Supraclavicular node metastasis from thoracic esophageal carcinoma: A surgical series from a Japanese multi-institutional nationwide registry of esophageal cancer

Yuji Tachimori, MD,^a Soji Ozawa, MD,^b Hodaka Numasaki, PhD,^c Hisahiro Matsubara, MD,^d Masayuki Shinoda, MD,^e Yasushi Toh, MD,^f and Harushi Udagawa, MD,^g The Registration Committee for Esophageal Cancer of the Japan Esophageal Society

Objectives: In the present TNM classification, involvement of supraclavicular nodes is defined as distant metastases. However, the therapeutic value of supraclavicular node dissection remains controversial. The purpose of this study was to evaluate the survival benefit of dissection of metastases to the supraclavicular lymph nodes in patients with thoracic esophageal carcinoma by using a large nationwide registry of esophageal cancer maintained by the Japanese Esophageal Society.

Methods: The study group comprised 1309 patients with thoracic esophageal carcinoma treated in 2001, 2002, and 2003, who underwent esophagectomy with 3-field dissection for curative intent, and in whom the locations of pathologic metastatic lymph nodes and outcome evaluations were available.

Results: Of 1309 patients, 559 (42.7%) had no nodal metastases, 560 (42.8%) had at least 1 positive node but were supraclavicular node-negative, and 190 (14.5%) had supraclavicular node metastases. The 5-year survival was 73.7% for patients with N0, 40.4% for node-positive patients without supraclavicular node disease, and 24.1% for patients with supraclavicular node metastasis. In a multivariate analysis, male sex ($P < .001$), deeper T category ($P < .001$), and more positive nodes ($P < .001$) retained statistical significance as adverse prognostic factors for overall survival. Supraclavicular node metastasis was not significant ($P = .062$).

Conclusions: The survival benefit of dissection of metastases to the supraclavicular lymph nodes was indicated in patients with thoracic esophageal carcinoma. Supraclavicular nodes appear to be regional nodes similar to other regional nodes. (J Thorac Cardiovasc Surg 2014;148:1224-9)

In the present 7th Union for International Cancer Control (UICC) TNM classification¹ and the 7th AJCC *Cancer Staging Manual*,² celiac axis nodes and paraesophageal nodes in the neck are included in the regional lymph nodes, irrespective of the site of the primary tumor. However, supraclavicular nodes remain as distant metastases (M1). Most clinicians believe that the presence of M1 disease

precludes curative treatment approaches. The presence of supraclavicular node metastasis, similar to visceral organ metastasis, may be considered a contraindication for curative surgery, and supraclavicular node dissection may be considered not associated with any survival benefit. However, patients who had supraclavicular node metastasis appeared to have a better survival than patients with visceral metastasis in several studies.³⁻⁶ Thus, the therapeutic value of supraclavicular node dissection remains controversial.

The purpose of this study was to evaluate the survival benefit of dissection of metastases to the supraclavicular lymph nodes in patients with thoracic esophageal carcinoma who undergo surgical treatment with curative intent, by using a large, multi-institutional, nationwide registry of esophageal cancer maintained by the Japanese Esophageal Society.

MATERIALS AND METHODS

Patients

A comprehensive registry of esophageal cancer in Japan was established and has been maintained by the Registration Committee for Esophageal Cancer of the Japan Esophageal Society since 1976. The first report was published in 1979. The registration did not restrict for patients who underwent surgery but included patients who underwent nonsurgical therapy. All patients' data, including demographic characteristics, symptoms, clinical stage, treatment features, and survival information, were collected.

