

# The Accuracy of the international ovarian tumor analysis (IOTA) simple rules in predicting malignant ovarian tumors with biopsy as the reference standard\*

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## ABSTRACT

**Background:** The IOTA Simple Rules provide a standardized ultrasound description in order to correctly classify ovarian tumors as benign or malignant even among non-expert readers. Its high accuracy rate was noted in foreign studies but was never validated in the local setting. The IOTA inconclusive tumors that were either assumed to be malignant or referred to experts in other studies were separately addressed in this research.

**General Objective:** To determine the accuracy of the IOTA Simple Rules to predict malignant ovarian tumors

**Materials and Methods:** *Subjects:* Patients with ovarian tumors admitted for surgery with complete ultrasound records done at Women's Health Unit and those with histopathologic report from the Department of Pathology. *Setting:* Department of Obstetrics and Gynecology in a tertiary hospital from August 2015 to February 2017. *Design:* Cross-sectional Diagnostic Accuracy Test. *Data Collection:* After obtaining approval from the IRB and Office of the Medical Director, the ovarian tumors were tallied and categorized according to their IOTA classification and final histopathologic diagnoses. The sensitivity, specificity, positive and negative predictive values, and accuracy were obtained using a 2x2 table. The biopsy reports of the inconclusive tumors were also reviewed and the sonographic characteristics of those which turned out to be malignant were noted.

**Results:** A total of 110 adnexal masses were included, with the IOTA Simple Rules applicable in 84.55% of cases. It produced an accuracy rate of 100%. Among the 17 inconclusive tumors, two proved to be truly malignant with the presence of only one papillarity in a borderline tumor and the complex appearance of a germ cell tumor.

**Conclusion:** The IOTA Simple Rules is an accurate preoperative diagnostic tool in predicting ovarian malignancy. Two malignant tumors were classified as inconclusive and their sonographic characteristic of only one papillarity and the complex appearance of these tumors may warrant malignancy.

*Keywords:* Inconclusive, IOTA Simple Rules, Ovarian cancer

## INTRODUCTION

### A. Background of the Study

Ovarian masses are frequent findings on pelvic examination and pelvic imaging.<sup>1</sup> The task of the clinician is to determine whether the mass should be removed or may be managed expectantly.<sup>1</sup> Considerations for removal include the symptoms produced by the mass, the likelihood of spontaneous resolution and any suspicion of malignancy. The overall incidence of a symptomatic ovarian cyst in a premenopausal female being malignant is approximately 1 in 1000, increasing to 3 in 1000 at the age of 50 years.<sup>2</sup>

The evaluation of ovarian masses begins with careful physical examination, including an abdominal and a bimanual pelvic examination. The size and physical characteristics of the cyst are as important as the other laboratory parameters.<sup>1</sup> Transvaginal ultrasonography is the single effective tool in the evaluation of an ovarian mass and is usually preferable over the transabdominal route due to its increased sensitivity. Larger masses and extra-ovarian disease may require a combination of both routes. Although histopathology remains the only definitive diagnosis of an ovarian mass, typical characteristics of ovarian pathology maybe seen on ultrasonography which help determine whether the mass is more likely to be benign or malignant.

Prediction models have been developed to aid clinicians in directing patients toward appropriate treatment pathways which include morphologic indices, risk of malignancy indices and mathematical models.

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However, the disadvantage of ultrasound-based prediction models is that it is subjective and is operator dependent.

The International Ovarian Tumor Analysis (IOTA) Group has developed a list of characteristics for benign and malignant masses with the aim of producing rules that may help less experienced examiners replicate the results of expert sonologists. The IOTA Group simple rules are defined as benign or B-rules and malignant or M-rules.<sup>2</sup> The benign or B-rules include unilocular cysts, presence of solid components where the largest solid component is less than 7 mm, presence of acoustic shadows, smooth multilocular tumor with largest diameter of less than 100 mm and a color score of 1. On the other hand, the malignant or M-rules are as follows: irregular solid tumor, presence of ascites, at least four papillary structures, irregular multilocular solid tumor with largest diameter greater than 100 mm and a color score of 4 which indicates a strong blood flow (Appendix A). If one or more M-features apply without the presence of B-features, the ovarian mass is likely malignant. If one or more B-features apply without the presence of M-features, the ovarian mass is likely benign. If no features present or if both B and M-features apply, the result is inconclusive.

