

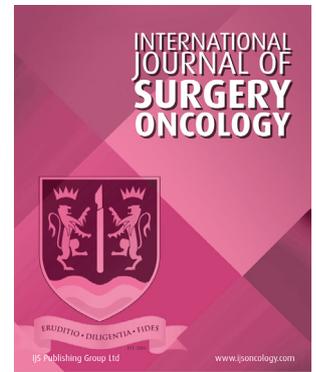


# Comparison of Local Recurrence Patterns of Postoperative Radiotherapy with Surgery Alone for Esophageal Carcinoma Patients

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EXPERIMENTAL  
RESEARCH



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## ABSTRACT

**Background:** We analyzed local regional recurrence patterns of thoracic esophageal carcinoma after three-field lymph node dissection (3-FLD) with and without postoperative radiotherapy, and assessed the postoperative radiation value for local control.

**Methods:** The study reviewed 239 local recurrences of esophageal squamous cell carcinoma after 3-FLD from 2010 to 2018 in our hospital, retrospectively, and compared local regional recurrence patterns between surgery followed by radiotherapy (S+RT) and surgery alone (SA).

**Results:** In 239 thoracic esophageal carcinomas that underwent curative surgery, the lymph node recurrence was the most common type of local recurrence for patients in both groups. The sequence of lymph node recurrence rate in both groups from highest to lowest was mediastinal, cervical, and abdominal. The recurrence rate of superior mediastinal lymph node in patients without radiotherapy was significantly higher than that in patients with radiotherapy (67.72% vs. 47.54%,  $\chi^2 = 7.615$ ,  $P = 0.006$ ). The recurrence rate of abdominal lymph node in the upper TEC was significantly lower than that in the middle and lower TEC ( $\chi^2 = 9.452$ ,  $P = 0.009$ ). The abdominal lymph node recurrence rate in patients with preoperative abdominal LNM was very significantly higher than that in patients without preoperative abdominal LNM (43.63% vs. 6.66%,  $P < 0.001$ ).

**Conclusions:** The dangerous lymph node recurrence regions included superior, middle mediastinum, and neck. Postoperative radiotherapy shows great value for patients in reducing superior mediastinal lymph node recurrence rate. The lower segment of thoracic esophageal carcinoma and preoperative abdominal lymph node metastasis, especially para-aortic lymph node metastasis, may be risk factors for abdominal lymph node recurrence.

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## INTRODUCTION

At present, the overall 5-year survival rate of esophageal carcinoma is 45.7% [1]. Despite recent advances in minimally invasive oesophagectomy [2], there was no significant improvement in survival. The main treatment failure causes after surgery were local recurrence and distant metastasis. The local recurrence rates after surgery ranged from 42.9% to 57.9% [3–7]. Although there is no common consensus for postoperative radiotherapy, a growing number of researchers [8–11] suggest that postoperative radiotherapy, which can reduce local recurrence, was associated with better survival rates for patients with node-positive thoracic esophageal carcinoma (TEC). However, the universally accepted prophylactic radiotherapy target volume for TEC has not yet been established. Initially, the target volume includes the entire mediastinum, bilateral supraclavicular area, and left gastric area. However, patients frequently had side effects, such as gastrointestinal reaction or bone marrow suppression. Latest researchers [12–16] thought supraclavicular, and station 1–5 and 7 lymph nodes should be included in postoperative radiotherapy. In this way, many patients could avoid many adverse effects.

This study compared the recurrence rate and relapse site in TEC patients after three-field lymph node dissection (3-FLD) between surgery followed by radiotherapy (S+RT) and surgery alone (SA), and may show its possible impact on target delineation for postoperative radiotherapy.

## METHODS

### GENERAL INFORMATION

From January 2010 to December 2018, 980 patients with thoracic esophageal squamous cell carcinoma (ESCC) were treated with three-field lymph node dissection (3-FLD) [17]. 239 patients with ESCC who had local-regional recurrence, including 175 cases in SA group and 64 cases in S+RT group, were identified in our hospital. Patients with palliative surgical treatment or apparent residual tumors were excluded.

