Carcinogenesis and treatment of adenocarcinoma of the oesophagus and gastric cardia
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Chapter 3

The recurrence pattern of oesophageal carcinoma after transhiatal resection

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Abstract

Background. There is much controversy about the optimal resection for carcinoma of the oesophagus. Little is known about the pattern of recurrence after transhiatal resection for oesophageal carcinoma.

Patients and Methods. We retrospectively reviewed the charts of 149 patients who underwent transhiatal oesophagectomy for carcinoma of the mid or distal oesophagus or gastro-oesophageal junction between June 1993 and June 1997. Recurrence was classified as either loco-regional or distant recurrence. Nine patients with macroscopically tumour left after resection and three patients (2.0%) who died in the hospital were excluded from the analysis. This left 137 patients; 105 men and 32 women with a median age 65 years (range: 37 – 84).

Results. There were 95 adenocarcinomas (69.3%) and 42 squamous cell carcinomas (30.7%). Overall the median follow-up was 24.0 months (range: 1.4 – 69.2). For the patients alive at the end of follow-up without recurrence the median follow-up was 36.5 (range: 23.6 – 69.2). Seven patients died of other causes. The median interval between operation and recurrence was 11 months (range: 1.4 – 62.5) for patients who had recurrence, with no significant difference in interval between loco-regional or systemic recurrence. Seventy-two of the 137 patients (52.6%) developed recurrent disease. Thirty-two patients (23.4%) developed loco-regional recurrence only, 21 patients (15.3%) developed systemic recurrence only and 19 patients (13.9%) had a combination of both. In only 8.0% of all patients was there recurrence in the cervical lymph nodes. The most frequent sites of distant recurrence were liver (37.5%), bone (25.0%) and lung (17.5%). Recurrence was related to postoperative lymph node status (p<0.001) and the radicality of the operation (p<0.001) in multivariate analysis. Recurrence was not associated with localisation or histologic type of the tumour.

Conclusion. Recurrence after transhiatal resection is an early event. Almost 40 % of the patients developed loco-regional recurrent disease. For this patient group a more extended procedure may be of benefit, especially in the patients (23.4%) with loco-regional recurrence in whom this is the only site of recurrent disease. However, the potential benefit of a more extended procedure has to be balanced against a possible increase in peri-operative morbidity and/or mortality.
Introduction

Surgery is the best curative option in patients with cancer of the oesophagus. It is indicated only in patients without signs of distant metastases, local irresectability or both. Because of the late onset of symptoms, many patients already have distant metastases, locally irresectable tumour or both at first presentation.

The type of ‘curative’ operation that should be performed is controversial. Opinions range from a relatively limited transhiatal (abdominocervical) resection of the tumour to an extended resection including the primary tumour with its adjacent structures combined with a complete lymph node dissection of upper abdomen, posterior mediastinum and sometimes even the neck.

Advocates of an extended lymphadenectomy argue that lymph nodes at a relatively large distance from the primary tumour are frequently involved; protagonists of a less extended resection argue that the larger operation probably carries an increased morbidity and mortality, while the advantages of a complete lymph node dissection for survival have never been proved.\(^1\)

We performed a retrospective analysis of the pattern of recurrence after transhiatal oesophagectomy. Insight into the recurrence pattern might offer an indication of the possible advantages of a more extensive loco-regional procedure.

Patients and methods

We performed a retrospective chart review of all patients who underwent a transhiatal resection for adeno- or squamous cell carcinoma of the mid or distal oesophagus or gastro-oesophageal junction between June 1993 and June 1997. Patients with tumours of the oesophagus proximal to the carina were preferentially operated transthoracically, so they were not included. Follow-up ended July 1999, ensuring a follow-up of at least two years for surviving patients.

All patients were operated on with curative intent, that is, in the absence of distant metastases or signs of local irresectability. Preoperative analysis included oesophagogastroscopy with histologic biopsy, endosonography, external ultrasonography of the abdomen and neck, indirect laryngoscopy, sometimes combined with computed tomography of chest and abdomen. In selected patients, bronchoscopy was performed to rule out involvement of the trachea or bronchi. Staging was done according to the pathological tumour node metastasis (pTNM) criteria for carcinoma of the oesophagus (UICC-AJCC 1987). This classification can also be applied to carcinomas of the gastro-oesophageal junction, because the biological behaviour of the tumour is considered to be comparable.\(^4\)
Six patients with squamous cell carcinoma received pre-operative chemotherapy as part of a randomised trial. Operations were performed by or under direct supervision of a senior staff member (JJBvL or HO). Transhiatal oesophagectomy starts with a midline laparotomy. After careful exploration of the abdominal cavity the diaphragm is incised to facilitate intrathoracic mobilization of the oesophagus including the tumour and the peri-oesophageal tissue up to the carina. No formal lymphadenectomy is done in either abdomen or mediastinum, but when resectable positive lymph nodes around the coeliac trunc are encountered, these are removed when possible. When the oesophagus has been mobilised up to several centimetres proximal of the tumour, a gastric tube is constructed. In the cervical phase of the operation the oesophagus is mobilised circumferentially and transected low in the neck. A vein stripper is then inserted distalwards and the normal oesophagus proximal to the tumour is extracted from the mediastinum by inversion. An anastomosis is performed cervically. No lymph node dissection is carried out in the neck.

