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Pathological analysis of extracapsular extension of metastatic lymph node and its potential impact on nodal clinical target volume in the radiotherapy of esophageal squamous cell carcinoma

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There is no consensus regarding the clinical target volume (CTV) margins which surround the gross tumor volume of metastatic lymph nodes (LN) in radiotherapy of esophageal squamous cell carcinoma (ESCC). This study retrospectively assessed the distance of extracapsular extension (ECE) of metastatic LN in thoracic ESCC and defined nodal CTV margins. Histological sections of metastatic LNs from 217 patients with thoracic ESCC were re-examined. The incidence and maximal distance of ECE of metastatic LNs were assessed. The relationships between ECE and clinicopathologic features were also investigated. The ECE was found in 37.3% of patients (81/217) and 23.1% of metastatic LN (159/689), and the incidences had a significant relationship with N stage and LN size. The median distance of ECE was 1.0 mm (range, 0.2–9.7 mm). The distance of ECE showed a positive correlation with LN size (Spearman's correlation coefficient = 0.419; $p<0.001$). The ECE distances of LN with <10 mm diameter were significantly smaller than LN with 10–30 mm diameter ($p<0.001$). The 95th percentiles of ECE distances for these two groups were 3 mm and 5 mm, respectively. For pathologic LN <10 mm in diameter, a 3-mm CTV margin appears to be adequate to encompass 95% of the microscopic ECE, and for LN 10–30 mm, a 5-mm CTV margin is recommended.

Key words: esophageal squamous cell carcinoma, radiotherapy, clinical target volume, extracapsular extension, lymph node

Esophageal cancer is a highly aggressive malignancy with a poor prognosis. Worldwide, it is the sixth most common cancer and fifth most common cause of cancer deaths in males, and in females it rank as the eleventh most common cancer and eighth most common cause of cancer deaths [1,2]. In China, esophageal cancer was the fifth and sixth most common cancer in males and females, respectively, and the majority of cases are esophageal squamous cell carcinoma (ESCC) with a high proportion of patients diagnosed with locally advanced disease [3,4]. The current preferred treatment for locally advanced ESCC is either neoadjuvant chemoradiotherapy followed by surgery, or concurrent chemoradiotherapy alone [5,6]. Obviously, Radiotherapy plays an important role in the treatment of locally advanced ESCC. However, local failure still occurs in more than 50% of the patients when definitive concurrent chemoradiotherapy is given [7-9].

With the development of radiotherapy, three-dimensional conformal and intensity-modulated radiotherapy have been routinely used in clinical practice. These new technologies could accurately deliver radiation to shaped target areas and increase the radiation dose to the tumor while reducing radiation exposure to the normal organs at risk [10-12]. The superiority of new technologies in radiotherapy may generate promising treatment effects. However, the superiority depends on the accurate delineation of the target volume.

Unfortunately, there are still many controversies regarding target delineation for ESCC. Previous studies about nodal clinical target volume (CTVn) were often concerned about whether CTVn should encompass the areas at risk for nodal metastases and which areas were at risk. However, few studies were concerned about another important issue: what margins of CTVn should be added to the gross tumor volume (GTV)

of nodal disease. Up to now, no consensus has been reached on this question. Different institutions have different CTVn standards which range from 0 mm to 15 mm [8,13-16]. Unfortunately, these standards are empirically developed without pathological evidence to support them and may be excessive or insufficient.

Microscopic extracapsular extension (ECE) in metastatic lymph nodes (LN) is an important factor that should be taken into account in the delineation of CTVn in ESCC. Several studies have reported that ECE of ESCC is associated with recurrence and poor prognosis [17-19]. Because the optimal CTVn can ensure adequate radiation dose to the areas at a high risk for ECE and may improve the local control rate and prognosis, it is necessary to define the appropriate CTVn margins based on pathological evidence. Several investigators have previously measured the extent of ECE of metastatic LNs in patients with non small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC), respectively [20-22]. However, to our knowledge, no previous studies reported the extent of ECE in metastatic LN of ESCC. In the study, we want to determine optimal CTVn margins in radiotherapy through measuring the distance of ECE beyond the capsule of metastatic LN in thoracic ESCC.

