Prognostication in esophageal cancer
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Prognostic factors in adenocarcinoma of the esophagus or gastroesophageal junction

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

The incidence of adenocarcinoma of the esophagus is rising rapidly in Western Europe and North America. It is an aggressive disease with early lymphatic and hematogenous dissemination. TNM cancer staging systems predict survival on the basis of the anatomic extent of the tumor. However, the adequacy of the current TNM staging system for adenocarcinoma of the esophagus or gastroesophageal junction (GEJ) is questioned repeatedly. Numerous prognostic factors have been described, but are not included in the TNM system. This review describes clinical parameters, aspects of operative technique, response to preoperative chemoradiation therapy, complications and established pathological determinants found in the resection specimen that have a prognostic impact. Furthermore, their potential application in the clinical setting in patients with adenocarcinoma of the esophagus or GEJ is discussed. Future directions to improve staging systems are given.
Introduction

Adenocarcinomas are predominantly located in the distal esophagus and at the gastroesophageal junction (GEJ). Adenocarcinoma is an aggressive disease with early lymphatic and hematogenous dissemination. Surgery is the best curative treatment option, but is accompanied by a high morbidity and substantial mortality rate. Advances in surgical techniques together with improvements in perioperative care have reduced risks to an acceptable level. Despite comprehensive preoperative staging to select patients for potentially curative surgery, many patients present with recurrences within two years after esophagectomy and 5-year survival rates rarely exceed 25%. Recently, better long-term survival results after esophagectomy have been presented. It is suggested that large hospital volume, early detection, improved patient selection based on novel staging modalities, but also increased use of preoperative neoadjuvant therapy, might be responsible for this.

Well-known prognostic factors of esophageal and GEJ adenocarcinomas form the basis of the prognosis-orientated TNM-staging systems. However, for the esophagus, the staging system originally based on squamous cell carcinoma is now also applied for adenocarcinoma, despite their potentially different biological behavior. For adenocarcinoma of the GEJ, staging systems for cancer of both the esophagus and the stomach are used. To improve the currently available staging systems, additional clinical and pathological factors have been suggested.

This review describes clinical parameters, aspects of operative technique, response to preoperative chemoradiation therapy, complications and established pathologic determinants found in the resection specimen, which have a prognostic effect. Furthermore, their potential clinical application in staging patients is discussed. The prognostic value of specific gene and protein expressions will not be discussed in this review. Future directions to improve staging systems are given.

Methods

A review of the recent English-language literature (January 1990 through July 2005) concerning esophageal adenocarcinoma was performed. This review is focusing on clinical, surgical, neoadjuvant and pathological factors with prognostic power to predict survival.
Clinical prognostic factors (Table 1)

Age and sex
Several studies did not show any prognostic significance for age. In case of comparable therapy, survival was similar in all age groups\textsuperscript{23-27}. Only two studies have reported a survival benefit for female compared with male patients with adenocarcinoma of the esophagus\textsuperscript{28,29}.

Barrett’s mucosa
A clear relationship between gastroesophageal reflux disease, Barrett’s mucosa, and esophageal adenocarcinoma has been identified. GEJ tumors without associated Barrett’s mucosa might represent a different tumor type that originates from the cardia. Patients with Barrett’s mucosa seem to have a better survival, because tumors with a Barrett’s segment are more differentiated, have a smaller diameter and are detected earlier\textsuperscript{30-32}. This suggests that tumors without a Barrett’s segment are not of a different origin, but are rather more advanced tumors that may have overgrown areas of preexisting Barrett’s mucosa\textsuperscript{24,33}. This theory is further supported by the fact that Barrett’s mucosa was unmasked by neoadjuvant chemotherapy in 23\% of patients, who did not have a Barrett’s segment at initial presentation\textsuperscript{34}.

Tumor location
Tumors are mostly classified according to location: type I (adenocarcinoma of the distal esophagus), type II (true carcinoma of the cardia) and type III (subcardial gastric carcinoma that infiltrates the GEJ). Although this classification has some limitations, it has been

<table>
<thead>
<tr>
<th>Clinical factor</th>
<th>Prognostic impact</th>
<th>Favoring survival benefit</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>none</td>
<td>-</td>
<td>23-27,69</td>
</tr>
<tr>
<td>sex</td>
<td>dubious</td>
<td>female</td>
<td>28,29</td>
</tr>
<tr>
<td>Barrett’s mucosa</td>
<td>minor</td>
<td>Barrett’s mucosa present</td>
<td>24,30-32</td>
</tr>
<tr>
<td>tumor location</td>
<td>minor</td>
<td>location in esophagus</td>
<td>7,12,35</td>
</tr>
<tr>
<td>dysphagia at presentation</td>
<td>minor</td>
<td>dysphagia absent</td>
<td>10,133,134</td>
</tr>
<tr>
<td>weight loss</td>
<td>considerable</td>
<td>weight loss absent</td>
<td>40-42</td>
</tr>
<tr>
<td>type of operation*</td>
<td>minor</td>
<td>extended esophagectomy</td>
<td>12,44,46-49</td>
</tr>
<tr>
<td>surgical complications</td>
<td>dubious</td>
<td>complications absent</td>
<td>18,51,52</td>
</tr>
</tbody>
</table>

NOTE: Prognostic impact in clinical factors is scored as none (no evidence), dubious (conflicting evidence), minor (only evidence from univariate analysis), considerable (evidence from uni- and multivariate analysis) and strong (evidence of prognostic value in several multivariate analyses).
* The prognostic impact of this therapeutic intervention is scored as minor since only one subgroup analysis of a randomized trial showed a survival benefit.
suggested that there is a relation between tumor localization and long-term outcome irrespective of type of operation\textsuperscript{7,12,35}. It is possible that cancer is earlier detected in the esophagus due to surveillance. Moreover, cancer in the relatively narrow esophagus presents earlier with dysphagia than tumors arising around the cardia.

