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Diagnostic role and prognostic impact of positron emission tomography / computed tomography in patients treated for uterine corpus cancer

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SUMMARY

Introduction/Objective The goal of our research was to evaluate diagnostic and prognostic role of positron emission tomography/computed tomography (PET-CT) in patients previously treated for uterine cancer and compare it to conventional imaging methods (CIM).

Methods We analyzed 37 patients examined on PET-CT for follow-up or suspicion of uterine cancer recurrence, and who were previously treated with surgery and/or chemoradiotherapy. All patients underwent computed tomography or magnetic resonance imaging prior to PET-CT, and were followed-up for at least one year.

Results PET-CT showed sensitivity, specificity and diagnostic accuracy in uterine cancer relapse detection of 96.3%, 70% and 89.2%, while those values for CIM were 92.6%, 40% and 78.4 %, respectively. Correlation of PET-CT and CIM findings was 78% (29/37). In 13 out of 25 true positive patients on CIM, PET-CT found greater number of active sites missed by conventional imaging. Positive findings on PET-CT were associated with shorter progression free survival (p = 0.023, logrank test).

Conclusion PET-CT constitutes an important diagnostic method in management of recurrent cancer of uterine corpus, demonstrating high sensitivity and accuracy. In comparison to CIM, PET-CT can discover larger number of active tumor sites, and also shows better specificity. PET-CT positive patients have worse prognosis with shorter progression free survival.

Keywords: endometrial cancer; fluorodeoxyglucose; progression free survival; sensitivity; specificity; uterine sarcoma

САЖЕТАК

Увод /Циљ Циљ ове студије био је да се испита дијагностичка и прогностичка улога позитронске емисионе томографије са компјутеризованом томографијом (ПЕТ-ЦТ) код пацијенткиња претходно лечених од малигних тумора утеруса, уз поређење са конвенционалним визуелизационим методама (КВМ).

Метод Евалуирано је 37 испитаница које су упућене на ПЕТ-ЦТ преглед у склопу праћења или сумње на рецидив након лечења малигнитета утеруса хирургијом, хеморадиотерапијом или комбинацијом наведеног. Све пацијенткиње подвргнуте су компјутеризованој томографији или магнетној резонанци пре ПЕТ-ЦТ прегледа, уз минимално праћење 12 месеци.

Резултати Укупна сензитивност, специфичност и дијагностичка тачност у детекцији рецидива рака утеруса износиле су 96,3%, 70% и 89,2% за ПЕТ-ЦТ и 92,6%, 40% и 78,4 % за КВМ, респективно. Корелација ПЕТ-ЦТ и КВМ била је присутна у 29/37 случајева (78%). Код 13/25 стварно позитивних испитаница на КВМ, ПЕТ-ЦТ је детектовао додатне лезије. Позитиван налаз ПЕТ-ЦТ био је повезан са краћим преживљавањем без прогресије болести (p = 0,023, логранк тест).

Закључак ПЕТ-ЦТ представља важно дијагностичко средство код пацијенткиња лечених од рака тела материце, показујући високу сензитивност и дијагностичку тачност. Посебан допринос хибридног имиџинга представља његова већа специфичност и способност да детектује већи број активних лезија у поређењу са КВМ. ПЕТ-ЦТ позитивне пацијенткиње такође имају лошију прогнозу, са краћим временом преживљавања без прогресије болести.

Кључне речи: ендометријални карцином; флуородеоксиглукоза; преживљавање без прогресије болести; сарком утеруса; сензитивност; специфичност

INTRODUCTION

Uterine cancers represent most common gynecological cancer in developed countries, being the fourth most common malignant tumor and participating with up to 5% in cancer-related death among women [1, 2]. Over 400.000 newly-developed cases of uterine cancers were documented in 2020. in world [3]. During the last decades, slight increase in uterine cancer incidence has been observed, which could be attributed to ageing of population, fertility decrease and increase in prevalence of certain risk factors such as obesity, polycystic ovarian syndrome, lack of physical activity etc. [4]. Uterine malignant tumors can be of epithelial (endometrial carcinoma) and mesenchymal (uterine sarcoma) origin. Histopathological classification of uterine cancers should be performed according to World Health Organization (WHO) criteria [5].

