Carcinogenesis and treatment of adenocarcinoma of the oesophagus and gastric cardia

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Chapter 1

Adenocarcinoma of the oesophagus: the role of lymph node dissection

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Introduction

For some tumours optimal loco-regional treatment including a formal lymph node dissection leads to a decrease in loco-regional recurrence, an improved disease-free survival and/or an increase in overall survival. For instance, total mesorectal excision (TME), with wide excision of the tumour and resection of all regional lymph nodes, has become the standard practice in many Western countries for the treatment of rectal cancer, leading to improved loco-regional control and perhaps even increased survival-rates. However, it is uncertain whether this is due to an improved lymph node clearance or an increase in the number of patients with microscopically radical resection. In the same way elective lymph node dissection might improve loco-regional control and survival in patients with intermediate thickness melanomas.

There are limits to the extent of the lymph node dissection. An extended (D2) dissection for gastric carcinoma is propagated by many Japanese surgeons, claiming more favourable outcomes when compared with non-extended resections. However, a randomised study from the Netherlands showed that an extended resection for gastric carcinoma is associated with a significant increase in postoperative morbidity and mortality when compared with limited resection (43% vs 25% and 10% vs 4% resp.), while long-term results were not significantly improved (risk of relapse 37% vs 43%, p=0.22).

In the same way the role of lymph node dissection is debated among oesophageal surgeons. Oesophageal carcinoma is an aggressive disease with a poor chance of definite cure. Approximately 50% of the patients already present with irresectable local ingrowth and/or distant metastases, thus precluding curative resection. Surgery remains, until today, the best curative option. But even after 'curative surgery' the average five-year survival rates do not exceed 20%. Up to three-quarters of the patients undergoing resection have metastases to the abdominal and/or mediastinal lymph nodes, a factor that also accounts for the dismal prognosis. Many studies focus on the optimal surgical approach, but great controversy still exists among oesophageal surgeons as to the value of (extended) lymphadenectomy.

Two main strategies for improving the results of surgical therapy for oesophageal carcinoma have emerged. The first aims to decrease early morbidity and mortality by minimising surgical trauma. This might be achieved by performing a transhiatal resection, thus avoiding a formal thoracotomy with its alleged (mainly pulmonary) complications. The second aims to improve the long-term cure rates by performing a more radical (transthoracic) resection, with a wide excision of the tumour and its adjacent tissues in combination with a lymph node dissection in abdomen and chest, thereby accepting a potential increase in early morbidity and mortality. This rests on the belief that in some patients with
lymph node metastases cure can be obtained by an aggressive surgical resection of peri-tumoural tissue combined with a lymph node dissection of all possibly involved nodes.

Arguments in favour of more extensive surgery are an improved (if not optimal) staging, and an improved loco-regional control leading to a possibly prolonged disease-free survival and perhaps an improved long-term survival as well. Opponents of this strategy object that post-operative morbidity and mortality might be increased, and that the alleged beneficial effects on disease-free survival and/or overall long-term survival have not been proven (yet). Also, the natural protective filter for tumour cells may be removed when an extensive lymph node dissection is performed, and the injury of major surgery may have detrimental immuno-suppressant effects.

The extent of lymph node infiltration in oesophageal carcinoma

Due to the non-segmental lymph drainage of the oesophagus lymph node metastases may occur on distant sites relatively early in the course of disease. Little is known about the preferential spreading pattern of lymph node metastases in adenocarcinoma of the oesophagus and/or gastric cardia. Knowledge hereof might be of assistance in deciding upon the optimal surgical approach regarding lymph node dissection.

