Prognostication in esophageal cancer
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Citation for published version (APA):

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Postoperative complications after esophagectomy for adenocarcinoma of the esophagus are related to timing of death due to recurrence

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Fiebo JW ten Kate
Olivier RC Busch
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J Jan B van Lanschot
Abstract

Introduction
Esophagectomy is frequently accompanied by substantial complications with secondary disturbance of the immune system. After esophagectomy for adenocarcinoma of the distal esophagus and/or gastroesophageal junction, the majority of patients develops an early recurrence and dies within two years. The aim of this study was to determine the relevance of perioperative complications on the timing of death due to recurrence.

Patients and Methods
A consecutive series of 351 patients who underwent esophagectomy for adenocarcinoma of the esophagus and gastroesophageal junction was reviewed.

Results
Of the 351 included patients, 191 patients (54%) died due to recurrence of esophageal adenocarcinoma. Of these 191 patients, 77 (40%), 138 (72%) and 186 patients (97%) died before 12, 24 and 60 months respectively. Multivariate Cox regression analysis demonstrated that T-stage, lymph node ratio > 0.20, the presence of extracapsular LNI, but not complications were significant factors for the prediction of death due to cancer recurrence. However, in the patients who died, multivariate Cox regression analysis demonstrated that not only the presence of extracapsular LNI but also the occurrence of complications were significantly related with a shorter time interval until death due to recurrence.

Conclusions
The relation between perioperative complications and cancer recurrence per se is not causal. However, postoperative complications are independently associated with the early timing of death due to cancer recurrence. A possible explanation for this phenomenon is that immunological host factors enhance microscopic residual disease to develop more rapidly into clinically manifest recurrence.
Introduction

The incidence of adenocarcinoma of the esophagus is rapidly rising\textsuperscript{1-3}. Esophageal adenocarcinoma is an aggressive disease with early lymphatic and hematogenous dissemination. Surgery is the best curative treatment option. Centralization of surgical resections, advances in surgical techniques and improvements in peri-operative care (e.g. epidural analgesia, early extubation) have reduced the risk of esophagectomy to an acceptable level\textsuperscript{4-8}. However, these advances have failed to translate into a substantial improvement of long-term survival after surgical resection with 5-year survival rates rarely exceeding 30\%\textsuperscript{6,8-11}. Despite comprehensive preoperative staging to select patients for potentially curative surgery, many have unrecognized metastatic disease at the time of first presentation and later present with locoregional, hematogenous and or transcelomic recurrences. Disappointingly, even in patients who were operated on with curative intent, the majority develops recurrence and dies within two years\textsuperscript{7,12-16}. Only a minority of patients developing recurrence suffers from relatively late recurrence. This marked difference in biological behavior probably depends both on tumor characteristics and on host factors. It has been suggested that potent immunosurveillance is of pivotal importance to eradicate microscopic residual disease after surgical resection\textsuperscript{17-19}. Major surgical resection is frequently accompanied by substantial complications with secondary disturbance of the immune system\textsuperscript{17-19}. It could be hypothesized that these complications might have a negative impact on immunosurveillance and thus on tumor recurrence and long term survival.

To our knowledge, no attention has been paid to the predictors of timing of death due to recurrence after esophagectomy. It remains unknown if patients who die due to an early recurrence had more advanced disease at the time of operation or had a secondary disturbance of the immune system due to the presence of perioperative complications. Therefore, the aim of the present study was to determine factors associated with survival due to cancer recurrence after intentionally curative esophagectomy for adenocarcinoma of the distal esophagus and gastroesophageal junction and especially to determine the relevance of complications to the time-interval until death due to cancer recurrence.

Patients and Methods

Between January 1993 and January 2003, a consecutive series of 351 patients underwent esophagectomy for adenocarcinoma of the esophagus and / or gastro-esophageal junction (GEJ). Patients did not receive pre- or postoperative chemo- and/ or radiation therapy. Clinicopathological data, including complications, from all operated patients were permanently collected in a prospective database.

