

Original Research

Adjuvant radiotherapy of endometrial cancer: role of ¹⁸F-FDG-PET/CT in treatment modulation

Martina Ferioli^{1,2,*}, Anna Myriam Perrone^{3,4}, Paolo Castellucci⁵, Valeria Panni², Anna Benini^{1,2}, Gabriella Macchia⁶, Andrea Galuppi¹, Milly Buwenge^{1,2}, Elisa Lodi Rizzini¹, Lidia Strigari⁷, Luca Tagliaferri⁸, Claudio Zamagni⁹, Pierandrea De Iaco^{3,4}, Stefano Fanti⁵, Alessio Giuseppe Morganti^{1,2}

¹Radiation Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, 40138 Bologna, Italy

²Radiation Oncology, Department of Experimental, Diagnostic and Specialty Medicine – DIMES, University of Bologna, 40138 Bologna, Italy

³Oncologic Gynaecology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, 40138 Bologna, Italy

⁴Department Medical and Surgical Sciences (DIMEC), University of Bologna, 40138 Bologna, Italy

⁵Nuclear Medicine Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, 40138 Bologna, Italy

⁶Radiotherapy Unit, Gemelli Molise Hospital, Fondazione Policlinico Universitario A. Gemelli, IRCCS, 86100 Campobasso, Italy

⁷Medical Physics, IRCCS Azienda Ospedaliero-Universitaria di Bologna, 40138 Bologna, Italy

⁸UOC di Radioterapia Oncologica, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario “A. Gemelli” IRCCS, 00168 Rome, Italy

⁹Oncologia Medica Addarii, IRCCS Azienda Ospedaliero-Universitaria di Bologna, 40138 Bologna, Italy

*Correspondence: martina.ferioli4@unibo.it (Martina Ferioli)

Academic Editor: Enrique Hernandez

Submitted: 31 October 2021 Revised: 19 December 2021 Accepted: 28 December 2021 Published: 15 April 2022

Abstract

Objective: Residual disease after surgery is related to an unfavorable prognosis in patients with endometrial cancer (EC). An early diagnosis and treatment of this condition could improve patients' outcome. Aim of this study was to define the role of postoperative ¹⁸F-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography (¹⁸F-FDG-PET/CT) in patients with high risk of residual disease after EC surgery. **Methods:** Patients operated for EC, with one or more risk factors, who underwent ¹⁸F-FDG-PET/CT before adjuvant treatment were included in this observational study. The primary endpoint was the rate of patients in whom ¹⁸F-FDG-PET/CT changed the treatment strategy and/or the radiotherapy (RT) planning. **Results:** Our analysis included 58 patients (median age: 67.5 years, range: 48.0–86.0) with the following risk factors: lymphadenectomy not performed (26 patients; 44.8%), inadequate lymphadenectomy (23 patients; 39.7%), and high risk of residual disease due to advanced stage (nine patients; 15.5%). Postoperative ¹⁸F-FDG-PET/CT imaging was positive in 18 patients (31%) in the following sites: pelvic extra-nodal disease (one patient), pelvic and/or paraaortic lymph nodes (12 patients), distant metastases (one patient), or combination of previous sites (four patients). Based on these results, the adjuvant therapeutic strategy was changed in five patients, three of whom were referred to chemotherapy alone due to distant metastases and two of whom were referred to nodal-directed treatment due to lymph node metastases (lymphadenectomy and pelvic chemoradiation plus boost, respectively). Furthermore, based on the ¹⁸F-FDG-PET/CT results, the RT plan was modified in 13 patients (addition of a boost on residual pelvic/abdominal disease in 12 and target modification in one, respectively). Therefore, based on postoperative ¹⁸F-FDG-PET/CT findings, the therapeutic strategy and the RT plan were changed in 5 patients (8.6%) and 13 patients (22.4%), respectively. **Conclusion:** In this analysis, the adjuvant treatment was modified after post-operative ¹⁸F-FDG-PET/CT in about one third of patients. Further studies are needed to better define the risk factors (or their combinations) correlated with higher probability of residual disease after radical hysterectomy-adnexectomy for EC.

Keywords: Endometrial cancer; Postoperative treatment; ¹⁸F-FDG-PET/CT; Radiotherapy; Concurrent chemoradiation; Brachytherapy

1. Introduction

Endometrial cancer (EC) is the fourth most frequent tumor in the female European population and its incidence is increasing in developed countries [1]. In 2018, as reported in the International Agency for Research on Cancer (IARC) database [2], the crude incidence rate was 31.6/100,000/year. Most cases are diagnosed at an early stage [3] with 90–95% five-year survival rate. However, these rates decrease to 57% in patients with pelvic lymph-

nodes (LNs) metastases and to 49% in case of abdominal LNs metastases [4].