From the Division of Esophageal Surgery,^a National Cancer Center Hospital, Tokyo, Japan; Department of Gastroenterological Surgery,^b Tokai University School of Medicine, Isehara, Japan; Department of Medical Physics and Engineering,^c Osaka University Graduate School of Medicine, Osaka, Japan; Department of Frontier Surgery,^d Chiba University Graduate School of Medicine, Chiba, Japan; Department of Thoracic Surgery,^e Aichi Cancer Center Hospital, Nagoya, Japan; Department of Gastroenterological Surgery,^f Kyushu Cancer Center, Fukuoka, Japan; and Department of Gastroenterological Surgery,^g Toranomon Hospital, Tokyo, Japan. This study was supported by Grants-in-Aid for Cancer Research (H22-3rd Term Cancer Control-General-043) from the Ministry of Health, Labor and Welfare of Japan. Disclosures: Hisahiro Matsubara reports consulting fees from Taiho Pharmacy, Danchi-Sankyo Pharmacy, and Oregai Pharmacy. All other authors have nothing to disclose with regard to commercial support.

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Address for reprints: Yuji Tachimori, MD, Division of Esophageal Surgery, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan (E-mail: ytachimo@ncc.go.jp).

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Abbreviation and Acronym

UICC = Union for International Cancer Control

Surgical features, pathologic stage, and detailed lymph node metastatic status also were collected for the patients who underwent surgery.

A total of 12,880 patients with primary esophageal carcinoma treated in 2001, 2002, and 2003 were registered in 2008, 2009, and 2010, respectively, from 241 institutions in Japan.⁷⁻⁹ Of 12,880 patients, 10,896 had thoracic esophageal carcinoma, 5734 underwent esophagectomy, 5111 received R0 resection, and 623 who underwent R1 and R2 resections were excluded because of limited node dissection. Of 5111 patients who received R0 resection, 1768 had 3-field esophagectomy including supraclavicular dissection. Because the study was based on a multi-institutional, nationwide registry, the selection of patients and indication for 3-field dissection were dependent on each institution and not specified. Of 1768 patients who had 3-field esophagectomy for R0 resection, 1427 had information about the locations of pathologic metastatic lymph nodes. Outcome evaluations were available in 1309 patients. Thus, the total study group comprised 1309 patients who had R0 resection and 3-field esophagectomy from 155 institutions.

Tumor Classification

Pathologic stages for all patients were reassessed according to the 7th edition of the UICC TNM classification system.¹ The clinical stage using the 7th edition of UICC/American Joint Committee on Cancer TNM staging system was not available in this registration for patients treated in 2001, 2002, and 2003. The TNM classification divides the intrathoracic esophagus into the following 3 anatomic subsites: upper, middle, and lower. Areas of lymph nodes were defined by the Japanese Classification of Esophageal Cancer (10th Edition).^{10,11} The supraclavicular nodes and cervical paraesophageal nodes were dissected via the cervical approach in 3-field dissection. The paraesophageal nodes, recurrent laryngeal nerve nodes, paratracheal nodes, aortopulmonary nodes, subcarinal nodes, tracheobronchial nodes, posterior mediastinal nodes beside the thoracic duct, pulmonary ligament nodes, and supradiaphragmatic nodes were dissected during thoracotomy. Abdominal lymph nodes dissected during the routine procedures were the paracardial nodes and nodes around the left gastric artery and the celiac axis. Nodes other than the supraclavicular nodes are regarded as regional in the TNM classification, whereas metastases in supraclavicular nodes from tumors of the esophagus are defined as distant (M1). The lymph node metastatic pattern was investigated according to tumor location. To examine whether the supraclavicular nodes are regional for thoracic esophageal carcinoma, the incidence of supraclavicular node involvement was compared with that of nodes other than supraclavicular nodes. In addition, the long-term outcomes of patients with lymph node metastases involving supraclavicular areas versus patients without supraclavicular lymph node metastases were examined to investigate the survival benefit of dissection of the supraclavicular nodes.

Statistical Methods

Statistical analysis was performed and relevant curves were created using SPSS 19.0 (SPSS Inc, Chicago, Ill). Unless otherwise stated, mean values and standard deviations are reported. Student *t* test was used for comparisons between subgroups. For categorical variables, the chi-square test or Fisher exact test was used, as appropriate. The kappa test was used to evaluate the consistency between clinical stage and pathologic stage. Survival curves were constructed using the Kaplan–Meier method, which was also used for univariate analysis. Variables with a *P* value less than .1 were included in the Cox proportional hazards model.

