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PET/MR Imaging of the Female Pelvis

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High-quality imaging diagnostics play a fundamental role in patient and therapy management of cancers of the female pelvis. Magnetic resonance imaging (MRI) and positron emission tomography (PET) represent two important imaging modalities, which are frequently applied for primary tumor evaluation, therapy monitoring, and assessment of potential tumor relapse. Based on its high soft-tissue contrast, MRI has been shown superior toward CT for the determination of the local extent of primary tumors and for the differentiation between post-therapeutic changes and tumor relapse. Molecular imaging utilizing ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET facilitates an insight into tumor metabolism depending on the glycolytic activity of tumorous cells. As the current gold standard of hybrid imaging, ^{18}F-FDG-PET/CT has been demonstrated highly accurate and superior to conventional imaging modalities for the detection of tumorous tissue due to the combined analysis of metabolic and morphologic data. Therefore, ^{18}F-FDG-PET has emerged to become a well-established imaging modality for the detection, re-/staging and therapy response monitoring of a variety of solid tumors, including gynecologic cancers. Integrated PET/MRI systems have been successfully introduced into scientific and clinical applications within the past 8 years. This new-generation hybrid imaging technology enables the simultaneous acquisition of PET- and MR Datasets, providing complementary metabolic, functional, and morphologic information of tumorous tissue. Combining the high soft-tissue contrast of MRI and the metabolic information derived from PET, PET/MRI bears the potential to be utilized as an accurate and efficient diagnostic tool for primary tumor staging, therapy monitoring and restaging of tumors of the female pelvis and plays a valuable role in the management of targeted tumor therapies in the future.

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Patient Preparation and PET/MR Protocols

Patient Preparation

Patient preparation is of great importance when dealing with hybrid imaging. The majority of the below-mentioned recommendations equally apply to PET/MRI and PET/CT imaging. One of the main objectives of patient preparation is the reduction of physiologic tracer uptake in healthy tissue while preserving tracer uptake in the target structures (tumorous tissue). To ensure adequate blood glucose levels (≤150 mg/dl.) at the time of radiotracer injection patients should be instructed to fast for a period of at least 6 hours prior to the examination. In case of increased blood glucose levels, regular human insulin may be administered intravenously and blood glucose levels should be evaluated again prior to tracer injection. ^{18}F-fluorodeoxyglucose is the current tracer of choice for imaging of female pelvic oncologic diseases with recommended dosages of 4 MBq/kg body weight.[1] As new-generation PET detector systems containing lutetium oxyorthosilicate-based avalanche photodiodes have been shown highly sensitive for PET-measurements[2] and dedicated protocols for female pelvis imaging require fairly long examination times per bed position, reduced ^{18}F-FDG doses of 2 MBq/kg bodyweight have also been shown feasible.[3,4] Simultaneous PET and MR imaging should be started approximately 1 hour after tracer injection. One important difference between PET/CT and PET/MRI imaging lies in the susceptibility of MR imaging for artifacts due to increased peristalsis of the bowel system. Hence, antiperistaltic

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Table 1 Dedicated pelvic and whole-body MR sequence protocols recommended for primary tumor staging of female pelvic malignancies by integrated PET/MRI

	Cervical Cancer	Endometrial Cancer	Ovarian Cancer
Pelvis	T2w TSE (Axial)	T2w TSE (Sagittal)	T2w TSE (Axial)
	T2w TSE (sagittal)	T2w TSE (Axial oblique, perpendicular to the endometrial cavity)	T2w TSE (Sagittal)
	T2w TSE (Axial oblique, perpendicular to the cervix)	DWI (Axial oblique, perpendicular to the endometrial cavity)	Fat saturated T1w (axial)
	3D fat-saturated T1w dynamic imaging (Sagittal)	3D fat-saturated contrast-enhanced T1w (Axial oblique, perpendicular to the endometrial cavity); single phase after 2 minutes 30 seconds or as a party of dynamic imaging	3D fat-saturated T1w dynamic imaging (Axial)
	Fat-saturated contrast-enhanced T1w TSE (Axial)	T2w TSE (Sagittal)	DWI (Axial)
Whole-body	Fast T2w spin echo sequence (Axial)		
	DWI (Axial)		
	3D fat-saturated contrast-enhanced T1w gradient echo sequence (Axial)		

DWI, diffusion-weighted imaging; TSE, turbo-spin echo.

agents (eg, hyoscine butylbromide) may be applied to reduce bowel activity and limit the occurrence of motion artifacts.[5] Furthermore, in case of utilization of gadolinium-based contrast agents, special attention must be paid toward potential contraindications (eg, allergic reactions toward Gd-based contrast agents, kidney disease, or renal dysfunction).[6]

PET/MR Protocols

Over the past few years, a number of PET/MR protocol proposals for dedicated local and or whole-body imaging have been published.[7-10] As specific protocols and MR sequences are subject to change depending on the user, vendor and indication, the below-mentioned proposals should be considered as recommendations.