When feasible, surgery is the mainstay of EC treatment [5] and the standard option is total hysterectomy with bilateral salpingo-oophorectomy [6]. The main aims of surgery are complete tumor resection and knowledge of the prognostic factors needed to guide adjuvant treatments. In fact, the EC staging is based on a surgical-pathological-based system, according to the International Federation



of Gynecology and Obstetrics (FIGO) [7]. In particular, pelvic lymphadenectomy provides important prognostic information and can guide the choice of postoperative treatments. While sentinel-lymph-node mapping may be used in uterine-confined disease especially in centers with specific expertise, pelvic and paraaortic lymphadenectomy is recommended in patients with higher risk of treatment failure (G3, non-endometrioid histological type, stage \geq IB) [6,8].

In case of high risk of residual disease due to high pathological stage or incomplete surgical staging, postoperative imaging is recommended by international guidelines [8,9]. The latter, in order to detect both local or metastatic residual disease, suggest both chest/abdominal/pelvic Computed Tomography (CT) (or abdominal/pelvic Magnetic Resonance Imaging (MRI)) and chest CT without contrast. ^{18}F -FDG-Positron Emission Tomography/Computed Tomography (^{18}F -FDG-PET/CT) is recommended only in selected cases, mainly to clarify ambiguous findings [8].

However, the multidisciplinary oncological-gynecological team of our institution introduced an operative protocol including postoperative ^{18}F -FDG-PET/CT in EC patients with high-risk features.

Therefore, the aim of this retrospective analysis was to define the impact of ^{18}F -Fluorodeoxyglucose -PET/CT in the adjuvant management of high-risk EC patients.

2. Material and methods

2.1 Study design and inclusion criteria

This is an observational study approved by the local Ethical Committee (ESTHER study, code CE 973/2020/Oss/AOUBo). We included EC patients who underwent postoperative ^{18}F -FDG-PET/CT in our institution before any adjuvant treatment due to one or more of the following risk factors: grade 3, stage \geq IB, histological types other than adenocarcinoma, and inadequate surgery based on the tumor stage.

In case of negative ^{18}F -FDG-PET/CT, patients were treated with adjuvant radiotherapy (RT) based on our institutional guidelines. The latter include: (i) vaginal brachytherapy (endometrioid carcinoma, stage \leq II, grading 1–2, and pN0; endometrioid carcinoma, stage IA, grading 3 and pN0; serous or clear cells carcinoma, stage IA and pN0); (ii) RT \pm concurrent chemotherapy followed by brachytherapy (BRT) boost (stage IA–B N1; stage IB, grading 3 pN0; stage II, grading 3 or grading 1–2 pN1); (iii) chemoradiation (CRT) followed by BRT boost (endometrioid carcinoma stage \geq III; serous or clear cells carcinoma, stage \geq IB, carcinosarcoma). Instead, patients with positive ^{18}F -FDG-PET/CT were referred to individualized treatment, planned through multidisciplinary discussion, and based on sites and characteristics of the residual disease.

2.2 Endpoints

Endpoints of the study were: (i) percentage of patients with modified therapeutic strategy (i.e., omitted RT) after ^{18}F -FDG-PET/CT; (ii) percentage of patients with modification of adjuvant RT dose (in particular delivery of a boost) and/or RT target definition after ^{18}F -FDG-PET/CT; (iii) outcomes (local control (LC), disease-free survival [DFS] and OS) in patients with positive ^{18}F -FDG-PET/CT; (iv) comparison between these outcomes and those of patients with negative postoperative ^{18}F -FDG-PET/CT. In order to assess the rate of patients with modified treatment based on ^{18}F -FDG-PET/CT, we recorded the adjuvant therapy settled by the multidisciplinary group only on the basis of the pathologic assessment of the surgical specimen.

2.3 PET/CT

Whole body ^{18}F -FDG-PET/CT was performed using the same positioning systems used in the planning and delivery of adjuvant pelvic RT. Three MBq/kg of ^{18}F -FDG were intravenously injected and after an uptake time of 60 min, images were acquired on a 3D tomograph, for two min per bed position, after defining the isocenter slice. In order to obtain anatomical information and for the attenuation correction, a low-dose CT scan (120 kV, 80 mA) was also performed. ^{18}F -FDG-PET/CT images were reconstructed using an iterative 3D ordered subsets expectation maximization method with two iterations and 20 subsets, followed by smoothing with CT-based attenuation, scatter, and random coincidence event correction. Then, three skin tattoo marks were then made in the abdominal region to ensure set-up reproducibility and treatment accuracy.

