BMC Medicine

RESEARCH ARTICLE

Open Access

Postoperative tumor bed radiation versus T-shaped field radiation in the treatment of locally advanced thoracic esophageal squamous cell carcinoma: a phase IIb multicenter randomized controlled trial

Ya Zeng[1†], Jiancheng Li[2†], Jingjun Ye[3†], Gaohua Han[4†], Wenguang Luo[5†], Chaoyang Wu[6†], Songbing Qin[7†], Wendong Gu[8†], Shengguang Zhao[9†], Yufei Zhao[10†], Bing Xia[11†], Zhengfei Zhu[12†], Xianghui Du[13†], Yuan Liu[14], Jun Liu[1], Hongxuan Li[1], Jiaming Wang[1], Jindong Guo[1], Wen Yu[1], Qin Zhang[1], Changlu Wang[1], Wentao Fang[15], Zhigang Li[15], Xiaolong Fu[1,12*] and Xuwei Cai[1,12*]

Abstract

Background Postoperative radiotherapy (PORT) is crucial for patients with thoracic locally advanced esophageal squamous cell carcinoma (LA-ESCC, pT3-4aN0-3M0) following esophagectomy. However, the appropriate radiation volume has not been well established. This study aimed to determine the optimal PORT volume for LA-ESCC patients.

Methods LA-ESCC patients post-esophagectomy were randomly assigned to either the large-field irradiation (LFI, primary lesion and lymph node tumor bed plus elective nodal irradiation) group or the small-field irradiation (SFI, primary lesion and lymph node tumor bed alone) group. Stratification was based on T stage and the number of lymph node metastases. The primary endpoint was disease-free survival (DFS), while the secondary endpoints included overall survival (OS), adverse events, and patterns of initial failure.

Results A total of 401 patients were randomly assigned to the intention-to-treat analysis(LFI group, $n=210$; SFI group, $n=191$). The median DFS of patients in the LFI group was 47.9 months and 48.1 months in the SFI group (HR = 0.87, 95%CI, 0.65 to 1.16; $p=0.32$). The estimated one-year and three-year OS rates were 89.2% and 63.2% for patients in the LFI group, compared to 86.6% and 60.7% for the SFI group, respectively. The difference of OS between the two groups was not significant (HR = 0.86, 95%CI, 0.63 to 1.16; $p=0.35$). Fewer patients in the LFI group experienced locoregional recurrence compared to the SFI group (12.9% vs 20.4%, $p=0.013$). Additionally, locoregional recurrence-free survival of the LFI group was significantly longer than that of SFI group (HR = 0.54, 95%CI, 0.34–0.87;

†Ya Zeng, Jiancheng Li, Jingjun Ye, Gaohua Han, Wenguang Luo, Chaoyang Wu, Songbing Qin, Wendong Gu, Shengguang Zhao, Yufei Zhao, Bing Xia, Zhengfei Zhu and Xianghui Du contributed equally to this work.

*Correspondence:
Xiaolong Fu
xlfu1964@hotmail.com
Xuwei Cai
birdhome2000@163.com
Full list of author information is available at the end of the article

$p = 0.01$). The most common toxicity was grade 2 esophagitis, observed in 22.9% of the LFI group and 16.8% of the SFI group. Grade 3 adverse events occurred in 6.7% of the LFI group and 2.6% of the SFI group. No grade 4 or 5 toxicities were observed. Adverse events did not significantly differ between the two groups.

Conclusions Postoperative radiotherapy, with the specified radiation volume shows encouraging survival outcomes that are comparable to those of neoadjuvant chemoradiotherapy in patients with thoracic LA-ESCC. Both postoperative irradiation fields were found to be feasible and safe.

Keywords Locally advanced esophageal squamous cell carcinoma, Postoperative radiotherapy, Radiation volume, Locoregional control, Survival outcomes

Background

Esophageal cancer ranks among the most aggressive malignant tumors worldwide. Neoadjuvant chemoradiotherapy followed by surgery is the standard care for operable thoracic esophageal cancer [1–3]. However, in China, a considerable number of patients opt for primary surgery rather than neoadjuvant chemoradiotherapy, as indicated by a database analysis conducted from January 2009 to December 2014 [4]. Notably, many patients many patients initially diagnosed with stage T1-2 are pathologically upgraded to advanced stages (T3-4 or N+) after surgery. Consequently, more than half of the patients with locally advanced esophageal squamous cell carcinoma (LA-ESCC) undergo esophagectomy without prior neoadjuvant treatment. For these LA-ESCC patients, adjuvant therapy is essential. Previous research has shown that postoperative radiotherapy (PORT) or chemoradiotherapy is crucial for selected LA-ESCC patients, particularly those with T3-4 stages or positive lymph nodes, who undergo initial radical surgery [5–9].

However, the debate over the optimal clinical target volume (CTV) for PORT persists, with consensus yet to be reached [10, 11]. An extensive irradiation field including tumor bed, bilateral supraclavicular area, mediastinal lymph nodes and left gastric and pericardial lymphatic might offer better disease control, However, this approach has resulted in pronounced toxicities in ESCC patients. Additionally, PORT with extensive irradiation field has not shown survival benefits over locoregional irradiation fields [10, 11].

Delineating an appropriate CTV for postoperative radiotherapy in thoracic LA-ESCC patients after esophagectomy is essential. Therefore, a multicenter, prospective randomized, phase IIb clinical trial was designed to evaluate the efficacy of two different postoperative radiotherapy CTVs.

Methods

Patients

Patients meeting the following criteria were eligible for this randomized trial conducted in 13 hospitals in China: they had initially undergone radical surgery and received pathological confirmation of locally advanced thoracic ESCC (pT3-4a, any N, M0, according to the UICC TNM staging for esophageal and esophagogastric junction cancers, seventh edition); patients were between 18 and 70 years old; radical surgery entailed the removal of at least 12 lymph nodes [12]; an ECOG performance score of 0 or 1; adequate hematologic, renal, hepatic, and pulmonary function; no prior neoadjuvant treatment, and no past or present history of other malignancies. The main exclusion criteria included: the presence of lymph nodes with a short axis diameter of at least one centimeter on computed tomography (CT) scans or suspicious residual disease detected via positron emission tomography (PET)-CT scans during postoperative evaluations; prior neoadjuvant or adjuvant treatments before randomization, and a weight loss exceeding 10% of their presurgery body weight at randomization. The protocol was approved by each institution's research ethics board, and all patients provided written informed consent before any study-related procedures were initiated. The study adhered to the standards of the Helsinki Declaration of 1975.

