Diagnostic accuracy of ultrasound in the differential diagnosis between uterine leiomyomas and sarcomas

Diagnostic accuracy of ultrasound in the differential diagnosis between uterine leiomyomas and sarcomas

Antonio RAFFONE, MD[1,2]; Diego RAIMONDO, MD, PhD[2]; Daniele NEOLA, MD[3]; Antonio TRAVAGLINO, MD[4,5]; Arianna RASPOLLINI, MD[1-2]; Matteo GIORGI, MD[6]; Angela SANTORO, MD[4]; Lucia DE MEIS, MD[2]; Gian Franco ZANNONI, MD[4]; Renato SERACCHIOLI, MD, PhD[1,2]; Paolo CASADIO, MD[2]* and Maurizio GUIDA, MD, PhD[5]*

[1] Department of Medical and Surgical Sciences (DIMEC), University of Bologna, 40138 Bologna, Italy

[2] Division of Gynaecology and Human Reproduction Physiopathology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, 40138 Bologna

[3] Gynecology and Obstetrics Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

[4] Anatomic Pathology Unit, Department of Advanced Biomedical Sciences, School of Medicine, University of Naples Federico II, Naples, Italy

[5] Gynecopathology and Breast Pathology Unit, Department of Woman's Health Science, Agostino Gemelli University Polyclinic, Rome, Italy

[6] Department of Molecular and Developmental Medicine, Obstetrics and Gynecological Clinic, University of Siena, 53100 Siena, Italy

*: The authors equally contributed to the study

CORRESPONDING AUTHORS:

Diego RAIMONDO, Division of Gynaecology and Human Reproduction Physiopathology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Via Giuseppe Massarenti 13, 40138, Bologna, Italy. Email: diego.raimondo@aosp.bo.it; raidie@libero.it

SYNOPSIS: This systematic review assesses the accuracy of ultrasound in the differential diagnosis between uterine leiomyomas and sarcomas, demonstrating only a moderate diagnostic accuracy.

ABSTRACT

Background: Differential diagnosis between uterine leiomyomas and sarcomas is challenging. Ultrasound shows an uncertain role in the clinical practice as pooled estimates about its diagnostic accuracy are lacking.

Objectives: To assess the accuracy of ultrasound in the differential diagnosis between uterine leiomyomas and sarcomas.

Data sources: A systematic review was performed searching 5 electronic databases (MEDLINE, Web of Sciences, Google Scholar, Scopus, and ClinicalTrial.gov) from their inception to June 2023.

Methods of study selection: All peer-reviewed observational or randomized clinical trials that reported an unbiased postoperative histological diagnosis of uterine leiomyoma or uterine sarcoma which also comprised a preoperative ultrasonographic evaluation of the uterine mass.

Tabulation, Integration and Results: Sensitivity, specificity, positive and negative likelihood ratios, diagnostic odds ratio, and area under the curve on summary receiver operating characteristic were calculated for each included study and as pooled estimate, with 95% confidence interval. 972 women (694 with uterine leiomyomas and 278 with uterine sarcomas), were included. Ultrasound showed pooled sensitivity of 0.76 (95%CI:0.70-0.81), specificity of 0.89 (95%CI:0.87-0.92), LR+ and LR- of 6.65 (95%CI:4.45-9.93) and 0.26 (95%CI:0.07-1.0) respectively, DOR of 23.06 (95%CI:4.56-116.53), and AUC of 0.8925.

Conclusions: Ultrasound seems to have only a moderate diagnostic accuracy in the differential diagnosis between uterine leiomyomas and sarcomas, with a lower sensitivity than specificity.

WORD COUNT: 3,063

KEYWORDS: malignancy; neoplasia; myomata; uterus; leiomyosarcoma; prediction; preoperative assessment

INTRODUCTION

Uterine sarcomas are rare malignant tumors arising from the mesenchymal tissues of the uterus, i.e. the endometrial stroma, uterine muscle and connective tissue[1].

Uterine sarcomas represent 1% of female genital tract malignancies and 3–7% of all uterine malignances[2], with a prevalence of 0.46%[3].

Malignant sarcomas comprise leiomyosarcoma, endometrial stromal sarcoma, adenosarcoma and undifferentiated sarcoma[4]. Leiomyosarcoma has been reported to be the most common type of sarcoma, with an incidence of 41 – 60%. Overall, uterine sarcomas are very aggressive tumors with a poor prognosis[5].

