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Diagnostic interpretation of non-contrast qualitative MR imaging features for characterisation of uterine leiomyosarcoma

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Introduction

Uterine sarcomas include leiomyosarcoma (LMS), low- and high-grade endometrial stromal sarcoma, undifferentiated uterine sarcoma and adenosarcoma, with LMS being the most common gynaecological sarcoma.[1] There were 2383 new LMS diagnoses between 1985 and 2008, according to the published data from the English National Cancer Data Repository, accounting for 54% of all uterine sarcomas and 86% of all gynaecologic LMS.[2] However, LMS of the uterus can represent an imaging challenge for accurate pre-operative diagnosis due to overlap in features with benign leiomyomas.[3]

Magnetic resonance imaging (MRI) is the best imaging method for preoperative evaluation of possible LMS.[4] The use of several qualitative and quantitative features on conventional MRI, diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI for the diagnosis of uterine sarcomas have been reported in the literature.[5-8] Certain qualitative MRI features such as ill-defined margins, increased signal intensity on T1- and T2-weighted images, haemorrhage, central necrosis and true diffusion restriction of the solid tissue with high signal intensity (SI) (ie. higher than cerebrospinal fluid) on high b value DWI images and low SI (ie. lower than skeletal muscle) on apparent diffusion coefficient (ADC) maps raise the concern for a uterine sarcoma.[9-10] Amongst quantitative features, ADC values are shown to be lower than that of benign uterine tumours due to high cell density of uterine sarcomas.[7,11-12] Concordantly, T2 and DWI characteristics of the solid tissue and corresponding low ADC value ($<0.905 \times 10^{-3}$ mm^2/s) were used as decision steps in a new diagnostic algorithm for the differential diagnosis of atypical uterine masses in a recent study.[13] However, given the low incidence of LMS, there are small numbers in the study cohorts in the current literature and inclusion of all types of uterine sarcomas have led to inconsistencies regarding qualitative or quantitative MRI features. According to European Society of Urogenital Radiology guidelines, particular features in a leiomyoma which raise the possibility of sarcoma should be mentioned in the report, including large size, growth, necrotic or haemorrhagic changes, ill-defined margin and strong enhancement .[14] However, those features have not yet been validated in large prospective multicentric studies. In addition, atypical

leiomyomas, leiomyomas with atypical MRI characteristics, may share some of those features with LMS and subsequently, the differentiation from LMS becomes problematic.[9]

Gynaecological oncology multidisciplinary teams (MDT) in the specialist cancer centres provide opinions on cases with clinical or radiological suspicion of LMS from different hospitals. However, MRI protocols may differ between those centres excluding particularly DCE, which may depend on the preference of the referring centres or certain clinical scenarios to avoid intravenous contrast. The basic MR imaging key sequences, such as conventional T1, T2 and DWI, tends to be consistent across different sites. This supports the importance of thorough investigation of these sequences and reflects the "real-life" assessment for the radiologist providing the MDT opinion.

The aim of this study was to evaluate the interpretation of non-contrast qualitative and quantitative MRI features for characterisation of uterine LMS between readers of varying experience and develop a clinical and radiological model to differentiate LMS from benign leiomyomas with atypical imaging features.

Materials and Methods

Study design and patient population

This single-institution retrospective study was performed as part of a gynaecological MRI service evaluation according to local trust's information governance policy. The local ethics committee waived the need for informed consent for data analysis (clinical project registration CUH/2640). All consecutive patients who were referred to the tertiary centre for specialist gynae-oncology MDT review due to suspicion for possible uterine sarcomas between November 2014 and November 2019 were reviewed for eligibility. The referrals were the cases that the referring centres have assessed as suspicious following their own MDT discussion. The inclusion criteria included clinical or radiological suspicion of uterine leiomyosarcoma, presence of a pelvic MRI with standard sequences (detailed below) and confirmed pathological diagnosis of the uterine mass. The exclusion criteria were patients

with classical MRI features of leiomyomas such as T2 hypointensity without diffusion restriction, pathologically confirmed smooth muscle tumour of uncertain malignant potential (STUMP) which have insufficient histological features for a diagnosis of LMS and endometrially-based uterine sarcomas other than LMS which have distinct MRI features. The final cohort included 73 female patients with MR imaging and pathological correlation of a uterine myometrially-based mass initially referred to the specialist MDT as suspected to represent leiomyosarcoma.

The patients' electronic health records were reviewed and clinical data (ie. age, menopausal status, body mass index, weight, symptoms, type of operation, CA125 and haemoglobin levels before the operation) and histopathological features of the masses were noted, if available. All patients were diagnosed, treated in the same gynaecology oncology department which is a specialist cancer centre for gynaecological malignancies.

MR imaging protocol

Amongst the study population, 40 patients were scanned in our university hospital, 33 patients were scanned in other centres including 10 different hospitals which refer into the tertiary specialist MDT. Eight patients were scanned in 3.0T and the remaining in 1.5T machines from three different vendors (GE healthcare, Siemens and Philips). All MRI protocols for characterisation of uterine masses included standard conventional sequences (ie. sagittal, axial, and coronal T_2-weighted fast spin-echo sequences, axial T_1-weighted gradient-echo sequences with and without fat-suppression) and DWI with *b*-values of 0 and 800-1000 s/mm^2. The MRI protocol analysed in this study included only non-contrast sequences for the purposes of the study, and to avoid bias, contrast-enhanced sequences were not viewed if present.

Image Interpretation and Analysis

Five readers including three consultant radiologists with 8, 10 and 13 years of experience in gynaecological imaging, a genitourinary radiology clinical fellow and a junior radiology trainee (not

FRCR accredited) took part in image interpretation and analysis. The readers were blinded to all clinical and pathological information as well as ADC measurements to avoid bias. Another consultant radiologist reviewed the images for eligibility, chose the eligible lesion, completed regions of interest (ROI) for ADC measurements and collected the clinical data. When multiple uterine masses were present, only the suspicious lesion with concerning imaging features was chosen for evaluation. Location of the eligible mass was described according to the FIGO classification.[15] Uterine diameters were measured in three orthogonal planes to calculate the uterine volume. Maximum diameter of the uterine mass was recorded.

For the qualitative evaluation, morphological MRI features of the tumour were assessed as following; tumour margins (smooth-regular / nodular-irregular), tumour shape (round-oval / irregular), intratumoural haemorrhage (Yes (Y)/No (N)), flow voids (Y/N), tumour morphology (homogeneous / heterogenous), cystic and necrotic alterations in the tumour (Y/N), T2-weighted imaging (T2WI) signal of the solid tissue (low / intermediate), T2 dark signal areas (Y/N), DWI signal of the tumour (low / intermediate / high), diffusion restriction in the tumour (Y/N), interruption of the endometrial interface (Y/N) and interruption of the uterine serosal border (Y/N) and endometrial stripe (normal / thickened / not seen). In addition, accompanying important MRI features (ascites, peritoneal implants, lymphadenopathy, invasion in the adjacent organs and presence of adnexal tubular solid structures favouring intravascular tumour growth) were dichotomised as Y/N. Each feature was assessed by each reader independently. Subsequently, readers assigned a Likert score to each mass, wherein 1=highly unlikely to have leiomyosarcoma, 2=leiomyosarcoma is unlikely, 3=indeterminate for leiomyosarcoma, 4=leiomyosarcoma is likely, 5=highly likely to have leiomyosarcoma. Following a one-month interval after all readers' assessment, the discrepancies between readers for various MRI features and Likert score were solved with consensus decision of the most experienced two readers. The specialty registrar and the clinical fellow evaluating these masses had been trained during the formal gynaecological imaging trainee programme. In addition, for this study, the imaging features, and the definitions were discussed prior to the feature assessment.