A microscopically radical resection (histologically negative margins) is called R0, a microscopically irradical resection (histologically positive resection margins but no macroscopic tumour remaining) is called R1, and a macroscopically irradical resection is called R2. Patients with an R2-resection were excluded from the analysis.

Patients were routinely seen in the outpatient clinic at three-month intervals for two years and at six month intervals thereafter. Apart from a careful history and physical examination additional diagnostic procedures were only performed if indicated. During follow-up loco-regional and distant recurrence was scored. Peri-anastomotic recurrence (tumour-recurrence in the gastric tube near the anastomosis, as identified by endoscopy or endoscopic ultrasonography and confirmed by histologic biopsy) was considered loco-regional recurrence. Recurrent disease was most often diagnosed radiologically by external ultrasonography, CT-scan, chest X-ray or bone-scan. Whenever possible, histologic confirmation was obtained. In some cases however, the diagnosis was established solely on clinical grounds. At follow-up cervical and coeliac trunc nodes were scored as indicating loco-regional recurrence; they were scored as indicating distant metastasis for the pTNM-classification of the primary tumour.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL). The chi-square or Fisher’s exact test and Student’s t-test were used when appropriate. Disease-free survival curves were calculated by the Kaplan-Meier method, and curves were compared statistically using the log-rank test. Patients who died from non-oesophageal-cancer related causes are included in the disease-free survival analysis and are treated as censored when they died. The Cox proportional hazards model was used to examine the impact of covariates (differentiation grade, the presence of lymph node metastases [pTNM-stage I and IIA versus IIb, III and IV] and radicality of the operation) on recurrence. Covariates were dichotomised in two categories, (a) an index group for which the risk was assumed to be increased was assigned a value of 1, versus (b) the reference group.
that constituted all other cases, which was attributed a value 0. The ratio of risk of the index group over the reference group is the hazard ratio.

Results

One hundred and forty-nine patients were identified. There were three early post-operative deaths (2.0%). These patients were excluded from the analysis. Also excluded were nine patients with a macroscopically irradical (R2) resection.

Follow-up was complete in the remaining 137 patients. At operation the median age was 65 years (range: 37 – 84). There were 105 men and 32 women. Ninety-five patients had adenocarcinoma (69.3%), and 42 (30.7%) suffered from squamous cell carcinoma.

The main characteristics of the patients and tumours are depicted in table I.

The median period of follow-up was 24.0 months (range 1.4-69.2) for all patients, in patients still alive without signs of tumour recurrence this was 36.5 months (range 23.6-69.2). During the follow-up period 72/137 patients (52.6%) developed tumour recurrence, 52 of 95 patients (54.7%) with an adenocarcinoma and 20 of 42 patients (47.6%) with a squamous cell carcinoma (p=0.46, Fisher’s exact test). The median interval between operation and recurrence was 11 months (range 1.4-62.5) for patients developing recurrence. There was no statistically significant difference between time to recurrence in adenocarcinoma and squamous cell carcinoma with a median disease-free interval of 9.1 months (range 1.4-62.5) versus 17.2 months (range 2.7 - 40.1; p=0.43) as estimated by the Kaplan-Meier curves, resp.

The cumulative disease-free survival curve is depicted in figure 1. Seven patients died of other causes without signs of recurrent disease. Causes of death in these patients were: cardiac arrest (4), progressive Parkinson’s disease (1), cerebro-vascular accident (1) and primary lung carcinoma (1).

In 32 patients (23.4% of all 137 patients or 44.4% of the 72 patients with recurrence) there was loco-regional recurrence only; systemic disease only developed in 21 patients (15.3% of all patients or 29.2% of the patients with recurrence). Nineteen patients (13.9% of all patients or 26.4% of the patients with recurrence) developed a combination of both loco-regional and distant recurrent disease (tables II and III).

