pT2 Adenocarcinoma of the Esophagus: Early or Advanced Cancer?

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Background. There is an increasing trend to include patients with esophageal carcinoma invading the muscularis propria (pT2) in neoadjuvant therapy regimens. But it is unclear which patients have prognostic benefit from this strategy. The aim of this study was to assess the prognosis and prognostic factors in patients with pT2 esophageal adenocarcinoma to further optimize treatment strategies.

Methods. Included were patients with pT2 esophageal adenocarcinoma treated operatively at three centers specializing in upper gastrointestinal surgery. There were 159 patients (139 male) without induction therapy; median age was 64.5 years. Survival was analyzed by univariate and multivariate analysis.

Results. In 37% of patients (n = 59), no lymph node involvement (pN0) was detected. Overall 5-year survival rate for all patients was 37%; for pN0 patients it was 62%, and for patients with lymph node metastases (pN+) it was 24%. Median number of examined lymph nodes was 26. Extracapsular lymph node involvement (ELNI) was evident in 55 of 100 pN+ patients with a 5-year survival rate of 14%. Patients without ELNI had a 5-year survival rate of 36% (p = 0.041). Results were comparable in all participating hospitals. Thirty-day and 90-day mortality rates of the entire collective were 2.6% and 3.8%, respectively. Multivariate analysis of prognosis revealed the lymph node ratio (p < 0.001) and the pN-ELNI category (p = 0.005) as significant parameters (pN0 hazard ratio 1 [reference]; pN+ without ELNI hazard ratio 2.2, 95% confidence interval: 1.2 to 3.8); pN+ with ELNI hazard ratio 2.5, 95% confidence interval: 1.5 to 4.5).

Conclusions. The prognosis of patients with esophageal adenocarcinoma invading the muscularis propria without lymph node metastasis is very good. However, in this study, about 30% had extracapsular lymph node involvement, which reflects particularly aggressive biological tumor behavior.


Regarding treatment strategies for adenocarcinoma of the esophagus, there is general consensus that endoscopy or surgery alone is appropriate for patients with localized tumors of the esophagus and gastro-esophageal junction (clinical T1) and no evidence of distant metastases [1, 2]. Locally advanced tumors (clinical T3/4) are treated preferably with induction therapy followed by surgery [3]. Conversely, optimal identification and management of patients with clinical T2 esophageal cancer remains problematic. With this stage, patients are often presumed to have node-negative disease, and thus are targeted for primary surgery. However, studies show that the prevalence of nodal disease in pathologic stage T2 (pT2) cancers is approximately 45% to 75% [4, 5].

The presence and extent of lymphatic dissemination are among the most important predictors for survival in gastrointestinal malignancies [6–8]. In addition, the extent of lymphadenectomy appears to influence the long-term prognosis for esophageal cancer [9–11]. More recently, the presence of extracapsular lymph node infiltration (ELNI) has been considered as a relevant prognostic factor. The impact of ELNI has been studied for several malignancies, including gastric, colon, breast, and head/neck cancers [12–21]. In esophageal cancer, the correlation of ELNI with advanced tumor stage has been made [17–19]. One recently published review identified seven studies showing a significant correlation with survival rates [17]. To date, however, little attention has been paid to its biological significance for earlier tumor stages.

Studies with neoadjuvant treatment strategies include more and more patients with clinical T2 tumor. Until now, there exists only small evidence about the benefit for those patients. The aim of this study was to assess the prognosis and prognostic factors in patients with resected
T2 (pT2) esophageal adenocarcinoma to further optimize treatment strategies for patients with this tumor stage.

Patients and Methods

Patients

One hundred fifty-nine patients with pT2 adenocarcinoma of the esophagus were included in this retrospective study. The patients were treated in three high-volume centers for upper gastrointestinal surgery between July 1, 1996, and June 30, 2010. Only patients without neoadjuvant therapy were included. Relevant patient characteristics are summarized in Table 1. The study was approved by the Local Ethics Committee of the three hospitals.

Surgical Resection

Surgical treatment of choice was subtotal en bloc esophagectomy using a right transthoracic approach, including two-field lymphadenectomy of the mediastinal and abdominal lymph nodes (LN). For 61 patients, a transhiatal subtotal esophagectomy with standardized lymphadenectomy was performed because of distal localization, circumscribed lesions, or impaired lung function. The specimens were removed en bloc, including the LNs. To ensure primary tumor integrity, the LNs were dissected partially in the operating theater and partially by pathologists according to a standardized protocol. The examined LNs were documented according to the seventh edition of the TNM classification [22]. The median number of examined LNs was 26 (minimum 3, maximum 75).

