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Original Research

Appropriate extent of lymphadenectomy for squamous cell carcinoma of the esophagogastric junction

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HIGHLIGHTS

- Metastasis in the upper/middle mediastinal nodes: seen in 25% of ECJ SCC patients.
- Tumor length was an independent risk factor, with the cutoff value of 54 mm.
- The therapeutic value of upper/middle mediastinal lymphadenectomy was high.
- Extended mediastinal lymphadenectomy may be required for patients at risk.

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ABSTRACT

Aim: To investigate the appropriate extent of lymphadenectomy for squamous cell carcinoma (SCC) of the esophagogastric junction (ECJ).

Methods: We retrospectively reviewed the cases of 52 patients with SCC of the ECJ who underwent extended mediastinal lymphadenectomy. We assessed potential risk factors for lymph node metastasis (LNM) in the upper/middle mediastinum by conducting univariate and multivariate analyses, and a receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value. Survival rates were calculated using the Kaplan-Meier method, and the therapeutic value index of each nodal basin dissection was calculated by multiplying the frequency of metastasis at the basin and the 5-year overall survival rate of patients with metastasis at that basin.

Results: Twenty patients (38%) had mediastinal LNM; 13 (25%) had metastasis in the upper/middle mediastinum, and 13 (25%) had metastasis in the lower mediastinum. Tumor length ($P = 0.03$) and pathological nodal status ($P = 0.01$) were independent risk factors for upper/middle mediastinal LNM. The optimal ROC cutoff value of tumor length was 54 mm. The 5-year overall survival rate of the patients with LNM in the upper/middle mediastinum was 46%. The therapeutic value index of upper/middle mediastinal lymphadenectomy was 11.6, which was inferior to that of perigastric lymphadenectomy at 17.3, but superior to that of lower mediastinal lymphadenectomy at 5.8.

Conclusion: An upper/middle mediastinal lymphadenectomy may be required for patients with tumors that are ≥54 mm long, and in those with suspected LNM.

1. Introduction

A recent topic of interest in medicine in Japan is the gradual increase in the incidence of carcinoma of the esophagogastric junction (EGJ) and the establishment of a treatment strategy for this disease. Many previous studies have focused on adenocarcinoma (AC) of the EGJ [1–3]; however, squamous cell carcinoma (SCC) is another histological type that is often seen in this area. In the International Union against Cancer (UICC) tumor-node-metastasis (TNM) classification, a tumor whose epicenter is within 5 cm of the EGJ and also extends into the esophagus is classified and staged using the esophageal scheme [4], which mainly reflects the Siewert classification and is mainly applied to ACs [5]. On the other hand, carcinoma of the EGJ is defined in the Japanese Classification of Esophageal Cancer and Gastric Carcinoma as a tumor whose

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epicenter is within 2 cm of the EGJ [6,7], a classification that is almost identical to that of a Siewert type II tumor but is applied to both ACs and SCCs in Japan.

Siewert type II tumors are often treated with a transhiatal extended gastrectomy including a distal esophageal resection with a lower mediastinal and abdominal lymphadenectomy, based on the clinical observation of lymphatic drainage from the EGJ [5]. It is uncertain, however, whether SCCs of the EGJ should be treated in the same way as ACs of the EGJ in terms of the operative approach, the extent of esophageal and gastric resection and that of mediastinal lymphadenectomy, and adjuvant therapy. We conducted the present retrospective study to elucidate the clinicopathological characteristics of SCCs of the EGJ and to investigate the appropriate extent of lymphadenectomy for this disease, using the therapeutic value index of each nodal basin dissection.

2. Materials and methods

2.1. Patients

Between January 1982 and December 2012, esophageal resection was performed in 107 patients who had SCC, the epicenter of which was located in the area extending from 2 cm above to 2 cm below the EGJ. Of these patients, 53 patients underwent limited resection via the transthoracic approach ($n = 7$), transhiatal approach ($n = 45$), and abdominal approach ($n = 1$), mainly because of no mediastinal lymph node metastasis (LNM) on clinical staging. Two patients underwent incomplete resection due to local tumor extension. A total of 55 patients were therefore excluded from this study. We selected the remaining 52 patients who underwent curative esophagectomy with an extended mediastinal lymphadenectomy from a prospectively maintained database and entered them in this study. Of these patients, 27 patients had tumors whose epicenters were located 1 cm–2 cm above the EGJ, corresponding to Siewert type I tumors. The remaining 25 patients had tumors corresponding to Siewert type II tumors. The median follow-up period of the censored cases was 167 months (range, 61–320 months). This study was reviewed and approved by the Institutional Review Board.

