



Understanding the pattern of lymph node metastasis for trans-segmental thoracic esophageal cancer to develop precise delineation of clinical target volume for radiotherapy

Liyuan Huang, Chen Chen, Mingqiang Lin, Jiancheng Li

Department of Radiation Oncology, Fujian Cancer Hospital & Fujian Medical University Cancer Hospital, Fujian 350014, China

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Correspondence to: Jiancheng Li. Department of Radiation Oncology, Fujian Cancer Hospital & Fujian Medical University Cancer Hospital, No. 420, Fumalu Road, Jinan District, Fuzhou 350014, China. Email: jianchengli6@163.com.

Background: This study was conducted to explore the lymph node metastasis (LNM) pattern of thoracic esophageal cancer (TEC) depending upon the location of the primary tumor and provide a reference for the design of clinical target volume (CTV).

Methods: The data of patients who underwent radical esophagectomy and three-field lymph node dissection at Fujian Cancer Hospital from 2006 to 2010 were retrospectively analyzed. We segmented the esophagus according to the anatomical landmarks on computed tomography (CT) and defined the trans-segmental and mono-segmental esophageal carcinoma. The LNM pattern in trans-segmental and mono-segmental esophageal cancer was explored and the CTV delineation was determined based on LNM pattern.

Results: A total of 852 patients were included in this study. The top five sites of LNM for upper-middle TEC were cervical, upper and middle paraesophageal, and zone 1, 2, 4 regions. The most common sites of LNM for lower-middle TEC were cervical and middle paraesophageal, group 3, 7, and zone 7 regions. The top five sites of LNM for middle-upper TEC were cervical, middle paraesophageal, zone 1, 7, and group 7 regions. The most common sites of LNM for middle-lower TEC were cervical, middle paraesophageal, zone 7, and group 2, 7 regions. The top five sites of LNM for TEC involving all the segments were cervical, middle paraesophageal, zone 7, group 2 and 7 regions.

Conclusions: LNM pattern of trans-segmental and mono-segmental TEC varies depending upon the primary tumor location. The irradiation field must be designed according to the primary tumor location.

Keywords: Esophageal cancer (EC); lymph node metastasis (LNM); clinical target volume (CTV)

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Introduction

Esophageal cancer (EC) is a common upper digestive tract malignant tumor especially in eastern Asia and Africa. It is the seventh most common cause of morbidity and sixth most common cause of mortality among the malignant tumors worldwide (1). Despite advances in the multimodality treatment of EC, the 5-year survival rate of esophageal

cancer continues to remain low (~40%) (2). Lymph node metastasis (LNM) is one of the most significant prognostic factors affecting the survival of EC (3).

The Union for International Cancer Control (UICC) divided the esophagus into four segments. Different tumor locations have different patterns of LNM, which plays an important role in the evaluation and treatment of EC. Usually, radiation oncologists delineate clinical

target volume (CTV) focusing on areas with high rates of LNM based on the location of tumor, which still remains disputed. Moreover, thoracic esophageal cancer (TEC) spanning segments are often encountered, whose LNM characteristics can be different from mono-segmental TEC. But the principles of TEC spanning are poorly understood. The benefits of precision radiotherapy may be offset by following the same criteria of CTV delineation. This retrospective study aimed to investigate the LNM pattern of trans-segmental TEC which can help in designing CTV.

Methods

This retrospective study was approved by Fujian Cancer Hospital Institutional Review Board. All patients provided written informed consent prior to treatment, and all information was anonymized prior to analysis.

In this study, we included patients with TEC who underwent surgery during the study period from January 2006 to December 2010 at Fujian Cancer Hospital. The patients who satisfied the following conditions were included: (I) histologically proven primary esophageal squamous cell cancer, (II) the upper and lower boundaries of the tumor were clearly defined by endoscopy, esophageal barium meal, and high-resolution CT chest examination before operation in our hospital, and (III) underwent radical esophagectomy and three-field lymph node dissection. The exclusion criteria were: patients who received preoperative radiotherapy or chemotherapy, those having cervical esophageal cancer and those with distant metastasis. Patients with prior thoracic surgery before esophagectomy were also excluded.