Patients and methods

Specimen selection. A retrospective search in the pathology database of our institution was conducted for patients with thoracic ESCC who had at least one metastatic LN. All patients received transthoracic esophagectomy with extensive lymphadenectomy, using either two-field or three-field approach between January 2011 and December 2012. Patients were excluded if they had received preoperative cancer therapy. A total of 248 patients were identified in the initial screening.

The histological sections of metastatic LN from 246 patients except for 2 patients whose specimens were not available were re-examined for ECE status and the ECE-positive LN were measured for the distance of ECE. All pathological analysis for

Table 1. Clinicopathological characteristics of patients and ECE incidence

Features	Patients			*P* values
	ECE negative (*n*)	ECE positive (*n*)	ECE incidence (%)	
Sex				0.882
Male	108	65	37.6	
Female	28	16	36.4	
Primary tumor site				0.149
Upper esophagus	9	4	30.8	
Middle esophagus	89	44	33.1	
Lower esophagus	38	33	46.5	
Primary tumor stage				0.508
T1	8	2	20.0	
T2	21	10	32.3	
T3	88	54	38.0	
T4	19	15	44.1	
Nodal stage				<0.001
N1	100	32	24.2	
N2	29	28	49.1	
N3	7	21	75.0	
Disease stage				<0.001
IIB	27	10	27.0	
IIIA	64	20	23.8	
IIIB	23	21	47.7	
IIIC	22	30	57.7	
Length of Tumor				0.252
≤4cm	68	34	33.3	
>4cm	68	47	40.9	
Tumor differentiation				0.301
Well	28	10	26.3	
Moderate	66	44	40.0	
poor	42	27	39.1	

Abbreviations: ECE, extracapsular extension.

ECE was performed by the single pathologist (D.M.) with 20 years of experience. Lymph node specimens would be excluded from this study if the normal architecture of the LN could not be recognized or LN specimens were not intact. The LN specimens with diameter larger than 3cm were also excluded, because the space of slide was limited to show the full range of ECE. Twenty-nine out of 246 patients were excluded from the study based on the criterion above.

Patient characteristics. The general characteristics of 217 patients (male 173, female 44) with thoracic ESCC identified in the initial analysis are listed in Table 1. The median age was 59 years ranging from 37 to 85 years. Concerning the location of primary tumors, 204 (94%) of the patients were recorded as the middle or lower thoracic ESCC and only 13 (6%) the upper thoracic ESCC. Tumor stage was classified according to the American Joint Committee on Cancer 2010 guidelines [23]. There were 10 (4.6%) patients with T1 stage, 31 (14.3%) with T2 stage, 142 (68.6%) with T3 stage and 34 (15.7%) with T4 stage. The distribution of N stage was: 132 (60.8%) patients with N1 stage, 57 (26.3%) with N2 stage, and 28 (12.9%) with N3 stage.

ECE measurement. According to the similar studies previously reported [20,24], ECE was defined as microscopic cancer cells spreading to extranodal connective tissues including microscopic extension of tumor cells through the capsule of LN into the extranodal tissues, deposits of metastatic cancer cells and tumor emboli cancer cell in fibrofatty tissue surrounding nodes. These could be recognized by tumor cells outside the capsule which were sometimes accompanied by tumor reaction including desmoplastic response and giant cell reaction to extracellular keratin. The specimens of ECE positive LNs were measured for the distance of ECE by a micrometer. The distance of ECE was defined as the distance from the LN capsule to the furthest identified tumor cells. In cases in which the capsule partly disappeared because of tumor invasion, the distance was measured from a capsular equivalent which was extrapolated from the nearest normal portion of the capsule. The pathologic features of each metastatic LN including the largest axial diameter and location were also recorded. Fig. 1 shows the examples of three kinds of microscopic ECE in metastatic LNs.