For quantitative DWI analysis, minimum, maximum and mean ADC values of the uterine mass were measured by manual tracing of the outer edge of the lesion on the slice with largest diameter in the ADC map. In addition, a standard ROI with minimum size (0.44 cm^2) was placed on solid areas avoiding haemorrhage and cystic degeneration areas and mean ADC values were calculated after three measurements for each lesion (Figure 1). Solid area was defined as tissue within the uterine mass displaying low-intermediate SI on T2WI and low SI on T1WI. SI of the solid area on T2WI and ADC map was defined relative to skeletal muscles whilst on DWI, it was compared to cerebrospinal fluid.

For quantitative evaluation of the lesion-based ADC ratios, the reference tissues used were normal-appearing myometrium and iliopsoas muscle. Standard ROIs were randomly drawn from three different slices in those tissues and mean ADCs of the whole lesion and solid areas were standardised with mean ADCs of the myometrium and iliopsoas muscle for further analysis.

Statistical analysis

Statistical analyses were conducted using "R" version 3.5.3 (2019; The R Foundation for statistical Computing). Mean and standard deviation (SD) or median and interquartile range (IQR) were used to describe continuous variables. T-test or Mann-Whitney test for continuous and Chi-squared test or Fisher exact test for categorical variables were used to compare the clinical variables between groups. To evaluate inter-reader reliability for the assessment of Likert score, intraclass correlation coefficient (ICC) values were calculated using two-way mixed effects, absolute agreement and multiple raters model.[16] To evaluate inter-reader reliability for the assessment of MRI features, Cohen's Kappa values were calculated for any pair of reader. ICC and average Kappa values were interpreted as follows: 0.00-0.20, poor agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, good agreement; and 0.81-1.00 excellent agreement. Lasso regression with 20 random partitions into 5 folds cross-validation procedure was used to perform variable selection. Binary logistic regression was used to produce the uni- and multi-(lasso selected) variable estimates of Odds Ratio (OR) and their Wald's

95% confidence interval (CI). To test the model fit, we binned the model predictions using Youden Index and produced the performance metrics (accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)). Using the lasso selected variables, our dataset was further explored using a Classification And Regression Tree (CART) model. We used the reduction in the loss function attributed to each variable to estimate the reader importance. A *p* value <0.05 was considered statistically significant.

Results

Study population and pathological outcomes

73 patients with a mean age of 50 years (range 25-79) who met the inclusion criteria were retrospectively reviewed. Among them, 45 patients had multi-fibroid uterus while the remaining had a single uterine mass. According to PALM-COEIN leiomyoma subclassification, locations of the masses were as follows; 4, pedunculated intracavitary; 1, less than 50% intramural; 3, more than 50% intramural; 4, contacts endometrium and 100% intramural; 14, intramural; 22, subserous ≥50% intramural; 14, subserosal < 50% intramural; 9, subserosal pedunculated; and 2 other (cervical and adnexa).

There were 57 uterine leiomyoma, and 16 leiomyosarcoma in the study population. Characteristics of patients, CA125 and haemoglobin values before the operation, uterus volume and diameter of the uterine masses in the related groups are given in Table 1.

Among leiomyomas, some pathological characteristics such as myxoid features, intralesional fat, cellular leiomyoma features or intravenous leiomyomatosis were detected at pathology and 23 (40%) leiomyomas had at least one of those features (Supplementary Table 1). Cellular leiomyoma was the most prevalent characteristic detected at pathology (n=15; apparent prevalence, 0.26; CI, 0.16-0.40). Only one leiomyosarcoma had myxoid features.

Identification of radiological features and inter-reader reliability

According to the consensus reading, T2 signal intensity of the solid areas in the mass (ie, at least intermediate SI) (n=15, 93.8%) and the cystic or necrotic alterations (n=15, 93.8%) were the most prevalent features in the LMS group (Figure 2) (Table 2). Interruption of the endometrial interface, thickened or not seen endometrial stripe, intratumour hemorrhage and irregular tumour shape were significantly different between the LMS and leiomyoma group ($p \leq 0.001$) (Table 2). Likert score was given as 1 in 14 patients (19.1%), 2 in 27 (36.9), 3 in 17 (23.2%), 4 in 10 (13.6%) and 5 in 5 patients (6.8%) in the study population.

Every feature had Kappa value above 0.2, which is considered a "fair" agreement (Table 2). Seven features had Kappa value over 0.4 which represented "moderate" reliability (Average kappa range, 0.41-0.55). Intratumoural haemorrhage represented highest reliability between readers with "substantial" reliability (average kappa= 0.72) (Figure 3). The reliability of the Likert score between 5 readers with various experience was excellent (ICC, 0.86; 95% CI, 0.76-0.92).

Quantitative DWI analysis

ADC measurements from whole uterine mass, solid tissue in the mass, reference tissues and reference standardised ADC ratios in the leiomyoma and leiomyosarcoma group are given in Table 3. All myometrium and iliopsoas measurements were consistent between measurements. All ADC measurements (min, max, mean, single ROI, robust ROI) were consistently lower in the leiomyosarcoma group, however, not enough to reach statistical significance except mass ADC_{min} ($p=0.032$).

Leiomyosarcomas had on average the same or slightly lower mean ADC and lower robust ADC than iliopsoas muscle with whole mass/reference ADC ratio less than or close to 1. Leiomyomas had on average higher ADC value compared to leiomyosarcoma and when both are standardised on each patient iliopsoas mean ADC. However, none of the mass ADC measurements standardised by myometrium ADC was significantly different between the two groups (for all, $p > 0.05$).

Assessment of radiological feature prediction capability

In the univariate analysis, interruption of the endometrial interface had the highest OR (64.00; 95%CI, 9.79-1285; p<0.001), followed by irregular tumour shape (OR, 12.00; 95%CI, 2.98-81.34; p=0.002) (Figure 4, Figure 5, Table 4). Likert score of the mass was also significant in prediction of the leiomyosarcoma (OR, 3.14; 95%CI, 1.83-6.00; p<0.001).

Multivariable estimation of the risk of leiomyosarcoma

Clinical features and reference standardised ADC values were considered for multivariable logistic regression analysis. Older age or post-menopausal status and the lower haemoglobin values remained the most relevant predictors of higher leiomyosarcoma risk (OR 1.10 per year vs. 9.07 vs. 0.75 per g/dL; *p*= 0.020 vs. 0.030 vs. 0.050, respectively) (Supplementary Table 2). Our results did not provide enough evidence to show association between the standardised ADC ratio and leiomyosarcoma. Although all ORs were consistent in direction, none of the associations was significant.

To assess feature prediction capability of all clinical characteristics, ADC values and consensus radiological features, multivariable analysis and variable selection process was performed to fit into a model. The menopausal status, interruption of endometrial interface and thickened endometrial stripe were most predictive variables among all. Adjusted OR and *p* values are given in Table 5. The performances of the proposed model were as follows; accuracy, 0.88 (95%CI 0.78, 0.94); sensitivity, 0.88 (95%CI 0.76, 0.95); specificity, 0.87 (95%CI 0.60, 0.98); PPV, 0.96 (95%CI 0.87, 0.99); NPV, 0.65 (95%CI 0.41, 0.85).

We further explored our dataset using a CART model and used LMS as classification target and lasso selected variables (ie, endometrial stripe (normal vs thickened or not seen), menopausal status, interruption of the endometrial interface) and the reader experience as predictor. Using the CART model (Figure 6), the observed risk of LMS was 7% when endometrial stripe is normal (cover: 80%), 15% when endometrial stripe is not seen or thickened & pre-menopausal status & endometrial

interface is normal (not interrupted) (cover: 4%); 53% when endometrial stripe is not seen or thickened & pre-menopausal status & endometrial interface is abnormal (interrupted) (cover: 5%); and 86% when endometrial stripe is not seen or thickened & post-menopausal status (cover: 11%). The CART model variable importance for the reader was about 30 times less the importance of the other three used variable (estimate was 37.96 for menopausal status, 36.62 for endometrial stripe, 29.98 for endometrial interface and 1.19 for reader).

