Advances in Endometrial Cancer Diagnosis

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Endometrial cancer is staged according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines which are developed independently from imaging [1]. Major prognostic factors for endometrial cancer comprise histologic grade and lymphovascular invasion, local tumor extent including depth of myometrial invasion and cervical stromal involvement, and extrauterine tumor spread including nodal and distant metastatic spread [2]. Although FIGO guidelines do not recommend cross-sectional imaging as routine diagnostic modalities, CT, MRI, and FDG-PET/CT have an increasing role in the management of endometrial cancer patients as they also allow assessment of distant nodal or visceral disease spread [3]. At the time of diagnosis of endometrial cancer, imaging is most important for staging of locoregional and distant tumor extent and for prognostication. The purpose of this chapter is to present a general overview of conventional and newly developed imaging concepts for endometrial cancer.

4.1 Local Staging

Depth of myometrial invasion (Stage IA vs. IB) and cervical stromal invasion are key features in the imaging assessment of local disease extent as both are highly associated with nodal metastases. Deep myometrial invasion >50% is associated with higher frequency of nodal metastases up to 46% [4].

CT has the advantage of widespread availability at a relatively low cost, providing fast and reproducible image acquisition compared to MRI and FDG-PET/CT. CT is usually performed after the injection of iodinated contrast-agent using multidetector technology, which enables data acquisition of large anatomical areas and high-quality thin-slice multiplanar image reformatting. However, the major

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disadvantage is the low soft tissue contrast, which hampers the depiction of small endometrial cancers and inhibits accurate assessment of local tumor spread such as myometrial or uterine cervical invasion. For assessment of deep myometrial invasion, a sensitivity of 83% with specificity of 42% and overall staging accuracy between 58 and 76% have been described [5, 6]. A study, using multidetector CT, reported better diagnostic accuracy of 95% for evaluating myometrial invasion and 81% for assessing cervical infiltration. However, the authors acknowledged small patient number and large percentage of cases with deep myometrial invasion [7]. In clinical practice, CT is mostly used to assess extrauterine diseases including regional and para-aortic lymph nodes and shows similar accuracy as MRI for the detection of extrauterine disease spread and identifying nodal metastases [8].

For local staging, MRI benefits from a superior contrast resolution and excellent soft tissue differentiation. Other benefits of MRI include absent radiation exposure, absent need of iodinated contrast-agent and a high flexibility in its performance allowing the adaptation of image protocols to the specific needs of the patient and easy integration of functional imaging sequences such as dynamic contrast-enhanced imaging (DCE-MRI) and diffusion-weighted imaging (DWI). Disadvantages included lower availability compared to CT, lower patient compliance related to longer imaging times, claustrophobia, and contraindications such as pacemakers.

Standardization of the MRI protocol is pivotal to optimize diagnostic accuracy and reproducibility and a protocol has been recommended in the European Society of Urogenital Radiology (ESUR) Endometrial Cancer Staging guidelines [8]. Routine sequences in the imaging protocol consist of T2-weighted images in the sagittal and oblique transverse plane, perpendicular to the endometrial cavity and fat-saturated post-contrast T1-weighted images. Combination with dynamic contrast-enhanced (DCE)-MRI—which is acquired by repetitive imaging with high temporal resolution over a predefined lesion prior to and during the injection of a gadolinium contrast agent—is highly recommended as it allows better delineation of the tumor [9]. Although not routinely recommended, studies have shown that DWI can be of additional value for endometrial characterization, assessment of myometrial invasion, response assessment, and prognostication [9, 10].

DWI distinguishes itself from conventional MRI sequences by detecting water molecule displacements at a cellular scale allowing functional characterization of tissue microstructural properties. The signal intensity of lesions depends on the amount of impediment of water molecule displacements. The more tissue restricts water molecule displacement (e.g. tumoral lesions), the brighter lesions appear at heavily weighted DWI (b = 800–1000 s/mm^2), compared to the suppressed background tissue. The typical signal decay with increasing b-value can be quantified using the apparent diffusion coefficient (ADC). In a simplified model, image analysis comprises combined reading of the signal intensity at high b-value images and quantification of ADC to differentiate malignant from benign tissue. Tissue, with a relatively increased cellular density (Tumor) will typically be bright on high b-value images and dark on the ADC-image while tissue with a relatively decreased cellular density (most benign tissues, inflammation and necrosis) will be dark on high b-value images and bright on the ADC-images [11].

