Diagnosis and Surgical Outcomes for Primary Malignant Melanoma of the Esophagus: A Single-Center Experience

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Background. We summarize the experience of diagnosis and surgical therapy for primary malignant melanoma of the esophagus (PMME).

Methods. Clinical data of 13 patients diagnosed as having PMME treated by surgery as their primary therapy from 2000 to 2012 were retrospectively analyzed, and survival information was collected through follow-up.

Results. The average age (± standard deviation) of participants in this study was 66.4 ± 7.6 years, and 84.6% were male. Overall, 61.5% of tumors were located in the lower thoracic esophagus. The accuracies of clinical T stage, N stage, and TNM stage were 53.9%, 46.2%, and 38.5%, respectively, compared with pathological staging (kappa = 0.252, p = 0.023). Surgical mortality and morbidity were 7.7% and 53.9%, respectively. The incidence of lymph node metastasis for patients with tumor invading within the mucosa was 0, but increased to 42.9% (3 of 7) with tumor invading to the submucosal layer. Primary malignant melanoma of the esophagus in the mid third of the thoracic esophagus had a greater chance to metastasize to perigastric lymph nodes (2 of 5) than to middle mediastinal lymph nodes (1 of 5). For PMME located at the lower third of the thoracic esophagus, upper mediastinal lymph node metastasis was more likely to occur (2 of 4) with tumor invasion penetrating the proper muscle layer. Recurrence occurred within 1 year in all patients with tumor later than Stage Ib. The most common recurrent organ was the liver. The overall 1-year and 5-year postoperative survival rates were 54.0% and 35.9%, respectively, and lymph node metastasis was the independent predictive factor for postoperative survival (p = 0.013; odds ratio, 15.05).

Conclusions. Despite the similarity in lymph node metastatic patterns to squamous cell carcinoma, PMME is more inclined to distant metastasis. Clinical staging was inconsistent with pathological staging for PMME based on endoscopy and computed tomography. Surgical therapy was the optimal treatment for PMME at an earlier stage. Early diagnosis and aggressive lymph node dissection were beneficial for accurate staging, potentially reducing recurrence and thus improving survival.

Material and Methods

Patients
Computerized and manual searches with the keyword PMME were conducted in our patient database, and a total of 16 patients were found from January 1, 2000, to September 30, 2012. Among these patients, 2 received only palliative therapy because of old age or poor performance, and 1 patient with tumor at Stage IIb received chemoradiotherapy (four courses of fluorouracil and cisplatin, 60 Gy), who had complete remission and survived 57.9 months. The remaining 13 patients who received surgical therapy as their primary treatment comprised the study population, which accounted for 0.81% of esophagectomy cases (13 of 1603) in the same period. The present study was approved by the ethics committee in our institute.

Data Collection
All patients’ data, including demographic characteristics, symptoms, clinical stage, surgical features, pathological
stage, detailed lymph node metastatic status, immuno-
histochemical results, and recurrence and survival informa-
tion, were collected retrospectively.

Follow-Up
The follow-up assessments were conducted by telephone
and personal interviews until September 30, 2012. Complete
follow-up details were obtained in all patients, including survival status and cause of death.

Diagnostic Evaluation
Clinical and pathological stages for all patients were
reassessed according to the 7th edition of the UICC TNM
classification system [2]. Clinical stage was compared
with pathological stage to evaluate the accuracy of
preoperative staging.

Surgical Outcomes
Surgical features such as operation time and blood loss
were reviewed, and surgical morbidity and mortality were
calculated. Long-term results were evaluated by the
disease-free survival rate, and overall survival rate was
calculated through survival curves. The lymph node
metastatic pattern of PMME was investigated according
to the tumor location and tumor invasion depth. The
lymph node areas were divided as follows: supra-
clavicular area; upper mediastinal area including para-
tracheal nodes and nodes along both recurrent laryngeal
nerves and upper paraesophageal nodes (from the sternal
notch to the tracheal bifurcation); mid mediastinal area
including middle paraesophageal (from the tracheal
bifurcation to the caudal margin of the inferior
pulmonary vein), subcarinal, and bilateral hilar nodes;
lower mediastinal area from the caudal margin of the
inferior pulmonary vein including lower paraesophageal
nodes and diaphragmatic nodes; perigastric area
including paracardial nodes and left gastric nodes; and
the celiac area including common hepatic nodes, splenic
nodes, and celiac nodes.

