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Pattern of lymph node metastasis in thoracic esophageal squamous cell carcinoma with poor differentiation

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Abstract. The aim of the present study was to explore the pattern of lymph node metastasis (LNM) in poorly-differentiated esophageal squamous cell carcinoma (pdESCC) and the implication of postoperative irradiation. A total of 690 patients with pdESCC were retrospectively investigated. The rates of intro-thoracic and extra-thoracic LNM in pdESCC were investigated and compared to previous research on ESCC en bloc. The comparison of the rates between pdESCC and ESCC were performed using the Cochran-Mantel-Haenszel test. The clinicopathological factors associated with LNM in pdESCC were analyzed by Chi-squared tests, and Fisher's exact test was used to assess the rate difference of extra-thoracic LNM. Logistic-regression analysis was used to explore risk factors associated with lymph node (LN) station. Results demonstrated that the distribution pattern of LNM in pdESCC was significantly different compared with that of ESCC ($P<0.05$). Univariate and multivariate analysis indicated that risk factors associated with LNM were depth and length ($P<0.001$ and $P<0.001$) and multivariate analysis also indicated that the location of the tumor ($P=0.042$) was a risk factor associated with LNM in pdESCC. Metastasis in the abdominal cavity was significantly higher than in the neck in the middle and lower thoracic pdESCC (both $P<0.01$). LN station 102 and 7 for upper thoracic ESCC, 101 and 105 for middle thoracic ESCC, and 100 for lower thoracic ESCC were identified as high-risk stations for metastases in pdESCC compared to ESCC. Several parameters, including location and neck metastasis, were identified as risk factors of metastasis for the above sites, respectively. In conclusion, postoperative therapy should include more LN stations in pdESCC depending on risk factors of tumor metastasis individually.

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Introduction

Esophageal squamous cell carcinoma (ESCC) is the most common pathological type of esophageal cancer in Asia, and the high rate of lymph node metastasis (LNM) has been demonstrated to be closely associated with local tumor recurrence (1). Besides adjuvant chemotherapy, postoperative irradiation has been a major treatment used to decrease the local recurrence rate in patients with ESCC (2,3). According to the nomination of lymph node (LN) stations by the Japanese Society for Esophageal Disease (JSED) (4), it is accepted that 101, 104, 105 and 106 LN stations should be included in the treatment planning of postoperative irradiation in upper thoracic ESCC, as well as 106, 107, 108, 110, 1, 2, 3 and 7 LN stations for middle thoracic ESCC while 107, 108, 110, 112, 1, 2, 3 and 7 LN stations for lower thoracic ESCC, respectively, which were based on the pattern of LNM in ESCC reported by various researchers (4-6).

As well as the depth of tumor invasion and lesion length, the pathological differentiation of the tumor is also considered as a very important risk factor for LNM. It has been widely recognized that poorly-differentiated (pd)ESCC has a higher tendency of early lymphatic metastasis and skip metastasis in distant LN stations (7). However, the pattern of LNM in pdESCC has been rarely reported, and it is not clear whether there are significant differences between pdESCC and ESCC en bloc on the pattern of LNM. If a difference is confirmed, LN stations included in the treatment planning for postoperative irradiation should be adjusted according to this pattern in the patient with pdESCC. To investigate this problem, the present study was designed to limit the inclusion criterion only to thoracic pdESCC in order to exclude potential confounders.

Patients and methods

Patient population. The medical records of 690 patients consisting of 508 males and 182 females admitted to Linyi People's Hospital (Linyi, China) who underwent radical surgery for esophageal carcinoma between December 2012 and July 2016 were retrospectively collected. The age range of patients was 39-85 years with mean age of 60.597 years. The exclusion criteria were as follows: No conformity with pdESCC histologically; preoperative chemotherapy and/or radiotherapy received; <15 LNs resected; and co-current malignant disease. The present study was approved by the Ethics Review Board of Linyi People's Hospital and written informed consent was collected from each patient.

