

RESEARCH

Open Access



Propensity-matched study on locally advanced esophageal cancer: surgery versus post-operative radiotherapy

Ya Zeng¹, Xi Su¹, Tongfang Zhou¹, Jingyi Jia¹, Jun Liu¹, Wen Yu¹, Qin Zhang¹, Xinyun Song¹, Xiaolong Fu^{1*} and Xuwei Cai^{1*}

Abstract

Background This study aims to delineate the long-term outcomes and recurrence patterns of locally advanced thoracic esophageal squamous cell carcinoma (TESCC) patients managed with or without postoperative radiotherapy (PORT).

Methods A retrospective cohort from two academic centers, encompassing patients who initially underwent esophagectomy and were pathologically staged T3-4, was analyzed. Survival outcomes were constructed using Kaplan–Meier method, with survival significance was evaluated using the log-rank test. Propensity score matching (PSM) was utilized to balance potential selection bias.

Results Among the 506 patients, 251 underwent surgery alone and 255 received radiotherapy following radical surgery. With a median follow-up of 49.1 months, PORT significantly improved 5-year overall survival (53.8% vs. 25.3%; $p < 0.001$) and 5-year disease-free survival rates (45.3% vs. 8.5%; $p < 0.001$) compared to surgery alone. These differences in survival outcomes persisted even after PSM ($p < 0.001$ for both). Treatment failure was significantly less frequent in the PORT group (46.7%) compared to the surgery-only group (90.0%; $p < 0.001$), with corresponding reductions in locoregional recurrence (9.4% vs. 54.1%; $p < 0.001$). This underscores the significant association between PORT and disease control.

Conclusion The absence of neoadjuvant chemoradiotherapy highlights the importance of PORT in improving survival and reducing recurrence in advanced T3-4 TESCC patients. This study underscores the importance of PORT as a salvage treatment for locally advanced TESCC patients without neoadjuvant chemoradiotherapy.

Keywords Postoperative radiotherapy, Locally advanced esophageal squamous cell carcinoma, Survival outcomes, Recurrent pattern

Introduction

Esophageal cancer ranks among the most aggressive malignancies. Neoadjuvant chemoradiotherapy is the standard care for operable thoracic esophageal cancer [1, 2]. However, a considerable number of esophageal cancer patients opt for esophagectomy as their initial treatment strategy and some of these patients experience an upgrade in pathological staging postoperatively [3, 4]. A majority experience local failure within two years after

*Correspondence:

Xiaolong Fu
xlfu1964@hotmail.com

Xuwei Cai
birdhome2000@163.com

¹ Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, 241 West Huaihai Road, Shanghai 200030, China



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

radical surgery [5–7], resulting in a dismal survival outcome [8–10]. Adjuvant treatment becomes imperative for patients who undergo esophagectomy alone, especially those who receive a pathological diagnosis of locally advanced thoracic esophageal squamous cell carcinoma (TESCC). The significance of postoperative adjuvant therapy, particularly postoperative radiotherapy (PORT), has been under investigation for decades in esophageal cancer patients, particularly those with the ESCC subtype. Previous studies have indicated that PORT could improve local control and potentially increase overall survival among patients with positive lymph nodes or stage T3-4 disease [11–16]. However, these conclusions were drawn from retrospective or database studies, making them susceptible to selection bias and group imbalances [17]. Two prospective clinical trials also concluded that PORT can improve survival for certain patients, specifically those with stage III disease or positive lymph nodes [11, 16], albeit in the era of older radiation technology. However, given the advancements in modern radiotherapy techniques, their findings may not be insufficient to convincingly support its efficacy under current treatment conditions. The official recommendation for adjuvant PORT is limited to TESCC patients with residual disease after surgery. Conducting a large prospective study to compare outcomes between patients with and without PORT is challenging, given the decreasing number of patients opting for surgery initially in the context of the standard neoadjuvant therapy plus surgery treatment strategy.

This study aimed to compare outcomes between patients who received adjuvant radiotherapy and those who did not after undergoing curative esophagectomy using propensity-score matching method. Additionally, nomogram models were developed to predict the risk of disease progression or local recurrence in individuals with locally advanced TESCC.

Methods

Patients included in this study were retrospectively collected from two academic treatment centers between 2007 and 2016 for the surgery alone group. Patients in the postoperative radiotherapy (PORT) group were recruited from a randomized clinical trial conducted between 2011 and 2021 in the same two centers. Eligible participants were those who had undergone radical esophagectomy and were pathologically diagnosed with stage T3-4 thoracic esophageal squamous cell carcinoma, with any N and M0 status. Patients with present or prior other malignancies, those who received any neoadjuvant therapy, individuals who underwent adjuvant immunotherapy or received prior thoracic radiation therapy, and patients with mixed cancer cells or other histologic subtypes were excluded from the study. Additionally, patients who underwent surgery were not to receive adjuvant radiation treatment after surgery.