Statistical Methods
Statistics were analyzed and relevant curves were created
using the SPSS 13.0 Statistics Software Package (SPSS Inc,
Chicago, IL). Unless stated otherwise, mean values and
standard deviations are reported. Student’s t test was
used for comparisons between subgroups. For categorical
variables, the χ² test or Fisher’s exact test was used as
appropriate. The kappa test was used to evaluate agree-
ment between clinical stage and pathological stage. Sur-
vival curves were constructed using the Kaplan-Meier
method, which was also used for univariate analysis.
Variables with a probability value less than 0.1 were
included in the Cox proportional hazards model. For all
statistical analyses, probability values less than 0.05 were
considered significant.

Results
Demographic Characteristics and Preoperative
Investigation
The average age was 66.4 ± 7.6 years, and the majority of
the patient population was male (84.6%; Table 1). Six
patients (46.2%) presented with dysphagia, 2 patients
(15.4%) had retrosternal pain or burning, and the other

Table 1. Patients With Primary Malignant Melanoma of the Esophagus in the National Cancer Center Hospital (Tokyo, Japan)
From 2000 to 2012

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Locationa</th>
<th>Size (mm)</th>
<th>Macroscopic Classificationb</th>
<th>cStage</th>
<th>pStage</th>
<th>Disease-Free Survival (m)/ Primary Recurrent Organ</th>
<th>Survival (m)</th>
<th>Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>M</td>
<td>L</td>
<td>110 × 65</td>
<td>Protruding</td>
<td>IIIIB</td>
<td>IVc</td>
<td>0.8/liver</td>
<td>4.1</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>M</td>
<td>L</td>
<td>125 × 80</td>
<td>Protruding</td>
<td>IIIIB</td>
<td>IIIC</td>
<td>9.8/Jejunum</td>
<td>13.1</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>M</td>
<td>L</td>
<td>160 × 48</td>
<td>Pedunculated</td>
<td>IIB</td>
<td>IA</td>
<td>36.2+</td>
<td>36.2</td>
<td>Y</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>M</td>
<td>L</td>
<td>75 × 55</td>
<td>Pedunculated</td>
<td>IA</td>
<td>IIB</td>
<td>5.8/mediastinal lymph node</td>
<td>12.0</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>M</td>
<td>L</td>
<td>110 × 55</td>
<td>Ulcerative and localized</td>
<td>IIA</td>
<td>IIIB</td>
<td>1.7/liver</td>
<td>3.7</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>M</td>
<td>M</td>
<td>70 × 45</td>
<td>Flat</td>
<td>IA</td>
<td>0</td>
<td>93.7+</td>
<td>93.7</td>
<td>Y</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>F</td>
<td>M</td>
<td>20 × 15</td>
<td>Pedunculated</td>
<td>IB</td>
<td>IIB</td>
<td>1.6/liver</td>
<td>3.7</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>M</td>
<td>M</td>
<td>55 × 45</td>
<td>Slightly elevated</td>
<td>IA</td>
<td>IA</td>
<td>114.1+</td>
<td>114.1</td>
<td>Y</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>M</td>
<td>L</td>
<td>70 × 70</td>
<td>Ulcerative and localized</td>
<td>IB</td>
<td>IIB</td>
<td>11.9/mediastinal lymph node</td>
<td>26.8</td>
<td>N</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>M</td>
<td>M</td>
<td>110 × 50</td>
<td>Protruding</td>
<td>IIIA</td>
<td>IIIC</td>
<td>1.8/stomach</td>
<td>2.1</td>
<td>N</td>
</tr>
<tr>
<td>11</td>
<td>62</td>
<td>F</td>
<td>L</td>
<td>170 × 60</td>
<td>Slightly elevated</td>
<td>IA</td>
<td>IA</td>
<td>46.1+</td>
<td>46.1</td>
<td>Y</td>
</tr>
<tr>
<td>12</td>
<td>75</td>
<td>M</td>
<td>L</td>
<td>90 × 60</td>
<td>Pedunculated</td>
<td>IB</td>
<td>IB</td>
<td>5.5/liver</td>
<td>10.6</td>
<td>N</td>
</tr>
<tr>
<td>13</td>
<td>75</td>
<td>M</td>
<td>M</td>
<td>50 × 23</td>
<td>Slightly elevated</td>
<td>IA</td>
<td>IIB</td>
<td>12.8+</td>
<td>12.8</td>
<td>Y</td>
</tr>
</tbody>
</table>

