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Preoperative Evaluation of Myometrial Invasion in Endometrial Carcinoma: Prospective Intra-individual Comparison of Magnetic Resonance Volumetry, Diffusion-weighted and Dynamic Contrast-enhanced Magnetic Resonance Imaging

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Abstract. *Aim: The purpose of this prospective study was to compare the diagnostic performance of diffusion-weighted (DWI) and dynamic contrast-enhanced imaging (DCE) and volumetric analyses in the preoperative assessment of myometrial invasion in patients with endometrial carcinoma. Materials and Methods: Thirty-five patients with endometrial cancer underwent preoperative magnetic resonance imaging including DWI and DCE for evaluation of the depth of myometrial invasion and volumetric analyses [tumor volume (TV), uterine volume (UV), tumor to volume ratio (TVR=(TV/TU)×100)]. The results of the evaluations were compared to the histopathological examinations. Results: DWI and DCE showed a sensitivity and specificity in evaluating the depth of myometrial invasion of 92% and 96% and 92% and 86%, respectively, while volumetric analyses showed a sensitivity and specificity of 85% and 86% (TVR cut-off=10%) and 69% and 100% (TVR cut-off=25%), respectively. Conclusion: DWI and DCE are both good diagnostic tools for the preoperative assessment of myometrial invasion. From our results and literature research, there is potential for omitting gadolinium-based contrast agents given the high diagnostic value of DWI. In our patient collective, the predictive power of volumetric analyses was lower than that of DWI.*

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Endometrial cancer (EC) is the most frequent gynecological malignancy worldwide with approximately 300,000 new cases every year (1). Clinical staging under-stages 13-22% of carcinomas and, therefore, since 1988 the official International Federation of Gynecology and Obstetrics (FIGO) staging combines surgical and histological findings (2), which was again revised in 2009 (3, 4). The prognosis of EC depends upon histological type, tumor grade, stage (myometrial infiltration >50% in apparent early stage) (5, 6), and lymph-node status (7-9).

Since the definition of lymph-node status allows for a precise determination of prognosis and accurate tailoring of adjuvant therapy (10), it is crucial to identify preoperative and intraoperative risk factors for recognizing the patients who may have lymph-node dissemination (5, 11-17). Depth of myometrial invasion is the most important risk factor in apparent early-stage EC, but it is difficult to determine preoperatively. Magnetic resonance imaging (MRI) has been shown to be the most sensitive imaging modality, with promising results (18, 19) and dynamic contrast-enhanced (DCE)-MRI improves the accuracy of the assessment of the depth of myometrial invasion, which can be more improved by performing of diffusion-weighted MRI (DWI) (20, 21).

In a recent retrospective study, Nougaret *et al*. evaluated the use of tumor volumetry as a tool for the initial staging of

EC and demonstrated a positive correlation of tumor volume with deep myometrial invasion, tumor grade, and lymphovascular invasion (22).

The aim of the present study was to compare the diagnostic accuracy of endometrial tumor volumetry with that of DCE imaging and DWI for detecting deep myometrial invasion in patients with EC.

Materials and Methods

General setup. This prospective, intra-individual comparative study was carried out at a single institution. The study protocol was approved by the Institutional Ethics Board with this approval number: EA1/065/12. All patients signed an approved informed consent form before study enrollment.

Study population. Between September 2012 and April 2015, 38 patients with histopathologically confirmed EC (established by means of tissue sampling with fractional dilatation and curettage) were enrolled. Three patients were excluded from the study population due to incomplete MRI examinations. Thirty-five patients were found to be eligible for final analysis.

For the majority of patients (n=33), preoperative MRI examination was performed before total hysterectomy with bilateral salpingo-oophorectomy. Histopathology after surgery served as the standard of reference. Curettage and histopathological analysis was performed in one 28-year-old patient who did not undergo hysterectomy in order to preserve fertility. One patient with FIGO stage II EC left the study before surgery.