In order to identify the pattern difference of LNM between pdESCC and ESCC en bloc, the results of previous research conducted by the authors of the present study were cited as a comparison, which were collected from the medical records of 1,893 ESCC cases coming from Shandong Cancer Hospital (Jinan, China) between February 2003 and September 2011 (1474 males and 419 females; mean age, 60.511 years) (4). The metastasis rates in the neck, upper mediastinum, middle mediastinum, lower mediastinum and abdominal cavity were compared. Further investigation on the difference of metastasis rate in every LN station was performed.

Surgical procedures and histopathological assessment. Patients received two-field or three-field lymphadenectomy during esophagectomy. Three-field lymphadenectomy was performed when cervical LN metastases were considered by ultrasound examination or computed tomography scan prior to surgery. Tumor-node-metastasis staging system (7th edition) was used to evaluate tumor T and N stages (6).

The tumor tissue and lymph nodes were resected and labeled corresponding to their sites by the surgeon at the end of the surgical procedure. LNs were labeled under the instruction of LN nomination principles of the Japanese Society for Esophageal Diseases (8). The specimens were sent to the Department of Pathology in Linyi People's Hospital (Linyi, China) and fixed in 10% formalin at room temperature for 24 h, embedded with the thickness of 2 mm tissue in paraffin and stained at room temperature for 0.5 h by haematoxylin-eosin. Two pathologists evaluated the differentiation grade of tumor tissue based on the morphological characteristics of tumor cells and LNM under an optical microscope. The differentiation grades were classified into three grades: Well-, moderately- and poorly-differentiated, depending on the difficulty and extent of identifing adenocarcinoma cell or squamous cancer cell under the optical microscope. Patients with poorly-differentiated squamous cell carcinoma was defined as pdESCC.

Statistical analysis. Results were presented as a number and percentage for categorical variables. The Cochran-Mantel-Haenszel test was used to assess the difference of LNM pattern between pdESCC and ESCC in the neck, upper mediastinum, middle mediastinum, lower mediastinum and abdominal cavity. The clinicopathological factors associated with LNM were analyzed using Chi-squared tests, and Fisher's exact test was used to assess the difference of LNM rates between the neck and abdominal cavity. Risk factors associated with LNM were identified by forward step-wise logistic-regression analysis, and this method was also used to evaluate the risk factors associated with LN stations that were not included in conventional treatment planning of postoperative irradiation. All analyses were performed using Stata IC 10.1 (Stata software v. 11.0; StataCorp LP., College Station, TX, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Clinicopathological characteristics of patients. The risk factors associated with LNM using univariate analysis are demonstrated in Table I. Tumor location (P=0.250), depth of tumor invasion (P<0.001), age of patients (P=0.450) and length of tumor (P=0.001) were evaluated using univariate analysis and further assessed in a multivariate analysis model. For multivariate analysis, tumor location (P=0.042), depth of tumor invasion (P<0.001) and length of tumor (P<0.001) were identified as significant risk factors that were closely associated with LNM (Table II). The above results of pdESCC were similar to our previous report in ESCC (4,5). In the present study, LNM was identified in 211 of 508 males and 70 of 182 females. LNM was confirmed in 17 cases with upper thoracic ESCC (41 cases totally), 160 cases with middle thoracic ESCC (524 cases totally) and 44 cases with the lower thoracic ESCC (125 cases totally). In total, 11,360 LNs were collected after surgery and metastases were identified in 1,366 LNs.

Difference in LNM pattern between pdESCC and ESCC en bloc. For the tumor metastasis happened in the site of neck, upper mediastinum, middle mediastinum, lower mediastinum and abdominal cavity, the rates of LNM in patients with upper thoracic pdESCC were significantly different than that of patients with upper thoracic ESCC (P<0.001). Compared with the LNM rate in upper mediastinum, the extra-thoracic LNM rate was relatively higher in patients with upper thosracic pdESCC than that of patients with upper thoracic ESCC. Similar results could be identified in the patients with middle and lower thoracic pdESCC, who had different rate of LNM than patients with middle and lower thoracic ESCC in the site of neck, upper mediastinum, middle mediastinum, lower mediastinum and abdominal cavity (P<0.001 and P=0.026, respectively; Fig. 1). Significant differences of LNM distribution in LN stations between patients with pdESCC and ESCC were demonstrated in this study, and further investigation revealed that the upper, middle and lower thoracic pdESCC cases had higher remote LNM rates than those of the upper, middle and lower thoracic ESCC cases (P<0.001, P<0.001 and P=0.029, respectively; Fig. 2).

