
Metabolic Tumor Volume on ^{18}F -FDG PET/CT Improves Preoperative Identification of High-Risk Endometrial Carcinoma Patients

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Our objective was to prospectively explore the diagnostic value of ^{18}F -FDG PET/CT for preoperative staging in endometrial carcinomas and to investigate whether ^{18}F -FDG PET-specific quantitative tumor parameters reflect clinical and histologic characteristics. **Methods:** Preoperative ^{18}F -FDG PET/CT was prospectively performed on 129 consecutive endometrial carcinoma patients. Two physicians who did not know the clinical findings or staging results independently reviewed the images, assessing primary tumor, cervical stroma involvement and metastatic spread, and determining maximum and mean standardized uptake value (SUV_{max} and SUV_{mean} , respectively) for tumor, metabolic tumor volume (MTV), and total lesion glycolysis (TLG). All parameters were analyzed in relation to histomorphologic and clinical tumor characteristics. Receiver-operating-characteristic curves for identification of deep myometrial invasion and lymph node metastases were generated, and MTV cutoffs for predicting deep myometrial invasion and lymph node metastases were calculated. **Results:** The sensitivity, specificity, and accuracy of ^{18}F -FDG PET/CT for the detection of lymph node metastases were 77%–85%, 91%–96%, and 89%–93%, respectively. SUV_{max} , SUV_{mean} , MTV, and TLG were significantly related to deep myometrial invasion, presence of lymph node metastases, and high histologic grade ($P < 0.015$ for all) and independently predicted deep myometrial invasion ($P < 0.015$) and lymph node metastases ($P < 0.025$) after adjustment for preoperative histologic risk (based on subtype and grade) in endometrial biopsies. Optimal cutoffs for MTV in predicting deep myometrial invasion (20 mL) and the presence of lymph node metastases (30 mL) yielded odds ratios of 7.8 ($P < 0.001$) and 16.5 ($P = 0.001$), respectively. **Conclusion:** ^{18}F -FDG PET/CT represents a clinically valuable tool for preoperatively evaluating the presence of lymph node metastases in endometrial carcinoma patients. Applying MTV cutoffs for the prediction of deep myometrial invasion and lymph node metastases may increase diagnostic accuracy and aid preoperative identification of high-risk patients, enabling restriction of lymphadenectomy for patients with a low risk of aggressive disease.

Key Words: endometrial carcinoma; ^{18}F -FDG PET/CT; cancer staging; metabolic tumor volume; incidental findings

J Nucl Med 2015; 56:1191–1198
DOI: 10.2967/jnumed.115.159913

Endometrial carcinoma is the most common gynecologic malignancy in the Western world, and the incidence is increasing (1). Preoperative risk profile, based on assessment of histologic subtype and grade in endometrial biopsies, combined with imaging methods to detect deep myometrial invasion, cervical stromal invasion, and lymph node metastases is applied to tailor primary surgery. Further assessment of histologic type and grade in hysterectomy specimens and results from surgical International Federation of Gynecology and Obstetrics (FIGO) staging are further used to individualize adjuvant therapy (1–3). These methods are, however, suboptimal, and improved imaging tools to preoperatively exclude lymph node metastases would reduce the need for staging lymphadenectomy, currently frequently performed despite lack of documented survival benefit from the procedure in randomized trials (4). More advanced preoperative risk stratification models could thus safely allow less extensive surgery and reduced postoperative morbidity in low-risk patients (5) and could allow radical hysterectomy or lymphadenectomy to be reserved for the approximately 20% of high-risk endometrial carcinoma patients who follow an aggressive course (4,6).

MR is presently the preferred imaging method for preoperative evaluation of endometrial carcinoma patients (1,7,8), although limitations in the accuracy and reproducibility of MR-based staging parameters have been reported (8–10). ^{18}F -FDG PET/CT combines morphologic and physiologic techniques and is the preferred imaging method for various cancers (11). Although several studies have suggested that ^{18}F -FDG PET/CT can be beneficial preoperatively in endometrial cancer patients (12–23), its clinical role in risk stratification of such patients is not well defined. Furthermore, the value of various quantitative tumor parameters and the corresponding optimal cutoffs for the prediction of tumor stage and prognosis are largely unexplored.

The aim of the present study was to prospectively explore the diagnostic value of preoperative ^{18}F -FDG PET/CT for staging of

Received Apr. 23, 2015; revision accepted May 20, 2015.

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Published online Jun. 4, 2015.

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endometrial carcinoma and to investigate the extent to which ^{18}F -FDG PET-specific quantitative tumor parameters reflect clinical and histologic tumor characteristics. To further explore clinical applicability, we assessed interobserver agreement for ^{18}F -FDG PET/CT staging parameters and quantitative tumor parameters and the prevalence and significance of incidental findings on prospective and consecutive ^{18}F -FDG PET/CT investigations of a population-based endometrial carcinoma cohort.

MATERIALS AND METHODS

Subjects and Study Setting

From October 2011 to November 2013, preoperative whole-body ^{18}F -FDG PET/CT was performed on 129 prospectively included, consecutive patients with endometrial carcinoma. The diagnoses were established through preoperative endometrial biopsy and verified in hysterectomy specimens, and stage was assessed according to the FIGO 2009 criteria for surgical staging. The images were acquired prospectively, and the results were reported to the responsible clinician together with the results of all relevant preoperative imaging. The patients gave written informed consent for the collection of data and specimens for biomarker studies under institutional review board-approved protocols. Image interpretation for staging parameters, reproducibility assessments, and quantifications were conducted retrospectively. All patients were diagnosed and treated at Haukeland University Hospital, a European Society for Gynecologic Oncology-accredited training center for gynecologic oncology, serving a population of about 1 million.

