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Comparison of the determination of the local tumor extent of primary endometrial cancer using clinical examination and 3 Tesla magnetic resonance imaging compared to histopathology

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Abstract

Purpose The aim of this study is to analyze the correct staging of primary endometrial cancer (EC) using clinical examination and 3 Tesla (T) magnetic resonance imaging (MRI) results compared to histopathology.

Methods In this prospective, non-randomized, single-center study, 26 women with biopsy-proven EC were evaluated. All women underwent clinical examination including transvaginal ultrasound (CE/US) and 3T MRI (T2-weighted, diffusion-weighted and dynamic contrast-enhanced sequences) prior to surgery. Spearman's correlation coefficient was employed to analyze the correlation between both staging methods and histopathology and generalized estimation equation analysis to compare their staging results. Main outcome measures are determinations of local tumor extent for EC on CE/US and 3T MRI compared to histopathology (gold standard).

Results Sixteen women had an early-stage pT1a tumor, 10 a locally advanced ≥ pT1b tumor. The early stage was correctly diagnosed at CE/US in 100%, by MRI in 81%. Spearman's correlation coefficient was $r = 1.0$ ($p < 0.001$) for correlation of CE/US and histopathology, $r = 0.93$ ($p < 0.001$) for correlation of MRI and pathology. A locally advanced tumor stage was exactly diagnosed by MRI in 70% and at CE/US in 50%.

Conclusions CE/US is sufficient for staging T1a endometrial cancer, while MRI provides higher sensitivity in detecting locally advanced tumors. Based on our results, combining CE/US and 3T MRI in patients with at least suspected deep myometrial invasion offers a more reliable workflow for individual treatment planning.

Keywords Endometrial cancer staging · Myometrial invasion · Ultrasound · 3 Tesla magnetic resonance imaging

Introduction

The lifetime risk of a woman developing endometrial cancer (EC) is approximately 2.8% in the US, whereas women aged 45–74 (median age at diagnosis 62 years) are mostly affected [1]. Due to an irregular, mostly postmenopausal, vaginal bleeding, EC is often detected at an early tumor stage, which leads to a good prognosis [2, 3]. The diagnosis is routinely made by clinical examination (CE) combined with transvaginal ultrasound (TVUS) (CE/US). TVUS is

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easily accessible, its cost is low and it gives a profound look into the female pelvis. It is minimally invasive and generally causes no pain, which makes it a well-established diagnostic method [4–7]. However, in case of EC, TVUS is limited in fully judging deep pelvic invasion, parametrial and surrounding tissue infiltration, as well as metastatic pelvic and paraaortic lymph node participation, all which are aspects called for in presurgical interdisciplinary patient management [5, 7–9].

The visualization of the entire pelvis can be very well performed using magnetic resonance imaging (MRI). In several studies, MRI was propagated to play an important role in the preoperative assessment of local tumor extent in patients with primary EC, complementing CE/US [10–13]. This was strengthened by a meta-analysis by Kinkel et al., summarizing that MRI provides the highest efficacy for evaluating the depth of myometrial invasion, cervical invasion, and nodal metastases with an overall accuracy of 80–90% [14].

The first objective of our prospective study was to evaluate the performance of 3T MRI and CE/US to determine early-stage and advanced EC compared to the "gold-standard" of histopathology on hysterectomy. Second, we compared the staging rates of the two diagnostic approaches to one another with regard to early and advanced tumor stages.

Materials and methods

This clinical prospective, non-randomized, single-center trial was approved by the local ethics committee (clinical trial number: S-528/2010, date of approval: 02-08-2011) and was conducted in accordance with the Declaration of Helsinki 2008. Informed consent was obtained from all individual participants included in the study.

Clinical examination

A pretreatment clinical examination was performed with Graves' specula, manual palpation, and 2D transvaginal ultrasound (Voluson e, General Electric Healthcare, Frankfurt, Germany) (CE/US) by experienced gynecologists in the outpatient department (each greater 9 years of experience) to stage the tumor according to the classification of the International Federation of Gynecology and Obstetrics (FIGO) [9]. The IETA (International Endometrial Tumor Analysis) terminology was used to assess the sonographic gray-scale and vascular pattern criteria [15]. The assessment of the presence of deep (≥ 50%) myometrial invasion (yes/no) and cervical invasion (no invasion or stromal invasion suspected) and objective measurements (e.g., tumor extension/size) were performed. Women were examined in the lithotomy position with an empty bladder. Treatment planning for each woman was decided upon the CE/US results.

