

Predicting Malignancy in Adnexal Masses by the International Ovarian Tumor Analysis-Simple Rules

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INTRODUCTION

According to Globocan 2018, Ovarian cancers are the 7th common cancers in females worldwide but have the highest mortality rates among all gynecological cancers.^[1] This high mortality is due to late diagnosis in an advanced stage where mortality is high. Infertility, early menarche and late menopause, exogenous hormonal use, high body mass index (BMI), and genetic mutations are considered some of the risk factors for ovarian cancers.

Why is it important to diagnose ovarian malignancies early? The answer to this lies in the fact that the majority of ovarian malignancies are epithelial ovarian cancers (EOC), which are rapidly progressing tumors. Timely diagnosis of the nature of the mass

ensures appropriate referral to gyne-oncologist and treatment.^[2] Preoperative diagnosis of adnexal mass as benign or malignant can change the approach to treatment, nonetheless is found to be most challenging. Various diagnostic tests available to date are not very dependable, and the need for a reliable method cannot be ignored. The commonly available tests are tumor markers or radiological imaging.

Few of the tumor markers include-alpha-fetoprotein, beta-human chorionic gonadotrophin, CA 19-9, CA 125,

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ABSTRACT

Background: Accurate prediction of adnexal tumors preoperatively is critical for optimal management of ovarian cancers. The International Ovarian Tumor Analysis Algorithms (IOTA) is a newer tool to characterize adnexal masses as benign or malignant. **Objective:** This study is aimed to predict malignancy in adnexal masses and differentiates benign from malignant, applying the sonography features of simple rules given by IOTA. **Methodology:** A prospective study was carried out at AIIMS Jodhpur for 1½ years. Women presenting with adnexal masses planned for surgery were recruited. Ultrasonography-transabdominal combined with transvaginal was done, and pelvic masses were characterized using IOTA simple rules. Patients underwent their planned surgery. Histopathology is considered the gold standard and was compared with the IOTA simple rules. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. **Results:** One hundred and seventy-four women were included in the study, of which the majority (82.75%) were benign, the rest being frankly malignant or borderline cancer. The sensitivity of IOTA is 96.6%, specificity of 92.3%, PPV of 72.5%, NPV of 99.2%, where indeterminate cases were considered malignant. **Conclusion:** IOTA simple rule is an effective tool for identifying malignant adnexal masses. It also suggests that IOTA-simple rules can be used as a diagnostic criterion for differentiating adnexal masses into benign and malignant on an out-patient department basis.

KEYWORDS: Adnexal mass, histopathology, International Ovarian Tumour Analysis Algorithms simple rules

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carcinoembryonic antigen, human epididymis 4 (HE-4), lactate dehydrogenase, inhibin A and B and many more. In younger patients generally, germ cell markers are used, while for middle age and older women, epithelial markers are preferred. CA-125 is the most common tumor marker in all the cases, but it has also shown to have false-positive results as may be raised in many nonmalignant pathologies too.

Imaging techniques such as ultrasound, computerized tomography (CT) scan, magnetic resonance imaging (MRI) are used to see the soft-tissue architecture, growth, and lymph nodes. Ultrasound be it trans-vaginal or trans-abdominal sonography is the first-line preoperative investigation for ovarian masses. It is the most common and widely tool used in diagnosing pelvic and abdominal pathology. CT scan and MRI are done later to see nodal involvement, disease extent in the upper abdomen, the architecture of the masses, and if doubt arises for the origin of mass, for example, gastro-intestinal tract, urinary or retro-peritoneum. Ultrasonography (USG)-based subjective pattern recognition assessment depends on the operator's experience, hence is operator dependent. Moreover, clear guidelines on terminology and classification for the USG-based description of the adnexal masses were lacking.

To overcome these drawbacks, various classification systems have been designed, taking USG findings and combining them with other modalities to differentiate adnexal masses. These led to the formation of different types of the scoring system for categorizing adnexal masses into benign and malignant; namely, risk of malignancy index (RMI), Risk of Ovarian Malignancy Algorithm (ROMA), International Ovarian Tumor Analysis (IOTA)-simple rules, IOTA-AdneXa model, Sassone morphology index, etc., RMI, ROMA use CA 125 values along with USG findings and menopausal state, calculation often being complex.

