

The Relationship between Recurrent Site of Esophageal Carcinoma and Preoperative Lymph Node Status

Xu ZC^{*1}, Su BA¹, Li J² and Chen J²

¹First Hospital of Quanzhou Affiliated to Fujian Medical University, China

²Fujian Provincial Cancer Hospital, Fujian Province, China

*Corresponding author:

Zhi-Chen Xu,

First Hospital of Quanzhou Affiliated to Fujian Medical University, Quanzhou (362000), People's Republic of China, E-mail: 609108007@qq.com

Received: 05 Feb 2022

Accepted: 15 Mar 2022

Published: 21 Mar 2022

J Short Name: JCMI

Copyright:

©2022 Xu ZC, This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Citation:

Xu ZC, The Relationship between Recurrent Site of Esophageal Carcinoma and Preoperative Lymph Node Status. J Clin Med Img. 2022; V6(5): 1-5

Keywords:

Esophageal carcinoma; Three-Field lymph node dissection; Recurrence; Lymph node status before operation

1. Abstract

1.1. Purpose: To analyse local regional recurrence pattern and site of thoracic esophageal carcinoma and discuss the relationship between lymph node status before operation and the lymph nodes recurrent site so as to provide evidence for target setting of radiotherapy.

1.2. Methods and Materials: We reviewed 175 cases with esophageal squamous cell carcinoma who had a local-regional recurrence after Three-Field Lymph Node Dissection (3-FLD) without prophylactic radiotherapy from 2005 to 2010 and analyzed local regional recurrent pattern and sites of thoracic esophageal carcinoma, lymph node metastasis rate in each site and relationship between lymph node status before operation and the lymph nodes recurrent site after operation.

1.3. Results: Among 175 patients with Thoracic Esophageal Carcinomas (TECs) who were underwent curative surgery, the lymph node metastasis, anastomosis recurrence and tumor bed recurrence rates were 90.29%, 19.43% and 9.71% ($\chi^2=282.564$, $P=0.000$), respectively. As to the 158 cases with lymph node metastasis, the mediastinal, cervical and abdominal lymph node metastasis rates were 72.78%, 49.37% and 20.25% ($\chi^2=87.769$, $P=0.000$), respectively. Furthermore, there was no significant difference among different segments of the primary tumor in cervical or mediastinal lymph node metastasis rates. The frequency of abdominal lymph node metastasis of the upper thoracic esophageal carcinoma was lower than those of the middle thoracic and lower thoracic location ($\chi^2=9.452$, $P=0.009$). In 175 cases, superior, middle and inferior mediastinal lymph node metastasis

rates were 67.72%, 28.48% and 1.27%, respectively. There was very significant difference among the three groups ($\chi^2=160.802$, $P=0.000$). The location of cervical Lymph Node Metastasis (LNM) before operation was not significantly associated with locoregional recurrence after operation ($\chi^2=0.557$, $P=0.455$). The location of subcarinal LNM before operation was significantly associated with locoregional recurrence after operation ($\chi^2=4.533$, $P=0.033$). The location of abdominal LNM before operation was also significantly associated with locoregional recurrence after operation ($\chi^2=34.498$, $P=0.000$).

Conclusions: The main pattern of local-regional recurrence may be lymph node metastasis after radical 3-FLD without prophylactic radiotherapy in esophageal squamous cell carcinoma. The abdominal and subcarinal LNM before operation may be associated with corresponding locoregional recurrence after operation.

2. Introduction

At present overall 5-year survival rate of Esophageal Carcinoma (EC) is only 16% [1]. Despite recent advances in multidisciplinary approaches including radiotherapy and chemotherapy, no significant improve was seen in 5-year survival rate [2]. Surgery remains the standard treatment for potentially resectable esophageal carcinoma. Three-field Lymph Node Dissection (3-FLD) for carcinoma of the esophagus has been practiced by Japanese surgeons since the early 1980s [3-4]. However, the significance of 3-FLD for survival remains controversial: Some patients may be offered significant survival benefit by extended radical esophagotomy with 3-FLD, whereas some patients still experience recurrent diseases after this highly invasive surgery. The purpose of this re-

search is to analyze local regional recurrence pattern of thoracic esophageal carcinoma after three-field lymph node dissection without prophylactic radiotherapy and relationship between lymph node status before operation and the site of recurrent lymph nodes after operation, so as to provide evidence for target setting of radiotherapy.

