Original Article

Fluorodeoxyglucose positron-emission tomography-magnetic resonance hybrid imaging: An emerging tool for staging of cancer of the uterine cervix

ABSTRACT

Positron-emission tomography-magnetic resonance imaging (PET-MRI) is an emerging hybrid imaging modality that utilizes the superior soft tissue resolution of MR with the metabolic data from PET. In this study, we sought to assess the clinical value of fluorodeoxyglucose (FDG) PET-MRI with dedicated pelvic PET-MR in the initial staging of cervical cancer. In this institutional-approved study, we identified 23 adult females who underwent FDG PET-MRI on hybrid camera for staging of primary uterine cervical cancer that included a dedicated PET-MR of the pelvis. A nuclear medicine physician and a radiologist reviewed the PET, MRI, and fusion-body and pelvis images alone and then with consensus read characterizing PET and MR abnormal findings. There were 23 patients who underwent FDG PET-MRI for initial staging of cervical cancer with an average age of 52.2 ± 14.0 years. A total of 23 suspected lymph nodes in eight different patients were detected within the pelvis with increased metabolic activity on PET. Both the dedicated pelvis and whole-body PET imaging detected the same corresponding pelvic lymph nodes, although the pelvic PET imaging had better lymph node uptake delineation due to longer acquisition time. Using a 10-mm short-axis criterion, MRI identified only 43.5% of the FDG avid lymph nodes. The average SUVmax on the pelvis PET sequences was higher with SUV 8.9 ± 5.2 compared to the whole-body PET with SUV 7.8 ± 5.4 but was not statistically significant ($P > 0.05$). Primary cervical cancer was identified in 18 patients on both PET imaging and MRI with dedicated MR pelvis providing better characterization. Based on our results of the patients with cervical cancer evaluated for initial staging, combining dedicated pelvic PET-MRI with whole-body PET/MR provides the most complete status of malignant disease in reference to delineation of primary tumor, involvement of surrounding tissues, and regional lymph nodes.

Keywords: Cervical cancer, fluorodeoxyglucose, lymph nodes, positron-emission tomography-magnetic resonance imaging

INTRODUCTION

Uterine cervical cancer is the fourth most common cancer among women worldwide and is the fourth most frequent cause of cancer death.[1] Global cancer statistics estimate that in 2018, there were 570,000 new diagnoses of cervical cancer and 311,000 deaths from this disease.[2] Transmission of the human papillomavirus (HPV) through sexual contact is thought to be the principal contributing factor in the development of cervical cancer. There are 15 HPV types categorized as oncogenic, with the majority of invasive cervical cancer related to types 16 and 18 representing 50% and 10% of the infections, respectively.[3] However, HPV

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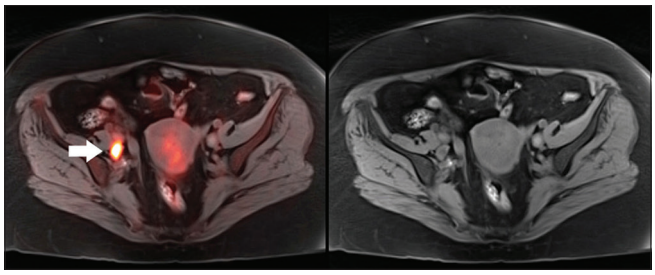

Figure 1: A 47-year-old female with squamous cell carcinoma of the exocervix. Positron-emission tomography-magnetic resonance fusion body sequence (left) showing a hypermetabolic right internal iliac lymph node (arrow) with SUV 14.8 which is enlarged on the T1-weighted radial volumetric interpolated breath-hold examination image (right). Mild heterogeneous uptake is noted in the uterine fundus due to benign fibroid activity

infection cannot act alone and other cofactors are necessary to induce the oncogenic changes in the development of cervical cancer, including immunodeficiency, smoking, higher number of pregnancies, genital hygiene, and oral contraceptive use.[3]

The initial diagnosis of cervical cancer is usually made by abnormal cervical cancer screening test or Pap smear during a routine gynecological visit or through cervical biopsy on initial colposcopy.[4] Patients who are determined to have large primary lesions in the cervix may undergo more invasive staging procedures, such as cystoscopy, proctoscopy, or laparoscopy. Imaging can also play a significant role in assessing the stage of advanced cervical cancer by detecting and visualizing invasion of surrounding pelvic organs, including the uterine appendages, rectum, and bladder, as well as identifying lymph node and distant metastases. Imaging modalities may include pelvic ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) of the pelvis or whole-body fluorodeoxyglucose (FDG) positron emission tomography (PET).[5]