Whole-body coverage comprises imaging from skull-base to mid-thighs entailing four to five bed positions (BP) depending on the patient height, utilizing a combination of dedicated (attenuation-corrected) radiofrequency (RF) head and neck coils and phased-array body surface RF.[11] Whole-body PET/MRI scans for primary tumor evaluation as well as for whole-body staging of patients with female pelvic malignancies are generally performed in supine position with arms placed next to the torso, with imaging starting in the pelvic region to ensure minimal impairment of lesions in the vicinity of the bladder due to increased (^{18}F)-FDG activity of the bladder.

In a first-step MRI, localizers are obtained to define the axial range for the examination. Following, prescanning of the shimming and adjustment of the magnetic field as well as the attenuation correction (AC) sequence are acquired for every BP. Whole-body staging should be categorized into (1) primary local and whole-body staging and (2) whole-body staging without dedicated pelvis imaging. In case of primary staging of cancers of the female pelvis or for the purpose of therapy monitoring whole-body staging protocols should comprise a dedicated MR protocol of the female pelvis. In general, the protocols comprise high-resolution T2-weighted imaging (in sagittal and axial plane), contrast-enhanced T1-weighted sequences, and diffusion-weighted imaging. Nevertheless, to ensure best possible assessment of the tumor extent the MR protocols require adaptations in dependence of the imaged tumor entity (Table 1). Thus, for example, T2-weighted imaging in axial oblique plane is recommended for exclusion of parametrial invasion in cervical cancer, while delayed postcontrast T1-weighted imaging (minimum 2:30 minutes post injection) has been demonstrated to yield best tumor-myometrial contrast in endometrial cancer.[12,13] In contrary to the standardized protocol recommendations in cervical and endometrial cancer, imaging of ovarian cancer is fairly complex due to the heterogeneous structure of the tumor.[14]

Complementary to dedicated imaging of the pelvic tumor region, PET/MRI enables a dedicated and combined work up of the primary cancer and whole-body staging in one examination[15] (Fig. 1). Over the past years, a number of studies investigated different imaging algorithms focusing on protocol optimization to enable high-quality PET/MR diagnostics while preserving short acquisition times to comply with economic and time efficiency as well as patient comfort.[7-10] Different algorithms for whole-body imaging in a primary staging as well as restaging setting were recently published in a consensus recommendation paper comprising fast and ultra-fast protocols for whole-body coverage.[16,17] Previous studies on fast and ultra-fast PET/MR imaging showed the potential for a significant shortening of the examination time comparable to PET/CT acquisition times (27.5 ± 2.0 minutes [fast PET/MRI]) and 18.5 ± 1 minutes. [ultra-fast PET/MRI]) vs 18.2 minutes [PET/CT]), while preserving an equivalent diagnostic performance when compared to PET/CT.[9,10] The application of these or other short imaging protocols enables the utilization of PET/MR imaging as an

