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ORIGINAL ARTICLE

**Yoshiaki Kajiyama · Yoshimi Iwanuma · Natsumi Tomita
Takayuki Amano · Fuyumi Isayama
Toshiharu Matsumoto · Masahiko Tsurumaru**

Size analysis of lymph node metastasis in esophageal cancer: diameter distribution and assessment of accuracy of preoperative diagnosis

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Abstract
Background. In esophageal cancer, lymphatic spread occurs more frequently and at an earlier stage than in other gastrointestinal cancers, and both preoperative and intraoperative diagnoses of lymph nodes metastases are sometimes incorrect. Our objective was to measure the sizes of lymphatic metastases and to examine the accuracy of clinical diagnosis of lymphatic spread in patients with squamous cell carcinoma of the esophagus.
Methods. The sizes of 320 metastatic lymph nodes of 9254 dissected nodes from 92 consecutive esophagectomy patients over 1 year were measured and compared with the sizes of the actual metastases within the nodes. These data allowed investigation of the correct rate of preoperative diagnosis of lymph node metastasis.
Results. The mean diameter of the metastases was 4.8 mm, which was significantly smaller than that of the involved lymph nodes. Among the metastatic lymph nodes, 37.2% were less than 5 mm in diameter, and 63.1% of the metastases were less than 5 mm in diameter. The true-positive and true-negative diagnosis rate for all lymph node stations in three fields (neck, thorax, and abdomen) was only 23.2%, and the false-negative rate for diagnosis of lymph node metastasis was 53.7%.
Conclusions. Two-thirds of involved lymph nodes had very small metastases (<5 mm), suggesting that limited confidence should be placed in the preoperative diagnosis of lymphatic spread. Therefore, extensive lymph node dissection appears appropriate in esophageal cancer surgery, given the small sizes of many metastases and the difficulty with preoperative diagnosis.

Key words Size of lymph node metastasis · Esophageal cancer · Accuracy of preoperative diagnosis · Lymphatic spread

Introduction

Esophageal carcinoma has fulminant biological characteristics and shows a higher rate of lymph node metastasis than other gastrointestinal malignancies [1]. Lymph node metastasis has been recognized as a predictive factor for prognosis of esophageal cancer, and the number of metastatic lymph nodes is thought to be one of the most powerful predictors of prognosis [2]. Accordingly, accurate diagnosis of lymph node metastasis in patients with esophageal cancer is essential for correct preoperative staging and for selecting a proper treatment modality. Various methods can be used for detection of lymph node metastases in esophageal cancer, including computed tomography (CT), ultrasonography (US), endoscopic ultrasonography (EUS), and positron emission tomography (PET). However, it is sometimes difficult to diagnose lymph node metastasis accurately before pathological examination, even with use of the most advanced imaging methods. Furthermore, misdiagnosis of a metastatic lymph node as normal and vice versa may even occur during surgery.

Patients with esophageal cancer with a depth of tumor invasion of submucosal or deeper based on preoperative examination are considered to have "advanced esophageal cancer," and we have uniformly performed thoracic esophagectomy with so-called three-field systematic lymph node dissection as the standard surgery for these patients. Three-field dissection involves extension of en bloc lymph node dissection throughout the cervical, thoracic, and abdominal fields [3], and this operation allows sufficient and reliable information to be obtained regarding lymphatic spread. The objective of the current study was to measure the actual sizes of metastases in involved lymph nodes, to assess the accuracy of preoperative clinical diagnosis of lymphatic spread, and to use this information to propose a reliable and

Y. Kajiyama (✉) · Y. Iwanuma · N. Tomita · T. Amano · F. Isayama · M. Tsurumaru
Department of Surgery, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
Tel. +81-3-3813-3111; Fax +81-3-3813-0731
e-mail: kaji@med.juntendo.ac.jp

T. Matsumoto
Department of Pathology, Juntendo University School of Medicine, Tokyo, Japan

curative surgical procedure for patients with squamous cell carcinoma of the esophagus.