Imaging Protocol

PET/CT was performed on a Biograph 40 True Point scanner (Siemens). Both PET and low-dose CT scanning covered the skull to the proximal thigh. The protocol included 6 h of fasting before image acquisition, and all patients were asked to void before undergoing scanning. ^{18}F -FDG (322–414 MBq) was given intravenously 60–120 min before the CT scan, and the patients rested in a semidark, temperate room between injection and scanning. Low-dose CT (120 kV, 50 mAs) for attenuation correction of the PET data was performed before the static emissions, which were obtained at a rate of 3 min per bed position; immediately thereafter, intravenous contrast agent (Iomerol, 350 mg iodine/mL; Bracco Imaging Scandinavia, AB) and negative oral contrast agent (water) were administered for the subsequent diagnostic CT scan (120 mV, 240 mAs), covering a region from the meatus of the ear to the proximal thigh. The total scanning time was about 25 min per patient. Images were reconstructed and stored in axial, coronal, and sagittal slices 3.0–5.0 mm thick in the department's PACS (Impax 6; Agfa Healthcare BV).

Data Analyses

A standard imaging report was generated by the responsible nuclear physician and radiologist and reported to the clinical team as part of

the routine clinical diagnostic work-up. This imaging report was read and approved by a specialist in nuclear medicine and a radiologist subspecialist in pelvic imaging as part of the standard interpretation setup at our institution.

After being used for routine diagnosis, all images were anonymized, processed, and reviewed retrospectively and independently by 2 physicians experienced in both nuclear medicine and radiology, on a Segami Oasis workstation (version 1.9.4.2; Segami Corp.). Both interpreters had about 4 y of experience with PET/CT before the study. They were unaware of the clinical data and the results of surgical staging, and they reported imaging findings on a standardized form. This form included information on tumor avidity and uptake intensity, as well as metabolic tumor volume (MTV). Information on the presence of increased ^{18}F -FDG uptake in the cervix (interpreted as cervical stroma invasion), in lymph nodes (interpreted as lymph node metastases), and at distant sites (interpreted as likely metastases) was also recorded. The depth of myometrial invasion based on ^{18}F -FDG uptake was not recorded, because the low resolution of the PET signal was perceived to preclude such assessment.

The PET images were fused with both the diagnostic and the low-dose CT images on the Oasis workstation. All measurements were performed using the low-dose fusion images, whereas diagnostic fusion was used for staging. For the measurements of MTV and mean standardized uptake value (SUV_{mean}), voxels with an SUV of more than 2.5 were included in the volume of interest (Fig. 1). Total lesion glycolysis (TLG) in the tumor was also estimated using the following equation: $\text{TLG} = \text{SUV}_{\text{mean}} \times \text{MTV}$ (24). For the statistical analyses of continuous variables, the mean of the 2 observers' measurements was applied.

To achieve a common understanding of the criteria for assessing tumor avidity, uptake intensity, and MTV, the 2 observers independently recorded 5 selected training cases on the standardized form and then discussed any disagreements or differences in interpretation. These 5 cases were excluded from the study data.

Surgical Staging and Clinical Outcome

In total, 125 (97%) of the 129 patients were surgically staged according to the FIGO 2009 criteria; the responsible physicians of the remaining 4 patients considered them to have inoperable disease, and their diagnoses were based on the uterine biopsies. Depth of myometrial invasion and presence of cervical stromal invasion were assessed macroscopically and confirmed microscopically according to standard procedures. Routine histopathology reports were generated without knowledge of preoperative PET/CT results. Number, size, and localization of lymph node metastases were documented in the histopathology report.

To determine how the clinical team had dealt with follow-up of incidental findings, the medical records were examined retrospectively about 1 y after the PET/CT scans. All additional workups due to the reported incidental PET findings were recorded, together with the results of any repeated examinations.

Statistical Analyses

PET/CT results suggesting cervical stromal invasion or lymph node metastases were compared with the final histopathologic report as the reference standard to calculate sensitivity, specificity, accuracy, positive and negative predictive values, and number of false-positive or -negative findings for each observer and for the imaging report. The relationship between quantitative tumor parameters on PET/CT (SUV_{max} , SUV_{mean} , MTV, and TLG) and the clinical and histologic tumor characteristics were analyzed by the Mann-Whitney

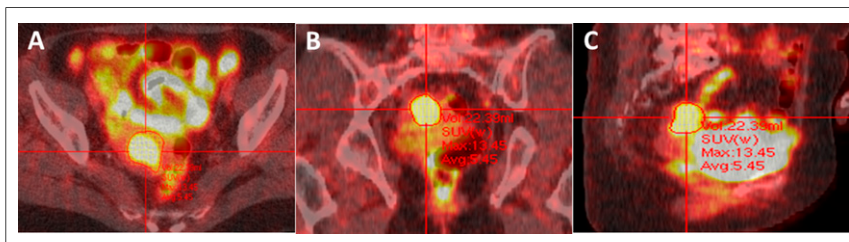


FIGURE 1. ^{18}F -FDG PET/CT images depicting manually drawn MTV in 3 planes: axial (A), coronal (B), and sagittal (C) in 63-year-old woman with FIGO stage 1A endometrioid grade 1 endometrial cancer. In this patient, MTV was 22.4 mL, SUV_{max} 13.5, and SUV_{mean} 5.5.

TABLE 1
Diagnostic Performance of ¹⁸F-FDG PET/CT Compared with Surgical Staging

Parameter	Cervical stroma invasion	Lymph node metastases
Sensitivity		
Observer 1	8/24 (33%)	10/13 (77%)
Observer 2	8/24 (33%)	10/13 (77%)
Clinical report	6/24 (25%)	11/13 (85%)
Specificity		
Observer 1	75/102 (74%)	81/89 (91%)
Observer 2	75/102 (74%)	85/89 (96%)
Clinical report	89/102 (87%)	82/89 (92%)
Accuracy		
Observer 1	83/126 (66%)	91/102 (89%)
Observer 2	83/126 (66%)	95/102 (93%)
Clinical report	96/126 (76%)	93/102 (91%)
Positive predictive value		
Observer 1	24/49 (49%)	13/21 (62%)
Observer 2	24/49 (49%)	13/17 (76%)
Clinical report	24/37 (65%)	13/20 (65%)
Negative predictive value		
Observer 1	102/118 (86%)	89/92 (97%)
Observer 2	102/118 (86%)	89/92 (97%)
Clinical report	102/120 (85%)	89/91 (98%)
False-positive/-negative findings		
Observer 1	25/16	8/3
Observer 2	25/16	4/3
Clinical report	13/18	7/2

Data are numbers of patients or findings.