Discussion

In this study, we evaluated the non-contrast qualitative MR imaging features and ADC values for characterisation of LMS. We aimed to depict the "real-life" issue at the time of MDT discussion. Therefore, we chose to look at only atypical leiomyomas rather than ordinary leiomyomas for comparison with LMS and we wanted to look at the non-contrast sequences to see if on basic imaging (which can be easily replicated in any centre) and for any patient (including the elderly patients who may not be able to have contrast) and at all radiologist reader levels (including junior) if there were consistent results that allow for differentiation. Our data demonstrated that interruption of the endometrial interface and irregular tumour shape had the highest OR in prediction of LMS. When clinical characteristics were included into the model, postmenopausal status, interruption of endometrial interface and thickened endometrial stripe were predictive of leiomyosarcomas after multivariable analysis and variable selection process. However, neither the mass ADC measurements nor the reference standardised ADC ratios were significant in differentiating LMS from atypical leiomyomas. Evaluation of qualitative MRI features by readers with various experiences had fair to good reliability. According to the results of CART model, at any level of expertise as a radiologist reader, the loss of the normal endometrial stripe (either thickened or not seen) in a post-menopausal patient with a myometrial mass was highly likely to be LMS.

A rapidly growing uterine mass usually warrants a detailed clinical and radiological assessment due to possibility of uterine sarcoma particularly in post-menopausal women. However, accurate diagnosis of

LMS and distinction from other uterine sarcomas and atypical leiomyomas such as cellular or degenerating leiomyomas, may possess a diagnostic challenge especially when those tumours exhibit heterogeneity and rapid growth.[9] Although leiomyomas are obviously much more common than LMS, they can represent a clinical dilemma and may present with similar clinical symptoms. None of the serum markers (e.g., CA125, LDH), when used alone, are proved to be significant in differentiation since they may overlap between leiomyomas and early-stage LMS.[17] Radiological diagnosis is challenging even though MRI, with superior soft tissue resolution, is used for characterisation.

With developments in sequence acquisitions and capability to perform functional imaging, MRI has become an excellent technique for uterine mass characterisation. The review of Food and Drug Administration (FDA) regarding higher prevalence of unsuspected uterine sarcoma and LMS among patients undergoing myomectomy or hysterectomy for presumed benign leiomyomas has raised the concerns in pre-operative diagnosis of those patients and MRI has become widely used for pre-treatment assessment.[18] This also has led to increased pressure on radiologists to differentiate LMS from leiomyoma.[3] Therefore, the evidence-based for MRI differentiation of LMS from leiomyoma is relatively recent.[3,8,19] The most common presentation of LMS is a large, often solitary heterogeneous mass with irregular margins.[5,20] In addition, hyperintense areas resulting from areas of haemorrhage on T1-weighted images, cystic necrotic T2 hyperintense areas, diffusion restriction and intense contrast enhancement also suggest the diagnosis.[3,9,21] However, overlapping features may occur especially in cellular or degenerating leiomyomas. Lakhman et al. identified four qualitative MRI features with the strongest association with LMS (nodular borders, haemorrhage, T2 dark areas and central unenhanced areas) and found that the presence of ≥3 of them could accurately differentiate LMS from atypical leiomyomas.[19] In our study, those features, except central unenhanced areas, were assessed and found to be significant in predicting LMS with odds ratios between 5.4 and 8.8 in univariate analysis. When they were used in combination (ie, having all three features vs not having the three), predictability increased with OR 21.39 ($p<0.001$). However, those three features were not selected as significant variables when Lasso regression was used. This could be due to overlap in the

given features with the atypical leiomyoma group. Although we used a purely atypical leiomyoma cohort similar to the study of Lakhman et al. to compare with LMS, we had more atypical leiomyomas (57 vs 22) in our study.[19]

In our study, we have found that the most predictive feature with highest OR was the interruption of the endometrial stripe which was also selected in multivariable analysis. This was comparable with the study of Xie et al, in which interruption of endometrial cavity was also proved to be significant in multivariable model.[22] Moreover, we aimed to develop a five-level Likert score reflecting the overall impression of the radiologist following consideration of all features and imaging findings. This score was significant in prediction of LMS with an excellent agreement between different readers at different levels of experience. In few studies, inter-reader agreement in the assessment of qualitative MRI features was studied and reported as substantial to almost perfect, in which number of readers was limited (e.g., 2).[12,19] With higher number of readers (i.e., 5), our study shows that junior readers can focus on qualitative features safely and use the Likert score as a practical assessment tool in the differentiation of LMS and atypical leiomyoma.

The utility of diffusion weighted imaging and quantitative measurement of ADC values has been reported previously with mean ADC values of uterine sarcomas less than or around $1x10^{-3}$ mm^2/s in several studies.[6,11-12,23] However, there was overlap with those of ordinary leiomyomas and cellular leiomyomas.[6] Although some studies demonstrate that the presence of restricted diffusion with an ADC value below a certain threshold (range 0.905-1.272 $x10^{-3}$ mm^2/s) within a uterine mass is suggestive of malignancy [13,24], our results did not provide enough evidence to show significant association between ADC and LMS, and none of ADC values were significant to calculate a threshold. This may be related to relatively low number of LMSs and inclusion of only atypical leiomyomas rather than ordinary leiomyomas in our cohort. However, in our opinion this reflects the clinical conundrum where ordinary leiomyomas are easily differentiated from LMS by conventional sequences, but atypical leiomyomas constitute the real diagnostic challenge. On the other hand, our results were also

consistent with a recent systematic review which did not demonstrate a significant statistical correlation between ADC values of LMSs and benign uterine pathology.[25] Moreover, all those studies included various types of uterine sarcomas (e.g., LMS, endometrial stromal sarcoma, carcinosarcoma) into one category despite their distinct MR features and clinical outcomes. Of note, we excluded sarcomas other than LMS to avoid conflicting results. We also used reference standardised ADC ratios to overcome impacts of ADC measurement differences from different vendors, however they were not significant either.

Several studies combined a variety of clinical findings with MRI features since it is challenging to differentiate uterine sarcoma from atypical leiomyoma based on a single clinical or MRI parameter. Those studies have proposed accuracies over 0.90 with their models combining different parameters.[24,26-27] In our study, postmenopausal status, interruption of endometrial interface and thickened endometrial stripe were remained significant after multivariable analysis. Although this model achieved an accuracy of 0.88, the overall predictive capability of all clinical and radiological characteristics did not allow an acceptable stratification of the leiomyosarcomas risk in our sample. This could be related to exclusion of ordinary leiomyomas, which often do not possess a diagnostic challenge and our results supports the presence of difficulties in distinction of LMS from atypical leiomyomas statistically, like the real clinical scenario. When we used the lasso selected variables as predictors for CART model, in the combination of post-menopausal status and thickened/not seen endometrial stripe, the observed risk of LMS was 86%, which did not differ with the level of reader's expertise. However, this method is strongly data-driven and larger scale studies are required for assessment of combined clinical and radiological models.

There were several limitations in our study. First, it was a retrospective audit of patients who were discussed in a specialist MDT meeting due to concerning features for uterine sarcoma. Therefore, it may be prone to selection bias which can be unavoidable. Second, the rate of tumour growth was not calculated since large myometrial masses were discovered at the initial encounter. Third, the number

of LMSs was low in our cohort, because we excluded other subtypes of uterine sarcomas to avoid confounding results. However, we believe that conclusions from a much more homogeneous population including only leiomyosarcomas on the malignant counterpart could be more reliable since other uterine sarcoma subtypes have distinct radiological features. Lastly, we were not able to validate our results in an external validation set.

