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^{18}F-Fludeoxyglucose–Positron Emission Tomography/Computed Tomography and Laparoscopy for Staging of Locally Advanced Gastric Cancer

A Multicenter Prospective Dutch Cohort Study (PLASTIC)

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IMPORTANCE The optimal staging for gastric cancer remains a matter of debate.

OBJECTIVE To evaluate the value of ^{18}F-fludeoxyglucose–positron emission tomography with computed tomography (FDG-PET/CT) and staging laparoscopy (SL) in addition to initial staging by means of gastroscopy and CT in patients with locally advanced gastric cancer.

DESIGN, SETTING, AND PARTICIPANTS This multicenter prospective, observational cohort study included 394 patients with locally advanced, clinically curable gastric adenocarcinoma (≥cT3 and/or N+, M0 category based on CT) between August 1, 2017, and February 1, 2020.

EXPOSURES All patients underwent an FDG-PET/CT and/or SL in addition to initial staging.

MAIN OUTCOMES AND MEASURES The primary outcome was the number of patients in whom the intent of treatment changed based on the results of these 2 investigations. Secondary outcomes included diagnostic performance, number of incidental findings on FDG-PET/CT, morbidity and mortality after SL, and diagnostic delay.

RESULTS Of the 394 patients included, 256 (65%) were men and mean (SD) age was 67.6 (10.7) years. A total of 382 patients underwent FDG-PET/CT and 357 underwent SL. Treatment intent changed from curative to palliative in 65 patients (16%) based on the additional FDG-PET/CT and SL findings. FDG-PET/CT detected distant metastases in 12 patients (3%), and SL detected peritoneal or locally nonresectable disease in 73 patients (19%), with an overlap of 7 patients (2%). FDG-PET/CT had a sensitivity of 33% (95% CI, 17%-53%) and specificity of 97% (95% CI, 94%-99%) in detecting distant metastases. Secondary findings on FDG/PET were found in 83 of 382 patients (22%), which led to additional examinations in 65 of 394 patients (16%). Staging laparoscopy resulted in a complication requiring reintervention in 3 patients (0.8%) without postoperative mortality. The mean (SD) diagnostic delay was 19 (14) days.

CONCLUSIONS AND RELEVANCE This study's findings suggest an apparently limited additional value of FDG-PET/CT; however, SL added considerably to the staging process of locally advanced gastric cancer by detection of peritoneal and nonresectable disease. Therefore, it may be useful to include SL in guidelines for staging advanced gastric cancer, but not FDG-PET/CT.

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Invited Commentary
Supplemental content

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Gastric cancer is the third leading cause of cancer-related death worldwide and accounted for more than 1 million patients with newly diagnosed gastric cancer in 2018.[1] In Western countries, the recommended treatment with curative intent is subtotal or total gastrectomy with lymphadenectomy, with perioperative chemotherapy in case of locally advanced tumors.[2,3] Prognosis mainly depends on tumor stage; recurrences occur in up to 60% of patients after surgery,[4] with the peritoneum most frequently involved.[5,6] For detecting noncurable disease, the accuracy of staging using gastroscopy and computed tomography (CT) of the thorax and abdomen is limited.[7,8] As a result, some patients incorrectly undergo treatment with curative intent, exposing them to the risk of complications of surgery and perioperative chemotherapy. If noncurable disease could be detected accurately before initiation of treatment, more tailored and less toxic palliative treatment can be offered.[9-11]

To accurately detect noncurable gastric cancer, the role of other preoperative staging modalities, such as ^{18}F-fludeoxyglucose-positron emission tomography with CT (FDG-PET/CT) and staging laparoscopy (SL) has increased over the years. A study in patients with locally advanced gastric cancer reported that FDG-PET/CT detected additional distant metastases in 10% of patients, whereas SL detected peritoneal metastases in 19%, preventing futile treatment and improving quality of life of patients and cost-effectiveness.[12] As a result, several international guidelines now advise to perform FDG-PET/CT and SL in patients with locally advanced gastric cancer in addition to initial staging with CT and gastroscopy.[2,3,13] Although the evidence for performing SL is strong in Asian populations, the evidence for both SL and FDG-PET/CT in Western populations is limited. Therefore, the aim of the present study (Evaluation of FDG-PET/CT and Laparoscopy in Staging Advanced Gastric Cancer [PLASTIC], a Dutch multicenter prospective study) was to evaluate the value of FDG-PET/CT and SL in addition to initial staging in patients with locally advanced gastric cancer.

