CURRENT ONCOLOGY

ORIGINAL ARTICLE

Computed tomography–based distribution of involved lymph nodes in patients with upper esophageal cancer

M. Li PhD,* Y. Liu MD,† L. Xu PhD,† Y. Huang MD,† W. Li MD,† J. Yu PhD,* and L. Kong MD*

ABSTRACT

Background Delineating the nodal clinical target volume (CTVN) remains a challenging task in patients with cervical or upper thoracic esophageal carcinoma (EC). In particular, the extent of the lymph area that should be included in the irradiation field remains controversial. In the present study, the extent of the CTVN was determined based on the incidence of lymph node involvement mapped by computed tomography (CT) imaging.

Methods Our study included 468 patients who were diagnosed with cervical and upper thoracic EC and who received staging information between June 2005 and April 2011. The anatomic distribution of metastatic regional lymph nodes was mapped using CT images and grouped using the levels established by the Radiation Therapy Oncology Group. The probability of the various groups being involved was examined. If a lymph node group had a probability of 10% or more of being involved, it was considered at high risk for metastasis, and elective treatment as part of the CTVN was recommended.

Results Lymph node involvement was mapped by CT in 256 patients (54.7%). Not all lymph node groups should be included in the CTVN. For cervical lesions, the involved lymph nodes were located mainly between the hyoid bone and the arcus aortae; the recommended CTVN should consist of the neck lymph nodes at levels III and IV (supraclavicular group) and thoracic groups 2 and 3P. In upper thoracic EC patients, most of the involved lymph nodes were distributed between the cricoid cartilage and the subcarinal area; the CTVN should cover the supraclavicular group and thoracic nodal groups 2, 3P, 4, 5, and 7.

Conclusions Our CT-based study indicates a specific distribution and incidence of metastatic lymph node groups in patients with cervical and upper thoracic EC. The results suggest that regional lymph node groups should be electively included in the CTVN for precise radiation administration.

Key Words Esophageal squamous cell carcinoma, lymph node metastasis, computed tomography, radiation, clinical target volume

Curr Oncol. 2015 June;22(3):e178-e182 www.current-oncology.com

BACKGROUND

Esophageal carcinoma (EC) is the 8th most common cancer worldwide and the 6th most common cause of cancer-related mortality[1]. Cervical and upper thoracic lesions account for approximately 15% of all ECs. A complicated anatomy limits the surgical procedures that can be used for these lesions[2]. Definitive radiotherapy or chemoradiotherapy are options for advanced EC patients[3]. However, delineating the nodal clinical target volume (CTVN) for EC remains a challenging task.

The esophagus is marked by a rich network of lymphatic vessels that facilitate tumour spread longitudinally, radially, and to lymph nodes far from the primary tumour. The relative risk of nodal metastases at specific nodal locations is suggested to depend on the site of the primary tumour. The recommended elective CTVN for treatment of upper EC includes the supraclavicular lymph nodes and the para-esophageal lymph nodes of the upper mediastinum[4,5]. Those data are helpful for delineating the CTVN in radiotherapy, but technologic advances in radiation treatment (for example, three-dimensional conformal

Correspondence to: Minghuan Li or Li Kong, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jiyan Road 440, Jinan, Shandong Province 250117 PR China.
E-mail: sy_lmh2001@163.com or kongli7@sina.com ■ **DOI:** http://dx.doi.org/10.3747/co.22.2365

radiotherapy and intensity-modulated radiotherapy) have progressively changed such practices. Optimal conformal radiation therapy requires precise target identification and delineation to minimize toxicity. Most surgical studies thus far have provided information about nodal metastasis in a certain region (neck; upper, middle, or lower mediastinum; abdominal area) rather than in a specific lymph node group in patients with EC, which might not be adequate for delineating the CTVN for conformal irradiation. We thought that a careful choice of the nodal sites or groups to be included in the CTVN is important when determining the precise radiation target volume.

Several modalities—CT, endoscopic ultrasonography, and positron-emission tomography—have been used in diagnosing and staging EC patients[6,7]. The mainstay for staging EC has been CT, which is commonly applied to determine the extent of local invasion, lymph node malignancy, or distant metastasis. With respect to radiation treatment, CT also provides information about the densities of various tissues, which is essential to obtaining dose distributions in treatment planning systems.