According to the 8th edition of the American Joint Committee on Cancer (AJCC), the location of esophageal tumor was defined based on the center of the tumor. In the present study, the location of the tumor was determined using the anatomical landmarks on preoperative high-resolution CT examination. The term 'upper/middle/lower thoracic esophageal cancer' (U/M/L TEC) were specifically used for the tumors whose boundaries were in the same segment. For larger tumors located in more than one segment, we used the term 'trans-segmental esophageal carcinoma'. The upper-middle thoracic esophageal cancer (U-M TEC) referred to the tumor whose center was within upper esophagus while the lower border extended in to the middle esophagus. Similarly, the middle-upper thoracic esophageal cancer (M-U TEC) referred to the tumor whose center was in the middle esophageal segment while

the upper border was extending in to the upper esophagus. The middle-lower thoracic esophageal cancer (M-L TEC) referred to the tumor whose center was within middle esophagus while the lower border was extending in to the lower esophageal segment. The lower-middle thoracic esophageal cancer (L-M TEC) refers to the tumor whose center was within the lower esophagus while the upper boundary extended in to the middle esophagus. The tumors extending to all the three segments of the thoracic esophagus were termed as 'all thoracic esophageal cancer' (ATEC).

To accurately describe the pattern of LNM, the regional lymph nodes were named as described by the Japanese Society for Esophageal Diseases (JSED) and AJCC. The characteristics of LNM pattern were collected retrospectively from postoperative pathological LN status. Then we compared the differences in LNM between trans-segmental and mono-segmental TEC, to make precise delineation of CTV for routine clinical practice.

Categorical data are presented as numbers and percentages. The LNM rates were compared between the groups by Chi-square test or Fisher's exact test as applicable. Data were analyzed using Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) version 22.0 for Windows. A two-tailed P value <0.05 was considered statistically significant.

Results

A total of 852 patients with TEC were included in this study. The median age was 57 years (range, 31 to 84 years). There were 649 males (76.2%) and 203 females (23.8%). The numbers of patients with U, U-M, M, M-U, M-L, A, L, and L-M TEC were 88 (10.3%), 44 (5.2%), 285 (33.5%), 150 (17.6%), 198 (23.3%), 25 (2.9%), 48 (5.6%), and 14 (1.6%), respectively. The demographic details of the patients are shown in *Table 1*.

The incidence of LNM varied depending upon the location of the primary tumor. Even for the TEC of the same segment of esophagus, the LNM pattern of trans-segmental and mono-segmental TEC were different. The rates of LNM in neck, upper mediastinum, middle mediastinum, lower mediastinum, and abdominal cavity were 36.8% (313/852), 8.3% (71/852), 23.5% (200/852), 9.4% (80/852), and 23.4% (199/852), respectively (*Table 2*). The LNM rates of patients with U TEC in neck, upper mediastinum, middle mediastinum, lower mediastinum, and abdominal cavity were 47.7% (42/88), 5.7% (5/88), 8.0% (7/88), 2.3% (2/88), and 2.3% (2/88), respectively.

Table 1 The clinical characteristics of 852 patients with TEC

Characteristics	U	U-M	M	M-U	M-L	A	L	L-M	Total
Total	88	44	285	150	198	25	48	14	852
Sex									
Male	60	36	213	119	150	23	37	11	649
Female	28	8	72	31	48	2	11	3	203
T									
Tis	1	0	4	0	0	0	0	0	5
T1	16	0	52	10	3	1	11	0	94
T2	20	11	49	25	34	2	10	2	155
T3	31	26	135	89	125	15	21	11	446
T4	20	7	45	26	36	7	6	1	152
N									
N0	39	17	135	49	66	7	16	5	334
N1	23	14	69	48	62	9	17	6	248
N2	21	9	59	33	40	3	10	2	177
N3	5	4	22	20	30	6	5	1	93
Differentiation									
High	3	3	30	24	18	1	2	1	82
Middle	66	31	203	93	145	21	37	10	606
Low	12	8	36	25	19	0	7	1	108
Unknow	7	2	16	8	16	3	2	2	56
Length of tumor									
<4 cm	56	14	152	60	56	4	20	2	364
4–6 cm	28	27	118	71	103	13	21	12	393
>6 cm	4	3	15	19	39	8	7	0	95

TEC, thoracic esophageal cancer; U, upper thoracic esophageal cancer; U-M, upper-middle thoracic esophageal cancer; M, middle thoracic esophageal cancer; M-U, middle-upper thoracic esophageal cancer; M-L, middle-lower thoracic esophageal cancer; A, all thoracic esophageal cancer; L, lower thoracic esophageal cancer; L-M, lower-middle thoracic esophageal cancer.

