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Original Research Article

## Evaluation of simple International ovarian tumor analysis ultra sound rules in differentiating between benign and malignant ovarian tumors and their histopathological correlation

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### ABSTRACT

**Background:** IOTA (International ovarian tumor analysis) study is considered one of the largest studies on ultrasound diagnosis of ovarian pathology conducted in literature till date. It was started in 1999 and included nine European countries. It is a standardized technique for preoperative classification of ovarian pathology defined by IOTA group.

**Methods:** A retrospective study was analyzed from a period of January 2016 to December 2017 (2-year period). The records of all the patients operated for benign and malignant ovarian pathology in the gynae department of hospital were retrieved from medical record sections. USG findings were redefined as per IOTA simple rules by sonologist and its histopathological correlation was done using kappa statistical method.

**Results:** In the present study, out of 61 patients IOTA was applicable to 57 patients. The sensitivity where IOTA simple rules were applicable was 92.8% and the specificity was 93%. The accuracy turned out to be 92.9%. If inconclusive results were taken as malignant then sensitivity increased to 94% and specificity decreased to 87%. Good level of agreement was found between sonological and histopathological findings with Kappa statistics application ( $K = 0.59$ ).

**Conclusions:** The IOTA simple rules can be considered as an important diagnostic modality in differentiation of benign and malignant ovarian tumors, it has an added advantage of abolishing the subjectivity of routine ultrasound. However inconclusive results demand further expertise in the field and need to be taken care of before interpretation of ovarian pathologies.

**Keywords:** B-Rules, International ovarian tumor analysis, Kappa statistics, M-Rules, Ovarian pathology, Ultrasound

### INTRODUCTION

Distinguishing ovarian pathologies as benign or malignant preoperatively is of paramount importance as the therapeutic approach of management of each kind is

entirely different. One such approach for distinction is IOTA (International ovarian tumor analysis). The study on IOTA is considered as one of the largest study conducted on ultrasound diagnosis till date. It was started in 1999 and included nine European countries. It is a

standardized technique for preoperative classification of ovarian pathology defined by IOTA group. The rules are based on simple demonstration of certain sonographic findings, some of which are indicative of malignancy (M-rules) and others of benign behaviour (B-rules) and if neither is applicable, the mass could not be classified and was labelled inconclusive (Table 1).

**Table 1: Simple IOTA rules for predicting benign or malignant ovarian tumor.**

Rules for predicting a malignant tumor (M -rules)	Rules for predicting a benign tumor (B - rules)
M1 - Irregular solid tumor	B1 - Unilocular cyst
M2 - Presence of ascites	B2 - Presence of solid component where largest solid component is less than 7mm in largest diameter
M3 - AT least 4 papillary structure	B3 - Presence of acoustic shadows
M4 - Irregular multilocular solid tumor with largest diameter greater 100 mm	B4 - Smooth multilocula tumor with largest diameter less than 100 mm
M5 - Very strong blood flow (color score 4)	B5 - No blood loss (color score 1)

It is well known that the five-year survival rate associated with ovarian cancer is less than 30%. One of the contributing factors of such a low survival rate is lack of reproducibility of standardized terms and procedures in gynecological sonography. The use of IOTA simple ultrasound rules may eliminate this issue being highly sensitive and specific in predicting ovarian malignancy. The observation according to IOTA is reproducible, easy to train for and can be used with ease.<sup>1</sup> In literature there are tremendous studies conducted on the applicability of IOTA rules on distinguishing the benign and malignant behaviour, however there is lack of prospective studies carried in this regard.

This study was conducted to truly establish the diagnostic performance of these rules and to estimate and correlate the sensitivity and specificity of given rules with histopathological diagnosis and establish their use as a tool in early diagnosis of ovarian malignancy.

**METHODS**

A retrospective study was conducted from a period of January 2016 to December 2017 (2-year period).

**Inclusion criteria**

- All the patients who had been operated for suspected ovarian pathology (benign or malignant) in the

hospital in the above-mentioned period were included in the study.

**Exclusion criteria**

- All the patients where tubal pathology is also suspected in addition to ovarian pathology like tubo ovarian mass because of pelvic inflammatory disease or tuberculosis
- Patients with suspected chronic ectopic masses
- Para ovarian cysts.

Study population constitutes all the patients included in the study.

The medical records of the patients included in the study were retrieved from medical record section. The ultrasound findings of all the cases attached with their respective medical files were summarized according to IOTA simple ultrasound rules, were divided into benign, malignant, and inconclusive categories by sonologist and were matched with histopathological reports and then the sonological and histopathological correlation was established using kappa statistics to establish the usefulness of IOTA simple rules.