Statistical analysis. The normality of quantitative variables was assessed on residuals with Shapiro-Wilks test. The impact of clinical parameters of patients and LNs on incidence of ECE was assessed using the chi-square test. Multiple step-wise logistic regression analysis was used to examine the independent relationship between the incidence of ECE and these clinical parameters. The Student *t* test was applied to compare the mean axial diameter of LNs with and without ECE. For the distances of ECE were highly skewed and could not be transformed to normality, the differences between groups of ECE distance were analyzed by the Mann-Whitney U test or the Kruskal-Wallis test followed by the Mann-Whitney U test. A bonferroni correction was applied to correct for multiple comparisons of the distances of ECE. Spearman's rank correlation was performed to evaluate the relationship between the distance of ECE and LN size. A p value of less than 0.05 on two-sided tests was set as the threshold of significance. The statistical analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, USA).

Results

Clinicopathological characteristics of patients and ECE incidence. As shown in Table 1, 37.3% of patients (81/217) exhibited the evidence of ECE. ECE incidence showed significant associations with nodal stage (p<0.001) and disease stage (P<0.001) in all patients. Step-wise logistic regression analysis identified only N stage as the independent influence factor (p<0.001; OR=3.049; 95% confidence interval: 1.994–4.662). The incidences of ECE stratified by N stage were 24.2% (32/132) in N1, 49.1% (28/57) in N2, and 75% (21/28) in N3. However, ECE incidence was not found to be associated with the other clinicopathological factors.

Characteristics of metastatic LN and ECE incidence. A total of 3,792 nodes were removed from 217 patients, with a mean of 17.5 nodes per patient. The ratio of positive lymph

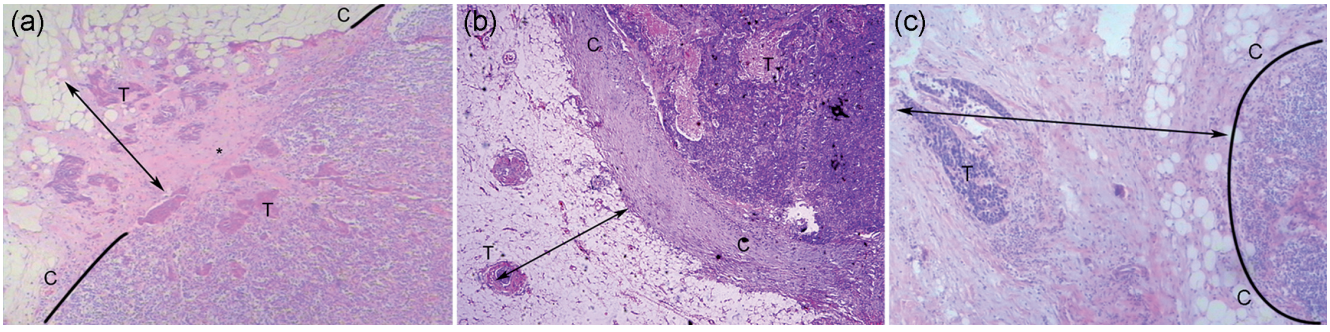

Figure 1. Histological specimens (hematoxylin-eosin staining, ×40) demonstrating three kinds of extracapsular extension of esophageal squamous cell cancer. Microscopic extension of tumor cells through the capsule of lymph nodes into the extranodal tissues (a), tumor emboli cancer cell (b) and deposits of metastatic cancer cells (c) in fibrofatty tissue surrounding nodes. Capsule of lymph nodes was denoted by C, tumor was denoted by T, the site where the tumor ruptured the capsule is denoted by an asterisk and the measured distance was marked by straight line.

node to all lymph nodes resected was 18.2% (689/3792). The characteristics of the metastatic LNs and incidence of ECE are listed in Table 2. ECE was detected in 23.1% (159/689). The mean axial diameter for LN with ECE was 14.0mm, while the mean axial diameter for LN without ECE was 11.9 mm. The diameters of nodes with and without ECE were significantly different (p<0.001). When the metastatic LN were divided into three groups by size (<10 mm, 10–19 mm, 20–30 mm), the ECE incidences were 15.7% (36/230), 25.1% (97/386) and 35.6% (26/73), respectively (p<0.001). In addition, the ECE incidence also correlated significantly with the number of nodes involved (p=0.047) and disease stage (p=0.027). However, step-wise logistic regression analysis identified only lymph node size (p<0.001; OR=1.808; 95% confidence interval: 1.352–2.420) and N stage (p=0.006; OR=1.377; 95% confidence interval: 1.094–1.733) as the independent influence factor.

