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Original Research

Rapid rate of growth in adnexal masses, despite benign appearance on ultrasound, was associated with malignancy. A retrospective analysis of 48 consecutive cases from a single institution

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Background: To compare the rate of malignancy in adnexal masses with benign appearance on ultrasound and low Risk of Malignancy Index (RMI) based on their rate of growth. *Methods*: All patients in our obstetrics and gynecology practice undergoing surgery between 2015 and 2020 for adnexal masses with only benign appearance on ultrasound were analyzed. Ultrasound findings of the adnexa up to 3 years prior to surgery, cancer antigen 125 (CA-125) levels and RMI were evaluated. *Results*: Patients ranged in age from 22 to 84. All adnexal masses appeared benign on ultrasound using International Ovarian Tumor Analysis (IOTA) *Simple Rules*. CA-125 levels ranged from 4 to 127 U/mL. The RMI ranged from 7 to 127 (200 is indicative of malignancy). Ultrasound findings up to three years prior to surgery were available for 43 patients. In 39 patients, the adnexal mass grew slowly, and the histopathology was benign. In 4 patients, the adnexal mass grew rapidly (increased in size by more than 50% or first appeared in 6–12 months prior to surgery), and all were found to have borderline or early stage ovarian/tubal carcinomas. The rate of malignancy was 9.3%. *Conclusions*: Despite benign appearance on ultrasound and low RMI, adnexal masses with a rapid rate of growth were associated with a risk of malignancy of 9.3%.

Keywords

Adnexal mass; Risk of malignancy index; IOTA *Simple Rules*; Benign ovarian mass; Adnexal ultrasound

1. Introduction

Adnexal masses are a common problem facing obstetricians/gynecologists in practice and although most of these masses will prove to be benign, it is important to identify the ones more likely to be malignant while avoiding overtreatment of those likely to be benign. Masses with a high likelihood of being malignant require rapid further evaluation and proper surgical planning, either primary referral to a gynecologic oncologist, intra-operative surgical consultation as deemed necessary, or a discussion with the patient that a second surgery may be needed if the mass is found to be malignant [1].

The discrimination between benign and malignant adnexal masses has long been challenging and findings such as pelvic exam, tumor marker, and diagnostic imaging (i.e., computer tomography (CT) scan, ultrasound, MRI) taken alone have inadequate sensitivity and specificity [2, 3].

Efforts to improve on discrimination of individual tests led to the development of algorithms combining tumor markers, clinical factors, and ultrasound findings. One such algorithm is the Risk of Malignancy Index (RMI), initially described by Jacobs *et al.* [4] in 1990. This index uses the CA-125 level, menopausal status and ultrasound features to calculate a score above which the likelihood of malignancy is higher. A higher score is associated with menopausal status, higher CA-125 levels and ultrasound findings such as bilaterality, solid areas, multilocularity, and ascites. The RMI 1 of Jacobs *et al.* [4] with a cut-off of 200 showed a sensitivity of 85% and specificity of 97% in discriminating between malignant and benign lesions. The Risk of Malignancy Index 1 and subsequent modifications are simple, practical, and sensitive tools which have entered clinical practice after being studied and validated in larger patient cohorts [5–9].

Among imaging modalities, transvaginal ultrasound remains the method of choice for evaluating adnexal masses, based on its ease, availability, and patient tolerance. Other methods, such as CT scan and MRI, are not superior for the initial evaluation and are reserved for further evaluation in patients when the suspicion for malignancy is high to assess for lymph node enlargement, peritoneal disease, or possible distant metastases [3, 10–12].

Many research efforts have been made into using ultrasound morphologic criteria and scoring algorithms to differentiate between benign and malignant adnexal masses. In 2005, the International Ovarian Tumor Analysis (IOTA) group described two models (M1 and M2) based on a logistic regression analysis of clinical and ultrasound parameters collected in a standard fashion in a large patient cohort by experienced sonographers in a small number of centers using

a common protocol. The larger model M1, using 12 parameters, achieved a sensitivity of 93% and a specificity of 76% in distinguishing between benign and malignant masses [13]. To obtain a simpler and clinically useful model, the IOTA group found in a later analysis that 10 of the ultrasound parameters had the highest predictive value and were easily and widely applicable. This set of 10 ultrasound findings—the *Simple Rules*—was published in 2008 [14]. Five were indicative of benign masses: unilocular; solid components with the largest being <7 mm; smooth; multilocular with largest diameter <10 cm; presence of acoustic shadows; no blood flow. The other five were indicative of malignancy: irregular solid tumor; presence of ascites; >4 papillary structures; irregular multilocular solid tumor with largest diameter >10 cm; strong blood flow signal.

