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1 **O-RADS MRI Scoring system has the potential to reduce the frequency of avoidable**
2 **adnexal surgery**

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44

45 **Precis**

46 In pelvic masses sonographically indetermined, stratification using O-RADS MRI scoring
47 system could allow avoidance of adnexal surgery in 88.2% of asymptomatic patients without
48 history of infertility.

49

50

51 **Abstract**

52 **Objective:** To assess the potential impact of the O-RADS MRI score on the decision-making
53 process for the management of adnexal masses.

54 **Methods:** EURAD database (prospective, European observational, multicenter study) was
55 queried to identify asymptomatic women without history of infertility included between
56 March 1st and March 31st 2018, with available surgical pathology or clinical findings at 2-year
57 clinical follow-up. Blinded to final diagnosis, we stratified patients into five categories
58 according to the O-RADS MRI score (absent i.e. non adnexal, benign, probably benign,
59 indeterminate, probably malignant). Prospective management was compared to theoretical
60 management according to the score established as following: those with presumed benign
61 masses (scored O–RADS MRI 2 or 3) (follow-up recommended) and those with presumed
62 malignant masses (scored O–RADS MRI 4 or 5) (surgery recommended).

63 **Results:** The accuracy of the score for assessing the origin of the mass was of 97.2%
64 (564/580, CI_{95%} 0.96 – 0.98) and was of 92.0% (484/526) for categorizing lesions with a
65 negative predictive value of 98.1% (415/423, CI_{95%} 0.96 – 0.99). Theoretical management
66 using the score would have spared surgery in 229 patients (87.1%, 229/263) with benign
67 lesions and malignancy would have been missed in 6 borderline and 2 invasive cases. In
68 patients with a presumed benign mass using O-RADS MRI score, recommending surgery for
69 lesions \geq 100 mm would miss only 4/77 (4.8%) malignant adnexal tumors instead of 8 (50%
70 decrease).

71 **Conclusion:** The use of O-RADS MRI scoring system could drastically reduce the number of
72 asymptomatic patients undergoing avoidable surgery.

73 **Keywords:** neoplasms; ovary; magnetic resonance imaging; decision making process;

74
75

76 **Introduction**

77 Balancing the risks and benefits of expectant versus surgical management of adnexal
78 masses is a common challenging dilemma amongst the gynecological community.

79 Ovarian cancer remains the leading cause of death from gynecological neoplasms in
80 developed countries [1]. The lack of effective screening modalities results in the majority of
81 patients being diagnosed at an advanced stage [2]. This is unfortunate since patients with
82 early stage disease limited to the ovary have an excellent prognosis with 95% overall survival
83 at 5 years when compared to patients with advanced-stage disease that have limited survival
84 of 30% at 5 years [3]. The concern of missing or undertreating an early invasive lesion in
85 patients with isolated ovarian masses often leads to avoidable surgical procedures since the
86 majority of ovarian masses will be benign at final pathology [4].

87 Ultrasonography is the first line imaging technique to evaluate adnexal masses but
88 between 18% and 31% of adnexal masses remain indeterminate following ultrasonography
89 using International Ovarian Tumor Analysis (IOTA) Simple Rules or other ultrasonography
90 scoring systems [5]. As demonstrated in the recent publication from Jha et al., O-RADS US
91 in a non-selected population shows a high VPN (US acts as a Gate keeper) but a low PPV of
92 31.4%. Thus, a second line technique is required to limit unnecessary surgeries. On this
93 cohort of selected women by US, MR has largely proven to be the best technique to
94 reclassify as benign masses rated as suspicious or indeterminate at US [6]. Although MRI is
95 the most accurate imaging technique to characterize sonographically indeterminate adnexal
96 masses, with an accuracy >80% [7], MRI remains largely underused, as demonstrated in one
97 study where only 25% of surgeons performed MR imaging before surgery [8].

