Thai Journal of Obstetrics and Gynaecology
November 2021, Vol. 29, No. 6, pp. 331-339

GYNAECOLOGY

Diagnostic Performance of International Ovarian Tumor Analysis-simple Rules Versus Risk Malignancy Index 2 Scoring System to Differentiate Between Benign and Malignant Adnexal Masses

Jaishree Bamniya, M.S.*,
Pooja Singh, M.S.*,
Devanshi Patel, M.S.*,
Arpita Chaudhary, M.S.*,
Harshad Ladola, M.S.*

** Gujarat Cancer Society Medical College and Research Centre, Ahmedabad, Gujarat, India*

ABSTRACT

Objectives: To compare International ovarian tumor analysis-simple rules (IOTA-SR) versus risk of malignancy index 2 (RMI 2) scoring system to differentiate benign and malignant adnexal mass.

Materials and Methods: A prospective cohort study was conducted at Gynecology department of GCS (Gujarat Cancer Society) Medical College and Research center, Ahmedabad, Gujarat, India. One hundred and twenty-four patients from period of June 2018 to Dec 2020 with persistent adnexal tumors with informed consent underwent transvaginal and transabdominal gray-scale and Doppler ultrasound examination using a standardized examination technique and standardized terms and definitions.

Results: Diagnostic accuracy of IOTA-SR and RMI 2 scoring was assessed by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). In our study IOTA-SR had a sensitivity, specificity, PPV and NPV of 92.30%, 93.87%, 80% and 97.87%, respectively. On the other hand, RMI 2 scoring had a sensitivity, specificity, PPV and NPV of 62.50%, 91.30%, 71.42% and 87.50%, respectively. IOTA had better diagnostic performance than RMI 2 (chi square test 83.33 vs 39.31).

Conclusion: A management protocol based on triaging women using the IOTA-SR performed significantly better than the RMI 2 -based protocol. IOTA-SR was very easy to be done by gynecologist and could be used in practice to differentiate between benign and malignant adnexal masses ensuring timely and proper referral to gynecologic oncologists in developing country like India with burden of patients and limited resources.

Keywords: adnexal mass, doppler ultrasound, predictive value, India.

Correspondence to: *Jaishree Bamniya , M.S., Gujarat Cancer Society Medical College and Research Centre, Ahmedabad, Gujarat, India. E-mail: jaishreeskumar@yahoo.co.in*

Received: 12 May 2021, **Revised:** 25 June 2021, **Accepted:** 30 June 2021

Introduction

Adnexal masses are frequently observed in women of all ages particularly in mid and late age[1]. Malignant lesion if picked up at earlier stage have a better prognosis than at advanced stage. Therefore, it is crucial to adequately characterize such masses to ensure that women are triaged appropriately and thus receive optimal treatment. The limiting factor for early diagnosis of ovarian tumor is lack of standardized terms and procedures in gynecological sonography[2].

The World Ovarian Cancer Coalition Atlas 2018 reports that India has the world's second highest ovarian carcinoma incidence. The incidence of ovarian carcinoma is estimated to increase to 371,000 a year by 2035 (55%), while the death rate increases by 67% to 254,000[3].

India with its 1.37 billion population has a huge burden of the disease in comparison to the number of comprehensive cancer centers and trained Gynaec-oncological surgeons. Therefore, to optimize the care, referring the right women to specialist centers is crucial. This hinges on an accurate preoperative assessment of the likely pathology.

For correct characterization of ovarian tumors, several ultrasound-based prediction models have been developed to help operators accurately differentiate between benign and malignant adnexal masses, which are Sassone Morphology Index (1991), Risk of Malignancy Index (RMI) (Jacob, 1991) and International Ovarian Tumor Analysis (IOTA, 2000-2013).

However, IOTA and RMI scoring systems are most commonly used. Auekitrungrueng et al in study of 479 masses concluded that IOTA simple rules had higher diagnostic accuracy compared with RMI to discriminate between benign and malignant adnexal masses[4].