Several studies have validated the *Simple Rules* prospectively [15, 16] and a 2014 systematic review and meta-analysis found the IOTA *Simple Rules* algorithm to be the best risk assessment algorithm, with a sensitivity of 0.93 [95% confidence interval (CI), 0.89–0.95] and a specificity of 0.81 [95% CI, 0.76–0.85] based on pooled data [17]. One drawback of the *Simple Rules* is that approximately 25% of adnexal masses cannot be classified, either because none of the rules apply or because rules from both benign and malignant categories apply. Despite this drawback, the *Simple Rules* remain one of best simple tools to assess 75% of adnexal masses for the likelihood of being benign or malignant [18].

Among adnexal masses judged to be benign according to ultrasound appearance, using different models including the IOTA *Simple Rules*, the risk of malignancy is very low (less than 1–8%) [19–21]. The rate at which a benign-appearing adnexal mass grows has not been described as a risk factor for malignancy and this observation is the basis of this report.

2. Methods

All patients in our obstetrics and gynecology group practice found to have a presumably benign adnexal mass requiring surgery between 2015 and 2020 were reviewed for the evaluation. Patients with presumably malignant adnexal masses were referred directly for surgery in gynecologic oncology centers and were not considered for the analysis. Forty-eight masses were classified as benign according to ultrasound findings using IOTA *Simple Rules* and formed the study group. Benign masses could have only benign criteria and none of the malignant. Benign criteria are: unilocular masses; masses with solid components the largest being <7 mm; smooth, multilocular masses with a maximum diameter <10 cm; presence of acoustic shadows and no blood flow. Approximately 10 masses, presumably benign, could not be classified according to the *Simple Rules* and were not included in the analysis.

Benign-appearing masses were initially followed by ultrasound, if asymptomatic and small (<3 cm). The indications for surgery included patient symptoms (pain, pressure, abnormal bleeding), persistence or changes on ultrasound (i.e., growth or morphologic features).

Ultrasound exams were performed by the three practice partners (gynecologists each having over 15 years of sonography training and experience) following a generally standard procedure. The exam was begun transvaginally with a General Electric (GE) Voluson, 730 Pro or Voluson E6 6.5 MHz transvaginal probe and if the mass was too large to be assessed transvaginally, a transabdominal approach was performed. Color Doppler was performed at low velocity (5–10 cm/s), low pulse repetition frequency and high sensitivity settings.

A total of forty-eight consecutive cases meeting the criteria were found and included in the evaluation. Because of its retrospective chart review nature of data which is anonymous and personally unidentifiable, IRB and ethics approval was not required.

Ultrasound findings of the adnexa up to 3 years prior to surgery and CA-125 levels when available were reviewed. The ultrasound findings (adnexal mass morphology) were assessed by the authors and described according to standard terminology and definitions as described by Timmerman *et al.* [22] in 2000.

A Risk of Malignancy Index was calculated using the following formula: RMI 2 (Risk of Malignancy Index) = M × U × CA-125 according to Tingulstad *et al.* [5], where M (menopausal score) is 1 point for premenopausal patients or 4 points for postmenopausal patients. Menopause is defined as >1 yr amenorrhea or age >50 if status post hysterectomy. The ultrasound score (U) is based on the ultrasound morphologic criteria: bilaterality, solid areas, multilocularity, ascites and metastases. For 0–1 criteria, U = 1, for >2 criteria, U = 4. CA-125 levels are measured in U/mL. CA-125 levels were not performed in every patient, but rather at the discretion of the treating physicians.

A rapid rate of growth was defined when a mass increased in size by more than 50% in 6–12 months or when a mass felt to indicate surgery first appeared 6–12 months prior to surgery.