Figure 1 illustrates the flow of patient selection of this study (Fig. 1). Baseline characteristics and treatment details were systematically enrolled from patients' medical records; these encompassed demographic information

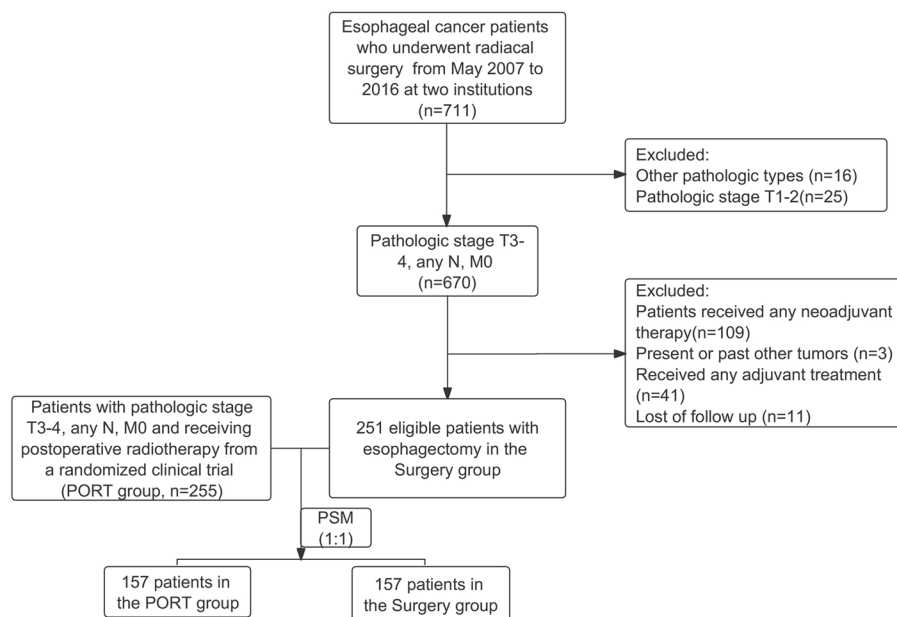


Fig. 1 Flowchart for patient selection

such as age and gender, as well as clinical data, including pathological findings, the extent of lymph node dissection, and the regime of adjuvant chemotherapy administered. The study secured approval from the Research Ethics Boards of the respective institutions involved, and the requirement for written informed consent from the patients was waived, attributable to the retrospective nature of the research. This study is in accord with the ethical standards of the 1975 Declaration of Helsinki.

Postoperative radiation treatment

Adjuvant radiotherapy was administered within eight weeks following surgery. Among the 255 patients undergoing postoperative radiotherapy, prophylactic irradiation was received by 122 with a radiation field that included the primary tumor bed and adjacent lymph node regions. For the remaining 133 patients, those with upper or middle third thoracic cancer underwent modified T-shaped field radiation, targeting bilateral supraclavicular and upper mediastinal lymph node areas, extending from the lower edge of cricoid to 3 cm beneath the subcarinal region or the primary lesion's lower boundary. Conversely, the clinical target volume (CTV) for patients with lower third thoracic cancer encompassed the mediastinal lymph node area, delineated from the T1 vertebral body to the primary tumor bed's lower margin. The CTV received a cumulative dose of 50.4 Gy across 28 fractions, complemented by a 9.8–12.6 Gy boost to the tumor bed, utilizing a simultaneous integrated-boost intensity-modulated radiotherapy technique.

Follow up

Patient follow-ups were conducted tri-monthly for the initial two years after treatment, semi-annually for the subsequent two years, and then annually.

The final follow-up for this study was conducted in March 2023. Routine assessments of treatment response encompassed thoracic computed tomography (CT), esophageal radiography or endoscopy, and abdominal and cervical ultrasound. Ancillary investigations such as bone scintigraphy, fine-needle aspiration cytology, and positron emission tomography-CT were not mandatory during these follow-up sessions. The primary recurrence pattern was meticulously documented, and any subsequent relapses detected within a one-month interval were recorded as concurrent. Evaluations of treatment responses adhered strictly to the RECIST 1.1 criteria.