Preoperative discrimination between benign and malignant adnexal masses is a crucial step in planning an individualized therapeutic approach to avoid any delay in intervention that may lead to disease progression, as well as avoid unnecessary surgical intervention. Thus, the use of the IOTA simple rules by a general gynecologist has the potential to improve the management of women with adnexal masses. The IOTA Simple Rules have been validated in a number of foreign studies. However, it has never been tested for reproducibility in the local setting particularly in this institution.

## B. Significance of the Study

The use of the IOTA Simple Rules by the sonologists in this institution started in 2015. Although the accuracy of the use of these simple rules is high in other countries, it has never been validated in this institution. The findings of this study compare the accuracy rating of the IOTA simple rules to the results of previous studies and strengthen its diagnostic performance as being a reliable preoperative classification of ovarian masses. Clinical practitioners will then be given the correct preoperative reading of the ovarian mass whether it is benign or malignant as well as be guided in the optimal management for these patients. And for those read as “inconclusive” by the IOTA, this study aims to determine the truly malignant tumors among the inconclusive and discover their most likely sonographic feature of malignancy. A better understanding of the

characteristics of ovarian tumors difficult to classify as benign or malignant using IOTA will be developed. Thus, this study provides gynecologists an insight as to the likelihood of malignancy when these specific sonographic characteristics will be present.

## C. Research Objectives

### General Objective

To determine the accuracy of the International Ovarian Tumor Analysis (IOTA) Simple Rules to predict malignant ovarian tumors

### Specific Objectives

1. To determine the proportion of subjects with ovarian tumor read as malignant by IOTA Simple Rules among those confirmed to be malignant by biopsy (Sensitivity)
2. To determine the proportion of subjects who were confirmed to be malignant by biopsy among those screened by IOTA as malignant (Positive Predictive Value)
3. To determine the proportion of subjects with ovarian tumor read as benign by IOTA Simple Rules among those confirmed to be benign by biopsy (Specificity)
4. To determine the proportion of subjects who were confirmed to be benign by biopsy among those screened by IOTA as benign (Negative Predictive Value)
5. To determine the proportion of malignant ovarian mass confirmed by biopsy among those tumors considered to be inconclusive by IOTA
6. To describe the specific sonographic characteristics of the malignant tumors that were considered Inconclusive by IOTA Simple Rules

## Definition of Terms

1. IOTA Simple Rules - a preoperative classification system for ovarian tumors, consisting of five features typical for benign tumors (B-features) and five features typical for malignant tumors (M- features)
2. IOTA Benign – an ovarian mass with one or more benign or B - features present without malignant or M - features
3. IOTA Malignant – an ovarian mass with one or more malignant or M – features without benign or B - features
4. IOTA Inconclusive – an ovarian mass with either the presence of both B and M – features or none at all
5. Two by two table showing the accuracy of IOTA Simple Rules with Biopsy as reference standard

IOTA Simple Rules	Pathologic Diagnosis (Biopsy)	
	Malignant Disease	Benign Disease
Malignant	A True Positive	B False Positive
Benign	C False Negative	D True Negative

6. Sensitivity – refers to the ability of the test (IOTA Malignant) to correctly identify the true positive (malignancy on histopathology)

$$\text{Sensitivity} = \frac{A}{A + C} \times 100$$

7. Specificity – refers to the ability of the test (IOTA Benign) to correctly identify the true negative (Benign on histopathology)

$$\text{Specificity} = \frac{D}{B + D} \times 100$$

8. Positive Predictive Value – refers to the probability of the presence of disease (malignancy) among those who had a positive screening test (IOTA Malignant)

$$\text{Positive Predictive Value} = \frac{A}{A + B} \times 100$$

9. Negative Predictive Value – refers to the probability of the absence of disease (Malignancy) among those who had a negative screening test (IOTA Benign)

$$\text{Negative Predictive Value} = \frac{D}{C + D} \times 100$$

10. Accuracy – refers to the correctness of the IOTA Simple Rules to detect malignant ovarian tumors when compared to its histopathologic findings

$$\text{Accuracy} = \frac{A + D}{A + B + C + D} \times 100$$

### Ethical Considerations

Prior to the conduct of the study, an approval from the Institutional Review Board of the institution was obtained. The permission to use the data of the patients for the purpose of this research was granted by the Office of the Medical Director. Confidentiality of the patient's data was observed during the data collection and in the writing of the manuscript.

