



Original Research

Prognostic significance of the number of lymph nodes examined in node-negative Siewert type II esophagogastric junction adenocarcinoma



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HIGHLIGHTS

- The prognostic value of the number of examined LNs remains unclear in node-negative (pN0) Siewert type II EGJ adenocarcinoma.
- The number of LNs dissected had an important influence on the prognosis of the patients with Siewert type II EGJ adenocarcinoma.
- Dissection of more than 15 lymph nodes might improve the long-term survival of patients with pN0 Siewert type II EGJ adenocarcinoma.

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ABSTRACT

Background: Involvement status of lymph node (LN) is one of the most important prognostic factors for esophagogastric junction (EGJ) adenocarcinoma. However, the prognostic value of the number of examined LNs remains unclear in node-negative (pN0) Siewert type II EGJ adenocarcinoma.

Methods: A cohort of 262 patients who underwent curative surgery for pN0 Siewert type II EGJ adenocarcinoma from January 2000 to August 2013 were retrospectively analyzed from high-volume center database. All enrolled patients were categorized into 3 groups according to the number of examined LNs (≤ 14 , 15 to 21, ≥ 22). Kaplan-Meier curves were used for comparing the differences of cancer-specific survival among groups; Correlation between survival and the number of examined LNs were analyzed by using stratified, uni- and multivariate analyses.

Results: The hazard ratio for cancer-specific mortality decreased sequentially with increasing number of LNs examined. The 5-year cancer-specific survival rates were 45.1%, 58.4% and 65.7% for patients with ≤ 14 LNs, 15 to 21 and ≥ 22 LNs removed, respectively. The number of removed LNs was significantly correlated with survival in stratified analyses according to T stage. In multivariate model controlling for gender, age, surgical approach, tumor grade, and postoperative chemotherapy, the number of removed LNs and T stage were confirmed to be independent prognostic factors and significantly correlated with disease-specific survival.

Conclusion: The number of examined LNs is an independent prognostic factor of survival for patients with pN0 Siewert type II EGJ adenocarcinoma. Adequate dissection of LNs (more than 15 LNs) is recommended for patients undergoing curative resection.

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1. Introduction

Esophagogastric junction (EGJ) adenocarcinoma is an important clinical entity, defined as tumor with involvement of the anatomic

border between the esophagus and the proximal stomach. According to the widely accepted Siewert system, EGJ adenocarcinomas are usually classified into 3 categories (types I, II, and III) based on anatomic location of the tumor center [1]. Siewert type I was reported with dramatically incidence in Western countries, whereas Siewert type II and III are the predominant ones in eastern Asian countries [2–4]. Especially for type II, called true carcinoma of the cardia, an increasing trend has recently been observed in our center. Acceptance has been gained on that standardized surgical resection combined with lymphadenectomy could benefit patients

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in terms of more accurate staging and higher overall survival.

Involvement status of LNs is the most important prognostic factor for Siewert type II EGJ adenocarcinoma, and the seventh American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) classification of the esophageal carcinoma had been reported to be more compatible with Siewert type II EGJ adenocarcinoma [5,6]. According to the TNM classification, the N stage is totally based on the number of metastatic lymph nodes (LNs). The 7th edition defines node-negative (pN0) disease as any EGJ carcinoma with all examined LNs negative, without consideration of the value of total number of examined LNs. The prognostic significance of the number of dissected LNs EGJ adenocarcinoma patients remains unclear. However, several previous studies have confirmed that the postoperative prognosis of pN0 cancer patients, such as gastric cancer and esophageal cancer [7,8], was associated with the number of dissected LNs.

Although previous studies have studied on the optimal extent of lymphadenectomy of Siewert type II EGJ adenocarcinoma [9,10], none of them discussed the significance of number of examined LNs; And there is no consensus on the optimal number of nodes should be examined during a curative resection for pN0 patients with Siewert type II EGJ adenocarcinoma. Therefore, current study was designed to explore the correlation between the total number of examined LNs during surgery and the prognosis of Siewert type II EGJ adenocarcinoma without LNs metastasis.

