Use of ultrasonographic rules and tumour marker HE4 level to predict malignancy of a pelvic mass: abridged secondary publication

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KEY MESSAGES

1. In Hong Kong women, the International Ovarian Tumor Analysis (IOTA) simple rules are 94% accurate in diagnosing malignancy of a pelvic mass detected on ultrasound when the IOTA results are conclusive.
2. IOTA simple rules are more accurate than other assessment methods such as the Risk of Malignancy Index (RMI) and the Risk of Malignancy Algorithm (ROMA).
3. When results of IOTA simple rules are inconclusive in 25% of patients, addition of ultrasound assessment by an expert results in higher sensitivity than addition of ROMA or RMI, despite similar specificity and accuracy.
4. Our findings suggest that pelvic masses detected on ultrasound should be assessed by the IOTA simple rules first. If results are inconclusive, ultrasound assessment by an expert should be added. If expertise is not available, RMI or ROMA should be added to improve accuracy.

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Introduction

Pelvic ultrasound is commonly used to investigate gynaecological symptoms. Accurate prediction of a malignant mass enables appropriate referral to specialised care. The International Ovarian Tumor Analysis (IOTA) simple rules are based on assessment of various pre-defined benign and malignant ultrasound features.[1] The IOTA simple rules can be inconclusive in 25% of cases. In inconclusive cases, addition of ultrasound assessment by an expert is recommended. This study compared various combinations of methods in predicting malignancy of a pelvic mass: the IOTA simple rules with or without ultrasound assessment by an expert, the Risk of Malignancy Index (RMI),[2] or the Risk of Malignancy Algorithm (ROMA).[3] IOTA predicts malignancy by assessing the presence of five benign and five malignant ultrasound features. RMI predicts the risk of malignancy by assessing the menopausal status, ultrasound features, and the tumour marker CA-125 levels. ROMA uses levels of two tumour markers (HE4 and CA-125) to calculate the risk of malignancy. This study aims to determine whether ROMA/RMI can replace ultrasound assessment by an expert when IOTA outcome is inconclusive.

Methods

Consecutive women from one cancer centre and three general units who were scheduled for operation for a pelvic mass were recruited. Before surgery, the women underwent a pelvic ultrasound by a gynaecologist, and the pelvic mass was assessed according to the RMI and IOTA criteria. The risk of ovarian cancer was calculated using each all three methods: IOTA, RMI, and ROMA. For those with inconclusive IOTA results, ultrasound assessment by an expert was performed (Table 1). The final histology of the mass was obtained from the operative sample. The sensitivity, specificity, and accuracy for each combination of methods were

TABLE 1. Various methods to predict malignancy of a pelvic mass detected on ultrasound

Method	Detail
Ultrasound assessment by an expert	Most accurate method. Depends heavily on the level of expertise
International Ovarian Tumor Analysis simple rules	Ultrasound assessment using five benign and five malignant features. Simple to use by operators with basic training
Risk of Malignancy Index	Calculation of risk by five ultrasound features, menopausal status, and biomarker CA-125 level
Risk of Malignancy Algorithm	Calculation of risk by an algorithm that includes menopausal status, biomarkers CA-125 and HE4 levels. No ultrasound features involved.

compared with the McNemar test. The primary outcome was to determine the best method for predicting malignancy in women with inconclusive IOTA results. We assumed that the accuracy for ROMA was around 85%, and that the actual difference between the two methods was 5%, and that the range of non-inferiority was at 5%. A sample size of 160 subjects was expected to have 90% power to show non-inferiority between the two correlated accuracy rates. The one-sided non-inferiority test of two correlated proportions was used. A minimum of 640 women undergoing operation was needed.

Results

A total of 690 women with a histological/cytological diagnosis were included in the analysis (Table 2). Of them 519 (75.2%) had a conclusive IOTA result and 171 (24.8%) had an inconclusive IOTA result. Ultrasound assessment by an expert was more sensitive than the ROMA in diagnosing a malignant mass (81% vs 63%, P=0.009), with no significant difference in specificity (72% vs 73%) or accuracy (76% vs 68%). Among those with conclusive IOTA results, IOTA was more accurate than ROMA in diagnosing a malignant mass (94% vs 84%, P<0.001).

