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# $^{18}$FDG-PET-CT improves specificity of preoperative lymph-node staging in patients with intestinal but not diffuse-type esophagogastric adenocarcinoma

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## Abstract

*Introduction*: The accuracy of preoperative lymph-node staging in patients with adenocarcinoma of the esophagogastric junction (AEG) or gastric cancer (GC) is low. The aim of this study was to assess the accuracy of [18F]fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT) for lymph-node staging in patients with AEG or GC, with or without neoadjuvant treatment.
*Patients and methods*: 221 consecutive patients with GC (n = 88) or AEG (n = 133) were evaluated. Initial staging included endoscopic ultrasound (EUS), multidetector spiral CT (MDCT) and PET-CT. PET-CT was performed for restaging in patients after neoadjuvant treatment (n = 94). Systematic lymphadenectomy was routinely performed with histopathological assessment of individual mediastinal and abdominal lymph-node stations. Preoperative staging from EUS, MDCT, and PET-CT was correlated with histopathological results.
*Results*: PET-CT showed a high specificity (91%) and positive predictive value (89%) for the preoperative detection of lymph-node metastases. In comparison, EUS was more sensitive (73% versus 50%, $P < 0.01$) but less specific (60%, $P < 0.01$). In patients with intestinal/mixed-type tumors, PET-CT improved the detection of extra-regional lymph-node metastases ($P = 0.01$) and distant metastases ($P = 0.01$) compared to CT alone. In contrast, lymph-node assessment by PET/CT after neoadjuvant treatment (32%, $P < 0.01$) and in diffuse-type cancers (24%, $P < 0.01$) is futile because of low sensitivities.
*Conclusion*: PET-CT does not improve the overall accuracy of N staging, but does improve specificity compared to EUS and MDCT in AEG and GC. We do not recommend routine PET-CT for the initial staging in patients with diffuse-type cancer or for restaging of lymph nodes after neoadjuvant treatment.


*Keywords:* Gastric cancer; PET-CT; Preoperative staging

## Introduction

Adenocarcinomas of the stomach (gastric cancer, GC) and esophagogastric junction (AEG) (types I–III according to the Siewert classification[1]) are among the most lethal tumors worldwide.[2,3] Lymph-node status is a major prognostic factor,[4] and the influence of extended

*Abbreviations:* AEG, adenocarcinoma of the esophagogastric junction; CT, computed tomography; EUS, endoscopic ultrasound; GC, gastric cancer; LAD, lymphadenectomy; LN, lymph node; MDCT, multidetector spiral computed tomography; PET, 18-fluorodeoxyglucose ($^{18}$FDG) positron emission tomography; PET-CT, combined positron emission tomography and computed tomography.

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lymphadenectomy (LAD) has been studied in, for example, patients with Barrett's cancer (AEG Siewert type I). In these patients, two-field LAD, including the abdominal and mediastinal nodes, resulted in a survival advantage of approximately 10%,[5] and was significant when up to eight positive lymph nodes were present.[6] In a Dutch randomized trial[7] in patients with gastric cancer, D2-LAD, compared to D1-LAD, reduced locoregional recurrence rates and resulted in a significant survival benefit after 15 years of follow-up.

Current preoperative staging includes endoscopic ultrasound (EUS), multidetector spiral computed tomography (MDCT),[8,9] and laparoscopy prior to neoadjuvant treatment for locally advanced GC and AEG Siewert types II–III.[10] EUS is considered the most accurate diagnostic modality for determining tumor invasion (T category), although the accuracy depends on the examiner's experience, and evaluation of distant lymph-node stations is not possible.[11,12] Despite a known low sensitivity and specificity, CT is performed for the assessment of lymph nodes and metastases (N and M categories).[13] In the current clinical setting, prediction of lymph-node involvement is therefore poor, with a low overall accuracy, and low positive and negative predictive values.[8]

