Review Article

The role of fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) in staging and restaging of patients with uterine sarcomas: a systematic review

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Abstract: To evaluate the role of fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) in staging and in detecting recurrence in uterine sarcomas (US), a systematic review was performed on PubMed and Medline, for studies reporting the diagnostic performance of ^{18}F-FDG-PET/CT, 16a-^{18}F-fluoro-17b-estradiol (^{18}F-FES)-PET/CT, 30-deoxy-30-[^{18}F]-fluorothymidine (^{18}F-FLT)-PET, conventional imaging (CT, magnetic resonance imaging and ultrasonography) in staging or in detecting recurrence/post therapy surveillance in US published up to October 2018. Out of 70 studies initially identified, 39 articles were chosen concerning the role of ^{18}F-FDG-PET/CT in staging and restaging in US, combined with other PET tracers or conventional imaging. To date, the preoperative evaluation of US is problematic. However, there is some evidence in favor of the use of ^{18}F-FDG-PET/CT in association with the study of certain clinicopathological factors, and metabolic parameters that showed good accuracy in the staging of US. This helps the stratification of patients according to the identified risk, contributing to avoid unnecessary surgery. Whereas, the majority of the studies included in this review article showed that ^{18}F-FDG-PET/CT is an accurate method for the detection and localization of local and distant relapses in patients affected by US, especially when combined conventional imaging and immunohistochemical analysis. This combination had a good impact on clinical decision making of these patients. All the PET study results reported in this review have demonstrated the possible use of PET/CT in order to improve the assessment of this rare disease for the initial staging, therapeutic planning and subsequent follow-up. Given the small body of literature concerning this topic, further and larger studies are, therefore, an essential next step in confirming the value of this promising imaging tool.

Keywords: Uterine sarcomas; positron emission tomography (PET); fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT); 16a-^{18}F-fluoro-17b-estradiol-positron emission tomography/computed tomography (^{18}F-FES-PET/CT); 30-deoxy-30-[^{18}F]-fluorothymidine-positron emission tomography (^{18}F-FLT-PET)

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Introduction

Uterine sarcomas (US) are infrequent gynecologic tumors representing 3% to 7% of all uterine malignant cancers (1). This group of neoplasms presents differing tumor biology, natural history and response to treatment (2). Histologic classification of US is based on the differentiation and growth pattern of the neoplastic cells and their presumed cell of origin (3). This group of tumors includes leiomyosarcoma (LMS), the most common subtype of US, endometrial stromal sarcomas (ESS), and undifferentiated endometrial sarcomas (UES) (4). At the beginning, uterine carcinosarcoma (UCS) was categorized as a type of sarcoma (malignant mixed Mullerian tumor), afterward it has been regarded as a dedifferentiated or metaplastic form of endometrial carcinoma (3,5). There is also a particular type of uterine smooth muscle tumor (USMT) that has histological characteristics similar to the LMS for which a differential diagnosis must be made. This tumor is called an atypical smooth muscle tumor (STUMP) (6). Although there is no universal staging system for sarcomas, a staging system for US has been created by the International Federation of Gynecology and Obstetrics (FIGO). This staging system has two classifications, one for LMS and ESS and one for adenosarcoma, while UCS uses the endometrial cancer staging system (5,6). No validated clinical or imaging modality can offer a reliable preoperative diagnosis (7,8). The first line investigation when a woman has suggestive symptoms of uterine cancer is pelvic ultrasound (9), usually followed by computed tomography (CT) or magnetic resonance imaging (MRI). In addition to conventional morphological imaging that allows to assess spreading disease into surrounding tissue, metabolic imaging using fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) is now used to evaluate doubtful neoplasms or advanced metastatic disease (10). PET is an advanced diagnostic method for tumor diagnosis, staging and restaging (11). This nuclear-medical investigation technique allows to study the metabolic behavior of tumor cells. ^{18}F-FDG is a glucose analogue that follows glucose metabolism, enters cancer cells via glucose transporter proteins known as GLUT transporters and it is phosphorylated by the hexokinase into FDG-6-phosphate. Since FDG-6-phosphate is not recognized by the glucose-6-phosphate isomerase it gets stuck, builds up in cells and appears in ^{18}F-FDG-PET. In particular, neoplastic cells have an intense glycolytic activity due to an increase in the expression of GLUT transporters, mainly the GLUT-1 subtype and to the increase of hexokinase enzyme. Therefore, the uptake of FDG in cancer cells reflects tumor metabolism which is measured semi quantitatively using the standardized uptake value (SUV) and identifying the maximum metabolic activity within the tumor (SUVmax) (12). Moreover, some studies have shown that in addition to SUVmax, which reflects only the point of maximum metabolic activity within cancer cells, there are volume-based metabolic PET parameters that could provide additional information regarding cancer behavior, considering activity metabolic rate of the entire tumor, and that have been reported as possible prognostic factors (12). These parameters include tumor metabolic volume (MTV), defined as total tumor volume, and total lesion glycolysis (TLG), automatically calculated by multiplying the primary cancer MTV by the mean SUV (13). Therefore, ^{18}F-FDG-PET/CT is now widely used in the evaluation of many oncological diseases (14), both in staging and in the search for metastatic lesions or suspected recurrence. ^{18}F-FDG is a radiopharmaceutical that accumulates not only in malignant cells, but also in normal and inflamed tissues, and in benign lesions (15) thus generating sources of error that can cause false positives and false negatives (14). Potential false positives include physiological absorption of FDG in utero and ovaries during ovulation and menstruation, inflammatory and infectious processes in the pelvic area, benign lesions such as leiomyomas, focal ureteral/urethral or bladder activity which may mimic the disease; and vesicovaginal fistulas which may limit the assessment of the disease. Instead, potential false negatives include reduced spatial resolution of PET, movement artifacts, and physiological bowel activity that can mask peritoneal disease and small lymph nodes. ^{18}F-FDG low avidity tumors, slow growth, with low degree of malignancy or well differentiated, with mucinous component, lesions adjacent to the bladder that can be masked by high physiological activity excreted from the urinary tract and metal implants/devices that can cause attenuation correction artifacts on PET/CT masking small volume peritoneal disease (14,16). Anyway, metabolic imaging with FDG-PET has assumed an important role in the therapeutic decision of malignancies, such as in lung cancer, colorectal cancer, melanoma, head and neck cancers, and breast cancer (11). In particular, this imaging tool is effective in certain situations such as the recognition of doubt lesions at CT, monitoring response to therapy, and early detection of non-responsive tumors, which can provide a basis for alternative treatment strategies in specific tumors. Some studies have shown that PET has