Conclusion

The assessment of qualitative MRI features such as interruption of the endometrial interface and irregular tumour shape can be helpful in prediction of LMS with high inter-reader reliability. A combined clinical and radiological model including the post-menopausal status, interruption of endometrial interface and thickened endometrial stripe can predict LMS with high accuracy in non-contrast MR imaging amongst junior as well as senior readers of MRI.

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Figure legends

Figure 1. Demonstration of ROI measurements from diffusion-weighted imaging (DWI) of a patient with a benign leiomyoma. Axial DWI image with *b* value 800 (a) shows high signal intensity (SI) in the solid parts of the uterine mass (arrows) with low SI in the central cystic area (star). ADC map (b) shows three ROI measurements from the solid, mostly restricted areas of the tumour (ie. high SI on high b value DWI and low SI on ADC map). Haemorrhage and cystic degeneration areas were avoided during measurements. Mean ADC values were calculated after three ROI measurements for each lesion.

Figure 2. 85-year-old woman with leiomyosarcoma. Sagittal T2-weighted image (a) demonstrates a large heterogeneous uterine mass with irregular borders (solid arrows). Endometrial interface is delineated as a smooth hyperintense line and was not interrupted in this patient (dashed arrows). Axial T2-weigted image (b) shows T2 dark areas in the lesion (arrow). There is focal intratumoural haemorrhage (c) and intracavitary haemorrhage (d) on T1-weighted fat-supressed images (arrows). The nodular borders on the right side (arrows in e), irregular shape of the tumour and diffusion restriction with high signal intensity on diffusion-weighted image (e) and low signal intensity on ADC map (f) are seen. The mean ADC value of the mass was measured as 1.19×10^{-3} mm^2 /s.

Figure 3. 52-year-old woman with cellular leiomyoma. Sagittal (a) and axial (b) T2-weighted images show an intramural lesion with intermediate T2 signal intensity. The endometrial cavity is delineated separately and not involved (dashed arrows in b and c). Heterogeneous diffusion restriction is seen with high signal intensity areas on high b-value diffusion weighted image (c) and low - intermediate signal intensity on ADC map (d). The mean ADC value of the mass was measured as 1.51×10^{-3} mm^2 /s. Five readers were all in agreement in assessment of nodular/irregular outline and diffusion restriction. Lesion was regarded as Likert 3 (indeterminate for leiomyosarcoma) in consensus reading.

Figure 4. 70-year-old woman with leiomyosarcoma. Sagittal T2-weighted image (a) demonstrates a large heterogeneous uterine mass with irregular nodular borders and serosal breach. The endometrial cavity is interrupted and cannot be defined separately to the mass. There is intratumoral haemorrhage

(arrow) on T1-weighted fat-supressed image (b). The nodular outline and diffusion restriction is clearly demonstrated on diffusion-weighted image (c) and ADC map (d). The mean ADC value of the mass was measured as $1.53x10^{-3}$ mm^2 /s.

Figure 5. 51-year-old woman with cellular leiomyoma complicated by cystic degeneration. Sagittal (a) and axial (b) T2-weighted images show an intrauterine lesion with T2 hyperintense cystic areas and solid areas with intermediate T2 signal intensity. Endometrial interface is preserved with normal thickness (arrows). Diffusion-weighted image and ADC map of this patient are shown in Figure 1. The mean ADC value of the mass was measured as $2.39x10^{-3}$ mm^2 /s.

Figure 6. Tree plot. The coloured box represent the final prediction (leaf of the tree). The report in the first line represents the prediction class (leiomyoma or leiomyosarcoma), in the second line the proportion of patients observed to have LMS in that branch, and in the third line the percentage of patients in the branch. For example, 86% of our patients with endometrial stripe thickened and post-menopausal status had LMS. These two characteristics are simultaneously present in the 11% of our cohort.

Table legends

Table 1. Description of the study population.

Table 2. Prevalence of radiological features in atypical leiomyoma and leiomyosarcoma groups and inter-reader reliability.

Table 3. Univariate analysis to detect associations of apparent diffusion coefficient (ADC) with leiomyosarcoma.

Table 4. Univariate associations between radiological features and leiomyosarcoma.

Table 5. Results from multivariable analysis and variable selection process.

Supplementary Table 1. Detected pathological characteristics of leiomyomas.

Supplementary Table 2. Odds Ratio (OR) of the risk of leiomyosarcoma in the group including leiomyoma (n=57) vs. leiomyosarcoma (n=16).

Figure 1

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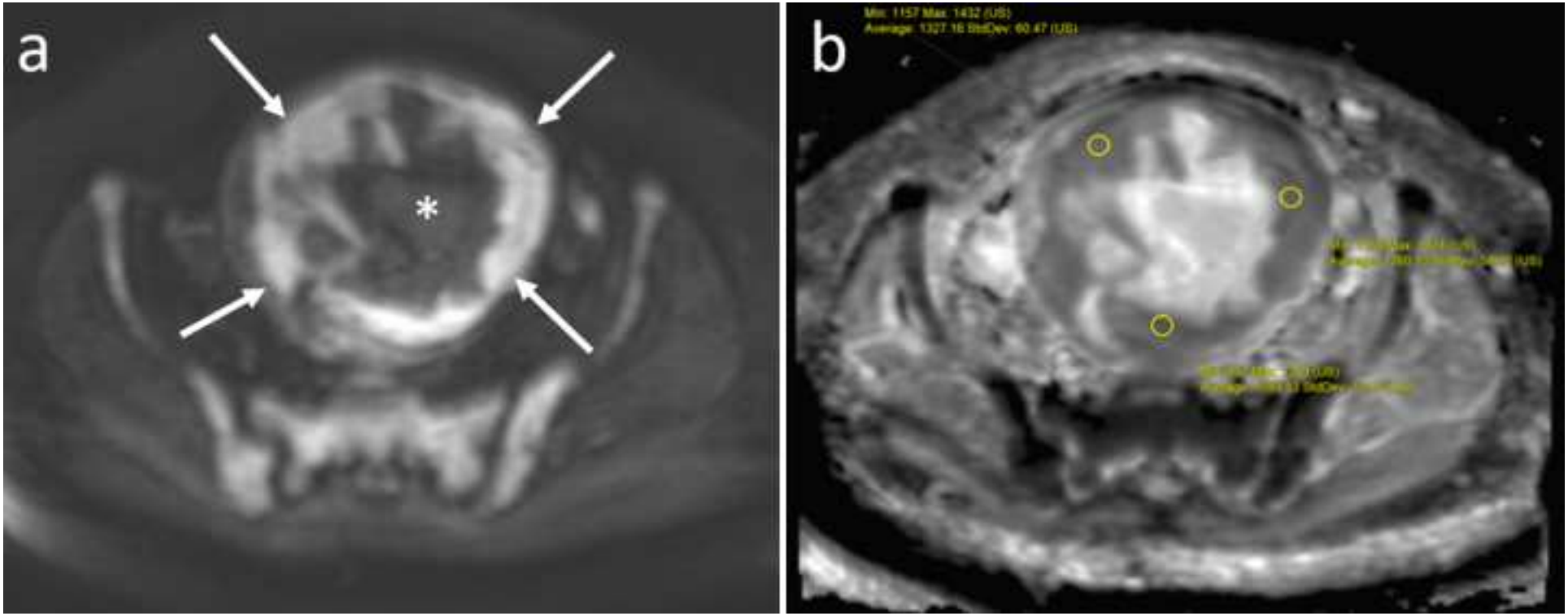