Unfortunately, these tumors can show similar symptoms, such as abnormal uterine bleeding (56%), a palpable pelvic mass (54%) or abdominal pain (22%), and overlapping imaging characteristics with benign lesions (i.e. uterine myomas) at preoperative workup[1]. As a result, an accurate preoperative differential diagnosis appears challenging, with a serious impact on management options (e.g. follow-up, medical therapy, or surgery) and surgical strategy. On these bases, indeed, in 2014, a Food and Drugs Administration (FDA) safety communication warned against the use of the uterine morcellator during minimally invasive surgery of uterine myomas as it could promote the dissemination of malignant debris in case of an occult malignant lesion[6]. The reported prevalence of occult sarcoma at surgery for a symptomatic leiomyoma ranges from 0.01% to 0.28%[7]. In 2020, the FDA released an updated communication reaffirming that laparoscopic power morcellation for myomectomy should be performed only with a tissue containing system (e.g. in-bag morcellation) and only in appropriately selected patients[8]. Therefore, an accurate preoperative diagnosis of myometrial tumors would be essential to plan the surgical route (endoscopy *vs* laparotomy), avoiding worsening the patient's prognosis in case of uterine sarcoma and allowing minimally invasive surgery so as not to increase the patient's morbidity in case of uterine myoma. Moreover, an accurate preoperative differential diagnosis would be crucial even for planning surgical treatment. In fact, while uterine myomas can be treated by myomectomy, uterine sarcomas require total abdominal hysterectomy, oophorectomy and debulking of the tumor outside the uterus[9].

In this scenario, several tools, such as ultrasound, magnetic resonance imaging (MRI) and serum markers, have been assessed to improve this preoperative differential diagnosis. In

particular, ultrasound represents the first-line imaging technique for the assessment of myometrial tumors, being non-invasive, quick, cheap and feasible in every setting. This technique allows a correct evaluation of the number, volume, location, and vascularity of uterine leiomyomas[10]. However, ultrasound has limitations in displaying the global image of large tumors and tissue characterization, and its diagnostic accuracy in the detection of uterine sarcomas may be affected by significant overlap in ultrasound appearance between degenerating leiomyoma and malignancy[11]. Moreover, despite ultrasound has been assessed in several studies[12,13], pooled estimates about its accuracy in the preoperative differentiation between leiomyomas and sarcomas are lacking. As a result, its role in the clinical practice is still uncertain.

The aim of this study was to assess the accuracy of ultrasound in the differential diagnosis between uterine leiomyomas and sarcomas.

MATERIALS AND METHODS

Study protocol

Two authors independently concluded each study step according to an *a priori* defined study protocol. In the case of disagreements, a discussion among all authors was adopted as a solution. The Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement and checklist[14] and the Synthesizing Evidence from Diagnostic Accuracy Tests (SEDATE) guidelines[15] were followed for reporting the whole study.

Search strategy

We performed several searches in 5 electronic databases (MEDLINE, Web of Sciences, Google Scholar, Scopus, and ClinicalTrial.gov) from their inception to June, 2023, by using a combination of the following text words: “uter*”, “cancer”; “carcinoma”; “tumor”; “tumour”; “malignancy”; “neoplas*”; “myom*”; “leiomyom*”; “sarcoma”, “different*”; “distinguis*”; “diagnos*”; “preoperat*”; “before surgery”; “presurg*; ”ultrasound”; “ultrasonograph*”; “ultrasound”; “scan”.

References list from each eligible study were also screened for missed studies.

Study selection

We included all peer-reviewed studies that allowed to calculate the accuracy of ultrasound in the differential diagnosis between uterine sarcomas and leiomyomas. In particular, we included all peer-reviewed observational studies (both retrospective and prospective studies) or randomized clinical trials, in English language, that reported an unbiased postoperative histological diagnosis of uterine leiomyoma or uterine sarcoma which also comprised a preoperative ultrasonographic evaluation of the uterine mass.

We *a priori* defined reviews and case reports as exclusion criteria.

Data extraction

We extracted original data from included studies without modification (Table S1). Two by two contingency tables were built for each included study, reporting two qualitative variables:

- ultrasound diagnosis (index test), alternatively dichotomized as “uterine leiomyoma” vs “uterine sarcoma”;
- pathological diagnosis (reference standard), as “uterine leiomyoma” vs “uterine sarcoma”.

We extracted the following data from the included studies: country in which the study was conducted, setting, number of patients include in each study, number of leiomyomas, number of sarcomas, study design, inclusion criteria, ultrasound criteria used in each study for the diagnosis of sarcoma or myoma, period of enrollment (Table 1). We also extracted the following patients characteristics from each included study: age, number of premenopausal women, number of asymptomatic women, number of women with abnormal uterine bleeding, number of women with abdominal or pelvic pain (Table 2).

Cases in which was not possible to exclude malignancy at ultrasound were considered as “uterine sarcoma” during data extraction.

