differences in other clinical characteristics between the two groups. However, there was a trend that the IMRT group was enriched for clinical N0 disease (P=0.0850).

Response

The response rates are summarized in *Table 2*. The overall response rate (ORR) for all the patients (n=72) was 73.6%. Thirty-six patients had a complete response (CR), and 17 patients had a partial response (PR). Thirty-one patients in the CRT group achieved CR or PR, while 22 patients in the IMRT alone group had a CR or PR. The ORR in the CRT group was significantly higher than that in the IMRT group (P=0.0309).

Follow-up

The last follow-up day was December 31st, 2015, and the median follow-up was 19.6 months [inter-quartile range (IQR), 8.3–31.8]. Of the 72 patients, 26 patients were still alive (17 of 36 patients in the IMRT plus chemotherapy group and 9 of 36 patients in the IMRT group). Median OS for patients was 29.7 months in the IMRT plus chemotherapy group and 12.9 months in the IMRT alone group [P=0.0287, hazards ratio (HR) 0.52 (95% CI, 0.29–0.93), *Figure 2A*]. OS was 83.3% [95% confidence interval

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Table 1 Baseline clinical characteristics of patients in this cohort

Characteristics	CRT (n=36)	IMRT (n=36)	P value
Age (median, IQR)	63 (55.50–71.00)	76.5 (64.5–80.50)	0.0002
Sex, n (%)			1.0000
Male	27 (84.4)	24 (75.0)	
Female	9 (15.6)	8 (25.0)	
Tumor length (median, IQR)	5.5 (3.3–7.0)	5.0 (3.3–6.0)	0.26
Tumor location, n (%)			0.3099
Proximal third esophagus	12 (33.3)	7 (19.4)	
Middle third esophagus	18 (50.0)	19 (52.8)	
Distal third esophagus	6 (16.7)	10 (27.8)	
Clinical tumor (cT) stage, n (%)			0.8857
cT2	3 (8.3)	3 (8.3)	
cT3	15 (41.7)	17 (47.2)	
cT4	18 (50.0)	16 (44.4)	
Clinical node (cN) stage, n (%)			0.0850
cN0	19 (52.8)	27 (75.0)	
cN1	17 (47.2)	9 (25.0)	
TNM stage, n (%)			0.3366
II	12 (33.3)	17 (47.2)	
III	24 (66.7)	19 (52.8)	
Hb, n (%)			0.6142
≥10 g/dL	35 (97.2)	33 (91.7)	
<10 g/dL	1 (2.8)	3 (8.3)	
Neutrophils count, n (%)			1.0000
$\geq 2\times 10^{9}$/L	35 (97.2)	36 (100.0)	
$<2\times 10^{9}$/L	1 (2.8)	0 (0)	
PLT count, n (%)			1.0000
$\geq 100\times 10^{9}$/L	33 (91.7)	34 (94.4)	
$<100\times 10^{9}$/L	3 (8.3)	2 (5.6)	
ALT, n (%)			0.2394
≤50 U/L	36 (100.0)	33 (91.7)	
>50 U/L	0 (0.0)	3 (8.3)	
AST, n (%)			1.0000
≤40 U/L	35 (97.2)	35 (97.2)	
>40 U/L	1 (2.8)	1 (2.8)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	CRT (n=36)	IMRT (n=36)	P value
Bilirubin, n (%)			0.4290
≤19.0 µmol/L	34 (94.4)	31 (86.1)	
>19.0 µmol/L	2 (5.6)	5 (13.9)	
Creatinine, n (%)			1.0000
≤133.0 µmol/L	33 (100.0)	32 (97.0)	
>133.0 µmol/L	0 (0)	1 (3.0)	
Albumin, n (%)			0.4637
≥40 g/L	23 (63.9)	19 (52.8)	
<40 g/L	13 (36.1)	17 (47.2)	
Presence of comorbidities, n (%)			0.2355
Yes	13 (36.1)	19 (52.8)	
No	23 (63.9)	17 (47.2)	

CRT, chemoradiotherapy; Hb, hemoglobin; IMRT, intensity modulated radiotherapy; IQR, interquartile range; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate transaminase.

Table 2 Response rates in our cohort

Treatments	CR, n (%)	PR, n (%)	PD, n (%)	SD, n (%)
CRT	21 (58.3)	10 (27.8)	2 (5.6)	3 (8.3)
IMRT	15 (41.7)	7 (19.4)	8 (22.2)	6 (16.7)

CR, complete response; PR, partial response; PD, progression of disease; SD, stable disease; CRT, chemoradiotherapy; IMRT, intensity modulated radiotherapy.

