

Preoperative Risk Assessment of Adnexal Masses Using Simple Rules from the International Ovarian Tumor Analysis Group

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ABSTRACT

Introduction: Pelvic sonography is easily available, economical and a consistent method for diagnosing ovarian or adnexal masses. The incidence rate of ovarian malignancy is maximum among the post-menopausal women. The gold standard of ovarian tumor markers is CA-125, which together with Ultrasound findings is used in predicting the malignancy of an adnexal tumor.

Aims and objectives: To predict the risk of malignancy using ultrasonography in adnexal masses based on the simple rules given by international ovarian tumor analysis and to evaluate the diagnostic performance of IOTA simple rules in differentiating between benign and malignant ovarian tumors and their correlation with histopathological study.

Materials and methods: A total of 76 women participated in the study. All the patients were subjected to trans abdominal/ trans vaginal ultrasonography after taking informed consent. They were classified as benign and malignant according to simple rules given by IOTA group, and they were compared to gold standard histopathological study for final analysis.

Results: The analysis of IOTA SR (benign features) in our study shows high sensitivity and relatively low specificity (93.7% and 76.9% respectively). The IOTA SR (malignant features) shows 81.8% sensitivity and 97% specificity. Out of 76 patients a total of 21 (28%) patients had raised Ca-125 (>35U/ml), out of which, 11 patients were found to have malignancy, confirmed on final HPE.

Conclusion: IOTA simple rules are considered to have a high diagnostic accuracy to discriminate adnexal masses even when performed by non-expert sonographer after a course of training

Keywords:

International ovarian tumor analysis (IOTA), Ca-125, benign and malignant tumors.

Introduction

In gynecological practice, the first investigation done in patients with complaints of pain abdomen or with palpable/ suspected abdominal mass is Ultrasonography.¹ Pelvic sonography is easily available, economical and a consistent method for diagnosing ovarian or adnexal masses. Ovarian tumors are common in women of all age groups.²⁻⁴ The risk of undergoing surgery for a suspected ovarian neoplasm in the female population is 5–10%.⁵ Around 2,39,000 new cases of ovarian cancer (OC) are found worldwide annually, and the incidence rate is maximum among the post-menopausal women⁶. As the prognosis improves significantly when Ovarian cancer is diagnosed at an early-stage, better diagnostic methods are needed.

The subjective evaluation of the findings in an ultrasound is the best method to differentiate between malignant and benign adnexal masses when performed by an ultrasound examiner with sufficient experience⁷⁻⁹. Since such experience is difficult to come by, the IOTA (international ovarian tumor analysis) study had tried to develop algorithms for diagnosis, which aid physicians in differentiating adnexal pathology, without depending on the expertise of the physician.

The gold standard of ovarian tumor markers is CA-125, which together with Ultrasound findings

is typically used in predicting the malignancy of an adnexal tumor.

MATERIALS AND METHODS

A prospective observational study was conducted in which total of 76 cases were enrolled presenting with adnexal masses, admitted in department of obstetrics and gynecology, Institute of medical sciences and SUM hospital, Bhubaneswar over a period of 1year 6months, after formal written consent.

Inclusion criteria:

- Women who presented with adnexal masses willing for surgery.
 - ✓ In case of bilateral adnexal masses, we include the mass with the most complex ultrasonic morphology.
 - ✓ If both the masses have similar morphology on ultrasound, the one which is most easily accessible by trans abdominal/ trans vaginal ultrasound or the largest one is included.
- Patients who have given informed consent.

Exclusion criteria:

- Pregnancy at the time of examination.
- Refusal for USG.
- Patients declining participation.
- Surgical intervention >120 days after the ultrasound examination.