a The main tumor location is that with the deepest tumor invasion, U, M, and L represent upper, middle, and lower thoracic segments, respectively.
b Protruding; according to the Japanese classification of esophageal cancer, 10th edition. c Lower esophageal carcinoma with supraclavicular lymph node metastasis.
5 patients (38.4%) were referred to us for an esophageal lesion detected during examination for various reasons.

All patients underwent preoperative barium esophagography, endoscopy, and computed tomography (CT) to confirm the diagnosis and determine the macroscopic classification and clinical stage (Table 1). Eight cases (61.5%) of tumor were located in the lower thoracic esophagus, followed by the middle thoracic esophagus (5 cases, 38.5%). A lobular, polypoid, protruding, or segmented intraluminal tumor was commonly present on the esophagogram, except for some extremely early patients, in whom it was difficult to detect the lesion. In most patients, endoscopy showed a dark gray superficial lesion or endoluminal and polylolobulated mass that was inclined to bleed easily after biopsy. Immunohistochemical examination of biopsy specimens was performed in 8 patients. The diagnosis was confirmed by endoscopic biopsy in 12 patients (92.3%) and suspected in only 1 patient, for whom PMME could not be differentiated from carcinosarcoma.

As for clinical staging, the clinical T stage by endoscopy was accurate in 7 patients (53.9%), understaged in no cases, and overstaged in 6 patients (46.2%) compared with the pathological T stage, and the clinical N stage by CT was accurate in 6 patients (46.2%), understaged in 6 patients (46.2%), and overstaged in 1 patient (7.7%) compared with the pathological N stage. Endoscopic ultrasound was used in 4 patients with superficial lesions to help in T staging, and positron emission tomography/CT was used in 2 patients to rule out distant metastases. The median standard uptake value for the primary lesion was 5.8. Based on the complete preoperative workup, the clinical TNM stage was accurate in 5 patients (38.5%), understaged in 6 patients (46.1%), and overstaged in 2 patients (15.4%) compared with pathological staging ($kappa = 0.252, p = 0.023$; Table 1).

**Surgical and Pathological Features**

Subtotal esophagectomy with anastomosis in the left neck plus three-field lymph node dissection was the standard operation for esophageal cancer in our institute and was used for nearly all patients with PMME except for 1 patient, who was clinically diagnosed as having an esophagogastric junction tumor and thus underwent a left transthoracoabdominal procedure plus lower mediastinal and abdominal lymph node dissection. The operation time was $378.4 \pm 108.0$ minutes, and blood loss was $345.4 \pm 237.0$ g. One patient (7.7%) died of sepsis subsequent to empyema caused by leakage on postoperative day 64. Leakage occurred in 3 patients (23.1%), and left recurrent laryngeal nerve palsy, chylothorax, and incision infection occurred in 1 patient each (7.7%). The overall morbidity was 53.9% (7 of 13).

The number of dissected lymph nodes was 53.2 ± 22.7. Primary malignant melanoma of the esophagus at the mid third of the thoracic esophagus was more likely to metastasize to perigastric lymph nodes (2 of 5) than to middle mediastinal lymph nodes (1 of 5). For PMME located at the lower third of the thoracic esophagus, there was still 1 patient with a cervical lymph node metastasis, and upper mediastinal lymph node metastasis was more likely to occur (2 of 4), with tumor invasion depth pene- trating the proper muscle layer (Table 2). No lymph node metastasis was detected in 2 patients with tumor invasion depth restricted to the mucosa (Tis or T1a), and 3 of 7 patients with tumor invasion to the submucosal layer (T1b) had lymph node metastasis.

