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Role of 18F-FDG PET/CT in the Carcinoma of the Uterus: A Review of Literature

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In the present review we reported the value of 18F-fluorodeoxyglucose (FDG) PET/CT in face of uterine cancer, in terms of sensitivity, specificity and accuracy. Moreover, we made a comparison with the other imaging techniques currently used to evacuate these tumors including contrast-enhanced CT, contrast enhanced-MRI and transvaginal ultrasonography. FDG PET/CT has been reported to be of particular value in detecting occult metastatic lesions, in prediction of response to treatment and as a pro-gnostic factor.

Key Words: Uterine cancer, cervical cancer, FDG PET/CT, contrast enhanced CT, MRI, accuracy, predictive value, prognosis

INTRODUCTION

Uterine malignancies including cervical and endometrial cancer, represent an important cause of morbidity and death among women.

In 2014, the American Cancer Society projected 12360 new cases and 4020 deaths for invasive cervical cancer in the United States. For uterine body cancer (including both endometrial cancer and uterine sarcomas), estimates for 2014 are about 52630 new cases with about 8590 deaths.[1,2] European statistics for 2012 reported 98984 new patients with uterine cancer with 23733 deaths, and projects 102423 new European cervical cancer cases for 2015. There were 58373 new cases of uterine cancer in 2012 with 24385 deaths, with a projection of 58868 new cases for 2015.[3] Following the most recent guidelines, preoperative evaluation includes clinical and gynaecological examination, chest radiography, transvaginal ultrasound, blood counts and liver and renal function profiles.[4,5] Abdominal contrast-enhanced computed tomography (CECT) is indicated to detect the presence of extrapelvic disease, while dynamic contrast-enhanced magnetic resonance imaging (MRI) seems to be the best tool to assess cervical involvement.[6] Molecular

imaging with 18F-FDG PET/CT has been proposed for inclusion in these guidelines, mainly to detect distant metastases.[4,5] Herein, we review current literature on FDG PET/CT in cervical and endometrial cancer, with respect to staging and restaging, treatment response monitoring, prognosis and surveillance.

CERVICAL CANCER

With the introduction of Papanicolau test (Pap-test) between 1955 and 1992, the cervical cancer (CC) related-death rate declined by almost 70%, because this screening procedure is able to early find tumoral changes in the cervix at its most curable stages.[1] The main cause of CC is a persistent human papilloma virus (HPV) infection, in particular the oncogenic subtypes HPV 16 and 18, which are detected in 99% of cervical tumors. Currently available vaccines seem to be effective, safe and capable of preventing HPV CC-related neoplasms.[7] Despite the strong recommendation of HPV vaccination in the at-risk population, along with regular gynaecologic examinations and Pap-test, CC still represents a major worldwide public health problem. CC remains the 3rd most common cancer among female population worldwide, representing 9% of all female cancers.[3]

As is typical for gynaecological cancers, early stage CC is usually asymptomatic until it extends to the nearest anatomic structures, causing pain, dyspareunia, discharge or abnormal bleeding.[4]

The International Federation of Gynecology and Obstetrics (FIGO) classification is based on tumor size, surrounding structure involvement (parametria, vagina, bladder, rectum) and distant metastases.[8]

There is growing evidence that the N status correlates with prognosis. Despite advancements in minimally invasive surgical techniques, FIGO encourages the use of imaging for pelvic and abdominal lymph node assessment.[8-11]

FIGO guidelines recommend CECT and MRI as first line imaging techniques for treatment planning in cervical cancer, while FDG PET/CT is emerging as an additional tool for N staging rather than T extension. FDG PET/CT parameters may be useful in estimating disease-free survival (DFS), time-to-relapse (TTR), and overall survival (OS). In addition to the well-known maximum standardised uptake value (SUVmax), there are other parameters measurable with PET/CT including the metabolic tumor volume (MTV). The MTV represents the viable metabolic tumor extent. Kim, et al.[12] evaluated 45 early FIGO stage cervical cancer patients with both SUVmax and MTV, and MTV proved to be an important independent prognostic marker for DFS.

Sironi, et al.[13] conducted a prospective study on 47 patients with early stage cervical cancer, carefully verifying that lymph nodes results as the analysed with pathology correlated with the FDG PET assessment, as demonstrated by labelling them by site and side and sectioning each surgical specimen in the same transverse plane used at PET/TC. The overall node-based sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of FDG PET/CT in revealing cancer spread irrespective of the node size (for a total amount of 1081 examined nodes) were 72%, 99.7%, 81%, 99.5%, and 99.3%, respectively. These values were even greater when calculated for nodes larger than 0.5 cm in short axis diameter.