Standard reconstruction for patients receiving transhiatal esophagectomy was done by stomach interposition with high intrathoracic esophagogastrostomy. The R0 resection rate was 93.1% (n = 148; R1/2 n = 11).

Pathology

The TNM staging was performed according to the criteria of the seventh edition of the International Union Against Cancer (UICC) [22]. Histopathologic examination of all resected specimens consisted of thorough evaluations of tumor stage, residual tumor (R category), grading, and number of examined and involved LNs (LN). The specimens were fixed in 5% formaldehyde and set in paraffin. The LNs were counted and the maximum diameter of each node was measured with a slide gauge. A series of sections from each node was selected and stained with hematoxylin and eosin as well as with periodic acid-Schiff (PAS). All dissected LNs were microscopically analyzed for metastatic disease.

The ELNI was defined as metastatic cancer extending through the nodal capsule into the perinodal fatty tissue. Examinations of LNs were reevaluated by experienced pathologists of the different institutes. Deposits of metastatic cancer cells without a recognizable LN were considered ELNI, unless these deposits were associated with perineural or vessel involvement. In cases of desmoplastic reaction resulting in difficulties identifying the preexisting LN capsule, an imaginary line representing the original capsule was drawn to facilitate interpretation (see also Lagarde and associates 2006 [6]).

The ratio of the number of involved to examined regional LNs was termed the “lymph node ratio” (LN ratio). A cut-off value of 0.2 was selected for differentiation of prognosis [9, 23, 24]. Other cut-off values were tested to optimize the prognostic relevance.

Statistics

In the three centers, the data were collected prospectively according to a standardized protocol beginning in 1996. The median, with the minimum and maximum values,
was used for descriptive statistics; χ² statistics were calculated for frequencies of factors with a significance level of p less than 0.05. The Kruskal-Wallis test or the Wilcoxon test was used for testing differences between nonparametric data. Binary logistic regressions analysis was used to find dependent factors for LN metastases with ELNI.

The median follow-up time of all patients was calculated using the time between study entry and the date of the actual analysis and the time between the study entry and the date of censoring for censored patients [25]. The median follow-up time was 4.1 years (range, 0.5 to 10.5). All surviving patients had follow-up of more than 1 year.

Kaplan-Meier plots were used to depict survival distribution. The log rank test was used to evaluate for survival differences. In addition, 95% confidence intervals (CI) were calculated for the different survival curves. Postoperative mortality was not included in the calculation of prognosis. The multivariate analysis of survival used Cox regression analysis to identify independent prognostic variables. The level of significance was set to p less than 0.05. All statistical analyses were performed using the statistics program SPSS for Windows version 20.0 (SPSS, Chicago, IL). For graphic presentation of the results, MedCalc version 12.0 (MedCalc Software, Ostend, Belgium) was used.

Results

Demographics

One hundred fifty-nine patients not undergoing neoadjuvant therapy were included in this study. The median age of the 159 patients was 64.5 years (minimum 36, maximum 84). The demographics and prognostic factors for the patients are shown in Table 1. There were no significant differences among the three surgical centers according to age of the patients (p = 0.882), sex (p = 0.259), pN category (p = 0.638), pM category (p = 0.923), R category (p = 0.469), or follow-up of the patients (p = 0.234).

Lymph Node Metastases

In 159 patients, 4,395 LNs (median 26; minimum 3, maximum 75) were resected. Lymph node metastases were detected in 100 patients (63%). All positive LNs (n = 533) were reexamined for the presence of ELNI (ELNI+). These were found in 55 patients. Tumor growth beyond the LN capsule was detected in 159 LNs (29.8%).

The number of resected and identified LNs did not differ between patients without LN metastasis (pN0) or with LN metastasis (pN+). The same was true for pN+ patients with or without ELNI (Fig 1A, Table 2). The number of LNs with ELNI was significantly (p < 0.001) correlated with the number of positive nodes (Fig 1B). ELNI+ was seen more often with higher LN ratios (Table 2).

The multivariate regression analysis including the variables, sex, age, grading, number of resected LNs, and number of metastatic LNs showed that females had a higher risk for ELNI+ with an odds ratio of 7.9 (95% CI: 1.01 to 69.11) compared to males (p = 0.049). In addition, a higher number of LN metastasis was an independent predictor of ELNI+ (p = 0.001).

Surgical Procedure

Transhiatal esophagectomy was performed in 91 patients and transhiatal esophagectomy in 61 patients. The median number of resected LNs was significantly higher in the group of patients with the transhiastic approach (median 29 LNs; minimum 10, maximum 75) versus patients undergoing transhiatal esophagectomy (median 22 LNs; minimum 3, maximum 49; p < 0.001). The frequency of patients with LN metastases was not different after transthoracic (63%) or transhiatal (62%) esophagectomy. The number of LN metastasis as well as the number of LNs with ELNI did not significantly differ between the two surgical approaches (p = 0.176 and p = 0.384). As a consequence, the LN ratio did differ significantly (p = 0.003).