MRI. All patients were examined with the same 3-Tesla system (Somatom Skyra; Siemens Healthcare, Erlangen, Germany) using an 18-channel phased-array coil. The MRI protocol included standard T1-weighted and T2-weighted turbo spin-echo, DWI and gadolinium-enhanced T1-weighted sequences. T1-weighted turbo spin-echo images were obtained in the axial plane (mean field of view: 400 mm; echo time (TE): 21 ms; repetition time (TR): 900 ms; number of slices: 49; slice thickness: 4 mm; matrix: 448×336). T2-weighted turbo spin-echo images were obtained in the axial (mean field of view: 240 mm; TE: 101 ms; TR: 4500 ms; number of slices: 20; slice thickness: 5 mm; matrix: 448×358.4) and sagittal (mean field of view: 240 mm; TE: 101 ms; TR: 6100 ms; number of slices: 20; slice thickness: 5 mm; matrix: 448×358.4) planes. T2-weighted images were also obtained in the axial oblique plane perpendicular to the major axis of the uterine body (mean field of view: 220 mm; TE: 91 ms; TR: 4960 ms; number of slices: 30; slice thickness: 3 mm; matrix: 220×220). DWI with echo-planar technique (field of view: 220 mm; number of slices: 30; slice thickness: 3 mm; TE: 112 ms; TR: 8600 ms; b-value of 0 and 800 s/mm^2; matrix: 220×220) were acquired in the axial and sagittal planes. DCE images were obtained using T1-weighted fat-suppressed volumetric-interpolated breath-hold examination (VIBE) images (field of view: 395 mm; number of slices: 50; slice thickness: 2 mm TE: 2.1 ms; TR: 4.3 ms; matrix 256×196). Images were acquired in the axial, sagittal and oblique coronal planes after injection of gadobutrol (Gadovist; Bayer Health Care, Berlin, Germany) at a dose of 1 ml/kg body weight and an injection flow of 2 ml/s. Images were obtained at 0, 30, 60, 120, 180 and 300 s after injection of the contrast agent. In order to reduce peristalsis artifacts, intramuscular administration of butylscopolamine (20 mg) was performed prior to the MRI examination.

Image analysis. Evaluation of myometrial infiltration: MR images were anonymized and stored in a picture archiving and communication system (Centricity RA1000; GE Healthcare, Waukesha, WI, USA). One radiologist with over 8 years of experience in gynecological imaging assessed all images. The depth of myometrial invasion was scored according to the revised FIGO staging system (4) using standard anatomic images and DCE or DW images at two separate readings. The reader was blinded to the patients' names, clinical histories, and to the results of the histopathological studies. The tumor was staged as FIGO IA if the tumor infiltrated up to 50% of the myometrium and as stage FIGO IB if the tumor infiltrated more than 50% of the myometrial thickness. A cervical stromal involvement defined FIGO stage II.

Tumor volumetry: DCE and DW images were transferred to a workstation for 3D-image analysis and analyzed using a semiautomatic 3D segmentation software (Medisys; Philips Research, Suresnes, France). Tumor volume was assessed semi-automatically by outlining the lesion on each image. The total tumor volume was automatically calculated by the software. The tumor contour was defined as areas of low signal intensity compared to the homogeneously enhancing normal myometrium. The volume of the uterus was measured on the basis of axial DCE images during the equilibrium phase (180 s after injection of contrast medium).

The cervix as well as uterine fibroids were carefully excluded from measurements. The tumor:volume ratio (TVR) was calculated as follows: TVR=(TTV/TUV)×100, where TTV was the total tumor volume and TUV the total uterine volume (22).

Surgery and histopathology. Total hysterectomy with bilateral salpingo-oophorectomy was performed in 33 out of 35 patients 1 to 7 days after MRI examination. Curettage only was performed in one young patient. One patient with clinically and imaging-evident FIGO stage II left the study without undergoing surgery. Experienced Board-certified gynecological oncologists performed all surgical procedures. Patients received once-off intravenous antibiotic prophylaxis (1.5 g cefuroxime and 0.5 g metronidazole) at induction and low-molecular-weight heparin (0.3-0.4 ml/24 h fraxiparine) subcutaneously 12 h after the operation. Lymph node dissection was performed only for patients with grade 3, type II-histopathology in the same session or in confirmed FIGO stage IB or higher after receiving the final histopathological study in a second session. Expert pathologists, who were blinded to the imaging results, performed histopathological examination of all tumors. Depth of myometrial invasion (superficial invasion, confined to the endometrium or inner half of the myometrium; deep invasion, invading the outer half of the myometrium) and the presence of cervical stromal invasion were confirmed microscopically. Patients were enrolled in a follow-up program of assessments at 3-month intervals.

Statistical analysis. Diagnostic performance of the different modalities were calculated as follows: sensitivity=true positives (TP)/all positive samples (P); specificity=true negatives (TN)/all negative samples (N); accuracy=(TP+TN)/(P+N); positive predictive value (PPV)=TP/all positive calls; negative predictive value (NPV)=TN/all negative calls.