(CI), 82.9–95.4%] at 1 year, 54.8% (95% CI, 54.3–71.2%) at 2 years, and 47.2% (95% CI, 46.7–64.4%) at 3 years in the IMRT plus chemotherapy group, compared with 50.0% (95% CI, 49.5–66.3%), 38.9% (95% CI, 38.4–54.8%), and 28.9% (95% CI, 28.4–44.4%) respectively, in the IMRT alone group. Median PFS was 14.0 months in the IMRT plus chemotherapy group and 6.5 months in the IMRT alone group [P=0.0186, HR 0.50 (95% CI, 0.28–0.89), *Figure 2B*]. PFS in the in the IMRT plus chemotherapy group was 55.6% (95% CI, 55.1–71.9%) at 1 year, 41.7% (95% CI, 41.2–57.8%) at 2 years, and 41.7% (95% CI, 41.2–57.8%) at 3 years, compared with 36.1% (95% CI, 35.6–51.8%), 27.8% (95% CI, 27.3–42.5%), and 18.0% (95% CI, 17.6–31.1%) respectively, in the IMRT alone group [HR 0.53 (95% CI, 0.28–0.87)]. Analysis of disease-specific survival (DSS) showed that patients in the IMRT plus chemotherapy group had a significantly higher DSS compared with patients in the IMRT group [median DSS:

41 *vs.* 15.2 months, P=0.0396, HR 0.52 (95% CI, 0.27–0.96)] (*Figure 3*).

Univariate analysis and multivariate Cox analysis of OS and PFS

Gender, age, clinical tumor stage (cT2/cT3 *vs.* cT4), clinical node stage (cN0 *vs.* cN1), and inclusion of chemotherapy were included in the univariate analysis. Only being female [P=0.036, HR 0.456 (95% CI, 0.219–0.949), *Table 3*] and inclusion of chemotherapy [P=0.032, HR 0.525 (95% CI, 0.291–0.946)] predicted better OS in our study. There was a trend that clinical lymph node involvement predicted worse survival [P=0.062, HR 1.777 (95% CI, 0.972–3.247)]. Multivariate Cox analysis revealed that being female and use of chemotherapy independently predicted a better OS [HR 0.439 (95% CI, 0.211–0.913), P=0.028; HR 0.505 (95%CI 0.280–0.913), P=0.024]. Regarding PFS, being female
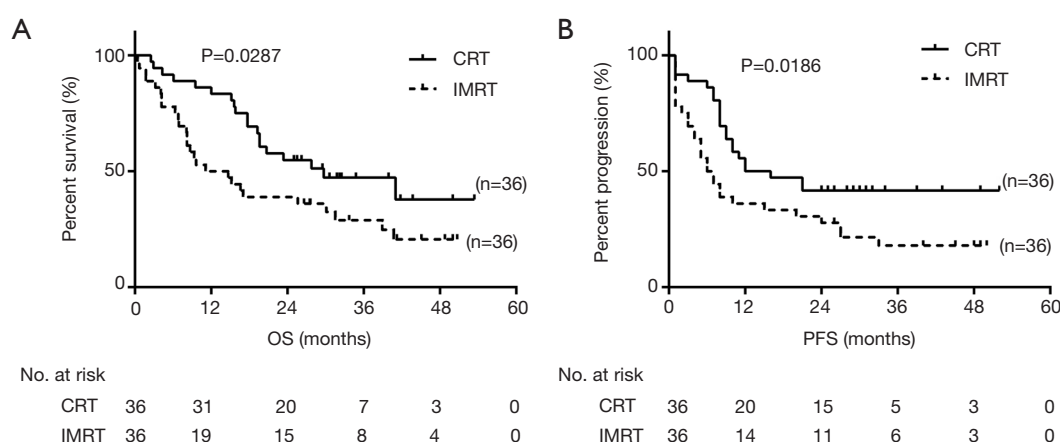
Figure 2 Kaplan-Meier estimates of overall survival (OS) (A) and progression-free survival (PFS) (B) by intensity-modulated radiotherapy (IMRT) alone and IMRT plus chemotherapy.
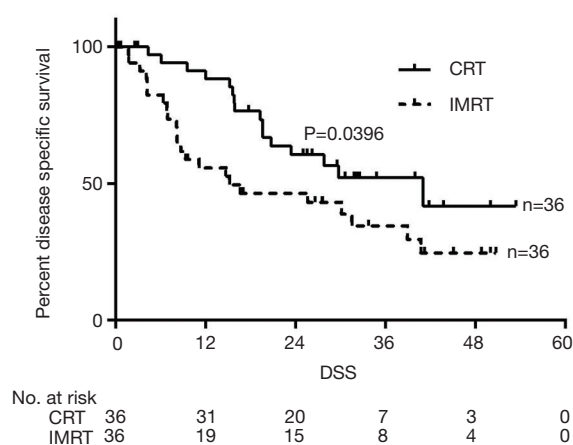

Figure 3 Kaplan-Meier estimates of disease-specific survival (DSS) by intensity-modulated radiotherapy (IMRT) alone and IMRT plus chemotherapy.

