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Metabolic tumor volume (MTV) at 18F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F-FDG-PET/CT) improves preoperative identification of high-risk endometrial carcinoma patients

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Short running title: MTV predicts high-risk endometrial cancer

Abstract

Objectives

Prospectively explore the diagnostic value of 2-deoxy-2-[^{18}F]fluoroglucose positron emission tomography/computed tomography (18F-FDG-PET/CT) for preoperative staging in endometrial carcinomas. Investigate if 18F-FDG-PET specific quantitative tumor parameters reflect clinical and histological characteristics.

Methods

Preoperative 18F-FDG-PET/CT was prospectively performed in 129 consecutive endometrial carcinoma patients. Two physicians, blinded for clinical findings and staging results, independently reviewed the images assessing primary tumor, cervical stroma involvement and metastatic spread, and measured tumor standardized uptake value (SUV)max, SUVmean and metabolic tumor volume (MTV) with calculation of total lesion glycolysis (TLG). All parameters were analysed in relation to histomorphological and clinical tumor characteristics. Receiver operating characteristics (ROC) curves for identification of deep myometrial invasion and lymph node metastases were generated and MTV cut-off values for predicting deep myometrial invasion and lymph node metastases were calculated.

Results

Sensitivity (specificity) and accuracy of 18F-FDG-PET/CT for the detection of lymph node metastases were 77-85% (91-96%) and 89-93%, respectively. SUVmax, SUVmean, MTV and TLG were significantly related to deep myometrial invasion, presence of lymph node metastases and high histological grade ($p<0.015$ for all), and independently predicted deep myometrial invasion ($p<0.015$) and lymph node metastases ($p<0.025$) after adjusting for preoperative histological risk (based on subtype and grade) in endometrial biopsies. Optimal cut-off values for

MTV in predicting deep myometrial invasion (20 ml) and presence of lymph node metastases (30 ml), yielded ORs of 7.8 ($p<0.001$) and 16.5 ($p=0.001$), respectively.

Conclusions

18F-FDG-PET/CT represents a clinically valuable tool to evaluate presence of lymph node metastases preoperatively for endometrial carcinoma patients. Applying MTV cut-off values 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 low risk of aggressive disease.

Key words: Endometrial carcinoma, 18F-FDG-PET/CT, cancer staging, metabolic tumor volume, incidental findings

Introduction

Endometrial carcinoma is the most common gynecological 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, cervical stromal invasion and lymph node metastases is applied to tailor primary surgery. Further assessment of histologic type and grade in the hysterectomy specimens and results from the surgical International Federation of Gynecology and Obstetrics (FIGO) staging is 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 post-operative morbidity in low-risk patients (*5*), and reserve radical hysterectomy and/or lymphadenectomy for the ~20% high-risk endometrial carcinoma patients that follow an aggressive course (*4, 6*).

Magnetic resonance imaging (MRI) is presently the preferred imaging method for pre-operative evaluation of endometrial carcinoma patients (*1, 7, 8*) although limitations in accuracy and reproducibility of staging parameters based on MRI have been reported (*8-10*). Positron emission tomography / computed tomography (PET/CT) with 2-^{18}F-Fluoro-2-deoxy-D-glucose (18F-FDG) is an imaging method that combines morphological and physiological imaging techniques, and it is the preferred imaging method for various cancers (*11*). Although several studies have suggested that 18F-FDG-PET/CT can be beneficial preoperatively in endometrial cancer (*12-23*), the role of 18F-FDG-PET/CT for risk-stratification in endometrial carcinoma patients in clinical care is not well defined. Furthermore, the value of various quantitative tumor parameters and the corresponding optimal cut-off values for the prediction of tumor stage and prognosis are largely unexplored.

The aim of the present study is to prospectively explore the diagnostic value of preoperative 18F-FDG-PET/CT for staging purposes in endometrial carcinomas, and to investigate to what extent 18F-FDG-PET-specific quantitative tumor parameters reflect clinical and histological tumor characteristics. To further explore clinical applicability we have assessed interobserver agreements for 18F-FDG-PET/CT staging- and quantitative tumor parameters in relation to the prevalence and significance of incidental findings in the context of prospective and consecutive 18F-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 18F-FDG-PET/CT imaging was performed in 129 prospectively included consecutive endometrial carcinoma patients to evaluate the usefulness of advanced methods for imaging staging in the context of surgical staging and assessment of molecular biomarkers for aggressive disease. The diagnoses were established through preoperative endometrial biopsy and verified in hysterectomy specimens, while stage was assessed according to FIGO 2009 criteria for surgical staging. The images were acquired prospectively and results reported to the responsible clinician together with all relevant preoperative imaging performed. The patients signed informed consent for collection of data and specimens for biomarker studies under institutional review board-approved protocols. Image reading 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 ~1 million inhabitants.