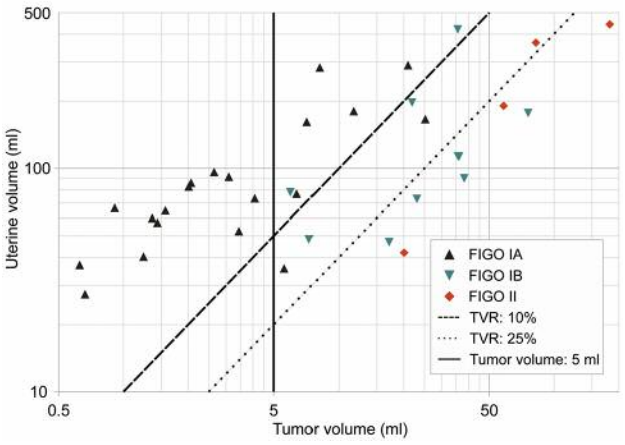

Figure 1. *Distribution of different International Federation of Gynecology and Obstetrics (FIGO) stages according to tumor and uterine volume. Diagonal lines symbolize tumor:volume ratios (TVR) of 25% and 10%. Tumors with a TVR higher than 25% were all FIGO stage IB or II. Most of the stage IA tumors had a TVR smaller than 10%, primarily owing to their smaller tumor volumes: all tumors <5 ml were stage IA tumors in our collective.*

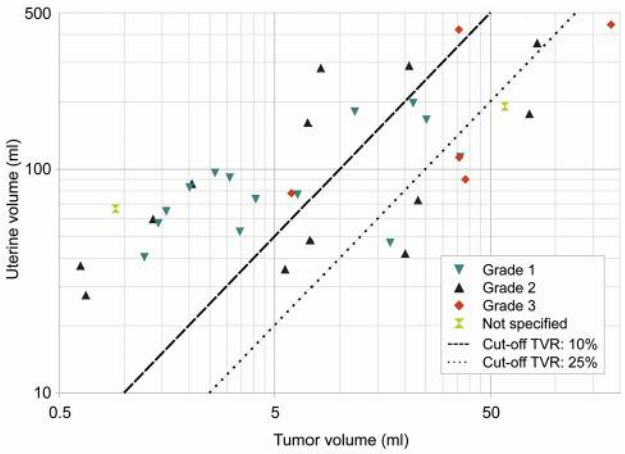

Figure 2. *Distribution of histopathological grading according to tumor and uterine volume. Diagonal lines symbolize tumor:volume ratios (TVR) of 25% and 10%. Unlike for regarding tumor staging, no correlation was found between tumor grade and tumor volume or tumor:volume ratio (TVR), with half of the G3 tumors having a TVR <10% (note that one of them was not visible in imaging and therefore is not shown in the plot).*

Results

Baseline patient demographic and clinical characteristics were as follows: The median patient age was 60 (range=28-83) years, 28 out of 35 being at least 56 years of age (80%), 11 of them between 56 and 60 years of age. Hysterectomy and histopathological studies were performed in 33 out of 35 patients. Thirty-one patients were diagnosed with type I endometrial cancer, nine of them with squamous differentiation. In two patients, serous carcinoma was found. Fourteen out of 31 patients had a well-differentiated tumor (G1), 13 had G2 tumors (moderately differentiated) and six patients had a poorly differentiated tumor (G3). There were no undifferentiated tumors in our collective. At histopathology, 22 out of 35 (62.9%) patients had a tumor with no or less than 50% myometrial invasion. One of the 22 patients had cervical stromal invasion (FIGO stage II), while the remaining 21 were staged as FIGO stage IA EC. Thirteen out of 35 patients (37.1%) had deep myometrial invasion. Disease in three out of these 13 patients was staged FIGO stage II due to combined cervical stromal invasion; in 10 it was staged FIGO stage IB.

For detecting deep myometrial invasion, DWI achieved an accuracy, sensitivity and specificity of 94.3%, 92.3% and 95.5%, respectively, with PPV and NPV of 92.3% and 95.5%, respectively. DWI underestimated the depth of infiltration in one patient with deep myometrial infiltration and overstaged another patient with superficial myometrial infiltration at histopathology.

Accuracy, sensitivity and specificity of DCE-MRI were 88.6%, 92.3% and 86.4% with PPV and NPV of 80.0% and 95.0%. DCE imaging overestimated the myometrial infiltration in three patients.

The TUV showed a large variability from 27 to 440 ml. The TTV ranged from 20 to 181 ml for FIGO II tumors, 0 (no tumor detected in one patient) to 25 ml for FIGO IA tumors and 6 ml to 76 ml for FIGO II tumors (Figure 1).

By using a TVR cut-off value of 25%, deep myometrial invasion was predicted with an accuracy, sensitivity and specificity of 88.6%, 69.2% and 100%, respectively, with a PPV and NPV of 100% and 84.6%, respectively. Choosing a lower cut-off of 10% improved the weak sensitivity to 84.6% at the expense of accuracy and specificity (85.7% and 86.4%) with PPV and NPV of 78.6% and 90.5%, respectively. For a summary and comparison of test characteristics see Table I.