2.4 Radiotherapy

2.4.1 External beam

Pelvic external beam RT (EBRT) was planned and delivered using intensity modulated RT (IMRT) technique. The dose was prescribed according to the International Commission on Radiation Units and Measurements (ICRU) 83 report [10]. In patients with negative ^{18}F -FDG-PET/CT, the total dose was 45 Gy (1.8 Gy/fraction) and the clinical target volume (CTV) was defined including surgical bed, vaginal cuff, and pelvic lymph-nodes (obturator, external iliac, internal iliac, and presacral). The planning target volume (PTV) was defined as the CTV plus an isotropic margin of 1 cm. Patients with a pelvic nodal or extra-nodal residual disease at ^{18}F -FDG-PET/CT were treated by adding a simultaneous integrated boost (SIB) (boost dose: 14–20 Gy based on the dose delivered to the surrounding organs at risk [OARs]). In case of residual vaginal disease deemed amenable to endovaginal BRT, a local boost after EBRT was delivered (26 Gy in 4 fractions). In patients with para-aortic nodal metastases on ^{18}F -FDG-PET/CT, the prophylactic CTV was extended to the upper border of L1 and metastatic LNs were treated with SIB (14 Gy). Concurrent and adjuvant chemotherapy (CHT) was considered in ^{18}F -

Table 1. Patients characteristics.

	All patients, N (%)	PET negative, N (%)	PET positive, N (%)	<i>p</i>
Patients number	58 (100)	40 (69)	18 (31)	
Age, years				0.463
Median (range)	67.5 (48–86)	67 (48–81)	69 (51–86)	
Lymphadenectomy				0.559
No	27 (46.6)	18 (45.0)	9 (50.0)	
Pelvic	22 (37.9)	17 (42.5)	5 (27.8)	
Pelvic and paraaortic	9 (15.5)	5 (12.5)	4 (22.2)	
FIGO stage				0.049
I	25 (43.1)	21 (52.5)	4 (22.2)	
II	5 (8.6)	4 (10)	1 (5.6)	
III	28 (48.3)	15 (37.5)	13 (72.2)	
Histological type				0.353
Endometrioid carcinoma	41 (70.7)	30 (75.0)	11 (61.1)	
Non-endometrioid carcinoma	5 (8.6)	2 (5.0)	3 (16.7)	
Mixed	12 (20.7)	8 (20.0)	4 (22.2)	
Grading				0.355
1	6 (10.3)	4 (10.0)	2 (11.1)	
2	24 (41.4)	19 (47.5)	5 (27.8)	
3	28 (48.3)	17 (42.5)	11 (61.1)	

FIGO, International Federation of Gynecology and Obstetrics; PET, positron emission tomography.

FDG-PET/CT positive patients and prescribed taking into account any comorbidities. All patients with para-aortic metastatic nodes received both concomitant and adjuvant CHT.

2.4.2 Brachytherapy

After pelvic RT, most ¹⁸F-FDG-PET/CT negative patients underwent BRT boost to the vaginal cuff, delivered with high dose rate (HDR). Vaginal cylinder or ovoids were placed after local anesthesia. The BRT treatment plan was calculated with 3D-technique on a CT scan, after OARs delineation. The dose was prescribed 5 mm from the external surface of the applicator at the mid-point of the activated dwell positions length [11]. The BRT dose, in ¹⁸F-FDG-PET/CT-negative patients, ranged between 6 and 21 Gy in one-three fractions. Six Gy in one fraction or 10 Gy in two fractions were delivered after postoperative pelvic EBRT, while 21 Gy in three fractions were prescribed in postoperative exclusive BRT.

2.4.3 Chemotherapy

Concurrent cisplatin-based (40 mg/m²) CHT was administered weekly by intravenous infusion. Adjuvant CHT was prescribed according to patients' characteristics and EC stage (loco-regional or metastatic) with Carboplatin and Taxanes being the most used drugs.

2.5 Statistical analysis

Demographic and clinical data were analyzed with descriptive statistics and presented as numbers and percentages. Continuous variables were presented in terms of medians and ranges. The Chi-square test and the Mann-Whitney U test were used to compare categorical and continuous variables, respectively. Survival curves were calculated with the Kaplan-Meier method and compared with the log rank test. A value of *p* < 0.05 was used to define statistical significance. Data were analyzed using SPSS for Windows (version 20.0; SPSS Inc., Chicago, IL, USA).