### REVIEW OF RELATED LITERATURE

Ovarian cancer is the second most common malignancy of the lower part of the female genital tract. A major contributing factor to the high death rate from the disease stems from its frequent detection after metastatic spread.<sup>1</sup> Thus, early detection of ovarian

carcinoma continues to be a difficult challenge. Since the advent of ultrasound evaluation of the female pelvis, the characteristics of the normal and abnormal ovary has been extensively studied and has improved visualization of ovarian function and ovarian tumors. An important goal of ovarian ultrasound evaluation is to determine the differences between normal physiologic findings, inflammatory changes, benign neoplastic processes and ovarian cancer.<sup>4</sup> Different scoring systems have been proposed to standardize ovarian tumor characteristics.

The principal IOTA investigators set out to study a large cohort of patients with a persistent adnexal mass in different clinical centers, using a standardized ultrasound protocol. The primary aim of the study was to develop rules and models to characterize ovarian pathology and subsequently to demonstrate their utility by both temporal and external validation in the hands of examiners with different levels of ultrasound expertise.<sup>5</sup>

Several studies done by different investigators sought to validate the IOTA Simple Rules by calculating sensitivity, specificity, positive and negative predictive values. The IOTA simple rules yielded good diagnostic performance in different institutions including oncology centers with a high sensitivity of 89%, specificity of 84.7%, positive predictive value of 75.4% and negative predictive value of 93.9% as presented by Timmerman et al.<sup>5</sup>

Likewise, many authors agree that the IOTA simple rules showed a high - quality reproducibility among non - expert examiners including residents, fellows and trainee sonologists. Meta - analysis by Nunes (2014) highlighted IOTA simple rules as an accurate test for discriminating between benign and malignant adnexal lesions in the hands of a less experienced reader, applicable in 80% of women.<sup>14</sup> In the Philippines, Declarador and Pangilinan (2016) assessed the reliability of these simple rules analyzed by an ultrasound trainee and reported a 100% accuracy rate in 93% of cases.<sup>8</sup>

In this institution, though all sonologists are expert readers, the IOTA Simple Rules is relatively a novel method to describe ovarian features. This study intends to validate the predictive accuracy of the IOTA Simple Rules as compared to the histopathologic diagnosis of the ovarian mass.

In a recently published systematic review and meta - analysis by Kaijser et al, all tumors designated as inconclusive by the IOTA simple rules were classified in the malignant group and results of validation studies produced the same level of sensitivity but a lower specificity.<sup>13</sup> With this in mind, the malignant tumors read as inconclusive is of special interest to the researcher. Thus, this study seeks to determine the specific sonographic characteristics of the malignant tumors classified as IOTA inconclusive.

## RESEARCH METHODOLOGY

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**Study Design:** Cross-sectional Diagnostic Accuracy Test

**Study Setting:** Department of Obstetrics and Gynecology in a tertiary hospital from August 2015 to February 2017

**Study Population:** All patients who will fulfill the inclusion and exclusion criteria will be consecutively evaluated in the study.

C1. Inclusion Criteria:

1. Transvaginal ultrasound with adnexal or ovarian mass with an IOTA Simple Rule classification
2. Availability of the histopathologic report

C2. Exclusion Criteria:

1. Surgery beyond 120 days after ultrasound examination
2. Incomplete records
3. Known diagnosis of adnexal masses such as ovarian cancers scheduled for second look operation, or endometrioma diagnosed by previous laparoscopy

C3. Sample Size Calculation:

Sample size calculated was 101, given 95% confidence level, precision of 0.05 and an assumed proportion of 93% based on a study by Nunes et al.<sup>14</sup>

### Data Collection

After obtaining both the approval from the Institutional Review Board and the permission from the Office of the Medical Director, the census of the Department of Obstetrics and Gynecology were reviewed as to the patients admitted with ultrasound findings of ovarian or adnexal mass who underwent surgical procedure from August 2015 to February 2017. The surgical treatments include cystectomy and oophorectomy either by open laparotomy or laparoscopy, and debulking surgery done within 120 days from the time of ultrasound examination. The transvaginal or transrectal ultrasound of the subjects were from the Women's Health Unit with complete evaluation of the ovarian or adnexal mass including the sonographic morphology and color Doppler study using the advanced ultrasound machines GE Logiq S6 and Samsung Medison WS80A. The characteristics of the masses were analyzed according to IOTA simple rules done by the three IOTA certified obstetric sonologists. The histopathologic report from the Department of Pathology were reviewed after the scheduled operation. The following data were extracted: IOTA classification and the specific sonographic description of the ovarian mass, and the final histopathologic report.

