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Short title: O-RADS MRI score to spare avoidable adnexal surgeries

Precis

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

Abstract

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

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

Results: The accuracy of the score for assessing the origin of the mass was of 97.2% (564/580, $CI_{95\%}$ 0.96 – 0.98) and was of 92.0% (484/526) for categorizing lesions with a negative predictive value of 98.1% (415/423, CI95% 0.96 – 0.99). Theoretical management using the score would have spared surgery in 229 patients (87.1%, 229/263) with benign lesions and malignancy would have been missed in 6 borderline and 2 invasive cases. In patients with a presumed benign mass using O-RADS MRI score, recommending surgery for lesions >= 100 mm would miss only 4/77 (4.8%) malignant adnexal tumors instead of 8 (50% decrease).

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

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

Introduction

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

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

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

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

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

Methods

Study design and study cohort

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

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

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

Population

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

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

Imaging Technique

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

Data collection

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

Reference standard

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

Statistical analysis

All statistical analyses were performed using R software (version 1.3.1093, available online). Descriptive analysis included frequencies and percentages for qualitative variables and median (interquartile range (IQR)) for quantitative variables. Statistical analysis was based on the Student's t test for continuous variable and the $\chi 2$ test or Fisher's exact test for categorical variables. P – values < 0.05 were considered to denote significant differences.

Firstly, we analyzed the accuracy of O-RADS MRI score to determine the origin of the lesion. Secondly, we compared theoretical management by O-RADS MRI score to the prospective management of these patients: patients with a lesion with O-RADS MRI score 2 or 3 or 1 non-suspicious were considered as "presumably benign" whilst patients with at least one lesion assigned as O-RADS MRI score 4 or 5 or 1 suspicious were considered as "presumably malignant".

Results

Final diagnosis

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Prospective management in O-RADS MRI score 2 or 3 masses (presumed benign) was surgery in 56.7% (240/423 including 232 benign and 8 malignant tumors), and non-surgical follow-up in 43.3% (183/423) (Table 3). In the group of patients with presumably benign lesions, surgery was more frequent if the lesion was larger than 100mm (OR= 10. 9 CI95% 2.7 – 96.5, p < 0.001), had a solid portion in a mixed mass (OR 3.41 CI95% 1.22 - 11.79, p = 0.01), solid papillary projections (OR 3.1 CI95% 1.2 - 9.6, p = 0.01), or was bi or multilocular lesion (OR 1.91 CI95% 1.17 - 3.15, p = 0.01). In contrast, patients that were selected for non-surgical follow-up more often had purely cystic lesions (OR 0.38 $CI_{95\%}$ 0.25 – 0.59; p < 0.001).

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

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

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

Discussion

Main findings

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

Interpretation

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

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

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

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

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

Strength and limitations

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

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

Conclusion

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

Aknowledgment: /

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Tables / Figures caption list

Table 1: Description of pelvic masses

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Table 3: Characteristics of the patients with O–RADS MRI presumed benign lesions, by prospective management

Table 4: Comparison of prospective and theoretical management

Figure 1: Flow chart of the study

Figure 2: Prospective and Theoretical management according to O–RADS MRI score in the 526 patients with asymptomatic adnexal masses and no history of infertility. B: Benign. BL: Borderline. I: Invasive.

Supplementary Figure 1: MRI performance for the diagnostic of non-adnexal masses

Supplementary Table 1: Characteristics of the surgical procedure by menopausal status

Supplementary Document 1: List of including centers in the EURAD study

Supplementary Document 2: STROBE Checklist