The Range of Tumor Extension Should Have Precedence over the Location of the Deepest Tumor Center in Determining the Regional Lymph Node Grouping for Widely Extending Esophageal Carcinomas

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Background: The Japanese Guide Lines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus (9th edn) give precedence to the location of the deepest tumor center rather than the range of tumor extension when determining regional lymph node grouping. We evaluated the validity of this recommendation.

Methods: The subjects were 49 patients with carcinomas of the distal thoracic esophagus and cardia who had undergone esophagectomy with three-field lymph node dissection. We measured variables defining tumor location, such as the distance from the esophagogastric junction (EGJ) to the proximal margin of the tumor (DJP), the distance from the EGJ to the distal margin of the tumor (DJD), and the distance from the EGJ to the deepest tumor center (DJC). To examine the relation of tumor location to lymph node metastasis in the proximal direction, the patients were divided into two groups according to the presence (14 patients) or absence (35 patients) of middle-upper mediastinal and/or cervical lymph node metastases. These two groups were compared with respect to the above variables. To analyze lymph node metastasis in the distal direction, the patients were also divided into two groups according to the presence (12 patients) or absence (37 patients) of distant abdominal lymph node metastases. These two groups were similarly compared with respect to the above variables.

Results: DJP was significantly longer in the patients with middle–upper mediastinal and/or cervical lymph node metastases than in those without such metastases. Multiple logistic regression analysis showed that the DJP was a better predictor of middle–upper mediastinal and/or cervical lymph node metastases than was the DJC. The DJD was significantly longer in the patients with distant abdominal lymph node metastases. Multiple logistic regression analysis also showed that the DJD was a better predictor of distant abdominal lymph node metastases than was the DJC.

Conclusions: The range of tumor extension is a more reliable predictor of the risk of distant lymph node metastases than is the location of the deepest tumor center in esophageal carcinoma.

Key words: esophageal cancer — cardia cancer — tumor extension — tumor center — lymph node metastasis

INTRODUCTION

Carcinomas of the distal thoracic esophagus and cardia have peculiar clinicopathologic characteristics because of the unique anatomic features of this region. The esophagus has squamous epithelium, and the stomach has columnar epithelium.
epithelium. The mechanisms of carcinogenesis, histological features, extent of lymph node metastases, operative methods, and prognoses of these carcinomas remain controversial (1–3). The operative approach and range of lymph node dissection should be based on an accurate evaluation of the extent of primary tumor and nodal metastases. A better understanding of clinicopathologic features and the development of improved classification systems are needed.

Most of the currently used classification systems are based on variables defining tumor location, such as the location of the tumor center (the point of deepest tumor invasion) and the range of tumor extension (4–6). The Japanese Guide Lines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus (9th edn) regard the location of the deepest tumor center to be the most important variable defining tumor location and regional lymph node grouping (6). Furthermore, in widely extending esophageal carcinomas, the location of the deepest tumor center has precedence over the range of tumor extension in determining regional lymph node grouping. According to the Guide Lines, both widely extending and narrowly extending esophageal cancers are considered to have the same lymph node grouping if the deepest tumor centers reside in the same area (Fig. 1). We questioned the validity of the regional lymph node grouping in the Japanese Guide Lines.

In this study of carcinomas of the distal thoracic esophagus and cardia, we used the distance from the esophagogastric junction (EGJ) to the margin of the tumor as an index of the range of tumor extension. Our results suggest that the range of tumor extension is a more accurate predictor of lymph node metastases than is the location of the deepest tumor center.

**Patients and Methods**

**Patients**

We studied 49 patients with primary carcinomas of the distal thoracic esophagus and cardia with at least part of the primary tumor present in the abdominal esophagus (Ae), as defined by the Japanese Guide Lines. We could thus investigate various tumors with different patterns of extension. Extension ranges of the tumors were divided into the following four types: 32 patients had widely extending carcinomas that occupied the lower thoracic esophagus (Lt), Ae, and stomach (G) (LtAeG); six had carcinomas that occupied both the Lt and Ae (LtAe); eight had carcinomas that occupied both the Ae and G (AeG); and three had carcinomas that were localized to the Ae. All patients had undergone esophagectomy with three-field lymph node dissection (curative R0 resection) at the Department of Surgery, Division of Digestive Surgery, Kyoto Prefectural University of Medicine, between January 1987 and December 2003. We categorized their regional lymph nodes into cervical, upper mediastinal, middle mediastinal, lower mediastinal, and abdominal lymph nodes. In accordance with the Japanese Guide Lines, we defined celiac artery, common hepatic artery, and splenic artery lymph nodes as distant abdominal lymph nodes.