Methods

Study design

The study was conducted at a single teaching hospital at which almost 100 esophagectomies are performed each year. Eligible patients had histologically proven squamous cell carcinoma of the thoracic esophagus and a depth of tumor invasion that was preoperatively diagnosed as submucosal or deeper; this included patients who had resectable cervical or abdominal lymph nodes suspected to be associated with the tumor, but did not have unresectable local disease. Exclusion criteria were previous esophageal surgery, concurrent multiple cancers elsewhere, and age more than 90 years old. Eligible consecutive patients treated in the year 1999 were enrolled in the study: in this year, 92 esophagectomies were performed and 320 lymph nodes were proven to have metastasis among a total of 9254 dissected nodes. The mean age of the patients was 64 years old, and there were 80 men (87.0%) and 12 women (13.0%); the distribution of the depth of tumor invasion is summarized in Table 1. The dissected lymph nodes were prepared and classified immediately after the operation by the surgeons who performed the esophagectomy. The classification was made according to the Japanese *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* [4] (Fig. 1), which provide a more detailed lymph node classification than the *AJCC Cancer Staging Manual* [5]. The accurate location of each lymph node was recorded, and the nodes were delivered to the pathology department with precise information sheets regarding their stations. The final pathological diagnosis of lymph node metastasis was compared with the preoperative clinical diagnosis to determine the accuracy of preoperative diagnosis for each lymph node station. The diameters of all metastatic lymph nodes and the actual sizes of the metastases in these nodes were then measured microscopically. Using these data, the extent of the metastatic area in each lymph node was calculated as the "metastasis occupational rate" for each lymph node, using the following formula: metastasis occupational rate = (mean diameter of metastasis/mean diameter of metastatic lymph node)^2.

The preoperative diagnostic workup for lymph node metastasis comprised endoscopic ultrasonography (EUS), external ultrasonography (US) of the neck and abdomen, and computed tomography (CT) from the neck to the lower abdomen; positron emission tomography (PET) was also performed when indicated. Before surgery, written informed consent for esophagectomy with three-field lymph node dissection was obtained from all patients.

Table 1. Distribution of depth of tumor invasion

Tumor depth	T1	T2	T3	T4
Number of patients	31	14	41	6

Surgical procedures and pathological examination

The operations were performed by two surgeons (M.T. and Y.K.) using the same surgical procedure. The thoracic duct, azygos vein, pleura, and all the periesophageal tissues in the mediastinum were dissected en bloc. While directly viewing