Imaging protocol

PET/CT imaging was performed on a Siemens Biograph 40 True Point scanner. Both PET and low dose CT scans covered a region from the skull to the proximal thigh. The protocol included six hours fasting before image acquisition, and all patients were asked to void before scanning. Intravenous injection of 322-414 MBq was carried out 60-120 min before the CT scan, and the patients were rested in a semi-dark, 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 that were obtained in 3 min/bed, and immediately thereafter, intravenous contrast agent (Iomerol, 350 mg iodine/mL; Bracco Imaging Scandinavia, AB; Gotenburg, Sweden) and negative oral contrast (water) was administrated for the subsequent diagnostic CT scan (120 mV, 240 mAs) covering a region from the meatus of the ear to the proximal thigh. Total scan time was ~25 minutes per patient. Images were reconstructed and stored in axial, coronal and sagittal slices with slice thickness of 3.0-5.0 mm in the department's Picture Archiving and Communication System (PACS) (Agfa Impax 6, Agfa Healthcare BV, Antwerp, Belgium).

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 subspecialized in the field of pelvic imaging as part of the standard reading set-up at our institution.

After use for routine diagnosis, all images were deidentified, processed and reviewed retrospectively and independently by two physicians (JAH and BCR) experienced in both nuclear medicine and radiology, on a Segami Oasis workstation (v. 1.9.4.2; Segami Corporaton Columbia, MD, USA). Both readers had ~ four years' experience with PET-CT prior to the study. They were blinded to clinical data and results of surgical staging, and reported imaging findings

in a standardized form. This registration form included information on tumor avidity and uptake intensity as well as metabolic tumor volume. Information on presence of increased 18F-FDG uptake of 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 18F-FDG uptake was not registered, due to the low resolution of PET signals, perceived to preclude myometrial invasion 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, whereas the diagnostic fusion was used for staging. For the measurements of metabolic tumor volume (MTV) and average standardized uptake value (SUVmean), voxels with SUV >2.5 were included in the volume of interest (VOI) (Fig 1). Total lesion glycolysis (TLG) in the tumour was also estimated using the following equation: TLG = SUV_{mean} * MTV (*24*). For the statistical analyses of continuous variables, the mean of the two observers' measurements was applied.

To achieve a common understanding of the image reading criteria for assessing tumor avidity and uptake intensity as well as metabolic tumor volume, the two observers independently recorded five selected pilot cases in the registration form as a training set, and disagreements and different interpretations were discussed to reach a common understanding of the criteria applied. These five cases were excluded from the data presented in the present cohort.

Surgical staging and clinical outcome

In total, 125 of the 129 (97%) patients included in this study were surgically staged according to the FIGO 2009 criteria; the remaining four patients were considered to be inoperable by the responsible physicians, 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.

For the registration of how the clinical team had dealt with follow-up of incidental findings, the medical records were examined retrospectively ~ one year after the PET-CT scans. All additional work-up due to the reported incidental PET-findings were registered together with results from renewed examinations.

Statistical analyses

PET/CT imaging results suggesting cervical stromal invasion and/or lymph node metastases were compared to the findings in the final histopathological report as reference standard to calculate sensitivity, specificity, accuracy, positive and negative predictive values and number of false positives / negative findings for each observer and for the imaging report. The relationship between quantitative tumor parameters on PET/CT (SUVmax, SUVmean, MTV and TLG) and the clinical and histological tumor characteristics were analyzed by Mann-Whitney U Test, Jonckheera-Terpsta Trend Test and multivariate logistic regression analyses. Intraclass correlation coefficient (ICC) was used to assess the consistency and reproducibility of the quantitative PET/CT parameters, and minimal detectable change (MDC; 1.96 x SEM x $\sqrt{2}$) 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 presence of lymph node metastases. From these analyses, the optimal cut-off values (rounded to cl) for MTV were estimated by aiming for values achieving the best separation between groups by the Youden index. Statistical analyses were performed using SPSS 22.0 (Chicago, IL, USA) and STATA 12.1. All reported p-values were two-sided and considered significant when $p < 0.05$.