98 In 2013, an MRI scoring system was developed [9]. The score was based on MRI
99 features with high negative predictive value in distinguishing benign from malignant masses
100 that were considered indeterminate on ultrasonography. This score was prospectively
101 validated in a large multicenter European study (EURAD study), with a high reproducibility
102 and accuracy, and was published as the O-RADS MRI score [10].

103 The objective of this study was to evaluate whether the O-RADS MRI score could
104 potentially optimize patients' management, in particular by limiting the number and the extent
105 of surgical procedures in asymptomatic patients without compromising oncologic safety.

106 **Methods**

107 *Study design and study cohort*

108 The EURAD database was queried to identify asymptomatic women without history of
109 infertility (Infertile women could be advised surgery independently of the presumed nature of
110 the pelvic mass). The EURAD study was a prospective observational European multicentre
111 study conducted between March 1st 2013 and March 31st 2018 where patients underwent a
112 study MRI but patient management followed standard of care. The list of including centers is
113 available in the Supplementary document 1.

114 The study was approved by the « Comité Consultatif sur le Traitement de
115 l'Information en matière de Recherche dans le domaine de la Santé » (approval no 13.090),
116 and by the Ethics Committee of each participating site. All participating women provided
117 written informed consent.

118 This study followed the STROBE (Strengthening the Reporting of Observational Studies in
119 Epidemiology) guidelines as the original publication did (Supplementary document 2).

120

121 *Population*

122 The EURAD database includes 1340 women of whom 1194 were evaluable patients who
123 underwent pelvic MRI to characterize adnexal masses with subsequent pathological
124 diagnosis or 2-year follow-up. We excluded patients with symptoms (n=523), those being
125 managed for infertility at the time of inclusion (n=57), or without a pelvic mass at the time of
126 MRI (disappearance of ultrasonographic described mass) (n=34). Patients were considered
127 symptomatic when they had self – reported symptoms or answered physician questions
128 during initial management. Symptoms could include pain, pelvic heaviness, urinary or

129 digestive symptoms. The final population consisted in 580 patients with a prevalence of
130 malignancy of 14.3% (83/580) (figure 1).

131

132 *Imaging Technique*

133 MRI scans followed study protocol and were acquired on a 1.5 T or 3.0 T machine
134 [10] and included morphological sequences (T2-weighted sequence, T1-weighted before and
135 after fat saturation and T1-weighted sequence after gadolinium injection) and functional
136 sequences (dynamic contrast-enhanced sequence, T1-weighted sequence and diffusion-
137 weighted sequence) as recommended.

138 *Data collection*

139 At each participating center, MRI examinations were prospectively evaluated and readers
140 were asked to categorize each adnexal lesion according to O–RADS MRI classification [9].
141 This scoring system can be accessed online: <http://oradsmricalc.com/>. In cases where the
142 lesion was not located within the adnexa, the lesion was rated O-RADS MRI score 1 and
143 then classified as suspicious or non-suspicious for malignancy. For each patient with more
144 than one lesion, the highest score was retained for analysis.

145

146 *Reference standard*

147 Patient management was decided by a multidisciplinary team according to standard
148 clinical practice in each center, based on standard MRI report, without reference to the O-
149 RADS MRI score. The use of biomarkers such as CA125 was at the discretion of the team
150 managing the patient and usually based on national guidelines. The final diagnosis recorded
151 for each patient was based on pathology or follow-up, as published in the princeps study
152 [10]; if the lesion did not disappear or decrease at imaging follow-up, a minimum of 24
153 months of observation was performed (with or without imaging) from the date of the study
154 MRI. In the EURAD study and in this manuscript, “malignant” refers to invasive and
155 borderline adnexal masses.

156

157 *Statistical analysis*

158 All statistical analyses were performed using R software (version 1.3.1093, available online).
159 Descriptive analysis included frequencies and percentages for qualitative variables and
160 median (interquartile range (IQR)) for quantitative variables. Statistical analysis was based
161 on the Student's t test for continuous variable and the χ^2 test or Fisher's exact test for
162 categorical variables. P – values < 0.05 were considered to denote significant differences.
163 Firstly, we analyzed the accuracy of O-RADS MRI score to determine the origin of the lesion.
164 Secondly, we compared theoretical management by O-RADS MRI score to the prospective
165 management of these patients: patients with a lesion with O-RADS MRI score 2 or 3 or 1
166 non-suspicious were considered as "presumably benign" whilst patients with at least one
167 lesion assigned as O-RADS MRI score 4 or 5 or 1 suspicious were considered as
168 "presumably malignant".