RESULTS

Patients' characteristics and findings are listed in Table 1. The location of the tumors was the upper esophagus in 222 patients (17.0%), the middle esophagus in 761 patients (58.1%), and the lower esophagus in 326 patients (24.9%). By histology, most patients (97.7%) had squamous cell carcinomas, and only 7 patients had adenocarcinomas. According to the selection criteria, most patients with junctional tumor and those with adenocarcinoma were excluded because of limited or no dissection of supraclavicular nodes. Approximately half of patients had at least T3 disease (46.2%).

There were 559 patients without nodal metastases (42.7%) and 750 patients with nodal metastases (57.3%). Of the 750 patients with nodal involvement, 560 (42.8%) had at least 1 positive node, but were supraclavicular node-negative, and 190 patients (14.5%) had supraclavicular node metastases. According to tumor location, the frequency of supraclavicular node metastases was 19.4% in patients with upper esophageal tumors, 15.0% in patients with middle esophageal tumors, and 9.3% in patients with lower esophageal tumors. A supraclavicular node was the only positive node in 19 (10%) of 190 patients with positive supraclavicular nodes. The number of resected nodes was not collected in this registration. The median number of positive nodes was 6 in 190 patients with positive supraclavicular nodes and 3 in 560 patients with positive nodes without supraclavicular node metastasis.

Neoadjuvant chemoradiotherapy was administered to 174 patients (13.3%), 92 patients (7.0%) received neoadjuvant chemotherapy, and 14 patients (1.1%) received definitive chemoradiotherapy and underwent salvage esophagectomy. Preoperative therapy was not standard for esophageal cancer in Japan 10 years ago. The selection of patients and indication and therapeutic means for preoperative therapy were dependent on each institution and not specified.

The 30-day operative mortality rate was 1% (13 patients). The median follow-up duration of surviving patients was 6.4 years. The median overall survival for all patients was 74.2 months, and the 3- and 5-year survivals were 60.2% and 52.6%, respectively.

On univariate analysis for survival (Table 2), male sex (*P* = .05), deeper T category (*P* < .001), more positive nodes (*P* < .001), and metastasis of supraclavicular nodes (*P* < .001) were associated with worse overall survival. Tumor location was not found to be associated with survival (*P* = .078).

The 5-year survival was 73.7% for patients with N0, 40.4% for node-positive patients without supraclavicular node disease, and 24.1% for node-positive patients with supraclavicular node metastasis (Figure 1). These differences were significant.

TABLE 1. Patients' characteristics and tumor findings

Characteristic and finding	No. (%)
Median age (range), y	62.0 (20-84)
Sex	
Male	1138 (86.9)
Female	171 (13.1)
Tumor location	
Upper	222 (17.0)
Middle	761 (58.1)
Lower	356 (24.9)
Histologic cell type	
Squamous cell carcinoma	1279 (97.7)
Adenocarcinoma	7 (0.5)
Others	23 (1.8)
Preoperative therapy	
Neoadjuvant chemotherapy	92 (7.0)
Neoadjuvant chemoradiotherapy	174 (13.3)
Definitive chemoradiotherapy	14 (1.1)
Pathologic T classification	
TX	15 (1.2)
T0	22 (1.7)
Tis	11 (0.8)
T1a	105 (8.0)
T1b	355 (27.1)
T2	195 (14.9)
T3	583 (44.5)
T4a	22 (1.7)
Pathologic positive node no. (including supraclavicular node)	
N0	559 (42.7)
N(1-2)	292 (22.3)
N(3-6)	279 (21.3)
N(7-)	179 (13.7)
Pathologic M classification	
M1 (supraclavicular node)	190 (14.5)

TABLE 2. Univariate analysis of factors for survival

Factor	5-y Survival (%)	P value
Sex		<.001
Male	50.1	
Female	69.5	
Tumor location		.078
Upper	49.0	
Middle	55.6	
Lower	48.0	
Histologic cell type		.666
Squamous cell carcinoma	52.7	
Adenocarcinoma	47.6	
Others	47.2	
T		<.001
Tx	75.7	
T0	53.0	
Tis	80.0	
T1a	77.1	
T1b	68.9	
T2	52.7	
T3	37.5	
T4a	30.0	
No. of positive nodes including supraclavicular		<.001
N0	73.7	
N(1-2)	53.9	
N(3-6)	34.7	
N(7-)	11.1	
Supraclavicular node		<.001
Negative	40.4	
Positive	24.1	