Statistical analysis

Baseline characteristics of the groups were analyzed using the Chi-square test. Survival rates were estimated using the Kaplan–Meier method, and differences in disease-free survival (DFS) and overall survival (OS)

between the PORT group and the surgery group were evaluated through the log-rank test. DFS was defined from the date of surgery to the occurrence of the first failure pattern, death from any cause, or the last follow-up date. OS was measured from the date of surgery to the date of death from any cause or the last follow-up date. Prognostic factors affecting survival were analyzed using univariable and multivariable Cox proportional hazard regression models. To balance potential baseline factors, including lymph node dissection field, primary tumor location, number of dissected lymph nodes, N stage, and chemotherapy, propensity score matching (PSM) analysis was performed (caliper = 0.1). Factors related to disease progression or local recurrence in patients with locally advanced TESCC were assessed using logistic regression analysis. A nomogram model was generated based on the results of the logistic regression. The area under the curve (AUC) values of time-dependent receiver operating characteristics were calculated, and calibration curves were plotted to assess the consistency between actual recurrence probability and predicted recurrence probability. Calibration was determined using the Unreliability test, and $S: p > 0.05$ indicated that the model passed the calibration test. Statistical significance was defined as a two-sided p -value less than 0.05. Data analyses were conducted using SPSS 22.0 software, GraphPad Prism 7, and R-4.2.2 software.

Results

Baseline characteristics and treatment

This study included a total of 506 patients. Among them, 255 patients underwent postoperative adjuvant radiotherapy with or without chemotherapy (PORT group), while 251 patients underwent radical surgery alone (surgery group). A significant majority, 94.9% of patients, presented with stage T3 disease. Notably, 13.4% of patients underwent three-field lymph node dissection. It's worth mentioning that patients who underwent three-field lymph node dissection were less likely to receive postoperative radiotherapy (surgery vs. PORT, 21.1% vs. 5.9%; $p < 0.001$). Furthermore, the PORT group had a higher proportion of patients with lower third thoracic diseases compared to the surgery group (60.8% vs. 38.6%; $p < 0.001$). Patients with stage N2 or N3 disease were also more inclined to receive adjuvant radiotherapy (surgery vs. PORT, 8.0% vs. 31.4%; $p < 0.001$). Surprisingly, almost half of the patients with locally advanced ESCC, specifically 49.2%, did not undergo adjuvant chemotherapy. A summary of the baseline characteristics of the study population is presented in Table 1.

Table 1 Baseline characteristics

		Before PSM			After PSM		
		surgery group (n = 251, %)	PORT group (n = 255, %)	p value	Surgery group (n = 157, %)	PORT group (n = 157, %)	p value
Gender				0.94			0.36
	Male	222 (88.4)	225 (88.2)		84 (53.5)	138 (87.9)	
	Female	29 (11.6)	30 (11.8)		73 (46.5)	19 (12.1)	
Age				0.43			0.17
	≤ 60	132 (52.6)	143 (56.1)		84 (53.5)	96 (61.1)	
	> 60	119 (47.4)	112 (43.9)		73 (46.5)	61 (38.9)	
Differentiation				0.43			0.56
	Well	16 (6.4)	22 (8.6)		9 (5.7)	9 (5.7)	
	Moderate	135 (53.8)	143 (56.1)		89 (56.7)	98 (62.4)	
	Poor	100 (39.8)	90 (35.3)		59 (37.6)	50 (31.8)	
Dissection field				<0.001			0.19
	Three field	53 (21.1)	15 (5.9)		19 (12.1)	12 (7.6)	
	Two field	198 (78.9)	239 (94.1)		138 (87.9)	145 (92.4)	
Tumor location				<0.001			0.58
	Upper TEC	21 (8.4)	16 (6.3)		5 (3.2)	8 (5.1)	
	Middle TEC	133 (53.0)	84 (32.9)		63 (40.1)	67 (42.7)	
	Lower TEC	97 (38.6)	155 (60.8)		89 (56.7)	82 (52.2)	
Dissection LN				<0.001			0.65
	≤ 21	158 (62.9)	109 (42.7)		82 (52.2)	78 (49.7)	
	> 21	93 (37.1)	146 (57.3)		75 (47.8)	79 (50.3)	
T stage				0.39			0.24
	T3	236 (94.0)	244 (95.7)		153 (97.5)	149 (94.9)	
	T4	15 (6.0)	11 (4.3)		4 (2.5)	8 (5.1)	
N stage				<0.001			1.00
	N0-1	231 (92.0)	175 (68.6)		139 (88.5)	139 (88.5)	
	N2-3	20 (8.0)	80 (31.4)		18 (11.5)	18 (11.5)	
Chemotherapy				0.01			0.65
	No	138 (55.0)	111 (43.5)		82 (52.2)	78 (49.7)	
	Yes	113 (45.0)	144 (56.5)		75 (47.8)	79 (50.3)	

PSM propensity-score matching, PORT postoperative radiotherapy, TEC thoracic esophageal cancer, LN lymph node

Survival outcomes and prognostic factors

With a median follow-up duration of 49.1 months (95%CI, 50.6–61.8) for the surviving patients, the 3-year and 5-year DFS rates for patients in the PORT group were 49.8% and 45.3%, respectively, in contrast to 12.3% and 8.5% for patients who did not receive adjuvant radiotherapy. Those who underwent postoperative radiotherapy exhibited significantly prolonged DFS compared to those who underwent surgery alone, with a median DFS of 35.8 months versus 8.0 months (HR, 0.36; 95%CI, 0.29–0.44; $p < 0.001$; as illustrated in Fig. 2A). The 3-year and 5-year OS rates were 64.8% and 53.8% for patients in the PORT group, while in the surgery group, these rates were 35.2% and 25.3%, respectively. Importantly, PORT demonstrated a significant improvement in OS compared to surgery

alone for locally advanced TESCC, with a median OS of 74.6 months versus 21.3 months (HR, 0.41; 95%CI, 0.33–0.52; $p < 0.001$; Fig. 2B).

