Three-field lymphadenectomy and pattern of lymph node spread in T3 adenocarcinoma of the distal esophagus and the gastro-esophageal junction

C. van de Ven, P. De Leyn, W. Coosemans, D. Van Raemdonck, T. Lerut*

Department of Thoracic Surgery, U.Z. Gasthuisberg, Catholic University of Leuven, Herestraat 49, 3000 Leuven, Belgium

Abstract

Objective: Lymph node metastasis in carcinoma of the esophagus and the gastro-esophageal junction is often underestimated by clinical staging. It is the aim of this study to provide support to the fact that three-field lymphadenectomy leads to a better pathological staging also in adenocarcinoma. Methods: The pattern of lymph node metastasis in adenocarcinoma of the gastro-esophageal junction (GEJ) and the distal esophagus was charted in a prospective way by using a database. An analysis was performed with regard to lymphatic spread in T3, N0 adenocarcinomas of the distal esophagus and the GEJ junction, which were treated with a radical resection including a three-field lymphadenectomy. Out of 324 patients with adenocarcinoma of the esophagus and GEJ, we selected a group of 37 patients with an adenocarcinoma T3, N0 of the distal (n = 17) or GEJ junction (n = 20), treated with a radical resection and three-field lymphadenectomy (> 25 lymph nodes resected). Results: In total, 2240 lymph nodes were removed, with a mean of 59.5 per patient. In the GEJ group the ratio of positive nodes was 15.9, in the distal 1/3 group this ratio was 12.7%. Abdominal lymph nodes were positive in all GEJ tumors and in 70% of the distal third carcinomas. Thoracic lymph nodes were positive in 40% of GEJ tumors, and 70.6% of the distal group. Cervical lymph nodes were positive in 20% of the GEJ tumors and in 35.3% of the distal tumors. In six patients only right-sided cervical nodes were affected. Three patients in the GEJ group had positive lymph nodes in the neck without any involvement of thoracic lymph nodes. Conclusions: (1) Three-field lymphadenectomy improves accuracy of staging. (2) Cervical nodes are frequently involved. (3) Especially in tumors of the GEJ there is an important skipping phenomenon, i.e. positive lymph nodes in the neck in the absence of involvement of thoracic nodes. (4) Clinical staging remains deficient in regard to lymph node metastasis, especially cervical nodes. (5) The frequent unforeseen involvement of cervical lymph nodes in adenocarcinoma of the distal esophagus and GEJ tumors makes the interpretation of results of induction chemoradiotherapy questionable. (6) For the same reason, cervical lymph nodes should be included in the radiation field in case of induction chemoradiotherapy. (7) The similar pattern of lymph node involvement suggests similar oncological behavior of adenocarcinoma of the distal esophagus and the GEJ, questioning the actual TNM classification of these tumors as gastric carcinomas. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Adenocarcinoma pathology; Lymphatic metastasis; Lymph node excision; Esophageal neoplasms; Lymph node pathology

1. Introduction

Over the last decades a dramatic increase in adenocarcinoma, mainly in the distal part of the esophagus and the gastro-esophageal junction has been reported [1]. Controversy exists about the behavior of especially gastro-esophageal tumors. They are still classified as gastric carcinoma whereas the increasing and often underestimated incidence of intestinal metaplasia suggests common origin of all adenocarcinomas of the esophagus and the gastro-esophageal junction [2–4].

The long-term survival after resection remains poor because of the often advanced stage at the time of diagnosis. Undoubtedly one of the reasons is the high rate of lymph node metastasis at the time of diagnosis, in some reports reaching 80% [5]. Besides TNM stage grouping, lymph node metastasis seems the most important factor in predicting survival [6]. Lymph node metastasis in squamous cell carcinoma has been studied extensively [7]. On the contrary, little is known about the lymphogenic spread in adenocarcinoma of the distal esophagus and the gastro-esophageal junction.

The aim of this study is to analyze the pattern of lymph node metastasis of patients with adenocarcinoma of the...
distal esophagus and the gastro-esophageal junction and to study the behavior of lymphatic spread in these two groups.

2. Materials and methods

Between January 1994 and June 1998, carcinoma of the hypopharynx, the esophagus and the gastro-esophageal junction was resected in 324 patients. One-hundred and ninety-seven patients (60.8%) had an adenocarcinoma. All patients underwent a preoperative staging including a clinical examination, an esophago-gastroscopy, bronchoscopy, an endoscopic ultrasonography, a computed tomography of chest and upper abdomen as well as a sonography of the cervical region. As from January 1996, positron emission tomography (PET scan) was used in some patients to look for metastatic disease. We selected patients with transmural disease (T4), with nodal involvement (106 patients). Early stages were excluded because they were too few number to draw conclusions.