To examine the relation of tumor location to lymph node metastasis in the proximal direction, the patients were divided into two groups according to the presence or absence of middle–upper mediastinal and/or cervical lymph node metastases. Among the 49 patients, 14 were positive and 35 negative for middle–upper mediastinal and/or cervical lymph node metastases. Furthermore, to examine the relation of tumor location to lymph node metastasis in the distal direction, the patients were divided into two groups according to the presence or absence of distant abdominal lymph node metastases. Among the 49 patients, 12 were positive and 37 negative for distant abdominal lymph node metastases.

**Clinicopathologic Features**

We compared patients positive for distant lymph node metastasis and those negative for metastasis with respect to age, sex, tumor size, depth of tumor invasion, histological type, gross type, lymphatic invasion, and blood vessel invasion. The depth of tumor invasion was evaluated on specimens stained with hematoxylin and eosin and was classified according to the Japanese Guide Lines as being from pTis to pT2 (nine patients) or from pT3 to pT4 (40 patients). Histologically, tumors were classified into two types: squamous cell carcinoma (41 patients) or others (adenocarcinoma,
five patients; adenosquamous carcinoma, two patients; basaloïd carcinoma, one patient). Macroscopically, tumors were classified as elevated (27 patients) or depressed (22 patients). Lymphatic invasion and blood vessel invasion were evaluated microscopically and categorized as positive or negative.

**Measurement of Variables Defining Tumor Location**

Using resected organs, we measured and recorded several variables defining tumor location. As recommended by the *Japanese Guide Lines*, each resected specimen was stretched to a length most closely approximating that in the human body. The specimen was then fixed, and variables were assessed by macroscopic examination. The EGJ was decided macroscopically by inspecting the border between the esophageal epithelium and the gastric mucosa. We used three variables to define tumor location: the distance from the EGJ to the proximal margin of the tumor (DJP), the distance from the EGJ to the distal margin of the tumor (DJD), and the distance from the EGJ to the deepest tumor center (DJC). We retrospectively examined the relations of these variables to lymph node metastases (Fig. 2).

**Statistical Analysis**

Statistical analysis was done with Fisher’s exact tests and Student’s t-tests for clinicopathological characteristics and variables defining tumor location. Differences were considered statistically significant when \( P \) values were less than 0.05. Logistic regression analysis was used to identify risk factors associated with distant lymph node metastases. Statistical analyses were performed with the statistical software JMP, version 5.

![Diagram](https://example.com/diagram.png)

**Figure 2.** Three variables defining tumor location. DJC, distance from the EGJ to the deepest tumor center; DJP, distance from the EGJ to the proximal margin of tumor; DJD, distance from the EGJ to the distal margin of tumor.

**RESULTS**

**Relation of Tumor Location to Lymph Node Metastasis in the Proximal Direction**

Patients with and without middle–upper mediastinal and/or cervical lymph node metastases did not differ significantly with respect to age, sex, tumor size, depth of tumor invasion, histological type, gross type, lymphatic invasion, or blood vessel invasion (Table 1). The DJP was significantly longer in patients with middle–upper mediastinal and/or cervical lymph node metastases. However, the DJC and the DJD were similar in patients with and those without middle–upper mediastinal and/or cervical lymph node metastases (Table 1).

Logistic regression (univariate) analysis was performed with middle–upper mediastinal and/or cervical lymph node metastases as the dependent variable. The DJP, used as an independent variable, was found to significantly correlate with middle–upper mediastinal and/or cervical lymph node metastases. In contrast, when the DJC was used as the independent variable, there was no correlation with middle–upper mediastinal and/or cervical lymph node metastases. Similarly, when the DJD was used as the independent variable, there was no correlation (Table 2a). When multiple logistic regression analysis was performed with the DJP, DJC and DJD as independent variables, \( P \) values were 0.105, 0.762, and 0.805, respectively. These data indicate that the range of tumor extension is a stronger predictor of the risk of middle–upper mediastinal and/or cervical lymph node metastases than is the location of the deepest tumor center.

We compared patients with and those without middle–upper mediastinal and/or cervical lymph node metastases with respect to tumor location as defined by the *Japanese Guide Lines*. We found no clear correlation between the location of the deepest tumor center (the variable used to define tumor location by the *Japanese Guide Lines*) and metastases to these lymph nodes. As for the range of tumor extension, most of the tumors with middle–upper mediastinal and/or cervical lymph node metastases widely occupied three areas: Lt, Ae, and G (LtAeG). In addition, all tumors with metastases to these lymph nodes occupied Lt (Table 2b). These results suggest that the range of tumor extension correlates more closely with middle–upper mediastinal and/or cervical lymph node metastases than does the location of the deepest tumor center, the variable used to define tumor location by the *Japanese Guide Lines*.

