Original Article

Preliminary analysis of the benefits of different irradiation types on patients with postoperative locoregional recurrence of esophageal cell squamous carcinoma

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Background: To explore the benefits of different types of irradiation on patients with postoperative locoregional recurrence (LRR) of thoracic esophageal squamous cell carcinoma (ESCC).

Methods: We analyzed the medical records of 344 patients with recurrent esophageal cancer (EC) at the Fourth Hospital of Hebei Medical University. All patients met an inclusion criteria that included having postoperative LRR (without distant metastasis), and having received either chemotherapy, radiotherapy, or chemoradiotherapy after LRR. Patients either received elective nodal irradiation (ENI) or involved field irradiation (IFI), with a stratified analysis performed on both groups. SPSS 19.0 software (IBM Corporation, Armonk, NY USA) was then used for statistical analysis.

Results: The median overall survival time of all patients after surgery was 33 months [95% confidence interval (CI): 28.3–37.7 months]; the median overall survival time of patients after recurrence after radiotherapy was 12.8 months (95% CI: 11.3–14.3 months). There were 276 cases (80.2%) of single local recurrence after surgery, and 68 cases (19.8%) of multiple local recurrence (≥2). The results of our multivariate analysis showed that the patient's gender, log odds of positive lymph nodes (LODDS), and the number of courses of chemotherapy were all independent factors affecting the patient's prognosis (P=0.003, P<0.001, and P<0.001). The results of stratified analysis showed that patients with esophageal lesion length <5.0 cm, stage N0, ≤9 surgically dissected lymph nodes, no positive regional lymph node metastasis (LNM), and LODDS ≤0.030 could benefit from ENI treatment (X^2=4.208, P=0.032; X^2=6.262, P=0.012; X^2=10.359, P=0.001; X^2=6.327, P=0.012; X^2=6.026, P=0.014); and patients with ≥16 surgically dissected lymph nodes could benefit from IFI treatment (X^2=4.429, P=0.035).

Conclusions: Chemotherapy, radiotherapy, and chemoradiotherapy are all effective modes of treatment for patients with postoperative LRR of EC. Patients with shorter esophageal lesions determined by preoperative esophagography, earlier postoperative pathological N staging, lower LODDS scores, and fewer surgically dissected lymph nodes might benefit more from ENI treatment than from IFI. However, patients with a larger number of lymph nodes dissected during surgery might benefit more from IFI treatment. To further confirm this study's conclusions, multiple prospective studies should be undertaken in the future.

Keywords: Esophageal neoplasms/esophageal squamous cell carcinoma (ESCC); surgical treatment; postoperative recurrence; types of irradiation; stratified analysis

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Introduction

In patients with esophageal squamous cell carcinoma (ESCC), locoregional recurrence (LRR) is the main reason for treatment failure (1-4). For those with postoperative recurrent ESCC, surgical resection, radiotherapy, chemotherapy, or chemoradiotherapy are the key treatments in clinical practice. The suitability of each of these treatments varies from patient to patient, and each produces diverse therapeutic effects (5-8). Due to the range of recurrent regions and a patient's willingness to undergo a second operation, chemoradiotherapy is currently the most common treatment for ESCC patients. However, there has been no consensus on the radiotherapy target volume for postoperative recurrent ESCC. Discrepancies are present in the understanding of the postoperative target volume in various hospitals and medical institutions across the country. Theoretically, the volume of elective nodal irradiation (ENI) is greater than that of involved field irradiation (IFI), which may increase the control rate of regional lymph nodes, as well as the incidence of toxicities (9-12). In our cancer center at the Fourth Hospital of Hebei Medical University, radiotherapy with or without chemotherapy remains a key treatment for patients with postoperative recurrentt esophageal cancer (EC). To further clarify the advantages and disadvantages of the two different irradiation methods, we performed a retrospective analysis on a diverse group of 344 patients experiencing postoperative recurrent EC after chemoradiotherapy. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2080).

Methods

Each patient included in the study met the following inclusion criteria: (I) patient underwent radical surgery for EC (with no adjuvant chemoradiotherapy before or after surgery) in the Department of Thoracic Surgery, Fourth Hospital of Hebei Medical University; (II) thoracic ESCC was confirmed by postoperative pathology; (III) pT1-4N0-3M0 EC was diagnosed according to the eighth edition of the tumor-node-metastasis (TNM) staging system outlined by the American Joint Committee on Cancer (AJCC)/the Union for International Cancer Control (UICC); (IV) first recurrence occurred at the time of enrollment; (V) the Karnofsky score was ≥70 points; (VI) multiple and simultaneous LRR in the thoracic cavity was detected, but distant metastasis was not; (VII) patient showed no serious underlying diseases affecting treatment and had undergone chemoradiotherapy with a radiation dose of ≥45 Gy; and (VIII) no other malignant tumors were present. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (2021KT254) and individual consent for this retrospective analysis was waived.

