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Wide-spread Distribution of Sentinel Lymph nodes in Esophageal Cancer

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Abstract

Sentinel lymph nodes are the first draining nodes that contain tumor cells. Identification of sentinel nodes may help to determine the suitable extent of lymphadenectomy. To assess the location of sentinel lymph nodes, a series of 41 patients with single and two metastatic lymph nodes who underwent esophagectomy and 3-field lymphadenectomy between 1991 and 1999 were investigated retrospectively. Only 29 (47.5%) of 61 metastatic nodes showed correspondence between the tumor site and the regional metastatic lymph nodes by routine histologic examination. In the patients with tumors in the upper and middle thoracic esophagus, metastatic lymph nodes were distributed in the cervix, mediastinum and abdomen. Although sentinel nodes were limited to the regional and adjusting compartments in 82%, nodes were found beyond the adjusting compartments in 18%. The sentinel nodes were broadly distributed depending on the location of the tumor in esophageal cancer. (J Nippon Med Sch 2001; 68: 393—396)

Key words: sentinel lymph node, esophageal cancer, esophagectomy, lymphadenectomy, skip metastasis

Introduction

Esophageal cancer has a poor prognosis despite recent advances in treatment^{1,2}. It has been reported that lymph node metastasis is an important prognostic factor and necessitates extensive lymphadenectomy for cure³⁻⁷. However, extensive procedures increase the incidence of postoperative complications such as anastomotic leakage, pneumonia and recurrent laryngeal nerve paralysis, and decrease the quality of life of patients who undergo esophagectomy^{3,4,7}.

The sentinel node concept has recently been generally accepted. That is, the first draining node is also the first node to contain tumor cells. The sentinel node biopsy technique has been applied for correcting

the nodal status and the stage in various solid tumors⁸⁻¹³. Identification of sentinel nodes may help to determine the suitable extent of lymphadenectomy, and to thereby improve the outcome of esophageal cancer surgery. To detect the sentinel node during surgery, radiolabeled compounds and a blue dye are utilized. However, it has been difficult to identify sentinel nodes in gastrointestinal cancers because of high false-negative rates^{12,13}. Therefore, the aim of this study was to determine the prevalence of sentinel nodes prior to performance of sentinel node biopsy in esophageal cancer surgery. We retrospectively evaluated the pattern of metastatic nodes in relation to the location of the primary tumors in patients undergoing esophagectomy.

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Patients and Methods

Of 162 patients who underwent esophagectomy with systemic lymphadenectomy for carcinoma of the esophagus between 1991 and 1999, 41 had single or two metastatic nodes by routine histologic examination. The location of the tumors and regional lymph nodes were divided into five compartments according to the guidelines for clinical and pathologic studies on carcinoma of the esophagus¹⁴: cervix, upper, middle and lower thorax or mediastinum, and abdomen. All patients underwent esophagectomy via thoracotomy with dissection of at least 10 lymph nodes from the cervix, mediastinum and abdomen, and had primary tumors which had not undergone any preoperative chemotherapy or radiotherapy. The patients' characteristics are shown in **Table 1**. The disease was squamous cell carcinoma in 39, mucoepidermoid carcinoma in one, and malignant melanoma in one. The mean number of dissected lymph nodes was 29 (17) (mean (SD)) (range 10 to 74). A total of 61 metastatic nodes from 41 patients were mapped, and the correlation between the location of the primary tumor and the metastatic nodes was examined. The chi-square test with Yate's correction was applied for comparison of the data. $P < 0.05$ was defined as statistically significant.

Results

Metastatic lymph nodes were found in the deep cervix, bilateral recurrent nerve at the top of the mediastinum, intrathoracic, perigastric and the route of the left gastric artery. The distribution of metastatic lymph nodes is shown in **Table 2**. The overall correspondence rate between the primary tumors and the regional metastatic lymph nodes was 47.5%. It was 71.4% in the cervical compartment, 57.1% in the upper, 29.2% in the middle and 50% in the lower thoracic compartments, and 75% in the abdominal esophagus. The rate of 29.2% (7/24) for tumors in the middle thoracic esophagus was significantly lower compared with the 59.5% (22/37) for the tumors located in the other compartments ($p < 0.05$). Although metastatic lymph nodes were limited to the regional

Table 1 Patient characteristics

Age		62 (28–78)
Sex	male	37
	female	4
Tumor site*	cervix	4
	upper	8
	middle	18
	lower	7
	abdomen	4
Number of dissected lymph nodes		29 (10–74)

* According to guidelines for the clinical and pathologic studies on carcinoma of the esophagus (Reference 14).