Primary treatment of uterine cancer consists of hysterectomy with ovariectomy, with or without lymph nodes dissection, and in case of positive risk factors adjuvant therapy (chemotherapy and/or irradiation) should be taken into consideration. Despite optimal surgical and adjuvant treatment, 7-15% women who initially had early stage endometrial canrcinoma (stages I and II as defined by The International Federation of Gynecology and Obstetrics - FIGO) develop recurrent disease, and women with more advanced disease at diagnosis have much higher chances of recurrence [6]. Endometrial cancer relapse can be difficult to treat, particularly in patients who already received radiotherapy, or have oligometastatic disease. In the past couple of years, 5-year survival rate of women with relapsed endometrial carcinoma registered 3-fold increase, from 25% to 75%, due to better selection for treatment [6]. Therefore, for better patient selection, research of predictive biomarkers and prospective outcome analysis in larger study population is of key importance [6]. In patients with uterine sarcomas, high recurrence rate is present in all disease stages, despite surgery and adjuvant

therapy, with the recurrence rate of 53–71%, from which 22% pelvic, 58% distant and 20% mixed [7].

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) represents functional imaging modality which is used in initial staging, therapy evaluation, restaging and follow-up of cancer patients. Combined with computed tomography (CT) in the same device, PET-CT represents hybrid imaging which evaluates both, functional metabolic parameters assessing disease activity in loco-regional and distant tumor sites and their morphological characteristics. Another important characteristic of FDG PET-CT imaging is its standard procedure of assessing the whole body, i.e. from head to thighs, with possibility to discover distant lesions together with loco-regional status evaluation, which could suggests its superiority compared to computed tomography and particularly magnetic resonance imaging (MRI). Furthermore, it was shown that certain FDG PET-CT parameters could have potential role as predictive biomarkers in endometrial carcinoma and uterine sarcoma patients [8, 9]. However, current guidelines recommend conventional imaging methods (CIM), that is CT and/or MRI, as imaging modalities of choice in suspected recurrent uterine cancer, with PET-CT being considered only in selected cases [10]. With increase in number of studies regarding the use of diagnostic imaging methods in oncological patients, it was shown that the data obtained by FDG PET-CT could be beneficial in management of these patients. However, information with regard to role of FGD PET-CT in gynecological malignancies are still relatively limited, with no agreement in FDG PET diagnostic accuracy in comparison to CIM among recent studies when it comes to women with uterine neoplasms, and further investigations are needed to precisely determine the validity and usefulness of these methods [11].

Based on the above mentioned, primary aim of our research was evaluation of FDG PET-CT role in women who underwent treatment for uterine cancer, with assessment of its

diagnostic performances. Additional goals were to compare performances of FDG PET-CT to morphological imaging methods – CT and MRI, and to determine their potential prognostic role in these patients.

METHODS

Study population

Our research was designed as retrospective cohort study which included women who received treatment for cancer of the uterus. Patients were referred to Center for nuclear medicine with PET, University clinical center of Serbia for FDG PET-CT examination between January 2015. and December 2019, for following indications: clinical suspicion for disease relapse, new lesions on conventional imaging, or routine follow-up. All patients fulfilled certain criteria, and inclusion criteria were: 1) pathohistologically proven malignant tumor of uterine corpus, 2) completed primary therapy (surgery ± chemo/radiotherapy), 3) CT or MRI of abdomen and pelvis no more than three months before PET-CT, 4) minimum patient follow-up time of 12 months after PET-CT. Exclusion criteria were: 1) previously proven other malignant tumor, 2) less than three months after surgery/irradiation and less than four weeks after chemotherapy until PET-CT imaging. Approval for this study was obtained from the institutions' Ethics board (number 668/6), while all patients have signed written consent.

FDG PET-CT protocol

Hybrid PET-CT machine Biograph True 64 (Siemens AG, Erlangen, Germany) was used for imaging of all patients. After minimum 6 hours of fasting, mean dose of 5.5 MBq/kg of FDG was intravenously administered to examinees. Blood glucose level had to be less than 11 mmol/l, measured just before FDG administration. Patients subsequently rested for 60–90 minutes post-injection, before the imaging. Imaging protocol consisted of non-contrast low-

dose computed tomography (120 kV, 40 mAs, slice thickness 5 mm, pitch 1.5, time of rotation 0.5s), and immediately after that 3D acquisition by positron emission tomography. Images were acquired from scull base to upper femurs. Syngo Multimodality workstation VE31A (Siemens Medical Solutions, USA, Inc.) was used for image interpretation. Qualitative and semi-quantitative analysis of PET-CT findings was performed. All lesions which demonstrated elevated FDG accumulation on PET, even in the absence of morphological lesions on CT, were considered as positive for relapse, after the benign and physiological causes of FDG uptake were excluded. In semi-quantitative analysis, SUVmax values of pathological lesions were calculated, with following formula: activity in the tissue (count/pixel/s) multiplied by calibrating factor, divided by administered radioactive dose (MBq/kg body weight). SUVmax is represented by voxel with greatest activity in designated volumes of interest - pathological areas of elevated fluorodeoxyglucose accumulation on reconstructed PET images. However, semi-quantitative analysis using SUVmax was only used as an additional mean of interpretation, with no threshold value for diagnosing recurrence. Two nuclear medicine specialists analyzed PET-CT findings separately, with no available information from previous conventional imaging results. If no agreement was achieved, expert team reviewed the images and made final decision. PET-CT results were assigned as 1. positive for recurrence, or 2. normal PET-CT findings. Positive PET-CT results were then divided in three categories: only loco-regional relapse, distant metastasis without locally active tumor, and both local and distant recurrence.

