Carcinogenesis and treatment of adenocarcinoma of the oesophagus and gastric cardia

Hulscher, J.B.F.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
A prospective analysis of the diagnostic yield of extended en bloc resection for adenocarcinoma of the oesophagus or gastric cardia

Jan B.F. Hulscher JBF¹, Johanna W. van Sandick JW¹, G. Johan A. Offerhaus²,
Hugo W. Tilanus HW³, Hugo Obertop¹, Van Lanschot JJB¹

Academic Medical Center/University of Amsterdam: Departments of Surgery¹ and
Pathology², Erasmus University Hospital Rotterdam: Department of Surgery³

Published as:
Abstract

**Background:** The extent of lymph node dissection can affect TNM-staging. The resulting “stage-migration” might hamper stage-by-stage comparison between different forms of oesophageal resection. Aim of the study was to assess the diagnostic impact of extended en-bloc lymphadenectomy in staging (adeno)-carcinoma of the mid/distal oesophagus or gastric cardia.

**Patients and Methods:** Prospective study.

**Results:** Between 1994 and 2000 74 patients underwent extended oesophagectomy: 67 men and 7 women, median age 63 (40 - 78) years. A median of 31 (15-78) lymph nodes was resected (and identified), with a median of 5 (0-31) positive nodes. Twenty-seven patients (36.5%) showed tumour-positive nodes in extended fields: 15 patients (20.3%) in the abdomen, 15 patients (20.3%) in the mediastinum. Subcarinal nodes were most affected (19%). Extended resection led to tumour-upstaging in 17 patients (23.0%): two patients had isolated positive subcarinal nodes, 15 other tumours became M1a due to positive nodes near coeliac axis, hepatic - or splenic artery. Tumour positivity in paratracheal - or aorta-pulmonary nodes occurred in 8% of patients, without influencing staging.

**Conclusion:** extended en-bloc lymphadenectomy alters staging in 17/74 patients (23.0%) with adenocarcinoma of the oesophagus or cardia: mainly into M1a due to positive coeliac nodes (20.3%). Subcarinal nodes are often affected, but rarely change staging.

**Introduction**

Lymph node dissection for oesophageal carcinoma serves three purposes: it aids in the staging of the disease, it may decrease or postpone the incidence of loco-regional tumour recurrence, and finally it may prolong the (disease-free) survival. A proper staging offers important prognostic information, for both physician and patient, and might influence the decision to apply adjuvant chemo- and/or radiation therapy.

During a transhiatal oesophageal resection, the left gastric artery is transected as it branches from the coeliac axis, and only the nodes at the origin of the left gastric artery are routinely removed. Nodes near the coeliac axis (i.e. nodes near the hepatic and splenic arteries and the coeliac axis itself) are not routinely resected. Metastases in these nodes are considered distant metastases (M1) for oesophageal carcinoma according to the UICC '97 TNM-classification. The subcarinal lymph nodes are also not included in the resection during a transhiatal procedure. The positivity of these nodes affects the N-status, but not the M-status.
In general, variability in the extent of lymph node dissection and number of lymph nodes examined per lymph node station can significantly affect nodal staging and thus TNM-staging. This can lead to so-called stage migration, *i.e.* the migration of disease into a more advanced stage, by demonstrating (more distant) lymph node metastases, which would not have been identified by a less extended lymphadenectomy. This phenomenon might hamper the stage-by-stage comparison between different forms of oesophageal resection. In this study the effect of an extended *en-bloc* resection on staging adenocarcinoma of the mid/distal oesophagus or gastric cardia is evaluated.

**Patients and Methods.**

Patients undergoing right-sided transthoracic oesophagectomy with an extended *en-bloc* lymph node dissection for adenocarcinoma of the mid/distal oesophagus or gastric cardia as part of a randomised trial comparing transhiatal resection with transthoracic oesophagectomy with extended *en-bloc* lymph node dissection were enrolled. Operations were performed with curative intent, which is in the absence of local irresectability and/or distant metastases (including positive cervical lymph nodes or resectable coeliac lymph nodes).

The diagnostic work-up consisted of endoscopy with biopsy, endosonography, external sonography of abdomen and neck, and laryngoscopy to evaluate the function of the vocal cords. Routine chest X-ray and EKG were also performed. Laparoscopy with laparoscopic ultrasonography was added for cardia-carcinoma. Cardia-carcinoma was defined as a tumour with the tumour bulk at or distal from the gastro-oesophageal junction as seen endoscopically/endosonographically.