In the evaluation of locoregional spread, contrast-enhanced MRI pelvis is usually the imaging choice outperforming CT in the staging and overall assessment of pelvic malignancies. MRI is more accurate than CT in determining tumor size, local extension, and lymph node involvement. PET-CT with FDG is also used in staging of invasive cervical cancer providing the status of locoregional and distant spread of disease, and predicting overall survival, as well.[6]

PET-MR is an emerging imaging modality using hybrid imaging technique that combines the metabolic biomarker data derived by PET imaging with the superior soft tissue quality of MRI obtaining benefits from both modalities. The authors hypothesized that simultaneous PET and MRI for the initial assessment of cervical cancer would be helpful in determining accurate status of disease. The purpose of this study was to evaluate the clinical value of whole-body FDG PET-MRI with dedicated pelvic PET-MR for the initial staging of cervical cancer.

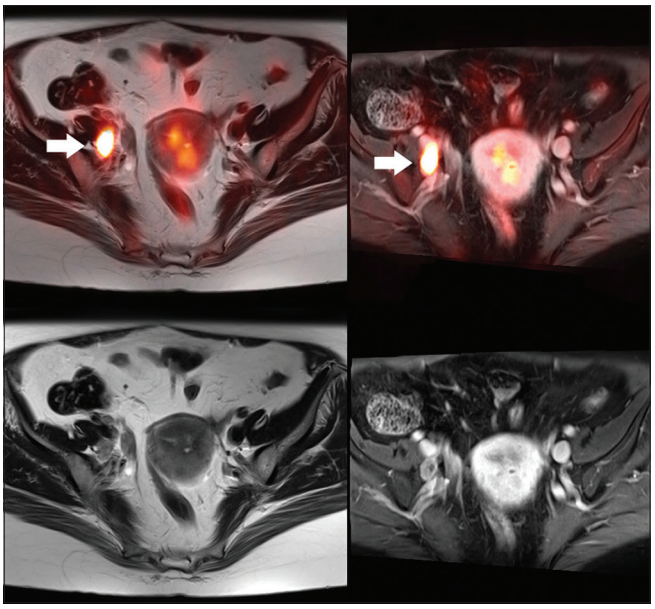

Figure 2: A 47-year-old female with squamous cell carcinoma of the exocervix. Dedicated pelvis imaging showing the same hypermetabolic right internal iliac lymph node (arrows) on T2-weighted fusion(top left) and T1-weighted volumetric interpolated breath-hold examination contrast-enhanced fusion images (top right). T2-weighted images showing the enlarged lymph node (bottom left) which demonstrates enhancement (bottom right)

MATERIALS AND METHODS

Patients

The institutional review board approved the retrospective study (Project No. 833707/01-2016, extension 12-2019). We identified 23 adult female patients who underwent FDG PET-MRI from September 2013 to December 2018 for clinically indicated primary uterine cervical cancer staging. Each patient had a whole-body FDG PET-MR scan from the top of the head to the mid-thigh followed by a multisequence, multiplanar dedicated pelvis PET-MRI with gadolinium contrast. We excluded all female patients younger than 18 years old, pregnant women, and patients with inadequate fasting, fasting blood glucose levels >160 mg/dl, metastatic malignancy to the cervix, and vaginal or uterine body malignancies with cervical invasion. Studies with technical issues were also excluded such as missing sequences, inadequate or lack of gadolinium contrast administration, whole-body imaging without adequate dedicated pelvic PET-MR, excessive motion artifact, and altered FDG distribution.

Imaging acquisition

All PET-MRI was performed on a dedicated hybrid 3 Tesla Siemens Biograph mMR (Siemens Healthcare, Malvern, PA, USA) acquiring PET and MRI data simultaneously. The PET detector consists of a lutetium oxyorthsilicate scintillation detector combined with avalanche photodiodes composed as a block. Each block detector is composed of 64 crystal elements with each crystal measuring 4 mm × 4 mm × 20 mm and a block area of 32 mm × 32 mm. The PET ring detector has 56 LSO-APD block detectors with 64 detector element rings arranged along the Z-axis. MRI is equipped with a 3 Tesla magnet fully integrated with the PET detector complex.

