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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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Imaging by ^{18}FDG positron emission tomography

PET-CT imaging was performed as a clinical procedure on an in-line system (Discovery LS or Discovery ST; GE Healthcare). These systems integrate a PET scanner (Advance Nxi; GE Healthcare) with a multi-slice helical CT (LightSpeed Plus or LightSpeed 16; GE Healthcare) allowing for acquisition of co-registered CT and PET images in one session. In PET-negative tumors, LNs were considered metastatic according to the criteria used for CT (short-axis diameter $\geq$ 10 mm) whereas in PET-positive tumors only LNs with FDG uptake were considered positive.

Statistical analysis

Data were prospectively collected and entered in an SPSS database (Version 18.0, Chicago, IL). For categorical variables the chi-square or Fischer's exact test were used. All statistical tests were two-sided. All statistical analyses were performed using SPSS (Version 18.0, Chicago, IL). A P-value <0.05 indicated statistical significance.

Results

Patient characteristics

Two hundred and twenty-one consecutive patients with adenocarcinoma of the stomach or esophagogastric junction (Siewert type I–III) were included in this study (Table 1). The majority of patients presented with advanced (T2–4) tumors; only 46 patients (21%) had early cancer, defined by tumor invasion limited to the mucosa/submucosa (uT1) on EUS. Ninety-four patients (43%) received 3–4 cycles of neoadjuvant chemotherapy or chemoradiation. Surgery was finally performed in 193 patients; 28 patients had palliative treatment only because of systematic metastases or peritoneal carcinomatosis (Supplementary Fig. 1).

PET-CT imaging of the primary tumor

Overall, PET-CT detected the primary tumor in 79% of patients. Higher detection rates were found for AEG (86%) compared to GC (70%, $P < 0.01$), and for intestinal/mixed-type tumors compared to diffuse-type cancers according to Laurén's classification (86% versus 63%, $P < 0.01$).

PET-CT for preoperative lymph-node staging

Lymph-node staging by EUS, MDCT, and PET-CT was compared and correlated to staging by histopathology. Overall, EUS demonstrated the highest sensitivity (73%) in detecting positive LNs compared to PET-CT (50%) and MDCT (48%). However, PET-CT had a higher specificity (91%) and positive predictive value (90%) compared to EUS and MDCT (Fig. 1). The low accuracy and predictive values were disappointing for all three modalities and did not translate into clinically relevant differences. Looking at the 108 patients that were directly operated, PET-CT showed a lower sensitivity of 35%, as shown in Fig. 1, indicating that this group of patients includes earlier stages than patients with neoadjuvant therapy.

Table 1
Clinicopathological features (TNM 7th Edition, AJCC/UICC).[29] Overall, 193 patients underwent tumor resection. Radical lymphadenectomy was defined as ≥D2 for gastric cancer or two-field lymphadenectomy for AEG I.

Parameter	n = 221	%
Age (median, years)	62	
Gender		
Male	158	71
Female	63	29
Localization		
AEG Siewert Type I	66	30
AEG Siewert Type II	38	17
AEG Siewert Type III	29	13
Gastric cancer	88	40
Grading		
G1	7	3
G2	86	40
G3	128	58
Laurén's classification		
Intestinal	138	62
Mixed	26	12
Diffuse	57	26
Depth of invasion (EUS) (n = 193)		
uT1	46	21
uT2	54	24
uT3	74	34
uT4	19	9
Histopathologic T category (n = 193)		
ypT0	8	4.1
pT1	59	30.5
pT2	31	16.0
pT3	76	39.4
pT4	19	9.8
Histopathological N category (n = 193)		
pN+	112	58
pN0	81	42
Metastatic disease		
Extra-regional LN	23	10.4
Hematogenic metastases	24	10.2
Peritoneal metastases	22	10
Type of surgery (n = 193)		
Transthoracic esophagectomy	45	23
Transmediastinal esophagectomy	19	10
Transhiatally extended gastrectomy	62	32
Total gastrectomy	21	11
Subtotal (4/5) gastrectomy	46	24
Lymphadenectomy		
Patients with ≥D2 or two-field LAD	177	92
Number of harvested lymph nodes (median)	36	