3. Results

Fifty-eight patients were included in the analysis (median follow-up: 41 months; range: 5–146) and 18 (31.0%) of them had a positive postoperative ¹⁸F-FDG-PET/CT (median SUV-max: 13.7, range: 1.5–27). Patients referred to our institution for adjuvant treatment between 2009 and 2018, coming from different local centres. Table 1 reports patient characteristics with a comparison between positive versus negative ¹⁸F-FDG-PET/CT cases. The only statistically significant difference between the two groups was the FIGO stage (*p* = 0.049), moreover we described the higher FIGO stage III percentage in ¹⁸F-FDG-PET/CT positive patients (72.2% versus 37.5%).

The site of macroscopic residual disease and both planned and delivered treatment are shown in Table 2. Briefly, the postoperative ¹⁸F-FDG-PET/CT was positive in the following sites: residual tumor on the vaginal cuff

Table 2. Sites of residual disease at PET/CT and their treatments.

Patients	Site of residual disease	Planned treatment (before PET)	Delivered treatment (after PET/CT)
1	Pelvic NM	BRT	Lymphadenectomy that reported negative pelvic nodes
2	Pelvic NM	CRT on pelvis + BRT	Prophylactic CRT on the pelvis with SIB on positive nodes + BRT to vaginal cuff
3	Pelvic NM	CRT on pelvis and paraaortic nodes + BRT	Prophylactic RT on the pelvis and paraaortic nodes (stage IIIC2) with SIB on positive nodes + adjuvant CHT
4	Pelvic NM	CRT on pelvis + BRT	Prophylactic CRT on the pelvis with SIB on positive nodes
5	Pelvic NM	RT on pelvis + BRT	Prophylactic RT on the pelvis with SIB on positive nodes + BRT to vaginal cuff
6	Pelvic NM	CRT on pelvis + BRT	Prophylactic RT on the pelvis with SIB on positive nodes + BRT to vaginal cuff
7	Pelvic extra-NM	CRT on pelvis + BRT	CRT on the pelvis with BRT boost on the lesion over vaginal cuff + adjuvant CHT
8	Pelvic extra-NM + NM	BRT	Indication to CRT on pelvis with SIB on positive sites and BRT, but postoperative treatment not performed due to surgical complications
9	Pelvic extra-NM + NM	CRT on pelvis + BRT + CHT	Prophylactic RT on the pelvis with SIB on positive areas + adjuvant CHT
10	Para-aortic NM	CRT on pelvis + BRT + CHT	Prophylactic CRT on pelvic and para-aortic nodes with SIB on NM (planned but not delivered due to surgical complications & early tumor progression)
11	Para-aortic NM	CRT on pelvis + BRT + CHT	Prophylactic CRT on pelvic and para-aortic NM without SIB because of closeness to an intestinal loop + BRT to vaginal cuff + adjuvant CHT
12	Pelvic + Para-aortic NM	CRT on pelvis and paraaortic nodes + BRT	Prophylactic CRT on the pelvis and para-aortic nodes with SIB on positive nodes + BRT on vaginal cuff + adjuvant CHT
13	Pelvic + Para-aortic NM	CRT on pelvis and paraaortic nodes + BRT	Prophylactic CRT on the pelvis and para-aortic nodes (stage IIIC2) with SIB on positive nodes + BRT on vaginal cuff + adjuvant CHT
14	Pelvic + Para-aortic NM	CRT on pelvis and paraaortic nodes + BRT	Prophylactic CRT on the pelvis and paraaortic nodes (stage IIIC2) with SIB on positive nodes + BRT to vaginal cuff
15	Pelvic + Para-aortic NM	CRT on pelvis + BRT	Prophylactic RT on the pelvis and paraaortic nodes with SIB on positive nodes+ BRT to vaginal cuff
16	DM	CRT on pelvis + BRT	CHT
17	Pelvic ± para-aortic NM + DM	CRT on pelvis and paraaortic nodes + BRT	CHT
18	Pelvic ± para-aortic NM + DM	CRT on pelvis + BRT + CHT	CHT

BRT, brachytherapy; CRT, chemoradiation; CHT, chemotherapy; DM, distant metastases; NM, nodal metastases; PET, positron emission tomography; RT, radiotherapy; SIB, simultaneous integrated boost.

Table 3. High-risk features in PET-positive patients.