3. Results

Between 2015 and 2020, forty-eight patients in our obstetrics and gynecology group practice (consecutive cases) were operated for adnexal masses benign in appearance on ultrasound according to IOTA *Simple Rules.* Patient characteristics, types of surgery performed, and histology results are shown in Table 1 (Ref. [5, 14]). CA-125 levels, when performed, and the Risk of Malignancy Index 2 [5] are also reported in Table 1. Small, asymptomatic, benign-appearing masses were followed initially with serial ultrasound. Once patients became symptomatic or masses grew larger than 3 to 4 cm, the indication for surgery was made. The histology confirmed benign pathology such as endometriosis, benign teratoma, cystadenoma etc. in most cases.

Table 1. Adnexal mass ultrasound findings, CA-125, risk of malignancy index, surgery performed and histology.

Case number	Menopausal status	Histology	Ultrasound 0–6 mo prior	Ultrasound 6–12 mo prior	Ultrasound 12–18 mo prior	Ultrasound 18–24 mo prior	Ultrasound 24–36 mo prior	CA-125 (U/mL)	Risk of Malignancy Index 2 (Tingulstad *et al.* [5])
1	Pre-menopausal	Mucinous Ov CA pT1aN0L0V0G3	9 cm B2 Adnexal mass		Adnexal ultrasound wnL	Adnexal ultrasound wnL		127	1 × 1 × 127 = 127
2	Post-menopausal	Serous borderline tumor of left ovary pT1a	4.5 cm B2 Adnexal mass	3.0 cm B2 Adnexal mass	Adnexal ultrasound wnL			25	4 × 1 × 25 = 100
3	Pre-menopausal	Left ovarian endometriosis cyst	5.3 cm B3 Adnexal mass	4.0 cm B3 Adnexal mass				N/A	
4	Pre-menopausal	Left ovarian endometriosis cyst		3.0 cm B3 Adnexal mass		2.2 cm B1 Adnexal mass		N/A	
5	Post-menopausal	Right ovary with adenomatoid and mesothelial hyperplasia and serosal cyst	2.8 cm B1 Adnexal mass		2.2 cm B1 Adnexal mass	2 cm B1 Adnexal mass		N/A	N/A
6	Post-menopausal	Para-ovarian cyst right	3 cm B1 Adnexal mass	3 cm B1 Adnexal mass	2.8 cm B1 Adnexal mass			12	4 × 1 × 12 = 48
7	Pre-menopausal	Right ovarian dermoid cyst	5.3 cm B4 adnexal mass		4 cm B4 adnexal mass			N/A	
8	Post-menopausal	Left ovarian cystadenoma	2.6 cm B1 Adnexal mass		1.8 cm B1 Adnexal mass			N/A	
9	Pre-menopausal	Bilateral ovarian dermoid cysts	3.8 cm B3 Adnexal mass		3 cm B3 adnexal mass			N/A	
10	Post-menopausal	Right ovary with serous inclusion cyst	5.3 cm B4 adnexal mass					N/A	
11	Pre-menopausal	Left ovarian endometriosis cyst	7 cm B2 + B3 Adnexal mass	6.3 cm B2 + B3 Adnexal mass	2.8 cm B3 Adnexal mass			N/A	
12	Pre-menopausal	Left ovarian endometriosis cyst	3.4 cm B3 adnexal mass	3.1 cm B3 adnexal mass	2.9 cm B3 adnexal mass	3 cm B1 adnexal mass	2.5 cm B1 adnexal mass	65	1 × 1 × 65 = 65
13	Pre-menopausal	Right ovarian dermoid cyst	5.3 cm B3 adnexal mass		2.59 cm B3 adnexal mass		1.7 cm B3 + B5 adnexal mass	N/A	
14	Pre-menopausal	Serous papillary cystadenoma of the left ovary	3.4 cm B4 adnexal mass		3.4 cm B4 adnexal mass		3.1 cm B1 adnexal mass	N/A	
15	Post-menopausal	Left ovarian mucinous cystadenoma	3.8 cm B4 adnexal mass	3.6 cm B1 adnexal mass	3.8 cm B1 adnexal mass		3.3 cm B1 adnexal mass	9	4 × 1 × 9 = 36
16	Pre-menopausal	Left ovarian endometriosis cyst	5.5 cm B3 adnexal mass		5 cm B3 adnexal mass			N/A	
17	Post-menopausal	Right serous ovarian cyst	5.5 cm B1 Adnexal mass		5.2 cm B1 Adnexal mass		4.7 cm B1 Adnexal mass	N/A	
18	Pre-menopausal	Ovarian theca luteal cyst	5.4 cm B4 Adnexal mass		4 cm B4 Adnexal mass	3.4 cm B4 Adnexal mass	3.1 cm B1 Adnexal mass	N/A	
19	Pre-menopausal	Ovarian endometriosis cyst	3.5 cm B3 Adnexal mass		2.9 cm B3 Adnexal mass			N/A	
20	Pre-menopausal	Right para-ovarian cyst	4.3 cm B3 Adnexal mass		4.2 cm B3 Adnexal mass		3 cm B1 Adnexal mass	N/A	