The attenuation correction map was based on a Dixon segmentation using a dual echo T1-weighted gradient recalled echo sequence performed from the top of the head to the mid-thigh. PET data set was reconstructed using an iterative 3D ordinary Poisson ordered subsets expectation–maximization algorithm at four iterations and 21 subsets with a 4 mm Gaussian postreconstruction image filter. The spanning length was 25.8 cm in the Z-direction. For the body PET images, the voxel size was 4.17 mm × 4.17 mm × 2.03 mm with a slice thickness of 2 mm. The transaxial field of view (FOV) was 59.4 cm × 59.4 cm with a matrix size of 172 × 172 × 515. For the dedicated PET pelvis images, the voxel size was 2.80 mm × 2.80 mm × 2.03 mm with a slice thickness of 2 mm. The transaxial FOV was 59.4 cm × 59.4 cm with a matrix size of 256 × 256 × 127.

Before FDG injection, all patients fasted for a minimum of 4 h. Blood glucose level was checked to be 160 mg/dL or lower. Each patient received approximately 10 mCi (370 MBq) of FDG administered intravenously with modification of the dose according to the patient's body weight. Afterward, the patient was placed in a warm, quiet room and told not to move or talk excessively. Approximately 1 h after the radiotracer injection, the patient underwent body imaging with the hybrid PET-MR scanner from the top of the head to the mid-thigh using five bed stations at 5 min each. A body surface coil was used for both MRI of the body and dedicated pelvis imaging. Sequences obtained for the MR body imaging were T1-weighted radial volumetric-interpolated breath-hold examination (VIBE) with fat suppression in the axial plane, T2-weighted HASTE in the axial plane, and either short T1-weighted inversion recovery sequence of the spine in the sagittal plane or T1 Dixon sequence of the spine in the sagittal plane.

Afterward, multiplanar multisequence PET-MRI was obtained of the pelvis for 30 min. Pre- and post-dynamic contrast-enhanced imaging of the pelvis was included using gadopentetate dimeglumine as an intravenous contrast agent. Pelvis MRI protocol included a T1-weighted axial large FOV to evaluate the entire pelvis and lower abdomen for lymphadenopathy, as well as high-resolution sequences for the evaluation of the primary tumor and determination of the extent of local involvement.

Imaging analysis

A board-certified nuclear medicine physician reviewed all the PET body images fused with T1 radial VIBE axial with fat suppression. Next, he/she looked at the dedicated pelvis PET images fused with the T1 VIBE axial with fat suppression. Visual assessment of the fusion was performed on a MIM workstation using MIM 6.4 fusion and contouring software (MIM Software, Cleveland, Ohio, USA). A board-certified radiologist reviewed the MRI sequences for the whole-body acquisition, and afterward, the dedicated pelvis MRI. The nuclear medicine physician and radiologist then concurrently reviewed the whole-body PET-MRI and dedicated pelvis PET-MRI with fusion alignment of all acquired MRI sequences giving a single consensus read. The readers characterized PET and MRI abnormal findings based on the pattern of FDG uptake, maximum standardized uptake value, lesion location, size and involvement of surrounding structures, diagnostic confidence, along with MRI signal characteristics. Lymph node sizes were determined using cross-sectional short-axis measurements. A chart review was conducted to look at the clinical history and other pertinent radiological studies. Student's *t*-test was performed for statistical analysis.

RESULTS

There were a total of 23 patients who underwent FDG PET-MRI for initial staging of cervical cancer which included PET-MR whole-body imaging from the top of the head to the mid-thigh and dedicated pelvic PET-MRI. The average age was 52.2 ± 14.0 years, with an age range 27–76 years. There were seven patients with adenocarcinoma of the endocervix, 15 with squamous cell carcinoma of the exocervix, and one with poorly differentiated carcinoma of the exocervix.

A total of 23 suspected lymph nodes in eight different patients were detected within the pelvis with increased metabolic activity on PET. Five of these patients had squamous cell carcinoma and three were adenocarcinoma. Both the dedicated pelvis PET and whole-body PET imaging detected the same corresponding pelvic lymph nodes, although the pelvic PET imaging had better lymph node uptake delineation due to longer acquisition time. All abnormal hypermetabolic foci corresponded to the lymph nodes on the dedicated pelvic

MRI study range, in short axis, from 5 to 20 ± 3.7 mm. There were 13 lymph nodes ranging from 5 to 9 mm in short-axis diameter with mean pelvis SUVmax 8.5 and 10 lymph nodes ranging from 10 to 20 mm in short-axis diameter with mean pelvis SUVmax 9.4. Using a 10-mm short-axis criterion, MRI identified only 43.5% of the FDG avid lymph nodes. There were no lymph nodes smaller than 5 mm short axis that had increased FDG activity on pelvis or body PET imaging. No lymph nodes were identified on either the whole-body or pelvic MRI with abnormal signal, size, or morphology that were not active on the PET imaging. The dedicated higher resolution pelvis MR identified the same enlarged lymph nodes on the body MR sequences, but with better resolution and confidence on the pelvis MR sequences [Figures 1 and 2]. The average SUVmax on the pelvis PET sequences was higher with SUV 8.9 ± 5.2 compared to the whole-body PET with SUV 7.8 ± 5.4, although this was not statistically significant ($P > 0.05$).