Patients	Age	Lymphadenectomy	LVSI	Grading	Histological type	FIGO pathological stage
1	60	No	NA	2	Endometrioid	IB
2	58	Pelvic	Positive	2	Endometrioid	IIIC1
3	78	Pelvic+LA	Positive	3	Non-endometrioid	IIIC2
4	53	Pelvic	Positive	1	Endometrioid	IIIC1
5	80	NA	NA	2	Endometrioid	II
6	74	Pelvic	NA	3	Endometrioid	IIIA
7	66	No	Negative	3	Endometrioid	IIIA
8	72	No	Negative	1	Endometrioid	IB
9	67	Pelvic	NA	3	Mixed type	IIIA
10	85	No	NA	3	Mixed type	IIIB
11	73	No	NA	3	Non-endometrioid	IB
12	66	Pelvic	Positive	3	Mixed type	IIIC1
13	67	Pelvic+LA	Positive	3	Endometrioid	IIIC2
14	51	Pelvic+LA	Positive	2	Endometrioid	IIIC2
15	84	No	NA	3	Endometrioid	IIIB
16	69	No	NA	3	Non-endometrioid	IB
17	69	Pelvic+LA	Positive	2	Endometrioid	IIIC2
18	86	No	NA	3	Mixed type	IIIA

LA, Lomboarctic; LVSI, Lymphovascular invasion; NA, not available; FIGO, International Federation of Gynecology and Obstetrics.

(one patient), pelvic and/or para-aortic lymph nodes (12 patients), distant metastases (one patient), or combination of previous sites (four patients with nodal disease and pelvic residual tumor and/or distant metastases). Based on these results, the adjuvant therapeutic strategy was changed in five patients: three were referred to chemotherapy alone due to distant metastases and two were referred to nodal-directed treatment due to lymph node metastases (lymphadenectomy and pelvic chemoradiation plus boost, respectively). Furthermore, based on the ^{18}F -FDG-PET/CT results, the RT plan was modified in 13 patients (addition of a boost on residual pelvic/abdominal disease in 12 and target modification in one, respectively). Therefore, based on postoperative ^{18}F -FDG-PET/CT findings, the therapeutic strategy and the RT plan were changed in 5 patients (8.6%) and 13 patients (22.4%), respectively. However, the treatment established on the basis of ^{18}F -FDG-PET/CT was not performed in two patients, in one case due to postoperative complications and in the other for the same reason and due to early tumor progression (Table 2).

The main possible high-risk features in PET-positive patients were shown in Table 3: eight patients did not performed lymphadenectomy, mainly for clinical comorbidities; 11 patients had grade 3 or undifferentiated tumors; a non-endometrioid or mixed histological type was reported in seven cases.

Three-year OS was 55.6% and 57.1% in the whole group of ^{18}F -FDG-PET/CT-positive patients including subjects with hematogenous distant metastases and in the sub-

group of ^{18}F -FDG-PET/CT-positive patients with residual disease only in the pelvis or in extra-pelvic lymph nodes, respectively. Furthermore, three-year DFS in the same patient populations was 22.9% and 27.8%, respectively. Compared to ^{18}F -FDG-PET/CT-positive patients, OS was significantly higher in ^{18}F -FDG-PET/CT-negative patients ($p < 0.001$) (Fig. 1). Even when compared with ^{18}F -FDG-PET/CT-positive patients but without hematogenous metastases, OS was significantly higher in ^{18}F -FDG-PET/CT-negative patients ($p < 0.001$) (Fig. 2). Among ^{18}F -FDG-PET/CT-positive patients, 11 had died at the last observation: nine due to tumor progression and two due to non-cancer-related reasons.

4. Discussion

In our real-life analysis on patients with high-risk EC, evaluated with postoperative ^{18}F -FDG-PET/CT, the latter was positive in 31.0% of patients leading to a change of the treatment planned based on the pathological examination of the surgical specimen in all subjects.

We showed that, in patients with inadequate surgical staging, postoperative ^{18}F -FDG-PET/CT can frequently and drastically change the adjuvant therapy plan. Table 3 reports the main risk factors in our PET-positive patients: lack of lymphadenectomy, Grade 3, non-endometrioid histological type, and advanced FIGO stage (\geq IIIC). Lymphadenectomy is recommended in these high-risk patients (Grade 3, FIGO stage \geq IB, non-endometrioid histology) and in cases without surgical nodal staging, the European

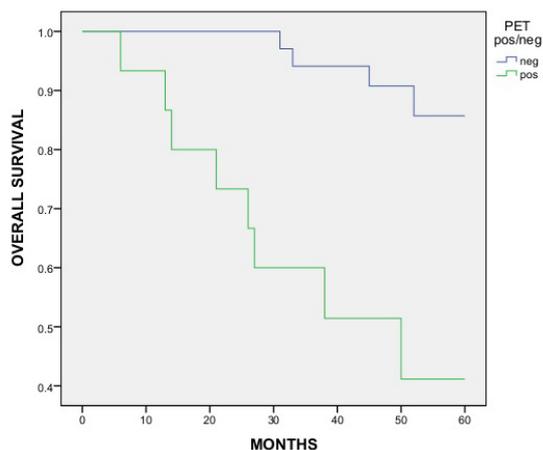


Fig. 1. Overall survival in patients with negative versus positive PET/CT.