For staging the TNM-classification from the UICC '97 was used. Oesophageal carcinoma and cardia-carcinoma (with substantial ingrowth in the oesophagus) were considered as one clinical entity and staged by the classification for oesophageal carcinoma. Nodes near the coeliac axis, the hepatic artery and the splenic artery were considered M1a. Histologically proven tumour positive lymph nodes in the neck (M1b) were considered a contraindication for curative surgery, while resectable enlarged lymph nodes near the coeliac axis (formally M1a) were not.

All study-patients underwent a cervico-thoraco-abdominal subtotal oesophageal resection with dissection of the right-sided paratracheal - (up to three cm from the subclavian artery, thus leaving the right recurrent nerve chain in situ), aorta pulmonary window -, subcarinal -, mediastinal -, paracardial -, lesser and greater curvature -, left gastric artery -, common hepatic artery -, splenic artery -, and coeliac trunc lymph nodes. The left para-tracheal/recurrent laryngeal nerve chain was not dissected. Paratracheal -, aorta-pulmonary window-, and subcarinal lymph nodes were considered extended lymph nodes, just as nodes near the hepatic artery, near the splenic artery or near the coeliac trunc. Nodes at the origin of the left gastric artery were not considered extended nodes, as they are also
removed during non-extended transthiatal resection without formal lymph node dissection. The anastomosis was made in the neck, approaching the neck from the left side for reasons described elsewhere.\textsuperscript{3} No formal lymphadenectomy was performed in the neck.

Surgery was performed/supervised by one of three experienced oesophageal surgeons (HWT, HO, JJBvL) at the Academic Medical Centre/University of Amsterdam and the University Hospital Rotterdam – Dijkzigt, both tertiary care centres with a wide experience in oesophageal surgery (>70 resections each annually).

The origin of the left gastric artery and the subcarinal nodes were marked in the resection specimen. Separate lymph nodes were marked by localisation and submitted in separate bottles. Peri-oesophageal tissue and lesser and greater omentum were palpated on the presence of lymph nodes by the pathologist, and subsequently dissected. Routine H&E staining was performed using a standardised protocol in which lymph nodes were cut in two and both sides stained with hematoxylineosin. Patients were only eligible for the present study when 15 or more lymph nodes had been resected and identified by the pathologist and the subcarinal and left gastric artery lymph nodes were marked adequately. An experienced (gastro-intestinal) pathologist reviewed the resection specimens, and pathological findings were described on a standardised form. The pTNM-stage, tumour diameter, differentiation grade, radicality, total number of resected lymph nodes and total number of positive lymph nodes, including their localisation, were recorded. No additional immuno-histochemical staining techniques to detect micro-metastases were used.

Statistical analysis was performed using the SPSS-package. For categorical data the Chi-square or Fisher Exact tests were used as appropriate, the Mann Whitney U test was used to compare continuous variables.

Results

Between 1994 and 2000 74 patients underwent extended transthoracic oesophagectomy while meeting the inclusion criteria: 67 men and 7 women with a median age of 63 (40 - 78) years, amounting to 75\% of all patients undergoing transthoracic resection with extended en bloc resection in the study period. There were 60 tumours of the distal oesophagus (81.1\%) and 14 tumours of the cardia (18.9\%). Median operation time was 6 hours (3.5 - 8.5), in-hospital mortality 5/74 (6.8\%). Median stay in intensive care/high care was 6 days (1 - 79), median hospital stay was 22 days (7 - 154).

The median number of resected and identified lymph nodes per patient was 31 (15-78), with a median number of 5 (0-31) positive nodes. There were no positive lymph nodes found in nine patients with T1 tumours (all T1 submucosal) while lymph node metastases were found 9/9 and 50/56 patients with
T2 and T3 tumours respectively. The distribution of lymph nodes is shown in table 1. Tumour positive lymph nodes were most frequently encountered in the non-extended fields. Overall, 27 patients (36.5%) showed tumour-positivity in lymph nodes of the extended fields: 15 patients (20.3%) had positive nodes in the extended fields of the mediastinum, and 15 patients (20.3%) had positive nodes in the extended fields of the abdomen. Three of these patients had positive nodes in the extended fields of both abdomen and chest. There was no difference between oesophageal carcinoma and cardia-carcinoma regarding the presence of nodal metastases in the extended fields (p=0.59).

