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GENERAL GYNECOLOGY

The ENZIAN score as a preoperative MRI-based classification instrument for deep infiltrating endometriosis

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Abstract

Purpose Comparison of preoperative magnetic resonance imaging (MRI) with intraoperative findings in patients with deep infiltrating endometriosis (DIE) by means of the ENZIAN score.

Methods This retrospective two-center study includes 63 patients with deep infiltrating endometriosis, who underwent surgery between 2012 and 2016 at both the University Hospital of Zurich and the Cantonal Hospital of Schaffhausen. Inclusion criteria were a preoperative pelvic MRI and intraoperative or bioptic confirmation of DIE. The preoperative MRI findings were compared with the intraoperative results by means of the ENZIAN score. Furthermore, the various MRI sequences were analyzed for their diagnostic value based on a Likert scale.

Results Sensitivity and negative predictive values of MRI confirmed by surgery were 95.2% and 91.7% (lesions in the vaginal/rectovaginal space), 78.4% and 56% (uterosacral ligaments), 91.4% and 89.7% (rectum/sigmoid colon), 57.1% and 94.1% (myometrium), 85.7% and 98.3% (bladder), and 73.3% and 92.2% (intestine), respectively. T2 axial and sagittal MRI sequences in combination with a T1 sequence were diagnostically sufficient.

Conclusions The MRI-based ENZIAN score correlates well with the intraoperative findings, enabling a better planning of the surgical procedure for patients and physicians. However, considerable difficulty and a poorer comparability result from the variations in sequences used in the detection of this multifaceted disease. Therefore, a standardization of MRI protocols used in the detection of DIE will be a crucial step towards increased diagnostic validity and the ENZIAN score may be used as an anatomical land map and valuable communication tool between radiologists and gynecologists.

Keywords Preoperative planning in deep infiltrating endometriosis · Deep infiltrating endometriosis · ENZIAN score · MRI · Endometriosis

Introduction

Endometriosis is a chronic inflammatory disease, defined as growth of endometrial glands and stroma outside the uterine cavity, which affects 5–10% of women in their reproductive age [1, 2]. The disease occurs in different locations such as the peritoneum, ovaries or as deep infiltrating endometriosis (DIE) in the retroperitoneum and rarely in other localizations. Although the clinical presentation is variable, common symptoms include dysmenorrhea, dyspareunia, non-cyclic pelvic pain and infertility. Despite its high incidence, the time between first symptoms and diagnosis of endometriosis is often very long, with an average of 6–11 years [3, 4].

Routine clinical examination and transvaginal sonography (TVS) have shown a limited benefit especially for DIE, where TVS has a high false-negative rate and further

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limitations such as the examiner's experience or limited field of vision [5–8]. Magnetic resonance imaging (MRI) is a reliable diagnostic procedure for diagnostic investigation including both localization of the endometriosis lesions and planning of the surgical procedure, in particular for DIE. A recent review showed that although they are continuously improving, the non-invasive diagnostic methods available are not yet able to supersede diagnostic laparoscopy [9]. So far, international consensus reports regarding the diagnostic protocols of preoperative MRI in DIE are sparse [10].

The most accepted and widely used endometriosis classification system worldwide is the revised score of the American Society for Reproductive Medicine (rASRM) [11]. A disadvantage of the rASRM is that it neglects the retroperitoneal organs and the deep infiltrating form of endometriosis [12].

Therefore, the ENZIAN score was introduced in 2005 and, after its revision in 2011, it became a useful supplemental scoring system for DIE and should be applied additionally to the rASRM score in patients with DIE [12–14]. As the predictive power has so far not been sufficiently examined and its international level of acceptance is still poor, further studies are needed [12, 15].

An improved preoperative classification could yield considerable benefit regarding preoperative planning and patient information.

The aim of this study was to compare preoperative MRI findings with intraoperative surgical results as reference standard in patients with DIE using the ENZIAN score as primary outcome. The secondary outcome was the analysis of the diagnostic value of different MRI sequences used in DIE diagnosis with assistance of a Likert scale.