Data collection procedure:

- Oral and or written informed consent were taken as required by the local ethics committee.
- A standardized history was taken for clinical information from each patient.
- ✓ All the participants were subjected to trans-abdominal /Trans vaginal ultrasonography and the simple rules given by IOTA were followed.
- ✓ All adnexal masses were categorized finally into two groups - benign and malignant, in accordance with the simple-rules protocol:
 - The benign features are B1, unilocular cyst; B2, presence of solid components (largest diameter < 7 mm); B3, presence of acoustic shadowing; B4, smooth multilocular tumor with largest diameter < 100 mm; and B5, no blood flow (color score 1).
 - The malignant features are: M1, irregular solid tumor; M2, ascites present; M3, at least four papillary structures present; M4, irregular, multilocular solid tumor with largest diameter ≥ 100 mm; and M5, very strong blood flow (color score 4).
- ✓ Tumors displaying features of both benign and malignant were categorized as unclassified. In case of a women having bilateral tumors, both the tumors were assessed and categorized. If either of the tumor is categorized as malignant then the malignant tumor was used in the final analysis. If the assessment of one tumor is benign and that of the other is indetermined, then the tumors were categorized as indeterminate.
- The final diagnosis was based on histopathological examination, which is considered as gold standard. Only patients with a histological diagnosis were included in the final analysis.
- Serum levels of CA 125 were estimated

RESULTS

Our study population includes 76 patients who had adnexal mass and underwent surgery.