3. Methods and Materials

3.1. Patients

From January 2005 to December 2010, 175 patients with thoracic esophageal Squamous Cell Carcinoma(SCC), who had local-regional recurrence after three-field lymph node dissection, were identified in the Fujian Provincial Cancer Hospital. The median age of the patients (150 men and 25 women) was 57.5 (from 38 to 77) years. All patients underwent three-field lymph node dissection [5] and did not receive any preoperative or postoperative radiotherapy. Patients with palliative resection or apparent residual tumors were excluded. The distribution of the tumor location was 34 cases in the upper thoracic segment, 124 in the middle thoracic segment, and 17 in the lower thoracic segment esophagus. The distribution of the T category in the TNM classification (AJCC / UICC, 2009) was 6 in T1, 38 in T2, 130 in T3, and 1 in T4. That of pN category was 52 in N0, 47 in N1, 31 in N2 and 45 in N3.

3.2. Diagnostic criteria

Local-regional recurrence included lymph node recurrence, anastomosis recurrence and tumor bed recurrence. In this study the time interval from operation to recurrence for all patients was 1-108 months, the median recurrent time was 14.6 months. Any additional recurrences, including other lymph nodes or organs found within 1 month after the initial detection of recurrent tumors, were considered to have occurred simultaneously.

As one criterion, detected nodes were considered recurrent tumors if the long axis was greater than 1cm [6-7]. In addition, we also took node shape (round or flat), uptake of contrast medium or FDG and difference from the previous node into consideration when evaluating for recurrence. Anastomotic recurrence was determined by histologic analyses following biopsy or surgery. Tumor bed recurrence was diagnosed by CT or PET-CT.

3.3. Terminology of the regional lymph nodes in esophageal cancer

According to a lymph node mapping system for esophageal carcinoma (AJCC-UICC in 1996), 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 (paraaortic nodes); 7(subcarinal nodes); 8M(middle paraesophageal lymph nodes); 8L(Lower paraesophageal lymph nodes); 9(pulmonary ligament nodes); 10R(Right hilar nodes); 10L(Left hilar nodes). The lymph nodes in the 1,2,3,4,5

and 6 level were included in the superior mediastinal lymph node; the lymph nodes in the 7, 8M, 10 level were included in the middle mediastinal lymph node; the lymph nodes in the 8L, 9 level were included in the inferior mediastinal lymph node.

4. Statistical Analysis

All analyses were performed with the statistical package SPSS for Windows (release 11.5; SPSS Inc., Chicago, IL, USA). The chi-square test was used for Categorical variable. A p value of less than 0.05 was considered statistical significant.

5. Results

5.1. Pattern of recurrence

Among 175 recurrent patients who underwent curative surgery without prophylactic radiotherapy, the lymph node metastasis, anastomosis recurrence and tumor bed recurrence rate were 90.29% (158 cases), 19.43% (34 cases) and 9.71% (17 cases), respectively. There was very significant difference among three groups ($\chi^2=282.564$, $P=0.000$). the lymph node metastasis was the main pattern.

Among 158 patients with lymph node metastasis after operation, mediastinal, cervical and abdominal lymph node metastasis rate was 72.78% (115 cases), 49.37% (78 cases) and 20.25% (32 cases), respectively. There was very significant difference among three groups ($\chi^2=87.769$, $P=0.000$). There was no significant difference among different segments of the primary tumor in cervical or mediastinal lymph node metastasis rates. However, the frequency of abdominal lymph node metastasis of the upper thoracic esophageal carcinoma was lower than those of the middle thoracic and lower thoracic location ($\chi^2=9.452$, $P=0.009$) (Table 1).