U test, the Jonckheera–Terpsta trend test, and multivariate logistic regression analysis. The intraclass correlation coefficient was used to assess the consistency and reproducibility of the quantitative PET/CT parameters, and the minimal detectable change ($1.96 \times \text{SEM} \times \sqrt{2}$) for these parameters was also calculated.

Receiver-operating-characteristic (ROC) analyses were performed to evaluate the diagnostic value of the different tumor quantifications in identifying deep myometrial invasion and the presence of lymph node metastases. From these analyses, the optimal cutoffs (rounded to cL) for MTV were estimated by aiming for the values that best separated groups by the Youden index. Statistical analyses were performed using SPSS, version 22.0 (IBM), and Stata, version 12.1 (StataCorp). All reported *P* values were 2-sided and considered significant when less than 0.05.

RESULTS

Patient Characteristics

Mean age for the 129 patients was 66 y (median, 67 y; range, 26–88 y), and 93% (120/129) of the patients were postmenopausal. Surgical FIGO 2009 staging criteria identified stage IA

in 57% (73/129, tumor invading < 50% of the myometrium), stage IB in 17% (22/129; tumor invading \geq 50% of the myometrium), and unclassified stage I in 1% (1/129). Stage II was detected in 13% (17/129; cervical stromal invasion), stage III in 9% (12/129; local or regional spread), and stage IV in 3% (4/129). Among the 98 patients with the endometrioid subtype, data for grade were available in 92 cases: 57% (52/92) grade 1, 30% (28/92) grade 2, and 13% (12/92) grade 3. Clear cell histology was reported in 5% (6/129), serous histology in 12% (15/129), carcinosarcoma in 5% (6/129), and undifferentiated histology in 3% (4/129). Among the 4 patients with stage IV disease, one had bone metastases; one had abdominal carcinomatosis, including omental metastases; and two had locally advanced tumors with growth into the bladder and rectum, one of whom also had ovarian metastases. All metastases were confirmed by gynecologic examination with ultrasound, MR imaging (bone metastases), biopsy, or perioperative inspection.

Simple hysterectomy with bilateral salpingo-oophorectomy was performed on 91% (118/129) of patients, 7 patients were treated with radical hysterectomy and bilateral salpingo-oophorectomy, and 4 patients underwent palliative procedures (tumor reductive surgery [*n* = 1] or uterine biopsy [*n* = 3]). Pelvic lymph nodes were sampled in 75% (97/129), among whom 19% (25/129) also had paraaortic lymph nodes removed as part of the surgical staging procedure. Adjuvant therapy was given to 37% (48/129); chemotherapy to 33% (42/129), pelvic radiation to 3% (4/129), and antihormonal treatment to 2% (2/129).

Diagnostic Performance of ¹⁸F-FDG PET/CT in Preoperative Staging

For detecting cervical stromal involvement and lymph node metastases, the observers (including the routine clinical report) had a sensitivity of 25%–33% and 77%–85%, respectively, a specificity of 74%–87% and 91%–96%, respectively, a positive predictive value of 49%–65% and 62%–76%, respectively, and a negative predictive value of 85%–86% and 97%–98%, respectively (Table 1). The 4 cases with confirmed distant metastases were correctly identified and described by observer 1, by observer 2, and in the routine report in 2, 3, and 3 cases, respectively. In a different patient previously treated for breast cancer, widespread malignant disease (metastases in the lungs, mediastinum, bones, and liver) was noted by both observers and in the clinical report, all correctly perceiving this as likely breast cancer metastases in addition to the newly diagnosed localized primary endometrial cancer. No false-positive distant metastases were identified on the basis of PET/CT imaging, yielding a positive predictive value of 100% for both interpreters.

¹⁸F-FDG PET Quantification Measures Associated with Surgicopathologic Findings

The mean SUV_{max}, SUV_{mean}, MTV, and TLG of the uterine tumors were 14.2, 5.8, 30 mL, and 215 g, respectively, and the corresponding median values were 14.1, 5.7, 19 mL, and 119 g, respectively. All values were significantly higher in tumors microscopically invading at least 50% compared with less than 50% of the uterine wall and in tumors that had lymph node metastases compared with those that did not (Table 2). The same parameters were also significantly higher in high-grade endometrioid tumors, and MTV and TLG were significantly higher in aneuploid tumors. Apart from a significantly higher MTV in tumors with cervical stromal involvement, there was no significant difference in the quantitative parameters related to presence of cervical stroma invasion, histologic subtype, or age (Table 2).

TABLE 2
Quantitative Tumor Parameters Assessed by ¹⁸F-FDG PET/CT in Relation to Clinical and Histologic Characteristics