### Data Analysis

All the adnexal masses were tallied and categorized into three groups as benign, malignant and inconclusive. The masses with pathological diagnosis of borderline

or low malignant potential tumors were included in the malignant group. The sensitivity, specificity and predictive values of the IOTA simple rules in predicting malignancy were calculated. The adnexal masses categorized under IOTA Inconclusive were also tallied and followed up on histopathology whether they were benign or malignant and reviewed as to which specific characteristic made it unclassifiable. Descriptive statistics such as proportion was used to summarize the data.

## RESULTS

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A total of 110 women with adnexal mass were included in the study. The IOTA Simple Rules was used to classify the 110 adnexal masses as benign, malignant and inconclusive. It was applicable in 84.55% of cases as it specifically characterized the benign tumors according to the B – features as well as the malignant tumors according to the M - features. A summary of the IOTA classification and corresponding final diagnoses of the cases is shown in Tables 1 and 2 and findings confirmed all 79 benign tumors as truly benign and all 14 malignant tumors as truly malignant by histopathology.

Table 3 shows the IOTA inconclusive tumors and their final diagnoses by biopsy. Among the 17 tumors that could not be classified using the IOTA simple rules, 2 cases proved to be malignant and 15 cases emerged as benign.

Comparison of the results of the IOTA simple rules and histopathologic findings for the benign and malignant adnexal masses showed no significant difference as shown in Table 4. In the 93 masses for which the IOTA simple rules could be applied, sensitivity was 100%, specificity 100%, positive predictive value 100%, and negative predictive value 100%. The accuracy of IOTA simple rules in discriminating adnexal masses as benign or malignant was 100%.

Among the seventeen inconclusive tumors, no B-rule or M-rule could be applied in 16 (94.12%) lesions such as in cases of smooth multiloculated cyst measuring >100 mm, huge solid mass with no color flow, tumors with minimal or moderate color flow, and tumors with less than four papillary like densities or with irregular solid structures <7 mm. And the remaining 1 (5.88%) case, the lesion exhibited 2 B-rules and 1 M-rule being a unilocular cyst measuring <100 mm with absent color flow containing irregular hyperechoic solid looking components in the cyst wall.

The sonographic characteristics of the two malignant tumors classified as IOTA inconclusive are itemized in Table 6. Both tumors manifested similar features namely irregular and thick walled, less than 100 mm in size, no solid densities and no color flow present. However, one tumor was unilocular and contained medium level echoes with

one papillarity while the other tumor was multilocular, and complex in appearance.

## DISCUSSION

Accurate characterization before surgery of an ovarian pathology is essential for adequate clinical decision – making. To date, ultrasound examination has been largely used to predict ovarian malignancy. Hence, the advent of the IOTA simple rules in 2008 paved a

simpler way of characterizing benign or malignant adnexal masses that is equally useful for sonologists both experts and novices alike. When tested prospectively by the IOTA group, the simple rules provided conclusive results in 76% of adnexal masses, with a sensitivity and specificity of 95% and 91%, respectively. Similarly, Hartman et al in 2012 also reported that the IOTA simple rules was applicable in 82.7% of adnexal tumors resulting in a sensitivity of 90%, specificity of 87%, positive predictive value of 69% and negative predictive value of 97%.<sup>18</sup>

