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FULL PAPER

Phase II study of concurrent selective lymph node late course accelerated hyper-fractionated radiotherapy and pemetrexed and cisplatin for locally advanced oesophageal squamous cell carcinoma

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Objective: To determine the clinical efficacy and toxicity of pemetrexed combined with low-dose cisplatin (CDDP) concurrent with late-course accelerated hyperfractionated (LCAF) intensity-modulated radiation therapy (IMRT) in patients with inoperable locally advanced oesophageal squamous cell carcinoma (ESCC).

Methods: Patients with locally advanced ESCC (less than or equal to 75 years of age, clinical stages IIB–IVA and Karnofsky performance status ≥ 70) were enrolled into the study. A target group size of 22 was projected based on the estimation that 2-year overall survival (OS) would increase from 20% to 40%. Patients were treated with pemetrexed, low-dose CDDP and LCAF IMRT concurrently. The main objective of the study was for a 2-year OS, and the secondary objectives were progression-free survival (PFS), objective response, locoregional failure rate, and acute and late toxicities.

Results: 25 patients were recruited from October 2008 to July 2011. The median OS was 21 months, with 2- and 5-year OS rates of 44% and 44%, respectively. The median PFS was 18.2 months. The objective response rate was 96% (24/25), with 11 complete responses and 13 partial responses. The locoregional failure rate was 16%. Grades 4 and 5 acute toxicity rates were 8% and 4%, respectively, while no Grade 3 or greater late toxicity was observed.

Conclusion: The findings of this Phase II study indicated that the therapeutic regimen appears to achieve an excellent response rate and favourable survival for locally advanced ESCC. However, the severe acute side effects should be considered cautiously in further studies.

Advances in knowledge: To our knowledge, this is the first study that introduced pemetrexed and low-dose CDDP combined with LCAF IMRT to treat locally advanced ESCC. The 5-year OS rate was as high as 44%, which was more favourable than other studies.

Oesophageal carcinoma (EC) is one of the common malignant tumours all over the world, with China having a high incidence, for about 150,000 people die of it each year, accounting for nearly a quarter of all cancer deaths worldwide.¹ According to a series of studies implemented by the Radiation Therapy Oncology Group (RTOG), such as the RTOG 8501² and RTOG 9405,³ concurrent chemoradiotherapy (CCRT) was established as a standard approach for locally advanced EC; however, the prognosis was still poor with a median overall survival (OS) of 14.1 and 18.1 months, respectively. In order to improve the prognosis, late-course accelerated hyperfractionated (LCAF) radiotherapy (RT) was scheduled on oesophageal squamous cell carcinoma (ESCC) by Shi et al⁴ in 1999. The results of LCAF RT were encouraging, with the 5-year survival rate

varying from 26% to 33%.^{4–6} Furthermore, patients with ESCC who were treated with concurrent LCAF RT and chemotherapy had a 5-year survival rate of 40% and a median survival time of 30.8 months in the study by Zhao et al.⁷ Therefore, this study indicated better survival in patients who received concurrent LCAF RT and chemotherapy than in those receiving LCAF RT alone. However, Grades 3–4 and Grade 5 toxicity rates were 46% and 6%, respectively, which were more severe than that in LCAF RT alone and might be mostly owing to chemotherapy.

In order to reduce the adverse effects and improve the outcome, new chemotherapy regimens combined with LCAF RT should be investigated. Pemetrexed, a novel antitumour drug, acting as a multitargeted antifolate by

inhibiting several key enzymes involved in nucleotide synthesis, has demonstrated broad antitumour activity in a wide variety of solid tumours.⁸ The interaction of pemetrexed and ionizing radiation has been investigated *in vitro* using different human tumour cell lines. It enhanced radiation-induced cell inactivation at moderately toxic exposures over several hours after drug removal.⁹ Myelosuppression and mucositis, the most significant toxicities induced by pemetrexed, have been significantly ameliorated by folic acid and vitamin B12 supplementation without compromising its antitumour effect. More importantly, vitamin supplementation has not demonstrated any adverse effects.⁸ Jatoi et al¹⁰ reported a clinical trial with concurrent pemetrexed, carboplatin and radiation followed by surgery to treat locally advanced EC and gastro-oesophageal-junction tumours. The pathological complete response (pCR) rate was 23%, higher than that in other studies.^{11,12}