Results

Patient characteristics

Mean (median; range) age for the 129 patients studied was 66 (67; 26-88) years and 93% (120/129) of the patients were postmenopausal. Surgical FIGO 2009 staging criteria identified FIGO stage IA in 57% (73/129, tumor invading <50% of the myometrium), FIGO stage IB in 17% (22/129; tumor invading ≥50% of the myometrium) while 1% (1/129) was unclassified stage I. FIGO stage II was detected in 13% (17/129; cervical stromal invasion), FIGO stage III in 9% (12/129; local or regional spread) and FIGO stage IV in 3% (4/129). Amongst the 98 patients with endometrioid subtype, data for grade was available in 92 cases, and reported to be 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). Amongst the four 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 these also had ovarian metastases. All metastases were confirmed by gynaecological examination with ultrasound, MRI (bone metastases), biopsy and/or perioperative inspection.

Simple hysterectomy with bilateral salpingo-oophorectomy (BSO) was delivered to 91% (118/129) patients, seven patients were treated with radical hysterectomy and BSO while four patients underwent palliative procedures (tumor reductive surgery (n=1) or uterine biopsy (n=3). Pelvic lymph node sampling was performed in 75% (97/129), among whom 19% (25/129) also had para aortic lymph nodes removed as a part of the surgical staging procedure. Adjuvant therapy was given to 37% (48/129); chemotherapy in 33% (42/129), pelvic radiation in 3% (4/129) and anti-hormonal treatment in 2% (2/129).

Diagnostic performance of 18F-FDG-PET/CT in preoperative staging

Sensitivity (specificity) for the observers (including the routine clinical report) ranged from 25-33% (74-87%) for detecting cervical stromal involvement and from 77-85% (91-96%) for detecting lymph node metastases while positive (negative) predictive values ranged from 49-65% (85-86%) and 62-76% (97-98%), respectively (Table 1). The four cases with confirmed distant metastases were correctly identified and described by observer 1, observer 2 and in the routine report in two, three and three cases, respectively. In a different patient previously treated for breast cancer, widespread malignant disease (metastases in the lungs, the 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 new localized primary endometrial cancer diagnosed. No false positives were identified based on the PET-CT imaging, yielding a positive predictive value of 100% for both readers.

18F-FDG-PET quantifications measures are associated with surgicopathological findings

Mean (median) SUVmax, SUVmean, MTV and TLG of the uterine tumors were 14.2 (14.1), 5.8 (5.7), 30 (19) ml and 215 (119) g respectively, all significantly higher in tumors microscopically invading ≥50% compared to <50% of the uterine wall, and in tumors with lymph node metastases compared to no lymph node spread (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 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).

SUVmax, SUVmean, MTV and TLG uterine tumor measures significantly predicted deep myometrial invasion and lymph node metastases (all p-values≤0.008; Table 3) also when adjusting for high-risk based on preoperative endometrial biopsy (all p-values≤0.023; Table 3). In contrast, SUVmax, SUVmean, MTV and TLG did not predict presence of cervical stromal involvement (Table 3).

ROC curves showed that MTV had the highest area under curve with AUCs of 0.77 and 0.86 to predict deep myometrial invasion and lymph node metastases respectively (Fig 2a and b). Based on these ROC curves, cut-off value for MTV 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 MTV ≥ 30 yielded an OR of 16.5 (CI 3.4-80.3, $p=0.001$) for lymph node metastases. When adjusting for preoperative biopsy suggesting high risk (non-endometrioid subtype or endometrioid grade 3), MTV ≥ 20 ml yielded an OR of 7.3 (CI 2.9-18.3, $p<0.001$) for deep invasion and MTV ≥ 30 ml 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 (ICC) of 0.56 and 0.57, respectively (Table 4). For SUVmax and SUVmean, the ICC was very good yielding values of 0.98 and 0.87, respectively (Table 4).

Incidental findings

Based on the clinical report, significant incidental findings (defined as 18F-FDG uptake with a possible therapeutic consequence) suggesting additional work-up were reported in 18% (23/129) of the patients. In 17 of the patients, further examinations were performed; leading to an additional cancer diagnosis in four of them (lung cancer, thyroid cancer, low-grade B-cell lymphoma and breast cancer) in addition to colonic polyps in two patients (Figure 3). For the remaining 11 patients, either no pathology was confirmed (six patients), non-malignant pathology was found and treated (thyroiditis or abnormal thyroid function parameters; in four patients), in one patient, the peritoneal 18F-FDG-avid lesion was part of widespread metastatic disease from endometrial cancer confirmed per-operatively, and in one different patient, the 18F-FDG-avid perineal lesion was confirmed as a metastasis from endometrial cancer three months later (Figure 3). Six patients are still under surveillance for their incidental findings.