Preoperative staging was done with endoscopy with histological biopsy, endosonography, external sonography of the neck, CT scan and, on indication, PET-scan. Surgery was
performed / supervised by one of three experienced surgeons (ORCB, HO, JJBvL) at the Academic Medical Center at the University of Amsterdam, a tertiary referral center with a wide experience in esophageal surgery. Operations were performed with curative intent, i.e. in the absence of local irresectability and/or distant metastases (including tumor positive cervical lymph nodes or irresectable celiac nodes). Operations were performed via the transhiatal or transthoracic approach. During transhiatal esophagectomy, the mid- to distal esophagus was dissected under direct vision through the widened hiatus of the diaphragm. The tumor and its adjacent lymph nodes were dissected en-bloc. During transthoracic esophagectomy, a right-sided postero-lateral thoracotomy was performed. The esophagus was resected en-bloc with all (peri-) esophageal tissue in the mediastinum including the thoracic duct, azygos vein, ipsilateral pleura and lymph nodes.

The subcarinal nodes and the origin of left gastric artery were marked in the resection specimen. Pathologic findings were described on a standardized form. The pTNM-stage, differentiation grade, radicality of resection, total number of resected lymph nodes and total number of positive lymph nodes, including their location were recorded. The lymph node ratio was defined as the ratio between the total amount of positive lymph nodes divided by the total amount of resected nodes. Lymph nodes were cut in two and routine H&E staining was performed using a standardized protocol. Extracapsular lymph node involvement (LNI) was defined as metastatic adenocarcinoma extending through the nodal capsule into the perinodal fatty tissue.

Definition of complications
Complciations were categorized as medical (including infectious complications) or complications directly attributable to surgical technique. Medical complications included cardiac complications (atrial fibrillation, myocardial ischemia, heart failure, cerebral infarction), respiratory failure (diagnosed with blood gas criteria with or without mechanical ventilatory support), atelectasis, pulmonary embolism and renal failure. Infectious complications included wound infection, pleural empyema, pneumonia (defined as a new infiltrate on chest x-ray, accompanied by purulent sputum or fever, for which treatment with antibiotics was started), and sepsis. Technical complications were recorded as chylothorax, chyloperitoneum, anastomotic leakage (including both radiological and clinical leakages), ischemia of the gastric tube, haemorrhage, recurrent laryngeal nerve palsy, diaphragmatic herniation and dehiscence of the fascia.

Follow-up
All patients were seen at the outpatient clinic at three to four months intervals during the first two years and every six months thereafter for three years. After five years, follow-up was obtained by telephone from the patient or the patient’s family practitioner. Follow-up extended to August 2005 ensuring a minimal potential follow-up of 32 months. Follow-up was complete in all patients. Recurrence of disease was only diagnosed on clinical grounds. Radiological modalities were not routinely used. When recurrence was suspected, additional investigations were performed on indication.
Definition of recurrence pattern
Recurrences were classified as hematogenous recurrence, locoregional recurrence and transcelomic (pleural / peritoneal) recurrence. Recurrence at cervical-, celiac, or paraaortic lymph nodes was classified as locoregional recurrence. Simultaneous locoregional and hematogenous disease was classified as hematogenous recurrence.

Statistics
Statistical calculations were performed using SPSS® version 12.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). The primary end point of the analysis was disease specific survival (defined as time from date of surgery to date of death as a result of disease recurrence). To perform statistical analysis in a homogeneous group, patients who died due to postoperative complications and patients who died due to unrelated causes were excluded. Cox regression models were used to examine the association between potential predictors and the time until death as a result of esophageal cancer. The following potential predictors were analyzed; age, sex, operative approach, ASA classification, pT-stage, pN-stage, presence of positive truncal nodes, lymph node ratio (categorized into ≤ 0.20 or >20%20), the presence of extracapsular LNI, presence of Barrett’s mucosa, differentiation grade, microscopically irradical resection and the presence of medical or surgical complications. The Cox proportional hazards regression model was used for both univariate and multivariate analyses. The models in the present analysis were constructed (1) to identify factors associated with death due to recurrence and (2) to identify prognostic factors in patients who died due to recurrence. Variables achieving a probability value of less than 0.1 in the univariate analysis were subsequently introduced in a multivariate stepwise proportional-hazard analysis (Cox model) to identify those variables significantly associated with death due to recurrence and timing of death due to recurrent disease. Results are given as hazard ratios with their 95% confidence interval. P-values less than 0.05 (two-sided) were considered statistically significant.