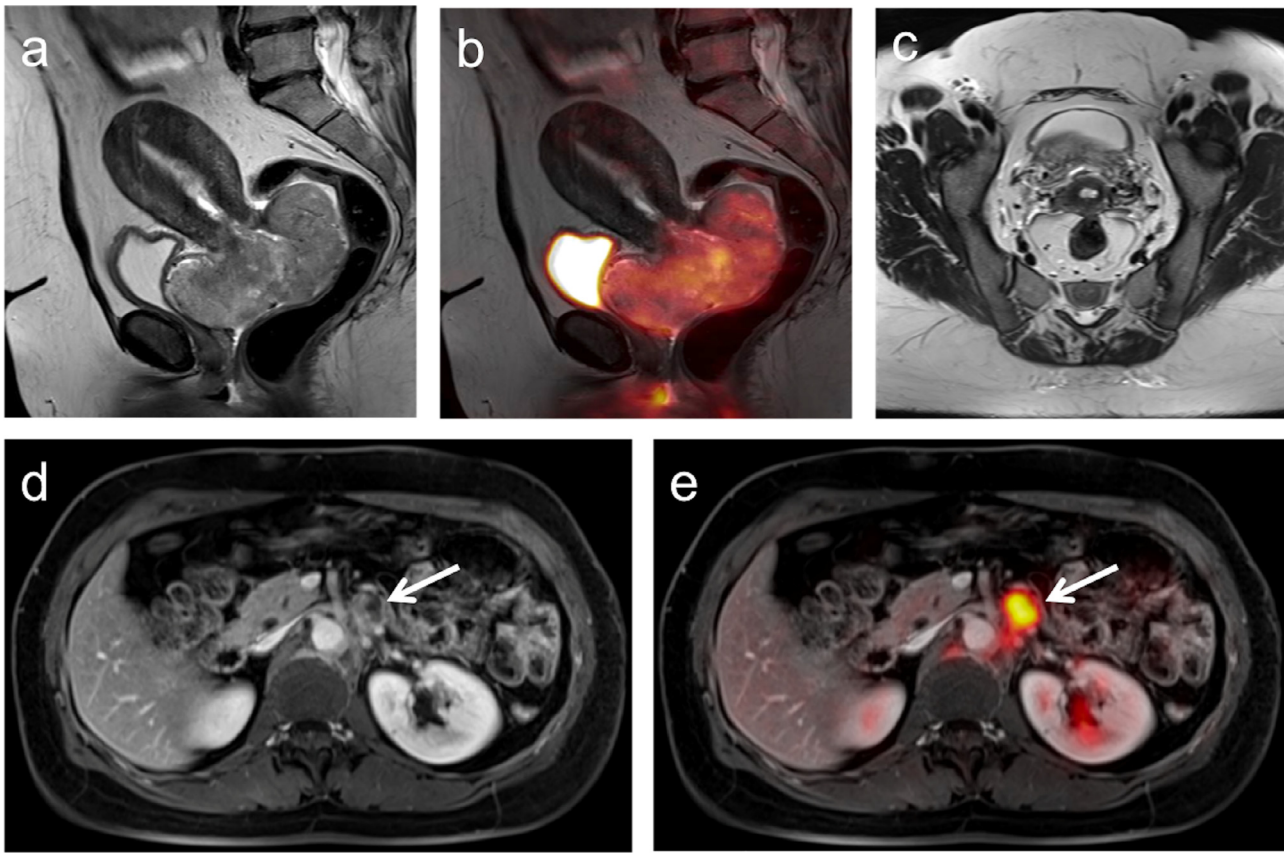

Figure 1 Images of a 43-year-old patient with an exophytic growing cervical cancer (a, T2w) with pathologically increased glucose metabolism (b, PET/MRI). No parametrial tumor invasion was detected (c, T2w). Whole-body MR (d, contrast-enhanced T1w) and PET/MR (e) images reveal an enlarged ^{18}F-FDG-PET-positive para-aortic lymph node metastasis.

efficient and high-quality staging tool for whole-body staging and/or whole-body restaging.

Cervical Cancer

The widespread use of cervical screening programs and recommendations for prevention has significantly reduced the overall rates of cervical cancer over the last years. Nevertheless, it remains to be the second most common female-specific cancer after breast cancer as well as the five most common causes of cancer death.[18] While survival rates of early stages of cervical cancer may be as high as 100%, survival rates of stage 3 and/or higher significantly decrease to less than 40%.[19] With curative options such as surgery and concurrent chemoradiotherapy being limited to small local tumors, patient management and the choice of therapy depends on accurate assessment of the local extent of the primary cancer as well as its metastatic spread. Apart from histopathologic sampling to provide information about tumor histology and aggressiveness, cervical cancers are commonly clinically staged in accordance with to the International Federation of Gynecology and Obstetrics (FIGO).[20] However, distinct discrepancies between clinical and surgical staging, in particular in patients with locally advanced cancers, have underpinned the diagnostic importance of advanced imaging techniques.[21,22] The combination of high soft-tissue contrast, high-resolution imaging, as well as potential for functional data acquisition has sustained the role of MRI as the imaging tool of choice for cross-sectional assessment of cervical cancer and its recognition in the revised FIGO recommendations for staging and therapy monitoring.[20,23-25] Facilitating sensitivity and specificity rates ranging from 75% to 100% and 96% to 99%, MRI is recommended as an adjunct to clinical staging for assessment of therapy-crucial factors such as tumor size, tumor extent, and parametrial or sidewall-infiltration.[26,27] While MRI has been shown superior for evaluation of the local tumor extent (over other cross-sectional imaging modalities), molecular imaging, by means of ^{18}F-FDG-PET/CT, has been demonstrated superior for lymph node staging, overall restaging and treatment monitoring of gynecologic malignancies.[28,29] The presence of lymph node metastases is considered an important prognostic factor to progression-free and overall survival[30-32] with survival rates significantly decreasing in early tumor stages (IB, IIA) when lymph node metastases are present.[33-34] Furthermore, the detection of lymph node metastases requires important changes regarding adjuvant radiation or radiochemotherapy as well as planning of the radiation field.[29] Hence, due to its superiority in lymph node detection when compared to CT or MRI based on the combined assessment of metabolic and