Discussion

The majority of the typically elderly endometrial carcinoma patients have an excellent prognosis for their cancer disease. In this context, they have been and still are subjected to extensive overtreatment, surgically with lymphadenectomy as staging procedure, and with adjuvant chemo- and radiotherapy, where 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, is proposed in the STATEC (Selective Targeting of Adjuvant Therapy for Endometrial Cancer) trial (*25*). Patients are planned to be randomized to lymphadenectomy versus no lymphadenectomy, followed by adjuvant therapy for the node positive patients subjected to lymphadenectomy versus adjuvant therapy for all patients not subjected to lymphadenectomy. A sentinel node sub study for patients undergoing lymphadenectomy will compare sentinel lymph node mapping to 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 18F-FDG-PET/CT applied as tool to detect lymph node metastases in endometrial carcinomas yielded sensitivities (specificities) of 77-85% (91-96%) and accuracies of 89-93%. The sensitivity is within the higher range compared to most previous studies reporting sensitivities of 60-83% (*12-15, 22*), whereas the specificity is within the lower range compared to previous studies (93-100%) (*12-15, 22*). Accuracy seems quite similar to previously reported figures in the recent literature (90-95%) (*12, 13, 22*). Our ability to compare the staging results from 18F-FDG-PET/CT to sentinel lymph node (SNL) procedures is currently limited, as the true performance of the performance in endometrial carcinomas is not

well established due to small studies and often varying techniques applied (*26*). A recent update after 10 years of experience on SNL mapping in uterine cancer at the Memorial Sloan-Kettering cancer center, concluded that prospective studies are needed to validate the use of SNL mapping in patients with early stage endometrial cancer (*27*). Interestingly, the negative predictive value in the present study was very high (97-98%), confirming previous findings by Criverallo et al reporting NPV of 95% (*13*) and Antonsen et al reporting NPV of 96% (*22*). Thus, the combined high specificity and high NPV, confirms that 18F-FDG-PET/CT presently is the most promising imaging method to reliably exclude presence of lymph node metastases which may be helpful to avoid potentially harmful lymphadenectomy for staging purposes.

The present study also suggests that MTV measurements may represent a new tool to assess deep myometrial invasion and metastatic lymph nodes, and we propose potential cut-off values to aid identification of patients carrying a higher risk of having these two well-established surrogate markers for poor outcome. For deep myometrial invasion applying cut-off of ≥/< 20 ml for MTV yields sensitivity (specificity) of 79% (68%) whereas for lymph node metastases, cut-off of ≥/< 30 ml for MTV yields sensitivity (specificity) of 85% (76%). Interestingly, this new approach to risk assessment using MTV seems to outperform the clinically establishes method based on assessment of histologic subtype and grade in preoperative biopsies which in this cohort yielded sensitivity (specificity) for deep myometrial invasion of 47% (72%) and lymph node metastases of 85% (66%). In line with this, 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 one recent study of 56 endometrial carcinoma patients (*23*), emphasizing MTV and TLG as significant predictors of several clinicopathological characteristics, and superior to SUVmax in differentiating high-risk from low-risk patients. Also two studies of 76 endometrial carcinoma patients in each study (*13, 28*), suggest MTV as a promising marker for lymph node

metastases and poor outcome. No previous studies have, to our knowledge, proposed cut-offs for MTV based on ROC curves predicting deep myometrial invasion and presence of lymph node metastases. As opposed to our proposed cut-off, a recent smaller study of 56 patients, proposes a cut-off value of 9.4 ml for MTV for the differentiation between high-risk and low-risk tumors (based on surgicopathological assessment). This differing result is possibly explained by a larger proportion of patients with advanced FIGO stage in the cohort and unlike definitions of high- and low- risk groups (*23*).

All four measures for 18F-FDG-PET quantifications, SUVmax, SUVmean, MTV and TLG, applied in the present study were found to be independent predictors of deep myometrial invasion and lymph node metastases when adjusting for high-risk based on histological subtype and grade in preoperative uterine biopsies. The prognostic value of SUV max assessment has previously been reported for endometrial carcinomas (n=101, n=268 and n=56) (*19, 21, 23*), but these studies did not adjust for the routinely applied methods for preoperative risk assessment. A recent review, however, concluded that SUVmax has limited value in risk-stratification, although it may aid in the prediction of patient outcome (*16*). SUVmean, which has been less studied, was associated with FIGO stage, histologic grade, lymphovascluar space invasion and maximum tumor size (similar to SUVmax) in a previous study of 18F-FDG-PET/CT in 60 women with endometrial cancer (*17*). Our findings that MTV and TLG may be helpful to detect deep myometrial- and cervical stromal invasion are also in line with three previous smaller studies (n=76, n=84 and n=56) (*13, 18, 23*).

