Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(12) 1–11

DOI: 10.1177/0300060520977403
journals.sagepub.com/home/imr
SAGE

Risk factors for tumor recurrence in patients with $pT_3N_0M_0$ thoracic esophageal squamous cell carcinoma after esophagectomy

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Abstract

Objective: To analyze the factors contributing to recurrence in patients with $pT_3N_0M_0$ thoracic esophageal squamous cell carcinoma (ESCC).

Methods: Patients with $pT_3N_0M_0$ thoracic ESCC who underwent esophagectomy from January 2008 to December 2012 were included retrospectively. The last date of follow-up was 1 December 2016. Multivariate proportional hazard Cox models were used to identify factors associated with total (i.e., any) recurrence (TR), locoregional recurrence (LR), and distant metastasis (DM).

Results: A total of 692 patients were included. The median follow-up was 53 months (range: 3–107). The 3- and 5-year TR, LR, and DM rates were 35.8% and 41.0%, 28.7% and 32.1%, and 16.8% and 21.1%, respectively. The Cox analyses showed that the tumor location, number of dissected lymph nodes, and postoperative therapies were significantly associated with LR. The subgroup analysis showed that postoperative therapies could significantly decrease LR in the mediastinum but not in the neck and upper abdomen regions.

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Conclusions: The recurrence rate of $pT_3N_0M_0$ thoracic ESCC patients was high, especially for LR in the mediastinum. Postoperative therapies can significantly reduce the incidence of mediastinal recurrence.

Keywords
Esophageal squamous cell carcinoma, esophagectomy, recurrence, adjuvant radiotherapy, adjuvant chemotherapy, distant metastasis

Date received: 14 July 2020; accepted: 6 November 2020

Introduction

Esophageal cancer (EC) is the seventh most common cancer worldwide.[1] The incidence of EC is higher in developing countries than in developed ones.[2] Over half of newly diagnosed EC cases occur in China.[3] Esophageal squamous cell carcinoma (ESCC) has remained the predominant pathological type of EC in China, accounting for over 90% of EC patients.[4] Neoadjuvant chemoradiotherapy (NCRT) is recommended by the National Comprehensive Cancer Network (NCCN) for esophageal carcinoma in patients with node-positive disease and bulky tumors based on the results of many large scale studies, such as the CROSS trial.[5] A network meta-analysis by Huang Y et al. also confirmed that NCRT could increase the radical resection rate and lower the occurrence of complications, thereby prolonging the survival time for ESCC patients.[6] However, in China, radical esophagectomy is regarded as a curative treatment for resectable ESCC (e.g., $pT_{1–3}N_0$).

After surgery, many patients develop locoregional recurrence (LR) and distant metastasis (DM).[7–11] The reported 5-year survival rates of $pT_{1–3}N_0$ ESCC patients after radical esophagectomy in China is ~50%.[12–14] Postoperative radiotherapy (PORT) and chemotherapy (POCT) have been shown to improve the survival of locally advanced ESCC patients (e.g., $cN_{1–2}$ or $pN_{1–2}$).[15,16] However, their role in the treatment of pN_0M_0 ESCC patients, especially those with $pT_3N_0M_0$ ESCC, is unknown.[8] In this study, we investigated the impact of PORT, POCT, and other clinical factors on the LR, DM, and survival of $pT_3N_0M_0$ ESCC patients.

Methods

Patient selection

The clinical data of all patients with thoracic ESCC $pT_3N_0M_0$ (AJCC 2009), who underwent radical esophagectomy between January 2008 and December 2012 at the Fourth Hospital of Hebei Medical University in China, were retrospectively analyzed. The inclusion criteria were as follows: (1) survival of at least 3 months after radical R0 resection to minimize the impact of surgery-related deaths on the efficacy of postoperative adjuvant therapy, (2) a Karnofsky Performance Score (KPS) of at least 70 before surgery, (3) no preoperative neoadjuvant therapy, and (4) no history of other malignant tumors. The exclusion criteria were (1) non-squamous cell carcinoma of the esophagus, (2) R1/R2 resection, (3) preoperative neoadjuvant therapy, (4) survival of less than 3 months after surgery, (5)

history of other malignant tumors, and (6) incomplete clinical, radiological, and follow-up data. This study was approved by the Medical Ethics Committee of the Fourth Hospital of Hebei Medical University. Written informed consent forms were signed and obtained from all recruited individuals.

