

RESEARCH ARTICLE

IOTA Simple Rules in Differentiating between Benign and Malignant Ovarian Tumors

Charuwan Tantipalakov¹, Chanane Wanapirak¹, Surapan Khunamornpong², Kornkanok Sukpan², Theera Tongsong^{1*}

Abstract

Background: To evaluate the diagnostic performance of IOTA simple rules in differentiating between benign and malignant ovarian tumors. **Materials and Methods:** A study of diagnostic performance was conducted on women scheduled for elective surgery due to ovarian masses between March 2007 and March 2012. All patients underwent ultrasound examination for IOTA simple rules within 24 hours of surgery. All examinations were performed by the authors, who had no any clinical information of the patients, to differentiate between benign and malignant adnexal masses using IOTA simple rules. Gold standard diagnosis was based on pathological or operative findings. **Results:** A total of 398 adnexal masses, in 376 women, were available for analysis. Of them, the IOTA simple rules could be applied in 319 (80.1%) including 212 (66.5%) benign tumors and 107 (33.6%) malignant tumors. The simple rules yielded inconclusive results in 79 (19.9%) masses. In the 319 masses for which the IOTA simple rules could be applied, sensitivity was 82.9% and specificity 95.3%. **Conclusions:** The IOTA simple rules have high diagnostic performance in differentiating between benign and malignant adnexal masses. Nevertheless, inconclusive results are relatively common.

Keywords: Adnexal masses - IOTA simple rules - ultrasound - benign ovarian tumor - malignant ovarian tumor

Asian Pac J Cancer Prev, 15 (13), 5123-5126

Introduction

Preoperative discriminating between benign and malignant adnexal masses is essential for decision-making since they need different therapeutic approaches. For example benign adnexal masses like functional ovarian cysts may require only close monitoring or endometrioma may need laparoscopic conservative surgery, whereas ovarian cancers usually need more surgical expertise with well-planned consultation of available oncologists or referral to tertiary center. Several strategies have been proposed to differentiate the two entities, especially using pelvic ultrasound based on either morphological scoring (Sassone et al., 1991; Lerner et al., 1994; Arab et al., 2013; Hafeez et al., 2013; Yavuzcan et al., 2013), subjective assessment (Tongsong et al., 2007), spectral Doppler analysis (Tongsong et al., 2009; Alcazar et al., 2011; Guerriero et al., 2011), or simple rules for general practitioners (Timmerman et al., 2010a; Alcazar et al., 2013). In 2008, Timmerman et al. (2008), as the International Ovarian Tumor Analysis (IOTA) group, proposed simple ultrasound-based rules in predicting ovarian malignancy. The rules are based on the simple demonstration of certain sonographic findings, some of which are indicative of malignancy (M-features) and others of benignity (B-features). More than three-quarter of adnexal masses could be applied for the IOTA simple

rules and the diagnostic performance is high, sensitivity of 92% and specificity of 96% (Timmerman et al., 2010b). The use of the IOTA simple rules has the potential to improve the management of women with adnexal masses. Only a minority of adnexal masses, which the rules yield inconclusive results, need further evaluation by the experienced ultrasound examiners. Nevertheless the IOTA simple rules have never been tested for reproducibility in our population or in other groups of investigators. The objective of this study was to evaluate the diagnostic performance of IOTA simple rules in differentiating between benign and malignant ovarian tumors

Materials and Methods

This study was conducted on female patients admitted to Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, between April 2007 and March 2012, and scheduled for surgery because of the detection of an adnexal mass either by pelvic examination or previous ultrasonography or both. The study was ethically approved by the institute review board. The women were counseled and invited to participate the study with written informed consent.

Exclusion criteria consisted of 1) known diagnoses of adnexal masses, such ovarian cancers scheduled for second look operation, or endometrioma diagnosed by

¹Department of Obstetrics and Gynecology, ²Department of Pathology, Chiang Mai University, Thailand *For correspondence: ttongson@mail.med.cmu.ac.th

previous laparoscopy, etc; 2) patients undergoing surgery beyond 24 hours after ultrasound examination.

All participants underwent ultrasound examination within 24 hours of operation by the authors who had no any clinical information of the patients. All examinations were performed either transabdominal or transvaginal approach or both, using real-time 5-7.5 MHz transvaginal or 3.5-5 MHz transabdominal curvilinear transducer connected to and Aloka model SSD alpha-10 (Tokyo, Japan). During the examination, assessments of sonographic morphology of the masses together with color Doppler study were performed to characterize the masses and prospectively recorded in the report forms. The characteristics of the masses were subsequently analyzed according to the IOTA simple rules (Timmerman et al., 2008) to determine whether there were malignant (M) features or benign (B) features, as presented in Table 1 and Figure 1-2. 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 or inconclusive. Likewise, if no rule applies, the mass cannot be classified or inconclusive.

