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Chapter 6

Positive peri-truncal nodes for oesophageal carcinoma: not always a dismal prognosis

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Abstract

Background. For oesophageal carcinoma, positive truncal nodes are considered distant metastases, and might be a contraindication for potentially curative surgery. With the development of new diagnostic tools more/smaller peri-truncal nodes may be found positive pre-operatively. We evaluate whether it is justified to exclude all patients with positive peri-truncal nodes from curative surgery.


Results. 110 patients underwent transhiatal resection for oesophageal carcinoma. Sixteen patients had tumour positive, resectable peri-truncal lymph nodes not identified pre-operatively, changing pre-operative stage III into post-operative stage IV (M1a).

After follow-up of 2.9 years (0.07 – 7.6) 49 patients (45%) were alive. On multivariate analysis radicality and lymph node status were independent prognostic factors. There was no significant difference in survival between stage III and stage IV (M1a) tumours: 1.7 years and 1.5 years resp. (p=0.87). At the end of follow-up 4/16 patients (25%) with stage IV (M1a) disease were alive without evidence of disease.

Conclusion. The presence of malignant cells in small, resectable peri-truncal nodes does not preclude long-term survival. The results of new diagnostic modalities should be interpreted cautiously, until firm criteria for irresectability/incurability of positive truncal nodes are established.

Introduction

Oesophageal carcinoma is a highly aggressive disease. Many patients are not considered candidates for intentionally curative surgery due to the presence of locally irresectable disease or distant metastases. According to the '97 UICC TNM classification tumour positive lymph nodes near the coeliac axis are considered distant metastatic disease for mid/distal oesophageal carcinoma (M1a). In some centres, the presence of tumour positive lymph nodes at the coeliac axis is considered a contraindication for curative surgery. However, little is known about the prognostic value of small positive lymph nodes at this location. With the development of modern staging techniques such as endoscopic ultrasonography (EUS) with fine needle biopsy (EUS-FNA) smaller tumour positive lymph nodes can probably be detected and proven cytologically at an earlier stage.
To analyse the prognostic value of resectable tumour positive truncal nodes a survival-analysis of all patients undergoing transhiatal oesophageal resection for carcinoma of the mid/distal oesophagus was performed.

Patients and methods

Data from all patients operated upon for oesophageal carcinoma and carcinoma of the gastric cardia with substantial infiltration of the oesophagus in the Academic Medical Center/University of Amsterdam are collected in a prospective database. From this database the records of patients undergoing transhiatal resection for adeno- or squamous cell carcinoma of the mid/distal oesophagus between July 1993 and January 1997 were collected, ensuring a minimal follow-up of two years. Patients with cardia carcinoma (bulk of the tumour at or below the gastro-oesophageal junction endoscopically) were not included in this analysis, because this tumour might be considered as gastric carcinoma and is often staged accordingly.

Pre-operative work-up consisted of endoscopy with biopsy, external ultrasonography of abdomen and neck, routine chest X-ray, oesophageal endosonography and indirect laryngoscopy. Tumour positive lymph nodes at the coeliac trunc were considered a contraindication for resection only when proven by sonographically guided transcutaneous cytological puncture.

All patients in the present study were operated through the transhiatal route by or under supervision of one of the authors (HO or JJBvL). No formal lymph node dissection was performed in the chest, or near the hepatic- and splenic artery. Lymph nodes near the origin of the left gastric artery were always removed with the resection specimen. The surgeon routinely marked the origin of the left gastric artery. Nodes within one cm of this location in the specimen were considered truncal nodes in the present study.

Routine pathology (hematoxylin/eosin staining) was performed, no additional immuno-histochemistry was used to detect micro-metastasis. A microscopically radical resection (histologically negative proximal, distal and circumferential margins) is called R0, a microscopically irradical resection (histologically positive margins but no macroscopic tumour left behind) is called R1, and a macroscopically irradical resection is called R2. Patients with an R2-resection were excluded from the present analysis.

Patients were seen at a regular basis for five years in the outpatient clinic during follow-up. In the first two years patients were seen at three-four months intervals, afterwards at six months intervals. For the present study patients and/or their family practitioners were contacted by phone to assess their current status when the surgeon had discharged them after five years of follow-up. Additional diagnostic procedures such as sonography or endoscopy were performed on indication only. Adjuvant therapy

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was not administered. Palliative radiotherapy was considered for patients with symptomatic loco-regional recurrence

Statistical analysis was performed using the SPSS statistical package. The Chi-square or Fisher’s exact test and Student’s t-test were used when appropriate. Survival curves were calculated following the Kaplan-Meier method, using the log-rank test for significance. Patients who died from non-oesophageal-cancer related causes were included (not treated as censored) in the survival analysis, just as the patients who died in the hospital. The Cox proportional hazard model was used to analyse prognostic factors. We were especially interested in the prognostic value of tumour-positive truncal nodes demonstrated in the resection specimen.