Randomization and masking

This trial was registered in ClinicalTrials.gov with identifier NCT01391572. In this multicenter, prospective, randomized phase IIb trial, we aimed to investigate the optimal postoperative radiation volume for LA-ESCC patients. After completing routine post-surgical examinations, patients were randomly assigned (1:1) to either the large-field irradiation (LFI) or small-field irradiation (SFI) group. Stratification was based on the number of lymph node metastases ($LN \geq 3$ vs. $LN < 3$) and T stage (T3 vs. T4a). Enrolled patients then underwent postoperative radiotherapy, followed by sequential chemotherapy. The central randomization process was conducted by the Clinical Trial Center of Shanghai Chest Hospital (Shanghai, China) using computer-generated lists for each stratum, considering lymph nodes and T stage as block factors. Both patients and investigators were not blinded to the treatment assignments.

Procedures

Patients were scheduled for postoperative radiotherapy within eight weeks following radical surgery. Patients were positioned supine and immobilized with a thermoplastic mask. A simulation planning CT was performed, encompassing an area from the upper edge of the cricoid to the upper abdomen, utilizing a 5 mm slice thickness. Essential references for tumor bed delineation included preoperative and postoperative CT images, surgical records, and pathology reports. Upper gastrointestinal endoscopy and esophagography were crucial in identifying the primary tumor's location. In the SFI group, the clinical tumor volume (CTV) was limited to the primary and metastatic lymph nodes' tumor bed. Conversely, the LFI CTV included the tumor bed and bilateral supraclavicular and upper-middle mediastinal lymph node drainage areas. This configuration forms a modified T-shaped radiation field, extending from the lower edge of cricoid to 3 cm below the subcarinal region. For tumors situated in the lower or middle-third of the esophagus, the LFI region was defined to include upper-middle mediastinal lymphatic drainage areas, excluding the supraclavicular lymphatic drainage areas. The upper boundary was set at T1, with the lower boundary defined by the primary tumor bed (e.g., Additional file 1: Fig. S1, Additional file 2: Fig. S2). The planning target volume (PTV) was defined as the clinical target volume (CTV) with an additional uniform margin of 0.8–1.0 cm. Critical structures including the lungs, heart, and spinal cord were contoured to facilitate the evaluation of the treatment plan. Treatment planning employed a simultaneous integrated-boost intensity-modulated radiotherapy (SIB-IMRT) technique with the Pinnacle treatment planning system (Philips Medical Systems).

In the LFI group, patients received 50.4 Gy in 28 fractions (1.8 Gy per fraction) over five weeks. With SIB-IMRT, the tumor bed received 63 Gy for T4a or 60.2 Gy for T3, delivered in 28 fractions (2.25 Gy or 2.15 Gy per fraction) over five weeks. Patients in the SFI group received 60.2 Gy or 63 Gy in 28 fractions. Positioning reproducibility was ensured using an orthogonal laser beam and an electron beam imaging device. A 6-MV X-ray linear accelerator was used for radiotherapy, featuring a multiple field technique and external beam radiation.

The treatment plan was evaluated, and the organs at risk (OARs) documented using isodose contours and dose-volume histograms. Established dose constraints for OARs, with slight variations, included the following: for the lungs, V20 was set below 25% of the total volume, with a mean dose not exceeding 15 Gy; for the spinal cord, the maximum dose was below 45 Gy; for the heart, V30 was set below 40%, and V40 below 30%.

Following postoperative radiotherapy, patients were typically scheduled for four cycles of cisplatin-based chemotherapy, involving a dual-drug regimen. The regimen included cisplatin (25 mg/m^2, days 1–3) and either 5-fluorouracil (5-FU, 600 mg/m^2, days 1–5) or paclitaxel (75 mg/m^2, day 1), administered at three- to four-week intervals. Laboratory assessments were conducted weekly during chemotherapy cycles, and imaging evaluations were performed as needed. Adverse events (AEs) were closely monitored and classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0, throughout the study.

Follow-up and assessment

Upon treatment completion, patients had follow-up visits every three months for the first two years, every six months for the next two years, and annually from the fifth year onward. These visits were dedicated to monitoring potential disease relapse, progression, and mortality. Mandatory routine imaging included enhanced chest CT scans, esophagography, and ultrasonography of the bilateral supraclavicular fossa and upper abdomen. If symptoms such as unexplained weight loss or pain emerged, interim imaging was permitted before the next scheduled visit. If routine examinations suggested a potential recurrence, additional steps were planned, including histological confirmation when feasible or PET-CT scans. Treatment assessments were carefully conducted by the respective investigators, according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines.

Statistical analyses

Data analyses included all patients who were randomly allocated, adhering to the intention-to-treat (ITT) principle. Additionally, A per protocol analysis was also conducted, with detailed results furnished in the supplementary appendix (Additional file 3: Fig. S3, Additional file 4: Fig. S4 and Additional file 5: Table S1). The primary endpoint of this study was disease-free survival (DFS), defined as the time from randomization to the initial occurrence of disease progression or death from any cause. Based on the findings of Schreiber et al. [13], the estimated 5-year DFS rate for the SFI group is 25%. The present study was designed to assess the potential differences in DFS between the LFI and SFI groups. To ensure 81% statistical power to detect a hazard ratio of 0.65 with a significance level of 0.047, a two-sided log-rank test was used. The study planned a 3-year enrollment period and a 2-year observation period, including a scheduled interim analysis. Considering a 10% drop-out rate and aiming for balanced cohort sizes, a minimum of 320 patients was required, with 160 per group.

The secondary endpoints included overall survival (OS), AEs and initial failure patterns. OS was defined as the time from randomization to death from any cause or the last follow-up. Both locoregional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) were key components of the data analysis. Locoregional recurrence included failures in regional lymph nodes, anastomotic sites, and the tumor bed, while distant metastasis involved non-regional lymph nodes (e.g., celiac lymph nodes for upper third thoracic esophageal cancer, cervical lymph nodes for lower third thoracic ESCC) and hematogenous spread. LRFS was measured from randomization to the first locoregional recurrence, with isolated distant metastases censored if no locoregional failure was observed by the final follow-up. DMFS was measured from randomization to the initial distant metastasis, being censored at locoregional recurrence only, if that was the sole event at the last follow-up. Survival outcomes were estimated using the Kaplan–Meier method, and differences in survival were assessed using the log-rank test. Subgroup analyses for OS and DFS utilized a univariate Cox regression model, with a subsequent Cox proportional hazards model to examine prognostic factors associated with DFS and OS. Differences in treatment failure patterns and AE were evaluated using the Chi-square test. Statistical analyses were performed using SPSS 22.0 and GraphPad Prism 7, with a significance level set at 0.05(two-sided).