In 640 women with ovarian pathology, IOTA with ultrasound assessment by an expert was more sensitive than IOTA with ROMA (79.9% vs 73.2%, P=0.015, Table 3). Both IOTA with ROMA and ROMA alone were similarly sensitive (73.2% vs 74.3%) and were more sensitive than RMI alone (66.5%, P=0.030). Both IOTA with ROMA and IOTA with RMI as well as IOTA with ultrasound assessment by an expert were similarly accurate. Various combinations of IOTA with ultrasound assessment by an expert or ROMA or RMI were all more accurate than ROMA alone or RMI alone (89.2% vs 88% vs 88% vs 81.6% vs 84.2%, P=0.004 to P<0.001).

Both IOTA with ultrasound assessment by an expert and IOTA with ROMA were similarly sensitive in pre- and post-menopausal women (81% vs 79%) but both were more accurate in pre-menopausal women (92% vs 84%, P=0.009 and 90% vs 83%, P=0.017, respectively). Both ROMA alone and RMI alone were similarly sensitive and specific in pre- and post-menopausal women, but RMI alone was more accurate in pre-menopausal than post-menopausal women (87% vs 77%, P=0.003).

In 315 women from the cancer centre, IOTA with ultrasound assessment by an expert was more sensitive (83% vs 76%, P=0.033) but less specific (87% vs 91%, P=0.040) than IOTA with ROMA, with similar accuracy (85% vs 85%). Both ROMA alone and RMI alone were similarly sensitive, but RMI alone was more specific (87% vs 80%). In 325 women from the three general units, both IOTA with ultrasound assessment by an expert and IOTA with ROMA were similar in sensitivity, specificity, and accuracy. IOTA with ultrasound assessment by an expert or ROMA, or ROMA alone were more sensitive than RMI alone. IOTA with RMI was more sensitive than RMI alone (60% vs 42%, P=0.008).

TABLE 2. Characteristics of patients

Characteristic	One cancer centre*	Three general units*	Total*
No. of patient	341	349	690
Age, y	47 (18-85)	45 (19-89)	46 (18-89)
Menopausal status			
Post-menopausal	113	99	212
Pre-menopausal	228	250	478
Ovarian malignancy	112 (32.8)	30 (8.6)	142 (20.6)
Ovarian			
Benign	184	275	459
Endometriotic cyst	84	97	181
Dermoid	32	71	103
Serous/mucinous cystadenoma	34	57	91
Fibroma	5	7	12
Functional cyst	6	8	14
Hydrosalpinx	1	2	3
Mixed	3	1	4
Others/unspecified	19	32	51
Malignant	112	30	142
Serous	28	9	37
Mucinous	5	2	7
Clear cell	25	5	30
Endometrioid	18	7	25
Mixed	13	0	13
Sex cord stromal/germ cell	4	2	6
Metastatic	10	4	14
Others	9	1	10
Borderline	16	20	36
Malignant/borderline	1	0	1
Non ovarian			
Benign	10	23	33
Malignant	18	1	19
International Federation of Gynecology and Obstetrics staging			
I	36	15	51
II	11	4	15
III	23	2	25
IV	10	2	12
Unstaged	11	0	11
Inconclusive results of International Ovarian Tumor Analysis simple rules	105 (30.8)	66 (18.9)	171 (24.8)

* Data are presented as median (range) or No. (%) of patients

TABLE 3. Diagnostic accuracy of five different methods in women with an ovarian pathology (n=640)