Dysphagia and weight loss at initial presentation
The majority of patients present with dysphagia\textsuperscript{36-39}, which might reflect relatively advanced disease. If the presenting symptom is not dysphagia but, for example, anemia or hematemesis, the patient might have a smaller tumor and a better T-stage. Only one study described its prognostic effect in univariate analysis, but this effect was not confirmed in multivariate analysis\textsuperscript{10}. Also weight loss can be a reflection of advanced disease. In several studies weight loss prior to treatment was a prognostic factor in both univariate and multivariate analysis\textsuperscript{40-42}.

Surgical prognostic factors (Table 1)

Type of operation
It is uniformly accepted that patients with type I tumors should undergo esophagectomy. However, there is controversy about the extent of surgical resection\textsuperscript{11}. Some authors state that survival is comparable after extended surgery as compared with limited resection, whereas morbidity is higher. To minimize surgical trauma a transhiatal resection is therefore preferred\textsuperscript{43}. Others believe that the course of the disease can be influenced positively by aggressive surgery. Proponents advocate an extended two- or three field en bloc resection. Obviously, for staging purposes an extended lymphadenectomy is superior\textsuperscript{44} and can affect TNM-staging. This so-called stage migration happens if positive nodes in the extended fields change N-stage or M-stage (in case of positive truncal or cervical nodes)\textsuperscript{44-46}. However, the prognostic effect of the extended resection per se seems only limited. In a subgroup analysis of a randomized study comparing limited transhiatal esophagectomy with transthoracic esophagectomy with extended lymph node dissection, the long-term benefit for a transthoracic resection could be attributed to patients with type I tumors. The effect was marginal in patients with type II tumors\textsuperscript{12,44,46-49}. Other data suggest that extended total gastrectomy (with lower morbidity rates compared with transhiatal resection) is sufficient in these patients\textsuperscript{7}. However, debate remains open and these procedures need randomized evaluation\textsuperscript{50}. Type III tumors are seen as gastric cancer by most authors and an extended total gastrectomy is performed\textsuperscript{50}.

Surgical complications
A prognostic relation between technical complications after esophagectomy and overall survival has been hypothesized\textsuperscript{18,51}, possibly explained by a weakened immune function.
enabling cancer recurrence. Alternatively, unrecognized (micro-) metastatic disease might make the patient more susceptible for complications. However, no effect of complications was described on tumor-specific survival, and thus the prognostic impact of complications is yet unclear. A study focusing solely on anastomotic leakage did not find a survival effect resulting from this complication.\textsuperscript{52}

### Table 2: Pathologic prognostic factors in adenocarcinoma of the esophagus or gastroesophageal junction

<table>
<thead>
<tr>
<th>Pathologic factor</th>
<th>Prognostic impact</th>
<th>Favoring survival benefit</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM-staging systems</td>
<td>strong</td>
<td>early stage</td>
<td>8,10,43,53-60</td>
</tr>
<tr>
<td>T-stage</td>
<td>strong</td>
<td>early stage</td>
<td>8,10,43,49,56, 62,64</td>
</tr>
<tr>
<td>N-stage</td>
<td>strong</td>
<td>N0</td>
<td>7,27,56,57, 60,64,66-69</td>
</tr>
<tr>
<td>micrometastases in lymph nodes*</td>
<td>considerable</td>
<td>micrometastases absent</td>
<td>70-80</td>
</tr>
<tr>
<td>No. of positive nodes and ratio</td>
<td>strong</td>
<td>fewer positive nodes</td>
<td>7,13,49,55,60,62,6 8,69,81,83-86</td>
</tr>
<tr>
<td>extracapsular lymph node involvement</td>
<td>strong</td>
<td>extracapsular LNI absent</td>
<td>82,88</td>
</tr>
<tr>
<td>location of positive nodes†</td>
<td>minor</td>
<td>regional lymph nodes</td>
<td>8,55,57,69,81, 83,86,93</td>
</tr>
<tr>
<td>micrometastases in bone marrow</td>
<td>dubious</td>
<td>micrometastases absent</td>
<td>74,94-101</td>
</tr>
<tr>
<td>differentiation grade</td>
<td>minor</td>
<td>good differentiation</td>
<td>60,67,104</td>
</tr>
<tr>
<td>radicality</td>
<td>strong</td>
<td>R0 resection</td>
<td>7,9,16,57,62,67, 81,105-113</td>
</tr>
<tr>
<td>tumor size</td>
<td>strong</td>
<td>small tumor</td>
<td>27,69</td>
</tr>
<tr>
<td>lymphatic vessel invasion</td>
<td>considerable</td>
<td>no invasion</td>
<td>60,114</td>
</tr>
<tr>
<td>blood vessel invasion</td>
<td>minor</td>
<td>no invasion</td>
<td>60,67,102</td>
</tr>
<tr>
<td>perineural invasion</td>
<td>minor</td>
<td>no invasion</td>
<td>60,67,102,112</td>
</tr>
<tr>
<td>response to chemoradiation therapy</td>
<td>minor</td>
<td>complete pathologic</td>
<td>119-121</td>
</tr>
</tbody>
</table>