Risk of bias within studies assessment

The latest Quality assessment of Diagnostic Accuracy Studies (QUADAS-2) was used to assess the risk of bias within studies[16]. In particular, we assessed each included study for 4 domains related to risk of bias: 1) Patient selection (i.e. if patients were randomly or consecutively selected for inclusion in the study); 2) Index test (i.e. if ultrasound was unbiased, e.g. exam performed by expert sonographers blinded to ultimate pathological diagnosis); 3) Reference standard (i.e. if pathological examination was unbiased, e.g. blinded evaluation by at least 2 pathologists and updated pathological criteria); 4) Flow and Timing (i.e. if all patients were assessed with both ultrasound and pathological examination; if interval between ultrasound and pathological examination was less than 1 year).

Authors judged each study at “low risk”, “unclear risk” or “high risk” of bias if data about the domain were “reported and adequate”, “not reported” or “reported but inadequate”,

153 respectively.
154

155 **Data analysis**

156 Sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-) and diagnostic
157 odds ratio (DOR), and area under the curve (AUC) on summary receiver operating
158 characteristic (SROC) were calculated for each included study and as pooled estimate.
159 Values were reported graphically on forest plots with 95% confidence interval (CI).

160 The diagnostic accuracy in differentiating uterine leiomyomas and sarcomas was
161 categorized as absent for AUC≤0.5, low for 0.5<AUC≤0.75, moderate for 0.75<AUC≤0.9,
162 high for 0.9<AUC<0.97, very high for AUC≥0.97, as previously reported[17,18].

163 Statistical heterogeneity among the included studies was estimated with the Higgins I^2
164 statistic; in particular, heterogeneity was categorized as null for I^2=0%, minimal for
165 0%<I^2≤25%, low for 25<I^2≤50%, moderate for 50<I^2≤75% and high for I^2>75%, as previously
166 reported[19–21].

167 The random effect model of DerSimonian and Laird was adopted independently from the
168 statistical heterogeneity, as recommended for meta-analysis of diagnostic accuracy by the
169 SEDATE guidelines.

170 Meta-DiSc version 1.4 (Clinical Biostatistics Unit, Ramon y Cajal Hospital, Madrid, Spain)
171 and Review Manager 5.4 (Copenhagen: The Nordic Cochrane Centre, Cochrane
172 Collaboration, 2014) were used as software for analysis.

173

RESULTS

Study selection

At the end of the databases searches, 4,491 studies were identified. Duplicates removal and title screening processes led to 671 and 88 studies, respectively. Abstract screening led to 14 studies which were evaluated for eligibility[22,23,32–35,24–31]. Of them, 4 studies were excluded because data about suspicion of uterine sarcoma at ultrasound were not reported[22–25], while 7 studies were excluded because they did not assess patients with uterine leiomyoma [26–32]. Finally, 3 studies were included in both qualitative synthesis and quantitative synthesis[33–35] (Figure 1).

Studies and patients' characteristics

Included studies assessed a total of 972 women (694 with uterine leiomyomas and 278 with uterine sarcomas) and were observational totally retrospective in two cases[34,35] and prospective/retrospective in another one[33](Table 1). Proportions between benign and malignant uterine lesions differ from general population due to the need to include the highest number of malignancies in the individual studies.

Age of women with uterine leiomyomas ranged from to 29 to 81 years and age of women with sarcoma ranged from 36 to 76 years. In our population, 92% (639/694; 95% CI: 90.1%-94.1%) of women with uterine leiomyomas and 44.6% (124/278; 95% CI: 38.8%-50.4%) of women with uterine sarcoma were premenopausal. 49.7% (332/668; 95% CI: 45.9%-53.5%) of women with leiomyomas and 56% (135/241; 95% CI: 49.7%-62.3%) with sarcoma were asymptomatic. About symptoms, 13.8% (96/694; 95% CI: 11.3%-16.4%) of women with uterine leiomyomas and 47.8% (133/278; 95% CI: 42%-53.7%) of women with uterine sarcoma showed abnormal uterine bleeding, while 21% (16/76; 95% CI: 11.9%-30.2%) and 42.1% (24/57; 95% CI: 29.3%-54.9%) had pelvic/abdominal pain, respectively (Table 2).

In the study by Chiappa *et al.*[34] ultrasound images were stored and elaborated by a radiomics platform for the differential diagnosis between myomas and sarcomas. However, we extracted and analyzed for our meta-analysis data referred to subjective ultrasound evaluation before application of radiomics and machine-learning models.

Risk of bias within studies evaluation

During the risk of bias within studies evaluation, all included studies were judged at low risk of bias in the “Index test” and “Flow and Timing” domains.

In the “Patient selection”, two studies were judged at unclear risk of bias because they did not clearly report if patients were randomly or consecutively selected for inclusion in the study[33,35]. The patient selection of these two studies might underlie the difference in proportions between benign and malignant uterine lesions that we reported in our study population compared to general population.