General clinicopathological data were collected from patients with EC who were treated at the Fourth Hospital of Hebei Medical University from January 2009 to December 2014. Among them, 344 cases (male-to-female ratio, 2.5:1) were eligible for enrollment. The median age at surgery was 59 years (age range, 39–79 years), and the median age of patients with postoperative recurrent EC receiving chemoradiotherapy was 60.2 years (age range, 39.8–81.9 years). There were 83, 15, and 15 patients with a past history of hypertension, diabetes, and coronary heart disease, respectively. The length of lesion determined by esophageal barium meal examination before surgery was 1.0–11.0 cm (median 5.0 cm). The main surgical methods included a left thoracotomy for 292 cases (84.9%), a right thoracotomy for 26 cases (7.6%), 2 incisions (neck and abdomen) for 13 cases (3.8%), and 3 incisions (neck, chest, and abdomen) for 13 cases (3.8%). In addition, postoperative pathology showed positive stumps in 30 cases, and postoperative pathology showed no nerve invasion. This general information is listed in *Table 1*.

For our study, postoperative LRR was detected by anastomotic recurrence (AR) and lymph nodal recurrence. AR was confirmed by a biting biopsy analyzed under electron gastroscopy. Superficial lymph node metastasis (LNM) was confirmed pathologically by a needle biopsy, and the diagnosis of LNM in the remaining regions was confirmed by computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT), or B-ultrasound.

The location of recurrent lymph nodes was mainly

Table 1 Results of univariate analysis of prognostic factors in 344 postoperative LRR EC patients

Factor	N	Survival rate (%)			MST (M)	X^2	P
		1-year	3-year	5-year			
Sex						10.814	0.001
Male	247	47.2	18.2	12.2	11.3		
Female	97	70.1	33.5	26.6	18.9		
Age (years)						0.571	0.450
≤59	181	54	22.9	20.2	12.8		
≥60	163	53.2	22.3	11.6	12.7		
Underlying diseases						0.293	0.588
No	247	52	22.3	18.4	12.8		
Yes	97	57.8	21.6	10.3	12.7		
History of smoking						6.091	0.014
No	166	61.5	27.9	19.6	15.5		
Yes	178	45.9	17	13.3	11.1		
History of drinking						8.468	0.004
No	200	59	28.6	20.1	15		
Yes	144	45.7	13.6	10.9	11		
Family history						2.412	0.120
No	293	53.3	25.4	18.3	13.4		
Yes	51	54.5	3.8	3.8	12.4		
Differentiation						0.434	0.510
Not or poorly	76	53.8	27.1	20.3	13.8		
Moderately or well	268	53.5	21.5	15.5	12.7		
Primary tumor location						2.445	0.294
Upper	43	48.5	29.5	25.3	11		
Middle	184	54.1	27.4	18.9	13.9		
Lower	117	54.6	11.3	9.4	12.6		
Types of thoracotomy						0.714	0.398
Left thoracotomy	292	53.1	23.6	16.9	12.7		
Other types	52	56.1	16.3	13.1	13.9		
Length of esophageal lesion determined by esophagography (cm)						9.287	0.002
<5.0	150	59.2	29.5	25	18.9		
≥5.0	194	49.1	17.6	10.8	11.8		
pT staging						8.257	0.041
pT1	45	55.6	28.1	24.6	17.8		
pT2	69	68.5	32.2	25.2	19.4		
pT3	220	48.7	18.7	13.4	11.8		
pT4	10	40	10	10	5.9		

Table 1 (*continued*)

Table 1 (*continued*)

