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Original article

Prognostic significance of lymph node metastasis in esophageal squamous cell carcinoma

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ABSTRACT

Prediction of lymph node metastasis in esophageal squamous cell carcinoma (ESCC) is very important to have prognostic significance. The objective of this study which involved a relatively large number of ESCC patients was to investigate the correlated factors for lymph node metastasis and prognosis in ESCC. We analyzed a retrospective review of 446 patients with ESCC treated by esophagectomy between January 2010 and July 2016. The relationship between lymph node metastasis and clinicopathological parameters were analyzed. The association between overall survival and clinicopathological factors were evaluated using univariate and multivariable Cox regression models. In the present study, 36.8% esophageal squamous cell carcinoma patients were histologically shown to have lymph node metastasis. Lymph node metastasis was closely correlated with tumor differentiation ($p = 0.016$), perineural invasion ($p = 0.022$), advanced stage tumor ($p < 0.001$) and venous invasion ($p < 0.001$). Kaplan-Meier survival analysis revealed that patients with tumor size, higher T stage, perineuronal invasion, lymph node metastasis, N stage and LNR higher than 0.2 had unfavorable prognosis ($p < 0.05$). The univariate analysis revealed for overall survival that tumor size, pathological stage, perineuronal invasion, lymph metastasis, N stage, involved LNR were relevant prognostic indicators. Furthermore, tumor size, lymph metastasis, N stage and LNR could as independent prognostic factors.

1. Introduction

Esophageal carcinoma is one of the most frequently diagnosed cancers, as well as one of the most fatal cause of cancer-related mortality worldwide [1]. In Asian, especially in China, most esophageal carcinomas (95%) are the squamous cell histology type [2]. The overall survival of esophageal carcinoma remains poor although some improvements have been achieved in treatment [3]. It is important to investigate the initiation and progression of ESCC and to study the associated prognostic factors.

The lymph node metastasis incidence of ESCC is reported to be approximately 38.2%–43% [4,5]. Lymph node metastasis is the important prognosis factor in patients with invasive ESCC [6]. According to previous studies, ESCC patients without nodal metastases generally have a more favorable prognosis after surgical resection [7,8]. ESCC is associated with a risk of extensive lymphatic spread, even when the cancer is confined to the submucosa. As a result, lymph node status is an important issue that has attracted considerable attention in centers dedicated to the management of this disease.

The TNM staging system has become accepted worldwide as the most important reference for treatment planning in clinical oncology and prognosis prediction for esophagus cancer [9]. In the American Joint Committee on Cancer (AJCC) TNM system, N is classified according to the number of metastatic lymph nodes as N0, no lymph node metastasis; N1, 1–2 metastatic lymph nodes; N2, 3–6 metastatic lymph nodes; and N3, more than 7 metastatic lymph nodes [10]. The concept of lymph node ratio(LNR) was discussed by some reports recently. LNR has been found to have prognostic significance in several kinds of tumors, such as lung, breast, colorectal cancer [11–13]. The superiority of LNR classification has been reported by some investigators, and they also showed that it is an independent prognostic indictor for Esophageal cancer [14].

China has a relatively high incidence of ESCC, but there are not sufficient data about ESCC. We began to search for tumor characteristics related to lymph node metastasis. And we assessed whether classification of lymph node metastasis enhanced of prediction of outcomes in patients with ESCC. The present study involved a relatively large number of ESCC patients and the condition of lymph

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node metastasis. In addition, the relation between the other clinicopathological factors and survival was also evaluated.

2. Materials and methods

2.1. Patients

In this retrospective study, data were collected from the medical records of 446 consecutive patients who underwent esophagectomy at the first teaching hospital of Xinjiang medical university, from January 2010 and July 2015. All patients were followed up every 3 months for the first years, and once a year thereafter. Overall patient survival, defined as the time from operation to death or last follow up, was used as a measure of prognosis.