Table 2 Location of primary tumors and metastatic lymph nodes

Tumor site	Location of metastatic nodes				
	Cervix	Upper	Middle	Lower	Abdomen
Cervix	5	2	0	0	0
Upper	2	8	3	0	1
Middle	1	6	7	2	8
Lower	0	0	1	6	5
Abdomen	0	1	0	0	3

and adjusting compartments in 50 (82%), metastatic nodes beyond the adjusting compartments were found in 11 (18%). Of 33 patients with tumors in the intrathoracic esophagus, 12 (36.4%) had metastases in the abdominal lymph nodes. Furthermore, metastatic lymph nodes spread to all five compartments in the patients with tumors in the middle thoracic esophagus.

Discussion

In carcinomas of the breast and penis, sentinel node biopsy of the axillary and inguinal nodes is feasible and highly accurate^{8–10}. Thus, large studies are addressing sentinel node dissection surgery¹⁵. However, there is controversy regarding the accuracy of sentinel node identification in gastrointestinal tumors^{12,13}. In the present study, we investigated the distribution of sentinel nodes, and they corresponded to the regional nodes in only 47.5% of esophageal cancers. Although the location of sentinel nodes was limited to the regional and adjusting compartments in 82%, sentinel

nodes were beyond the adjusting compartments in 18%. Furthermore, for tumors in the upper and middle mediastinum, the sentinel nodes were distributed in the cervix, mediastinum and abdomen. However, the sentinel nodes of tumors located in the cervix and abdomen were mostly regional and adjusting nodes. These results suggest that the location of sentinel nodes depends on the tumor site, and that skip metastases may be frequent in esophageal cancer.

To identify the sentinel nodes during surgery, radiolabeled compounds and a blue dye were utilized^{10,11}. However, in colon cancer, the regional nodes were frequently stained with a blue dye, but there was a high false-negative rate¹³. The rates of skip metastasis in stomach and esophageal cancers were also reported to be high¹⁶⁻¹⁹. This may be due to more complicated drainage routes in the case of gastrointestinal tumors. Furthermore, the clinical significance of micrometastases in various gastrointestinal cancers, including the esophagus, has been reported²⁰⁻²⁴. Endoscopic ultrasonography and computed tomography scanning have been employed to estimate the nodal status, but it is difficult to detect the micrometastasis by these procedure. Immunohistochemistry using anti-cytokeratin antibodies detects micrometastases even in nodes that are tumor-negative by routine pathologic examination. However, there are great variations in the positive rates obtained by immunohistochemical staining for tumor-negative nodes by routine pathologic examination. Recently, it has been reported that the rate of positive staining is only 1% in five serial sections of tumor-negative nodes by routine pathologic examination²¹. We previously reported that only 65% of the primary tumors are positive by immunohistochemical staining using anti-cytokeratin 19 antibody²⁵. It has also been reported that RT-PCR using CEA mRNA detects micrometastases more frequently than immunohistochemistry^{22,23}. Furthermore, there is controversy regarding the presence of micrometastases and the prognosis in esophageal cancer^{20,21,24}. Although difficult to apply during surgery, these methods may provide new information for the estimation of the nodal status.

Esophageal cancer metastasizes to the lymph nodes at an early stage of the disease^{3,16}. Furthermore, skip metastases have been reported to be frequently found

since the introduction of extended lymphadenectomy¹⁷. Three-field lymphadenectomy has been reported to improve the outcome of surgery^{3,4,6}. The findings of the present study suggest that patients who have tumors other than in the thoracic esophagus may require sentinel lymph node biopsy in the regional and adjusting compartments for estimation of the nodal status. On the other hand, extensive examination of the cervical, thoracic and abdominal lymph nodes may be necessary for patients with tumors in the thoracic esophagus. In our hospital, a low dose (10 mg/kg) of glucocorticoid decreases the surgical stress of esophagectomy, and improves postoperative condition²⁶.

In summary, sentinel nodes are quite broadly distributed in esophageal cancer. Although further studies need to investigate the detection of metastatic nodes during surgery, skip metastasis is frequently found in tumors located in the thoracic esophagus. Extensive lymphadenectomy may be beneficial in these patients with node-positive tumors.

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