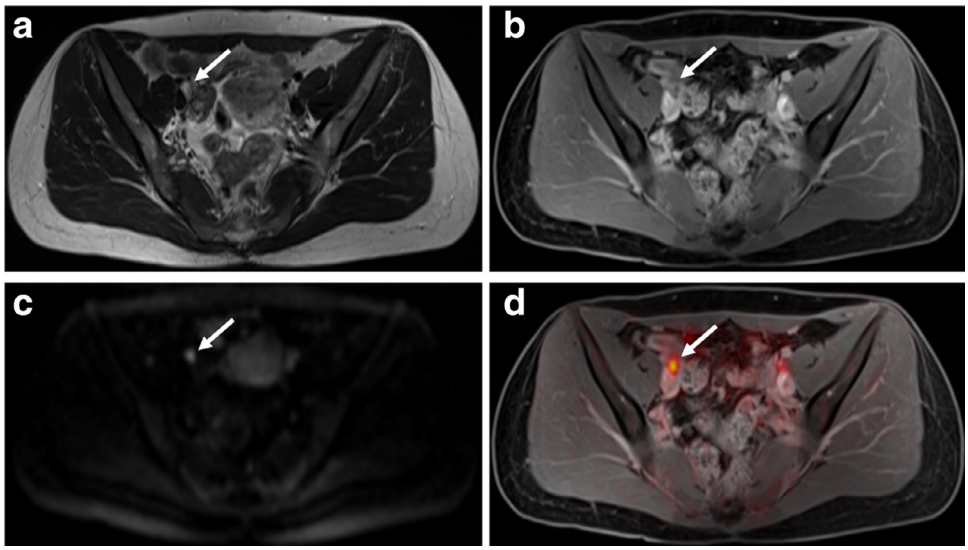

Figure 2 Images of a 59-year-old patient with primary cervical cancer and an ^{18}F-FDG-PET positive lymph node metastasis in the right hemipelvis. MR images (a, T2w; b, contrast-enhanced T1w) show a nonenlarged, hence morphologically nonsuspicious lymph node adjacent to the right iliac vessels. The correct diagnosis could be made based on its restricted diffusivity (c, DWI) and pathologically increased glucose metabolism (d, PET/MR).

morphologic information, PET/CT is considered an accurate imaging alternative to surgical lymph node dissection in advanced tumor stages and recommended as an adjunct to local tumor assessment by MRI to provide complementary information.[35,36] The realization of the value and diagnostic potential of the combined strength of MRI and PET initiated the utilization of PET/MR imaging early in its implementation into female imaging. Kitajima et al were one of the first to investigate the diagnostic potential of retrospectively fused ^{18}F-FDG-PET- and MR data for the assessment of the tumor extent as well as nodal staging in cervical cancer patients.[37] Based on the superior soft-tissue contrast of MRI, the results of their comparison trial underlined the higher diagnostic accuracy of PET/MRI and MRI for T-staging when compared to PET/CT. Comparable to studies by Queiroz et al and Grüneisen et al, the metabolic component in PET/MRI helped to surpass the diagnostic potential of MRI alone for lymph node detection[15,38] (Fig. 2). A recently published systematic review and meta-analysis on the diagnostic potential of integrated PET/MRI by Nie et al supports these results in underlining the superiority of PET/MRI to PET/CT for T-staging and its diagnostic equivalence to PET/CT in regard of nodal staging.[25]

Apart from primary staging, PET/MRI also bears the potential to serve as a valuable treatment monitoring tool as it facilitates the simultaneous and combined analysis of morphologic, metabolic, and functional tumor data. As MRI is known to be impaired in the differentiation of post-therapeutic scar tissue and potential residual tissue, the combined analysis with PET has been shown helpful for treatment monitoring (Fig. 3). While the number of studies is limited, a number of initial studies have demonstrated the predictive power of the quantification of metabolic activity and tissue cellularity of cervical cancer tissue, revealing significant correlations with treatment response as well as patient survival.[39-43] According to Nakamura et al, the combination of higher SUVmax and lower ADCmin values may predict a shorter overall and disease-free survival in patients with cervical cancer.[39] Further studies revealed significant inverse correlations between SUV and ADC values of primary cancers of the uterine cervix.[44,45] Hence, integrated simultaneous PET/MRI may enable a more comprehensive characterization of tumor biology, which may aid to facilitate early treatment response assessment or maybe even prediction of treatment response.