Of the 23 cases, there were five patients who underwent surgical removal of cervical cancer before imaging. This included three women who underwent cone biopsy and two with hysterectomy. The primary cervical cancer was identified in the remaining 18 patients on both PET and MRI imaging. PET-dedicated pelvis images detected the abnormal cervical uptake in the same number of patients as the PET whole-body images although with better delineation from surrounding structures when assessing tumor extent. MR-dedicated pelvis imaging also had better delineation of the local tumor spread compared to whole-body MRI. In addition, pelvic MR was superior to PET in evaluating the primary cervical cancer by identifying parametrial spread in four tumors.

The average maximum SUV primary tumor was 14.3 ± 10.5 on the body imaging ranging from SUVmax of 2.7–41.6. The average size of the lesion on MRI was 19.2 ± 22.3 cm^2 using greatest transaxial measurement with a range of 0.91–42.21 cm^2.

One patient had widespread extrapelvic metastatic disease that included peritoneal metastases, lung lesions, mediastinal lymph nodes, and lymph nodes of the neck. The lesions were equally detected on the PET and MRI body sequences.

DISCUSSION

PET-CT and PET-MRI offer the combined benefits of both functional and anatomic imaging. FDG PET-CT has been demonstrated to be a valuable tool in the staging of cervical cancer, including evaluating the primary tumor site, determining the status of pelvic lymph nodes, and identifying distant metastatic disease. A meta-analysis of 67 studies showed MRI to have a sensitivity of 54% and specificity of 93% in detecting pelvic lymph node metastases.[7] For locally advanced cervical cancer, MRI performed better identifying pelvic lymph node metastases, with a specificity of 88% compared to 52% in early-stage disease. PET-alone and PET-CT combined both demonstrated a sensitivity of 76% in recognizing patients with any positive pelvic lymph node and a sensitivity of 55% in identifying a metastatic lymph node in a defined pelvis anatomic region. PET-alone and PET-CT combined specificity were highest among imaging modalities with 94% recognizing patient with any positive pelvic lymph node and 98% based on specific regional pelvic lymph node detection.[7] As a limitation for PET, imaging including PET-CT and PET-MRI has a much lower accuracy in detecting FDG avid lymph node metastases <5 mm in short-axis diameter. PET is also not reliable in detecting peritoneal metastatic disease where lesions are either less FDG avid or difficult to discern from physiological uptake. False-positive findings with PET may also occur with inflammatory processes, such as postsurgical inflammation, granulomatous reactions, tuberculosis, or sarcoidosis.[8]

In our study, we found that performing a 30-min extended PET acquisition of the pelvis did not detect more FDG positive lymph nodes than the 5-min PET body sequence acquisition. Using the extended time acquisition increased confidence in interpreting the study but did not result in nodal upstaging in any of the cervical cancer patients. Likewise, the multisequence multiplanar pelvis MRI also did not detect additional pelvic lymph nodes that were not found on the whole-body MR sequences, although smaller lymph nodes were easier to identify and better defined on the pelvis images. Dedicated MRI pelvic imaging was better than whole-body MRI and superior to PET in assessing tumor extent in our study, better identifying parametrial spread in four malignancies.

Our results were not concordant with previous studies that compared PET-MR whole-body sequences with dedicated PET-MR pelvis imaging, including Bailey *et al*. looking at rectal cancer lymph node metastases and Lake *et al*. evaluating prostate cancer lymph node metastases using ^{68}Ga-PSMA-11. In these studies, either a 15 min (for Bailey *et al*.) or 8 min (for Lake *et al*.) dedicated pelvis PET-MR acquisition detected more positive lymph nodes than the corresponding 3-min whole-body acquisition.[9,10] One possible explanation for the discrepancy compared to our study is that the 5-min acquisition that we used on our body sequences was sufficient to detect small lesions not seen on 3-min acquisitions in the other studies. In addition, we did not detect lymph nodes

smaller than 5 mm that were identified in the other studies. The current PET-MR hybrid camera has a wider FOV along the Z-axis compared to a typical PET-CT being currently used. Hence, a whole-body PET-MR scan using a 5-min acquisition time per bed position with five separate bed positions is not much longer in total time for a patient to lie still compared to a PET-CT study using a 3-min acquisition time per bed position with seven separate bed positions.

