Prognostic and Clinical Evaluation of Axillary Lymph Node Metastasis in Esophageal Cancer

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Axillary lymph node metastasis (ALNM) from esophageal cancer is rare. Its prognosis and effective treatments remain unknown. Between 1997 and 2005, esophagectomy was performed in 361 patients with esophageal cancer in our hospital. ALNM was identified in four patients (1.1%). All patients had left ALNM with ipsilateral left supraclavicular lymph node metastasis. In two patients ALNM developed after radical esophagectomy with regional lymphadenectomy and in the other two patients after chemoradiotherapy of primary lesions. Axillary lymphadenectomy with chemoradiotherapy was given to all patients. Median survival time and disease-free survival (DFS) after initial treatment for primary esophageal cancer were 30.5 months and 11.5 months, respectively. One patient, who had a small number of regional lymph node metastases (two lymph nodes) at esophagectomy and prolonged DFS (22 months) until axillary node recurrence, is still alive, 67 months after axillary lymphadenectomy. The other three patients, who had larger numbers of regional lymph node metastases (average, 8.3) and shorter DFS (average, 9.7 months), died of recurrence an average of 13.3 months after axillary lymphadenectomy. In conclusion, although ALNM is considered a type of distant organ metastasis, if it is a solitary recurrence, good survival may be obtained after appropriate loco-regional therapy. The number of metastatic regional lymph nodes at initial esophagectomy and the duration of DFS until axillary node recurrence can help to guide the decision whether aggressive treatments are warranted.

Key words: esophageal cancer – lymph node metastasis – axillary lymph node – salvage surgery – prognosis

INTRODUCTION

Cervical lymph node recurrence is often encountered after curative surgery for esophageal cancer, but if it is a solitary recurrence, reasonably good survival can be attained by appropriate loco-regional therapy (1, 2). However, axillary lymph node metastasis (ALNM) from esophageal cancer is classified as a distinct type of distant lymph node metastasis and appears to be rare. To our knowledge, no cases have been reported in the English-language literature to date. Thus, its prognosis and effective treatments remain unknown.

At our institute, ALNM following radical esophagectomy was identified in four patients (1.1%), one of whom is still alive 67 months after axillary lymphadenectomy, with no further recurrence. We describe these four patients, propose likely mechanisms of metastasis, and discuss the response to loco-regional therapy.

PATIENTS AND METHODS

Between 1997 and 2005, esophagectomy with regional lymphadenectomy was performed in 361 patients in our hospital. Axillary lymph node metastasis was identified in four of these patients (1.1%), all of whom received radical axillary lymphadenectomy plus chemoradiotherapy. We retrospectively examined the clinical and histopathological features of these patients. Histopathological factors such as tumor
location, depth of tumor invasion, histological type and pathological stage (pStage) were classified according to both the Japanese Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus (9th edn) (JGCE) (3) and the TNM staging system (4).

**RESULTS**

**CLINICOPATHOLOGICAL FEATURES OF THE PATIENTS**

Clinicopathological features of the four patients (three men, one woman) are shown in Table 1. Their average age was 62.8 years (range, 55–73). Primary lesions were located in the middle thoracic esophagus in three patients and in the upper thoracic esophagus in one. Histologically, all patients had squamous cell carcinomas (well differentiated in two, moderately differentiated in one and poorly differentiated in the other). The average tumor length was 39.3 mm (range, 18–60). Lymphatic invasion was evident in all patients. Lymph node involvement at esophagectomy was graded as pathological N4 (cases 1, 3 and 4) or N3 (case 2) according to the JGCE classification and as M1b in all patients according to the TNM classification. Median numbers of metastatic and dissected lymph nodes were 6.8 (range, 2–13) and 47 (range, 39–61) respectively. The left supraclavicular lymph nodes were involved in all patients.

**TREATMENTS FOR AXILLARY LYMPH NODE METASTASIS**

Patients were followed-up every 3–6 months by upper gastrointestinal endoscopy and computed tomography (CT) and ultrasonography (US) of the neck, chest and abdomen after initial treatments (esophagectomy with regional lymphadenectomy or chemoradiotherapy). Treatments for axillary lymph node recurrence are summarized in Table 2. Left axillary lymph node metastasis developed in all patients. Median disease-free survival (DFS) until axillary node recurrence was 11.5 months (range, 6–22).