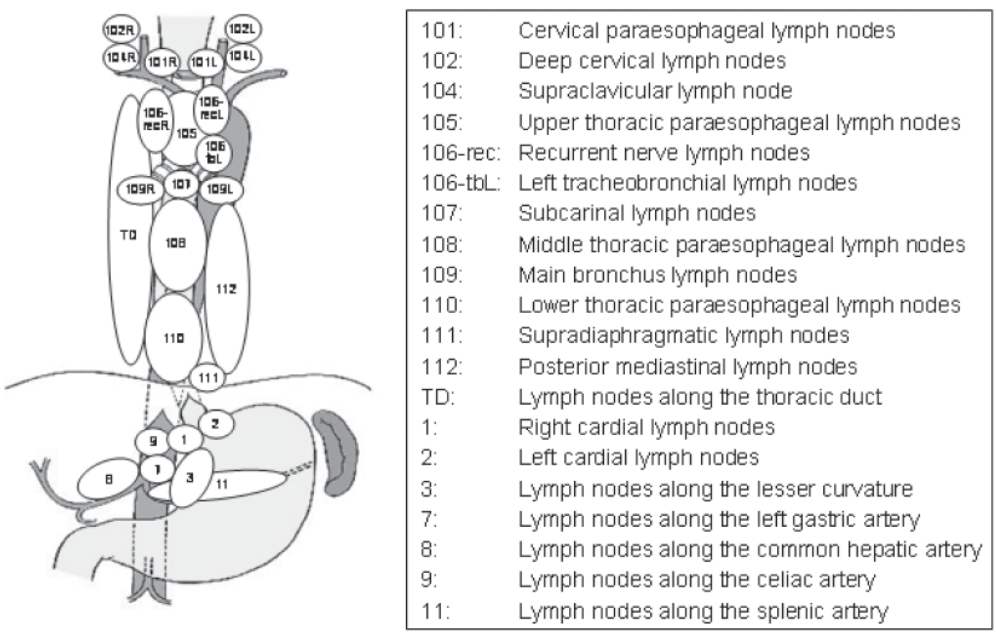


Fig. 1. Precise classification and station numbers of regional lymph nodes according to the Japanese Guidelines on Carcinoma of the Esophagus

the right and left recurrent laryngeal nerves, the upper mediastinal lymph nodes (including the nodes along each recurrent laryngeal nerve) were completely cleared. The bilateral paratracheal lymph nodes, subcarinal and bilateral hilar lymph nodes, posterior mediastinal lymph nodes adjacent to the descending aorta and left pleura, and diaphragmatic lymph nodes were then dissected en bloc (see Fig. 1). The lymph nodes in the aortopulmonary window (left tracheobronchial nodes) were dissected separately. For the abdominal procedure, after upper midline laparotomy, en bloc dissection of lymph nodes was performed along the cardia, lesser curvature, left gastric artery, celiac axis, common hepatic artery, and splenic artery. The left gastric artery was cut at its origin. Along with all these dissected lymph nodes, the proximal stomach was cut between the right and left gastric artery and resected with the esophagus using a linear stapler, after which a gastric tube was constructed. The extent of abdominal lymph node dissection was the same as that for D2 lymph node dissection in gastric cancer surgery [6]. For the neck, a collar incision was made and the middle deep cervical and supraclavicular lymph nodes were removed en bloc (102 and 104 in Fig. 1). The lymph nodes were then removed along the cervical recurrent laryngeal nerve, which is located between the common carotid artery and the trachea (101 in Fig. 1).

In the pathological examination, each lymph node was cut along its maximum diameter and stained with hematoxylin and eosin. Detection of metastasis was performed by pathologists working under the supervision of a senior gastroenterological pathologist. For all positive lymph nodes detected in 1999, we measured the longer and shorter diameters of the entire lymph node and the actual sizes of the metastatic lesions under a microscope.

Criteria for preoperative diagnosis of lymph node metastasis

Lymph nodes were judged to be metastatic when the largest diameter was >10 mm, the shape of the node was round, the internal CT density or US echogenicity was homogeneously low, and the margin of the node was clear. The same criteria were used for cervical lymph nodes, except that the requirement for the diameter was set at greater than 5 mm [7,8].

A CT was obtained after an infusion of 150 ml nonionic contrast with 5-mm-thick slices from neck to lower border of bilateral kidneys. Patients underwent ultrasonography examination, and images were obtained at 3.5 MHz in the abdomen and 5.0 MHz in the neck.

Statistical analysis

A chi-square test or analysis of variance (ANOVA) was used to compare categorical data, and Student's *t* test was used for continuous variables. The SPSS program (SPSS Inc.) was used for all analyses. All reported p values are two sided, and $P < 0.05$ was considered to indicate statistical significance.

Results

Rate of metastasis and number of metastatic nodes

Twenty-six patients had no lymph node metastases and 66 had at least one metastatic lymph node, giving a 71.7% rate of lymphatic metastasis. This rate increased with the depth of tumor invasion: 47.8%, 64.7%, 82.4%, and 85.7% for pT1, pT2, pT3, and pT4 tumors, respectively. The mean number of dissected lymph nodes per patient was 111, with an average of 42 in the neck, 37 in the mediastinum, and 32 in the abdomen. The mean number of metastatic lymph nodes was 1.2 in the neck, 2.0 in the mediastinum, and 1.5 in the abdomen.

