Association of Location of Lymph Node Metastases with Postoperative Recurrence of Esophageal Squamous Cell Carcinoma

HIROAKI TANAKA, MASAICHI OHIRA, NAOSHI KUBO, KAZUYA MUGURUMA, YOSHITO YAMASHITA, TETSUJI SAWADA and KOSEI HIRAKAWA

Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan

Abstract. *Lymph node (LN) metastasis in patients with esophageal squamous cell carcinoma (ESCC) has important prognostic implications. In this study, we examined the association between postoperative recurrence and the location of LN metastases in patients with clinical stage II/III ESCC. Of 90 patients who underwent curative esophagectomy with systemic lymphadenectomy at our Department between 2000 and 2007, we identified 49 recurrences and 37 deaths during follow-up. UICC pathological stage, pathological intramural metastasis, total number of LN metastases, and number of involved LNs in upper paraesophageal, subcarinal, lower paraesophageal, post mediastinal, perigastric, and celiac locations were significantly associated with recurrence-free survival (RFS) in univariate analysis. In multivariate analysis, the number of involved subcarinal and lower paraesophageal LNs were independent factors predictive of postoperative recurrence. Our findings suggest that patients with LN metastases at these locations are at risk of recurrence and should be considered for more aggressive adjuvant therapies.*

Although there have been recent improvements in surgical procedures, the overall prognosis for patients with esophageal squamous cell carcinoma (ESCC) remains poor, with 5-year survival rates of 5-45% even after curative resection (1, 2). Analysis of survival and disease-free survival curves showed that more than 30% of patients who underwent R0 resection developed recurrence within a year (3-5). Surgical resection is generally considered as the best treatment for clinical stage II/III ESCC, although one report indicated that approximately 40-50% of patients develop fatal hematogenous recurrence after curative resection (6). Thus, accurately predicting the risk of recurrence and choosing an appropriate postoperative therapeutic strategy is very important for high-risk patients. Some prognostic factors after surgery are known, such as depth of tumor, tumor length, pathological stage and percentage of involved lymph nodes (LNs) (7, 8). LN metastasis was reported to be an important independent factor in predicting the prognosis of patients with ESCC who had undergone surgical resection (9, 10). However, there has been controversy regarding the significance of the location of LN metastases in patients who were treated with surgery only. Moreover, it remains uncertain whether the location of LN metastases affects outcomes after preoperative therapy. Therefore, we investigated whether the recurrence of clinical stage II/III ESCC after curative resection is influenced by the location of LN metastases.

Correspondence to: Hiroaki Tanaka, Department of Surgical Oncology, Osaka City University Graduate School of Medicine, 1-4-3, Asahimachi, Abeno-ku, Osaka 545-8585, Japan. Tel: +81 666453838, Fax: +81 666466450, e-mail: hiroakitan@med.osaka-cu.ac.jp

Key Words: Esophageal cancer, recurrence, lymph node location, subcarinal lymph node, lower paraesophageal lymph node.

Patients and Methods

Patients and clinical data. The retrospective analysis included 90 patients who presented with ESCC at the Department of Surgical Oncology in Osaka City University Hospital between January 2000 and December 2007. Inclusion in the study was limited to patients who had clinical stage II/III (UICC International Union Against Cancer TNM classification of malignant tumor) tumors, excluding T4, and who had been offered surgery without preoperative treatment. The main procedures for staging included chest X-ray, upper gastrointestinal endoscopy, and enhanced computed tomography of the neck, thorax and abdomen. Two types of systematic lymphadenectomy were performed, two-field and three-field. Two-field lymphadenectomy was performed for limited lower thoracic or abdominal esophageal cancer. Seven LN locations were defined, according to the Japanese Classification of Esophageal Cancer (11). All nodal material was dissected separately from the specimen by the surgeon and analyzed by pathologists. Histologic staging was based on the pathological TNM classification (12).