Key Points

Question Do ^{18}F-fludeoxyglucose-positron emission tomography with computed tomography (FDG-PET/CT) and staging laparoscopy provide benefit in patients with locally advanced gastric cancer?

Findings In this multicenter cohort study comprising 394 patients, FDG-PET/CT detected metastatic disease in 3% of patients and staging laparoscopy detected metastatic or noncurable disease in 19% of patients with locally advanced gastric cancer. Treatment intent changed from curative to palliative in 16% of the patients.

Meaning These findings suggest that FDG-PET/CT has limited additive value, but staging laparoscopy adds considerably to the staging process in patients with locally advanced gastric cancer.

Methods

Study Design

The protocol of this multicenter prospective, observational cohort study has been published.[13] Inclusion criteria consisted of patients with a histologically proven adenocarcinoma of the stomach or gastroesophageal junction (Siewert type III); patients having undergone a CT scan of the thorax/abdomen; patients with locally advanced gastric cancer, defined either as transmural and invading the outer layer of the stomach or involving at least 1 lymph node, as reported on CT (≥cT3 and/or N+, M0 category according to the seventh edition of the American Joint Committee on Cancer TNM staging system)[13,14]; surgically resectable gastric cancer (<cT4b); and patients considered fit for treatment with curative intent (surgery with or without chemotherapy), as determined by the multidisciplinary team (MDT). In all centers in the Netherlands with patients included in the study, MDTs are composed of upper gastrointestinal surgeons, radiologists/nuclear medicine physicians, medical oncologists, gastroenterologists, radiation oncologists, and pathologists. Patients in whom it was not possible to make a clear distinction between cT2 and cT3 cancer based on CT scan or endoscopic ultrasonographic findings were also included. Data on race and ethnicity were not included in the electronic case report forms.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and later versions.[15] Because this study does not allocate patients to interventions other than standard of care according to national guidelines, this study does not fall within the Medical Research Involving Human Subjects Act (WMO). A non-WMO declaration (METC 16-633/C) has been obtained from the Medical Ethical Review Board of the University Medical Center Utrecht, Utrecht, the Netherlands. In addition, the trial was approved by the institutional review board in each of 18 participating centers (eAppendix in Supplement 1). Because questionnaires and financial hospital data were required for a side study, written informed consent was obtained. Patients did not receive financial compensation.

Patients who met the inclusion criteria as determined by the MDT were invited to participate in the study in 1 of the 18 Dutch centers. All 18 centers participated in a regional MDT including at least 1 surgical high-volume center (>20 procedures). Surgical procedures were performed in 13 high-volume centers. In the Netherlands, centralization of gastric cancer treatment was initiated in 2013, meaning that only hospitals in which at least 20 gastrectomies are performed annually are considered sufficiently competent to perform this type of surgery.

Procedures

After written informed consent was obtained, patients were enrolled in the study and underwent FDG-PET/CT and/or SL as standard of care according to Dutch national guidelines. Ideally, FDG-PET/CT was performed first, followed by SL if no distant metastases were found on FDG-PET/CT. Staging laparoscopy was performed as a separate procedure in patients scheduled for neoadjuvant chemotherapy or otherwise at the

onset of gastrectomy. The protocol for performing FDG-PET/CT and SL is summarized in the eMethods in Supplement 1 and was previously published.[13] The FDG avidity of the primary tumor and lymph nodes and the presence of distant metastases were scored as yes, equivocal, or no, and distant metastases were scored as suspicious, equivocal, or no at the discretion of the nuclear medicine physician. Staging laparoscopy reported the location and extent of peritoneal metastases and local resectability, and it was recommended to perform peritoneal lavage with cytologic testing. Based on the results of both investigations, the final treatment strategy was determined at the subsequent MDT meeting.