Why choose International Ovarian Tumor Analysis Algorithms-simple rules?

IOTA – is a multidisciplinary group founded by Dirk Timmerman, Lil Valentin, Tom Bourne, William Collins, Herman Verrelst, Sabine Van Huffel, and Ignace Vergote in 1999 to develop standard terms, definition, and simple descriptors to describe sonographic features of adnexal masses.^[3] This group was a multidisciplinary team having clinicians, basic scientists, mathematicians, biostatisticians, etc., They developed a predictive model for the assessment of malignancy in an adnexal mass. IOTA described Simple Rules, which are easy to use in clinical practice to estimate the risk of malignancy. They found the sensitivity to be 91% and the specificity of 93% for their model, which were better compared to other known models.^[2,3]

“IOTA Simple Rules” are a preoperative USG-based classification system for ovarian tumors, consisting of five features typical for benign tumors called the B-features and five features typical for malignant tumors termed M-features. Based on B- or M-features, tumors are classified as benign, malignant, or inconclusive (if both B and M-features are present).^[3] “B features” included-unilocular, presence of solid components <7 mm, presence of acoustic shadow, smooth multilocular tumor with the tumor measuring <100 mm, and no blood flow on color Doppler (color score 1). “M features” included– irregular solid tumor, presence of ascites, at least four papillary structures, irregular multilocular solid tumor with the largest diameter \geq 100 mm, very strong blood flow (color score 4).

The primary objective was to find the utility of IOTA simple rules in the studied population for differentiating adnexal masses as benign or malignant.

The secondary objective was:

- To find the histopathological subtypes of these adnexal masses
- The find prevalence of malignancy in pre- and post-menopausal women.

METHODOLOGY

This study was approved by the Institutional Ethics committee. Eligible patients coming to the out-patient department in Obstetrics and Gynaecology with adnexal mass and planned for surgery were recruited into the study after written informed consent

Study design

This is a prospective study done over 18 months at a tertiary referral center in western India. The primary objective was to find the utility of IOTA simple rules in the studied population for differentiating adnexal masses as benign or malignant.

The secondary objective was:

- To find the histopathological subtypes of these adnexal masses
- The prevalence of malignancy in pre- and post-menopausal women.

Inclusion criteria

Women with adnexal masses planned for surgery.

Exclusion criteria

Young girls who have not yet attained menarche, pregnant women, already diagnosed cancer of the ovary by histopathology (fine needle aspiration cytology or biopsy).

By considering the results obtained from different studies carried out over the years, the sensitivity of IOTA with histopathological examination (HPE) is 88% with 5% precision based upon those studies. Considering a 95%

confidence interval, the sample size came out to be 162; 10% extra is added to cover the loss of data making a total of 180.

A routine complete history, including presenting complaint, menstrual, obstetrical, family, personal, and past history, was taken. They also underwent a routine physical examination, including breast examination, abdominal examination, and pelvic examination. Sonography (transvaginal/trans-abdominal), routine investigations, CA-125 serum levels, and other tumor markers as per need were done. Further radiologic (CT scan or MRI etc.) and other investigations were also advised as per the decision of the treating consultant. USG was repeated after admission, and adnexal masses were classified according to IOTA simple rules by a gynecologist not involved in decision making for the surgery for that particular case. Most of the USG for IOTA categorization was done by the first author, who also has IOTA certification. The second and third authors are senior gynecologists of >8 years and have been doing USG regularly and have learnt from the literature and undergone informal training. Any difference of opinion was sorted by consensus among these authors.

The gynecologist doing USG was blinded to the earlier USG findings. The type of surgical procedure was decided by the operating surgeon; histopathology was obtained after the surgery. The primary report from the sonologist was according to their experience and subjective assessment and not based on the IOTA.