Statistical analysis. All statistical analyses used SPSS II for Windows (SPSS Inc., Chicago, IL, USA). Univariate logistic regression was used to explore the predictive utility of the number of LN metastases with defined recurrent disease. Cox regression models were used to evaluate the association between clinicopathological features and recurrence-free survival (RFS). Any variable that attained a significance of $p<0.05$ was entered into multivariate analysis. Survival was calculated from the date of surgery by the Kaplan Meier method, and groups were compared by log-rank test. Significance was defined as $p<0.05$ throughout the study.

Results

Patient characteristics. From January 2000 to December 2007, 90 patients were identified with clinical stage II/III ESCC. The patients were 70 men and 20 women with a mean age of 63.5 years. All patients underwent R0 esophagectomy and regional systematic lymphadenectomy without preoperative therapy. Two-field lymphadenectomies were performed in 24 patients and three-field lymphadenectomies in 66 patients. Nineteen patients (21%) had thoracotomies assisted by thoracoscopy as a component of their surgical management. The median follow-up time for patients who survived was 42 months (range 8-115 months). The overall 5-year survival rate for the entire cohort was 41.4%.

Conventional risk factors for recurrence. Of the 90 patients, 49 were found to have recurrent disease. The cumulative 1- and 2-year recurrence rates were 33% and 51%, respectively (Figure 1A). The median time to recurrence from surgical resection was 12 months. The 5-year overall survival rate for patients with recurrence was 14.5% (Figure 1B). Various recurrent lesions were observed in this cohort. In the recurrence group of 49 patients, LN recurrences were observed in 18 patients, distant metastasis in 14 patients and both together in 17 patients. There were no significant associations between the recurrent lesion and location of LN metastases. The general characteristics of patients who did and did not experience recurrent disease are shown in Table I. Univariate analysis revealed no significant differences in RFS in terms of age, sex, cancer history, tumor location, pathological differentiation, UICC TNM stage, and vascular invasion. However, significant differences were observed in relation to UICC pathological stage, intramural metastasis and postoperative therapy.

Impact of the location of disease-positive LNs on recurrence. The association between the number of LN metastases and recurrence is shown in Table II. The mean number of LNs removed in 90 patients was 60.2 (range 15-112) and the mean number of LN metastases was 3.5 (range 0-15). In the recurrence group, the mean number of LN metastases was 4.6 and the percentage of patients with LN metastasis was 85.7%; corresponding values in the no-recurrence group