Outcomes

The primary outcome of the study was the number of patients in whom the treatment intent was changed from curative to palliative based on the results of the FDG-PET/CT or SL. Secondary outcomes were the diagnostic performance (sensitivity and specificity) of both modalities, number of incidental findings on FDG-PET/CT, morbidity of SL, diagnostic delay, quality of life, and cost-effectiveness. All patient data were prospectively registered using electronic case report forms.[13]

Statistical Analysis

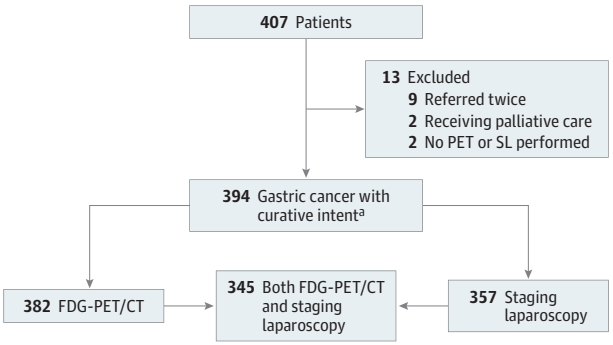
Factors associated with FDG avidity were evaluated using the χ^2 test or Fisher exact test when appropriate. For modality-specific performance, sensitivity and specificity with 95% CIs were calculated. By means of cross tabulation of the index test results against those of the reference standard, the sensitivity and specificity of the index test were estimated.[16,17] A priori-determined subgroup analyses for specific patient and tumor characteristics were performed as described in the study protocol.[13] For FDG-PET/CT, the reference standard for positivity was biopsy or additional imaging, and for negativity, clinical follow-up of 6 months. For SL, biopsy findings from macroscopically suspicious lesions were the reference standard for positivity, and false-negative findings were defined as peritoneal metastases found at the onset of gastrectomy or within 6 months after an initially negative SL result. Members of the study team were not blinded to the results. All statistical analyses were performed using SPSS, version 25.0 (IBM Corp), and a 2-sided, unpaired *P* value <.05 was considered statistically significant.

Results

Study Population

Between August 1, 2017, and February 1, 2020, a total of 407 patients with locally advanced gastric cancer were included in 18 centers in the Netherlands. Two centers included more than 40 patients, 6 centers included 20 to 40 patients, and the remaining centers included fewer than 20 patients. In total, 13 patients were excluded: 9 patients were registered twice (in the referring and tertiary hospitals), a palliative intent was already decided for 2 patients during the first MDT meeting, and 2 patients were excluded because neither FDG-PET/CT nor SL was performed (**Figure**). Of the 394 included patients, 256 (65%) were men and 138 (35%) were women; mean (SD) age was 67.6 (10.7) years; other patient characteristics are presented in **Table 1.**

Figure. Flowchart of Inclusion and Exclusion Criteria



FDG-PET/CT indicates ^{18}F-fludeoxyglucose–positron emission tomography/computed tomography; PET, positron emission tomography; and SL, staging laparoscopy.

[a] cT3 and/or N+, M0 category.

FDG-PET/CT Scan

Of the 394 patients, 382 patients underwent FDG-PET/CT, revealing an FDG-avid primary tumor in 302 patients (79%). A more frequent association was noted between FDG avidity and male sex, positive lymph nodes on CT imaging, gastroesophageal junction tumor location, and intestinal type tumor (**Table 2**).