Although MRI is considered the most accurate imaging modality for staging and preoperative assessment of endometrial cancer, the value of pretreatment MRI is not unequivocally accepted as the majority of cases are treated by surgery [12]. According to the European Society of Urogenital Radiology (ESUR) Endometrial Cancer Staging guidelines, indications for MRI with proven or suspected endometrial cancer include: high-grade, serous or clear-cell adenocarcinomas; suspicion of advanced disease, including cervical stroma extension and confirmation of stage III and IV disease; screening for lymph node enlargement as a roadmap for lymph node sampling; medical contraindication for surgical staging; and suspected endometrial cancer with inability of curettage (e.g., cervical stenosis) [8].

For assessment of deep myometrial invasion, a meta-analysis in 47 studies aiming to compare the utility of CT, endovaginal ultrasound, and MRI described sensitivity between 78.6% and 100%, respectively, specificity between 71.4% and 100% for contrast-enhanced MRI compared to sensitivity between 40% and 100%, respectively, specificity between 66.7% and 100% for CT and sensitivity between 50% and 100%, respectively, specificity between 65% and 100% for endovaginal ultrasound. For assessment of cervical involvement, sensitivity in the included studies ranged between 55.6 and 100% and specificity between 92.3 and 100% for MRI, compared to 40–71.4% sensitivity with 100% specificity for CT and 66.7–80% sensitivity with 95.2–100% specificity for endovaginal ultrasound [13]. Importantly, the superiority of MRI over endovaginal ultrasound could not be unequivocally shown. However, MRI harbors the important advantage that it is the only modality that allows for simultaneous accurate assessment of myometrial, cervical, and nodal involvement (Fig. 4.1).

Another more recent meta-analysis including 52 eligible studies, showed 80.7% pooled sensitivity and 88.5% pooled specificity for the assessment of deep (>50%) myometrial invasion and 57% pooled sensitivity and 94% pooled specificity for assessment of cervical stromal involvement. Importantly, the addition of the functional MRI sequences, DCE-MRI and DWI, increases sensitivity compared to contrast-enhanced MRI alone [14]. DCE-MRI allows for better differentiation of tumor from blood products and debris as well as tumor from the myometrium due to differential timing of enhancement [9]. Although less established compared to DCE-MRI, DWI improves MR assessment of myometrial invasion with diagnostic accuracies ranging between 62–90% [15, 16]. In a study of Beddy et al., DWI showed superior accuracy over DCE-MRI (90% vs. 71%) for assessment of myometrial invasion [10]. In a study by Rechichi et al., DWI showed not only higher accuracy for tumor staging but also higher interobserver agreement for assessing tumor extension [17]. These findings suggest that DWI adds to the overall diagnostic performance of MRI for local tumor staging, not only by improving diagnostic accuracy but also by improving radiologist confidence. Alternatively, these findings indicate that DWI can obviate the need of contrast-injection, in case of contraindication. An additional important advantage of DWI over conventional MRI for local tumor assessment is the ability for quantification of tissue properties by means of the ADC. This allows DWI to differentiate endometrial cancer from benign endometrial polyps and could be of particular importance in patients difficult to biopsy. A previous study showed that endometrial cancer has significantly lower ADC