NOTE: Prognostic impact in clinical factors is scored as none (no evidence), dubious (conflicting evidence), minor (only evidence from univariate analysis), considerable (evidence from uni- and multivariate analysis) and strong (evidence of prognostic value in several multivariate analyses). Abbreviations: LNI, lymph node involvement; R0, microscopically radical resection
\# = staging systems according to AJCC (American Joint Committee on Cancer) and the UICC (Union Internationale Contre le Cancer)\textsuperscript{53,54}
* = only in patients with conventionally staged negative lymph nodes, LNI = Lymph Node Involvement
† = certain distant positive lymph nodes are considered as M-stage disease in TNM classifications, R0 = microscopically radical resection
Pathological prognostic factors (Table 2)

Pathological staging systems

The current staging systems (AJCC = American Joint Committee on Cancer and UICC = Union Internationale Contre le Cancer), for adenocarcinoma of the esophagus and GEJ are TNM based\textsuperscript{53,54}. Obviously stage groupings are strong independent prognostic parameters in several studies, with a higher stage implying more advanced disease\textsuperscript{8,43,55}.

Usually adenocarcinoma of the distal esophagus is staged as esophageal cancer. However, the UICC suggests classifying adenocarcinoma of the GEJ as esophageal carcinoma if more than 50% of the tumor mass involves the esophagus and as gastric carcinoma if more than 50% involves the stomach. There are clear differences between these classifications (Table 3). Classification problems obviously arise for junctional tumors because of the borderline location. These junctional tumors are staged as esophageal cancer by some authors\textsuperscript{55-59} and as gastric cancer by others\textsuperscript{8,10,60}.

### Table 3: Staging systems according to AJCC (American Joint Committee on Cancer) and the UICC (Union International Contre le Cancer)\textsuperscript{53,54}

<table>
<thead>
<tr>
<th>TNM esophagus*</th>
<th>stage 0</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>stage IIa</td>
<td>T2-3</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>stage IIb</td>
<td>T1-2</td>
<td>N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>stage III</td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
<td>M1a = metastasis in celiac lymph nodes</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N0-1</td>
<td>M0</td>
<td>M1b = other distant metastasis</td>
</tr>
<tr>
<td>stage IVa</td>
<td>T1-4</td>
<td>N0-1</td>
<td>M1a</td>
<td></td>
</tr>
<tr>
<td>stage IVb</td>
<td>T1-4</td>
<td>N0-1</td>
<td>M1b</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TNM stomach†</th>
<th>stage 0</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>stage Ia</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>stage Ib</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>N1 = metastasis in 1 to 6 regional nodes</td>
</tr>
<tr>
<td>stage II</td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
<td>N2 = metastasis in 7 to 15 regional nodes</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
<td>N3 = metastasis &gt; 15 regional nodes</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>M1 = distant metastasis</td>
</tr>
<tr>
<td>stage IIIa</td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>stage IIIb</td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>stage IV</td>
<td>T4</td>
<td>N1-3</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1-4</td>
<td>N3</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1-4</td>
<td>N1-3</td>
<td>M1</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Adenocarcinoma of the GEJ is staged as esophageal cancer if >50% of the mass is located in the esophagus. \* = mediastinal resection specimen should contain at least six lymph nodes, † = resection specimen contains at least 15 lymph nodes
T-stage
Increasing depth of tumor invasion is associated with the presence of lymphatic dissemination\textsuperscript{27,27,61-63} and is a known important independent prognostic parameter\textsuperscript{8,10,43,49,56,62,64}.

N-stage
Adenocarcinoma of the esophagus and GEJ is known for its early lymphatic dissemination. Already 30\% of the T1b tumors have positive lymph nodes and 5-year survival of these patients is only 33\%\textsuperscript{63}. This can be explained by the presence of extensive lymphatics in the submucosa. As soon as the cancer breaches the muscularis mucosae, it invades encountered lymphatics, which drain into regional lymph nodes, but also directly into the thoracic duct\textsuperscript{27,65}. In many studies the presence of lymphatic dissemination is the most important independent prognostic factor\textsuperscript{27,56,64,66-69}.

Micrometastases in lymph nodes
Routine histopathologic examination of lymph nodes will underestimate the prevalence of lymph node metastasis. Micrometastases can be revealed when tumor mRNA is detected with use of immunohistochemistry and/or polymerase chain reaction. Studies indicate that 1 to 17\% of conventionally negative lymph nodes and 11 to 50\% of pN0 patients have nodal metastases that are missed by routine pathological evaluation\textsuperscript{70-80}. All but one\textsuperscript{76} of the studies with clinical follow-up show a significant correlation of micrometastasis in routinely lymph node negative patients with a poor outcome\textsuperscript{70-75,77-79}. In some studies, the presence of micrometastasis in lymph node negative patients is an independent prognosticator\textsuperscript{70,74}.