MRI examination and parameters

All women underwent pretreatment MRI at a 3T scanner (TIM Trio, Siemens, Erlangen, Germany) according to a standardized protocol for the diagnosis of EC [6, 16, 17]. This included high-resolution T2-weighted images (T2WI) in the sagittal and transverse oblique planes, diffusion-weighted images with *b*-values from 0–1000 in the sagittal and transverse oblique planes, a dynamic contrast-enhanced (DCE) sequence in the sagittal plane and post-contrast T1-weighted images (T1WI) with fat saturation in the transverse oblique plane. For a better delineation of the cervix and the anterior and posterior vaginal wall, sterile ultrasonic gel (20 ml) was applied to the vagina of each patient (Endosgel®, Farco-Pharma GmbH, Cologne, Germany). Additionally, bowel motion artifacts were reduced by administering 20 mg butyl-scopolamine bromide (Buscopan®, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) per 60 kg body weight intravenously prior to the examination after contraindications were excluded (cardiac arrhythmia or glaucoma). All women were examined in a supine position with their knees elevated on a pillow. To stage myometrial invasion correctly, high-resolution oblique transverse slice orientation was used along the short axis of the endometrial cavity (Fig. 1) [16, 17]. Each MR image was interpreted by one radiologist with 9 years of experience in oncologic gynecologic imaging. The radiologist was not blinded to the diagnosis of EC but remained unaware of the CE/US results. EC may present on MRI as of either low or high signal intensity on T2WI and as less enhanced than the surrounding myometrium on CE T1WI [18]. A diagnosis

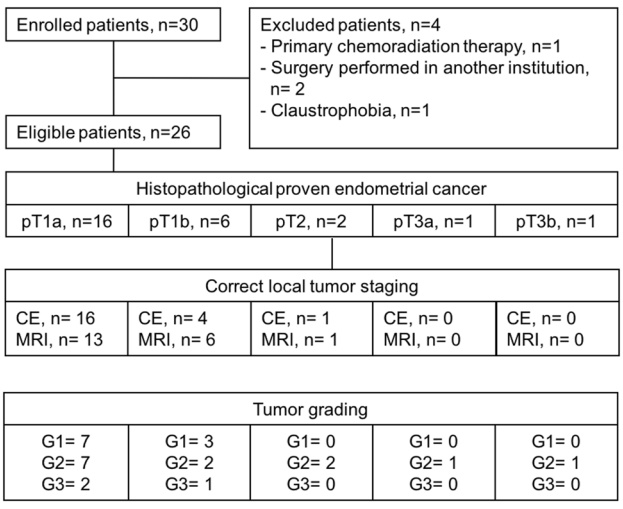

Fig. 1 Flow diagram of enrolled and eligible patients, including exclusion criteria, histopathological results, correct local tumor staging and tumor grading

was made using the T2WI, DWI, and DCE sequences, using the extent of the tumor signal intensity extending into the myometrium to define the depth of myometrial invasion on transverse oblique images. A cervical stromal invasion on the midsagittal plane was diagnosed if the cervical junctional zone was disrupted and the interface between the tumor and the cervical stroma was irregular [10]. The tumor was staged according to the latest version of the TNM classification system [19].

Surgical procedure and histopathological analysis

Primary surgery was performed by an expert gynecological surgeon with experience in gynecologic-oncological surgery (> 10 years) in median 2 weeks after CE/US and 3T MRI. The surgeon was not blinded towards the presurgical biopsy, CE/US or MRI results. Surgery was performed via an open abdominal or a laparoscopic approach and according to the decision of the pretreatment interdisciplinary tumor board. The surgical approach was planned based on the FIGO classification derived from CE/US. All samples were analyzed by a pathologist experienced in gynecological pathology (> 10 years) who was blinded to the CE/US or MRI staging results.