Table 1. Continued.

Case number	Menopausal status	Histology	Ultrasound 0–6 mo prior	Ultrasound 6–12 mo prior	Ultrasound 12–18 mo prior	Ultrasound 18–24 mo prior	Ultrasound 24–36 mo prior	CA-125 (U/mL)	Risk of Malignancy Index 2 (Tingulstad *et al.* [5])
21	Pre-menopausal	Benign ovarian cystic teratoma	3.8 cm B2 Adnexal mass	3 cm B2 Adnexal mass				7	1 × 1 × 7 = 7
22	Post-menopausal	Right ovarian fibroma	3.2 cm B1 Adnexal mass		2.8 cm B3 Adnexal mass		2.6 cm B3 Adnexal mass	8	4 × 1 × 8 = 32
23	Post-menopausal	Right ovarian cystadenoma	4.9 cm B4 Adnexal mass		4 cm B1 adnexal mass			N/A	
24	Pre-menopausal	Serous borderline tumor of the right ovary, pT1a NxL0V0R0	6 cm B2 Adnexal mass		Adnexal ultrasound wnL			N/A	
25	Pre-menopausal	Right ovarian mucinous adenofibroma	3.8 cm B2 adnexal mass		3.1 cm B1 adnexal mass		3.2 cm B1 adnexal mass	26	1 × 1 × 26 = 26
26	Pre-menopausal	Right ovarian desmoid cyst	3.2 cm B3 adnexal mass	3.0 cm B3 adnexal mass				N/A	
27	Pre-menopausal	Sactosalpinx bilaterally	7 cm and 4 cm B1 Adnexal masses	7 cm and 3.5 cm B1 adnexal masses	6.6 cm and 4 cm B1 adnexal masses			N/A	
28	Post-menopausal	Simple cyst	4.6 cm B4 adnexal mass	4.3 cm B4 adnexal mass	4.2 cm B4 adnexal mass		2.7 cm B1 adnexal mass	N/A	
29	Post-menopausal	Hyalinized follicular cyst	3.8 cm B4 adnexal mass	Same	2.9 cm B1 adnexal mass		Same	N/A	
30	Pre-menopausal	Endometriosis cyst	5.6 cm B3 adnexal mass	Same		Same	6 cm B3 adnexal mass	26	1 × 1 × 26 = 26
31	Post-menopausal	Serous cyst adenofibroma of the right ovary	6.7 cm B1 adnexal mass	5.7 cm B1 adnexal mass	5.7 cm B1 adnexal mass			4	4 × 1 × 4 = 16
32	Post-menopausal	Serous cystadenoma of the right ovary	3.2 cm B1 adnexal mass		2.8 cm B1 adnexal mass		1.9 cm B1 adnexal mass	N/A	
33	Post-menopausal	Tubal hydatid cyst	4 cm B1 adnexal mass	5 cm B1 adnexal mass				N/A	
34	Post-menopausal	Serous adenofibroma of both ovaries	1 cm and 3 cm B1 adnexal masses					18	4 × 1 × 18 = 72
35	Post-menopausal	Corpus albicans cysts bilaterally	1.7 and 1.9 cm B3 Adnexal masses					N/A	
36	Pre- menopausal	Right ovary with serosal cyst, left paratubal cyst	6.6 cm B3 adnexal Adnexal mass					N/A	
37	Pre-menopausal	Mucinous cystadenoma	6 cm B3 Adnexal mass					N/A	
38	Pre-menopausal	Left ovarian pseudocyst	9 cm B4 adnexal mass	8.8 cm B4 + B5 adnexal mass				N/A	
39	Post-menopausal	Serous fallopian tube cancer pT2pN0M0G3	9 cm B4 adnexal mass	Same	Adnexal ultrasound wnL	Adnexal ultrasound wnL		24	4 × 1 × 24 = 96
40	Pre-menopausal	Left ovarian endometriosis cyst	4.5 cm B3 + B5 adnexal mass	3.2 cm B3 adnexal mass				21	1 × 1 × 21 = 21
41	Pre-menopausal	Left ovarian endometriosis cyst	8 cm B3 adnexal mass	6.9 cm B3 adnexal mass	5.2 cm B3 adnexal mass			N/A	