One of the most challenging issues is the limited accuracy of FDG PET/CT with respect to smaller lymph nodes. In a multicenter prospective study, 237 patients with FDG PET/CT negative para-aortic lymph nodes underwent a laparoscopic lymphadenectomy. Upon pathological correlation, FDG PET/CT was falsely negative in 12% of cases, especially for lymph nodes of 5 mm or less.[14]

Nakamura, et al.[15] retrospectively investigated the prognostic value of FDG PET/CT and MRI parameters, comparing SUVmax and MRI-minimum apparent diffusion coefficient (ADCmin) in pelvic lymph nodes confined to the pelvis in patients with CC of stages Ib1 to Iva. DFS and OS were significantly lower in patients with greater nodal SUVmax; Chung, et al.[16] examined the relationship between recurrence and SUVmax in pelvic lymph nodes of patients with FIGO stage Ib to IIa. Multivariate analysis demonstrated that both lymph node SUVmax and parametrial invasion were independent risk factors for recurrence Patients with nodal SUVmax $\geq$2.36 and $<$2.36 differed significantly in terms of recurrence ($p<0.001$). Furthermore, the involvement of higher and deeper lymph nodes (not only para-aortic, but also retrocrural and supraclavicular) correlated with a worse prognosis.[17] SUVmax of pelvic lymph nodes is also predictive of treatment response, risk of pelvic disease recurrence, disease-specific survival and overall survival. In a recent series of 83 patients the presence of extrapelvic lymph nodes was even more significant.[18]

Some new interesting advances for T staging have been demonstrated with fused PET and MRI. Kitajima, et al.[19] retrospectively investigated the fusion of pelvic MRI and PET images, finding that accuracy for T status for fused vs.

non fused PET/MRI was significantly higher than PET/CT (83.3% vs. 53.3%, respectively). In another study, fused FDG PET/CT and MRI T2-weighted images were superior to CECT and MRI T1-weighted images in evaluating uterine and other gynaecological malignancies.[20]

FDG PET/CT has been shown to be helpful for therapy response assessment for several tumors,[21] included gynaecological malignancies.[22,23] One point to be elucidated is the evaluation of the best timing to be chosen to perform the interim PET and its correlation to the post-therapy PET results, as well as the correspondence to pathological findings. The main advantage for FDG PET in tumors undergoing therapy is the potential to timely differentiate responder from non-responder patients. Yoon, et al.[24] studied the at-interim and post-radiotherapy metabolic response on baseline PET-positive lymph nodes. Patients with poor or no response at inter-radiotherapy PET/CT had significant delayed failure on post-radiotherapy PET/CT. The 3-year DFS rate was significantly higher in the group who achieved a complete response respect to the other (71% vs. 18%, respectively). Similar behaviour was observed about the 3-year distant metastasis-free survival (79% vs. 27%, respectively). Another study suggested that a percentage change of SUVmax ≥60% at 4 week after the administration of concurrent chemoradiotherapy could be useful to predict complete response and progression-free survival.[25] A comparison between a FDG PET/CT obtained after 4 weeks of treatment and the baseline PET/CT, has been demonstrated to represent the best time point to evaluate the prediction to therapy also in the study of Kidd, et al.[26]

As frequently reported in literature of PET/CT in oncology, FDG PET/CT is most useful in visualizing local and distant recurrent disease, often more accurately than CECT or MRI for contributing to treatment adjustments. Percentages ranges are 90.3–96% for sensitivity and 81–100% for specificity, with ranges of accuracy, PPV and NPV of 86.5–99%, 86–100%, and 91.7–96%, respectively.[27-30]