[P=0.035, HR 0.471 (95% CI, 0.234–0.948)] and inclusion of chemotherapy [P=0.025, HR 0.525 (95% CI, 0.298–0.923)] predicted better PFS. In multivariate Cox analysis, being female [P=0.036, HR 0.475 (95% CI, 0.236–0.954)] and use of chemotherapy [P=0.027, HR 0.528 (95% CI, 0.300–0.929)] were independently associated with superior PFS.

Subgroup analysis

We explored the clinical impact of the addition of chemotherapy in patients with stage II and stage III diseases. In patients with stage III disease, we found that

patients treated with CRT had a significantly superior OS (20.7 vs. 8.2 months, respectively, P=0.0017, *Figure 4A*) and PFS (10.5 vs. 4 months, respectively, P=0.0008, *Figure 4B*) as compared to patients receiving IMRT alone. However, in patients with stage II disease, CRT did not show a significant advantage over IMRT, in terms of OS (40.9 vs. 30.1 months, respectively, P=0.7539, *Figure 4C*) and PFS (35 vs. 20 months, respectively, P=0.3969, *Figure 4D*).

Safety

Adverse events for each arm are summarized in *Table 4*. The most common nonhematologic toxicities included grade 1 to 2 nausea, radiation esophagitis, and radiation pneumonitis. The incidence of grade 1 to 2 nausea was significantly higher in the IMRT plus chemotherapy group than in the IMRT alone group. The incidence of radiation esophagitis or radiation pneumonitis was similar between the two groups. Among hematologic toxicities, grade 3 to 4 neutropenia and thrombocytopenia were experienced by 11 patients and 3 patients, respectively. Grade 3 to 4 neutropenia and thrombocytopenia were more common in the IMRT plus chemotherapy group (P=0.0002, P=0.0425, *Table 4*). Also, grade 3 to 4 vomiting was more common in the IMRT plus chemotherapy group (P=0.0324, *Table 4*).

Discussion

In the present study, we discovered that IMRT combined with chemotherapy significantly improved both the OS and PFS of patients with locally advanced ESSC as compared

Table 3 Univariate and multivariate Cox regression analysis of OS and PFS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
OS				
Sex (female)	0.456 (0.219–0.949)	0.036	0.439 (0.211–0.913)	0.028
Age (>60 years)	1.179 (0.660–2.106)	0.579	–	–
cT4	1.131 (0.634–2.019)	0.677	–	–
cN1	1.777 (0.972–3.247)	0.062	–	–
Chemoradiotherapy	0.525 (0.291–0.946)	0.032	0.505 (0.280–0.913)	0.024
PFS				
Sex (female)	0.471 (0.234–0.948)	0.035	0.475 (0.236–0.954)	0.036
Age (>60 years)	1.160 (0.666–2.022)	0.599	–	–
cT4	1.203 (0.690–2.099)	0.514	–	–
cN1	1.673 (0.945–2.961)	0.078	–	–
Chemoradiotherapy	0.525 (0.298–0.923)	0.025	0.528 (0.300–0.929)	0.027