Flow chart of simple rules as triage test

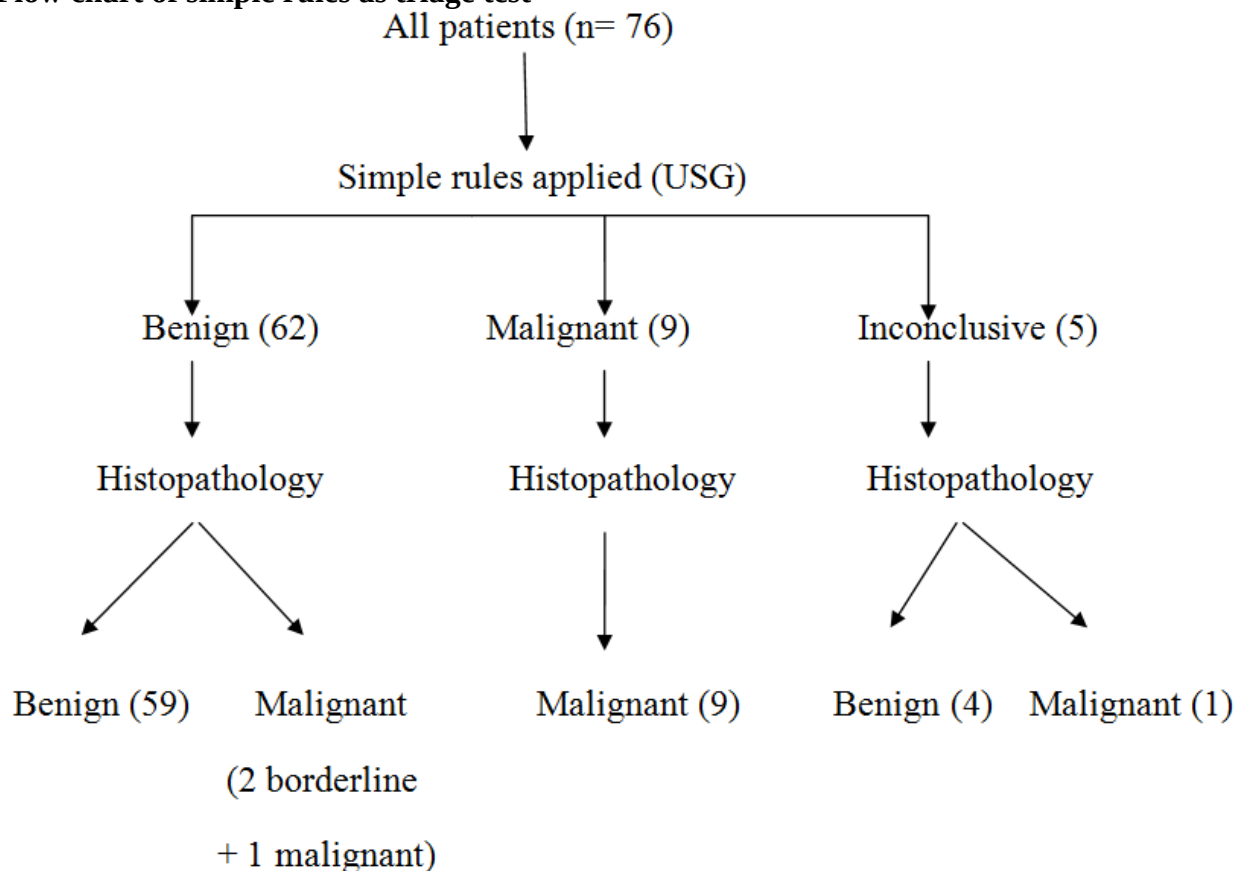


Table 1 Age in years

Age in years	No. of cases	Percentage
≤20yrs	5	7%
21-30yrs	24	32%
31-40yrs	23	30%
41-50yrs	14	18%
≥50yrs	10	13%

The majority of patients included in the study were between 21-30yrs (32%) followed by 31-40yrs (30%).

Table 2 Presenting Complaint

Presenting Complaint	No. of Cases	Percentage
Abdominal Distension	1	1.3%

Amenorrhea	2	2.6%
Dysmenorrhea	7	9.2%
Inability to Conceive	3	3.9%
Irregular Cycles	2	2.6%
Mass per Abdomen	2	2.6%
Menorrhagia	1	1.3%
Pain in Abdomen	56	73.7%
Post- Menopausal Bleeding	2	2.6%
Total	76	100%

The maximum number of patients had Pain abdomen (73.7%) as the presenting complaint. 9.2% of patients had Dysmenorrhea and 3.9% of patients came with complaints of inability to Conceive. Similarly, 2.6% of patients had Amenorrhea and 2.6% of patients had Irregular Cycles. Also 2.6% of patients had mass per Abdomen and 2.6% of patients had Post-Menopausal Bleeding. 1.3% of patients had Abdominal Distension and 1.3% of patients had Menorrhagia.

Table 3 Relation between Age in years and Histopathology Report

Histopathology Report	N	Mean	SD	t Value	P Value
Benign	63	33.721	10.985	-3.451	< 0.001*
Malignant	13	47.091	15.972		

***Significant**

The independent 't' test results shows that there is a significant difference in mean of Age in years for benign and malignant tumors with respect to the Histopathology Report (t value=-3.451, P< 0.001*).

Table 4 Average CA-125 (u/ml) level in Benign and Malignant group

Group	N	Mean	SD	t Value	P Value
Benign	63	22.849	24.284	-5.152	< 0.001*
Malignant	13	157.145	205.325		

***Significant**

Average CA-125 (u/ml) level in Benign group is 22.849 (u/ml) and in malignant group is 157.145 (u/ml). The independent 't' test results shows that there is a significant difference in mean of CA-125 (u/ml) level between benign and malignant groups (t value=-5.152, P< 0.001*).

Table 5 Ultrasound Diagnosis

Ultrasound Diagnosis	No. of Cases	Percentage
Benign	62	81.6%
Malignant	9	11.8%

Unclassified	5	6.6%
Total	76	100%

The result shows that majority of patients had Benign (81.6%). 11.8% of patients had Malignant and 6.6% of patients were Unclassified.

Table 6 Histopathology Report

Histopathology Report	No. of Cases	Percentage
Benign	63	82.83%
Malignant	11	14.4%
Borderline	2	2.6%
Total	76	100%

The result shows that majority of patients had Benign (82.8%). 14.4% of patients had Malignant and 2.6% of patients were in Borderline.

Table 7 IOTA Benign Features

IOTA Benign Features	Yes		No	
	N	%	N	%
B1	47	61.8%	29	38.2%
B2	3	3.9%	73	96.1%
B3	29	38.2%	47	61.8%
B4	15	19.7%	61	80.3%
B5	63	82.9%	13	17.1%

The result shows that out of 76 cases, 47 (61.8%) patients have the B1 criteria, 3 (3.9%) patients have the B2 criteria, 29 (38.2%) patients have the B3 criteria, 15 (19.7%) patients have the B4 criteria and 63 (82.9%) patients have B5 criteria.