In the “Reference standard” domain, one study was judged at unclear risk of bias because it did not report data[33] and another study at high risk of bias because it did not adopt updated pathological criteria[35].

Risk of bias within studies evaluation is graphically shown in Figure 2.

Meta-analysis

In the differential diagnosis between uterine leiomyomas and sarcomas, ultrasound showed pooled sensitivity of 0.76 (95% CI: 0.70-0.81; I^2: 94.5%; Figure 3a), specificity of 0.89 (95% CI: 0.87-0.92; I^2: 0%; Figure 3b), LR+ and LR- of 6.65 (95% CI: 4.45-9.93; I^2: 35.1%; Figure 3c) and 0.26 (95% CI: 0.07-1.0; I^2: 96.9%; Figure 3d) respectively, DOR of 23.06 (95% CI: 4.56-116.53; I^2: 80.2%; Figure 3e), and AUC of 0.8966 (Figure 3f).

DISCUSSION

Main findings and interpretation

Despite the inclusion of only 3 studies and the high statistical heterogeneity for some outcomes (i.e. sensitivity, LR- and DOR), this study showed that ultrasound has only a moderate diagnostic accuracy (AUC=0.89) in the differential diagnosis between uterine leiomyomas and sarcomas, with a lower sensitivity (76%) than specificity (89%).

In the clinical practice, the preoperative differentiation between uterine myomas and sarcomas is a challenging and unsolved issue.

In order to improve and standardize ultrasound assessment of uterine lesions, The Morphological Uterus Sonographic Assessment (MUSA) group defined the ultrasound characteristics of uterine fibroids and sarcomas. In fact, a uterine fibroid appears as a well-defined round lesion, often showing shadows at the edge of the lesion and/or inside it, with circumferential flow on color- or power-Doppler imaging. On the other hand, uterine sarcomas present as purely myometrial lesions and are typically single, large tumors, with a regular or irregular outline, frequent irregular anechoic areas due to necrosis and irregular vascularization[10] (Figures 4-6). These findings are the result of several studies which described ultrasound appearance and the most common ultrasound signs of uterine sarcomas. In detail, in 2007, Exacoustos *et al.* suggested that the presence of a single, large, rapidly growing myometrial lesion, with cystic degeneration and with marked peripheral and central vascularization is suggestive of the presence of a uterine leiomyosarcoma[27]. Bonneau *et al.* analyzed ultrasound findings in 85 benign myomas and 23 uterine sarcomas of different types, describing that uterine sarcomas appeared more frequently as a single mass with no acoustic shadowing[26]. In 2019, reporting the largest series in the literature, Ludovisi *et al.* concluded that the ultrasound features suggestive for uterine mesenchymal malignancy are the presence of a large myometrial lesion , with inhomogeneous echogenicity , irregular cystic areas , absence of shadows and calcifications, in symptomatic women (in particular with abnormal uterine bleeding)[29]. Kim *et al.* suggested that sarcomas affect mostly women in late reproductive age, are usually larger than 5 cm and show heterogeneous echogenicity and irregular cystic degeneration[28]. A recent systematic review assessed the most frequent ultrasound signs of uterine sarcomas, showing that they more commonly appear as solid tumor > 8 cm, with unsharp borders,

heterogeneous echogenicity, no acoustic shadowing, rich vascularization, and cystic changes within[36].

Unfortunately, ultrasound features of uterine sarcomas may be indistinct from those of benign fibroids. In fact, data on the prediction of uterine sarcoma by ultrasound examination are overall scarce and based mainly on small retrospective case series[37]. Moreover, the right prevalence of preoperative ultrasound characteristics suspicious of malignancy in uterine sarcomas is still unclear. Yet, the overall diagnostic accuracy of ultrasound in the preoperative differentiation of uterine leiomyomas and sarcomas was never estimated. Thus, despite the low number of eligible studies, in order to improve the knowledge in the field, we also performed a meta-analysis.In particular, we found that ultrasound has only a moderate diagnostic accuracy (AUC=0.89) in the differential diagnosis between uterine leiomyomas and sarcomas, with a lower sensitivity (76%) than specificity (89%). Our study assessed such accuracy for the first time in the literature.

Therefore, ultrasound does not appear reliable enough in identifying women with uterine sarcoma preoperatively, explaining the risk for occult sarcoma in the clinical practice[38]. On the other hand, a higher specificity could more consistently detect women with benign lesions. In other words, the accuracy and sensitivity of ultrasound would not allow to exclude malignancy in the case of a diagnostic uncertainty, while its specificity would make us more confident about the benign nature of the lesion in the presence of benign ultrasound signs.