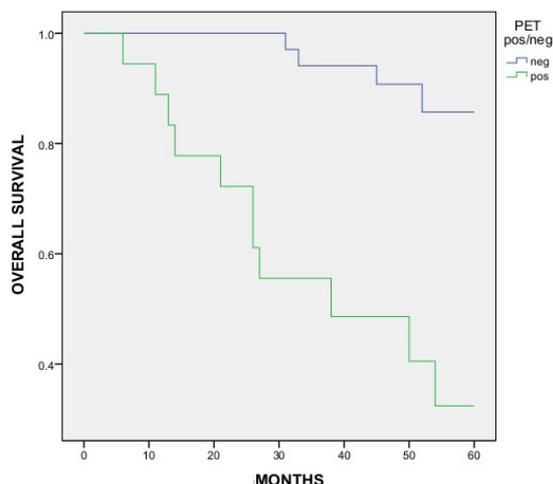


Fig. 2. Overall survival in patients with negative versus positive PET/CT (only patients without distant metastases included).

guidelines suggest intensified adjuvant treatment strategies [6]. This recommendation is particularly important in patients with metastatic pelvic and/or abdominal lymph nodes, in whom the risk of residual cancer is higher. However, in our series many patients did not undergo lymphadenectomy, due to their advanced age and/or relevant comorbidities. Furthermore, due to its still controversial role, not even sentinel lymph node analysis was performed. Finally, particularly in patients with nodal residual disease at ^{18}F -FDG-PET/CT, an intensified local treatment (lymphadenectomy followed by chemotherapy \pm chemoradiation) would probably have been justified, at least in selected patients.

In most cases, nodal uptake was detected on postoperative ^{18}F -FDG-PET/CT in patients with: (i) disease con-

finned only to the uterus (based on initial imaging) but surgically inadequately staged, especially at the nodal level, or (ii) with metastatic lymph nodes on pathological examination and in which ^{18}F -FDG-PET/CT was performed to optimize target volumes and doses of postoperative radiotherapy. In fact, in some of these patients, preoperative imaging raised the suspicion of nodal involvement but clearly, even in patients undergoing lymphadenectomy, there is a risk of incomplete removal of metastatic lymph nodes. It is impossible to predict the outcome of positive ^{18}F -FDG-PET/CT patients if they had received the previously planned treatment. However, considering that in the case of macroscopic residual tumor the international guidelines recommend doses of 60–70 Gy [8], if these patients had received only a “prophylactic” dose (45–50 Gy) it is easily conceivable that adjuvant radiotherapy would have been ineffective. It should be noted that, despite an early detection of residual disease, the outcome of positive ^{18}F -FDG-PET/CT patients was very poor, being the 3-year DFS rate below 25.0%. Considering that most tumor progressed with distant metastases, it can be speculated that a more intensive use of systemic treatments could improve the prognosis in this setting. Indeed, excluding three patients with distant metastases, only four out of 15 patients with positive ^{18}F -FDG-PET/CT underwent CHT. Similarly, in patients with ^{18}F -FDG-PET/CT showing distant metastases, in all but one cases with ≤ 5 lesions, the question might be: “would a metastasis-directed therapy (such as stereotactic RT), applied based on current evidence [12], have improved the outcome?”. Finally, particularly in patients with nodal residual disease at ^{18}F -FDG-PET/CT, an intensified local treatment (lymphadenectomy followed by chemoradiotherapy) would probably have been justified, at least in selected patients.

Our analysis has obvious limitations. First, the retrospective study design leads to unavoidable risks of bias. Moreover, the patients included in our analysis were referred for adjuvant treatment to our institution from very heterogeneous centres, where the preoperative staging protocols and the experience and surgical volumes in oncological gynaecology were strongly different. Furthermore, the small sample size limits the possibility of clearly identifying patients to be candidates for postoperative ^{18}F -FDG-PET/CT. Moreover, the rate of patients not undergoing lymphadenectomy can also be surprisingly high in our case series, limiting their generalizability in terms of frequency of positive PET/CT. However, it should be considered that our study was based on the selection of patients with a high risk of residual cancer after surgery, which at least partially justifies the high percentage of patients without surgical staging. Furthermore, ^{18}F -FDG-PET/CT positive patients were treated inhomogeneously, particularly in terms of systemic therapies. Moreover, the results of this analysis would likely have been different if international guidelines [8] on clinical management of EC had been followed,

particularly regarding the recommendation to perform preoperative lymph node staging in high-risk patients. Therefore, this aspect also limits the generalizability of our results since they were recorded in a partially incorrect therapeutic setting. However, even in this case, we must stress that our analysis was aimed at assessing the impact of PET/CT in a real-world clinical situation not uncommon in our experience. Finally, the only postoperative imaging examination was ^{18}F -FDG-PET/CT, thus preventing the comparison between the results of the latter with those of other imaging techniques (CT or MRI) currently suggested by international guidelines in this setting [8].