**RESULTS**

In the present study total 61 patients were included, the youngest was 16 years old and eldest was 68. The mean age was 42.5 years. In our study we found that malignancy was more common in elderly (6<sup>th</sup> decade) and postmenopausal women (Table 2) and (Table 3) where the figures are maximum 53.33 and 66.6 percent respectively. Out of 61 patients IOTA rules were applicable to 57 patients, in rest of the 5 patients' rules were not applicable and were termed as inconclusive. Among 57 applicable patients 41 were indicative of benign and 16 of malignant (Table 4).

**Table 2: Age distribution in benign and malignant ovarian masses (n = 61).**

Age group (in years)	Benign		Malignant	
	Number	%	Number	%
11-25 years	7	15.21%	0	0%
26-40 years	32	69.56%	3	20%
41-55 years	3	6.5%	2	13.33%
56-70 years	3	6.5%	8	53.33%
71-85 years	1	0.02%	1	6.66%
<b>Total</b>	<b>46</b>	<b>100%</b>	<b>15</b>	<b>100%</b>

In the present study 18 different combinations of benign and malignant simple ultrasound features were encountered (Table 5). Out of 18 combinations most common was B1 and B3 combination frequency of which was 9. Out of these 9 patients one had final

histopathological diagnosis of malignancy, so the rate of malignancy in this particular combination was 11.1%. Out of 4 combinations of 100% rate of malignancy, most

frequent combination was application of rule M2, M3 and M5, having frequency of five.

**Table 3: Relation of menopausal status with ovarian tumors.**

Menopausal status	Benign	%	Malignant	%
Postmenopausal	6	13%	10	66.66%
Premenopausal	40	86.9%	5	33.33%
<b>Total</b>	<b>46</b>	<b>100%</b>	<b>15</b>	<b>100%</b>

**Table 4: Classification of cases as per IOTA simple ultrasound rules.**

Nature of the mass as per ITOA rules	No
Benign	41
Malignant	16
Indeterminate	4
<b>Total</b>	<b>61</b>

Out of all benign factors, B1 is the most common occurring factor, however B2, B4 and B5 predicted the

result most correctly (100%) followed by B1 and B5 (Table 6).

Among M factors M2 was the most common factor but the predictability of M3 factor was maximum which correctly predicted malignancy in seven patients (Table 7).

Kappa statistics (K = 0.59) (Table 8) shows good level of agreement between sonology and histopathological findings (> 0.75 - excellent, 0.4-0.75-good, < 0.4-poor).

**Table 5: Observed combinations of benign and malignant ultrasound features of IOTA simple rules ranked by frequency.**

SN	Applicable B factors					Applicable M factors					FREQ	Benign	Malignant	Rate of malignancy
	B1	B2	B3	B4	B5	M1	M2	M3	M4	M5				
1	1	0	1	0	0	0	0	0	0	0	9	8	1	11.15%
2	1	0	0	0	1	0	0	0	0	0	8	8	0	0%
3	1	1	0	0	1	0	0	0	0	0	5	5	0	0%
4	0	0	0	0	1	0	0	0	0	0	6	6	0	0%
5	1	0	0	0	0	0	0	0	0	0	5	5	0	0%
6	1	0	1	0	1	0	0	0	0	0	2	2	0	0%
7	0	0	1	1	0	0	0	0	0	0	2	2	0	0%
8	1	0	0	0	0	0	0	0	0	0	3	3	0	0%
9	1	1	0	1	1	0	0	0	0	0	1	1	0	0%
10	0	0	0	0	0	0	1	1	0	1	5	0	5	100%
11	0	0	0	0	0	0	1	0	0	0	4	2	2	50%
12	0	0	0	0	0	0	1	1	1	0	2	0	2	100%
13	0	0	0	0	0	1	1	0	0	0	3	1	2	66.6%
14	0	0	0	0	0	1	1	0	0	0	2	0	2	100%
15	0	1	0	0	0	0	1	0	0	0	1	1	0	0%
16	0	0	1	0	0	0	0	0	1	1	1	1	0	0%
17	0	1	0	0	0	0	1	0	0	0	1	1	0	0%
18	0	0	1	0	0	0	0	0	1	1	1	0	1	100%

In our study the sensitivity of IOTA simple rules for the detection of malignancy where applicable was 92.8%, whereas specificity was 93%, it had the positive predictive value of 81.2%, with a comparatively high

negative predictive value of 97.5% and the accuracy of 92.9% (Table 9). There was one false negative case in our study where there were presence of acoustic shadows and

later on it turned out to be serous epithelial ovarian cancer in histopathological diagnosis.