Interobserver agreement is a critical factor for any biomarker in order to become clinically applicable in a routine setting. In the present study this was moderate for MTV and TLG, and very good for SUVmax and SUVmean. This difference is probably due to the subjective steps involved in the metabolic volume measurement, where the size of the VOI is determined manually in three planes. The SUV measurements are more robust, as SUVmax only depends on the one single voxel with the highest value being included in the VOI. No previous studies in

endometrial cancer has assessed the interobserver reproducibility for PET assessed parameters, but for other cancer types, interobserver agreement on PET-assessed tumor parameters have reported ICC of 0.60-1.00 and 0.85-0.97 for SUVmax and SUVmean, respectively (*29-31*), which appears to be in line with our findings. Although not directly comparable to our study due to its whole-body tumor burden assessment, one 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 from other cancer types support that agreement on PET measurements seems lower for volume dependent parameters than the SUV measurements alone. However, the very similar ROC curves of MTV for the different observers (fig. 2 C and D) suggest that in spite of some interobserver variability, MTV may represent a robust imaging biomarker for the prediction of deep myometrial invasion and lymph node metastases. Furthermore, the observed agreement for MTV is similar to that reported for other radiological quantitative methods in daily use within the same field suggesting that the method may be feasible in a routine clinical context (*33, 34*).

Incidental findings and detection of second primary cancers at 18F-FDG-PET/CT is interesting and not previously reported for a population based endometrial carcinoma patient 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 cost-effectiveness of 18F-FDG-PET/CT, since follow-up examinations are costly and often yield negative results. However, four synchronous cancers, all of which had a potentially worse prognosis than the primary endometrial cancer, were diagnosed and treated with curative intent. In addition, one precancerous colonic polyp was successfully removed. Although comprehensive and systematic cost-benefit analyses are difficult in this mixed, casuistic group, we assume that these patients in our study may in particular have benefitted from the preoperative 18F-FDG-PET/CT examinations unraveling

incidental pathology leading to intentionally curative treatment that most likely increased their life expectancy and future working ability.

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

Conclusion

The present study has shown that 18F-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 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 cut-offs outperforms endometrial biopsy histologic subtyping and grading currently used for preoperative risk stratification.

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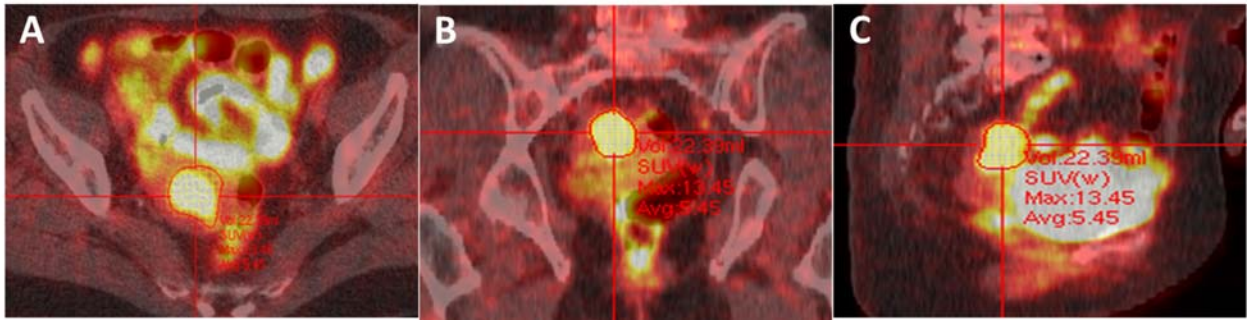

FIGURE 1 18F-FDG-PET/CT images depicting a manually drawn metabolic tumor volume (MTV) in three planes: (A) axial, (B) coronal and (C) sagittal in a 63 year-old woman with FIGO stage 1A endometrioid grade 1 endometrial cancer. In this patient, MTV was 22.4 ml, SUVmax 13.5 and SUVmean 5.5.