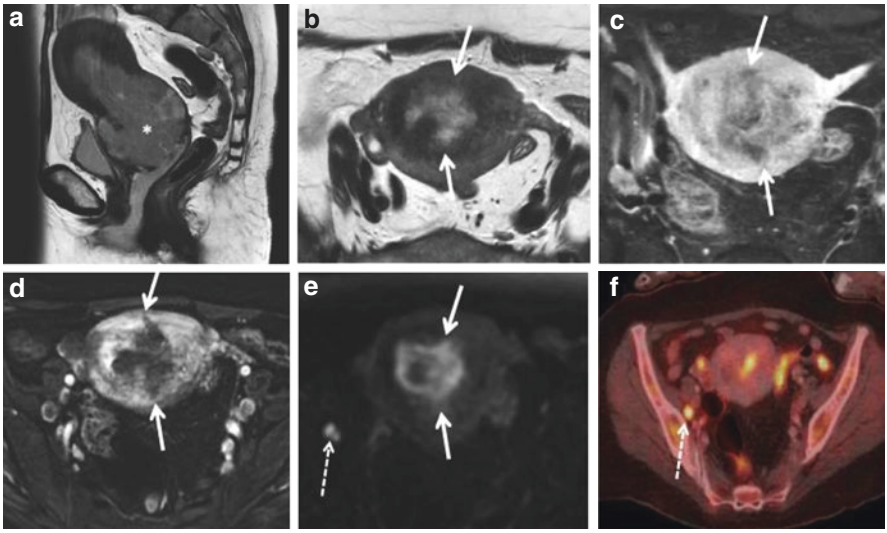

Fig. 4.1 Patient with advanced endometrial cancer: (**a**) Sagittal T2-weighted MRI shows large mass in the endometrial cavity with gross cervical invasion (asterisk). (**b**, **c**) Transverse T2-weighted and contrast-enhanced T1 image shows multifocal deep myometrial invasion (arrows). (**d**, **e**) This is better appreciated at DCE-MRI and DWI due to the high tumor-to-background contrast (arrows). DWI also allows the depiction of a bright right iliac lymphadenopathy, confirmed by FDG-PET/CT (**f**, dashed arrow)

compare to benign polyps allowing differentiation with 92% accuracy [18]. Moreover, Studies have shown that the ADC measured over the endometrial mass can predict tumor grade, for which a lower ADC correlates to higher tumor grade [19–21]. However, substantial overlap between ADC of different tumor grades does not allow its clinical application at this time. Recently, a study has shown that tumor volumetry combined with volumetric ADC measurements or ADC histographic analysis may allow accurate preoperative risk stratification of patients with endometrial cancer. ADC histographic analysis depicts the ADC heterogeneity and thus better reflection of the tumoral microstructural heterogeneity. Lower histographic ADC values were shown to correlate significantly with lymphovascular invasion and allow differentiation grade 3 from grade 2 and 1 tumors. Although further development is required, DWI could further help to stratify treatment according to risk of local or distant recurrence [22].

FDG-PET/CT takes advantage of the fact that endometrial cancer demonstrates an increased rate of glycolysis for visualization. In a comparative study, FDG-PET/CT showed 61% accuracy for myometrial invasion and 83% accuracy for cervical invasion similar to MRI [23]. It should however be noted that neither DCE-MRI nor DWI were included in the scan protocol. Overall, FDG-PET/CT has a limited role for local staging whereas it has greater value for staging extrauterine disease. Importantly, similar as for DWI, assessment of the tumoral metabolical properties

may hold prognostic information. Previous studies have shown a statistical correlation between the maximum standard uptake value (SUVmax) of the primary tumor and FIGO stage, histological grade, depth of myometrial invasion, lymph nodes metastases and lymphovascular invasion [24, 25]. In a study by Husby et al., Metabolic tumor volume and PET-derived quantitative parameters including the SUVmax were independent predictors of deep myometrial invasion and nodal metastases and may aid in the preoperative identification of high-risk patients and enable the restriction of lymphadenectomy in patient with low risk of aggressive disease [26]. Furthermore, a high SUVmax has been shown to be an independent prognostic factor for overall survival [27].

4.2 Staging of Extrauterine Disease Spread

For detection of nodal metastases, CT and conventional MRI rely on size-related (1 cm threshold) and morphologic criteria like shape or internal architecture. These features are highly variable predictors of nodal involvement and bare the inherent disadvantage that small nodal metastases remain undetected and or that enlarged reactive—and thus benign—lymph nodes are falsely interpreted as malignant. Although the presence of intranodal necrosis at conventional imaging has positive predictive value of 100% for predicting metastatic involvement, its occurrence is too infrequent to significantly influence diagnostic performance [5]. The sensitivity of CT ranges between 52 and 92% for assessing pelvic and para-aortic lymphadenopathy, is not significantly improved by conventional MRI which has described diagnostic accuracy between 55 and 77% [9, 28].

Due to its ability to probe the tissue microstructure—irrespective of lesion size by differences in ADC, DWI has the potential to improve nodal staging compared to conventional MRI.

Differences in ADC between malignant and benign lymph nodes likely result from differences in microstructure with metastatic lymph nodes expected to have increased cellularity, enlarged cell size and nuclei compared to benign lymph nodes. This should result in lower ADC for metastatic lymph nodes due to the restriction of extracellular water molecules.