From these 106 patients with a T3 (UICC classification, 4th edition) adenocarcinoma of the esophagus and proximal stomach, with nodal involvement we selected a subgroup of 37 patients. Those 37 patients all had an adenocarcinoma of the distal third of the esophagus (dist 1/3, n = 17) or gastro-esophageal junction (GEJ, n = 20) which all underwent a radical resection and a three-field lymphadenectomy (abdominal, thoracic and bilateral cervical dissection). While no strict definition of carcinoma of the gastro-esophageal junction exists, we considered all tumors with the core of the tumor located on the Z-line or within an area of 5 cm orally or aborally from the anatomic junction between the esophageal and the gastric wall. Three-field lymphadenectomy was considered representative when more then 25 nodes were recovered. The reasons for not performing three-field lymphadenectomy were diverse: advanced age (40/106 patients > 70 years old), co-morbidity, peropera-tive instability or R2 situation (macroscopically incomplete resection). Patients who received induction chemo- or radio-therapy were excluded from this series. In all 37 patients clinical staging of the cervical region was negative for lymph node involvement.

In all 37 patients subtotal esophagectomy was performed through a thoracophrenolaparotomy using tubulated stomach for the reconstruction after resecting the complete lesser curvature. A cervical esphago-gastrostomy was performed to restore continuity. In the abdominal compart-

Table 1

<table>
<thead>
<tr>
<th>Dist 1/3 (n = 17)</th>
<th>GEJ (n = 20)</th>
<th>Total (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total amount of resected nodes</td>
<td>1020</td>
<td>1220</td>
</tr>
<tr>
<td>Total amount in the cervical field</td>
<td>339</td>
<td>371</td>
</tr>
<tr>
<td>Ratio positive/total nodes (3-field)</td>
<td>12.7% (129/1020)</td>
<td>15.9% (194/1220)</td>
</tr>
<tr>
<td>Ratio positive/total nodes (cervical field)</td>
<td>3.5% (12/339)</td>
<td>2.7% (10/371)</td>
</tr>
</tbody>
</table>

3. Results

The study group consisted of 17 patients with distal third adenocarcinoma and 20 patients with a GEJ adenocarci-noma.

The total amount of nodes excised was 2240 (mean 59.5 ± 16.5, range 26–91). Mean number of resected lymph nodes per region was: 18.6 for the cervical region, 19.8 for the thoracic region and 24.2 for the abdominal region. The overall ratio of positive nodes was 12.7% (129/1020) for the dist 1/3 and 15.9% (194/1220) for the GEJ (Table 1).

For the cervical region alone 710 nodes were resected. In distal third carcinomas 3.5% of resected cervical lymph nodes were positive (12/339), the number being 2.7% in GEJ tumors (10/371).

Table 2 shows the number of patients with positive nodes in different locations. 20% (n = 4, one bilateral, two right sided, one left sided) of patients with a GEJ tumor had positive cervical lymph nodes, the percentage being 35.3% (n = 6, one bilateral, four right sided, one left sided) for distal third carcinomas. Abdominal lymph nodes were positive in all patients of the GEJ group and in 70.6% of patients with dist 1/3 tumors. Thoracic lymph nodes were involved in up to 40% of patients with a GEJ tumor and 70.6% in distal third tumors.
Patients with positive cervical nodes

Table 2

<table>
<thead>
<tr>
<th>Patients with positive cervical nodes</th>
<th>Dist 1/3 (17 patients, %)</th>
<th>GEJ (20 patients, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>11.7</td>
<td>10</td>
</tr>
<tr>
<td>Right</td>
<td>29.4</td>
<td>15</td>
</tr>
<tr>
<td>Patients with positive thoracic nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carina/mainstem/paratracheal</td>
<td>23.5</td>
<td>25.0</td>
</tr>
<tr>
<td>Pulmonary hilum/AP window</td>
<td>21.4</td>
<td>16.6</td>
</tr>
<tr>
<td>Thoracic duct</td>
<td>46.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Peritumoral</td>
<td>67.7</td>
<td></td>
</tr>
<tr>
<td>Patients with positive abdominal nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac axis</td>
<td>20.0</td>
<td>35.3</td>
</tr>
<tr>
<td>Splenic artery/hilum</td>
<td>23.0</td>
<td>16.6</td>
</tr>
<tr>
<td>Hepatic artery/vein</td>
<td>6.6</td>
<td>7.1</td>
</tr>
<tr>
<td>Left gastric artery and lesser curvature</td>
<td>58.8</td>
<td></td>
</tr>
<tr>
<td>Left gastric artery</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>Peritumoral &lt;3 cm</td>
<td>89.5</td>
<td></td>
</tr>
<tr>
<td>Peritumoral &gt;3 cm</td>
<td>31.6</td>
<td></td>
</tr>
</tbody>
</table>