2. Material and methods

2.1. Patients

From January 2000 to August 2013, a cohort of 262 patients with node-negative Siewert type II EGJ adenocarcinoma who underwent curative surgery in the thoracic surgery departments were retrospectively analyzed from our center database. The diagnosis was precisely confirmed based on the following methods: the preoperative esophagogram, computed tomography scan and endoscopic findings, intraoperative observation, and postoperative pathology examination. Clinicopathologic variables, including tumor staging according to the EGJ adenocarcinoma TNM classification (seventh edition), were retrieved from the patient's hospital records. The protocol of current study was approved by the Research Ethics Committee of Anhui Provincial Hospital Affiliated with Anhui Medical University; and the requirement for written informed consent of individual patient was waived owing to the retrospective nature of this study.

The exclusion criteria were as follows: patients who received neoadjuvant therapy, who died within 60 days after operation, who were complicated with other malignancies or with lymph node or distant metastasis were excluded from the study. We also eliminated patients with exploratory surgery only, with unknown surgery status or unknown number of lymph nodes examined. Additionally, T4 stage patients were not enrolled in this study because of more complicated status and unverified R0 resection. Finally, 262 patients of stage I (T1N0M0) and stage IIA (T2-3N0M0) Siewert type II EGJ adenocarcinoma were enrolled.

2.2. Surgical treatment

The surgical methods of resection included transthoracic approach and transabdominal hiatal approach. For transthoracic group, only an incision was made in the seventh left intercostal space. According to the anatomy of the lower esophagus and the stomach, proximal gastrectomy through the esophageal hiatus was performed, and the type of digestive tract reconstruction was esophagogastrostomy. Lymphadenectomy mainly involved the

lower thoracic paraesophageal, supra and infradiaphragmatic, lymph nodes in the esophageal hiatus of the diaphragm and perigastric lymph nodes. For transabdominal hiatal group, proximal gastrectomy was performed through an upper abdomen midline incision. The type of anastomosis was the same as in the transthoracic group. D2 lymph node dissection and limited lower mediastinal lymphadenectomy were adopted.

2.3. Follow-up

All patients were visited at the outpatient clinic or by telephone follow-up or by other information. The quality-of-life indicators, including dietary intake and reflux information, tumor markers, and imaging data (endoscopy, computed tomography) were the main postoperative evaluation indicators. The principles of postoperative follow-up were as follow: including every 3-month radiological examination for the first 2 years, then every 6-month for following 3 years, and once a year afterwards. Survival time was defined as the time from the date of taking surgery to death or last follow-up. Owing the purpose of current study was to assess the correlation between the number of examined LNs and prognostic survival; cancer-specific mortality was used in all analyses for controlling of unrelated causes of death. During processing the data cancer-specific survival, unrelated causes of death were censored.

2.4. Statistical analyses

SPSS version 19.0 (Statistical Package for the Social Sciences, Chicago, IL) was used for statistical analyses. We used the χ^2 test to compare differences between categorical variables, the *t*-test and trend test for continuous variables. Survival curves were calculated by using the Kaplan-Meier method and compared by the log-rank test. A multivariate analysis of prognostic factors was performed by using the Cox proportional hazards model and a stepwise procedure. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated. All statistical tests were conducted 2-sided, and *p* values < 0.05 were considered to be statistically significant.

3. Results

3.1. Demographics and clinicopathological features

During the period from January 2000 to August 2013, 262 consecutive patients with stages of I (T1N0M0) and IIA (T2-3N0M0) Siewert type II EGJ adenocarcinoma were treated with R0 resection and were enrolled in present study. There were 107 (40.8%) women and 155 (59.2%) men. The age range was 41–80 years, with the median age of 67 years. The median number of lymph nodes examined was 16.4 (1–36). According to the number of LNs resected, all included patients were categorized into 3 groups: 1 to 14 (111, 42.4%), 15 to 21 (87, 33.2%), and ≥ 22 (64, 24.4%). Table 1 summarizes the demographic data and clinicopathological features stratified according to the number of removed LNs. Overall, no significant differences were found in terms of gender, age, surgical approach, T stage, tumor grade or postoperative chemotherapy among the 3 different groups.

3.2. Univariate and subgroup survival analyses

The median follow-up time for all patients was 43 months and EGJ adenocarcinoma mortality comprised 67.5% of all causes deaths. The 5-year cancer-specific survival rate of the entire cohort was 54.5%. Survival analysis for all patients indicated that EGJ adenocarcinoma specific survival increased sequentially with

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