Reports evaluating DWI quantified by the ADC for nodal staging in patients with endometrial and cervical uterine cancer show variable results. While in the study of Roy et al., ADC values were not statistically different between benign and malignant lymph nodes and thus did not allow for characterization of nodal metastases, Lin et al., showed that adding DWI substantially improved sensitivity compared to conventional MRI while maintaining specificity (83% vs. 25%) [29, 30]. The diverging results likely reflect difficulties encountered in the analysis of DWI. Impeded diffusion with similar low ADC with as for malignancy may be encountered in reactive lymph nodes due to hypercellularity of lymphoid cells. Further refinement of ADC-analysis could overcome this problem and overcome current limitations for differentiation of pelvic lymph nodes. Recently, Rechichi

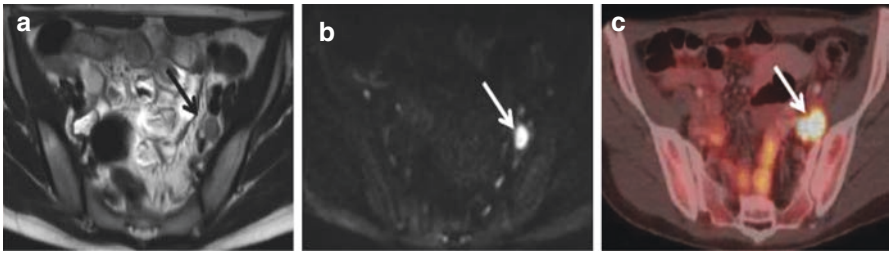

Fig. 4.2 (**a**) T2-weighted MR image shows enlarged lymph node posterior to the right external iliac vein. The lymphadenopathy is markedly hyperintense compared to surrounding lymph nodes on the (**b**) b1000 DWI-image facilitating its detection. The lymphadenopathy was confirmed by (**c**) PET/CT and subsequent lymphadenectomy

et al., found high accuracy for nodal differentiation in endometrial cancer of 98.3% by applying minimum ADC region values compared to 72.9% for the mean ADC—the current standard analysis [31]. Awaiting further development, standardization and larger studies that reproduce initial results, the use of DWI with quantitative ADC for nodal differentiation in endometrial cancer should currently not be considered clinical routine.

Nevertheless, when combined with conventional MRI, qualitative interpretation of high *b*-value DWI images has been shown to improve the detection of lymphadenopathy in abdominopelvic, compared with conventional imaging [9] (Fig. 4.2).

While the role of FDG-PET/CT seems more limited for local staging, it shows high value for assessing nodal and distant metastases [32]. Several studies have assessed the value of FDG-PET/CT for nodal staging in high-risk endometrial cancer patients. On a per-region based analysis, studies found sensitivities ranging between 36 and 72% with specificities between 88 and 99% [33]. A more recent meta-analysis showed good performance of FDG-PET/CT with an overall accuracy of 89.5% [34]. Currently, the spatial limitation of FDG-PET/CT limits the detection of lesions smaller than 5 mm and sensitivity decreases with lesions size. A study by Kitajima et al., showed 93.3% sensitivity for lesions larger than 1 cm, 66.7% sensitivity for lesions from 0.6 to 0.9 cm, and 16.7% sensitivity for lesions smaller than 0.4 cm [35]. Therefore, FDG-PET/CT is not generally accepted as and an adequate alternative to surgical staging [36]. Therefore, the integration of PET/CT and sentinel lymph node mapping has been proposed in high-risk endometrial cancer patients. The high specificity and positive predictive value of FDG-PET/CT allows to select patients for pelvic and aortic lymphadenectomy. The combination with sentinel lymph node mapping can overcome the spatial resolution limits of FDG-PET/CT and increase the ability to detect small nodal metastases [36]. In addition to nodal staging, FDG-PET also shows value for detecting intra- and extra-abdominal distant metastases with a described accuracy up to 96.9% [37] (Fig. 4.3).