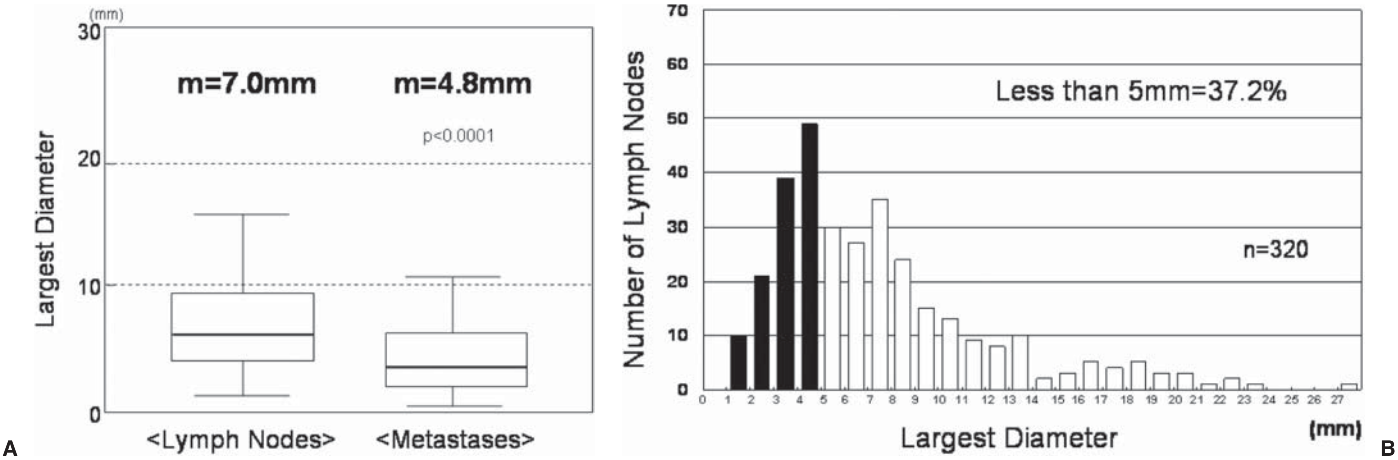
Size of lymphatic metastases

The mean largest diameter ± standard deviation (SD) of the metastatic lymph nodes was 7.0 ± 4.7 mm, the median size of the metastatic lymph nodes was 6.0 mm, and the mean largest diameter of the actual metastases in the involved nodes was 4.8 ± 4.1 mm. The mean diameter of the metastases was significantly smaller than that of the involved nodes ($P < 0.0001$, Student's *t* test) (Fig. 2A). The size distributions of the largest diameters of the metastatic lymph nodes and the metastatic lesions in the involved nodes are shown using 1-mm intervals in Fig. 2B,C. There were 119 metastatic lymph nodes with a largest diameter less than 5 mm, corresponding to 37.2% of all metastatic nodes (Fig. 2B), and metastatic lesions of less than 5 mm in largest diameter were found in 202 (63.1%) of the 320 metastatic lymph nodes (Fig. 2C).

The sizes of the metastases were also analyzed according to tumor depth and AJCC-TNM stage [5]. The mean diameters of the metastases were 4.4, 4.7, 4.9, and 4.6 mm for pT1, pT2, pT3, and pT4 tumors, respectively; there was no significant difference in size with respect to the depth of tumor invasion ($P = 0.92$). Based on the TNM stages as defined in the American Joint Committee on Cancer (AJCC) staging manual (5th edition) [5], the mean diameters of the metastases were 4.2, 4.4, 4.1, and 5.1 mm for stages 2B, 3, 4A, and 4B, respectively; there was also no significant difference in size among these stages ($P = 0.88$).

