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

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- 23 **SYNOPSIS:** This systematic review assesses the accuracy of ultrasound in the differential
- 24 diagnosis between uterine leiomyomas and sarcomas, demonstrating only a moderate
- 25 diagnostic accuracy.
- 26

### 27 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.

31 **Objectives:** To assess the accuracy of ultrasound in the differential diagnosis between 32 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.

36 **Methods of study selection:** All peer-reviewed observational or randomized clinical trials 37 that reported an unbiased postoperative histological diagnosis of uterine leiomyoma or 38 uterine sarcoma which also comprised a preoperative ultrasonographic evaluation of the 39 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.

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

### 50 **WORD COUNT:** 3,063

51 **KEYWORDS:** malignancy; neoplasia; myomata; uterus; leiomyosarcoma; prediction; 52 preoperative assessment

### 54 **INTRODUCTION**

55 Uterine sarcomas are rare malignant tumors arising from the mesenchymal tissues of the 56 uterus, i.e. the endometrial stroma, uterine muscle and connective tissue<sup>1</sup>.

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

59 Malignant sarcomas comprise leiomyosarcoma, endometrial stromal sarcoma, 60 adenosarcoma and undifferentiated sarcoma<sup>4</sup>. Leiomyosarcoma has been reported to be 61 the most common type of sarcoma, with an incidence of 41 - 60%. Overall, uterine sarcomas 62 are very aggressive tumors with a poor prognosis<sup>5</sup>.

63 Unfortunately, these tumors can show similar symptoms, such as abnormal uterine bleeding 64 (56%), a palpable pelvic mass (54%) or abdominal pain (22%), and overlapping imaging 65 characteristics with benign lesions (i.e. uterine myomas) at preoperative workup<sup>1</sup>. As a 66 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 67 68 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 69 70 surgery of uterine myomas as it could promote the dissemination of malignant debris in case 71 of an occult malignant lesion<sup>6</sup>. The reported prevalence of occult sarcoma at surgery for a symptomatic leiomyoma ranges from 0.01% to 0.28%<sup>7</sup>. In 2020, the FDA released an 72 73 updated communication reaffirming that laparoscopic power morcellation for myomectomy 74 should be performed only with a tissue containing system (e.g. in-bag morcellation) and only 75 in appropriately selected patients<sup>8</sup>. Therefore, an accurate preoperative diagnosis of myometrial tumors would be essential to plan the surgical route (endoscopy vs laparotomy), 76 77 avoiding worsening the patient's prognosis in case of uterine sarcoma and allowing 78 minimally invasive surgery so as not to increase the patient's morbidity in case of uterine 79 myoma. Moreover, an accurate preoperative differential diagnosis would be crucial even for 80 planning surgical treatment. In fact, while uterine myomas can be treated by myomectomy, 81 uterine sarcomas require total abdominal hysterectomy, oophorectomy and debulking of the 82 tumor outside the uterus<sup>9</sup>.

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

85 particular, ultrasound represents the first-line imaging technique for the assessment of 86 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 87 88 uterine leiomyomas<sup>10</sup>. However, ultrasound has limitations in displaying the global image of large tumors and tissue characterization, and its diagnostic accuracy in the detection of 89 90 uterine sarcomas may be affected by significant overlap in ultrasound appearance between 91 degenerating leiomyoma and malignancy<sup>11</sup>. Moreover, despite ultrasound has been assessed in several studies<sup>12,13</sup>, pooled estimates about its accuracy in the preoperative 92 differentiation between leiomyomas and sarcomas are lacking. As a result, its role in the 93 94 clinical practice is still uncertain.

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

### 98 MATERIALS AND METHODS

#### 99 Study protocol

100 Two authors independently concluded each study step according to an *a priori* defined study 101 protocol. In the case of disagreements, a discussion among all authors was adopted as a 102 solution. The Preferred Reporting Item for Systematic Reviews and Meta-analyses 103 (PRISMA) statement and checklist<sup>14</sup> and the Synthesizing Evidence from Diagnostic 104 Accuracy Tests (SEDATE) guidelines<sup>15</sup> were followed for reporting the whole study.

105

### 106 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".

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

114

### 115 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.

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

### 124 Data extraction

125 We extracted original data from included studies without modification (Table S1). Two by 126 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.

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### 141 **Risk of bias within studies assessment**

The latest Quality assessment of Diagnostic Accuracy Studies (QUADAS-2) was used to 142 assess the risk of bias within studies<sup>16</sup>. In particular, we assessed each included study for 4 143 domains related to risk of bias: 1) Patient selection (i.e. if patients were randomly or 144 145 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 146 147 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 148 149 Timing (i.e. if all patients were assessed with both ultrasound and pathological examination; 150 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

Sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-) and diagnostic odds ratio (DOR), and area under the curve (AUC) on summary receiver operating characteristic (SROC) were calculated for each included study and as pooled estimate. 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 $\leq$ 0.5, low for 0.5<AUC $\leq$ 0.75, moderate for 0.75<AUC $\leq$ 0.9, 162 high for 0.9<AUC<0.97, very high for AUC $\geq$ 0.97, as previously reported<sup>17,18</sup>.

