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Original Article

Clinical characteristics and prognostic factors of patients with lymph node metastasis of thoracic esophageal squamous cell carcinoma

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Abstract: Objective: To investigate clinical characteristics and prognostic factors of patients with lymph nodes metastasis (LNM) of thoracic esophageal squamous cell carcinoma (ESCC) so as to provide reference basis for the clinical prevention and treatment of LNM of thoracic ESCC. Methods: Through a retrospective analysis on the clinical and follow-up data collected from 96 patients with LNM of thoracic ESCC admitted in our hospital from 1 February 2008 to 1 March 2012, this study described clinical characteristics of these patients. Meanwhile, Cox proportional hazard regressive model was used to investigate factors influencing the prognosis of patients with LNM of thoracic ESCC. Results: 121 patients with LNM of thoracic ESCC accounted for 39.0% of ESCC patients (121/310) in the same period. During operation, a total of 2531 lymph nodes were dissected. 312 were found to be positive nodes in postoperative pathological diagnosis. The rate of lymphatic metastasis was 12.3%. For 57.9% (70/121) patients, the carcinoma metastasized to ≥ 3 nodes. For 28.9% (35/121) patients, LNM involved ≥ 2 areas. Among these cases, there were 33 patients with neck lymphatic metastasis (19.1%), 90 patients with thoracic lymphatic metastasis (52.0%) and 50 patients with abdominal lymphatic metastasis (28.9%). The median survival time of patients with LNM of thoracic ESCC postoperation was 35 months with a 1-, 3- and 5-year survival rate of 80.2%, 48.8% and 21.5%, respectively. Univariate analysis showed that there was statistically significant difference ($P < 0.05$) in terms of postoperative survival condition for patients with LNM of thoracic ESCC of different sex, length, degree of differentiation and invasion depth of tumor, blood vessel invasion, with different number of nodes and areas involved, as well as rate of lymphatic metastasis (%). Multivariate Cox regression analysis indicated that poorly differentiated esophageal carcinoma (*HR* = 2.14, 95% *CI*: 1.08-4.26), depth of invasion in T3/T4 (*HR* = 1.87, 95% *CI*: 1.02-3.45), rate of lymphatic metastasis > 20% (*HR* = 3.07, 95% *CI*: 1.72-5.47) and areas involved ≥ 2 (*HR* = 2.60, 95% *CI*: 1.44-4.70) were factors influencing the prognosis of patients with LNM of thoracic ESCC. Conclusion: The prognosis of patients with LNM of thoracic ESCC is poor. In particular, the prognosis of patients with LNM of thoracic ESCC combined with poorly differentiated esophageal carcinoma, depth of invasion in T3/T4, high rate of lymphatic metastasis and multiple areas involved is poor. Comprehensive treatment measures should be taken to prolong patients' survival time and improve their quality of life.

Keywords: Esophagus carcinoma, squamous cell carcinoma, lymphatic metastasis, clinical characteristics, prognostic analysis

Introduction

Esophageal carcinoma is currently one of the most common malignant tumors in the world. Annually, about 500,000 people are diagnosed with esophageal carcinoma and 300,000 die of this disease [1]. In China, its incidence and mortality rank the third among malignant tumors. Moreover, along with changes of environment and diet as well as the aggravation of the aging population, the incidence of esophageal carcinoma is increasing gradually [2, 3]. Esophageal carcinoma is subject to metastasis. It can be metastasized/diffused by such approaches as diffusion in esophageal wall, direct diffusion, lymphatic metastasis and metastasis by blood supply, among which lymphatic metastasis is the most important one [4]. Once lymphatic metastasis occurs, the prognosis of patients with esophageal carcino-

ma will be worsened and their 3-year survival rate will be less than 20% [5]. Therefore, it is of important clinical significance to know about clinical characteristics and prognostic factors of patients with LNM of ESCC. Based on the site of growth, esophageal carcinoma can be classified into three types-neck, thoracic and abdominal. The overwhelming majority of it is thoracic. In addition, squamous carcinoma can be found most frequently (70%-90%) based on histological classification (squamous carcinoma and adenocarcinoma) [6]. Through a retrospective analysis on the clinical and follow-up data collected from patients with LNM of thoracic ESCC admitted in our hospital from 1 February 2008 to 1 March 2012, this study is intended to investigate clinical characteristics and prognostic factors of these patients so as to provide reference basis for improving their prognosis.

Patients and methods

Object of study

Objects of this study were patients with thoracic ESCC admitted in the oncology department of our hospital from 1 February 2008 to 1 March 2012 who had lymphatic metastasis. Inclusion criteria were as follows: a. Esophageal carcinoma confirmed by postoperative pathological diagnosis; b. Squamous carcinoma by histological classification; c. Thoracic esophageal carcinoma; d. At least one lymphatic metastasis demonstrated pathologically; e. Underwent esophagectomy and lymph node dissection; f. Complete clinical and follow-up data in our hospital. Exclusion criteria were as follows: a. Combined with tumors at other sites; b. Preoperative adjuvant radio-chemotherapy; c. Distant metastasis found in preoperative examination.

