Predictors of Lymph Node Metastasis in Surgically Resected T1 Esophageal Cancer

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Background. The application of endoscopic therapies for early cancers of the esophagus is limited by the possible presence of regional lymph node metastases. Our objective was to determine the prevalence and predictors of lymph node metastases in patients with pT1 carcinoma of the esophagus and the gastric cardia.

Methods. The National Cancer Institute’s Surveillance Epidemiology and End Results Database (2004 to 2010) was used to identify all patients with pT1 carcinomas who underwent primary surgical resection for squamous cell carcinoma (SCC) or adenocarcinoma (EAC) of the esophagus and of the esophagogastric junction (AEG). Prevalence of lymph node metastases was assessed, and survival in all types of cancer was calculated. Multivariate logistic regression was used to identify factors predicting positive lymph node status.

Results. There were 1,225 patients (84% male), with a mean age of 64 ± 10 years, and 90% were white. Intramucosal disease was present in 44% of patients, and submucosal invasion (T1b) was present in 692 (56%). Prevalence of lymph node metastases in EAC, SCC, and AEG was 6.4%, 6.9%, and 9.5% for pT1a tumors and 19.6%, 20%, and 22.9% for pT1b tumors, respectively. In patients with more than 23 lymph nodes removed during resection, prevalence of lymph node metastases in EAC, SCC, and AEG was 8.1%, 25%, and 7.4% for pT1a tumors and 27.8%, 33.3%, and 22% for pT1b tumors, respectively. Positive lymph node status was associated with worse overall 5-year survival in EAC (N0 vs N+: 78% vs 52%) and AEG (N0 vs N+: 83% vs 44%) but did not have a significant effect on the long-term survival of patients with SCC. Infiltration of the submucosa, tumor size exceeding 10 mm, and poor tumor differentiation were independently associated with the risk of nodal disease. Prevalence of lymph node metastasis negative for these three risk factors was only 4.8%.

Conclusions. Prevalence of lymph node metastasis in early esophageal cancer is high in patients with T1 cancer. Inadequate lymphadenectomy underestimates lymph node status. Endoscopic treatment can be considered only in a select group of patients with early esophageal cancer.

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Management of early esophageal cancer arising from Barrett mucosa is controversial [1]. Although radical esophagectomy and extended lymphadenectomy are still considered the gold standard in treating early esophageal neoplasia by many centers, less invasive endoscopic approaches are increasingly propagated despite some serious concerns about the oncologic adequacy of these methods and the lack of high-level evidence [2]. Theoretically, endoscopic mucosal resection (EMR) embodies the long sought after, ideal treatment of early cancer. On one hand, it is organ preserving without the long-term consequences of radical resection and can be performed with practically zero mortality and very low morbidity [3]. On the other hand, an indiscriminate use of these techniques may compromise long-term survival of patients with early esophageal neoplasia, particularly if lymph node metastases are present.

The success of endoscopic treatment is based on two premises: (1) most patients with superficial esophageal cancer have no lymph node metastasis, and (2) it is possible to predict lymph node involvement, thus selecting patients where endoscopic resection of the cancerous mucosa is sufficient and a surgical lymphadenectomy is unnecessary. Published single-center studies of esophagectomy specimens indicate that the prevalence of lymph node metastases is 0% to 16% [4] for intramucosal esophageal cancer and up to 54% for tumors involving the submucosa [5]. In addition, current methods of patient
selection and the available diagnostic procedures and immunohistochemical predictors are unreliable for predicting nodal disease [6, 7], emphasizing the need for descriptive data to estimate the risk of lymphatic spread in patients with early esophageal cancer.

In this study, we used the Surveillance, Epidemiology, and End Results (SEER) database to assess the prevalence of lymph node metastases in a large number of patients with early squamous cell cancer (SCC) and adenocarcinoma (EAC) of the esophagus and the esophagogastric (AEG) junction and to identify factors predicting nodal positive disease.