Table 2. Characteristics of metastatic lymph nodes and ECE incidence

Group	Specimens (*n*)	ECE incidence *n* (%)	*P* value
Sex			0.956
Male	571	132(23.1)	
Female	118	27(22.9)	
Lymph node size			0.001
<10mm	230	36(15.7)	
10-19mm	386	97(25.1)	
20-30mm	73	26(35.6)	
Nodal location			0.558
Cervical	43	14(32.6)	
Upper thoracic	39	8 (20.5)	
Middle thoracic	232	50(21.6)	
Lower thoracic	100	21(21.0)	
Abdominal	275	66(24.0)	
Primary tumor stage			0.493
T1	13	2(15.4)	
T2	83	24 (28.9)	
T3	429	94(21.9)	
T4	164	39(23.8)	
Nodal stage			0.047
N1	183	34(18.6)	
N2	233	49(21.0)	
N3	273	76(27.8)	
Disease stage			0.027
IIB	49	12(24.5)	
IIIA	123	19 (15.4)	
IIIB	175	34(19.4)	
IIIC	342	94(27.5)	
Tumor differentiation			0.930
Well	75	16(21.3)	
Moderate	347	81(23.3)	
poor	267	62(23.2)	

Abbreviation as in Table 1.

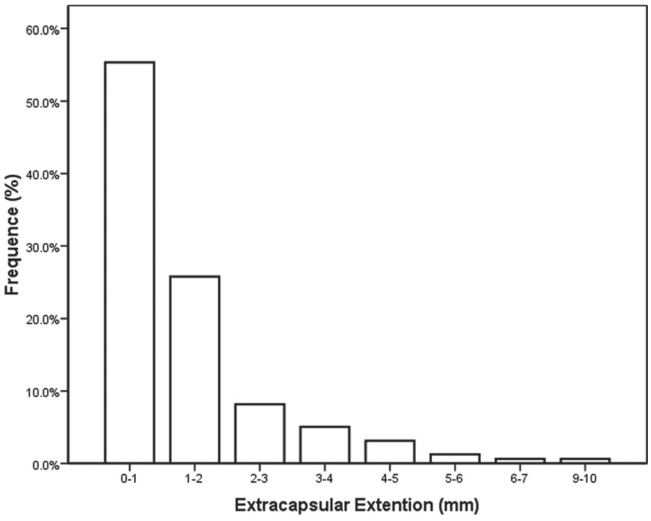

Figure 2. Distributions of the extracapsular extension distance.

Distance of ECE. The mean and median distances of ECE were 1.4mm and 1.0mm, respectively, with the range from 0.2 mm to 9.7mm. Among the LN with ECE, 81.1% (129/159) had ECE ≤ 2mm, 89.3% (142/159) ≤ 3mm, 94.3% (150/159) ≤ 4mm, 97.5% (155/159) ≤ 5mm. Histogram distributions (Fig. 2) showed a positively skewed, leptokurtic distribution of ECE (skewness 2.548, kurtosis 8.992). Among the 38 LNs with ECE ≥2 mm, there were only three LNs <10 mm in diameter. The specimens of these nodes were examined again, but no special pathologic feature was found.

Relationship between distance of ECE and clinicopathological parameters of LN. As shown in the scatter plot of distance of ECE versus LN size for all 159 individual LNs (Fig. 3), there was a positive correlation between distance of

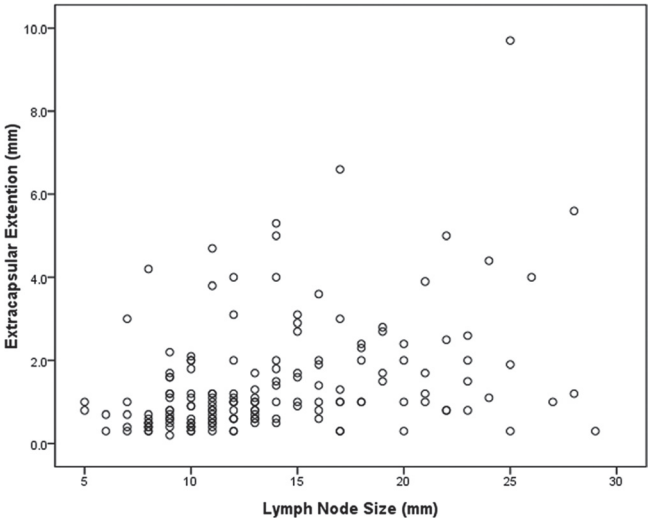

Figure 3. Scatter plot of distribution of extracapsular extension (ECE) distance versus lymph node size for all 159 ECE-positive lymph nodes.