A Phase I clinical trial¹³ that combined pemetrexed and cisplatin (CDDP) with concurrent selective lymph node (SLN) LCAF RT was conducted in our institution (Shandong Cancer Hospital, Jinan, China). Although toxicities were common, the protocol was safe and well tolerated and achieved an encouraging outcome. To further determine the efficacy and side effects, the Phase II study was then performed in patients with locally advanced ESCC.

METHODS AND MATERIALS

Eligibility criteria

Patients with histologically confirmed ESCC without previous treatment, clinical stage ranging from IIB to IVA, indications for chemoradiotherapy, and who were inoperable or refused surgery were enrolled in this study. They all had bidimensionally measurable disease, lumen size >5 mm diameter, Karnofsky performance status ≥ 70 and a life expectancy of 3 months or longer. The criteria for laboratory examination were as follows: haemoglobin ≥ 10 g dl⁻¹; absolute white blood cell count ≥ 4000 ml⁻¹; platelet count $\geq 100,000$ ml⁻¹; total bilirubin level ≤ 1.5 mg dl⁻¹; serum creatinine level ≤ 1.5 times the upper limit of normal; and aspartate/alanine aminotransferase levels ≤ 2.5 times the upper limit of normal.¹⁴

Exclusion criteria

Exclusion criteria were patients with distant metastases except for M1a, oesophageal perforation that reflected on radiographic imaging or oesophagoscope, and some other serious underlying medical conditions, such as significant cardiac disease, uncontrolled diabetes, serious infections, central nervous system disorders or psychological disability that cannot withstand the treatment protocol. Patients who participated in other clinical trials were also excluded.

Pre-treatment evaluation

Physical examination and a history inquiry were performed before treatment. Pre-treatment staging examination included barium oesophagogram, oesophagoscope, bone scan with single photon emission CT, CT scan of the brain, neck, chest and abdomen, and complete blood count with differential, serum chemistry tests, liver function tests, coagulation panel, urinalysis and electrocardiogram. Bronchoscopy was also performed if

clinically necessary. Patients were staged according to the American Joint Committee on Cancer TNM Classification of Carcinoma of the Oesophagus and Oesophagogastric Junction (6th ed, 2002). All patients signed the informed consent form.

Chemotherapy

Chemotherapy began on Day 1, concurrent with the beginning of RT. Based on our Phase I study, patients were treated with 400 mg m⁻² pemetrexed, which was administered intravenously over 10 min on Days 1 and 22, and 10 mg m⁻² CDDP was given intravenously on Days 1–5 and 22–26. All patients received folic acid, vitamin B12 and steroid prophylaxis treatment.

