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Review Article

PET/MR hybrid imaging of cervical and endometrial cancer

I-Lun Shih [a, b], Tiffany Ting-Fang Shih [a, b, *]

[a] Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan
[b] Department of Radiology, College of Medicine, National Taiwan University, Taipei, Taiwan

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ABSTRACT

Integrated positron emission tomography/magnetic resonance imaging (PET/MRI) is a recently developed imaging modality that can provide simultaneous PET and MRI data in a single examination. MRI has high soft tissue contrast and is an excellent tool for evaluating local disease in patients with cervical and endometrial cancers, whereas positron emission tomography/computed tomography (PET/CT) is more useful for detecting extrauterine spread. As it combines the strengths of both PET and MRI and reduces radiation exposure from the CT component of PET/CT, PET/MRI represents a promising tool for evaluating cervical and endometrial cancers. In addition, PET/MRI can also serve as a functional imaging platform to provide quantitative imaging biomarkers derived from PET and functional MRI techniques. These imaging biomarkers can then be used to assess treatment response and they have been shown to have prognostic significance. This review article summarizes recent developments in the application of PET/MRI in cervical and endometrial cancers, and emphasizes its benefit as a one-stop, comprehensive imaging modality.

1. Introduction

Integrated positron emission tomography/magnetic resonance imaging (PET/MRI) has been clinically applied in recent years. This technique can simultaneously acquire PET and MRI data, and has the advantage of combining the morphological and functional information of MRI with the metabolic information of PET.[1,2] The high soft tissue contrast of MRI is mandatory to delineate details of the female pelvic organs, and it is the best single imaging tool to evaluate the local tumor extent in patients with cervical and endometrial cancers.[3] In contrast, positron emission tomography/computed tomography (PET/CT) is useful for identifying lymphadenopathy, distant metastasis, and tumor recurrence.[4] Since MRI and PET have complementary roles in the evaluation of these patients, integrated PET/MRI can be expected to be beneficial as a one-stop examination. In this review, we summarize the recent developments in the clinical application of PET/MRI in patients with cervical and endometrial cancers.

2. Imaging protocol

There is currently no standard imaging protocol for PET/MRI, and practices may differ across institutions and may depend on the clinical setting. In general, for the evaluation of gynecologic cancers, whole-body MRI and dedicated pelvic MRI are performed with PET data being obtained simultaneously.

In our institution, PET/MRI examinations are performed with an integrated PET/MRI system (Biograph mMR, Siemens Healthcare, Erlangen, Germany). For whole-body scans, PET and MRI are performed simultaneously from above the head to mid-thighs, with five bed positions and an acquisition time of 4 min per bed position. The pulse sequences of MRI include an axial T2-weighted half-Fourier single-shot turbo spin-echo (HASTE) sequence, a coronal short tau inversion recovery sequence, and an axial Dixon-based volumetric interpolated breath-hold examination (VIBE) sequence. The whole-body layout of PET/MRI is shown in Fig. 1. For the dedicated pelvic MRI, the pulse sequences include axial, sagittal, and coronal T2-weighted turbo-spin echo sequences and an axial diffusion-weighted imaging (DWI) sequence. After injecting intravenous contrast medium, whole-body imaging is performed with an axial VIBE sequence. Dynamic contrast-enhanced (DCE) MRI can also be performed to evaluate perfusion parameters of the tumor.

Because the longer scanning time compared with PET/CT is a

* Corresponding author. Department of Medical Imaging and Radiology, National Taiwan University Medical College and Hospital. No.7, Chung-Shan South Road, Taipei, Taiwan.
E-mail address: ttfshih@ntu.edu.tw (T. Ting-Fang Shih).
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drawback of PET/MRI, Grueneisen et al. attempted to optimize the imaging protocol. They reported that DWI in PET/MRI has no additional diagnostic benefit for whole-body staging of women with pelvic malignancies, and therefore that it could be eliminated to reduce examination time and increase patient comfort.[5] They also proposed a FAST PET/MRI protocol to evaluate recurrent gynecologic malignancies, including only three MRI sequences (DWI, T2-weighted HASTE, and post-contrast VIBE). This FAST protocol showed comparably high diagnostic performance compared to PET/CT, with a slightly longer scan duration and markedly decreased radiation exposure.[6] Furthermore, Grueneisen et al. also proposed another ultra-fast PET/MRI approach including only two diagnostic MRI sequences (T2-weighted HASTE and post-contrast VIBE), and showed that it could provide equivalent diagnostic performance and examination time to PET/CT.[7]

3. PET/MRI in cervical cancer

Cervical cancer is the fourth most commonly diagnosed cancer in women worldwide, and the most common gynecologic malignancy and third leading cause of cancer death in less developed countries.[8] The two primary treatment strategies are surgery for early-stage disease (stage IA, IB1, and IIA1) and concurrent chemoradiotherapy for patients with bulky tumors (>4 cm, stage IB2 and IIA2) or locally advanced disease (stage IIB or greater). Therefore, accurate pretreatment diagnosis is important, and imaging studies play a central role in treatment planning.