Factor	N	Survival rate (%)			MST (M)	X^2	P
		1-year	3-year	5-year			
pN staging						8.256	0.016
pN0	175	57.5	30.5	22.6	13.9		
pN1	113	49.4	14.6	10.7	11.8		
pN2+3	56	49.7	13.2	6.6	11.3		
Postoperative stump						0.501	0.479
Negative	314	53.7	22.9	16.6	12.7		
Positive	30	52.3	20.7	20.7	13.8		
Vessel carcinoma embolus						3.524	0.06
No	325	54.3	23.9	17.1	13.4		
Yes	19	42.1	5.3	5.3	8.6		
Total no. of surgically dissected lymph nodes						0.538	0.764
≤9	139	52.4	24.3	17.8	12.6		
10–15	126	54	20.1	14.7	12.7		
≥16	79	54.7	22.9	16.6	12.8		
LODDS						21.63	0
≤0.030	194	61.2	32.3	23.9	14.7		
>0.030	150	43.6	11.2	7.5	9.8		
Postoperative chemotherapy						0.012	0.912
No	156	50.2	25.8	16.2	12.2		
Yes	188	56.3	20.1	15.7	13.9		
No. of courses of chemotherapy						13.957	0
0–2	232	45.8	17.9	11.6	10.6		
≥3	112	68.6	32.1	26.7	19.4		
Types of irradiation						0.851	0.356
IFI	214	53.4	21.5	13.5	12.5		
ENI	130	53.9	24.3	20.8	13.9		
Irradiation dose (Gy)						10.446	0.005
<60	47	40	10.3	6.9	9		
60	186	–	27.7	22.9	14		
>60	111	52.2	19.1	11.4	12.3	111	
Interval between surgery and recurrence (month)						22.605	0
≤24	262	48.2		16	12	11.6	
>24	82	70.1		42.5	26.6	28.9	
No. of recurrent regions after surgery						0.784	0.376
1	276	55.6		30.6	17	13.4	
≥2	68	44.7		18.6	13.9	10.9	

LRR, locoregional recurrence; EC, esophageal cancer; MST, median survival time; LODDS, log odds of positive lymph nodes; IFI, involved field irradiation; ENI, elective nodal irradiation.

defined according to the eighth edition TNM staging system for EC. This included stations 1–8 M being defined as lymph nodes in the middle and upper mediastinal region (the upper boundary included the supraclavicular region, tracheoesophageal groove, and the paratracheal region at the level of the lung apex to the lower edge of the inferior pulmonary vein); stations 8Lo, 9, and 15 being defined as lymph nodes in the inferior mediastinal region (the upper boundary was the lower edge of the lymph node drainage area in the middle and upper mediastinal region, and the lower boundary was at the top of the diaphragm); and stations 16–20 being defined as the upper abdominal lymph node area (the upper boundary was connected to the lower boundary of the lymphatic drainage area in the inferior mediastinal region, and the lower boundary was at the level of the abdominal trunk).

All patients underwent intensity-modulated radiation therapy (IMRT) with 6 MV X-rays. For the 214 patients who received IFI, the target volume included recurrent lymph nodes or recurrent tumor tissues and was expanded by 2–3 cm margins (avoiding damage to surrounding normal tissues and vital organs). The prescribed dose ranged from 45–70 Gy (median 60 Gy). The remaining 130 patients underwent ENI using the same target volume as IFI. In addition, preventive irradiation was performed on the corresponding lymph node drainage areas of patients with recurrence in different segments. For patients with recurrence in the upper thoracic segment, drainage areas encompassed the bilateral supraclavicular region and paraesophageal region (zones 2, 4, 5, and 7). As for those with recurrence in the middle thoracic segment, drainage areas included the paraesophageal region (zones 2, 4, 5, and 7). For recurrence in the lower thoracic segment, drainage areas encompassed the paraesophageal region (zones 2, 4, 5, 7, and 8), paracardial area, and left gastric area. The upper and lower boundaries of the target volume were adjusted according to the anatomical barrier and the recurrent regions. In addition, 74 patients were initially treated 18–28 times with conventional segmented irradiation (36–50.4 Gy) in the drainage area, and the target volume was localized for late course accelerated hyperfractionated irradiation, with a dose of 12–24 Gy (6–12 times). For all patients with lymph nodal recurrence in the supraclavicular region, if there was any residual after IMRT, the residual part was irradiated with an electronic beam. All patients in this group completed the treatment according to the clinical treatment regimen.

A total of 188 patients (54.7%) also received a regimen of chemotherapy, which was mainly platinum-based combination chemotherapy. The number of courses of this treatment varied from 1–7 (median 3), with 112 patients receiving ≥3 courses. All 188 patients received concurrent chemotherapy, with several patients also undergoing radiotherapy prior to this.

Patient follow-up was mainly performed by combining a telephone interview or outpatient visit with case data. The follow-up ranged from the day the patient received either chemotherapy, radiotherapy, or chemoradiotherapy for postoperative LRR up to December 31, 2019. The patients were re-examined every 3–6 months in the first year, and every 6–12 months thereafter. Thirteen cases did not take part in the follow-ups (3.8%) and were subsequently censored at the last date of follow-up.