Methods

Population

In this retrospective two-center study, a total of 65 surgical cases in 63 female patients were included (Figs. 1, 2). All patients had surgically verified DIE and were operated between 2012 and 2016 either at the University Hospital Zurich ($n = 31$) or the Cantonal Hospital Schaffhausen ($n = 32$). Inclusion criteria were a preoperative assessment by means of pelvic MRI and intraoperative or bioptic verification of DIE.

Patient age ranged from 22 to 49 years (mean age 33.5 years). In 61 patients (1 case corresponding to 1 patient), 1 preoperative MRI and 1 surgical intervention were performed. Two patients underwent two different MRI examinations before two different surgical interventions.

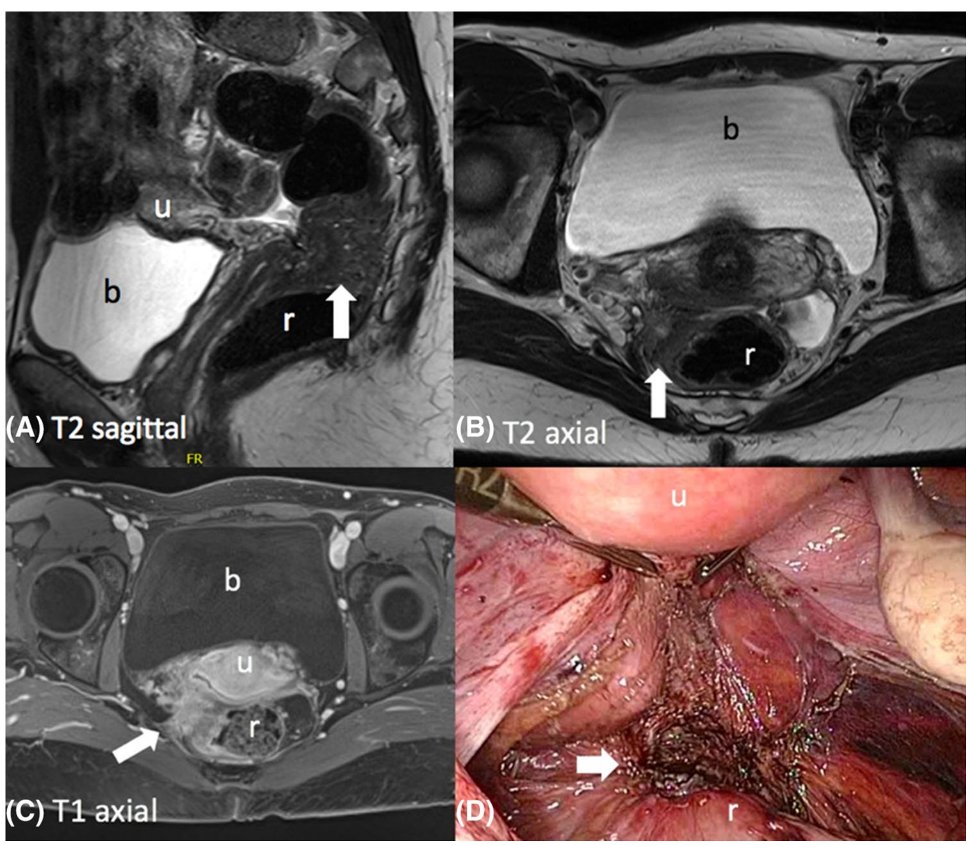

Fig. 1 A case of a 35-year-old patient (ENZIAN score preoperative MRI/intraoperative A2B3C1) with a lesion infiltrating the rectum, the right USL and the cervix (arrow = lesion; u = uterus; b = bladder; r = rectum); **a** hypointense in T2 sagittal, **b** hypointense in T2 axial, **c** hyperintense in T1 axial after application of contrast agent, **d** intraoperative imaging through laparoscopy