The first three investigators of this study performed the USG and reported according to IOTA simple rules. USG machines, Mindray Z and Philips CV 550 were used for this study. Sonographic assessment of the given adnexal masses was made using a 2–5 Mhz curved transducer for transabdominal sonography and a transducer with a frequency 5–7.5 Mhz for transvaginal sonography. Power doppler with a setting of PRF 0.3, velocity scale 3–6 cm/s was used to score the color flow.

All pertinent data were recorded in an excel sheet. SPSS version 21 was used for analysis. Chi-square test was used for comparison of categorical data, and Student's *t*-test was used for comparison of means. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the International ovarian tumor analysis-simple rules (IOTA) was calculated in comparison to the gold standard reference, histopathology reports.

RESULTS

One hundred and eighty women were enrolled, of which 6 patients were excluded due to – mass arising from

appendix or retro-peritoneum, histopathology awaited, and one deferred from surgery due to uncontrolled diabetes and one had incomplete records. Out of the 174 cases analyzed, 144 (82.75%) were benign and 28 (16.09%) malignant cases, and two borderline cases (1.15%). Women with malignant tumors were older (statistically significant); had more medical problems and higher BMI though not found to be statistically significant [Table 1].

The premenopausal group formed 140 patients and the postmenopausal group had 34 patients [Table 2]. Although the number of postmenopausal women was less, postmenopausal females had a larger proportion of malignant cases (35.29%) than the premenopausal group (12.85%). Thus, malignancy was more prominent in the higher age group postmenopausal women which were found to be statistically significant ($P < 0.003$). Borderline tumors were grouped with malignancy as both patients had completed their family and were managed similarly as malignant tumors. There was not much difference between the groups for the age of menarche, menopause, or BMI.

Histopathology types of adnexal masses are listed in Table 3.

We observed 13/144 (7.47%) were inconclusive, of which 30.76% were found to be malignant on HPR [Table 4].

On analyzing the data, it was observed that, IOTA-simple rules had a sensitivity of 96.67% (95% confidence interval 82.78–99.92), specificity of 92.36% (95% confidence interval 86.74–96.1), PPV of 72.5%, NPV of 99.25%. This data were calculated considering indeterminate cases in IOTA as malignant. Furthermore, borderline tumors on histopathology were grouped in malignant as the surgical management of these tumors is similar to malignant in women who have completed their family as was the case in our two patients.

We can observe that IOTA simple rules have a high sensitivity, specificity, and NPV. These overall make IOTA simple rules an excellent predictor of malignant adnexal mass.

DISCUSSION

Adnexal masses must be classified as benign or malignant to best manage them. This differentiation has been achieved by clinical judgment, tumor markers, especially CA 125 or HE-4, Sassone sonographic morphology, sonography by an expert, spectral Doppler.^[2-7] etc., RMI scoring system using a combination of age, menopausal status, tumor markers, and USG morphology has also

Table 1: Demographic details in benign, borderline, and malignant tumors according to histopathology report

Variables studied	Benign 144		Malignant 30**		P
	Mean	Range	Mean	Range	
Age	37.6	19-55	56.7	41-63	0.003
Age of menarche	14.5	10-15	13.3	11-15	0.072
Age of menopause (in postmenopausal women only)	46.6	42-50	49.7	44-52	0.675
BMI	24.5	17.5-27.2	27.4	23-29.4	0.21
		n (%)		n (%)	
Diabetes		7 (4.9)		3 (10)	
Hypertension		14 (9.73)		4 (13.3)	
Tobacco		9 (6.25)		3 (10)	
Hypothyroidism		7 (4.9)		2 (6.7)	

**Borderline cases included with malignant. BMI: Body mass index

Table 2: Benign and malignant adnexal masses according to histopathology and menopausal status

	Premenopausal (%)	Postmenopausal (%)	Total (%)
Benign	122 (87.14)	22 (64.7)	144 (82.75)
Malignant + borderline	18 (12.85)	12 (35.29)	30 (17.24)
Total	140 (80.45)	34 (19.54)	174

