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Para-aortic Lymph Node Invasion in High-risk Endometrial Cancer: Performance of ^{18}FDG PET-CT

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Abstract. *Aim: ^{18}F-Fluorodeoxyglucose positron-emission tomography integrated with computed tomography (^{18}FDG PET-CT) is a non-invasive examination that could be helpful for the management of endometrial cancer. This study investigated the performance of ^{18}FDG PET-CT in assessing para-aortic (PA) lymph-node involvement in high-risk endometrial cancer. Materials and Methods: This was a retrospective, single-center study carried out between 2009 and 2018. The inclusion criteria were high-risk and locally advanced type 1 or 2 endometrial cancer with ^{18}FDG PET-CT before PA lymphadenectomy. Results: During the study period, among 142 patients with high-risk endometrial cancer, 35 patients (24.6%) underwent ^{18}FDG PET-CT followed by PA lymphadenectomy. In 25% of cases, PA lymphadenectomy was not performed due to the discovery of metastasis. ^{18}FDG PET-CT had a sensitivity of 50%, a specificity of 100%, a positive predictive value of 100%, a negative predictive value of 75%, accuracy of 80% and an area under the curve of 0.75 for the evaluation of PA involvement. Conclusion: According to its high specificity in PA lymph-node evaluation, a positive PET scan might allow PA lymphadenectomy to be avoided.*

Endometrial cancer is the fourth most frequent cancer in women, with more than 8,000 cases per year in France (1). A knowledge of lymph-node status and International Federation of Gynecology and Obstetrics (FIGO) stage is necessary to establish the most appropriate treatment strategy. The risk of lymph-node involvement is strongly correlated with the characteristics of the tumor, and depends on its histological type, grade, the degree of local extension (myometrium and cervical stroma), and the presence of lymphovascular space invasion (2). Since the European Society for Medical Oncology (ESMO) congress of 2009 (3) and the publication of the French National Institute of Cancer (INCA) recommendations in 2010 (4), para-aortic lymphadenectomy (PAL) has been recommended for stage I tumors of histological type 1 (endometrioid adenocarcinoma) with a high risk of recurrence (stage IB and grade 3, or with the presence of lymphovascular space invasion, regardless of grade), for tumors of stage II and above, and for histological type 2 tumors (clear-cell carcinoma, papillary serous carcinoma, and carcinosarcoma) of all stages.

PAL is a surgical procedure associated with non-negligible morbidity, particularly in elderly patients with associated comorbid conditions (5). Its therapeutic impact on survival is a matter of debate (6). Knowledge of pelvic and para-aortic (PA) lymph-node status guides therapeutic decisions, determining whether there are indications for more or less extensive radiotherapy and systemic treatment (7). The PORTEC-3 study showed that adjuvant chemotherapy, in addition to radiotherapy, was beneficial in stage III high-risk endometrial cancer (8).

^{18}F-Fluorodeoxyglucose positron-emission tomography integrated with computed tomography (^{18}FDG PET-CT) is a non-invasive examination that can modify the management of endometrial cancer. It was cited in the 2016 INCA and ESMO guidelines as an option (3, 4). It is widely used in the management of locally advanced cervical cancer (9, 10). ^{18}FDG PET-CT may help clinicians decide whether or not to perform lymphadenectomy in cases of endometrial cancer with an indication for PAL. Few studies have evaluated its potential utility for lymph-node staging in endometrial cancer.

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Key Words: Endometrial cancer, PET-CT, para-aortic, lymphadenectomy.

We investigated the performance of ^{18}FDG PET-CT for assessing PA involvement in high-risk type 1 and 2 endometrial cancer.

Materials and Methods

Patients. We performed a retrospective, single-center study to evaluate the diagnostic performance of preoperative ^{18}FDG PET-CT for assessing PA lymph-node involvement in high-risk and advanced endometrial cancer at Limoges University Hospital between 2009 and 2018. The inclusion criteria were high-risk and locally advanced type 1 or 2 endometrial cancer and the performance of ^{18}FDG PET-CT before PAL. Patients with recurrent cancer or on neoadjuvant chemotherapy were excluded.

PET-CT was not performed in patients for whom no treatment was planned due to poor general condition, or in patients for whom stage IVB disease had already been demonstrated by standard imaging.