As a comparison of every LN station between pdESCC and ESCC, the LNM rates of station 102 and 7 in the upper thoracic pdESCC were higher than those of in upper thoracic pdESCC. Similarly, the LNM rates of station 101 and 105 in pdESCC were higher than those of ESCC in the middle thoracic

Table I. Univariate analysis of clinicopathological factors associated with LNM in poorly-differentiated esophageal squamous cell carcinoma.

Characteristics	n	Cases with LNM (n)	X^2	P-value
Sex			0.22	0.630
Male	508	211		
Female	182	70		
Tumor location			2.73	0.250
Upper thoracic esophagus	41	17		
Middle thoracic esophagus	524	190		
Lower thoracic esophagus	125	74		
Depth of tumor invasion			24.7	<0.001
T1	94	13		
T2	185	62		
T3	366	175		
T4	45	31		
Age, years			1.57	0.450
≤40	4	1		
41-59	295	132		
≥60	391	148		
Length of tumor, cm			17.8	0.001
≤2.0	55	8		
2.1-4.0	276	99		
4.1-6.0	271	118		
6.1-8.0	59	37		
>8.0	29	19		

LNM, lymph node metastases.

Table II. Multivariate analysis of risk factors associated with lymph node metastasis in poorly-differentiated esophageal squamous cell carcinoma.

Parameters	Odds ratio	Standard error	Z	P-value	95% confidence interval
Location of tumor	1.430663	0.251992	2.03	0.042	1.013001-2.020529
Length of tumor	1.5345	0.152081	4.32	<0.001	1.26359-1.863493
Depth of tumor	1.925458	0.224064	5.63	<0.001	1.532782-2.418732

pdESCC, while the LNM rate of 100 station in pdESCC was higher than that of ESCC in lower thoracic pdESCC. All of these LN stations were not delineated in conventional treatment planning of postoperative irradiation, which was based on the pattern of LNM in ESCC.

Differences in extra-thoracic metastases between upper, middle and lower thoracic pdESCC. In the neck, significant differences in LNM were not identified among the upper, middle and lower thoracic pdESCC (P>0.05). However, in the abdominal cavity, significant differences of LNM were confirmed among the upper, middle and lower thoracic pdESCC (P<0.05). Further analysis indicated that significant differences of bi-directional lymphatic metastasis (up to neck and down to abdominal cavity, simultaneously) were demonstrated in the middle (P<0.01) and lower thoracic pdESCC (P<0.01), and not indicated in upper thoracic pdESCC (P=0.27; Table III). Furthermore, higher number of metastases was identified in the abdominal cavity compared with the neck for middle and lower thoracic pdESCC (98 cases vs. 59 cases; 39 cases vs. 8 cases, respectively; Table III).

Risk factors associated with metastases of 102, 7, 101, 105 and 100 LN stations. Tumor location and upper mediastinum metastasis were demonstrated to be the LNM risk factors of station 102 (P=0.01 and P=0.001, respectively, Table IV), while neck and middle mediastinum metastasis were identified as the LNM risk factors of station 7 (P=0.03 and P=0.04, respectively, Table IV). Despite this, station 102 and 7 were not included in treatment planning of postopera-