Radiotherapy

RT was performed using a Varian® linear accelerator (Varian Medical Systems, Palo Alto, CA). All patients were immobilized in the supine position with the arms above the head in a vacuum-bag restriction system (Vac-Lock™; CIVCO Medical Solutions, Kalona, IA) and, then, consecutively underwent enhanced CT scanning under normal respiration with 5 mm slice thickness scans throughout the entire neck and thorax. All the CT images acquired were transferred to and registered in the treatment planning system. The targets and organs at risk were delineated according to the following criteria. The gross target volume (GTV) included primary tumour and metastatic lymph nodes. The SLN areas were defined as groups 104–107 and part of 108 in the upper thoracic oesophageal cancer; groups 104, 106–108, part of 110, 1 and 2 in the middle thoracic oesophageal cancer; and groups 104, part of 106 and 108, 1–3, 7 and 9 in the lower thoracic oesophageal cancer. The lymph node groups were named according to Japanese guidelines.¹⁵ For primary tumour, a 3 cm margin was added superiorly and inferiorly and 1 cm laterally to create a planning target volume (PTV), and for involved lymph nodes, a 1 cm margin was added around the entire lymph node. The fields of the first phase RT involved the above GTV, selective high-risk lymph node areas and PTV, which received 40 Gy in total, 2 Gy per fraction and five fractions a week. In the second phase, accelerated hyperfractionated radiation was employed with a total dose of 19.6 Gy, 1.4 Gy per fraction, twice a day with a minimum interval of 6 h, ten fractions a week. The selective high-risk lymph node areas were spared. The total dose of the 2-phase irradiation was 59.6 Gy per 34 fractions in 5.4 weeks. All plans aimed to achieve a minimum dose >95% and a maximum dose <107% of the prescribed dose, and that no 2 cc region (either within or more of the PTV) may receive >110% of the dose. The dose with inhomogeneity correction was prescribed to the 95% isodose line, which encompassed 95% PTVs. The dose–volume histogram constraints of the organs at risk were as follows: bilateral lung V20 $\leq 30\%$, spinal D_{max} ≤ 50 Gy, heart V50 $\leq 33\%$ and V45 $\leq 67\%$, hepatic V35 $\leq 50\%$, gastric D_{max} ≤ 50 Gy and intestinal D_{max} ≤ 50 Gy. No modifications in fraction size or total dose were permitted during the whole process.

Adverse effect assessment

During the intensity-modulated radiation therapy (IMRT) and chemotherapy period, assessment of the acute adverse effects was performed weekly using the National Cancer Institute

Table 1. Clinical features of 25 patients with oesophageal squamous cell carcinoma

Characteristic	n (%)
Sex	
Male	23 (92)
Female	2 (8)
Age (years)	
Median	62
Range	40–75
Subsection	
Cervical	3 (12)
Upper thoracic	9 (36)
Middle thoracic	11 (44)
Lower thoracic	2 (8)
Stage	
IIB	7 (28)
III	11 (44)
IVA	7 (28)
Karnofsky performance status	
Median	90
Range	80–100

Common Toxicity Criteria v. 3.0.¹⁶ 3 months after the treatment, late RT effects were recorded according to the RTOG/EORTC late radiation morbidity scoring schema.¹⁷ Side effects were managed aggressively using standard supportive measurements; granulocyte colony stimulating factor and interleukin-11 were provided if medically necessary. Treatment interruption was allowed for patients with \geq Grade 3 toxicity lasting more than 7 days.

Table 2. Acute toxicity

Toxicity	Grade 0, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Skin reaction	1 (4)	24 (96)	0 (0)	0 (0)	0 (0)	0 (0)
Oesophagitis	2 (8)	17 (68)	5 (20)	1 (4)	0 (0)	0 (0)
Oesophageal stricture	22 (88)	3 (12)	0 (0)	0 (0)	0 (0)	0 (0)
Fistula	24 (96)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
Nausea	10 (40)	9 (36)	6 (24)	0 (0)	0 (0)	0 (0)
Vomiting	17 (68)	3 (12)	4 (16)	1 (4)	0 (0)	0 (0)
Pneumonia	15 (60)	9 (36)	1 (4)	0 (0)	0 (0)	0 (0)
Leukopenia	1 (4)	3 (12)	8 (32)	12 (48)	1 (4)	0 (0)
Anaemia	11 (44)	10 (40)	0 (0)	4 (16)	0 (0)	0 (0)
Thrombocytopenia	8 (32)	6 (24)	6 (24)	3 (12)	2 (8)	0 (0)
Maximum severity per patient	0 (0)	3 (12)	6 (24)	13 (52)	2 (8)	1 (4)

Follow-up

After treatment, patients were followed up every 2 months for the first year, every 4 months for the second year and every 6 months thereafter. Each visit included medical history, physical examination, complete blood count, chest X-ray, oesophageal barium radiography, and chest and abdomen CT. Biopsy of the primary tumour site was required when locoregional recurrence was suspected.