However, our study is original being one of the very few evidence on the role of ^{18}F -FDG-PET/CT in detecting post-surgical residual EC. In fact, to the best of our knowledge, only Simcock *et al.* [13] analyzed the results of PET/CT in 48 patients with intermediate or high-risk EC after total hysterectomy and bilateral salpingo-oophorectomy \pm lymphadenectomy. In their analysis, ^{18}F -FDG-PET/CT was positive in 35% of patients and led to a change in the planned treatment in 31% of cases. Therefore, the results of that series are surprisingly similar to those of our analysis and seem to confirm the usefulness of ^{18}F -FDG-PET/CT in selected patients with resected EC.

Instead, other studies tested PET/CT in patients with suspected EC recurrence during the post-surgical follow-up. OzcanKara *et al.* [14] reported higher sensitivity, specificity, and diagnostic accuracy of ^{18}F -FDG-PET/CT, compared to conventional imaging (CT, MRI, ultrasound) and CA-125 levels, in the evaluation of post-treatment EC with suspected recurrence. Moreover, Sharma *et al.* [15] reported higher specificity (96% versus 62%), accuracy (92% versus 76%), and comparable sensitivity (89% versus 85%) of ^{18}F -FDG-PET/CT, compared to CT and MRI, in EC with suspected recurrence. Finally, the systematic reviews by Kadkhodayan *et al.* [16] and Bollineni *et al.* [17], showed a high accuracy of ^{18}F -FDG-PET/CT in detecting EC recurrences and a clear impact on their treatment. More generally, Crivellaro *et al.* [18] reported that, in high-risk EC, ^{18}F -FDG PET/CT demonstrated moderate sensitivity but high specificity and accuracy for the nodal status assessment.

Taken together, the available evidence seems to suggest that in adequately early-stage radiologically and surgically staged patients, postoperative ^{18}F -FDG-PET/CT could be omitted, unless suspicious residual disease at surgery. Moreover, preoperative staging is recommended in all patients, with more attention if known high-risk features are present at diagnosis [8], in order to make an oncological adequate surgical staging, but none of the imaging modality can totally replace the surgical act [19]. Furthermore, the surgical staging and the possible postoperative imaging become even more important considering that nodal disease can not be excluded also if preoperative imaging was negative [20].

In conclusion, ^{18}F -FDG-PET/CT seems useful both in the post-surgical restaging of selected patients and in the whole body restaging of patients with proven or suspected local EC recurrence. Furthermore, the results of our analysis suggest that, in daily clinical practice, postoperative ^{18}F -FDG-PET/CT may be justified at least in some categories of patients with high risk of undertreatment. In particular, postoperative ^{18}F -FDG-PET/CT seems particularly useful in patients with both incomplete surgical nodal staging and advanced FIGO stage (\geq FIGO III), or both incomplete surgical nodal staging and grading 3 EC. In fact, in our analysis, the rates of ^{18}F -FDG-PET/CT positive patients within these two subgroups were 47.4% and 41.0%, respectively.

5. Conclusions

The results of our analysis warrant further studies in this setting. Such analyses could have the purpose of: (i) a more precise definition of the patient populations to be referred to postoperative ^{18}F -FDG-PET/CT; this objective could be pursued through the collection of clinical, pathological, bio-molecular and radiomics data from large patient series in order to develop predictive models of post-surgical residual disease; (ii) to test more intensive and possibly more personalized integrated treatments in order to improve the outcome of these patients with poor prognosis; this intensification could involve the administration of systemic therapies in patients with increased risk of distant metastasis and the use of dose-escalated RT in patients with increased risk of local failure (dose-escalated SIB, boost delivered with stereotactic RT).

Author contributions

Conception and design—MF, AMP, PC, VP, AB, GM, AG, MB, ELR, LS, LT, CZ, PDI, SF, AGM. Research and data collection—MF, VP, AB and AMP. Analysis and interpretation of data—MF, GM, ELR, LT, & AG. Manuscript writing—MF, AMP, PC, VP, AB, GM, AG, MB, ELR, LS, LT, CZ, PDI, SF, AGM. Approval of final article—all authors.

Ethics approval and consent to participate

This is an observational study approved by the local Ethical Committee (AVEC - Comitato Etico Area Vasta Emilia Centro): ESTHER study, code CE 973/2020/Oss/AOUBo. All subjects gave their informed consent for inclusion in this study.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions that improved the paper.