In the univariable analyses, DFS exhibited associations with primary tumor location, the number of dissected lymph nodes, T stage, and PORT. Meanwhile, OS displayed correlations with gender, age, tumor differentiation, the number of dissected lymph nodes, T stage, N stage, and PORT.

The multivariable analyses revealed that stage T3 (HR, 0.55; 95%CI, 0.36–0.84; $p = 0.01$) and PORT (HR, 0.34; 95%CI, 0.27–0.43; $p < 0.001$) were associated with prolonged DFS. Furthermore, female patients (HR, 1.78; 95%CI, 1.16–2.72; $p = 0.009$), well-differentiated tumors (HR, 0.49; 95%CI, 0.28–0.88; $p = 0.02$), dissected

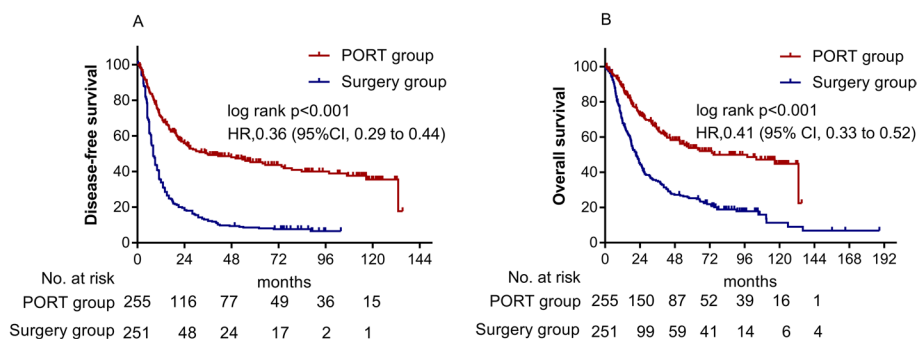


Fig. 2 Survival outcomes of the entire population. **A** Disease-free survival; **B** overall survival. PORT, postoperative radiotherapy; HR, hazard ratio; CI, confidence Interval; No, number

lymph nodes exceeding 21 (HR, 1.30; 95%CI, 1.02–1.65; $p=0.03$)), stage T3 (HR, 0.44; 95%CI, 0.28–0.70; $p<0.001$), N0-1 (HR, 0.38; 95%CI, 0.27–0.53; $p<0.001$), and PORT (HR, 0.32; 95%CI, 0.24–0.42; $p<0.001$) were identified as independent favorable prognostic factors for OS (see additional file-Table s1).

In the PSM cohort, the well-matched population confirmed the survival findings. The PORT group exhibited 3-year and 5-year DFS rates of 50.9% and 45.7%, respectively, while the surgery group showed rates of 9.8% and 7.8%, respectively. Furthermore, the 3-year and 5-year OS rates of PORT group were 64.6% and 53.1%, respectively, whereas the surgery group had rates of 33.1% and 24.2%, respectively. These differences remained statistically significant for both DFS (median DFS, 47.9 vs. 8.0 months; HR, 0.34; 95%CI, 0.26–0.44; $p<0.001$; Fig. 3A) and OS (median OS, 73.5 vs. 20.3 months; HR, 0.39; 95%CI, 0.29–0.52; $p<0.001$; Fig. 3B).

In the PSM population (see additional file-Table s2), univariable analyses revealed associations between survival outcomes and pathological N stage as well as PORT. Furthermore, in the multivariable analyses, N0-1 stage (HR, 0.48; 95%CI, 0.40–0.58; $p<0.001$) and PORT (HR, 0.29; 95%CI, 0.22–0.38; $p<0.001$) emerged as

independent prognostic factors for DFS. Similarly, in the well-balanced cohort, N stage (HR, 0.51; 95%CI, 0.41–0.62; $p<0.001$) and PORT (HR, 0.36; 95%CI, 0.27–0.48; $p<0.001$) were identified as independent factors associated with OS.