Statistical analyses

Clinical and demographic parameters of the study population, as well as FIGO and T-stage results of CE/US, MRI, and histopathology were descriptively analyzed (Fig. 1, Table 1). The detection rates of CE/US and MRI as compared to that of histopathology were analyzed using the sensitivity both for an exact match of the T-stage and for the detection of advanced T-stages (>T1a). We also conducted a correlation analysis between both diagnostic methods and the histopathological T-stage using Spearman's correlation analysis. The absolute value of r was defined as very weak (0.00–0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79) and very strong (0.80–1.0). To examine the statistical differences between CE/US and MRI in detecting all carcinomas, T1a carcinomas, and>T1a carcinomas, we performed McNemar's test. To perform a non-inferiority analysis of MRI and CE/US, we used matched-pair analysis of the difference between the detection rates with 95% confidence intervals (95% CI) (generalized estimation equation analysis, GEE analysis) [20].

Statistical analyses were performed using IBM SPSS Statistics®V20 (Armonk, USA) and SAS (SAS Institute, Inc., Cary, North Carolina) for the non-inferiority analysis with the PROC GENMOD. A p value < 0.05 was considered statistically significant. Since the study was exploratory in design, and multiple tests without adjustment for multiplicity were performed, the reported p values can be interpreted only descriptively. The reporting followed Standards of Reporting of Diagnostic Accuracy [21].

Table 1 Primary staging results from CE/US and MRI compared to histopathological results ($n = 26$)

Patient	T-stage histopathology	T-stage CE/US	T-stage MRI
Early stage $n = 16$			
No. 2	1a	1a	1a
No. 3	1a	1a	*1b*
No. 4	1a	1a	1a
No. 5	1a	1a	*1b*
No. 8	1a	1a	1a
No. 9	1a	1a	1a
No. 11	1a	1a	1a
No. 12	1a	1a	1a
No. 15	1a	1a	*1b*
No. 18	1a	1a	1a
No. 19	1a	1a	1a
No. 20	1a	1a	1a
No. 21	1a	1a	1a
No. 24	1a	1a	1a
No. 25	1a	1a	1a
No. 26	1a	1a	1a
Advanced stage $n = 10$			
No. 6	1b	*1a*	1b
No. 7	1b	1b	1b
No. 13	1b	1b	1b
No. 14	1b	*1a*	1b
No. 17	1b	1b	1b
No. 22	1b	1b	1b
No. 16	2	*1a*	*1a*
No. 23	2	2	2
No. 1	3a	*1b*	*1b*
No. 10	3b	*2*	*2*

CE/US clinical examination including transvaginal ultrasound, *MRI* magnetic resonance imaging; tumor stage highlighted in italics indicates false imaging staging result

Results

From February 2011 to May 2013, 30 consecutive patients with biopsy-proven EC underwent presurgical staging according to the latest version of the FIGO classification and the TNM system. In all the cases, transvaginal ultrasound was applicable and in no case endoanal or abdominal ultrasound was needed for tumor evaluation due to suboptimal transvaginal conditions. In total, 26 consecutive women (median age 65 years; interquartile range (IQR) 59–70) underwent surgical treatment in median within 2 weeks of presurgical diagnostics, while four women had

to be excluded from the study (Fig. 1). Of the 26 women, 19 (73%) had presented to the physician with postmenopausal bleeding and 7 (26%) had been diagnosed with a suspicious endometrium in their routine gynecological checkup. The histopathological result was endometrial adenocarcinoma in 25 patients and a combined mucinous endometrial cancer in one patient. 62% had pT1a EC, 23% had pT1b EC and 15% had pT2 and higher stage EC (Fig. 1). An example of a T1a cancer is given in Fig. 2. In two women a lymphadenectomy was performed according to presurgical CE/US staging. These women had positive lymph nodes, resulting in histopathological FIGO staging of IIIC / pT1b N1 (one with G1 and one with a G2 tumor grading). One woman had serosal invasion with small peritoneal implants resulting in a histopathological FIGO stage of IVB/pT3a N0 M1. 54% had accompanied uterine fibroids (14/26).