Among the 239 patients, there were 212 male patients and 27 female patients. Ages ranged from 38 to 78 years, with a median age of 57 years old. 43 patients had upper TEC, 176 had middle TEC, and 20 had lower TEC. Patients were staged according to TNM classification (AJCC/UICC, 2009). Patient characteristics are shown in **Table 1**. In this study, the median time to recurrence was 16.6 months (range 10–43 months).

### POSTOPERATIVE RADIATION

Radiotherapy with 18-MV X-rays was started 4 weeks after surgery. For upper and middle TEC, the supraclavicular, and station 1–5 and 7 lymph nodes regions, anastomosis and tumor bed were irradiated. For lower TEC, supraclavicular, station 1–5 and 7 lymph nodes

VARIABLE	SA	S+RT	$\chi^2$ VALUE	P VALUE
<b>Age (years)</b>				
>60 years	104	45	2.365	0.124
≤60 years	71	19		
<b>Sex</b>				
Male	150	58	0.190	0.663
female	25	8		
<b>Localization of the tumors</b>				
Upper thoracic third	34	9	2.852	0.240
Middle thoracic third	124	52		
Lower thoracic third	17	3		
<b>Length of tumor on X-ray</b>				
>5cm	82	28	0.182	0.670
≤5cm	93	36		
<b>Tumor differentiation</b>				
Low (G3)	43	16	1.202	0.548
Moderate (G2)	103	41		
High (G1)	29	7		
<b>pT category</b>				
T1/T2	45	13	0.744	0.388
T3/T4	130	51		
<b>pN category</b>				
N0	12	52	5.075	0.166
N1	17	47		
N2	10	31		
N3	25	45		
<b>Postoperative chemotherapy</b>				
YES	134	52	0.594	0.441
NO	41	12		

**Table 1** Patient and tumor characteristics. Abbreviations: SA = surgery alone; S+RT = surgery plus postoperative radiotherapy; G = grad.

and upper abdominal lymph nodes area, anastomosis and tumor bed were irradiated. The median radiation dose was 50 Gy in 25 fractions at 2 Gy per fraction, 5 days per week.

### DIAGNOSTIC CRITERIA

Preoperative lymph node metastasis was confirmed pathologically after 3-LND. All patients were followed up every 3–6 months. Local-regional recurrence included lymph node, anastomosis, and tumor bed recurrence.

Supraclavicular lymph node recurrence diagnosis was mainly based on physical examination, Doppler

ultrasound, CT, and fine needle aspiration cytology if necessary. Mediastinal lymph node recurrence diagnosis was mainly based on CT or PET-CT. Abdominal lymph node recurrence diagnosis was based mainly on Doppler ultrasound and CT.

As diagnostic criterion, detected nodes were considered recurrence if the short axis was greater than 1cm [18–19]. Additionally, we also took uptake of contrast medium or FDG into consideration. Anastomotic recurrence was determined pathologically by gastric endoscopy. Tumor bed recurrence was diagnosed by CT or PET-CT.

**TERMINOLOGY OF THE REGIONAL LYMPH NODES IN ESOPHAGEAL CANCER**

According to a lymph node mapping system for esophageal carcinoma (AJCC-UICC in 2009), the fields of lymph nodes were as follows: 1R (right highest mediastinal nodes); 1L (left highest mediastinal nodes); 2R (right upper paratracheal nodes); 2L (left upper paratracheal nodes); 3P (posterior mediastinal nodes); 4R (right lower paratracheal nodes); 4L (left lower paratracheal nodes); 5 (subaortic nodes); 6 (paraortic nodes); 7 (subcarinal nodes); 8M (middle paraesophageal lymph nodes); 8L (lower paraesophageal lymph nodes); 9 (pulmonary ligament nodes); 10R (right hilar nodes); and 10L (left hilar nodes). The lymph nodes in the 1, 2, 3, 4, 5 and 6 levels were included in the superior mediastinal lymph node; the lymph nodes in the 7, 8M, and 10 level were included in the middle mediastinal lymph node; the lymph nodes in the 8L and 9 level were included in the inferior mediastinal lymph node.