FDG-PET/CT results were suspicious for distant metastases in 16 patients (4%) and equivocal in 22 patients (6%). Metastatic disease was confirmed in 12 patients (3%); findings were suspicious on FDG-PET/CT in 10 patients and equivocal in 2 patients. These metastases were located in distant lymph nodes (n = 4), liver (n = 3), peritoneum (n = 3), uterus (n = 1), and bone (n = 1). Of these 12 patients with confirmed M1 category, 11 also had clinically positive locoregional lymph nodes and 2 patients had a cT4 tumor.

The sensitivity of FDG-PET/CT for detection of distant metastases was 33% (95% CI, 17%-53%), and for specificity, 97% (95% CI, 94%-99%) (eTable, A in Supplement 1). In the subgroup of patients with an FDG-avid primary tumor, sensitivity was 31% (95% CI, 14%-55%), and for specificity, 98% (95% CI, 95%-99%) (eTable, B in Supplement 1). In subgroup analyses for patients with peritoneal metastases, cT4 tumors or cN+ status, the diagnostic accuracy of FDG-PET/CT did not improve (eTables, C-E in Supplement 1).

Of the total cohort of 382 patients, a clinically relevant lesion was found in 83 (22%) of 132 patients with suspected relevant secondary findings, resulting in additional investigations in 60 patients (**Table 3**). In 7 of 83 patients (8%) a second primary tumor was confirmed (3 colon, 2 lung, and 2 prostate cancers), but in most of these 83 patients, follow-up was not reported.

Staging Laparoscopy

Of the 394 patients, 357 underwent SL and 264 (74%) also underwent peritoneal lavage for cytologic testing. Staging lapa-

Table 1. Baseline Characteristics of 394 Included Patients[a]

Characteristic	No. (%)
Patients	
Age, mean (SD), y	67.6 (10.7)
Missing values	0
Sex	
Men	256 (65)
Women	138 (35)
Missing values	0
Diagnostic tests	
Gastroscopy	394 (100)
Missing values	0
CT thorax/abdomen	394 (100)
Missing values	0
Endoscopic ultrasonography	70 (18)
Missing values	1 (0.2)
Tumors	
cT category	
T1	0
T2	28 (7)
T3	301 (76)
T4	56 (14)
Tx	9 (2)
Missing values	0
cN category	
N0	177 (45)
N1	126 (32)
N2	72 (18)
N3	13 (3)
Nx	6 (2)
Missing values	0
Location	
Cardia	94 (24)
Corpus	110 (28)
Antrum	125 (32)
Pylorus	33 (8)
Diffuse	26 (7)
Missing values	6 (2)
Lauren classification	
Intestinal	118 (30)
Diffuse	135 (34)
Mixed	19 (5)
Unknown	122 (31)
Missing values	0
Differentiation	
Well	15 (4)
Moderate	92 (23)
Poor	108 (27)
Undifferentiated	3 (1)
Missing values	176 (45)
ERBB2 status[b]	
Positive	18 (5)
Negative	115 (29)
Missing values	261 (66)

Abbreviation: CT, computed tomography.

[a] Percentages may not total 100% owing to rounding.

[b] Formerly *HER2*/neu.

roscopy identified suspicious peritoneal lesions in 62 patients (17%), with metastatic disease confirmed in 44 of 357 patients (12%) patients: in 31 by histologic testing, 2 by cytologic testing, and 11 by both tests. Of 295 patients with no or low clinical suspicion during SL, biopsies were performed in 54 patients (18%) and peritoneal lavage was performed in 223 patients (76%). Metastatic disease was still found in 25 patients: in 6 by histologic characteristics of biopsy samples that were not expected by the surgeon to be metastases, 17 by cytologic examination, and in 2 by both tests. Of all 357 patients who underwent SL, a nonresectable tumor was identified in 13 patients: 4 patients solely because of a T4b tumor and 9 patients who also had peritoneal metastases. Altogether, SL findings were positive in 73 patients (19%). Positive SL findings were significantly associated with cT4 tumor category (39% vs 17% cT3 tumors; $P = .001$) and diffuse-type tumors (21% vs 14% intestinal types; $P = .006$).