Parameter	n	SUV _{max}		SUV _{mean}		MTV (mL)		TLG (g)	
		Mean	P	Mean	P	Mean	P	Mean	P
Myometrial invasion			0.008*		0.000*		0.000*		0.000*
<50%	86	12.9 (11.4–14.4)		5.3 (4.9–5.7)		20 (15–25)		141 (98–185)	
≥50%	38	16.4 (14.5–18.3)		6.6 (6.0–7.2)		53 (38–68)		361 (263–459)	
Cervical stroma invasion			0.05		0.05		0.034*		0.05
Yes	23	16.5 (14.1–18.8)		6.4 (5.6–7.2)		37 (24–51)		245 (157–333)	
No	100	13.5 (12.1–14.9)		5.6 (5.2–6.0)		28 (21–35)		203 (148–257)	
Lymph node metastases			0.010*		0.002*		0.000*		0.000*
Yes	13	20.7 (17.1–24.4)		7.6 (6.4–8.8)		65 (47–83)		479 (353–604)	
No	88	13.3 (12.0–14.7)		5.7 (5.3–6.1)		25 (19–32)		183 (132–233)	
Histologic subtype			0.88		1.00		0.55		0.47
Endometrioid	97	14.3 (12.9–15.6)		5.8 (5.4–6.2)		28 (22–35)		202 (153–252)	
Nonendometrioid	30	14.1 (11.5–16.6)		5.6 (5.0–6.3)		38 (22–55)		259 (146–372)	
Histologic grade†			0.013*		0.003*		0.001*		0.002*
1	51	12.8 (11.1–14.5)		5.3 (4.8–5.8)		20 (14–27)		135 (87–182)	
2	28	14.7 (11.7–17.8)		6.0 (5.1–6.9)		36 (19–53)		268 (141–394)	
3	12	19.0 (15.8–22.1)		7.6 (6.3–8.9)		49 (31–67)		370 (243–496)	
DNA ploidy			0.66		0.40		0.029*		0.026*
Diploid	48	15.9 (14.2–17.6)		6.2 (5.6–6.8)		35 (25–46)		252 (170–335)	
Aneuploid	15	16.8 (13.3–20.4)		6.7 (5.5–8.0)		58 (34–82)		383 (247–520)	
Age at diagnosis (y)			0.10		0.26		0.96		0.62
<66	60	15.4 (13.5–17.2)		6.1 (5.5–6.7)		27 (20–34)		211 (149–274)	
≥66	67	13.2 (11.7–14.7)		5.5 (5.1–5.9)		33 (23–44)		219 (152–186)	

*Statistically significant.

†Endometrioid subtype only.

Data in parentheses are 95% confidence intervals. *P* values were obtained using Mann–Whitney *U* test for 2 categories and Jonckheere–Terpsta trend test for multiple categories.

SUV_{max}, SUV_{mean}, MTV, and TLG significantly predicted deep myometrial invasion and lymph node metastases both with and without adjustment for high risk based on preoperative endometrial biopsy (all *P* ≤ 0.008 and all *P* ≤ 0.023; Table 3). In contrast, SUV_{max}, SUV_{mean}, MTV, and TLG did not predict the presence of cervical stromal involvement (Table 3).

ROC curves showed that MTV had the highest areas under the curve: 0.77 and 0.86 in predicting deep myometrial invasion and lymph node metastases, respectively (Figs. 2A and 2B). On the basis of these ROC curves, an MTV cutoff of 20 mL yielded an odds ratio (OR) of 7.8 (confidence interval [CI], 3.2–19.1; *P* < 0.001) for deep myometrial invasion, whereas an MTV cutoff of 30 mL yielded an OR of 16.5 (CI, 3.4–80.3; *P* = 0.001) for lymph node metastases. When adjusting for preoperative biopsy results suggesting high risk (nonendometrioid subtype or endometrioid grade 3), an MTV cutoff of 20 mL yielded an OR of 7.3 (CI, 2.9–18.3; *P* < 0.001) for deep invasion and an MTV cutoff of 30 mL yielded an OR of 10.9 (CI, 2.1–55.3; *P* < 0.005) for lymph node metastases.

Interobserver Agreement

The interobserver agreement for MTV and TLG was moderate, with intraclass correlation coefficients of 0.56 and 0.57, respectively (Table 4). For SUV_{max} and SUV_{mean}, the intraclass

correlation coefficient was very good, yielding values of 0.98 and 0.87, respectively (Table 4).

Incidental Findings

On the basis of the clinical report, significant incidental findings (defined as ¹⁸F-FDG uptake with a possible therapeutic consequence) suggesting additional workup were reported for 18% (23/129) of the patients. Further examinations were performed for 17 patients, leading to an additional cancer diagnosis in 4 patients (lung cancer, thyroid cancer, low-grade B-cell lymphoma, and breast cancer) and to the finding of colonic polyps in 2 patients (Fig. 3). For the remaining 11 patients, either no pathologic finding was confirmed (6 patients) or a nonmalignant disease was found and treated (thyroiditis or abnormal thyroid function parameters [4 patients]), the peritoneal ¹⁸F-FDG-avid lesion was found to be part of widespread metastatic disease from endometrial cancer confirmed peroperatively (1 patient), or the ¹⁸F-FDG-avid perineal lesion was confirmed to be a metastasis from endometrial cancer 3 mo later (1 different patient) (Fig. 3). Six patients are still under surveillance for their incidental findings.

DISCUSSION

Most endometrial carcinoma patients, who typically are elderly, have an excellent prognosis. They are subjected to

TABLE 3

ORs for ¹⁸F-FDG PET/CT Prediction of Deep Myometrial Invasion, Cervical Stroma Invasion, and Lymph Node Metastases

Parameter	SUV _{max}	SUV _{mean}	MTV (mL)	TLG (g)
Deep myometrial invasion (n = 124)				
Unadjusted OR	1.09	1.44	1.03	1.004
95% CI	1.02–1.16	1.16–1.79	1.02–1.05	1.002–1.005
P	0.008*	0.001*	<0.001*	<0.001*
Adjusted OR	1.08	1.40	1.03	1.003
95% CI	1.02–1.16	1.12–1.75	1.01–1.04	1.001–1.005
P	0.013*	0.003*	<0.001*	0.001*
Cervical stroma invasion (n = 123)				
Unadjusted OR	1.07	1.22	1.01	1.00
95% CI	1.00–1.15	0.97–1.52	1.00–1.02	1.00–1.00
P	0.06	0.09	0.23	0.47
Adjusted OR	1.06	1.15	1.003	1.00
95% CI	1.00–1.15	0.91–1.46	0.99–1.02	1.00–1.002
P	0.10	0.23	0.63	0.98
Lymph node metastases (n = 101)				
Unadjusted OR	1.22	1.53	1.03	1.004
95% CI	1.09–1.38	1.14–2.05	1.01–1.05	1.002–1.006
P	0.001*	0.005*	0.001*	0.001*
Adjusted OR	1.24	1.51	1.02	1.003
95% CI	1.08–1.43	1.07–2.13	1.005–1.04	1.001–1.005
P	0.002*	0.021*	0.013*	0.008*

*Statistically significant.