Table 8 IOTA Malignant Features

IOTA Malignant Features	Yes		No	
	N	%	N	%
M1	9	11.8%	67	88.2%
M2	7	9.2%	69	90.8%
M3	5	6.6%	71	93.4%
M4	7	9.2%	69	90.8%
M5	12	15.8%	64	84.2%

The result shows that out of 76 cases, 9 (11.8%) patients have the M1 criteria, 7 (9.2%) patients have the M2 criteria, 5 (6.6%) patients have the M3 criteria, 7 (9.2%) patients have the M4 criteria and 12 (15.8%) patients have M5 criteria.

Table 9 Histopathology of the included cases (Benign)

HPS	No. of Cases	Percentage
Serous Cystadenoma	19	30.1%
Mature Teratoma	15	23.8%
Endometriotic cyst	11	17.4%
Corpus luteal cyst	6	9.5%
Mucinous cystadenoma	5	7.9%
Paraovarian/ tubal cyst	4	6.3%
Meso/ Paramesonephric cyst	2	3.1%
Broad ligament fibroid	1	1.5%
Total	63	100%

Among the benign cases, Serouscystadenoma accounted for 30.1% followed by Mature Teratoma and Endometriotic cyst (23.8 and 17.4% respectively).

Table 10 Histopathology of included cases (malignant + borderline)

HPS	No. of Cases	Percentage
Serous Cystadenocarcinoma	6	46.1%
Mucinous cystadenocarcinoma	3	23%
Mucinous borderline	2	15.3%
Granulosa cell tumor	1	7.6%
Immature teratoma	1	7.6%
Total	13	100%

Among the malignant cases, Serouscystadenocarcinoma accounted for about 46.1% followed by mucinous cystadenocarcinoma 23%. Among the borderline cases two were of mucinous type (15.3%).

Table 11 Comparison of Ultrasonography and Histopathology findings in inconclusive cases

ultrasonographic features (IOTA rules)
B3+M1+M4+M5
B3+M3+M4+M5
B4+B5+M2
B5+M1+M2
B3+M2+M4+M5

Histopathological study
Broad ligament fibroid
Serous cystadenocarcinoma
Mature cystic teratoma
Serous cystadenoma with torsion
Mature cystic teratoma

The percentage of inconclusive results was 6.7%.

Among the inconclusive cases 4 were benign and one was malignant according to histopathology

study.

Table 12 Comparison of USG findings and Histopathology reports of Benign cases

		HPE findings		
		Benign		
		Yes	No	Total
USG findings	Yes	59	3	62
	No	4	10	14
Benign	Total	63	13	76
Chi-square value = 35.716		P value < 0.001		Significant

Out of 62 benign cases in USG findings, 59 were benign in Histopathology report. Chi-square test result shows that there is a significant correlation between USG findings and HPE findings in terms of Benign.

Analysis of IOTA SR for benign cases

Sensitivity	93.7%
Specificity	76.9%
Positive Likelihood Ratio	4.06
Negative Likelihood Ratio	0.08
Positive predictive value	95.2%
Negative predictive value	71.4%

Table 13 Comparison of USG findings and Histopathology reports of Malignant cases

		HPE findings		Total
		Malignant		
USG findings	Yes	9	0	9
	No	2	65	67
	Total	11	65	76
Chi-square value = 60.326		P value < 0.001		Significant

Out of 9 malignant cases in USG findings, all 9 of them were malignant in Histopathology report. Chi-square test result shows that there is a significant correlation between USG findings and HPE findings in terms of Malignant.