Results

Patients and treatment

From May 2011 to July 2021, thirteen treatment centers enrolled 401 patients, who were then randomized to undergo either large-field irradiation ($n=210$) or small-field irradiation ($n=191$, Fig. 1). The demographic and baseline characteristics were generally well-balanced between two groups in the intention-to-treat population (Table 1). The study population was predominantly male, comprising 88.0%. The average number of lymph node dissections was comparable between the LFI and SFI groups, recorded at 25 ± 11 and 25 ± 12, respectively. A significant proportion of participants, precisely 63.3%, were diagnosed with moderately differentiated ESCC. In the LFI group and SFI group, 5.7% and 7.3% of patients, respectively, were diagnosed with stage T4a. Lymph node negativity was reported in 32.9% of the LFI group and 31.9% of the SFI group. Furthermore, a notable proportion of patients, 43.3% in the LFI group and 40% in the SFI group, did not receive adjuvant chemotherapy after radiotherapy.

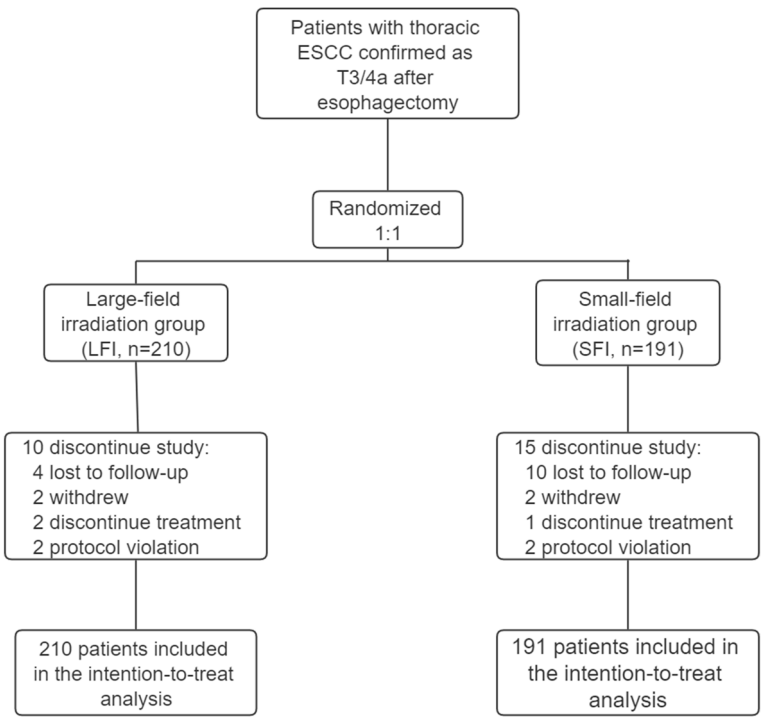

Fig. 1 CONSORT diagram of patients. ESCC, esophageal squamous cell carcinoma; LFI, large-field irradiation; SFI, small-field irradiation; AE, adverse event

Table 1 Baseline characteristics of the intention-to-treat population

		LFI group ($n=210$)	SFI group ($n=191$)	*p*-value
Age, years	Median (range)	61(39–70)	62(38–70)	0.45
Gender				0.57
	Female	27(12.9%)	21(11.0%)	
	Male	183(87.1%)	170(89.0%)	
Primary Lesions				0.47
	Upper TEC	14(6.7%)	12(6.3%)	
	Middle TEC	90(42.9%)	71(37.2%)	
	Lower TEC	106(50.5%)	108(56.5%)	
Dissection of LN	Mean ± SD	25 ± 11	25 ± 12	0.77
Tumor Length, cm	Mean ± SD	4.3 ± 1.4	4.4 ± 3.4	0.45
Tumor Differentiation				0.69
	Well	17(8.1%)	12(6.3%)	
	Moderate	134(63.8%)	120(62.8%)	
	Poor	59(28.1%)	59(30.9%)	
Pathologic T stage				0.51
	T3	198(94.3%)	177(92.7%)	
	T4a	12(5.7%)	14(7.3%)	
Pathologic N stage				0.09
	N0-N1	153(72.9%)	124(64.9%)	
	N2-3	57(27.1%)	67(35.1%)	
Chemotherapy cycles				0.42
	0	91(43.3%)	76(40.0%)	
	1	19(9.0%)	12(6.3%)	
	2	22(10.5%)	23(12.1%)	
	3	9(4.3%)	14(7.4%)	
	4	61(29.0%)	62(32.6%)	
	5	2(1.0%)	0	
	6	6(2.9%)	3(1.6%)	

Abbreviation: LFI large-field irradiation, *SFI* small-field irradiation, *TEC* thoracic esophageal cancer, *LN* lymph nodes, *SD* standard deviation

Disease-free survival

With a median follow-up time of 41.8 (95%CI, 38.0 to 45.7) months for survivors, disease progression occurred in 46.6% (95%CI, 39.8% to 53.7%) of the LFI group and 47.6% (95%CI, 40.4% to 55.0%) of the SFI group. The one-year, three-year DFS rates for the entire cohort were 72.0% (95%CI, 68.9% to 77.8%) and 51.6% (95%CI, 46.4% to 56.4%), respectively. The median DFS was 47.9 (95%CI, 22.2 to 73.6) months in the LFI group, closely similar to the 48.1 (95%CI, 12.1 to 84.0) months of the SFI group (HR = 0.87, 95%CI, 0.65 to 1.16; $p=0.32$, Fig. 2A). In the LFI group, the one-year and three-year DFS rates were 76.4% (95% CI, 70.7% to 82.5%) and 51.5% (95% CI, 44.4% to 63.9%), respectively. In the SFI group, these rates were 67.6% (95% CI, 62.5% to 76.0%) and 51.6% (95% CI, 44.5% to 59.1%), respectively. Multivariable analyses identified the primary esophageal cancer lesion (HR = 0.71, 95%CI, 0.52 to 0.98; $p=0.03$), T stage (HR = 0.47, 95%CI, 0.28 to 0.81; $p=0.006$), and the number of lymph node metastases (HR = 0.47, 95%CI, 0.35 to 0.63; $p<0.001$) as significant prognostic factors for DFS (Additional file 6: Fig. S5A). Notably, patients in both groups had a consistent DFS benefit across stratified factors (Fig. 2C).

Overall survival

The median OS for the entire cohort was 74.6 (95%CI, 35.8 to 111.1) months. Specifically, the LFI group had a median OS of 133.0 (95% CI, 32.1 to 233.9) months, compared to 73.5 (95% CI, 32.3 to 114.7) months in the SFI group. Predominantly, mortality was attributable to ESCC, with the exception of one patient who died of primary lung cancer; three patients who died of bowel obstruction and two patients who died of malnutrition; and two patients who died suddenly due to cardiovascular ailments. For the entire cohort, the one-year and three-year OS rates were 88.0% (95%CI, 84.9% to 91.4%) and 62.0% (95%CI, 57.1% to 66.8%), respectively.