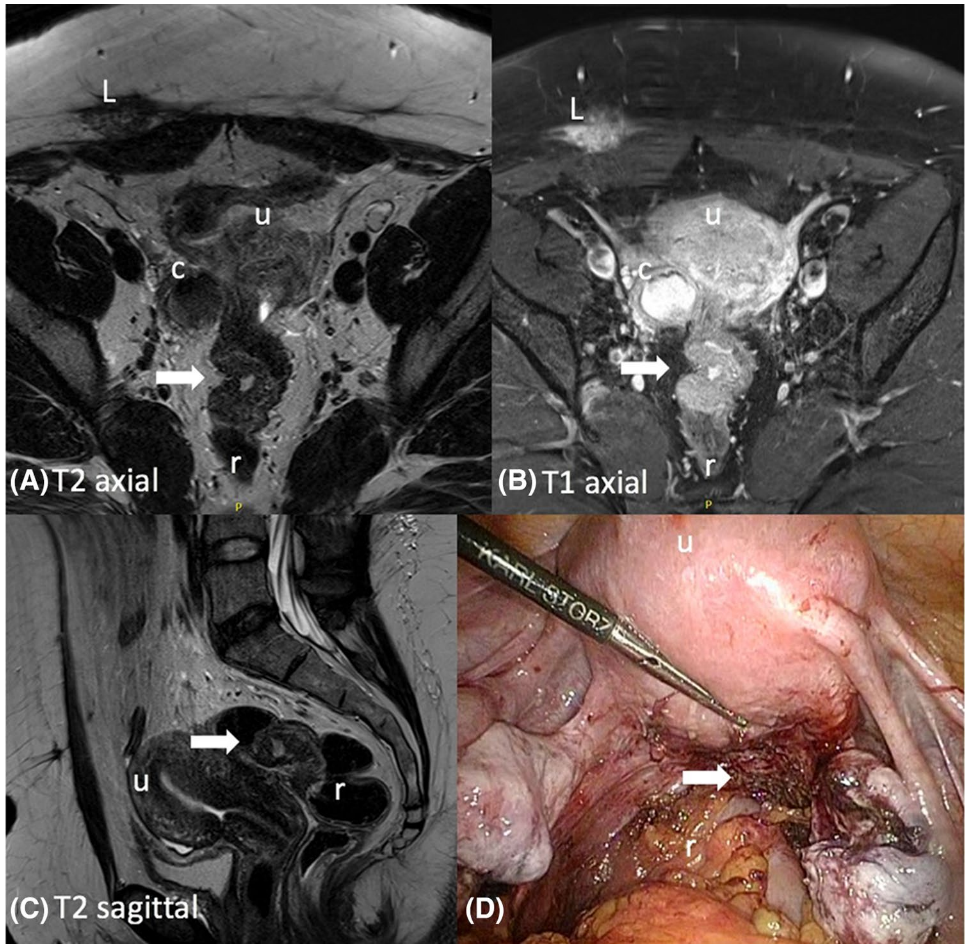

Fig. 2 A case of a 31-year-old patient (ENZIAN score preoperative MRI/intraoperative A0B0C3FO) with a lesion infiltrating the rectum and a lesion in the abdominal wall (arrow = lesion; u = uterus; r = rectum; c = ovarian cyst; L = a further lesion in the abdominal wall); **a** hypointense in T2 axial, **b** hyperintense in T1 axial after application of contrast agent, **c** hypointense in T2 sagittal, **d** intraoperative imaging of the lesion through laparoscopy

Surgical technique

The surgical procedures were typically conducted as minimal invasive technique, at the University Hospital Zurich in 88% (29/33) and at the Cantonal Hospital Schaffhausen in 100% (32/32) cases. Four cases required a laparotomy. Intraoperative photo or video documentation was made in all laparoscopic cases. In four cases with laparotomy, the intraoperative ENZIAN score was assessed when analyzing the operation report and verified by the responsible surgeon.