Study design and end points

A single centre open-label Phase II study was designed to further evaluate the effectiveness and safety of the recommended dose of pemetrexed and low-dose CDDP when given concurrently with SLN LCAF IMRT to the patients with locally advanced ESCC. This study was approved by the ethical committees of our hospital and registered with the Chinese Clinical Trial Registry (<http://www.chictr.org/cn/>); the registration number was ChiCTR-TRC-09000568.

6–8 weeks after completion of CCRT, the treatment response was evaluated using CT and barium oesophagogram. In accordance with the solid tumour's effect evaluation criterion of the World Health Organization, all responses were defined as follows: complete response (CR), complete disappearance of all tumours; partial response (PR), 50% decrease in the sum of products of the largest perpendicular diameters of all measurable lesions; stable disease (SD), failure to observe remission; and progressive disease, the appearance of new lesions or $>25\%$ increase in size of existing lesions.

The primary end point of this Phase II study was a 2-year OS. Secondary end points included progression-free survival (PFS), objective response, locoregional failure rate, and acute and late toxicities rates. OS was observed from the first day of treatment until death or last follow-up time, and PFS was observed from the first day of treatment until progress, death or last follow-up time.

Table 3. Late radiotherapy toxicity

Toxicity	Grade 0, n (%)	Grade 1, n (%)	Grade 2, n (%)
Skin	22 (88)	3 (12)	0 (0)
Oesophagus	20 (80)	4 (16)	1 (4)
Larynx	24 (96)	1 (4)	0 (0)
Lung	22 (88)	2 (8)	1 (4)
Maximum severity per patient	17 (68)	6 (24)	2 (8)

Statistical analysis

Sample size was projected based on the estimate of the 2-year OS of 20% for CCRT. With our modified treatment protocol the 2-year OS was expected to increase to 40%. It was assumed that the one-sided Type I error was 10%, the statistical power was 0.80 and there was no dropout. Sample size was calculated by the Stata™ software v. 12.0 (StataCorp LP, College Station, TX), and 22 patients were expected to adequately detect the difference. The OS and PFS were estimated by the Kaplan–Meier model using SPSS® v. 17.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

25 patients (23 males and 2 females; with the following sub-sections: 3 cervical, 9 upper, 11 middle and 12 lower oesophageal squamous cell carcinoma) with Stages IIB–IVA were enrolled in this study from October 2008 to July 2011. The patients' characteristics are summarized in Table 1.

Treatment response

6–8 weeks after CCRT, the response was evaluated using both thoracic CT scan and barium oesophagogram. The CR, PR and SD were observed in 11 (44%) patients, 13 (52%)

Figure 1. Kaplan–Meier plot of overall survival.