Cervical and supraclavicular lymph node metastasis after operation: the left cervical Lymph Node Metastasis(LNM) accounted for 66.67% of cervical LNM and 32.91% of total LNM, while the right cervical LNM accounted for 66.67% of cervical LNM and 24.05% of total LNM. The cervical LNM rate in the left wasn't higher than those in the right ($\chi^2=3.045$, $P=0.081$) (Table 2). However, the supraclavicular LNM in the left was similar to those in the right ($\chi^2=0.928$, $P=0.335$).

Mediastinal lymph node metastasis after operation: in 175 TECs, the superior, middle and inferior mediastinal nodes rate were 67.72% (107 cases), 28.48% (45 cases) and 1.27% (2 cases), respectively. There is very significant difference among the three groups ($\chi^2=160.802$, $P=0.000$) (Table 2). As to superior mediastinal lymph node metastasis, locoregional recurrence was frequent in the 4R region, and there is very significant difference among these regions (Table 3). Lymph node metastasis rate of left recurrent laryngeal nerve nodes (including region 1L, 2L, 4L and 5) and right recurrent laryngeal nerve nodes (region 1R) were 43.04%(68 cases) and 12.66%(20 cases), respectively ($\chi^2=36.287$, $P=0.000$). As to middle mediastinal lymph node metastasis, locoregional recurrence was frequent in the 7 region, and there is significant difference

rence among these regions (Table 3). As to inferior mediastinal lymph node metastasis, locoregional recurrence was rare and lymph node metastasis rate in the 8L region and 9 region accounted for 1.27%(2cases).

Relationship between the location of lymph node metastases before operation and the location of the lymph node recurrence after operation

Cervical LNM before operation was found in 75 of 175 patients. Of these 75 patients, Cervical LNM after operation was recognized in 31 patients (41.33%), There was no obvious relationship between the location of two groups ($\chi^2=0.557, P=0.455$).

Mediastinal LNM before operation was found in 87 patients. Of these 87 patients, Mediastinal LNM after operation was recognized in 56 patients (64.37%). There was no obvious relation between the location of two groups ($\chi^2=0.139, P=0.709$). The same results were in superior mediastinal and middle mediastinal. However,

the site of subcarinal LNM before operation had an obvious relation to the location of subcarinal LNM after operation ($\chi^2=4.533, p=0.033$) (Table 4). Our findings indicate that the presence of subcarinal LNM before operation may be an important predictor of locoregional recurrence after operation. The positive predictive value, negative predictive value, sensitivity, and specificity were 32.43%, 83.33%, 34.29%, and 82.14%, respectively.

Abdominal LNM before operation was found in 55 patients. Of these 55 patients, recurrent disease was recognized in 24 patients (43.64%), The location of abdominal LNM before operation was significantly associated with locoregional recurrence after operation ($\chi^2=34.498, P=0.000$) (Table 5). These findings indicate that the presence of abdominal LNM may be an important predictor of locoregional recurrence after operation. The positive predictive value, negative predictive value, sensitivity, and specificity were 75%, 78.32%, 43.63% and 93.33%, respectively.

Table 1: Frequency of lymph node metastasis in 158 recurrent cases among different segment esophageal carcinoma (%)

Location	cases	Cervical nodes	mediastinal nodes	abdominal nodes
Ut	34	13(38%)	27(79%)	0(0%)
Mt	124	59(48%)	76(61%)	28(23%)
Lt	17	6(35%)	12(71%)	4(23%)
		$\chi^2=1.599$	$\chi^2=4.088$	$\chi^2=9.452$
		P=0.449	P=0.130	P=0.009

Abbreviations: Ut = upper thoracic; Mt = middle thoracic; Lt = lower thoracic

Table 2: Frequency of lymph node metastasis after operation in 158 cases (%)