Figure 2

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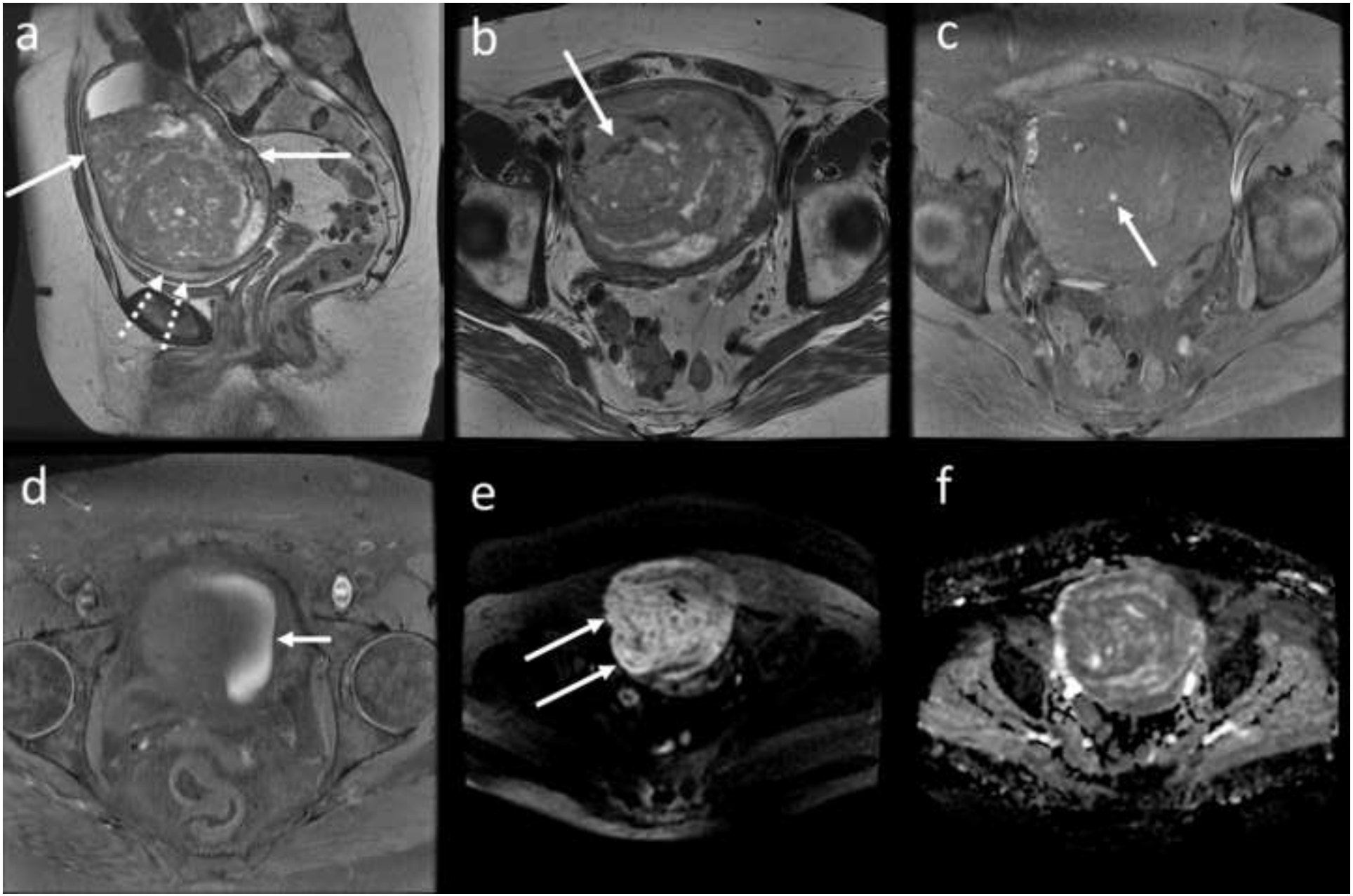

Figure 3

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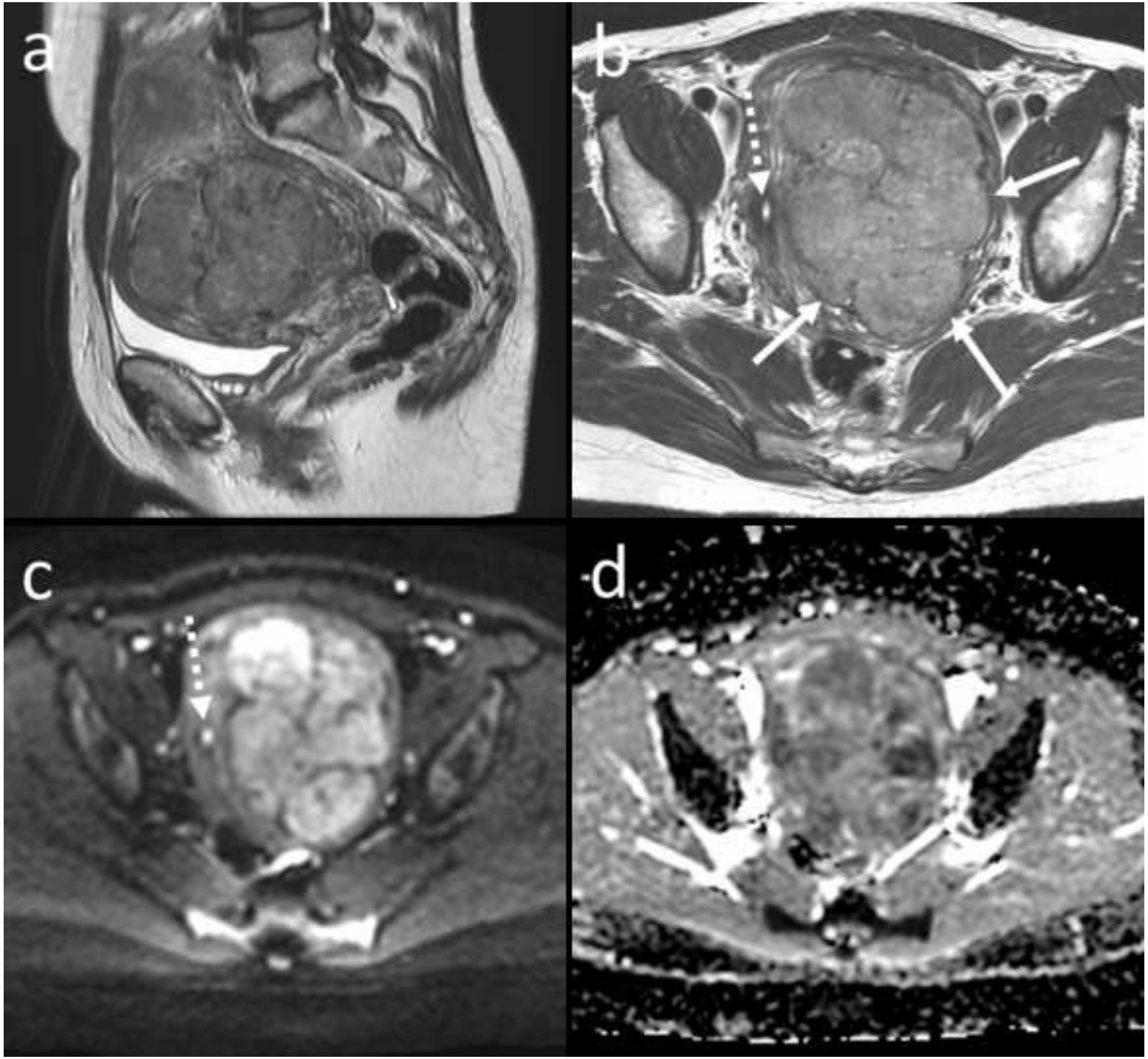