Table 1. Continued.

Case number	Menopausal status	Histology	Ultrasound 0–6 mo prior	Ultrasound 6–12 mo prior	Ultrasound 12–18 mo prior	Ultrasound 18–24 mo prior	Ultrasound 24–36 mo prior	CA-125 (U/mL)	Risk of Malignancy Index 2 (Tingulstad *et al.* [5])
42	Pre-menopausal	Benign hemorrhagic ovarian cyst	8 cm B4 adnexal mass	8 cm B4 adnexal mass				N/A	
43	Pre-menopausal	Benign ovarian cystic teratoma	7.4 cm B3 + B5 adnexal mass		7 cm B3 + B4 adnexal mass			29	1 × 1 × 29 = 29
44	Pre-menopausal	Benign ovarian mesothelial cyst	4.5 cm B2 adnexal mass	4.7 cm B2 adnexal mass	4.5 cm B2 adnexal mass			13	1 × 1 × 13 = 13
45	Post-menopausal	Benign right ovarian cyst, not otherwise classified	7 cm B1 adnexal mass		6 cm B1 adnexal mass			13	4 × 1 × 13 = 52
46	Post-menopausal	Left functional ovarian cyst	5.3 cm B1 adnexal mass	5 cm B1 adnexal mass	3.7 cm B1 adnexal mass			N/A	
47	Post-menopausal	Right ovarian serous cystadenoma	4.3 cm B4 adnexal mass		4 cm B4 adnexal mass		3 cm B1 adnexal mass	N/A	
48	Post-menopausal	Left ovarian serous cystadenoma	3.3 cm B4 adnexal mass	3.8 cm B4 adnexal mass	3.4 cm B4 adnexal mass			N/A	

Classification according to 10 *Simple Rules* (Timmerman, Testa, Bourne *et al.* 2008) [14]. If one or more B-rules apply in the absence of an M-rule, the mass is classified as benign. If no rule applies, the mass cannot be classified with the 10 simple rules.

B1 = Unilocular;

B2 = Presence of solid components, where the largest solid component has a diameter <7 mm;

B3 = Presence of acoustic shadows;

B4 = Smooth multilocular tumor with largest diameter <100 mm;

B5 = No blood flow (color score 1).

Masses were generally measured in 3 dimensions. The largest diameter is reported and used in the analysis.

Risk of Malignancy Index 2 (Tingulstad *et al.* 1996) [5] is calculated according to the following formula: CA-125 (U/mL) × Menopausal Status (M) × Ultrasound score (U), where:

M = 1 if premenopausal and 4 if postmenopausal;

U = 1 if ≤ 1 ultrasound feature;

4 if ≥ 2 ultrasound features.

Menopause is defined as either amenorrhea >1 year or age >50 if patient had a hysterectomy. Ultrasound features include bilaterality, solid areas, multilocularity, ascites and metastases.

Patients ranged in age from 22 to 84; 27 were premenopausal and 21 were postmenopausal. All adnexal masses appeared benign on ultrasound using IOTA *Simple Rules* [14]. Masses were generally measured in three dimensions. The largest diameter in centimeters is reported and used in the analysis. CA-125 levels ranged from 4 to 127 U/mL. The Risk of Malignancy Index 2 ranged from 7 to 127 and was never above 200 (indicative of malignancy).

Ultrasound findings up to three years prior to surgery were available for 43 patients. These findings (at 0–6 months, 6–12 months, 12–18months, 18–24 months and 24–36 months prior to surgery) are also reported in Table 1. In 39 of these patients, the adnexal mass was present and growing slowly (increased in size $<$50%) over several months prior to surgery. The surgical histology in these patients was benign.