Therapeutic method

After freeing by right anterolateral thoracotomy, total thoracic esophagectomy was performed. Median incision on upper abdomen was conducted for freeing stomach and clear away lymph nodes around the stomach. The stomach was then brought up to neck through esophagus bed and anastomosis was performed between esophageal stump and the neck of gastric fundus via the incision of the left or right neck. Lymph nodes located at the junction of the left neck and the top of recurrent laryngeal nerve, the superior, middle and inferior mediastinum of the chest as well as in the abdomen were cleared away. All cases received lymphadenectomy were marked by group and submitted for inspection together with excised esophagus. Postoperative adjuvant therapy included postoperative adjuvant chemotherapy, radiotherapy and radiochemotherapy.

Study methods

The clinical and follow-up data of patients with lymph node metastasis of thoracic esophageal squamous cell carcinoma were collected by retrieving hospitalization records, various auxiliary test reports and medical data including follow-up records, and the relevant information was extracted with uniform questionnaire, including sex, age, site of esophageal carcinoma, general type, lesion length, pathological type, degree of differentiation and infiltration, vascular invasion, number of lymph node metastasis, degree of lymph node metastasis (pathologically confirmed number of lymph node metastasis/number of dissected lymph nodes) and area of lymph node metastasis (divided into the neck, chest and abdomen), treatment characteristics, time of last follow-up and survival time etc.

Follow-up approach

The follow-up data were collected by outpatient review and telephone follow-up for the patients, who were followed up to March 1, 2016. The survival time was the time period when the patients were living after surgery, calculated in months.

Statistical analysis

Statistical analysis on data was performed with the IBM SPSS 21.0 software, mean ± standard deviation (Mean ± SD) was used for statistical description of the normal measurement data, and relative numbers like rate and constituent ratio were used for statistical description of counting data. The Kaplan-Meier method was adopted to estimate the post-surgery survival rate of patients with lymph node metastasis of thoracic esophageal squamous cell carcinoma showing different characteristics, the log-rank test was used for one-way ANOVA, and the Cox

Table 1. Clinical characteristics of patients with LNM of thoracic ESCC

Characteristics	Number of cases	Percentage (%)
Age (year) ($\bar{X}$±S) (*R*)	62.1±15.5 (28~80)	
Sex (M/F)	63/38	68.6/31.4
Site of esophageal carcinoma		
Upper thoracic portion	23	19.0
Middle thoracic portion	65	53.7
Lower thoracic portion	33	27.3
General type		
Medullary	20	16.5
Fungoid	12	9.9
Ulcerative	65	53.8
Constrictive	24	19.8
Tumor length (cm)		
< 3.0	19	15.7
3.0~5.0	43	35.5
> 5.0	59	48.8
Degree of differentiation		
High	6	5.0
Medium	83	68.6
Poor	32	26.4
Degree of infiltration		
T1	10	8.3
T2	28	23.1
T3	49	40.5
T4	34	28.1
Vascular invasion		
Yes	43	35.5
No	78	64.5
Invasion of the upper esophageal stump		
Yes	36	29.8
No	85	70.2
Number of lymph node metastasis		
1~2	51	42.1
≥ 3	70	57.9
Degree of lymph node metastasis (%)		
≤ 20.0	75	62.0
> 20.0	46	38.0
Number of areas with lymph node metastasis		
1	86	71.1
≥ 2	35	28.9
Number of dissected lymph nodes		
≤ 20.0	60	49.6
> 20.0	61	50.4

proportional hazards regression model was used to discuss the factors influencing survival of the patients. The test level was α = 0.05 and *P* < 0.05 indicated statistically significant differences.

Results

Clinical features

A total of 121 patients with LNM of thoracic ESCC were included in this study. It accounted for 39.0% (121/310) of patients with thoracic ESCC who received radical operation on esophageal carcinoma in the same period. There were 83 male and 38 female aging from 28 to 80 years, averaging 62.1±15.5 years, with a median age of 60 years. The site of esophageal carcinoma mainly located at thoracic with 65 cases (accounting for 53.7%); The gross type was primarily ulcerative type with 65 cases (accounting for 53.8%); In 59 cases, tumor length > 5.0 cm (accounting for 48.8%); The degree of differentiation was mainly medium, with 83 cases (accounting for 68.6%); The depth of invasion was predominantly in T3 with 49 cases (40.5%); 43 cases had blood vessel invasion (35.5%); And in 36 cases, the upper stump of esophagus was invaded (29.8%).