Method	Sensitivity*	Specificity*	Accuracy*	Histology malignant (misdiagnosed as low risk)*	Histology benign (misdiagnosed as high risk)*
International Ovarian Tumor Analysis simple rules (IOTA) + ultrasound assessment by an expert	79.9 (73.1-85.3)	92.8 (90.0-94.9)	89.2 (86.5-91.5)	20.1 (14.7-26.9)	7.2 (5.1-10)
IOTA + Risk of Malignancy Algorithm	73.2 (66.0-79.4)	93.7 (91.0-95.7)	88.0 (85.1-90.3)	26.8 (20.6-34)	6.3 (4.3-9)
IOTA + Risk of Malignancy Index	72.1 (64.8- 78.4)	94.1 (91.5- 96.0)	88.0 (85.1-90.3)	27.9 (21.6-35.2)	5.9 (4.0-8.5)
Risk of Malignancy Algorithm alone	74.3 (67.1-80.4)	84.4 (80.7-87.5)	81.6 (78.3-84.4)	25.7 (19.6-32.9)	15.6 (12.5-19.3)
Risk of Malignancy Index alone	66.5 (59.0-73.2)	91.1 (88.0-93.5)	84.2 (81.1-86.9)	33.5 (26.8-41)	8.9 (6.5-12)

* Data are presented as % (95% confidence interval)

Addition of IOTA improved the accuracy of ROMA alone or RMI alone.

Of 142 ovarian cancers, 51 were at stage 1. IOTA with ultrasound assessment by an expert was similar to IOTA with ROMA/RMI or ROMA alone in terms of sensitivity. All combinations of IOTA (with ultrasound assessment by an expert or ROMA or RMI) were more sensitive than RMI alone (81% vs 72% vs 70 % vs 58%, P=0.035 to P=0.003). ROMA alone was more sensitive than RMI alone (70% vs 58%), but the difference did not reach significance (P=0.061).

For 36 borderline tumours, all methods had poor sensitivity in diagnosing borderline tumours (36% to 57%). There was no significant difference between various methods.

Discussion

IOTA simple rules were more accurate than ROMA and RMI in diagnosing a malignant mass when the IOTA results were conclusive. When IOTA result is inconclusive in 25% of women, addition of ultrasound assessment by an expert enhances the accuracy the most.[1] In the present study, addition of ultrasound assessment by an expert increased sensitivity more than addition of ROMA, although differences in specificity and accuracy were not significant. We suggest that women with a pelvic mass detected on ultrasound should be first assessed using the IOTA simple rules by gynaecologists or radiologists. If the mass is at high risk of malignancy, woman should be referred to gynaecological oncologists for further assessment and management. Women with inconclusive results should be referred for an ultrasound assessment by an expert. If such an expert is not available, ROMA or RMI should be added to determine if the mass is malignant. Both ROMA and RMI require a blood test for tumour markers (HE4 and CA-125 for ROMA and CA-125 for RMI); it may be more cost-effective to add RMI than ROMA.

Various combinations of IOTA methods appeared to perform better in pre-menopausal women, consistent with a meta-analysis that reported a higher accuracy of IOTA simple rules in pre-menopausal women, likely owing to better diagnosis of endometriotic or dermoid cysts.[4] All methods were not sensitive in diagnosing borderline malignancies. This may reduce the overall performance of the tests. Borderline cases were excluded in other studies in the literature.

Other methods for predicting malignancy in pelvic masses include logistic regressions models, the IOTA simple rules risk model, and the ADNEX model. Ultrasound assessment by an expert has the best performance, but if such expertise is not available, the IOTA ADNEX model and the IOTA simple rule risk model are recommended.[5] The IOTA simple rules and RMI are most widely used in clinical practice in Hong Kong, mainly owing to the ease of use and recommendations by the Royal College of Obstetricians and Gynaecologists guidelines. We suggest using IOTA simple rules as the first step in assessing a pelvic mass, particularly in the general population setting. For those with inconclusive results, addition of ultrasound assessment by an expert is preferred, owing to a higher sensitivity. Nonetheless, addition of ROMA or RMI has similar accuracy.

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Disclosure

The results of this research have been previously published in:

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