Staging laparoscopy results were false-negative in 11 patients. Hence, the sensitivity of SL for detection of macroscopically peritoneal metastases was 82% (95% CI, 70%-91%) and specificity was 78% (95% CI, 73%-83%) (eTable, F in Supplement 1).

Staging laparoscopy resulted in postoperative complications in 3 patients (0.8%): luxation of a simultaneously placed feeding jejunostomy, a wound hematoma and bilateral adrenal bleeding, and a trocar incisional hernia with obstruction of the small intestine. All complications required surgical reintervention. No perioperative mortality was observed (**Table 4**).

Treatment Changes

The combination of FDG-PET/CT and SL detected metastatic disease in 78 of 394 patients (20%), metastases in 12 patients (3%) were detected by FDG-PET/CT, metastases in 73 patients (19%) were detected by SL, and metastases in 7 patients (2%) were identified by both examinations. Theoretically, this finding should have resulted in a change of treatment intent in all these patients. All confirmed positive FDG-PET/CT findings (12 of 394 [3%]) resulted in a change from curative to palliative treatment intent. After positive SL findings, intent of treatment was changed to palliative in 60 of 73 patients (60 of 394 [15%]). Of the remaining 13 patients, 3 did not undergo resection owing to death during or shortly after neoadjuvant chemotherapy (n = 2) or progression of disease (n = 1). The other 10 patients had limited peritoneal metastases (n = 3) or only positive cytologic test results (n = 7) and underwent perioperative chemotherapy or chemoradiotherapy and surgical resection. Overall, the number of patients in whom treatment strategy changed from a curative to palliative intent was 65 of 394 (16%).

Diagnostic Delay

Performing only FDG-PET/CT resulted in a mean (SD) of 17 (20) additional days, and performing only SL resulted in 17 (8) additional days until the second MDT meeting. When the investigations were performed consecutively, the delay was 19 (14) days if FDG-PET/CT had been initially performed and 18 (12) days if SL was performed first.

Table 2. FDG-PET/CT Avidity of Primary Tumor and Tumor Characteristics

Variable[a]	FDG avidity, primary tumor, No. (%)[b]			*P* value
	Yes	Equivocal	No	
Sex (n = 381)				
Male	206 (83)	33 (13)	9 (4)	.001
Female	96 (72)	18 (14)	19 (14)	
Site (n = 375)				
Gastroesophageal junction	90 (97)	3 (3)	0	<.001
Corpus	75 (71)	17 (16)	14 (13)	
Antrum	96 (81)	15 (13)	8 (7)	
Pylorus	23 (74)	7 (23)	1 (3)	
Diffuse	16 (62)	6 (23)	4 (15)	
cT category (n = 373)				
cT2	20 (71)	5 (18)	3 (11)	.42
cT3	232 (79)	39 (13)	21 (7)	
cT4	47 (89)	4 (8)	2 (4)	
cN category (n = 376)				
cN0	122 (72)	31 (18)	16 (9)	.03
cN1	98 (80)	17 (14)	8 (7)	
cN2	67 (94)	1 (1)	3 (4)	
cN3	11 (85)	2 (15)	0	
Lauren classification (n = 261)				
Intestinal	106 (91)	6 (5)	4 (3)	<.001
Diffuse	81 (63)	28 (22)	19 (15)	
Mixed	14 (82)	1 (6)	2 (12)	
Differentiation (n = 212)				
Well	12 (86)	2 (14)	0 (0)	.02
Moderate	84 (92)	4 (4)	3 (3)	
Poor	75 (72)	17 (16)	12 (12)	
Undifferentiated	3 (100)	0	0	

Abbreviation: FDG-PET/CT, ^{18}F-fludeoxyglucose–positron emission tomography with computed tomography.

[a] For this analysis, only patients in whom the designated tumor characteristics were registered were taken into account.