**Material and Methods**

The SEER program of the National Cancer Institute is the only comprehensive source of population-based cancer information in the United States. SEER currently collects and publishes incidence, treatment information, and survival data from population-based cancer registries covering more than 28% of the United States population. The registries maintain active follow-up of all cases. From this database, all patients with microscopically confirmed, first primary T1 EAC and SCC of the esophagus and AEG that were diagnosed between 2004 and 2010 were identified using the respective histology and tumor site codes. We limited our analysis to patients who were not diagnosed at autopsy or from death certificate data and selected those who underwent surgical resection (partial or total esophagectomy). Patients who received neoadjuvant therapy were excluded.

**Definitions**

Patients were stratified to T1a (tumor invades lamina propria or into but not beyond the muscularis mucosae) and T1b (tumor invades the submucosa without invasion of the muscularis propria) groups based on information provided by SEER. Analyzed variables included age at diagnosis, sex, race, tumor size in millimeters, histologic evaluation, grade, depth of tumor invasion, lymph node status, number of resected nodes, and cancer-related survival. Race was dichotomized into “white” or “nonwhite.” Adequate lymphadenectomy was defined as at least 23 lymph nodes removed during the operation [8].

**Statistics**

The Kaplan-Meier method was used to assess and compare disease-related survival of patients with various variables. Survival curves were compared by log-rank analysis. Multivariate logistic regression was used to identify significant independent predictors of lymph-node positivity and that of survival. The level of statistical significance was set at $p$ of less than 0.005. Analyses were conducted using R 3.1.0 software [9].

**Results**

The study included 1,225 patients with undergoing surgical resection for T1 EAC, SCC, and AEG between 2004 and 2010 who met the inclusion criteria. Mean age was 64.2 years. Most patients were male (84%) and white (90%). Only 8% of all patients had SCC histologies. Table 1 summarizes patient characteristics and tumor-related variables. The percentage of men, those of white race, and the percentage of intramucosal cancer were significantly different between the distinctive histologies. Distribution of grade, and the percentage of tumor size exceeding 10 mm and of patients undergoing operations with adequate lymphadenectomy did not show any significant difference. A median number of 10 lymph nodes were resected during the operation. Lymphadenectomy was adequate in 159 patients (13%).

**Prevalence of Lymph Node Metastasis**

Overall, 186 of 1,225 patients (15.2%) had lymph node metastasis. Table 2 reports the rates of lymph node metastasis in each histologic classification and histologic subgroup. Limiting our analysis to the 159 patients with

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**Table 1. Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Variables</th>
<th>EAC (n = 674)</th>
<th>SCC (n = 98)</th>
<th>AEG (n = 453)</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean y</td>
<td>63.7</td>
<td>65.6</td>
<td>64.7</td>
<td>0.132</td>
</tr>
<tr>
<td>Male, %</td>
<td>89.9</td>
<td>67.4</td>
<td>78.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White, %</td>
<td>95.1</td>
<td>69.4</td>
<td>88.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T1a, %</td>
<td>48.8</td>
<td>31.6</td>
<td>38.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T1b, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1, %</td>
<td>15.6</td>
<td>14.3</td>
<td>13.9</td>
<td>0.0029</td>
</tr>
<tr>
<td>Grade 2, %</td>
<td>42.3</td>
<td>46.9</td>
<td>44.8</td>
<td></td>
</tr>
<tr>
<td>Grade 3, %</td>
<td>25.5</td>
<td>25.5</td>
<td>32.9</td>
<td></td>
</tr>
<tr>
<td>Tumor size &gt;10 mm, %</td>
<td>74.2</td>
<td>81.23</td>
<td>79.6</td>
<td>0.1063</td>
</tr>
<tr>
<td>No. of Lymph nodes removed, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6.6</td>
<td>4.1</td>
<td>6.4</td>
<td>0.7464</td>
</tr>
<tr>
<td>&gt;15</td>
<td>31.6</td>
<td>39.8</td>
<td>38</td>
<td>0.04607</td>
</tr>
<tr>
<td>&gt;23</td>
<td>10.9</td>
<td>19.4</td>
<td>15</td>
<td>0.01916</td>
</tr>
</tbody>
</table>

AEG = adenocarcinoma of the esophagogastric junction; EAC = esophageal adenocarcinoma; SCC = squamous cell carcinoma.
adequate lymphadenectomy, the prevalence of cancer-positive lymph nodes was 18% in patients with EAC, 32% in patients with SCC, and 16% in patients with AEG. Less than 4% of all patients had more than two cancer-positive lymph nodes. Multivariate logistic regression analysis identified depth of tumor invasion, tumor size, and grade of tumor differentiation as independent predictors of positive lymph node status (Table 3).