Prognosis

The 30-day and 90-day postoperative mortality rates were 2.6% and 3.8%, respectively. There were no differences between patients without or with LN metastases (30-day mortality: pN0 1 of 59, pN+ 3 of 100; 90-day mortality: pN0 2 of 59, pN+ 4 of 100). The 5-year survival rate for all patients was 37% (95% CI: 28% to 45%). Patients without LN metastases had a 5-year survival rate of 62% (95% CI: 48% to 78%) and patients with positive LNs had a 5-year survival of 24% (95% CI: 18% to 32%; p < 0.001). The
established prognostic factors for esophageal cancer (pN, pM, and R category) were significant in the univariate analysis (Table 1).

The number of resected LNs was not different between patients with pN0 or pN+. In the group of 59 patients without LN metastasis, we found no significantly prognostic benefit for the different cut-off values of resected LNs (<20, <25, and <30). For 100 patients with LN metastasis the following cut-off values of LN ratios were tested: LN ratio 0.1 or less, 0.2 or less, 0.25 or less, and 0.3 or less. The cut-off value with an optimal prognostic relevance was a LN ratio of 0.2 or less with a \( \chi^2 \) value of 22.6 in log rank test (\( \chi^2 \) for LN ratio 0.1 or less, =11.3; LN ratio 0.25 or less, 15.2; and LN ratio 0.3 or less, 0.11).

Analyzing the prognostic relevance of LN ratio 0.2 or less in the subgroups of pN category according to the seventh edition of UICC classification, it could be shown that patients with pN2, 3 to 6 LN metastases, and LN ratio 0.2 or less (n = 20; 5-year survival rate 34%) had a significantly better prognosis than patients with a LN ratio greater than 0.2 (n = 15; 5-year survival rate 7%; \( p = 0.025 \)). The prognostic relevance of the LN ratio 0.2 or less could be confirmed for pN+ patients with ELNI (\( \chi^2 \) = 13.8, log rank-test) and without ELNI (\( \chi^2 \) = 9.3, log rank test).

The median survival of patients with ELNI was 16 months (95% CI: 12 to 24), in comparison to 25 months (95% CI: 18 to 36) for pN+ patients without ELNI (\( p = 0.045 \)). The 5-year survival rate was 36% for patients rated pN+ without ELNI and 14% for patients with ELNI (\( p = 0.041 \); Fig 2).

Multivariate analysis for R0 resected patients included age, sex, esophagectomy type, number of resected LNs, LN ratio, number of LN metastasis, number of LN metastasis ELNI+, pN category seventh edition UICC, and pN category ELNI; and identified LN ratio and pN ELNI as independent variables for prognosis (backward elimination of nonsignificant variables): LN ratio (\( p < 0.001 \)); pN0 (hazard ratio [HR] 1 [reference]); LN ratio 0.2 or less (HR 2.3, 95% CI: 1.4 to 3.9; \( p = 0.002 \)), LN ratio 0.2 or greater (HR 7.3, 95% CI: 4.1 to 12.5; \( p < 0.001 \)), pN+ELNI (HR 1 [reference]); and pN+ELNI+ (HR 1.7, 95% CI: 1.1 to 3.1; \( p = 0.039 \)).

Comment
In this study, we could show that patients with adenocarcinoma of the esophagus limited to the muscularis propria and no lymphatic tumor invasion (pT2pN0) have a very good prognosis with a median survival rate of more than 8 years. The 5-year survival rate of 62% is lower than that of published data for patients with “early” adenocarcinoma of the esophagus at approximately 74% [2]. In our series, the prognosis for patients with pT2pN0 carcinoma is comparable to data from 66 patients with submucosal infiltration including 24% of patients with LN metastasis [2].