Magnetic resonance imaging and computed tomography imaging

For comparison with hybrid imaging, written reports of conventional imaging modalities (CT or MRI) were acquired. MRI examinations contained of T1 and T2 sequences, post-contrast and diffusion-weighted (DWI) images, with abdominal and pelvic region included, in

all women who underwent magnetic resonance imaging. High resolution contrast enhanced CT images, with minimum one portal-venous phase acquisition included, were acquired from remaining patients. All conventional imaging results were also defined as positive or negative for recurrence, according to current interpretation guidelines.

For calculation of conventional and hybrid imaging diagnostic performances final diagnosis (reference standard) was obtained histopathologically (biopsy or surgery) when possible, while in other cases women were followed-up clinically and by imaging, for minimum six months, in order to confirm/refute diagnosis made by index (imaging) tests.

Patients follow-up

Information about disease progression was acquired from patients' medical records. Follow-up of all patients consisted of anamnesis, clinical examinations, and diagnostic imaging in form of CT/MRI/PET-CT according to clinical indications. Longest follow-up period was 3.5 years (41 months), with median follow-up time of 13 months. Progression of disease was declared in cases of new disease sites or progression in size/number/FDG uptake level detected on imaging during follow-up, and in cases of death due to tumor. Progression free survival time was calculated from the day of PET-CT examination until detection of progression, or until the end of follow-up time if there was no progression.

Statistical analysis

Descriptive and analytical statistical methods were used in data analysis. Sensitivity, specificity and diagnostic accuracy of conventional imaging (CT/MRI) and PET-CT were calculated using standard formula, on patient basis. Survival analysis in settings of positive and negative CIM findings, positive and negative hybrid imaging results, and with different types of PET-CT positive results (loco-regional relapse only/distant lesions only/both local and

distant disease) was performed using Kaplan-Meier and Log Rank tests. IBM SPSS Statistics program, Version 25.0 (IBM Corp, Armonk, NY, USA) was used for all statistical calculations, and p value ≤0.05 was considered statistically significant.

RESULTS

Total of 37 women was included in the study, average age 60 ± 16 years. Most of the patients had FIGO I or II initial disease stage, which were present in 25/37 females (68%), whereas the remaining patients were diagnosed with advanced disease (FIGO stages III and IV). Endometrioid type endometrial carcinoma was the most common histological tumor type, proven in 27/37 women, while the remaining examinees had some of the other types: carcinosarcoma in 4 cases, 3 patients with endometrial stromal sarcoma, 2 leiomyosarcoma and 1 case of serous endometrial adenocarcinoma. In 28/37 cases we managed to acquire information on histological tumor grade, with even distribution of grades among patients. In Table 1, an overview of patients' clinical data, pathohistological and imaging results is displayed.

Results of conventional imaging (CT or MRI) were positive for relapse in 31 women (84%), while 6 patients (16%) had negative CT/MRI results. Calculated sensitivity and diagnostic accuracy of CT/MRI in detection of uterine cancer recurrence were 92.6% and 78.4%, respectively, with much lower specificity of only 40%. Positive predictive value was 80.6% and NPV was 66.7%.

In eight patients (22%), positron emission tomography/computed tomography results were negative for uterine cancer recurrence. Out of remaining 29 women with positive PET-CT, 9 (24%) had loco-regional lesions only, in 10 patients (27%) only distant metastatic sites were detected, and 10 women (27%) were presented with both local and disseminated active lesions on FDG PET-CT (Figures 1 and 2). FDG PET-CT displayed better diagnostic abilities

in comparison to CIM, with sensitivity of 96.3%, specificity of 70%, PPV and NPV 89.7% and 87.5% respectively, and diagnostic accuracy of 89.2% (Table 2). Concordance of hybrid imaging with CIM findings was present in 29/37 patients (78%). With regard to conventional imaging true positive examinees, in 52% (13/25) of cases additional active disease sites were seen on hybrid imaging, missed by CT/MRI.