a significant value in staging and restaging of US but there are still few studies regarding this topic due to the rarity of the disease. The present review discusses the current role of ^{18}F-FDG-PET/CT in the management of US, discussing its usefulness and limitations in the imaging of these patients.

We present the following article in accordance with the PRISMA reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-20-76/rc).

Materials and methods

A literature search until October 2018 was performed in PubMed and Medline with no language limit. Of the 70 studies initially identified, 39 articles were chosen concerning staging and restaging and combined assessment with other PET tracers or conventional imaging, including reviews (17), case reports (18-20), prospective and retrospective studies. The following words and key phrases were searched: "endometrial stromal sarcoma" or "uterine sarcoma" or "mesenchymal uterine tumors" or "uterine stromal sarcoma" or "uterine leiomyosarcoma" or "carcinosarcomas" and "magnetic resonance imaging", "positron emission tomography" or "^{18}F-FDG PET/CT" or "18-F FES PET/CT" or "^{18}F-FLT PET" and "computed tomography".

Results

Literature search and selection of studies

Our research yielded 70 records, of which 5 records of duplicated abstracts were excluded. Also, non-relevant 20 studies and 5 letters were excluded. The remaining forty full text articles were assessed for eligibility and one article was excluded due to insufficient data for the calculation of sensitivity and specificity of ^{18}F-FDG-PET in evaluation of patients with US. Finally, 39 studies were selected that were eligible for systematic review, including reviews, case reports, prospective and retrospective studies.