Both intramucosal (T1im) and submucosal (T1sm) tumours are considered as T1 (early tumours) according to the UICC'97 staging system. (see Introduction) However, there is a considerable difference in T1 im and T1 sm tumours when the prevalence of lymph node metastases is concerned. Different studies have shown that lymph node metastases are rare in T1im tumours (0-7%), but increase in incidence when there is submucosal spread (22-50%). We have found lymphatic spread in 30% of the patients with T1sm tumours, while none of the patients with T1 im tumours showed positive lymph nodes. This is in accordance with a recent report by Nigro et al., which mentions positive lymph nodes in 10% of the patients with occult (not visible on endoscopy) carcinoma of the oesophagus. Lymph node metastases therefore occur already early in the course of the disease, as up to 50% of the patients with a T1 tumour already have positive nodes. When there is transmural tumour spread, over three-quarters of the patients have nodal metastases. Many groups report a higher incidence of distant (not in the same anatomical compartment) lymph node spread in larger tumours with often more than one field positive for lymph node metastases. The distribution of lymph node metastases probably fans out according to the depth of tumour invasion. In distal adenocarcinomas the paracardial and lesser curvature nodes are often the first to become affected, up to 30% of the patients with submucosal adenocarcinoma show already tumour positivity in these nodes (±15% for both lymph node stations). The paracardial and lesser curvature nodes can adequately be resected during a transhiatal resection. When there is intramural spread the
The percentage of patients with positive nodes near the lesser curvature increases from ±15% to ±33%. The para-oesophageal (±33%), tracheo-bronchial (±10%) and subcarinal nodes (±10%) might also become affected, just as the nodes near the greater curvature (±10%), the left gastric artery (±10%) and the celiac trunc (±10%). While the subcarinal nodes can sometimes be reached through the widened diaphragm during transhiatal resection, the tracheo-bronchial nodes cannot be reached. Some centres routinely perform a lymph node dissection in the abdomen during transhiatal resection, including the lymph nodes near the coeliac axis, while others consider positive nodes near the coeliac axis distant metastasis and therefore a contraindication for curative surgery. When there is transmural carcinoma the percentage of patients with positive nodes near the celiac axis increases to 30%, while 50% show tumour positivity at the parahiatal and lesser curvature nodes.

The number of tumour positive nodes (or the lymph node ratio, i.e. the ratio of positive to removed nodes) might also be an indicator for distant lymph node metastases. Nigro and co-workers describe a high risk for distant lymph node metastases when more than four local nodes are affected. The frequency and the extent of nodal metastases therefore apparently increase with greater wall penetration.

Some (mostly) Japanese authors report high incidences of tumour positive cervical lymph nodes after three-field lymphadenectomy, even in tumours located in the distal oesophagus. Akiyama and co-workers describe a ±30% incidence of positive lymph nodes in patients with a middle or distal carcinoma. In some studies the recurrent nerve node group is most frequently infected: up to 70% of the patients with invaded lymph nodes had positive recurrent nerve nodes regardless of tumour site and depth of invasion. These results are confirmed by a few Western studies: Altorki and Skinner find positive cervical lymph nodes also in 30% of their patients with a distal carcinoma, without a difference between T1 and T3 tumours. This suggests that oesophageal carcinoma is a systemic disease from the moment it invades the basement membrane. This is why many (mostly Japanese) surgeons favour a three-field approach, in which a formal lymph node dissection in the neck is carried out together with lymph node clearance in chest and abdomen, claiming survival benefits even when the cervical nodes are positive.

The clinical significance of lymph node dissection

Staging and prognosis

The pre-operative staging procedures serve to select patients with potentially curable tumours. Positive lymph nodes in the neck and/or irresectable lymph nodes near the coeliac axis are often considered metastatic disease for (distal and proximal resp.) oesophageal carcinoma (M1), thus...
precluding long term survival. Because oesophagectomy is generally not considered appropriate as a palliative option, tumour spread in these lymph nodes is considered a contraindication for resection in most Western centres. However, a recent study by Clark et al. showed no significant survival disadvantage for patients with (resectable) coeliac node involvement versus patients without celiac node involvement, although the number of patients was small and there seemed to be a tendency to a lower survival.22

Nodal metastasis is correlated with survival. In multivariate analyses R-category (R0= microscopically radical resection, R1=macroscopically radical but microscopically irrAdical resection, R2=macroscopic tumour remaining) and nodal status are often the predominant prognostic factors.29 Steup et al. even mention five year survival rates of 60-70% for patients without coeliac nodal involvement versus 10-20% for patients with such nodal involvement (all regarding tumours of the gastro-oesophageal junction and the oesophagus).30