Metastasis occupational rate in lymph nodes

A scatter plot of the "metastasis occupational rate" of each lymph node according to the largest diameter of the lymph node is shown in Fig. 3. The mean metastatic occupation rate per lymph node was 0.51 ± 0.31, and the mean rates for lymph nodes with a largest diameter below and above 10 mm were 0.48 and 0.61, respectively. There was a significant difference in metastasis occupational rate between small and large lymph nodes ($P = 0.002$).



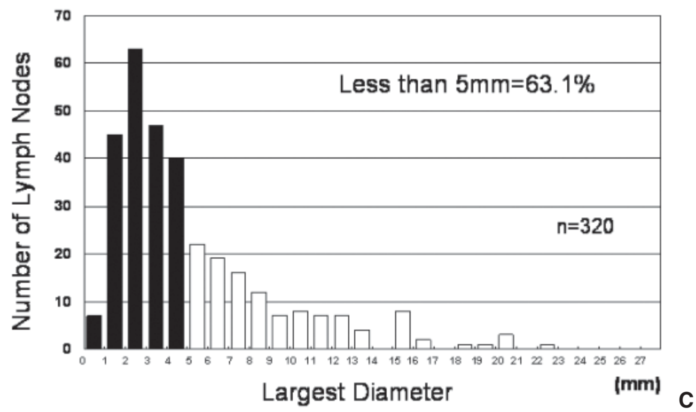


Fig. 2. Size of metastatic lymph nodes and metastatic lesions in the nodes. **A** Mean diameter. **B** Distribution of sizes of metastatic lymph nodes. **C** Distribution of sizes of metastases in the nodes

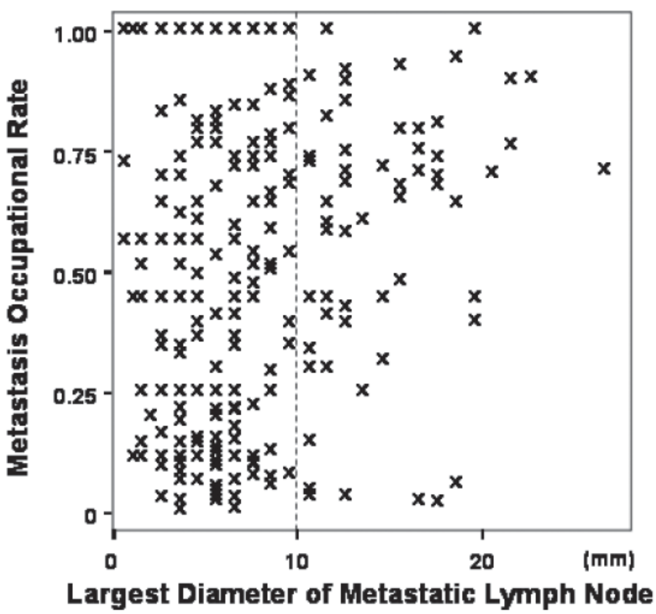
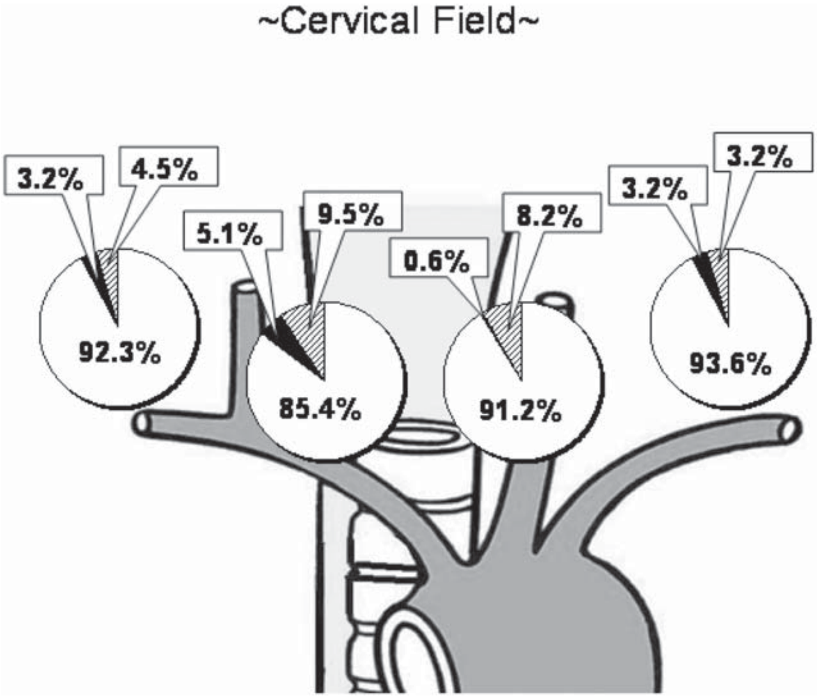