Staging

Preoperative evaluation of US is problematic. Although there is still no real score for the preoperative assessment of US, a retrospective analysis developed a scoring system that combined several predictive factors considered useful for the preoperative diagnosis of this disease in order to avoid unnecessary surgery (21). This score, called PREoperative Sarcoma Score (PRESS), consists of a maximum score of 7 points and examines preoperative clinical, laboratory results such as lactate dehydrogenase (LDH) levels, imaging such as MRI and cytological results. Concerning serum LDH values, a study saw that ^{18}F-FDG-PET/CT combined with serum LDH levels (≥229 U/L) was more accurate than either method alone for the diagnosis of LMS (accuracy of 100%) (22). Whereas Kusunoki *et al.* showed that combining a SUVmax cutoff value of 7.5 in ^{18}F-FDG-PET/CT with LDH serum levels decreases false-positive rate in patents with MRI suspicious for US. This might help to avoid unnecessary surgery in patients who may only have leiomyoma (23,24). In other studies, the preoperative evaluation has focused on the analysis of different metabolic parameters determined by ^{18}F-FDG-PET/CT, that may have prognostic potential; in particular, a study has shown that the parameter of SUV max in ^{18}F-FDG-PET/CT performed preoperatively in patients with LMS can be an important predictive prognostic factor, helping in therapeutic decision-making based on risk (25). Another study, showed that MTV and TLG parameters but not the SUVmax, defined by ^{18}F-FDG-PET/CT performed preoperatively in patients with primary UCS, were associated with clinical pathological prognostic characteristics such as cancer antigen 125 (CA-125) levels, FIGO stage, histology, vascular lymphatic invasion, myometrial and adnexal invasion, and they could influence prognosis in terms of progression-free survival (PFS) and overall survival (OS), thus helping in the stratification of patients to high risk not eligible for primary surgery (26).

Lee *et al.* has shown that the metabolic parameter TLG measured preoperatively is an important independent prognostic marker of relapse in patients with UCS (13). In a multicenter retrospective study, it has been examined the prognostic value of tumor heterogeneity determined in terms of negative linear MTV regression slope (nMLRS) on ^{18}F-FDG-PET/CT performed preoperatively in patients with uterine LMS, demonstrating that nMLRS is a potential and important prognostic marker in the detection of recurrence (27). Moreover, Ho *et al.* demonstrated that there is a characteristic pattern of FDG absorption visible in PET/CT to better differentiate LMS/STUMP from benign leiomyomas, called "hollow ball" (28). This sign is observed in the presence of areas of coagulative tumor necrosis, typical of LMS and STUMP but not of leiomyomas. As a further confirmation tool for the differential diagnosis, a new parameter such as the metabolic tumor/necrosis ratio was also studied.

Monitoring response and restaging/post-therapy surveillance

Most research has shown how the application of ^{18}F-FDG-PET/CT in the monitoring response and restaging of US had good impacts on clinical decision making.

A retrospective study has shown that ^{18}F-FDG-PET/CT has good sensitivity and specificity in identifying local and distant relapses (29). Also, Park *et al.* have shown that PET or PET/CT are very useful in detecting disease in patients with suspected relapse, with good sensitivity especially in asymptomatic patients (30). These studies had an important influence on the clinical management of a good percentage of patients (29,30). A prospective pilot study suggests that ^{18}F-FDG-PET/CT is useful in planning palliative therapy in patients with inoperable UCS in order to achieve a better quality of life, avoiding aggressive curative treatments (31). Another study demonstrated that ^{18}F-FDG-PET/CT is an effective method in the follow-up (FU) of patients with US, both in the evaluation of patients undergoing surgical removal of the uterus for other reasons where the sarcoma is found histologically and randomly on the operative specimen and in the exclusion or in proving the presence of localized or disseminated relapses (32). Moreover, Inoue *et al.* showed that ^{18}F-FDG-PET/CT is useful in the detection of ESS with a high proliferative index (Ki-67 index) as they observed that the uptake of the radiotracer was related to the index of proliferation (33).

^{18}F-FDG-PET/CT compared to conventional imaging (CT, MRI and ultrasonography)

Several studies have evaluated the efficiency of ^{18}F-FDG-PET/CT in finding suspected tumor relapse or in FU, focusing on its impact on patient clinical management compared to conventional imaging. Umesaki *et al.* in a series of five cases compared the value of ^{18}F-FDG-PET/CT in the diagnosis of US against the value of MRI imaging and power Doppler ultrasound (34). Additional work was done in which greater sensitivity of ^{18}F-FDG-PET/CT was demonstrated in early research of FU relapse after treatment in patients with US at FIGO stage I, compared with CT and ultrasound (35). For these authors, the major application of ^{18}F-FDG-PET/CT in US is the recognition of local or diffuse relapse of the disease in FU. On the contrary, Sharma *et al.* have shown that ^{18}F-FDG-PET/CT is a very specific diagnostic method for the recognition of relapses in treated US patients, however it offers no more help than conventional imaging for this goal (36). Also, Lee *et al.* demonstrated that ^{18}F-FDG-PET/CT, performed preoperatively, allows to identify UCS at the onset and extrauterine localizations of the disease, with high precision similar to MRI (37). Furthermore, ^{18}F-FDG-PET/CT has a high sensitivity in the search for lymph node metastases in patients with UCS compared to MRI, and it could be useful in avoiding unnecessary lymphadenectomy. There is some evidence that the performance of multiparametric MRI (mp-MRI) was better than that of PET to distinguish between US and leiomyoma (38). In contrast, a study conducted on patients with suspicion non-benign USMT, showed that ^{18}F-FDG-PET in combination with MRI is more advantageous compared to MRI alone, and can help to avoid unnecessary surgical treatments, directing towards a conservative therapy (39).