Table 2 LNM rates at different sites taking all the TEC cases in to consideration

	Neck (%)	Um (%)	Mm (%)	Lm (%)	Ac (%)
TEC	313/852 (36.8)	71/852 (8.3)	200/852 (23.5)	80/852 (9.4)	199/852 (23.4)

LNM, lymph node metastasis; TEC, thoracic esophageal cancer; Um, upper mediastinum; Mm, middle mediastinum; Lm, lower mediastinum; Ac, abdominal cavity.

The LNM rate was 45.5% (20/44), 25.0% (11/44), 6.8% (3/44), 2.3% (1/44), and 6.8% (3/44) for patients with U-M TEC respectively (Table 3). The LNM rates were 12.5%

(6/48), 4.2% (2/48), 25.0% (12/48), 10.4% (5/48), and 47.9% (23/48) in patients with L TEC and 42.9% (6/14), 0% (0/14), 21.4% (3/14), 8.3% (4/14), and 42.9% (6/14) in

Table 3 LNM rates at different sites for upper (U) and upper-middle (U-M) TEC

U/U-M TEC	Neck (%)	Um (%)	Mm (%)	Lm (%)	Ac (%)	n
U	42 (47.8)	5 (5.7)	7 (8.0)	2 (2.3)	2 (2.3)	88
U-M	20 (45.5)	11 (25.0)	3 (6.8)	1 (2.3)	3 (6.8)	44
X ²	0.061	10.277	0	0	0.650	
P	0.805	0.001	1	1	0.420	

LNM, lymph node metastasis; U, upper thoracic esophageal cancer; U-M, upper-middle thoracic esophageal cancer; Um, upper mediastinum; Mm, middle mediastinum; Lm, lower mediastinum; Ac, abdominal cavity.

Table 4 LNM rates at different sites for lower (L) and lower-middle (L-M) TEC

L/L-M TEC	Neck (%)	Um (%)	Mm (%)	Lm (%)	Ac (%)	n
L	6 (12.5)	2 (4.2)	12 (25.0)	5 (10.4)	23 (47.9)	48
L-M	6 (42.9)	0 (0)	3 (21.4)	4 (8.3)	6 (42.9)	14
X ²	4.602	0	0	1.602	0.111	
P	0.032	1	1	0.206	0.739	

LNM, lymph node metastasis; L, lower thoracic esophageal cancer; L-M, lower-middle thoracic esophageal cancer; Um, upper mediastinum; Mm, middle mediastinum; Lm, lower mediastinum; Ac, abdominal cavity.

Table 5 LNM rates to different regions for M, M-U, M-L and A TEC

M/M-U/M-L/A TEC	Neck (%)	Um (%)	Mm (%)	Lm (%)	Ac (%)	n
M	90 (31.6)	14 (4.9)	54 (18.9)	20 (7.0)	61 (21.4)	285
M-U	76 (50.7)	21 (14.0)	42 (28.0)	20 (13.3)	28 (18.7)	150
M-L	65 (32.8)	14 (7.1)	68 (34.3)	23 (11.6)	69 (34.9)	198
A	7 (28.0)	4 (16.0)	11 (44.0)	5 (20.0)	7 (28.0)	25
X ²	17.936	13.349	18.658	7.711	15.504	
P	0.001	0.004	0.001	0.052	0.001	

LNM, lymph node metastasis; M, middle thoracic esophageal cancer; M-U, middle-upper thoracic esophageal cancer; M-L, middle-lower thoracic esophageal cancer; A, all thoracic esophageal cancer; Um, upper mediastinum; Mm, middle mediastinum; Lm, lower mediastinum; Ac, abdominal cavity.

patients with L-M TEC respectively (*Table 4*). The LNM rates in neck, upper mediastinum, middle mediastinum, lower mediastinum, and abdominal cavity were 31.6% (90/285), 4.9% (14/285), 18.9% (54/285), 7.0% (20/285), and 21.4% (61/285), respectively in patients with M TEC. The LNM rates were 50.7% (76/150), 14.0% (21/150), 28.0% (42/150), 13.3% (20/150), and 18.7% (28/150) in patients with M-U TEC, 32.8% (65/198), 7.1% (14/198), 34.3% (68/198), 11.6% (23/198), and 34.9% (69/198) in patients with M-L TEC and 28.0% (7/25), 16.0% (4/25), 44.0% (11/25), 20.0% (5/25), and 28.0% (7/25) in patients

with A TEC respectively (*Table 5*).