By subdividing the different levels of lymphadenectomy, a more precise image of nodal involvement can be made (Table 2). Arbitrarily we divided the thoracic nodal sites into subgroups: Carina/mainstem/paratracheal, pulmonary hilum/Aortapulmonary window, thoracic duct, and peritumoral. The abdominal nodes were divided into celiac axis, splenic artery/hilum, hepatic artery/vein and left gastric artery/lesser curvature. In the GEJ group a further division was made in peritumoral lymph nodes more or less then 3 cm from the tumor (i.e. N1-N2 in UICC classification, version 1987, 4th edition). Nodal involvement in dist 1/3 tumors and GEJ tumors was comparable. Analyzing more closely the pattern of lymph node metastasis in the cervical compartment revealed involvement of only the right-sided cervical nodes in two (10%) patients in the GEJ group and in four (23.5%) patients in the distal 1/3 group. Interestingly, in the GEJ group three patients (15%) had positive cervical lymph nodes without any thoracic nodal involvement. Since skip metastasis is an important problem in esophageal cancer, we have analyzed the pathology in the group of 10 patients with cervical nodal involvement in this study. In all these tumors, lymphatic, vascular and perineural invasion was demonstrated. In four patients submucosal spread was found with submucosal metastatic lesions in the esophageal wall in three patients and submucosal metastatic lesion in the stomach (corpus) in one patient.

4. Discussion

There is no doubt that adding the third field, i.e. cervical lymph node dissection contributes to the accuracy of the final staging of the disease. This has most impressively been proved by mainly Japanese groups in squamous cell carcinoma of the thoracic esophagus. Akiyama extensively studied the lymph node metastasis pattern in a series of 290 patients [7]. In his study the frequency of nodal metastases was studied according to the location of the tumor and each of the three dissected fields. According to the location of the tumor in upper, middle or distal third of the esophagus, cervical lymph node involvement was seen in 46, 29 and 27% of patients. Our present study confirms the importance of adding the third, cervical field to improve the accuracy of the final staging, with 35% of patients having positive lymph nodes in the neck for distal third and a striking 20% of patients with positive lymph nodes in tumors of the gastro-esophageal junction.

In all patients lymph node involvement was unforeseen, clinical staging with the ultrasound of the neck, computed tomography of neck and chest and endoscopic ultrasonography all being negative. Surprisingly three of the patients with a gastro-esophageal junction tumor with positive cervical lymph nodes had no positive lymph nodes in the chest. One of them only had involvement of lymph nodes in the vicinity of the tumor, another one only had positive lymph nodes in the vicinity of the tumor and in the hepato duodenal ligament. Consequently those three patients changed from stage 3 to stage 4 disease.

The consequence of these findings is evident. Diagnosis of positive lymph nodes in the neck by clinical staging remains problematic because of the shortcoming of ultrasound, CAT scan and EUS in this particular region [8]. Adding a PET scan to the preoperative work-up probably will improve the detection of positive lymph nodes and could have a major impact on diagnosis and treatment. Although PET scan seems promising, taking into account the very accurate diagnosis of mediastinal nodal involvement in non-small-cell lung cancer [17], we cannot make any conclusion for the reason why this investigation was not performed systematically in all patients. Further prospective study is currently being carried out.

The finding of positive cervical lymph nodes in a substantial fraction of advanced tumor stage questions the interpretation of the accuracy of induction therapy modalities. Furthermore when using chemoradiotherapy as an induction therapy modality the question arises whether to include the entire mediastinum but also the supraclavicular area and the neck in the field of irradiation. Needless to stress that enlarging the area to irradiate to such an extent will increase morbidity and possibly mortality.