Statistical analysis

Statistical analysis was undertaken using SPSS 19.0 software (IBM Corporation, Armonk, NY, USA). The comparison of numerical data was performed using a chi-square test. A log-rank test and the Kaplan-Meier (KM) method were used for the univariate survival analysis, while a Cox proportional hazard model was used for multivariate analysis. Propensity score matching (PSM) was used to test patient results under different types of irradiation. Patients were divided into groups to reduce confounding bias. The level of significance was set at α=0.05, and a P value <0.05 was considered statistically significant.

Results

To ensure the success of the number of lymph nodes dissected during the operation, we used the log odds of positive lymph nodes (LODDS) system. The calculation method of LODDS was as follows (13): log (the number of positive lymph nodes + 0.5)/(the number of negative lymph nodes + 0.5). The subsequent LODDS value in this study ranged from −1.204 to 0.638 (median 0.030).

The 1-, 3-, and 5-year overall survival (OS) rates of all patients after postoperative radiotherapy (PORT) were 91.3%, 47.1%, and 32.2%, respectively [median 33 months; 95% confidence interval (CI): 28.3–37.7 months]. The 1-, 3-, and 5-year OS rates of patients with LRR after PORT were 53.6%, 22.6%, and 16.4%, respectively (median 12.8 months; 95% CI: 11.3–14.3 months). The 1-, 3-, and 5-year recurrence-free survival (RFS) rates after PORT were 46.5%, 16.9%, and 12.0%, respectively (median 11.0 months; 95% CI: 9.6–12.4 months). The 1-, 3-, and

Table 2 Multivariate analysis results of prognostic factors in 344 postoperative LRR EC patients

Factor	B	SE	Wald	P	HR	95.0% CI	
						Upper	Lower
Sex	−0.448	0.151	8.839	0.003	0.639	0.475	0.858
LODDS	0.374	0.084	19.630	0.000	1.454	1.232	1.715
No. of courses of chemotherapy	−0.531	0.144	13.666	0.000	0.588	0.444	0.779

LRR, locoregional recurrence; EC, esophageal cancer; CI, confidence interval; LODDS, log odds of positive lymph nodes.

5-year progression-free survival (PFS) rates after PORT were 39.8%, 11.3%, and 6.7%, respectively (median 7.9 months; 95% CI: 5.8–10.0).

The analysis results of all patients with postoperative LRR found the interval between surgery and recurrence was 0.3–87.4 months (median 11.6 months). Based on the distribution of specific recurrent regions, the results were as follows: 50 (14.5%) cases had simple supraclavicular lymph node recurrence (SCLNR), 182 (52.9%) cases had simple mediastinal lymph node (MLN) recurrence, 23 (6.7%) cases had simple AR; 21 (6.1%) cases had simple abdominal lymph node recurrence (ALNR); 21 (6.1%) cases had both SCLNR and MLN; 12 (3.5%) cases had both SCLNR and ALNR; 4 (1.2%) cases had both SCLNR and AR; 16 (4.7%) cases had both MLN and AR; 9 (2.6%) cases had both MLN and ALNR; 1 (0.3%) case had both ALNR and AR; 3 (0.9%) cases had SCLNR, MLN, and ALNR; and 2 (0.6%) cases had SCLNR, MLN, and AR.

The results of our univariate analysis of all patients showed that the patient's gender, smoking history, drinking history, esophageal lesion length determined by angiography, pathological T staging, pathological N staging, LODDS, number of courses of chemotherapy, irradiation dose, interval between surgery, and recurrence were risk factors affecting patient prognosis (X^2=10.814, P=0.001; X^2=6.091, P=0.014; X^2=8.468, P=0.004; X^2=9.286, P=0.002; X^2=8.257, P=0.041; X^2=8.256, P=0.016; X^2=21.630, P<0.001; X^2=13.957, P<0.001; X^2=10.446, P=0.005; X^2=22.605 P<0.001). Detailed information of this analysis is listed in *Table 1*.

We conducted a multivariate analysis of all patients by entering all statistically significant factors identified by the univariate analysis into a Cox multivariate analysis model. The results revealed that the patient's gender, LODDS, and the number of courses of chemotherapy were all independent factors affecting the prognosis of the patient (P=0.003, P<0.001, P<0.001). Detailed information of this analysis is listed in *Table 2*.

Our stratified analysis compared the two different types (ENI and IFI) of irradiation used in our study, and the general clinical and pathological indicators of the two groups were compared. The results suggested that there was a statistically significant difference in the composition ratio between the method of thoracotomy (X^2=22.703, P=0.000) and the length of lesion determined by esophageal barium meal examination in both groups (X^2=9.527, P=0.002). According to the results of Cox multivariate analysis, the PSM method was used to achieve a balanced distribution of patients in the two groups (1:1). The results showed that there were 130 patients in each group, and that the composition ratio of the two groups was balanced, indicating no significant difference. Detailed information of this analysis is listed in *Table 3*.