In this scenario of uncertainty and preoperative diagnosis extremely dependent on ultrasound examiner subjective assessment, the implementation of additional and more reproducible tools, such as MRI, radiomics methods and serum biomarkers, and the evaluation of specific symptoms, appears crucial. Chiappa *et al.* tried to implement the use of radiomics in the ultrasonographic evaluation of uterine mesenchymal masses[34]. However, this tool showed a diagnostic performance similar to that of ultrasound demonstrated in our study. Indeed, ultrasonographic radiomics showed a moderate accuracy, with an AUC of 0.85 and a specificity higher than sensitivity.

Najibi *et al.* compared MRI to ultrasound in the diagnosis of uterine leiomyosarcoma and found a higher diagnostic value of MRI. In particular, MRI resulted both more sensitive and specifical than ultrasound, with a sensitivity of 94.6% and a specificity of 92.3%[35]. In fact, in North America, the medical community has moved beyond ultrasound for differentiating

leiomyosarcoma from leiomyomas to use of MRI with intravenous contrast, which is recognized as the gold standard technique[39]. Our data seem to support these recommendations.

Regarding serum tumor markers and risk assessment scores, no reliable preoperative test is available in the clinical practice to differentiate benign and malignant uterine mesenchymal lesions[40]. Lactate Dehydrogenase (LDH) isoenzymes have been studied as a possible tool for preoperative diagnosis, but they still lack validation. In detail, although LDH is considered a nonspecific tumor marker, some of its isoenzymes have been found to be altered in some malignancies, especially in malignancies of the genital tract[41]. In this regard, a mathematical index based on analysis of LDH isoenzymes has shown promising results, with a 100% sensitivity and a 99.6% specificity for diagnosing uterine sarcoma[42].

Moreover, malignancy should be particularly suspected in cases of tumor growth in postmenopausal women who are not on hormone replacement therapy[43]. Occasionally, the presenting symptoms can be tumor rupture (hemoperitoneum), extrauterine growth (from one-third to one-half of cases) or metastases[44]. On these bases, Kohler *et al.* proposed a preoperative risk score (pLMS score) for uterine masses undefined or suspicious for leiomyomas or leiomyosarcomas, and tested it on a large cohort through a multicenter retrospective study. In detail, after assessing 13 variables in a multivariable analysis, abnormal uterine bleeding, dysmenhorrea, suspicious sonography and tumor diameter were included in the preoperative risk score as key variables[33].

Lastly, needle biopsies of suspected myometrial masses have recently been proposed as a novel, accurate, diagnostic tool[45]. Indeed, preoperative, MRI-guided, percutaneous uterine needle biopsy with microscopic examination or array-comparative genomic hybridization showed a diagnostic accuracy of 94% and 100%, respectively[46]. Such procedure seems also feasible under ultrasound guidance, as showed by a recent case-series reporting a 100% accuracy[47].

Further studies are encouraged for improving diagnostic accuracy of ultrasound (with a systematic assessment of ultrasound sings of uterine mesenchymal malignancy) and other proposed tools.

Strengths and limitations

To our knowledge, this may be the first systematic review and meta-analysis to evaluate the diagnostic accuracy of ultrasound in this field. Moreover, the included studies showed a good overall quality as shown by the risk of bias within studies assessment: in fact, only one study was judged at high risk of bias in only one domain[35].

However, some major limitations may affect our findings, such as the low number of included studies, the retrospective study design and the high heterogeneity in some outcomes (i.e. sensitivity, LR- and DOR). Given these limitations, our meta-analysis should be considered as an exploratory analysis that needs to be updated over the time with additional future studies. Anyway, given the rarity of uterine sarcomas, prospective studies appear difficult to be performed; conversely, an international registry with clear reporting standards could be a sensible approach for improving evidence about such rare conditions. Moreover, despite ultrasound was performed by expert sonographers, another limitation may be the subjectivity of ultrasound assessment and the absence of homogeneous and clearly stated ultrasonographic criteria for malignancy in all included studies. In detail, in two out of three included studies[33,35], the ultrasonographic suspicion of benignity or malignancy was based on a subjective evaluation by an expert sonographer without reporting specific ultrasonographic signs.

CONCLUSION

Ultrasound seems to have an only moderate diagnostic accuracy in the differential diagnosis between uterine leiomyomas and sarcomas, with a lower sensitivity than specificity. Therefore, it would not allow to exclude malignancy in the case of a diagnostic uncertainty at ultrasound evaluation, while it would make us more confident in the benign nature of the lesion in the presence of benign ultrasound signs.

Further studies are encouraged for confirming these findings and improving diagnostic accuracy of ultrasound for uterine mesenchymal lesions.