The following data were collected: Age at diagnosis, body mass index (BMI), positivity or negativity of preoperative ^{18}FDG PET-CT for PA lymph nodes, positivity or negativity of preoperative magnetic resonance imaging (MRI) for PA lymph nodes, surgical approach, and pathology findings (histological type, grade, presence of vascular emboli, FIGO stage, number of lymph nodes involved, and the number of lymph nodes removed). We compared the pathology results for PAL with preoperative MRI and ^{18}FDG PET-CT findings.

All treatment decisions were taken at multidisciplinary medical team meetings, in accordance with the recommendations of the INCA and ESMO, according to the general condition of the patient.

^{18}FDG PET-CT. Patients underwent ^{18}FDG PET-CT on a SIEMENS Symbia T6 machine (from January 2009 to August 2015) or a SIEMENS Biograph mCT20 machine (since November 2015) at the Department of Nuclear Medicine, University Hospital Center of Limoges, Limoges, France. The results were interpreted by a senior nuclear physician. A second centralized reading was then performed for each ^{18}FDG PET-CT scan.

The patients received an injection of ^{18}FDG (5 MBq/kg). All patients fasted for at least 6 hours before the examination. Peripheral glucose concentration was systematically evaluated. ^{18}FDG PET-CT was performed only in patients with a blood glucose concentration below 140 mg/dl. PET recordings were acquired 60 to 115 minutes after the injection. Image quality and diuresis were increased by injecting 0.5 mg of furosemide per kilogram body weight (40 mg maximum) intravenously into the patients 45 minutes before data acquisition.

Lymph nodes were considered to be positive on ^{18}FDG PET-CT if FDG uptake was greater than that of the surrounding tissue in a structure corresponding to a lymph node of more than 5 mm in diameter localized on CT sections.

MRI. MRI was performed with a 1.5 Tesla system (Philips Achieva Best, Eindhoven, NL) and pelvis- and body-phased array antennas. For transaxial and transverse sections of the pelvis and abdomen, and for sagittal and coronal sequences, T2 spin -echo, T1 spin-echo, diffusion and T1 spin-echo with intravenous gadolinium injection, and fat-suppression sequences were used, with a slice thickness of 3 mm. The criterion for lymph-node involvement on MRI was a short diameter of greater than 8 mm for pelvic lymph nodes and 10 mm for PA lymph nodes.

Pathology analysis. Lymph nodes were evaluated macroscopically and counted by a pathologist. Pathology analysis was performed according to the standard procedure, with hematoxylin-eosin-saffron staining. Slides giving false-negative results on ^{18}FDG PET-CT were reread.

Surgical protocol. The patients underwent laparotomy, robot-assisted laparoscopy, or retro- or transperitoneal laparoscopy. The choice of approach was based on BMI, age, comorbid conditions and FIGO stage. PAL extended from the left renal vein to the iliac bifurcations (including the promontory and common iliac vein). The internal, external, and obturator iliac lymph nodes were considered to lie within the zone of pelvic lymphadenectomy.

Statistical analysis. All the data were recovered from a computerized database (Filemaker Pro 13.0v5®, FileMaker®, Inc., Santa Clara, CA, USA). Quantitative data are expressed as means and ranges, and qualitative data are expressed as percentages. The diagnostic performance of ^{18}FDG PET-CT and MRI was assessed by calculating sensitivity specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. The gold standard evaluation was the definitive pathological examination of the PA lymph nodes.

Our main objective was to study the performance of ^{18}FDG PET-CT for evaluating PA involvement in high-risk or locally advanced endometrial cancer. Our secondary objective was to study its performance as a function of histological type.

Student's *t*-test was used for comparisons of continuous variables and Fisher's exact test was used for comparisons of categorical variables. Comparisons of two areas under the receiver operating characteristics curve (AUC) were performed with the comproc or roccomp module of STATA®. McNemar or Fisher's exact test was used to compare the intrinsic characteristics of a test (according to the independence or non-independence of the samples). All analyses and calculations were performed with STATA 15.1 SE® software (StataCorp, College Station, TX, USA). Values of $p<0.05$ were considered statistically significant.

Results

Between 2009 and 2018, 273 patients were treated for endometrial cancer at Limoges University Hospital, 142 (52%) of whom had cancer with a high risk of recurrence or at an advanced stage. In total, 81 (57%) out of these 142 patients underwent ^{18}FDG PET-CT during their initial examinations, and 42 (52%) of these patients did not undergo PAL (Figure 1). Among the 142 patients with high-risk endometrial cancer, 61 (43%) did not undergo ^{18}FDG PET-CT due to the optional nature of this examination or because advanced-stage cancer was identified on standard imaging examinations.