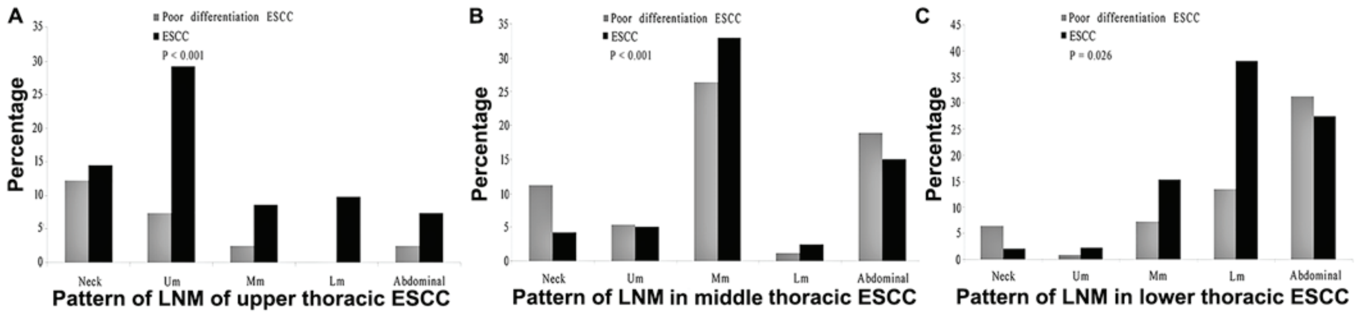

Figure 1. Comparison of LNM distribution between ESCC and pdESCC in the neck, Um, Mm, Lm and abdominal cavity. The difference of LNM distribution in the site of neck, Um, Mm, Lm and abdominal cavity between patients with thoracic ESCC and pdESCC were significant. (A) upper thoracic ESCC vs. upper thoracic pdESCC, P<0.001. (B) Middle thoracic ESCC vs. middle thoracic pdESCC, P<0.001. (C) Lower thoracic ESCC vs. lower thoracic pdESCC, P=0.026). LNM, lymph node metastasis; ESCC, esophageal squamous cell carcinoma; pd, poorly-differentiated; Um, upper mediastinum; Mm, middle mediastinum; Lm, lower mediastinum; EC, Esophageal cancer.

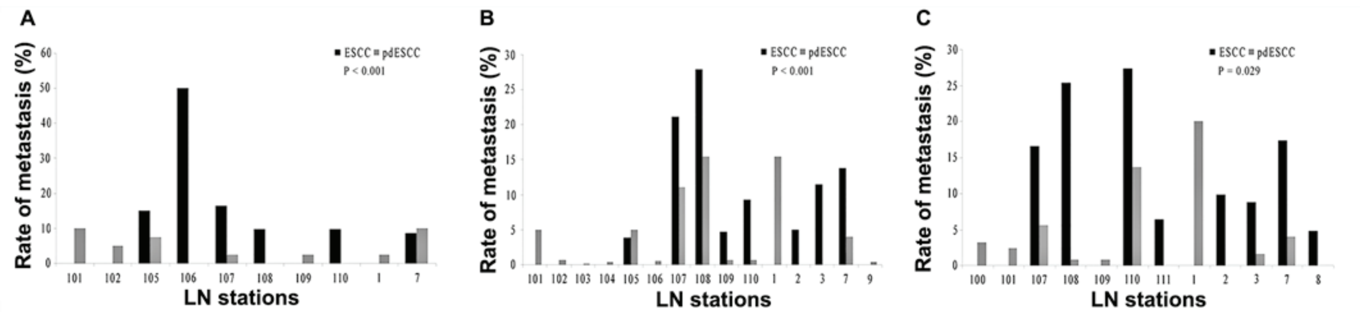

Figure 2. Comparison of LNM distribution in LN stations between ESCC and pdESCC. The difference of LNM distribution inthe site of every LN station between patients with thoracic ESCC and pdESCC were significant. (A) Upper thoracic ESCC vs. upper thoracic pdESCC, P<0.001. (B) Middle thoracic ESCC vs. middle thoracic pdESCC, P<0.001. (C) Lower thoracic ESCC vs. lower thoracic pdESCC, P=0.029). LNM, lymph node metastasis; LN, lymph node; ESCC, esophageal squamous cell carcinoma; pd, poorly-differentiated.

tive irradiation in upper thoracic pdESCC Station 101 and 105 were not included in the treatment planning in middle thoracic pdESCC Accordingly, tumor location, middle mediastinum metastasis, T stage of tumor and abdominal metastasis (P=0.04) were the risk factors for metastasis of station 101, while tumor location (P=0.04), upper and lower mediastinum metastasis (P=0.01) were the risk factors for metastasis of station 105 in middle thoracic pdESCC (Table IV). The T stage of tumor was excluded from Table IV because of the low impact of it on tumor metastasis. In lower thoracic pdESCC, station 100 was excluded from the treatment planning of postoperative irradiation conventionally in ESCC.

