Peer Review File

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The paper titled “The Role of 18F-FDG PET/TC in staging and restaging of patients with uterine sarcomas: A Systematic Review” is interesting. 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. However, there are several minor issues that if addressed would significantly improve the manuscript.

Comment 1. What is the difference between this study and published study [Role of 18F-FDG PET/CT in restaging and follow-up of patients with uterine sarcomas, Rev Esp Med Nucl Imagen Mol, PMID: 30396849]? What is the innovation? These should be described in the discussion.

Reply 1: The article written by *D'Albano et al* is based to the study of 18FDG PET/CT exclusively with the FDG tracer only and to the evaluation of patients with US in restaging and post-treatment surveillance; our study instead aims to review the role of 18F-FDG / CT PET in US not only in restaging and follow up but also in staging and preoperative evaluation, also taking into consideration the possibility of using other radiopharmaceuticals and comparing it with the conventional imaging.

Comment 2: How to evaluate the diagnostic performance of 18F-FDG PET/CT and MRI for uterine sarcoma?

Reply 2: The 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.

Comment 3: Does 18-FDG-PET/CT have a role to play in the lung metastases from benign uterine leiomyoma?

Reply 3: Yes, it does. There are still not many studies in this regard, however some case reports described in the literature have shown that in the PET / CT evaluation of patients with uterine leiomyoma and suspected lung lesions, most of these lesions show little or no metabolic activity, therefore, it is hypothesized that 18F-FDG-PET /

CT may play an important role in differentiating Pulmonary benign metastasizing leiomyoma (PBML) from malignant metastases.

Dai HY, Guo SL, Shen J, Yang L. Pulmonary benign metastasizing leiomyoma: A case report and review of the literature. *World J Clin Cases* 2020; 8(14): 3082-3089

Abu Saadeh F, Riain CO, Cormack CM, Gleeson N. Lung metastases from benign uterine leiomyoma: does 18-FDG-PET/CT have a role to play? Ir J Med Sci. 2019 May;188(2):619-624.

Sawai Y, Shimizu T, Yamanaka Y, Niki M, Nomura S. Benign metastasizing leiomyoma and 18-FDG-PET/CT: A case report and literature review. Oncol Lett. 2017;14(3):3641-3646.

Comment 4: What is the potential role of 18-FDG-PET/CT in other gynecological malignancies?

Reply 4: The posted literature on the role of 18F-FDG PET/CT in gynecological neoplasms is still maturing and recent literature has shown how the use of this imaging tool in staging and restaging these patients can have a significant impact on targeted treatment choice and disease management.

In particular, in a recent meta-analysis it was shown that PET / CT in patients with **ovarian cancer** plays an important role in the re-evaluation in case of documented or suspected relapse with an increase in CA125; it has a promising role in predicting response to chemotherapy in patients undergoing neoadjuvant chemotherapy, on the contrary in staging, although it has been shown that PET/CT is effective in detecting extra-abdominal lesions of the disease compared to CT, this superiority does not translate into a significant management change for the patient.

The 18F-FDG PET / CT in **cervical cancer** plays an established role in visualizing distant and lymph node metastases in advanced patients and is essential in patient selection for exenterative surgery; it can also be useful for evaluating the response to therapy in terms of survival.

The primary role of 18 F-FDG PET CT in **endometrial cancer** is the detection of extra uterine disease. It does not yet play a role in primary tumor staging and detection but has modestly better accuracy for lymph node staging than conventional imaging, however its effectiveness depends on node size. This diagnostic tool is also effective in detecting disease recurrence and has potential value as a predictive biomarker but requires better standardization of metabolic cut-offs.

Narayanan P, Sahdev A. The role of 18F-FDG PET CT in common gynaecological malignancies. Br J Radiol. 2017 Nov;90(1079):20170283.

Comment 5: How to evaluate the role of 18F-FDG PET/CT in detecting recurrent disease in patients after treatment for uterine sarcoma? How's the effect? And compare it with conventional imaging, what are the advantages?

Reply 5: According to study of *Sharma P et al* and as observed in previous works, the FDG PET-CT has a good specificity and sensitivity in the evaluation of recurrence in post-therapy patients with uterine sarcoma, however, does not provide any significant advantage over conventional imaging.

Comment 6: How about the application research of 18F-FDG PET/CT in the diagnosis and staging of lymphoma?

Reply 6: Several studies have now consolidated the role of FDG-PET / CT in lymphomas, in particular in staging where it plays a central role in the choices of the most appropriate treatment. It plays an important position also on the interim and post therapy evaluation and in the post-treatment evaluation of relapsing disease to guide in salvage therapy, on the contrary, it currently does not play a fundamental role in routine follow-up after completion metabolic response to therapy. Although the FDG PET/CT has more sensitivity compared to other conventional imaging methods, the positive predictive value of FDG for lymphoma remains moderate, with numerous causes of non-neoplastic FDG avidity (e.g. granulomatous inflammation, lymphoid hyperplasia) potentially resulting in false positives interpretations of the stage of the disease o relapsed / refractory lymphoma, therefore it would be useful to deepen this aspect, in order to reduce false positives and avoid inappropriate treatments.

Comment 7: What is the value of 18F-FDG PET/CT combined with pelvic enhanced CT in preoperative TNM staging of cervical cancer?

Reply 7:

The most important role of 18F-FDG CT-PET in the staging of cervical cancer patients is the detection of distant lymph nodes or metastases compared to conventional MRI and CT with contrast, significantly influencing the therapeutic management and prognosis of patients. On the contrary, the evaluation of the primary lesion, MRI still plays a primary role today**.**

Narayanan P, Sahdev A. The role of 18F-FDG PET CT in common gynaecological malignancies. Br J Radiol. 2017 Nov;90(1079):20170283.

Comment 8: At present, there are few reports in the literature, and the pathological incidence is low. A large number of further studies are needed for verification.

Reply 8: Exactly, at the moment there are few studies in the literature regarding the role of FDG PET / CT in uterine sarcomas due to the low incidence of disease that limits the population sample of patients to be studied, therefore it would be desirable to confirm the validity of this promising diagnostic investigation through numerous and larger studies.