As shown in Fig. 1, we sometimes find a shift of the tumor center in patients with esophageal cancer. Therefore, we analyzed the shift of the tumor center in all 49 patients and examined the relation between this variable and lymph node metastases. We calculated the diameter of the tumor in the direction of the esophageal axis by measuring the DJP and DJD. The true anatomical center point of the tumor was then decided. The shift of the tumor center (the distance from the location of deepest tumor invasion to the true
anatomical center point of the tumor) was calculated, and the data were normalized with the radius of the tumor in the direction of the esophageal axis. As shown in Fig. 3, shifts in tumor centers were within one tenth of radiuses in 42.9% of the patients. The maximum shift in the tumor center was 0.509 proximally and 0.508 distally. The shift in the tumor center was similar in patients with and those without middle–upper mediastinal and/or cervical lymph node metastases (positive, $-0.035 \pm 0.038$; negative, $-0.002 \pm 0.038$, $P = 0.605$). These results suggest that middle–upper mediastinal and/or cervical lymph node metastases are not influenced by shifts of the tumor center.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Middle–upper mediastinal and/or cervical lymph node metastases</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive ($n = 14$)</td>
<td>Negative ($n = 35$)</td>
</tr>
<tr>
<td>Age (younger than 60 years/60 years or older)</td>
<td>6/8</td>
<td>15/20</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>12/2</td>
<td>31/4</td>
</tr>
<tr>
<td>Tumor size (less than 50 mm/50 mm or more)</td>
<td>5/9</td>
<td>20/15</td>
</tr>
<tr>
<td>Depth of tumor invasion (pTis-T2/pT3-4)</td>
<td>2/12</td>
<td>7/28</td>
</tr>
<tr>
<td>Histological type (squamous cell carcinoma/others)</td>
<td>11/3</td>
<td>30/5</td>
</tr>
<tr>
<td>Gross type (elevated/depressed)</td>
<td>7/7</td>
<td>20/15</td>
</tr>
<tr>
<td>Lymphatic invasion ($-/+$)</td>
<td>1/13</td>
<td>11/24</td>
</tr>
<tr>
<td>Blood vessel invasion ($-/+$)</td>
<td>6/8</td>
<td>18/17</td>
</tr>
<tr>
<td>DJP (mm)</td>
<td>49.6 ± 6.8</td>
<td>31.4 ± 3.1</td>
</tr>
<tr>
<td>DJC (mm)</td>
<td>15.2 ± 3.5</td>
<td>8.6 ± 2.1</td>
</tr>
<tr>
<td>DJD (mm)</td>
<td>15.1 ± 3.3</td>
<td>14.1 ± 2.7</td>
</tr>
</tbody>
</table>

DJP, distance from the EGJ to the proximal margin of tumor; DJC, distance from the EGJ to the deepest tumor center; DJD, Distance from the EGJ to the distal margin of tumor. Values are means ± SE (standard error). Statistical analysis was carried out using Fisher’s exact tests and Student’s $t$-tests.

* $P < 0.05$.

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Estimate</th>
<th>Standard error</th>
<th>$P$ value</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DJP</td>
<td>0.038</td>
<td>0.016</td>
<td>0.015*</td>
<td>1.039</td>
<td>1.007–1.071</td>
<td>0.115</td>
</tr>
<tr>
<td>DJC</td>
<td>0.042</td>
<td>0.026</td>
<td>0.112</td>
<td>1.043</td>
<td>0.990–1.098</td>
<td>0.046</td>
</tr>
<tr>
<td>DJD</td>
<td>0.005</td>
<td>0.021</td>
<td>0.833</td>
<td>1.004</td>
<td>0.964–1.047</td>
<td>0.001</td>
</tr>
</tbody>
</table>

DJP, distance from the EGJ to the proximal margin of tumor; DJC, distance from the EGJ to the deepest tumor center; DJD, Distance from the EGJ to the distal margin of tumor; 95% CI, 95% confidence interval.