ENDOMETRIAL CANCER

Corpus uteri cancer is the 4th common cancer in women in developed countries, accounting for 7.1% of female cancers based on 5-years-prevalence estimates.[3] Most cases are fortunately detected at early stages, because uterine bleeding is the most frequent presentation.[5] Surgeons and clinicians continue to debate whether standard approach of early stage endometrial cancer should include lymphadenectomy. In a large randomised series, systematic lymphadenectomy did not improve disease-free or overall survival.[31] In another selected population of 385 women with low-risk endometrial cancer, lymphadenectomy increased morbidity and was not cost-effective.[32] Thus, finding a reliable N staging technique could help in proper patient selection, by reducing unhelpful surgical interventions. In a recent large multicentric study on 318 patients, Antonsen, et al.[33] compared the diagnostic performance of PET/CT, MRI and transvaginal ultrasonography (TVUS) in preoperative staging endometrial cancer. PET/CT and MRI were found to be quite similar in assessing myometrial invasion with satisfactory NPV but TVUS had the best accuracy (71.6% vs. 60.7% for PET/CT and 65.6% for MRI); PET/CT, and MRI showed similar results for lymph node evaluation, with better results for PET/CT in estimating cervical invasion. The authors suggest that, although no single modality can replace surgical staging, combinations could improve accuracy. Due to their high NPV, PET/CT, and MRI could be used to select patients who should not be candidate for surgical staging. This is concordant with previous studies dealing on the same issue comparing FDG PET/CT to CECT and MRI for the pre-operative lymph node staging of 40 patients, Kitajima, et al.[34] showed that FDG PET/CT was superior CECT and MRI, but only moderately sensitive in predicting lymph node metastasis preoperatively. The overall node-based sensitivity, specificity, and accuracy of PET/CT for detecting nodal metastases were 53.3%, 99.6%, and 97.8%, respectively. The sensitivity for detecting metastases decreased with the diameter of the lesions (from 93.3% to 16.7% from lesions of size 10 and 4 mm, respectively).

Similar results were obtained in a pilot study by Nayot, et al.[35] on a small series. In high-risk early stage patients, the role of FDG PET/CT for "N" assessment is imperfect but promising. In this population, PET/CT demonstrated high specificity and accuracy, despite moderate sensitivity for nodal status, but did not correlate with relapse.[36]

There is also interest in the prognostic value of PET/CT with respect to "T" staging. A prospective study demonstrated that patients with high initial SUVmax had significantly lower DFS and OS compared with patients with low FDG uptake values. Multivariate analysis revealed that SUVmax is an independent prognostic factor of both DFS and OS that is superior to CA-125 serum levels[37] and ADCmin MRI.[38]

Another Japanese study compared retrospectively fused

PET/MRI images with contrast-enhanced PET/CT and contrast-enhanced dynamic MRI. PET/MRI was most effective for the assessment of the primary tumor and "N" staging.[39]

There are few papers investigating FDG PET/CT in monitoring treatment response. As with other tumors, PET/CT is useful for therapy management. In an ongoing trial with PET/CT performed at baseline and after 2 and 6 weeks of therapy, changes in total lesion glycolysis (TLG) after 2 weeks predicted partial response (PR) after 10 weeks and a rise in SUVmax between the second and sixth week predicted progression and was associated with worse progression free survival. In addition, early response evaluation with FDG PET/CT was useful in predicting subsequent radiological PR and progression disease.[40] Given the limited reported data on this issue, more investigation is needed.

Guidelines suggest a higher sensitivity and specificity of PET/CT in assessing suspected relapse of endometrial cancer.[5] FDG PET/CT results modified both the diagnostic and the treatment plan in 22.6% of patients in a series by Chung, et al.[41] similarly to the data reported by Park, et al.[42] in a population of 88 women (21.9%).

Several articles demonstrated that FDG PET/CT is superior to CECT and MRI for relapse assessment. Sensitivity, specificity and accuracy ranged between 89.5–100%, 94.7–96.4%, and 92.1–97%, respectively for PET/CT,[41,43,44] while the same parameters for CECT, ultrasound and MRI taken together reported in one study resulted in 85.1% sensitivity, 62% specificity, and 76.3% accuracy, though statistical analysis revealed only specificity to be significantly different.[43] One study compared the diagnostic yield of full-dose contrast-enhanced PET/CT vs. low-dose non-enhanced FDG PET/CT in endometrial cancer relapse, both by patient-based analysis and lesion-based analysis showed no significant difference in a small cohort.[45]

CONCLUSION

From the data reported above, we may highlight that in "T" staging of uterine malignancies FDG PET/CT is a secondary technique compared with CECT and MRI. In some series, FDG PET/CT results have matched MRI. The most promising role of metabolic imaging may be its ability to quantitatively predict DFS, OS, and TTR by assessing "N" status with SUVmax, MTV, and TLG.

For endometrial cancer, these techniques could be used to select patients who do not require surgical staging, thus sparing unhelpful lymphadenectomies. There is an important limitation regarding the staging of very small lymph nodes (<0.5 cm). FDG PET/CT is generally superior to CECT and MRI for detecting distant metastasis in advanced stage patients. PET/CT is recommended for detecting distal metastases in current clinical practice guidelines.[4,5] PET/CT may change the management in a significant percentage of patients regarding recurrence monitoring and follow up, resolving uncertain findings of CECT and MRI. In addition, there is growing interest in PET and MRI fusion imaging for the evaluation and follow-up of uterine and cervical cancers.

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