3.1. Diagnostic accuracy

MRI is the best single imaging tool to assess local tumors, particularly when evaluating tumor size and the presence of parametrial invasion.[3] Using surgical pathology as a reference standard, MRI has been shown to be superior to CT and clinical examination for measuring tumor size.[9] MRI has been reported to have a high accuracy (88%–97%) to evaluate parametrial invasion.[3] In contrast, PET/CT has been shown to be more sensitive than CT or MRI to evaluate lymph node metastasis.[4] In a patient-based meta-analysis, PET or PET/CT showed the highest pooled sensitivity (82%) and specificity (95%) for detecting lymph node metastasis, while the values for CT and MRI were 50% and 92%, and 56% and 91%, respectively.[10] In addition, PET imaging has also been reported to be useful when planning radiation therapy, for the early evaluation of therapeutic response, and long-term follow-up.[11–13]

Considering the complementary advantages of MRI and PET/CT in cervical cancer, it would appear to be potentially beneficial if these two imaging modalities could be combined. Kim et al. fused PET images from PET/CT and pelvic MRI in 79 patients with cervical cancer, and reported the sensitivity (54%) of fused PET/MRI in detecting lymph nodal metastases was higher than that of PET/CT (44%), and receiver operating characteristic curve analysis demonstrated a higher diagnostic performance of fused PET/MRI.[14]

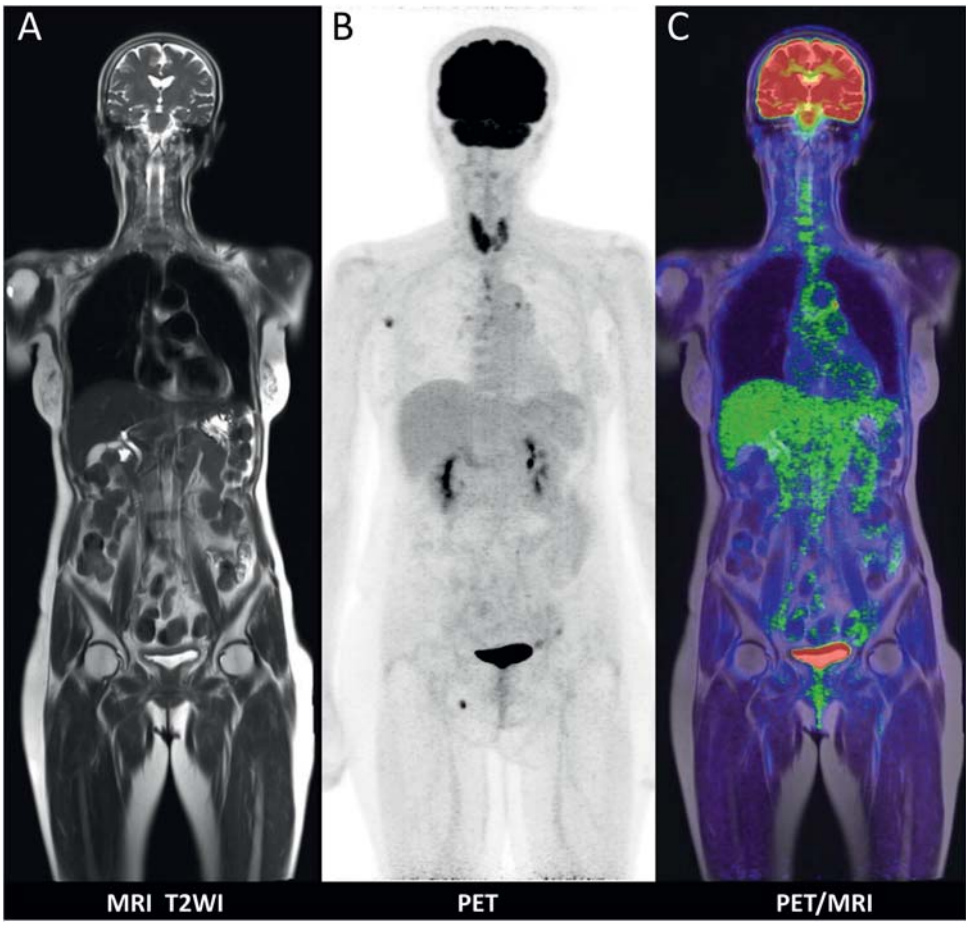

Fig. 1. Whole-body layout for integrated PET/MRI scanning. (A) Coronal plane of fast T2-weighted MRI, from skull to mid-thigh. (B) Coronal maximum intensity projection of a PET image. (C) Registration of integrated whole-body PET and MRI.