Site of recurrence	cases	Frequency(%)	Site of recurrence	cases	Frequency(%)
Cervical nodes	78	49.37%	Mediastinal nodes	115	72.78%
right cervical nodes	38	24.05%	Superior mediastinal nodes	107	67.72%
left cervical nodes	52	32.91%	Middle mediastinal nodes	45	28.48%
			Inferior mediastinal nodes	2	1.27%

Cervical lymph node metastasis: $\chi^2=3.045, P=0.081$; Mediastinal lymph node metastasis: $\chi^2=160.802, P=0.000$

Table 3: Frequency of mediastinal lymph node metastasis at recurrence in 158 cases (%)

group	No.	Frequency (%)	group	No.	Frequency (%)
Superior mediastinal LNM	107	67.72%	6 region	4	2.53%
1R region	20	12.66%	Middle mediastinal LNM	45	28.48%
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%	Inferior mediastinal LNM	2	1.27%
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%			

Abbreviations: LNM: lymph node metastasis;

Superior mediastinal lymph node metastasis $\chi^2= 155.416, P=0.000$; Middle mediastinal lymph node metastasis $\chi^2= 35.726, P=0.000$

Table 4: Relationship between subcarinal mediastinal lymph node status before operation and the lymph node metastases after operation

subcarinal nodal metastasis	subcarinal nodal recurrence	
	recurrent	normal
Positive	12	23
Negative	25	115

Comparison of subcarinal nodal recurrence: $\chi^2=4.533, P=0.033$

Table 5: Relationship between abdominal mediastinal lymph node status before operation and the lymph node metastases after operation

abdominal nodal metastasis	abdominal nodal	
	recurrent	normal
Positive	24	31
Negative	8	112

Comparison of abdominal nodal recurrence: $\chi^2=34.498$, $P=0.000$.

6. Discussion

At present, surgical treatment remains the preferred treatment method for thoracic esophageal squamous cell carcinoma of T1-3N0-1M0 stage. Most Japanese scholars believed that the 3-FLD could improve survival rate of esophageal carcinoma. Satoru et al. [8-9] reported after extended radical esophagectomy with 3FL, the overall 5-year survival rate of patients could reach 55.6%, however, the local recurrence rate was 17.5% -21%. In our hospital, 3-FLD had been mostly performed [5] since it was established in 1986, and the local recurrence rate after this curative surgery was 15.7% -41.1% [10]. Many researches [11-14] had reported recurrence patterns after extended radical esophagectomy with 3FL. But there is rare article talking about the relationship between the location of lymph node metastases before operation and the site of lymph node recurrence after operation. The purpose of postoperative radiotherapy is to reduce the local recurrence rate. The local recurrent site after operation is very important for target setting of radiotherapy. So we selected recurrent cases of esophageal carcinoma after operation without prophylactic radiotherapy to analyse relationship between the location of lymph node metastases before operation and the site of lymph node recurrence after operation.

In this study, lymph node metastasis rate of recurrent cases was 90.29%, which indicated that lymph node metastasis was the main local regional recurrence patterns after extended radical esophagectomy with 3FL. The main regions of lymph node metastasis after operation included mediastinum (72.78%) and neck (49.37%). On the contrary, abdominal recurrence is rare. Nakagawa et al. [15] reported a study of 171 patients with thoracic esophageal carcinomas who underwent 3-FLD; of the 30 patients who experienced locoregional recurrence, 28.6% of recurrences appeared in the cervical region, 62.9% in the mediastinum, 17.1% in the abdominal region, and 2.9% at the anastomotic stoma, which is similar to our study. In our series, the main region of mediastinal lymph node recurrence was the superior and middle mediastinum. Some articles [13-16] reported the main region of mediastinal lymph node recurrence after extended radical esophagectomy with 3FL was mainly cervicomedial, which is similar to our study. In superior and middle mediastinal, lymph node metastasis after operation occurred mainly in 4R level, 7 level and the recurrent laryngeal nerve area. A possible reason for this result was the technical difficulty of lymph node dissection in the lower neck, superior and middle mediastinal regions owing to the complex anatomy with the abundance of nerves and lymphatic vessels and adjoining large blood vessels and critical organs in these regions. On the other hand,

the inferior mediastinal and upper abdominal areas can be well exposed, and lymph node dissection is comparatively more thorough. So our researchers suggested the target volume of radiotherapy after 3-FLD should not depend completely on the regularity of lymphatic spread [5].