In the present study, we used CT images to evaluate the anatomic distribution of involved lymph nodes in newly diagnosed patients with cervical and upper thoracic EC. We aimed to elucidate the distribution of metastatic lymph nodes according to the Radiation Therapy Oncology Group's definition of lymph node groups, which could be helpful in determining the CTVN for precise radiation therapy in patients with upper EC.

METHODS

Patients

Between June 2005 and April 2011, more than 3000 patients with esophageal lesions underwent CT imaging in the CT centre of the Shandong Cancer Hospital and Institute. We retrospectively analyzed patients who had cervical and upper thoracic EC without distant metastasis at diagnosis. Esophageal lesions in the reviewed patients were assessed and characterized using examinations that included esophagography, endoscopy, CT imaging, and for some patients, combined positron-emission tomography–CT and endoscopic ultrasonography. Patients were excluded if they had any history of other malignant tumours. The institutional review board approved the study.

CT Diagnosis of Metastatic Nodes

The cervical esophagus begins at the level of the lower margin of the cricoid cartilage and ends at the thoracic inlet. The thoracic esophagus extends from the thoracic inlet to the gastroesophageal junction and is subdivided into 3 parts. On CT images, the planes through the upper border of the suprasternal notch, the azygos vein, and the lower left pulmonary vein serve as the anatomic borders separating the parts. If the EC lesion extended more than 1 cm into an adjacent segment, the patient was excluded. Esophagography and endoscopy were performed to determine the presence, location, and length of the EC lesion.

All reviewed patients underwent dedicated neck, chest, and upper abdominal CT imaging with contrast to assess the extent of circumferential lymph node involvement and the locoregional lymph node status. A slice thickness of 5 mm was used. Based on the American Joint Committee on Cancer staging system (7th edition), a regional lymph node includes any para-esophageal lymph node extending from the cervical lymph nodes to the celiac lymph nodes. Lymph nodes were classified into groups according to the mapping system for EC proposed by the Radiation Therapy Oncology Group[8,9].

In thoracic malignant disease, most CT studies have recorded the short-axis diameter of nodes, because that measurement is the most reproducible[6,7,10]. In our CT centre, lymph nodes with a short-axis diameter greater than 10 mm in EC images are generally considered to be metastatic. Other criteria, including the nodal enhancement pattern, the number of nodes, extranodal tumour extension, and the presence of necrosis are also used to assess nodes.

RESULTS

Our study identified 97 patients with cervical EC and 371 patients with upper thoracic EC without distant metastasis. Of those patients, 84% had a histologic diagnosis of squamous cell carcinoma, and 16% were diagnosed with nonspecific carcinoma. At diagnosis, 256 patients (54.7%) showed regional lymph node involvement on CT imaging, including 51 with cervical EC and 205 with upper thoracic EC. The rates of metastatic regional node involvement were 52.6% and 55.3% for cervical and upper thoracic EC respectively. In those patients, the number of the affected lymph node groups ranged from 0 to 7 (median: 1). Table I shows the clinical characteristics of the patients.

TABLE I Characteristics of the study patients

Characteristic	Location of EC lesion	
	Cervical	Upper thoracic
Patients (*n*)	97	371
Sex (*n*)		
Men	81	282
Women	16	89
Age (years)		
Median	58	60
Range	37–83	36–85
Histologic grade (*n*)		
I	33	76
II	45	154
III	12	71
NOS	7	70
Length (cm)		
Median	3.5	4
Range	1.5–5.5	1.5–7.5
Clinical stage (*n*)		
T1–3	79	299
T4	18	72
N0	46	166
N+	51	205

EC = esophageal cancer; NOS = not otherwise specified.

Distribution of Involved Lymph Node Groups

First, we assessed the regional distribution (neck, mediastinum, and abdomen) and incidence of lymph node metastasis. For patients with cervical EC, the proportions of lymph node involvement in the neck (levels II, III, and the supraclavicular lymph nodes) was 39.2%; in the upper mediastinum (groups 2–6), 38.1%; in the mid- to lower mediastinum (groups 7–10), 3.1%; and in the abdominal cavity (groups 15–20), 2.1%. For patients with upper thoracic EC, the percentages were 21.8%, 49.3%, 16.7%, and 3.2% respectively [Table II, Figure 1(A,B)].