Kitajima et al. also evaluated the diagnostic accuracy of fused PET (from PET/CT) and MRI in primary tumors and nodal staging of cervical cancer. They analyzed the results of 30 patients and found that the accuracy of T staging of PET/MRI (83.3%) and MRI (83.3%) was better than that of PET/CT (53.3%). The sensitivity and specificity (92.3% and 88.2%) of fused PET/MRI for detecting nodal metastasis were the same as those of PET/CT. In addition, fused PET/MRI was more sensitive, although less specific, than non-fused PET/MRI (sensitivity 84.6% and specificity 94.1%) and MRI (sensitivity 69.2% and specificity 100%). The authors concluded that fused PET/MRI combines the individual advantages of MRI and PET.[15] Nakajo et al. also reported that fused PET/MRI was superior to PET/CT for the detection and localization of gynecological malignancies, mainly cervical cancers.[16] Queiroz et al. used a trimodality system with sequential MRI and PET/CT to evaluate patients with gynecologic cancers, including seven patients with cervical cancer. They showed that PET/MRI was superior to PET/CT to delineate primary tumors.[17]

For recurrent tumors, Kitajima et al. investigated the diagnostic value of fused PET/MRI in 30 patients with suspected recurrent gynecologic cancers (15 cervical, nine ovarian, and six endometrial cancer), and found that the patient-based sensitivity for detecting local recurrence, pelvic lymph nodes, bone metastasis, and peritoneal lesions were 87.5, 87.5, 100, and 80.0%, respectively, for fused PET/MRI. In addition, the sensitivity of fused PET/MRI for detecting local recurrence was significantly better than that of PET/CT.[18] Vargas et al. reported the use of fused PET/MRI in patients with recurrent gynecologic cancers (16 cervical, eight endometrial, and seven vaginal/vulvar cancer) undergoing pelvic exenteration, and found greater diagnostic confidence and inter-reader agreement for fused PET/MRI than for either MRI or PET/CT.[19]

However, a limitation of fused PET/MRI is mis-registration between the separate PET and MRI studies. The location of the pelvic organs may be affected by the varying extent of urinary bladder distension as well as movement of the intestines. This limitation is expected to be overcome by new integrated PET/MRI systems, which can allow for the simultaneous acquisition of PET and MRI data. Zhang et al. performed a one-stop sequential whole-body PET/MRI study in 25 patients with cervical cancer, and evaluated the accuracy of image coregistration, and found that the coregistration of cervical lesions was usually accurate, and was better between T2-weighted MRI and PET than between apparent diffusion coefficient (ADC) map and PET.[20]

Using an integrated PET/MRI system, Grueneisen et al. examined 27 patients with cervical cancer and assessed the diagnostic value of whole-body staging.[21] The T stage, N stage, and M stage were correctly determined in 85%, 80%, and 100% of the patients, respectively. Later, the same study group reported the results of a larger patient cohort ($n = 53$) comparing the accuracy of PET/MRI with that of MRI alone,[22] and found that PET/MRI and MRI alone correctly determined the T stage in 85% and 87% of the patients, respectively. To detect nodal-positive patients, the sensitivity, specificity, and accuracy of PET/MRI were 83%, 90%, and 87%, respectively, which were higher than those of MRI alone (71%, 83%, and 77%, respectively). PET/MRI also performed better than MRI alone in detecting distant metastases (sensitivity: 87% vs. 67%, specificity: 92% vs. 90%, diagnostic accuracy: 91% vs. 83%). The results were promising, and the authors concluded that integrated PET/MRI is valuable for whole-body tumor staging in patients with cervical cancer (Fig. 2 and Fig. 3).

Grueneisen et al. also reported the diagnostic value of integrated PET/MRI in patients with suspected recurrent gynecological pelvic