Surgery

Before surgery, patients were examined with thoracic and abdominal computed tomography (CT), esophagogram, gastroscopy, and pathology to confirm ESCC. A left thoracotomy was the most common surgical approach for middle and lower thoracic EC. Radical surgical resection consisted of a transthoracic subtotal esophagectomy, including abdominal and mediastinal lymphadenectomy. A right thoracotomy was the most common surgical approach for upper thoracic EC. A gastric tube through the posterior mediastinal route was then used as a substitute for the resected esophagus to restore the continuity of the alimentary tract, and a cervical esophagogastric anastomosis was performed. Pathology and staging were conducted according to the 7th TNM cancer staging criteria.

Postoperative therapies

The postoperative therapies depended upon the stage of the disease, physical condition of the patient, economic status, and personal will of the patient. The demographic and clinical variables, including the preoperatively assigned upper, middle, or lower locations of thoracic ESCCs, were collected for analysis. All patients were categorized into three groups based on the treatment they received as follows: (1) surgery alone, (2) POCT alone, and (3) PORT (with or without sequential chemotherapy). The postoperative adjuvant therapies were administered within 3 months after surgery.

The administered chemotherapy drugs mainly consisted of cisplatin/nedaplatin, fluorouracil, and paclitaxel/docetaxel. Chemotherapy was initiated 3 to 4 weeks after surgery. The median number (range) of chemotherapy cycles prescribed was 3 (range 1–6).

All PORTs used three-dimensional conformal radiotherapy or intensity-modulated radiotherapy. None of the PORT patients received concurrent chemotherapy. The principle of postoperative clinical target volume delineation was to contour the lymphatic drainage regions depending on the location of the tumor as follows: (1) upper mediastinum, supraclavicular region, and lower neck for upper thoracic ESCC, (2) whole or partial mediastinum for middle thoracic ESCC, and (3) middle and lower mediastinum and the region around the left gastric artery for lower thoracic ESCC. All patients in this study had completed the prescribed PORT. The radiotherapy dosage delivery was 50 to 54 Gy/25 to 28 fractions (f), 1.8 to 2.0 Gy/f, and 5 f per week.

Follow-up and outcomes

All patients were followed up until death or 1 December 2016. The follow-up was scheduled every 3 months for 2 years, every 6 months for the next 3 years, and annually thereafter. Contrast-enhanced CT of the neck, thorax, and upper abdomen and routine blood and biochemistry investigations were performed at each follow-up visit. Ultrasonography of the neck and upper abdomen, a nuclear bone scan, gastric endoscopy, positron emission tomography, or cytologic puncture were performed, if indicated. Three outcomes were analyzed in this study: total recurrence (TR), LR, and DM. Specifically, TR was defined as any recurrence or metastasis during the

follow-up period. LR was defined as any locoregional tumor recurrence and/or metastatic lymph node at cervical, mediastinal, and upper abdomen regions defined by AJCC 2009. DM was defined as any event of recurrence or metastasis other than LR. Tumor recurrence and DM were diagnosed by imaging studies [any combination of ultrasound, CT, magnetic resonance imaging, single-photon emission CT, and position emission tomography/CT (PET/CT)] with or without pathological confirmation by biopsy. Recurrence-free survival days were calculated from the date of surgery to the date of each analyzed outcome (TR, LR, and DM) or last follow-up date plus one.

Statistical analysis

A Kaplan–Meier curve and proportional hazard Cox regression model were used to determine the factors affecting tumor recurrence and compare events, such as overall survival (OS), among the subgroups. Logistic regression was used to analyze the association between clinical variables and binary outcomes. All statistical analysis was conducted with SPSS version 22.0. The statistical significance level was a two-sided *p*-value equal to 0.05.

Results

Patient characteristics

From 2008 to 2012, 2350 EC patients underwent esophagectomy at our hospital, of which 692 $pT_3N_0M_0$ thoracic ESCC patients were included in this study. Their median age was 60 (range: 33–86) years, and 30% were women (Table 1). The surgery alone, POCT alone, and PORT subgroups included 278 (40%), 331(48%), and 83 (12%) patients, respectively. Two hundred and sixty-eight patients had mediastinal lymph nodes with a transverse diameter less than 1 cm (defined as "Med. large LN") on CT imaging before surgery. Regarding the surgical approach, 611 (88%) patients underwent an esophagectomy via a left thoracotomy, and 679 (98%) patients received a two-field lymph node dissection (thorax and abdomen). The surgery of adhesions (defined as "Sur. Adhesions") was recorded according to the difficulty in separating esophageal tumors from peripheral normal tissues or organs at surgery, which likely varied among surgeons. The median number of dissected lymph nodes was 9 (range: 1–27).