Results
Between January 1993 and January 2003 a consecutive series of 351 patients underwent esophagectomy for malignant disease of the esophagus and / or GEJ. The following patients were excluded from this study; eight patients in whom tumor was left behind macroscopically and ten patients who died of postoperative complications (3%). Furthermore, 22 patients who died during follow-up due to unrelated disease were excluded from this analysis; eight patients due to myocardial infarction, six patients due to cerebral infarction, five patients due to pulmonary disease, one patient due to pathologically proven primary pancreatic cancer, one patient due to pathologically proven primary lung cancer and one patient with
Table 1: Clinicopathological characteristics of patients with adenocarcinoma of the distal esophagus or gastroesophageal junction. Patients are divided in those who died of cancer recurrence and those who were alive at least 32 months after date of operation.

<table>
<thead>
<tr>
<th>Factor</th>
<th>died of recurrence</th>
<th>alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>age*</td>
<td>64 (35-85)</td>
<td>64 (37-83)</td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- male</td>
<td>162 (85%)</td>
<td>100 (83%)</td>
</tr>
<tr>
<td>- female</td>
<td>29 (15%)</td>
<td>20 (17%)</td>
</tr>
<tr>
<td>operative approach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- THE</td>
<td>137 (72%)</td>
<td>88 (73%)</td>
</tr>
<tr>
<td>- TTE</td>
<td>52 (28%)</td>
<td>32 (27%)</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1</td>
<td>43 (23%)</td>
<td>25 (21%)</td>
</tr>
<tr>
<td>- 2</td>
<td>113 (56%)</td>
<td>78 (65%)</td>
</tr>
<tr>
<td>- 3</td>
<td>33 (17%)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>- 4</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>pT-stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- pT1</td>
<td>12 (6%)</td>
<td>48 (40%)</td>
</tr>
<tr>
<td>- pT2</td>
<td>19 (10%)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>- pT3</td>
<td>148 (77%)</td>
<td>54 (45%)</td>
</tr>
<tr>
<td>- pT4</td>
<td>12 (7%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>pN-stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- pN0</td>
<td>28 (15%)</td>
<td>69 (58%)</td>
</tr>
<tr>
<td>- pN1</td>
<td>163 (85%)</td>
<td>51 (43%)</td>
</tr>
<tr>
<td>presence positive truncal node (M1a)</td>
<td>52 (27%)</td>
<td>16 (13%)</td>
</tr>
<tr>
<td>lymph node ratio*</td>
<td>0.30 (0.0-1.0)</td>
<td>0.0 (0.0-0.6)</td>
</tr>
<tr>
<td>Presence extracapsular LNI</td>
<td>122 (64%)</td>
<td>19 (16%)</td>
</tr>
<tr>
<td>Presence Barrett’s mucosa</td>
<td>101 (53%)</td>
<td>75 (63%)</td>
</tr>
<tr>
<td>Differentiation grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- good</td>
<td>4 (2%)</td>
<td>13 (11%)</td>
</tr>
<tr>
<td>- moderate</td>
<td>61 (32%)</td>
<td>63 (53%)</td>
</tr>
<tr>
<td>- poor</td>
<td>126 (66%)</td>
<td>44 (37%)</td>
</tr>
<tr>
<td>microscopically irradical resection (R1)</td>
<td>47 (25%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>medical or surgical complications</td>
<td>121 (63%)</td>
<td>55 (46%)</td>
</tr>
<tr>
<td>ICU-stay*</td>
<td>2 (1-70)</td>
<td>2 (1-73)</td>
</tr>
<tr>
<td>hospital stay*</td>
<td>17 (10-104)</td>
<td>15 (10-129)</td>
</tr>
</tbody>
</table>

* Values depicted are median (range). THE = transhiatal esophagectomy, TTE = transthoracic esophagectomy. ASA = The American Society of Anesthesiologists. LNI = lymph node involvement. ICU = Intensive Care Unit
Parkinson’s disease. Five (1%) patients who experienced recurrence at last follow-up, but were still alive, were censored in survival analyses.

