6 Clinical Staging of Adenocarcinoma of the Esophagogastric Junction

Julia Cordin, Kuno Lehmann, and Paul M. Schneider

Abstract Tumors of the esophagogastric junction are among the most frequent and cause lethal cancers. Patients often do not present until late in the disease when the tumor is sufficiently large to cause obstruction or invasion of the adjacent structures, and thus becomes symptomatic. Preoperative staging is critical to select those patients whose disease is still locally confined for curative surgery. Ideally, clinical staging should accurately predict tumor invasion, lymph node involvement, and distant metastases. Upper endoscopy establishes the tumor diagnosis by multiple biopsies and defines the tumor type (Siewert I-III), based on tumor localization in relation to the endoscopic cardia. Preoperative TNM staging has a strong impact on treatment strategy. Endoscopic Ultrasound (EUS) determines the T category, and to a lesser extent, the presence of lymph node metastases. Multislice Computed Tomography (CT) and ^{18}Fluorodeocxglucose Positron Emission Computed Tomography (^{18}FDG-PET-CT) provide further information, especially about systemic metastases. Diagnostic laparascopy is suggested in advanced (CT3/4) Siewert type II-III tumors to exclude peritoneal carcinomatosis. This chapter summarizes current staging modalities and their accuracy in clinical practice.

6.1 Introduction

Tumors of the esophagogastric junction are among the most frequent and lethal cancers. In addition, their incidence is increasing (Botterweck et al. 2000). Patients often do not present until late in the disease when the tumor is sufficiently large to cause obstruction or invasion of the adjacent structures, and thereby becomes symptomatic. Preoperative staging is critical to select those patients whose disease is still locally confined for curative surgery. Ideally, clinical staging should accurately predict tumor invasion, lymph node involvement, and distant metastases.

6.2 Establishing the Diagnosis

Upper endoscopy with multiple biopsy-sampling establishes the diagnosis (Lerut et al. 2006). The procedure enables tissue diagnosis

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and visualizes the upper gastrointestinal tract, if the endoscope can pass the tumor. Early-stage cancers appear endoscopically, as superficial, elevated, flat, or ulcerated lesions. Advanced lesions can impose as strictures, ulcerated masses, circumferential masses, or large ulcerations (Japanese Gastric Cancer Association 1998). Although the endoscopic visualization of a large, suspect mass is nearly pathognonomic for cancer, biopsies are mandatory to confirm the diagnosis. Taking multiple biopsies increases the diagnostic accuracy as shown in a series including patients with esophageal and gastric cancer (Graham, et al. 1982). The accuracy for the first biopsy was 93%, and increased to 95% for four, and 98% for seven biopsies.

6.3 The Tumor Center Localization Determines the Classification

Upper endoscopy enables the diagnosis of cancer, and also classifies adenocarcinoma of the esophagogastric junction. Adenocarcinomas of the gastric cardia have distinct pathological and clinical characteristics as compared to distal gastric tumors (MacDonald 1972). However, adenocarcinoma of the gastric cardia and the distal esophagus also show many similarities and were also classified as one group of tumors (Kalish et al. 1984). The use of different classification systems made a comparison of epidemiology, diagnosis, management, and outcome difficult. This confusion is mainly due to the borderline location of these tumors between the distal esophagus and the stomach, the ambiguous use of the term "cardia carcinoma," and the lack of clear UICC recommendations for classification and staging of these tumors (Hermanek and Sobin 1997).

Siewert and colleagues established a classification for adenocarcinoma of the esophagogastric junction (AEG) that is now widely accepted and used (Siewert et al. 1987; Siewert and Stein 1998). AEG tumors were defined by a tumor center within 5 cm proximal or distal to the endoscopic cardia. This "endoscopic cardia" is defined as the area where the longitudinal gastric folds end. The Siewert classification of AEG divides them into three types (Fig. 6.1). The location of the AEG does influence the prognosis and affects the therapeutic management (Siewert et al. 1998). Until now, AEG type I has been staged like esophageal cancers and AEG type II and type III like gastric cancers. The new 7th edition of the UICC TNM classification stages adenocarcinoma of the esophagogastric junction (Siewert type I-III) as one clinical entity alike esophageal cancers. Lymph nodes at the celiac trunc are considered regional lymph nodes (see chapter 3).