**Table 6: Prevalence and predictive power of benign factors.**

Benign	Predicted	Result	Percentage
B1	33	32	96.96%
B2	11	11	100%
B3	15	13	86.66%
B4	3	3	100%
B5	22	22	100%

**Table 7: Prevalence and predictive power of malignant factor.**

Malignant	Predicted	Result	Percentage
M1	5	4	80%
M2	18	13	72.22%
M3	7	7	100%
M4	3	2	66.66%
M5	6	5	83.33%

**Table 8: Comparison of results of IOTA simple rules with histopathological findings.**

Nature of the mass as per iota rules	No	Benign	Malignant
Benign	4	40	1
Malignant	16	3	13
Indeterminate	4	4	1

Table 10 depicts the comparison between the sonographic and histopathological diagnosis of inconclusive cases.

**Table 9: Efficacy of IOTA simple rules.**

Efficacy of IOTA simple rules	
Sensitivity	92.8%
Specificity	93%
PPV	81.2%
NPV	97.5%
Accuracy	92.9%

**Table 10: Comparison between sonographic and histopathological findings of inconclusive cases.**

Sonographic findings (IOTA rules)	Histopathology
M2+ B2	Mucinous cystadenoma
B3+M4+M5	Serous cystadenoma
B2+M2	Endometrioma
B3+M4	Immature teratoma

In addition to it, the study group had been divided into premenopausal and postmenopausal group and the results were depicted as in Table 11. The sensitivity was higher in postmenopausal (91%) as compare to premenopausal (83.3%) while specificity was lower (88% and 97.5% respectively) (Table 12). If inconclusive results are considered as malignant sensitivity index increased from 92.8% to 94% and specificity decreased from 93% to 87% respectively (Table 13).

**Table 11: Comparison of results of present study with the published data is shown.**

Author and year to study	No. of patients	Patients in whom rule is applicable	Malignant tumor	Benign tumor	Prevalence	True positive	False positive	False negative	True negative	Sensitivity	Specificity
Timmerman D et al <sup>10</sup>	507	386	-	-	29	106	25	6	249	95	91
Timmerman D et al <sup>8</sup>	1938	1501	542	1396	25	34	49	29	1083	92	96
Fathallah K et al <sup>9</sup>	122	109	14	108	10.10	8	3	3	95	73	97
Hartman CA et al <sup>11</sup>	103	91	30	73	24.20	20	9	2	60	91	87
Sayasneh A et al <sup>12</sup>	255	214	74	181	24.80	46	3	7	158	87	98
Alcazar JL et al <sup>13</sup>	340	270	55	285	12.20	29	6	4	231	88	97
Nunes N et al <sup>14</sup>	303	237	135	168	44.30	101	15	4	117	96	89
Garg et al <sup>15</sup>	50	45	14	36	28.00	11	5	1	28	91.66	84.84
Present study	61	57	15	46	24.6	13	3	1	40	92.8	93

**DISCUSSION**

The differentiation of benign and malignant tumors is based on several diagnostic modalities such as clinical assessment, CA125, (Erdogan et al; Mousavi et al),

sonographic morphology (Sassone et al; Timmerman et al) or doppler evaluation (Kurjak et al; Tongsong et al).<sup>2-7</sup> However the most proposed sonographic assessment requires higher degree of expertise, limiting their wider use in clinical practice. To overcome this factor Timmerman et al, elicited IOTA simple rules and

validated it for diagnostic performance.<sup>8</sup> The simple rules seem to be more attractive and practical because they are uncomplicated and user-friendly in categorizing an adnexal mass as benign or malignant. Nevertheless, only few studies from other groups in the world have been conducted to test the accuracy and reproducibility of the simple rules.

The present study is a retrospective one, where the sonographic data is collected from the record section and evaluated by the sonologist according to the prediction

model and later on its histopathological correlation was done. 61 patients were included in the study, out of which IOTA rules were applicable to 57 (93.4%) patients. Rest of the 5 patients were termed as inconclusive as they were not applicable. Among 57 applicable patients 41 (67.2%) were suggested as benign and 16 (26.2%) as malignant. Whereas Fathallah et al, performed a prospective study using the IOTA simple rules in a series of 122 masses.<sup>9</sup> The malignancy rate was 11.5% (14 malignancies). The IOTA simple rules were applicable in 89.3% of masses.