In two patients [cases 1 and 2 (Fig. 1)], ALNM developed after radical esophagectomy with three-field lymphadenectomy, including cervical, mediastinal, and abdominal lymph node dissection (5). In the other two patients [cases 3 and 4 (Figs. 1b and 2)], ALNM developed after chemoradiotherapy for primary lesions. After receiving additional chemoradiotherapy, these patients underwent salvage esophagectomy with three-field lymphadenectomy plus axillary lymphadenectomy to treat local recurrence and ALNM. The former patients (cases 1 and 2) additionally received adjuvant chemoradiotherapy and the latter (cases 3 and 4) were given further chemotherapy after axillary lymphadenectomy. There was no major treatment-related complication.

**OUTCOMES OF PATIENTS WITH AXILLARY LYMPH NODE METASTASIS**

Median survival time was 30.5 months (range, 21–89) after initial treatments for primary esophageal cancer. As of October 2006, one patient (case 2) has remained alive for 89 months (67 months after axillary lymphadenectomy). The remaining patients (cases 1, 3 and 4) died of recurrence. One patient (case 1) survived for 19 months after axillary lymphadenectomy, but died of multiple lung metastases. Another patient (case 3) survived for 11 months after salvage esophagectomy with regional lymphadenectomy plus axillary lymphadenectomy, but died of multiple organ metastases.

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**Table 1. Clinicopathological features of four patients with axillary lymph node metastasis from thoracic esophageal cancer**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/gender</td>
<td>55/female</td>
<td>62/male</td>
<td>73/male</td>
<td>61/male</td>
</tr>
<tr>
<td>Tumor location</td>
<td>Middle</td>
<td>Middle</td>
<td>Middle</td>
<td>Upper</td>
</tr>
<tr>
<td>Tumor length (mm)</td>
<td>49</td>
<td>18</td>
<td>60</td>
<td>22</td>
</tr>
<tr>
<td>Histology</td>
<td>Well diff. sc</td>
<td>Well diff. sc</td>
<td>Mod. diff. sc</td>
<td>Poor. diff. sc</td>
</tr>
<tr>
<td>Initial treatment for primary esophageal cancer</td>
<td>Esophagectomy with three-field lymphadenectomy</td>
<td>Esophagectomy with three-field lymphadenectomy</td>
<td>Chemoradiation (63Gy + CDDP/5-FU)</td>
<td>Chemoradiation (50Gy + CDGP/5-FU)</td>
</tr>
<tr>
<td>Salvage esophagectomy with three-field lymphadenectomy plus axillary lymphadenectomy</td>
<td>No (out of adaptation)</td>
<td>No (out of adaptation)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Metastatic node number and sites according to JGCE</td>
<td>6 No. 1,106recL,108,104R,104L (61) + (Lt: 3/7)</td>
<td>2 No. 104L (44) + (Lt: 2/4)</td>
<td>13 No. 104L,105,106recR,108,110 (39) + (Lt: 1/9)</td>
<td>6 No. 104L,105,110,3 (44) + (Lt:1/7)</td>
</tr>
<tr>
<td>(Dissected node number)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraclavicular node metastasis</td>
<td>pJGCE-stage: pT3N4M0 (Stage IVa)</td>
<td>pT1bN3M0 (Stage III)</td>
<td>pT3N4M0 (Stage IVa)</td>
<td>pT3N4M0 (Stage IVa)</td>
</tr>
<tr>
<td>pTNM-stage</td>
<td>pT3N1M1b (Stage IVB)</td>
<td>pT1N1M1b (Stage IVB)</td>
<td>pT3N1M1b (Stage IVB)</td>
<td>pT3N1M1b (Stage IVB)</td>
</tr>
</tbody>
</table>

CDGP, nedaplatin; CDDP, cisplatin; JGCE, Japanese Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus.
recurrence, including metastases to the brain and lung. The final patient (case 4) survived for 10 months after salvage esophagectomy with regional lymphadenectomy plus axillary lymphadenectomy, but died of abdominal lymph node recurrence (Table 2).