In the other 4 patients, the adnexal mass grew rapidly—either increasing in size $>$50% over 6–12 months prior to surgery or first appearing 6–12 months prior to surgery. Two of these patients were premenopausal (aged 40–50), the other two were postmenopausal (aged 65–75). In three of the four patients, the benign-appearing mass measured 6 to 9 cm in largest diameter at presentation and had not been present on an ultrasound 6 to 12 months prior. In the other patient, the mass measured 3cm in largest diameter at initial presentation and had grown to 4.5 cm 3–6 months later. Surgery was performed either due to pain or size greater than 3–4 cm. In these four patients, all were found to have borderline or early stage ovarian or tubal carcinomas. The rate of malignancy was 9.3%.

4. Discussion

The management of adnexal masses is dependent on the symptoms they produce as well as on their likely nature (benign versus suspicious for malignancy). Much research has been dedicated to determining which clinical factors, imaging modalities and laboratory markers can best distinguish the nature of adnexal masses. Among imaging modalities, transvaginal ultrasound remains the best first-line method due to its convenience, ease of use and ability to distinguish likelihood of malignancy based on certain morphologic criteria. CT scan and MRI have been shown to have higher specificity but lower sensitivity than ultrasound at predicting malignancy [3, 11] and are better suited for evaluating extent of disease if suspicion is high for malignancy.

Diagnostic algorithms which have been found to have a high sensitivity and specificity for differentiating benign from malignant adnexal masses include the Risk of Malignancy Index (RMI). First described in 1990 by Jacobs *et al.* [4], the RMI 1 is calculated using the product of the serum CA-125 level (U/mL), the ultrasound scan result (expressed as a score of 0, 1 or 3 depending on ultrasound findings) and the menopausal status score (1 if premenopausal and 3 if postmenopausal). Ultrasound findings included bilaterality, solid areas, multilocularity, ascites and metastases. If no abnormality was found, the score was 0. For one abnormality, the score was 1 and for 2 or more abnormalities, the score was 3. Menopause was defined as one year of amenorrhea or the age of 50 for women who had had a hysterectomy. The RMI 1 with a cut-off of 200 showed a sensitivity of 85% and specificity of 97% in discriminating between malignant and benign lesions.

Several modifications of the Risk of Malignancy Index have been developed to improve on sensitivity and specificity. Tingulstad *et al.* [5] described the RMI 2 in 1996, which is calculated similarly to the RMI 1, but differing in weight of the ultrasound score (1 if $\leq$1 ultrasound feature and 4 if $\geq$2 ultrasound features) and the menopausal status (1 if premenopausal and 4 if postmenopausal). The RMI 3 was another modification by Tingulstad described in 1999 [6] and the RMI 4 was developed by Yamamoto in 2009 [7]. Several prospective studies and systematic reviews comparing the four indices have since been published. In 2009, Geomini *et al.* [8] found the RMI 1 and 2, both with a cut-off of 200, to be the best predictors with an estimated sensitivity of 78% [95% confidence interval (CI), 0.71–0.85] and a specificity of 87% [95% CI, 0.83–0.91] for malignancy. In 2014, Yamamoto *et al.* [9] found RMI 2 to have the highest sensitivity for malignancy, and RMI 2 and 4 to have similar ability to distinguish between benign and malignant adnexal masses. Because of these considerations, we chose to use the RMI 2 in our analysis. None of the patients in our analysis had a RMI 2 above 200.

Another algorithm based on ultrasound criteria alone is called the IOTA *Simple Rules* and was developed by the IOTA group in 2008. Five were indicative of benign masses: unilocular; solid components less than 7 millimeters; smooth, multilocular less than 10 centimeters; presence of acoustic shadows; no blood flow. The other five were indicative of malignancy: irregular solid tumor; presence of ascites; more than 4 papillary structures; irregular, solid tumor greater than 10 centimeters; strong blood flow signal. The IOTA *Simple Rules* have high sensitivity (0.93) and specificity (0.81) as found by a systematic review and meta-analysis in 2014 [8]. Furthermore, they are easy to apply and approximately 75% of adnexal masses can be classified with a high likelihood either as benign or malignant. For a quantification of risk of malignancy, the IOTA group published new data in 2016 showing that the *Simple Rules*, if applicable, individually or in certain combinations, can accurately estimate an individual patient's risk of malignancy [19]. We chose to use the IOTA *Simple Rules* to assess the ultrasound morphology of the adnexal masses and only those masses which could be classified by the *Simple Rules* and which were judged to be benign were included.