PAL was not performed in 20 (25%) out of the 81 patients who underwent ^{18}FDG PET-CT due to the discovery of metastasis. Four out of the 39 patients who underwent PAL were excluded from the study (three because they received neoadjuvant chemotherapy and one due to recurrence) (see Figure 1).

The data for the 35 patients who underwent ^{18}FDG PET-CT followed by PAL are presented in Table I. Fourteen (40%) had type 1, and 21 (60%) had type 2 tumors. PAL findings were

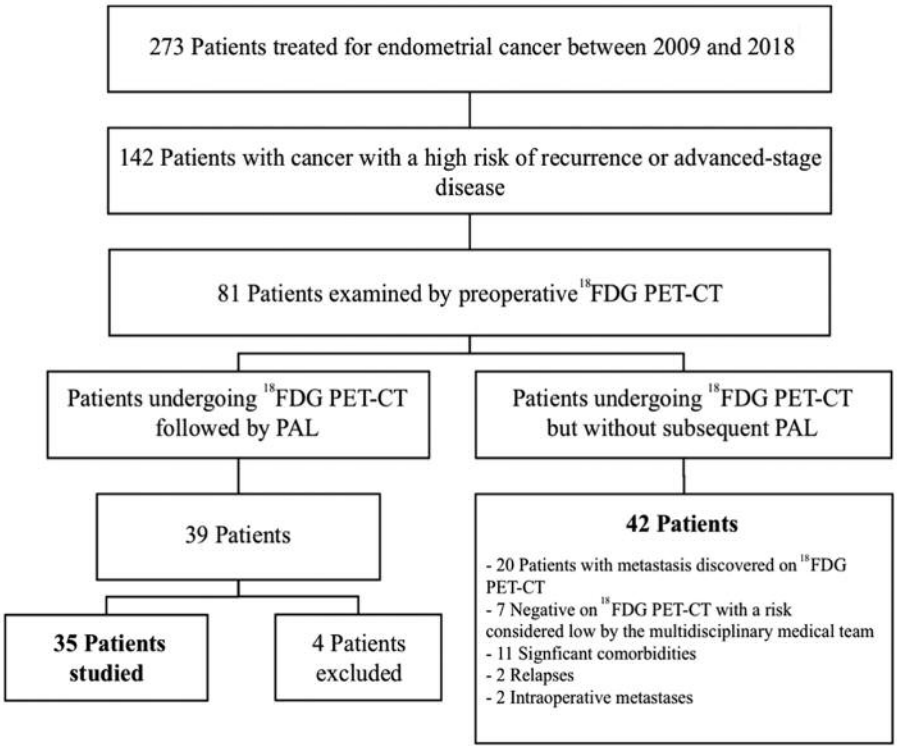

Figure 1. *Flowchart of the study. ^{18}FDG PET-CT: ^{18}F-Fluorodeoxyglucose positron-emission tomography integrated with computed tomography. PAL: para-aortic lymphadenectomy.*

positive for 14 patients (40%). The mean number of positive lymph nodes was three (range=1-12) for these patients. Eleven out of the 14 patients with positive PAL results (78.6%) had type 2 tumors (eight papillary serous carcinomas, one clear-cell carcinoma, and two carcinosarcomas). The PA invasion rate for type 1 cancer was 21.4% and that for type 2 cancer was 52.4% (p=0.09). The mean number of positive lymph nodes in cases of PA involvement was 2.7 for those with type 1 and 3.2 for those with type 2 (p=0.8) tumors. PA lymph-node involvement was associated with pelvic lymph-node involvement in half of the cases. FIGO stage distribution differed significantly between the two histological types after complete surgical staging, especially for tumors advanced beyond stage 3 (p=0.007). No significant differences in overall characteristics were found between the two groups.

^{18}FDG PET-CT had a sensitivity of 50%, specificity of 100%, PPV of 100%, NPV of 75%, an accuracy of 80%, and an AUC of 0.75 for the evaluation of PA involvement.
MRI had a sensitivity of 33.3%, specificity of 100%, PPV of 100%, NPV of 70.4%, an accuracy of 74.2%, and an AUC of 0.67 for the evaluation of PA involvement. The difference in diagnostic performance between the two examinations was not significant (p=0.13).

Table II shows a comparison of the performance of ^{18}FDG PET-CT for tumors of different histological types. The differences in sensitivity and in AUC according to tumor type were not significant (p=0.500 and p=0.565, respectively).