MRI technique

MRI imaging was conducted with 3.0 T MRI scanners; MRI Siemens Skyra (University Hospital Zurich), MRI Philips Achieva (Cantonal Hospital Schaffhausen). The MRI protocols exhibited a relatively high degree of variability. However, all protocols included T2-weighted FSE (fast spin-echo) sequences with small FoV (field-of-view) in transverse, sagittal and coronal orientation, a T1-weighted FSE or gradient-echo (GRE) sequence with large FoV in transverse orientation, a T2*-weighted GRE sequence in transverse orientation and a T1-weighed fat-saturated post-contrast GRE sequence in transverse orientation.

In both institutions, patients were given spasmolytics (butylscopolamine) before the examination and prior to the administration of the contrast agent. In the absence of contraindications, intravenous contrast medium was applicated (standard dose of a Gadolinium chelate, 0.2 ml (= 0.1 mmol)/kilo bodyweight). The examination was conducted independently of the menstrual cycle and no special preparation was used in term of enema or purgatives.

rASRM and ENZIAN scores

The rASRM score for endometriosis focuses on endometriotic lesions and adhesions in the peritoneum, ovaries and tubes as well as an obliteration of the Douglas cavitiy. A numeric score divides the disease into four stages according to the extent of the findings [11].

The ENZIAN score for DIE is divided into three main compartments: A (vagina and rectovaginal space), B (uterosacral ligaments and pelvic wall), and C (rectum and sigmoid colon). Compartments are subdivided according to the extent of the lesions into 0 (no lesion), 1 (< 1 cm), 2 (1–3 cm) and 3 (> 3 cm). Additional localizations are FA (adenomyosis), FB (bladder), FU (ureter, intrinsic), FI (intestine except rectum/sigmoid colon), and FO (other, e.g., diaphragm). These localizations are not subdivided according to the extent of the lesion and should only be mentioned if they occur [13, 14].

Data collection

In each center, a radiologist responsible for MRI diagnostics (Zurich: A.B., Schaffhausen: S.S.) as well as a gynecologist responsible for treatment, including surgery (Zurich: P.I., Schaffhausen: M.E.), inspected the archive research (performed by L.B.) and applied the ENZIAN score and rASRM score separately and without awareness of the comparative classification in preoperative MRI or the intraoperative findings, respectively.

To evaluate the various MRI sequences for their diagnostic validity, they were compared with the intraoperative findings based on a five-point Likert scale (1 = not diagnostic; 2 = poor, definitely affecting interpretation; 3 = moderate, potentially affecting interpretation; 4 = good, not affecting interpretation; 5 = excellent). Moreover, a score was assigned to each sequence regarding the accordance of imaging findings with the intraoperative findings by means of the ENZIAN score as a reference: 1 (no accordance with compartments), 2 (missing accordance with > 1 compartment), 3 (accordance regarding compartments except 1), 4 (accordance regarding compartments), and 5 (accordance regarding compartments and extent of lesion).

Statistical analysis

Data were described as numbers and percentages, or mean and standard deviation, as appropriate. Statistical evaluation was undertaken using Intercooled Stata 14.0 (StataCorp LP, College Station, TX) by means of Fisher's exact or Chi-square test for categorical data and Kruskal–Wallis test for continuous variables. Preoperative MRI findings were compared with intraoperative surgical findings with the surgical findings considered as standard. Sensitivity, specificity, PPV, NNP, accuracy, and association (*k*-Cohen coefficient) of the scores were calculated. In addition, the scores for the compartments A, B, and C were calculated by means of the Kendall's tau *b* test to take into account their subdivision (size 1–3). Data for the compartments A, B, and C were dichotomized into A0 (respectively, B0, C0, for no lesion) and A1 (respectively, B1, C1 for any lesion) and compared with each other. *p* values below 0.05 indicate statistical significance (two-sided).

Results

Preoperative MRI showed 41 A, 40 B, 36 C, 14 FA, 7 FB and 14 FI lesions (total lesions $n = 152$). Intraoperative findings were scored with 42 A, 51 B, 35 C, 7 FA, 7 FB and 15 FI lesions (total lesions $n = 157$). The overall accordance of the main compartments (A–C) and the additional compartments (FA, FB, FI) is presented in Table 1.