ECE and LN size (Spearman's correlation coefficient=0.419; $p<0.001$). There were significant differences among the three groups of LN (<10 mm, 10–19 mm, 20–30 mm, $p<0.001$). In the subgroup analysis through bonferroni correction, there were differences between the subgroups <10 mm and 10–19 mm, but the differences between 10–19 mm and 20–30 mm vanished (<10 mm vs 10–19 mm, $p=0.002$; 10–19 mm vs 20–30 mm, $p=0.048$; corrected $p=0.017$). Based on the above results, the LNs were divided into two groups (<10 mm, 10–30 mm) and the differences between them were significant ($p<0.001$). The 95th percentile of ECE distances for these two groups was 3 mm and 5 mm, respectively. The other clinicopathological parameters, such as age, gender, nodal location, nodal stage, tumor stage and differentiation, were not associated with the distance of ECE (Table 3).

Discussion

The purpose of the study was to clarify CTVn margins in ESCC through a retrospective pathological analysis of microscopic extracapsular extension of metastatic LNs. The incidence of ECE had a significant relationship with N stage and diameter of LNs. The distance of ECE was correlated to the diameter of LNs. The median distance of ECE was 1.0mm with a range from 0.2mm to 9.7mm. The ECE distances of LNs with <10 mm diameter were smaller than LNs with a diameter of 10–30 mm. The 95th percentile of ECE distances for these two groups was 3 mm and 5 mm, respectively. Our results suggest 3-mm and 5-mm CTVn margins around nodal GTV to encompass 95% of the microscopic ECE of metastatic LN <10 mm and 10–30 mm in size, respectively.

Unlike the similar studies about the CTVn of HNSCC and NSCLC [20-22], we not only assessed the microscopic extension of tumor cells through the capsule of LN into the extranodal tissues, but also assessed the tumor deposits and emboli cancer cells emboli in fibrofatty tissue surrounding nodes. This was because in an earlier study about ESCC, Baba M *et al.* [24] reported the perinodal tissue tumor involvement which we called ECE was composed of these three kinds of subclinical lesions as mentioned above. The similar phenom-

Table 3 Relationship between distance of ECE and clinicopathological parameters

Group	No. of Lymph node (%)	Median ECE extent (mm) (Interquartile range)	*P* value
Total LN (n=159)	159(100)	1.0(0.6-1.9)	
Lymph node size			<0.001
<10mm	36(20.8)	0.6(0.4-1.0)	
10-19mm	97(62.7)	1.0(0.6-1.8)	
20-30mm	26(16.5)	1.7(1.0-3.1)	
Nodal location			0.250
Cervical	14(8.8)	1.0 (0.5-2.1)	
Upper thoracic	8(5.0)	0.8(0.5-1.0)	
Middle thoracic	50(31.4)	1.2(0.6-2.0)	
Lower thoracic	21(13.2)	0.8(0.6-1.2)	
Abdominal	66(41.5)	1.0(0.6-2.0)	
Differentiation			0.543
Well	16(10.1)	1.1(0.4-1.9)	
Moderate	81(51.0)	1.0(0.6-2.0)	
Poor	62(39.0)	1.0(0.5-1.7)	
Sex			0.197
Male	141(88.7)	1.0(0.6-1.7)	
Female	18(11.3)	1.2(0.7-2.9)	
Age			0.636
<60	71(44.7)	1.0(0.6-1.8)	
≥60	88(55.3)	1.0(0.6-2.0)	
Primary tumor stage			0.379
T1,2	26(16.4)	1.0(0.5-1.6)	
T3	94(59.1)	1.0(0.6-2.0)	
T4	39(24.5)	0.8(0.5-1.4)	
Nodal stage			0.277
N1	34(21.4)	1.2(0.8-2.0)	
N2	49(30.8)	1.0(0.5-2.0)	
N3	76(47.8)	1.0(0.6-1.5)	

Abbreviation as in Table 1.

enon was also observed also by some other investigators [25]. Although the mechanism of their formation has not been elucidated, it is obvious that the three kinds of subclinical disease represent the characteristics of metastatic LNs and the CTVn should cover all of them.