ORs are given both unadjusted and adjusted for risk from preoperative endometrial biopsy indicating nonendometrioid subtype or endometrioid grade 3. P values were obtained using logistic regression analysis.

extensive overtreatment, surgically with lymphadenectomy as a staging procedure, and with adjuvant chemo- and radiotherapy, although the survival benefit from such treatments is undocumented. A follow-up randomized phase 3 trial for women with clinical early-stage high-risk endometrial cancer has been proposed in the STATEC (Selective Targeting of Adjuvant Therapy for Endometrial Cancer) trial (25). The plan is for patients to be randomized to lymphadenectomy versus no lymphadenectomy, followed by adjuvant therapy for node-positive lymphadenectomy patients versus adjuvant therapy for nonlymphadenectomy patients. A sentinel node substudy for patients undergoing lymphadenectomy will compare sentinel lymph node mapping with full lymphadenectomy. It may be a challenge to include preoperative PET/CT in such a study, although further studies also including state-of-the-art advanced imaging methods would be highly valuable in this setting. Including preoperative imaging in future clinical trials could potentially clarify whether advanced imaging tools may contribute to further tailoring of surgical and systemic therapies, which is critical to reduce overtreatment and related side effects.

In the present study, we found that the application of ¹⁸F-FDG PET/CT to detect lymph node metastases in endometrial carcinomas yielded sensitivity of 77%–85%, specificity of 91%–96%, and accuracy of 89%–93%. The sensitivity is within the higher range compared with most previous studies (60%–83%) (12–15,22), whereas the specificity is within the lower range compared with previous studies (93%–100%) (12–15,22). Accuracy seems quite

similar to that reported recently (90%–95%) (12,13,22). Our ability to compare staging using ¹⁸F-FDG PET/CT with that using sentinel lymph node procedures is currently limited, as the true performance in endometrial carcinomas is not well established because the studies have been small and the techniques applied have often varied (26). A recent update from the Memorial Sloan Kettering Cancer Center after 10 y of experience with sentinel lymph node mapping in uterine cancer concluded that prospective studies are needed to validate the use of sentinel lymph node mapping in early-stage endometrial cancer (27). Interestingly, the negative predictive value in the present study was very high (97%–98%), confirming the 95% reported by Criverallo et al. (13) and the 96% reported by Antonsen et al. (22). Thus, the combined high specificity and high negative predictive value confirm that ¹⁸F-FDG PET/CT is presently the most promising imaging method to exclude lymph node metastases and thus help avoid potentially harmful lymphadenectomy for staging.

The present study also suggested that measurement of MTV may represent a new tool to assess two well-established surrogate markers for poor outcome: deep myometrial invasion and metastatic lymph nodes; we therefore proposed potential cutoffs to help identify patients at higher risk of having these markers. For deep myometrial invasion, an MTV cutoff of 20 mL yielded sensitivity and specificity of 79% and 68%, respectively, whereas for lymph node metastases a cutoff of 30 mL yielded sensitivity and specificity of 85% and 76%, respectively. Interestingly, this new approach to risk assessment seems to outperform the clinically established

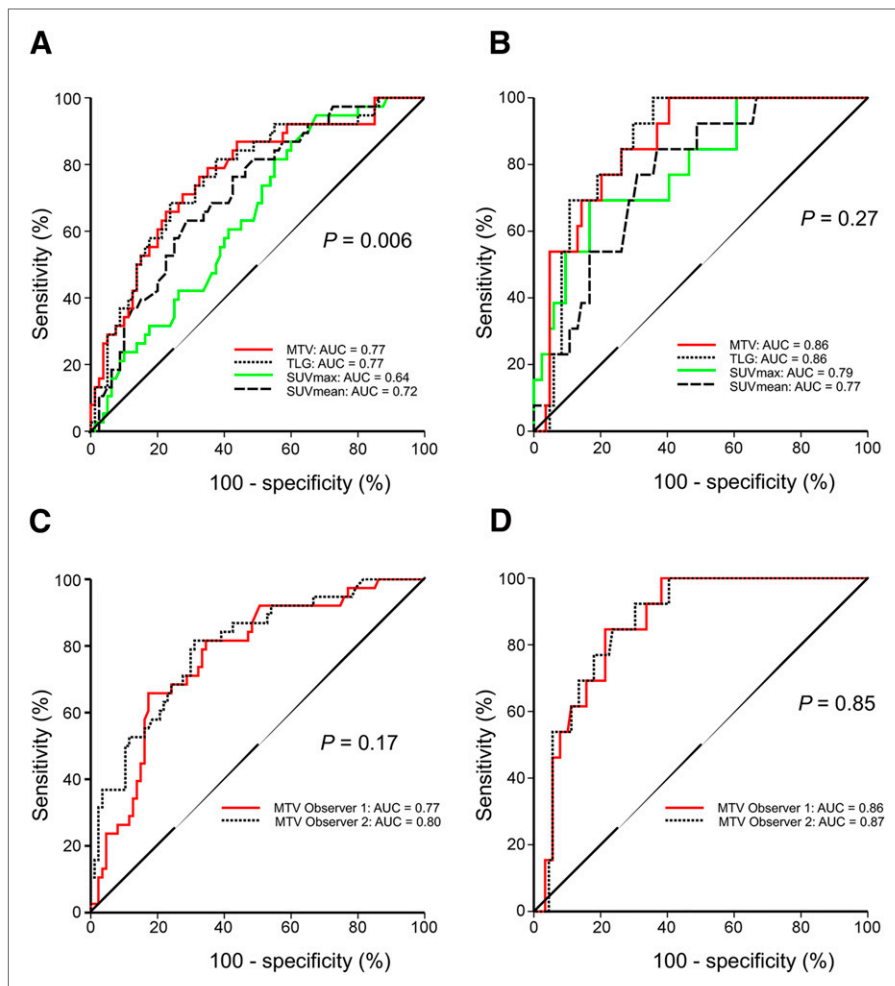


FIGURE 2. Receiver-operating-characteristic curves for various tumor quantifications for prediction of myometrial invasion (A) and lymph node metastases (B) and ROC curves for 2 observers for MTV to predict myometrial invasion (C) and MTV to predict the presence of lymph node metastases (D) in patients with endometrial carcinoma. *P* values refer to test of equal areas under the curve across tumor quantifications. AUC = area under the curve.