In 21/37 cases, there were signs of progressive disease during follow-up. Women with pathological CT/MRI results had mean PFS time of 19.8 ± 2.8 months, while in patients with normal conventional imaging findings mean PFS was 34.3 ± 5.2 months ($p = 0.114$) (Figure 3). On the other hand, women with positive PET-CT findings had shorter mean PFS of 18.3 ± 2.8 months than PET-CT negative patients, with mean progression free survival time of 31.4 ± 3.4 months ($p = 0.023$) (Figure 4). Moreover, women who had both loco-regional and distant disease relapse on hybrid imaging had the shortest PFS of 9.4 ± 2.4 months, followed by patients with only distant metastasis (PFS 20.9 ± 4.7 months), and women with loco-regional disease only (PFS 26.3 ± 5.6 months) ($p = 0.002$) (Figure 5).

DISCUSSION

This study analyzed diagnostic abilities and prognostic role of FDG PET-CT in patients treated for uterine corpus cancer, and compared it to conventional imaging (CT and MRI). Our results suggest high sensitivity and accuracy of FDG PET-CT in detection of uterine cancer relapse, with also better specificity comparing to conventional imaging. Furthermore, PET-CT positive patients show shorter progression free survival.

In our research, obtained values of sensitivity and accuracy of PET-CT in patients treated for uterine cancer were high, reaching 96.3% and 89.2%, respectively. Systematic review and meta-analysis by Bollineni et al. [12], which included 8 papers, also reported high sensitivity and diagnostic accuracy of PET-CT in detection of recurrent endometrial cancer, with values

of 95% and 93%, respectively, which is in concordance with our results. On the other hand, specificity in our study was only 70%, somewhat lower than in aforementioned meta-analysis where it reached 91%. One of the main drawbacks of FDG PET-CT is its lack of specificity, since both malignant and benign (mostly inflammatory) lesions can show elevated fluorodeoxyglucose uptake, and our results could be explained by high prevalence of post-therapeutic and unspecific inflammation in our patients, combined with relatively low number of true negatives. False positive PET-CT results in our study were caused by granulomatous post-treatment inflammation, reactive inflammatory changes in lymph nodes, and bone osteoporosis. When it comes to uterine sarcomas, literature data show somewhat different results of PET-CT diagnostic abilities in patients after primary treatment. In a paper by Albano et al. that evaluated 41 women treated for uterine sarcoma, obtained values of FDG PET-CT diagnostic capabilities were 88% for sensitivity, 98% for specificity and 93% for accuracy [13]. With regard to low number of uterine sarcoma patients in our research (n = 5), that could explain partial discrepancies with our results.

In women treated for uterine neoplasms in our research, PET-CT showed somewhat better sensitivity than conventional imaging (96.3% for PET-CT vs. 92.6% for CT/MRI). However, the main advantage of hybrid imaging comparing to conventional methods in our study was considerably higher specificity (70% for PET-CT vs. 40% for CT/MRI) and subsequently higher overall accuracy (89.2% for PET-CT vs. 78.4% for CT/MRI). Higher specificity of PET-CT comparing to CIM could be the result of morphologically still present lesions (post-therapy sequels) on conventional imaging, but without metabolic activity. Ozcan Kara et al. also evaluated post-treatment PET-CT in 31 patients with endometrial carcinoma, showing its superiority over conventional imaging, but with main difference in sensitivity values (100% PET-CT vs. 46% CIM), while both PET-CT and CIM had relatively high specificity [14]. However, overall accuracy of both PET-CT and CIM (97% and 74%) in their

research was similar to ours. One of the possible explanations of only partial agreement with our results was relatively small sample size in both studies, with significantly higher fraction of negative vs. positive imaging results in the work of Ozcan Kara et al. [14] comparing to our sample. On the other hand, Albano et al. [15] did an analysis on 157 women with suspicion of relapsed endometrial cancer, where they obtained high values of sensitivity, specificity and accuracy for FDG PET-CT (96%, 99%, 97%, respectively), with inferior results of conventional imaging, particularly concerning specificity (sensitivity 97%, specificity 62%, accuracy 80%), which is in agreement with our results. Similar results were attained in a study by Sharma et al. [16], where PET-CT showed higher specificity and accuracy (96.4% and 92.1%, respectively) in detecting recurrent endometrial cancer than CIM (62% and 76.3%, respectively), with comparable sensitivity (85.1% PET-CT vs. 89.5% CIM), thus being in concordance with our research. With regard to imaging of uterine sarcoma after primary treatment, Sharma et al. [17] also demonstrated superior sensitivity, specificity and accuracy of hybrid imaging over CT/MRI (85.7%, 100% and 93.3% vs. 57.4%, 87.5% and 73.3%, respectively) in their analysis on 12 patients, with higher fraction of negative vs. positive imaging findings than in our sample, which can explain partial discrepancies with our results.