Discussion

ESCC has been demonstrated to be characterized with high LNM rate, which was closely related to poor progression-free survival and overall survival (9). Postoperative irradiation on LN stations with high metastasis risk may be very important to decrease the local recurrence rate in postoperative treatment (10). However, bi-directional metastasis (downward and upward metastasis at the same time) and skip metastasis have been observed to occur in the early stage of ESCC (11,12). From our previous study, using a large sample size, it was observed that pathological differentiation was an important predictor for LNM, which was consistent with other research (13).

To the best of our knowledge, the distribution pattern of LNM in pdESCC has not previously been reported and the difference of LNM pattern between pdESCC and ESCC was unclear. Based on the present study, there was a significant difference in the LNM pattern between pdESCC and ESCC, which existed not only in the neck, upper mediastinum, middle mediastinum, lower mediastinum and abdominal cavity, but also in every LN station.

The present study further demonstrated that there were differences in the extra-thoracic metastasis ability among the upper, middle and lower thoracic pdESCC. The abdominal cavity was the major LNM area in middle and lower thoracic pdESCC, while not in upper thoracic pdESCC. For the upper thoracic pdESCC, the frequency of LNM in the abdominal cavity was not significantly lower than in the neck. For the middle and lower thoracic pdESCC, the frequency of LNM in the abdominal cavity was significantly higher than that in the neck. This finding may indicate that the anatomy structure in the upper mediastinum is different to that of the middle and lower mediastinum; the upper mediastinum is rich in lymphatic vessels, nerves and blood vessels making it possible for metastasis to spread along them (14). It would be beneficial to understand the mechanism of LNM in pdESCC.

Similar to the results of previously published papers, tumor location, depth of tumor invasion and length of tumor were demonstrated to be the risk factors associated with LNM in univariate and multivariate analysis in the present

Table III. Pattern of LNM in the neck and abdominal cavity from poorly-differentiated esophageal squamous cell carcinoma.

	Neck			Abdominal		
Area	Total cases	Cases of LNM (n)	P-value	Total cases	Cases of LNM	P-value
Ut EC	41	5	>0.05	41	2[a]	<0.05
Mt EC	524	59		524	98[b]	
Lt EC	125	8		125	39[c]	

Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; EC, Esophageal cancer; LNM, lymph node metastases. [a]P=0.27 vs. Ut EC cases with LNM in the neck; [b]P<0.01 vs. Mt EC cases with LNM in the neck; [c]P<0.01 vs. Lt EC cases with LNM in the neck.

Table IV. Risk factors of metastasis for lymph node stations in pdESCC.

Risk factors	Odds ratio	Standard error	Z	P-value	95% confidence interval
102 station in UtpdESCC					
Tumor location	0.10	0.10	-2.46	0.01	0.02-0.63
Um metastasis	15.20	13.46	3.07	0.001	2.68-86.23
7 station in UtpdESCC					
Neck metastasis	3.03	1.52	2.21	0.03	1.13-8.11
Mm metastasis	2.47	1.06	2.11	0.04	1.07-5.73
101 station in Mt pdESCC					
Abdominal metastasis	3.31	1.93	2.05	0.04	1.05-10.38
105 station in Mt pdESCC					
Tumor location	0.16	0.14	-2.11	0.04	0.03-0.88
Lm metastasis	35.17	46.64	2.69	0.01	2.62-472.97

pdESCC, poorly-differentiate desophageal squamous cell carcinoma; Um, upper mediastinum; Mm, middle mediastinum; Lm, lower mediastinum; Ut, upper thoracic; Mt, middle thoracic.

study (15-17). Age was not identified to be a significant risk factor for LNM, which was concluded in our previously study of ESCC. The possible reason for this may be that the influence of age on LNM was weaker than that of differentiation in the multivariate analysis model in pdESCC. This result implied that tumor differentiation was a more powerful prognostic factor compared to age in pdESCC.

