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1 **Diagnostic accuracy of ultrasound in the differential diagnosis between uterine**
2 **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**

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

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

33 **Data sources:** A systematic review was performed searching 5 electronic databases
34 (MEDLINE, Web of Sciences, Google Scholar, Scopus, and ClinicalTrial.gov) from their
35 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.

40 **Tabulation, Integration and Results:** Sensitivity, specificity, positive and negative
41 likelihood ratios, diagnostic odds ratio, and area under the curve on summary receiver
42 operating characteristic were calculated for each included study and as pooled estimate,
43 with 95% confidence interval. 972 women (694 with uterine leiomyomas and 278 with uterine
44 sarcomas), were included. Ultrasound showed pooled sensitivity of 0.76 (95%CI:0.70-0.81),
45 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
46 (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

53

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 tissue¹.

57 Uterine sarcomas represent 1% of female genital tract malignancies and 3–7% of all uterine
58 malignances², with a prevalence of 0.46%³.

59 Malignant sarcomas comprise leiomyosarcoma, endometrial stromal sarcoma,
60 adenosarcoma and undifferentiated sarcoma⁴. 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 prognosis⁵.

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 workup¹. As a
66 result, an accurate preoperative differential diagnosis appears challenging, with a serious
67 impact on management options (e.g. follow-up, medical therapy, or surgery) and surgical
68 strategy. On these bases, indeed, in 2014, a Food and Drugs Administration (FDA) safety
69 communication warned against the use of the uterine morcellator during minimally invasive
70 surgery of uterine myomas as it could promote the dissemination of malignant debris in case
71 of an occult malignant lesion⁶. The reported prevalence of occult sarcoma at surgery for a
72 symptomatic leiomyoma ranges from 0.01% to 0.28%⁷. In 2020, the FDA released an
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 patients⁸. Therefore, an accurate preoperative diagnosis of
76 myometrial tumors would be essential to plan the surgical route (endoscopy vs laparotomy),
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 uterus⁹.

83 In this scenario, several tools, such as ultrasound, magnetic resonance imaging (MRI) and
84 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
87 technique allows a correct evaluation of the number, volume, location, and vascularity of
88 uterine leiomyomas¹⁰. However, ultrasound has limitations in displaying the global image of
89 large tumors and tissue characterization, and its diagnostic accuracy in the detection of
90 uterine sarcomas may be affected by significant overlap in ultrasound appearance between
91 degenerating leiomyoma and malignancy¹¹. Moreover, despite ultrasound has been
92 assessed in several studies^{12,13}, pooled estimates about its accuracy in the preoperative
93 differentiation between leiomyomas and sarcomas are lacking. As a result, its role in the
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.

97

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 checklist¹⁴ and the Synthesizing Evidence from Diagnostic
104 Accuracy Tests (SEDATe) guidelines¹⁵ were followed for reporting the whole study.

105

106 **Search strategy**

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

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

114

115 **Study selection**

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

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

123

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:

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

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

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

140

141 **Risk of bias within studies assessment**

142 The latest Quality assessment of Diagnostic Accuracy Studies (QUADAS-2) was used to
143 assess the risk of bias within studies¹⁶. In particular, we assessed each included study for 4
144 domains related to risk of bias: 1) Patient selection (i.e. if patients were randomly or
145 consecutively selected for inclusion in the study); 2) Index test (i.e. if ultrasound was
146 unbiased, e.g. exam performed by expert sonographers blinded to ultimate pathological
147 diagnosis); 3) Reference standard (i.e. if pathological examination was unbiased, e.g.
148 blinded evaluation by at least 2 pathologists and updated pathological criteria); 4) Flow and
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).

151 Authors judged each study at “low risk”, “unclear risk” or “high risk” of bias if data about the
152 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 $AUC \leq 0.5$, 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^{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 $0\% < I^2 \leq 25\%$, low for $25 < I^2 \leq 50\%$, moderate for $50 < I^2 \leq 75\%$ and high for $I^2 > 75\%$, as previously
166 reported¹⁹⁻²¹.

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

174 **RESULTS**

175 **Study selection**

176 At the end of the databases searches, 4,491 studies were identified. Duplicates removal and
177 title screening processes led to 671 and 88 studies, respectively. Abstract screening led to
178 14 studies which were evaluated for eligibility^{22,23,32-35,24-31}. Of them, 4 studies were
179 excluded because data about suspicion of uterine sarcoma at ultrasound were not
180 reported²²⁻²⁵, while 7 studies were excluded because they did not assess patients with
181 uterine leiomyoma ²⁶⁻³². Finally, 3 studies were included in both qualitative synthesis and
182 quantitative synthesis³³⁻³⁵ (Figure 1).

183

184 **Studies and patients' characteristics**

185 Included studies assessed a total of 972 women (694 with uterine leiomyomas and 278 with
186 uterine sarcomas) and were observational totally retrospective in two cases^{34,35} and
187 prospective/retrospective in another one³³(Table 1). Proportions between benign and
188 malignant uterine lesions differ from general population due to the need to include the
189 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%-
192 94.1%) of women with uterine leiomyomas and 44.6% (124/278; 95% CI: 38.8%-50.4%) of
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
197 sarcoma showed abnormal uterine bleeding, while 21% (16/76; 95% CI: 11.9%-30.2%) and
198 42.1% (24/57; 95% CI: 29.3%-54.9%) had pelvic/abdominal pain, respectively (Table 2).