Number of positive nodes and lymph node ratio
As in gastric cancer\textsuperscript{53,54}, the number of metastatic lymph nodes is an important independent prognostic factor in adenocarcinoma of the esophagus and GEJ; as a higher number indicates further progression of disease\textsuperscript{49,55,56,60,62,68,69,81-85}. Some prefer to use the lymph node ratio, which is the ratio between number of involved to resected nodes\textsuperscript{7,13,62,69,85,86}. The chance of identifying involved nodes increases with the number of resected (and identified) lymph nodes and can be markedly influenced by the extent of lymph node dissection\textsuperscript{47,49,85}. It has been suggested that the total number of resected and identified nodes should exceed 15 nodes\textsuperscript{87}. It is reported that patients who have at least four involved lymph nodes (reported range 3-6\textsuperscript{49,55,60,68,69,81,83-85}) have a worse prognosis. Patients with a lymph node ratio less than 0.2 have a better prognosis\textsuperscript{7,13,62,85,86} (reported range 0.10-0.30\textsuperscript{62,69,81}).

Extracapsular lymph node involvement
Extracapsular lymph node involvement is the extension of cancer beyond the lymph node capsule. In adenocarcinoma of the esophagus and GEJ, reports are limited\textsuperscript{82,88} but the presence of extracapsular lymph node involvement was an independent prognostic indicator in both studies.
Location of positive lymph nodes

The extensive lymphatic plexus of the esophagus fosters a pattern of bidirectional metastatic dissemination\(^81,89,90\). Involvement of distant lymph nodes is unpredictable because of the high incidence of skip metastasis\(^49,91\). In adenocarcinomas of the esophagus, as many as 26-30% of the patients had positive nodes in the cervical field\(^46,92\). The prognostic effect of these nodes is still unclear, because only 6% of the patients who underwent esophagectomy without cervical node dissection experienced cervical recurrence\(^9\). Lymphatic dissemination beyond the regional nodes is considered as M1 disease in the TNM classification. However, long-term survival is still possible for some of these patients; e.g. tumor positive lymph nodes near the celiac trunc are considered distant metastatic disease in the TNM-classification of the esophagus, but the presence of resectable positive peritruncal nodes did not have a prognostic effect\(^93\). Some studies described no prognostic effect at all for distant positive lymph nodes\(^57,81,86\), whereas others described only a small prognostic effect. The presence of distant lymph node metastasis was not fatal for all patients\(^8,55,69,83\).

M-stage

Patients with presence of visceral organ dissemination, are not curable by surgery. Its prognostic effect will not be discussed. In the TNM-classification certain distant positive lymph nodes are classified as M1 (see location of positive lymph nodes).

Micrometastases in bone marrow

Although the skeleton is not a preferred site for overt dissemination in patients with adenocarcinoma of the esophagus or GEJ, the detection of tumor cells in bone marrow might be considered as metastatic disease and is seen in 17 to 89% of the patients\(^74,94-99\). Its prognostic impact has been shown in one study\(^99\) and needs further investigation\(^98\). It remains unclear which percentage of these cells can escape from their dormant state and which percentage can effectively be eradicated by immunosurveillance\(^95,96\). Moreover, recent evidence suggests that these (pseudo-) epithelial cells can be identified in almost half of the patients with a benign disorder of the colon\(^100\), and in about one third of the patients who undergo cardiac surgery and are not known to have cancer\(^101\). This suggests an immense proportion of false positivity.

Differentiation grade

Microscopically, adenocarcinomas are graded as well-, moderately or poorly differentiated. The majority of tumors are well or moderately differentiated\(^67,102\). Tumors can show variation in grade within the same tumor and the highest (i.e. poorest) grade is usually recorded for prognostic purposes\(^103\). Although grade is routinely reported in pathologic reports, its prognostic impact remains to be elucidated. Lack of differentiation increases the risk on lymphatic dissemination\(^27\) and has a negative effect on survival in univariate analysis\(^60,67,104\).
Radicality
A consistent determinant of long-term survival after potentially curative resection of the esophagus is the completeness of surgical resection\textsuperscript{7,9,16,57,62,67,81,105}. The completeness of resection can be described with respect to the proximal, distal and circumferential resection margin.

Microscopic spread of esophageal cancer is usually far more extensive than the macroscopic boundaries of the tumor. Most studies have evaluated the proximal resection margin for squamous cell carcinoma\textsuperscript{106,107}. In one study it was reported that 9\% of the patients had tumor infiltration at the proximal resection margin\textsuperscript{109}. In uni- and multivariate analysis their survival was significantly worse. The influence of tumor infiltration at the distal resection margin has been described in one study\textsuperscript{110}. It was shown that survival of patients with tumor cells at the distal resection margin had a significantly worse survival. Recently, the prognostic significance of the presence of tumor cells at the circumferential margin has been investigated\textsuperscript{110-113}. In a prospective study, the presence of tumor cells within 1mm of the circumferential margin following potentially curative resection of the esophagus was an independent prognostic variable for survival\textsuperscript{104,110}. However, in a large retrospective analysis no difference in survival was found, not even in prognostic subgroups\textsuperscript{111,112}.

Tumor size
Longitudinal tumor growth indirectly reflects increasing depth of tumor invasion. In one study, it was shown that tumor length independently worsened survival, and was more important than T-stage\textsuperscript{69}. It is thought that longitudinal tumor growth in the lymphatic plexus results in regional lymph node metastases\textsuperscript{27}.