The subsequent results showed that patients who had any of the following could benefit from ENI treatment: an esophageal lesion length <5.0 cm, ≤9 surgically dissected lymph nodes, 0 positive regional LNM, ≤0.030 LODDS, or N0 stage (X^2=4.208, P=0.032; X^2=6.262, P=0.012; X^2=10.359, P=0.001; X^2=6.327, P=0.012; X^2=6.026, P=0.014). We also found that patients with ≥16 surgically dissected lymph nodes could benefit from IFI treatment (X^2=4.429, P=0.035). Detailed information of this analysis is listed in *Table 4*.

Discussion

LRR is the main cause for treatment failure in ESCC patients. Chemotherapy, radiotherapy, and chemoradiotherapy are effective and safe treatment options widely used in clinical practice (14,15). However, in clinical application, there has been no consensus regarding whether ENI or IFI should be applied to these patients. Currently, there are only a few reports which stipulate the volume of the target area for patients receiving irradiation for postoperative LRR of EC. Unfortunately, these studies exhibit several disadvantages, including analyzing only a small number of EC patients, not

Table 3 The composition ratio of patients under different irradiation types before and after PSM

Factor	Before PSM (N)		X^2	P	After PSM (N)		X^2	P
	IFI	ENI			IFI	ENI		
Sex			0.110	0.740			0.484	0.486
Male	155	92			97	92		
Female	59	38			33	38		
Age (years)			1.555	0.212			0.990	0.320
≤59	107	74			66	74		
≥60	107	56			64	56		
Underlying diseases			1.325	0.250			1.229	0.268
No	149	98			90	98		
Yes	65	32			40	32		
History of smoking			0.004	0.953			0.246	0.602
No	103	63			67	63		
Yes	111	67			63	67		
History of drinking			0.102	0.749			0.063	0.801
No	123	77			75	77		
Yes	91	53			66	53		
Family history			1.36	0.244			0.027	0.870
No	186	107			108	107		
Yes	28	23			22	23		
Differentiation			1.315	0.251			1.074	0.300
Not or poorly	43	33			26	33		
Moderately or well	171	97			104	97		
Primary tumor location			3.335	1.189			2.044	0.360
Upper thoracic segment	22	21			14	21		
Middle thoracic segment	121	63			72	63		
Lower thoracic segment	71	46			44	46		
Types of thoracotomy			22.703	0.000			3.196	0.074
Left thoracotomy	197	95			107	95		
Other types	17	35			23	35		
Length of esophageal lesion determined by esophagography (cm)			9.527	0.002			3.462	0.063
<5.0	82	72			57	72		
≥5.0	132	58			73	58		
pT staging			7.729	0.052			4.463	0.216
pT1	20	25			13	25		
pT2	42	27			30	27		
pT3	146	74			83	74		
pT4	6	4			4	4		

Table 3 (*continued*)

Table 3 (*continued*)

Factor	Before PSM (N)		X^2	P	After PSM (N)		X^2	P
	IFI	ENI			IFI	ENI		
pN staging			0.443	0.801			0.589	0.745
pN0	107	68			74	68		
pN1	70	43			38	43		
pN2+3	37	19			18	19		
Postoperative stump			0.068	0.794			0.044	0.833
Negative	196	118			11	118		
Positive	18	12			13	12		
Vessel carcinoma embolus			1.884	0.170			1.066	0.302
No	205	120			124	120		
Yes	9	10			6	10		
Total no. of surgically dissected lymph nodes			1.702	0.427			2.694	0.260
≤9	83	56			48	56		
10–15	77	49			46	49		
≥16	54	25			36	25		
LODDS			0.683	0.428			0.064	0.800
≤0.030	117	77			79	77		
>0.030	97	53			51	53		
Postoperative chemotherapy			0.055	0.815			0.000	0.001
No	96	60			60	60		
Yes	118	70			70	70		
No. of courses of chemotherapy			0.099	0.753			0.018	0.893
0–2	143	89			90	89		
≥3	71	41			40	41		
Irradiation dose (Gy)			0.929	0.628			1.185	0.553
<60	30	17			20	17		
60	119	67			72	67		
>60	65	46			38	46		
Interval between surgery and recurrence (month)			5.531	0.019			3.398	0.065
≤24	172	90			103	90		
>24	42	40			27	40		
No. of recurrent regions after surgery			3.370	0.071			0.484	0.486
1	177	97			97	97		
≥2	37	33			33	33		

PSM, propensity score matching; IFI, involved field irradiation; ENI, elective nodal irradiation; LODDS, log odds of positive lymph nodes.