169 **Results**

170 *Final diagnosis*

171 The population included 580 pelvic masses. Adnexal and non-adnexal masses
172 represented 90.7% (526/580) and 9.3% (54/580), respectively. (Table 1).

173 Non-adnexal masses were invasive in 11.1% (6/54) and benign in 88.9% (48/54)
174 (Supplementary Fig. 1). Most of them were solitary lesions (81.5%, 44/54). The origin was
175 uterine (66.7%, 36/54), peritoneal (20.3%, 11/54), urological (1.9%, 1/54), lymphatic (3.8%,
176 2/54), or other (7.4%, 4/54) (Table 1). The sensitivity, specificity, PPV, NPV and accuracy of
177 the score for categorizing the mass as non-adnexal were 79.6% (43/54, CI_{95%} 0.66 – 0.89),
178 99.0% (521/526, CI_{95%} 0.98 – 1.00), 90% (43/48, CI_{95%} 0.77 – 0.97), 98% (521/532, CI_{95%}
179 0.96 – 0.99), 97.2% (564/580, CI_{95%} 0.96 – 0.98) respectively. Ten benign non-adnexal
180 masses (91%, 10/11) (1 adenomyoma, 1 hematoma, 5 uterine fibroids, 1 peritoneal inclusion
181 cyst and 2 indeterminate lesions) and one malignant non adnexal mass (9%, 1/11) (a
182 urothelial carcinoma of 70 mm) were considered as adnexal masses on MRI while 3 benign
183 adnexal lesions (2 serous cystadenomas and 1 functional cyst) and 2 invasive
184 cystadenocarcinomas were considered as non-adnexal masses. These serous and
185 endometrioid cystadenocarcinomas were considered suspicious on MRI and underwent
186 surgery and thus were not considered as missed cancers.

187 Prospective and theoretical management for patients with adnexal masses at final
188 pathological analysis were compared (Fig. 2).

189

190 *Prospective management of patient with adnexal masses (n=526)*

191 Surgery was performed in 340 patients including 18 patients after initial follow up (14
192 benign and 4 malignant corresponding to 2 metastasis, 1 tubal cancer and 1 high grade
193 serous cystadenocarcinoma).

194 Patients with benign lesions who underwent surgery (n = 263) had a laparoscopy in
195 73.0% (192/263) and laparotomy in 27.0% (71/263). These patients underwent salpingo-
196 oophorectomy in 62.7% (165/263) including bilateral procedure in 44.8% (74/165),

197 cystectomy in 23.6% (62/263), total hysterectomy in 14.8% (39/263) including laparotomy in
198 76.9% (30/39), only peritoneal biopsy for pathological analysis before neoadjuvant
199 chemotherapy in 3.8% (10/263), pelvic and/or para-aortic lymphadenectomy in 1.9% (5/263)
200 and omentectomy in 2.7% (7/263).

201 Patients with borderline lesions (n=20) underwent laparotomy in 40% (8/20) and the
202 remaining had laparoscopy (60%, 12/20). Eleven patients underwent radical treatment of the
203 adnexa, including 7 bilaterally.

204 All patients with invasive lesions (n=57) underwent surgery and 52.6% of them
205 (30/57) had laparotomy. Histology includes 16 metastases (16/57, 28%) and 37 tubo-ovarian
206 cystadenocarcinomas (37/57, 64.9%), 14 of whom had extensive non-resectable peritoneal
207 carcinomatosis (14/37, 37.8%).

208 In the prospective contributing study, clinical follow up was the planned standard of
209 care management in 186 patients (186/526, 35.4%) with adnexal lesions, which were all
210 considered benign at final reference standard.