**DISCUSSION**

Metastasis of esophageal cancer to the axillary lymph nodes is rare. The prevalence of ALNM among patients with esophageal cancers who underwent esophagectomy was only 1.1% (4/361) in our hospital. Indeed, little is known about the clinical behavior of ALNM in esophageal cancer. We analyzed the characteristics of four cases of ALNM encountered and treated during the past 9 years to gain better insight into the clinical significance and possible pathways leading to the development of ALNM from esophageal cancer.

Non-regional lymph node dissemination such as ALNM is classified as a type of distant metastasis according to both the JGCE and TNM staging systems (3, 4). Such cases of distant lymph node metastasis are usually managed as systemic disease in all solid cancers. Patients with distant metastasis are considered incurable and only palliative treatment is instituted. The prognosis of patients with non-regional metastasis can also be negatively affected by the

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**Table 2.** Treatments and outcomes of four patients with axillary lymph node metastasis from thoracic esophageal cancer

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS after initial treatment for primary esophageal cancer (months)</td>
<td>17</td>
<td>22</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Side of axillary node recurrence</td>
<td>Left</td>
<td>Left</td>
<td>Left</td>
<td>Left</td>
</tr>
<tr>
<td>Conservative therapy before axillary lymphadenectomy</td>
<td>—</td>
<td>—</td>
<td>Chemoradiation (40Gy + docetaxel/5-FU)</td>
<td>Chemoradiation (40Gy + CDP/5-FU)</td>
</tr>
<tr>
<td>Surgical treatment for axillary lymph node metastasis</td>
<td>Left axillary lymphadenectomy</td>
<td>Left axillary lymphadenectomy</td>
<td>Left axillary lymphadenectomy</td>
<td>Left axillary lymphadenectomy</td>
</tr>
<tr>
<td>Metastatic axillary node number (Dissected node number)</td>
<td>9 (25)</td>
<td>6 (8)</td>
<td>3 (13)</td>
<td>0 (4)</td>
</tr>
<tr>
<td>Additional therapy after axillary lymphadenectomy</td>
<td>Chemoradiation (50Gy + CDDP/5-FU)</td>
<td>Chemoradiation (50Gy + CDDP/5-FU)</td>
<td>Chemotherapy* (CDGP/docetaxel)</td>
<td>Chemotherapy** (docetaxel/5-FU)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Dead</td>
<td>Alive</td>
<td>Dead</td>
<td>Dead</td>
</tr>
<tr>
<td>(Survival time after axillary lymphadenectomy [months])</td>
<td>(19)</td>
<td>(67)</td>
<td>(11)</td>
<td>(6)</td>
</tr>
<tr>
<td>(Overall survival [months])</td>
<td>(38)</td>
<td>(89)</td>
<td>(23)</td>
<td>(21)</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; 5-FU, 5-fluorouracil.*Chemotherapy: docetaxel 50 mg/body/tri-weekly + 5-FU 300 mg/body/day. **Chemotherapy: nedaplatin 120 mg/body/tri-weekly + docetaxel 45 mg/body/tri-weekly.

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**Figure 1.** Computed tomographic scan of ALNM in Case 2 and Case 4. A 62-year-old man with squamous cell carcinoma of the middle thoracic esophagus underwent radical esophagectomy with three-field lymphadenectomy. Computed tomography shows ALNM, developing 22 months after esophagectomy (arrow) (Fig. 1a). A 61-year-old man with squamous cell carcinoma of the middle thoracic esophagus received chemoradiotherapy for the primary lesion and had an almost complete response clinically. SCLNM (Fig. 1b) and ALNM developed 6 months after initial chemoradiotherapy (detailed in Fig. 2). ALNM, axillary lymph node metastasis; SCLNM, supraclavicular lymph node metastasis.
high risk of simultaneous distant metastasis, a feature shared by all cancers with massive regional dissemination. Exceptionally, however, ALNM and supraclavicular lymph node metastasis (SCLNM) can represent a contiguous regional dissemination of esophageal cancer. Such mechanisms of metastasis may be conducive to long-term survival in selected patients.