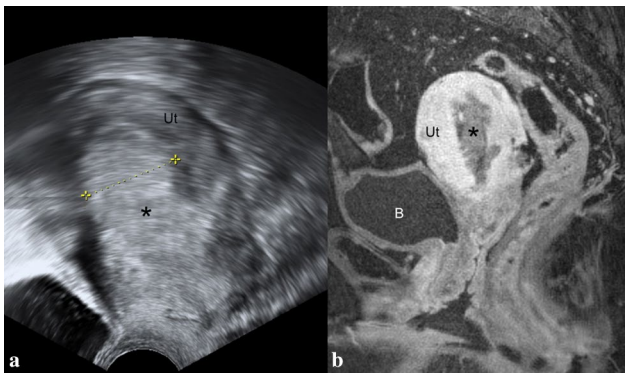

Fig. 2 Case of a 53-year-old woman with histopathological proven endometrioid adenocarcinoma pT1a pN0, correctly diagnosed by CE/US and MRI. **a** Transvaginal ultrasound shows a homogenous hyperechoic mass in the uterine cavity with suspicion for myometrial invasion (asterisk). **b** contrast-enhanced T1-weighted MR sequence with fat saturation in sagittal plane showing the hypointense tumor of the endometrium with invasion of the myometrium with less than 50% of the thickness (asterisk). The cervix is not involved. *Ut* Uterus; *B* Bladder

The overall staging with CE/US was correct in 81% (21/26). CE/US understaged 19% (5/26) compared to histopathology and did not overstage any patient (Table 1). Overall staging with MRI was correct in 77% (20/26). MRI understaged and overstaged with 11.5% (3/26) each (Table 1). Both modalities missed the T2 cancer due to only histopathologically visible cervical invasion determining a T1a cancer (patient no. 16). Both modalities also missed the T3a cancer due to a stretched uterine cavity and a compressed myometrium layer of the histopathologically proven combined mucinous endometrial cancer, falsely determined as T1b tumor (Table 1, patient no. 1). Third, both modalities determined cervical invasion in one patient but missed the beginning vaginal invasion which was histopathologically proven as T3b cancer (Fig. 3).

Second, we focused on the correct prediction of the T-stage for each individual method. In total, CE/US determined 81% of all cancer stages correctly (Table 2). The sensitivity of MRI in determining all cancer stages correctly was 77%. Spearman`s correlation analysis revealed a statistically significant correlation for both CE/US ($r = 0.785$, $p < 0.001$) and MRI ($r = 0.705$, $p < 0.001$). Additionally, we investigated the sensitivity of determination of tumor extent and the correlation of the diagnostic method for histopathology, dichotomized for T1a and > T1a cancers (Table 2, Fig. 2). CE/US matched perfectly for early T1a cancer in our study cohort and showed a very

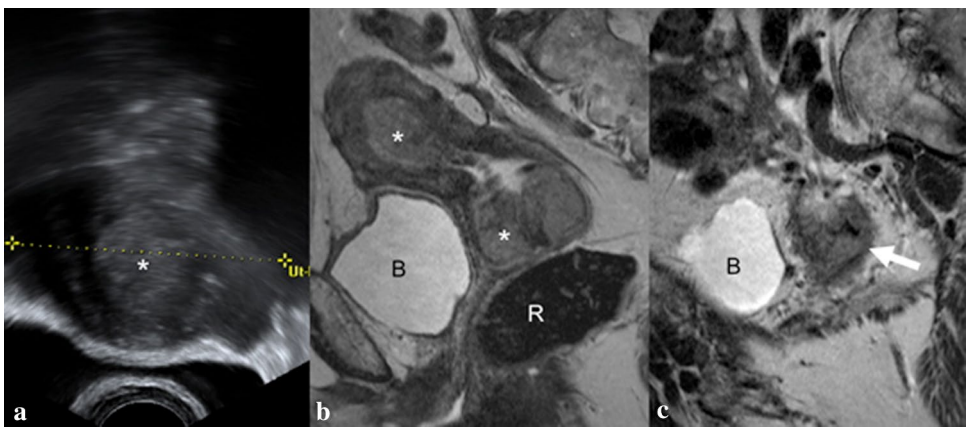

Fig. 3 Case of a 75-year-old woman with histopathological-proven endometrioid adenocarcinoma staged pT3b pN0 due to an infiltration of the vagina. **a** Transvaginal ultrasound of the uterus presents a hyperechoic mass in the uterine cavity with partial invasion of more than 50% of the myometrial thickness (asterisk). Cervical invasion was revealed (not shown), but vaginal infiltration was missed. **b** High-resolution T2-weighted image in sagittal plane shows a hyperintense mass in the uterine cavity with enlarged invasion into the cervix (asterisk). *B* bladder; *R* rectum. **c** The sagittal T2-weighted image at the edge of the uterine cervix left sided shows blurry margins of the vaginal fornix (arrow). This correlates with the histopathological result but was misdiagnosed by MRI on primary staging