The pTNM stage of the tumours is depicted in table 2. It shows that an extended resection in chest and abdomen led to upstaging of the tumour in 17/74 patients (23.0%), 14/60 patients with oesophageal carcinoma (23.3%), and 3/14 patients with cardia carcinoma (21.4%). Two of these 17 patients had isolated positive subcarinal nodes, changing N0 into N1-status. The other 15 patients had M1a-nodes in the abdomen: positive (resectable) lymph nodes near the coeliac axis, near the hepatic artery or near the splenic artery. Eight patients had positive nodes near the coeliac axis without positive nodes at the origin of the left gastric artery. There was no upgrading due to tumour positive paratracheal or aorta-pulmonary nodes, although in three patients these were the only positive node locations in the chest (but the patients also had positive nodes in the – non-extended – abdominal fields).

Discussion

In the present series, tumour positive lymph nodes in the extended fields changed staging in 17/74 (23.0%) of the patients, offering potentially important diagnostic and prognostic information. This stage migration has been clinically demonstrated for gastric carcinoma, but as yet not for oesophageal carcinoma. Fifteen tumours became M1a due to positive nodes near the coeliac axis, common hepatic artery or splenic artery. Fourteen of the patients (18.9%) had positive subcarinal nodes, changing N0-status into N1-status in only two patients. Only six patients (8%) showed positive nodes in the aorta-pulmonary window or right paratracheal nodes, but all of these patients had also positive lymph nodes in the non-extended fields.

During routine transhiatal resection in our institution the nodes near the origin of the left gastric artery are removed. Adding a formal dissection near the coeliac axis changed staging in 20% of the patients. Eight of these patients showed some form of skip-metastases: nodes near the coeliac axis being positive without positive nodes near the origin of the left gastric artery. A formal lymphadenectomy near the coeliac axis can probably be done without adding substantial morbidity or mortality, and supplies important diagnostic information. Based on this assumption, a routine lymph node dissection might be recommended for staging purposes in the upper abdomen, if this diagnostic information leads to an altered adjuvant post-operative strategy.
During a transthoracic *en bloc* resection the subcarinal (and sometimes the lower paratracheal) nodes are routinely removed, while the nodes in the aorta-pulmonary window are not dissected. In the present protocol the nodes in the aorta-pulmonary window were resected together with the (right sided) paratracheal nodes, which led to the term “extended *en bloc*” resection.

The subcarinal nodes are positive in 19% of the cases. This is in accordance with the literature, in which the percentage of patients with positive nodes ranges from 10 to 40%. These nodes might sometimes be reached through the widened hiatus of the diaphragm during transhiatal resection, but this would imply the use of large retractors, possibly leading to more manipulation of the heart, and a dissection under sub-optimal vision. In our routine transhiatal resection, these nodes are therefore only rarely removed. Although not important for staging (only two patients changed from N0 into N1 due to isolated positive subcarinal nodes), the large percentage of tumour positive lymph nodes at this site suggests a possible benefit of routine clearance of the subcarinal nodes. Whether or not removal of these positive subcarinal nodes lowers the incidence of loco-regional recurrence and perhaps even improves long-term survival is beyond the scope of the present analysis.

Adding a thoracotomy probably increases the physiologic impact of the operation, leading to an increased post-operative morbidity and mortality. Therefore, adding a formal thoracotomy for staging purposes only seems unwarranted based on the present data: although 14/74 (18.9%) of the patients showed tumour positive subcarinal nodes, a change in staging due to positive subcarinal nodes occurred in only two patients (3%).

Some authors propose using a classification system in which adenocarcinoma of the distal oesophagus and adenocarcinoma of the gastric cardia are considered as one entity. In the present paper the TNM-classification for carcinoma of the distal oesophagus is used. There seems no difference in lymph node spread between oesophageal carcinoma and cardia-carcinoma. However, when the TNM-classification of stomach cancer is used, the nodes located along the left gastric, common hepatic, splenic, and coeliac arteries and the hepatoduodenal nodes are considered regional lymph nodes, and thus not as distant metastases. Only the involvement of other intra-abdominal lymph nodes such as the retro-pancreatic, mesenteric and para-aortic nodes is classified as distant metastasis. In the present series, dissection of these latter nodes was not performed. When the stomach-cancer criteria would be applied to the lymph nodes in the abdomen, there would not have been any stage migration due to removal of the peri-truncal nodes. However, 28 tumours (38%) would have been re-staged as M1 due to the presence of intra-thoracic nodal disease when a thoracic lymph node dissection would have been performed.