[b] Percentages may not total 100% owing to rounding.

Discussion

This multicenter prospective, observational cohort study evaluated the outcomes associated with adding FDG-PET/CT and SL to the staging process of locally advanced gastric cancer. We found that FDG-PET/CT identified distant metastatic disease in 12 of 394 patients (3%) and SL identified noncurable disease in 73 patients (19%). In all 12 patients with positive FDG-PET/CT results, the finding of metastatic disease resulted in a change of treatment strategy from curative to palliative intent. In the 73 patients with positive SL findings, treatment strategy was changed to palliative intent in 60 patients (15%), with an overlap of 7 patients (2%) who also had a positive FDG-PET/CT. These results suggest a limited additional role of FDG-PET/CT and what appears to be a considerable benefit of SL on the staging process of gastric cancer.

Retrospective studies reported a possible additional role of FDG-PET/CT in the identification of distant metastatic disease in gastric cancer being positive in 6% to 16% of patients,[18-22] but limited additional value in detecting other noncurable disease.[18,19,21,23-28] The present study found a much lower detection rate of 3% for distant metastases. Moreover, in 7 of 12 patients with positive FDG-PET/CT findings, metastatic disease was detected by SL, resulting in a negligible value of FDG-PET/CT. A possible reason for this difference may be that some patients with positive FDG-PET/CT results may not have been included in this study because regional centers may not have referred them to a participating center. To reduce this risk of this bias, multidisciplinary consultation lists were checked, and centers were asked to discuss all FDG-PET/CTs in the MDT meeting. In addition, the study by Smyth et al[12] applied the sixth edition of the TNM classification system, whereas our staging was based on the seventh and, when available, the eighth edition. The T3 and T4 tumors according to TNM-6, included by Smyth et al, correspond to category T4a and T4b tumors according to TNM-7 and TNM-8. Therefore, we included lower T-category tumors (T3, T4a, and T4b) than Smyth et al. However, the accuracy of PET/CT did not increase in subgroup analyses with T4 tumors. In our study, 79% of tumors were FDG avid, which is comparable to other studies,[8,12,24,29,30] but less than has been reported in other types of cancer, such as esophageal cancer.[18] FDG avidity of the primary gastric tumor has previously been reported to be associated with male sex, intestinal type tumors, gastroesophageal junction tumors, and larger tumor size and depth.[12,18,19,21,23-25,30-32] Determining FDG avidity of diffuse-type gastric cancer is challenging in clinical practice, because it may be interpreted as physiological uptake. Moreover, because FDG avidity of this type of tumor is generally lower, FDG-

Table 3. FDG-PET/CT Results in 382 Patients With Advanced (≥cT3 and/or N+) Gastric Adenocarcinoma With Curative Intent

Variable	No. (%)[a]
FDG avidity of primary tumor	
No	28 (7)
Equivocal	51 (13)
Yes	302 (79)
Missing values	1 (<1)
Maximum SUV, median (SD)	10.5 (8.0)
Missing values	270 (68)
Lymph nodes avid	
No	225 (60)
Equivocal	20 (5)
Yes, location	132 (35)
Lesser curvature	98 (26)
Greater curvature	13 (3)
Paracardial	12 (3)
Locoregional NOS	45 (12)
Missing values	5 (1)
Suspicion of metastatic disease	
No	344 (90)
Equivocal	22 (6)
Yes, location	16 (4)
Liver	8 (2)
Lung	8 (2)
Bone	4 (1)
Peritoneum	4 (1)
Distant lymph nodes	15 (4)
Corpus uteri	1 (<1)
Missing values	0
cM1 category confirmed (n = 38)	
No	26 (7)
Yes	12 (3)
Missing values	0
Secondary findings	
No	249 (65)
Yes	
Clinically irrelevant[b]	49 (13)
Clinically relevant, location	83 (22)
Pulmonary	8 (2)
Gastrointestinal	38 (10)
ENT	5 (1)
Thyroid	10 (3)
Soft tissue	4 (1)
Adrenal	1 (2)
Prostate	3 (1)
HPB	5 (1)
Other	9 (2)
Additional examination, yes[c]	60 (16)
Missing values	1 (<1)

Abbreviations: cM1, clinically M category; ENT, ear, nose, and throat; FDG-PET/CT, ^{18}F-fludeoxyglucose–positron emission tomography with computed tomography; HPB, hepato-pancreato-biliary; NOS, not otherwise specified; SUV, standardized uptake value.