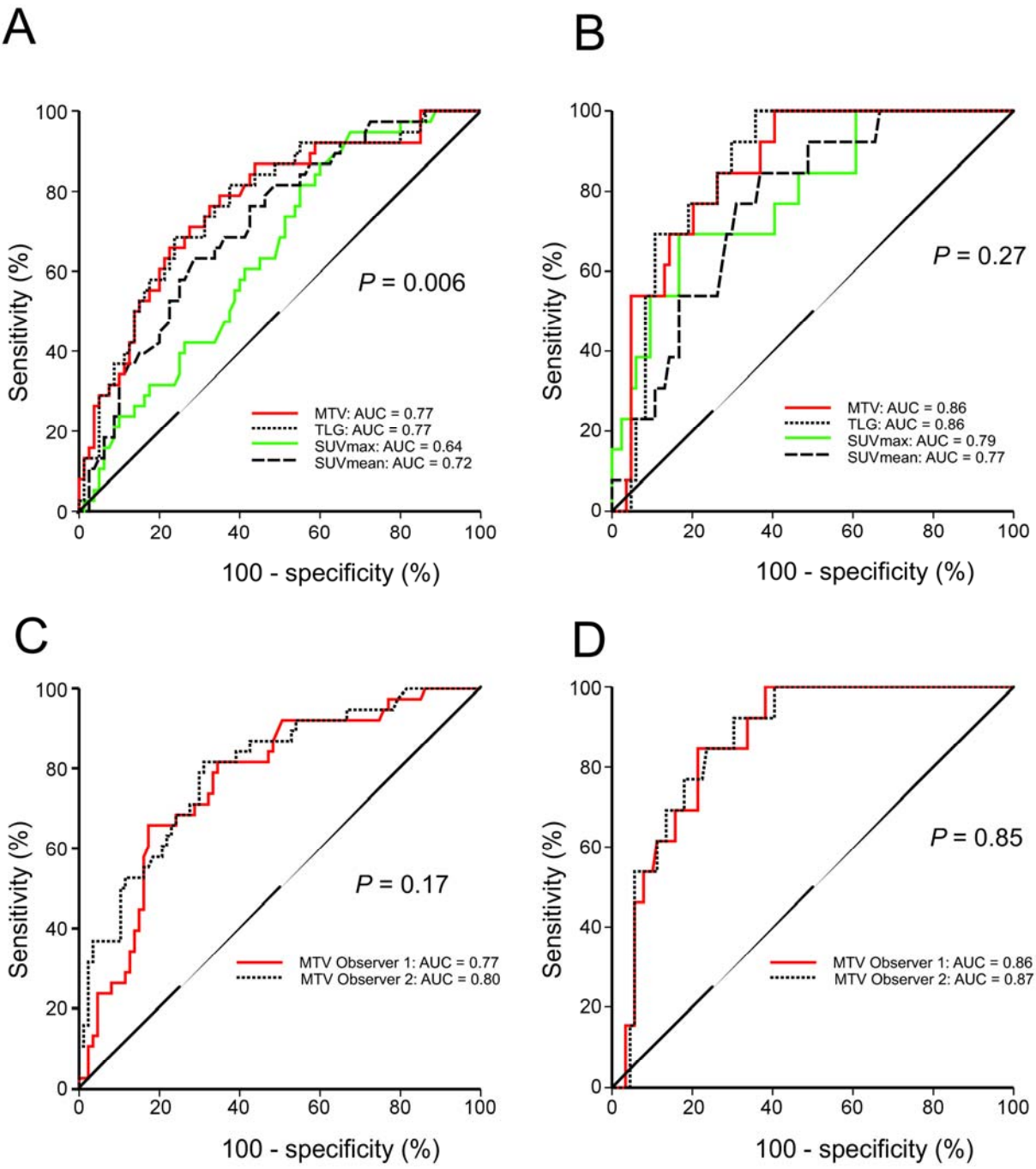

FIGURE 2 Receiver operator characteristic curves for the various tumor quantifications for prediction of (A) myometrial invasion and (B) lymph node metastases and ROC curves for the two observers for (C) metabolic tumor volume (MTV) to predict myometrial invasion and (D) MTV to predict the presence of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