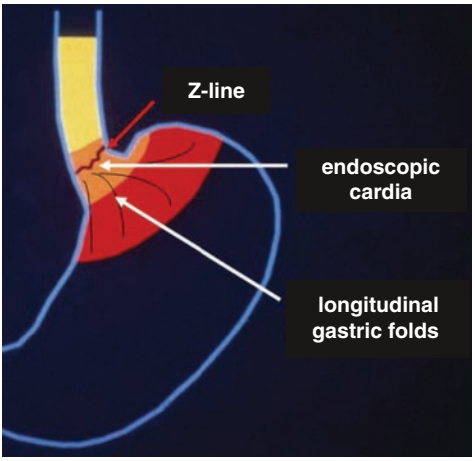

Fig. 6.1 Siewert classification of AEG. Type I (*yellow*): Adenocarcinoma of the distal esophagus with the tumor center more than 1 cm above the endoscopic cardia. These tumors generally originate from an area of Barrett's metaplasia in the esophagus. Type II (*orange*): True carcinoma of the cardia (tumor center from 1 cm above to 2 cm below the endoscopic cardia), arising from the cardiac epithelium or a short segment with intestinal metaplasia. Type III (*red*): subcardial gastric carcinoma infiltrating the cardia ± distal esophagus from below (tumor center 2–5 cm below the endoscopic cardia)

6.4 Preoperative TNM Staging Defines Further Treatment Strategies

The main goal of preoperative TNM staging is to select patients with early disease for limited surgery, and to avoid unnecessary radical surgery in patients with systemically (M+) advanced disease. Depending on the tumor stage, current treatment options for esophageal and gastric cancer range from endoscopic mucosal resection (EMR) to preoperative chemoradiation followed by esophagectomy or transhiatally extended gastrectomy (Lerut et al. 2001). Evaluation of the T-category is critical for AEG tumors. Only T1 tumors are considered as early cancers. In patients with categories T1-2 at presentation, primary resection and lymph node dissection is the treatment of choice, and is potentially curative. Extension into the esophageal adventitia results in a locally advanced T3 carcinoma, which is still resectable, but usually asks for multimodality treatment (preoperative neoadjuvant chemotherapy or chemoradiation). Invasion of the tumor into adjacent organs, such as aorta, diaphragm, liver, or pancreas, indicates T4 disease. Approximately 80% of patients in Western countries have locally advanced disease at the time of diagnosis. Neoadjuvant chemotherapy or chemoradiation may improve the rate of curative resections and potentially overall survival (Cunningham et al. 2006).

Approximately, 50% of patients have metastatic disease at presentation. With a few exceptions (e.g., single organ metastasis), no curative treatment is available and local tumor therapy is applied exclusively for palliation of symptoms (Lerut et al. 2006).

According to the current UICC/AJCC classification, metastatic disease is subdivided into M1a (metastases to nonregional lymph nodes) and M1b (distant organ metastases) for AEG Siewert type I (Greene et al. 2002). In the new UICC/AJCC classification, AEG Siewert Type I-III will be staged identically and lymph node metastases to the celiac trunk will be classified as regional lymph node metastases and will no longer be classified as M1a for Siewert Type I tumors.

6.5 Imaging Techniques for AEG

Currently, the most frequently used imaging techniques for the clinical staging of AEG are endoscopic ultrasound and multislice CT of the chest and abdomen. The ^{18}FDG-PET or the combined ^{18}FDG-PET/CT is not yet widely available. Barium studies may suggest the presence of adenocarcinoma of the esophagogastric junction and help defining unclassified AEG (e.g., impassable tumor stenosis), but are not routinely performed. The MRI may play a role in selected patients with suspected liver metastases.