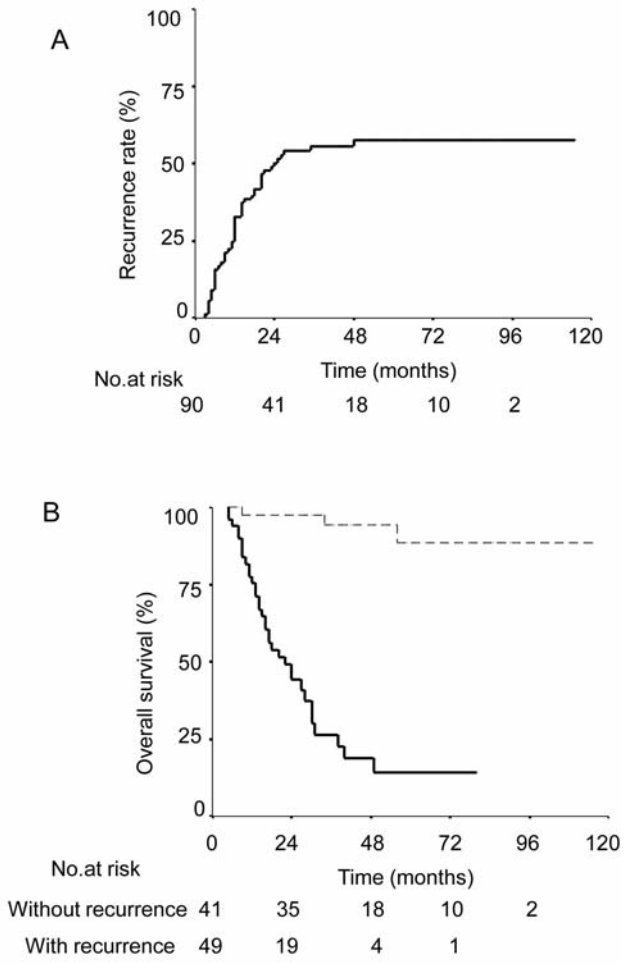

Figure 1. *A: Recurrence rate for the 90 patients who underwent R0 resection for esophageal squamous cell carcinoma. Of the 90 patients, 49 had recurrent disease.The mean recurrence-free survival time was 13.4 months. B: Overall survival rate of patients with and without recurrence. The survival of patients with recurrence (solid line) was significantly worse than that of those without recurrence (dashed line) (log-rank test, p<0.001). The number of subjects at risk at each time interval is shown in the table below the graph.*

were 2.0 and 70%, respectively ($p<0.05$). Both groups had a similar metastasis profile, which involved three fields. However, there were some differences in metastasis location between the two groups. Cox univariate regression analysis of RFS demonstrated that the total number of LN metastases and location in the upper paraesophageal, subcarinal, lower paraesophageal, postmediastinum, perigastric, and celiac regions were significantly associated with RFS. However, these significant locations were not associated with organs of recurrence (Table III).

Multivariate analysis. In a multivariate analysis, including pathological stage and intramural metastasis, the number of

Table I. *Chracteristics of the 90 patients studied and association with recurrence.*

Charateristics	Recurrence	Non-recurrence	*p*-Value
No. of patients	49	41	
Age, years	63.1±8.2	63.2±7.8	0.964
Gender			
Male/female	38/11	32/9	0.895
History of other cancer			
Yes/no	39/10	34/7	0.447
Main tumor location			
Ut/Mt/Lt/Ae	5/22/14/8	6/14/15/6	0.997
Tumor length (cm)	5.0±1.3	5.1±2.0	0.55
Differentiation			
Well/moderate/poor	7/18/24	5/20/16	0.235
UICC pTNM			
T1/T2/T3/T4	2/5/41/1	1/13/26/1	0.228
N0/N1	7/42	12/29	0.078
M0/M1a/M1b	38/2/9	34/4/3	0.186
UICC pStage			
IIa/IIb/III/IVa/IVb	6/4/28/2/9	11/7/16/4/3	0.022
Vascular invasion			
ly0/ly1/ly2/ly3	6/16/21/6	4/20/14/3	0.225
v0/v1/v2/v3	27/14/5/3	27/12/2/0	0.074
Intramural metastasis			
Positive/negative	7/42	1/40	0.046
Postoperative therapy			
Yes/no	41/8	25/16	0.043

Table II. *Association of site of lymph node (LN) metastases with recurrence.*

	Recurrence (n=49) % of metastasis	Non-recurrence (n=41) % of metastasis	*p*-Value
Total LN metastases	4.6±3.2	2.0±2.8	<0.001
Site of LN metastases			
Cervical paraesophageal	12.2%	4.9%	0.459
Supraclavicular	12.2%	12.2%	0.741
Upper paraesophageal	16.3%	2.4%	<0.001
Paratracheal	40.8%	24.3%	0.113
Subcarinal	14.2%	0.0%	<0.001
Middle paraesophageal	24.4%	4.9%	0.834
Main bronchus	10.2%	0.0%	0.045
Lower paraesophageal	26.5%	4.9%	<0.001
Supradiaphragm	6.1%	4.9%	0.449
Postmediastinal	8.1%	0.0%	0.001
Perigastric	61.2%	43.9%	0.014
Celiac	10.2%	2.4%	0.028
Total cervical metastases	20.4%	14.6%	0.506
Total thoracic metastases	67.3%	34.1%	0.001
Total abdominal metastases	63.2%	48.9%	0.010

Table III. *Distribution of lymph node (LN) metastases and region of recurrence of esophageal squamous cell carcinoma (no. of patients=49).*