Table 1. Patient and tumor characteristics.

Variable	Class	N (%)
Sex	Male	487 (70.4%)
	Female	205 (29.6%)
Age (years)	≤ 65	529 (76.4%)
	> 65	163 (23.6%)
Tumor location	Upper	92 (13.3%)
	Middle	471 (60.1%)
	Lower	129 (26.6%)
Med. large LN	No	424 (61.3%)
	Yes	268 (38.7%)
Tumor length (cm)	≤ 5	507 (73.3%)
	> 5	185 (26.7%)
Sur. adhesions	No	33 (4.8%)
	Mild	279 (40.3%)
	Severe	303 (43.8%)
	Data missing	77 (11.1%)
LN dissected	< 12	452 (65.3%)
	≥ 12	240 (34.7%)
Tumor Diff.	High/Moderate	612 (88.4%)
	Low	80 (11.6%)
Post. treatment	Neither	278 (40.2%)
	PORT	83 (12%)
	POCT	331 (47.8%)

Med., mediastinal; LN, lymph node; Sur., surgical; Diff., differentiation; Post., postoperative; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy.

Recurrence rates

The median follow-up period of the entire group was 53 months (range: 3–107).

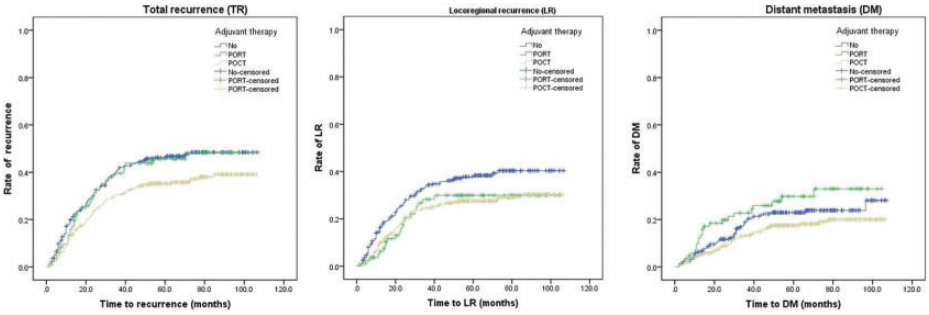

Figure 1. Kaplan–Meier curves of TR (A), LR (B), and DM (C) by adjuvant therapy status in patients with $pT_3N_0M_0$ thoracic esophageal squamous cell carcinoma.
TR, total recurrence; LR, locoregional recurrence; DM, distant metastasis; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy.

Overall, the rates of TR, LR, and DM were 40%, 29.9%, and 19.1%, respectively. The 1-, 3-, and 5-year rates were 16.1%, 35.8%, and 41.0% for TR, 12.0%, 28.7%, and 32.1% for LR, and 6.4%, 16.8%, and 21.1% for DM, respectively. There were significant differences in the TR ($p = 0.018$), LR ($p = 0.016$), and DM ($p = 0.031$) rates of the three groups (Figure 1).

Univariate and multivariate Cox regression analysis showed that the tumor location, number of dissected lymph nodes, tumor differentiation, and POCT were significantly associated with TR, whereas the tumor location, number of dissected lymph nodes, PORT, and POCT were significantly associated with LR. Only tumor location and tumor differentiation were significantly associated with DM (Tables 2 and 3).

Statistically, POCT was associated with reduced TR [hazard ratio (HR) = 0.682; $p = 0.004$] and LR (HR = 0.665; $p = 0.008$), and PORT was associated with reduced LR (HR = 0.580; $p = 0.027$).

Subgroup analysis based on tumor location

We performed a subgroup analysis to determine the benefits of PORT and POCT among different subgroups of $pT_3N_0M_0$ ESCC patients based on tumor location. We found that PORT was significantly associated with reduced TR ($p = 0.011$) and LR ($p = 0.029$) for upper ESCC alone and unexpectedly associated with higher DM for middle ESCC (HR = 1.944; $p = 0.043$). POCT was significantly associated with reduced TR ($p = 0.011$) and LR ($p = 0.038$) for middle ESCC (Table 4). No benefit of POCT or PORT was observed for lower ESCC compared with surgery alone.