CONTRIBUTION

AR (Antonio Raffone), AT, and DN independently assessed electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. DR, AR (Arianna Raspollini), MG and AS contributed to the elaboration of methods for risk of bias assessment, data extraction and analysis. AR (Antonio Raffone), DR, AT, DN, DR, LDM, GFZ, RS, PC and MG conceived the study; AR (Antonio Raffone), DR, DN, AR, MG and LDM worked on the design of the study; AR (Antonio Raffone), AT, DN, DR, MG and AS worked on the manuscript preparation; GFZ, RS, PC and MG supervised the whole study.

CONFLICT OF INTEREST STATEMENT

Authors report no conflict of interest.

FUNDING INFORMATION

None.

REFERENCES LIST

1. D'Angelo E, Prat J. Uterine sarcomas: A review. *Gynecol Oncol*. 2010;116(1). doi:10.1016/j.ygyno.2009.09.023
2. Tropé CG, Abeler VM, Kristensen GB. Diagnosis and treatment of sarcoma of the uterus. A review. *Acta Oncol (Madr)*. 2012;51(6). doi:10.3109/0284186X.2012.689111
3. Coffin PH, Ascher S, Spies J. The Risk of Uterine Malignancy in a Population Being Evaluated for Uterine Fibroid Embolization. *J Comput Assist Tomogr*. 2020;44(6):893-900. doi:10.1097/RCT.0000000000001104
4. Zaloudek CJ, Hendrickson MR, Soslow RA. Mesenchymal Tumors of the Uterus. In: *Blaustein's Pathology of the Female Genital Tract*. ; 2011. doi:10.1007/978-1-4419-0489-8_10
5. Nagai T, Takai Y, Akahori T, et al. Novel uterine sarcoma preoperative diagnosis score predicts the need for surgery in patients presenting with a uterine mass. *Springerplus*. 2014;3(1). doi:10.1186/2193-1801-3-678
6. Hampton T. Use of morcellation to remove fibroids scrutinized at FDA hearings. *JAMA - J Am Med Assoc*. 2014;312(6). doi:10.1001/jama.2014.10041
7. Hindman N, Kang S, Fournier L, et al. MRI Evaluation of Uterine Masses for Risk of Leiomyosarcoma: A Consensus Statement. *Radiology*. 2023;306(2). doi:10.1148/RADIOL.211658
8. U.S. Food and Drug Administration. Update: perform only contained morcellation when laparoscopic power morcellation is appropriate. https://www.fda.gov/medical-devices/safety-communications/update-perform-only-contained-morcellation-when-laparoscopic-power-morcellation-appropriate-fda. Published 2020.
9. Giuntoli RL, Metzinger DS, DiMarco CS, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: Prognostic indicators, surgical management, and adjuvant therapy. In: *Gynecologic Oncology*. Vol 89. ; 2003. doi:10.1016/S0090-8258(03)00137-9
10. Van Den Bosch T, Dueholm M, Leone FPG, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: A consensus opinion from the Morphological Uterus Sonographic

Assessment (MUSA) group. *Ultrasound Obstet Gynecol*. 2015;46(3). doi:10.1002/uog.14806

11. Amant F, Coosemans A, Debiec-Rychter M, et al. Clinical management of uterine sarcomas. *Lancet Oncol*. 2009;10(12). doi:10.1016/S1470-2045(09)70226-8

12. Stoelinga B, Juffermans L, Dooper A, et al. Contrast-Enhanced Ultrasound Imaging of Uterine Disorders: A Systematic Review. *Ultrason Imaging*. 2021;43(5). doi:10.1177/01617346211017462

13. Sun S, Bonaffini PA, Nougaret S, et al. How to differentiate uterine leiomyosarcoma from leiomyoma with imaging. *Diagn Interv Imaging*. 2019;100(10). doi:10.1016/j.diii.2019.07.007

14. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Rev Esp Nutr Humana y Diet*. 2016;20(2). doi:10.1186/2046-4053-4-1

15. Sotiriadis A, Papatheodorou SI, Martins WP. Synthesizing Evidence from Diagnostic Accuracy TEsts: The SEDATE guideline. *Ultrasound Obstet Gynecol*. 2016;47(3). doi:10.1002/uog.15762

16. Whiting PF, Rutjes AWS, Westwood ME, et al. Quadas-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8). doi:10.7326/0003-4819-155-8-201110180-00009

17. Raffone A, Travaglino A, Cerbone M, et al. Diagnostic Accuracy of Immunohistochemistry for Mismatch Repair Proteins as Surrogate of Microsatellite Instability Molecular Testing in Endometrial Cancer. *Pathol Oncol Res*. 2020;26(3). doi:10.1007/s12253-020-00811-5