	Regional (n=12) (% of metastasis)	Non-regional (n=37) (% of metastasis)	*p*-Value
Total LN metastases	91.7%	89.1%	0.959
Site of LN metastases			
Cervical paraesophageal	16.7%	10.8%	0.311
Supraclavicular	8.3%	13.5%	0.641
Upper paraesophageal LN	16.7%	16.2%	0.877
Paratracheal LN	50.0%	37.8%	0.513
Subcarinal LN	8.3%	16.2%	0.427
Middle paraesophageal LN	8.3%	29.7%	0.167
Main bronchus LN	16.7%	8.1%	0.538
Lower paraesophageal LN	33.3%	24.3%	0.208
Supradiaphragm LN	0.0%	8.1%	0.837
Postmediastinal LN	0.0%	10.8%	0.849
Perigastric LN	66.7%	59.5%	0.695
Celiac LN	8.3%	10.8%	0.806
Total of cervical metastasis	25.0%	18.9%	0.342
Total of thoracic metastasis	66.7%	67.6%	0.543
Total of abdominal metastasis	75.0%	59.5%	0.628

subcarinal and lower paraesophageal LN metastases remained significantly correlated with RFS (Table IV). Subcarinal and lower paraesophageal metastases were significantly associated with the total number of LNs involved, and the number in the thoracic, upper paraesophageal and supradiaphragm regions (Table V). In addition, patients with subcarinal and lower paraesophageal LN metastases had a 1-year RFS of 14% and 23%, respectively, compared with 80% in patients without LN metastases at those locations (Figure 2A and 2B). The overall median survival of patients with either subcarinal or lower paraesophageal LN metastases was 22 months, whereas median survival was not reached for patients without metastases at these locations (Figure 2C).

Discussion

This study retrospectively demonstrated that the presence of subcarinal and lower parasesophageal LN metastases were independent predictors for postoperative recurrence in patients with resectable ESCC. The median RFS of patients with subcarinal or lower esophageal LN metastases was only 9 months after surgical resection. Moreover, the number of LN metastases at these locations was significantly associated with the total number of LN metastases, which has been recognized as an independent factor of prognosis in esophageal carcinoma. Therefore, our results indicate that the presence of subcarinal LN metastases could be as significant as the M category of the TNM classification.

Complete resection plus adjuvant chemotherapy is the standard treatment in Japan for clinical stage II/III ESCC

Table IV. *Risk factors for recurrence of esophageal squamous cell carcinoma (multivariate analysis).*

Factor	HR	95% CI	*p*-Value
Intramural metastasis	1.69	0.56-5.12	0.353
UICC pStage	1.25	0.83-1.87	0.281
Location of LN metastases			
Upper paraesophageal	1.05	0.33-3.28	0.937
Subcarinal	2.72	1.19-6.25	0.018
Main bronchus	1.45	0.81-2.62	0.211
Lower paraesophageal	1.45	1.03-2.04	0.032
Postmediastinal	1.69	0.64-4.45	0.287
Perigastric	0.97	0.36-2.63	0.952
Celiac	0.67	0.12-3.73	0.648
Total no. of thoracic LN metastases	1.20	0.66-2.21	0.547
Total no. of abdominal LN metastases	1.31	0.44-3.84	0.628
Total no. of LN metastases	0.87	0.48-1.57	0.641

CI: Confidence interval; HR: hazard ratio.

Table V. *Characteristics of patients with metastases in subcarinal or lower paraesophageal regions.*

	Metastases (+) (% of metastasis)	Metastases (–) (% of metastasis)	*p*-Value
No. of patients	18	72	
Total LN metastases	6.2±3.1	2.8±3.2	0.002
Site of LN metastases			
Cervical paraesophageal	11.1%	8.3%	1.000
Supraclavicular	5.5%	18.1%	0.921
Upper paraesophageal	22.0%	6.9%	0.042
Paratracheal	44.4%	30.5%	0.638
Middle paraesophageal	38.9%	9.7%	0.514
Main broncus	16.7%	2.7%	0.175
Supradiaphragm	16.7%	2.7%	0.042
Postmediastinal	5.6%	4.2%	0.528
Perigastric	72.2%	48.6%	0.153
Celiac LN	16.7%	4.2%	0.078