A total of 2531 lymph nodes were dissected in 121 patients. The number of dissected nodes ranged from 8 to 49, averaging 20.9 per case. 312 were found to be positive nodes in postoperative pathological diagnosis. The rate of lymphatic metastasis was 12.3%. 10 cases had carcinoma metastasized to 1

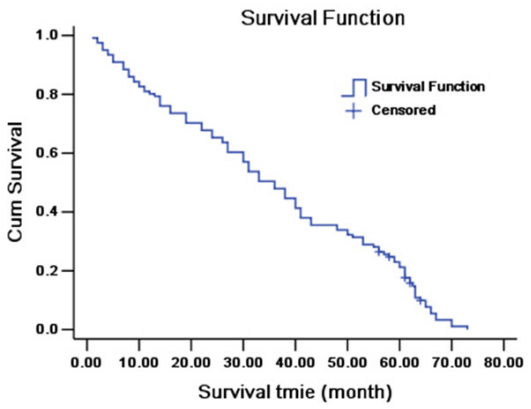

Figure 1. The survival curve of 121 patients with LNM of thoracic ESCC.

nodes (8.3%), 41 cases had carcinoma metastasized to 2 nodes (33.9%), and 70 cases had carcinoma metastasized to ≥ 3 nodes (57.9%). For 86 cases, LNM involved 1 area (71.1%); For 35 cases, LNM involved ≥ 2 areas (28.9%). Among these cases, there were 33 patients with neck lymphatic metastasis (19.1%), 90 patients with thoracic lymphatic metastasis (52.0%) and 50 patients with abdominal lymphatic metastasis (28.9%) (**Table 1**).

Overall survival of patients with LNM of thoracic ESCC

The survival time of 121 patients with LNM of thoracic ESCC ranged from 1 to 73 months with a median survival time of 35 months. The 1-, 3- and 5-year survival rate was 80.2% (97/121), 48.8% (59/121) and 21.5% (26/121), respectively (**Figure 1**).

Univariate prognostic analysis of patients with LNM of thoracic ESCC

Univariate analysis (log-rank test) showed that there was statistically significant difference ($P < 0.05$) in terms of postoperative survival condition for patients with LNM of thoracic ESCC of different sex, length, degree of differentiation and invasion depth of tumor, blood vessel invasion, with different number of nodes and areas involved, as well as rate of lymphatic metastasis (%). By contrast, there was no statistically significant difference ($P > 0.05$) in terms of postoperative survival condition for these patients of different age group, diseased location and gross type of thoracic ESCC, as well as different invaded upper stump of esophagus and number of dissected lymph node (**Table 2**).

Multivariate prognostic analysis of patients with LNM of thoracic ESCC

Multivariate Cox stepwise regressive analysis indicated that four factors, including poorly differentiated esophageal carcinoma, depth of invasion in T3/T4, rate of lymphatic metastasis > 20% and areas involved ≥ 2, were independent prognostic risk factors for patients with LNM of thoracic ESCC ($\chi^2 = 5.670$-19.937, $P < 0.05$) (**Table 3**).

Discussion

Esophageal carcinoma is a malignant tumor frequently found on the mucous membrane of esophagus in the digestive tract. The most common type is squamous carcinoma (accounting for more than 90% of various types of esophageal carcinoma). Esophageal squamous carcinoma (ESCC) is of high malignant degree and poor prognosis in patients. It can be further classified into three types-neck, thoracic and abdominal, among which the overwhelming majority is thoracic [7, 8]. Major factors affecting the survival rate of patients with esophageal carcinoma are its metastasis and local recurrence. In these two factors, lymphatic metastasis is most common route of metastasis for esophageal carcinoma. In this study, a total of 121 patients with LNM of thoracic ESCC were included. It accounted for 39.0% (121/310) of patients with thoracic ESCC who received radical excision of esophageal carcinoma in the same period. This is consistent with previous relevant studies [10, 11], suggesting that patients with LNM of thoracic ESCC were subject to lymphatic metastasis. Possible reasons are as follows [12, 13]: a. Lacking serosa in esophagus, which facilitates local diffusion of tumor; b. Esophagus communicating with collateral lymph vessels of the neck, chest and abdomen as well as extensive mediastinal lymph nodes connecting with blood vessels. This anatomical structure makes thoracic ESCC liable to metastasis to thoracic, mediastinal, supraclavicular and celiac lymph nodes. Therefore, LNM of thoracic ESCC is very complicate, involving both deep sites and an extensive range of more than 20 lymph nodes in the neck, chest and abdomen. The route of metastasis is generally consistent with normal lymph node drainage. Over a quarter of patients (28.9%) in this study had carcinoma metasta-