**Table 1.** Distribution of IOTA Benign Tumors According to Final Histopathological Diagnoses

IOTA Classification	Final Diagnoses	Frequency	Percentage (%)
Benign Tumors	Benign Serous Ovarian Cyst	3	3.8
	Cystic Struma Ovarii	1	1.27
	Endometriotic Cyst	12	15.19
	Hemorrhagic Corpus Luteum	1	1.27
	Hemorrhagic Cystic Follicle	1	1.27
	Hemorrhagic Fibrocollagenous Cyst	1	1.27
	Hemorrhagic Paratubal Cyst, Paratubal Cyst	6	7.59
	Mature Cystic Teratoma	17	21.52
	Mucinous Cystadenoma	19	24.05
	Multiple Cystic Follicles	1	1.27
	Ovarian Inclusion Cyst	1	1.27
	Serous Cystadenofibroma	1	1.27
	Serous Cystadenoma	14	17.72
	Serous Papillary Cystadenoma	1	1.27
<b>Total</b>		<b>79</b>	<b>100</b>

**Table 2.** Distribution of IOTA Malignant Tumors According to Final Histopathological Diagnoses

IOTA Classification	Final Diagnoses	Frequency	Percentage (%)
Malignant Tumors	Adult Granulosa Cell Tumor	2	14.29
	Clear Cell Carcinoma	2	14.29
	Endometrioid Adenocarcinoma	1	7.14
	Follicular Carcinoma	1	7.14
	Serous Borderline Tumor with Intraepithelial Carcinoma and Microinvasion	1	7.14
	Low Grade Papillary Serous Cystadenocarcinoma	1	7.14
	Serous Papillary Adenocarcinoma	1	7.14
	Poorly Differentiated Serous Papillary Adenocarcinoma	1	7.14
	Mucinous Borderline Tumor	3	21.43
	Mucinous Cystadenocarcinoma	1	7.14
<b>Total</b>		<b>14</b>	<b>100</b>

**Table 3.** Distribution of IOTA Inconclusive Tumors According to Final Histopathological Diagnoses

IOTA Classification	Final Diagnoses	Frequency	Percentage (%)
Inconclusive Tumors	Adult Granulosa Cell Tumor	1	5.88
	Borderline Serous Tumor	1	5.88
	Endometriotic Cyst	3	17.65
	Fibrothecoma	1	5.88
	Mature Cystic Teratoma	1	5.88
	Mucinous Cystadenoma	7	41.18
	Serous Cystadenoma	1	5.88
	Simple Cyst	1	5.88
	Ovarian Cyst with Torsion	1	5.88
Total		17	100

**Table 4.** Diagnostic Indices of IOTA Simple Rules in Predicting Malignant Adnexal Masses

IOTA Simple Rules	Histopathologic Diagnosis		
	Malignant Disease	Benign Disease	Total
Malignant	A True Positive	B False Positive	14
Benign	C False Negative	D True Negative	79
Total	14	79	93

Sensitivity = 100%  
 Specificity = 100%  
 Positive Predictive Value = 100%  
 Negative Predictive Value = 100%  
 Accuracy = 100%

In this study, the application of IOTA simple rules yielded comparable results as it was able to classify 84.55% of cases as benign and malignant. Consequently, the sensitivity and specificity of the IOTA simple rules were both 100% which confirmed its ability to precisely identify the truly benign and truly malignant tumors. In the same manner, the positive and negative predictive values increased to 100% which indicate the presence of ovarian malignancy among the IOTA malignant and its absence among the IOTA benign tumors, with an overall accuracy rate of 100%. This finding is rather expected since sonologists in the study were all IOTA certified and expert readers.

Despite having obtained a high diagnostic performance, the application of IOTA Simple Rules by the original IOTA group had a relatively high rate of inconclusive results of 20%. In contrast, this study produced a lower

**Table 5.** Distribution of IOTA Inconclusive Tumors and their features According to Final Histopathologic Diagnoses

IOTA Inconclusive	Histopathology		
	Benign	Malignant	Total
Neither B or M Features*	14	2	16
With B or M Features	1	0	1
<b>Total</b>	<b>15</b>	<b>2</b>	<b>17</b>

\* Based on IOTA

rate of inconclusive readings at 15.45%. It can be inferred that this study utilized ultrasound machines equipped with faster frame rates and powerful data processing to provide clearer images and more stable signals, thus helping to improve diagnostic accuracy.

While some studies assumed these nonclassifiable tumors to be malignant, others opted not to include them for data analysis and instead, referred them to expert readers for pattern recognition. Hartman et al found that germ cell tumors and serous and mucinous borderline tumors were the more difficult types to classify.<sup>19</sup> Considering that the sonologists in this institution were all IOTA certified readers, this research focused and analyzed further the seventeen IOTA inconclusive tumors. Upon follow - up of their respective histopathologic results, two turned out to be malignant. Both tumors were 70-80 mm in size and had thick and irregular cyst walls. Striking differences were noted between malignant neoplasms, the presence of only one papillarity in the borderline serous tumor and the complex appearance of the adult granulosa cell tumor.

