A prospective evaluation of the IOTA Logistic Regression Model LR2 for the diagnosis of ovarian cancer

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KEYWORDS: diagnosis; IOTA; logistic regression; ovarian cancer; ultrasound

ABSTRACT

Objectives To assess the accuracy of the IOTA Logistic Regression Model LR2 for the diagnosis of ovarian cancer.

Methods This was a prospective single-center study of women with an ultrasound diagnosis of an adnexal tumor. They were all examined by a single Level II ultrasound operator, who had received training in the systematic examination of ovarian tumors in accordance with the IOTA guidelines. In all women the likelihood of the adnexal lesion being malignant was calculated using the IOTA LR2 model. All women underwent surgery within 120 days of ultrasound examination and the ultrasound findings were compared with operative findings and the final histological diagnosis.

Results 124 women were included in the final analysis. The mean age was 53.2 (range, 20–91) years and 61/124 (49.2%) women were postmenopausal. 66/124 (53.2%) women had malignant lesions on postoperative histological examination. The IOTA LR2 model had a sensitivity of 97.0% (95% CI, 89.5–99.6%) and a specificity of 69.0% (95% CI, 55.5–80.5%). The area under the receiver-operating characteristics curve was 0.93 (SE, 0.022; 95% CI, 0.89–0.97), which was not significantly different from 0.92 (SE, 0.018) reported in the original study (P > 0.05).

Conclusion When evaluated prospectively the accuracy of the IOTA LR2 model was similar to that reported in the original study: Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Preoperative differentiation between benign and malignant ovarian tumors is difficult. A large number of scoring systems and diagnostic models have been developed in recent years in order to facilitate the detection of ovarian cancer on ultrasonography1–3. The majority of these tests were based on retrospective analysis of small datasets, and their accuracy tends to be poor when evaluated prospectively4–5.

The International Ovarian Tumor Analysis (IOTA) collaboration started several years ago and included nine European centers that participated in the recruitment of patients6. The strengths of this collaboration are a uniform approach to ultrasound assessment of adnexal lesions, a large dataset and the use of robust statistical methods. The main aim of the collaboration was to design models for the diagnosis of ovarian cancer, which could be used in routine clinical practice by non-expert operators of average skill and experience. The majority of routine gynecological ultrasound examinations worldwide are carried out by sonographers who are usually classified as Level II operators7–8. Level II examiners tend to describe morphological appearances of adnexal tumors in detail, but unlike the experts (Level III operators), they are not trained to differentiate subjectively between benign and malignant tumors on ultrasound8. At present the subjective assessment of adnexal tumor morphology or ‘pattern recognition’ method is the most accurate way of diagnosing ovarian cancer on ultrasonography9. It has been hypothesized that a well designed and accurate diagnostic model would help Level II sonographers and other examiners without particular expertise in gynecological ultrasound to differentiate between benign and malignant adnexal tumors. Although the initial published results of the IOTA models were promising, the models have been developed and subsequently tested by expert ultrasound operators (Level III), who were also able to use the pattern recognition method to determine the nature of adnexal lesions6,10,11. This

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could have contributed positively to the accuracy of the IOTA diagnostic models. It is therefore unknown whether the IOTA models would perform equally well if used by operators with less expertise in gynecological ultrasonography.

The aim of our study was to prospectively evaluate the diagnostic accuracy of the IOTA Logistic Regression Model LR2 on a representative sample of adnexal lesions when all ultrasound examinations were performed by a non-expert ultrasound operator.

**METHODS**

This was a prospective single-center study conducted over a 17-month period from May 2009 to September 2010. All women attending our gynecological diagnostic unit routinely undergo a detailed transvaginal and transabdominal scan, which includes a systematic examination of the uterus, ovaries and adnexa. Women with ultrasound evidence of an adnexal tumor were first examined by a single non-expert operator, who performed a detailed assessment of the tumor characteristics using the IOTA protocol. The non-expert operator (N.N.) had received training in the systematic examination of ovarian tumors in accordance with the IOTA guidelines. She was not trained in tumor ‘pattern recognition’ and she was discouraged from attempting to differentiate subjectively between benign and malignant tumors on ultrasound scan.