Restaging of lymph nodes by PET-CT after neoadjuvant therapy

Ninety-four patients received neoadjuvant treatment. We compared the lymph-node status on the initial PET-CT

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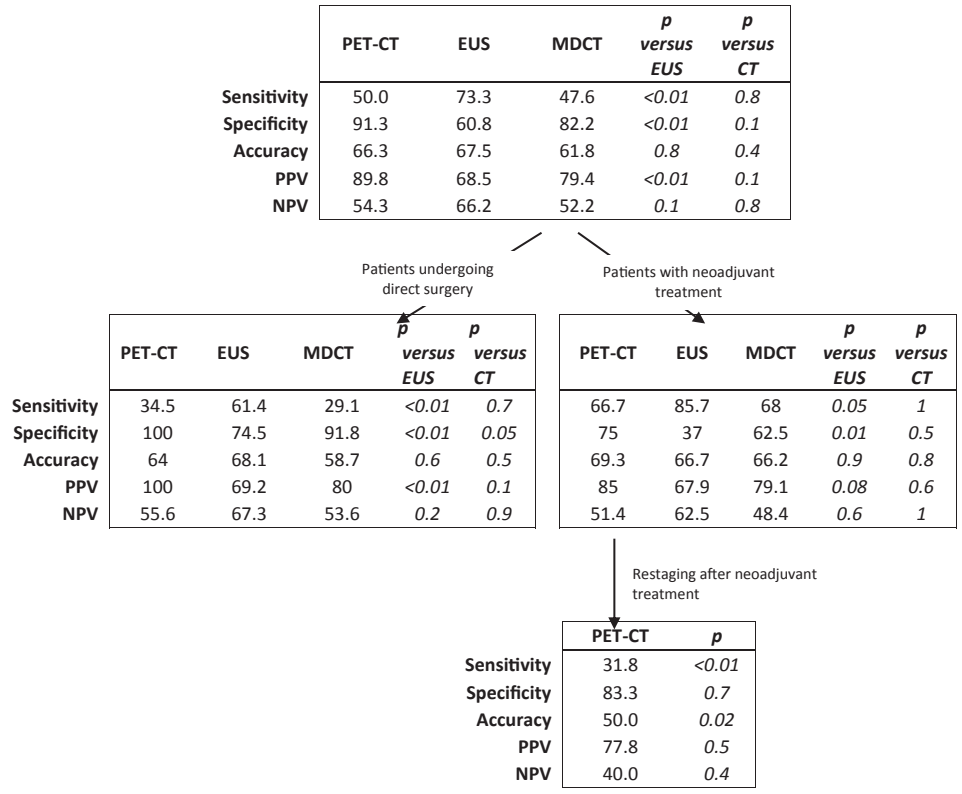

Figure 1. N staging by positron emission tomography and computed tomography (PET-CT), endoscopic ultrasound (EUS) and multidetector spiral computed tomography (MDCT). Preoperative lymph-node staging was evaluated by PET-CT, EUS and MDCT, and compared to staging by histopathology. Analysis was performed for the whole cohort of patients using initial staging results, then separately using initial staging for the groups with and without neoadjuvant treatment, and finally restaging PET-CT following neoadjuvant treatment prior to surgery.

prior to chemotherapy or chemoradiation to a second PET-CT performed for restaging (Fig. 1). After neoadjuvant treatment, LNs became PET-CT-negative in 37% of patients. Consequently, in the second PET-CT, the false-negative rate increased, and the sensitivity dropped to only 32% ($P < 0.001$) compared to the initial staging PET-CT. N staging in patients with neoadjuvant treatment should therefore always be interpreted on the basis of the initial PET-CT staging.

N staging according to tumor localization and Laurén's subtypes

We compared the accuracy of N staging by PET-CT for different tumor locations, and found a higher sensitivity (62% versus 38%, $P = 0.01$) and accuracy (72% versus 49%, $P = 0.07$) for AEG tumors compared to gastric cancer (Table 2). AEG-type tumors showed a higher rate of intestinal-type carcinomas compared to GC. Indeed, looking at the Laurèn type, the accuracy of N staging for intestinal/mixed-type tumors was significantly better than for diffuse-type tumors (Table 2). Additionally, we assessed whether PET-CT improves staging in a specific lymph-node compartment. However, we found only a poor accuracy in the D1 and D2 compartments.