Table 3: Histopathology of adnexal masses

Benign (n=144)	Malignant (n=30)
Dermoid tumour-21	Epithelial cancers-17
Endometriosis-18	Mucinous carcinoma-6
Mucinous tumours-16	Serous carcinoma-10
Serous cystadenoma-27	Seromucinous tumour-1
Sero-mucinous cystadenoma-2	Germ cell tumors: 8, (3 - dysgerminoma, 2 - immature teratoma, and 1-yolk sac tumor)
Others: 57	Metastatic-2
	Others: 1
	Borderline-2

Table 4: Comparison of international ovarian tumor analysis simple rules findings to histopathology report

	HPR analysis		Total
	Malignant	Benign	
IOTA-simple rules			
Benign	1	133	134
Inconclusive	4	9	13
Malignant	25	2	27
Total	30	144	174

IOTA: International ovarian tumor analysis, HPR: Histopathology report

been used to increase sensitivity and specificity in predicting malignancy in the adnexal masses. USG is a simple, noninvasive, nowadays widely available modality. Accurate assessment for malignancy by USG requires high expertise, limiting them from being widely practiced. Simple Rules developed by the IOTA group seems attractive and practical as they are user friendly. With a little practice, it is possible to reach an

acceptable proficiency incorrectly identifying them as benign or malignant. Till now, it has been validated by a few studies only across the world. Most of these studies are retrospective in nature.

Some studies have compared these simple rules to CA 125, RMI, or ROMA and have found that the IOTA prediction model performs better in predicting malignancy.^[6,7] Studies involving CA 125 are known to be confounded as this marker is raised in many nonmalignant conditions too for example, pelvic inflammatory disease, adenomyosis, pregnancy, endometriosis, fibroids, and many non-gynecologic conditions, for example, appendicitis, colitis, tuberculosis, etc., HE-4 levels are not influenced by these benign conditions and may be helpful in some conditions.^[8]

IOTA simple rules have been validated in studies with good sensitivity and specificity for correctly identifying malignancy. In 2013, Stefano Guerriero *et al.*, studied the reproducibility of IOTA simple rules for adnexal masses for classifying them as benign or malignant among examiners with different levels of expertise using stored images. Intra-observer reproducibility was moderate or good for all observers (Kappa index 0.59–0.74). They concluded that IOTA simple rules were easy to use and learn.^[9]

Nunes *et al.* in 2014, in their study, found that IOTA simple rules can be accurate in 76%–89% of tumors for the diagnosis of ovarian cancer.^[10] Dodge *et al.* did a meta-analysis comparing various classification and scoring systems existing for pre-operative diagnosis of adnexal masses and concluded the similar results in favor of IOTA simple rules.^[11]

Few other studies which have used IOTA simple rules are listed in Table 5, which show the type of study and the sensitivity and specificity obtained.

Few studies have compared it with RMI, Sassone morphological scoring and found good results with IOTA.^[12]

Table 5: Sensitivity, specificity of International ovarian tumor analysis simple rules in some studies