Approximately one-third of cervical cancer patients suffer from tumor relapse, with higher relapse rates in patients with nodal metastases and/or more locally advanced tumors at initial diagnosis.[46,47] Up to current status, CT and/or MRI are considered the standard imaging procedures for the evaluation of a potential tumor relapse. However, various studies demonstrated the superiority of PET/CT over conventional cross-sectional imaging modalities, providing sensitivity and specificity values >80% and support the implementation of PET/CT for the detection of recurrence in patients potentially treatable with curative intent.[48-50] Hence, over the past few years, PET/CT has been introduced into a number of guidelines as a recommended tool for assessment of tumor relapse of female pelvic (and other) malignancies.[36] Comparable to PET/CT, PET/MRI may also be applied for whole-body restaging. Numerous studies investigated the diagnostic competence of integrated PET/MRI compared to MRI alone as well as to PET/CT for restaging of various tumor entities.[51-57] Kitajima et al assessed the diagnostic performance of ^{18}F-FDG-PET/CT in comparison to ^{18}F-FDG-PET alone and contrast-enhanced CT alone in 90 patients with a suspected tumor recurrence of cervical or endometrial cancer.[50] The results revealed a significantly higher accuracy of PET/CT for the detection of

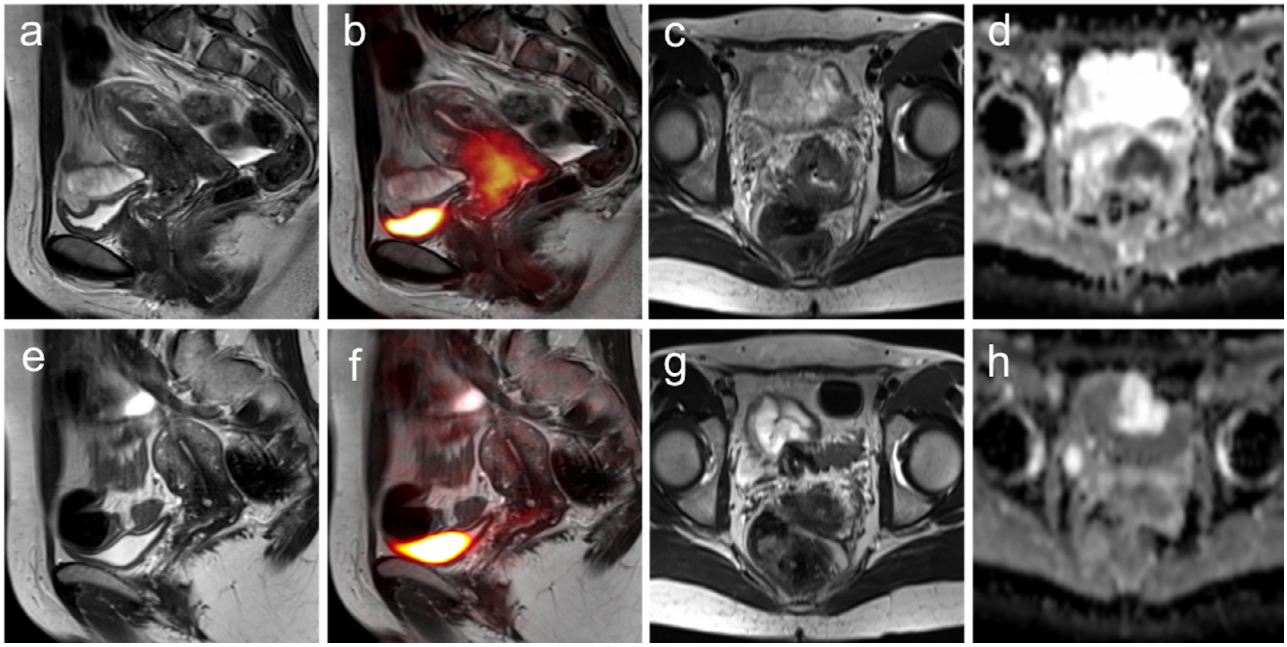

Figure 3 Images of pre- (a-d) and post-therapeutic (e-h) PET/MR examination of a 67-year-old patient with primary cervical cancer (a, c, T2w). Pretherapeutic MR images show a parametrial tumor invasion (c, T2w) as well as a pathologically increased glucose metabolism (b, PET/MRI) and restricted diffusion of the primary tumor (d, ADC map). On post-therapeutic PET/MR images 3 months after concurrent chemoradiation, the cervical tumor manifestation cannot be delineated in the morphologic images any more (e,g T2w) and in addition, no pathologic tracer uptake (f, PET/MR) or restricted diffusion (h, ADC map) can be determined. Imaging follow-up confirmed therapeutic complete response.

recurrent cancers, leading to changes in subsequent treatment recommendations in 42% of the patients. With regard to staging of patients with suspected recurrence of gynecologic pelvic cancer, current studies also indicate a promising role for PET/MRI.[10,52] In a recent study by Sawicki et al, the authors evaluated the diagnostic performance of ^{18}F-FDG-PET/MRI for whole-body staging and potential changes in therapeutic management of women with suspected recurrent pelvic cancer in comparison with MRI alone. PET/MRI yielded superior diagnostic accuracy with significantly better identification of patients with cancer recurrence (100% with PET/MRI vs 83.6% with MRI alone, $P< 0.01$), superior diagnostic accuracy (99.2% vs 79.3%, $P< 0.001$) and superior diagnostic confidence in the categorization of malignant lesions compared with MRI alone (2.7 ± 0.5 vs 2.4 ± 0.7, $P< 0.001$).[52] When compared with PET/CT, PET/MRI has been shown to facilitate a comparable whole-body staging performance in patients with tumor recurrences of female pelvic malignancies.[58-60] Only minor differences between the two modalities were described regarding the delineation of suspect lesions in dependence of their localization.[9] While PET/CT was shown to yield a higher detection rate of pulmonary lesions, PET/MRI offered a higher accuracy for the identification and characterization of liver metastases and better detectability of bone metastases when compared to PET/CT.[57,61-63]