PET-CT in the staging of early cancer

Despite a negative predictive value of 79%, PET-CT did not detect small positive LN metastases in ten patients; three of them had micrometastases. Compared to MDCT,

Table 2
N staging according to tumor localization and Laurén's subtypes. Lymph-node staging by combined positron emission tomography and computed tomography (PET-CT) was assessed in adenocarcinoma of the esophago-gastric junction (AEG) versus gastric cancer (A), and in intestinal versus diffuse-type carcinomas (B). Mixed types were grouped within intestinal types.

A	AEG I–III	Gastric cancer	*P*
Sensitivity	61.8	38.3	0.01
Specificity	85.7	91.9	0.5
Accuracy	70.9	58.8	0.08
PPV	87.5	88.5	1
NPV	58.1	47.9	0.3
B	**Intestinal**	**Diffuse**	***P***
Sensitivity	58.6	24	<0.01
Specificity	88.9	100	0.6
Accuracy	71.8	48.6	0.02
PPV	87.2	100	1
NPV	62.3	38.7	0.03

PPV, positive predictive value; NPV, negative predictive value.

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PET-CT therefore did not improve lymph-node staging in pT1 tumors (Table 3).

PET-CT for extra-regional lymph nodes and systemic metastases

Overall, there was no difference in the detection rate for systemic metastases by PET-CT and MDCT (Table 4). The main reason for this, despite a high specificity of both modalities, was missed peritoneal carcinomatosis. When peritoneal metastasis was excluded, the sensitivity of PET-CT increased significantly compared to that of MDCT (82% versus 48%, $P = 0.01$, Table 4). Analyzing only the PET-sensitive intestinal/mixed-type tumors, the sensitivity for detecting LN metastases outside regional compartments further increased and was significantly better for PET-CT than for MDCT (95% versus 63%, $P = 0.01$).

Discussion

Our data confirm the moderate diagnostic value of EUS and CT in preoperative N staging for AEG and GC in this Western series. The major benefit of the combined PET-CT is a higher specificity and positive predictive value, particularly in intestinal/mixed-type tumors. In contrast, staging of diffuse-type tumors by PET-CT and evaluation of lymph nodes after neoadjuvant treatment are inaccurate. The strength of this study is its detailed histopathological analysis after systematic radical lymphadenectomy, often not available in other reports. To the best of our knowledge no large trial with standardized radical LAD using EUS, CT and integrated PET/CT comparing AEG I–III and GC has been reported in a Western population.

The good results of EUS in our study are not uniformly reproducible in the literature, and some studies demonstrate a high variability for sensitivity (16.7–96.7%) and specificity (48.4–100%).[13,32] Both EUS and CT generally use a diameter ≥1 cm as a diagnostic criterion for LN involvement.[33] LN size alone, however, is not a reliable indicator in AEG and GC since more than 50% of resected metastatic LNs are ≤5 mm in diameter.[34] One study therefore defined all identifiable LNs as metastatic,[35] and surprisingly this study still reported a sensitivity of 89.5% and a specificity of 75.0%.

Table 3
N staging for early versus advanced tumors. N staging by positron emission tomography and computed tomography (PET-CT): accuracy and predictive values for early and advanced tumors (TNM 7th Edition, AJCC/UICC).[29]

	Advanced (>pT1)	Early (pT1)	*P*
Sensitivity	49.5	28.6	0.2
Specificity	88.9	95	0.4
Accuracy	58.3	77.8	0.02
PPV	93.9	66.7	0.08
NPV	33.8	79.2	<0.01

PPV, positive predictive value; NPV, negative predictive value.

Table 4
Comparison of positron emission tomography and computed tomography (PET-CT) and multidetector spiral computed tomography (MDCT) in the detection of metastases. (A) Overall detection of metastases. (B) Detection of systemic metastases with exclusion of peritoneal carcinomatosis.