6.6 Endoscopic Ultrasound (EUS)

EUS is nowadays the most precise imaging technique to evaluate the depth of tumor invasion (uT) and to a lesser extent, lymphatic (uN) involvement (Bentrem et al. 2007; Kienle et al. 2002). The ability to display distinct wall layers is the particular advantage of EUS in the staging of esophageal and gastric cancer. EUS at 7.5 MHz (conventional EUS) produces a five-layer image (superficial mucosa, mucosa, including the lamina muscularis mucosae, submucosa, muscularis propria, adventitia/serosa) of the organ wall (Messmann and Schlottmann 2001). Accurate staging of early AEG is helpful if a local therapy like EMR is planned. The risk for positive regional lymph nodes is below 5% if the tumor is limited to the mucosa (T1a). Deeper infiltration to the submucosa (T1b) will raise this risk to >20% (Katai and Sano 2005; Stein et al. 2005). Subsequently, higher invasion grades (uT2-3) frequently show

the involvement of the regional lymph nodes. Mucosal tumors (T1a) are frequently undetectable in conventional EUS. Therefore, there is a high chance for a submucosal infiltration (T1b), if the 7.5 MHz EUS is positive (Kelly et al. 2001).

EUS can also be performed with a high-frequency (up to 30 MHz) miniprobe-EUS, which is able to demonstrate up to nine different layers. This kind of EUS is primarily used to distinguish disease involving the mucosa from disease penetrating into the submucosa. A successful differentiation of mucosal and submucosal cancers is hereby possible in 84% (Murata et al. 1996). With high-frequency EUS (20–30 MHz), correct identification of T1a ranges from 70 to 100%. A clear disadvantage of high-frequency EUS compared to conventional EUS is its lower depth of penetration. Therefore, high-frequency EUS cannot be used for lymph node staging and assessment of locally advanced tumors (Murata et al. 2003). The accuracy of conventional EUS in differentiating lower T-categories uT1/T2 from advanced categories uT3/T4 in gastric and esophageal cancers were 93% and 91% in very experienced hands, respectively. Some studies, however, showed a lower accuracy for T-staging in the daily clinical routine and it is obvious that reported accuracies are clearly lower in more recent studies (Meining et al. 2002). Unfortunately, the accuracy of EUS is highly dependent on the experience of the examiner and showed only a rather modest performance in some studies (Meining et al. 2003; Polkowski et al. 2004).

In general, EUS tends to overestimate the depth of tumor infiltration, when inflammatory reactions or edema is present. This is likely the reason for the low accuracy (50% or less) of EUS to predict histopathologic response to neoadjuvant therapy (Beseth et al. 2000; Schneider et al. 2008). Furthermore, local advancement of the disease may lead to stenosis, which is already a rather poor prognostic sign (Hiele et al. 1997). In this condition, the accuracy of T-staging falls below 50% (Lerut et al. 2006). The accuracy of EUS staging appears to be better in Siewert type I than type II/III cancers (Byrne and Jowell 2002).

EUS can assess structures up to a distance of approximately 5 cm from the probe. This allows assessment of the regional lymph node involvement. EUS is probably more accurate to assess regional lymph nodes than CT (Kienle et al. 2002) (Table 6.1). To improve specificity, EUS can be combined with fine-needle aspiration (FNA). This is a highly sensitive method to assess lymph nodes (Fritscher-Ravens et al. 2000). Despite this, FNA can lead to false negative results due to sampling

Table 6.1 Assessment of the lymph node involvement by CT, EUS, and ^{18}FDG-PET

Reference	Tumor type	*n*	CT		EUS		^{18}FDG-PET	
			Sens (%)	Spec (%)	Sens (%)	Spec (%)	Sens (%)	Spec (%)
Flamen et al. 2000	E	39	22	96	63	88	39	97
Kim et al. 2001	E	53	15	97			52	94
Kienle et al. 2002	B	117	84	47	84	71		
Romagnoulo et al. 2002	E	48	53	86				
Hunerbein et al. 2003	B	97			71	71		
Wu et al. 2003	E	86	77	79	68	75		
Yoon et al. 2003	E	81	11	95			30	82
Polkowski et al. 2004	G	88	84	50	68	64		

The table shows sensitivity and specificity for multislice CT, EUS, or PET in patients with gastric (G), esophageal (E), or both esophageal and gastric cancer (B). Adapted from (Weber and Ott 2004)

errors, and rarely to false positive results, when the needle passes through the primary tumor.