Table 2 Analysis for the exact match of any stage of endometrial cancer and for T1a and > T1a cancers separately for clinical examination and MRI (A). Analysis for determination of at least T1b cancer (> T1a) by clinical examination and MRI (B)

	Value (significance)	95% CI
(A) Analysis for exact match		
Analysis for all cancers ($n=26$)		
Clinical examination		
Sensitivity in %	81	(61–96)
Spearman's correlation r	0.785 ($p<0.001$)	(0.55–0.99)
MRI		
Sensitivity in %	77	(58–92)
Spearman's correlation r	0.705 ($p<0.001$)	(0.36–0.93)
Analysis for T1a cancers ($n=16$)		
Clinical examination		
Sensitivity in %	100	(100–100)
Spearman's correlation r	1.0 ($p<0.001$)	(1.0–1.0)
MRI		
Sensitivity in %	81	(61–100)
Spearman's correlation r	0.930 ($p<0.001$)	(0.74–0.98)
Analysis for cancers> T1a ($n=10$)		
Clinical examination		
Sensitivity in %	50	(15–81)
Spearman's correlation r	0.360 ($p=0.307$)	(0.27–0.92)
MRI		
Sensitivity in %	70	(33–93)
Spearman's correlation r	0.458 ($p=0.184$)	(0.45–0.91)
(B) Analysis for determination of T-stage> T1a		
Analysis for all cancers ($n=26$)		
Clinical examination		
Sensitivity in %	85	69–96
Spearman's correlation r	0.768 ($p<0.001$)	(0.53–0.99)
MRI		
Sensitivity in %	81	65–96
Spearman's correlation r	0.695 ($p<0.001$)	(0.39–0.93)

CI confidence interval

strong correlation; however, it showed only a weak correlation regarding the exact match of advanced stage (at least T1b cancer) (Table 2). In comparison, MRI presented a moderate correlation for the exact match of advanced cancer, with a very strong correlation as well as for the exact match of early T1a cancer. Both examinations showed a strong correlation for determining advanced tumor stage (≥ T1b) in general (Table 2).

The statistical differences between CE/US and MRI in determining the correct tumor stage of all cancers, T1a cancers, and cancers > T1a are given in Table 3. McNemar's test did not show any statistically significant difference in the correct tumor staging of all cancers ($p=1.000$), T1a cancers ($p=0.226$), and > T1a cancers ($p=0.649$) between CE/US and MRI (Table 3). Lastly, the GEE analysis shows that MRI was neither inferior to CE/US for the correct tumor staging of all tumors nor for the detection of T1a or locally advanced tumors (Table 3).

Discussion

Ultrasound employed during clinical examination (CE/US) in women with suspicion of primary endometrial cancer (EC) is an established diagnostic imaging method for tumor detection, complemented with an endometrial sampling for histological tumor grading which is performed during hysteroscopy [22]. Although affected women with EC frequently undergo primary surgery, the surgical approach depends on the local tumor extent, with hysterectomy and bilateral oophorectomy used in low-risk patients and lymphadenectomy with omental and peritoneal biopsies performed in selected high-risk patients [7, 23]. As ultrasound has its limits in the evaluation of the entire pelvis due to a limited wave depth, additional cross-sectional imaging modalities such as computed tomography (CT) and MRI are beneficial for the evaluation of tumor extension [4]. While CT is generally performed for extra pelvic diseases or the

Table 3 Statistical differences between the staging results of CE/US and MRI using McNemar's test (A). Noninferiority analysis of CE/US and MRI using a matched-pair analysis of the differences in the staging results with 95% confidence intervals (B)