We further evaluated in detail the lymph node involvement frequency for each lymph node group. In patients with cervical lesions, the lymph node spread affected mainly the neck lymph nodes (14.43% at level III and 30.9% in the supraclavicular group) and also those at the highest level in the upper mediastinum (above the arcus aortae: 11.34% in group 2 and 23.7% in group 3P). The lower paratracheal (8.3%), aortopulmonary (8.3%), anterior mediastinal (7.2%), subcarinal (3.1%), and lower mediastinal (0%) groups were less frequently affected [Figure 2(A)]. Among patients with upper thoracic EC, the peri-esophageal (39.1%) and supraclavicular (20.5%) groups showed the highest involvement. Involvement rates were 13.8%, 12.1%, and 17.5% for groups 2, 4, and 5 respectively. Lymph node involvement was less frequent in the subcarinal area (12.9%), the middle-lower mediastinal group (3.2%), and the abdominal group (3.2%). The probabilities for involvement of the upper-neck lymph nodes (2.2%) and the anterior mediastinal group (5.7%) were also lower [Figure 2(B)]. Table III shows the full results.

TABLE II Distribution and incidence of involved lymph nodes, by region

Lymph node region	Patients [*n* (%)] with EC lesion	
	Cervical (*n*=97)	Upper thoracic (*n*=371)
Neck (levels II and III and group 1)	38 (39.2)	81 (21.8)
Upper mediastinum (groups 2–6)	37 (38.1)	183 (49.3)
Mid- to lower mediastinum (groups 7–10)	3 (3.1)	62 (16.7)
Abdomen (groups 15–20)	2 (2.1)	12 (3.2)

EC = esophageal cancer.

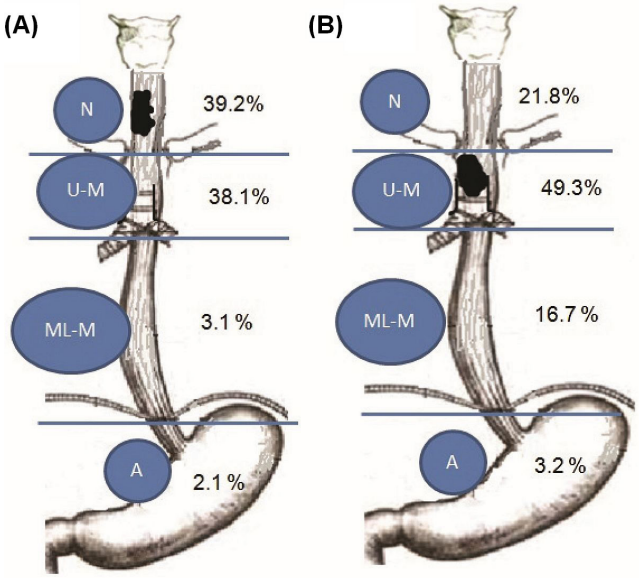

FIGURE 1 Regional distribution and incidence of lymph node metastasis for (A) cervical and (B) upper thoracic esophageal carcinoma. N = neck; U-M = upper mediastinum; ML-M = middle-lower mediastinum; A = abdomen.

Suggested CTVn for Cervical and Upper Thoracic EC

In the present study, when the probability of a lymph node group being affected by nodal metastasis was 10% or greater, we recommended that group's elective inclusion in the CTVn. For the cervical esophagus, the elective node groups should include level III, the supraclavicular group, and thoracic groups 2 and 3P [Figure 2(A)]. For the upper thoracic esophagus, elective treatment should cover the supraclavicular group and thoracic groups 2, 3P, 4, 5, and 7 [Figure 2(B)].

DISCUSSION

Together with surgery and chemotherapy, radiotherapy represents a main treatment modality for EC. The central aim of the present study was to use CT data to characterize involved lymph node distribution, and to use that evidence to suggest contours that could potentially reduce the CTVn.