Table 4 Analysis results of the impact of different irradiation types on patient prognosis

Factor	Types of irradiation								X^2	P
	IFI				ENI					
	1-year	3-year	5-year	MST (M)	1-year	3-year	5-year	MST (M)		
Male	45.6	15.8	8.0	10.9	45.0	17.7	14.2	10.6	0.346	0.556
Female	72.2	32.7	22.4	15.0	26.5	40.5	36.0	22.2	1.060	0.303
≤59 years of age	51.5	23.0	15.9	12.3	54.3	22.3	22.3	13.4	0.482	0.488
≥60 years of age	53.4	16.3	4.4	12.5	53.4	27.3	19.5	14.0	1.309	0.253
Not or poorly differentiated	75.1	23.9	15.9	20.9	44.8	30.3	30.3	10.0	0.384	0.535
Moderately or well differentiated	46.8	19.0	10.1	11.0	56.4	22.9	18.8	14.2	2.313	0.128
Upper thoracic segment	53.1	29.5	29.2	12.3	48.6	30.4	30.4	10.6	0.059	0.808
Middle thoracic segment	50.1	24.5	12.5	12.3	53.6	29.8	23.8	13.9	1.380	0.240
Lower thoracic segment	56.4	10.0	5.0	12.5	56.8	13.1	13.1	12.8	0.605	0.437
Lesion length <5.0 cm	59.8	25.1	16.7	15.4	63.4	39.5	39.5	20.8	4.208	0.032
Lesion length ≥5.0 cm	47.9	17.4	8.1	11.4	42.0	8.0	4.0	10.6	0.066	0.797
T1+2	64.6	21.1	13.2	15.0	65.1	43.0	38.7	19.4	2.742	0.098
T3+4	46.4	20.2	11.4	10.9	44.5	8.9	6.7	10.6	0.080	0.777
N0	53.0	22.3	10.2	12.3	63.4	40.3	33.6	21.5	6.262	0.012
N1+2	52.0	17.7	11.8	12.3	43.2	4.7	4.7	10.6	2.242	0.134
Total no. of surgically dissected lymph nodes ≤9	45.2	12.5	5.0	11.7	64.3	37.0	32.4	21.0	10.359	0.001
Total no. of surgically dissected lymph nodes 10–15	51.2	23.5	17.6	12.2	47.1	16.3	13.0	10.8	0.049	0.825
Total no. of surgically dissected lymph nodes ≥16	65.1	29.6	19.9	19.6	42.3	6.8	6.8	10.6	4.429	0.035
No. of positive regional lymph node metastasis 0	57.9	25.3	10.0	13.8	65.7	42.0	35.0	21.0	6.327	0.012
No. of positive regional lymph node metastasis 1	47.8	20.1	15.0	10.2	38.6	4.6	4.6	7.9	1.436	0.231
No. of positive regional lymph node metastasis ≥2	39.4	5.6	5.6	9.7	42.5	3.9	3.9	10.0	0.027	0.870
No. of courses of chemotherapy ≤2	44.8	15.3	7.9	10.2	44.4	18.4	14.7	10.6	0.542	0.462
No. of courses of chemotherapy ≥3	68.3	30.1	17.6	14.7	73.7	38.0	25.3	21.9	1.055	0.304
LODDS ≤0.030	58,7	25.8	10.7	13.9	63.4	42.2	35.7	21.0	6.026	0.014
LODDS >0.030	42.5	12.5	10.0	9.7	38.2	2.1	2.1	7.9	1.516	0.218
Interval between surgery and recurrence ≤24 months	50.4	18.5	12.0	12.2	45.8	14.6	13.2	10.8	0.023	0.880
Interval between surgery and recurrence >24 months	60.4	26.5	0.0	20.9	71.4	45.5	34.1	28.5	2.807	0.094
No. of recurrent regions after surgery 1	52.0	21.1	12.8	12.3	58.4	26.4	22.3	16.1	2.526	0.113
No. of recurrent regions after surgery ≥2	55.5	18.5	0.0	15.0	38.3	17.5	17.5	9.8	0.780	0.377

IFI, involved field irradiation; ENI, elective nodal irradiation; MST, median survival time; LODDS, log odds of positive lymph nodes.