Table III presents the main characteristics of the ^{18}FDG PET-CT scans. The mean number of positive lymph nodes was two (range=1-5) for the seven patients with false-negative ^{18}FDG PET-CT results. Six of the false-negative tumors were of type 2 (four papillary serous carcinomas, one clear-cell carcinoma, and one carcinosarcoma), including three tumors with a preoperative stage of 1A. The mean lesion size for the 15 positive lymph nodes was 2.7 mm, but three lymph nodes had lesions of more than 5 mm in diameter.

Discussion

^{18}FDG PET-CT appears to be useful for evaluating PA involvement in high-risk or locally advanced endometrial cancer, given its high specificity. Its performance appeared to vary with histological type. Sensitivity and accuracy appeared lower for type 2 than for type 1 tumors, but this difference was not statistically significant: 66.7% and 92.9% for type 1, and 45.5% and 71.4% for type 2, respectively.

Our results are similar to the published results presented in Table IV, which summarizes the series focusing specifically on the performance of ^{18}FDG PET-CT for the assessment of PA lymph nodes.

Table I. *Patient characteristics according to histological type.*

Characteristic	Type 1 (N=14)	Type 2 (N=21)	Total (N=35)	*p*-Value
Age at diagnosis, years				
Mean (range)	62.7 (49-78)	64.3 (43-76)	63.7 (43-78)	0.617*
BMI, kg/m^2				
Mean (range)	28.6 (21.1-36.3)	25.4 (14.4-38.6)	26.6 (14.4-38.6)	0.101*
Histological type, n (%)				
Endometrioid	14 (100)	NA	14 (40.0)	<0.001#
Clear cell	NA	5 (23.8)	5 (14.3)	
Carcinosarcoma	NA	4 (19.1)	4 (11.4)	
Papillary serous	NA	12 (57.1)	12 (34.3)	
FIGO stage (after surgery), n (%)				
IA	1 (7.1)	6 (28.6)	7 (20.0)	0.007#
IB	2 (14.3)	2 (9.5)	4 (11.4)	
II	2 (14.3)	0 (0.0)	2 (5.7)	
IIIA	3 (21.4)	0 (0.0)	3 (8.6)	
IIIB	0 (0.0)	1 (4.8)	1 (2.9)	
IIIC1	2 (14.3)	0 (0.0)	2 (5.7)	
IIIC2	3 (21.4)	11 (52.4)	14 (40.0)	
IVA	0 (0.0)	1 (4.8)	1 (2.9)	
IVB	1 (7.1)	0 (0.0)	1 (2.9)	
LVSI, n (%)				
Yes	5 (35.7)	13 (61.9)	18 (51.4)	0.176#
No	9 (64.3)	8 (38.1)	17 (48.6)	
Procedure, n (%)				
Laparoscopy	9 (64.3)	11 (52.4)	20 (51.1)	0.511#
Robot-assisted	0 (0.0)	3 (14.3)	3 (8.6)	
Laparotomy	5 (35.7)	7 (33.3)	12 (34.3)	
Number of PALN				0.985*
Mean	16.6	16.7	16.7	
Range	2-46	5-39	2-46	

NA: Not applicable; BMI: body mass index; FIGO: International Federation of Gynecology and Obstetrics; LVSI: lymphovascular space invasion; PALN: para-aortic lymph node. *Student's *t*-test, #Fisher's exact test.

Our study is original in that it is the only study to date as far as we are aware to have focused on the performance of ^{18}FDG PET-CT according to histological type. In previous studies evaluating the performance of ^{18}FDG PET-CT, particularly in the large series of Atri *et al.* (16), the proportion of type 2 tumors was not clearly stated. Our series revealed a trend towards lower accuracy for type 2 tumors than for type 1 tumors. The high proportion of type 2 lesions in our series and the high rate of PA lymph-node involvement may account for the lower accuracy in this study than in previous studies. Indeed, the extrinsic diagnostic qualities (PPV, NPV, and accuracy) of this technique vary with disease prevalence, whereas the intrinsic diagnostic qualities of the test (sensitivity and specificity) are independent of disease prevalence. Furthermore, the study by Park *et al.* (12) performed in 2008, that included 39.6% type 2 lesions, had one of the lowest accuracy rates of the published reports, although the exact proportion of type 2 lesions in patients undergoing PAL was not stated.

We currently have no reasonable explanation for this difference in performance according to histological type.