Adnexal masses predicted to be benign according to these diagnostic algorithms have an extremely low likelihood of being malignant and can in general be followed by serial ultrasound if patients are asymptomatic. The unexpected finding of malignancy after surgery for an anticipated benign adnexal mass led to this evaluation and review of the literature. In two

large series of unilocular adnexal masses followed with ultrasound, the rate of malignancy was less than 1% and factors associated with malignancy were menopausal status, history of breast and ovarian cancer, as well as the development of abnormal morphologic features on ultrasound [19, 20]. Furthermore, the authors noted that intra-cystic solid structures were indeed found by pathology after removal and may have been missed on ultrasound, making a point for careful ultrasound evaluation prior to surgery looking specifically for intra-cystic solid/papillary structures.

A factor which we noted to be associated with malignancy in our consecutive series of patients operated for benign appearing adnexal masses was the rate of growth. Patients in whom the adnexal mass had grown by over 50% in 6–12 months prior to surgery or in whom the adnexal mass first appeared 6–12 months prior to surgery had a higher likelihood of malignant histology as compared to those in whom the adnexal mass had been growing at a slower pace. The rate of malignancy was 9.3%. This observation is biologically plausible since most ovarian cancers grow rapidly and present in advanced stages. Despite lack of elevated CA-125 levels or Risk of Malignancy Index and despite benign ultrasound features, rapid growth was associated with a high likelihood of malignancy.

Our study has several limitations: its small size, it's retrospective nature, the lack of CA-125 values and ultrasound findings in several patients, the lack of a formal statistical analysis. It is not meant to change current practice, but rather to report an interesting and clinically relevant finding. These findings need to be validated in a larger group of patients evaluated and treated in a standard fashion before a practice-changing conclusion can be drawn.

5. Conclusions

In our series of forty-eight consecutive patients taken to surgery for adnexal masses judged to be benign according to ultrasound criteria (IOTA *Simple Rules*) and low Risk of Malignancy Index, those adnexal masses with a rapid rate of growth (increases in size greater than 50% in 6–12 months prior to surgery) were associated with a high risk of malignancy (9.3%). This finding warrants further study and may be useful in the planning of surgery for adnexal masses.

Author contributions

CM-T contributed to patient management, to data collection and analysis, and to writing of the manuscript. NV contributed to patient management. NG provided conceptual guidance and review of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Because this is a retrospective observational analysis of anonymous, personally unidentifiable clinical data, IRB and ethics approval was not sought at the outset of performing this study.

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Conflict of interest

The authors declare no conflict of interest. NG is the Editor of this journal, given his role as Editor, had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

References

[1] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. Practice Bulletin No. 174: Evaluation and Management of Adnexal Masses. Obstetrics and Gynecology. 2016; 128: e210–e226.

[2] Padilla LA, Radosevich DM, Milad MP. Limitations of the pelvic examination for evaluation of the female pelvic organs. International Journal of Gynecology & Obstetrics. 2005; 88: 84–88.

[3] Grab D, Flock F, Stöhr I, Nüssle K, Rieber A, Fenchel S, *et al.* Classification of asymptomatic adnexal masses by ultrasound, magnetic resonance imaging, and positron emission tomography. Gynecologic Oncology. 2000; 77: 454–459.

[4] Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. British Journal of Obstetrics and Gynaecology. 1990; 97: 922–929.

[5] Tingulstad S, Hagen B, Skjeldestad FE, Onsrud M, Kiserud T, Halvorsen T, *et al.* Evaluation of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. British Journal of Obstetrics and Gynaecology. 1996; 103: 826–831.

[6] Tingulstad S, Hagen B, Skjeldestad FE, Halvorsen T, Nustad K, Onsrud M. The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. Obstetrics & Gynecology. 1999; 93: 448–452.

[7] Yamamoto Y, Yamada R, Oguri H, Maeda N, Fukaya T. Comparison of four malignancy risk indices in the preoperative evaluation of patients with pelvic masses. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2009; 144: 163–167.