Authors	Year	Type of study	Number of participants	Parameters studied	Results	comments
Kaijser <i>et al.</i> ^[7]	2014	Meta-analysis	195 studies, 26,438 adnexal mass	RMI-1, LR2, IOTA SR	RMI-1 Sn- 79%, Sp- 90% IOTA SR Sn- 93%, Sp-76%	IOTA better than RMI
Nunes <i>et al.</i> ^[10]	2014	Prospective Meta-analysis	303	IOTA simple rules and its accuracy	IOTA SR Sn- 93%, Sp- 95%	IOTA has good sensitivity for
Beatriz Ruiz de Gauna, <i>et al.</i> ^[13]	2015	Prospective	247	IOTA simple rules in 2 different centers	IOTA SR Sn- 100%, Sp- 93.9%	
Feharsal and Putra ^[12]	2016	Retrospective	119	IOTA- simple rules, RMI 4 and sassone morphological index	IOTA- Sn- 98%, Sp- 74% RMI-4- Sn- 86%, Sp- 61%	IOTA better than RMI and Sassone score
Niemi <i>et al.</i> ^[14]	2017	Retrospective	96	IOTA simple rules, LR1, LR2, RMI, 3D doppler	IOTA-SR Sn- 90.6%, Sp- 84.6% subjective assessment- Sn- 87.5%, Sp- 92.4% RMI Sn- 71.9%, Sp- 80.3%	IOTA SR has better sensitivity that RMI and subjective assessment
Meys <i>et al.</i> ^[15]	2017	Retrospective	326	IOTA simple rules, AdneXa, RMI, Subjective assessment	IOTA-SR Sn- 89%, Sp- 90% AdneXa- Sn- 98%, Sp- 62% Subjective assessment- Sn- 90%, Sp-91% RMI-2 Sn-74%, Sp-73%	IOTA SR and subjective assessment by an expert are comparable
Froyman <i>et al.</i> ^[16]	2017	Prospective	2403	IOTA simple rules and AdneXa model and subjective assessment	IOTA-SR Sn-97%, Sp-69.1% AdneXa- Sn- 97.4%, Sp- 69.5%	IOTA simple rules and AdneXa model had very good sensitivity
Garg <i>et al.</i> ^[17]	2017	Prospective	50	IOTA- simple rules and HPE	IOTA- simple rules Sn-91.6% Sp- 84.84%	
Tantipalakorn <i>et al.</i> ^[18]	2014	Prospective	319	IOTA SR and HPR	IOTA SR Sn 82.9% Sp 95.3%	IOTA SR had good sensitivity
Auekitrungrueng <i>et al.</i> ^[19]	2019	Retrospective	479	IOTA and RMI	IOTA SR Sn 83.8% Sp 92% RMI Sn 77.2%, Sp 86.8%	
Dakhly <i>et al.</i> ^[20]	2019	prospective	396	IOTA SR and pattern recognition	IOTA SR Sn 88%, Sp 90.9% pattern recognition Sn 88.3% Sp 92.7%	
Present study	2020	Prospective	174	IOTA with HPR	Sn 96.67% Sp 92.36%	IOTA SR had good sensitivity

IOTA: International ovarian tumor analysis, RMI: Risk of malignancy index, HPR: Histopathology report

We can see that most studies are showing sensitivity and specificity of 89%–97% and 69.1%–96%, respectively. The study shows a similar result of sensitivity of 96.6% and specificity of 92.36%.

Timmerman *et al.* in 2016^[21] concluded that “individual risk estimates can be derived from these 10 USG features of simple rules and may form the basis of a clinical management system.” Sayasneh *et al.* did a prospective study and found that the IOTA model performs satisfactorily even in sonographers of varying levels of training.^[22-24] Garg *et al.*^[25] in a prospective study on 50 patients also found that IOTA simple rules are 90% sensitive in predicting ovarian masses correctly, similar to our study. The clinical diagnosis must be complemented with sonography and other radiological investigation to accurately predict malignancy in adnexal masses for optimal management.^[25]

Most of the studies using IOTA simple rules are conducted in American and European countries and it has not been validated enough in other parts of the world. Most studies are retrospective and very few prospective studies have been done. This prospective study planned to find the efficacy of IOTA simple rules in women presenting with adnexal masses is one of a kind. Our study validates the findings of IOTA simple rules and concludes that these can be easily learned and applied. It can be of great clinical value in deciding the nature of adnexal masses.

Study limitation was that cases planned for surgery were included

CONCLUSION

IOTA simple rules – have good sensitivity and specificity for identifying malignant adnexal masses and differentiating benign from malignant. With the available evidence, IOTA is emerging as a single modality, cost-effective, feasible, with a short learning curve to differentiate the adnexal mass from a benign or malignant, thus priding the patients a chance for early diagnosis, treatment, and better survival rate. IOTA may be incorporated in clinical practice as a tool for assessing an adnexal mass.

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Conflicts of interest

There are no conflicts of interest.

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