Evaluation of FDG–PET for Detecting Lymph Node Metastasis in Uterine Corpus Cancer

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Abstract. *Background: In order to decrease surgery-related morbidity, we evaluated the reliability of the evaluation of lymph node metastasis in patients with uterine corpus cancer by positron-emission tomography (PET) with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) before surgical staging. Materials and Methods: Patients with newly diagnosed uterine corpus cancer scheduled for surgical staging, including lymphadenectomy, underwent PET imaging within 30 days before surgery. PET results and postoperative histopathology were compared for each patient and each nodal site. Sensitivity, specificity, positive and negative predictive value (PPV/NPV) as well as accuracy of FDG–PET in predicting nodal disease was determined by joined meta-analysis of the present data and the data available in the literature. Results: Of 21 patients examined, 13 patients were eligible to enter this pilot study. Only one patient had lymph node metastasis, which was preoperatively detected by FDG–PET scan. Additionally, another patient was considered to have lymph node metastasis according to increased focal FDG uptake; however, all lymph nodes were free of malignant disease upon final pathology. In contrast, all other patients without lymph node metastasis upon final pathology showed negative preoperative FDG–PET scans. The meta-analysis yielded a sensitivity, specificity, PPV, NPV and accuracy of 0.53, 0.91, 0.57, 0.90 and 0.84, respectively. Conclusion: In patients with uterine corpus cancer, FDG–PET had an insufficient positive predictive value in detecting lymph node metastases, indicating that this method cannot replace surgical staging. However, due to its high NPV, FDG–PET might be beneficial in selected patients who are poor candidates for surgical staging.*

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In accordance with the International Federation of Obstetrics and Gynecology (FIGO), endometrial cancer has been staged surgically since 1988. Such a staging procedure includes an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, as well as a pelvic and para-aortic lymphadenectomy. However, the management of women with endometrial cancer in terms of the necessity for a full lymphadenectomy is growing more complex in light of two recently published large randomized controlled trials, neither of which have been able to demonstrate a survival advantage for women who did undergo a systematic pelvic lymphadenectomy compared to women who did not (1, 2).

Even if performing a systematic lymphadenectomy does not seem to have an impact on survival, the information about the lymph node status is of important value, since lymph node involvement, including either pelvic or para-aortic lymph nodes, results in a worse prognosis (3). Moreover, a greater use of complete surgical staging is accompanied by a marked decrease in the use of adjuvant treatment reducing potential morbidity (4). On the other hand, performing a systematic lymphadenectomy entails a significant morbidity related to the procedure, with up to 31% combined postoperative early and late complications being reported in one of the above randomized trials (1).

In light of these pros and cons for performing a systematic lymphadenectomy in all patients with endometrial cancer, having a preoperative method to assess lymph node status would help to tailor optimal surgical management and adjuvant therapy when needed. Unfortunately, conventional imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) are unreliable in detecting pelvic and/or para-aortic lymph node involvement (5-7).

Like the majority of malignant neoplasms, endometrial cancer demonstrates an increased rate of glycolysis. Positron-emission tomography (PET) with the radioactive glucose analog 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) exploits this metabolic characteristic of malignant tissue to identify tumor foci. Over the last decade, FDG-PET has become an established method for imaging of different gynecological tumors (8).

Table I. *Stage and pathologic characteristics in patients with uterine corpus cancer undergoing surgical staging after a pre-operative FDG-PET.*

FIGO stage	
IA	0
IB	10
IC	2
II	0
III	1
IV	0
Histology	
Endometrioid adenocarcinoma	12
Papillary serous	1
Clear cell	0
Others	0
Grade	
G1	3
G2	7
G3	3
Lymph nodes removed	
Median [±SD]	16 [±6]
Pelvic	181
Para-aortic	4

To our knowledge, five studies so far have tested the reliability of FDG–PET and FDG–PET/CT in the preoperative assessment of the nodal status in patients with endometrial cancer (9-13). These studies have been able to demonstrate a good specificity of between 87% and 100%; however, in terms of the sensitivity, the results varied between 0 and 100%.

With respect to these conflicting results, we conducted a prospective study of the evaluation of preoperative FDG PET scan for the detection of lymph node metastasis in patients with newly diagnosed uterine corpus cancer.

Materials and Methods

All patients were evaluated with history, physical examination, routine laboratory tests, endometrial biopsy or dilatation and curettage, and chest radiography. If advanced disease was suspected, an additional CT of the pelvis and/or abdomen was performed.