For patients with upper esophageal tumors, 5-year survival was 66.3% for patients with N0, 35.3% for node-positive patients without supraclavicular node disease, and 38.1% for patients with supraclavicular node metastasis (Figure 2, A). The difference between node-positive patients without supraclavicular node disease and node-positive patients with supraclavicular node disease was not significant. For patients with mid-thoracic tumor, 5-year survival was 77.3% for N0 patients, 44.0% for node-positive patients without supraclavicular node disease, and 21.6% for patients with supraclavicular node disease (Figure 2, B). The difference between node-positive patients without supraclavicular node disease and patients with supraclavicular node metastasis was significant. For patients with lower esophageal tumors, 5-year survival was 70.0% for patients with N0, 35.9% for node-positive patients without supraclavicular node disease, and 10.9% for patients with supraclavicular node metastasis (Figure 2, C). The difference between node-positive patients without supraclavicular node disease and patients with supraclavicular node metastasis was significant. In the analysis

according to the number of involved lymph nodes including supraclavicular nodes, patients with more positive nodes had significantly worse survival (Figure 3).

A multivariate analysis was performed using factors that were significant on univariate analysis. Table 3 shows that male sex ($P < .001$), deeper T category ($P < .001$), and more positive nodes ($P < .001$) retained statistical

FIGURE 1. Survival by involved lymph node location. pN0, pN positive without supraclavicular node metastasis; pN, positive with supraclavicular node metastasis.

FIGURE 2. Survival by tumor location and involved lymph node location. A, Tumor located in the upper esophagus. B, Tumor located in the middle esophagus. C, Tumor located in the lower esophagus. *pN0*, pN positive without supraclavicular node metastasis; *pN*, positive with supraclavicular node metastasis.

significance as adverse prognostic factors for overall survival. However, supraclavicular node metastasis was not significant ($P = .062$). As shown in Figure 4, in patients with the same number of positive nodes, supraclavicular node status did not predict survival outcome. Survival was worse overall in patients with positive supraclavicular node, but this is not simply because of the supraclavicular node but primarily because of the number of involved nodes.

FIGURE 3. Survival by number of involved lymph nodes including supraclavicular nodes.

DISCUSSION

A large series of patients who underwent esophagectomy with supraclavicular node dissection for thoracic esophageal cancer was reported. The frequency of supraclavicular node metastases was 14.5%. Although patients with supraclavicular node metastases had a worse prognosis than patients without supraclavicular node disease, 24.1% of patients with supraclavicular node disease resected for curative intent (R0) achieved long-term survival. The supraclavicular node status did not predict survival outcome when patients had the same number of metastatic nodes. The number of positive nodes including supraclavicular nodes predicted survival better, as reported previously.¹²⁻¹⁴ Survival was worse overall in patients with positive supraclavicular node, not simply because of the supraclavicular node but primarily because of the number of involved nodes. This indicates the survival benefit of dissection of metastases to the supraclavicular lymph nodes in patients with thoracic esophageal carcinoma who undergo surgical treatment with curative intent.

The frequency of supraclavicular node metastases and the 5-year survival after dissection of patients with supraclavicular node metastasis were 19.4% and 38.1%

TABLE 3. Multivariate analysis of factors for survival

Factor	Risk ratio	95% CI	P value
Sex			
Male/female	1.721	1.286-2.304	<.001
T category			
T3, T4, Tx/T0, Tis, T1a, T1b, T2	1.592	1.335-1.899	<.001
No. of positive nodes including supraclavicular nodes			
N(1-2)/N0	1.904	1.500-2.416	<.001
N(3-6)/N0	2.701	2.132-3.423	<.001
N(7-)/N0	5.144	3.939-6.717	<.001
Supraclavicular node			
Positive/negative	1.224	0.990-1.514	.062

CI, Confidence interval.