Demographic data including the patient’s age, menopausal status, medical history and family history were recorded as part of the routine assessment. Women ≥ 50 years of age who had previously had a hysterectomy were defined as postmenopausal. In addition, morphological and Doppler characteristics of adnexal tumors were recorded in accordance with the IOTA protocol. A family history that included the number of first-degree relatives with ovarian or breast cancer was taken from each patient.

As with the original IOTA study, pregnant women, those unable to undergo a transvaginal scan and those who had surgery later than 120 days after the ultrasound scan were excluded from the final data analysis. In women with bilateral lesions, the lesion that was more likely to be malignant according to the IOTA model was included in the analysis.

The probability of an adnexal mass being malignant was estimated using the IOTA LR2 model. Six variables were used for the calculation: (1) age of the patient (in years); (2) presence of ascites (yes = 1, no = 0); (3) presence of blood flow within a solid papillary projection (yes = 1, no = 0); (4) maximum diameter of the solid component (expressed in mm, but with no increase if > 50 mm); (5) irregular internal cyst walls (yes = 1, no = 0); and (6) presence of acoustic shadows (yes = 1, no = 0). The probability of malignancy was calculated using the formula

\[ y = \frac{1}{1 + e^{-z}}, \]

where \[ z = -5.3718 + 0.0354 \times (1 + 1.6159 \times (2 + 1.1768 \times (3 + 0.0697 \times (4 + 0.9586 - 5) - 2.9486 \times 6)), \]

as described in the original IOTA study. The probability \( y \) is dichotomized at 0.1 to give a predictive diagnosis.

The non-expert operator had recorded the assessments of the IOTA variables in the research file and they were not made available to the clinicians who made the decisions about the patients’ management.

All women were then re-examined by expert ultrasound operators who advised the women on their management in accordance with our standard clinical protocols. Only women who underwent surgery were included in the data analysis. Surgical options varied from laparoscopic ovarian cystectomy to primary ovarian debulking surgery.

The IOTA LR2 model calculation of the risk of malignancy was performed only at the end of the study when data collection had been completed, and its accuracy was assessed using histology as the gold standard. Tumors were classified according to the criteria recommended by the International Federation of Gynecology and Obstetrics. Statistical analysis was performed using the software package Stata 11.1® (Stata Corp., College Station, TX, USA). The diagnostic accuracy of the IOTA LR2 model was assessed by calculating its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR−) and the area under the receiver–operating characteristics curve (AUC). The \( \chi^2 \) method was used to compare differences in proportions between the results of the original IOTA study and those of the current study. As morphological analysis of the tumors using the IOTA protocol is performed routinely in our department and no therapeutic decisions were based on the IOTA model, our local research and development department advised that the study did not require formal ethical assessment and approval.

**RESULTS**

A total of 332 women were diagnosed with adnexal tumors during the study period. Of these, 141 (42.5%) women had surgery or a biopsy, while the remaining 191 (57.5%) were managed conservatively. Seventeen of the 141 (12.1%) women were excluded; three were pregnant and 14 did not have surgery within 120 days of their ultrasound examination, thus a total of 124 women were included in the final analysis (Figure 1). Their mean age was 53.2 (range, 20–91) years. There were 63 (50.8%) premenopausal and 61 (49.2%) postmenopausal women. 47 (37.9%) were referred by their general practitioner, 67 (54.0%) were tertiary referrals from another unit, eight (6.5%) attended as an emergency and two (1.6%) were referred via other routes. There were 58 (46.8% (95% CI, 38.2–55.5%)) benign, 9 (7.3% (95% CI, 3.9–13.2%)) borderline, 42 (33.9% (95% CI, 26.1–42.6%)) primary invasive malignant adnexal tumors and 15 (12.0% (95% CI, 7.5–19%)) metastatic tumors of the ovary. Of the 42 primary invasive malignant lesions there were 14 (33.3 %) Stage I, three (7.1%) Stage II, 13 (31.0%) Stage III and 12 (28.6%) Stage IV. Primary invasive
Prospective evaluation of IOTA LR2 model

Figure 1 Study flowchart.