This study was performed to establish the diagnostic performance of IOTA SR and RMI 2 scoring with estimating and comparing the sensitivity and specificity of given models with histological diagnosis and establish which was better tool in differentiating malignant and benign adnexal masses in Indian population.

Materials and Methods

As per formula of sample size $N = z^2 p (1-p)/ d^2$. We have taken z value of 1.96, p value of 0.013, so 1-p is 0.987 and with precision of 0.02, N comes to 123.22, in our study we had taken sample size of 124.

All patients who presented with adnexal masses and who consented to participate in study were taken as study subject. The exclusion criteria were the patients with already diagnosed cases of malignancy, incomplete medical records, subjects who refused the surgery and who were lacking histopathology reports. All study subjects were subjected to both IOTA SR and RMI 2 scoring to differentiate between benign and malignant mass. IOTA –Simple rules comprised five ultrasonic features (including shape, size, solidity, and results of colour Doppler examination) to predict a malignant tumour (M features) and five to predict a benign tumour (B features) as depicted in Table 1[5]. Fig. 1 shows the Malignant (M) and Benign (B) sonographic features used in IOTA-SR[6].

Table 1. Simple rules for classifying adnexal masses as benign or malignant, as defined by the International Ovarian Tumor Analysis Group.[5]

Rules for predicting Malignant tumor (M Rules)	Rules for predicting Benign tumor (B Rules)
M1 Irregular solid tumor	B1 Unilocular
M2 Presence of ascites	B2 Presence of solid components where the largest solid component has a largest diameter <7 mm
M3 At least four papillary structures	B3 Presence of acoustic shadows
M4 Irregular multilocular solid tumor with largest diameter ≥100 mm	B4 Smooth multilocular tumor with largest diameter < 100 mm
M5 Very strong blood flow (color score 4)	B5 No blood flow (color score 1)