undertaking a stratified analysis of most patients, and (as in most studies) failing to comprehensively compare the efficacy of different irradiation methods on patient prognosis. For our study, we conducted a retrospective analysis of 344 patients with postoperative LRR of EC at a single center. The results of our univariate and multivariate analyses showed that the mode of radiotherapy (ENI or IFI) was not a prognostic factor in this group of patients. To clarify prognosis of different patients under different types of irradiation, we conducted a stratified analysis. The results indicated that ENI treatment was beneficial to patients with early lesions, specifically patients with an esophageal lesion length less than 5.0 cm, pathological stage T1+2, stage N0, and LODDS ≤0.030. In addition, patients with ≤9 surgically dissected lymph nodes could also benefit from ENI, whereas patients with ≥16 surgically dissected lymph nodes and LODDS >0.030 could benefit from IFI treatment. Taken together, the choice of irradiation mode for treating patients with postoperative LRR of EC can vary from person to person, and different groups of people might benefit more from ENI, IFI, or other radiotherapy treatments.

Currently, there is no consensus on the delineation of the target area for patients receiving salvage radiotherapy for LRR of EC. Unlike older forms of two-dimensional radiotherapy, the wide clinical application of precision radiotherapy technology requires the precise delineation of the target area in clinical practice. However, to our knowledge, there are few related reports on this subject, and these report diverse conclusions. Jingu *et al.* (12) analyzed 30 patients with postoperative LRR EC; a T-shaped field (including bilateral supraclavicular, mediastinal and abdominal regions) was used for 11 patients, and IFI was used for the remaining 19 patients. The results showed that other than benefiting patients, irradiation with a T-shaped field was more likely to lead to acute adverse events of grade 3 or higher. In another of their related studies (16), they analyzed 35 patients with postoperative recurrent EC, with a T-shaped field used for 15 patients and IFI used for the remaining 20. Among them, 2 patients who underwent irradiation with a T-shaped field experience other types of LNM. In another study (14), they analyzed 80 patients with postoperative LRR of EC who received chemoradiotherapy. In this study, the interval between surgery, recurrence, and AR were independent factors affecting the prognosis of patients. After a matched-pair analysis, they found 26 patients in both the IFI and ENI groups. The OS rate and local control (LC) rate of the patients in the IFI and ENI groups were 50.9% vs. 21.1% (P=0.016) and 79.0% *vs.* 42.2% (P=0.014), respectively. ENI was therefore considered unnecessary for patients with postoperative LRR of EC. In a study conducted by Kawamoto *et al.* (5), the prognosis of 21 patients with lymph node recurrence (LNR) after surgery for EC were retrospectively evaluated. The 2-year OS rate of these patients was 78%. After treatment, 9 (42.9%) patients were found to have failed, including 4 patients (19%) with recurrence within the irradiation field, while another 5 (23.8%) patients had distant metastases. The authors indicated that IFI was an effective radiotherapy regimen for patients with postoperative LRR of EC. In another study by Kawamoto *et al.* (8), they retrospectively analyzed 57 patients with postoperative LRR of EC who received radiotherapy, including 15 (26.3%) patients who received ENI, and 42 (73.7%) patients who received IFI; the median survival period of the two groups was 21 and 22 months, respectively (P=0.38). In the abovementioned studies, the researchers asserted that preventive irradiation should not be recommended for patients with LRR of EC. However, these studies have several disadvantages, including the small number of patients who took part in their studies, the amount of patients with solitary LNR, a T-shaped field design that was different from the current delineation standard of an elective nodal drainage area under precise treatment, and a lack of a stratified analysis across a diverse group of patients. To add to this research, our study results show that different types of irradiation have no significant effect on the number of recurrent regional lymph nodes. Therefore, we believe that for different types of patients, a further stratified analysis should be carried out to pinpoint which patients will benefit more from a given irradiation field.

Additional research, such as that by Zhang *et al.* (11) also retrospectively analyzed the clinical data of 50 patients. This group (except for SCLNR patients who received irradiation of the supraclavicular lymphatic drainage area) underwent IFI, with 1-year and 3-year survival rates of 56% and 14%, respectively. The median PFS and OS rate were 9.8 and 13.3 months, respectively. Unfortunately, this study failed to further compare and analyze different types of irradiation. Chen *et al.* (15) also retrospectively analyzed the survival rate and prognostic factors of 83 patients with local LNR after radical resection of ESCC. Among them, 41 cases received radiotherapy alone, 42 cases received radiotherapy combined with chemotherapy, and all received IMRT. In addition to the target volume of the target area, the adjacent drainage area was irradiated. The 1-, 3-, and 5-year OS rates of all patients were 83.0%, 40.1%, and 35.1%, respectively, with a median survival period of