Besides aforementioned, PET-CT showed another advantage over CIM in uterine cancer, since it detected additional metabolically active recurrent lesions in 13 out of 25 CT/MRI true positive women, which can be of great importance in further patient management and change treatment approach, e.g. by choosing systemic over local treatment. Accordingly, it was previously shown by Panagiotidis et al. [18] that in patients with intra-abdominal malignancies (including uterine cancer patients) and with negative CIM results, PET-CT can often detect missed peritoneal and other active lesions. In a paper by Ferioli et al. [19] it was demonstrated that postoperative PET-CT can change treatment plan endometrial cancer patients in 8.6-22.4% of cases, which was afterwards also confirmed by Albano et al. who showed that PET-CT

influenced therapeutic approach in 33/157 suspected recurrent endometrial carcinoma patients [15]. Impact of hybrid imaging on therapy decision was also shown in women with suspected recurrent uterine sarcoma [13, 20].

Although CT/MRI negative patients had shorter progression free survival in comparison with CIM positive women treated for uterine cancer in our study, that did not reach statistical significance. However, PET-CT positive patients had significantly shorter PFS than women with normal PET-CT findings (18.3 ± 2.8 months vs. 31.4 ± 3.4 months). These results are concordant with findings of Albano et al. [15] which also showed longer PFS but also longer overall survival in patients with suspected recurrent endometrial cancer and negative PET-CT. In addition, in our research we also demonstrated PFS differences in PET-CT positive patients depending on disease spread: in cases with only loco-regional disease detected PFS was longest (26.3 ± 5.6 months), followed by that in women with distant lesions only (PFS 20.9 ± 4.7 months), and patients with both local and distant active disease present on PET-CT who had shortest PFS of only 9.4 ± 2.4 months. In a study on 61 patients treated for endometrial carcinoma, Chung et al. [21] found that post-treatment PET SUVmax values correlated with disease free survival (DFS), such as that patients with SUVmax <4.25 had statistically longer DFS. Saga et al. [22] also analyzed possible prognostic role of PET in 21 women treated for endometrial carcinoma, and suggested that negative PET finding could be a predictor of good prognosis.

One of the limitations in our study was relatively small sample size. The other drawback is lack of histopathological confirmation in all of our patients as a gold standard. Furthermore, this study included somewhat heterogeneous sample of tumor histopathological types, which can have different prognosis in general, but with endometrioid type endometrial cancer being most common by far. However, this can better reflect role of FDG PET-CT in everyday clinical practice.

CONCLUSION

Our results suggest important role of FDG PET-CT in clinical practice in follow-up and suspicion for recurrence of uterine cancers, with high sensitivity and overall accuracy. Additional advantage of PET-CT over CT and MRI could be its capability to discover larger number of active tumor sites, and also better specificity. Moreover, PET-CT results in these patients can also have prognostic impact, with PET-CT negative women showing significantly longer progression free survival.

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Table 1. Patients' characteristics

Characteristic	**Value**
Age (years)	
mean ± sd	60 ± 16
Initial FIGO disease stage, n (%)	
I	14 (38%)
II	11 (30%)
III	8 (21%)
IV	4 (11%)
Tumor histological type, n (%)	
Endometrial carcinoma	32 (86%)
Endometrioid type	27 (73%)
serous adenocarcinoma	1 (3%)
carcinosarcoma	4 (11%)
Uterine sarcoma	5 (14%)
Leiomyosarcoma	2 (5%)
Endometrial stromal tumor	3 (8%)
Tumor grade, n (%)	
Low grade	9 (24.3%)
Intermediate grade	9 (24.3%)
High grade	10 (27%)
Unknown	9 (24.3%)
CT/MRI findings, n (%)	
Positive	31 (84%)
Negative	6 (16%)
PET-CT findings, n (%)	
Positive	29 (78%)
Negative	8 (22%)

FIGO – the International Federation of Gynecology and Obstetrics; CT – computed tomography, MRI – magnetic resonance imaging; PET-CT – positron emission tomography / computed tomography

Table 2. Diagnostic performance of CT/MRI and PET-CT

	TP (n)	TN (n)	FP (n)	FN (n)	Sensitivity (%)	Specificity (%)	Accuracy (%)
CT/MRI	25	4	6	2	92.6%	40%	78.4%
PET-CT	26	7	3	1	96.3%	70%	89.2%

CT – computed tomography; MRI – magnetic resonance imaging; PET-CT – positron emission tomography / computed tomography; TP – true positive; TN – true negative; FP – false positive; FN – false negative