Initial recurrence patterns and risk factors for progression

During the follow-up period, disease recurrence was observed in 90.0% (226/251) of patients in the surgery group and 46.7% (119/255) of patients in the PORT group, with a statistically significant difference ($p<0.001$). As indicated in Table 2, distant metastases were noted in 19.5% (49/251) of surgery group patients and 28.6% (73/255) of PORT group patients, demonstrating a significant difference ($p<0.001$). Notably, hematologic metastasis emerged as the predominant failure pattern in patients who had undergone adjuvant radiotherapy. In contrast, locoregional recurrence (54.2% vs. 9.4%, $p<0.001$) and anastomosis recurrence (6.4% vs. 0.8%, $p=0.03$) were more frequently observed in the surgery group compared to the PORT group. These differences in distant metastases and locoregional relapse between the two groups remained statistically significant (both $p<0.001$) in the PSM cohort. It is noteworthy that,

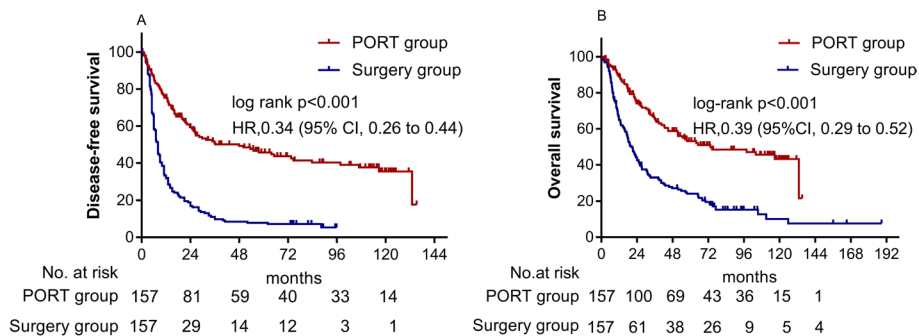


Fig. 3 Survival outcomes of patients after propensity-score matching. **A** Disease-free survival; **B** overall survival. PORT, postoperative radiotherapy; HR, hazard ratio; CI, confidence Interval; No, number

Table 2 Failure patterns of two groups in the entire population and PSM cohort

Recurrence patterns	Before PSM			After PSM		
	Surgery group (n=251, %)	PORT group (n=255, %)	p value	Surgery group (n=157, %)	PORT group (n=157, %)	p value
Distant metastasis	49 (19.5)	73 (28.6)	<0.001	28 (17.8)	43 (27.4)	<0.001
Locoregional recurrence	136 (54.2)	24 (9.4)	<0.001	86 (54.8)	19 (12.1)	<0.001
Anastomosis recurrence	16 (6.4)	2 (0.8)	0.03	10 (6.4)	1 (0.6)	0.10
Mixed recurrence	25 (10.0)	20 (7.8)	0.13	19 (12.1)	13 (8.3)	0.45

PORT postoperative radiotherapy

for patients experiencing locoregional recurrences, 87.8% (40/46) of cases occurred within the radiation field in the PORT group. While 96% (170/177) of locoregional recurrences in the surgery group were within the specified radiation field.

The logistic regression results revealed that T stage (OR, 1.87; 95%CI, 1.19–2.95; $p=0.007$), age (OR, 0.40; 95%CI, 0.25–0.60; $p<0.001$), PORT (OR, 0.06; 95%CI, 0.04–0.10; $p<0.001$), and adjuvant chemotherapy (OR, 0.53; 95%CI, 0.32–0.87; $p=0.01$) were identified as independent factors associated with locoregional recurrence. Furthermore, T stage (OR, 0.18; 95%CI, 0.04–0.86; $p=0.03$), N stage (OR, 1.75; 95%CI, 1.32–2.33; $p<0.001$), and PORT (OR, 0.08; 95%CI, 0.05–0.14; $p<0.001$) were strongly correlated with disease progression. These significant associations led to the development of two separate nomogram models (Fig. 4A, B) designed to

predict the likelihood of locoregional recurrence and overall disease progression in patients who had undergone esophagectomy for locally advanced TESCC.

These models exhibited commendable predictive accuracy, as evidenced by their area under the curve (AUC) values: 0.833 for locoregional recurrence and 0.805 for disease progression. Moreover, calibration curves were employed to assess the models' accuracy in predicting locoregional recurrence (S: $p=0.802$, Fig. 4C) and overall progression (S: $p=0.474$, Fig. 4D).

Discussion

This study emphasizes that patients undergoing esophagectomy without adjuvant treatment experienced short-term treatment failures, leading to unfavorable outcomes. Adjuvant radiotherapy significantly improves local control and overall survival in patients with stage