18 months (range, 5–75 months). However, these authors did not compare the efficacy of different irradiation fields in patients. In our study, we retrospectively analyzed 344 patients with postoperative LRR of EC, including 130 patients who received ENI, and 214 patients who received IFI. The 1-, 3-, and 5-year OS rates of patients receiving ENI and IFI were 53.9%, 24.3%, 20.8%, and 53.4%, 21.5%, 13.5%, respectively, with a median survival period of 13.9 months for ENI patients and 12.5 months for IFI patients. Although no significant difference was found between the two groups, the 5-year survival rate of the two groups indicated that patients receiving ENI might have a more advantageous long-term prognosis.

The length of esophageal lesion and postoperative pathological staging are important factors affecting the prognosis of patients with EC after surgery (17). Most research results show that the lesion length of EC is closely related to the postoperative pathological stage T and N, and that patients with shorter lesions have relatively early T and N staging (18,19). According to the calculation formula of LODDS, it is clear that LODDS is related to the number of lymph nodes, with smaller LODDS correlating to the earlier stages of a patient's disease. The location, size, mobility, relationship with surrounding organs, and local LNM of esophageal tumors are closely related to the scope of surgery. Therefore, the patient's preoperative condition directly affects the extent of resection and lymph node dissection during surgery. In the case of resection, the extent of resection is often relatively large for patients with an advanced illness. Compared with a smaller area, a larger surgical area will inflict considerable trauma to the patient and lead to a variety of unpredictable surgical complications, as well as a longer period of recovery and recuperation (20).

Immune function status is known to be an important indicator that affects the prognosis of patients with malignant tumors. Numerous researchers (21,22) believe that the occurrence and development of tumors are caused by low immunity or weakened immunogenicity of mutant cells. Changes in the number and function of immunocytes may lead to immune function disorder and resultant tumors. Andaluz-Ojeda *et al.* (23) even believe that tumor staging, patient survival time, and the prognostic effect of surgery could be estimated by a T lymphocyte count, T lymphocyte subgroup count, and the degree of the disorder. Surgery has a dual effect on the immune function of patients. On the one hand, surgical trauma, anesthesia, and blood transfusion can lead to decreased immunity to a certain extent, but on the other hand, with the recovery of surgical trauma, the immune function of patients with EC can be improved (24). Moreover, postoperative chemoradiotherapy for EC may result in T cell immunosuppression and the compromised function of immune cells, thereby resulting in a prolonged period of lower immune function of the T cells and adversely affecting the recovery of a patient's immune functions. This suggests that different treatment methods have selective effects on the recovery of immune function (25). For example, EC patients in more advanced stages often have lower local and systemic immune function. For patients whose immune function has not fully recovered, larger irradiation fields may contribute to a further decline in the patient's immunity and affect the prognosis, thereby offsetting the benefits of large irradiation fields. In addition, patients with late-stage EC and those with lower immunity are more likely to have distant metastasis. This means that even larger irradiation fields can only serve as a local treatment option and cannot reduce the rate of distant metastasis. This may explain why the stratified analysis results of this study show that after ENI treatment, prognosis is more favorable in patients at the early-stage of EC than in patients at the advanced-stage.

This study has several limitations. First, as this study is retrospective, there is an inherent bias in the cases selected. Second, in addition to the effects of different irradiation fields, there are many factors effecting the treatment and prognosis of patients with postoperative LRR of EC, including radiation dose, chemotherapy regimen, and the timing of chemotherapy treatment. Third, due to word count limitations, this study did not conduct further analysis on the toxic effects, other side effects, or the recurrence patterns of the two types of irradiation. Lastly, due to the limited amount of literature available on using irradiation fields for treating patients with postoperative LRR of EC, discussion and comparison with other relevant findings were limited in this paper.

In conclusion, chemotherapy, radiotherapy, or chemoradiotherapy are effective treatment modes for patients with postoperative LRR of EC in the thoracic cavity, but different types of irradiation fields may benefit different patients in clinical settings. In respect to survival, patients who would benefit the most from ENI therapy were found to have a shorter esophageal lesion (determined through preoperative esophagography), early postoperative T/N staging, lower LODDS score, and a small number of lymph nodes dissected, whereas patients with a larger number of lymph nodes dissected during surgery and a higher LODDS score were found to benefit more from

IFI. To further confirm these results, a large number of prospective controlled studies should be conducted in the future.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (2021KT254) and individual consent for this retrospective analysis was waived.

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