Patients with four or less involved lymph nodes may have a survival advantage over patients with more than four metastatic nodes, which is correlated with the finding that patients with more than four involved nodes have a higher risk of distant positive nodes.21,24 The extent of nodal metastases is also correlated with survival: patients with involvement of only the abdominal lymph nodes have a survival advantage over patients with metastatic lymph nodes in both abdomen and chest.30 For squamous cell carcinoma this relationship has also been described: when nodal spread involved two (or three) anatomic compartments, 2-year survival was 0%, versus 29.8% when only one compartment was involved.31 Other authors argue that it is not (or not only) the absolute amount of positive lymph nodes, but the ratio of positive to removed nodes. This might better reflect the state of disease than the absolute number of positive nodes, especially when one takes in account that the number of lymph nodes removed per patient (or per surgeon!) may vary greatly. This also holds true for transthiatal resections, in which by definition a formal lymph node dissection is not carried out, certainly not in the chest. In a recent analysis of 115 patients undergoing transthiatal resection with curative intent multiple stepwise regression analysis identified the lymph node ratio (with a ratio of positive to removed nodes >0.30) as the strongest independent predictor of long-term survival.32 Also after extended transthoracic resection for squamous cell carcinoma, the ratio of invaded to removed mediastinal nodes was (after the presence of residual tumour after resection, R1 and R2) the second most important independent prognostic factor on multivariate analysis.33 The prognosis for patients with nodal metastases deteriorates when more than 20 - 30 percent of the removed nodes are invaded by tumour. Some authors consider this an indirect argument in favour of more extended lymph node dissections.

This approach also underlies the phenomenon of stage migration. Dissecting more lymph nodes increases the chance of finding a tumour positive node. This might influence the pTNM stage significantly. pTNM-stage (and thus estimation of prognosis) is based on the resection specimen with its resected lymph nodes. In transthiatal resections, the lymph node dissection is far from complete:
unresected tumour positive lymph nodes may remain, which might lead to understaging. The specimens obtained after transhiatal resections might therefore not reflect the true state of disease. When in the same patient a formal lymph node dissection would have been performed, a positive lymph node might have been found, leading to a different pTNM-stage. When the results of the different resection forms are compared, this is frequently done on a stage-by-stage basis. Stage migration might seriously hamper this comparison, because patients with the same stage might be staged differently based on extent of the lymph node dissection and the increased possibility of finding a positive node in more extended resections.

Another problem frequently encountered is the sensitivity of routine pathological staging procedures. Sampling error and the sensitivity of the techniques used might have a large impact on the results. There might also be a large inter-observer variation in the staging of resected specimens. Furthermore, routine pathological (histological) techniques may not be able to identify all (micro)-metastases. A recent German study of the prognostic value of immuno-histochemically identifiable tumour cells in lymph nodes of patients with completely resected (RO) oesophageal cancer showed that of 399 lymph nodes tumour-free on routine analyses, 67 (17 percent) showed tumour-cells on immuno-histochemical analysis. The presence of tumour cells not detected on routine histology but demonstrated with immuno-histochemistry was a significant independent prognostic factor, both for disease-free survival and for overall survival. In a smaller series this was confirmed by Bonavina et al, who found micrometastases in 33% of the patients after resection for adenocarcinoma of the oesophagogastric junction considered N0 after routine histology. An impact on survival was also found in this series.

However, although there was a significant relation between the presence of immuno-histochemically detected tumour-cells in lymph nodes and relapse with distant metastases, no correlation could be proven between the presence of such cells and local recurrence. The predisposition to have distant metastases among patients with immuno-histochemically detected tumour cells in their lymph nodes suggests that these cells are the consequence of advanced tumours and/or aggressive tumour behaviour, rather than indicators of sites of subsequent disease. Lymph node (micro)-metastases may therefore indeed be only indicators, not governors, of survival. The clinical significance of these findings thus remains uncertain. Although in a rat model it has been shown that remaining cells (isolated from human micrometastases as mentioned above) are able to develop into carcinomas, as yet there are no conclusive data that these tumour cells are indeed viable cells in humans. The growth of single tumour cells into overt metastases is also determined by the local environment and the capacity of the cells to respond to it. It is unlikely (due to the short time frame in which recurrence occurs) that lymph node recurrence primarily occurs and hematogenic dissemination from the recurrent lymph nodes to the organs results in distant recurrence. Until more data regarding the biologic behaviour of these remaining tumour cells become available, the clinical significance of removing these residual micrometastases by routine extended nodal clearance remains uncertain. The immuno-histochemical
techniques currently in use are rather time-consuming and at present (in most hospitals) impossible to be implemented in routine clinical practice.