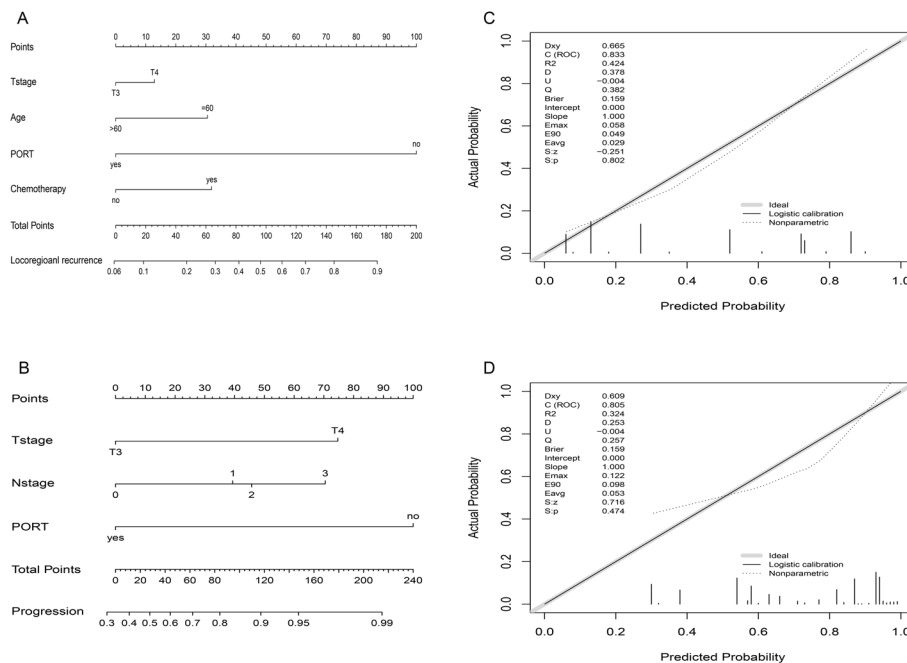


Fig. 4 Nomogram models to calculate risk score and predictions of progressive probability and calibration curves. **A** Local recurrence model; **B** Total progression model; **C** calibration curves for (A); **D** calibration curves for (B). PORT, postoperative radiotherapy

T3-4N0-3M0 disease, consistent with previous research. The role of postoperative adjuvant radiotherapy in the management of locally advanced TESCC patients is pivotal. Notably, the survival outcomes in the PORT group indicate that patients receiving adjuvant radiotherapy can achieve survival outcomes comparable to those who undergo standard neoadjuvant chemoradiotherapy followed by surgery [1, 18].

Postoperative radiotherapy is not considered the standard treatment for esophageal cancer patients, encompassing both ESCC and adenocarcinoma, as indicated by recommended clinical guidelines. Nonetheless, in the real-world clinical practice, a significant number of patients opt for surgery as their primary treatment approach, as documented in various studies [4, 9]. It's worth noting that the underutilization of preoperative endoscopic ultrasound has been associated with disease upstaging following esophagectomy. Patients diagnosed with stage T3-4, any N, M0 disease who undergo surgery alone face a substantial risk of experiencing treatment failure. This study provides compelling evidence that adjuvant PORT plays a pivotal role in reducing the risk of locoregional recurrence and overall disease progression among patients with locally advanced TESCC, as indicated by our nomogram models. Furthermore, patients in the PORT group revealed superior survival outcomes compared to those who underwent surgery alone. The effectiveness of postoperative radiotherapy in the treatment of stage III TESCC or lymph node-positive cases is not only supported by this study but also corroborated by numerous previous retrospective and prospective investigations [3, 11, 16, 18–22]. Importantly, this study identifies PORT as an independent prognostic factor for patients with locally advanced TESCC. Consequently, it can be inferred that adjuvant radiotherapy should be considered a vital therapeutic option for patients diagnosed with locally advanced TESCC who initially choose surgery as their primary treatment strategy.

It is well-established that preoperative chemoradiotherapy is considered the standard of care for esophageal cancer, encompassing both squamous cell carcinoma and adenocarcinoma. Remarkably, our findings reveal promising outcomes for patients with locally advanced TESCC who may not have initially received the standard neoadjuvant chemoradiotherapy [1, 2]. Specifically, patients diagnosed with locally advanced TESCC after upfront surgery and subsequently treated with PORT exhibit a remarkable 5-year DFS rate of 45.3% and a 5-year OS rate of 53.8%. While it's important to note that direct comparisons across different studies are not valid, we do observe that the survival outcomes in our study appear numerically similar to those reported for patients who underwent neoadjuvant chemoradiotherapy in the CROSS

study (5-year PFS, 44%; 5-year OS rate, 47%). It's crucial to clarify that our intention was not to directly compare these two distinct studies. Rather, we aimed to emphasize the significant potential for patients who did not initially receive neoadjuvant therapy plus surgery to benefit from postoperative radiotherapy, as evidenced by these promising results.