Figure 4

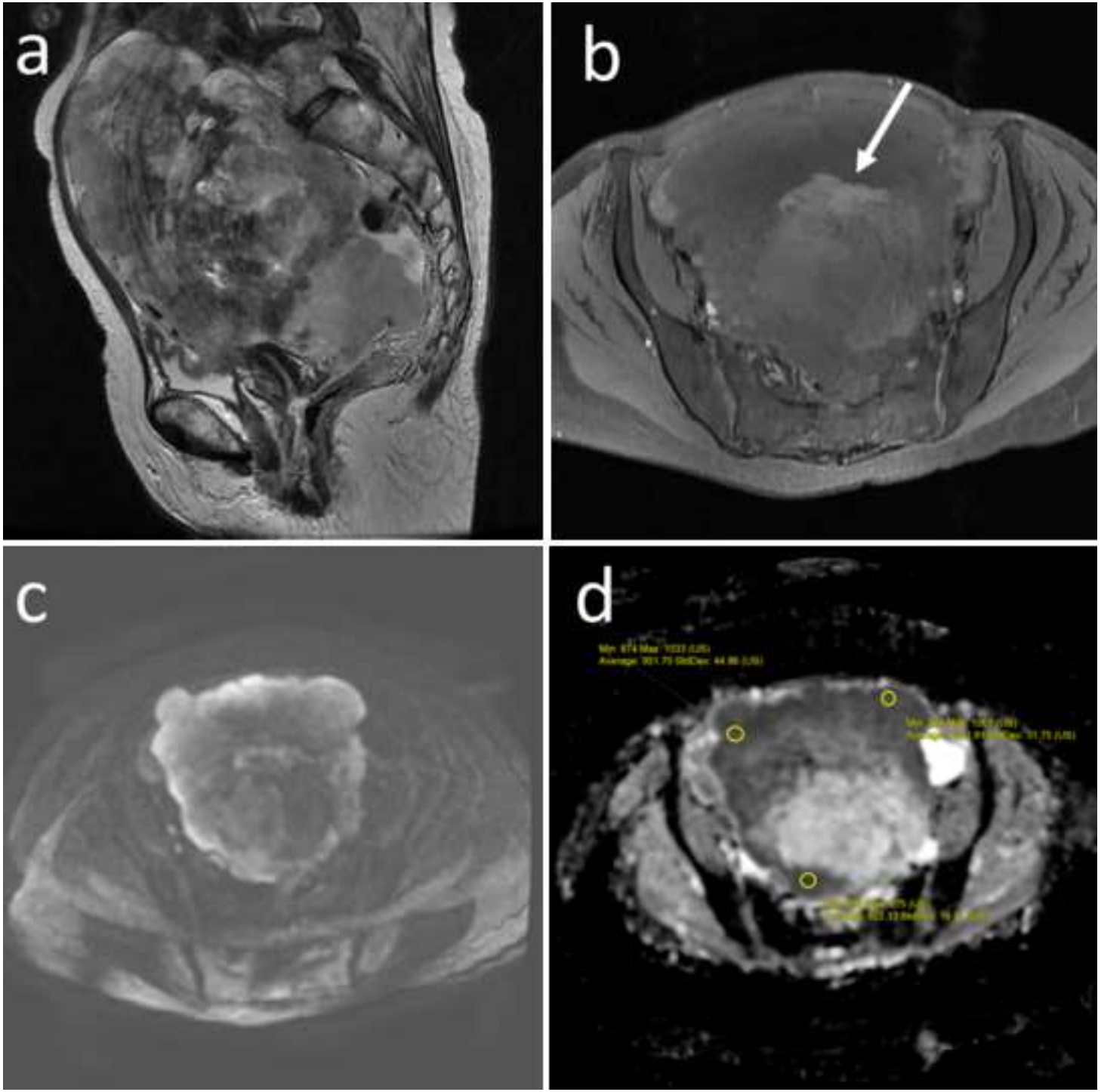

Figure 5

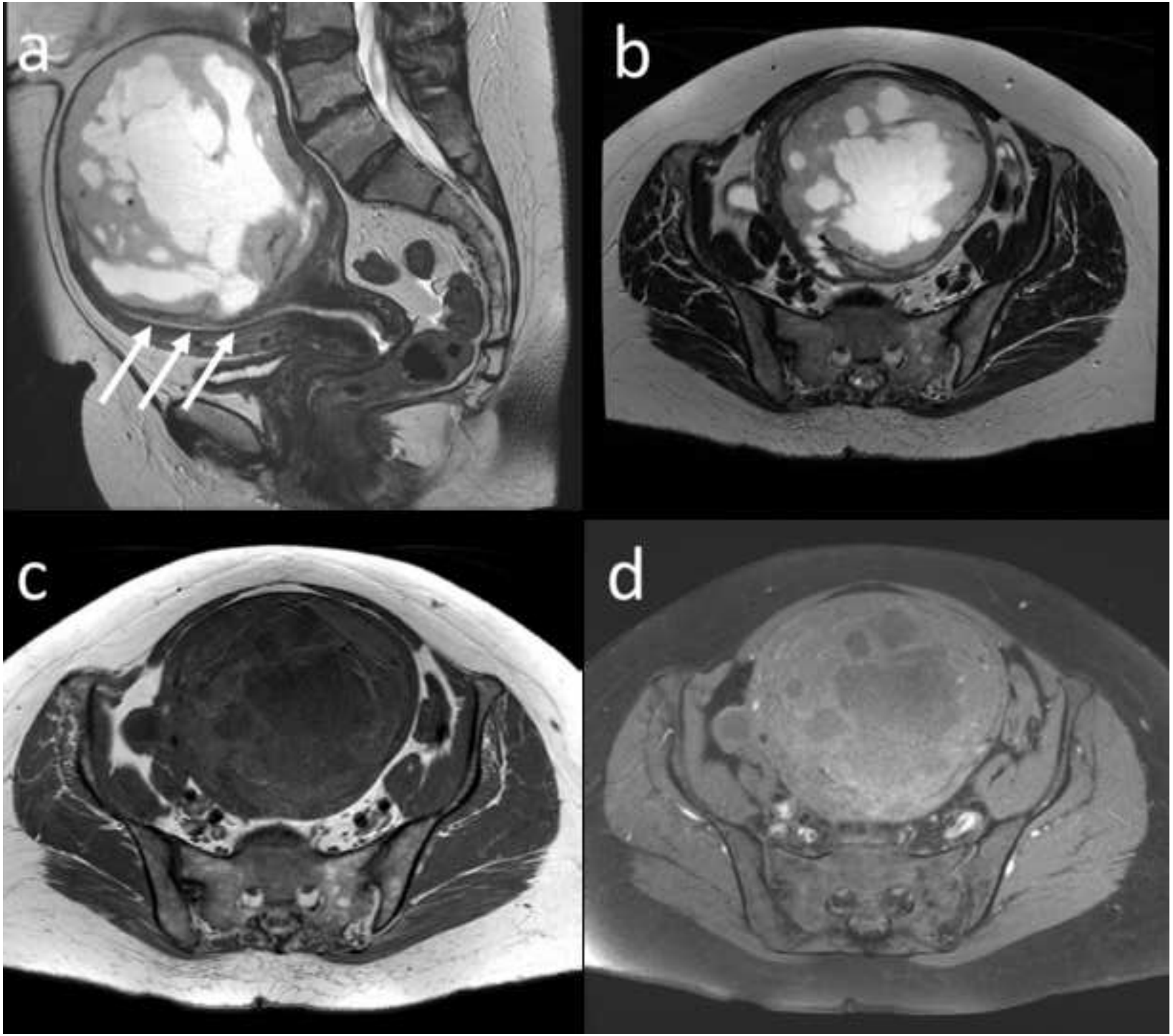

Figure 6

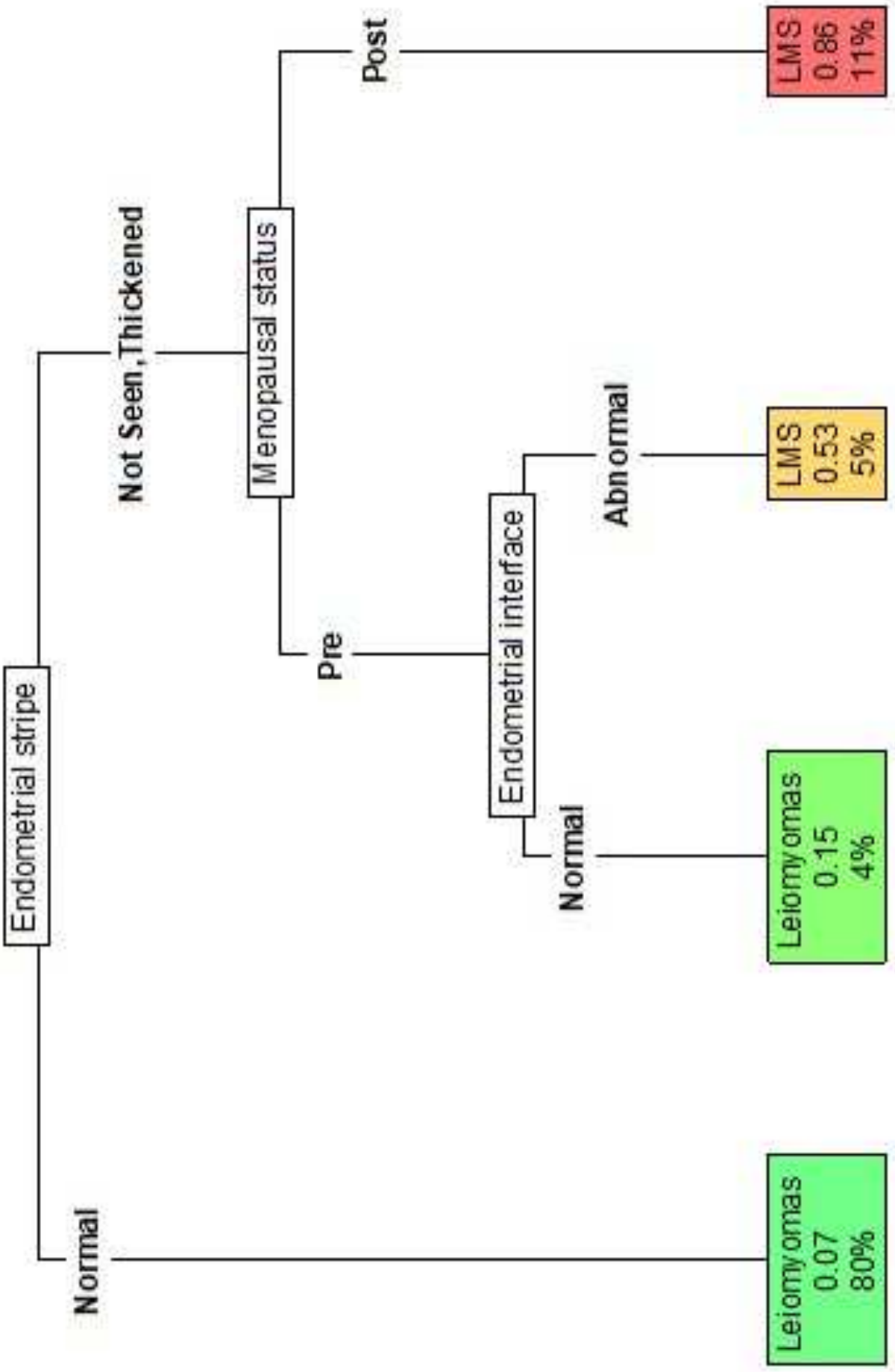
Endometrial stripe
Normal
Leiomyomas
0.07
80%
Not Seen, Thickened
Menopausal status
Post
LMS
0.86
11%
Pre
Endometrial interface
Abnormal
LMS
0.53
5%
Normal
Leiomyomas
0.15
4%

Table 1

Table 1. Description of the study population.

	Overall, N = 73	**Leiomyoma, N = 57**	**LMS, N = 16**	p
Age at exam, Mean (SD)	50.51 (10.38)	48.42 (8.12)	57.94 (13.99)	0.001
Pre-menopausal, N (%)	55 (75.3)	49 (86.0)	6 (37.5)	<0.001
BMI [kg/m^2], Mean (SD)	29.87 (8.83)	29.50 (7.87)	31.12 (11.75)	0.524
Weight [kg], Mean (SD)	80.08 (23.14)	80.11 (21.18)	79.99 (29.51)	0.986
Abnormal vaginal bleeding*, N (%)	24 (32.9)	16 (28.1)	8 (50.0)	0.032
Menstrual changes#, N (%)	26 (35.6)	24 (42.1)	2 (12.5)	0.001
Abdominal pain, N (%)	29 (39.7)	24 (42.1)	5 (31.2)	0.137
Newly diagnosed pelvic mass, N (%)	50 (68.5)	38 (66.7)	12 (75.0)	0.102
Increase in size of uterus, N (%)	57 (78.1)	46 (80.7)	11 (68.8)	0.136
Pelvic pressure symptoms, N (%)	16 (21.9)	14 (24.6)	2 (12.5)	0.108