There were 18 false positive and two false-negative cases (Table 1). Benign ovarian cystadenomas and mature cystic teratomas were responsible for 10/18 (55.6%) of all false-positive diagnoses of ovarian cancer. The first false-negative case was that of a premenopausal woman with large bilateral ovarian tumors whose histology showed a borderline mucinous tumor and an incidental finding of an appendix goblet cell carcinoid tumor. The other patient was a postmenopausal woman, also with bilateral ovarian tumors, which were metastatic from a gastrointestinal primary. The tumors were smooth and multilocular with no solid areas and no ascites. Tumor deposits were, however, seen in the pouch of Douglas.

In order to test for the possibility of bias due to increased operator experience during the study period we divided the data set into two halves. The performance of the IOTA LR2 model in the first 62 consecutive patients was not significantly different from the results in the 62 subsequently recruited women (sensitivity 94% vs. 100% (P = 0.152); specificity 61% vs. 78% (P = 0.063)).

The AUCs were not significantly different between the current study, the original IOTA report and the prospective IOTA validation study (Table 2).6,14 Sensitivity in our study was significantly better than in the original study (χ² = 6.162, P = 0.013), but it was not statistically different from the sensitivities in the validation study. Specificities in the IOTA validation study were significantly higher than in our study (external χ² = 21.1, P = 0.001; temporal χ² = 6.96, P = 0.008). The specificities in our study and the original study, however, were not significantly different.

Alternative cut-off points were investigated for our data. A cut-off of 6.4% instead of 10% would have given us 100% sensitivity, but the specificity would have fallen to 36.9% (Figure 2).

Table 1 Histological findings in women with a false-positive diagnosis of ovarian cancer using the International Ovarian Tumor Analysis Group logistic regression model LR2 (n = 18)

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystadenoma/cystadenofibroma</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Mature cystic teratoma</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Dermoid with cystadenoma</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Pedunculated leiomyoma</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Benign aspirate/pseudocyst</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Torsion of benign cyst</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Brenner tumor</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Fat necrosis and inflammation—suspected actinomycosis</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Total</td>
<td>18 (100)</td>
</tr>
</tbody>
</table>

DISCUSSION

Our study has shown that the accuracy of the IOTA LR2 model was similar, in the hands of a non-expert operator, to that found in the original IOTA study. Although AUCs were not significantly different in our and the two previous studies conducted by experts, there were some differences. The specificity was marginally higher in our study than in the original studies6,14, which were conducted by experts. The specificity in our study was lower than that reported in the two previous studies, particularly in comparison with the validation study. These differences could be explained by the operator effect on the performance of the model. It has previously been documented that the specificity of ultrasound diagnosis is higher when expert operators perform the examinations.10,12 Assessment of ovarian tumors during previous IOTA studies was performed by ultrasound experts. During data collection, the operators were also able to assess tumor characteristics using “pattern recognition”. In many cases the operators could have determined the type of ovarian tumor before collecting the data using the IOTA protocol. This is a potential source of bias that could have led to an overestimation of the model’s specificity.

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We considered the possibility that prior knowledge that the population was high risk could have contributed to the high false-positive rate and lower specificity of the test. We found that in fact, the proportion of false-positive findings was less in women who presented as tertiary referrals than in low-risk women. While it is true that our study population was smaller than those in the original and validation IOTA studies, the number of cancer cases was more than 10 per model variable, which is sufficiently large for statistical analysis of its accuracy.