* $P < 0.05$.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Middle–upper mediastinal and/or neck lymph node metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive ($n = 14$)</td>
</tr>
<tr>
<td>Location of deepest tumor center</td>
<td>Lt/Ae/G</td>
</tr>
<tr>
<td>Range of tumor extension</td>
<td>LtAeG/LtAe/Ae/AeG</td>
</tr>
</tbody>
</table>

Lt, lower thoracic esophagus; Ae, abdominal esophagus; G, stomach.
RELATION OF TUMOR LOCATION TO LYMPH NODE METASTASIS

whether resection of these lymph nodes is indicated. We considered this value a landmark that can be used to decide whether resection of these lymph nodes. As shown in Fig. 4a, no patient in whom DJD were less than 0 mm had distant abdominal lymph node metastases. In contrast, when the DJD was used as the independent variable, there was no correlation with distant abdominal lymph node metastases. Similarly, when the DJP was used as the independent variable, there was no correlation (Table 4a). When multiple logistic regression analysis was performed with the DJD, DJC, and DJP as independent variables, P values were 0.049, 0.777, and 0.772, respectively. These data indicate that the range of tumor extension was a stronger predictor of the risk of distant abdominal lymph node metastases than was the location of the deepest tumor center.

With respect to tumor location as defined by the Japanese Guide Lines, patients with and those without distant abdominal lymph node metastases were compared. We found no clear correlation between the location of the deepest tumor center and distant abdominal lymph nodes metastases. In contrast, with respect to range of tumor extension, all tumors with distant abdominal lymph nodes metastases widely occupied three areas. Similar to the results of analysis in the proximal direction, all tumors with distant abdominal lymph nodes metastases occupied G (Table 4b). These results suggest that the range of tumor extension correlates more closely with distant abdominal lymph node metastases than does the location of the deepest tumor center, the variable used to define tumor location by the Japanese Guide Lines. Furthermore, the shift of the tumor center was similar in patients with and those without distant abdominal lymph node metastases (positive, 0.009 ± 0.050; negative, −0.018 ± 0.035, P = 0.691). These results suggest that distant abdominal lymph node metastases were unrelated to shifts of the tumor center.

We investigated the relation between the DJD and distant abdominal lymph node metastases to determine whether there was a clear cut-off point. As shown in Fig. 4b, no patient in whom DJD were less than 0 mm had distant abdominal lymph node metastases. This finding indicates that distant abdominal lymph nodes, such as the celiac artery lymph nodes, should be resected in patients who have esophageal cancers that involve the stomach.

DISCUSSION

Esophagectomy with three-field lymph node dissection is considered to be the standard procedure for the treatment of cancer of the thoracic esophagus (7–10). However, the operative procedure for cancers involving the distal thoracic esophagus and cardia remains controversial because the region is very complex anatomically as well as histologically (11–13). Differences in operative procedure can affect both curability of cancer and patients’ postoperative quality of life (14, 15).

Preoperative diagnosis of the extent of primary tumor and nodal metastasis has an important role in deciding whether operation should be done through a transthoracic, transabdominal, or transhiatal approach (16, 17). Esophagectomy by
a left thoracoabdominal approach is often used for carcinomas of the distal thoracic esophagus or cardia, but its value is questionable because mediastinal lymphadenectomy is limited almost exclusively to the lower mediastinum. Transhiatal esophagectomy is also inappropriate for mediastinal lymphadenectomy. It is thus very important to accurately predict middle–upper mediastinal lymph node metastasis when selecting the operative approach. Because the stomach is usually used for reconstruction after esophagectomy, preoperative prediction of abdominal lymph node metastases is also essential.

The appropriate range of lymphadenectomy for distal thoracic esophageal cancer remains controversial, especially with regard to whether middle–upper mediastinal and/or cervical lymphadenectomy should be performed (18–20). Baba et al. proposed that the range of mediastinal lymphadenectomy for distal esophageal cancer should be based on the anatomic location of the deepest tumor center (21). They recommended that the recurrent nerve lymph nodes, representing the upper margin of the mediastinal lymph nodes, should be dissected in esophageal cancers in which the tumor center is located within 1–5 cm from the EGJ. Furthermore, they pointed out that upper mediastinal lymphadenectomy could be omitted in esophageal cancers in which the deepest tumor center is located within 1 cm from the EGJ. Our analysis of carcinomas arising in the distal thoracic esophagus or cardia showed no significant relation between the DJC and middle–upper mediastinal and/or cervical lymph node metastases. However, we showed a positive correlation between the frequency of these lymph node metastases and the DJP. In our analysis, the cut-off point of the DJP used to predict middle–upper mediastinal and/or cervical lymph node metastases was 20 mm. The range of the abdominal esophagus is generally considered to be about 20 mm from EGJ in Japan (5). Therefore, our results indicate that middle–upper mediastinal lymph node dissection by a right thoracoabdominal approach should be performed in patients whose cancers extend to the lower thoracic esophagus.