An important advantage of PET/MRI lies in the radiation exposure savings which amount to 73%-77% in comparison to a full-dose PET/CT scan,[64] which may be of particular importance considering the application of repetitive follow-up examinations in cancer patients and a young peak age of cervical cancer patients.

Overall, it can be concluded that PET/MRI provides a high-quality alternative for whole-body cancer staging to PET/CT with excellent soft-tissue contrast and significantly lower radiation exposure.

Endometrial Cancer

Endometrial cancer is the third most common cause of death in cancers, which only affect women and is the most frequently diagnosed gynecologic malignancy in developed countries.[65] Typical clinical symptoms include abnormal or postmenopausal bleeding and commonly occur at an early stage of the disease. Transvaginal ultrasound and endometrial biopsy are commonly applied to aid in the diagnosis of endometrial cancer. As endometrial cancer is surgically staged, further preoperative imaging is generally only recommended if imaging is needed for further treatment planning, for example, in high-risk patients, advanced cancers or to assess potential myometrial invasion or endocervical tumor extent. Due to its high soft-tissue contrast MRI is considered highly accurate and superior toward CT or ultrasound for the assessment of the local tumor extent and the depth of myometrial tumor invasion, representing one of the most important prognostic factors.[65-67] Sensitivities and specificities of MRI for the determination of the depth of myometrial tumor invasion range between 70%-95% and 80%-95%,

respectively.[23,68] Apart from the local tumor extent, further important prognostic factors include the occurrence of lymph node and distant metastases.[69] The occurrence of pelvic and/or para-aortic lymph node metastases in endometrial cancer impacts treatment planning, in terms of surgical treatment and adjuvant radiochemotherapy options, and designates the patient to a stage IIIC or higher.[70-72] As demonstrated in other cancers of the female pelvis, hybrid imaging has been proven superior for the detection of lymph node metastases over conventional imaging modalities like CT or MRI.[35] Kim et al compared MRI and PET/CT for detection of lymph node metastases in a fairly large cohort with 287 patients with endometrial cancer. Their results underline the superiority of PET/CT in facilitating a significantly higher sensitivity, specificity, PPV, NPV, and accuracy of PET/CT compared to MRI as well as excellent rates in high sensitivity, specificity, and NPV for the detection of distant metastases.[72] Comparable to their studies in cervical cancer, Kitajima et al investigated the diagnostic value of a retrospective fusion of pelvic MR- and ^{18}F-FDG-PET datasets for locoregional tumor staging of primary endometrial carcinoma in comparison to MRI alone and PET/CT.[73] Following the promising results of fused PET/MRI for assessment of the local tumor extent and lymph node staging in endometrial cancer, the utilization of integrated PET/MRI seems even more promising as potential misregistration artifacts due to different bladder fillings (and corresponding positioning of the uterus) can be reduced thanks to simultaneous scanning of PET and MRI. Nevertheless, current studies on PET/MRI in primary endometrial cancer are yet to be published.