The recurrence rate was significantly associated with the pTNM-stage: there was only one recurrence in the stage I group (5.9%), while in stages IIA, IIB, III and IV the recurrence rates were 42.4%, 63.6%, 69.8% and 76.9%. Lymph node status (corresponding with stages I and Ila versus stage IIB, III and IV) was an independent prognostic factor in multivariate analysis (p<0.001, Cox proportional hazards
model, see table IV). The same holds for radicality: of the 109 patients in whom a R0-resection could be achieved 50 (45.9%) developed recurrence, which is significantly less than the 78.6% recurrence rate in the 28 patients in whom microscopic tumour remained (R1) (p<0.001, Cox proportional hazards model, see table IV). There was no relation between the localisation of the tumour (mid or distal oesophagus or cardia) and the development of loco-regional recurrence or distant metastases.

Discussion

Oesophageal cancer is still a highly lethal disease. Despite all efforts, five-year survival rates after ‘curative surgery’ rarely exceed 30%. This is mainly because of the advanced stage of the disease by the time of presentation. Curative resection is possible only when there are no signs of distant metastases or local irresectability.

Because of the longitudinal lymphatic drainage via the extensive submucosal plexus, lymph node metastases can occur relatively early in all three body compartments (abdomen, chest, neck), regardless of the location of the primary tumour. Matsubara and associates and Altorki and colleagues report a 30% incidence of preoperatively unsuspected cervical nodal metastases, irrespective of the stage of the tumour, implying that cervical dissemination may be an early event. Some surgeons therefore perform not only a two-field lymphadenectomy (abdomen and chest), but also include a formal cervical lymphadenectomy. However, no survival benefit has been demonstrated after two- or three-field dissections in randomised trials so far.

Theoretically it is possible that mediastinal and peri-truncal lymph nodes might remain in situ after transhiatal resection without formal two-field lymph node dissection. However, a lymph node dissection up to the carina can be performed most of the time even when operating transhiatally. Secondly, the involved nodes along the greater curvature of the stomach might be transposed into the chest if the stomach is used to re-establish gastrointestinal continuity. This might lead to a higher incidence of loco-regional recurrence when compared with resections in which e.g. the colon is used to establish gastrointestinal continuity.

Our results are quite similar to those of Clark and colleagues who found (overall) nodal recurrence in 39.5%, systemic recurrence in 39.5% and anastomotic recurrence in 10.5% of the cases after en-bloc resections for adenocarcinoma with a mean follow-up of 16.5 months. However, in his series the percentage of patients with loco-regional recurrence only was 13%, as compared with 23.4% in the present series. Our overall recurrence rate of 55.4% is comparable with their 52.6%, suggesting that the addition of a wide local excision including a radical lymphatic dissection does not necessarily lead to better results. Recent reports by the same group are much more favourable and mention only a 2.2% incidence of loco-regional recurrence after en-bloc resection for transmural tumours after a median
follow up of two years. However, 43% of these patients developed systemic recurrent disease. This might indicate that addition of an en-bloc dissection might be able to improve loco-regional control, but might not improve survival.

After a median follow-up of two years 52.6% of the patients have developed recurrent disease. This is in accordance with the literature. However, there is a high percentage of patients with relatively early tumours (stage I and IIa account for 38% of the patients in this series). This might also reflect the fact that lymph node clearance is far from complete in transhiatal resections, which might lead to understaging of the tumour. This could be an explanation of the relatively high recurrence rate in these early tumours (approximately 40% in stage IIa).

Twenty-three percent (6 of 26) of the patients with stage IV tumours did not develop recurrence (yet), which might be due to the fact that positive celiac axis nodes are considered M1, but were still removed when possible. All six patients underwent a radical R0 resection with removal of positive lymph nodes near the celiac axis. This might argue in favour of a lymph node dissection around the celiac axis.

Lymphatic and hematogenic dissemination probably occurs in a parallel pattern. Loco-regional and distant metastases occur often within one year after surgery, indicating that both must have been present already at the time of operation, because metastases arising from other metastases are exceptional and probably need more time to develop. Theoretically, this implies that of those patients developing metastases, only those who develop loco-regional recurrence without distant metastases might have benefited from a more radical resection when survival is concerned. In the present study this amounts to 32 of the 137 patients, or 23.4%, but this number is bound to increase over the years as more patients will develop recurrent disease.