Table II. *Comparison of the performance of ^{18}F-fluorodeoxyglucose positron-emission tomography integrated with computed tomography (^{18}FDG PET-CT) for tumors of different histological types.*

Performance of ^{18}FDG PET-CT	Type 1	Type 2	*p*-Value
Sensitivity	66.7%	45.5%	0.500
Specificity	100.0%	100.0%	
PPV	100.0%	100.0%	
NPV	91.7%	62.5%	
Accuracy	92.9%	71.4%	
AUC	0.833	0.727	0.565

PPV: Positive predictive value; NPV: negative predictive value; AUC: area under the receiver operating characteristics curve.

However, histological type may be a determinant of the sensitivity of ^{18}FDG PET-CT. The cellular uptake of ^{18}FDG appears to depend partly on cellular grade (17). In ovarian cancer, patients with clear-cell carcinoma have been shown to have a lower mean maximal standardized uptake value than

Table III. *Characteristics of the cases that were false-negative by ^{18}F-fluorodeoxyglucose positron-emission tomography integrated with computed tomography.*

Patient	Age (years)	BMI (kg/m^2)	Preoperative stage[#]	Results of PAL: N+/NT	Involvement (mm)/ size of lymph node (mm)	Results of PL: N+/N_T	Histological type	Grade	LVSI
1	63	33.8	IA	1+/9	3/32	NP4	Endometrioid	2	Yes
2	72	31.3	IA	5+/29	1/3, 1/5, 1/9, 1/5, 1/4	0/27	Clear cell	3	No
3	51	22.3	IA	2+/7	7/7, 6/6	0/16	Carcinosarcoma	1	Yes
4	56	23	IB	2+/13	1/15, 2/6	0/16	Papillary serous	3	No
5	72	21.5	IA	1+/34	7/14	2+/17	Papillary serous	3	No
6	70	38.5	IIIA	2+/9	1/8, 1/23	0/10	Papillary serous	3	Yes
7	76	23.2	IB	2+/14	5/9, 2/2	0/5	Papillary serous	3	Yes
Mean	65.6	27.7		2.1/16.4	2.7/9.9	0.3+/15.2			

[#]Evaluated by magnetic resonance imaging. N+/NT: number of positive lymph nodes/number of lymph nodes removed; PAL: Para-Aortic Lymphadenectomy; PL: pelvic lymphadenectomy; NP: not performed; BMI: body mass index; LVSI: lymphovascular space invasion.

Table IV. *Principal studies on the performance of ^{18}F-fluorodeoxyglucose positron-emission tomography integrated with computed tomography for assessing para-aortic lymph nodes.*

Study	Patients, n	PAL, n		Distribution, n (%)		Performance of ^{18}FDG PET-CT, %				
		Total	Positive	Type 1	Type 2	Sensitivity	Specificity	PPV	NPV	Accuracy
Suzuki *et al*., 2007 (11)	30	19	1	29 (97%)	1 (3%)	0	100	0	94.7	94.7
Park *et al*., 2008 (12)	53	31	7	32 (60%)	21 (40%)	57.1	87.5	57.1	87.5	80.6
Kitajima *et al*., 2008 (13)	40	34	NC	37 (93%)	3 (7%)	51.7	99.4	83.3	97.3	96.8
Crivellaro *et al*., 2013 (14)	76	15	6	66 (87%)	10 (13%)	85.7	96	87.5	96.3	94.3
Gholkar *et al*., 2014 (15)	20	13	1	15 (75%)	5 (25%)	100	66.7	20	100	69.2
Atri *et al*., 2017 (16)	160	160	23	NR		65	88	48.4	93.8	85
Our study	81	35	14	14 (40%)	21 (60%)	50	100	100	75	80

NR: Not reported; PAL: para-aortic lymphadenectomy.

patients with serous adenocarcinoma or endometrioid adenocarcinoma (18-20). Clear-cell carcinomas seem to prefer the glutaminolysis pathway over glycolysis, resulting in lower ^{18}F-FDG concentrations in cells and a weaker signal (19).