[8] Geomini P, Kruitwagen R, Bremer GL, Cnossen J, Mol BWJ. The accuracy of risk scores in predicting ovarian malignancy: a systematic review. Obstetrics and Gynecology. 2009; 113: 384–394.

[9] Yamamoto Y, Tsuchida A, Ushiwaka T, Nagai R, Matsumoto M, Komatsu J, *et al.* Comparison of 4 Risk-of-Malignancy Indexes in the Preoperative Evaluation of Patients with Pelvic Masses: a Prospective Study. Clinical Ovarian and other Gynecologic Cancer. 2014; 7: 8–12.

[10] Harris RD, Javitt MC, Glanc P, Brown DL, Dubinsky T, Harisinghani MG, *et al.* Clinically suspected adnexal mass. ACR Appropriateness Criteria. American College of Radiology. Ultrasound Quarterly. 2013; 29: 79–86.

[11] Sohaib SA, Mills TD, Sahdev A, Webb JAW, Vantrappen PO, Jacobs IJ, *et al.* The role of magnetic resonance imaging and ultrasound in patients with adnexal masses. Clinical Radiology. 2005; 60: 340–348.

[12] Levine D, Patel MD, Suh-Burgmann EJ, Andreotti RF, Benacerraf BR, Benson CB, *et al.* Simple Adnexal Cysts: SRU Consensus Conference Update on Follow-up and Reporting. Radiology. 2019; 293: 359–371.

[13] Timmerman D, Testa AC, Bourne T, Ferrazzi E, Ameye L, Konstantinovic ML, *et al.* Logistic regression model to distinguish between the benign and malignant adnexal mass before surgery: a multicenter study by the International Ovarian Tumor Analysis Group. Journal of Clinical Oncology. 2005; 23: 8794–8801.
[14] Timmerman D, Testa AC, Bourne T, Ameye L, Jurkovic D, Van Holsbeke C, *et al.* Simple ultrasound-based rules for the diagnosis of ovarian cancer. Ultrasound in Obstetrics & Gynecology. 2008; 31: 681–690.
[15] Timmerman D, Ameye L, Fischerova D, Epstein E, Melis GB, Guerriero S, *et al.* Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by the IOTA group. British Medical Journal. 2010; 341: c6839.
[16] Alcázar JL, Pascual MÁ, Olartecoechea B, Graupera B, Aubá M, Ajossa S, *et al.* IOTA simple rules for discriminating between benign and malignant adnexal masses: prospective external validation. Ultrasound in Obstetrics & Gynecology. 2013; 42: 467–471.
[17] Kaijser J, Sayasneh A, Van Hoorde K, Ghaem-Maghami S, Bourne T, Timmerman D, *et al.* Presurgical diagnosis of adnexal tumors using mathematical models and scoring systems: a systematic review and meta-analysis. Human Reproduction Update. 2014; 20: 449–462.
[18] Andreotti RF, Timmerman D, Strachowski LM, Froyman W, Benacerraf BR, Bennett GL, *et al.* O-RADS us Risk Stratification and Management System: a Consensus Guideline from the ACR Ovarian-Adnexal Reporting and Data System Committee. Radiology. 2020; 294: 168–185.
[19] Timmerman D, Van Calster B, Testa A, Savelli L, Fischerova D, Froyman W, *et al.* Predicting the risk of malignancy in adnexal masses based on the Simple Rules from the International Ovarian Tumor Analysis group. American Journal of Obstetrics and Gynecology. 2016; 214: 424–437.
[20] Modesitt SC, Pavlik EJ, Ueland FR, DePriest PD, Kryscio RJ, van Nagell JR. Risk of malignancy in unilocular ovarian cystic tumors less than 10 centimeters in diameter. Obstetrics and Gynecology. 2003; 102: 594–599.
[21] Valentin L, Ameye L, Franchi D, Guerriero S, Jurkovic D, Savelli L, *et al.* Risk of malignancy in unilocular cysts: a study of 1148 adnexal masses classified as unilocular cysts at transvaginal ultrasound and review of the literature. Ultrasound in Obstetrics & Gynecology. 2013; 41: 80–89.
[22] Timmerman D, Valentin L, Bourne TH, Collins WP, Verrelst H, Vergote I. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. Ultrasound in Obstetrics & Gynecology. 2000; 16: 500–505.