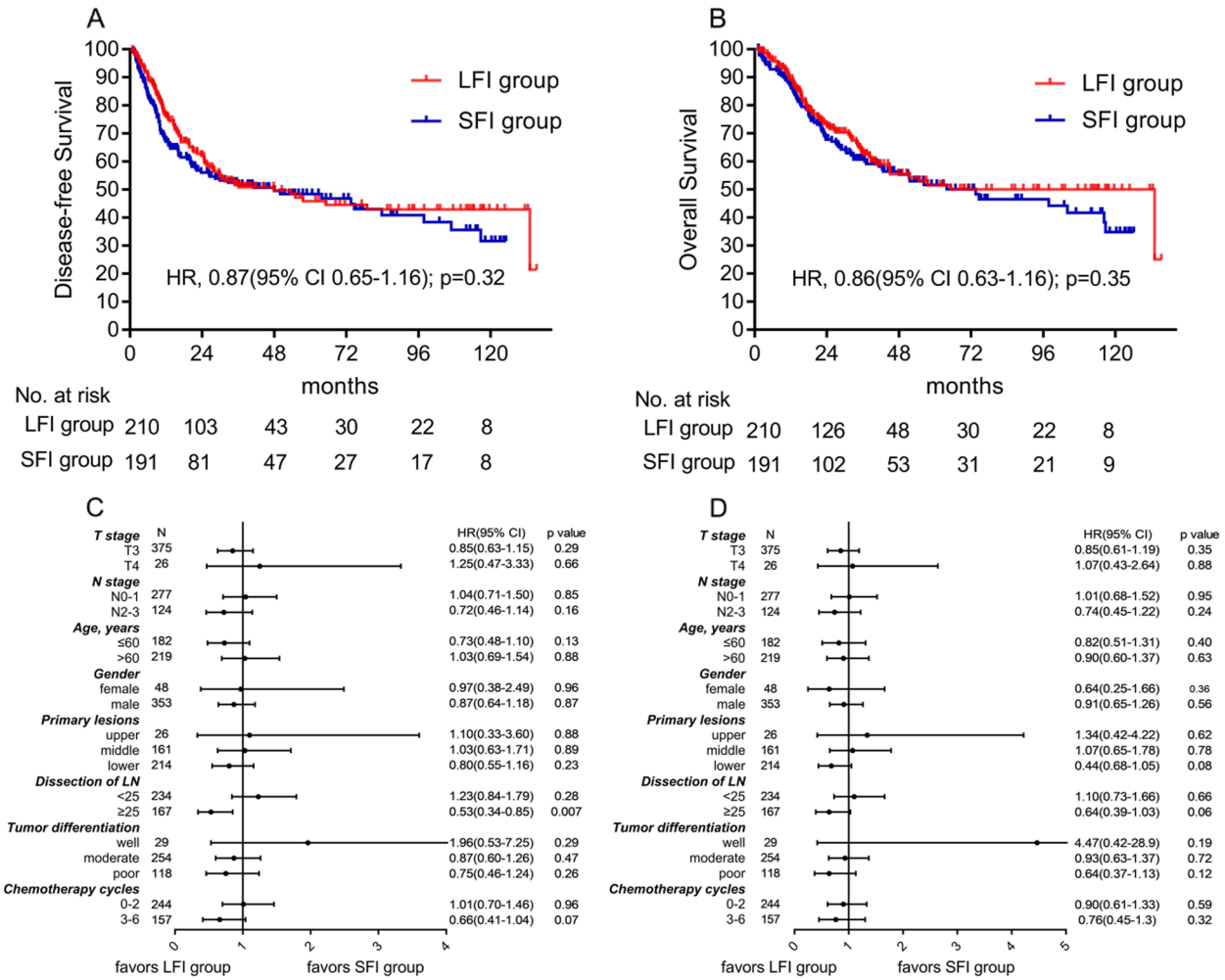

Fig. 2 Disease-free survival and overall survival of the ITT population. Comparing rates of disease-free survival (**A**) and overall survival (**B**) between two groups. Panel (**C**-**D**) shows subgroup analysis. No, number; HR, hazard ratio; LN, lymph node

The estimated one-year and three-year OS rates were 89.2% (95%CI, 84.4% to 93.2%) and 63.2% (95%CI, 56.4% to 69.8%) for the LFI group, and 86.6% (95%CI, 81.1% to 91.2%) and 60.7% (95%CI, 52.9% to 67.1%) for patients in the SFI group, respectively. The difference of OS between the groups was not statistically significant (HR = 0.86, 95%CI, 0.63 to 1.16; $p = 0.35$, Fig. 2B). Multivariable analyses showed that patients undergoing over three cycles of adjuvant chemotherapy (HR = 1.61, 95% CI, 1.07 to 2.10; $p = 0.02$), those with T3 stage (HR = 0.37, 95% CI, 0.22 to 0.62; $p < 0.001$), and those with fewer than three lymph node metastases (HR = 0.50, 95% CI, 0.36 to 0.69; $p < 0.001$) had extended OS with PORT (Additional file 6: Fig. S5B). However, subgroup analyses revealed no notable differences in OS relative to baseline characteristics and treatment groups (Fig. 2D).

Locoregional recurrence-free survival and distant metastasis-free survival

At the data cutoff for this analysis, twenty-seven patients (12.9%, 95%CI, 9.0% to 18.1%) in the LFI group and 20.4% (95%CI, 16.0%-28.1%) in the SFI group experienced locoregional relapse. The median LRFS of both groups has not been reached. The one-year and three-year LRFS rates were 92.3% (95% CI: 88.3%-95.8%) and 83.7% (95% CI: 78.0%-88.4%) in the LFI group, and 87.0% (95% CI: 81.7%-91.6%) and 74.7% (95% CI: 68.0%-80.7%) in the SFI group. Patients in the LFI group had better locoregional control than those in the SFI group (HR = 0.54, 95%CI, 0.34—0.87; $p = 0.01$; Fig. 3A).