Less invasive (non-operative) techniques are being developed to supply more accurate diagnostic information about the status of specific lymph node stations. When combined with fine needle aspiration, endosonography might (in experienced hands) be able to reliably identify patients with cytologically positive nodes. When the subcarinal or paratracheal nodes are found positive, an *en bloc* resection might be considered. However, even in experienced hands it is difficult to distinguish
between nodes near the origin of the left gastric artery (N1) and nodes near the coeliac axis (M1),
which is why only the presence of enlarged, irresectable (> 2cm on external ultrasonography),
histologically proven tumour positive nodes near the coeliac axis was used as a contra-indication for
surgery in the present series. In the present series, there was one patient with endosonographically
suspicious nodes near the coeliac axis undergoing resection, in the other 14 patients the presence of
nodal metastases became apparent in the resection specimen. Laparoscopy in combination with
laparoscopic ultrasonography, performed only in patients with a cardia carcinoma, had also not been
able to detect these small metastases. The development of positron emission tomography and
magnetic resonance imaging with iron contrast might also aid in the pre-operative staging of patients
with carcinoma of the oesophagus. However, until long-term recurrence and survival data are
known, the therapeutic effect of a more extended lymphadenectomy remains uncertain.

Conclusion

An extended lymphadenectomy in the abdomen and chest altered staging in 23% of the patients with
(adeno)carcinoma of the mid/distal oesophagus and/or gastric cardia, offering valuable diagnostic and
prognostic information. Tumour staging changed most of the times due to the presence of tumour
positive lymph nodes near the coeliac axis (M1a). Positive subcarinal nodes were found in one-fifth
of the patients, changing N-status in only 2/74 (3%). Lymphatic metastases in the paratracheal/aorto-
pulmonary window region were identified in only 8% of the patients, and when they occurred they did
not alter staging because positive lymph nodes were always found elsewhere in the non-extended
fields as well.

Based on these data, stage migration in oesophageal cancer occurs mainly due to positive nodes in the
upper abdomen. If dissection of these nodes can be performed without adding substantial morbidity or
mortality, a routine extended lymphadenectomy can be recommended for staging purposes along the
celiac axis. Although often positive, subcarinal nodes changed staging only in a small minority of
patients. A routine clearance of the subcarinal nodes, implying a thoracotomy or a technically
demanding extended transhiatal resection, is probably not warranted for staging purposes only. Less-
invasive pre-operative diagnostic modalities (esp. EUS-guided FNA) might be able to identify patients
with positive subcarinal or paratracheal nodes, but whether removal of these nodes offers any (disease-
free) survival benefit has yet to be demonstrated.
Acknowledgements

The authors thank Dr. B.P.L. Wijnhoven from the Erasmus University Hospital Rotterdam, Department of Surgery, Dr. P. Fockens from the Academic Medical Center/University of Amsterdam, Department of Gastroenterology, and Prof. F.J.W. ten Kate from the Academic Medical Center/University of Amsterdam, Department of Pathology for their assistance in obtaining the data presented in the study and their critical comments during the preparation of the manuscript.

References:


Table 1: Lymph node distribution among 74 patients with adenocarcinoma of the mid/distal oesophagus and/or gastric cardia who underwent an extended lymphadenectomy in chest and abdomen.

<table>
<thead>
<tr>
<th>Lymph node station</th>
<th>LN identified No. of patients (%)</th>
<th>LN Positive No. of patients (%)</th>
<th>Positive/removed* No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paratrach./Aorta-pulm. window</td>
<td>61 (82.4)</td>
<td>6 (8.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>Subcarinal</td>
<td>69 (93.2)</td>
<td>14 (18.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Mediastinal/paracardial</td>
<td>68 (91.9)</td>
<td>35 (47.3)</td>
<td>0.52</td>
</tr>
<tr>
<td>Lesser curvature</td>
<td>58 (78.4)</td>
<td>37 (50.0)</td>
<td>0.64</td>
</tr>
<tr>
<td>Origin of left gastric artery</td>
<td>57 (77.0)</td>
<td>27 (36.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Hepatic-/splenic art./coeliac axis</td>
<td>53 (71.6)</td>
<td>15 (20.3)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Aorta-pulum: aorta-pulmonary; LN: lymph nodes; Paratrach: paratracheal

* The percentage between brackets is the percentage of all 74 patients.

* Positive/removed: the ratio of positive to removed and identified lymph nodes

Table 2: pTNM stage of tumours in 74 patients after extended en bloc resection compared with pTNM stage when only the non-extended lymph node stations were taken into account.

<table>
<thead>
<tr>
<th>Extended Stage</th>
<th>Stage I</th>
<th>Stage IIa</th>
<th>Stage IIb</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ext Stage I</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>Stage IIa</td>
<td>-</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Stage IIb</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>-</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Stage III</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>37</td>
<td>12</td>
<td>49</td>
</tr>
<tr>
<td>Stage IV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>5</td>
<td>7</td>
<td>38</td>
<td>15</td>
<td>74</td>
</tr>
</tbody>
</table>