Overall, conventional EUS at 7.5 MHZ appears to be an acceptable local T-staging modality that allows a reasonably safe stratification for primary resection for uT1/2 tumors and neoadjuvant treatment for uT3/4 tumors. Its value in the prediction of lymph node involvement is limited even in experienced hands. The future role of the miniprobe is rather questionable since EMR is now frequently used as a combination of a staging and treatment modality and therefore makes high frequency EUS unnecessary. EUS-guided FNA of lymph nodes should be performed only if clinical consequences are drawn from this examination.

6.7 Computed Tomography (CT)

Today, multislice, contrast-enhanced CT is probably the most frequently used staging modality for adenocarcinoma of the esophagogastric junction. The introduction of multislice computed tomography (CT) into clinical radiology constitutes a major improvement in CT technology. It will most likely widen the scope of CT endoscopy, CT angiography, and multiplanar imaging in the near future. The advantages over helical CT have been quantitative, mainly in terms of increased image acquisition speed which provides acquisition of a large volume of the body and an optimal contrast between vessels, tumors, and various tissues. Therefore, new challenges are faced that require the development of novel strategies in order to take full advantage of the increased capabilities of multislice CT in its current form and future generations of CT scanners (Gretschel et al. 2004).

CT is of limited value for loco-regional staging. It is not capable of differentiating the depth of primary tumor invasion and often leads to overestimation of T2 tumors as T3 or even T4 tumors, especially in AEG type II and III. Although CT can detect enlarged lymph nodes, the sensitivity, specificity, and accuracy for nodal disease are low (Table 6.1). The accuracy for the prediction of lymph node metastases is between 62 and 73% and therefore within the range of conventional EUS (van Vliet et al. 2008). Thus the major role of CT is the detection of tumors infiltrating adjacent structures and predominantly systemic metastases at the most common sites (liver, lung). The reported values for the sensitivity of CT for the detection of distant metastases vary from less than 50% to more than 90% (Kinkel et al. 2002; van Vliet et al. 2008). However, a major drawback of all noninvasive imaging modalities including multislice CT is the limited sensitivity for the detection of small metastases on the peritoneum.

For good quality CT examination of the upper gastrointestinal tract, up to 1,500 mL of water should be used as a negative contrast medium (Horton and Fishman 1998). Intravenous contrast medium is necessary and data acquisition at the time of peak enhancement of the liver enables optimal contrast between tumor and normal mucosa.

In conclusion, CT clearly has its role in the detection of metastases at the most common sites (liver, lung, lymph nodes) and the identification of locally advanced tumors (T3/T4) in AEG types I-III (Fig. 6.2).

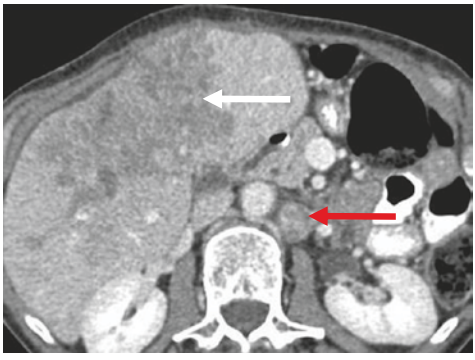

Fig. 6.2 CT image of metastases in AEG type III. The CT scans shows diffuse metastases in the liver (*white arrow*) and a large para-aortic lymph node metastasis (*red arrow*)

6.8 ^{18}Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET)

^{18}FDG-PET is unique in its ability to visualize areas of increased metabolic activity within tissues. It is based on the application of the glucose analog 2-deoxy-2-(18F)-fluoro-D-glucose (^{18}FDG). ^{18}FDG is preferentially taken up by tumor cells due to their high metabolic turnover, but cannot be metabolized inside the cell. The detection of lesions by ^{18}FDG-PET is dependent on the size and ^{18}FDG uptake. Therefore, even very small lesions, with a diameter of less than 1 cm can be visualized, if the metabolic activity of the tissue is high. In contrast, large tumor masses can be falsely negative if the tumor is metabolically inactive (De Potter et al. 2002; Stahl et al. 2003). Usually, AEG show a high ^{18}FDG-uptake.