Mechanisms underlying metastasis to the axillary lymph nodes have not been reported to date for esophageal cancer, but are well documented for lung cancer (6–8). Three hypothetical routes have been proposed for ALNM. The first is newly developed lymphatic channels arising from pleural lesions of adhesive lung tumors. The second is retrograde spread, leading to the development of SCLNM. The third possible route is the development of ALNM from systemic disease. Marcantonio and Libshitz reported the retrograde flow of contrast material from the supraclavicular lymph nodes to the axillary lymph nodes in four (2%) of 200 consecutive lymphangiograms (6). Riquet also suggested that retrograde flows could be caused by lymphatic blockade owing to the presence of simultaneous SCLNM and ALMN may develop when the vascular competence of lymphatic vessels is lost in bronchogenic carcinoma (9). All four of our patients presented with left ALNM with ipsilateral SCLNM. This finding provides further evidence that ALMN may be caused by retrograde flow owing to lymphatic blockade by SCLNM in esophageal cancer.

The left supraclavicular (Virchow’s) lymph nodes are intercalated nodes draining from the thoracic duct and are occasionally involved with advanced gastrointestinal cancers as one of the clinical conditions for far advanced disease. However, in esophageal cancer, solitary metastasis to cervical lymph nodes, such as the supraclavicular nodes, is not rare and develops independently of tumor location, depth of invasion and histological type (10–12). In other words, so-called ‘jumping metastasis’ can occur in patients with thoracic esophageal cancer (13). Therefore, if lymphatic blockade is caused by ‘jumping SCLNM’ in surgically curable and potentially early-stage esophageal cancer, ALNM can also develop even in patients with early disease.

We previously showed that salvage cervical lymphadenectomy produced relatively good outcomes in patients with solitary supraclavicular lymph node recurrence (1). Patients who have cervical lymph node recurrence after esophagectomy should undergo cervical lymphadenectomy. We believe that good outcomes can be obtained by appropriate loco-regional treatments in patients with ALNM caused by retrograde spread owing to the presence of SCLNM.

We also hypothesized that variables such as the number of metastatic regional lymph nodes or the duration of DFS after initial treatment of primary lesions might be significantly related to the outcomes of patients with ALNM. Consistent with the findings of previous studies (14, 15), indeed, cases 1, 3 and 4 had poor outcomes and an average of 8.3 metastatic regional lymph nodes. In contrast, case 2, who had only two metastatic regional lymph nodes at esophagectomy, is still alive. Mean DFS until axillary node recurrence in cases 1, 3 and 4 was 9.7 months (range 6–17 months). DFS in case 2, who is still alive, was 22 months. Our results suggest that the number of metastatic regional lymph nodes and the duration of DFS until axillary node recurrence might assist in deciding whether to perform salvage axillary lymphadenectomy. Treatment planning for patients with recurrence should also consider the likelihood of recurrence to other sites.

Potential benefits of more extended procedures for recurrence have to be weighed against possible increases in peri-operative
morbidity and mortality, but axillary lymphadenectomy was associated with minimal morbidity. Therefore, if the axilla is the only site of recurrence, standard axillary dissection with chemotherapy or chemoradiotherapy should be considered.

In conclusion, the possibility of axillary lymph node recurrence should be considered during follow-up of patients with esophageal cancer after curative surgery or definitive chemoradiotherapy. Routine palpation of the axillae is recommended if SCLNM is found at initial treatment. Although axillary node metastasis is generally considered a type of distant organ metastasis, good survival may be obtained after appropriate loco-regional therapies such as axillary lymphadenectomy and chemoradiotherapy in patients with solitary site of recurrence, such as case 2 in our series. The duration of DFS after initial treatment for the primary lesion and the number of metastatic regional lymph nodes can help to guide the decision whether aggressive treatments are warranted.

Conflict of interest statement
None declared.

References