In ESCC, LN stations with metastasis rates higher than 15% have been identified as high-risk areas that should be included inside the clinical target volume (CTV) in the treatment planning of postoperative irradiation (18-20). However, in pdESCC, the threshold of LNM rate that should be considered as the high-risk area may change, because the trend oflymphatic skip metastasis in pdESCC was stronger than in ESCC (21). It has been demonstrated that the average rate of LNM in all LN stations may be a reasonable threshold for metastasis risk in ESCC (22). Based on the result of the present study, the rates of LNM of stations 102 and 7 were higher than the average LNM rate in all LN stations in upper thoracic pdESCC (4.9 and 9.8 vs. 3.9%); the rates of LNM in station 101 and 105 were higher than that in middle thoracic pdESCC (5.0 and 5.0 vs. 3.9%); and the rate of LNM in station 100 was close to that in lower thoracic pdESCC (3.2 vs. 4.3%). Coincidentally, station 102 and 7 were not included in the conventional treatment planning of postoperative irradiation in upper thoracic ESCC. Similarly, it was widely accepted that station 101 and 105 could not be included in the conventional treatment planning of postoperative irradiation in middle thoracic ESCC and station 100 could not be included in lower thoracic ESCC. This result suggested that the average LNM rate in all LN stations may be a reasonable cutoff value to determine high-risk LN stations for metastasis in pdESCC.

However, more LN stations receiving irradiation would mean that a larger CTV would be delivered to patients in the treatment planning of radiotherapy, and a larger CTV may lead to heavier toxicity of normal tissue. To solve this problem, it may be effective to only consider the above LN stations when the risk factors of tumor metastasis have been identified. Due to the different LNM pattern between pdESCC and ESCC, treatment planning of postoperative irradiation should be designed individually depending on risk factors for the particular LN station in pdESCC.

Based on the results of the present study, it can be recommended that in the upper thoracic pdESCC, station 102 should receive irradiation when upper mediastinum metastasis has been confirmed, while station 7 is recommended to be delineated inside CTV when neck and middle mediastinum metastases are identified. In middle thoracic pdESCC, station 101 should be drawn inside the CTV when middle mediastinum metastasis, T3-4 stage tumor and abdominal metastasis are identified, while station 105 should be included inside CTV iflower mediastinum metastasis is confirmed. The above results suggested that the adjacent LN stations with metastases were usually risk factors for metastasis in the next LN station, which was similar to a report by Juloori *et al* (23). A much more interesting result found in the present study was that neck metastasis was a significant risk factor for LNM of station 7 in the upper thoracic pdESCC and metastasis in the abdominal cavity was a risk factor for LNM of station 101 in middle thoracic pdESCC, which were consistent with the characteristic of ESCC that bi-directional and skip metastases appeared frequently, particularly in pdESCC (24).

Based on the results of the present study, it is strongly recommended that the distant LN stations should be included in irradiation in postoperative radiotherapy individually when risk factors have been confirmed. This outcome may also be used as an implication to explore the distant LNM in lymphadenectomy for patients with pdESCC.

The present study had some limitations. Firstly, although the comparison of LNM pattern between pdESCC and ESCC was performed, more results may be identified if the comparison between pdESCC and moderate- or well-differentiated ESCC was conducted. Secondly, the impact on prognosis of LNM pattern between pdESCC and ESCC was not investigated, which may provide more important recommendation for treatment planning design of postoperative radiotherapy in pdESCC.

In summary, higher metastases were identified in regional LN in pdESCC, and the LNM pattern was different compared with that of ESCC. Distant LN stations should be individually considered in postoperative radiotherapy when risk factors have been identified in patients with pdESCC.

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Availability of data and materials

The datasets used and/or analysed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JZ, XH and BL designed the study. YL and FC collected the information of patients and analyzed the data. JZ and YL wrote the paper. XH and BL reviewed and edited the manuscript. All authors read and approved the manuscript.

Ethics approval and consent to participate

All procedures used in this study involving human participants were in accordance with the ethical standards of the institutional research committee, and with the 1964 Helsinki declaration and its later amendment or comparable ethical standards.The present study was approved by the Ethics Review Board of Linyi People's Hospital and written informed consent was collected from each patient.

Consent for publication

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

Competing interests

The authors declare that they have no competing interests.

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