Several previous studies have examined the clinical features of esophageal cancer involving the stomach, including involvement patterns, histological characteristics, and outcomes (22–24). To our knowledge, however, no previous study has assessed the relation of abdominal lymph node metastasis to tumor location as defined by variables such as the length of stomach invasion and site of deepest invasion. Our study clearly showed that the DJD is a more reliable predictor of the risk of distant abdominal lymph node metastases than is the DJC. Further, our results concerning the cut-off point of the DJD indicated that distant abdominal lymph nodes, such as the celiac artery lymph nodes, should be resected in addition to the perigastric lymph nodes in patients with cancer involving the stomach.

In this study, we examined the relations of variables defining tumor location to lymph node metastases by
macroscopically evaluating resected organs because important morphologic landmarks, such as tumor margins, tumor center, and the EGJ could be clearly defined. Clinically, however, the ability to preoperatively assess these variables by means of techniques such as endoscopy and esophagography would greatly facilitate selection of the surgical procedure of choice before operation. In our analyses of distal thoracic esophageal and cardia cancers, variables defining tumor location were measured using resected specimens stretched to a length most closely approximating that in the human body. We therefore believe that our post-operatively measured values would not significantly differ from those obtained by pre-operative examinations. With resected specimens, however, measurement error may increase as the distance from the EGJ becomes longer. Ultimately, therefore, pre-operatively measured values should be used.

Table 4a. Results of logistic regression using distant abdominal lymph node metastases as the dependent variable (univariate analysis)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Estimate</th>
<th>Standard error</th>
<th>P value</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>DJD</td>
<td>0.060</td>
<td>0.026</td>
<td>0.024*</td>
<td>1.061</td>
<td>1.008–1.118</td>
<td>0.118</td>
</tr>
<tr>
<td>DJC</td>
<td>0.018</td>
<td>0.028</td>
<td>0.511</td>
<td>0.982</td>
<td>0.930–1.037</td>
<td>0.008</td>
</tr>
<tr>
<td>DJP</td>
<td>0.008</td>
<td>0.015</td>
<td>0.581</td>
<td>1.008</td>
<td>0.980–1.038</td>
<td>0.006</td>
</tr>
</tbody>
</table>

DJD, distance from the EGJ to the distal margin of tumor; DJC, distance from the EGJ to the deepest tumor center; DJP, distance from the EGJ to the proximal margin of tumor.

Values are means ± SE (standard error). Statistical analysis was carried out using Fisher’s exact tests and Student’s t-tests. *P < 0.05.

Table 4b. Comparison between patients positive for distant abdominal lymph node metastases and those negative for such metastases according to tumor location as defined by the Japanese Guide Lines

<table>
<thead>
<tr>
<th>Variable</th>
<th>Distant abdominal lymph node metastases</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of tumor center</td>
<td>Lt/Ae/G</td>
<td>Positive (n = 12)</td>
<td>Negative (n = 37)</td>
</tr>
<tr>
<td>Range of tumor extension</td>
<td>LtAeG/LtAe/Ae/G</td>
<td>12/0/0/0</td>
<td>20/6/3/8</td>
</tr>
</tbody>
</table>

Lt, lower thoracic esophagus; Ae, Abdominal esophagus; G, stomach.
We focused our attention on the range of tumor extension and the location of deepest tumor invasion in this analysis of widely extending esophageal carcinomas. The latter value, i.e. the location of deepest tumor invasion, has precedence in determining the regional lymph node grouping of widely extending esophageal carcinomas according to the Japanese Guide Lines. We consider it more difficult to diagnose the location of deepest tumor invasion rather than the range of tumor extension on preoperative examinations such as endoscopy and esophagography. In this sense, we believe that a revised classification of lymph node metastases that better reflects the range of tumor extension should be established.

In conclusion, our results clearly show that the range of tumor extension is a more reliable predictor of the risk of distant lymph node metastases than is the location of the deepest tumor invasion rather than the range of tumor extension should be established. The location of deepest tumor invasion, has precedence in determining the regional lymph node grouping of widely extending esophageal carcinomas according to the Japanese Guide Lines. We consider it more difficult to diagnose the location of deepest tumor invasion rather than the range of tumor extension on preoperative examinations such as endoscopy and esophagography. In this sense, we believe that a revised classification of lymph node metastases that better reflects the range of tumor extension should be established.

In conclusion, our results clearly show that the range of tumor extension is a more reliable predictor of the risk of distant lymph node metastases than is the location of the deepest tumor invasion rather than the range of tumor extension should be established.

References