**Table 12: Comparative sensitivity and specificity of published data with the current study in pre and postmenopausal women.<sup>3,5-8</sup>**

Author and year of study	Patients with rules applicable	Prevalence of malignancy	Sensitivity	Specificity
<b>All women</b>				
Timmerman D et al <sup>8</sup>	796	22.2	96	96
Hartman CA et al <sup>11</sup>	91	24.2	87	87
Sayasneh A et al <sup>12</sup>	214	24.8	98	98
Alcazar JL et al <sup>13</sup>	270	12.2	97	97
Nunes N et al <sup>14</sup>	237	44.3	89	89
Garg et al <sup>15</sup>	45	28	91.66	84.84
Present study	57	24.6	92.8	93
<b>Premenopausal</b>				
Timmerman D et al <sup>8</sup>	526	9.5	90	97
Hartman CA et al <sup>11</sup>	39	23.1	89	90
Sayasneh A et al <sup>12</sup>	143	15.4	82	100
Alcazar JL et al <sup>13</sup>	217	7.4	88	97
Nunes N et al <sup>14</sup>	130	22.3	90	89
Garg et al <sup>15</sup>	30	3.33	100	86.2
Present study	43	11	83.3	97.5
<b>Postmenopausal</b>				
Timmerman D et al <sup>8</sup>	270	47	91	94
Hartman CA et al <sup>11</sup>	36	30.6	91	80
Sayasneh A et al <sup>12</sup>	71	43.7	90	93
Alcazar JL et al <sup>13</sup>	53	32.1	88	100
Nunes N et al <sup>14</sup>	107	71	99	87
Garg et al <sup>15</sup>	15	73.33	90.9	75
Present study	14	72	91	88

**Table 13: Test performance of different simple rules (SR) strategies in the IOTA studies.**

Study	Sensitivity if SR applicable	Specificity if SR applicable	Sensitivity With SR+MA	Specificity with SR+MR
Timmerman D et al <sup>8</sup>	91	96	94	80
Fathallah K et al <sup>9</sup>	73	97	79	88
hartman CA et al <sup>11</sup>	91	87	94	76
Alcazar JL et al <sup>13</sup>	88	97	93	81
Nunes N et al <sup>14</sup>	96	89	97	70
Tantipalakorn C et al <sup>16</sup>	83	95	87	81
Garg et al <sup>15</sup>	92	85	93	80
Present study	92.8	93	94	87

SR-simple rules; SR+MA- simple rules+ inconclusive result considered as malignant.

In our study the sensitivity of IOTA simple rules for the detection of malignancy where applicable was 92.8%, whereas specificity was 93%, it had the positive predictive value of 81.2%, with a comparatively high negative predictive value of 97.5% and the accuracy of 92.9%. The sensitivity and specificity of our study is comparable to the study of Timmerman et al (92% and 96% respectively) where as Fatallah et al has decreased sensitivity (73%) and increased specificity (97%) as compare to our study.<sup>8,9</sup> On contrary Timmerman et al, has increased sensitivity and decreased specificity as compare to our study (95% and 91% respectively), the comparison of sensitivity and specificity of our study with various studies in literature is depicted on Table 9.<sup>10</sup>

Furthermore, the study group had been divided into premenopausal and postmenopausal and the results were reflected as in Table 11. It depicted that the sensitivity was higher in postmenopausal (91%) as compare to premenopausal (83.3%) while specificity was lower (88% and 97.5% respectively). In the study of Hartman et al the sensitivity is lower in premenopausal group (89%) as compare to postmenopausal group (91%) and specificity is higher In premenopausal (90%) as compare to postmenopausal group (80%).<sup>11</sup> where as in the study of Sayashneh et al, the sensitivity and specificity are 82% and 100% respectively in premenopausal group where as in post-menopausal group the sensitivity and specificity are 90% and 93% respectively. The rate of inconclusive results was 4 out of 61 patients (7.14%). Using a strategy classifying the inconclusive cases as malignant was adopted by many other authors in their respective studies as depicted in Table 13.<sup>12,13</sup>

If inconclusive results are considered as malignant sensitivity index increased from 92.8% to 94% and specificity decreased from 93% to 87% respectively. The result well correlated with the study of Timmerman D et al, Alcazar et al, Nunes et al, Garg et al and Tantipalakorn C et al.<sup>8,13-16</sup>

## CONCLUSION

The most important prognosticating factor in any malignancy is its diagnosis well in time. With early and timely detection, the survival rates of patient improve effectively. USG offers inherent benefits of easy availability and low cost. Furthermore, it has an additional advantage of lack of radiation exposure; nevertheless, the problem often faced with USG is it is more subjective as compare to other diagnostic modalities. IOTA simple ultrasound rules can abolish this issue, as they are highly sensitive and specific in predicting ovarian malignancy yet being reproducible, easy to train and use. In conclusion, the IOTA simple rules have high diagnostic accuracy in differentiating between benign and malignant adnexal masses. Application of the IOTA simple rules yielded acceptable results in terms of sensitivity and specificity and its

histopathological correlation proved to be effective statistically.

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