Type of intervention, N (%)				0.058
Myomectomy	6 (8.2)	5 (8.8)	1 (6.2)	
Hysterectomy	63 (86.3)	51 (89.5)	12 (75.0)	
Uterine mass biopsy	3 (4.1)	1 (1.8)	2 (12.5)	
Other¥	1 (1.4)	0 (0.0)	1 (6.2)	
Previous malignancy, N (%)	3 (4.1)	2 (3.5)	1 (6.2)	0.99
CA125 value §, Median (IQR)	17 [13, 34]	15.5 [13, 33.25]	24 [16.5, 55]	0.521
Hb value §, Mean (SD)	12.40 (2.83)	12.75 (2.48)	10.87 (3.77)	0.046
Uterus volume ¤ [ml], Median [IQR]	935 [470, 1492]	994 [576, 1506]	764 [387, 966]	0.167
Max diameter of uterine mass [mm], Median[IQR]	109 [68, 139]	109 [68, 140]	101 [92, 126]	0.844

BMI, body mass index; CA125, Cancer antigen 125; Hb, Haemoglobin; IQR, interquartile range; LMS, leiomyosarcoma; SD, standard deviation

*Intermenstrual bleeding or postmenopausal bleeding; # among pre-menopausal women; §CA125 and Hb values were detected in the last two months prior to the intervention; ¥ Other refers to embolization, debulking surgery or diagnostic laparoscopy.

¤ Uterus volume [ml] = x * y * z * 0.523 / 1000

Table 2

Table 2. Prevalence of radiological features in atypical leiomyoma and leiomyosarcoma groups and inter-reader reliability.