The finding of unforeseen positive lymph nodes in the neck and especially in the absence of thoracic lymph node metastasis in the distal third and gastro-esophageal adenocarcinoma raises the question about the value of extensive lymphadenectomy in particular the three-field lymphadenectomy in relation to prolonged tumor-free survival and improvement of cure rate [9]. In this study we only analyzed the pattern of lymph node metastasis, we did not look at survival and recurrence rates firstly because the group we
selected was very small and secondly because 5-year survival is not reached yet. Within due course, results will become available.

Over recent years there is overwhelming evidence that R0 dissection (no residual tumor left behind) is the most important prognostic variable after surgery. To achieve R0 resection, organ dissection and lymphadenectomy must be radical. It has to be emphasized that local disease free survival is an important goal to achieve in carcinoma of the esophagus and gastro-esophageal junction, the majority of patients presenting themselves with advanced stage at the time of diagnosis. Clark et al. [10] analyzed in detail the operative specimen for 43 patients undergoing a transthoracic en bloc esophagectomy for adenocarcinoma of the esophagus and the cardia in relation to the pattern of recurrence at follow-up. They found that nodal recurrence occurred only in 8% within the area of dissection. This low percentage of local recurrence is in sharp contrast to the rate of local recurrence after transmediastinal blunt dissection of the esophagus.

Barbier et al. [11] found local recurrence in more than 50% of cases after standard esophagectomy, i.e. after incomplete lymphadenectomy. Whether adding the cervical field to the lymphadenectomy will be beneficial in the prophylaxis of recurrence for adenocarcinoma of the distal third and gastro-esophageal junction is a question that cannot be answered at this moment and still awaits confirmation.

The most important question to be answered of course is whether more radical dissection really contributes to improvement of survival.

Hagen et al. [12] performed a prospective randomized trial on 69 patients comparing extended en bloc resection versus transhiatal standard esophagectomy for carcinoma of the lower esophagus and cardia and showed a 5-year survival being significantly better after en bloc resection: 41% versus 21% for transhiatal resection. This study is lacking sufficient power as only 69 patients were involved and as patient material both included squamous cell carcinoma and adenocarcinoma of the distal third of the esophagus. Kato et al. [16] compared two-field versus three-field lymphadenectomy. The differences in 5-year survival were 48.7% in three-field lymphadenectomy versus 33.7% in two-field lymphadenectomy. The major critic on this study however was the difference in patient characteristics.

Similarities between the pattern of lymph node spread in adenocarcinoma of the distal esophagus and the GEJ, especially in relation to the findings in the cervical field, raises the question about the oncological behavior of these tumors, the actual TNM classification of adenocarcinomas of the distal third and tumors of the gastro-esophageal junction and consequences related to surgical strategies.

The UICC suggests classifying adenocarcinoma involving more then 50% of the esophagus as esophageal carcinoma and those involving more then 50% of the stomach including those equally distributed as gastric carcinoma. In our opinion this UICC TNM classification ignores one of the essential questions: carcinoma of the esophago-gastric junction, because of its particular anatomical location, behaves differently from carcinoma of the esophagus or stomach. Recent data from the literature showed Barrett metaplasia as the source of adenocarcinoma of the cardia in up to 50% of adenocarcinomas of the Gastro-esophageal junction. This data suggests a common origin of adenocarcinoma of the esophagus and adenocarcinoma at the GEJ and a behavior similar to that of esophageal carcinoma [3,9]. Further evidence on Japanese study and some western studies suggest that carcinoma of the esophagus and the GEJ largely share patterns of age distribution sex distribution and morphological characteristics [2,13]. When compared with infracardiac gastric carcinoma, there seems to be highly significant differences in age distribution and micro and macroscopic appearances between gastro-esophageal junction tumors and gastric carcinoma. These differences suggest that GEJ tumors are more closely related to the esophagus than to the stomach. The data from previous literature and from the present experience seem to support the thesis that gastro-esophageal carcinomas should be classified as esophageal carcinomas in the TNM classification. These findings question the value of the actual TNM staging for carcinoma of the GEJ especially in relation to lymph node status. In the actual TNM classification tumors of the GEJ are classified as gastric carcinomas and therefore the finding of positive lymph nodes in the chest equals stage 4 disease which means incurable disease. However from our own earlier published experience with 95 resections for GEJ tumors [14], 5-year survival of 11% was obtained in stage 4 disease. Analyzing the survival with both abdominal and thoracic involvement of lymph nodes showed a 5-year survival of 13%. These survival figures are very much similar to the 15% 5-year survival obtained in patients with carcinoma of the thoracic esophagus with positive lymph nodes [6]. The consequence of these findings in view of the frequent involvement of thoracic lymph nodes in up to 40% in tumors of the GEJ are clear. Lymph node dissection of the posterior mediastinum up to the carina is necessary to obtain a correct pathological staging. This favors a transthoracic approach, which will always result in a better and more complete removal of mediastinal lymph nodes then any other approach [15]. Furthermore the detection of disease of intrathoracic lymph nodes by different staging methods, either non-invasive (endoscopic ultrasonography) or invasive (thoracoscopy), should not exclude patients from treatment modalities with curative intent in particular surgery. For these reasons we suggest that diseased intrathoracic lymph nodes should no longer be considered as incurable stage 4 disease; we suggest rather that GEJ tumors should be classified as esophageal carcinomas and staged accordingly, i.e. positive intra-thoracic lymph nodes as stage 3 disease.
References