In our study, 20 (24.7%) out of 81 patients had metastases (stage IVB) discovered on the basis of a positive ^{18}FDG PET-CT result. This examination therefore avoided the need for irrelevant and potentially invasive lymph-node surgery. Kim *et al*. showed that ^{18}FDG PET-CT had an excellent performance for the detection of distal metastases, with a sensitivity of 92.9%, specificity of 98.9%, PPV of 81.3%, NPV of 99.6% and an accuracy of 98.6% (21). They thus proposed an algorithm in which ^{18}FDG PET-CT was the first examination performed to detect distal metastases and evaluate lymph-node involvement. MRI, on the other hand, was used only for the evaluation of tumor characteristics, such as the degree of myometrial invasion, in particular. In their meta-analysis of seven studies performed in 2013, Kakhki *et al*. found that ^{18}FDG PET-CT had a sensitivity of 95.7% and specificity of 95.4% for the detection of distant metastasis (22).

The sampling of sentinel lymph nodes (SLN) may be an alternative to imaging that is less drastic than lymphadenectomy. The French SENTI-ENDO study, which evaluated the feasibility of SLN biopsy in endometrial cancer, reported a detection rate of 89% [95% confidence intervaI (CI)=82-93%] by double labeling (patented blue and 99technetium) (23). In their study, the sensitivity of the technique was 84% (95% CI=62-95%) and the NPV was 97% (95% CI=91-99%). They reported three false negatives, all corresponding to type 2 lesions, confirming the singularity of histological type 2.

It is unclear whether the search for SLN would have identified the affected PA lymph nodes not picked up by PET in our series. An evaluation of the characteristics of the false negatives in our study showed most to correspond to patients with type 2 lesions, with a small number of positive lymph nodes, invasion of a few millimeters, and mostly negative pelvic lymphadenectomies. This result is discordant with published findings. Widschwendter *et al*. reported that only 3% of isolated PA lesions were affected, with no pelvic involvement. However, the proportion of type 2 tumors was low (10%) (24). Soliman

et al. evaluated the performance of SNL in high-risk endometrial cancers. They reported a promising sensitivity of 95%, with a false-negative rate of 5%. Only one patient had PA involvement, with no pelvic involvement (25). However, the low rate of PA lymph-node involvement in this high-risk population and the small number of lymph nodes removed necessitate confirmation of the utility of SLN in high-risk endometrial cancer. A multicenter French study (SENTIRAD, Identifier: NCT02598219) is currently underway.

Our study had several limitations, including the small number of participants and the absence of information about the size of some lymph-node lesions, despite the importance of this element. Indeed, the poor sensitivity of ^{18}FDG PET-CT probably reflects the need for a sufficient number of neoplastic cells to induce ^{18}F-FDG hypermetabolism. In our series, re-assessment of the 15 false-negative lymph nodes revealed lesions of less than 6 mm in diameter for 80% of these nodes. Kitajima *et al*. showed that the sensitivity of ^{18}FDG PET-CT depended on lymph node size, with values of 13 to 17% for lymph nodes of less than 4 mm, 67% for lymph nodes of 5 to 9 mm, and 97 to 100% for lymph nodes of more than 10 mm in diameter (13, 26). Park *et al*. focused on the performance of ^{18}FDG PET-CT for lymph nodes giving negative results on MRI. They showed that true positives had a mean size of 8 mm for the long axis and 5 mm for the minor axis, whereas the false-positive lymph nodes had a mean size of 6 mm for the long axis and 3 mm for the minor axis (27).

In conclusion, ^{18}FDG PET-CT can detect a metastasis in approximately 25% of cases of high-risk endometrial cancer. Given its high specificity in PA lymph-node evaluation, a positive PET scan might make it possible to avoid PAL, that would be advantageous given that the actual therapeutic value of lymphadenectomy remains unclear. In cases of high-risk endometrioid endometrial cancer and in patients with high levels of comorbidity, the high accuracy of PET might help guide decisions as to whether or not to perform PAL. In cases of ^{18}FDG-negative PET-CT for type 1 lesions, SLN evaluation may be a viable alternative to PAL. For type 2 lesions, ^{18}FDG PET-CT cannot currently replace PAL because of the risk of false negatives. However, more highly powered prospective studies are required to confirm these results.

Conflicts of Interest

The Authors declare no conflicts of interest in regard to this study.

Authors' Contributions

Maxime Legros, François Margueritte, Tristan Gauthier are the principal authors and investigator of this study. Aymeline Lacorre, Yves Aubard, and Tristan Gauthier carried out all surgical procedures. Alexandru Ceuca interpreted all MRI. Jacques Monteil interpreted all ^{18}FDG PET-CT. Camille Sallèe and Antoine Tardieu participated in data collection. Valère Mbou interpreted all pathology analyses. Elise Deluche participated in multidisciplinary medical team meetings for the management of patients. All Authors helped to evaluate and edit the manuscript.

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