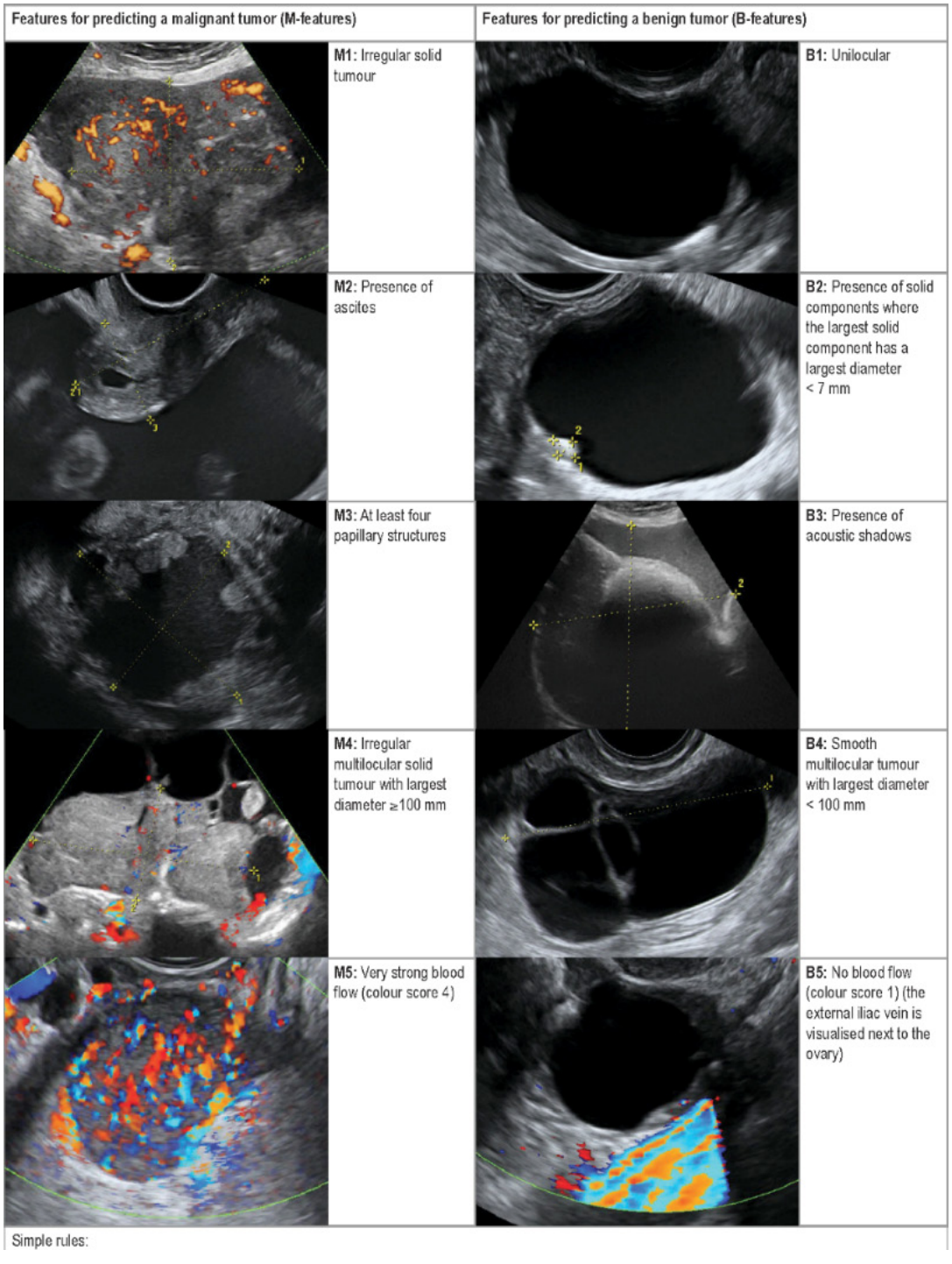

Fig. 1. International ovarian tumor Analysis-Simple rules[6]

RMI 2 Scoring by Tingulstad considered Menopausal status and CA-125 levels also along with sonographic features of adnexal mass also using the following formula (Risk scoring = U × M × CA-125).

Sonographic assessment of the given adnexal masses was done by gynaecologist with fellowship in sonography with 12 years of experience using a wide band transvaginal transducer having frequency 5-7.5

MHz and 5 MHz curved transducer (GE Logiq P3) for transabdominal sonography, which was available in department. In inconclusive cases referral to radiology department was done.

Transvaginal scan was performed in all cases except unmarried females. Transabdominal sonography was used to examine large masses that could not be seen in their entirety using a transvaginal probe. Gray-scale and color Doppler imaging was performed. If the adnexal mass was diagnosed as malignant in any of the study arm, the patients were referred to gynecological oncologist in our hospital. (Fig. 2.)