Fig. 3. Distribution of metastasis occupational rates in metastatic nodes based on the largest diameter of each node

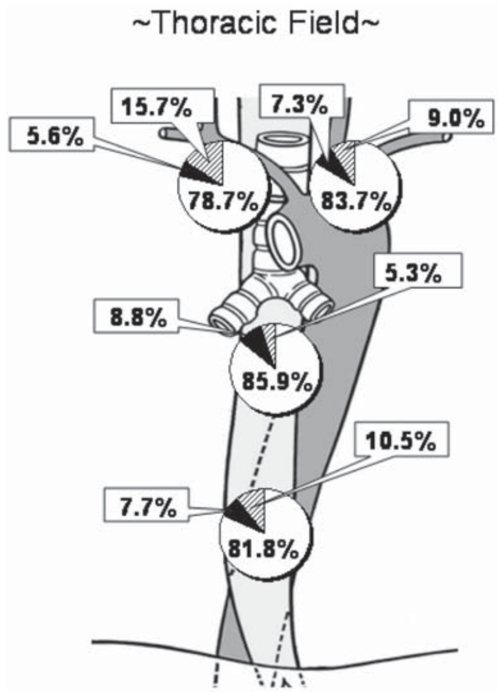
Accuracy of preoperative diagnosis of lymphatic spread

The accuracy rate in preoperative diagnosis of lymph node metastasis is shown in Fig. 4. For each lymph node station, the true-positive and true-negative diagnostic rates were 85%–94% in the cervical field (Fig. 4A), 79%–86% in the thoracic field (Fig. 4B), and 78%–86% in the abdominal field (Fig. 4C). The false-negative and false-positive diagnostic rates for metastatic lymph nodes are also shown in Fig. 4. A strict assessment of the success of preoperative diagnosis of lymphatic spread requires that a diagnostic failure at any lymph node station should be judged as a misdiagnosis. According to this strict criterion, the true positive and negative rates for lymphatic spread were 71.3% in the cervical field, 42.0% in the thoracic field, and 57.9% in the abdominal field. Application of this criterion reduced the true-positive and true-negative rate for all lymph node stations in the three fields to 23.2%. The false-negative rates for lymph nodes metastases were 13.9% in the cervical field, 35.6% in the thoracic field, 33.5% in the abdominal field, and 53.7% across the three fields based on the strict criterion.