Funding

This research received no external funding.

Conflict of interest

PDI is serving as one of the Editorial Board members and AMP is serving as one of the Review Board members of this journal. We declare that PDI and AMP had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Enrique Hernandez. The other authors declare no conflict of interest.

References

- [1] McAlpine JN, Temkin SM, Mackay HJ. Endometrial cancer: not your grandmother's cancer. *Cancer*. 2016; 122: 2787–2798.
- [2] Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, *et al*. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. 2018. Available at: <https://gco.iarc.fr/today> (Accessed: 18 March 2019).
- [3] National Cancer Institute. SEER Stat Fact Sheets: Endometrial Cancer. 2020. Available at: <https://seer.cancer.gov/statfacts/html/corp.html> (Accessed: 18 March 2020).
- [4] Lewin SN, Herzog TJ, Medel NIB, Deutsch I, Burke WM, Sun X, *et al*. Comparative Performance of the 2009 International Federation of Gynecology and Obstetrics' Staging System for Uterine Corpus Cancer. *Obstetrics & Gynecology*. 2010; 116: 1141–1149.
- [5] Lin MY, Dobrotwir A, McNally O, Abu-Rustum NR, Narayan K. Role of imaging in the routine management of endometrial cancer. *International Journal of Gynecology & Obstetrics*. 2018; 143: 109–117.
- [6] Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, *et al*. ESMO–ESGO–ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. *Annals of Oncology*. 2016; 27: 16–41.
- [7] Erdemoğlu E, Çerçi SS, Erdemoğlu E, Yalçın Y, Tatar B. Role of positron emission tomography-computed tomography in endometrial cancer. *Turkish Journal of Obstetrics and Gynecology*. 2017; 14: 203–209.
- [8] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Uterine Neoplasms Version 1.2020. 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf (Accessed: 3 July 2020).
- [9] Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, *et al*. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2013; 24: vi33–vi38.
- [10] Grégoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report no. 83). *Cancer/Radiothérapie*. 2011; 15: 555–559.
- [11] Small W, Beriwal S, Demanes DJ, Dusenbery KE, Eifel P, Erickson B, *et al*. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. *Brachytherapy*. 2012; 11: 58–67.
- [12] Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, *et al*. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *The Lancet*. 2019; 393: 2051–2058.
- [13] Simcock B, Narayan K, Drummond E, Bernshaw D, Wells E, Hicks RJ. The Role of Positron Emission Tomography/Computed Tomography in Planning Radiotherapy in Endometrial Cancer. *International Journal of Gynecologic Cancer*. 2015; 25: 645–649.
- [14] Ozcan Kara P, Kara T, Kaya B, Gedik GK, Sari O. The value of FDG-PET/CT in the post-treatment evaluation of endometrial carcinoma: a comparison of PET/CT findings with conventional imaging and CA 125 as a tumour marker. *Revista Española De Medicina Nuclear E Imagen Molecular*. 2012; 31: 257–260.
- [15] Sharma P, Kumar R, Singh H, Jeph S, Sharma DN, Bal C, *et al*. Carcinoma Endometrium. *Clinical Nuclear Medicine*. 2012; 37: 649–655.
- [16] Kadkhodayan S, Shahriari S, Treglia G, Yousefi Z, Sadeghi R. Accuracy of 18-F-FDG PET imaging in the follow up of endometrial cancer patients: Systematic review and meta-analysis of the literature. *Gynecologic Oncology*. 2013; 128: 397–404.
- [17] Bollineni VR, Ytre-Hauge S, Bollineni-Balabay O, Salvesen HB, Haldorsen IS. High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. *Journal of Nuclear Medicine*. 2016; 57: 879–885.
- [18] Crivellaro C, Signorelli M, Guerra L, De Ponti E, Pirovano C, Fruscio R, *et al*. Tailoring systematic lymphadenectomy in high-risk clinical early stage endometrial cancer: the role of 18F-FDG PET/CT. *Gynecologic Oncology*. 2013; 130: 306–311.
- [19] Antonsen SL, Jensen LN, Loft A, Berthelsen AK, Costa J, Tabor A, *et al*. MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer — a multicenter prospective comparative study. *Gynecologic Oncology*. 2013; 128: 300–308.
- [20] Kitajima K, Suzuki K, Senda M, Kita M, Nakamoto Y, Sakamoto S, *et al*. Preoperative nodal staging of uterine cancer: is contrast-enhanced PET/CT more accurate than non-enhanced PET/CT or enhanced CT alone? *Annals of Nuclear Medicine*. 2011; 25: 511–519.