PET has a limited role in evaluating the T-category because of its inability to differentiate between individual organ layers. Compared with ^{18}FDG-PET or CT, EUS was more accurate for T-staging (Lowe et al. 2005). For loco-regional N-staging, ^{18}FDG-PET has a limited value due to its low sensitivity of 20% (Flamen et al. 2000; Lerut et al. 2000). However, there is still additional information due to a high specificity of the ^{18}FDG-PET (Chen et al. 2005). Results for N-staging by ^{18}FDG-PET are summarized in Table 6.1.

The ^{18}FDG-PET, however, increases the diagnostic accuracy for distant metastases (Heeren et al. 2004; Meltzer et al. 2000). For the detection of liver metastases, ^{18}FDG-PET shows a specificity of 85% and is therefore more sensitive than CT and ultrasound (Kinkel et al. 2002).

Furthermore, the assessment of tumor response by ^{18}FDG-PET has been shown to correlate with histopathologic tumor regression and patient survival in patients with AEG tumors (Ott et al. 2006; Weber et al. 2001). Responders were defined as those with a >35% decrease in the metabolic activity of the tumor tissue. Residual ^{18}FDG uptake after chemo-radiotherapy shows residual tumor tissue and is associated with a poor prognosis.

In the future, the combined ^{18}FDG-PET/CT may improve the accuracy of lymph node staging and the assessment of distant metastases by combining the advantages of two modalities (Fig. 6.4). However, a comparative study on that topic is currently not available.

6.9 MRI

There is little benefit of magnetic resonance imaging (MRI) in routine staging of AEG. The few studies that exist mostly compare multislice CT with MRI. These studies did not show a substantial benefit of one over the other method (Anzidei et al. 2009; Wang et al. 2000). The same was found for the staging of regional lymph nodes. MRI did not improve the already weak accuracy of multislice CT (Sohn et al. 2000). Thus, for the staging of the T and N categories, MRI does not add any benefit. However, MRI may play a role for metastatic disease, mostly for liver metastases and helps to differentiate malignant from benign lesions. The choice of the contrast media during the MRI scan is important (Gretschel et al. 2004). The use of contrast media containing supramagnetic iron oxide particles (SPIO) facilitates the detection of low-vascularized liver lesions like metastases, and thereby enhances the diagnostic sensitivity (Kim et al. 2003) (Fig. 6.3).

6.10 Staging Laparoscopy Excludes Peritoneal Disease

Peritoneal carcinomatosis is an important problem in patients with AEG type II and particularly III. The incidence ranges from 7% in a large Japanese series including many early stages

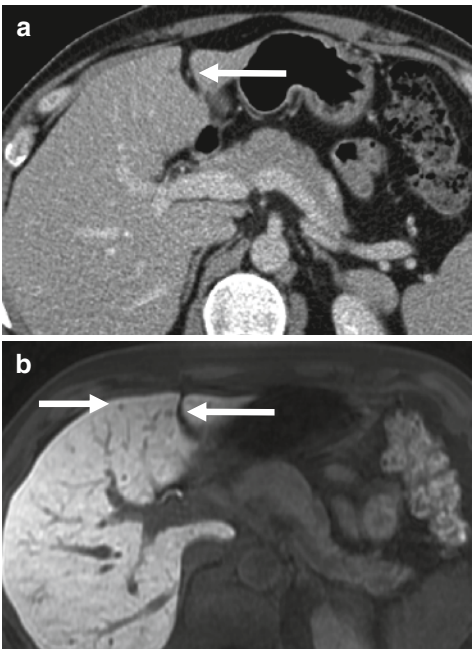

Fig. 6.3 CT and MRI Image of liver metastases. The CT (**a**) and MRI (**b**) scans show the same level in the same patient at identical time points. One lesion was hardly visualized by CT (**a**, *arrow*). By MRI, two lesions were found at the same level and appeared well demarcated (**b**, *arrows*)