Appendix A. Conference discussion

Dr H. Ellis (Boston, MA): I agree that gastroesophageal junction tumors should be considered as cancers of the esophagus. They behave similarly. The surgical approach is the same for each, and their postoperative survival rate is the same. Furthermore, more and more junctional tumors are being recognized as developing from metaplastic Barrett’s epithelium lining the esophagus. Whether one stages these tumors according to gastric or esophageal staging criteria is the point at issue, and I am not sure that it makes that much difference, although my associates and I have always staged cancers of the cardia using esophageal staging criteria. Whether or not to perform a neck dissection in all patients with T3 distal esophageal and gastroesophageal cancers is, in my opinion, a controversial issue, since only 10% or so of these patients have positive cervical nodes. This means that in 90% of cases a neck dissection is an unnecessary procedure (except for staging purposes) and may lead to complications such as recurrent nerve injury. In the presence of positive cervical nodes, may there not be micrometastases elsewhere that will result in a low long term survival rate? I realize that this presentation concerned the pattern of lymph node metastases and not survival data, but do the authors have any evidence in terms of 5-year survival rates that support the use of cervical lymphadenectomy in these cases? Dr De Leyn: First of all, how do we stage these patients? We follow the international classification. So in our department, gastroesophageal junction tumors are still staged according to gastric cancer staging. Regarding survival, this is indeed a very difficult question. And there are some articles from Professor Skinner’s group which show that in stage III disease, and mainly in stage III disease, there seems to be a better survival: 30% for patients with radical en bloc dissection, part of them had three-field lymphadenectomy: versus 11 or 12%. The question is, of course, is this not a better selection of stage III patients? I mean, if you do a two-field lymphadenectomy and you find stage III disease, it is possible that with bilateral it would have been stage IV. So are the better results of three-field lymphadenectomy not just a better staging (with stage migration) of patients? It is very difficult to answer. We did not attempt to answer this question, and I don’t know if there is an effect on survival.

On the question of morbidity: this is also a very important question, because it’s important, of course, to look at morbidity because that surgery is more demanding. It depends on the experience, but it takes 2–2.5 h more. Maybe I can show you one discussion slide. (Slide) In an earlier experience we have looked at about 40 patients with three-field lymphadenectomy and looked at the morbidity. We had no mortality in this group. Pulmonary complications were found in about one-third of the patients, but this is very comparable to our overall problem with pulmonary complications. Recurrent nerve palsy was seen in two patients. But in this group we didn’t find a higher morbidity. For the local regional recurrence: when you look at the literature, again Altorki and other groups, who are doing radical surgery, the local regional recurrence will be somewhere around 10%. In our experience it was 17%.

Dr Ellis: May I make one last comment on the question of staging esophageal cancers? The new classification of the AJCC, which is supposedly the same as that of the UICC, now stages tumors of the lower esophagus with celiac node involvement as M1a which places them in Stage IV. Both Professor Lerut and I agree that this is probably not appropriate. Furthermore, the new staging criteria don’t take into account the number of nodes involved which both Dr Skinner and others, including ourselves, think is essential for proper staging of these tumors. While perhaps this isn’t the best venue for discussing staging criteria, I would like to make a plea to all of us involved in this field to be sure that the next published esophageal cancer staging criteria include some of these suggestions, since, in the opinion of many of us, the new 1997 AJCC staging criteria is suboptimal.