**STATISTICAL ANALYSIS**

SPSS 19.0 statistical software was used for data analysis. A chi square test was used for enumeration data. A P value less than 0.05 was considered statistically significant.

**RESULTS**  
**RECURRENCE PATTERNS**

Among 239 patients, lymph node recurrence was the most common pattern of local regional recurrence in both group. There was no significant difference between S+RT and SA regarding lymph node recurrence (95.31% vs. 90.29%, P = 0.214), anastomosis recurrence (10.94% vs. 19.43%, P = 0.123), and tumor bed recurrence (4.69% vs. 9.71%, P = 0.214) (*Table 2*).

**LYMPH NODE RECURRENCE**

The mediastinal lymph node recurrence was the most common lymph node recurrence in both groups. The difference was not statistically significant between S+RT and SA in the cervical (40.98% vs. 49.37%, P = 0.265), mediastinal (69.93% vs. 72.78%, P = 0.199), and abdominal lymph node recurrence (20.25% vs. 27.87%, P = 0.225) (*Table 3*). In patients without postoperative radiotherapy, there was no significant difference in the cervical lymph node recurrence among different primary tumor segments ( $\chi^2 = 1.599$ , P = 0.449). In patients without postoperative radiotherapy, there was no significant difference in the mediastinal lymph node recurrence among different primary tumor segments ( $\chi^2 = 4.088$ , P = 0.130). However, the recurrence rate of abdominal lymph node in the upper TEC was significantly lower than that in the middle and lower TEC ( $\chi^2 = 9.452$ , P = 0.009).

**MEDIASTINAL LYMPH NODE RECURRENCE**

The superior mediastinal lymph node recurrence was the most common mediastinal recurrence both groups. The recurrence rate of superior mediastinal lymph node in patients (SA) was significantly higher than that in patients (S+RT) (67.72% vs. 47, 54%,  $\chi^2 = 7.615$ , P = 0.006). However, there was no significant difference between two groups of middle and inferior mediastinal lymph node recurrence.

GROUPS	LYMPH NODES RECURRENCE	ANASTOMOSIS RECURRENCE	TUMOR BED RECURRENCE
SA	158(90.29%)	34 (19.43%)	17 (9.71%)
S+RT	61(95.31%)	7 (10.94%)	3 (4.69%)
statistics	$\chi^2 = 1.544$ , P = 0.214	$\chi^2 = 2.377$ , P = 0.123	$\chi^2 = 1.544$ , P = 0.214

**Table 2** The comparison of local recurrence patterns between two groups. Abbreviations: SA = surgeryalone; S+RT = surgery plus postoperative radiotherapy.

GROUPS	THE CERVICAL LYMPH NODE RECURRENCE	THE MEDIASTINAL LYMPH NODE RECURRENCE	THE ABDOMINAL LYMPH NODE RECURRENCE
SA	78 (49.37%)	115 (72.78%)	32 (20.25%)
S+RT	25 (40.98%)	39 (63.93%)	17 (27.87%)
statistics	$\chi^2 = 1.242$ , P = 0.265	$\chi^2 = 1.652$ , P = 0.199	$\chi^2 = 1.470$ , P = 0.225

**Table 3** The comparison of lymph node recurrence between two groups. Abbreviations: SA = surgeryalone; S+RT = surgery plus postoperative radiotherapy.

Local recurrence of superior mediastinal lymph nodes occurred mostly in 4R region. There was very significant difference in the recurrence among these regions in patients with postoperative radiotherapy ( $\chi^2 = 38.812, P < 0.001$ ). It was the same case for patients without postoperative radiotherapy ( $\chi^2 = 155.416, P < 0.001$ ).

Local recurrence of middle mediastinal lymph nodes occurred mostly in 7 region, and there was significant difference in the recurrence among these regions in patients with postoperative radiotherapy postoperative radiotherapy ( $\chi^2 = 11.186, P < 0.001$ ). It was the same case for patients without postoperative radiotherapy ( $\chi^2 = 35.726, P < 0.001$ ). However, the recurrence of inferior mediastinal lymph nodes was rare in both groups (*Tables 4 and 5*).