PET alone may be of additional diagnostic value when compared to CT because of its higher specificity, demonstrated in some series.[14,15] However, the main disadvantage of PET is the low overall sensitivity and spatial resolution. It is therefore not yet clear whether PET is useful for staging in every patient.[13] Metabolic response assessment of the primary tumor in patients receiving neoadjuvant therapy correlated with an improved survival after resection.[16] This prognostic information is interesting for a subset of patients. However, it is unclear whether a PET-based restaging would allow adaptation of the surgical strategy. So far, EUS has already been demonstrated to be of little use for restaging after neoadjuvant treatment.[17] The availability of combined PET-CT scanners provides simultaneous information about anatomy and cancer metabolism in one image, and may therefore improve anatomical assignment of PET signals and preoperative decision-making: i.e. selection of patients for preoperative chemotherapy or chemoradiation,[18,19] targeted or systematic extension of LAD,[20,21] limited versus systematic resection in patients with early cancer,[22–24] or sophisticated individually tailored approaches.[25]

The aim of this study was to determine the staging accuracy of combined PET and CT, compared to EUS and MDCT, for N staging of patients with AEG and GC (with or without neoadjuvant treatment) in a large Western series.

## Patients and methods

Patients referred to our institution during the years 2008–2013 with a biopsy-proven adenocarcinoma of the stomach or AEG Siewert types I–III were included. Exclusion criteria comprised previous treatment for AEG or GC, or any previous malignancy. Patients underwent routine staging procedures – including medical history, physical examination, laboratory tests, upper gastrointestinal endoscopy with EUS, MDCT, and PET-CT for initial staging – and were presented in a specialized upper gastrointestinal tumor board. Locally advanced tumors received neoadjuvant chemotherapy (ECF[18] or FLOT[26]) or chemoradiation,[27] and were restaged by PET-CT 2 weeks after the last chemotherapy cycle and 4–5 weeks after chemoradiation.

The study was approved by the local ethics committee.

### *Surgery*

Standardized resections were performed, including systematic D2 lymphadenectomy (LAD) with individual pathological assessment of lymph-node (LN) stations 1–12 (Japanese Gastric Cancer Association),[28] and additionally LAD of the lower mediastinum for AEG types II and III. The D1 compartment includes perigastric LN stations 1–6; D2 includes stations 7–12 along the celiac axis. In patients with AEG Siewert type I, a transthoracic en bloc esophagectomy together with a two-field lymphadenectomy (extended mediastinal LAD) was the surgical standard.[5] All LNs were separately labeled during the operation according to their localization in the mediastinum (Japan Esophageal Society) and abdominal LN compartments (Japanese Gastric Cancer Association) by P.M.S, who was present at all operations. LNs outside regional compartments – e.g. the axillary, supraclavicular, or para-aortic – were considered as "extra-regional" LNs (TNM 7th Edition, AJCC/UICC).[29] Extra-regional LNs were biopsied by ultrasound or EUS-guided fine-needle aspiration, or dissected during surgery if enlarged ($\geq$10 mm) or PET positive on preoperative scans.

### *Endoscopic ultrasound*

EUS procedures were performed by two gastroenterologists (P.B. and C.G.) with Olympus echoendoscopes GF UE 160 (ALOKA, Holding Europe, Zug, Switzerland) with a 360° radial scanner (5–10 MHz, balloon contact method) in combination with an Aloka ProSound alpha 10. An LN was considered metastatic if the following criteria were present: hypoechogenic internal echo pattern, sharp borders and rounded shape, or a diameter $\geq$10 mm.[30]

### *Imaging by multidetector spiral computed tomography*

Contrast-enhanced MDCT was performed using a 128-slice dual-source CT (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) or a 64-slice dual-source CT (Somatom Definition, Siemens Healthcare, Forchheim, Germany) in all patients. LNs were considered positive if the short-axis diameter was $\geq$10 mm.[31]

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