Association between postoperative therapy and the site of local recurrence

LR was found to be distributed along cervical, mediastinum, and upper abdomen lymphatic drainage regions. We conducted univariate Cox regression to determine the impact of postoperative treatments on location-specific LR (Table 5). Compared with surgery alone, the addition of PORT and POCT reduced LR in the mediastinum ($p = 0.018$ and $p = 0.011$, respectively) but not in the cervix or upper abdomen.

Discussion

In this study, we observed that the TR rate among $pT_3N_0M_0$ thoracic ESCC patients was as high as 40%. The LR and DM

Table 2. Univariate Cox regression analysis of outcomes.

		TR		LR		DM	
Item	Group	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Gender	Male	1.161 (0.874–1.541)	0.303	1.151 (0.850–1.559)	0.364	1.162 (0.795–1.700)	0.438
	Female	1		1		1	
Ages	≤ 65	1		1		1	
	> 65	1.040 (0.771–1.403)	0.797	1.158 (0.848–1.583)	0.356	1.093 (0.734–1.628)	0.661
Tumor location	Upper	1		1		1	
	Middle	0.552 (0.406–0.750)	0.000	0.605 (0.422–0.869)	0.006	0.456 (0.297–0.699)	0.000
	Lower	0.337 (0.219–0.518)	0.000	0.333 (0.199–0.557)	0.000	0.343 (0.191–0.616)	0.000
Tumor length	≤ 5 cm	1		1		1	
	> 5 cm	1.012 (0.781–1.311)	0.931	1.111 (0.842–1.465)	0.457	0.774 (0.539–1.111)	0.165
Med. large LN	No	1		1		1	
	Yes	1.177 (0.885–1.564)	0.263	1.206 (0.891–1.634)	0.226	1.394 (0.964–2.016)	0.078
LN dissected	< 12	1.499 (1.132–1.985)	0.005	1.452 (1.074–1.964)	0.015	1.395 (0.959–2.027)	0.081
	≥ 12	1		1		1	
Sur. adhesion	No	1		1		1	
	Slight	1.517 (0.766–3.006)	0.232	2.323 (0.942–5.727)	0.067	2.008 (0.730–5.528)	0.177
	Severe	1.637 (0.829–3.232)	0.155	2.357 (0.958–5.801)	0.062	1.779 (0.645–4.908)	0.266
	No record	1.664 (0.782–3.540)	0.186	2.716 (1.043–7.076)	0.041	1.527 (0.492–4.738)	0.464
Tumor Diff.	Middle-high	1		1		1	
	Low	1.894 (1.348–2.661)	0.000	1.350 (0.906–2.011)	0.140	2.817 (1.882–4.216)	0.000
Post. treatment	Neither			1		1	
	PORT	0.999 (0.675–)1.478	0.995	0.686 (0.428–1.099)	0.117	1.407 (0.865–2.290)	0.169
	POCT	0.718 (0.547–0.943)	0.017	0.669 (0.502–0.892)	0.006	0.748 (0.514–1.089)	0.130

TR, total recurrence; LR, locoregional recurrence; DM, distant metastasis. HR, hazard ratio; CI, confidence interval; LN, lymph node; Sur., surgical; Diff., differentiation; Post., postoperative; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy.

rates were 21% and 19%, respectively. Mediastinal LR accounted for 81% of LR. These results are similar to those reported by other Chinese studies.[9,11,12] The current study demonstrated that tumor location was an independent risk factor for TR, LR, and DM. Upper thoracic ESCC had the highest LR rates, followed by middle and lower thoracic ESCC. This finding is in contrast to that reported by previous studies.[17,18] We believe that this might be due to the difference in surgical approaches. In this study, most of our patients underwent two-field lymphadenectomy via a left thoracotomy. Many previous studies have suggested three-field lymph node dissection via a right thoracotomy, especially for upper or middle thoracic ESCC.

We found that the higher number of dissected lymph nodes was associated with higher TR among $pT_3N_0M_0$ ESCC patients. In fact, the NCCN guidelines recommend that at least 15 lymph nodes should be dissected during radical esophagectomy for EC. Previous studies also support this recommendation.[19,20] Greenstein et al.[19] demonstrated that a high number of dissected lymph nodes was associated with an improved survival rate among pN_0 ESCC patients. Dutkowski et al.[20] suggested that at least 12 lymph nodes should be dissected to ensure the accuracy of N staging in EC patients. Although all patients had pN_0 disease, most patients in this study did not receive PET/CT prior to surgery. Therefore, the possibility of unobserved metastatic lymph nodes cannot be

Table 3. Multivariate Cox regression analysis of outcomes.