### THE LOCAL CONTROL EFFICACY OF POSTOPERATIVE RADIOTHERAPY FOR PATIENTS WITH PREOPERATIVE SUBCARINAL OR ABDOMINAL LYMPH NODE METASTASES

In patients without postoperative radiotherapy, the subcarinal lymph node recurrence rate in patients with preoperative subcarinal LNM was significantly higher than that in patients without preoperative subcarinal LNM (34.28% vs. 17.85%,  $P = 0.033$ ). There was no significant difference in the subcarinal lymph node recurrence between SA and S+RT in patients with preoperative subcarinal LNM ( $\chi^2 = 0.005, P = 0.943$ ) (*Table 6*).

In patients without postoperative radiotherapy, the abdominal lymph node recurrence rate in patients with preoperative abdominal LNM was very significantly higher

GROUP	NO.(%)	GROUP	NO.(%)
<b>SMLNR</b>	<b>107(67.72%)</b>	6 region	4(2.53%)
1R region	20(12.66%)	<b>MMLNR</b>	<b>45(28.48%)</b>
2R region	22(13.92%)	7 region	37(23.42%)
4R region	55(34.81%)	8M region	8(5.06%)
1L region	11(6.96%)	10R region	11(6.96%)
2L region	21(13.29%)	10L region	12(7.59%)
4L region	35(22.15%)	<b>IMLNR</b>	<b>2(1.27%)</b>
5 region	30(18.99%)	8L region	2(1.27%)
3A region	0(0.00%)	9 region	0(0.00%)
3P region	0(0.00%)		

**Table 4** The distribution of mediastinal lymph node recurrence in the SA group.

Abbreviations: SMLNR = superior mediastinal lymph node recurrence. MMLNR = middle mediastinal lymph node recurrence. IMLNR = inferior mediastinal lymph node recurrence. SA = surgery alone.

Note: Superior mediastinal lymph node recurrence:  $\chi^2 = 155.416, p < 0.001$ ; Middle mediastinal lymph node recurrence:  $\chi^2 = 35.726, p < 0.001$ .

GROUP	NO.(%)	GROUP	NO.(%)
<b>SMLNR</b>	<b>29(47.54%)</b>	6 region	3(4.92%)
1R region	5(8.20%)	<b>MMLNR</b>	<b>18(29.51%)</b>
2R region	7(11.48%)	7 region	13(21.31%)
4R region	15(24.59%)	8M region	3(4.92%)
1L region	1(1.64%)	10R region	4(6.56%)
2L region	2(3.28%)	10L region	5(8.20%)
4L region	7(11.48%)	<b>IMLNR</b>	<b>2(3.28%)</b>
5 region	7(11.48%)	8L region	2(3.28%)
3A region	2(3.28%)	9 region	0(0.00%)
3P region	0(0.00%)		

**Table 5** The distribution of mediastinal lymph node recurrence in the S+RT group.

Abbreviations: SMLNR = superior mediastinal lymph node recurrence. MMLNR = middle mediastinal lymph node recurrence. IMLNR = inferior mediastinal lymph node recurrence. S+RT = surgery plus postoperative radiotherapy.

Note: Superior mediastinal lymph node recurrence:  $\chi^2 = 38.812, p < 0.001$ ; Middle mediastinal lymph node recurrence:  $\chi^2 = 11.186, P = 0.011$ .

than that in patients without preoperative abdominal LNM (43.63% vs. 6.66%,  $P < 0.001$ ), and it was the same case for patients with postoperative radiotherapy (52.38% vs. 13.95%,  $P = 0.001$ ). There was no significant difference in the abdominal lymph node recurrence between SA and S+RT in patients with abdominal subcarinal LNM ( $\chi^2 = 0.468, P = 0.494$ ) (*Table 7*).