A	PET-CT	MDCT	*P*
Sensitivity	56.9	40.0	0.1
Specificity	98.7	98.1	1
Accuracy	88.5	83.3	0.1
PPV	93.5	88.0	0.7
NPV	87.6	82.7	0.2
B	**PET-CT**	**MDCT**	***P***
Sensitivity	82.1	48.4	0.01
Specificity	98.9	98.9	1
Accuracy	96.7	91.6	0.04
PPV	92	88.2	1
NPV	97.3	91.9	0.02

PPV, positive predictive value; NPV, negative predictive value.

In the present study, the major advantage of the PET-CT is a good specificity and positive predictive value. The vast majority of previously reported studies were performed with PET only, and showed a high specificity, despite a low sensitivity in gastric[32] and esophageal cancers.[36] A possible reason for the reported low to moderate sensitivity of PET is its limited resolution. Current PET scanners have a 4–5-mm resolution,[35] but it has been reported that 15% of metastatic LNs in gastric cancer have a diameter of <3 mm.[34]

PET/CT fusion provides both anatomical and functional information, and theoretically allows more accurate localization of foci with increased ^{18}FDG uptake than standalone PET. Our results, however, are in line with published data using conventional PET.[14,37–39] Despite the combined PET-CT used in our study, the sensitivity remained too low for clinical prediction of regional lymph nodes. This may be a result of the intense uptake of ^{18}FDG by the primary tumor that complicates interpretation by obscuring the adjacent regional LN basins. Previously, PET alone demonstrated an improved detection of distant lesions compared to CT,[40,41] and sensitivities as high as 90% have been reported in the detection of metastatic LNs at distant sites, including cervical and abdominal locations.[14] Two recent reports suggest a role for PET-CT in the detection of metastatic disease, but they are retrospective and lack comparison with CT and/or histology.[42,43] The only available prospective study involving 113 Western patients found a benefit in about 10% of the patients compared to CT.[44] Our data strongly support these findings, especially for tumors with intestinal/mixed differentiation. In contrast, PET-CT does not provide an additional benefit in diffuse-type cancers or for exclusion of peritoneal involvement, where diagnostic laparoscopy remains the diagnostic standard.

A recent study in patients with esophageal cancer reported a poor diagnostic performance of a response PET-CT after chemoradiation.[45] This is in line with our results, and we extended our findings to patients with gastric cancer. Importantly, our results show that the initial PET-CT

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scan before neoadjuvant treatment is more accurate for N staging than the consecutive preoperative PET-CT scan after neoadjuvant treatment, which showed a high false-negative rate and is therefore not reliable for the prediction of lymph-node status. Despite the shown prognostic information by response evaluation of the primary tumor in the MUNICON II trial,[16] a restaging PET-CT therefore does not change the surgical strategy or extent of lymphadenectomy.

Based on our results, PET-CT should not be uniformly recommended. For regional N staging, PET-CT is useful only in patients with AEG tumors or GC with intestinal/mixed differentiation, where sensitivity and accuracy are clearly better than those of EUS and MDCT. In these patients, PET-CT may help to identify extra-regional lymph nodes for extended surgery. Routine extension of LAD to the para-aortic D3 compartment did not result in an overall survival benefit in GC, and is probably indicated only in selected patients.[21] Similarly, three-field LAD for esophageal cancer may improve the outcome in selected patients, but is currently also not recommended for routine use.[20] Radiological staging could be an option to select patients for targeted extension of the LAD since detection is improved by both PET[14] and PET-CT, as demonstrated. In contrast, sensitivity is insufficient for decision-making in patients with gastric cancer with diffuse-type tumors owing to a low FDG uptake and therefore poor sensitivity. In early tumors, a limited LAD cannot be recommended on the basis of PET-CT. The risk of missing small metastases or micrometastases by PET-CT in these patients is significant, and may have an impact on the patients' survival.[46]

In conclusion, PET-CT improves diagnostic specificity, but does not improve overall accuracy compared to EUS and MDCT, and therefore should not be performed in all patients with AEG or GC. In patients with AEG or GC with intestinal/mixed-type differentiation, PET-CT has a higher specificity and PPV than EUS and MDCT for N staging, improves the detection rate of extra-regional LNs and systemic metastases, and influences therapeutic strategies. In patients following neoadjuvant treatment, restaging of lymph nodes by PET-CT appears to be too inaccurate.

Conflict of interest statement

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejso.2016.08.020.

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