An analysis of FO was neglected due to comparatively few lesions (MRI: 0 vs. OP: 3). MRI showed the highest sensitivity for lesions in the rectovaginal septum/vagina (A) with 95.2% and the rectum/sigmoid (C) with 91.4%,

Table 1 Comparison of the preoperative MRI findings with the intraoperative surgical findings as reference by means of the ENZIAN score

OP	MRI +	MRI −	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	Kendall's tau b	Concordance (k-Cohen)	*p*
A +	40	2								
A −	1	22	95.2	95.7	95.4	97.6	91.7	0.8625	0.9001	< 0.0001
B +	40	11								
B −	0	14	78.4	100.0	83.1	100.0	56.0	0.6542	0.6104	< 0.0001
C +	32	3								
C −	4	26	91.4	86.7	89.2	88.9	89.7	0.8213	0.7828	< 0.0001
FA +	4	3								
FA −	10	48	57.1	82.8	80.8	28.6	94.1		0.2772	0.0076
FB +	6	1								
FB −	1	57	85.7	98.3	96.9	85.7	98.3		0.8399	< 0.0001
FI +	11	4								
FI −	3	47	73.3	94.0	89.2	78.6	92.2		0.6894	< 0.0001

Concordance (*k*-Cohen) A–C/FA–FI and additionally A–C (Kendall's tau *b*; in consideration of subsizing) [OP (surgical findings), PPV (positive predictive value), NPV (negative predictive value)] respectively. The lowest accordance was found in compartment FA. A1–A3 Tables present the main compartments A–C divided by the size of each lesion. Even though a strong accordance between preoperative MRI and intraoperative findings is evident, there is a tendency to underestimate lesions preoperatively in MRI. Especially when their size is borderline, lesions are often rated in the smaller category (1: < 1cm, 2: 1–3 cm, 3: > 3 cm). Therefore, in the statistical analysis, the anatomical locations A–C were compared collectively [A (B or C) 0] versus any lesion [A (B or C) 1–3], whereas the evaluation of lesion sizes regarding accordance of preoperative MRI with intraoperative findings was omitted. This is clinically acceptable, since the treating surgeon's primary interest is where to search for the lesions. Their size is of secondary importance.

The *p* value for each anatomic location mentioned was < 0.01 and indicated as statistically significant.

The agreement of the rASRM score regarding stage I–IV in preoperative MRI compared to surgical findings was 58% (A4 Table).

During surgery, the small lesions which were found ranged from early stage with more glandular tissue and a red vesicular appearance up to predominantly fibrotic tissue. More extensive lesions, as often seen in DIE of the retroperitoneum, presented themselves as coarse, fibrotic tumors, partially with hemorrhage, adherent to surrounding organs. The latter findings were often located in compartment C or A, occasionally involving compartment B.

In MRI, advanced lesions exhibit a scarring appearance with a diffuse margin, crooked with the surrounding tissue. These lesions appear hyperintense in T1, hypointense in T2 and show a pronounced enhancement after application of a contrast agent. In newer, small lesions with glandular tissue, which appear as small and well-defined nodules in MRI, T1 supersedes the other sequences. Blood degradation products (e.g., methemoglobin), in cases of recent hemorrhage, are well pictured in T2*. Adenomyosis can be best constituted in T2, showing a diffuse or local thickening of the junctional zone of more than 12 mm (physiologically around 5 mm).

Regarding the clinical relevance of the different MRI sequences, SAG T2 showed the highest diagnostic value, based on the Likert scale, with a mean of 4.4, followed by AX T2 (4.3), COR T2 (3.75), AX T2* (3.4), AX T1 pkm (3.3) and AX T1 (3.0) (A5 Table).

Discussion

Recent research evaluating MRI as a diagnostic instrument in endometriosis, particularly in DIE, has shown convincing results [9, 16-20]. The diagnostic and therapeutic procedures are surely demanding in view of the complex character of endometriosis and the lack of correlation between objective findings and the patient's symptoms.