OS, overall survival; PFS, progression-free survival; HR, hazards ratio; 95% CI, 95% confidence interval.
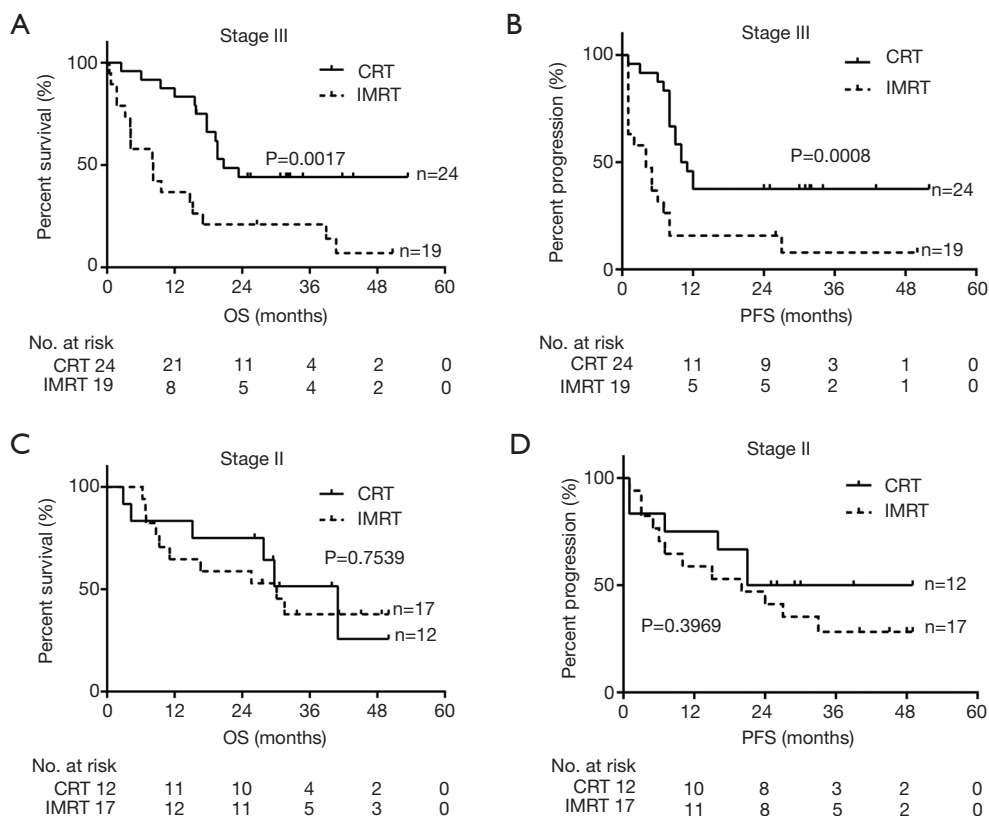

Figure 4 Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) by intensity-modulated radiotherapy (IMRT) alone and IMRT plus chemotherapy in patients with stage III disease (A,B) and stage II diseases (C,D), respectively.

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Table 4 Adverse events in the 72 patients during treatment

Adverse events	CRT (n=36)	IMRT (n=36)	P
Leukopenia, n (%)			0.0002
Level 1–2	21 (58.3)	20 (55.6)	
Level 3	10 (27.8)	1 (2.8)	
Level 4	0 (0)	0 (0)	
Thromcytopenia, n (%)			0.0425
Level 1–2	19 (52.8)	13 (36.1)	
Level 3	3 (8.3)	0 (0)	
Level 4	0 (0)	0 (0)	
Vomiting, n (%)			0.0324
Level 1–2	24 (66.7)	18 (50.0)	
Level 3	3 (8.3)	0 (0)	
Level 4	0 (0)	0 (0)	
Radiation esophagitis, n (%)			0.5605
Level 1–2	23 (63.9)	20 (55.6)	
Level 3	2 (5.6)	1 (2.8)	
Level 4	0 (0)	0 (0)	
Radiation pneumonitis, n (%)			0.5082
Level 1–2	14 (38.9)	12 (33.3)	
Level 3	1 (2.8)	0 (0)	
Level 4	0 (0)	0 (0)	

CRT, chemoradiotherapy; IMRT, intensity modulated radiotherapy.

to IMRT alone. Multivariate Cox analysis confirmed that the inclusion of chemotherapy as an independent factor is predictive of a favorable prognosis.

For patients with unresectable tumors or contraindications to surgery, radiation constitutes the backbone of treatment, which is of curative potential. With the advent of specialized CT scanners and planning software, IMRT has the ability to delineate tumors and organs accurately, thus allowing for optimal dose delivery to the tumor target volume and adjacent normal tissues (14). Furthermore, the development of effective drugs with fewer toxicities have made it possible to improve the outcome of patients with EC using concurrent CRT. Paclitaxel is a drug isolated from the bark of Taxus brevifolia, which interferes with the breakdown of microtubules during cell division (15). Preclinical and clinical data from studies in other cancers showed significant additive or synergistic activity for paclitaxel/cisplatin combination

chemotherapy (16). Infusional paclitaxel has shown promising efficacy in the treatment of advanced esophageal squamous cell cancer (17). Weekly chemotherapy with paclitaxel and cisplatin and concurrent radiotherapy has been used as preoperative treatment in locally advanced EC, achieving a 3-year survival rate of 35% (18).