Statistical heterogeneity among the included studies was estimated with the Higgins l<sup>2</sup> statistic; in particular, heterogeneity was categorized as null for l<sup>2</sup>=0%, minimal for  $0\% < l^2 \le 25\%$ , low for 25 < l<sup>2</sup>  $\le 50\%$ , moderate for 50 < l<sup>2</sup>  $\le 75\%$  and high for l<sup>2</sup> > 75\%, as previously reported<sup>19-21</sup>.

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.

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

#### 174 **RESULTS**

#### 175 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<sup>22,23,32–35,24–31</sup>. Of them, 4 studies were excluded because data about suspicion of uterine sarcoma at ultrasound were not reported<sup>22–25</sup>, while 7 studies were excluded because they did not assess patients with uterine leiomyoma <sup>26–32</sup>. Finally, 3 studies were included in both qualitative synthesis and quantitative synthesis<sup>33–35</sup> (Figure 1).

183

### 184 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<sup>34,35</sup> and prospective/retrospective in another one<sup>33</sup>(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.

190 Age of women with uterine leiomyomas ranged from to 29 to 81 years and age of women 191 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 192 193 women with uterine sarcoma were premenopausal. 49.7% (332/668: 95% CI: 45.9%-53.5%) 194 of women with leiomyomas and 56% (135/241; 95% CI: 49.7%-62.3%) with sarcoma were 195 asymptomatic. About symptoms, 13.8% (96/694; 95% CI: 11.3%-16.4%) of women with 196 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 197 198 42.1% (24/57; 95% CI: 29.3%-54.9%) had pelvic/abdominal pain, respectively (Table 2).

In the study by Chiappa *et al.*<sup>34</sup> 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. 203

# 204 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<sup>33,35</sup>. 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<sup>33</sup> and another study at high risk of bias because it did not adopt updated pathological criteria<sup>35</sup>.

- 215 Risk of bias within studies evaluation is graphically shown in Figure 2.
- 216

# 217 Meta-analysis

218In the differential diagnosis between uterine leiomyomas and sarcomas, ultrasound showed219pooled sensitivity of 0.76 (95% CI: 0.70-0.81;  $I^2$ : 94.5%; Figure 3a), specificity of 0.89 (95%220CI: 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%; Figure2213c) and 0.26 (95% CI: 0.07-1.0;  $I^2$ : 96.9%; Figure 3d) respectively, DOR of 23.06 (95% CI:2224.56-116.53;  $I^2$ : 80.2%; Figure 3e), and AUC of 0.8966 (Figure 3f).

#### DISCUSSION

#### 225 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 andsarcomas is a challenging and unsolved issue.

232 In order to improve and standardize ultrasound assessment of uterine lesions, The 233 Morphological Uterus Sonographic Assessment (MUSA) group defined the ultrasound 234 characteristics of uterine fibroids and sarcomas. In fact, a uterine fibroid appears as a well-235 defined round lesion, often showing shadows at the edge of the lesion and/or inside it, with 236 circumferential flow on color- or power-Doppler imaging. On the other hand, uterine 237 sarcomas present as purely myometrial lesions and are typically single, large tumors, with 238 a regular or irregular outline, frequent irregular anechoic areas due to necrosis and irregular 239 vascularization<sup>10</sup> (Figures 4-6). These findings are the result of several studies which 240 described ultrasound appearance and the most common ultrasound signs of uterine 241 sarcomas. In detail, in 2007, Exacoustos et al. suggested that the presence of a single, 242 large, rapidly growing myometrial lesion, with cystic degeneration and with marked 243 peripheral and central vascularization is suggestive of the presence of a uterine 244 leiomyosarcoma<sup>27</sup>. Bonneau *et al.* analyzed ultrasound findings in 85 benign myomas and 245 23 uterine sarcomas of different types, describing that uterine sarcomas appeared more 246 frequently as a single mass with no acoustic shadowing<sup>26</sup>. In 2019, reporting the largest series in the literature, Ludovisi et al. concluded that the ultrasound features suggestive for 247 248 uterine mesenchymal malignancy are the presence of a large myometrial lesion, with inhomogeneous echogenicity, irregular cystic areas, absence of shadows and 249 250 calcifications, in symptomatic women (in particular with abnormal uterine bleeding)<sup>29</sup>. Kim et 251 al. suggested that sarcomas affect mostly women in late reproductive age, are usually larger 252 than 5 cm and show heterogeneous echogenicity and irregular cystic degeneration<sup>28</sup>. A 253 recent systematic review assessed the most frequent ultrasound signs of uterine sarcomas, 254 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<sup>36</sup>.

257 Unfortunately, ultrasound features of uterine sarcomas may be indistinct from those of 258 benign fibroids. In fact, data on the prediction of uterine sarcoma by ultrasound examination 259 are overall scarce and based mainly on small retrospective case series<sup>37</sup>. Moreover, the 260 right prevalence of preoperative ultrasound characteristics suspicious of malignancy in 261 uterine sarcomas is still unclear. Yet, the overall diagnostic accuracy of ultrasound in the 262 preoperative differentiation of uterine leiomyomas and sarcomas was never estimated. 263 Thus, despite the low number of eligible studies, in order to improve the knowledge in the 264 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 265 266 leiomyomas and sarcomas, with a lower sensitivity (76%) than specificity (89%). Our study 267 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<sup>38</sup>. 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.