With 15% of tumor relapses within the first 3 years of initial diagnosis and treatment of endometrial cancer, the most common sites include lymph nodes or the vaginal vault.[74] As the occurrence of distant metastases drastically changes and limits therapeutic options, accurate whole-body restaging is indispensable. Comparable to other tumors of the female pelvis, PET/CT has been demonstrated superior over conventional modalities, yielding pooled sensitivity and specificity rates of 95.8% and 92.5% for the depiction and localization of recurrences in post-therapeutical follow-up of endometrial cancer patients.[75] Hence, the American College of Radiology assigned highest ratings toward the application of PET/CT restaging of endometrial cancer patients in their recommendations.[76] Up to current status, only a few studies investigated the diagnostic competence of PET/MRI in comparison to PET/CT in female pelvic cancers, mostly in mixed cohorts including cervical, ovarian, and endometrial cancer. Their results underline the comparable potential of PET/MRI whole-body restaging toward PET/CT, while facilitating the benefit of reduced radiation dosages.[9,10,15,38,52]

Ovarian Cancer

Ovarian cancers are among the most common neoplasms of the female pelvis and one of the leading causes of cancer-related deaths in western countries.[77] Early-stage ovarian cancer rarely causes any symptoms, often delaying the initial diagnosis to more advanced tumor stages. With more than 70% of patients being diagnosed at FIGO stage III or IV, the 5-year survival rate is less than 30%.[78] Clinical signs of advanced-stage ovarian cancer include symptoms like abdominal bloating, weight loss, or changes in bowel habits, which due to their rather nonspecific nature often amplify the delay in diagnosis. In case of suspicion for ovarian cancer, clinical evaluation, transvaginal ultrasonography, and blood tests for tumor markers (eg, cancer antigen (CA)-125) are initially applied.[14] Optimal cytoreductive surgery followed by postoperative chemotherapy are considered the cornerstones of treatment of advanced ovarian cancer patients.[79,80] Nevertheless, the success rate of cytoreduction varies significantly, ranging from 15% to 85%, hence, precise pretreatment discrimination of patients who are not amenable to optimal cytoreduction is a prerequisite of optimal patient management.[81]

While CT imaging is most commonly used for primary tumor staging, technical innovations, in particular, the implementation of diffusion-weighted imaging, have uplifted the diagnostic accuracy of MRI for detection of lymph node and peritoneal metastases.[82,83] In a study by Michielsen et al, whole-body MRI including diffusion-weighted imaging was shown to provide a higher accuracy than CT for the detection of peritoneal carcinomatosis (91% vs 75%), lymph node metastases (87% vs 71%), and the correct determination of the tumor stage (94% vs 56%).[22] Furthermore, the role of PET/CT for staging of ovarian cancer has been assessed in a number of trials. In a meta-analysis analyzing the potential for detection of lymph node metastases, higher sensitivity and specificity of PET or PET/CT (73.2% and 96.7%) was demonstrated when compared to CT (42.6% and 95%) and MRI (54.7% and 88.3%).[84] Fiaschetti et al investigated the diagnostic potential of retrospectively fused PET and MRI datasets for the characterization of suspicious ovarian lesions (100). According to their results, PET/MRI showed a higher sensitivity, specificity, and negative predictive value (94%, 100%, and 83%) than PET/CT (74%, 80%, and 44%) and MRI alone (84%, 60%, and 50%) for the identification of ovarian tumor manifestations.[85] In a previously mentioned study, Queiroz et al directly compared PET/CT and PET/MRI for staging female pelvic malignancies, comprising 12 of 26 patients with ovarian cancer.[38] While both modalities showed equivalent results for the identification of abdominal and regional lymph node metastases, PET/MRI facilitated better determination of the local tumor extent in 5 of the 12 cases. These findings go in line with studies on the diagnostic potential of integrated PET/MRI for restaging of patients with suspicion of ovarian cancer relapse. Although limited to a few studies with mostly mixed cohorts of patients with cancers of the female pelvis, the results underline the comparable diagnostic ability of PET/MRI toward PET/CT for whole-body restaging in ovarian cancer and its superiority toward MRI alone[9,10,53,86] (Fig. 4). Overall, the authors reported comparable to equivalent detection rates of tumor recurrence on a per-patient- and per-lesion basis, with only minor differences between the two imaging modalities for lesion detection in dependence of their localization. Apart from its potential for detection of metastatic lesions, the PET component may also aid to predict suboptimal cytoreduction