For patients with local but unresectable EC, CRT remains the only treatment of potentially curative intent. In the prospective randomized clinical trial, RTOG 85-01, combined chemotherapy, significantly prolonged OS compared with radiation alone (3). This study established the role of CRT in patients with localized advanced EC who opt for non-surgical treatment (3). In the JCOG 0604 study, CRT with concurrent S-1 and cisplatin showed acceptable toxicity and favorable 3-year survival (61.9%), which further affirmed the role of concurrent CRT in the treatment of localized advanced EC (19).

However, until now, there has been no standard

regimen for CRT of EC. The meta-analysis by Pöttgen *et al.* reported a 2-year OS rate between 35% and 58% of patients treated by definite CRT (20). The 2-year OS rate of IMRT plus chemotherapy group in our study was within this range. In our study, the chemotherapy regimen was composed of liposomal paclitaxel and cisplatin. The 3-year OS rate of IMRT plus chemotherapy group was higher than that of the study by Shim *et al.* (21), which used weekly docetaxel and cisplatin as chemotherapy. Although the chemotherapy regimen was similar to that of the IMRT plus chemotherapy group in our study, the patients in the study by Shim *et al.* were all in stage III and IV. The advanced stage in their study accounted for the inferior 3-year OS of patients treated by concurrent CRT. In the study by Hsieh *et al.*, 39 patients received IMRT plus chemotherapy, which consisted of intravenous cisplatin (20 mg/m^2) for 1 hour and continuous intravenous infusion of fluorouracil (5-FU; 800 mg/m^2) for 24 hours from day 1 to day 4 on week 1 and week 5 during radiotherapy (8). The 3-year OS was 28%, which was much lower than that of the patients treated by CRT in our study. Different regimens and intensities of chemotherapy in the two studies might have contributed to this difference; furthermore, the percentage of patients with clinical lymph node involvement (30/39, 76.9%) was much higher than that in our study.

Our study demonstrated that IMRT plus chemotherapy improved the outcome of patients with localized EC, compared with IMRT alone. Although the superiority of chemoradiotherapy to radiotherapy has already been proven in EC, the current study confirms this conclusion in the setting of IMRT. Despite the fact that there was a selection bias that younger patients were treated by concurrent CRT more frequently, survival analysis revealed that age was not a prognostic factor in our study. Multivariate Cox analysis demonstrated that inclusion of chemotherapy was an independent prognostic factor in predicting OS and PFS. In subgroup analysis, we found that IMRT plus chemotherapy significantly improved the outcome of patients with stage III disease, and this benefit was not observed in patients with stage II disease. This difference might be due to the fact that patients with stage II disease had a relatively favorable outcome (median OS: 30.1 month) with IMRT treatment; as a result, there was limited room for improvement in this subgroup of patients. In our cohort, being female independently predicted better OS and PFS; this might be due to the fact that females had a higher frequency of stage II disease compared with males

(57.1% *vs.* 33.3%, respectively, P=0.0708), although without statistical significance.

The toxicities were acceptable in patients treated with concurrent CRT. Only 27.8% (10/36) of patients experienced grade 3 hematologic toxicities, and no grade 4 hematologic toxicities were observed. In another Chinese study using concurrent CRT contained paclitaxel plus cisplatin, 12.2% patients experienced grade 4 leukopenia; however, the patients in that study were much older than the patients in our study (22). Only 2 patients and 1 patient in the IMRT plus chemotherapy experienced grade 3 esophagitis and radiation pneumonitis, respectively. All these findings suggest that this combination was well-tolerated in our cohort.

The current study has several limitations. This is a retrospective study, so we were unable to balance the baseline clinical characteristics between the two arms. The patients in the IMRT plus chemotherapy group were much younger than those in the IMRT alone group, which made the direct comparison of the prognosis between the two groups questionable. Moreover, this is a single-center study with a relatively small size, so there exists bias impacting the conclusion due to the small sampling, especially in the subgroup analysis. Overall, it remains to be determined whether chemoradiotherapy using liposomal paclitaxel and cisplatin is superior to chemoradiotherapy using the standard chemotherapy regimen.

In summary, our study indicated that chemotherapy significantly improved the outcome of patients treated with IMRT. Large prospective studies are warranted to validate this conclusion in the future.

Acknowledgments

Footnote

Conflicts of Interest: The authors declare no conflicts of interest.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This is a retrospective study, and the study was approved by the ethics committee of the First Affiliated Hospital of Nanjing

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