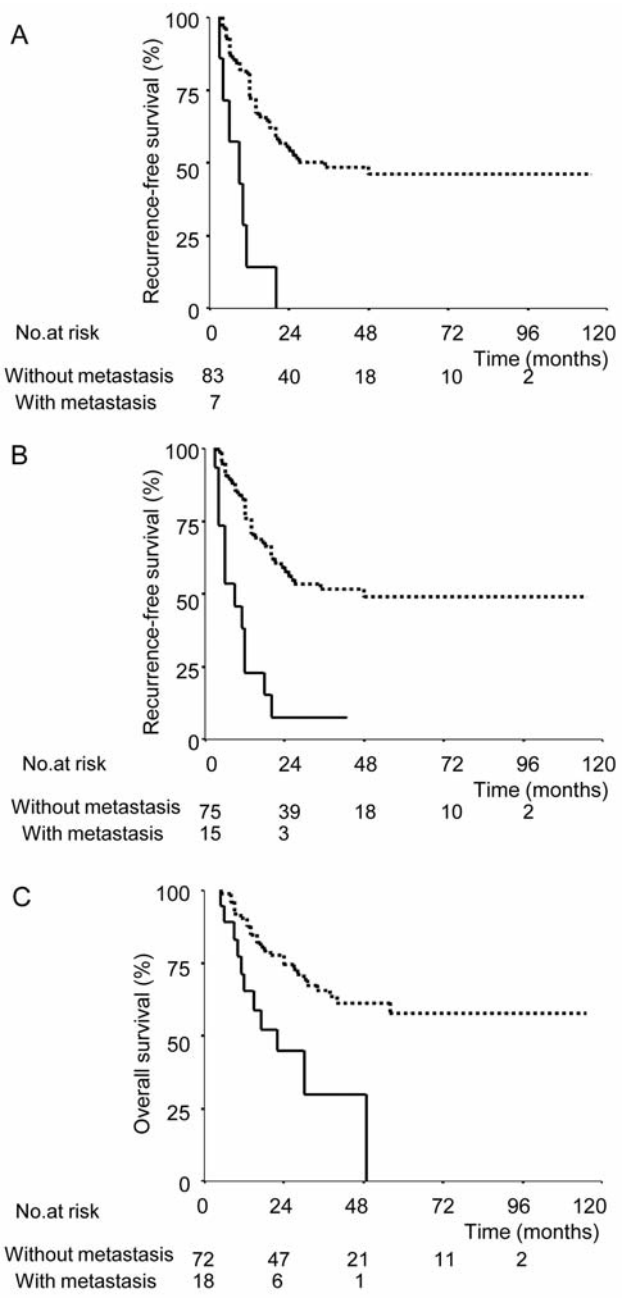

Figure 2. *Recurrence-free survival of patients with subcarinal metastasis (A) and lower paraesophageal metastasis (B). Survival was significantly better for patients without LN metastasis (dashed lines) (p<0.001). C: The overall survival rate was significantly worse for patient who had metastases (solid lines) in either the subcarinal or lower paraesophageal region (p<0.001).*

(13). Perioperative chemoradiotherapy has recently been reported to improve progression-free and overall survival in resectable ESCC (14-16). Patients with ESCC often have recurrent metastatic disease after curative resection despite multimodal therapy including chemotherapy and chemoradiotherapy (17). More accurate preoperative staging is needed in determining the most suitable therapy in clinical stage II/III ESCC. Thus, we limited this study to the subgroup of patients who underwent systemic lymphadenectomy without any preoperative therapy. Esophageal cancer recurs in almost half of all patients with stage II-III ESCC patients who undergo curative resection, with a 5-year overall survival rate of 42-47% (2, 11, 18). In this study, the incidence of recurrence was 50%, with a median follow-up of 42 months and the 5-year overall survival rate was 50.6%, values which are within the acceptable range. Pathological TNM classification is the current gold standard for predicting