Survival
At a median follow-up of 27 months, the overall 5-year survival was 75% for EAC (T1a: 86%, T1b: 65%), 62% for SCC (T1a: 77%, T1b: 54%), and 76% for AEG (T1a: 91%, T1b: 68%). Figure 1 demonstrates survival of patients according to lymph node status in all histologic classifications. Overall 5-year survival for N+ patients was significantly worse in patients with EAC (N0: 78% vs N+: 51%; all \( p < 0.001\)) and AEG (N0: 82% vs N+: 43%; all \( p < 0.001\)) showed no difference in patients undergoing surgical treatment for early SCC (N0: 61% vs N+: 65%; \( p = 0.591\)).

Comment
Our analysis of population-based data demonstrates that the prevalence of cancer-positive lymph nodes in patients with surgically resected T1 esophageal cancer is high: more than 15% of our study population had metastatic lymph nodes. We have found that the risk of cancer-positive lymph nodes in patients with intramucosal cancer is 7.5% and that the prevalence of nodal disease in T1b cancer is 21%, with a similar rate of nodal disease among patients with SCC and in those with AEC.

Our results are generally consistent with the prevalence of nodal disease for surgically resected pT1 esophageal cancer reported by others. For example, we previously reported 71 patients with pT1 adenocarcinoma of the distal esophagus and the gastric cardia. In this cohort, nodal metastases were not found in any of the patients with intramucosal adenocarcinoma, whereas the prevalence of N+ disease was 18% in patients with T1b cancer [10]. Similar findings of zero risk of lymph node metastasis in intramucosal cancer have been reported by other groups [11, 12].

However, Liu and colleagues [13] reported that lymph node metastases were present in 2 of 51 patients (3.9%) and that lymphovascular invasion, a tumor size greater than 1.2 cm, and poor tumor differentiation were all significantly associated with positive lymph node status. Rice and colleagues [14] reported that 1 of 38 (2.6%) patients with intramucosal adenocarcinomas had lymph node metastases compared with 6 of 27 patients (22%) with T1b adenocarcinoma. Altorki and colleagues [15] reported that 6.7% of their patients with T1a disease and 17.8% of those with invasion into the submucosa had nodal metastases. Pennathur and colleagues [16] analyzed 100 esophagectomy specimens and showed that N1 disease was present in 7% (2 of 29) in T1a cancer and in 27% (19 of 71) in patients with submucosal cancer.

Similarly, Ancona and colleagues [12] found that in 98 patients with pT1 esophageal cancer (67 with squamous

<p>| Table 2. Prevalence of Lymph Node Metastases in Esophageal Adenocarcinoma, Squamous Cell Carcinoma and Adenocarcinoma of the Esophagogastric Junction |
|---------------------------------|-----|-----|-----|-----|</p>
<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAC</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>T1a</td>
<td>309</td>
<td>94</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>T1b</td>
<td>280</td>
<td>81</td>
<td>65</td>
<td>19</td>
</tr>
<tr>
<td>SCC</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>T1a</td>
<td>27</td>
<td>87</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>T1b</td>
<td>218</td>
<td>78</td>
<td>56</td>
<td>20</td>
</tr>
<tr>
<td>AEG</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>T1a</td>
<td>157</td>
<td>91</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>T1b</td>
<td>218</td>
<td>78</td>
<td>56</td>
<td>20</td>
</tr>
</tbody>
</table>

AEG = adenocarcinoma of the esophagogastric junction; EAC = esophageal adenocarcinoma; SCC = squamous cell carcinoma.