		TR		LR		DM	
Variable	Class	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex	Female	1.000		1.000		1.000	
	Male	1.196 (0.912–1.567)	0.195	1.208 (0.883–1.652)	0.238	1.236 (0.836–1.827)	0.289
Age (years)	$\leq$ 65	1.000		1.000		1.000	
	$>$ 65	1.058 (0.796–1.407)	0.696	1.106 (0.801–1.527)	0.542	1.140 (0.754–1.723)	0.534
Tumor location	Upper	1.000		1.000	<0.001	1.000	
	Middle	0.604 (0.440–0.829)	0.002	0.627 (0.433–0.908)	0.014	0.551 (0.352–0.862)	0.009
	Lower	0.362 (0.232–0.567)	<0.001	0.322 (0.189–0.549)	0.000	0.434 (0.235-0.804)	0.008
Tumor length	$\leq$ 5 cm	1.000		1.000		1.000	
	$>$ 5 cm	1.189 (0.908–1.558)	0.209	1.225 (0.905–1.660)	0.189	0.886 (0.596–1.318)	0.551
Med. large LN	No	1.000		1.000		1.000	
	Yes	1.111 (0.852–1.449)	0.435	1.212 (0.887–1.656)	0.228	1.246 (0.847–1.832)	0.263
dissected LN	< 12	1.000		1.000		1.000	
	$\geq$ 12	0.724 (0.554–0.946)	0.018	0.693 (0.509–0.945)	0.021	0.799 (0.543–1.176)	0.256
Sur. adhesion	No	1.000		1.000		1.000	
	Slight	1.624 (0.818–3.224)	0.166	2.352 (0.947–5.840)	0.065	1.619 (0.583–4.500)	0.355
	Severe	1.456 (0.736–2.884)	0.281	1.979 (0.800–4.898)	0.140	1.436 (0.516–3.996)	0.489
	No record	1.778 (0.844–3.744)	0.130	2.749 (1.053–7.175)	0.039	1.481 (0.475–4.618)	0.498
Tumor. Diff.	High	1.000		1.000		1.000	
		1.684 (1.212–2.339)	0.002	1.289 (0.855–1.944)	0.226	2.431 (1.588–3.720)	0.000
Post. treatment	Neither	1.000		1.000		1.000	
	PORT	0.784 (0.535–1.151)	0.215	0.580 (0.358–0.941)	0.027	1.096 (0.658–1.827)	0.724
	POCT	0.682 (0.524–0.886)	0.004	0.665 (0.493–0.898)	0.008	0.702 (0.476–1.036)	0.075

TR, total recurrence; LR, locoregional recurrence; DM, distant metastasis. HR, hazard ratio; CI, confidence interval; LN, lymph node; Sur., surgical; Diff., differentiation; Post., postoperative; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy.

Table 4. Univariate logistic regression by tumor location.

		TR		LR		DM	
Location	Treatment	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Upper	Neither	1.000		1.000		1.000	
	PORT	0.147 (0.033–0.649)	0.011	0.091 (0.011–0.780)	0.029	0.467 (0.108–2.020)	0.308
	POCT	0.528 (0.209–1.331)	0.176	0.692 (0.285–1.682)	0.417	0.412 (0.156–1.084)	0.072
Middle	Neither	1.000		1.000		1.000	
	PORT	1.118 (0.637–1.962)	0.697	0.702 (0.381–1.292)	0.255	1.944 (1.022–3.698)	0.043
	POCT	0.594 (0.397–0.889)	0.011	0.640 (0.420–0.976)	0.038	0.737 (0.433–1.254)	0.261
Lower	Neither	1.000		1.000		1.000	
	PORT	0.750 (0.077–7.283)	0.804	0.917 (0.094–8.983)	0.940	–	–
	POCT	1.250 (0.562–2.778)	0.584	0.708 (0.285–1.754)	0.455	1.970 (0.696–5.575)	0.202

TR, total recurrence; LR, locoregional recurrence; DM, distant metastasis. HR, hazard ratio; CI, confidence interval; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy. Covariates included all variables listed in Table 2 except for the tumor location.

Table 5. Univariate logistic regression of postoperative treatments on location-specific LR.