## DISCUSSION

At present, the setting of postoperative radiation target volume in many centers is mostly based on the location of lymph nodes found during the operation. However, it is unclear whether the recurrence in the site of preoperative lymph node metastasis would occur after dissection. Fujita *et al.* [20] reported that in patients with upper TEC, metastasis before operation was commonly found in the cervicothoracic and periesophageal nodes, and recurrence mostly occurred in the cervical nodes. In patients with middle TEC, metastasis before operation was commonly found in the cervicothoracic nodes of the right side, whereas recurrence mostly occurred in that of the left side. In patients with lower TEC, metastasis before operation was commonly found in the periesophageal nodes and upper abdominal nodes, whereas recurrence mostly occurred in the celiac nodes. Therefore, postoperative radiation, whose target volume is based on lymphatic spread regularity, may result in missing the target area. And, the comparison of the recurrence rate in each site for patients with esophageal carcinoma between surgery followed by radiotherapy (S+RT) and surgery alone (SA)

SURGERY ALONE GROUP			SURGERY + RADIATION GROUP		
PSNM	SUBCARINAL NODES		PSNM	SUBCARINAL NODES	
	RECURRENT	NORMAL		RECURRENT	NORMAL
<b>Positive</b>	12	23	<b>Positive</b>	6	11
<b>Negative</b>	25	115	<b>Negative</b>	7	40
Statistics: $\chi^2 = 4.533, P = 0.033$			Statistics: $\chi^2 = 2.073, P = 0.150$		

**Table 6** The local control efficacy of postoperative radiotherapy for patients with preoperative subcarinal lymph node metastases. Abbreviations: PSNM = Preoperative subcarinal nodal metastasis. Note: Comparison of subcarinal recurrence between two groups in patients with preoperative subcarinal nodal metastasis:  $\chi^2 = 0.005, P = 0.943$ .

SURGERY ALONE GROUP			SURGERY + RADIATION GROUP		
PANM	ABDOMINAL NODES		PANM	ABDOMINAL NODES	
	RECURRENT	NORMAL		RECURRENT	NORMAL
<b>Positive</b>	24	31	<b>Positive</b>	11	10
<b>Negative</b>	8	112	<b>Negative</b>	6	37
Statistics: $\chi^2 = 34.498, p < 0.001$			Statistics: $\chi^2 = 10.681, P = 0.001$		

**Table 7** The local control efficacy of postoperative radiotherapy for patients with preoperative abdominal lymph node metastases. Abbreviations: PANM=Preoperative abdominal nodal metastasis. Note: Comparison of abdominal recurrence between two groups in patients with preoperative abdominal nodal metastasis:  $\chi^2 = 0.468, P = 0.494$ .

is very important to assess the value of postoperative radiation for local control. In this study, The lymph node recurrence was the most common local regional recurrence in patients with and without postoperative radiotherapy. The common recurrent regions were cervical, superior, and middle mediastinal in both groups. This result is consistent with some recent studies [13–16]. A possible reason for this result was the technical difficulty of lymph node dissection in the lower cervical, superior, and middle mediastinal regions. This is due to complex anatomy with abundant nerves, lymphatic vessels, and adjoining large blood vessels and critical organs in these regions. A few residual cancer cells are sometimes found in connective tissues, particularly in advanced ESCC, which may lead to relapse after surgery. Furthermore in our study, cervical and mediastinal recurrence was not significantly affected by TEC vertical location for patients without radiotherapy. Therefore, regardless of the location of tumor, irradiate supraclavicular and station 1–5 and 7 lymph nodes regions may decrease the risk of local recurrence and become an effective regimen for patients with high risk factors [10–11].