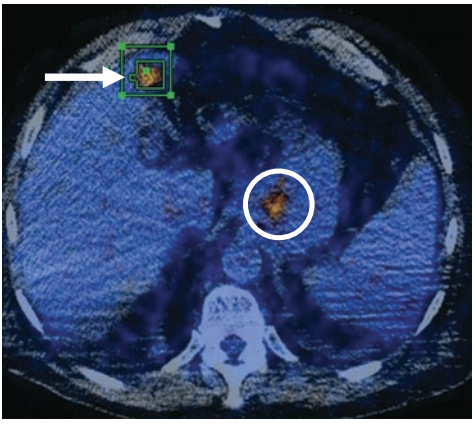

Fig. 6.4 Image of a ^{18}FDG-PET/CT. ^{18}FDG PET/CT images of a patient with an AEG type II, showing ^{18}FDG-uptake of the primary tumor (*circle*) and a single lesion in the liver (*arrow*)

(Maruyama et al. 2006) up to 56% in Western studies, where single cells were detected by immuno-histochemistry (Benevolo et al. 1998; Jonas et al. 2004). Small intraabdominal tumor deposits may not be visualized by abdominal imaging, because of the limited resolution of the conventional imaging methods such as CT, ^{18}FDG-PET, and MRI. Therefore, laparoscopy has been increasingly used for staging and exploration of intraabdominal disease in AEG Type II, and especially Type III tumors to avoid unnecessary laparatomy (D'Ugo et al. 1996; Hunerbein et al. 1995). Laparoscopy can be combined with diagnostic lavage cytology in the absence of ascites. This offers improved accuracy in the detection of intraabdominal tumor spread than CT (Chang et al. 2009). In general, staging laparoscopy is recommended in patients with locally advanced (uT3/4) AEG type II and III tumors where a neoadjuvant treatment is planned (Rau and Hunerbein 2005). Without preoperative chemotherapy, the laparoscopy can be performed in the setting of the planned primary resection. In patients with known metastatic disease, laparoscopy is unnecessary.

6.11 Conclusion

In conclusion, to establish the diagnosis for suspected adenocarcinoma of the esophagogastric junction, multiple biopsies during upper endoscopy are recommended. Endoscopy is crucial for the classification of AEG types I-III according to Siewert. The minimum staging requirement for an AEG type I-III is a CT of chest and abdomen with oral and intravenous contrast medium, preferentially as a multislice CT. In many centers, conventional EUS is performed in addition to CT and provides the uT category, and reasonably discriminates between T1/2 and T3/4 categories. In early AEG type I cancers, EMR is now frequently used as a combination

of a staging and treatment modality. In case of a submucosal cancer (pT1b) EMR/ESD is just diagnostic and a surgical resection is generally necessary. To exclude systemic metastases, a multislice CT or ^{18}FDG-PET/CT should be performed. MRI with supramagnetic iron oxide particles may be helpful in identifying liver metastases. A staging laparoscopy is recommended for occult peritoneal carcinomatosis in all locally advanced (uT3/4) AEG type II and III tumors, especially if neoadjuvant treatment is planned or within the setting of the planned primary resection.

Our current staging procedure consists of EUS and multislice CT. Within a prospective trial, we perform ^{18}FDG-PET-CT to evaluate its usefulness in detecting regional and extraregional lymph node metastases and systemic metastases. Diagnostic laparoscopy and lavage cytology is performed in all patients with cT3/T4 AEG type II-III to rule out occult peritoneal carcinomatosis prior to neoadjuvant chemotherapy or in the setting of a planned primary resection.

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