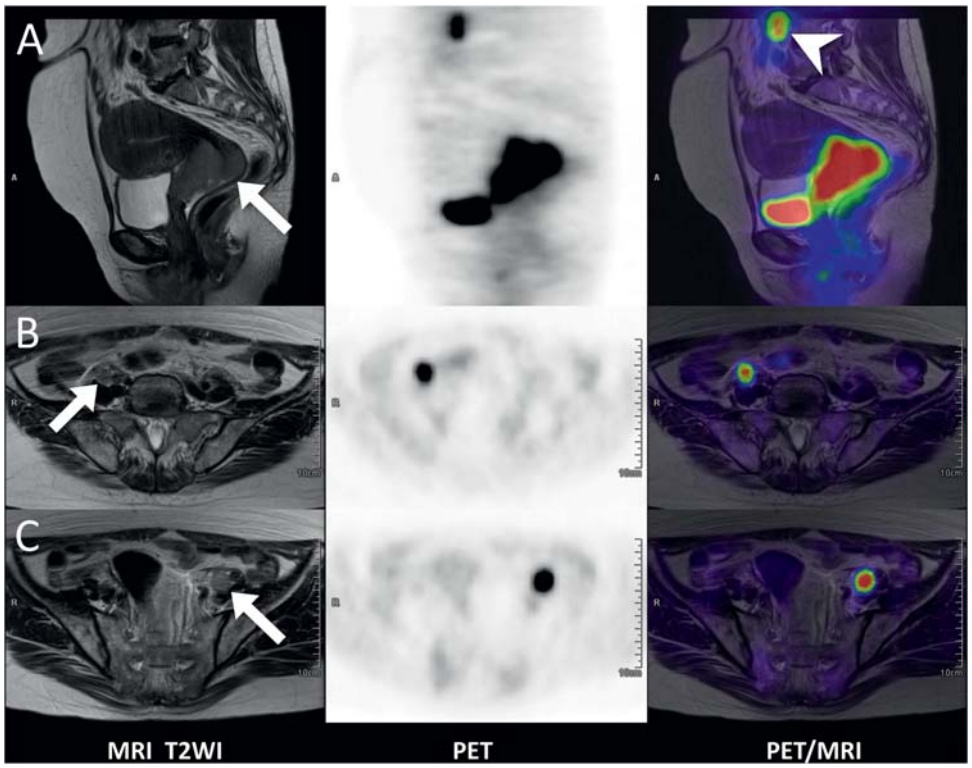

Fig. 2. A 51-year-old woman with cervical cancer, squamous cell carcinoma, stage IIIB. (A) MRI, PET, and PET/MRI showing a large primary tumor at the uterine cervix (arrow), with high fluorodeoxyglucose (FDG) uptake ($SUV_{max} = 13.4$). Hypermetabolic iliac lymphadenopathy was also noted (arrowhead). (B) FDG-avid right iliac lymphadenopathy (arrow). (C) Left iliac lymphadenopathy (arrow). Bilateral iliac lymph nodes were precisely coregistered.