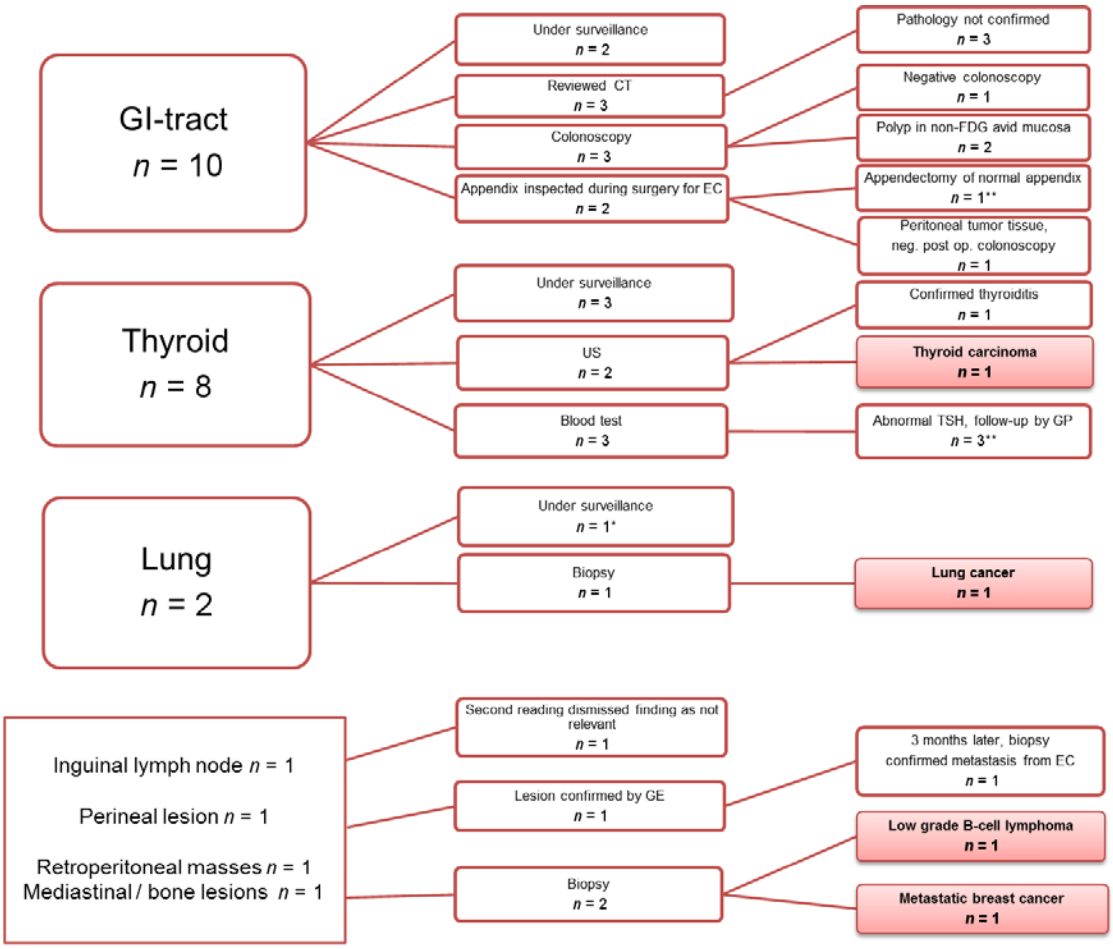

FIGURE 3 Flowchart on significant incidental findings (defined as 18F-FDG uptake with a possible therapeutic consequence) on 18F-FDG-PET/CT in 129 endometrial carcinoma patients. *One lesion did not have increased 18F-FDG uptake. **One patient had two separate incidental findings. EC=endometrial cancer,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

TABLE 1
Sensitivity, specificity, accuracy, positive predictive value, negative predictive value and number of false positive/negative findings for the different observers and routine clinical report for detection of cervical stroma invasion and lymph node metastases from endometrial carcinoma by 18F-FDG-PET/CT compare to the results from surgical staging (reference standard).

	Cervical stroma invasion % (Patient No)	Lymph node metastases % (Patient No)
Sensitivity		
Observer 1	33 (8/24)	77 (10/13)
Observer 2	33 (8/24)	77 (10/13)
Clinical report	25 (6/24)	85 (11/13)
Specificity		
Observer 1	74 (75/102)	91 (81/89)
Observer 2	74 (75/102)	96 (85/89)
Clinical report	87 (89/102)	92 (82/89)
Accuracy		
Observer 1	66 (83/126)	89 (91/102)
Observer 2	66 (83/126)	93 (95/102)
Clinical report	76 (96/126)	91 (93/102)
Positive predictive value		
Observer 1	49 (24/49)	62 (13/21)
Observer 2	49 (24/49)	76 (13/17)
Clinical report	65 (24/37)	65 (13/20)
Negative predictive value		
Observer 1	86 (102/118)	97 (89/92)
Observer 2	86 (102/118)	97 (89/92)
Clinical report	85 (102/120)	98 (89/91)
Number of false-positive/negative findings		
Observer 1	25/16	8/3
Observer 2	2/16	4/3
Clinical report	13/18	7/2