From analysis of the false-negative and false-positive rates of lymph node metastasis, we found that the ratio of false-negative to false-positive results differed among the three fields (Fig. 4A–C). This ratio ranged from 0.073 to 1.0



A



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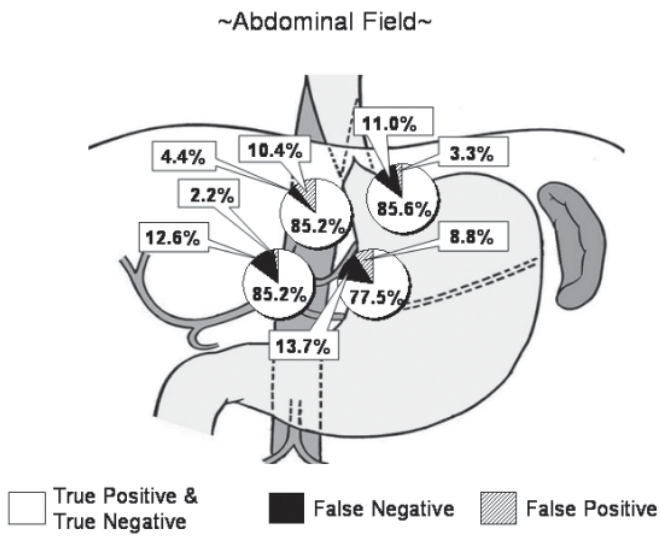

C

Fig. 4. True-positive and true-negative and false-negative and false-positive clinical diagnostic rates for lymph node metastasis at each regional lymph node station: cervical field (**A**); thoracic field (**B**); abdominal field (**C**)

in the cervical field, from 0.36 to 1.7 in the thoracic field, and from 0.42 to 5.7 in the abdominal field.

Discussion

In esophageal cancer, the clinical stage sometimes differs from the pathological stage [9], and one of the reasons for inaccurate preoperative staging is that correct clinical diagnosis of lymphatic spread is not always possible [10]. The data presented here indicate the accuracy with which lymph nodes metastasis can be predicted in patients with esophageal cancer, using the latest diagnostic techniques. For diagnosis at each lymph node station the true-positive and true-negative diagnostic rate ranged from 78% to 94%, which appears to be fairly good. For diagnosis based not on individual lymph node stations, but more strictly as a field diagnosis per patient (i.e., a requirement that all stations in a field are correctly diagnosed), the cervical field was still correctly diagnosed in 75% of patients as a result of the precision of external and endoscopic ultrasonography [11,12]. However, a correct diagnosis in the thoracic or abdominal field was only obtained in half the patients [13], and the true-positive and true-negative diagnostic rate (indicating a completely correct diagnosis over the three fields) was only 23.2%. Based on these results, only limited confidence can be placed in the preoperative diagnosis of lymph nodes metastasis or in TNM staging.

One of the reasons for the poor diagnostic rate of lymphatic spread in esophageal cancer is the small size of the actual lymph node metastases. The average size of the largest diameter of the lymph node metastases in our esophageal cancer patients was only 4.8mm (see Fig. 2A), and in many cases the metastasis was significantly smaller than the involved lymph node; this is problematic, because only the whole node can be assessed preoperatively. An analysis of the size distributions for the whole metastatic lymph nodes and the actual lesions showed that almost one-third of metastatic nodes (37.2%) had a diameter of less than 5mm (Fig. 2B) and nearly two-thirds of all metastatic nodes (63.1%) contained lesions that were less than 5mm in diameter (Fig. 2C). In such cases, precise diagnosis of lymph node metastasis before surgery is likely to be difficult using conventional radiographic or ultrasonographic examination, and many small metastases may be missed by current diagnostic methods. It is still difficult to diagnose small lymph node metastases of less than 5mm in diameter using functional imaging such as PET [14]. However, most lymph nodes more than 1cm in diameter should be suspected of containing metastases [15].