Risk factors for death due to cancer recurrence
The clinicopathologic characteristics of 191 patients (62%) who died of recurrence and 120 patients (38%) who were alive are given in Table 1. In univariate analysis, the radicality of resection, the depth of invasion (T-stage), the presence of lymphatic dissemination, the presence of positive celiac nodes, a lymph node ratio > 0.20, the presence of extracapsular LNI and the differentiation grade of the tumor and the presence of medical or surgical complications were all significantly associated with death from recurrence of adenocarcinoma of the distal esophagus and/or GEJ (Table 2). There were no significant differences in survival time between the three operating or supervising surgeons (p=0.258). Multivariate Cox regression analysis demonstrated that T-stage, a lymph node ratio > 0.20 and the presence of extracapsular LNI were significant factors for the development of cancer.

### Table 2: Univariate Cox-regression analysis for death due to cancer recurrence after esophagectomy for adenocarcinoma of the esophagus or gastroesophageal junction. Results are given as Hazard Ratios and their 95% confidence interval (CI)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age, one year increment</td>
<td>0.99</td>
<td>0.978-1.01</td>
<td>0.327</td>
</tr>
<tr>
<td>male gender</td>
<td>1.02</td>
<td>0.69-1.52</td>
<td>0.918</td>
</tr>
<tr>
<td>transthoracic approach</td>
<td>0.91</td>
<td>0.66-1.24</td>
<td>0.538</td>
</tr>
<tr>
<td>ASA classification (compared with ASA 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2</td>
<td>0.87</td>
<td>0.61-1.23</td>
<td>0.419</td>
</tr>
<tr>
<td>-3</td>
<td>1.04</td>
<td>0.66-1.64</td>
<td>0.878</td>
</tr>
<tr>
<td>-4</td>
<td>1.88</td>
<td>0.45-7.75</td>
<td>0.385</td>
</tr>
<tr>
<td>pT-stage (compared with pT1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- pT2</td>
<td>3.27</td>
<td>1.58-6.74</td>
<td>0.001</td>
</tr>
<tr>
<td>- pT3</td>
<td>6.52</td>
<td>3.61-11.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- pT4</td>
<td>12.89</td>
<td>5.76-28.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence lymph node metastasis (pN1)</td>
<td>4.69</td>
<td>3.13-7.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence positive truncal node (M1a)</td>
<td>2.01</td>
<td>1.46-2.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymph node ratio &gt;0.20</td>
<td>4.57</td>
<td>3.38-6.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence extracapsular LNI</td>
<td>4.42</td>
<td>3.28-6.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence Barrett’s mucosa</td>
<td>1.27</td>
<td>0.96-1.69</td>
<td>0.110</td>
</tr>
<tr>
<td>Differentiation grade (compared with good)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- moderate</td>
<td>2.19</td>
<td>0.80-6.04</td>
<td>0.128</td>
</tr>
<tr>
<td>- poor</td>
<td>4.53</td>
<td>1.67-12.28</td>
<td>0.003</td>
</tr>
<tr>
<td>microscopically irradical resection (R1)</td>
<td>2.34</td>
<td>1.68-3.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>medical and/or surgical complications</td>
<td>1.32</td>
<td>0.99-1.77</td>
<td>0.062</td>
</tr>
</tbody>
</table>

ASA = The American Society of Anesthesiologists. LNI = lymph node involvement
recurrence (Table 3). The presence of medical or complications was not related with cancer recurrence in multivariate analysis.

Table 3: Multivariate Cox-regression analysis for death due to recurrence after esophagectomy for adenocarcinoma of the esophagus or gastroesophageal junction. Results are given as Hazard Ratios and their 95% confidence interval (CI)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT-stage (compared with pT1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- pT2</td>
<td>2.28</td>
<td>1.07-4.88</td>
<td>0.034</td>
</tr>
<tr>
<td>- pT3</td>
<td>3.05</td>
<td>1.58-5.88</td>
<td>0.001</td>
</tr>
<tr>
<td>- pT4</td>
<td>5.43</td>
<td>2.28-12.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence lymph node metastasis (pN1)</td>
<td>1.24</td>
<td>0.73-2.09</td>
<td>0.430</td>
</tr>
<tr>
<td>Presence positive truncal node (M1a)</td>
<td>1.05</td>
<td>0.74-1.49</td>
<td>0.780</td>
</tr>
<tr>
<td>Lymph node ratio &gt;0.20</td>
<td>6.91</td>
<td>3.27-14.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence extracapsular LNI</td>
<td>1.91</td>
<td>1.28-2.85</td>
<td>0.002</td>
</tr>
<tr>
<td>Differentiation grade (compared with good)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- moderate</td>
<td>0.80</td>
<td>0.28-2.30</td>
<td>0.679</td>
</tr>
<tr>
<td>- poor</td>
<td>1.24</td>
<td>0.44-3.52</td>
<td>0.688</td>
</tr>
<tr>
<td>microscopically irradical resection (R1)</td>
<td>0.98</td>
<td>0.66-1.43</td>
<td>0.897</td>
</tr>
<tr>
<td>medical or surgical complications</td>
<td>1.21</td>
<td>0.90-1.63</td>
<td>0.214</td>
</tr>
</tbody>
</table>