211

212 *Theoretical management of patients with adnexal masses (n=526)*

213 Patients with benign adnexal masses based on the reference standard (n = 449)
214 were considered as presumably benign (true negative) using O-RADS MRI score in 92.4%
215 (415/449) and presumably malignant (false positive) in 7.6% (34/449). Among the 34 women
216 with false positive score, 31 were operated (91.2%) by laparoscopy (n=20) and laparotomy
217 (n=11) in prospective management. This group of 34 patients were menopausal in 58.8%
218 (20/34). Pathological analysis in these 34 patients revealed 10 mature cystic teratomas, 6
219 serous cystadenomas, 5 chronic pelvic inflammatory disease, 5 ovarian fibromas, 4
220 cystadenofibromas, 1 mucinous cyst, 2 benign Brenner tumors and 1 hydrosalpinx.

221 Patients with invasive or borderline adnexal masses were considered as presumably
222 malignant (true positive) using O-RADS MRI score in 89.6% (69/77) and presumably benign
223 in 10.4% (8/77) (false negative). Six out of the 8 women with a false negative score had a
224 borderline lesion (75%) and 2 had an invasive histology (25%) (table 2). Five patients had a

225 single lesion and 3 had two lesions on MRI rated also presumably benign using O-RADS
226 MRI score. The mean size of these lesions was of 88.6 mm (+/- 68.6) including 4 patients
227 with masses larger than 100mm. They were all mixed masses (solid and cystic). Three
228 patients had bi- or multilocular lesions.

229 Thus, the sensitivity, specificity, PPV, NPV, accuracy of the score for predicting
230 malignancy for adnexal masses (n=526) were 89.6% (69/77, CI95% 0.80 – 0.95), 92.4%
231 (415/449, CI95% 0.90 – 0.95), 67.0% (69/103, CI95% 0.57 – 0.76), 98.1% (415/423, CI95%
232 0.96 – 0.99), 92.0% (484/526), respectively.

233

234 *Potential impact of the score on patient with adnexal masses (n=526)*

235 The decision to proceed to surgery did not differ according to menopausal status (p =
236 0.5) (Supplementary table 1). When compared to premenopausal, a significantly higher
237 proportion of menopausal patients underwent non adnexa preserving approach (p < 0.001),
238 by laparotomy (p < 0.001).

239 Prospective management in O-RADS MRI score 2 or 3 masses (presumed benign)
240 was surgery in 56.7% (240/423 including 232 benign and 8 malignant tumors), and non-
241 surgical follow-up in 43.3% (183/423) (Table 3). In the group of patients with presumably
242 benign lesions, surgery was more frequent if the lesion was larger than 100mm (OR= 10.9
243 CI95% 2.7 – 96.5, p < 0.001), had a solid portion in a mixed mass (OR 3.41 CI95% 1.22 -
244 11.79, p = 0.01), solid papillary projections (OR 3.1 CI95% 1.2 - 9.6, p = 0.01), or was bi or
245 multilocular lesion (OR 1.91 CI95% 1.17 - 3.15, p = 0.01). In contrast, patients that were
246 selected for non-surgical follow-up more often had purely cystic lesions (OR 0.38 CI_{95%} 0.25
247 – 0.59; p < 0.001).

248 Prospective and theoretical management using the score were consistent in 214
249 patients with benign lesions (183 correctly classified underwent follow up and 31 false
250 positive underwent surgery) and 69 correctly classified patients with malignant lesions (Table
251 4). Theoretical management using the score would have spared surgery for benign adnexal
252 lesions in 232 patients (88.2%, 232/263). These patients underwent a laparoscopy in 74.1%

253 (172/232) and laparotomy in 25.9% (60/232) following prospective management. Three
254 patients with benign lesions that underwent follow-up by prospective management would
255 have been overtreated by surgery using O-RADS MRI score. O-RADS MRI score
256 misclassified 8 patients as presumably benign who would have wrongly undergone follow-up
257 instead of a surgery for a malignant lesion (6 borderline and 2 invasive).