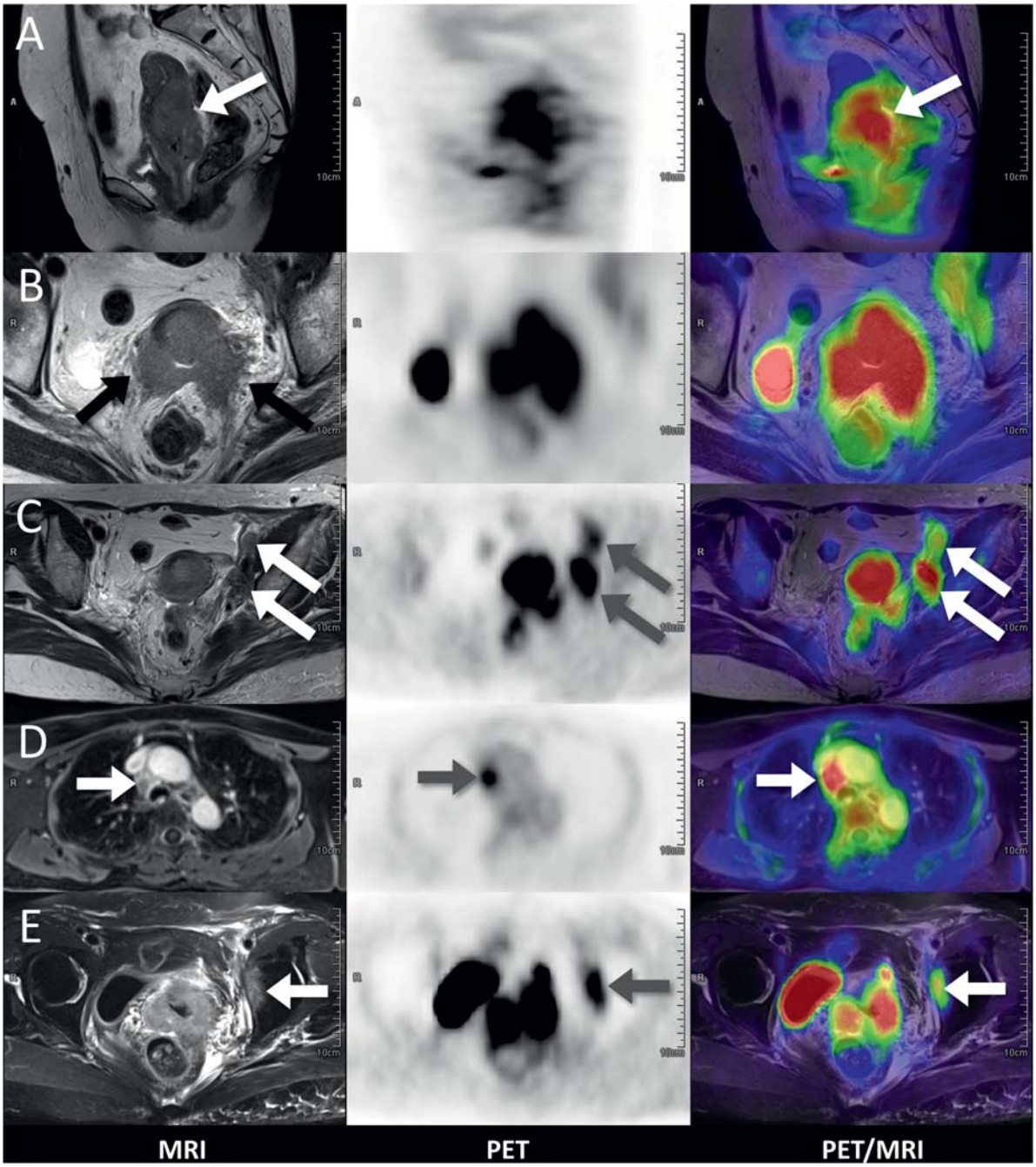

Fig. 3. A 70-year-old woman with cervical cancer, squamous cell carcinoma, with multiple lymphadenopathy and bone metastasis, stage IVB. (A) MRI, PET, and PET/MRI showing a large tumor at the uterine cervix (arrows), with high FDG uptake ($SUV_{max} = 9.03$). (B) Axial images show tumor invasion into the bilateral parametrium (arrows). (C) FDG-avid lymph nodes in the left iliac region (arrows). (D) An FDG-avid lymph node in the right mediastinum (arrows). (E) Bone metastasis at the left acetabulum (arrow).

malignancies including 18 patients with cervical cancer and 16 patients with ovarian cancer. They found that PET/MRI correctly identified all patients with cancer recurrence and 98.9% of all malignant lesions, which was better than MRI alone (92% of patients and 88.8% of malignant lesions).[23] A follow-up study including more patients (n = 71) with suspected recurrent gynecological pelvic malignancies (including 32 cervical, 26 ovarian, seven endometrial, four vulvar, and two vaginal cancers) was reported later by the same group,[24] and the results also showed that PET/MRI correctly identified all of the patients with cancer recurrence (100%) and all malignant lesions, and that these results were better than MRI alone (83.6% of the patients and 74.6% of the lesions). The same study group also compared the performance of PET/MRI and PET/CT to diagnose recurrent gynecologic cancers, and showed that PET/CT and PET/MRI had equivalently high diagnostic value for detecting recurrent pelvic malignancies, and that PET/MRI offered higher diagnostic confidence.[6,25] Therefore, considering the reduced radiation dose, PET/MRI may serve as a powerful alternative to PET/CT.