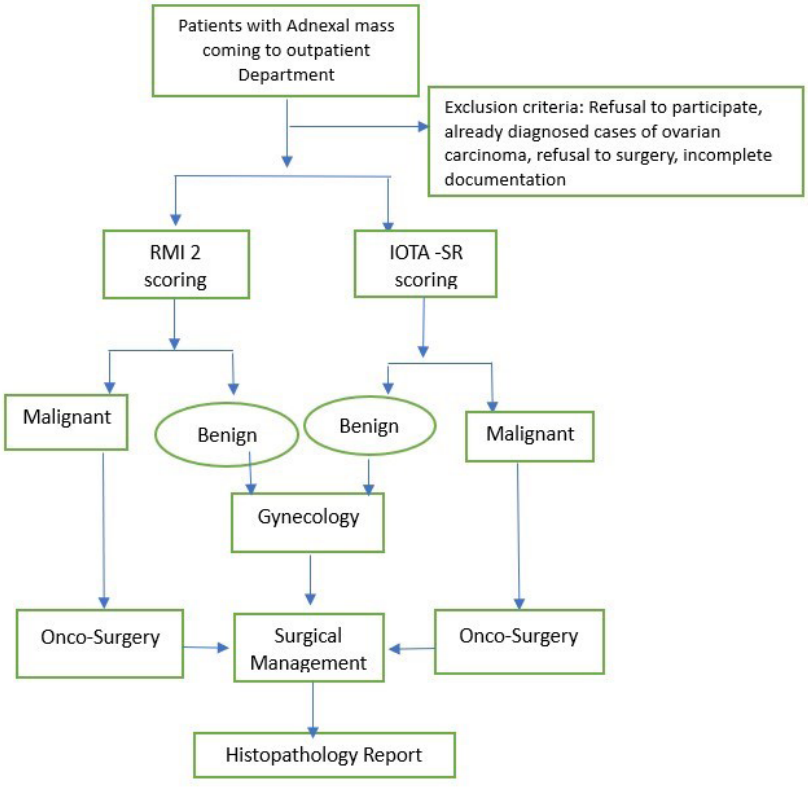

Fig. 2. Consort Flow Diagram for allocation of patients.

Histological diagnosis was considered gold standard. Tumours were classified according to the criteria recommended by the International Federation of Gynaecology and Obstetrics.

Study was approved by local Ethical Committee. The patients were selected and data related to age, menstrual history, symptoms at diagnosis, presence of ascites, CA-125 levels, and ultrasound findings were collected and coded into software SPSS version 26.

The exclusion criteria were the patients with already diagnosed cases of malignancy, incomplete medical records, subjects who refused the surgery and who were lacking histopathology reports.

If one or more M-rules apply in the absence of a B-rule, the mass is classified as malignant.

If one or more B-rules apply in the absence of an M-rule, the mass is classified as benign.

If both M-rules and B-rules apply, the mass cannot be classified. If no rule applies, the mass cannot be classified.

We chose RMI 2 scoring system which was calculated for each patient using formula:

RMI 2 (Tingulstad et al. 1996)[7] = U × M × CA-125, where a total ultrasound score of 0 or 1 made U=1, and a score of ≥ 2 made U=4; premenopausal status made M=1 and postmenopausal M=4. The classification

of "post- menopausal" is a woman who had no period for more than 1 year or a woman over 50 who had a hysterectomy.

Ultrasound score (U) was based on one point for each of the following:

1. Bilateral lesion
2. Multilocular cyst with septations
3. Evidence of solid areas
4. Evidence of metastasis
5. Presence of ascites

The serum levels of CA-125 were taken in U/ml and CA-125 were determined by using advanced chemiluminescence (ACS): 180 plus in the department of Biochemistry. The levels of < 35 U/ml were considered to be normal.

The cut-off levels for RMI 2 score were taken as 200 for the study group. The patients with RMI 2 score < 200 was labeled as benign and score > 200 was labeled as malignant.

The histopathological reports from surgically removed ovarian tissues were retrieved, and the tumors were classified according to FIGO (International Federation of Gynecological Obstetrics) recommendations. Histopathological diagnosis was considered as gold standard for defining outcome.

Excel sheet data tested with student t test and chi square test for demographic, biochemical and ultrasonographic data comparison for benign and malignant adnexal masses.

Results

124 women with adnexal mass were included in this prospective study with a mean age of 43.60 years (range 10-76 years). Ninety patients were premenopausal, of whom 79 had benign masses and 11 had malignant masses. The 30-40 age group had the highest number of adnexal masses. Maximum number i.e. 45.16% (56) had adnexal mass of < 10 cm while only 9.67% (12) subjects had mass of size > 20 cms (Table 1). Ninety-eight of the women had benign masses, whereas twenty-six women had malignant masses (Table 2).

Table 1. Distribution of cases according to size of adnexal mass.

Size of Adnexal mass	No.	Percentage
5-10 cm	56	45.16 %
11-15 cm	34	27.41%
16-20 m	22	17.74%
> 20 cm	12	9.67%

Maximum number of adnexal masses were in 5 to 10 cm size i.e. 45.16%. Only 9.67 % of masses were more than 20 cm in size

Table 2. Distribution of cases according to IOTA and RMI 2 Scoring.