Clinicopathologic data included the following information: name, gender, age, tumor stage, tumor size, nodal stage, degree of tumor differentiation. To be eligible for the study, patients were required to have pathologically confirmed ESCC. Lymph nodes were identified and retrieved from formalin-fixed surgical specimens. Paraffin-embedded nodes were stained with hematoxylin and eosin(HE) and were examined microscopically for metastases. And then the cytokeratin(CK) antibody was stained, in order to confirm lymph node metastasis of ESCC. The LNR was defined as the ratio of the number of metastatic lymph nodes to the total lymph nodes pathologically examined. The patients was classified into two groups(LNR1: <0.2; LNR2 ≥ 0.2). Perineural invasion (PNI) was assessed on HE-stained slides, as positive if cancer cells infiltrated into the perineurium. The CK were tested based on standard immunostaining. All specimens were evaluated by an expert pathologist in the matter of esophageal cancer.

2.2. Statistical analysis

All statistical analyses were performed using the SPSS 14.0 statistical program. The categorical variables were compared using the χ^2 test. The overall survival(OS) was calculated from the date of surgery to the date of death or until the date of the last time the patient was known to be alive. Survival analyses were constructed by Kaplan–Meier curves with log-rank tests for significance. Univariate and multivariate survival analyses ware performed using cox proportional hazards model. $P < 0.05$ was considered to be statistically significant. This study was approved by the ethics committee of this hospital.

3. Results

3.1. The correlations between lymph node metastasis and the clinicopathological characteristics of ESCC patients

There are totally 446 patients involved in this study at the first teaching hospital of Xinjiang medical university, including 310 males and 136 females. Table 1 shows the clinicopathological parameters of the studied patients. The average age was 62 years old (range, 35–84years). According to histological type, well differentiation tumors were observed in 64 (14.3%) patients, moderate in 249 (55.85%) patients, and poor in 133 (28.9%) patients. Lymph node metastasis was confirmed pathologically in 164 (36.8%) patients (Fig. 1). And PNI was confirmed pathologically in 91(25.3%) patients.

Of the 446 total patients, 282(63.2%) was classified as N0, 93 were classified as N1, 52 were classified as N2, and 14 were classified as N3. When classified into two groups according to LNR, Patients with a LNR less than 0.2 accounted for 84.5% of the whole cohort.

Table 1
Characteristics of ESCC patients.

Characteristics and finding	n = 446
Age(years)	
Range	35–84
median	62.40
Tumor size(cm)	
Range	0.2–9.0
median	3.6
Gender	
male	310(69.5%)
female	136(30.5%)
Differentiation	
well	64(14.3%)
moderate	249(55.8%)
poor	133(28.9%)
pathological stage	
T1	41 (9.2%)
T2	29(6.5%)
T3	132(29.6%)
T4	244(54.7%)
Lymph metastasis	
negative	282(63.2%)
positive	164(36.8%)
N stage	
N0	282(63.2%)
N1	98(21.9%)
N2	52(11.7%)
N3	14(3.1%)
Involved LNR	
<0.2	377(84.5%)
≥0.2	69(15.5%)
Venous invasion	
negative	339(76.1%)
positive	107(23.9%)
Perineuronal invasion	
negative	333(74.7%)
positive	113(25.3%)

In the present study, the rate of lymph node metastasis was 36.8%. The relationship between lymph node metastasis and clinicopathological findings are summarized in Table 2. χ^2 test analysis showed that poor differentiation, tumor with nervous invasion, advanced stage tumor and venous invasion were associated with lymph node metastasis(all $p < 0.05$). Poor differentiation carcinomas were more likely to have lymph node metastases than well differentiation and moderate differentiation ($p = 0.016$).There was no significant difference in gender, age, or tumor size for lymph node metastasis (Table 2). It was demonstrated that tumor differentiation, pathological stage, venous invasion and perineural invasion were predictive factors for lymph node metastasis.

3.2. Prognostic significance of lymph node metastasis on patients with ESCC

The Kaplan-meier method was performed to further analyze the association of lymph node metastasis with prognosis of the 446 ESCC patients. We found that the survival of patients with node metastasis positive was significantly worse than that of patients with node metastasis negative (Fig. 2A). thus, lymph node metastasis could affect the prognosis of ESCC patients. next, we reported a significant correlation between the N stage subgroups and the survival. We found that the survival of patients with N0 stage was significantly better than that of the patients with N1, N2 or N3 (Fig. 2B). As expected, we documented a correlation between the LNR and the overall survival. Likewise, the survival of the patients LNR < 0.2 was significantly better than that of the patients with