FIGURE 4. Survival by number of involved lymph nodes and supraclavicular node status: patients with 1 to 2 positive nodes (A), patients with 3 to 6 positive nodes (B), patients with 7 or more positive nodes (C).

in 222 patients with upper esophageal tumors, 15.0% and 21.6% in 761 patients with middle esophageal tumors, and 9.3% and 10.9% in 356 patients with lower esophageal tumors, respectively. The frequency of celiac node metastases and the 5-year survival after dissection of patients with celiac node metastasis were approximately 15% and 10%, respectively, in other reports.¹⁴⁻¹⁷ The regional nodes are defined irrespective of the site of the primary tumor in the 7th UICC TNM classification. With a 5-year survival of approximately more than 10% in patients with lower esophageal tumors, supraclavicular nodes seem to be regional nodes similar to other regional nodes, in such cases.

In the previous 6th UICC TNM classification, supraclavicular nodes and celiac axis nodes were not included in the regional lymph nodes of thoracic esophageal carcinoma, and involvement of these nodes was defined as distant metastasis (M1), as for visceral organ metastasis.¹⁸ During the past 2 decades, tumors of the distal esophagus or gastroesophageal junction have increased in patients in Western countries.¹⁹⁻²¹ As a result, an increasing number of patients with esophageal cancer were found to have lymph node metastasis at the celiac axis. Better survivals of patients with celiac node metastasis also were reported.^{14,16} Revision of the TNM staging system was recommended by a data-driven staging system based on data of the Worldwide Esophageal Cancer Collaboration.^{22,23} In this large series of international multicenter studies, tumor location was in the lower esophagus in 69% of patients. Celiac axis nodes are included in the regional lymph nodes in the present 7th UICC TNM classification.

In contrast, supraclavicular nodes are not included in the regional lymph nodes and remain as distant metastasis (M1) in the 7th UICC TNM classification. Two-field lymphadenectomy in the abdomen and mediastinum is commonly used in esophagectomy. Fewer data are available to evaluate the therapeutic value of dissection of metastatic supraclavicular nodes in patients with esophageal cancers, except for reports from Asia.^{24,25} Thus, the therapeutic value of supraclavicular lymph node dissection remains unclear. We believe this report to be the largest series of patients treated with esophagectomy and supraclavicular node dissection for esophageal cancer. This large database would have value in the revision of staging as great as that of the Worldwide Esophageal Cancer Collaboration data.

One potential criticism of the present study is that most patients (97.7%) had squamous cell carcinomas, and only a few had adenocarcinomas. In recent decades, a dramatic increase in the incidence of adenocarcinoma has been seen in Western patients.¹⁹⁻²¹ However, in Asian patients, including Japanese patients, squamous cell carcinoma remains the predominant type of esophageal cancer.^{26,27} The TNM staging system should be relevant to patients in Asia, as well as patients in the United States and Europe. With the limitations of the small number of patients with adenocarcinoma in Japan and the small number of patients undergoing supraclavicular dissection in Western countries, analysis of adenocarcinoma is difficult.

Study Limitations

Because the study was based on a multi-institutional, nationwide registry, it has limitations and biases. The selection of patients and indication for supraclavicular node dissection were not specified; however, more than 1300 patients treated with supraclavicular node dissection over 3

years were analyzed. The short period of the study overcomes the diagnostic and therapeutic variations in the previous historical studies with a long duration from a single institution.

CONCLUSIONS

The survival benefit of dissection of metastases to the supraclavicular lymph nodes was indicated in patients with thoracic esophageal carcinoma. Supraclavicular nodes appear to be regional nodes similar to other regional nodes and celiac axis nodes.

This registry complies with the Act for the Protection of Personal Information that was promulgated in 2003 and follows the ethical guidelines for epidemiologic studies published jointly by the Japan Ministry of Science, Culture, and Education and the Japan Ministry of Health, Labor and Welfare in 2002, which was revised in 2007.

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