258 Finally, a strategy combining a lesion size larger than 100mm and a presumed benign
259 O-RADS MRI score would have missed only 4 malignant tumors instead of 8 (50%
260 decrease). This strategy would still permit a reduction of 76.8% (202/263) of nonessential
261 surgeries (benign lesions at final pathological analysis).

262

263

264

265

266 **Discussion**

267 *Main findings*

268 Our study demonstrates that theoretical management of sonographically
269 indeterminate pelvic masses based on O-RADS MRI scoring system would have the
270 potential to allow avoidance of surgery in 88.2% (232/263) of asymptomatic patients without
271 fertility issues with only 8 false negative patients (6 with borderline and 2 with invasive
272 lesions with a median size of 69 mm). When further adding size of 100mm as a critical
273 parameter to stratify for surgery, the number of false negative patients (that would undergo
274 follow-up instead of surgery for a malignancy) would decrease by 50% (4/8), whilst still
275 allowing avoidance of surgery in 76.8% (202/263) of patients.

276 *Interpretation*

277 Recent report by Reding et al. found in a large prospective trial of screening that
278 among ovaries with one simple cyst detected, 53% retained a simple cyst the next year, 34%
279 had no cyst visualized, 7.5% had more than one simple cyst and 5.5% had a more complex
280 cyst present the next year [11]. They also reported the absence of correlation of the
281 occurrence of simple cysts with subsequent development of ovarian cancer. Similar natural
282 history was described in postmenopausal women by Greenlee et al. [12]. The increased use
283 of transvaginal (TVUS) and transabdominal ultrasound (US) as well as computed
284 tomography (CT)-examinations in recent years has resulted in a significant increase in the
285 number of incidentally detected pelvic masses [13]. Our study confirms the ability of MR
286 imaging to reclassify incorrect US origin of a pelvic lesion (accuracy=97.2%) and also to
287 predict benignity (accuracy= 91.1%). Both gynecologists and radiologists agree that most
288 adnexal lesions surgically removed are benign [14], no matter which criteria are elected to
289 decide surgery, and despite international guidelines in this setting. Indeed, in our cohort,
290 among the 449 asymptomatic patients with benign adnexal masses, 186 were followed-up
291 while 263 patients underwent surgery by laparoscopy (n=192) or even by laparotomy (n=71).
292 Pelvic surgery has a well-defined morbidity profile with potentially long term sequelae
293 especially in case of laparotomy [15,16]. The choice of performing laparoscopy or direct

294 laparotomy is mostly conditioned by the evaluated risk of malignancy, which is accurately
295 given by O-RADS MRI score now adopted in French national guidelines [17]. Moreover, even
296 if laparoscopic management of adnexal masses is associated with a lower morbidity, fertility
297 must be considered a main issue for pre-menopausal women [18]. In these asymptomatic
298 patients, immediate indication for surgery such as cystectomy would not be recommended,
299 to minimize the risk of ovarian reserve alteration, especially for cysts larger than 50mm in
300 diameter [19]. In our cohort, according to standard clinical practice, 47 premenopausal
301 patients underwent cystectomy and 40 underwent complete adnexal removal by laparoscopy
302 that could have been avoided with the use of the O-RADS MRI score. Furthermore, even in
303 postmenopausal women, endocrine function of the ovary remains functional for several years
304 and increased mortality has been reported following bilateral oophorectomy mostly due to
305 cardiac events and osteoporosis [20]. In our cohort, according to standard clinical practice,
306 87 menopausal patients underwent bilateral oophorectomy that could have been avoided
307 using the O-RADS MRI score.