Integrated PET/MRI has also been shown to play a potential role

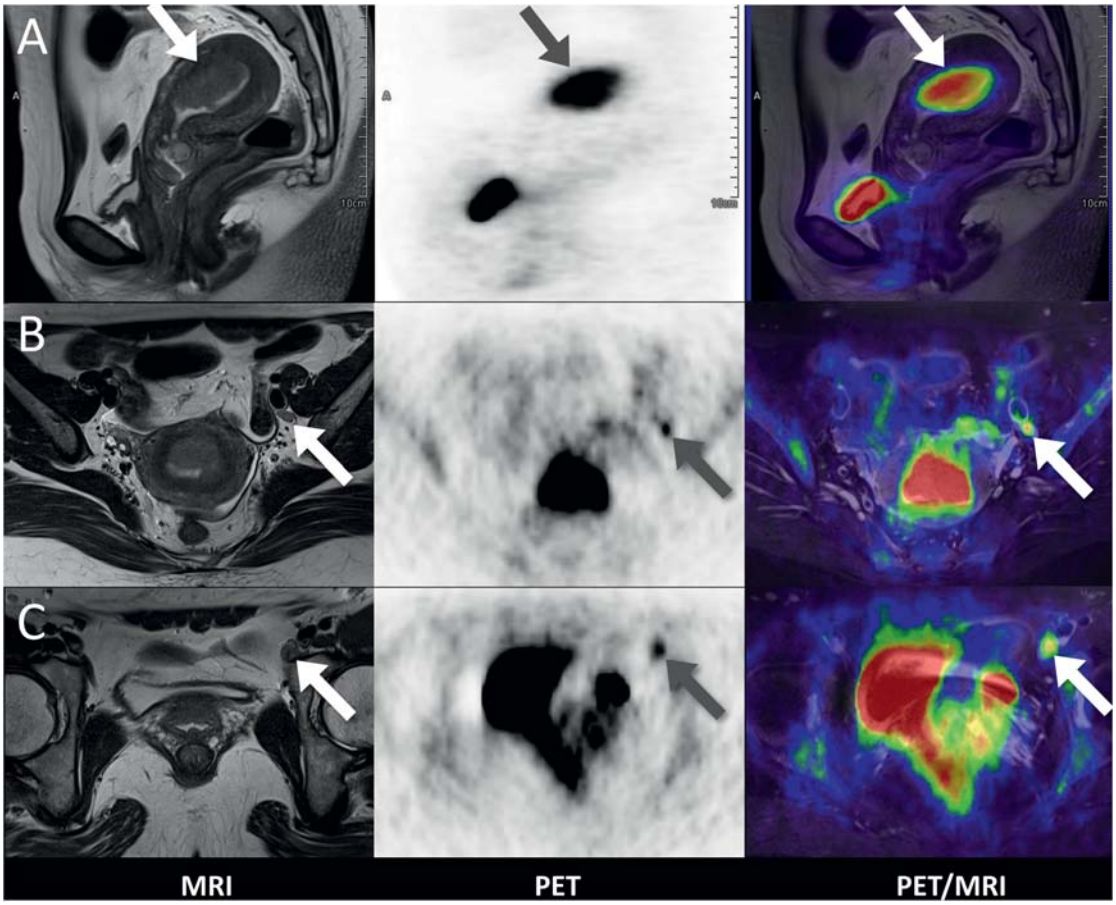

Fig. 4. A 40-year-old woman with endometrial cancer, endometrioid adenocarcinoma, with small left iliac lymphadenopathy, stage IIIC1. (A) MRI, PET, and PET/MRI showing a hypermetabolic tumor (arrows) in the uterine cavity ($SUV_{max} = 25.2$). The other hot-spot in the anterior pelvic cavity is the urinary bladder. (B, C) Two small lymph nodes (<1 cm) in the left external iliac region (arrows), which were not suggestive of metastasis by size criteria on MRI alone. However, high FDG uptake was noted on PET images, suggesting metastasis. Surgical pathology confirmed lymph node metastasis.

in assessing treatment response. Sarabhai et al. performed integrated PET/MRI in eight patients with cervical cancers before and after chemotherapy or concurrent chemoradiotherapy.[26] They used RECIST and PERCIST criteria to evaluate the treatment response, and verified their findings using histopathological studies based on radical hysterectomy and biopsy samples. There was a high correlation with the response criteria to differentiate between therapeutic responders and non-responders.

3.2. Imaging biomarkers

DWI is the most commonly used functional MRI technique. It is based on the diffusivity of water molecules and is inversely correlated with tissue cellularity, and is routinely used in clinical protocols to evaluate gynecologic malignancies and can facilitate lesion detection.[27–31] ADC is the quantitative parameter derived from DWI. It has been associated with tumor stage and lymph node metastasis in patients with cervical cancer, and it has been shown to be a predictor of disease-free and overall survival.[32,33] Maximum standardized uptake value (SUV_{max}) represents the strongest glucose metabolism of a tumor, and is the most commonly used imaging parameter in PET. Previous studies of PET/CT have shown that SUV_{max} is associated with tumor stage and lymph node metastasis in patients with cervical cancer, and is a predictor of disease recurrence and survival.[32–34]

Grueneisen et al. investigated the relationship between SUV_{max} and minimum ADC (ADC_{min}) of integrated PET/MRI in 19 patients with primary and recurrent cervical cancer, and reported a significant and strong inverse correlation between SUV_{max} and ADC_{min} ($r = -0.692$; $P < 0.001$) in primary tumors and lymphadenopathy, but no significant correlation in recurrent tumors.[35] Another similar study of 31 patients reported by Brandmaier showed inverse correlations between SUV_{max} and ADC_{min} in both primary ($r = -0.532$; $P = 0.05$) and recurrent tumors ($r = -0.747$; $P = 0.002$).[36]

In the above-mentioned study by Grueneisen et al.,[21] significant correlations between the quantitative functional parameters and pathological grade and tumor size were also reported. Tumors with higher grade and larger size tended to have higher SUV and lower ADC values. Furthermore, ADC_{min} was lower in tumors with an advanced tumor stage. In contrast, Surov et al. reported lower PET/MRI-derived ADC values in tumors with lymph node metastasis. They also evaluated histopathological parameters, and found that SUV and ADC were correlated with the proliferation index Ki-67, while SUV was also correlated with the percentage of epithelial area in the tumor.[37]

Sarabhai et al. investigated the use of PET/MRI to assess treatment response in patients with cervical cancer, and found that functional imaging parameters differed between therapeutic responders and non-responders.[26] They also found a decreased SUV,

increased ADC, and decreased perfusion parameters in tumors showing a therapeutic response. Taken together, these studies demonstrate the promising ability of PET/MRI to provide multiparametric functional information about tumors.