Lymphatic vessel invasion
Lymphatic vessel invasion is defined as tumor cell growth into lymphatic vessels. Lymphatic vessel invasion has prognostic significance in adenocarcinoma of the esophagus\textsuperscript{60,114}. It is associated with more advanced disease and precedes or coincidently occurs with lymph node metastasis. The presence and extent of lymph vessel invasion are associated with a decreased survival and are independent prognostic factors.

Blood vessel invasion
The prognostic impact of vascular invasion remains to be elucidated. In most studies it is significant in univariate analysis, but not in multivariate analysis\textsuperscript{60,67,102}.

Perineural invasion
Perineural invasion (or involvement) refers to growth of tumor along the nerve branches present within the esophagus. The tumor can easily grow along the plane of least resistance (i.e. the path created by the preexisting nerve). This mechanism of spread has shown its prognostic significance in a few studies in univariate analysis\textsuperscript{60,67,102}, but not in all\textsuperscript{112}. 
Response on chemoradiation therapy
The main goal of neoadjuvant chemoradiation therapy is improvement of loco-regional control. Despite its large-scale use there is only limited evidence for its effectiveness\textsuperscript{22,115-118}. The single most important prognostic factor is probably the pathological response on therapy, since patients with a complete pathological response demonstrated a significant improvement in survival in multiple studies in univariate analysis\textsuperscript{119-121}. However, the more favorable prognosis of responders compared to nonresponders might be independent of the applied neoadjuvant chemotherapy, because it might simply reflect a more favorable biological behavior of the responding tumors per se\textsuperscript{119}. Final evidence for the effectiveness of neoadjuvant chemoradiation can only come from randomized trials. So far, these trials have shown contradictory results\textsuperscript{22,115,116,121}.

Proposed revision of staging systems
The purpose of a conventional cancer staging system is to predict survival on the basis of the anatomic extent of the tumor. This information can be used to estimate prognosis (post-treatment) of the patient and to direct tailored therapy (mainly pre-treatment). The current TNM based staging systems for esophageal carcinoma are based primarily on patients with squamous cell carcinoma of the cervical and thoracic esophagus. The adequacy of the current staging systems is questioned repeatedly, and many authors propose a revision of these systems\textsuperscript{47,55,57,68,83,91,104,122,123}. This has many reasons. First, adenocarcinomas are of a different histological subtype. Second, the staging system does not adequately consider GEJ tumors, which are difficult to interpret due to their borderline location between stomach and esophagus. Third, lymph node involvement outside regional nodes is seen as M1 disease. Finally, it does not take into account other important prognostic variables (e.g. the number of involved lymph nodes, of which its importance has been shown in staging of gastric cancer). Different adaptations have been suggested (Table 4). Some authors consider adenocarcinoma of the esophagus and GEJ as one clinical entity and propose one classification system for both types\textsuperscript{57,91,122,124}, while others prefer two different staging systems based on the location of the tumor\textsuperscript{7,125}. Many studies propose to include the number of positive lymph nodes\textsuperscript{55,62,83,91,122} or the presence of distant positive nodes as a separate N-category in a new system\textsuperscript{55,57,91}. Additional clinicopathological factors have been proposed to be incorporated in TNM-staging\textsuperscript{69,104}.

Future
Simplicity is one of the reasons why TNM has been applied for such a long time. The three factors of classification can be remembered easily by clinicians. However, the biological diversity is high in patients with adenocarcinomas of the distal esophagus or GEJ, and many feel that additional factors can improve staging. Staging systems should be dynamic,
reflecting the increasing knowledge of cancer, its treatment and prognostic factors. To
develop better staging systems, other modalities such as nomograms and artificial neural
networks (ANN) have been designed. Nomograms are based on a Cox regression model
and incorporate factors included in any staging system, but can also add other clinical and
pathological factors known to have an impact on outcome.\(^{126}\) ANNs are highly complex
computational methodologies that perform multifactorial analyses, inspired by networks of
biological neurons. An ANN can correlate different predicting factors, find hidden interactions
among variables, predict an outcome for an individual patient or for groups of patients and
classify patients in risk groups.\(^{127}\)

Nomograms and artificial networks are more complex and can include nonanatomic factors
such as weight loss and age, but also gene expression data (not discussed in this review).
These models have been proven to predict disease outcome better than TNM-based staging
in several other gastrointestinal malignancies including squamous cell carcinoma of the
esophagus.\(^{128-132}\) The rising problem is that the more variables a model contains, the less
practical it becomes. However, with the widespread use of computer programs and Web-
based engines this problem might be easily overcome.

It is a challenge to develop a new staging system that includes diverse variables with a
prognostic impact. Furthermore, staging systems should be more dynamic and should be
able to add new knowledge of cancer easily. With use of computer programs, these goals
should be feasible. Possibly adenocarcinoma of the distal esophagus and GEJ is especially
suitable for this because it is mainly a disease of the West, where the use of computers is
getting more and more integrated in daily clinical practice.