Di Paola et al. [21] compared preoperative MRI findings with intraoperative surgical results by means of the ENZIAN score and found an overall correlation between MRI and intraoperative findings of 95%, with a sensitivity of 94% and NPV of 86%. In this study, the values are slightly lower which may be due to the two-centric setting but compartment A and C still exhibit an excellent association to the intraoperative findings (A Sens. 95.2%, NPV 91.7%/C Sens. 91.4%, NPV 89.7%) and the high value of the preoperative MRI-based ENZIAN score could be confirmed.

Lesions in compartment B showed the lowest accordance among the main compartments A–C (Sens. 78.4%, NPV 56.0%) and were distinctly lower compared to other studies [19, 21]. In one case, a big C3 lesion may have superseded a B3 lesion (MRI-classified B1) and aggravated the detection. In another case, big kissing ovaries led to the missing of a B2 lesion (classified as B0 in MRI). Though in many other cases, the B compartment was underestimated without any obvious reason when compared to the intraoperative findings. For future improvement of MRI diagnostics, this result should lead to a higher awareness regarding this compartment.

In the additional compartments FA, FB, FI, and FU, especially lesions in the compartment FB exhibited a very good accordance (Sens. 85.7%, NPV 98.3%).

As distinct from most preexisting data, this study was written primarily from the point of view of the clinician, as not only the radiologist should be familiar and trained in the interpretation of MRI in deep infiltrating endometriosis. Also the gynecologist/surgeon as conducting a relevant part of the diagnostic procedure (routine clinical examination, abdominal/transvaginal sonography, and laparoscopy) should be able to understand the findings on MRI and include this knowledge into the planning of treatment.

The MRI sequences T2 (sag/ax/cor), T1 (ax), T1 (ax) pkm and additive T2 (ax) * enable a precise staging of the different lesions. Further sequences should be used selectively on the basis of special questions. This is a clinical analysis, though consistent with actual guidelines [10]. The current extent of sequences used is vast, aggravates comparability and is not purposive. Even though lately MRI has been increasingly used as a diagnostic instrument for DIE, and despite important proceedings, there is still no sufficiently standardized diagnostic protocol [10]. This fact combined with the diverse characteristics of this disease, the inconsistent vocabulary in MRI reports and hectic everyday life inevitably make a detailed discussion of the results between radiologists and gynecologists difficult. Especially in a multifaceted disease such as endometriosis, detailed preoperative planning is required to improve preoperative patient information (e.g., stoma), intraoperative course (time management, bringing in of colorectal surgeons in case of bowel affection) as well as the postoperative course, e.g., rehabilitation time.

An anatomical and for radiologists easily applicable staging system as the ENZIAN score could assist in a systemic approach.

The widely used rASRM score showed in this population with DIE a low agreement (58%) between preoperative MRI findings and intraoperative results. This score tends to underestimate the severity in preoperative MRI. Most notably due to two issues: first, the nature of the rASRM classification neglects the occurrence of deep infiltrating form of endometriosis in the retroperitoneum [12, 15]. Second, MRI is indeed very sensitive regarding the detection of endometriomas, but not for small peritoneal lesions or adhesions which are a further part of this score [22]. In addition, the rASRM score is a numeric score and reflects the stage of the disease, but does not declare the location of lesions. Hence, the rASRM seems less suitable for the preoperative planning of DIE. A combination with the ENZIAN score could significantly improve clinical classification [13].

Recent studies indicate that the ENZIAN score could be of assistance in estimating the time of surgery and the extent of the intervention [21, 23].

Certainly, the most time-consuming compartment in the usually extensive surgeries in DIE is compartment C, particularly when bowel resection is required. However, even the excision of singular lesions in compartments A or B can be protracted due to strong adhesions.

Regarding the extent of surgical interventions in this study, seven out of nine preoperative MRI C3 and intraoperatively verified C3 and two out of eight preoperative C2 and intraoperatively verified C2 (though one was intraoperatively verified as C3) needed bowel resection. In the cases with the preoperative MRI rated as C1, no bowel resection was performed. In one case, preoperative C0 showed a C3 lesion intraoperatively, so that bowel resection was necessary.