Most studies report that the neck and upper mediastinum are the regions most commonly affected by nodal metastasis in patients with upper EC[11–13]. The present study

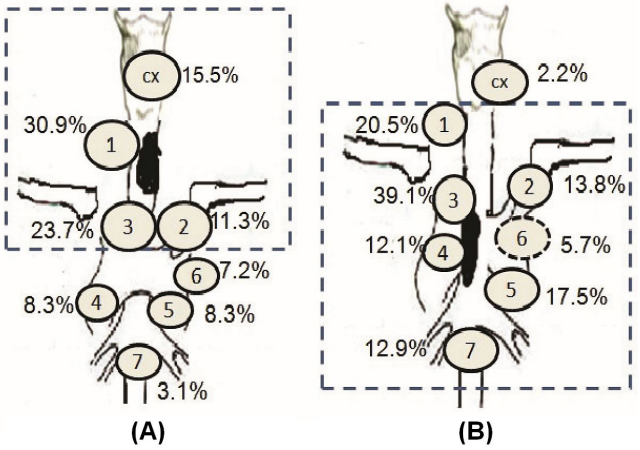

FIGURE 2 Distribution and incidence of involved lymph node groups for (A) cervical and (B) upper thoracic esophageal carcinoma. In cervical lesions, nodal spread occurs mainly in the neck group and the highest mediastinum (above the arcus aortae)—that is, the cervical lymph nodes of levels II and III and groups 1–3. In upper thoracic lesions, involvement is confined mainly to the nodes between the supraclavicular level and the subcarinal area (groups 1–5 and 7). CX = neck nodes of levels II and III.

TABLE III Distribution and incidence of involved lymph node groups, by RTOG classification

Node classification	Description	Patients [*n* (%)] with EC lesion	
		Cervical	Upper thoracic
Level II	Upper jugular	1 (1.0)	0
Level III	Middle jugular	14 (14.4)	8 (2.2)
Group 1	Supraclavicular	30 (30.9)	76 (20.5)
Group 2 R/L	Upper paratracheal	11 (11.3)	51 (13.7)
Group 3P	Posterior mediastinal (upper para-esophageal)	23 (23.7)	145 (39.1)
Group 4 R/L	Lower paratracheal	8 (8.2)	45 (12.1)
Group 5	Aortopulmonary	8 (8.2)	65 (17.5)
Group 6	Anterior mediastinal	7 (7.2)	21 (5.7)
Group 7	Subcarinal	3 (3.1)	48 (12.9)
Group 8	Middle para-esophageal	0	10 (2.7)
Group 9	Pulmonary ligament	0	2 (0.5)
Group 10 R/L	Tracheobronchial	0	8 (2.2)
Group 15	Diaphragmatic	0	0
Group 16	Paracardiac	0	2 (0.5)
Group 17	Left gastric arterial	2 (2.1)	10 (2.7)
Group 18	Common hepatic arterial	0	0
Group 19	Splenic arterial	0	0
Group 20	Celiac	0	0

RTOG = Radiation Therapy Oncology Group; EC = esophageal cancer; R/L = right or left.

also demonstrates a correlation between regional lymph node involvement and primary tumour location. In particular, for cervical EC, the most common area of nodal metastasis is the neck (39.2%), followed by the upper mediastinum (38.1%), the mid- to lower mediastinum (3.1%), and the abdominal cavity (2.1%). For upper thoracic lesions, the proportions of lymph node metastasis were 21.8%, 49.3%, 16.7%, and 3.2% for the neck, upper mediastinum, mid- to lower mediastinum, and abdominal cavity respectively. Those data are similar to findings reported in other surgical studies. In a cohort of upper EC patients receiving esophagectomy with 3-field lymph node dissection, Jang *et al.*[12] reported that the nodes of the mediastinum (74.2%) were most commonly affected, followed by the cervical lymph nodes (46.2%) and the abdominal lymph nodes (24.7%). In addition, Huang *et al.*[13] reported that the rate of lymph node metastasis in patients with upper thoracic tumours was 16.7% for cervical, 38.9% for upper mediastinal, 11.1% for middle mediastinal, 5.6% for lower mediastinal, and 5.6% for abdominal lymph nodes.

Metastatic rates for lymph nodes vary in different studies. One reason for that variation could be the difference in T stage (depth of tumour invasion) of the primary tumour. It was reported that the positivity rate for locoregional nodes increases from 0% for intra-epithelial tumours to 31%–56% for T1b, 58%–78% for T2, 74%–81% for T3, and 100% for T4 tumours[14–16].