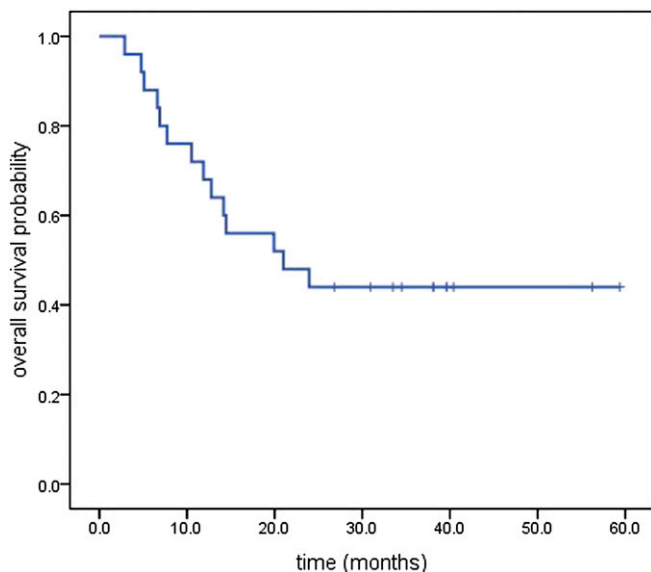
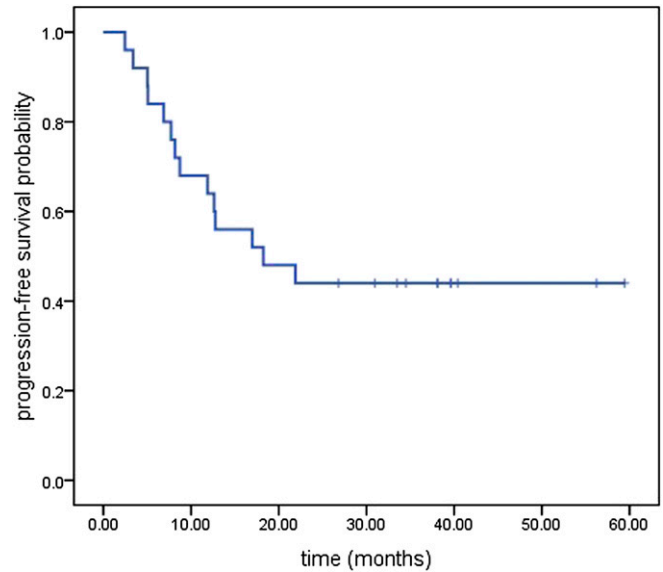


Figure 2. Kaplan–Meier plot of progression-free survival.



patients and 1 (4%) patient, respectively. So, the objective response rate was 96%.

Adverse effect

All patients were evaluated for toxicity. The acute toxicities for each patient are presented in Table 2. The major acute toxicities were myelosuppression, gastrointestinal reaction and oesophagitis. Grade 3 acute toxicity occurred in 13 (52%) patients, Grade 4 acute toxicity occurred in 2 (8%) patients and Grade 5 acute toxicity occurred in 1 (4%) patient. Two patients had a treatment interruption of less than 3 days owing to acute toxicities, and all the patients completed the treatment.

Late radiation toxicities are listed in Table 3. The major late radiation toxicity was oesophageal injury. There were no observations of late toxicities >Grade 3.

Survival and pattern of failure

The median follow-up was 21 months, with a range of 2.9–59.4 months until the last follow-up date of September 2013. Median OS for all the patients was 21 months [95% confidence interval (CI), 5.56–36.439 months], and the median PFS was 18.23 months (95% CI, 3.33–33.13 months). The OS and PFS are illustrated in Figures 1 and 2, respectively. The Kaplan–Meier estimated 1, 2 and 5 year OS rates and the PFS rates were 68%, 44%, 44% and 64%, 44%, 44%, respectively. The first failure patterns consisted of locoregional failure (16%) and distant metastasis (12%). Currently, a total of 11 patients are alive, 1 patient died of oesophageal fistula after therapy, 4 patients died of local disease recurrence, 3 patients died of distant metastasis, while the others died of non-tumour reasons (2 died of cardiac disease, 2 died of stroke and 2 died of unknown disease). The mean OS of the patients who died owing to non-tumour reasons was 8.42 months (ranging from 4.47 to 14.47 months). Of the living patients, there was no evidence of disease recurrence.