outcome. In our univariate analysis, the risk factors for recurrence were pathological TNM stage, intramural metastasis and total number of LN metastases. Because of the close association between depth of invasion and LN involvement, depth of tumor is not an independent prognostic factor. Our results are consistent with previous reports evaluating the prognostic significance of the number of LN metastases in esophageal cancer (8,19,20). However, to the best of our knowledge, few reports have analyzed the impact of the location of LN metastases on ESCC recurrence. A previous study showed the number and location of LN metastases to be prognostic variables (21). Lee *et al*. reported that patients with esophageal cancer with nonregional nodal metastasis had a 5-year survival of 25%; this included those who had complete surgical resection (22). However, analysis of LN metastasis location in that study showed that only M1a nodes were important and found no correlation between the number and location of LNs. Here, we observed no significant association between M0 and M1a or M1b in recurrence of ESCC. On the other hand, our results are consistent with a previous report that showed non-paraesophageal metastasis (such as subcarinal, main bronchial, and postmediastinal) to be significant in patients with thoracic nodal metastasis of ESCC (8).

In Japan, three-field LN dissection has been shown to improve the outcome of ESCC. Nevertheless, the effect of extended lymphadenectomy on improving survival is controversial. Our findings showed no association between cervical LN metastasis and RFS, suggesting that it might be possible to omit lymphadenectomy of this region in patients with middle and lower thoracic esophageal cancer.

There are several limitations to our study. Our cohort of patients was small, as they all came from a single hospital. Moreover, many patients in this cohort did not undergo a positron-emission tomographic scan in preoperative staging, subject to a prereferral selection bias. Large multicenter studies incorporating both preoperative diagnosis and surgical resections are necessary to confirm our findings.

In conclusion, metastasis in the subcarinal and lower paraesophageal lymph region was an independent predictive factor for recurrence of ESCC following curative resection. To improve the survival of patients with metastases in these regions, more accurate multimodal preoperative staging is necessary and more aggressive postoperative therapies should be considered.

References

1 Lv J, Cao XF, Zhu B, Ji L, Tao L and Wang DD: Effect of neoadjuvant chemoradiotherapy on prognosis and surgery for esophageal carcinoma. World J Gastroenterol *15*: 4962-4968, 2009.

2 Liu W, Zhang X and Sun W: Developments in treatment of esophageal/gastric cancer. Curr Treat Options Oncol *9*: 375-387, 2008.

3 Kosugi S, Kanda T, Yajima K, Ishikawa T and Hatakeyama K: Risk factors that influence early death due to cancer recurrence after extended radical esophagectomy with three-field lymph node dissection. Ann Surg Oncol *18*: 2961-2967, 2011.

4 Mal F, Perniceni T, Levard H, Denet C, Validire P and Gayet B: Pre-operative predictive factors of early recurrence after resection of adenocarcinoma of the esophagus and cardia. Gastroenterol Clin Biol *29*: 1275-1278, 2005.

5 Sano A, Kato H, Sakurai S, Sakai M, Tanaka N, Inose T, Saito K, Sohda M, Nakajima M, Nakajima T and Kuwano H: CD24 expression is a novel prognostic factor in esophageal squamous cell carcinoma. Ann Surg Oncol *16*: 506-514, 2009.

6 Yu E, Tai P, Malthaner R, Stitt L, Rodrigues G, Dar R, Yaremko B, Younus J, Sanatani M, Vincent M, Dingle B, Fortin D and Inculet R: What are the factors that predict outcome at relapse after previous esophagectomy and adjuvant therapy in high-risk esophageal cancer? Curr Oncol *17*: 46-51, 2010.

7 Kranzfelder M, Buchler P, Lange K and Friess H: Treatment options for squamous cell cancer of the esophagus: a systematic review of the literature. J Am Coll Surg *210*: 351-359, 2010.

8 Shimada H, Okazumi S, Matsubara H, Nabeya Y, Shiratori T, Shimizu T, Shuto K, Hayashi H and Ochiai T: Impact of the number and extent of positive lymph nodes in 200 patients with thoracic esophageal squamous cell carcinoma after three-field lymph node dissection. World J Surg *30*: 1441-1449, 2006.