LNI = lymph node involvement

Time interval until death due to cancer recurrence

Of the 191 patients who died due to recurrence of esophageal adenocarcinoma, 77 patients (40%), 138 patients (72%) and 186 patients (97%) died before 12, 24 and 60 months respectively. Almost three quarters died within two years and only 5 patients (3%) died due to recurrence after five years. To identify which factors are responsible for the time interval until death due to recurrence, univariate Cox-regression analysis was performed. This analysis revealed that besides conventional pathological factors, (such as depth of invasion, the presence of lymphatic dissemination, the lymph node ratio, the presence of extracapsular LNI), also the occurrence of medical and/or surgical complications was associated with a shorter time interval until death due to cancer recurrence (Table 4). Multivariate Cox regression analysis demonstrated that the presence of extracapsular LNI and the occurrence of medical and/or surgical complications were significantly related with a shorter time interval until death due to cancer recurrence (Table 5).

The presence of medical or surgical complications (p=0.030), especially more wound infections (p=0.033) and more sepsis (p=0.013) was related to a shorter time to death due to recurrence. Also the presence of surgical complications, especially chylothorax (p<0.001) was related with a shorter time to death due to recurrence (Table 6). The operating surgeon was not related with timing of death due to recurrence (p=0.439).
Discussion

Despite extensive preoperative staging, 60% of the patients treated in our hospital developed cancer recurrence within 60 months after (intentionally) curative surgery. Almost three quarters of cancer related deaths occurred within two years after surgery which is in line with other studies\textsuperscript{7,12-16}. Only a small proportion developed a recurrence after five years.
In various malignancies, a relation has been described between postoperative complications and recurrence of cancer\textsuperscript{21-23}. In esophageal cancer a prognostic relation between the presence of complications after esophagectomy and overall survival has been reported before\textsuperscript{6,24}. However, in those earlier studies, no effect of complications was identified on tumor specific survival and thus the impact of complications on cancer recurrence remained unclear. A study focusing only on anastomotic leakage did not find a long term survival effect due to this complication, but the number of patients with anastomotic leakage (n=14) was too small to draw definite conclusions\textsuperscript{25}.

Table 6: The influence of specific complications for the time interval until death due to cancer recurrence. Results are given as Hazard Ratios and their 95% confidence interval (CI). Hazard ratios and p-values were given if 5 or more events were present.