Table 6 showed the top five sites of LNM rates in TEC with different tumor location.

Discussion

EC is one of the commonest digestive tract cancers associated with high incidence of morbidity and mortality. In recent years, the prognosis has significantly improved with the multimodality treatment, however the 5-year survival rate is still low because of the early metastasis.

Table 6 The top five sites of LNM rates based on the primary tumor location

TEC	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)
U	C-P 40/88 (45.5)	Zone 1 6/88 (6.8)	U-P 5/88 (5.7)	Zones 2+4 4/88 (4.5)	M-P 3/88 (3.4)
U-M	C-P 19/44 (43.2)	U-P 10/44 (22.3)	Zone 1 4/44 (9.1)	Zones 2+4 3/44 (6.8)	M-P 2/44 (4.5)
L	Group 7 15/48 (31.3)	Group 3 9/48 (18.8)	Group 2 8/48 (16.7)	M-P 8/48 (16.7)	Zone 7 6/48 (12.5)
L-M	C-P 6/14 (42.9)	Group 7 4/14 (28.6)	Group 3 3/14 (21.4)	M-P 3/14 (16.7)	Zone 7 3/14 (16.7)
M	C-P 83/285 (29.1)	Group 7 36/285 (12.6)	Zone 7 31/285 (10.9)	Group 1 26/285 (9.1)	M-P 25/285 (8.8)
M-U	C-P 70/150 (46.7)	Zone 7 25/150 (16.7)	Group 7 21/150 (14.0)	Zone 1 21/150 (14.0)	M-P 20/150 (13.3)
M-L	C-P 62/198 (31.3)	Zone 7 44/198 (22.2)	Group 7 42/198 (21.2)	M-P 32/198 (16.2)	Group 2 29/198 (14.6)
A	Zone 7 8/25 (32.0)	M-P 8/25 (32.0)	C-P 6/25 (24.0)	Group 2 6/25 (24.0)	Group 7 5/25 (20.0)

TEC, thoracic esophageal cancer; U, upper thoracic esophageal cancer; U-M, upper-middle thoracic esophageal cancer; L, lower thoracic esophageal cancer; L-M, lower-middle thoracic esophageal cancer; M, middle thoracic esophageal cancer; M-U, middle-upper thoracic esophageal cancer; M-L, middle-lower thoracic esophageal cancer; A, all thoracic esophageal cancer; C-P, cervical paraesophageal; U-P, upper paraesophageal; M-P, middle paraesophageal.

Locoregional recurrence is the main cause for treatment failure after radical esophagectomy, and regional lymph nodes are the most common sites for recurrence (4). Some studies have LNM to be an important prognostic factor for the long-term survival of patients with EC after radical resection (5-7).

Radiotherapy, chemotherapy and surgery are the main components of multidisciplinary treatment of EC. Radiotherapy can improve local control and long-term survival rate significantly. Cheng *et al.* retrospectively analyzed 1,715 patients with TEC who underwent radical surgery. The 5-year overall survival rates of surgery and surgery plus postoperative radiotherapy were 21.3% and 34.2%, respectively. The median survival time was 21.9 and 35.4 months, respectively (8). A study based on the SEER database showed that multimodal therapy (preoperative or postoperative radiotherapy plus surgery) had a better prognosis than surgery only in the 3,292 patients with EC included in the study (9).

The LNM pattern of EC is one of the decisive factors in planning the radiotherapy. It's hard to define the CTV margin for radiotherapy in EC without clear understanding of LNM pattern. Due to the complex lymphatic drainage system of the esophagus, the LNM of EC is characterized by skipped and bidirectional spread (10). It has been systematically elucidated in the previous studies that the depth of tumor invasion, vascular invasion, tumor length, histological type and tumor differentiation affected the LNM pattern of EC, especially the primary tumor

location (3,11-13).

A study of 1,077 patients with EC indicated that the LNM was related to the location of the tumor (13). Another study by Cheng *et al.* involving 1,893 TEC patients from Shandong Cancer Hospital also found that the LNM distribution pattern was primarily dependent upon the location of the primary tumor (14). A meta-analysis of 18,415 patients enrolled in 45 studies by Ding *et al.* showed the LNM rates in upper, middle and lower TEC were 30.7%, 16.8% and 11.0% for cervical lymph nodes, 42.0%, 21.1% and 10.5% for upper mediastinal lymph nodes, 12.9%, 28.1% and 19.6% for middle mediastinal lymph nodes, 2.6%, 7.8% and 23.0% for lower mediastinal lymph nodes, and 9%, 21.4% and 39.9% for abdominal lymph nodes, respectively (15).