### Table 4: Adaptations of staging systems as proposed in the literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Tumor type</th>
<th>Location</th>
<th>Number</th>
<th>Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lerut et al (^{47,57,91})</td>
<td>both</td>
<td>yes</td>
<td>no</td>
<td>positive cervical nodes stages as N2</td>
</tr>
<tr>
<td>Korst et al (^{55})</td>
<td>both</td>
<td>yes</td>
<td>no</td>
<td>distant nodal location staged as N2</td>
</tr>
<tr>
<td>de Manzoni et al (^{68})</td>
<td>GEJ</td>
<td>yes</td>
<td>yes</td>
<td>including No. and location of positive nodes</td>
</tr>
<tr>
<td>Killinger et al (^{123})</td>
<td>esophagus</td>
<td>no</td>
<td>no</td>
<td>N0 disease must be stratified by T-stage; for N1 disease no further stratification by T-stage</td>
</tr>
<tr>
<td>Rice et al (^{83})</td>
<td>esophagus</td>
<td>no</td>
<td>yes</td>
<td>T1 reclassified in T1a and T1b, number of positive nodes N1(1 or 2) N2(&gt;2)</td>
</tr>
<tr>
<td>Dickson et al (^{104})</td>
<td>both</td>
<td>yes</td>
<td>no</td>
<td>location of nodes, radicality, grade included</td>
</tr>
<tr>
<td>Ellis et al (^{122})</td>
<td>both</td>
<td>no</td>
<td>yes</td>
<td>No. of positive nodes N1 (1-4) and N2 (&gt;4)</td>
</tr>
<tr>
<td>Wijnhoven et al (^{124})</td>
<td>both</td>
<td>yes</td>
<td>no</td>
<td>all positive nodes seen as N1 disease</td>
</tr>
<tr>
<td>Siewert et al (^{7})</td>
<td>both</td>
<td>-</td>
<td>-</td>
<td>classified as separate disease</td>
</tr>
<tr>
<td>Eloubeidi et al (^{83})</td>
<td>esophagus</td>
<td>no</td>
<td>yes</td>
<td>No. of positive nodes, tumor length</td>
</tr>
</tbody>
</table>

NOTE: Proposals are tabulated according to the tumor type for which recommendations have been
given. Furthermore, it is specified whether location and number of nodal metastasis are included in the proposa
References


Correspondence

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New proposal for postsurgery pathologic staging of esophageal or gastroesophageal Junction adenocarcinoma: Why Bother?

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To the Editor:
Lagarde et al1 should be commended for an extensive and painstaking review of the prognostic factors of esophageal or gastroesophageal adenocarcinoma. Their article serves as a useful reference for those interested in this disease process. They point out that the current classification of these tumors is outdated. For a long time, various groups have expressed considerable dissatisfaction with the current staging system. A variety of modifications have been proposed, but no group has provided a solution that is acceptable to all others. The authors have very clearly pointed out that surgery as primary therapy (most frequently diagnosed cancer is stage II or III) results in a dismal outcome (< 25% 5-year survival rate) and the results of randomized trials of preoperative chemoradiotherapy trials have been equivocal. The goal of preoperative chemoradiotherapy is not just to improve local control, but all such trials strived to improve overall survival (the primary end point) of the patients. Contrary to the authors’ assertion that response to preoperative chemoradiotherapy has a minor prognostic impact on prognosis, the pathologic stage after preoperative chemoradiotherapy remains the most important independent prognostic factor in a multivariate analysis of patients undergoing preoperative chemoradiotherapy2 and similar findings have been reported by other major institutions3,4. The authors do not point out that clinical stage (cT or cN) does not predict patient outcome whether surgery is used as primary therapy or not and certainly not in the setting of preoperative chemoradiotherapy2-4.

The authors go on to propose that a sophisticated postoperative staging system for localized esophageal and gastroesophageal junction adenocarcinoma should be developed. Such a new system may be of some academic interest, however, its value should be questioned, particularly when we consider the future approaches to improve the outcome of such patients. Should we continue to offer surgery as the primary therapy for clinical stage II or III esophageal or gastroesophageal junction cancer? No, not based on the utterly disappointing results. The 5-year survival rate of patients with postsurgery pathologic stage IIA after surgery as primary therapy is less than 35% and those with any stage higher than IIA results in a less than 20% 5-year survival rate5. What is to be accomplished by a new staging system with such poor results? The future improvements in the outcome are hardly likely from subjecting more and more patients with stage II or III cancer to surgery first and
developing a new postsurgery pathologic classification, as proposed. That would be just too simplistic and without considerations to failure of the current approaches in patients with localized carcinoma of the esophagus and esophageal junction. Moreover, the use of preoperative therapy (particularly chemoradiotherapy) has increased in North America and in Europe\textsuperscript{6,7}. This trend is not likely to subside and further reduces the value of a postoperative classification after surgery as primary therapy.

Clearly, obvious solutions are lacking, but the future is in confronting the bigger picture of the diversity in clinical biology of these tumors (that is to say that not all patients within a given clinical or postsurgical stage are the same after receiving the same therapy [surgery in this case]) and the true drivers of this clinical biologic diversity are the molecular biology of the cancer and patient genetics. We are just scratching the surface of our understanding that the considerable heterogeneity in molecular biology and patient genetics is the true determinant of patient outcome and gross pretreatment or postsurgical parameters have much less impact\textsuperscript{8-12}. Currently, we do not know what to do with such information, and much work needs to be done. I am hoping we would be diverting more resources to develop strategies in identifying biomarkers for individualization of therapy (molecular staging as a dominant component to clinical/pathologic parameters) and in the development of new therapeutic targets. Hopefully, that will lead to improved patient outcome and reduced complications.