Nature of lesion by IOTA	Malignant Lesion on HPE	Benign Lesion on HPE	Nature of lesion by RMI 2 scoring	Malignant Lesion on HPE	Benign Lesion On HPE
Malignant (n=30)	24 (19.35%)	6 (4.83%)	> 200 (n=28)	20 (16.12%)	8 (6.45%)
Benign (n=94)	2 (1.61%)	92 (74.19%)	< 200 (n=96)	12 (9.67%)	84 (67.74%)

IOTA: International Ovarian Tumour Analysis, RMI: Risk of Malignancy Index, HPE: Histo-pathological examination, PPV: positive predictive value, NPV: negative predictive value

The number of postmenopausal women was 34 and of these, 19 had benign lesions whereas 15 had malignant neoplasm. The average age of women with benign lesions was 32.16 ± 10 years and the average age for women with malignant masses was 60.16 ± 15.6 years.

Distribution of different adnexal masses in our study was benign serous cystadenoma (40.32%), benign mucinous cystadenoma (12.90 %), mature cystic teratoma (11.29%), parafimbrial cyst (8%), endometrioma (6.45%), ovarian cyst with torsion and haemorrhagic cyst each accounting for 1.61% of total cases.

In malignant category, serous cyst adenocarcinoma (3.22%), mucinous cystadenocarcinoma (1.61%), sex cord stromal tumor (4.83%) and dysgerminoma accounted for 4.83% of cases.

Diagnostic accuracy of IOTA SR and RMI 2 scoring was assessed by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). As shown in Table 3. IOTA SR had a sensitivity, specificity, PPV and NPV of 92.30%, 93.87%, 80% and 97.87%, respectively on the other hand RMI 2 scoring had a sensitivity, specificity, PPV and NPV of 62.50%, 91.30%, 71.42% and 87.50%, respectively.

Table 3. Efficacy of IOTA and RMI 2 scoring.

	IOTA -SR	RMI 2
Sensitivity	92.30 %	62.50 %
Specificity	93.87 %	91.30 %
Positive Predictive Value (PPV)	80	71.42
Negative Predictive Value (NPV)	97.87	87.50

IOTA: International Ovarian Tumour Analysis, RMI: Risk of Malignancy Index, PPV: positive predictive value, NPV: negative predictive value

Discussion

The aim of this observational study over a period of 2 year 6 months was to evaluate the role of IOTA simple rules and RMI 2 in distinguishing benign from malignant adnexal masses.

The strengths of this study were that the comparison of the two methods was performed on the same ultrasound examinations, making them perfect for comparison in terms of patients, the ultrasound machine, and time of examinations. Most of the research done was comparison between different RMI scoring systems but comparison between IOTA SR and RMI 2 were few. To the best of our knowledge, this is the first study aimed to directly compare the effectiveness of the two methods using the same settings of ultrasound examinations. Small sample size was the limitation of the study.

Many of the women in this study who had malignant pelvic masses were at stage 1. The lower numbers in stages 3 and 4 could be because most of the women at these stages would have presented with obvious symptoms of malignancy. Therefore, they would have had a computerized tomography rather than an ultrasound, which made them ineligible for inclusion into this study. The number of premenopausal females was also high as mostly menopausal females had a advanced or diagnosed stage of ovarian cancers.

As shown in Table 4. using a cut-off of 200, Tingulstad et al[7], in their study of 365 cases showed a sensitivity, specificity, PPV and NPV of 71%, 92%, 69%, and 92%, respectively. Andersen et al in study of 180 cases found a sensitivity, specificity, PPV and NPV of 70.6%, 89.3%, 66%, and 91%, respectively[9].

Table 4. Comparison of the present study results with previous studies on diagnostic performance of RMI 2.