Lu *et al.* [21] reported that after surgery, supraclavicular lymph node metastasis in patients in the lower and middle lower thirds were 1/43 and 1/18. So, it seems unnecessary that the bilateral supraclavicular area should be irradiated in the lower and middle lower thirds. Contrarily, Cai *et al.* [16] reported that the supraclavicular and station 1–5 and 7 lymph nodes had high recurrent rates for esophageal carcinomas

in all locations, and the supraclavicular area should be incorporated within the postoperative irradiation target volume. In our study, cervical recurrence rate in patients with and without postoperative radiotherapy was 40.98% and 49.37%, respectively. Therefore, we thought the supraclavicular area should be included in the postoperative radiotherapy target volume. In this study, the superior mediastinal lymph node recurrence rate in SA group was significantly higher than that in S+RT group (67.72% vs. 47.54%,  $\chi^2 = 7.615, P = 0.006$ ). Possible explanations include that it was technically difficult to dissect all lymph nodes in these areas and that the areas of these lymph nodes (station 1–5 lymph nodes) were incorporated within the postoperative irradiation target volume. The residual cancer cells then were killed by the postoperative radiotherapy with a sufficient dose. Therefore, we suggest the superior mediastinal area must be included in the postoperative radiotherapy target volume for all TEC segments.

Locoregional recurrence of the middle mediastinal lymph nodes was frequent in the 7 region. In patients without postoperative radiotherapy, the subcarinal lymph node recurrence occurred more frequently in those with preoperative subcarinal LNM. This suggested the presence of preoperative subcarinal LNM may be significantly associated with subcarinal recurrence. However, there was not a significant decrease in the recurrent rate of subcarinal lymph node in patients with preoperative subcarinal LNM after postoperative radiotherapy ( $\chi^2 = 0.005, P = 0.943$ ). We thought the

small sample sizes of recurrences with postoperative radiotherapy might influence this result.

Lower TEC mostly metastasizes downward to abdominal para-aortic lymph nodes [22–23]. In this study, the recurrent rate of abdominal lymph node in the upper TEC was significantly lower than that in the middle thoracic and lower TEC. Furthermore, the abdominal recurrence was significantly associated with the presence of preoperative abdominal LNM. This may be attributed to the technical difficulty in removing all lymph nodes in this area when some are adjacent to the abdominal aorta. These small numbers of residual cancer cells may result in recurrence [24]. In this study, postoperative radiotherapy did not significantly decrease the recurrent proportion of abdominal lymph nodes in patients with preoperative abdominal LNM. One possible explanation includes that the abdominal area was irradiated only in lower TEC and not in upper and middle TEC. Therefore, we suggest abdominal areas, including para-aortic lymph node areas, should be irradiated in patients with preoperative abdominal LNM, especially para-aortic LNM.

Anastomotic radiotherapy is still in dispute considering it may cause anastomotic stricture. In our study, the recurrence rate of anastomosis in patients without radiotherapy was higher than that in patients with radiotherapy (19.43% vs. 10.94%). Therefore, postoperative radiotherapy may reduce anastomotic recurrence if the target volume includes anastomosis.

There were some limitations to our study. First, because this study was a retrospective analysis of local recurrent cases with TEC, a clear conclusion cannot be exactly drawn. Second, we did not test gene expressions by immunohistochemical in every patient. Therefore, the existence of radiotherapy resistance in certain patients may also affect the results. A large sample prospective study with postoperative radiotherapy followed by 3-LND in patients with high risk factors is necessary to assess the postoperative radiation value for local control.

In conclusion, the main pattern of local esophageal squamous cell carcinoma recurrence after radical 3-FLD may be lymph node metastasis. The dangerous regions of lymph node recurrence included superior, middle mediastinum and neck. Postoperative radiotherapy shows great value in reducing superior mediastinal lymph node recurrence, and the fields of these lymph nodes should be delineated in the postoperative irradiation target volume. The lower segment of thoracic esophageal carcinoma and preoperative abdominal lymph node metastasis, especially para-aortic lymph node metastasis, may be risk factors for abdominal lymph node recurrence. Anastomosis should also be included in the target area.

## ETHICS AND CONSENT

No animal or human was involved in this study.

Informed consent was obtained from all individual participants included in the study.

## COMPETING INTERESTS

The authors have no competing interests to declare.

## AUTHOR CONTRIBUTIONS

ZX had the idea for the article and performed the literature search and data analysis, and ZX and BS drafted and/or critically revised the work.

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