Our data revealed another clinically important problem in preoperative diagnosis of lymph node metastasis: the average percentage area occupied by the metastasis in small lymph nodes with a largest diameter of less than 10mm is significantly lower than that in lymph nodes with a largest diameter of more than 10mm (see Fig. 3). Furthermore, we often found a minute metastatic lesion in a small lymph node of a few millimeters in diameter (Fig. 5). In small nodes, which are the majority of metastatic lymph nodes, diagnosis of metastasis is therefore very difficult, not only because the lymph nodes are small in diameter, but also because the area occupied by the metastasis is likely to be small. Therefore, although the number of involved nodes is a powerful prognostic factor, it is very difficult to determine the correct number of metastatic nodes preoperatively [6–18]. The clinical meaning of the size of a lymphatic metastasis also remains uncertain: sizes were independent of the depth of tumor invasion, and we were unable to find a relationship between the sizes of lymphatic metastases and cancer stage. Overall, these results suggest that preoperative diagnosis of lymphatic spread should be interpreted with care. Furthermore, in intraoperative complete dissection of possible lymph nodes, care should be taken not to leave residual small metastatic lymph nodes, and wide and systematic lymph node dissection surgery is recommended from a relatively early stage, such as submucosal cancer or TNM stage 2B, as well as in advanced cases.

The diagnostic results for lymphatic spread were better in the cervical field than in the abdominal field, because the latest ultrasonography devices allow identification of minute lymph nodes in the cervical field [12]. However, ultrasonographic diagnosis of minute lymph node metastases in the abdominal field is less certain because of the poor conditions for examination. Both metastatic size and accuracy of the diagnostic tools influence the diagnostic rate. Conventional imaging methods for detection of lymph node metastasis depend on analysis of factors such as size, shape, and the internal structure of the nodes. However, as shown in this study, these diagnostic methods have a limited ability to detect lymphatic spread in patients with esophageal cancer [19]. Therefore, at present, wide and systematic lymph node dissection may be preferable in esophageal cancer surgery at high-volume centers, considering the high rate of lymphatic spread, the low correct preoperative diagnostic rate, and the small size of lymph node metastases. To individualize therapeutic methods and minimize the morbidity of treatment for esophageal cancer, it will be necessary to increase the accuracy of functional imaging methods such as PET, or to develop new functional diagnostic tools for detection of small lymphatic spread in this disease.

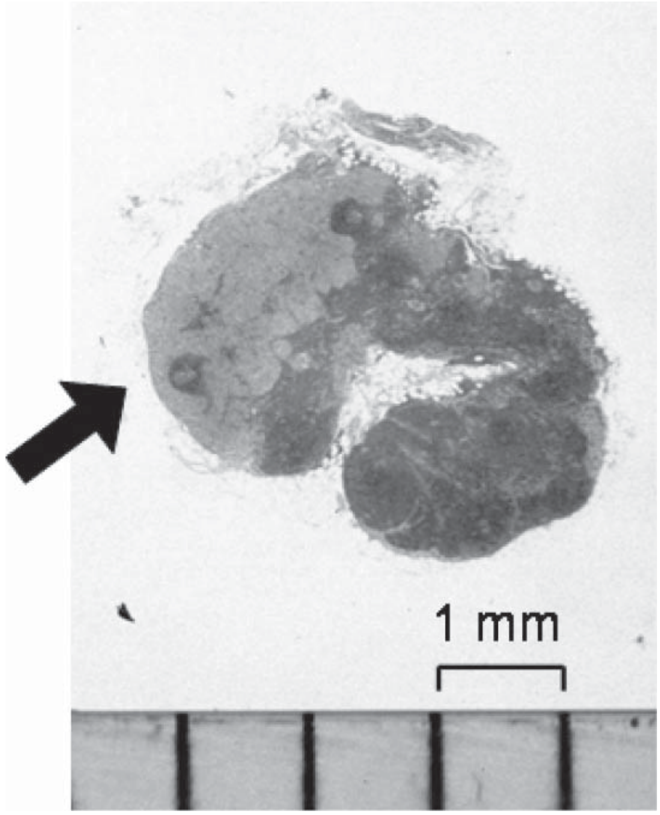

Fig. 5. A small metastatic lymph node: the *arrow* shows a minute metastasis occupying part of the node

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