PET imaging was carried out within 30 days prior to surgery, in most cases, the day before the operation. Scans were acquired on a CTI ECAT 922/47 tomograph in three-dimensional mode 60 min after intravenous injection of 387±61 MBq FDG and 20 mg furosemide. Reconstruction was by iterative reconstruction and datasets were fully corrected for random and scatter coincidences and photon attenuation using a $^{68}Ge/^{68}Ga$ transmission scan. Reconstructed FDG-PET images were analyzed on screen using maximum intensity projections and orthogonal cross-sectional display by an experienced nuclear medicine physician, blinded for clinical information and any additional imaging techniques of the patient. The location of any abnormal FDG-uptake was recorded prospectively, however, this was not communicated to the surgeon. Due to the proceeding gynecological intervention (see above) the primary tumor was not evaluated as (near-)total removal of the primary tumor and inflammatory changes may result in false-negative and false-positive findings.

Surgery was performed by one of the attending gynecological oncologists and included a total abdominal hysterectomy, bilateral salpingo-oophorectomy and peritoneal cytology, as well as a systematic bilateral pelvic lymphadenectomy. Systematic bilateral pelvic lymphadenectomy included the removal of all lymph nodes around the external iliac and common iliac vessels as well as from the obturator fossa. In cases of high-risk histology (papillary serous and/or clear cell), para-aortic lymph node sampling was additionally performed.

According to the guidelines of the German Society for Obstetrics and Gynecology (DGGG, http://www.uni-duesseldorf.de/AWMF/ll/032-034.htm#7), lymphadenectomy was omitted in cases of well-differentiated tumor (Grade 1) and absence of deep myometrial invasion on frozen section (pT1a/b).

After surgery, the results of FDG-PET were correlated with the pathological findings on a patient-by-patient basis. The sensitivity, specificity, positive (PPV) and negative predictive value (NPV), as well as accuracy of FDG-PET in predicting lymph node metastasis were determined.

Results

Overall, 21 patients with histologically confirmed endometrial cancer were enrolled into the study. In 8 patients, a systematic lymphadenectomy was omitted due to a well-differentiated tumor grading and early-stage disease. Thus, these patients had to be excluded from the final analysis.

The baseline characteristics of the remaining 13 patients are shown in Table I. A total of 181 lymph nodes were removed, with a median removal of 16 lymph nodes per patient (Table I).

The correlation of FDG-PET results with pathological findings is shown in Table II and compared in a meta-analysis with the present data.

Only one patient had extensive disease spread to the pelvic lymph node region which was correctly identified by a higher FDG uptake in the preoperative PET scan (n=1 true-positive). However, PET scan of another patient showed a focus of increased FDG uptake in the pelvic lymph node region. All lymph nodes in this region were free of disease upon final pathology (n=1 false-positive). All other PET scans gave true negative results (n=11; no false-negative result).

Given the limited number of patients and of affected lymph nodes in the present study, we conducted a meta-analysis including the present data and the data from the literature on a patient basis. The results of the meta-analysis are given in Table II for three studies using a stand-alone PET scanner [58 patients in total, 9 (*i.e.* 16%) patients with lymph node metastasis], three studies using a combined PET/CT scanner [105 patients in total, 21 (20%) patients with lymph node metastasis] and for the pooled data of all six studies [163 patients in total, 30 (18%) patients with lymph node metastasis].

Table II. *Meta-analysis of diagnostic accuracy of positron emission tomography using ^{18}F-fluorodeoxyglucose in detecting malignant lymph node metastases in patients with uterine corpus cancer.*

Study characteristic	No. of patients	Sensitivity	Specificity	Accuracy	PPV	NPV
PET						
Horowitz *et al*., 2004 (9)	19	0.67 (2/3)	0.94 (1/16)	0.89 (17/19)	0.67 (2/3)	0.94 (15/16)
Suzuki *et al*., 2007 (10)	26	0.00 (0/5)	1.00 (21/21)	0.81 (21/26)	n/a (0/0)	0.81 (21/26)
Klar *et al*., 2009	13	1.00	0.92	0.92	0.50	1.00
Total (95% CI)	58	0.33 (0.14-0.49)	0.96 (0.92-0.99)	0.86 (0.80-0.91)	0.60 (0.25-0.87)	0.89 (0.85-0.91)
PET CT						
Kitajima *et al*., 2008 (13)	40	0.50	0.87	0.78	0.56	0.84
Park *et al*., 2008 (11)	53	0.63	0.87	0.83	0.45	0.93
Nayot *et al*., 2008 (12)	12	1.00	1.00	1.00	1.00	1.00
Total (95% CI)	105	0.62 (0.44-0.76)	0.88 (0.84-0.92)	0.83 (0.76-0.89)	0.57 (0.40-0.70)	0.90(0.86-0.94)
PET and PET CT						
Combined (95% CI)	163	0.53 (039-0.66)	0.91 (0.88-0.94)	0.84 (0.79-0.89)	0.57 (0.42-0.71)	0.90 (0.87-0.92)

PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

Discussion

FDG-PET is used to map the increased metabolic activity of malignant cells. Thus, as a functional imaging modality, it provides attractive complementary information to structural imaging modalities such as CT and MRI in patients with gynecological malignancies. Since performing a systematic lymphadenectomy in every patient does not seem to have an impact on overall survival (1-2), one of the major goals of preoperative assessment should be to identify individual patients who have a negligible risk for lymph node metastasis in order to omit the morbidity of extensive retroperitoneal surgery. Against this background, we investigated whether FDG-PET may contribute to risk stratification and appropriate selection of patients.