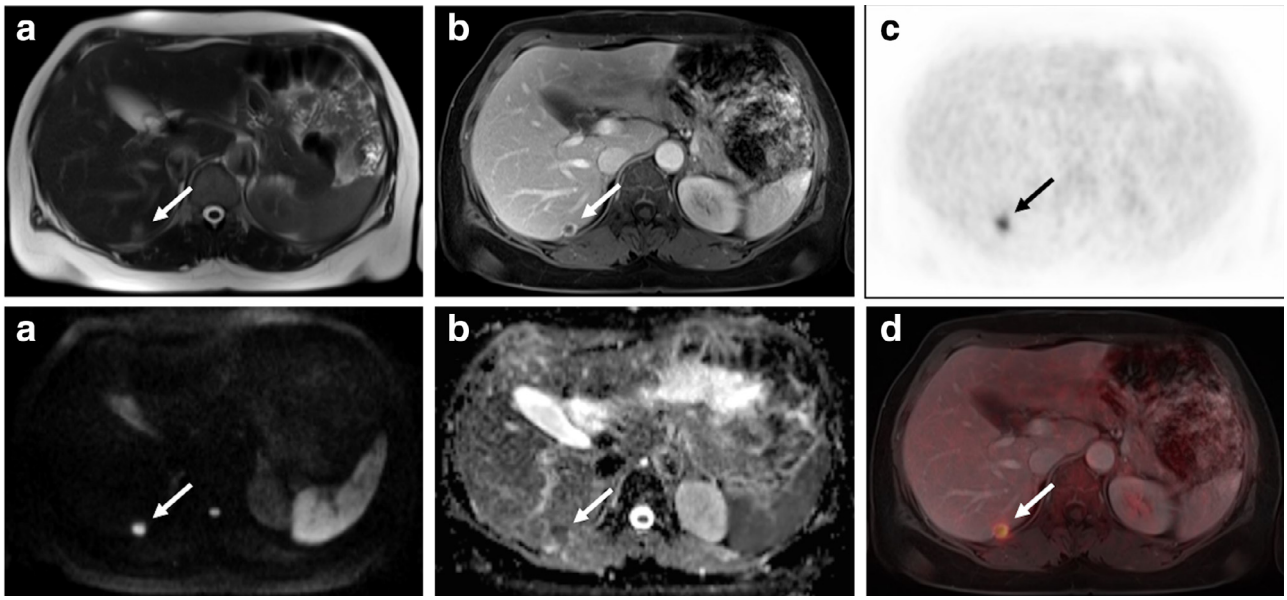

Figure 4 Restaging examination of a 62-year-old patient with a liver metastasis of an ovarian cancer. T2-weighted images (a) show a hyperintense subcapsular liver lesion with rim enhancement (b, contrast-enhanced T1w), which reveals restricted diffusivity (d, DWI; e, ADC-map) as well as a pathologically increased glucose metabolism of 18F-FDG PET (c,f).

during primary debulking surgery for advanced ovarian cancer.[87] In a recent publication by Chong et al, the authors aimed to evaluate the ability of ^{18}F-FDG-PET/CT parameters to predict suboptimal cytoreduction and to create a risk model for predicting suboptimal cytoreduction in advanced ovarian cancer. The hypothesis of their study was based on the reflection of the SUVmax as the aggressiveness and tumor activity of malignant lesions. To test their hypothesis, they obtained the SUVmax for nine different regions in the abdominal pelvic cavity. Their results could show that the presence of hypermetabolic lesions in the central, right upper, and left upper regions showed predictive value for suboptimal cytoreduction, concluding that their risk model may be helpful for selecting patients who may show suboptimal cytoreduction.[87] Combining the potential of PET and MRI for high soft-tissue contrast, integrated PET/MRI may help to triage the patient toward the most appropriate treatment strategy (eg, primary surgery vs neoadjuvant chemotherapy) as well as to predict the option of an optimal cytoreductive surgical intervention.

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