4. PET/MRI in endometrial cancer

Endometrial cancer is the sixth most commonly diagnosed cancer in women worldwide, and the most common gynecologic malignancy in developed countries.[8] Endometrial cancer is surgically staged based on the joint International Federation of Gynecology and Obstetrics (FIGO)/TNM classification system.[38] However, pretreatment imaging evaluation is still helpful for risk stratification and surgical treatment planning.[3]

4.1. Diagnostic accuracy

MRI is useful to evaluate local tumors, particularly for the high-risk features including a large tumor size, deep myometrial invasion, and cervical stromal invasion. Duncan et al. reported that the sensitivity and specificity for detecting deep myometrial invasion were 77% and 88%, respectively, and those for detecting cervical stromal involvement were 42% and 97%.[39] Similar to cervical cancer, MRI is limited in detecting lymph node metastasis based on size criteria alone, and PET/CT is more sensitive than CT or MRI for nodal metastasis.[4] The reported sensitivity and specificity of PET/CT for detecting lymph node metastasis range from 74% to 77% and 93%–100%, respectively, compared to 28%–64% and 78%–94% for CT and 59%–72% and 93%–97% for MRI.[40–42] PET/CT is also helpful to detect distant metastases in patients with high-grade tumors, with a reported sensitivity of 100% and specificity of 96%.[43] Whole-body PET or PET/CT has also been reported to be useful for detecting recurrent disease, with a sensitivity of 92%–93% and specificity of 93%–100%.[44,45]

To combine the complementary advantages of PET and MRI, Kitajima et al. retrospectively fused PET images from PET/CT and pelvic MRI in 30 patients with endometrial cancer, and found a higher diagnostic accuracy with fused PET/MRI in T staging (80%) than with PET/CT (60%), and a higher sensitivity in N staging (100%) than with MRI alone (66.7%).[46] Although the sample size was small and only 14 patients underwent pelvic lymphadenectomy, this study showed that fused PET/MRI may be valuable to evaluate