Results

Between July 1993 and January 1997, 139 patients were operated upon because of adeno- or squamous cell carcinoma of the mid/distal oesophagus. Twenty-two patients showed distant metastases or local irresectability during operation, precluding resection. They were not included in the study, just as the seven patients who had an R2-resection (macroscopic tumour left behind). This left 110 patients (85 men and 25 women, with a mean age of 64 ± 11 years) for further analysis.

Eighty-eight patients (80%) underwent radical (R0) resection; microscopic tumour was left behind (R1-resection) in the other 22 patients (20%). The pTNM stages of the tumours are depicted in table I. Sixteen patients had tumour positive, resectable lymph nodes within 1 cm of the ligature marking the origin of the left gastric artery. These nodes had not been identified as tumour positive coeliac trunc nodes by pre-operative work-up, changing pre-operative stage III into post-operative stage IV (M1a) disease.

Three patients (3%) died early post-operatively in the hospital, four patients (4%) died of non cancer-related causes during follow-up. After median follow-up of 2.9 years (range 0.07 – 7.6) 49 patients (45%) were alive. Follow-up in the surviving patients was 4.2 years (range 2.7 – 7.6). On univariate analysis the differentiation grade of the tumour, the radicality of the operation, and nodal status were statistically significant prognostic factors. On multivariate analysis only radicality and nodal status were independent prognostic factors (see table II). Kaplan Meier curves of pTNM stages and survival are depicted in figure I. As can be seen in the survival curves, there is no significant difference between stage III and stage IV tumours; with a median survival of 1.7 years (95% confidence interval 0.7 – 2.7) and 1.5 years (95% confidence interval 0.5 versus 2.5 years) resp. (p=0.87, log rank test). Four patients (25%) with stage IV (M1a) are still alive without evidence of recurrent disease after a follow-up of 3.0, 3.6, 3.9 and 4.0 years.
Discussion

In this retrospective study the prognostic value of lymph node status and radicality of surgery after oesophagectomy for cancer are confirmed. There was no survival difference between patients with stage III tumours and patients with positive nodes near the origin of the left gastric artery that can be staged as stage IV (M1a). It can be concluded that long term survival is possible when (resectable) truncal nodes are tumour positive. After a median follow-up of 3.6 years 25% of the patients with stage IV (M1a) disease were still alive, and the median survival of all patients with stage IV (M1a) disease is 1.5 years.

In the present study, enlarged lymph nodes near the coeliac axis were only accepted as contraindication for surgical resection when these nodes were proven positive by sonographically guided transcutaneous fine needle aspiration. This study therefore includes only patients with so-called negative nodes at the coeliac trunc on pre-operative staging. With the introduction of new diagnostic tools such as spiral computed tomography or endosonography with fine needle biopsy, substantially smaller nodes can probably also be detected and cytologically proven in the near future, possibly leading to an increase in patients with pre-operatively demonstrated stage IV (M1a) disease. Questions arise whether this will influence the selection of patients for curative resection.

At present endosonography is the most reliable tool for assessing T- and N-stage and computed tomography is useful for evaluating distant metastatic disease. In a recent series Reed and co-workers described a sensitivity and specificity of EUS of 72% and 97% resp. With EUS- guided fine-needle aspiration, tumour positivity could be confirmed in 88% of the cases called positive by EUS. In that paper, truncal nodes were considered a regional nodal basin of the tumour, not precluding resection. Hiele and others showed in 86 patients who underwent EUS for staging of tumours of the oesophagus or gastro-oesophageal junction that median survival was only three months when positive truncal nodes were present on EUS-FNA. Based on these results, other palliative treatment modalities should be applied instead of surgery for patients with EUS-FNA proven coeliac nodes. But of the ten patients with oesophageal carcinoma and metastatic disease at the coeliac axis in Hiele’s study, only one underwent a radical (R0) resection, and two did not undergo surgical treatment at all. Therefore it can not be concluded properly from that paper that the presence of nodal disease at the coeliac trunc is an independent prognostic factor for survival. The data in our study indicate that the presence of metastatic disease in the nodes near the origin of the left gastric artery does not necessarily imply a dismal prognosis.