Distant disease was observed in 33.3% of the LFI group and 29.3% of the SFI group, with the median DMFS not yet attained in either group. The one-year and three-year DMFS rates were 83.5% (95% CI: 77.4%–88.0%) and 63.6% (95% CI: 56.9%-70.2%) in the LFI group, compared

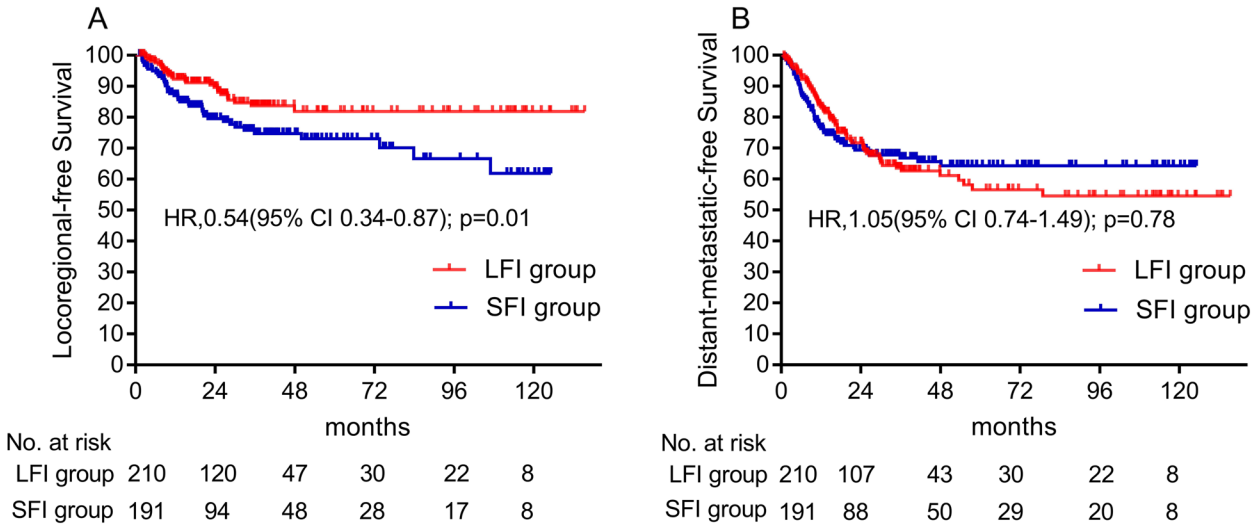

Fig. 3 Locoregional-recurrence-free survival and distant-metastasis-free survival. Comparing rates of locoregional-recurrence-free survival (**A**) and distant-metastasis-free survival (**B**) between two groups. No, number; HR, hazard ratio

to 76.3% (95% CI: 69.7%-82.1%) and 66.8% (95% CI: 59.3%-73.0%) in the SFI group. No significant difference in DMFS was found between the groups (HR = 1.05, 95%CI, 0.74–1.49; $p = 0.78$, Fig. 3B).

Failure patterns and safety

Fewer patients in the LFI group experienced locoregional recurrence compared to the SFI group (12.9% [27/210] vs. 20.4% [39/191]), with this difference being statistically significant ($p = 0.013$). While distant disease was more prevalent, encompassing 25.7% (103/401) of cases across both groups, compared to locoregional recurrence at 11.0% (44/401). However, no significant difference in the incidence of distant metastasis between the groups was found ($p = 0.326$). Concurrent locoregional recurrence and distant metastasis were documented in 4.3% (9/210) in the LFI group and 6.8% (13/191) of patients in the SFI group (Table 2).

The lung was the most common site of metastasis in both groups, followed by the bone and liver. A higher incidence of supraclavicular lymph node recurrences was observed in the SFI group compared to the LFI group,

Table 2 Failure patterns of the entire population

	LFI group ($n = 210$)	SFI group ($n = 191$)	*p*-value
Failure patterns			0.010
Local recurrence	18(8.6%)	26(13.6%)	
Distant metastasis	60(28.6%)	43(22.5%)	
Both	9(4.3%)	13(6.8%)	
UN	5(2.4%)	0	
Locoregional recurrence			0.013
Locoregional recurrence	27(12.9%)	39(20.4%)	
non-LR	65(31.0%)	43(22.5%)	
Local recurrence			0.022
In-field only	17(8.1%)	11(5.8%)	
Out-field only	10(4.8%)	27(14.1%)	
Both	1(0.5%)	2(1.0%)	
Distant metastasis (DM)			0.326
DM	69(32.9%)	56(29.3%)	
non-DM	23(11.0%)	26(13.6%)	

Abbreviation: LFI large-field irradiation, *SFI* small-field irradiation, *LN* lymph nodes, *LR* locoregional recurrence, *DM* distant metastasis, *UN* unknown

involving 15 and 4 patients, respectively. Similarly, celiac lymph node recurrence manifested in twelve patients from the LFI group and eleven from the SFI group (Additional file 7: Fig. S6).

Among patients with local recurrences, a higher proportion of individuals in the SFI group experienced out-of-field failure compared to those in the LFI group (14.1% [27/191] vs. 4.8% [10/210], $p < 0.05$). In-field recurrence was observed in 8.1% (17/210) of patients in the LFI group and 5.8% (11/191) of patients in the SFI group ($p < 0.05$, Table 2).

A total of 186 patients (46.4%) experienced adverse events related to the treatment. The most prevalent toxicity observed was grade 2 radiation esophagitis, affecting 22.9% (48/210) of patients in the LFI group and 16.8% (32/191) in the SFI group. This was followed by grade 2 hematologic toxicity, occurring in 14.3% (30/210) of the LFI group and 10.5% (20/191) of the SFI group. In the LFI group, 6.7% (14/210) of patients experienced grade 3 or higher adverse events, including four cases of grade 3 hematologic toxicity, seven cases (3.3%) of grade 3 esophagitis, and two cases of grade 3 pneumonitis. In contrast, the SFI group had one patient (0.5%) with grade 3 hematologic toxicity, two patients of grade 3 esophagitis, and two patients (1.0%) with grade 3 nausea or vomiting. There were no occurrences of grade 4 or 5 toxicities in either treatment group. No significant differences in treatment-related toxicities were observed, and all toxicities were manageable in this study (Table 3).

Discussion

This multi-center, prospective randomized clinical trial is the first to determine the optimal postoperative radiation volume for LA-ESCC patients. Comparing the PORT CTV of large-field irradiation, which encompasses the bilateral supraclavicular, upper mediastinal lymph node drainage areas along with the tumor bed (a modified T-shaped field), with tumor bed irradiation alone, shows that both groups achieved similar DFS. The results also showed that both PORT irradiation fields had promising OS with no significant differences between groups. Additionally, the LFI group achieved a superior locoregional control without a corresponding increase in adverse events. The 3-year DFS and 3-year OS rates reported in the CROSS study were 51% and 58%, respectively, while the NEOCRTEC5010 study reported rates were 68.9% and 65.8%, respectively. Notably, the survival outcomes in our study, which specifically included patients with stage pT3-4aN0-3M0, closely approached the remarkable survival rates observed in patients from the CROSS and NEOCRTEC5010 studies who underwent neoadjuvant chemoradiotherapy [14, 15]. These results suggest that both the modified T-shaped volume and tumor bed-only irradiation are viable options for LA-ESCC patients undergoing postoperative radiation therapy. This provides valuable alternatives for patients who did not receive standard neoadjuvant chemoradiotherapy.