18. Raffone A, Travaglino A, Santoro A, et al. Accuracy of One-Step Nucleic Acid Amplification in Detecting Lymph Node Metastases in Endometrial Cancer. *Pathol Oncol Res*. 2020;26(4). doi:10.1007/s12253-019-00727-9

19. Raffone A, Travaglino A, Saccone G, et al. Diabetes Mellitus Is Associated with Occult Cancer in Endometrial Hyperplasia. *Pathol Oncol Res*. 2020;26(3). doi:10.1007/s12253-019-00684-3

20. Travaglino A, Raffone A, Saccone G, et al. Congruence between 1994 WHO classification of endometrial hyperplasia and endometrial intraepithelial neoplasia system. *Am J Clin Pathol*. 2020;153(1). doi:10.1093/ajcp/aqz132

21. Travaglino A, Raffone A, Saccone G, et al. Significant risk of occult cancer in complex non-atypical endometrial hyperplasia. *Arch Gynecol Obstet*. 2019;300(5). doi:10.1007/s00404-019-05299-2

22. Aviram R, Ochshorn Y, Markovitch O, et al. Uterine sarcomas versus leiomyomas: Gray-scale and Doppler sonographic findings. *J Clin Ultrasound*. 2005;33(1). doi:10.1002/jcu.20075

23. Chen I, Firth B, Hopkins L, et al. Clinical characteristics differentiating uterine sarcoma and fibroids. *J Soc Laparoendosc Surg*. 2018;22(1). doi:10.4293/JSLS.2017.00066

24. Hata K, Hata T, Maruyama R, et al. Uterine sarcoma: Can it be differentiated from uterine leiomyoma with Doppler ultrasonography? A preliminary report. *Ultrasound Obstet Gynecol*. 1997;9(2). doi:10.1046/j.1469-0705.1997.09020101.x

25. Zhao F, Xu Y, Zhang H, et al. Ultrasonographic findings of uterine carcinosarcoma. *Gynecol Obstet Invest*. 2019;84(3):277-282. doi:10.1159/000481885

26. Bonneau C, Thomassin-Naggara I, Dechoux S, et al. Value of ultrasonography and magnetic resonance imaging for the characterization of uterine mesenchymal tumors. *Acta Obstet Gynecol Scand*. 2014;93(3). doi:10.1111/aogs.12325

27. Exacoustos C, Romanini ME, Amadio A, et al. Can gray-scale and color Doppler sonography differentiate between uterine leiomyosarcoma and leiomyoma? *J Clin Ultrasound*. 2007;35(8). doi:10.1002/jcu.20386

28. Kim JH, Kim HJ, Kim SH, et al. Sonographic and Clinical Characteristics of Uterine Sarcoma Initially Misdiagnosed as Uterine Fibroid in Women in the Late Reproductive Age. *J Menopausal Med*. 2019;25(3). doi:10.6118/jmm.19007

29. Ludovisi M, Moro F, Pasciuto T, et al. Imaging in gynecological disease (15): clinical and ultrasound characteristics of uterine sarcoma. *Ultrasound Obstet Gynecol*. 2019;54(5). doi:10.1002/uog.20270

30. Park GE, Rha SE, Oh SN, et al. Ultrasonographic findings of low-grade endometrial Stromal sarcoma of the uterus with a focus on cystic degeneration. *Ultrasonography*. 2016;35(2). doi:10.14366/usg.15045

31. Li D, Yin N, Du G, et al. A real-world study on diagnosis and treatment of uterine sarcoma in Western China. *Int J Biol Sci*. 2020;16(3). doi:10.7150/ijbs.39773

32. Skorstad M, Kent A, Lieng M. Preoperative evaluation in women with uterine leiomyosarcoma. A nationwide cohort study. *Acta Obstet Gynecol Scand*. 2016;95(11). doi:10.1111/aogs.13008

33. Köhler G, Vollmer M, Nath N, et al. Benign uterine mass—discrimination from leiomyosarcoma by a preoperative risk score: a multicenter cohort study. *Arch Gynecol Obstet*. 2019;300(6). doi:10.1007/s00404-019-05344-0

34. Chiappa V, Interlenghi M, Salvatore C, et al. Using rADioMIcs and machine learning with ultrasonography for the differential diagnosis of myometRiAL tumors (the ADMIRAL pilot study). Radiomics and differential diagnosis of myometrial tumors. *Gynecol Oncol*. 2021;161(3). doi:10.1016/j.ygyno.2021.04.004

35. Najibi S, Gilani MM, Zamani F, et al. Comparison of the diagnostic accuracy of contrast-enhanced/DWI MRI and ultrasonography in the differentiation between benign and malignant myometrial tumors. *Ann Med Surg*. 2021;70. doi:10.1016/j.amsu.2021.102813