method based on histologic subtype and grade in preoperative biopsies, which in this cohort yielded sensitivity and specificity of 47% and 72%, respectively, for deep myometrial invasion and 85% and 66%, respectively, for lymph node metastases. In line with this finding, adjusted for the preoperative biopsy risk assessment, MTV independently predicted deep myometrial invasion

and lymph node metastases (Table 3), suggesting that MTV may improve the preoperative identification of high-risk patients and the ability to tailor surgical and systemic therapies accordingly. Our results are in line with a recent study of 56 endometrial carcinoma patients (23) emphasizing MTV and TLG as significant predictors of several clinicopathologic characteristics and superior to SUV_{max} in differentiating high-risk from low-risk patients. Also two studies of 76 endometrial carcinoma patients each (13,28) suggested that MTV is a promising marker for lymph node metastases and poor outcome. To our knowledge, no previous studies have proposed cutoffs for MTV based on ROC curves predicting deep myometrial invasion and presence of lymph node metastases. As opposed to our proposed cutoff, a recent smaller study of 56 patients proposed a cutoff of 9.4 mL for MTV for differentiation between high-risk and low-risk tumors (based on surgicopathologic assessment). This differing result is possibly explained by a larger proportion of patients with an advanced FIGO stage in the cohort and differing definitions of high- and low-risk groups (23).

All 4 measures for ^{18}F -FDG PET quantification— SUV_{max} , SUV_{mean} , MTV, and TLG—in the present study were independent predictors of deep myometrial invasion and lymph node metastases after adjustment for high risk based on histologic subtype and grade in preoperative uterine biopsies. The prognostic value of SUV_{max} assess-

ment has previously been reported for endometrial carcinomas (19,21,23) ($n = 101, 268, \text{ and } 56$, respectively), but these studies did not adjust for the routinely applied methods of preoperative risk assessment. A recent review, however, concluded that SUV_{max} has limited value in risk stratification, although it may aid in the prediction of patient outcome (16). SUV_{mean} , which has been studied

TABLE 4
Interobserver Variability for Tumor SUV and Metabolic Volume Measurements

Parameter	Mean		Mean difference between 1 and 2	ICC	MDC
	Obs 1	Obs 2			
SUV_{max}	14.2	13.7	0.04 (SD, 1.3)	0.98	2.6
SUV_{mean}	6.0	5.4	0.5 (SD, 0.9)	0.87	2.1
Metabolic volume (mL)	26	38	12 (SD, 36)	0.56	74.1
TLG (g)	177	229	52 (SD, 183)	0.57	72.2

ICC = intraclass correlation coefficient; MDC = minimal detectable change.

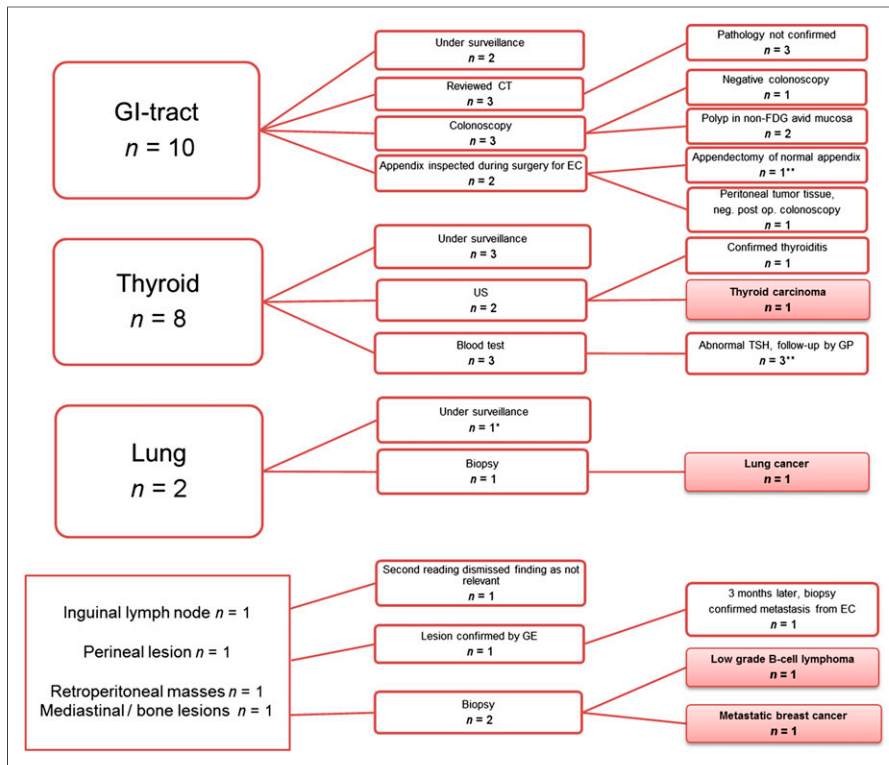


FIGURE 3. Flowchart of significant incidental findings (defined as ^{18}F -FDG uptake with possible therapeutic consequence) on PET/CT in 129 endometrial carcinoma patients. *One lesion did not have increased uptake. **One patient had 2 separate incidental findings. EC = endometrial cancer; GE = gynecologic examination; GI = gastrointestinal; GP = general practitioner; TSH = thyroid-stimulating hormone; US = ultrasound.

less, was found to be associated with FIGO stage, histologic grade, lymphovascular space invasion, and maximum tumor size (similar to SUV_{max}) in a study of ^{18}F -FDG PET/CT in 60 women with endometrial cancer (17). Our findings that MTV and TLG may be helpful in detecting deep myometrial and cervical stromal invasion are also in line with 3 smaller studies (13,18,23) ($n = 76, 84,$ and $56,$ respectively).