<table>
<thead>
<tr>
<th>Medical and infectious complications</th>
<th>N</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular complications#</td>
<td>27</td>
<td>1.37</td>
<td>0.91-2.06</td>
<td>0.134</td>
</tr>
<tr>
<td>- atrial fibrillation</td>
<td>20</td>
<td>1.55</td>
<td>0.98-2.48</td>
<td>0.064</td>
</tr>
<tr>
<td>- myocardial ischemia</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- heart failure</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- cerebral infarction</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARDS</td>
<td>6</td>
<td>1.37</td>
<td>0.91-2.06</td>
<td>0.134</td>
</tr>
<tr>
<td>atelectasis</td>
<td>51</td>
<td>1.27</td>
<td>0.92-1.75</td>
<td>0.154</td>
</tr>
<tr>
<td>pulmonary embolism</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>renal failure</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wound infection</td>
<td>6</td>
<td>2.44</td>
<td>1.07-5.53</td>
<td>0.033</td>
</tr>
<tr>
<td>pleural empyema</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sepsis</td>
<td>8</td>
<td>2.48</td>
<td>1.21-5.09</td>
<td>0.013</td>
</tr>
<tr>
<td>pneumonia</td>
<td>49</td>
<td>1.24</td>
<td>0.89-1.72</td>
<td>0.202</td>
</tr>
<tr>
<td>Total medical complications</td>
<td>96</td>
<td>1.38</td>
<td>1.03-1.83</td>
<td>0.030</td>
</tr>
<tr>
<td>chylothorax</td>
<td>9</td>
<td>3.47</td>
<td>1.75-6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>chyloperitoneum</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anastomotic leakage</td>
<td>28</td>
<td>0.88</td>
<td>0.59-1.33</td>
<td>0.556</td>
</tr>
<tr>
<td>- radiological</td>
<td>16</td>
<td>1.36</td>
<td>0.81-2.28</td>
<td>0.243</td>
</tr>
<tr>
<td>- clinical</td>
<td>12</td>
<td>0.61</td>
<td>0.347-1.09</td>
<td>0.096</td>
</tr>
<tr>
<td>hemorrhage</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>recurrent laryngeal nerve injury</td>
<td>15</td>
<td>1.48</td>
<td>0.87-2.52</td>
<td>0.152</td>
</tr>
<tr>
<td>diaphragmatic herniation</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dehiscence of the fascia</td>
<td>5</td>
<td>1.33</td>
<td>0.54-3.25</td>
<td>0.531</td>
</tr>
<tr>
<td>Total surgical complications</td>
<td>57</td>
<td>1.33</td>
<td>0.97-1.82</td>
<td>0.077</td>
</tr>
<tr>
<td>medical and/or surgical complications</td>
<td>121</td>
<td>1.47</td>
<td>1.08-2.00</td>
<td>0.013</td>
</tr>
</tbody>
</table>

# there were two patients with atrial fibrillation and myocardial ischemia
In the present study, classical pathological factors, which indicate advanced disease, such as advanced T-stage, lymph node ratio >0.20 and the presence of extracapsular LNI, were all independent prognostic factors associated with death due to cancer recurrence\textsuperscript{11,26-33}. Although the presence of complications was related with survival in univariate analysis in multivariate analysis, the occurrence of complications was not an independent predictor of death due to recurrence. This might indicate that the primary tumor biology determines who will die of recurrence and not a hypothetical negative impact of postoperative complications on oncological immunosurveillance. Possibly, the (indirect) relation between postoperative complications and death due to recurrence can be explained by the fact that the operative procedure is technically more demanding in patients with more advanced disease and therefore is accompanied with more postoperative complications. Another explanation might be that patients with more advanced disease have a higher load of unrecognized (micro) metastatic tumor that is left behind and makes the patient more susceptible for complications. Interestingly, the presence of postoperative complications did not have a significant effect on recurrence per se, but was related to the timing of death due to recurrence in multivariate analysis. The occurrence of postoperative complications was an independent predisposing factor for a short time-interval until death due to cancer recurrence. It is unlikely that this effect can be explained by a difference in preoperative comorbidity because ASA classification was not a significant factor in univariate analysis. It could be hypothesized that complications are accompanied by a secondary disturbance of the immune system. After major surgery there is a profound but self-limiting systemic inflammatory response in patients with an uncomplicated postoperative course. However, patients who develop postoperative complications suffer a ‘double hit’, the first as a result of surgery and the second from their complications. Possibly, these circumstances enhance that residual microscopic disease can develop more rapidly to become clinically manifest and fatal\textsuperscript{17-19,23}. This is further underlined by the fact that especially patients who developed sepsis and patients who had chyle leakage died earlier. The first group of patients probably suffers from a major double hit and the second group of patients suffers from an ongoing loss of fluids and proteins (consisting of e.g. lymphocytes and immunoglobulines)\textsuperscript{32,33} which further deteriorates the already malnourished and immunocompromised patient with adenocarcinoma of the esophagus and gastroesophageal junction\textsuperscript{34,35}.

In conclusion, the results of the present study indicate that the relation between postoperative complications and cancer recurrence per se is not causal. However, postoperative complications are significantly associated with a short time-interval until death due to cancer recurrence in multivariate analysis. A possible explanation for this phenomenon is that immunological host factors enhance microscopic residual disease to develop more rapidly into fatal recurrence.
References