Studies	RMI	N	Sensitivity (%)	Specificity (%)	PPV	NPV
Tingulstad, et al[7]	200	365	71	92	69	92
Morgante, et al[8]	125	124	81	90	74	
Andersen, et al[9]	200	180	70.6	89.3	66	91
Obeidat, et al[10]	200	100	90	89	96	78
Ulusoy, et al[11]	153	296	76.4	80	66	85.5
Our study	200	124	62.50	91.30	71.42	87.50

RMI: Risk of Malignancy Index, PPV: positive predictive value, NPV: negative predictive value

Obeidat et al in their study of 100 cases showed a sensitivity, specificity, PPV and NPV of 90%, 89%, 96%, and 78%, respectively[10]. Chopra Sunny et al stated in their study that the sensitivity of the RMI 2 for diagnosing malignant lesion was 96.7% (59/61) and the specificity was 84% (21/25). The PPV was 85.5% (59/69) and NPV was 67.7%[12].

Majority of research done in RMI 2 scoring showed a low specificity. A high specificity is important because it reduces the number of surgical procedures performed for benign cases in tertiary gynecological oncology centers, therefore optimizing resources for patients with malignant pelvic masses. In our study, we found that RMI 2 scoring had a sensitivity, specificity, PPV and NPV of 62.50%, 91.30%, 71.42% and 87.50%, respectively. On the other hand, IOTA SR protocol showed a sensitivity, specificity, PPV and NPV of 92.30%, 93.87%, 80% and 97.87%, respectively. In our study, IOTA SR scored over RMI 2 scoring system in all the diagnostic parameters proving it to be better tool in differentiating between benign and malignant adnexal mass and can be done easily by a gynecologist. Tongsong et al reiterated that because of simplicity to practice with no need of highly skilled expertise and high effectiveness, the IOTA SR are probably suitable for practice by general gynaecologists. They showed sensitivity and the specificity of the IOTA simple rules to be 82.9% and 94% respectively[13]. Sayasneh et al, in their multicentre study found sensitivity and specificity for IOTA SR in the hands of the examiners in their study was 87% and 98%, respectively. It suggested that when the IOTA SR are inconclusive, the patient should be referred to an expert in gynaecological scanning for further assessment (level III) as an optimal second-stage test which was also done as protocol in our study. It showed that IOTA SR perform well in the hands of both relatively inexperienced doctors and when used by sonographers and was better than the RMI. The study suggested that IOTA SR might replace the RMI in protocols designed to evaluate suspected adnexal pathology, particularly when dealing with premenopausal women[14].

For IOTA SR, statistically χ^2 was 83.33 and p value < 0.001, here p value was highly significant so we could say that there was association between nature of lesion by IOTA and histopathological report. For RMI 2, statistically χ^2 was 39.31 and p value < 0.001 and there was association. As χ^2 83.33 > 39.31, it showed that IOTA SR had better diagnostic per-formance.

Our study showed that the IOTA SR protocol was more accurate and easier than the RMI 2-based protocol classifying adnexal masses as being at low, moderate or high risk of malignancy. The IOTA protocol resulted in a substantial increase in the number of benign ovarian masses classified as low risk and in the number of invasive tumors classified as high risk. It was also associated with a reduction in the number of invasive tumors classified as low risk.

The difference between the protocols was similar in all subgroups considered. Further, the IOTA protocol

performed consistently in all histological types of invasive tumours, whereas the RMI protocol showed poorer performance in mucinous, non-epithelial primary invasive, and metastatic invasive tumours. This is likely to be explained by the lower expression of CA125 in these tumour types. Raised serum CA 125 levels found in association with benign ovarian cysts, endometriosis, and pelvic infection in addition to cancers of the endometrium, fallopian tube, breast, and colon decreased the specificity of RMI.

A recent study by Van Calster et al also founded that the IOTA SR protocol was more accurate for triage than the RCOG RMI protocol[15].