274 In this scenario of uncertainty and preoperative diagnosis extremely dependent on 275 ultrasound examiner subjective assessment, the implementation of additional and more 276 reproducible tools, such as MRI, radiomics methods and serum biomarkers, and the 277 evaluation of specific symptoms, appears crucial. Chiappa et al. tried to implement the use of radiomics in the ultrasonographic evaluation of uterine mesenchymal masses<sup>34</sup>. However, 278 279 this tool showed a diagnostic performance similar to that of ultrasound demonstrated in our 280 study. Indeed, ultrasonographic radiomics showed a moderate accuracy, with an AUC of 281 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%<sup>35</sup>. 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<sup>39</sup>. Our data seem to support these
 recommendations.

289 Regarding serum tumor markers and risk assessment scores, no reliable preoperative test 290 is available in the clinical practice to differentiate benign and malignant uterine mesenchymal 291 lesions<sup>40</sup>. Lactate Dehydrogenase (LDH) isoenzymes have been studied as a possible tool 292 for preoperative diagnosis, but they still lack validation. In detail, although LDH is considered 293 a nonspecific tumor marker, some of its isoenzymes have been found to be altered in some malignancies, especially in malignancies of the genital tract<sup>41</sup>. In this regard, a mathematical 294 295 index based on analysis of LDH isoenzymes has shown promising results, with a 100% sensitivity and a 99.6% specificity for diagnosing uterine sarcoma<sup>42</sup>. 296

297 Moreover, malignancy should be particularly suspected in cases of tumor growth in 298 postmenopausal women who are not on hormone replacement therapy<sup>43</sup>. Occasionally, the 299 presenting symptoms can be tumor rupture (hemoperitoneum), extrauterine growth (from 300 one-third to one-half of cases) or metastases<sup>44</sup>. On these bases, Kohler et al. proposed a 301 preoperative risk score (pLMS score) for uterine masses undefined or suspicious for 302 leiomyomas or leiomyosarcomas, and tested it on a large cohort through a multicenter 303 retrospective study. In detail, after assessing 13 variables in a multivariable analysis, 304 abnormal uterine bleeding, dysmenhorrea, suspicious sonography and tumor diameter were 305 included in the preoperative risk score as key variables<sup>33</sup>.

Lastly, needle biopsies of suspected myometrial masses have recently been proposed as a novel, accurate, diagnostic tool<sup>45</sup>. 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<sup>46</sup>. Such procedure seems also feasible under ultrasound guidance, as showed by a recent case-series reporting a 100% accuracy<sup>47</sup>.

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.

### 316 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<sup>35</sup>.

However, some major limitations may affect our findings, such as the low number of included 321 322 studies, the retrospective study design and the high heterogeneity in some outcomes (i.e. 323 sensitivity, LR- and DOR). Given these limitations, our meta-analysis should be considered 324 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 325 326 be performed; conversely, an international registry with clear reporting standards could be 327 a sensible approach for improving evidence about such rare conditions. Moreover, despite 328 ultrasound was performed by expert sonographers, another limitation may be the subjectivity 329 of ultrasound assessment and the absence of homogeneous and clearly stated 330 ultrasonographic criteria for malignancy in all included studies. In detail, in two out of three included studies<sup>33,35</sup>, the ultrasonographic suspicion of benignity or malignancy was based 331 332 on a subjective evaluation by an expert sonographer without reporting specific 333 ultrasonographic signs.

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335

## 337 CONCLUSION

- 338 Ultrasound seems to have an only moderate diagnostic accuracy in the differential diagnosis 339 between uterine leiomyomas and sarcomas, with a lower sensitivity than specificity. 340 Therefore, it would not allow to exclude malignancy in the case of a diagnostic uncertainty 341 at ultrasound evaluation, while it would make us more confident in the benign nature of the 342 lesion in the presence of benign ultrasound signs.
- Further studies are encouraged for confirming these findings and improving diagnosticaccuracy of ultrasound for uterine mesenchymal lesions.

# 346 **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.

354

# 355 CONFLICT OF INTEREST STATEMENT

- 356 Authors report no conflict of interest.
- 357

# 358 FUNDING INFORMATION

359 None.

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# 508 LEGENDS FOR TABLES AND FIGURES

509 **Figure 1.** Flowchart of study selection step of the systematic review and meta-analysis 510 (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).

511

512 **Figure 2.** Assessment of risk of bias. Summary of risk of bias for each study; Plus sign: low 513 risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias.

514

**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)

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523 **Figure 4.** Ultrasound image of uterine sarcoma showing a single, large lesion, with a solid 524 component of inhomogeneous echogenicity.

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

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

529

530 **Table 1.** Characteristics of the included studies.

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

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