9 Akutsu Y, Shuto K, Kono T, Uesato M, Hoshino I, Shiratori T, Isozaki Y, Akanuma N, Uno T and Matsubara H: The number of pathologic lymph nodes involved is still a significant prognostic factor even after neoadjuvant chemoradiotherapy in esophageal squamous cell carcinoma. J Surg Oncol, 2011.

10 Hsu WH, Hsu PK, Hsieh CC, Huang CS and Wu YC: The metastatic lymph node number and ratio are independent prognostic factors in esophageal cancer. J Gastrointest Surg *13*: 1913-1920, 2009.

11 Fujita H, Sueyoshi S, Tanaka T, Fujii T, Toh U, Mine T, Sasahara H, Sudo T, Matono S, Yamana H and Shirouzu K: Optimal lymphadenectomy for squamous cell carcinoma in the thoracic esophagus: comparing the short- and long-term outcome among the four types of lymphadenectomy. World J Surg *27*: 571-579, 2003.

12 Rice TW, Rusch VW, Ishwaran H and Blackstone EH: Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. Cancer *116*: 3763-3773, 2010.

13 Ando N, Iizuka T, Ide H, Ishida K, Shinoda M, Nishimaki T, Takiyama W, Watanabe H, Isono K, Aoyama N, Makuuchi H, Tanaka O, Yamana H, Ikeuchi S, Kabuto T, Nagai K, Shimada Y, Kinjo Y and Fukuda H: Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study – JCOG9204. J Clin Oncol *21*: 4592-4596, 2003.

14 Berger AC, Farma J, Scott WJ, Freedman G, Weiner L, Cheng JD, Wang H and Goldberg M: Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. J Clin Oncol *23*: 4330-4337, 2005.

15 Motoori M, Yano M, Ishihara R, Yamamoto S, Kawaguchi Y, Tanaka K, Kishi K, Miyashiro I, Fujiwara Y, Shingai T, Noura S, Ohue M, Ohigashi H, Nakamura S and Ishikawa O: Comparison Between Radical Esophagectomy and Definitive Chemoradiotherapy in Patients with Clinical T1bN0M0 Esophageal Cancer. Ann Surg Oncol, 2012.

16 Lv J, Cao XF, Zhu B, Ji L, Tao L and Wang DD: Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. World J Gastroenterol *16*: 1649-1654, 2010.

17 Stahl M, Lehmann N, Walz MK, Stuschke M and Wilke H: Prediction of prognosis after trimodal therapy in patients with locally advanced squamous cell carcinoma of the oesophagus. Eur J Cancer, 2012.

18 Saeki H, Morita M, Nakashima Y, Sonoda H, Hashimoto K, Egashira A, Oki E, Ohga T, Kakeji Y and Maehara Y: Neoadjuvant chemoradiotherapy for clinical stage II-III esophageal squamous cell carcinoma. Anticancer Res *31*: 3073-3077, 2011.

19 Greenstein AJ, Litle VR, Swanson SJ, Divino CM, Packer S and Wisnivesky JP: Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. Cancer *112*: 1239-1246, 2008.

20 Peyre CG, Hagen JA, DeMeester SR, Altorki NK, Ancona E, Griffin SM, Holscher A, Lerut T, Law S, Rice TW, Ruol A, van Lanschot JJ, Wong J and DeMeester TR: The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg *248*: 549-556, 2008.

21 Rizk N, Venkatraman E, Park B, Flores R, Bains MS and Rusch V: The prognostic importance of the number of involved lymph nodes in esophageal cancer: implications for revisions of the American Joint Committee on Cancer staging system. J Thorac Cardiovasc Surg *132*: 1374-1381, 2006.

22 Lee PC, Port JL, Paul S, Stiles BM and Altorki NK: Predictors of long-term survival after resection of esophageal carcinoma with nonregional nodal metastases. Ann Thorac Surg *88*: 186-192; discussion 192-183, 2009.

Received March 14, 2012
Revised April 23, 2012
Accepted April 25, 2012