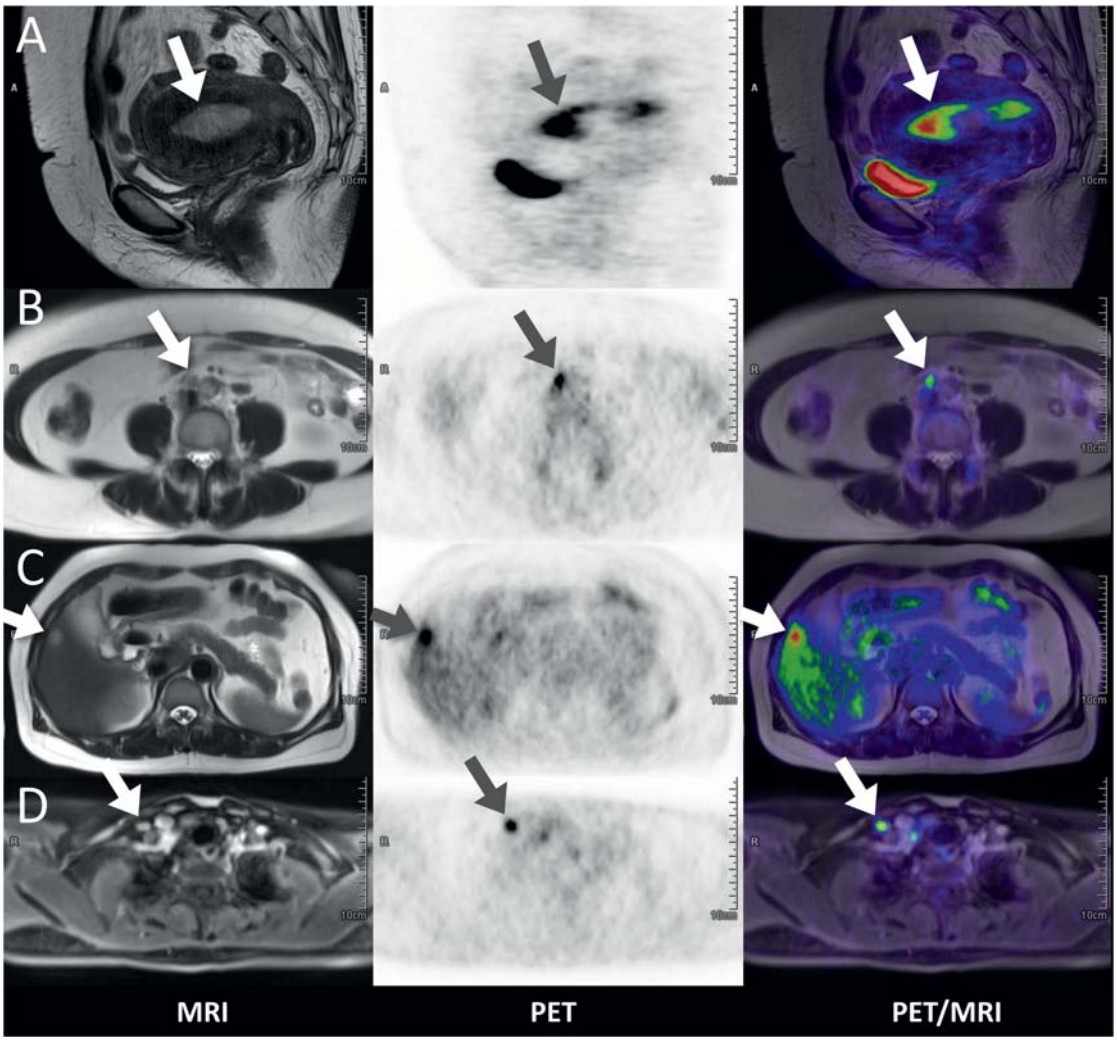

Fig. 5. A 58-year-old woman with endometrial cancer, neuroendocrine carcinoma arising from carcinosarcoma, with multiple metastases, stage IVB. (A) MRI, PET, and PET/MRI showing hypermetabolic tumors (arrows) in the uterine cavity ($SUV_{max} = 25.2$). (B) A small FDG-avid lymph node in the aortocaval space. (C) A hepatic tumor in segment 5 with high FDG uptake, suggestive of metastasis. (D) Distant lymph node metastasis in the right supraclavicular fossa. The local staging and all of the metastases could easily be evaluated in a single PET/MRI examination.

primary tumors and lymph node status in patients with endometrial cancer. Queiroz et al. used a trimodality system with sequential MRI and PET/CT studies to evaluate patients with gynecologic cancers, including four patients with endometrial cancer. They showed that PET/MRI was superior to PET/CT to delineate primary tumors.[17] For recurrent tumors, as described earlier in the cervical cancer section, Kitajima et al. and Vargas et al. reported the benefits of fused PET/MRI in patients with recurrent mixed gynecologic tumors, including endometrial cancer.[18,19]

Several studies have investigated the diagnostic accuracy of integrated PET/MRI to detect primary or recurrent tumors in heterogeneous groups of female patients with pelvic malignancies.[5,6,24] The majority of patients had cervical and ovarian cancers, with a few patients having endometrial cancer. The diagnostic accuracy of PET/MRI was reported to be better than that of MRI alone and comparable with PET/CT. Further investigations are needed to explore the diagnostic accuracy of integrated PET/MRI in the primary staging of endometrial cancer (Fig. 4 and Fig. 5).

4.2. Imaging biomarkers

Similar to cervical cancer, ADC and SUV are the most commonly used imaging biomarkers in endometrial cancer. Previous studies of MRI and PET/CT have demonstrated that both ADC_{min} and SUV_{max} of primary tumors are associated with pathological prognostic factors, including tumor stage, tumor grade, deep myometrial invasion, cervical involvement, and lymph node metastasis, and that they are independent predictive factors for disease recurrence.[47–49] In addition, SUV_{max} has also been shown to be an independent prognostic factor for overall survival.[50,51]

Shih et al. performed integrated PET/MRI in 47 patients with newly diagnosed endometrial cancer and evaluated correlations between imaging biomarkers and pathological prognostic factors, and reported a significant inverse correlation between SUV_{max} and ADC_{min} ($r = -0.53$; $P = 0.001$).[52] In addition, SUV_{max} was significantly higher in tumors with advanced stage, deep myometrial invasion, cervical invasion, lymphovascular space involvement, and lymph node metastasis, and ADC_{min} was lower in tumors with higher grade, advanced stage, and cervical invasion. In addition, a composite biomarker, the ratio of SUV_{max} to ADC_{min}, was shown to be more useful than SUV_{max} or ADC_{min} alone. The authors concluded that these two imaging biomarkers may provide additional information when evaluating patients with endometrial cancer.

5. Summary

Increasing evidence supports the clinical application of integrated PET/MRI in patients with cervical and endometrial cancers. Based on the high diagnostic accuracy and abundant functional information, PET/MRI has been shown to have a valuable role in pre-treatment staging, treatment monitoring, and post-treatment surveillance. Further studies with larger patient cohorts and longer follow-up periods are necessary to verify these findings and may reveal more clinical indications for this approach. Overall, this multiparametric hybrid imaging modality is a promising tool to evaluate patients with cervical and endometrial cancers.

Conflicts of interest

The authors declare no conflicts of interest.

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