As cited by Doki et al. [17], the tumor recurrence site was significantly affected by the location of esophageal carcinoma, and the regional recurrence (such as in the cervical and upper mediastinal nodes) was dominant in Ut (53%) and Mt (51%). However, we regarded the regional recurrence after operation was associated with more factors (e.g., lymph node status before operation, the size of T stage et al.).

There is rare article talking about the relationship between lymph node status at operation and the lymph node recurrence after 3-FLD. Fujita et al. [16] reported that in patients with upper thoracic esophageal carcinoma, metastasis before operation was most frequently found in the cervicothoracic and periesophageal nodes and recurrence after operation frequently occurred in the cervical nodes; in patients with middle thoracic esophageal carcinoma, metastasis before operation was most frequently found in the cervicothoracic nodes of the right side and in the upper abdominal nodes, whereas recurrence after operation frequently occurred in the cervicothoracic nodes in the left side; in patients with lower thoracic esophageal carcinoma, metastasis before operation was most frequently found in the periesophageal nodes and the upper abdominal nodes, whereas recurrence after operation most frequently occurred in the celiac nodes. However, his series had only few cases, which makes firm conclusions on external validity difficult. Nakagawa et al. [15] have shown that the location of cervical LNM before operation is significantly associated with locoregional recurrence, and may be an important predictor of locoregional recurrence. Yoichi et al. [18] have shown that recurrent nerve nodal involvement is associated with cervical nodes metastasis. However, our findings indicate the presence of cervical LNM before operation is not significantly associated with locoregional recurrence. Our findings also indicate mediastinal recurrence is not significantly associated with mediastinal LNM before operation. Therefore, we suppose that the recurrence of LNM after operation in esophageal carcinoma may be associated with many factors, and it should not be predicted merely by lymph node status before operation.

However, it is worth mentioning that the location of subcarinal LNM before operation was significantly associated with locoregional recurrence after operation. These findings might indicate

that the location of subcarinal LNM before operation maybe an important predictor of locoregional recurrence after operation. What is more, in our series, the abdominal mediastinal nodes recurrence after operation was dominant for Mt (23%) and Lt (23%) tumors but not for Ut (0%) tumors, and lymph node recurrence in abdominal regions after operation was associated with lymph node metastases before operation. These findings might also indicate that the presence of abdominal LNM before operation may be an important predictor of abdominal LNM after operation.