It Is Time for a Proper Staging System for Adenocarcinoma of the Gastroesophageal Junction

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To the Editor:
We read with great interest the article by Lagarde and colleagues entitled “Prognostic Factors in Adenocarcinoma of the Esophagus or Gastroesophageal Junction”1. As stated by the authors themselves, gastroesophageal junction (GEJ) adenocarcinoma is considered as a distinct clinical entity by the majority of authors, and the adequacy of the current TNM staging system has been questioned repeatedly; nonetheless, so far it has not been considered as a specific neoplasm in the International Union Against Cancer and American Joint Committee on Cancer guidelines2. According to the present TNM staging system, adenocarcinomas of the GEJ are classified as esophageal if more than 50% of the tumor mass involves the esophagus and as gastric if more than 50% involves the stomach2. While staging of tumors with the center clearly located in the distal esophagus or in the subcardial region is undemanding, classification problems arise for true junctional tumors because of their borderline location. Furthermore, many differences exist between subcardial gastric adenocarcinoma and stomach cancer as well as between adenocarcinoma of the distal esophagus and tumors of the thoracic esophagus. Siewert et al3 proposed an anatomotopographic classification for adenocarcinomas involving the GEJ which considers three types of tumors that, as already reported by Lagarde et al, did not show prognostic significance per se.

The authors analyzed a great number of prognostic factors and concluded that although TNM parameters have the advantage of the simplicity, they do not seem to completely reflect the biologic diversity of GEJ adenocarcinoma and that additional factors can improve staging.

In accordance with Lagarde et al and with many other authors, we firmly believe that GEJ adenocarcinoma needs a peculiar classification that differs both from esophageal and gastric staging systems. But, it is our own idea that, at the moment, depth of tumor invasion (pT), nodal involvement (pN), and presence of distant metastasis (M) together with residual tumor (R) are the main prognostic factors in gastrointestinal tumors and that TNM staging system certainly remains the most valid tool to stage esophageal as well as gastric carcinoma; particularly, no clinical, histopathologic, or biologic markers have been yet identified to have a comparable prognostic value. While the article by Lagarde et al openly highlighted the unquestionable importance of R-category, it is our idea that the necessity of considering GEJ adenocarcinoma separately from esophageal and gastric carcinoma in International
Union Against Cancer and American Joint Committee on Cancer guidelines should have been stressed more strongly. In addition, we believe that some peculiar issues on staging of this neoplasia should be considered: (1) depth of tumor invasion; several articles reported a similar prognosis between pT2 and pT3 subsets\textsuperscript{4,5}. This result seems to be due to the lack of the serosa in the GEJ region. Accordingly, some authors proposed to classify tumors with transmural growth and invasion of perigastric fat as pT2b and group this subset with pT3 tumors. (2) Nodal involvement; considering univariate survival analysis, both pT and pN classes usually result to be strong predictor of survival, otherwise, limiting the analysis to paper offering multivariate analysis, nodal involvement results to overweight the importance of pT class\textsuperscript{5-8}. In our series, Cox regression analysis showed lymph node involvement to be significantly the most important prognostic factor\textsuperscript{5,9}. (3) Number of nodal metastasis; as well described in the article by Lagarde et al, the number of metastatic nodes is a strong and an independent predictor of survival. Among the analyzed studies, an unfavorable prognosis has been reported for patients with more than three to six affected nodes\textsuperscript{7-10}. Gastric cancer pN staging system already considers the number of involved nodes, while a number-based revision of esophageal pN staging system has been proposed by several authors\textsuperscript{11-13}. (4) Site of nodal metastasis; celiac nodes are regarded as metastatic by TNM staging system for esophageal cancer. The review by Lagarde et al refers to the site of nodal metastasis as a minor prognostic factor. No study considered in the article analyzing the importance of location of positive nodes reports a lack of prognostic effect for nonregional lymph nodes. Particularly, the reported findings showed that patients with nodal metastasis outside the regional nodes had a poorer prognosis with respect to patients with regional node metastasis, even though better with respect to cases with systemic involvement\textsuperscript{13,14}. To our knowledge, no study except ours, has been published specifically correlating a number- and a site-based classification in GEJ adenocarcinoma\textsuperscript{9}. In our series, even among patients with a similar number of involved lymph nodes, the site of metastasis was found to be a strong and independent predictor of survival. Furthermore, we recently published our experience demonstrating that virtually no chance of survival is observed for patients with involvement of lymph nodes other than perivisceral\textsuperscript{15}. We demonstrated that patients with more than six metastatic nodes or involvement of second-tier nodes or beyond have little chance of survival and that the influence on survival showed by the Japanese Gastric Cancer Association as well as by the TNM staging systems was adequately represented after combining the two classifications. Consequently, the classes of the above mentioned classifications were joined together to build up a new pN classification which considers four categories: pN0, patients with fewer than seven metastatic nodes located within the first tier, patients with more than six involved nodes or involvement of second tier or beyond, and M1a\textsuperscript{15}. Finally, we would sincerely congratulate with Lagarde and colleagues for their great contribution to a better knowledge of this extremely aggressive disease in addition to advocate the refining of a proper staging system for GEJ adenocarcinoma.