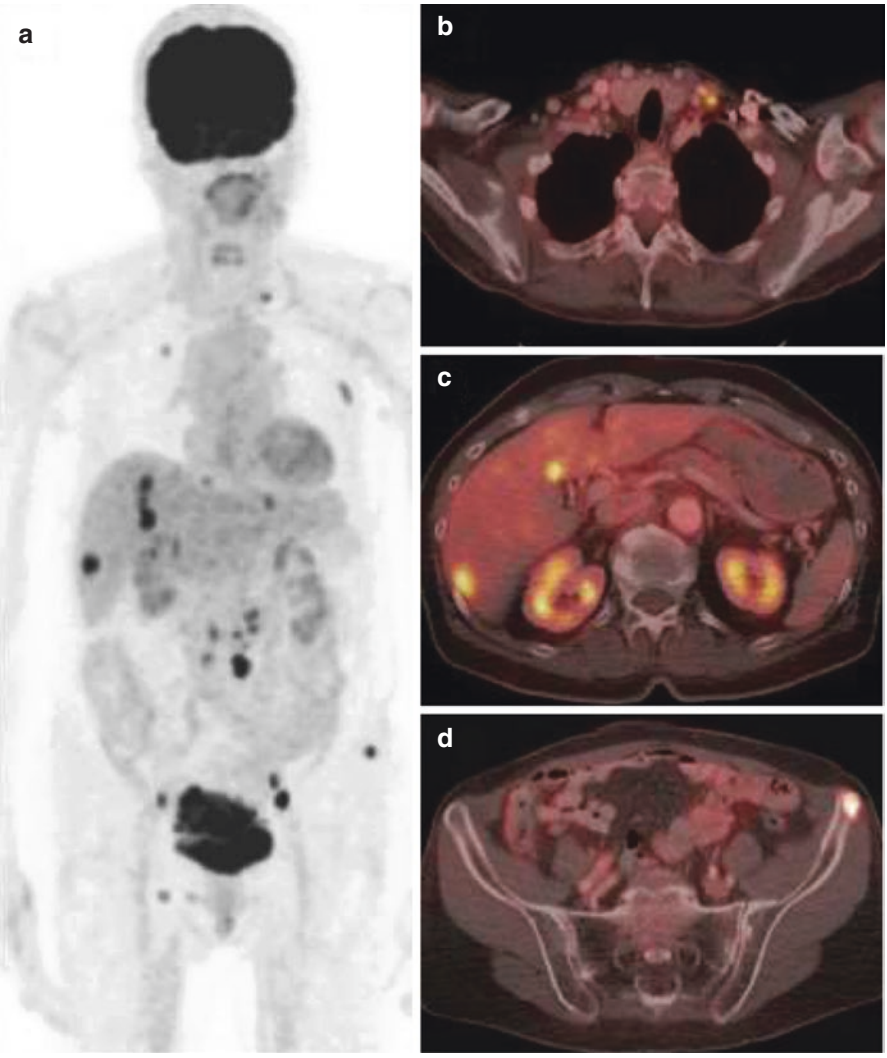

Fig. 4.3 Patient with advanced endometrial cancer: (**a**) MIP reconstruction of PET shows multifocal hypermetabolic lesions in lymph nodes, liver, and bone. Fused PET/CT images show (**b**) left supraclavicular lymphadenopathy, (**c**) liver metastases, and (**d**) bone metastasis in the left iliac crest

4.3 Conclusion

MRI complements clinical examination and ultrasound for local staging of endometrial cancer with the major advantage that it allows for accurate assessment of myometrial invasion. The addition of functional imaging techniques, including DWI and DCE-MRI, improves the accuracy of MRI for characterization of endometrial

lesions, local staging including the assessment of myometrial, and cervical involvement. In addition, DWI may also improve the ability of MRI for detection of lymph node metastases but requires further development before it can be reliably implemented as a clinical tool for nodal staging in endometrial cancer. While FDG-PET/CT has relatively low value for local staging it contributes mainly by the assessment of nodal and distant metastases. The high specificity enables adequate selection of patients for pelvic and aortic lymphadenectomy while the lower sensitivity for small nodal metastases can be overcome by additional surgical staging in high-risk endometrial cancer patients with negative nodal staging at FDG-PET/CT.

In addition, quantitative evaluation of DWI by the ADC and FDG-PET by the SUV may help in prognostication and risk stratification but requires validation in larger patient groups to validate its clinical utility. CT can be used as an alternative in endometrial cancer staging but is mostly used for detection of extrauterine disease spread. Due to its widespread availability at a relatively low cost, it is often used as a first d test.

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