Therefore, current literature shows different results on the accuracy of PET compared to MRI in the evaluation of patients with US; some studies show a comparable efficacy between both diagnostic tools instead other studies demonstrate a better accuracy of PET than MRI. Therefore, further studies and larger number of cases are needed to be able to affirm the validity of the methods, taking also into consideration the possibility of being able to combine the two methods to have a better diagnostic impact.

Alternative PET tracers in molecular imaging of US and correlation with immunohistochemical analysis

A number of studies have begun to examine the correlation between tumor uptake of 16a-^{18}F-fluoro-17b-estradiol (^{18}F-FES) and ^{18}F-FDG radiopharmaceuticals, the expression of sex hormone receptors, such as estrogen receptor (ER), progesterone receptors (PR) and other parameters such as GLUT-1 and Ki-67 studied with immunohistochemical analysis in patients with mesenchymal uterine cancers. In particular, a study showed that the uptake of ^{18}F-FES correlates with the expressions of the alpha subtype of ER and the PR, and the uptake of ^{18}F-FDG correlates with the expression of GLUT-1 and Ki-67 in all mesenchymal neoplasms (40). Also, Yamamoto *et al.* showed that ^{18}F-FDG SUVmax, ^{18}F-FES SUVmax, but in particular the ^{18}F-FDG/^{18}F-FES ratio could be a useful marker of the connection between sex hormone receptor expression (ERα, ERβ, PR, PR-B) and tumor proliferative activity (Ki-67, MIB-1, GLUT-1) in uterine tumors, especially in the US (41). Another study, showed that

FDG uptake was significantly higher and FES uptake was significantly lower for LMS than it was for leiomyoma (42). In contrast, Huang *et al.* showed that in UCS there is a high expression of ERβ, especially in advanced cancer and a repressed expression of the ERα and PR receptors (43). Additional efforts were directed to evaluate the efficacy of 30-deoxy-30-[^{18}F]-fluorothymidine (^{18}F-FLT)-PET in the differential diagnosis between malignant neoplasms and leiomyomas compared to ^{18}F-FDG-PET/CT (44). In particular, in a prospective study, the positive predictive value and accuracy of ^{18}F-FLT-PET were superior to those of ^{18}F-FDG-PET/CT. ^{18}F-FLT, analogue of thymidine, is phosphorylated by thymidine kinase 1, it is not incorporated into DNA, but accumulates inside the cell. Rapidly proliferating cells exhibit increased expression of this enzyme. Some papers have shown that the absorption of ^{18}F-FLT correlated well with index of cell proliferation (Ki-67), measured by immunohistochemical analysis, in several neoplasms, compared to ^{18}F-FDG (45). Also, Gokaslan *et al.*, in several studies, have reported that Ki-67 is a useful indicator for making the differential diagnosis between LMS and leiomyoma (46).

Conclusions

With this work, we aimed to review the available literature on the role of ^{18}F-FDG-PET/CT in staging and restaging of patients with US. This study has identified that several lines of evidence suggest that a promising role of metabolic imaging using FDG-PET/CT may be its skill to quantitatively foretell DFS, OS evaluating the disease not only with SUVmax, but also with others metabolic parameters (MTV, TLG). In addition, in a series of studies on the evaluation of US, great importance is given to the integration of radiological studies with immunohistochemical analysis. In addition, according to the evidences presented in this work, it would be desirable PET and MRI fusion imaging for the evaluation and FU of US, as it allows more precise characterization and localization of ^{18}F-FDG uptakes, by combining an anatomical and functional imaging technique (47). Together, the studies reported in this review support the use of PET/CT for improving the assessment of this US for the initial staging, therapeutic planning, and subsequent FU. In consideration of the limited number of articles in the literature at present and the low incidence of pathology, further and large studies are necessary to confirm the ability of this promising imaging tool.

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