Hematogenous metastasis has emerged as a new-found concern impacting the overall survival of patients who have undergone adjuvant radiotherapy. Although a prior study by Chen and colleagues [13] reported an 8.6% improvement in 5-year OS rates with postoperative radiotherapy concurrent with chemotherapy for ESCC patients with lymph node involvement, chemotherapy appears to have limited influence on improving survival in cases of locally advanced TESCC, as demonstrated by the Cox regression analyses conducted in this study. Furthermore, there were no significant differences in failure patterns between patients who received PORT with or without chemotherapy. Interestingly, hematogenous metastasis has become a predominant factor contributing to treatment failure, even in cases of neoadjuvant chemoradiotherapy [1, 18, 23, 24]. It appears that chemotherapy may have limited impact on addressing hematogenous metastasis. Immunotherapy has now become the standard approach for treating metastatic esophageal cancer [25]. Nivolumab, a PD-1 antibody, has been recommended as adjuvant treatment for patients who have undergone neoadjuvant chemoradiation and still exhibit residual pathologic disease after surgery according to the findings of the Checkmate 577 trial [26]. Further research is required to investigate whether immune checkpoint inhibitors can effectively target and eliminate potentially metastatic tumor cells in patients following esophagectomy. Ongoing clinical trials (NCT04688801, NCI-2018-01575) are investigating adjuvant immunotherapy for patients who have undergone primary surgery to evaluate its efficacy. Additionally, identifying molecular targets to control hematogenous metastasis in esophageal cancer patients is a pressing concern for the future.

The determination of the clinical target volume (CTV) for PORT holds equal significance in the context of TESCC patients. However, as of the present, a well-established standard for CTV has yet to be established [27–33]. The utilization of a modified elective nodal irradiation field, as employed in this study, appears to be a reasonable option for patients with locally advanced TESCC. The study's results indicate that patients who received PORT experienced significantly fewer locoregional recurrences compared to those treated with surgery alone. Furthermore, it's worth noting that most recurrences in the surgery group were observed within the referred radiation field, underscoring its validity

in the management of locally advanced TESCC (Additional file-Fig. s1). Currently, investigations are underway regarding the use of adjuvant immune checkpoint inhibitors in esophageal cancer patients. Radiotherapy has been considered a potential enhancer of the anti-tumor effect, opening up possibilities for exploring the combination of radiotherapy and immunotherapy. The delineation of the CTV for PORT emerges as another crucial area of interest in the era of immunotherapy, and it may warrant further examination in future research.

The retrospective cohort has some inherent limitations. Firstly, patients in the surgery group were retrospectively collected from two different academic treatment centers, and surgical strategies varied across centers and over the years. This variability may have led to an underestimation of the survival outcomes for patients in the surgery group. Additionally, patients with locally advanced disease who did not receive adjuvant treatment likely had a poor performance score post-surgery, potentially contributing to unfavorable outcomes. Studies have indicated that performance scores, along with other factors, can categorize patients into different risk groups and predict mortality within 90 days post-surgery [34]. It has been reported that a lower performance score negatively affects the survival of esophageal cancer patients [35]. Therefore, incorporating performance scores into survival prognosis assessments is advisable. Moreover, certain aspects remain unexplored, such as radiation dosage and treatment-related toxicity. The findings of this study suggest that the described PORT procedure may be considered acceptable; however, these concerns warrant validation in future investigations.

Conclusions

In summary, postoperative radiotherapy significantly decreased locoregional recurrence and improved overall survival for locally advanced TESCC patients after initial esophagectomy. These findings emphasize the crucial role of PORT as a salvage treatment strategy for locally advanced TESCC patients who, for various reasons, did not undergo neoadjuvant chemoradiotherapy.

Abbreviations

TESCC	Thoracic esophageal squamous cell carcinoma
PORT	Postoperative radiotherapy
PSM	Propensity score matching
CTV	Clinical target volume
OS	Overall survival
DFS	Disease-free survival
AUC	Area under the curve
OR	Odds ratio
CT	Computed tomography
HR	Hazard ratio

CI Confidence interval
LN Lymph node

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13014-024-02528-0>.

Supplementary material 1: Table s1. Cox regression analyses of DFS and OS before propensity-score matching. Table s2. Cox regression analyses of DFS and OS after propensity-score matching

Supplementary material 2: Fig.s1. A heatmap to show the details of failure patterns of two groups. PORT, postoperative radiotherapy.

Acknowledgements

Not applicable.

Author contributions

CXW and FXL generated the conception of the present study; LJ, YW, ZQ provided patient's material; SX, ZTF, JJY collected patient data; ZY, SXY analyzed and interpreted the patient data, and ZY was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by Emerging advanced technology joint research project of Shanghai Shenkang Hospital Development Center (SHDC12017103) and Shanghai science and Technology Fund (21Y11913000).

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This study is retrospective in nature, and as such, the requirement for ethics approval and consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 6 February 2024 Accepted: 18 September 2024

Published online: 27 September 2024

References

1. Yang H, Liu H, Chen Y, 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.
2. Eyck BM, van Lanschot JJB, Hulshof 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.
3. Yu J, Ouyang W, Li 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.
4. Mao YS, Gao SG, Wang Q, et al. Epidemiological characteristic and current status of surgical treatment for esophageal cancer by analysis of national registry database. *Zhonghua Zhong Liu Za Zhi.* 2020;42:228–33.