The results of this study will facilitate more appropriate referrals to the specialized gynecological oncology centers across India and help in determining the necessity of surgery, resulting in appropriate care for women with gynecological malignancies and optimization of healthcare resources

Conclusion

In conclusion, we have shown that a management protocol based on triaging women using the IOTA SR performed significantly better than the RMI 2-based protocol. IOTA has been developed on a large database of adnexal masses and undergone external validation in several different centres. We believe that the IOTA model should be considered as an alternative to the RMI for inclusion in triaging protocols for adnexal pathology. IOTA SR is very easy to be done by gynaecologist and can be used in practice to differentiate between benign and malignant adnexal masses ensuring timely and proper referral to gynaecologic oncologists in developing country like India with burden of patients and limited resources.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Kaijser J, van Hoorde K, van Calster B, Bourne T, Vergote I, Timmerman D. Diagnosing adnexal tumours before surgery: a critical appraisal of recent evidence. Obstet Gynaecol 2015;17:163-71.
2. Garg S, Kaur A, Kaur Mohi J, Sibia P, Kaur N. Evaluation of IOTA simple ultrasound rules to distinguish benign and malignant ovarian tumours. J Clin Diagn Res 2017; 11:TC06–9.
3. Murthy NS, Shalini S, Suman G, Pruthvisinh S Mathew A. Changing trend in incidence of ovarian cancer-the Indian scenario. Asian Pac J Cancer Prev 2009; 10:1025-30.
4. Auekitrungrueng R, Tinnangwattana D, Tantipalakorn C, Charoenratana C, Lerthiranwong T, Wanapirak C, et al. Comparison of the diagnostic accuracy of International Ovarian Tumor Analysis simple rules and the risk of malignancy index to discriminate between benign and malignant adnexal masses. Int J Gynecol Obstet 2019;146:364-9.
5. 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 Obstet Gynecol 2008;31:681-90.
6. Kaijser J, Bourne T, De Rijdt S, et al. Key findings from the International Ovarian Tumor Analysis (IOTA) study: an approach to the optimal ultrasound based characterisation of adnexal pathology. Australas J Ultrasound Med 2012;15:82-86.
7. Tingulstad S, Hagen B, Skjeldestad FE, Onsrud M, Kiserud T, Halvorsen T, Nustad K. Evaluation of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. Br J Obstet Gynaecol 1996;103:826-31
8. Morgante G, La Marca A, Ditto A, De Leo V. Comparison of two malignancy risk indices based on serum CA125, ultrasound score and menopausal status in the diagnosis of ovarian masses. Br J Obstet Gynaecol 1999;106:524-7.
9. Andersen ES, Knudsen A, Rix P, Johansen B. Risk of malignancy index in the preoperative evaluation of patients with adnexal masses. Gynecol Oncol 2003;90:109-12.
10. Obeidat BR, Amarin ZO, Latimer JA, Crawford RA. Risk of malignancy index in the preoperative evaluation of pelvic masses. Int J Gynecol Obstet 2004;85:255-8.
11. Ulusoy S, Akbayir O, Numanoglu C, Ulusoy N, Odabas E, Gulkilik A. The risk of malignancy index in discrimination of adnexal masses. Int J Gynecol Obstet 2007;96:186-91.
12. Chopra Sunny, Vaishya Richa, Kaur Jasbinder. An Evaluation of the applicability of the risk of malignancy index for adnexal masses to patients seen at a tertiary hospital in Chandigarh, India. J Obstet Gynecol India 2015;65:405-10.

13. Tongsong T, Tinnangwattana D, Vichak-ururote L, Tontivuthikul P, Charoenratana C, Lerthiranwong T, et al. Comparison of effectiveness in differentiating benign from malignant ovarian masses between IOTA simple rules and subjective sonographic assessment. Asian Pac J Cancer Prev 2016;17:4377-80.
14. Sayasneh A, Wynants L, Preisler J, Kaijser J, Johnson S, Stalder C, et al. Multicentre external validation of IOTA prediction models and RMI by operators with varied training. Br J Cancer 2013;108:2448-54.
15. Van Calster B, Timmerman D, Valentin L, Mclndoe A, Ghaem-Maghami S, Testa AC, et al. Triaging women with ovarian masses for surgery: observational diagnostic study to compare RCOG guidelines with an international Ovarian Tumour Analysis (IOTA) group protocol. BJOG 2012;119:662–71.