| Table 3. Predictors of Node-Positive Status for T1 Esophageal Cancer on Multivariate Analysis |
|---------------------------------|-----|-----|-----|
| Variable | OR  | OR1 | OR2 | \( \beta \) | p Value |
| Age <45 years | 0.601 | 0.215 | 1.675 | −0.510 | 0.330 |
| 45–65 years | 0.504 | 0.180 | 1.411 | −0.685 | 0.192 |
| >65 years | 0.816 | 0.485 | 1.371 | −0.204 | 0.442 |
| Male | 0.986 | 0.539 | 1.806 | −0.014 | 0.965 |
| Female | 1.998 | 1.269 | 3.147 | 0.692 | 0.003 |
| White | 0.312 | 0.175 | 0.555 | −1.165 | 0.000 |
| Nonwhite | 0.405 | 0.280 | 0.586 | −0.904 | 0.000 |
| T1a | 1.393 | 0.662 | 2.929 | 0.331 | 0.382 |
| T1b | 0.816 | 0.485 | 1.371 | −0.204 | 0.442 |
| Size >10 mm | 0.312 | 0.175 | 0.555 | −1.165 | 0.000 |
| Other | 0.405 | 0.280 | 0.586 | −0.904 | 0.000 |
| Grade 3 | 1.393 | 0.662 | 2.929 | 0.331 | 0.382 |
| Other | 0.816 | 0.485 | 1.371 | −0.204 | 0.442 |

OR = odds ratio; OR1 and OR2 = ranges of OR; SCC = squamous cell carcinoma.
cell carcinomas and 31 with adenocarcinomas), the rates of lymph node metastasis were 0% for the 27 mucosal carcinomas and 28% for the 71 submucosal cancers. Multivariate analysis showed depth of infiltration, lymphocytic infiltrate, and angiolymphatic and neural invasion were significantly associated with nodal-positive disease [12]. Bollschweiler and colleagues [11] reviewed the records of 60 patients with pT1 esophageal cancer (24 with SCCs and 36 with adenocarcinoma) and found that rates of lymph node metastasis were 0% for the 16 mucosal carcinomas and 45% for the 44 patients with submucosal carcinoma. In a multivariate analysis, submucosal infiltration and high grade showed a significant effect on nodal metastasis [8]. Sepesi and colleagues [17] analyzed tumor factors associated with lymph node metastases in EAC and found that nodal metastases were present in 0% (0 of 25) of intramucosal and 31% (9 of 29) of T1b cancers.

These differences in the reported rates of lymph node metastases in the literature are probably due to racial differences, the quality of lymphadenectomy during the operation, and intraobserver variations in the histopathologic workup of the esophagectomy specimen. Interestingly, a similar population-based study from Merkow and colleagues [18] found that the prevalence of lymph node metastasis was 5.0% for T1a and 16.6% for T1b lesions in patients undergoing esophagectomy based on the analysis of more than 5,000 patients from the National Cancer Data Base.

The second main finding of our study is that risk estimation for nodal-positive disease should not be based on depth of tumor infiltration alone but additional variables have to be considered as well. According to our data, depth of tumor invasion, tumor size, and grade of tumor differentiation are independent predictors of nodal-positive status. Others have shown submucosal tumor invasion, lymphovascular invasion, and high grade of tumor as independent predictors for nodal-positive disease in early esophageal cancer [5, 8, 12, 19].

Fig 1. Survival of patients with surgically resected T1 (A) esophageal adenocarcinoma, (B) squamous cell carcinoma, and (C) esophageal adenocarcinoma of the gastric cardia according to N+ (green line) or N0 (red line) lymph node status.
The absence of nodal metastases in T1a cancer in several of the published studies reporting on esophagectomy specimens is used to support the use of endoscopic resection for T1a lesions. The incidence of nodal-positive disease in T1a patients in our series is sufficiently low (7.5%) to warrant consideration of endoscopic therapy in selected patients. However, these results probably underestimate the true prevalence of nodal disease because most of the patients in this study underwent operations without optimal lymphadenectomy; therefore, nodal staging was insufficient. This is also demonstrated by our results: when our analysis was limited to patients with adequate lymph node dissection, the prevalence of nodal-positive disease was even higher.