Interobserver agreement is a critical factor if any biomarker is to become applicable in clinical routine. In the present study, interobserver agreement was moderate for MTV and TLG and very good for SUV_{max} and SUV_{mean} . This difference was probably due to the subjective steps involved in MTV measurement, where the size of the volume of interest is determined manually in 3 planes. SUV measurements are more robust, as SUV_{max} depends only on including in the volume of interest the single voxel with the highest value. The interobserver reproducibility of PET-assessed parameters has not previously been examined for endometrial cancer but has been examined for other cancer types, with intraclass correlation coefficients of 0.60–1.00 and 0.85–0.97 being reported for SUV_{max} and SUV_{mean} , respectively (29–31), which appears to be in line with our findings. Although not directly comparable to our study because of its assessment of whole-body tumor burden, a study of small-cell lung cancer found a similar low interobserver variability, with concordance correlation coefficients of 0.90 for assessment of whole-body MTV (32). Taken together, our data and current literature on other cancer types support the finding that agreement on PET measurements seems lower for volume-dependent parameters than for

SUV measurements alone. However, the very similar MTV ROC curves for the different observers (Figs. 2C and 2D) suggest that despite some interobserver variability, MTV may represent a robust imaging biomarker for prediction of deep myometrial invasion and lymph node metastases. Furthermore, the observed agreement for MTV is similar to that reported for other radiologic quantitative methods in daily use within the same field, suggesting that the method may be feasible in clinical routine (33,34).

Detection of incidental findings and second primary cancers on ^{18}F -FDG PET/CT is interesting and not previously reported for a population-based endometrial carcinoma cohort. Similar findings have been reported for cohorts with other primary cancer types (35,36), and the prevalence in our material is at a comparable level. The additional work-up generated by the findings is an important factor in evaluating the cost-effectiveness of ^{18}F -FDG PET/CT, since follow-up examinations are costly and often yield negative results. However, 4 synchronous cancers, all of which had a potentially worse prognosis than the primary endometrial cancer, were diagnosed and treated with curative intent. In addition, a precancerous colonic polyp was successfully removed.

Although comprehensive and systematic cost-benefit analyses are difficult in this mixed, casuistic group, we assume that our patients may have particularly benefited from the discovery of incidental pathology on preoperative ^{18}F -FDG PET/CT, leading to intentionally curative treatment that most likely increased their life expectancy and future ability to work.

This study had some limitations; the ROC analyses were conducted a posteriori, and it may be conceivable to prespecify a cutoff by a learning dataset including a smaller number of patients from the same patient population and achieve a priori cutoffs for utter validation (37). However, our patient cohort is presently considerably extended, and we plan to validate the proposed cutoffs in this larger, consecutive patient group.