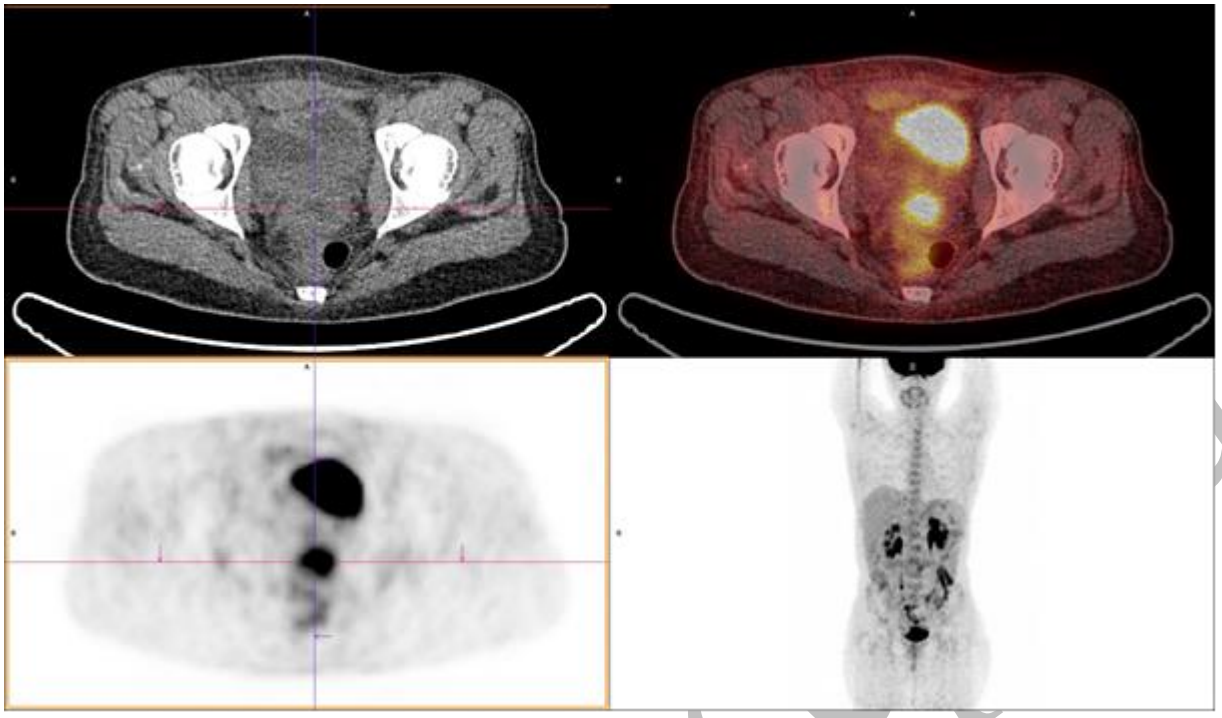

Figure 1. Local relapse after surgery for uterine sarcoma presented as ^{18}F-fluorodeoxyglucose avid lesion on positron emission tomography / computed tomography, without signs of distant disease spread