308 In our cohort, we found that surgical decisions in clinical practice were mainly based
309 on tumor morphology including size, the presence of solid tissue (papillary projection or
310 nodule) and bi or multilocularity. These criteria are the main (but not only) conventional
311 imaging features to predict malignancy issued from TVUS [21] and have a lower diagnostic
312 value than their combination with functional MR criteria, that explains the high accuracy of O-
313 RADS MRI score. ADNEX model historically demonstrated an individual estimated risk for
314 score 4 about 27-48% and for score 5 about 42%-99%. Recently, IOTA 2-step strategy was
315 demonstrated to predict malignancy in score 4 in 30% and score 5 in only 82% [22] Thus, if
316 these model allows to very accurately avoid malignancy if the mass is classified 1 or 2n they
317 present a poor PPV if the mass is classified 4 and 5. This is the reason why a second line
318 technique is needed to limit the number of unnecessary surgeries. In this setting, our study
319 demonstrates that theoretical management based on the score and prospective
320 management were highly concordant for malignant masses but mainly discordant for benign
321 masses with a potential of the O-RADS MRI score to allow an appropriate decrease in the

322 number of surgical procedures. Indeed, in 263 patients with a benign mass who underwent
323 surgery, 88.2% (232/263) were correctly assessed as presumably benign by O-RADS MRI
324 score and could have undergone follow-up. This is in line with the findings of Byrne et al. that
325 reported in a 2964 cohort patients with suspicion of ovarian lesion, the proportion of ovarian
326 malignancies was low (only 8%) but without presuming the possible management of these
327 patients in their work [14]. By applying an additional criterion of 100mm to the O-RADS MRI
328 score, we would reduce by 50% the number of missed malignancies. This cut-off is relevant
329 as it is also used in the IOTA classification as well as many other models apply to define
330 indeterminate masses [23,24]. Very large tumors (>100mm) result in difficult interpretation of
331 any imaging modality and should be referred for surgery even if the patient is asymptomatic,
332 as demonstrated in our study.

333 In our cohort, 34% of radical surgeries were performed in patients with benign lesions
334 that could have undergo conservative treatment by cystectomy. However, it has been
335 reported that even in patients with borderline or invasive tumors, the risk of inappropriate
336 procedures is real, with incomplete staging in 16% and 50% of cases, respectively [8]. Thus,
337 as recently underlined in a report on quality indicators in ovarian cancer surgery [25],
338 preoperative diagnosis of malignant tumors has an important role to transfer a patient to a
339 reference center.

340 *Strength and limitations*

341 Firstly, we defined “non-essential” surgery as surgery performed in asymptomatic
342 patients with presumed benign lesions (O-RADS MRI 2 or 3) without history of infertility.
343 However, some surgical indications are based on 1) the patients’ wish to undergo surgery (or
344 not). Indeed, patients’ preference was not collected but could have biased the number of
345 surgeries performed based solely on the score. 2) the concrete inability to undergo follow-up
346 (with the risk of loss to follow-up) and 3) the acceptance of some risks of complications in
347 follow-up cases such as torsion or hemorrhage [26]. Studies in patients who were included in
348 screening ovarian cancer trials demonstrated the psychological cost of undergoing intense
349 surveillance [27]. Surgery remains an option in patients (or physician) not willing to undergo

350 follow up. Moreover, there is a risk of torsion, as reported in the literature, even if this risk is
351 low (<1%) [28]. Secondly, we used only the O-RADS MRI score at baseline for the
352 theoretical decision-making process without considering other parameters such as the
353 Cancer Antigen 125 (CA125) level or HE4/ROMA score [29]. Thirdly, in patients with O-
354 RADS MRI 3 lesions (probably benign), the modality and timing of follow-up are not
355 determined yet. The two trials currently in process explore the potential benefit of O-RADS
356 MRI score in prospective management [30,31].

357

358 **Conclusion**

359 Our study demonstrates that management of sonographically indeterminate pelvic
360 masses based on O-RADS MRI score would allow avoidance of non-essential surgical
361 procedures in 88.2% of patients. When further adding size of greater than 100 mm as an
362 indication for surgery, the number of false negatives based on MRI (patients that would
363 undergo follow-up instead of surgery for a malignancy) would decrease by 50%. Further
364 studies, including prospective randomized trials are essential to evaluate its full potential in
365 the decision-making process.

366

367 **Aknowledgment: /**

368

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