Table 2. Univariate survival analysis of patients with LNM of thoracic ESCC

Factors	Number of cases	Median survival (months)	χ^2 value	*P* value
Age (year)				
< 65	70	36.0	0.315	0.574
≥ 65	51	33.5		
Sex				
M	83	33.0	8.451	0.015*
F	38	39.0		
Site of esophageal carcinoma				
Upper thoracic portion	23	33.0	1.311	0.252
Middle thoracic portion	65	34.5		
Lower thoracic portion	33	37.0		
General type				
Medullary	20	37.0	1.970	0.579
Fungoid	12	35.5		
Ulcerative	65	33.0		
Constrictive	24	36.0		
Tumor length (cm)				
< 3.0	19	21.0	12.324	0.001*
3.0~5.0	43	16.0		
> 5.0	59	5.0		
Degree of differentiation				
High/medium	89	40.0	19.574	< 0.001*
Poor	32	25.0		
Depth of infiltration				
T1+T2	38	42.0	15.325	< 0.001*
T3+T4	83	30.0		
Vascular invasion				
Yes	43	30.5	6.273	0.022*
No	78	38.0		
Invasion of the upper esophageal stump				
Yes	36	32.0	1.102	0.294
No	85	36.5		
Number of lymph node metastasis				
1~2	51	41.0	18.456	< 0.001*
≥ 3	70	26.0		
Degree of lymph node metastasis (%)				
≤ 20.0	75	42.0	23.548	< 0.001*
> 20.0	46	20.0		
Number of areas with lymph node metastasis				
1	86	41.0	18.132	< 0.001*
≥ 2	35	26.0		
Number of dissected lymph nodes				
≤ 20.0	60	33.5	1.230	0.267
> 20.0	61	37.0		

Note: *the survive in the first value compare with that in the second value of each variable, $P < 0.05$. (For example: the survive in patients with different number of areas with lymph node metastasis, *mean that the survive of patients with 1 area with lymph node metastasis (the first value of the variable) compared with that in patients with ≥ 2 area with lymph node metastasis (the second value of the variable)).

Table 3. Results of multivariate Cox stepwise regressive analysis on patients with LNM of thoracic ESCC (n = 121)

Independent variable	Regression coefficient	Standard error	Wald χ^2	*P* value	*HR* (95% *CI*)
Poorly differentiated esophageal carcinoma (reference group = high/medium differentiation)	0.763	0.350	6.479	0.011*	2.14 (1.08~4.26)
T3/T4 depth of infiltration (reference group = T1/T2)	0.629	0.310	5.670	0.017*	1.87 (1.02~3.44)
Degree of lymph node metastasis > 20% (reference group ≤ 20.0%)	1.121	0.295	19.937	< 0.001*	3.07 (1.72~5.47)
Number of areas with lymph node metastasis ≥ 2 (reference group = 1)	0.956	0.302	15.325	< 0.001*	2.60 (1.44~4.70)

Note: *compare with each reference group of variable, $P < 0.05$.

sized to 2 among 3 sites, i.e., the chest, neck and abdomen.

At present, the treatment for thoracic ESCC is still comprehensive therapy, mainly surgery, while one of the major causes of therapeutic failure is lymphatic metastasis. The median survival time of patients with LNM of thoracic ESCC was 35 months with a 1-, 3- and 5-year survival rate of 80.2%, 48.8% and 21.5%, respectively. This result was consistent with relevant studies both at home and broad [14, 15], suggesting that the prognosis of patients with LNM of thoracic ESCC was poor. Meanwhile, it was found in this study that poorly differentiated esophageal carcinoma (*HR* = 2.14, 95% *CI*: 1.08-4.26), depth of invasion in T3/T4 (*HR* = 1.87, 95% *CI*: 1.02-3.45), rate of lymphatic metastasis > 20% (*HR* = 3.07, 95% *CI*: 1.72-5.47) and involved areas ≥ 2 (*HR* = 2.60, 95% *CI*: 1.44-4.70) were prognostic risk factors of patients with LNM of thoracic ESCC. This was similar to results reported by Merkow et al. [16] and Chen Yuanmei et al. [17] Possible reasons are as follows [18]: a. The deeper the invasion of esophageal carcinoma is, the poorer of differentiation and the stronger invasion of esophageal squamous cells will be; b. The feature of longitudinal skip lymph node metastasis of ESCC determines the range of metastasis. The wider the range is, the more difficult the treatment and the poorer the prognosis will be. This suggests that for patients with abovementioned features, more attention should be paid to using proper comprehensive treatment so as to prolong life.

To sum up, lymphatic metastasis of patients with thoracic ESCC is extremely complex with deep sites and extensive ranges involved. The prognosis of those patients combined with LNM is poor and that of those with poorly differentiated ESCC, depth of invasion in T3/T4, high rate of lymphatic metastasis or multiple involved areas are poorer. Therefore, for high-risk patients with these features, a comprehensive treatment regimen should be adopted to prolong patients' survival time and improve their quality of life.

Disclosure of conflict of interest

None.

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