Baba M *et al.* [24] found the incidences of ECE were 43.3% in node-positive patients with ESCC and 22.2% in metastatic LN. Sakai M *et al.* [17] and Metzger *et al.* [19] reported the incidences of ECE were 41.2% and 35% in node-positive patients respectively and Sakai M, *et al.* [17] also showed a 24.5% incidence of ECE in metastatic LN. In our study the ECE incidences were 37.3% and 23.1%, respectively. It appears that our results are generally consistent with the previous studies in ESCC. In the present study, we found the incidence of ECE increased with N stage. The studies of ECE in ESCC mentioned above described the similar results [17,19,24,25]. However, the same phenomenon wasn't observed in HNSCC and NSCLC [20-22]. Thus, it may reflect a special biological behavior of ESCC.

It seems reasonable that ECE of metastatic LNs in advanced N stage have the ability to spread farther than those in early one. However, we failed to find a correlation between the distance of ECE and node stage. Yuan *et al.* have reported that poor differentiation of NSCLC may be significantly associated with farther ECE distance [21]. Similar results were not obtained in the studies about ECE in ESCC including ours. This may also reflect that there are different biological characteristics between ESCC and NSCLC.

Several authors have previously shown that the incidence of ECE in metastatic LN of HNSCC and NSCLC is positively correlated with LN size [21,22]. Similar results are obtained in our study about ECE. Further more, our study demonstrated that there was a correlation between the distance of ECE and LN size. ECE of larger LNs extended farther than the smaller ones. These are consistent with the studies by Yuan *et al.* and Ghadjar *et al* [21,22]. However, Apisarnthanarax *et al*. failed to demonstrate a correlation between the extent of ECE and LN size of HNSCC [20]. Thus, besides LN size, other biological mechanisms probably contribute to more aggressive growth.

There are several potential limitations in our study. Firstly, among the LNs assessed, there were only 74 metastatic LN >20 mm and no LN >30 mm in diameter was included in this study. The primary reason was that patients with bigger LNs were diagnosed as advanced stage and lost opportunity for surgery. The other reason was that the specimens of larger LN especially more than 30 mm in diameter were often disrupted and could not be measured. Thus, the incidence and distance of ECE of bigger LNs need to be further studied in a prospective way. Secondly, the pathological slices assessed in this retrospective study were the largest cross-sections of LN, but these could not demonstrate the ECE in every directions. Further more, the extent of tissue shrinkage due to fixation is hardly to be obtained retrospectively. So the incidence and distance of ECE could be somewhat underestimated. The third limitation is the relationships of the pathologic findings and preoperative computed tomography (CT) images have not been investigated. A minority of bigger lesions of ECE may be visible on CT images. For these situations, the CTVn margins based on pathological finding may be somewhat overestimated. But because the study was retrospective, it was hardly to get a one-to-one correspondence between the pathological cross-section of LN and its CT image.

To overcome these limitations, we will carry out a prospective study with the following characteristics: 1. Implementing entirely whole-mount sections of LNs to obtain more accurate pathologic data. 2. Collecting all the CT images of the LNs to get accurately one-to-one correspondence between the pathological cross-section of LN and its CT image. 3. Calculating the tissue shrinkage ratio. 4. Expanding the sample size of larger LNs.

In conclusion, the incidence of ECE had a positively relationship with N stage and diameter of LN and the extent of ECE was positively correlated to the diameter of LN. According to the pathologic results of our ECE investigations, we suggest 3-mm and 5-mm CTVn margins should be added to the nodal GTV for LN <10 mm and 10–30 mm of ESCC treated with radiotherapy, respectively.

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