Neoadjuvant chemoradiotherapy is currently the standard of care for operable locally advanced esophageal cancer. However, it is important to recognize the significance of adjuvant therapy for patients who initially opt for radical surgery as their primary treatment due to various reasons. Postoperative radiotherapy emerges as a potentially beneficial intervention for improving DFS and OS in ESCC patients with pathologically confirmed stage III or positive lymph nodes, especially when they have not undergone preoperative therapy [9, 16–19]. Furthermore, the prospective study's survival outcomes indicate that patients who received PORT achieved 3-year DFS and OS rates comparable to those observed in the CROSS study, even though this trial included patients with stage T3-4 disease. This highlights the potential effectiveness of PORT for improving outcomes in this patient population.

Defining an appropriate clinical target volume (CTV) for PORT is of paramount importance in the treatment of locally advanced esophageal cancer patients. Unfortunately, a consensus regarding the optimal extent of PORT CTV following esophagectomy for LA-ESCC has not yet

Table 3 Adverse events of the intention-to-treat population

		LFI group ($n = 210$)	SFI group ($n = 191$)
Hematological toxicities	Grade 2(%)	30(14.3)	20(10.5)
	Grade 3(%)	4(1.9)	1(0.5)
Esophagitis	Grade 2(%)	48(22.9)	32(16.8)
	Grade 3(%)	7(3.3)	2(1.0)
Pneumonitis	Grade 2(%)	8(3.8)	10(5.2)
	Grade 3(%)	2(0.9)	0
Nausea or vomiting	Grade 2(%)	11(5.2)	8(4.2)
	Grade 3(%)	1(0.5)	2(1.0)

Abbreviation: LFI large-field irradiation, *SFI* small-field irradiation, *LN* lymph node

been reached. One plausible approach is to include the tumor bed, bilateral supraclavicular area, mediastinal lymph nodes, cardia, and left gastric lymph nodes in the CTV. This strategy is based on the submucosal lymphatic drainage pattern and aims to reduce the risk of locoregional recurrence [16]. However, previous attempts with an extensive radiation field failed to reduce in-field recurrence and even resulted in increased adverse events [16, 19, 20]. Qiao et al. reported favorable outcomes with a regional PORT that targeted only the tumor bed and the immediate lymph node regions of the primary lesion, with survival rates comparable to those with an extensive radiation field [10]. This aligns with the findings from a recent prospective randomized study [21], which included 57 patients with stage pT2-4a or N + ESCC. In contrast, Lu et al. suggested that the extent of PORT CTV should be tailored to the primary esophageal cancer lesions [11]. The delineation of PORT clinical target volumes has been a topic of variation and debate for decades. In our study, we defined a modified CTV for the large-field irradiation group that included the bilateral supraclavicular area, upper mediastinal lymph node area (covering approximately 80% of recurrence sites [22–26], and the tumor bed. This CTV was then compared with that of patients in the SFI group.

Survival outcomes were remarkably similar between the two groups. The large-field irradiation volume, which included the bilateral supraclavicular, upper mediastinal lymph node drainage area and tumor bed, demonstrated superior locoregional control compared to the tumor bed-only approach without increasing adverse events. Although local disease control improved, it did not translate into significant differences in DFS, or the observed gap in OS. It's worth noting that patients experiencing local recurrence typically undergo aggressive salvage therapy [27], which may explain the marginal disparity observed between the groups. Considering the predominant location of primary tumors in the lower third of the thoracic esophagus, the occurrence of relapse in the celiac drainage area (12 patients in the LFI group and 9 in the SFI group) was considered acceptable due to the omission of the left gastric lymph node drainage area. Additionally, a significant proportion of patients in both groups experienced distant disease, which could potentially counterbalance the advantages of local control in terms of survival. In fact, most patients in this study ultimately developed distant metastases. These findings highlight the significance of addressing distant metastasis as a major contributor to treatment failure in ESCC patients, even when local control is significantly improved. Our ongoing research aims to further explore the mechanisms underlying distant metastasis in ESCC patients.

Toxicities remained under control and were well-tolerated throughout the duration of this study. Patients in the LFI group did not experience an increase in adverse events compared to those who received tumor bed-only irradiation. Notably, the transposed stomach is one of the most significant considerations for OAR during PORT. However, previous research has demonstrated the transposition stomach toxicity is manageable with conventional fractionation PORT [15]. Although not initially specified, a dose to the intrathoracic stomach with a V50 less than 14.05% was considered potentially acceptable during the PORT procedure [28]. This tolerable adverse events can be attributed to the sequential scheduling of chemotherapy after PORT, rather than concurrent administration with radiotherapy. While concurrent chemoradiotherapy (CCRT) may be considered a superior option for patients with locally advanced esophageal squamous cell carcinoma (LA-ESCC), as previous studies have suggested [6, 29, 30], it's important to acknowledge that CCRT could elevate treatment-related toxicities and potentially compromise survival outcomes [20, 31–34]. Notably, the survival outcomes observed in this study were not compromised when compared to the standard CROSS study, even in the context of a delay in chemotherapy administration.

Although this study provides valuable insights into rational PORT CTVs for LA-ESCC patients following radical surgery, several limitations must be acknowledged. First, given the long-term enrollment and follow-up period, some degree of bias was inevitable in this prospective study due to potential issues with compliance among participants. Second, the study exclusively focused on LA-ESCC patients, so the applicability of the proposed PORT volume regimen to esophagogastric junction adenocarcinoma, which is more prevalent in Western countries, remains to be investigated further. Additionally, an emerging question is whether the proposed radiation volume is suitable for use in combination with immunotherapy, warranting future exploration. Furthermore, several questions persist for future research, such as determining the optimal radiation dose, developing strategies for treating elderly patients, and evaluating the relative merits of CCRT versus sequential CRT within the proposed radiation volume.

Conclusions

In summary, LA-ESCC patients undergoing adjuvant radiotherapy following radical esophagectomy achieve survival outcomes comparable to those in neoadjuvant chemoradiotherapy clinical trials. The suggested radiation volume for PORT can be considered as a viable salvage therapy option for LA-ESCC patients who were initially treated with radical surgery. Notably, patients

who received either large-field or small-field irradiation after initial radical surgery achieved similar survival outcomes, making both approaches viable salvage therapy options comparable to neoadjuvant treatment.

Abbreviations

PORT	Postoperative radiotherapy
LA-ESCC	Locally advanced esophageal squamous cell carcinoma
CTV	Clinical target volume
LFI	Large-field irradiation
SFI	Small-field irradiation
DFS	Disease-free survival
OS	Overall survival
LN	Lymph node
CT	Computed tomography
PET-CT	Positron emission tomography- computed tomography
AE	Adverse event
LRFS	Locoregional recurrence-free survival
DMFS	Distant metastasis-free survival
CCRT	Concurrent chemoradiotherapy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03727-y.