(A) McNemar's test on statistical differences between clinical examination and MRI	
For all cancers	
McNemar's test on clinical examination versus MRI	$p = 1.000$
For T1a cancers	
McNemar's test on clinical examination versus MRI	$p = 0.226$
For> T1a cancers	
McNemar's test on clinical examination versus MRI	$p = 0.649$
(B) Generalized estimation equation analysis	
For all cancers	
Non-inferiority test using matched-pair analysis on differences D of proportions between clinical examination and MRI and 95% CI	$D = 0.106$ (95% CI 0.032–0.380)
For T1a cancers	
Non-inferiority test using matched-pair analysis on differences D of proportions between clinical examination and MRI and 95% CI	$D = 0.101$ (95% CI 0.001–0.506)
For> T1a cancers	
Non-inferiority test using matched-pair analysis on differences D of proportions between clinical examination and MRI and 95% CI	$D = 0.194$ (95% CI 0.001–0.624)

detection of distant metastases, MRI accurately evaluates the myometrial depth invasion and is the most accurate imaging modality for detecting cervical invasion [4, 22, 24]. MRI is, therefore, recommended for staging of endometrial cancer by radiologic societies since several years, e.g., by the European Society of Urogenital Radiology, but is meanwhile also recommended in clinical guidelines, e.g., in the ESMO Clinical Practice Guidelines [4, 16].

Regarding the depth of myometrial invasion as one of the most important prognostic factors for EC correlating with histopathological differentiation and tumor grading [22, 25, 26], MRI correctly diagnosed all 6 cases with a T1b tumor in our study cohort (100%), whereas CE/US correctly diagnosed only two-thirds of those (67%). CE/US understaged the two missing cases as T1a. Clinically, understaging EC by misdiagnosing a T1a instead of T1b cancer bares the risk of foregoing an extended primary surgery including lymphadenectomy of the pelvic and/or paraaortic lymph nodes, which is commonly indicated in advanced tumor stage [2, 27].

CE/US missed 50% of the cases with advanced tumor stages, whereas 3T MRI missed only 20%. However, no statistical differences were observed when both approaches are compared according to GEE model and McNemar's test. We acknowledge that this might be due to the small sample size of our study and further prospective analyses are needed to determine or refute the observed results.

Sensitivity of exact match was higher for CE/US in the early stage (100% versus 81%), whereas in the advanced stages the sensitivity was higher for 3T MRI (70% versus 50%). Additionally, the detection rate of deep myometrial invasion in our cohort was superior to published data in the literature using MRI (100%), which report correctly diagnosed tumors in 65–95%, and inferior to published data using CE/US (67%), which report correctly diagnosed tumors in 77–96% [5, 28–31]. The results of our study suggest that T1a stage EC could be reliably diagnosed by CE/US alone, whereby the role of MRI in primary EC might be disease staging with discrimination between advanced from early stages and the guidance of presurgical treatment planning [4, 14, 18, 32, 33].

Our study has some limitations. First, all patients in this single-center study had a biopsy-proven endometrial cancer. Thus, predictive values or overall accuracy could not be evaluated. Second, the study did not focus on tumor grading or the differentiation of endometrial cancer types due to the small number of patients. Third, lymph node samples were only available from two women. This is a consequence of the current standard operating procedures in our department and the fact that lymph node metastases are present in only around 10% of patients [19]. Therefore, evaluation of the lymph node detection rate was not an objective of the present analysis. Furthermore, we acknowledge additional costs of MRI examinations and time consumption required compared to CE/US, which is used for tumor detection. However, a cost analysis of MRI compared to conventional surgical staging with intraoperative uterine dissection for the staging of EC presented with similar costs and ability as defined by the Medicare reimbursement [36]. The use of MRI as a noninvasive pre-therapeutical tumor staging modality can be, therefore, justified in patients with a high risk of disseminated disease [14].

In conclusion, the well-established transvaginal ultrasound is sufficient to detect T1a endometrial cancer, whereas advanced tumor stages benefit from an additional MRI staging examination. Based on our results, the combination of both modalities in patients with at least suspected deep myometrial invasion offers a more reliable workflow for individual treatment planning.

Author contributions KAB: project development, data collection, data analysis, and manuscript writing/editing. JPR: data analysis and

manuscript editing. PH: protocol/project development and manuscript editing. CS: project development and manuscript editing. HPS: protocol/project development and manuscript editing. CDA: protocol/project development, data collection, and manuscript writing/editing.

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Compliance with ethical standards

Conflict of interest KA Brocker reports personal fees by Serag Wiessner, Naila, Germany, outside the submitted work. All the other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this trial involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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

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