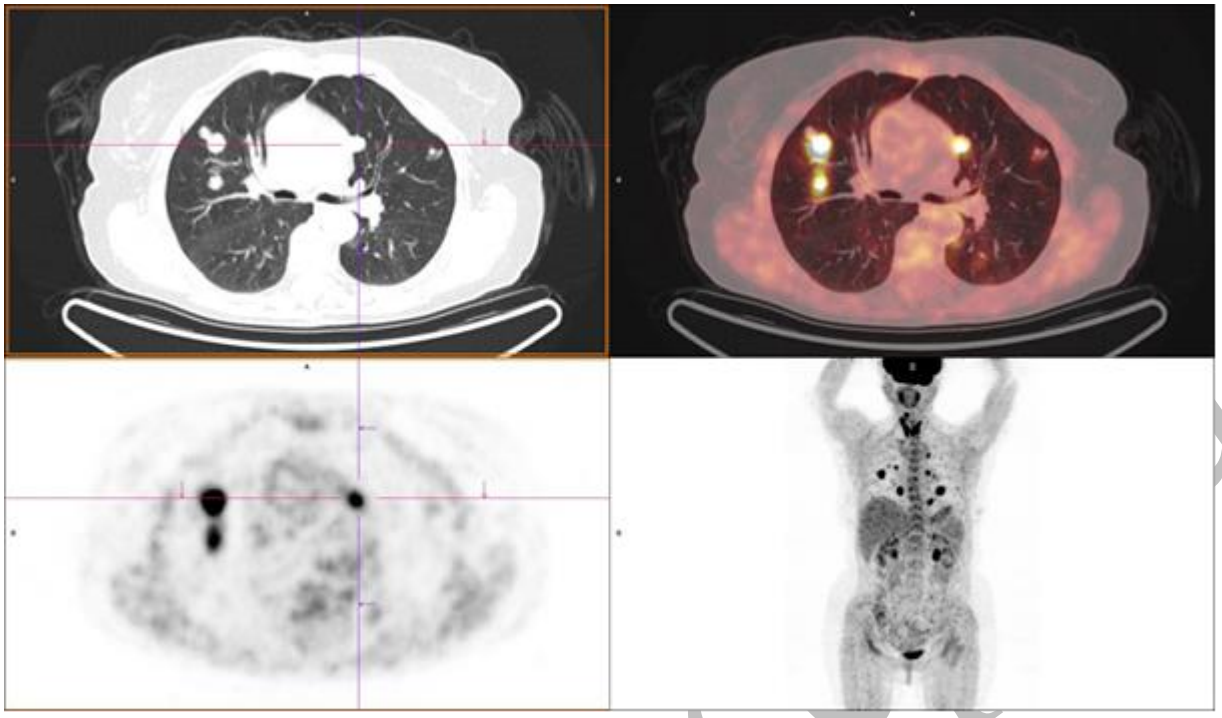

Figure 2. Lung metastasis on ^{18}F-fluorodeoxyglucose positron emission tomography / computed tomography in patient previously treated with surgery and irradiation for endometrial adenocarcinoma

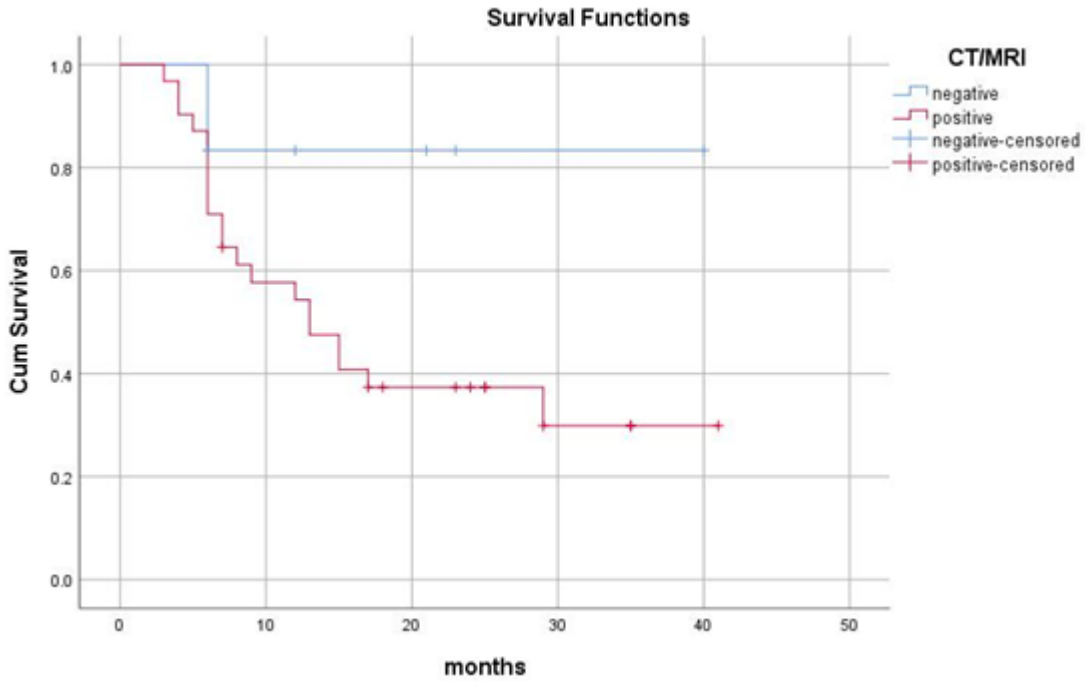

Figure 3. Kaplan–Meier survival curves showing progression free survival in patients with negative and positive computed tomography / magnetic resonance imaging (CT/MRI) findings; logrank, p = 0.114