In Reply

We appreciate the comments of Dr Ajani on our review concerning prognostic factors in adenocarcinoma of the esophagus and gastroesophageal junction. He questions the relevance of postsurgery pathological staging now that many centers apply preoperative chemo- and/or radiotherapy (CRT) to improve local control and overall survival.

Unfortunately, the randomized trials published so far on the value of neoadjuvant CRT have shown equivocal results. In our opinion preoperative CRT should still be considered experimental and should only be applied in the context of a clinical trial. We currently participate in a randomized multicenter Dutch trial comparing CRT plus surgery (41.4 Gy in 23 fractions of 1.8 Gy plus paclitaxel 50 mg/m2 and carboplatin area under the curve = 2 on days 1, 8, 15, 22, and 29) to surgery alone. The recently published favorable results of the British MAGIC trial, which compared perioperative chemotherapy and surgery versus surgery alone in gastric cancer, have changed the clinical management of (distal) gastric cancer, but in our view, these results are not applicable to esophageal and junctional cancer. The trial was originally designed specifically for gastric cancer patients. Only later during the course of the trial esophageal cancer patients also were allowed to enter the study because of the disappointing accrual, for which the trial was almost stopped. This afterthought should be considered as a major methodologic flaw.

Although the impact of currently available preoperative CRT on survival is unproven, we agree with Dr Ajani that patients who have a complete pathologic response have a better survival, also in multivariate analysis as recent research indicated.

Outside clinical trials, surgery is presently still offered as the primary therapy of first choice, to which all alternative (combinations of) therapies should be compared. The conventional postsurgery pathological TNM system is widely applied, but its prognostic accuracy is limited and can be substantially increased by simple, generally available pathologic parameters, such as lymph node ratio and extracapsular lymph node involvement.

The impact of neoadjuvant CRT on pathologic factors as described in our review remains unknown. A recent study showed that the number of positive lymph nodes remained an independent prognostic factor in patients with residual adenocarcinoma of the esophagus after preoperative chemoradiotherapy. This might indicate that, in patients who do not have a complete response, strong predictive factors may hold their prognostic value.

The genetic signature both of the tumor and of the patient play a pivotal role in the ultimate outcome of the patient. Until recently, most genetic studies focused on one or only a few molecular factors. Recently, microarray technology has become available, enabling whole genome analysis. This will supply detailed molecular insight into complex processes such as hematogenous and lymphatic dissemination. The original enthusiasm about the prognostic potential of this new technology has somewhat silenced because its bioinformatic analysis appears to be much more complicated and demanding than originally thought. But indeed individual tumor biology will ultimately be unraveled and thus (at least partly) replace TNM classification.
We are also grateful for the comments of Dr Pedrazzani et al on our review. They propose a separate classification system for gastroesophageal junction adenocarcinomas. There is an ongoing discussion about the classification of tumors originating at the gastroesophageal junction, mainly due to their borderline location between distal esophagus and cardia\textsuperscript{13}. While some investigators classify all these tumors as esophageal, others consider them to be gastric carcinomas and others (including the authors of the letter) regard them as separate entities. One factor contributing to this controversy is the precise identification of the gastroesophageal junction. The normal gastroesophageal junction is defined differently by anatomists (peritoneal reflection, muscle bundles), physiologists (lower esophageal sphincter), endoscopists (upper border of gastric folds), and pathologists (transition of squamous into columnar epithelium, presence of esophageal glands). Even bigger definition problems arise, when a Barrett’s esophagus or a sliding hernia is present\textsuperscript{13}. Also gastroesophageal junction cancers have been classified in three different subtypes by Siewert et al\textsuperscript{14,15}. One limitation is that in their original article, the gastroesophageal junction was defined as the Z-line\textsuperscript{16}. However, this reference point can move proximally into the esophagus when Barrett’s metaplasia develops. In addition, they claim that preoperative diagnostic tests can correctly classify gastroesophageal junction cancers in 95\% of cases, but this has never been properly and independently evaluated\textsuperscript{17}. Clearly, the classification of tumors arising at the gastroesophageal junction elicits substantial problems. Until these problems have been solved, the separate classification of gastroesophageal junction adenocarcinomas can hardly be recommended.

Staging systems should be dynamic, and increased knowledge of cancers will definitely change staging systems in the future. A large number of prognostic factors have already been described. Therefore, our aim was to supply a review of these factors. It can be used as a guideline for which factors to include in multivariate analysis when new prognostic factors are investigated. It is well possible that a single new factor, when compared with the conventional TNM system of the esophagus, has significant prognostic power in multivariate analysis. However, when additional factors (for example, the number of positive nodes and the presence of extracapsular lymph node involvement) are also included in the analysis, this new factor may lose its significance in multivariate analysis. In this respect, the site of nodal metastasis remains a controversial issue. Pedrazzani et al have shown that patients with involvement of second tier nodes or beyond have a very poor survival. However, it has been shown by others that patients with distal esophageal cancers and cervical lymph node metastasis still have a reasonable chance for survival\textsuperscript{18,19}. We also found that patients with cardiac cancer and relatively distant mediastinal nodes have a poor prognosis because it is a reflection of advanced disease\textsuperscript{20}. We look forward to the publication of the results of the new pN classification of Pedrazzani et al and hope that their classification system will show additional value when independently validated.