Patterns of Regional Lymph Node Recurrence After Radical Surgery for Thoracic Esophageal Squamous Cell Carcinoma

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Background. **This study aimed to investigate the patterns of regional lymph node recurrence after radical surgery for thoracic esophageal squamous cell carcinoma (ESCC).**

Methods. **We retrospectively reviewed clinical characteristics of ESCC patients admitted to two institutions from 1990 to 2011, and analyzed the patterns of regional lymph node recurrence.**

Results. **The records of 315 eligible patients with ESCC were reviewed. Of the 378 regional lymph node recurrence sites, 177 (46.8%) were in the supraclavicular areas, 120 (31.7%) in the mediastinum, and 81 (21.4%) in the upper abdominal areas. The most common sites of recurrence were the supraclavicular and mediastinum areas in patients with upper and middle thoracic ESCC. Approximately equal percentages of patients with lower thoracic tumors had supraclavicular, mediastinal, and upper abdominal (celiac) lymph node recurrence. Patients with tumor located in the lower thoracic esophagus had a lower probability of supraclavicular lymph node recurrence ($p = 0.013$). None of the assessed factors was associated with mediastinal lymph node recurrence. Celiac lymph node recurrence was more frequent among patients with lower thoracic ESCC ($p = 0.004$) and advanced pathologic nodal (pN) stage (pN2, $p = 0.034$; pN3, $p = 0.009$).**

Conclusions. **After radical surgery for thoracic ESCC, the patterns of regional lymph node recurrence are related to the tumor location and pN stage.**

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Esophageal cancer (EC) is a common malignant tumor of the gastrointestinal tract [1]. In China, approximately 90% of EC is classified as esophageal squamous cell carcinoma (ESCC), although esophageal adenocarcinoma is the predominant type in Western countries [2]. For resectable esophageal adenocarcinoma and ESCC, the standard surgical strategy is esophagectomy with lymphadenectomy with or without neoadjuvant chemoradiotherapy [3]. However, approximately half of the patients may have locoregional recurrence, especially regional lymph node recurrence (RLNR), and this adversely affects patient survival [4, 5].

The National Comprehensive Cancer Network guidelines recommend postoperative radiotherapy for patients with positive surgical margins [6]. However, recent studies of Chinese ESCC patients found that postoperative radiotherapy improved survival regardless of the margin status [7–10]. Lymph node drainage of the EC may present as multiple level and skipping metastasis [11]. Although it is difficult to determine the targets of lymph node regions for postoperative radiotherapy, the patterns of RLNR are the factors that can be used to determine the targets. Therefore, in this study, we investigated the patterns of RLNR with thoracic ESCC after esophagectomy and lymphadenectomy to assess the risk factors associated with RLNR. Our findings may provide a reference for identification of the targets for postoperative radiotherapy for ESCC patients.

Material and Methods

Patients

Clinical characteristics of ESCC patients who received radical surgery in the First Affiliated Hospital of Xiamen University, Xiamen Cancer Center (XMCC) and the Sun Yat-sen University Cancer Center (SYSUCC) from October 1990 to December 2011 were reviewed. Patients enrolled must have met the following criteria: (1) ESCC with no neoadjuvant radiotherapy, chemotherapy, or chemoradiotherapy; (2) postoperative pathology indicating negative surgical margins; and (3) postoperative RLNR with or without hematogenous metastasis during

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Abbreviations and Acronyms

CI = confidence interval
CT = computed tomography
EC = esophageal cancer
ESCC = esophageal squamous cell carcinoma
OR = odds ratio
PET = positron emission tomography
RLN = regional lymph node
RLNR = regional lymph node recurrence
SYSUCC = Sun Yat-sen University Cancer Center
XMCC = Xiamen Cancer Center

the follow-up period. This study protocol was approved by the Ethics Committee of the XMCC and SYSUCC.

Preoperative Staging Procedure

Sun Yat-sen University Cancer Center and Xiamen Cancer Center begun to use [18F]-fluorodeoxyglucose positron emission tomography (PET) with computed tomography (CT) scan for staging of EC in 2005 and 2007, respectively, but most patients still had CT scans for staging owing to economic problems. Endoscopic ultrasonography was begun to be used at SYSUCC and XMCC in 2008 and 2010, respectively. Therefore, the preoperative workup mainly relied on CT scans in this study. All patients underwent neck, chest, and upper abdomen contrast-enhanced scans to confirm the indications for surgery.

Diagnostic Criteria for Regional Lymph Node Recurrence

The boundaries of lymphatic drainage region were divided into the following five groups: cervical, upper mediastinal, middle mediastinal, lower mediastinal, and upper abdominal (celiac) areas [12]. The RLNR was confirmed by CT; PET/CT has been performed if necessary since the introduction of PET/CT scan in our hospitals. Suspected supraclavicular node recurrences were confirmed using histologic or cytologic testing when possible. Mediastinal and upper abdominal lymph nodes biopsy were not routinely performed. For the RLNR in the cervical, mediastinal and upper abdominal areas, a lymph node with a short axis greater than 10 mm or a lymph node with a short axis less than 10 mm combined with hoarseness or vocal cord paralysis was defined as recurrent disease.

Clinicopathologic Factors

The association of clinicopathologic factors with RLNR was determined, including age, sex, tumor location, pathologic tumor (pT) stage, pathologic nodal (pN) stage, tumor differentiation, the number of lymph node field dissected, the sites of lymph node involvement at the time of surgery, and the removed lymph nodes (RLN) count. Tumor staging was determined according to the TNM staging system for EC provided by the American Joint Committee on Cancer and the Union for International Cancer Control [13].

Statistical Analysis

All data were analyzed using the SPSS statistical software package (version 16.0; SPSS, Chicago, IL). The χ^2 and Fisher's exact tests were used to determine the significance of differences in qualitative data. The relationship between clinicopathologic factors and lymph node recurrence was examined by univariate and multivariate logistic regression analysis. Factors that were statistically significant in the univariate analysis were entered into multivariate logistic regression analysis. A p value less than 0.05 was considered statistically significant.

Results

Patient Characteristics

In all, 315 eligible patients with ESCC were identified during the study period, with 114 patients (36.2%) from XMCC and 201 patients (63.8%) from SYSUCC. The general characteristics of the enrolled patients from the two institutions are listed in Table 1. Overall, the median age was 55 years (range, 30 to 76); the male to female ratio was 3.1:1. Primary tumors were located in the upper

Table 1. Clinicopathologic Characteristics

Characteristic	n	XMCC	SYSUCC	p Value
Age, years				
≤60	221	83	138	0.439
>60	94	31	63	
Sex				
Male	238	92	146	0.109
Female	77	22	55	
Tumor location				
Upper thoracic	30	15	15	0.020
Middle thoracic	153	44	109	
Lower thoracic	132	55	77	
Tumor stage				
pT1	3	2	1	<0.001
pT2	113	58	55	
pT3	199	54	145	
Nodal stage				
pN0	69	26	43	0.142
pN1	127	40	87	
pN2	85	30	55	
pN3	34	18	16	
Tumor differentiation				
Well	41	6	35	0.009
Moderate	171	67	104	
Poor	103	41	62	
Number of fields dissected				
Two fields	243	96	147	0.024
Three fields	72	18	54	

SYSUCC = Sun Yat-sen University Cancer Center; XMCC = Xiamen Cancer Center.

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