2.2. Surgery, histopathological examination, and staging

The surgical procedure of extended mediastinal lymphadenectomy via the transthoracic approach is described elsewhere [8]. Cervical lymphadenectomy was added in 41 patients: bilateral in 16 patients and left in 25 patients. All patients underwent an R0 resection according to the UICC's residual tumor classification [4].

Preoperative imaging assessment included chest radiography, esophagography, esophagogastroduodenoscopy, and computed tomography of the neck, chest and abdomen. Endoscopic ultrasound, magnetic resonance imaging, positron emission tomography, bronchofiberscopy, and/or bone scintigraphy was performed if indicated for the determination of individual staging. We examined the patients' resected specimens histologically to determine the depth of the primary tumor invasion, nodal status, and presence or absence of vessel invasion. The EGJ was identified by the level of the macroscopic caliber change of the resected esophagus and stomach as defined by the Japanese Gastric Cancer Association classification of gastric carcinoma [7]. The length of esophageal invasion was defined as the distance between the EGJ and the proximal border of the tumor (Fig. 1). Clinical and pathological tumor staging and histopathological grading were performed according to the UICC's TNM classification [4].

The nodal basin classifications used in this study were as follows: cervical, upper/middle mediastinal, lower mediastinal, perigastric, and suprapancreatic. The lymph node stations included in each nodal basin were as described [9].

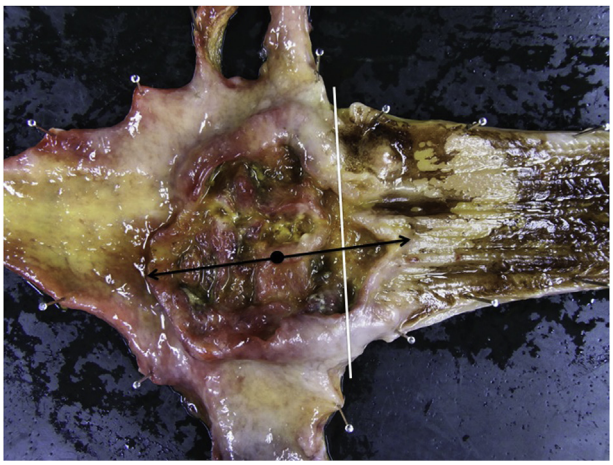

Fig. 1. Representative specimen of SCC of the EGJ. EGJ, white line; tumor epicenter, closed circle; tumor length, bidirectional arrow.

2.3. Evaluation of the benefit of lymphadenectomy, and statistical analyses

The clinicopathological characteristics noted included age; gender; tumor length; the length of esophageal invasion; macroscopic tumor type; histopathological grading; depth of primary tumor invasion; nodal status including cervical, mediastinal, and abdominal nodal basins; and lymphatic and venous invasion. We compared these factors between the patients with and without upper/middle mediastinal LNM. Differences were assessed using the Mann-Whitney *U* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Tukey's multiple comparison tests were used to analyze the correlation between the depth of tumor invasion and tumor length.

We performed a multivariate logistic regression analysis to identify independent risk factors for upper/middle mediastinal LNM. A receiver operating characteristic (ROC) curve analysis was used for the evaluation of predictive values. The overall performance of each predictive factor is expressed as the area under the ROC curve (AUC) with the 95% confidence interval (CI). We used the Youden index (sensitivity + specificity − 1) to estimate the optimal ROC cutoff values. A two-sided *P*-value < 0.05 was considered significant. All analyses were performed with the SPSS 22.0J software package (SPSS Japan, Tokyo).

Survival rates were calculated from the date of surgery until death or the last follow-up for surviving patients, using the Kaplan-Meier method. Differences between the survival curves were assessed using the log-rank test. To evaluate the benefit of lymphadenectomy, we used the therapeutic value index method described previously [1]. We calculated the index of the benefit produced by lymphadenectomy for each nodal basin by multiplying the frequency of metastasis at the basin and the 5-year overall survival rate of the patients with metastasis at that basin.

3. Results

3.1. Risk factors for LNM in the upper/middle mediastinum

The patient and tumor characteristics are summarized in Table 1. Cervical LNM was seen in four patients (8%). Twenty patients (38%) had mediastinal LNM; 13 (25%) had metastasis in the upper/middle mediastinum, and 13 (25%) in the lower mediastinum. Twenty-