Secondly, when weighing endoscopic therapy vs surgical resection for patients with intramucosal cancer, one must consider the predicted surgical mortality vs the possible presence of cancer-positive lymph nodes for the specific patient. In contrast to the often quoted 5% or higher mortality rate with local and regionally advanced tumors, recent publications from high-volume centers have reported that esophagectomy can be performed in patients with early esophageal neoplasia with a mortality rate of 0% to 1%, well below the average risk of nodal disease in these patients [20, 21]. Furthermore, a true preoperative determination of the depth of invasion and, therefore, isolation of a patient population with low risk of nodal disease may not be possible.

In a prospective, blinded study of high-resolution endoscopy and high-resolution endoscopic ultrasound imaging in the diagnosis of early esophageal cancer, submucosal infiltration was not diagnosed with either method in 40% of cases [22]. In an other report of 131 patients undergoing staging for early esophageal cancer, in 25 of 105 patients (24%) with no signs of submucosal invasion on endoscopic ultrasound, invasion of the submucosa was shown after pathologic workup of the EMR specimen, and in 7 of 26 patients (27%) with endoscopic ultrasound findings of T1b cancer, no submucosal invasion could be confirmed [23].

The excellent 5-year survival rates that have been reported after endoscopic resection of tumors confined to the mucosa by several expert centers [3, 24] might be puzzling considering that according to our results, these patients might have up to 8% prevalence of nodal disease. One possible explanation could be that the focus of the pathologists analyzing a surgical and an EMR specimen is different. On one hand, evaluation of the EMR specimen meticulously concentrates on differentiating between mucosal or submucosal infiltration; on the other hand, the focus after esophagectomy is usually on the detection of possible positive lymph nodes, which could result in an understaging of T1b cancer and results in a higher prevalence of lymph node metastasis in an esophagectomy specimen erroneously classified as T1a [25].

Lorenz and colleagues [26], from the Wiesbaden group, published the results of a series of patients undergoing esophagectomy for early EAC. According to the Wiesbaden treatment protocol, esophagectomy was recommended in all patients with cancers with a high risk for lymph node metastasis (infiltration of the submucosa or intramucosal infiltration with lymphovascular or vascular invasion) or after a “failed EMR.” In this population there was an approximate 10% chance of positive lymph nodes after esophagectomy for T1a cancer, and the prevalence of lymph node metastasis in patients with T1b EAC was 21% [26]. Admittedly this was a preselected population, but this was the only population published by the Wiesbaden group with histologic confirmation of lymph node status.

It is possible though, that because in our study we have analyzed population-based data without information on the individual therapeutic decisions in the patients, parts of our population might have been subjected to a similar pretherapeutic selection process as the patients in the study by Lorenz and colleagues.

However, it is also possible that the reasons behind these excellent outcomes after EMR could be the rigorous patient selection successfully excluding most patients with potential nodal disease [3] and the fact that the published 5-year survival rates are probably not the ideal markers of the long-term fate of patients with early esophageal cancer. A series from China of 17 patients without any treatment for early cancer of the gastric cardia showed an actual 5-year survival of 82% (14 of 17), with 12 patients (70%) eventually succumbing to locally advanced/metastatic cancer in an average of 6.7 years after diagnosis [27].

Our results show the quality of nodal staging in patients undergoing esophagectomy in our series was low. In concordance with other reports [28], the rate of adequate lymphadenectomy (>15 lymph nodes removed/examined) was less than 35% in our series, and only 13% of all patients underwent esophagectomy with more than 23 lymph nodes analyzed.

Although this can be caused by several factors and its importance is debated, it is still alarming that more than 6% of all patients underwent esophagectomy for T1 esophageal cancer with a D0 lymphadenectomy (0 lymph nodes removed/analyzed) in the 21st century in the United States.