	LR at cervical		LR at mediastinum		LR at upper-abdomen	
Treatment	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
No	1.000		1.000		1.000	
PORT	1.005 (0.390–2.592)	0.991	0.469 (0.250–0.879)	0.018	1.691 (0.304–9.402)	0.548
POCT	0.485 (0.233–1.011)	0.054	0.619 (0.429–0.895)	0.011	2.800 (0.903–8.688)	0.075

LR, locoregional recurrence; HR, hazard ratio; CI, confidence interval; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy.

ruled out. The impact of this possible scenario on the long-term outcomes in this study is not known.

The present study found that poorly differentiated ESCC had a significantly higher risk of TR and DM. Similar results were reported in other studies.[8,11,21] However, this study did not find any association between tumor differentiation and LR rates.

Most importantly, this study found that PORT was associated with significantly reduced TR and LR in patients with upper thoracic $pT_3N_0M_0$ ESCC. Moreover, the incidence of LR after PORT was lower for the mediastinal region. Liu et al.[8] found that PORT for the supraclavicular, upper mediastinal lymphatic drainage regions, and tumor bed could reduce intrathoracic lymph node recurrence in $pT_{2–3}N_0M_0$ ESCC patients. Chen et al.[22] concluded that PORT with T field irradiation was associated with reduced tumor bed LR without any improvement in the OS of $pT_{1–4}N_0M_0$ ESCC patients, and many other studies have suggested that PORT could significantly improve OS and disease-free survival (DFS) among $pT_3N_0M_0$ thoracic ESCC patients.[11,13,23]

In addition, this study showed that POCT was associated with significantly reduced TR and LR, especially in the middle thoracic segment in ESCC patients. Subgroup analysis showed that POCT was associated with reduced LR in the mediastinum. A meta-analysis by Zhang et al.[24] suggested that POCT could increase the 3-year DFS but not 3-year OS in stage III–IV ESCC patients. However, recent studies have shown that POCT could improve OS and DFS among pN+ patients.[25,26] Because these studies included different populations of ESCC patients, further prospective studies are needed to determine the exact roles of PORT and POCT in the treatment of pN_0 ESCC.

This study has several limitations. First, it was a retrospective single-center study, and the patients were included based on the selection criteria. Therefore, the possibility of selection bias cannot be excluded, despite the use of multivariate analysis. Second, in this study, 88% of patients underwent esophagectomy via a left thoracic approach, and 98% of patients received two-field lymphadenectomy. The impact of different surgical approaches was not considered in the analysis. Thus, the results likely cannot be extrapolated to those using alternative approaches. Indeed, dissection of the upper mediastinal lymph nodes via the left thoracic approach was inadequate, and the number of lymph nodes retrieved was significantly lower than that recommended by the NCCN guidelines. Moreover, most of the study patients did not receive PET/CT prior to or after surgery; thus, some patients with undetected lymph node metastasis may

have benefitted from postoperative adjuvant therapy leading to improved survival in these patients. However, several Chinese studies have shown that the OS for middle and lower thoracic EC patients treated using Sweet and Ivor Lewis techniques are similar.[27–30] Ma Q et al.[29] showed that the 3- and 5-year cancer-specific survival rates and OS were higher with the left transthoracic approach than the right transthoracic approach for pN_0 ESCC patients. Ma J et al.[30] reported that there was no significant difference in LR or distant recurrence with the Ivor Lewis or Sweet approach. Compared with the Ivor Lewis approach, the Sweet approach has a shorter operative time, less blood loss, a lower incidence of transfusion, and reduced postoperative complications.[27–30] Third, the individual dosages of PORT and POCT were slightly different and not analyzed in detail. However, because conducting randomized controlled trials on POCT and PORT aimed at improving the survival of $pT_3N_0M_0$ ESCC in our institution (or any institution in China) is difficult, we believe that the results of large sample-size studies from one or more high-volume institutions may be valuable. Prospective single-arm clinical studies can also partially verify the conclusions of this study.

In summary, LR was the main cause of treatment failure in $pT_3N_0M_0$ thoracic ESCC patients after two-field dissection. Tumor location and the number of dissected lymph nodes were significantly associated with LR. PORT could decrease LR in the upper third of the thoracic cavity in $pT_3N_0M_0$ patients, and POCT could reduce LR in the middle thoracic segment in $pT_3N_0M_0$ patients. Future studies are needed to validate our findings.

Acknowledgments

The authors would like to thank all clinical staff who provided years of care for the patients enrolled in this study.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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