Pathological examination showed intramural metastasis in 5 patients (38.5%), lymphatic invasion in 4 patients (30.8%), and venous invasion in 2 patients (15.4%). One patient (7.7%) was diagnosed as having amelanic PMME. Melanocytosis was found in all patients (100%), and there were satellite lesions in 9 patients (69.2%). Immunohistochemical examination was used for all surgical pathological examinations. The positive rate was as follows: S-100 (10 of 12); HMB-45 (12 of 13); Melan-A (10 of 11); CK-AE1 of 3 (0 of 1); Vim (1 of 1); SOX10 (2 of 2); aSMA (0 of 1); caldesmon (0 of 1); desmin (0 of 1); CD34 (0 of 1); and Ckit (0 of 1).

Five patients with their disease at later than Stage II underwent adjuvant chemotherapy consisted of two courses of dacarbazine, nimustine, and vincristine plus fluorouracil or not (DAV or DAVF).

**Survival and Predictors for Survival**

Follow-up was achieved in all patients. As shown in Table 1, recurrence was within 1 year in all patients with tumor later than Stage Ib. The most common recurrent organ was the liver, and chemotherapy consisted of dacarbazine, nimustine, vincristine, and tamoxifen (DAVTam), and in 1 case of brain metastasis, radiotherapy (30 Gy) was used to treat recurrence, but

<table>
<thead>
<tr>
<th>Area</th>
<th>Total (n = 13) (%)</th>
<th>Tumor Location</th>
<th>Tumor Invasive Depth</th>
<th>T1a (n = 2)</th>
<th>T1b (n = 7)</th>
<th>T2 (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraclavicular</td>
<td>1 (7.7)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Upper mediastinum</td>
<td>3 (23.1)</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mid mediastinum</td>
<td>2 (15.4)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lower mediastinum</td>
<td>1 (7.7)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Perigastric</td>
<td>6 (46.2)</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Celiac</td>
<td>1 (7.7)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
with a poor result. Almost all patients with a recurrence died within 1 year. The 1-year postoperative disease-free survival rate was 38.5% (Fig 1), and the 1- and 5-year postoperative survival rates were 54.0% and 35.9%, respectively (Fig 2).

Univariate and multivariate analyses of predictive factors for postoperative survival revealed that lymph node metastasis was the independent predictive factor for postoperative survival ($p = 0.013$; odds ratio, 15.05; Table 3).

**Comment**

It has been reported that the postoperative 5-year survival rate for PMME ranges from 2.2% to 37.5% [3, 4]. In the present study, the 5-year survival rate was 35.9%, which may have been mainly attributable to the fact that this cohort consisted of more early-stage patients.

Our previous study [5] showed that in patients with squamous esophageal carcinoma at the mid third of the esophagus, node metastasis was more frequent in the perigastric area than in the middle mediastinum; even in patients with squamous esophageal carcinoma located in the lower esophagus, node metastasis was more frequent in the upper mediastinum than in either the mid or lower mediastinum. In patients with tumor invading or penetrating the muscle layer, node metastasis in the mid and lower mediastinum was still less frequent than in the upper mediastinum or the perigastric area. The present study showed that the pattern of lymph node metastasis was somewhat similar to that of esophageal squamous cell carcinoma, but the most common form of recurrence for PMME was distant hematogenous metastasis rather than lymph node or regional recurrence, and almost all the patients with tumor later than Stage Ib recurred within about 1 year after operation. Ando and colleagues [6] summarized their 15-year experience in en-bloc esophagectomy plus three-field lymph node dissection for advanced squamous esophageal carcinoma and reported the overall 5-year survival rate in the range of 40% to 50%, which is higher than the overall survival rate of PMME in our result, which could be explained by the poor biological behavior of PMME [7].