Feature	Prevalence* leiomyoma, N = 57 N (%)	Prevalence* LMS, N = 16 N (%)	Fisher exact test p value	Overall agreement Average Kappa (min – max)	EA, Kappa	ENEA, Average Kappa (min – max)
Adnexal solid tubular structures favouring intravascular tumour growth	4 (7.0)	1 (6.2)	0.99	0.41 (0.14, 0.66)	0.14	0.38 (0.17, 0.65)
Ascites	2 (3.5)	1 (6.2)	0.530	0.29 (0.09, 0.79)	0.79	0.28 (0.12, 0.58)
Cystic/necrotic alterations	34 (59.6)	15 (93.8)	0.014	0.55 (0.49, 0.64)	0.51	0.57 (0.50, 0.64)
Diffusion restriction in the tumour	29 (50.9)	13 (81.2)	0.036	0.53 (0.42, 0.76)	0.76	0.52 (0.46, 0.61)
DWI signal of the tumour Low Intermediate High	 15 (26.3) 12 (21.1) 30 (52.6)	 2 (12.4) 1 (6.7) 13 (81.2)	0.178	0.41 (0.20, 0.64)	0.64	0.43 (0.31, 0.58)
Interruption of the endometrial interface	1 (1.8)	8 (50.0)	<0.001	0.37 (0.07, 0.80)	0.80	0.42 (0.34, 0.57)
Endometrial stripe Normal Thickened Not seen	 54 (94.7) 2 (3.5) 1 (1.8)	 7 (43.8) 8 (50.0) 1 (6.2)	<0.001	0.39 (0.17, 0.58)	0.51	0.34 (0.17, 0.49)
Flow voids in the tumour	27 (47.4)	10 (62.5)	0.398	0.39 (0.24, 0.51)	0.33	0.43 (0.34, 0.51)
Intratumour haemorrhage	9 (15.8)	10 (62.5)	0.001	0.72 (0.54, 0.90)	0.90	0.75 (0.63, 0.86)
Invasion in adjacent organs	0 (0.0)	2 (12.5)	0.046	0.53 (0.26, 0.79)	0.66	0.43 (0.26, 0.66)
Pelvic lymphadenopathy	1 (1.8)	0 (0.0)	0.99	-	-	-
Peritoneal implants	0 (0.0)	1 (6.2)	0.219	-	-	-
T2 dark/low signal areas in the tumour	32 (56.1)	14 (87.5)	0.038	0.37 (0.19, 0.67)	0.37	0.36 (0.19, 0.67)
T2-signal of the solid areas in the tumour	42 (73.7)	15 (93.8)	0.168	0.33 (0.14, 0.53)	0.50	0.33 (0.15, 0.53)
Tumour border (noduler/irregular)	24 (42.1)	13 (81.2)	0.010	0.47 (0.24, 0.59)	0.45	0.44 (0.24, 0.52)
Tumour morphology (homogeneous)	9 (15.8)	0 (0.0)	0.192	0.55 (0.25, 0.77)	0.59	0.61 (0.40, 0.77)
Tumour shape (irregular)	21 (36.8)	14 (87.5)	<0.001	0.48 (0.18, 0.75)	0.75	0.51 (0.36, 0.63)
Interruption of the uterine serosal border	12 (21.1)	6 (37.5)	0.200	0.43 (0.24, 0.66)	0.66	0.45 (0.29, 0.56)
Para-aortic lymphadenopathy	0 (0.0)	0 (0.0)	-	-	-	-

DWI, diffusion-weighted imaging; LMS, leiomyosarcoma

EA: Agreement between Experts (Two most experienced readers who had contributed to consensus decision were regarded as experts)

ENEA: Average agreement between any Expert-Non expert pair

*according to consensus reading.

Table 3

Table 3. Univariate analysis to detect associations of apparent diffusion coefficient (ADC) with leiomyosarcoma.

	Leiomyoma, N = 57	**Leiomyosarcoma, N = 16**	**p**
Iliopsoas ADC*			
robust ROI¥	1.425 [1.045, 1.599]	1.455 [0.892, 1.654]	0.783
Myometrium ADC			
robust ROI	1.564 [1.395, 1.749]	1.373 [1.253, 1.491]	0.055
Mass ADC#			
min (whole)	0.768 [0.636, 0.996]	0.482 [0.429, 0.697]	0.032
max (whole)	2.365 [1.934, 2.865]	2.326 [2.032, 2.829]	0.85
mean (whole)	1.484 [1.284, 1.722]	1.305 [1.137, 1.655]	0.216
robust ROI	1.383 [1.225, 1.610]	1.163 [0.978, 1.496]	0.074
Whole mass - Iliopsoas ADC ratio			
robust ROI iliopsoas measures	1.17 [0.96, 1.55]	0.98 [0.77, 1.51]	0.441
Whole mass - Myometrium ADC ratio			
robust ROI myometrium measures	0.95 [0.81, 1.18]	0.95 [0.74, 1.18]	0.814
Solid tissue - Iliopsoas ADC ratio			
robust ROI iliopsoas measures	1.09 [0.84, 1.43]	0.89 [0.59, 1.49]	0.310
Solid tissue - Myometrium ADC ratio			
robust ROI myometrium measures	0.95 [0.75, 1.16]	0.82 [0.68, 1.11]	0.365

ADC, apparent diffusion coefficient; IQR, interquartile range; ROI, region of interest

*****All calculated measures in the table are given as Median [IQR]. ADC value is given as $x10^{-3}$ mm^2 /s.

#minimum, maximum, and mean ADC values were obtained with manual tracing of ROI around the relevant tissue.

¥ Robust ROI values were calculated from ROI 1, 2 and 3 which were obtained by using a standard ROI (0.44 cm^2) and mean value was recorded.

Table 4

Table 4. Univariate associations between radiological features and leiomyosarcoma.

Radiological feature	**Univariate OR* (95% CI)**	**p**
Adnexal solid tubular structures favouring intravascular tumour growth	0.88 (0.04 - 6.55)	0.915
Ascites	1.83 (0.08 - 20.43)	0.630
Cystic/necrotic alterations	10.15 (1.85 - 189.78)	0.030
Diffusion restriction in the tumour	5.16 (1.26 - 35.13)	0.043
DWI signal of the tumour	2.64 (1.03 - 10.25)	0.082
Interruption of the endometrial interface	64.00 (9.79 - 1285)	<0.001
Endometrial stripe (thickened or not seen)	1.45 (1.18 - 1.78)	<0.001
Flow voids in the tumour	1.85 (0.60 - 6.09)	0.289
Intratumor haemorrhage	8.89 (2.67 - 32.60)	0.001
Invasion in adjacent organs	ne#	
Pelvic lymphadenopathy	ne	
Peritoneal implants	ne	
T2 dark/low signal areas in the tumour	5.47 (1.36 - 36.91)	0.034
T2-signal of the solid areas in the tumour	5.36 (0.95 - 100.98)	0.119
Tumour border (nodular/irregular)	5.96 (1.70 - 28.11)	0.010
Tumour morphology	ne	
Tumour shape (irregular)	12.00 (2.98 - 81.34)	0.002
Interruption of the uterine serosal border	2.25 (0.66 - 7.41)	0.184
Para-aortic lymphadenopathy	ne	
LIKERT score of the mass	3.14 (1.83 - 6.00)	<0.001

CI, confidence interval; DWI, diffusion-weighted imaging; OR, Odds ratio

***** Lasso regression was used to select the most relevant predictors.

ne (not evaluated), unable to estimate due to the absence of rate variability

Table 5. Results from multivariable analysis and variable selection process.

Selected clinical and radiological variables	**Adjusted OR (95% CI)**	**p**
Menopausal status [post vs pre]	1.31 (1.08 - 1.59)	0.010
Endometrial interface [interrupted vs not]	1.76 (1.40 - 2.20)	<0.001
Endometrial stripe [thickened vs normal / normal vs not seen]	1.28 (0.95 - 1.73)	0.110

CI, confidence interval; OR, Odds ratio.

Supplementary Table 1

Supplementary Table 2

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Supplementary material
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