Conventional MRI mainly uses size criteria for assessing for metastatic involvement of lymph nodes. Typically, pelvic lymph nodes for cervical cancer are suspicious if they measure 1 cm or greater in short-axis diameter. There is however an overlap in the size of normal lymph nodes, metastatic lymph nodes, and hyperplastic reactive lymph nodes. Micrometastases within normal size lymph nodes do occur. Accuracy for MRI detection of lymph node metastases based on size criteria ranges from 67% to 95%.[11] Other criteria for differentiating between normal and metastatic lymph nodes have been used with conflicting success. Diffusion-weighted imaging has been shown in a meta-analysis to be useful in helping to determine nonmetastatic from metastatic lymph nodes with sensitivity of 86% and specificity of 84%.[12] Looking at changes along the margin of the lymph nodes has low specificity for determining metastatic lymph nodes with lobulated or spiculated borders showing only a 21.0% sensitivity and 46.4% positive predictive value. Enhancement pattern of the lymph nodes following the administration of gadolinium intravenous contrast with MRI does not show any statistical advantage in detecting pelvic lymph node metastases.[13]

Integrated PET-MR cameras have been shown to be superior over MRI alone in the detection of metastatic cervical and gynecological malignancies. In a study of 71 women with gynecological malignancies, PET-MR correctly identified pelvic recurrence in 100% of patients compared to 83.6% with pelvic MRI.[14] In a study of 53 patients for staging of primary cervical cancer, positive lymph nodes were identified with PET-MR having an 83% sensitivity, 90% specificity, and 87% accuracy. For dedicated pelvic MRI, the sensitivity, specificity, and accuracy were 71%, 83%, and 77%, respectively. Both modalities were comparable in correctly determining the T-stage of the primary tumor with 85% accuracy using PET-MRI and 87% accuracy with MRI alone.[15] Similar lesion detectability with gynecological cancers has been found when comparing PET-MR and PET-CT. In a study looking at 19 patients with recurrent ovarian and cervical cancer, both PET-MR and PET-CT showed equivalent high diagnostic value for these recurrent malignancies. However, PET-MR had a higher diagnostic confidence in differentiating benign from malignant lesions for peritoneal and lymph node metastases compared to PET-CT.[16] A study done looking at fusion of PET and MRI compared to PET-CT and pelvic MRI showed sensitivity, specificity, and accuracy for lymph node metastases to be 92.3%, 88.2%, and 90.0% for both PET-MR fused and PET-CT. Contrast-enhanced pelvic MRI had sensitivity, specificity, and accuracy of 69.2%, 100%, and 86.7%.[17]

In regard to MR compared to FDG PET-CT in gynecological malignancies, MR is shown to be superior in T-staging of primary gynecological malignancy. In comparing fused PET/MRI, PET/CT, and MR, one study showed the accuracy of T-staging of cervical cancer for these modalities to be 83.3%, 53.3%, and 83.3%, respectively.[17] MRI using T2-weighted sequences does an excellent job at identifying parametrial fat invasion with high specificity of 96%–98%. Determining vaginal involvement is also high using MR with an overall accuracy of 86%–93,% with false positives for vaginal wall invasion occurring with large exophytic tumors distending the vaginal wall. MR can also accurately visualize bladder and rectum invasion.[18]

CONCLUSION

PET-MR hybrid technology is an emerging technology useful in the assessment and staging of various cancers. PET-MR combines the superior soft tissue imaging resolution obtained by MR with the sensitive functional component of PET imaging.

Although no additional lesions were detected by adding dedicated pelvic PET-MRI to whole-body PET-MR, the combination of these two acquisitions provides a more complete status of malignant disease in reference to delineation of primary tumor and involvement of surrounding tissues, as well as adds confidence in detecting regional lymph nodes. In addition, according to previously published data, PET-MRI has promising results in the detection of recurrence in cervical cancer and other gynecological malignancies. Compared to established PET-CT, PET-MR has a significant decrease in radiation exposure which is beneficial in middle-aged and younger adult patients diagnosed with cervical cancer. Larger prospective clinical validation studies are needed for PET-MR to make it an integral component of managing cervical cancer patients in the future.

Declaration of patient consent

The authors certify they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be

reported in this journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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