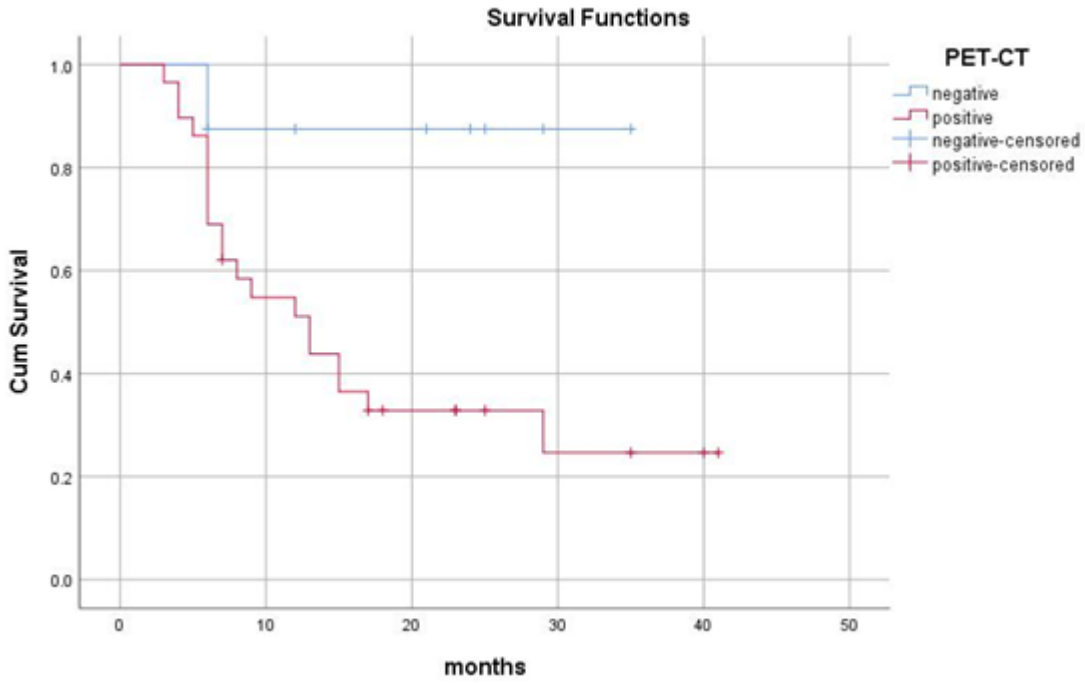

Figure 4. Kaplan-Meier survival curves showing progression free survival in positron emission tomography / computed tomography (PET-CT) negative and positive patients; logrank, p = 0.023

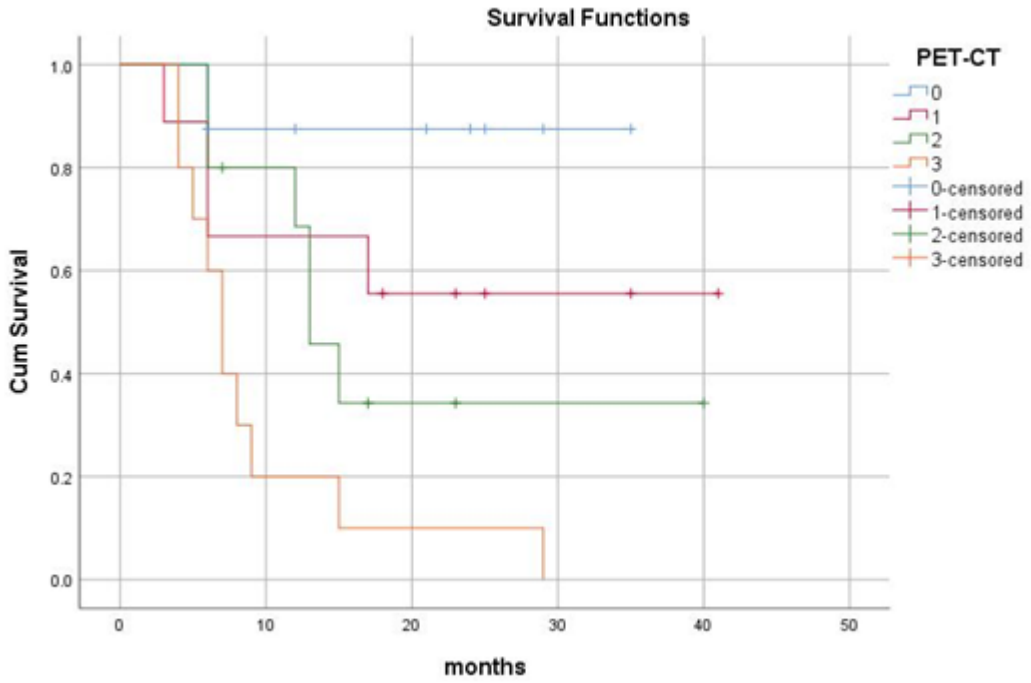

Figure 5. Kaplan–Meier survival curves showing progression free survival depending on type of positron emission tomography / computed tomography (PET-CT) findings: 0 – negative positron emission tomography / computed tomography, 1 – loco-regional lesions only, 2 – distant metastasis only, 3 – both loco-regional and distant active disease; logrank, p = 0.002