[a] Percentages may not total 100% owing to rounding.

[b] Clinically irrelevant secondary findings, such as hepatic cysts or adrenal adenomas.

[c] Excluding 2 patients with clinically irrelevant secondary findings in whom additional examination was conducted.

Table 4. Staging Laparoscopy Results of 357 Patients Who Were Diagnosed With Advanced (≥cT3 and/or N+) Gastric Adenocarcinoma With Curative Intent

Variable	No. (%)[a]
Performed staging	
Surgeon	215 (60)
Resident in presence of surgeon	97 (27)
Resident	37 (10)
Missing values	8 (2)
Operation time, mean (SD), min	34.6 (25.8)
Missing values	4 (1)
All quadrants scored	
No	14 (4)
Yes	256 (72)
Missing values	87 (24)
Ascites	
No	237 (66)
Yes	30 (8)
Missing values	90 (25)
Adhesions	
No	230 (64)
Yes	56 (16)
Missing values	71 (20)
Bursa opened	
No	202 (57)
Yes	72 (20)
Missing values	83 (23)
Suspicion of peritoneal metastases	
No	293 (82)
Yes	62 (17)
PCI score, median (IQR)	3 (1-8)
Missing values	5 (1)
Missing values	2 (1)
Histologic examination performed	
No	237 (66)
Yes	115 (32)
Positive	50 (14)
Missing values	5 (1)
Peritoneal washing performed	
No	88 (25)
Yes	264 (74)
Positive	32 (9)
Missing values	5 (1)
Missing values	5 (1)
Locally resectable	
No (cT4b)	13 (4)
Yes	331 (93)
Missing values	13 (4)
Positive SL[b]	
No	284 (80)
Yes	73 (20)
Missing values	0
SL performed	
As separate procedure	342 (96)
At the onset of gastrectomy[c]	15 (4)
Missing values	0

(continued)

Table 4. Staging Laparoscopy Results of 357 Patients Who Were Diagnosed With Advanced (≥cT3 and/or N+) Gastric Adenocarcinoma With Curative Intent (continued)

Variable	No. (%)[a]
Complicated postoperative course	
No	325 (91)
Yes[d]	3 (0.8)
Surgical intervention	3 (0.8)
Missing values	29 (8)
Hospital stay, median (IQR), d	0 (0-1)
Missing values	79 (22)

Abbreviations: PCI, peritoneal cancer index; SL, staging laparoscopy.

[a] Percentages may not total 100% owing to rounding.

[b] Positive SL is defined as positive cytologic test findings, positive histologic test findings, or nonresectable disease.

[c] In 1 patient, peritoneal as well as nonresectable disease was found. In this patient, the procedure was interrupted and no resection was performed.

[d] In a patient with a wound hematoma and bilateral adrenal bleeding, the hospital stay was prolonged to 30 days.

PET/CT will also be less sensitive for metastases of these tumors.[18,19,23,33]

The limited number of metastases detected by FDG-PET/CT alone, the additional waiting time of at least 17 days, and the high number of incidental findings leading to additional investigations raise questions regarding the routine use of FDG-PET/CT in patients with gastric cancer. Cost-effectiveness and quality-of-life analyses of our data will be performed after additional follow-up and may identify a subset of patients (eg, those with gastroesophageal junction or intestinal type tumors) that benefits from additional staging by FDG-PET/CT. In addition, patients with high FDG avidity of the primary tumor may have an increased risk of distant metastasis. Models to estimate the probability of this outcome, based on histopathological and other tumor characteristics, have been developed, such as the model reported by Kaneko et al.[34] However, this model has limited predictive value and may benefit from further optimization.