Until recently, the rather subjective criteria of size, shape, margins and echo pattern were the only criteria at hand for defining tumour positive lymph nodes at EUS. In a recent series by Heidemann et al. the accuracy of EUS in staging T and N stage decreased in more distal tumours, being 86% and 85% in thoracic tumours while dropping to 67% and 69% for N-staging. Unless all visible nodes are
punctured, including the non-suspect nodes, EUS-FNA will probably miss nodal metastatic disease. And even after EUS-FNA, sampling error might not be avoided. Deciding whether a node is suspect is difficult and deciding upon its precise location might be even more so. On (endo)sonography, it is hard to distinguish nodes along the left gastric artery from nodes near the coeliac axis itself. Distance to the coeliac trunc is hard to measure and it is not clear yet within which distance to the coeliac trunc a node should be considered as truncal node. In the present series, the peri-truncal nodes (within one cm of the origin of the left gastric artery as marked in the resection specimen) were dissected. We considered tumour positivity in these nodes as distant metastases, but this assumption can be criticised. We did not perform a lymph node dissection along the hepatic or splenic arteries. Performing a more extended lymphadenectomy in the upper abdomen might improve the adequacy of staging, but might also lead to an increase in morbidity, while long term benefits of such a more extended lymphadenectomy are still uncertain.

Pre-operative results of new diagnostic tools such as endosonography with fine-needle aspiration should therefore be interpreted with caution, to avoid denying patients a potentially curative treatment. Further studies are necessary to establish firm criteria regarding curability for patients with M1a-tumors, and to identify the proper role for new pre-operative diagnostic tools in the staging of patients with oesophageal carcinoma.

Conclusion

Although radicality and lymph node status were independent prognostic factors, there was no survival difference between patients with or without tumour positive lymph nodes near the origin of the left gastric artery (M1a) after transhiatal resection for oesophageal carcinoma when pre-operative work-up had not been able to identify these positive nodes. Median survival when these truncal nodes are positive was 1.5 years in this series, and long-term survival is possible in 25% of patients with involved truncal nodes. With the current possibility of more accurate and subtle staging of truncal lymph node involvement by e.g. EUS-FNA, more tumours might be classified as stage IV pre-operatively. However, these new findings should be interpreted with caution, until firm criteria for irresectability/incurability of positive nodes are established.
References


Table 1: Patient and post-resectional tumour characteristics of 110 patients undergoing macroscopically radical transhiatal resection for a mid/distal oesophageal carcinoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male : Female</td>
<td>85 : 25</td>
</tr>
<tr>
<td>Age (mean, standard deviation)</td>
<td>64 ± 11</td>
</tr>
<tr>
<td>Adenocarcinoma: Squamous cell carcinoma</td>
<td>70 : 40</td>
</tr>
<tr>
<td>R0 : R1*</td>
<td>88 : 22</td>
</tr>
<tr>
<td>Differentiation: Good</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>51 (46%)</td>
</tr>
<tr>
<td>Poor</td>
<td>53 (48%)</td>
</tr>
<tr>
<td>pTNM Stage I</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>Stage Ia</td>
<td>30 (27%)</td>
</tr>
<tr>
<td>Stage IIb</td>
<td>10 (9%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>39 (36%)</td>
</tr>
<tr>
<td>Stage IV‡</td>
<td>16 (15%)</td>
</tr>
</tbody>
</table>

*R0 = microscopically radical resection; R1 = microscopically tumour left behind
‡These are the patients in whom pre-operatively no positive lymph nodes were identified near the coeliac axis, but in whom there were positive nodes near the origin of the left gastric artery as identified in the resection specimen

Table 2: Multivariate analysis of differentiation grade of the tumour, radicality and the presence of lymph nodes (pTNM stages I and IIa versus IIb, III and IV) using Cox proportional hazards model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Differentiation grade</td>
<td>1.5</td>
<td>0.9 – 2.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Radicality</td>
<td>3.1</td>
<td>1.8 – 5.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lymph node status</td>
<td>2.8</td>
<td>1.5 – 5.1</td>
<td>0.0008</td>
</tr>
</tbody>
</table>
Figure 1: Kaplan Meier curves of 65 patients with carcinoma of the mid/distal oesophagus in whom nodal metastases were found after transhiatal resection. There were 10 patients with stage IIb, 39 patients with stage III and 16 patients with stage IV (M1a) disease.
Table 2: Relationship between patient survival and lymph node status (N+ only) for patients with different differentiation grade (G1: low, G2: medium, G3: high).

<table>
<thead>
<tr>
<th>Variable</th>
<th>N1 (n=10)</th>
<th>N2 (n=15)</th>
<th>N3 (n=20)</th>
<th>N4 (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation grade</td>
<td>G1</td>
<td>G2</td>
<td>G3</td>
<td>G4</td>
</tr>
<tr>
<td></td>
<td>3/4 (75%)</td>
<td>2/5 (40%)</td>
<td>1/5 (20%)</td>
<td>5/10 (50%)</td>
</tr>
<tr>
<td>Radicality</td>
<td>3/10 (30%)</td>
<td>4/15 (26.6%)</td>
<td>5/20 (25%)</td>
<td>10/25 (40%)</td>
</tr>
<tr>
<td>Lymph node status</td>
<td>3/10 (30%)</td>
<td>4/15 (26.6%)</td>
<td>5/20 (25%)</td>
<td>10/25 (40%)</td>
</tr>
</tbody>
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