36. Camponovo C, Neumann S, Zosso L, et al. Sonographic and Magnetic Resonance Characteristics of Gynecological Sarcoma. *Diagnostics (Basel, Switzerland)*. 2023;13(7). doi:10.3390/DIAGNOSTICS13071223

37. Horng HC, Wen KC, Wang PH, et al. Uterine sarcoma Part II—Uterine endometrial stromal sarcoma: The TAG systematic review. *Taiwan J Obstet Gynecol*. 2016;55(4). doi:10.1016/j.tjog.2016.04.034

38. Pritts EA, Vanness DJ, Berek JS, et al. The prevalence of occult leiomyosarcoma at surgery for presumed uterine fibroids: a meta-analysis. *Gynecol Surg*. 2015;12(3). doi:10.1007/s10397-015-0894-4

39. Petrocelli R, Hindman N, Reinhold C. Current Concepts in the Imaging of Uterine Sarcomas. *Radiol Clin North Am*. 2023;61(4). doi:10.1016/J.RCL.2023.02.008

40. Spivack LE, Glantz JC, Lennon C, et al. Specificity of the lactate dehydrogenase isoenzyme index as a preoperative screen for uterine sarcoma before myomectomy. *Fertil Steril*. 2021;115(1). doi:10.1016/j.fertnstert.2020.07.020

41. Mollo A, Raffone A, Travaglino A, et al. Increased LDH5/LDH1 ratio in preoperative diagnosis of uterine sarcoma with inconclusive MRI and LDH total activity but suggestive CT scan: A case report 11 Medical and Health Sciences 1103 Clinical Sciences. *BMC Womens Health*. 2018;18(1). doi:10.1186/s12905-018-0662-5

42. Di Cello A, Borelli M, Marra ML, et al. A more accurate method to interpret lactate dehydrogenase (LDH) isoenzymes' results in patients with uterine masses. *Eur J Obstet Gynecol Reprod Biol*. 2019;236. doi:10.1016/j.ejogrb.2019.03.017

43. Perri T, Korach J, Sadetzki S, et al. Uterine leiomyosarcoma: Does the primary surgical procedure matter? *Int J Gynecol Cancer*. 2009;19(2). doi:10.1111/IGC.0b013e31819a1f8f

44. Kurman RJ, Carcangiu ML, Herrington CS, et al. WHO Classification of Tumours of Female Reproductive Organs. *World Heal Organ Classif Tumours*. 2014.

45. Tamura R, Kashima K, Asatani M, et al. Preoperative ultrasound-guided needle biopsy of 63 uterine tumors having high signal intensity upon t2-weighted magnetic resonance imaging. *Int J Gynecol Cancer*. 2014;24(6). doi:10.1097/IGC.0000000000000189

46. Smadja J, El Zein S, Pierron G, et al. Percutaneous Uterine Needle Biopsy with Microscopic and Array-CGH Analyses for Preoperative Sarcoma Diagnosis in Patients with Suspicious Myometrial Tumors on MRI: A Prospective Pilot Study (SARCGYN). *Ann Surg Oncol*. 2022. doi:10.1245/s10434-022-12697-5

47. Alboni C, Mattos L, Malmusi S, et al. Ultrasound-guided needle biopsy for preoperative assessment of uterine fibroids: Our experience and a review of the literature. *Gynecol Minim Invasive Ther*. 2022;11(1). doi:10.4103/GMIT.GMIT_31_20

LEGENDS FOR TABLES AND FIGURES

Figure 1. Flowchart of study selection step of the systematic review and meta-analysis (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).

Figure 2. Assessment of risk of bias. Summary of risk of bias for each study; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias.

Figure 3 (a-e). Forest plots of individual studies and pooled sensitivity **(a)**, specificity **(b)**, positive likelihood ratio **(c)**, negative likelihood ratio **(d)**, diagnostic odds ratio **(e)** of ultrasound in the differential diagnosis between uterine leiomyomas and sarcomas.

Figure 3 (f). Pooled area under the curve (AUC) on summary receiver operating characteristic (SROC) with 95% confidence intervals of ultrasound in the differential diagnosis between uterine leiomyomas and sarcomas. Red circles refer to the included studies (in order from the top to the bottom: 2021 Chiappa; 2019 Kohler; 2021 Najibi)

Figure 4. Ultrasound image of uterine sarcoma showing a single, large lesion, with a solid component of inhomogeneous echogenicity.

Figure 5. Ultrasound image of uterine sarcoma showing cystic areas with irregular walls.

Figure 6. Ultrasound image of uterine sarcoma showing irregular vascularization.

Table 1. Characteristics of the included studies.

532 **Table 2.** Characteristics of the study population.

533

534 **Table S1.** Absolute numbers from included studies for diagnostic accuracy analyses.