Additional file 1: Fig. S1. Example diagram of radiation fields. The red lines show the primary tumor bed (this patient had a N0 disease); the green lines show the T-shaped field.

Additional file 2: Fig. S2. Detailed Illustration of Target Contouring.

Additional file 3: Fig. S3. Disease-free survival and overall survival with per protocol principle. Comparing rates of disease-free survival (A) and overall survival (B) between two groups. Panel C-D shows subgroup analysis. *SFI, small-field irradiation; LFI, large-field irradiation; No, number; HR, hazard ratio.*

Additional file 4: Fig. S4. Locoregional-recurrence-free survival and distant-metastasis-free survival with per protocol principle. Comparing rates of locoregional-recurrence-free survival (A) and distant-metastasis-free survival (B) between two groups. *SFI, small-field irradiation; LFI, large-field irradiation; No, number; HR, hazard ratio.*

Additional file 5: Table S1. Baseline characteristics of the per protocol population.

Additional file 6: Fig. S5. Cox regression analyses of disease-free survival and overall survival for ITT cohort. This forest plot shows hazard ratios for disease-free survival (A) and overall survival (B) and 95% confidence intervals (I bars) in the whole group, according to baseline and treatment characteristics. *LN, lymph node; HR, hazard ratio.*

Additional file 7: Fig. S6. The details of failure patterns in both groups. *LN, lymph node.*

Acknowledgements
We thank all patients who participated in this study and their families, along with the investigators and staff of each participating center for administrated patients and treatment planning.

Authors' contributions
Conception or design of the present study: FXL, CXW, ZY, LJC, YJJ, HGH, LWG, WCY, QSB, GWD, ZSG, ZYF, XB, ZZF, DXH, LJ, LHX, WJM, GJD, YW, ZQ, WCL, FWT, LZG. Acquisition, analysis, or interpretation of data: ZY, LY, FXL, CXW. Drafting of the manuscript: ZY, FXL, CXW, LJC, YJJ, HGH, LWG, WCY, QSB, GWD, ZSG, ZYF, XB, ZZF, DXH, LJ, LHX, WJM, GJD, YW, ZQ, WCL, FWT, LZG. Critical revision of the manuscript for important intellectual content: FXL, CXW. Statistical analysis: ZY, LY, FXL, CXW. Administrative, technical, or material support: FXL, CXW, LJC, YJJ, HGH, LWG, WCY, QSB, GWD, ZSG, ZYF, XB, ZZF, DXH, LJ, LHX, WJM, GJD, YW, ZQ, WCL, FWT, LZG. Supervision: FXL, CXW. All authors read and approved the final manuscript.

Funding
This trial was funded by Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support (20161433); Emerging advanced technology joint research project of Shanghai Shenkang Hospital Development Center (SHDC12017103) and Shanghai science and Technology Fund(21Y11913000).

Data availability
The datasets used during the current study are available from the corresponding author on reasonable request. Other data generated in this study are available within the article and its supplementary data files.

Declarations

Ethics approval and consent to participate
The study was approved by each participated institution's research ethics board (KS1714). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent to be included in the study, was obtained from all patients.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [2]Department of Radiation Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, China. [3]Department of Radiation Oncology, Jiangsu Cancer Hospital, The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, China. [4]Department of Radiation Oncology, Taizhou City People's Hospital, Taizhou, China. [5]Department of Radiation Oncology, Division of Life Sciences and Medicine, The First Affiliated Hospital of USTC, University of Science and Technology of China, Hefei, China. [6]Department of Radiation Oncology, Zhenjiang First People's Hospital, Zhenjiang, China. [7]Department of Radiation Oncology, The First Affiliated Hospital of Soochow University, Suzhou, China. [8]Department of Radiation Oncology, The Third Affiliated Hospital of Soochow University, Suzhou, China. [9]Department of Radiation Oncology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [10]Department of Radiation Oncology, The First Affiliated Hospital of USTC West District Anguish Provincial Cancer Hospital, Hefei, China. [11]Department of Radiation Oncology, Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province, Hangzhou Cancer Hospital, Hangzhou, China. [12]Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China. [13]Department of Radiation Oncology, Cancer Hospital of the University of Chinese Academy of Science/Institute of Cancer and Basic Medicine, Chinese Academy of Science, Zhejiang Key Laboratory of Radiation Oncology, Hangzhou, China. [14]Department of Statistics, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [15]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Received: 26 January 2024 Accepted: 24 October 2024
Published online: 07 November 2024

References

1. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366:2074–84.
2. Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16:1090–8.