7. Conclusion

The main pattern of local-regional recurrence of esophageal squamous cell carcinoma after radical 3-FLD without prophylactic radiotherapy may be lymph node metastasis. Common metastasis regions were cervical, superior and middle mediastinal regions (mainly located in 4R level, 7 level and the recurrent laryngeal nerve area). The presence of abdominal and subcarinal LNM before operation is significantly associated with LNM after operation, while cervical, other mediastinal LNM before operation are not associated with loco regional recurrence after operation. We regarded that abdominal or subcarinal lymph node status Before operation should be taken into consideration when we need postoperative radiotherapy.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ, et al. Cancer statistics. *CA Cancer Statistics*. 2009; 59(4): 225-249.
2. GebSKI V, Burmeister B, Smithers B M, Foo K, Jhon Z, Jhon S, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol*. 2007; 8(3): 226-234.
3. Tanabe G, Nishi M, Kajis T, et al. Analysis of lymph node metastases and surgical treatments for thoracic esophageal cancer: New method of the initial dissection of the cervix and abdomen. *Jpn J Gastroenterol Surg*. 1983; 16: 1890-1896.
4. Kato H, Tachimori Y, Watanabe H, Iizuka T, Terui S, Itabashi M, et al. Lymph node metastases in thoracic esophageal carcinoma. *J Surg Oncol*. 1991; 48: 106-111.
5. Chen J, Liu S, Pan J, Zheng X, Zhu K, Zhu J, et al. The pattern and prevalence of lymphatic spread in thoracic oesophageal squamous cell carcinoma. *Eur J Cardiothorac Surg*. 2009; 36: 480-486.
6. Shimada H, Kitabayashi H, Nabeya Y, Okazumi Si, Matsubara H, Funami Y, et al. Treatment response and prognosis of patients after recurrence of esophageal cancer. *Surgery*. 2003; 133(1): 24-31.
7. Kato H, Miyazaki T, Nakajima M, Fukuchi M, Manda R and Kuwano H. Value of positron emission tomography in the diagnosis of recurrent oesophageal carcinoma. *Br J Surg*. 2004; 91(8): 1004-1009.
8. Nakagawa S, Kanda T, Kosugi S, Kosugi Si, Ohashi M, Suzuki T, 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(2): 205-211.
9. Bhansali MS, Fujita H, Kakegawa T, Yamana H, Ono T, Hikita S, et al. Pattern of recurrence after extended radical esophagectomy with three-field lymph node dissection for squamous cell carcinoma in the thoracic esophagus. *World J Surg*. 1997; 21(3): 275-281.
10. Kunshou Z, Zhilian S, Junqian C, et al. Clinical significance of three field lymphadenectomy in thoracic carcinoma of esophagus and its prophylactic postoperative radiotherapy. *Chin J Cancer Prev Treat*. 2006; 13: 763-765.
11. Matsubara T, Ueda M, Takahashi T, et al. Localization of recurrent disease after extended lymph node dissection for carcinoma of the thoracic esophagus. *J Am Coll Surg*, 1996; 182: 340-366.
12. Kato H, Tachimori Y, Watanabe H, Igaki H, Nakanishi Y and Ochiai A. Recurrent esophageal carcinoma after esophagectomy with three-field lymph node dissection. *J Surg Oncol*. 1996; 61(4): 267-272.
13. Bhansali MS, Fujita H, Kakegawa T, Yamana H, Ono T, Hikita S, et al. Pattern of recurrence after extended radical esophagectomy with three-field lymph node dissection for squamous cell carcinoma in the thoracic esophagus. *World J Surg*. 1997; 21(3): 275-281.
14. Kyriazanos ID, Tachibana M, Shibakita M, Yoshimura H, Kinugasa S, Dhar DK, et al. Pattern of recurrence after extended esophagectomy for squamous cell carcinoma of the esophagus. *Hepato-gastroenterology*. 2003; 50(49): 115-120.
15. Nakagawa S, Kanda T, Kosugi S, Ohashi M, Suzuki T and Hatakeyama K. Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. *J Am Coll Surg*, 2004; 198(2): 205-211.
16. Fujita H, Kakegawa T, Yamana H, Shima I, Tanaka H, Ikeda S, et al. Lymph node metastasis and recurrence in patients with a carcinoma of the thoracic esophagus who underwent three-field dissection. *World J Surg*. 1994; 18(2): 266-272.
17. Doki Y, Ishikawa O, Takachi K, Miyashiro I, Sasaki Y, Ohigashi H, et al. Association of the Primary Tumor Location with the Site of Tumor Recurrence after Curative Resection of Thoracic Esophageal Carcinoma. *World J Surg*. 2005; 29(6):700-707.
18. Tabira Y, Yasunaga M, Tanaka M, Nakano K, Sakaguchi T, Nagamoto N, et al. Recurrent Nerve Nodal Involvement Is Associated with Cervical Nodal Metastasis in Thoracic Esophageal Carcinoma. *J Am Coll Surg*. 2000; 191(3): 232-237.