In our patients, only one patient had lymph node metastasis. In line with this, the fraction of patients with lymph node involvement was also fairly low in earlier studies on this topic (15-25% of patients) (9-13). Therefore, we decided to summarize the available evidence regarding the diagnostic accuracy of FDG-PET in detecting malignant lymph node metastasis by a meta-analysis which is shown in Table II. This analysis shows that FDG might be a suitable technique for risk stratification of patients who are poor candidates for surgical staging, since in our series, as well as according to the pooled data for PET and PET/CT, or the combined results, the NPV was fairly high, with a reasonable confidence interval. This high NPV seems to be of utmost importance when tailoring patients safely and deciding whether to rely on pre-operative FDG–PET scan to rule out lymph node metastasis, or alternatively, to perform a systematic lymphadenectomy to evaluate for lymph node metastasis by histology. According to the fraction of patients with lymph node involvement in these studies (*i.e*. pre-test likelihood of 18%), about 1 out of 5 patients will present with lymph node metastasis. In this setting, a negative FDG-PET has an NPV of about 90%, thus reducing the chance of missing a lymph node metastasis to 1 out of 10 patients if surgical staging is omitted, which appears to be acceptable given the questionable benefit and high morbidity of this procedure, especially in poor candidates for surgery.

Furthermore, it is of note that our results of 100% NPV are in concordance with the study by Horowitz and co-workers, who had only one false-negative result regarding lymph node assessment. However, in this patient, the primary uterine tumor was a malignant mixed mullerian tumor, which is a completely different entity itself due to its sarcomatous component (9).

Regarding the sensitivity of a preoperative FDG-PET scan in detecting lymph node metastasis in patients with endometrial cancer, the results of the published series are completely diverse. In comparison to previously published series, our results revealed a relatively high sensitivity (100% present study *vs*. 0 and 100% earlier studies) (9-10). These variable results in terms of sensitivity, however, are only of limited value since all series suffer from the low frequency of lymph node metastasis upon final histology. Suzuki and co-workers explain their low sensitivity by the fact that all of the missed lymph node metastases were less than 1 cm in diameter, concluding that FDG-PET is not able to detect microscopic nodal involvement. In this respect, it is of note that our meta-analysis demonstrates that the sensitivity for detecting lymph node metastasis was almost twice as high in studies using hybrid PET/CT systems in comparison to those relying on

stand-alone PET (62 % *vs*. 33%). This progress to improve the sensitivity of identifying metastatic lymph nodes in endometrial cancer patients provided by PET/CT (11-15) may be explained by two factors: On one hand, the PET component of most PET/CT systems tend to be newer generation systems with improved spatial resolution and system sensitivity compared to older, stand-alone, PET systems. On the other hand, and probably most importantly, the combined functional and structural information provided by hybrid PET-CT allows the metabolic activity of small and, according to CT criteria, unsuspicious lymph nodes (<1 cm), which would have been missed by PET alone (increase in sensitivity), to be systematically judged. At the same time, specificity is kept high since a false-positive finding due to focal radioactivity accumulation in the urinary system or bowel can be readily identified.

An alternative approach to reduce the morbidity associated with a systematic lymphadencetomy is the usage of a sentinel lymph node (SLN) detection concept in patients with endometrial cancer. The so-called SLN is the first lymph node which receives lymphatic drainage from the primary tumor, and theoretically represents the lymph node status in the same region. Therefore, an SLN which is negative for metastasis would predict the absence of metastasis in other regional nodes, and thus an extensive resection of all lymph nodes could be omitted. In this respect, Abu-Rustum and co-workers have recently published their promising results in a small series of patients with well differentiated endometrial cancer (16). By using a combined intracervical ^{99m}Tc microsulfur colloid and blue-dye injection technique in 42 patients, an SLN was identified in 86% of the cases. There were no false-negative cases and the sensitivity of the SLN procedure in the 36 patients who had an SLN identified was 100%.

According to our data and the literature, the strength of preoperative FDG-PET for detecting lymph node metastasis in patients with endometrial cancer is its high NPV, which may allow the safe omission of lymphadenectomy in selected patients who are poor surgical staging candidates. However, even after pooling the available evidence, the results suggest that a larger investigation specifically focusing on the detection of microscopic lymph node involvement is warranted.

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