However, multilocular findings, which occurred in the present study in 53/65 cases (81%), prolonged adhesiolysis before even reaching the lesions, and unexpected intraoperative complications impede an exact preoperative estimation of the surgical timeframe and extent of surgery per compartment in A1–C3.

In this study, the diagnosis of endometriosis was based on the intraoperative surgical findings, whereas the histopathologic results were used as second-line confirmation. We opted for this approach because in five cases, histology did not show a positive result for endometriotic lesions with glandular tissue, but described tissue fibrosis only. Thus, the histopathologic report did not certify endometriosis in these patients. This seems reasonable, due to the fact that in DIE most lesions consist of fibrotic tissue with only little endometriotic glandular and stromal tissue. As a further detriment, surgical diathermy impedes the histopathological specimen and most patients receive therapy with gestagens before surgery, as these have a destructive effect on endometriotic tissue. However, the cases were clear regarding the symptoms, the clinical presentation, the imaging and most of all the intraoperative findings.

Limitations of this study are its retrospective study design with a limited population and the varying diagnostic protocols that impede comparability. An unenhanced fat-suppressed T1-weighted sequence was not used standardly, although it has been considered as the most sensitive sequence for the detection of bloody foci and peritoneal endometriosis [10, 24, 25]. Further limitation is the involvement of the myometrium (adenomyosis, FA). Preoperatively, even slight manifestations can be detected in MRI. A hysterectomy and subsequent histopathalogic examination for the definitive confirmation of adenomyosis is conducted only in very severe forms and as rarely as possible, also due to the age of the patients and the often existing wish for a child. These preoperative findings remain unverified in most cases, leading to the low accordance found in this study.

Further prospective studies in a multicentric setting with consistent diagnostic protocols are needed [12]. Advances in non-invasive imaging modalities are of particular importance in the field of endometriosis as the diagnostic standard as only in a minority of diseases nowadays is still an invasive method. Not uncommonly multiple laparoscopic interventions are conducted in a single patient not last because of insufficient preoperative diagnostic information and thus the inoperative unexpected severity of disease. A systematic approach and improvement of staging and preoperative planning in this disease will lead to a reduction of recurrent interventions.

In the majority of cases, one could certainly concentrate on fewer MRI sequences as mentioned. Further sequences should be used for a specific question. Whether to use 1.5 T or 3 T MRI depends on the availability, a clear recommendation does not exist. As additional measures, spasmolytics improve the image quality and intravenous contrast agent has its benefit also with regard to differential diagnoses. The ENZIAN score could be used as standard in radiology findings. A certain point in time during the menstrual cycle for MRI diagnosis, vaginal or rectal filling showed no clear advantage in the literature, are controversially discussed and, therefore, not recommended [26].

In conclusion, MRI is a good and promising diagnostic instrument for DIE, enabling a better planning of the surgical procedure for patients and physicians. The ENZIAN score detected by MRI correlates well with the intraoperative findings. However, considerable difficulty and a poorer comparability result from the variations in sequences used in the detection of this multifaceted disease. Therefore, a standardization of MRI protocols used in the detection of DIE will be a crucial step towards increased diagnostic validity, and the ENZIAN score may be used as an anatomical land map and valuable communication tool between radiologists and gynecologists.

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Compliance with ethical standards

Conflict of interest The author Laurin Burla declares that he has no conflict of interest. The author David Scheiner declares that he has no conflict of interest. The author Eleftherios Pierre Samartzis declares that he has no conflict of interest. The author Stefan Seidel declares that he has no conflict of interest. The author Markus Eberhard declares that he has no conflict of interest. The author Daniel Fink declares that he has no conflict of interest. The author Andreas Boss declares that he has no conflict of interest. The author Patrick Imesch declares that he has no conflict of interest.

Ethical approval All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved prior to its initiation by the cantonal ethics committee of Zurich (2016–00613).

Informed consent Informed consent was obtained from all individual participants included in the study.

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