Table 4. Survival and toxicities of concurrent chemoradiotherapy for oesophageal cancer

Studies	Year	Histology	Radiation dose (Gy)	Radiation style	Chemotherapy	Median OS months	1 year OS rate (%)	2 year OS rate (%)	3 year OS rate (%)	5 year OS rate (%)	Grade 3 toxicity ^a (%)	Grade 4 toxicity ^a (%)	Grade 5 toxicity ^a (%)
al-Sarraf et al ¹⁸	1997	ADC, 10%; ESCC, 90%	50.0	CF RT	CDDP + 5-Fu	14.1	-	36	30.0	27.0	46.00 (25.00)	14 (4)	2.0 (0.0)
		ADC, 15%; ESCC, 85%	64.0	CF RT	-	9.3	-	10	0.0	0.0	19.00	4	0.0
INT0123 (RTOG 9405); Minsky et al ³	2002	ADC, 20%; ESCC, 80%	50.0	CF RT	CDDP + 5-Fu	17.2	-	-	30.0	-	49.00 (15.00)	13 (5)	0.0 (0.0)
		ESCC	64.8	CF RT	CDDP + 5-Fu	13.0	-	31	-	-	46.00, 34.00	21, 11	9.0, 1.0
Gao et al ⁶	2002	ESCC	50.4	CF RT	CDDP + 5-Fu	18.1	-	40	-	-	43.00, 24.00	26, 13	2.0, 0.0
		ESCC	60.0	LCAF RT	-	25.4	73.2	-	34.2	-	2.40, 0.00	2.4, 0	0.0, 0.0
Ishikura et al ¹⁹	2003	ESCC	60.0	CF RT	CDDP	32.6	80.7	-	40.0	-	10.00, 0.00	5, 0	0.0, 0.0
Zhao et al ⁷	2005	ESCC	68.4	LCAF RT	CDDP + 5-Fu	21.0	-	-	38.0	29.0	38.80, 9.35	5, 1.4	2.0, 1.4
Kang et al ²⁰	2007	ADC, 1.6%; ESCC, 98.4%	45.0-64.4	CF RT	CDDP + 5-Fu	30.8	67.0	58	44.0	40.0	40.00, 13.00	6, 2	6.0, 4.0
RTOG 8501; Cooper et al ²	1999	ADC, 21.5%; ESCC, 78.5%	50.0 randomized	CF RT	CDDP + 5-Fu	23.9	77.0	49	39.0	28.0	25.00, 23.00	0, 4	0.0, 4.0
		-	64.0	CF RT	-	-	-	-	-	16.0	-	-	-
RTOG 0113; Ajani et al ¹	2008	ADC, 65.28%; ESCC, 34.72%	50.4	CF RT	CDDP + 5-Fu + paclitaxel	28.7	76.0	56	-	-	-	27	3.0
		-	50.0 non-randomized	CF RT	Paclitaxel	14.9	69.0	37	-	-	-	43.00	40
KROSG0101/ JROSG021; Nishimura et al ²²	2009	ADC, 2.17%; ESCC, 97.83%	60.0	Split for 1 week	CDDP + 5-Fu, short term	-	-	46	-	35.0	-	-	-
		ESCC, 100%	60.0	Split for 1 week	CDDP + 5-Fu, protracted	-	-	44	-	24.0	-	-	-
Hurmuzlu et al ²³	2010	ADC, 34.78%; ESCC, 65.22%	66.0	CF RT	CDDP + 5-Fu	10.8	-	22	15.0	11.0	47.50	40	2.5
Sheng et al ²⁴	2011	ESCC	64.0-69.0	LCAF RT	Capecitabine	-	85.7	-	55.6	30.2	-	-	-

5-Fu, 5-fluorouracil; ADC, adenocarcinoma; CDDP, cisplatin; CF RT, conventional fractionated radiotherapy; ESCC, oesophageal squamous cell carcinoma; LCAF RT, late course accelerated hyper-fractionated radiotherapy; OS, overall survival.

^aToxicities were expressed as "acute toxicity rate, late toxicity rate" or "chemotherapy toxicity rate (radiotherapy toxicity rate)".