To achieve an accurate CTVN contour, we assessed the distribution of the involved lymph node groups in detail. In our study, lymph node metastasis in patients with cervical lesions was found mainly in the cervical node group and the upper mediastinum. However, very little nodal involvement was observed for the groups below the arcus aortae. Reports of neck node metastasis from cervical EC are rare. Hirano *et al.*[17] found that mediastinal metastases were more frequent in patients with disease in which cervical EC advances to the upper thoracic esophagus than in patients with cervical EC. In that study, the paraesophageal nodes (23.8%) were most frequently affected, followed by the paratracheal nodes (4.8%). No metastases below the tracheal carina were found in the cervical EC group. Guidelines from the U.S. National Comprehensive Cancer Network[5] recommended that the supraclavicular nodes and the even higher-echelon cervical nodes should undergo elective treatment in cervical EC. Our data show that, besides the cervical nodes, the highest mediastinal lymph nodes were also most commonly affected by nodal metastasis. The inferior border of the target volume should therefore be at the upper rim of the arcus aortae.

For upper thoracic EC, our data show that the supraclavicular lymph nodes should be included at the superior border of the target volume, and the subcarinal lymph nodes at the inferior border. Other lymph node groups located between the superior and inferior borders should also be included in the irradiation target volume. However, the anterior mediastinal group is less likely to be affected. Although we found subcarinal lymph node metastasis to be highly prevalent (12.9%), the lower mediastinal (3.2%) and abdominal (3.2%) groups were less frequently affected. Similar data were found in surgical studies. Jang *et al.*[12] also found that subcarinal lymph node metastasis is present in 15.1% of patients with upper EC. The recurrent laryngeal lymph node chains were the ones reported to be most commonly affected by nodal metastasis. The prevalence of cervical lymph node involvement is also high in surgical patients receiving 3-field dissection. In addition, a correlation between recurrent laryngeal and supraclavicular lymph node metastasis was observed, especially in upper thoracic EC[12,18].

It is difficult to accurately define the radiotherapeutic CTV because the lymph node metastasis rate and the affected node groups vary greatly in patients with EC. The inclusion of all lymph node groups in the irradiation field could lead to better outcomes, but it could also increase treatment-related toxicity. In our study, a lymph node group with a probability of 10% or more of being involved was recommended for elective treatment in the CTVN. Our data show that not all lymph node groups in a region should be included in the CTVN. For example, the anterior mediastinal group was less frequently affected in both cervical and upper thoracic EC. Node groups 4, 5, and 7 should not be included in the elective area for cervical EC. However, frequent node involvement in the subcarinal group was observed in upper thoracic EC. Our data show that, for patients with cervical EC, the CTVN should include the neck lymph nodes at level III, the supraclavicular group, and the thoracic lymph node groups 2 and 3P (upper thoracic and para-esophageal respectively). The supraclavicular and thoracic node groups 2, 3P, 4, 5, and 7 should be included in the CTVN for patients with upper thoracic EC.

Our data detail the distribution of high-risk node groups, which can potentially be used to reduce the target volume that must be irradiated.

Our study has some limitations. First, our findings are based on an interpretation of CT imaging and not on pathology assessments. Microscopic disease can occur in normal-sized lymph nodes, and lymph node enlargement can be caused by benign conditions, limiting the accuracy of CT for interpreting nodal involvement in EC to 39%–85%[10]. In addition, according to a meta-analysis, CT showed 0.50 sensitivity and 0.83 specificity for determining regional lymph node metastasis in thoracic tumours[19]. Second, our study focused on the affected groups (areas) of metastatic lymph nodes rather than on the number of affected lymph nodes. Surgical evaluations have reported that the number of metastatic lymph nodes is a prognostic factor for EC patients. However, the prognostic value of the affected node groups remains controversial. In addition, our study observed only the distribution of metastatic lymph nodes. In fact, elective nodal irradiation should consider tumour T stage, histology, and tumour length, among other factors[15,16]. Despite those limitations, CT is an important and common tool for EC care in nonsurgical patients. In combination with other tools, the clinical staging and target volume can be more precisely determined for EC.

CONCLUSIONS

Safe use of precise radiotherapy to prevent regional lymph node metastasis depends on accurate identification of the CTVn. We used CT imaging to create a probability map that sets out the incidence of nodal involvement by anatomic group in upper EC patients. Our data could be helpful in refining the CTVn and might result in improvements to the target contour during radiation treatment, with decreased treatment-related toxicity.