5. Li CL, Zhang FL, Wang YD, et al. Characteristics of recurrence after radical esophagectomy with two-field lymph node dissection for thoracic esophageal cancer. *Oncol Lett.* 2013;5:355–9.
6. Nakagawa S, Kanda T, Kosugi S, et al. Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. *J Am Coll Surg.* 2004;198:205–11.
7. Wu SG, Dai MM, He ZY, et al. Patterns of regional lymph node recurrence after radical surgery for thoracic esophageal squamous cell carcinoma. *Ann Thorac Surg.* 2016;101(2):551–7.
8. Gavin AT, Francisci S, Foschi R, et al. Oesophageal cancer survival in Europe: a EURO-CARE-4 study. *Cancer Epidemiol.* 2012;36:505–12.
9. Njei B, McCarty TR, Birk JW. Trends in esophageal cancer survival in United States adults from 1973 to 2009: a SEER database analysis. *J Gastroenterol Hepatol.* 2016;31:1141–6.
10. Zeng H, Zheng R, Guo Y, et al. Cancer survival in China, 2003–2005: a population-based study. *Int J Cancer.* 2015;136:1921–30.
11. Xiao ZF, Yang ZY, Liang J, et al. Value of radiotherapy after radical surgery for esophageal carcinoma: a report of 495 patients. *Ann Thorac Surg.* 2003;75:331–6.
12. Zhang W, Liu X, Xiao Z, 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.
13. Chen J, Pan J, Liu J, 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.
14. Chen J, Pan J, Liu J, et al. Number and location of positive nodes, postoperative radiotherapy, and survival after esophagectomy with three-field lymph node dissection for thoracic esophageal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys.* 2012;82:475–82.
15. Ni W, Yu S, Xiao Z, 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.
16. Xiao Z, Yang ZY, Miao YJ, et al. Influence of number of metastatic lymph nodes on survival of curative resected thoracic esophageal cancer patients and value of radiotherapy: report of 549 cases. *Int J Radiat Oncol Biol Phys.* 2005;62:82–90.
17. Wang Y, Wang F. Postoperative radiotherapy for thoracic esophageal carcinoma with upfront R0 esophagectomy. *Cancer Manag Res.* 2020;12:13023–32.
18. Shapiro J, van Lanschot JJB, Hulshof MCCM, 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.
19. Zhu Y, Li M, Kong L, et al. Postoperative radiation in esophageal squamous cell carcinoma and target volume delineation. *Onco Targets Ther.* 2016;9:4187–96.
20. Wong AT, Shao M, Rineer J, et al. The impact of adjuvant postoperative radiation therapy and chemotherapy on survival after esophagectomy for esophageal carcinoma. *Ann Surg.* 2017;265:1146–51.
21. Deng W, Yang J, Ni 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.
22. Lin HN, Chen LQ, Shang QX, et al. A meta-analysis on surgery with or without postoperative radiotherapy to treat squamous cell esophageal carcinoma. *Int J Surg.* 2020;80:184–91.
23. Oppedijk V, van der Gaast A, van Lanschot JJB, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol.* 2014;32:385–91.
24. Xi M, Yang Y, Zhang L, et al. Multi-institutional analysis of recurrence and survival after neoadjuvant chemoradiotherapy of esophageal cancer. *Ann Surg.* 2019;269:663–70.
25. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet.* 2021;398:759–71.
26. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. *N Engl J Med.* 2021;384:1191–203.
27. Lu JC, Tao H, Zhang YQ, et al. Extent of prophylactic postoperative radiotherapy after radical surgery of thoracic esophageal squamous cell carcinoma. *Dis Esophagus.* 2008;21:502–7.
28. Qiao XY, Wang W, Zhou ZG, et al. 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.
29. Yu E, Tai P, Younus J, et al. Postoperative extended-volume external-beam radiation therapy in high-risk esophageal cancer patients: a prospective experience. *Radiat Oncol.* 2009;16:48–54.
30. Zhang X, Ai D, Wang J, et al. The prognosis and feasibility of extensive clinical target volume in postoperative radiotherapy for esophageal squamous cell carcinoma: a phase II clinical trial. *Front Oncol.* 2021;11: 669575.
31. Ai D, Chen Y, Liu Q, 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.
32. Yang J, Zhang W, Xiao Z, 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.
33. Huang W, Li B, Gong H, 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.
34. D'Journo XB, Boulate D, Fourdrain A, et al. Risk prediction model of 90-day mortality after esophagectomy for cancer. *JAMA Surg.* 2021;156:836–45.
35. Pather K, Mobley EM, Guerrier C, et al. Long-term survival outcomes of esophageal cancer after minimally invasive Ivor Lewis esophagectomy. *World J Surg Oncol.* 2022;20:50.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.