3. Mao YS, Gao SG, Wang Q, Shi XT, Li Y, Gao WW, et al. Epidemiological characteristic and current status of surgical treatment for esophageal cancer by analysis of national registry database. Zhonghua zhong liu za zhi (Chinese Journal of Oncology). 2020;42:228–33.
4. Yu J, Ouyang W, Li Y, Hu J, Xu Y, Wei Y, et al. Value of radiotherapy in addition to esophagectomy for stage II and III thoracic esophageal squamous cell carcinoma: Analysis of surveillance, epidemiology, and end results database. Cancer Med. 2019;8:21–7.
5. Zhang W, Liu X, Xiao Z, Zhang H, Chen D, Feng Q, et al. Postoperative intensity-modulated radiotherapy improved survival in lymph node-positive or stage III thoracic esophageal squamous cell carcinoma. Oncol Res Treat. 2015;38:97–102.
6. Wang ZW, Luan ZP, Zhang W, Dong W, Fu CR, Wang YN, et al. Postoperative chemoradiotherapy improves survival in esophageal squamous cell cancer with extracapsular lymph node extension. Neoplasma. 2014;61:732–8.
7. Shridhar R, Weber J, Hoffe SE, Almhanna K, Karl R, Meredith K. Adjuvant radiation therapy and lymphadenectomy in esophageal cancer: a SEER database analysis. J Gastrointest Surg. 2013;17:1339–45.
8. Chen J, Zhu J, Pan J, Zhu K, Zheng X, Chen M, et al. Postoperative radiotherapy improved survival of poor prognostic squamous cell carcinoma esophagus. Ann Thorac Surg. 2010;90:435–42.
9. Deng W, Yang J, Ni W, Li C, Chang X, Han W, et al. Postoperative radiotherapy in pathological T2–3N0M0 thoracic esophageal squamous cell carcinoma: interim report of a prospective, phase III, randomized controlled study. Oncologist. 2020;25:e701–8.
10. Qiao XY, Wang W, Zhou ZG, Gao XS, Chang JY. Comparison of efficacy of regional and extensive clinical target volumes in postoperative radiotherapy for esophageal squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2008;70:396–402.
11. Lu JC, Tao H, Zhang YQ, Zha WW, Qian PD, Li F, et al. Extent of prophylactic postoperative radiotherapy after radical surgery of thoracic esophageal squamous cell carcinoma. Dis Esophagus. 2008;21:502–7.
12. Peng J, Wang WP, Yuan Y, Hu Y, Wang Y, Chen LQ. Optimal extent of lymph node dissection for siewert type II esophagogastric junction adenocarcinoma. Ann Thorac Surg. 2015;100:263–9.
13. Schreiber D, Rineer J, Vongtama D, Peter Han DS, Choi K, Rotman M. Impact of postoperative radiation after esophagectomy for esophageal cancer. J Thorac Oncol. 2010;5(2):244–50.
14. Eyck BM, van Lanschot JJB, Hulshof M, Peter Han DS, Choi K, Rotman M, et al. Ten-year outcome of neoadjuvant chemoradiotherapy plus surgery for esophageal cancer: the randomized controlled CROSS trial. J Clin Oncol. 2021;39:1995–2004.
15. Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z, et al. Long-term efficacy of neoadjuvant chemoradiotherapy plus surgery for the treatment of locally advanced esophageal squamous cell carcinoma: the NEOCRTEC5010 randomized clinical trial. JAMA Surg. 2021;156:721–9.
16. Xiao ZF, Yang ZY, Liang J, Miao YJ, Wang M, Yin WB, et al. Value of radiotherapy after radical surgery for esophageal carcinoma: a report of 495 patients. Ann Thorac Surg. 2003;75:331–6.
17. Yang J, Zhang W, Xiao Z, Wang Q, Zhou Z, Zhang H, et al. The impact of postoperative conformal radiotherapy after radical surgery on survival and recurrence in pathologic T3N0M0 esophageal carcinoma: a propensity score-matched analysis. J Thorac Oncol. 2017;12:1143–51.
18. Ni W, Yu S, Xiao Z, Zhou Z, Chen D, Feng Q, et al. Postoperative adjuvant therapy versus surgery alone for stage IIB-III esophageal squamous cell carcinoma: a phase III randomized controlled trial. Oncologist. 2021;26:e2151–60.
19. Wong AT, Shao M, Rineer J, Lee A, Schwartz D, Schreiber D. The impact of adjuvant postoperative radiation therapy and chemotherapy on survival after esophagectomy for esophageal carcinoma. Ann Surg. 2017;265:1146–51.
20. Ai D, Chen Y, Liu Q, Deng J, Zhang X, Zhang J, et al. Extensive clinical target volume in postoperative chemoradiotherapy for esophageal squamous cell carcinoma: A phase ii clinical trial (eso-shanghai 9). Radiat Oncol. 2023;18:26.
21. Yu E, Tai P, Younus J, Malthaner R, Truong P, Stitt L, Rodrigues G, et al. Postoperative extended-volume external-beam radiation therapy in high-risk esophageal cancer patients: a prospective experience. Radiat Oncol. 2009;16:48–54.
22. Liu R, Zhang XL, Zhang QN, Luo H, Wei S, Liu T, et al. Adjuvant radiotherapy of involved field versus elective lymph node in patients with operable esophageal squamous cell cancer: A single institution prospective randomized controlled study. J Cancer. 2021;12:3180–9.
23. Huang W, Li B, Gong H, Yu J, Sun H, Zhou T, et al. Pattern of lymph node metastases and its implication in radiotherapeutic clinical target volume in patients with thoracic esophageal squamous cell carcinoma: A report of 1077 cases. Radiother Oncol. 2010;95:229–33.
24. Liu J, Cai XW, Liu Q, Cheng HX, Fu XL. Characteristics of the local recurrence pattern after curative resection and values in target region delineation in postoperative radiotherapy for lower thoracic esophageal squamous cell cancer. Thorac Cancer. 2017;8:630–3.
25. Liu Q, Cai XW, Wu B, Zhu ZF, Chen HQ, Fu XL. Patterns of failure after radical surgery among patients with thoracic esophageal squamous cell carcinoma: implications for the clinical target volume design of postoperative radiotherapy. PLOS ONE. 2014;9(5):e97225.
26. Li CL, Zhang FL, Wang YD, Han C, Sun GG, Liu Q, et al. Characteristics of recurrence after radical esophagectomy with two-field lymph node dissection for thoracic esophageal cancer. Oncol Lett. 2013;5:355–9.
27. Cai WJ, Xin PL. Pattern of relapse in surgical treated patients with thoracic esophageal squamous cell carcinoma and its possible impact on target delineation for postoperative radiotherapy. Radiother Oncol. 2010;96:104–7.
28. Liu Q, Cai XW, Fu XL, Chen JC, Xiang JQ, et al. Tolerance and dose-volume relationship of intrathoracic stomach irradiation after esophagectomy for patients with thoracic esophageal squamous cell carcinoma. Oncotarget. 2016;6(31):32220–7.
29. Ni W, Yang J, Deng W, Xiao Z, Zhou Z, Zhang H, et al. Patterns of recurrence after surgery and efficacy of salvage therapy after recurrence in patients with thoracic esophageal squamous cell carcinoma. BMC Cancer. 2020;20(1):144.
30. Zou B, Pang J, Liu Y, Xu Y, Li L, Zhou L, et al. Postoperative chemoradiotherapy improves survival in patients with stage II-III esophageal squamous cell carcinoma: An analysis of clinical outcomes. Thorac Cancer. 2016;7:515–21.
31. Haefner MF, Lang K, Krug D, Koerber SA, Uhlmann L, Kieser M, et al. Prognostic factors, patterns of recurrence and toxicity for patients with esophageal cancer undergoing definitive radiotherapy or chemo-radiotherapy. J Radiat Res. 2015;56:742–9.
32. Chen J, Pan J, Liu J, Li J, Zhu K, Zheng X, et al. Postoperative radiation therapy with or without concurrent chemotherapy for node-positive thoracic esophageal squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2013;86:671–7.
33. Gupta A, Roy S, Majumdar A, Hazra A, Mallik C. A randomized study to compare sequential chemoradiotherapy with concurrent chemoradiotherapy for unresectable locally advanced esophageal cancer. Indian J Med Paediatr Oncol. 2014;35:54–9.
34. Zou B, Tu Y, Liao D, Xu Y, Wang J, Huang M, et al. Radical esophagectomy for stage II and III thoracic esophageal squamous cell carcinoma followed by adjuvant radiotherapy with or without chemotherapy: Which is more beneficial? Thorac Cancer. 2020;11:631–9.

Publisher's Note