CONCLUSION

The present study has shown that ^{18}F -FDG PET/CT represents a valuable imaging tool to detect lymph node metastases in endometrial carcinoma patients, and in particular a tool to precisely define patients with a low likelihood of lymph node metastases, in whom lymphadenectomy and adjuvant treatments have no documented survival benefit. All the quantitative parameters assessed were positively correlated with deep myometrial invasion and lymph node metastases. Our proposed approach applying MTV cutoffs outperforms the endometrial biopsy histologic subtyping and grading currently used for preoperative risk stratification.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. This work was supported by the Western Norway Regional Health Authority; Research Funds from the Department of Radiology, Haukeland University Hospital; MedViz (www.medviz.uib.no), a medical imaging and visualization R&D cluster in Western Norway founded by Haukeland University Hospital, the University of Bergen, and Christian Michelsen Research; the Norwegian Research Council; the University of Bergen; the Meltzer Foundation; the Norwegian Cancer Society (Harald Andersen's legacy); MedIm (the Norwegian Research School of Medical Imaging); and the Bergen Research Foundation. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. *Lancet*. 2005;366:491–505.
2. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri: FIGO 26th annual report on the results of treatment in gynecological cancer. *Int J Gynaecol Obstet*. 2006;95(suppl 1):S105–S143.
3. Tejerizo-García A, Jimenez-Lopez JS, Munoz-Gonzalez JL, et al. Overall survival and disease-free survival in endometrial cancer: prognostic factors in 276 patients. *Onco Targets Ther*. 2013;9:1305–1313.
4. Salvesen HB, Haldorsen IS, Trovik J. Markers for individualised therapy in endometrial carcinoma. *Lancet Oncol*. 2012;13:e353–e361.
5. Chan JK, Kapp DS. Role of complete lymphadenectomy in endometrioid uterine cancer. *Lancet Oncol*. 2007;8:831–841.
6. Plaxe SC, Mundt AJ. Overview of endometrial carcinoma. UpToDate website. http://www.uptodate.com/contents/overview-of-endometrial-carcinoma?detectedLanguage=en&source=search_result&search=endometrial+carcinoma&selectedTitle=2%7E150&provider=noProvider. Updated May 28, 2014. Accessed June 10, 2015.
7. Kinkel K, Kaji Y, Yu KK, et al. Radiologic staging in patients with endometrial cancer: a meta-analysis. *Radiology*. 1999;212:711–718.
8. Haldorsen IS, Salvesen HB. Staging of endometrial carcinomas with MRI using traditional and novel MRI techniques. *Clin Radiol*. 2012;67:2–12.
9. Haldorsen IS, Husby JA, Werner HM, et al. Standard 1.5-T MRI of endometrial carcinomas: modest agreement between radiologists. *Eur Radiol*. 2012;22:1601–1611.
10. Sala E, Rockall AG, Freeman SJ, Mitchell DG, Reinhold C. The added role of MR imaging in treatment stratification of patients with gynecologic malignancies: what the radiologist needs to know. *Radiology*. 2013;266:717–740.
11. Gambhir SS. Molecular imaging of cancer with positron emission tomography. *Nat Rev Cancer*. 2002;2:683–693.
12. Chang MC, Chen JH, Liang JA, Yang KT, Cheng KY, Kao CH. ¹⁸F-FDG PET or PET/CT for detection of metastatic lymph nodes in patients with endometrial cancer: a systematic review and meta-analysis. *Eur J Radiol*. 2012;81:3511–3517.
13. Crivellaro C, Signorelli M, Guerra L, et al. Tailoring systematic lymphadenectomy in high-risk clinical early stage endometrial cancer: the role of ¹⁸F-FDG PET/CT. *Gynecol Oncol*. 2013;130:306–311.
14. Horowitz NS, Dehdashti F, Herzog TJ, et al. Prospective evaluation of FDG-PET for detecting pelvic and para-aortic lymph node metastasis in uterine corpus cancer. *Gynecol Oncol*. 2004;95:546–551.
15. Suzuki R, Miyagi E, Takahashi N, et al. Validity of positron emission tomography using fluoro-2-deoxyglucose for the preoperative evaluation of endometrial cancer. *Int J Gynecol Cancer*. 2007;17:890–896.
16. Ghooshkhaneh H, Treglia G, Sabouri G, Davoodi R, Sadeghi R. Risk stratification and prognosis determination using ¹⁸F-FDG PET imaging in endometrial cancer patients: a systematic review and meta-analysis. *Gynecol Oncol*. 2014;132:669–676.
17. Lee HJ, Ahn BC, Hong CM, et al. Preoperative risk stratification using ¹⁸F-FDG PET/CT in women with endometrial cancer. *Nuklearmedizin*. 2011;50:204–213.
18. Shim SH, Kim DY, Lee DY, et al. Metabolic tumour volume and total lesion glycolysis, measured using preoperative ¹⁸F-FDG PET/CT, predict the recurrence of endometrial cancer. *BJOG*. 2014;121:1097–1106.
19. Walentowicz-Sadlecka M, Malkowski B, Walentowicz P, et al. The preoperative maximum standardized uptake value measured by ¹⁸F-FDG PET/CT as an independent prognostic factor of overall survival in endometrial cancer patients. *Biomed Res Int*. 2014;2014:234813.
20. Chung HH, Kang SB, Cho JY, et al. Accuracy of MR imaging for the prediction of myometrial invasion of endometrial carcinoma. *Gynecol Oncol*. 2007;104:654–659.
21. Antonsen SL, Loft A, Fisker R, et al. SUVmax of ¹⁸F-FDG PET/CT as a predictor of high-risk endometrial cancer patients. *Gynecol Oncol*. 2013;129:298–303.
22. Antonsen SL, Jensen LN, Loft A, et al. MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer: a multicenter prospective comparative study. *Gynecol Oncol*. 2013;128:300–308.
23. Kitajima K, Suenaga Y, Ueno Y, et al. Preoperative risk stratification using metabolic parameters of F-FDG PET/CT in patients with endometrial cancer. *Eur J Nucl Med Mol Imaging*. April 2, 2015 [Epub ahead of print].
24. Bai B, Bading J, Conti PS. Tumor quantification in clinical positron emission tomography. *Theranostics*. 2013;3:787–801.
25. Kitchener H. Selective targeting of adjuvant therapy for endometrial cancer: STATEG. Gynecologic Cancer Intergroup website. Published 2013. Accessed June 10, 2015.
26. Kang S, Yoo HJ, Hwang JH, Lim MC, Seo SS, Park SY. Sentinel lymph node biopsy in endometrial cancer: meta-analysis of 26 studies. *Gynecol Oncol*. 2011;123:522–527.
27. Abu-Rustum NR. Update on sentinel node mapping in uterine cancer: 10-year experience at Memorial Sloan-Kettering Cancer Center. *J Obstet Gynaecol Res*. 2014;40:327–334.
28. Chung HH, Lee I, Kim HS, et al. Prognostic value of preoperative metabolic tumor volume measured by ¹⁸F-FDG PET/CT and MRI in patients with endometrial cancer. *Gynecol Oncol*. 2013;130:446–451.
29. Huang YE, Chen CF, Huang YJ, Konda SD, Appelbaum DE, Pu Y. Interobserver variability among measurements of the maximum and mean standardized uptake values on ¹⁸F-FDG PET/CT and measurements of tumor size on diagnostic CT in patients with pulmonary tumors. *Acta Radiol*. 2010;51:782–788.
30. Goh V, Shastry M, Engledow A, et al. Integrated ¹⁸F-FDG PET/CT and perfusion CT of primary colorectal cancer: effect of inter- and intraobserver agreement on metabolic-vascular parameters. *AJR*. 2012;199:1003–1009.
31. Jackson T, Chung MK, Mercier G, Ozonoff A, Subramanian RM. FDG PET/CT interobserver agreement in head and neck cancer: FDG and CT measurements of the primary tumor site. *Nucl Med Commun*. 2012;33:305–312.
32. Liao S, Penney BC, Zhang H, Suzuki K, Pu Y. Prognostic value of the quantitative metabolic volumetric measurement on ¹⁸F-FDG PET/CT in stage IV non-surgical small-cell lung cancer. *Acad Radiol*. 2012;19:69–77.
33. Husby JA, Salvesen OO, Magnussen IJ, et al. Tumour apparent diffusion coefficient is associated with depth of myometrial invasion and is negatively correlated to tumour volume in endometrial carcinomas. *Clin Radiol*. 2015;70:487–494.
34. Ytre-Hauge S, Husby JA, Magnussen IJ, et al. Preoperative tumor size at MRI predicts deep myometrial invasion, lymph node metastases, and patient outcome in endometrial carcinomas. *Int J Gynecol Cancer*. 2015;25:459–466.
35. Tae CH, Lee JH, Choi JY, Min BH, Rhee PL, Kim JJ. Impact of incidental findings on integrated 2-[¹⁸F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in patients with gastric cancer. *Asia Pac J Clin Oncol*. 2015;11:34–40.
36. van Hooij FB, Keijsers RG, Loffeld BC, Dun G, Stadhouders PH, Weusten BL. Incidental colonic focal FDG uptake on PET/CT: can the maximum standardized uptake value (SUVmax) guide us in the timing of colonoscopy? *Eur J Nucl Med Mol Imaging*. 2015;42:66–71.
37. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155:529–536.