Radiation oncologists always design the CTV according to the location of primary tumor and its lymphatic drainage. Theoretically, the LNM of upper TEC tend to occur in upper mediastinum and neck. The LNM of middle TEC are skipped and bidirectional, so the upper, middle mediastinal and the abdominal lymph nodes all have high chances of metastasis. The lower TEC is prone to metastasize to abdominal lymph nodes. Irrespective of the segment of the esophagus involved, the paraesophageal lymph nodes always have high incidence of metastasis (16).

However, many patients in clinical practice have trans-segmental TEC. And there are very limited studies focusing on the difference in characteristics of LNM between trans-segmental and mono-segmental TEC. The present study

was designed to address this issue and provide reference for clinical use while planning radiotherapy.

The U TEC had a higher incidence of LNM in upper mediastinum than U-M TEC (25% *vs.* 5.7%). The most common lymph node regions (LNR) to develop metastases for U and U-M TEC were cervical, upper, middle paraesophageal and zones 1, 2, 4. NCCN guidelines recommend that the superior border of the CTV for U TEC should include zone 1 and cervical paraesophageal LNR and the inferior border to be extended up to the zone 4 LNR. So, for the U-M TEC, the zone 1, 2, 4 and 5, cervical, upper and middle paraesophageal LNR were recommended, the same to the U TEC.

Both the L and L-M TEC had high LNM rates in middle mediastinal and abdominal lymph nodes. Additionally, the L-M TEC was prone to metastasize to cervical LNR. The most common sites of LNM rates in L TEC were group 2, 3 and 7, middle paraesophageal, and zone 7. The cases of L-M TEC were limited in this study (n=14). The rates of LNM were 42.9% (cervical paraesophageal), 28.6% (group 7), and 21.4% (group 3), 16.7% (middle paraesophageal), and 16.7% (zone 7), respectively. It is recommended to include the middle mediastinal and abdominal LNR while delineating the CTV for L and L-M TEC. However, it may be extended up to zone 4 and down to group 7 LNR according to the results of this study. Moreover, unlike in L TEC, the cervical paraesophageal LNR should be covered in the CTV delineation of L-M TEC as per the findings of this study.

The M, M-U, M-L and A TEC were all characterized by high LNM rates in middle mediastinum with the LNM rates of 18.9%, 28.0%, 34.3%, and 44.0%, respectively. In the M-U TEC, the most common LNM site was the cervical nodes. LNM tended to appear in the upper mediastinum and neck in M-U and A TEC respectively. In M-L and A TEC, the common LNM site was the abdominal nodes. We also found that the A TEC had high incidence of LNM in all the LNR. Cervical paraesophageal lymph node region is traditionally not added to CTV for M TEC in clinical practice. However, the present study found the LNM rates in neck to be as high as 24.0–46.7%, even for the tumor extending to the lower third of thoracic esophagus. Hence, according to our study, the irradiation field for M-U TEC should be extended from neck to zone 7, including all the paraesophageal regions, zone 1, 2 and 4. For M-L TEC, the CTV should cover zone 2, 4, 7, left paracardial, lesser curvature, left gastric lymph nodes and all paraesophageal lymph nodes. For A TEC, the CTV may

include zone 2, 4, 7, left paracardial, lesser curvature, left gastric and all paraesophageal lymph nodes.

There are several limitations of this study. First, the sample size in our study was not large enough. Second, only cases of esophageal squamous cell carcinoma was included in this study. Third, we did not analyze the LNM pattern of cervical esophageal carcinoma. Moreover, we did not assess the impact of various other parameters such as depth of invasion, vascular invasion, and chemotherapy on LNM pattern. Future prospective studies are required to validate the findings of this study.

Conclusions

In general, the LNM pattern of trans-segmental and mono-segmental TEC are different. The irradiation field must be determined by experienced radiation oncologists according to the primary tumor location. Precise delineation of CTV may improve the local control rate and overall survival for patients with EC.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm.2020.04.10>). The authors have no conflicts of interest to declare.

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. This retrospective study was approved by Fujian Cancer Hospital Institutional Review Board. And the Ethical approval number is YKT2020-001-01. All information of patients was anonymized prior to analysis.

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