Pattern recognition among expert sonologists is considered superior in large multicenter studies in establishing a confident diagnosis of common ovarian

**Table 6.** Distribution of Malignant Tumors Classified as IOTA Inconclusive According to Sonographic Characteristics

Sonographic characteristics		IOTA Inconclusive		Malignant Tumor	
		N	(%)	N	(%)
Cyst wall	Smooth	8	47.1	0	0
	Irregular	9	52.9	2	100
Cyst wall thickness	Thin walled	5	29.4	0	0
	Thick walled	12	70.6	2	100
Locularity	Unilocular	5	29.4	1	50
	Multilocular	12	70.6	1	50
Internal contents	Anechoic	3	17.6	0	0
	Low level	7	41.2	0	0
	Medium level	1	5.9	1	50
	High level	1	5.9	0	0
	Mixed	2	11.8	0	0
	Complex	1	5.9	1	50
	Solid	2	11.8	0	0
Presence of Solid Density	None	9	52.9	2	100
	1	4	23.5	0	0
	2	1	5.9	0	0
	3	1	5.9	0	0
	4	1	5.9	0	0
	5 or more	1	5.9	0	0
Presence of Papillarity	None	14	82.4	1	50
	1	3	17.6	1	50
	2	0	0	0	0
	3	0	0	0	0
	4 or more	0	0	0	0
Size	<100 mm	10	58.8	2	100
	>100 mm	7	41.2	0	0
Color flow	No color	9	52.9	2	100
	Minimal	7	41.2	0	0
	Moderate	1	5.9	0	0
	Marked	0	0	0	0

masses. Findings of a large size greater than 70 mm, presence of septations and nodularities, papillary projections or frank solid masses, and lesions with irregular and thick walls greater than 3 mm, all increase the likelihood of a neoplastic nature. Moreover, the color content of the tumor reflects both the number and size of tumor vessels and malignancies often exhibit increased flow signals. In pattern recognition, papillarity is a characteristic of borderline tumors and stage I primary invasive epithelial ovarian cancers. Also, the “complex” appearance of an ovarian mass is a sonographic description prevalent among germ cell tumors because it contain various type of tissues. The above definitions

are evident in this study. Even though only one case was noted per sonographic characteristic, the presence of one papillarity may clinically signify an early stage of the disease such as in a low malignant potential tumor. Similarly, the complex appearance of the tumor may warn the clinician of a probable germ cell malignancy.

## CONCLUSION

The International Ovarian Tumor Analysis (IOTA) Simple Rules is an accurate diagnostic tool in predicting ovarian malignancy before surgery. In this institution, it has a sensitivity, specificity, positive and negative

predictive values of 100%, resulting in an overall accuracy of 100%. Along with its excellent diagnostic performance, a lesser number of inconclusive tumors were identified in this study at 15.45%, with two tumors diagnosed to be truly malignant. Their specific sonographic characteristics showed irregular and thick cyst walls with presence of only one papillarity in a low malignant potential tumor and the description of complex appearance in a germ cell tumor even with the absence of color flow. These two findings when present in any ovarian pathology warrants a high suspicion of malignancy.

## LIMITATION

All the transvaginal ultrasound readings and IOTA classification of ovarian masses were done by IOTA certified and expert sonologists in this institution. During the data analysis, only the IOTA classification of the ovarian mass and the final histopathologic diagnoses were included irregardless of patient related characteristics and presence of symptoms.

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## RECOMMENDATION

Further prospective studies using the IOTA Simple Rules in classifying ovarian masses with the analysis done by an ultrasound rotator resident physician in the local setting with a larger population is recommended. This is to test its applicability with a less experienced examiner. This research also serves as a benchmark for future studies to investigate on the specific sonographic characteristics of the IOTA inconclusive tumors as well as establish the probability of malignancy when cyst walls are irregular and thick, presence of only one papillarity or when the ovarian mass is described to be complex in appearance. This is to create an improved scoring system based on the results of patterns identified among inconclusive tumors. ■

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