While interpreting the results of our study, it is important to consider that our analyses are limited to the available variables in the SEER database with no information regarding completeness of the resection (R status), lymphovascular invasion, type of surgical procedure, or further subclassifications of the depth of cancer invasion in the esophageal wall. On the other hand, the multiple subdivisions of mucosa and submucosa are not included in current treatment guidelines or TNM classifications, probably because the definitions of these differ between centers in the East and the West [29, 30]. Furthermore, the diagnostic accuracy of EUS has been shown to be insufficient in depicting the further details of the different layers of the esophageal mucosa and submucosa [23, 31]. That several authors did not find any difference in the prevalence of nodal disease
between the different depths of submucosal infiltration is therefore not surprising [13, 32]. Secondly, a possible misclassification of patient information must always be considered when using a large, nationwide, administrative claims database. Despite these limitations, an analysis of the data set provided by SEER has several advantages: large, population-based data, rigorous quality control standards, and a patient follow-up rate of more than 95%. Therefore, that our conclusions are justified even with this limited data set can be reasonably assumed.

In summary, this is the first study to analyze population-based data on the prevalence of lymph node metastasis in early esophageal cancer. Our analysis of more than 1,200 patients showed that the rate of cancer-positive lymph nodes is high in patients with early cancer of the esophagus and that the prevalence of nodal-positive disease is markedly different in various histologies. In our opinion, based on the high prevalence of nodal-positive disease in our study, one could argue against EMR as a therapeutic modality of choice in most patients with T1 disease. Decision making in the therapy of patients with T1a tumors should be individualized according to the patient's overall status, presence of comorbidities, and histopathologic variables of the tumor: in highly selected patients with high surgical risk and with small, well-differentiated adenocarcinomas limited to the mucosa, EMR may be reasonable. In all other patients with early esophageal cancer, the prevalence of nodal metastases is probably unacceptably high to justify local therapies without regional lymphadenectomy.

References


DISCUSSION

DR THOMAS J. WATSON (Rochester, New York): Attila, great presentation. It is nice to see a former Rochester fellow going out in the world and doing a good job. Keep it up.

DR DUBECZ: Thank you.

DR WATSON: As you know, Christian Ell and his group in Wiesbaden, Germany, recently published their series of 1,000 endoscopic resections for T1 esophageal cancers. Notable from that series were a few bits of information. One is that of their 1,000 patients undergoing endoscopic resection, only 2 (0.2%) died of metastatic esophageal cancer at a follow-up of almost 5 years. You showed here that patients with T1 cancer undergoing esophagectomy had between a 5% and 10% incidence of nodal metastases. If these same patients had been treated with endoscopic resection, then presumably 5% to 10% would have died from progression of untreated nodal disease. How do we reconcile these conflicting series, one from an endoscopic center with a 0.2% incidence of death from metastatic cancer, and your surgical series demonstrating a much higher incidence of occult nodal disease?

DR DUBECZ: It is probably not impossible to survive 5 years with an untreated positive lymph node. There is a chance that the body can fight off some of these lymph node metastases. And, as I said in the presentation, I think the 5-year survival rates are not good markers of the long-term fate of a patient with an early cancer.

DR WATSON: I think you mentioned in your talk an important consideration as well. The quality of the pathology reports from these retrospective reviews of surgical specimens is a bit questionable. I suspect that pathologists tend to focus on lymph nodes when they are looking at esophagectomy specimens, and may not be as fastidious about assessing tumor depth of invasion, especially when the pertinent landmarks may be separated by microns. When they are looking at EMR [endoscopic mucosal resection] specimens, they are focused quite intensely on tumor depth.

DR DUBECZ: Yes. There is a theoretical chance that some of these T1as are actually T1bs. But this phenomenon of understaging of surgical specimens by the pathologists has not been described in the literature.

DR WATSON: I agree. Do you think one’s body can clear microscopic nodal disease when the main esophageal tumor has been resected endoscopically?

DR DUBECZ: No, I do not think so.

DR WATSON: Thank you for your insights.

DR MEHDI FAKHRAI (Los Angeles, CA): How many of these patients had sonograms to see if there were any lymph nodes there that they did not remove?

DR DUBECZ: We do not know. It is a population-based database, and there is no information about endoscopic ultrasound workup of these patients. That is one of the limitations of these data.

DR K. ROBERT SHEN (Rochester, MN): Your finding that the presence of nodal metastasis did not adversely affect survival in the squamous cell carcinoma patients is quite surprising and obviously is not consistent with other data. What do you think the explanation for that is? And if that really reflects reality, would that change your recommendation in terms of whether or not you would still offer EMR to a patient with a T1b lesion if it was a squamous cell?