Discussion

Over the past decade, the role of MRI in gynecological oncology has evolved dramatically. Especially in the context of EC, MRI has been established as a valuable tool in identifying deep myometrial invasion and thereby defining the local tumor stage. Thus, MRI helps in preoperative decision-making regarding the need for lymphadenectomy in patients with EC (23, 24).

In recent years, DWI has been evaluated with regard to whether it can facilitate determining the depth of myometrial

Table I. *Summary of test characteristics of diffusion-weighted (DWI) and dynamic contrast-enhanced imaging (DCE) and tumor:volume ratios (TVR) evaluating deep myometrial infiltration.*

Measure	DWI	DCE	TVR cut-off 10%	TVR cut-off 25%
Accuracy (%)	94.3	88.6	85.7	88.6
Sensitivity (%)	92.3	92.3	84.6	69.2
Specificity (%)	95.5	86.4	86.4	100
PPV (%)	92.3	80.0	78.6	100
NPV (%)	95.5	95.0	90.5	84.6

PPV: Positive predictive value; NPV: negative predictive value.

infiltration. DWI does not depend on the administration of gadolinium-containing contrast agents and its use is therefore independent of renal function or allergies to gadolinium-containing contrast agents. Therefore, several authors have proposed a prominent role of DWI in preoperative staging of EC (22, 25-26). More importantly, some studies have postulated that unlike DWI, DCE may overestimate the extent of myometrial tumor invasion due to peri-tumoral inflammation (26).

In our study, DWI compared to DCE imaging showed a slightly better diagnostic accuracy (94.3% *vs*. 88.6%), a higher specificity (95.5% *vs*. 86.4%; one *vs*. three FP samples) at the same level of sensitivity (92.3%, one FN sample in both imaging methods in two different patients) in assessing the depth of myometrial invasion. These results match the results of the study Beddy *et al*. conducted comparing the performance of DWI and DCE using a 1.5 T MRI scanner. They reported accuracy, sensitivity and specificity for two readers of 90/85% (reader 1/reader 2), 84/84% and 100/88%, respectively, in DWI compared to 71/79%, 61/77% and 88/82%, respectively, in DCE and found a significant improvement in diagnostic accuracy for reader 1 using DWI (25).

Concordantly, Rechichi *et al*. found in a prospective study that DWI was more accurate in assessing myometrial invasion than DCE. They reported sensitivity, specificity, PPV and NPV for assessing myometrial invasion of 84.6%, 70.6%, 52.4%, and 92.3%, respectively, for DWI compared to 69.2%, 61.8%, 40.9%, and 84%, respectively, for DCE (26).

In the volumetric analysis, we found discrepancies from the results of Nougaret *et al*. who reported that a TVR of 25% or more predicted deep infiltration, G3 tumors and lymphovascular invasion (22). For TVR and tumor volume, we did not find a correlation with a higher tumor grade: half of the G3 tumors in our collective exhibited a TVR<10%, while the other half had a TVR>25% (Figure 2). None of our patients had documented lymphovascular invasion.

Despite the finding that all tumors with a very large TVR>25% were stage IB or II tumors, this test only had a sensitivity of 69.2%, *i.e*. missing a large number of more advanced stage tumors. In our collective, the sensitivity of volumetric analyses was increased by lowering the cut-off to 10%, reaching a sensitivity and specificity of 84.6% and 86.4%, respectively, still not reaching the excellent values of DWI and DCE (Table I).

In our data set, volumetric analyses did not reliably contribute to better identification of deep myometrial infiltration given already existing information from DWI and DCE imaging. From our clinical experience, volumetric analyses are comparably time-consuming. Therefore, we conclude that in clinical practice, volumetric analyses should not be performed as routine.

Frei and co-workers calculated the pretest probability of myometrial invasion for G1, 2, and 3 tumors and concluded that MRI was reliably able to exclude deep myometrial disease in G1 and 2 disease and understaged 10% of patients with G3 disease (18). Our findings are consonant with these conclusions since one in six G3 tumors was reported FN in DWI in our study.

Taking into account previously published results, despite the small sample size of our study, we conclude that DWI and DCE-MRI are both valuable diagnostic tools for the preoperative assessment of myometrial invasion, whereas the predictive power of volumetric analyses should be interpreted with care. In future clinical routine, we see the potential for omitting gadolinium-based contrast agents given the high diagnostic value of DWI alone for our data set as well as in many previous studies (22, 25-27).

Conflicts of Interest

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