**Surgery for oesophageal carcinoma: an outline of the different resection forms with emphasis on lymph node dissection**

Over the years many resection forms have been developed. The different operative procedures vary mainly in one or more of the following aspects: type of incision, extent of resection, conduit for reconstruction, and type of anastomosis. We will focus on the first two differences: type of incision and extent of resection, which are closely related.

With increasing complexity, resections of the oesophagus can be (generally) divided into (with increasing complexity): a) transhiatal resection without thoracotomy, b) standard or limited resection, c) radical en-bloc resection, d) radical resection with two-field lymphadenectomy and finally e) radical resection with three-field lymphadenectomy.

A) **Transhiatal resection** is a resection through the abdomen and neck. The oesophagus is approached through a surgically widened hiatus of the diaphragm. Theoretically the avoidance of a formal thoracotomy might decrease peri-operative morbidity and mortality by lessening the physiologic impact of a combined thoracic and abdominal operation. In most patients the oesophagus can be dissected under direct vision up to the level of the lower pulmonary vein, with en bloc removal of the tumour and its adjacent lymph nodes, including nodes near the coeliac axis and hepatic and splenic arteries. Opponents of the transhiatal resection emphasise the uncontrolled part of the operation: proximal to the carina the (normal) thoracic oesophagus is dissected bluntly, i.e. not under direct vision. This might lead to damage to major intrathoracic structures such as trachea, (mainstem) bronchi, thoracic duct, azygos vein or aorta, implying, according to some, a higher per-operative risk when compared with transthoracic resections. It may also cause damage to the tumour itself with the associated tumour spill. A radical lymphadenectomy of all regional thoracic lymph nodes is impossible through a transhiatal incision, although lymph node clearance can be achieved up to (and sometimes including) the subcarinal nodes. Some opponents consider a transhiatal approach therefore a violation of radical oncological surgery, a claim that can also be supported by the assumption that transhiatal resections might limit the yield of tumour-negative dissection margins. Also, lymph node staging might be less effective because not all lymph nodes are dissected.

B) **Standard or limited resection** (as described by Ivor Lewis and Norman Tanner in 1946) implies a combined abdominal/thoracic approach. This has been the standard procedure until recently, and internationally many centres still consider this the procedure of first choice. The tumour and peri-oesophageal tissue with its adjacent lymph nodes are resected through a right-sided thoracotomy. A
margin of at least five centimetres proximally is required. When the tumour is situated in the lower third of the oesophagus a left thoracotomy can also be used. The position of the heart limits the extent of the resection and makes the intrathoracic anastomosis more difficult when using a left sided approach. No formal lymph node dissection is performed in chest or abdomen.

C) Radical en bloc resection includes a wide excision of the primary tumour (including the azygos vein, thoracic duct, overlying pleura and pericardium) combined with a complete lymph node dissection of the middle and lower third of the posterior mediastinum. The intrathoracic oesophagus is removed with an en bloc dissection of the adjacent bronchial, subcarinal, para-oesophageal and para-cardial nodes. The block of tissue is bounded superiorly by the upper border of the azygos vein and inferiorly by the superior border of the pancreas. Lateral margins are the right and left mediastinal pleura. Anteriorly, the membranous portions of the main bronchi and the pericardium bound the resection, while the aorta and vertebral column form the posterior border. The claimed advantage of this type of resection is a better loco-regional control without increasing peri-operative morbidity and mortality. This might diminish the number of patients with loco-regional recurrence and thus prolong the disease-free interval and perhaps even long-term survival.

D) Radical resection with two-field lymphadenectomy is an en-bloc resection combined with a complete lymph node dissection in chest and abdomen. In the two-field dissection all nodes in the posterior mediastinum and upper abdomen are removed. This comprises the paratracheal nodes, the nodes in the aorta-pulmonary window and the subcarinal nodes in the chest and in the abdomen the nodes near the coeliac axis, near the splenic and the common hepatic artery, and finally the nodes along the lesser curvature and the lesser omentum. Most of the time the anastomosis is, just as in a transhiatal resection, made in the neck.

E) Radical resection with three-field lymphadenectomy adds a formal dissection of the infraomohyoidal cervical lymph nodes (deep internal, deep external and the deep lateral nodes) to the dissection of the abdominal and mediastinal lymph nodes. Although results have been favourable in some (mostly Japanese) studies, most Western centres consider this approach associated with unacceptable morbidity and therefore do not perform this type of resection.
References


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