A very high sensitivity of the model, particularly in non-expert hands, is reassuring and indicates that it could be used as a primary test in women with adnexal tumors without fear of missing a significant number of malignant lesions. The LR of the model is also high and therefore women with negative results could be managed conservatively or by using minimally invasive surgery.

The large number of false-positive results in our study was mainly caused by the presence of solid content within 15/18 (83.3%) incorrectly classified benign lesions. In some cases hydropic areas in benign cystic teratomas or precipitated debris in ovarian endometriomas were misclassified as solid components within the cyst. Ascites due to other non-malignant medical conditions may also cause false-positive results, as the model assumes that the adnexal lesion is the cause of the ascites. The PPV was 78.0%, which means that more than a fifth of presumed malignant lesions were in fact benign. Women with positive results suggestive of cancer would therefore require additional tests to check the accuracy of the diagnosis in order to avoid subjecting those with benign lesions to unnecessary major gynecological staging operations.

It is not clear what would be the optimal secondary tests in women with suspected cancer on the LR2 model, but subjective assessment by an expert operator would probably be most helpful. The IOTA collaboration has developed another diagnostic model (LR1), which could potentially be more specific than the LR2 model evaluated in this study. The risk-of-malignancy calculation in the LR1 model is based on the analysis of 12 different demographic and ultrasound variables. The number of ovarian cancers in our dataset was not sufficiently large to assess the accuracy of the LR1 model as well, but our study is ongoing and we hope to report on our experience with the LR1 model in the near future.

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Table 2  Accuracy of the International Ovarian Tumor Analysis Group (IOTA) Logistic Regression Model LR2: comparison of findings in the original and prospective validation IOTA studies with those of the current study

<table>
<thead>
<tr>
<th>Study</th>
<th>AUC (95% CI)</th>
<th>SE</th>
<th>Sensitivity (% (95% CI)</th>
<th>Specificity (% (95% CI)</th>
<th>LR+ (95%CI)</th>
<th>LR− (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original IOTA study</td>
<td>0.92</td>
<td>0.018</td>
<td>89 (75–92)</td>
<td>73 (65–80)</td>
<td>3.3 (1.3–9.9)</td>
<td>0.15 (0.02–0.73)</td>
</tr>
<tr>
<td>Prospective validation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOTA study14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External (n = 997)</td>
<td>0.95 (0.93–0.96)</td>
<td>–</td>
<td>91.8 (80.8–100)</td>
<td>85.6 (70.1–94.2)</td>
<td>6.36 (3.33–7.63)</td>
<td>0.10 (0.06–0.14)</td>
</tr>
<tr>
<td>Temporal (n = 941)</td>
<td>0.92 (0.90–0.94)</td>
<td>–</td>
<td>99.2 (82.9–100)</td>
<td>79.8 (66.2–88.6)</td>
<td>4.42 (2.78–5.49)</td>
<td>0.14 (0.1–0.19)</td>
</tr>
<tr>
<td>Current study (n = 124)</td>
<td>0.93 (0.89–0.97)</td>
<td>0.022</td>
<td>97 (92.3–98.9)</td>
<td>69 (60.4–76.5)</td>
<td>3.12 (2.12–4.6)</td>
<td>0.044 (0.01–0.17)</td>
</tr>
</tbody>
</table>

AUC, area under receiver–operating characteristics curve; LR−, negative likelihood ratio; LR+, positive likelihood ratio; SE, standard error.

Figure 2 Receiver–operating characteristics curve of the International Ovarian Tumor Analysis Logistic Regression Model LR2.
In conclusion our study suggests that the overall accuracy of the IOTA LR2 model is maintained when used by a non-expert operator. Although the high test sensitivity is reassuring the specificity is too low to allow the use of the model as a sole test to diagnose ovarian cancer. Further larger studies including mainly low-risk women would be helpful to confirm these findings and to determine what secondary tests would need to be employed in order to reduce the number of false-positive findings.

ACKNOWLEDGMENT
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