In another 19 (13.9%) loco-regional recurrence might have been prevented or delayed by addition of a formal lymphadenectomy in the chest and abdomen, which might have led to a prolonged disease-free interval. However, these patients might still have developed distant recurrence. This is quite similar to the results reported earlier in a more heterogeneous group of patients who underwent either transthiatal or limited transthoracic resection.

Importantly, the present study shows that recurrence in cervical lymph nodes is more the exception than the rule, with cervical recurrence occurring in only 8.5% of all patients. In 50% of the patients with cervical recurrence, distant metastases occurred simultaneously. This corresponds well with the data of Clark and co-workers who found cervical nodal recurrence only in 7.9% of the cases. This suggests that a formal cervical lymphadenectomy (with its associated peri-operative morbidity, especially vocal cord paralysis due to injury to the recurrent nerve) may not be warranted in this population of middle and lower oesophageal cancers.
Conclusion

After a median follow-up of two years transhiatal resection of the oesophagus has led to tumour recurrence in 52.6% of the patients. Recurrence occurs relatively early; the median interval between operation and recurrence is 11 months for those patients in which recurrent disease developed. Loco-regional and systemic recurrences occur with similar frequencies and are related to the stage of the tumour and the radicality of the operation. The recurrence pattern after transhiatal oesophagectomy seems to be comparable to that after en-bloc oesophagectomy. The present study indicates that theoretically only a selective subgroup of patients might benefit from a more radical resection. However, it is (as yet) impossible to identify these patients pre-operatively. Whether the potentially better disease-free survival or overall survival after extended resection outweighs the expected increase in peri-operative morbidity and/or mortality is the subject of a randomised study currently undertaken in two academic centres in the Netherlands. In the present population singular cervical metastases are so rare that a three-field lymphadenectomy is probably not warranted.

References


Table 1: Patient and tumour characteristics of 137 patients with carcinoma of the mid/distal oesophagus or gastro-oesophageal junction (GEJ)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male : female</td>
<td>105 : 32</td>
</tr>
<tr>
<td>Adenoca. : squamous cell ca.</td>
<td>95 : 42</td>
</tr>
<tr>
<td>Pre-operative chemotherapy</td>
<td>6 (4.4%)</td>
</tr>
<tr>
<td>Oesophagus : GEJ</td>
<td>112 : 25</td>
</tr>
<tr>
<td>Differentiation:</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>8 (5.8%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>58 (42.3%)</td>
</tr>
<tr>
<td>Poor</td>
<td>71 (51.8%)</td>
</tr>
<tr>
<td>pTNM Stage:</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>17 (12.4%)</td>
</tr>
<tr>
<td>IIa</td>
<td>35 (25.5%)</td>
</tr>
<tr>
<td>IIb</td>
<td>11 (8.0%)</td>
</tr>
<tr>
<td>III</td>
<td>43 (31.4%)</td>
</tr>
<tr>
<td>IV</td>
<td>31 (22.6%)</td>
</tr>
<tr>
<td>Radicality:</td>
<td></td>
</tr>
<tr>
<td>R0 : R1</td>
<td>109 : 28</td>
</tr>
</tbody>
</table>

Table 2: Location of loco-regional recurrence in 51 patients

<table>
<thead>
<tr>
<th>Location of loco-regional recurrence</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>11 (21.6)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>25 (49.0)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>16 (31.4)</td>
</tr>
<tr>
<td>Perianastomotic</td>
<td>5 (9.8)</td>
</tr>
</tbody>
</table>

Footnote: there were six patients with loco-regional recurrence in more than one site.
### Table 3: Site of systemic recurrent disease in 40 patients

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Liver</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Bone</td>
<td>10 (25.0)</td>
</tr>
<tr>
<td>Skin</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Brain</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Parietal peritoneum</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Pleura</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Malignant ascites</td>
<td>3 (7.5)</td>
</tr>
</tbody>
</table>

Footnote: there were seven patients with systemic recurrence in more than one site

### Table 4: Multivariate analysis of tumour differentiation, radicality and lymph node status as predictors of recurrence.

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor differentiation</td>
<td>1.92</td>
<td>1.08 – 3.38</td>
<td>0.025</td>
</tr>
<tr>
<td>R1-resection</td>
<td>2.73</td>
<td>1.55 – 4.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive Lymph Nodes</td>
<td>3.12</td>
<td>1.63 – 5.95</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P-values from Cox proportional hazards multivariate analysis
Figure 1: Disease-free survival rates in 137 patients after potentially curative transhiatal oesophagectomy for oesophageal carcinoma. Patients who died of non-related causes are treated as censored at the time of death.