Analysis of IOTA SR for malignant cases

Sensitivity	81.8%
Specificity	97%
Positive Likelihood Ratio	-
Negative Likelihood Ratio	0.18
Positive predictive value	86.0%
Negative predictive value	97.0%

Table 14 CA-125 for Benign

		HPE findings		Total
		Benign		
CA-125		Yes	No	
	<35 (u/ml)	52	2	54
	>35 (u/ml)	11	11	22
	Total	63	13	76

Chi-square value = 23.629

P value < 0.001

Significant

Chi-square test result shows that there is a significant correlation between CA-125 level and HPE findings in terms of Benign.

Sensitivity	82.5%
Specificity	84.6%
Positive Likelihood Ratio	5.37
Negative Likelihood Ratio	0.21
Positive predictive value	96.3%
Negative predictive value	50.0%

Table 15 CA-125 for Malignant

		HPE findings		
		Malignant		
		Yes	No	Total
CA-125	>35 (u/ml)	9	13	22
	<35 (u/ml)	2	52	54
	Total	11	63	76

Chi-square value = 17.48

P value < 0.001

Significant

Chi-square test result shows that there is a significant correlation between CA-125 level and HPE findings in terms of Malignant.

Sensitivity	81.8%
Specificity	80.0%
Positive Likelihood Ratio	4.09
Negative Likelihood Ratio	0.23
Positive predictive value	40.9%
Negative predictive value	96.3%

DISCUSSION

With a wide range of potential causes, and treatment options, precise diagnosis of an adnexal mass is important. After diagnosis, a mass can be managed in different ways, varying from observation to surgical removal and chemotherapy. There are several controversial issues, which have to be kept in mind while outlining the plan of management for any patient with adnexal mass, so that the patient can be benefited. Our study showed that, the simple rules provide an accurate test for differentiating benign and malignant adnexal lesions.

The majority of patients included in our study were between 21-30 years of age (Table 1). Risk factors for ovarian carcinoma in general includes age greater than 50 years, inherited gene mutations, early menarche and late menopause, drugs used for fertility treatment, polycystic ovarian syndrome. Symptoms of pain, suspected/ palpable pelvic mass is the most common presenting complaint for patients with adnexal condition such as ovarian cyst or adnexal mass. 70% patients presented with pain abdomen as the chief complaint followed by dysmenorrhea in our study (table 2).

The mean age for benign and malignant cases was 33.7 and 47.0 (table 3). There is significant difference in the mean age for benign and malignant cases (p value<0.001) in our study (table 3).

The mean CA-125 level in benign group is 22.849 and in the malignant group is 157.145 (table 4). There is a significant difference in mean value of CA-125 in the benign and malignant group (p value< 0.001). In the statistical analysis the borderline tumors were grouped with malignant tumors.

Out of 76 cases sent for USG analysis, 62(81.6%) were benign, 9 were malignant and 5 were unclassified (table 5). According to the histopathological analysis 63(82.8%) were benign, 13(17.1%) were malignant (table 6). These findings are similar to the study by Ameye et al¹⁰, where in 74% were benign and 26% were malignant. In our study all the cases have been identified by histo- pathology.

In a study conducted by Timmerman et al¹¹, among benign tumors the most predictive feature was B1(Unilocular cyst), while the least predictive feature was B3(Presence of acoustic shadows) which is different when compared to our study i.e feature B5 (no Doppler blood flow- color score 1) was most predictive of a benign tumor 82.9% and feature B2 (presence of solid component <7mm) was least predictive(table 7).

And regarding the malignant tumors in our study M5(very strong blood flow) was the best predictive feature and M3(presence of papillary projections) was the least predictive feature(table 8) while the most predictive feature was M2 (presence of ascites) and the least predictive feature was M4 (irregular multi-locular solid tumor with largest diameter ≥ 100 mm) according to study by Timmerman et al.¹¹

Histopathology study of the benign category in our study shows that serous cystadenoma accounted for about 30.1% of cases followed by mature cystic teratoma 23.8% and endometriotic cyst 17.4% (table 9). These findings are almost similar to the studies of Ameye et al¹⁰ (endometrioma>teratoma> serous cystadenoma) and yabek et al¹² (teratoma> serous cystadenoma>endometrioma).