As for predictive factors for long-term survival, Yamaguchi and colleagues [8] reviewed 72 patients with PMME treated with surgery from 1993 to 2003 in Japan and addressed the predictive factors for prognosis, such as age older than 60 years, invasion deeper than T2, positive lymph node metastasis, and positive distant metastasis. The present results showed that lymph node metastasis was the independent predictive factor for postoperative survival. Although fewer cases were enrolled in the present analysis, taking the rarity of PMME into consideration, the sample appeared adequate for evaluating with Cox regression only three potential variables screened out by univariate analysis.

Both the clinical and pathological stages were not highly consistent in the present study. If endoscopic ultrasound had been used routinely in each patient, the accuracy may have been further improved. The actual accuracy of CT in N staging was even worse in the present study. Meta-analyses performed to examine the utility of sonography, CT, and positron emission tomography/CT for the staging and surveillance of patients with melanoma based on 10,528 patients between 1990 and 2009 found that positron emission tomography/CT was the most accurate modality for detection of metastases, with both a sensitivity and specificity of 95% [9]. Thus, we advocate routine use of endoscopic ultrasound and positron emission tomography/CT in the preoperative investigation of PMME.

The lower thoracic esophagus is the location most susceptible to PMME, followed by the midthoracic esophagus in the present cohort. The reason for this may be related to the greater concentration of melanocytes in...
Table 3. Univariate and Multivariate Analyses of Predictive Factors for Postoperative Survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate p Value</th>
<th>Multivariate p Value</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 y</td>
<td>0.745</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sex = female</td>
<td>0.907</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Location at low thoracic esophagus</td>
<td>0.584</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Surgical complication</td>
<td>0.865</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Tumor invasion depth ≥T2</td>
<td>0.184</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>0.001</td>
<td>0.013</td>
<td>15.05</td>
<td>1.757–128.795</td>
</tr>
<tr>
<td>pTNM stage</td>
<td>0.017</td>
<td>0.918</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Intramural metastasis</td>
<td>0.087</td>
<td>0.627</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>0.109</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Venous invasion</td>
<td>0.170</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

CI = confidence interval.

these regions [10]. Melanocytosis, which also presents as a black or gray appearance in the endoscopic view, is indicative of the lesion being the primary lesion rather than a secondary in cases of melanoma of the esophagus [11]. In the present study, melanocytosis was detected in all cases, justifying the view that they were all primary lesions. For lesions short of melanin, we advocate biopsy combined with immunohistochemical staining, which should be able to clearly define the melanocytic nature of the tumor cells, based on the expression by tumor cells of classic immunomarkers, such as vimentin, S-100 protein, HMB-45, and Melan-A, usually in the absence of expression of epithelial, smooth muscle, and lymphoid markers. In the present cohort, biopsies were conducted in all patients, and preoperative definitive diagnoses were made in 92.3% of the cases, which was higher than reported in the literature [12]. Because of the limitations of biopsy sampling, diagnosis failed to be confirmed preoperatively in only 1 patient in the present study, whose preoperative immunohistochemistry result was both HMB-45– and Melan-A-negative.

Our study has some limitations for its retrospective nature: (1) Routine preoperative workup only included endoscopy and CT, so the accuracy of clinical staging should be interpreted with caution. (2) Although great improvement has been made in chemotherapy for melanoma, there were no patients in the current study undertaking chemotherapy as neoadjuvant therapy. Based on the results that all the patients with tumor later than Stage Ib recurred within about 1 year after operation, it seems that neoadjuvant chemotherapy might have a role in downstaging the advanced disease for better surgical results, although until now we have no such experience, nor is there any such experience reported in the literatures. (3) The sample was small owing to the rarity of the disease.

Based on the pattern of lymph node metastasis, a high proportion of intramural metastasis, lymph node metastasis as the predictive factor of postoperative survival, and the fact that melanocytosis might be the precursor of melanoma [13], we conclude that early diagnosis and esophagectomy plus lymph node dissection are beneficial for accurate staging, potentially reducing recurrence and improving survival.

References