TABLE 2
Measures for quantitative tumor parameters assessed by 18F-FDG-PET/CT in relation to clinical and histological characteristics

		SUVmax		SUVmean		MTV (ml)		TLG (g)	
Variable	*n*	Mean (95% CI)	p*	Mean (95% CI)	p*	Mean (95% CI)	p*	Mean (95% CI)	p*
Myometrial invasion			**.008**		**.000**		**.000**		**.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			.05		.05		**.034**		.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			**.010**		**.002**		**.000**		**.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			.88		1.00		.55		.47
Endometrioid	97	14.3 (12.9-15.6)		5.8 (5.4-6.2)		28 (22-35)		202 (153-252)	
Non-endometrioid	30	14.1 (11.5-16.6)		5.6 (5.0-6.3)		38 (22-55)		259 (146-372)	
Histological grade**			**.013**		**.003**		**.001**		**.002**
Grade 1	51	12.8 (11.1-14.5)		5.3 (4.8-5.8)		20 (14-27)		135 (87-182)	
Grade 2	28	14.7 (11.7-17.8)		6.0 (5.1-6.9)		36 (19-53)		268 (141-394)	
Grade 3	12	19.0 (15.8-22.1)		7.6 (6.3-8.9)		49 (31-67)		370 (243-496)	
DNA ploidy			.66		.40		**.029**		**.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			.10		.26		.96		.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)

*Mann-Whitney U Test for two categories and Jonckheere-Terpsta Trend Test for multiple categories.
CI, confidence interval
Significant p-values are given in bold.

** endometrioid subtype only

TABLE 3
Odds ratios for the different tumor measurements by 18F-FDG-PET/CT to predict deep myometrial invasion, cervical stroma invasion and lymph node metastases. ORs are given unadjusted and adjusted for available preoperative histology risk group information from endometrial biopsies*

	SUVmax	SUVmean	Metabolic tumor volume (ml)	Total lesion glycolysis (g)
	OR [95% CI] (*p*-value)**	OR [95% CI] (*p*-value)**	OR [95% CI] (*p*-value)**	OR [95% CI] (*p*-value)**
Deep myometrial invasion (n=124)				
Unadjusted OR	**1.09 [1.02-1.16] (*p*=0.008)**	**1.44 [1.16-1.79] (*p*=0.001)**	**1.03 [1.02-1.05] (*p*<0.001)**	**1.004 [1.002-1.005] (*p*<0.001)**
Adjusted OR	**1.08 [1.02-1.16] (*p*=0.013)**	**1.40 [1.12-1.75] (*p*=0.003)**	**1.03 [1.01-1.04] (*p*<0.001)**	**1.003 [1.001-1.005] (*p*=0.001)**
Cervical stroma invasion (n=123)				
Unadjusted OR	1.07 [1.00-1.15] (*p*=0.06)	1.22 [0.97-1.52] (*p*=0.09)	1.01 [1.00-1.02] (*p*=0.23)	1.00 [1.00-1.00] (*p*=0.47)
Adjusted OR	1.06 [1.00-1.15] (*p*=0.10)	1.15 [0.91-1.46] (*p*=0.23)	1.003 [0.99-1.02] (*p*=0.63**)**	1.00 [1.00-1.002] (*p*=0.98)
Lymph node metastases (n=101)				
Unadjusted OR	**1.22 [1.09-1.38] (*p*=0.001)**	**1.53 [1.14-2.05] (*p*=0.005)**	**1.03 [1.01-1.05] (*p*=0.001)**	**1.004 [1.002-1.006] (*p*=0.001)**
Adjusted OR	**1.24 [1.08-1.43] (*p*=0.002)**	**1.51 [1.07-2.13] (*p*=0.021)**	**1.02 [1.005-1.04] (*p*=0.013)**	**1.003 [1.001-1.005] (*p*=0.008)**

* Preoperative endometrial biopsy indicating non-endometrioid subtype or endometrioid grade 3.
**Logistic regression analysis.
OR, odds ratio

TABLE 4

Interobserver variability for tumor SUV and metabolic volume measurements

	Mean		Mean difference (SD)		
	Obs 1	Obs 2	Obs 1/2	ICC	MDC
SUVmax	14.2	13.7	0.04 (1.3)	0.98	2.6
SUVmean	6.0	5.4	0.5 (0.9)	0.87	2.1
Metabolic volume (ml)	26	38	12 (36)	0.56	74.1
Total lesion glycolysis (g)	177	229	52 (183)	0.57	72.2

ICC, intra-class correlation; MDC, minimal detectable change; SD, standard deviation