Table 2. Demographic Data and Tumor Characteristics of 100 Patients With pT2 pN+ Esophageal Adenocarcinoma Comparing Patients Without and With Extracapsular Lymph Node Infiltration

<table>
<thead>
<tr>
<th>Variables</th>
<th>LN Metastasis Without ELNI</th>
<th></th>
<th>LN Metastasis With ELNI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients total (n = 100)</td>
<td>45</td>
<td>%</td>
<td>55</td>
<td>%</td>
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<tr>
<td>Sex</td>
<td>0.011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 89)</td>
<td>44</td>
<td>49</td>
<td>45</td>
<td>51%</td>
</tr>
<tr>
<td>Female (n = 11)</td>
<td>1</td>
<td>9</td>
<td>10</td>
<td>91%</td>
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<td>Median age, years</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1/G2 (n = 26)</td>
<td>9</td>
<td>35</td>
<td>17</td>
<td>65%</td>
</tr>
<tr>
<td>G3/G4 (n = 74)</td>
<td>36</td>
<td>49</td>
<td>38</td>
<td>51%</td>
</tr>
<tr>
<td>Median no. resected LN (min–max)</td>
<td>0.627</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN category 7th UICC</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN1 (n = 34)</td>
<td>28</td>
<td>82</td>
<td>6</td>
<td>18%</td>
</tr>
<tr>
<td>pN2 (n = 35)</td>
<td>11</td>
<td>31</td>
<td>24</td>
<td>69%</td>
</tr>
<tr>
<td>pN3 (n = 31)</td>
<td>6</td>
<td>19</td>
<td>25</td>
<td>81%</td>
</tr>
<tr>
<td>Median no. LNMs</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In pN+ cases (min–max)</td>
<td>1</td>
<td>(1–19)</td>
<td>6</td>
<td>(1–28)</td>
</tr>
<tr>
<td>LN ratio</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.2 (n = 57)</td>
<td>36</td>
<td>63</td>
<td>21</td>
<td>37%</td>
</tr>
<tr>
<td>&gt;0.2 (n = 43)</td>
<td>9</td>
<td>21</td>
<td>34</td>
<td>79%</td>
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<tr>
<td>Esophagectomy</td>
<td>0.384</td>
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<tr>
<td>Transthoracic (n = 62)</td>
<td>30</td>
<td>48</td>
<td>32</td>
<td>52%</td>
</tr>
<tr>
<td>Transhiatal (n = 38)</td>
<td>15</td>
<td>39</td>
<td>23</td>
<td>61%</td>
</tr>
</tbody>
</table>

ELNI = extracapsular lymph node infiltration; LN = lymph node; LNM = lymph node metastasis; UICC = Union Internationale Contre le Cancer.
pN category is based only on the number of metastatic LNs and does not consider the characteristics of the metastatic LN itself.

For all these patients the LN ratio—that means the number of LN metastasis divided by the number of resected LNs—has prognostic relevance. This was true for pN+ patients without and with ELNI. Hou and coworkers [30] analyzed the prognostic relevance of LN ratio for more than 1,000 patients with squamous cell carcinoma. They divided the LN ratio into four categories according to prognostic relevance: LN ratio 0; LN ratio 0 to 0.1 or less; LN ratio 0.1 to 0.3 or less; and LN ratio greater than 0.3 [30]. As have other researchers, we found an optimal cut-off value of 0.2 for prognostic relevance [9, 23, 24]. These findings confirmed the importance of adequate lymphadenectomy in patients with pT2 adenocarcinoma of the esophagus. Especially patients with less than 20% metastases in the resected LNs have the chance of improved long-term survival.

To examine the therapeutic consequences of the results of this study for patients with pT2 adenocarcinoma of the esophagus, we differentiated three separate groups of patients: pN0, pN+ELNI−, and pN+ELNI+. Patients without LN metastasis showed very good prognoses after transthoracic esophagectomy and adequate lymphadenectomy. In a population-based study using the Surveillance, Epidemiology and End Results database, Martin and coworkers [31] analyzed the influence of radiation therapy in patients with esophagectomy for T2N0 esophageal cancer. They found no prognostic benefit for additional radiation therapy for those patients. The prognosis of pN+ELNI− patients may be improved by neoadjuvant therapy. Bollschweiler and colleagues [32] have shown that patients with only a few LN metastasis yielded the greatest benefits from preoperative chemoradiation. The greatest therapeutic problem is the third group. It seems that patients with ELNI gain only minimal benefit from standard chemoradiation therapy [19].
Addressing the issue of whether pT2 is early or advanced cancer, our data demonstrate that patients without LN metastasis had a chance of survival after 5 years of approximately 60%. That implies that there is a group of patients with good or very good prognosis after surgery alone. In contrast, patients with LN metastasis had a 5-year survival rate of 24%, equal to the prognosis of advanced tumors. However, owing to the lack of diagnostic tools to further characterize LN involvement, it is not possible to make pretherapeutic treatment decisions. Consequently, new molecular diagnostic tools are required for an adequate therapeutic decision making.

In conclusion, the prognosis of pT2pN0 adenocarcinoma of the esophagus is very good. However, in this study, approximately 30% of pT2 carcinomas had ELNI, which reflects particularly aggressive biological tumor behavior.

References