Similarly histopathology study of the malignant tumors in our study revealed 76.9%(table 10) of the malignant tumors are of epithelial in origin, which is corresponding to studies conducted by Granberg¹³ and Aslam et al¹⁴ where the epithelial carcinoma cases accounted for about 80-90% of all ovarian cancers. There is a significant correlation between the ultrasound diagnosis and histopathology report in our study.

The percentage of inconclusive results in our study is 6.7% (table 11). Likely the rate of inconclusive results was 10% in other study by Garg S¹⁶. In a study conducted by Esmee et al¹⁷, showed 20% inconclusive results with simples rules.

The simples rules(SR) provided a definitive result in most benign tumors (81%) and in most primary invasive tumors(74%) but in only half of the borderline tumors(50%) in a study conducted by Timmerman et al.¹⁵

The sensitivity and specificity of simple rules compared with other studies

Author and year of study	No. of Patients	Patients in whom rules are applicable	Malignant Tumours	Benign Tumours	Sensitivity (%)	Specificity (%)
Timmerman D et al., ¹⁸ (2008)	507	386	-	-	95	91
Timmerman D et al., ¹⁵ (2010)	1938	1501	542	1396	92	96

Fathallah K et al., ¹⁹ (2011)	122	109	14	108	73	97
Hartman CA et al., ²⁰ (2012)	103	91	30	73	91	87
Sayasneh A et al., ²¹ (2013)	255	214	74	181	87	98
Alcazar JL et al., ²² (2013)	340	270	55	285	88	97
Nunes N et al., ²³ (2012)	303	237	135	168	96	89
Our study	76	73	9	62	93.7(B) 81.8(M)	76.9(B) 97(M)

The analysis of IOTA SR (benign features) in our study shows high sensitivity and relatively low specificity (93.7% and 76.9% respectively), and the IOTA SR (malignant features) shows 81.8% sensitivity and 97% specificity (table 12,13). In our study, out of 76 patients a total of 21 (28%) patients had raised Ca-125 (>35U/ml), out of which, 11 patients were found to have malignancy, which was confirmed on final HPE. Only two patients with Ca-125 value which is less than 35U/ml had malignancy (table 14,15). Ca-125 is the most abundantly studied tumor marker for anticipating the risk of malignancy. It is raised in 80% of epithelial ovarian cancer but efficacy is comparatively low in Stage 1 malignancy.²⁴ Its low specificity does not allow it to be used as a single preoperational diagnostic method.

Ca-125 has a sensitivity of 61%–90%, specificity of 71%–93%, positive predictive value of 35%–91%, and negative predictive value of 67%–90% in differentiating benign and malignant tumors.²⁴ McDonald *et al*²⁵ reported the association of Ca-125 >35U/ml and complex solid mass on USG with either borderline and malignant ovarian cancer in more than three fourth of patients.

CONCLUSION

- Time of detection is the most important factor in ovarian malignancy. Significant improvement in the survival is possible with early detection of the tumors.
- IOTA simple rules are considered to have a high diagnostic accuracy to discriminate adnexal masses even when performed by non-expert sonographer after a course of training.
- The simple ultrasound rules given by IOTA group are highly sensitive and specific in predicting ovarian malignancy.
- There is a significant correlation between ultrasound diagnosis and histopathology report in our study.
- Malignant tumor patients were significantly older (with mean age of malignancy being 47.091) and had high CA-125 level (mean 157.14) in our study.
- The analysis of IOTA SR (benign features) in our study showed high sensitivity and relatively low specificity (93.7% and 76.9% respectively), and the IOTA SR (malignant features) showed 81.8% sensitivity and 97% specificity.
- In our study, out of 76 patients a total of 21 (28%) patients had raised Ca-125 (>35U/ml), out of which, 11 patients were found to have malignancy, which was confirmed on final HPE. Only two patients with Ca-125 value which is less than 35U/ml had malignancy
- So, a classification system based on these 10 simple ultrasound rules of IOTA can form the basis of management of adnexal masses.

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