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

203

204 **Risk of bias within studies evaluation**

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

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

212 In the “Reference standard” domain, one study was judged at unclear risk of bias because
213 it did not report data³³ and another study at high risk of bias because it did not adopt updated
214 pathological criteria³⁵.

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

216

217 **Meta-analysis**

218 In the differential diagnosis between uterine leiomyomas and sarcomas, ultrasound showed
219 pooled sensitivity of 0.76 (95% CI: 0.70-0.81; I^2 : 94.5%; Figure 3a), specificity of 0.89 (95%
220 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
221 3c) and 0.26 (95% CI: 0.07-1.0; I^2 : 96.9%; Figure 3d) respectively, DOR of 23.06 (95% CI:
222 4.56-116.53; I^2 : 80.2%; Figure 3e), and AUC of 0.8966 (Figure 3f).

223

224 **DISCUSSION**

225 **Main findings and interpretation**

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

230 In the clinical practice, the preoperative differentiation between uterine myomas and
231 sarcomas 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 vascularization¹⁰ (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 leiomyosarcoma²⁷. 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 shadowing²⁶. In 2019, reporting the largest
247 series in the literature, Ludovisi *et al.* concluded that the ultrasound features suggestive for
248 uterine mesenchymal malignancy are the presence of a large myometrial lesion , with
249 inhomogeneous echogenicity , irregular cystic areas , absence of shadows and
250 calcifications, in symptomatic women (in particular with abnormal uterine bleeding)²⁹. 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 degeneration²⁸. 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,

255 heterogeneous echogenicity, no acoustic shadowing, rich vascularization, and cystic
256 changes within³⁶.

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 series³⁷. 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
265 moderate diagnostic accuracy (AUC=0.89) in the differential diagnosis between uterine
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.

268 Therefore, ultrasound does not appear reliable enough in identifying women with uterine
269 sarcoma preoperatively, explaining the risk for occult sarcoma in the clinical practice³⁸. On
270 the other hand, a higher specificity could more consistently detect women with benign
271 lesions. In other words, the accuracy and sensitivity of ultrasound would not allow to exclude
272 malignancy in the case of a diagnostic uncertainty, while its specificity would make us more
273 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
278 of radiomics in the ultrasonographic evaluation of uterine mesenchymal masses³⁴. However,
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.

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

286 leiomyosarcoma from leiomyomas to use of MRI with intravenous contrast, which is
287 recognized as the gold standard technique³⁹. Our data seem to support these
288 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 lesions⁴⁰. 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
294 malignancies, especially in malignancies of the genital tract⁴¹. In this regard, a mathematical
295 index based on analysis of LDH isoenzymes has shown promising results, with a 100%
296 sensitivity and a 99.6% specificity for diagnosing uterine sarcoma⁴².

297 Moreover, malignancy should be particularly suspected in cases of tumor growth in
298 postmenopausal women who are not on hormone replacement therapy⁴³. Occasionally, the
299 presenting symptoms can be tumor rupture (hemoperitoneum), extrauterine growth (from
300 one-third to one-half of cases) or metastases⁴⁴. 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 variables³³.

306 Lastly, needle biopsies of suspected myometrial masses have recently been proposed as a
307 novel, accurate, diagnostic tool⁴⁵. Indeed, preoperative, MRI-guided, percutaneous uterine
308 needle biopsy with microscopic examination or array-comparative genomic hybridization
309 showed a diagnostic accuracy of 94% and 100%, respectively⁴⁶. Such procedure seems
310 also feasible under ultrasound guidance, as showed by a recent case-series reporting a
311 100% accuracy⁴⁷.

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

315

316 **Strengths and limitations**

317 To our knowledge, this may be the first systematic review and meta-analysis to evaluate the
318 diagnostic accuracy of ultrasound in this field. Moreover, the included studies showed a
319 good overall quality as shown by the risk of bias within studies assessment: in fact, only one
320 study was judged at high risk of bias in only one domain³⁵.

321 However, some major limitations may affect our findings, such as the low number of included
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
325 studies. Anyway, given the rarity of uterine sarcomas, prospective studies appear difficult to
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
331 included studies^{33,35}, the ultrasonographic suspicion of benignity or malignancy was based
332 on a subjective evaluation by an expert sonographer without reporting specific
333 ultrasonographic signs.

334

335

336

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.

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

345

346 **CONTRIBUTION**

347 AR (Antonio Raffone), AT, and DN independently assessed electronic search, eligibility of
348 the studies, inclusion criteria, risk of bias, data extraction and data analysis. DR, AR (Arianna
349 Raspollini), MG and AS contributed to the elaboration of methods for risk of bias
350 assessment, data extraction and analysis. AR (Antonio Raffone), DR, AT, DN, DR, LDM,
351 GFZ, RS, PC and MG conceived the study; AR (Antonio Raffone), DR, DN, AR, MG and
352 LDM worked on the design of the study; AR (Antonio Raffone), AT, DN, DR, MG and AS
353 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

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359 None.

360

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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

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

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

522

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

525

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

527

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

529

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

531

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

533

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