DR DUBECZ: I do not think that that reflects reality. These data are probably skewed by the limited number of patients with T1b squamous cell carcinoma (SCC) in this study, therefore we did not even discuss this in the paper because we do not think that that reflects reality.

DR SHEN: So a T1b patient, even if it was squamous cell, you would still—

DR DUBECZ: We would resect.

DR SHEN: So which patients in your practice do you think it is reasonable to offer or at least discuss EMR management vs resection?

DR DUBECZ: Despite the data in this study, we still think that T1a patients with a slightly elevated surgical risk should undergo an endoscopic mucosal resection. But young patients in good overall health should be informed about the possibility of a lymph node metastasis, and the possibility of a curative resection.

DR SHEN: So in a T1a, if they are good risk, you would recommend that patient to go on for surgery?

DR DUBECZ: If they are young, yes.

DR SHEN: How many people in the audience would also recommend that patients go for a resection with T1a disease?

(A show of hands.)

DR SHEN: How about T1b?

(A show of hands.)

DR KATIE S. NASON (Pittsburgh, PA): What would you do with a patient who has a 1-cm poorly differentiated adenocarcinoma at the gastroesophageal (GE) junction with angiolymphatic invasion who is a poor candidate for surgical resection? It is endoscopically removed. You have your EMR specimen back. Do you recommend them for adjuvant therapy, radiation?
DR NASON: T1a, poorly differentiated, 1 cm, angiolymphatic invasion.

DR DUBECZ: You mean neoadjuvant therapy?

DR NASON: Well, you have resected it endoscopically and they are not a good candidate for surgery.

DR DUBECZ: You have to define the operative risk, if they are not a good candidate. There is the possibility for a transthiatal esophagectomy with much less morbidity.

DR NASON: So I suspect that the difference in the survival between what you are presenting and what they are presenting from Wiesbaden is the fact that the Wiesbaden patients are very highly selected. Poorly differentiated patients, larger tumors, those patients are being sent for esophagectomy, and they are no longer in that series.

DR DUBECZ: Yes. First, the Wiesbaden series is over 6,000 patients and they were selecting out 1,000. Secondly, their results have not really been reproduced in the literature. Thirdly, I showed the only patient group with a histology of the lymph nodes from Wiesbaden that Lorenz published last year, which is obviously a highly selected patient population with the failed EMRs; they have 10% lymph node metastases in T1as. That is the Wiesbaden data from Christian Ell as a coauthor in the *Annals of Surgery* last year.

DR WAYNE HOFSTETTER (Houston, TX): I think we all have to understand that patients who are T1a, there is a significant heterogeneity within that group, and we have to be careful about what we are discussing in terms of recognizing patients who need to be resected vs those who need to undergo organ-sparing therapy. The T1a is going to be potentially redesignated in the American Joint Committee on Cancer 8th Edition as stage 0 because the survival from a T1a is equivalent to a Tis. They have the same survival as their normal population. So to say that every T1a potentially deserves an esophagectomy I think is overkill, and I think we have to be very careful about that. Concurrently there are patients with Tis, high-grade dysplasia, or T1as who have extensive disease who have a bad esophagus that we need to consider resections on, but, as a group, we need to be very careful that we are not saying that just because any T1a is a low risk for surgery that we should be taking that esophagus out because those patients are probably more properly classified as a stage 0.

DR DUBECZ: In my opinion, there is no question about it that untreated patients with a T1a cancer will die of esophageal cancer, the question is when. As I mentioned in my presentation, there is a Chinese series with 30 patients who refused any treatment for early cancer of the esophagus and the gastric cardia, and these patients have an 8-year median cancer-related survival. So even without any treatment, you live for 8 years, but you will die of cancer, unlike the normal population.

DR HOFSTETTER: Just to be clear, the data I am quoting are 25,000 patients from the Worldwide Esophageal Cancer Collaboration (WECC) data. These are resected patients. These are patients with long-term follow-up who were resected. That is 25,000 patients, which is larger than any other data series that is out there.