ACKNOWLEDGMENTS

This work was supported by Natural Science Foundation of Shandong Province (no. ZR2012L35), PRC.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

* Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jinan, PR China; † Department of Radiology, Shandong Caner Hospital and Institute, Jinan, PR China.

REFERENCES

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006;24:2137–50.
2. Koshy M, Esiashvilli N, Landry JC, Thomas CR Jr, Matthews RH. Multiple management modalities in esophageal cancer: epidemiology, presentation and progression, work-up, and surgical approaches. *Oncologist* 2004;9:137–46.
3. Stahl M, Budach W, Meyer HJ, Cervantes A on behalf of the ESMO Guidelines Working Group. Esophageal cancer: clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(suppl 5):v46–9.
4. Minsky BD, Pajak TF, Ginsberg RJ, *et al.* INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002;20:1167–74.
5. International Commission on Radiation Units and Measurements (ICRU). *Prescribing, Recording, and Reporting Photon Beam Therapy.* ICRU report 62 (suppl to ICRU report 50). Bethesda, MD: ICRU; 2000.
6. Lowe VJ, Booya F, Fletcher JG, *et al.* Comparison of positron emission tomography, computed tomography, and endoscopic ultrasound in the initial staging of patients with esophageal cancer. *Mol Imaging Bio*l 2005;7:422–30.
7. Rasanen JV, Sihvo EI, Knuuti MJ, *et al.* Prospective analysis of accuracy of positron emission tomography, computed tomography, and endoscopic ultrasonography in staging of adenocarcinoma of the esophagus and the esophagogastric junction. *Ann Surg Oncol* 2003;10:954–60.
8. Casson AG, Rusch VW, Ginsberg RJ, Zankowicz N, Finley RJ. Lymph node mapping of esophageal cancer. *Ann Thorac Surg* 1994;58:1569–70.
9. Korst RJ, Rusch VW, Venkatraman E, *et al.* Proposed revision of the staging classification for esophageal cancer. *J Thorac Cardiovasc Surg* 1998;115:660–9.
10. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. *Br J Cancer* 2008;12;98:547–57.
11. Chen J, Liu S, Pan J, *et al.* The pattern and prevalence of lymphatic spread in thoracic oesophageal squamous cell carcinoma. *Eur J Cardiothorac Surg* 2009;36:480–6.
12. Jang HJ, Lee HS, Kim MS, Lee JM, Zo JI. Patterns of lymph node metastasis and survival for upper esophageal squamous cell carcinoma. *Ann Thorac Surg* 2011;92:1091–7.
13. Huang W, Li B, Gong H, *et al.* Pattern of lymph node metastases and its implication in radiotherapeutic clinical target volume in patients with thoracic esophageal squamous cell carcinoma: a report of 1077 cases. *Radiother Oncol* 2010;95:229–33.
14. Nishihira T, Sayama J, Ueda H, *et al.* Lymph flow and lymph node metastasis in esophageal cancer. *Surg Today* 1995;25:307–17.
15. Motoyama S, Maruyama K, Sato Y, *et al.* Status of involved lymph nodes and direction of metastatic lymphatic flow between submucosal and T2–4 thoracic squamous cell esophageal cancers. *World J Surg* 2009;33:512–17.
16. Tachimori Y, Nagai Y, Kanamori N, Hokamura N, Igaki H. Pattern of lymph node metastases of esophageal squamous cell carcinoma based on the lymphatic drainage system. *Dis Esophagus* 2011;24:33–8.
17. Hirano S, Nagahara K, Moritani S, Kitamura M, Takagita S. Upper mediastinal node dissection for hypopharyngeal and cervical esophageal carcinomas. *Ann Otol Rhinol Laryngol* 2007;116:290–6.
18. Lerut T, Nafteux P, Moons J, *et al.* Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. *Ann Surg* 2004;240:962–72.
19. de Langen AJ, Raijmakers P, Riphagen I, Paul MA, Hoekstra OS. The size of mediastinal lymph nodes and its relation with metastatic involvement: a meta-analysis. *Eur J Cardiothorac Surg* 2006;29:26–9.