DISCUSSION

In this Phase II trial, we tested pemetrexed, low-dose CDDP and concomitant RT in patients with locally advanced ESCC. In the present study, patients achieved a 44% 2 year OS, which reached the value of expectation. The 5 year OS was as high as 44%, which was more favourable than other studies (Table 4).

Seiwert et al²⁵ reported promising Phase I data with a combination of pemetrexed, carboplatin and radiation in patients with locally advanced oesophageal and lung cancers. The CR rate was 33%, and the incidence of oesophagitis as well as haematological, skin and pulmonary toxicities was lower than with other established chemoradiotherapy platforms. Jatoi et al¹⁰ also carried out a clinical trial with concurrent pemetrexed, carboplatin and radiation followed by surgery to treat locally advanced EC and gastro-oesophageal-junction tumours. The pCR rate was 23% and the median OS was 17.8 months. These data demonstrate that pemetrexed combined with platinum concurrent with RT achieved promising antineoplastic effects in patients with EC. However, the EC patients included in those studies were almost oesophageal adenocarcinomas. In the present study, we first applied pemetrexed in the treatment of ESCC and got a CR rate of 44% and a median OS of 21 months; the favourable results indicate that pemetrexed concurrent RT can be applied in the treatment of ESCC.

The studies RTOG 8501² and 9405³ have established the standard role of CCRT in the treatment of locally advanced EC, where the median OS was 14.1–18.1 months. Compared with these outcomes, the results of our present study seemed much better. In addition, the chemoradiotherapy followed by surgery for oesophageal cancer (CROSS) group had conducted a study²⁶ and found that neoadjuvant chemoradiotherapy followed by surgery to treat locally advanced EC resulted in a pCR rate of 29% and a 5-year OS rate of 57%. The finding indicated that patients with EC who underwent surgery could benefit from neoadjuvant chemoradiotherapy. Although the patients enrolled in our study were inoperable or refused surgery, the clinical stage was somewhat delayed, but the CR rate reached 44%, which was an

encouraging outcome. The high response rate may be due to the LCAF RT with 59.6 Gy higher radiation dose than CF RT with 41.4–50.4 Gy in other studies.²⁷ Shi et al⁴ compared the local control rate and the OS between CF RT and LCAF RT in patients with ESCC and demonstrated that the 5 year PFS in the LCAF RT group was improved significantly (42% vs 15%). The advantages of LCAF RT have been confirmed by many studies.²⁸

It is undeniable that toxicities obtained in our study were relatively severe, but fortunately, most of the acute side effects were manageable. The incidence of Grade 3 oesophagitis (4%) in our study was not notably higher than that obtained in other studies.²⁹ Although there were two patients who experienced treatment interruption, all patients completed the entire treatment process. There were no serious late toxicities, which may be attributed to the application of IMRT technology. Lin et al³⁰ had confirmed that IMRT was better than three-dimensional conformal RT (3D-CRT) when combined with chemotherapy in patients with oesophageal cancer. Compared with patients treated with IMRT, patients treated with 3D-CRT had a significantly greater risk of dying (72.6% vs 52.9%; $p < 0.0001$) and locoregional recurrence ($p = 0.0038$).

Given the overall size of this study, the follow-up time and the occurrence rate of acute toxicities, the results have been reviewed cautiously. However, the high response rate and 5 year OS when administering pemetrexed, CDDP and LCAF RT were encouraging and support further Phase III trial testing in locally advanced ESCC. But the formulation of specific schemes still needs further consideration to reduce side effects. Moreover, using radioprotectors to protect normal tissue could be favourable to patients' tolerability.

In conclusion, therapeutic regimens concurrent with SLN LCAF IMRT and pemetrexed with low-dose CDDP achieved excellent response rates and favourable survival rates for locally advanced ESCC. Further randomized studies could be carried out, but the severe and acute side effects should be reviewed cautiously, and additional measurements must also be taken to avoid and/or manage life-threatening acute toxicities.

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