By detecting noncurable disease in 19% of patients, SL was found to have a significant and clinically relevant added value in the staging of locally advanced gastric cancer. This finding supports the results of previous, mostly retrospective studies, reporting a yield of SL of 8% to 53%.[35] Treatment was not changed to a palliative approach in all 73 patients in the present study with a positive SL outcome; instead, some patients with limited peritoneal metastases and positive cytologic test findings were treated with curative intent. In line with previous studies,[36-38] the present study detected positive cytologic characteristics in 9% of the patients. Although positive cytologic findings are regarded as metastatic disease by the American Joint Committee on Cancer TNM-8 classification system[39] and some international guidelines,[2,40] no instructions exist on how to treat the patients with only positive cytologic findings. Some studies have reported a survival benefit when patients in whom a repeat SL showed a change from positive to negative cytologic findings following neoadjuvant chemotherapy undergo gastrectomy (hazard ratio, 0.42; 95% CI, 0.31-0.57; $P < .001$).[38,41,42] Adjuvant chemotherapy could also be considered in these patients, as other studies reported a survival gain in patients with positive cytologic test results who receive postoperative chemotherapy after a surgical resection compared with no chemotherapy (hazard ratio, 4.17; 95% CI, 3.01-5.78; $P = .01$).[43] Moreover, some studies have evaluated hyperthermic intraperitoneal chemotherapy in patients with positive cytologic findings, but no high-level evidence is yet available.[44,45] The PERISCOPE-II trial is evaluating a possible survival benefit of hyperthermic intraperitoneal chemotherapy and cytoreductive surgery after systemic chemotherapy, including both patients with limited peritoneal disease and those with solely positive cytologic test results of peritoneal fluid or peritoneal washing.[46]

Regarding the risks of SL, research has suggested that the morbidity of SL does not outweigh the benefits.[29] The present study noted metastatic disease in 19% of the patients, with a postoperative morbidity rate of 0.8%. This morbidity rate of less than 1% is in line with previously reported rates of 0% to 3%,[35] and, in our opinion, supports the additional value of SL. Despite these advantages of adding SL to the staging process, there is room for an improvement of the logistics because SL resulted in extra time in the diagnostic process.

Limitations

A limitation of this study is that the sensitivity and specificity of both FDG-PET/CT and SL could not be completely adequately assessed. Because follow-up of most patients who underwent FDG-PET/CT was lacking, the number of metastases detected at 6 months' follow-up is most likely underreported, resulting in an underestimation of sensitivity and specificity. Regarding sensitivity and specificity of SL, positive cytologic test results were not included in this analysis because peritoneal lavage was not repeated at the beginning of the gastrectomy and its clinical relevance is unclear, thereby precluding the adequate identification of true- and false-negative findings. Therefore, the sensitivity and specificity values reported herein should be interpreted with caution. In addition, no data on histopathological assessment of the resected specimens were collected, preventing examination of findings on FDG-PET/CT associated with tumor stage, nodal involvement, and metastatic status. Nevertheless, to our knowledge, the present study is the largest prospective study on the outcome of FDG-PET/CT and SL in patients with locally advanced gastric cancer in Western countries. The secondary outcomes (quality of life and cost-effectiveness) will be reported after the required 1-year follow-up for these end points has been reached.

Conclusions

In this study, FDG-PET/CT had limited value for detecting metastatic disease in patients with locally advanced gastric cancer. In contrast, SL detected metastatic or nonresectable disease in a considerable proportion of patients, resulting in a treatment change from curative to palliative intent. These findings suggest that it may be beneficial to include SL in guidelines for staging advanced gastric cancer, but not FDG-PET/CT.

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