The final diagnosis as a gold standard was based on pathological examinations or intraoperative diagnosis concluded by the surgeons in case of some benign conditions without pathological specimens. All of adnexal masses were finally categorized into 2 groups as benign and malignant group. The masses with pathological diagnosis of borderline or low malignant potential tumors were categorized in the malignant group. The sensitivity, specificity and predictive values of the IOTA simple rules in predicting malignancy were calculated, using IBM SPSS version 21.0 (IBM SPSS Statistics for Windows, Released 2012. Armonk, NY: IBM Corp).

Results

During the study period, 419 adnexal masses initially diagnosed as ovarian tumors were included in the study and underwent preoperative ultrasound examinations. Twenty-one masses were excluded because of pathological diagnoses of non-gynecologic conditions and surgery beyond 24 hours after ultrasound examination. The remaining 398 adnexal masses, in 376 women, were available for analysis. All were successfully performed either with transabdominal or transvaginal ultrasound. The mean (±SD) age of the women was 42.4±16.2 years

Table 1. The IOTA Simple Rules for Identifying a Benign or Malignant Tumor

Rules for predicting a malignant tumor (M-rules)		
M1	Irregular solid tumor	<input type="checkbox"/>
M2	Presence of ascites	<input type="checkbox"/>
M3	At least four papillary structures	<input type="checkbox"/>
M4	Irregular multilocular solid tumor with largest diameter ≥100 mm	<input type="checkbox"/>
M5	Very strong blood flow (color score 4)	<input type="checkbox"/>
Rules for predicting a benign tumor (B-rules)		
B1	Unilocular	<input type="checkbox"/>
B2	Presence of solid components with the largest diameter <7 mm	<input type="checkbox"/>
B3	Presence of acoustic shadows	<input type="checkbox"/>
B4	Smooth multilocular tumor with largest diameter <100 mm	<input type="checkbox"/>
B5	No blood flow (color score 1)	<input type="checkbox"/>

Table 2. Distribution of the Final Pathological Diagnoses of the Adnexal Masses

Diagnostic categories	Final diagnoses	No.	%
Benign tumors	Mucinous cystadenoma	26	8.2
	Serous cystadenoma	23	7.2
	Endometriotic cyst	66	20.7
	Mature teratoma (Dermoid cyst)	37	11.6
	Follicular cyst, Simple cyst	14	4.4
	Hemorrhagic cyst	5	1.6
	Subserous myoma	5	1.6
	Hydrosalpinx, TOA	5	1.6
	Thecoma, fibroma	7	2.2
	Other Benign tumors	24	7.5
	Borderline tumors	Mucinous borderline tumors	12
Malignant tumors	Serous cystadenocarcinoma	28	8.8
	Mucinous cystadenocarcinoma	11	3.4
	Endometrioid carcinoma	15	4.7
	Clear cell carcinoma	6	1.9
	Endodermal sinus tumor	4	1.3
	Immature teratoma	2	0.6
	Dermoid with squamous cell carcinoma	2	0.6
	Dysgerminoma	3	0.9
	Sex cord stromal tumor	6	1.9
	Other malignant tumors	8	2.5
	Metastatic adenocarcinoma	10	3.1
Total		319	100.0

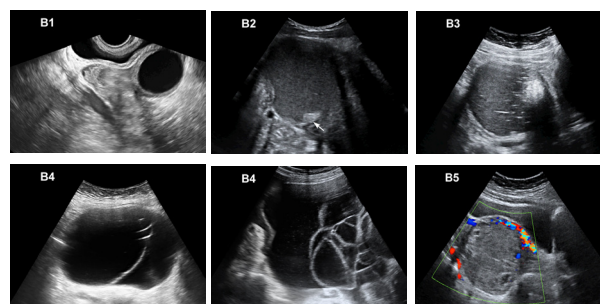


Figure 1. Examples Ultrasound Examinations Classified as B-rules

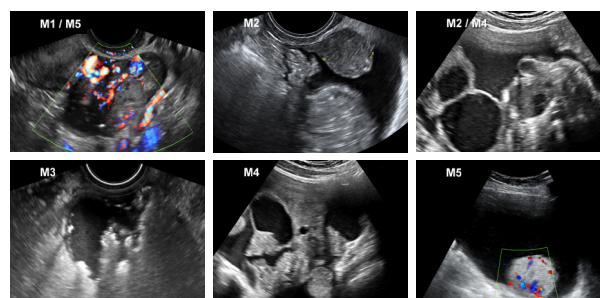


Figure 2. Examples Ultrasound Examinations Classified as M-rules

(range 13-82 years). One hundred and thirty-nine (37.0%) were nulliparous. Most women (255 women, 67.8%) were in reproductive age, 121 (32.2%) were menopausal and 4 of them were in pre-menarche period.

Of 398 masses, the IOTA simple rules could be applied in 319 (80.1%) masses. A total of 79 (19.9%) masses were inconclusive, including 55 benign masses and 24 malignant ones (p>0.05). Final diagnoses of all adnexal masses are summarized and presented in Table 2, including 212 (66.5%) benign tumors, 12 (3.8%) borderline tumors and 95 (29.8%) ovarian cancers. Therefore, the malignant group consisted of 107 (33.6%) masses and benign group had 212 masses. In the 319 masses for which the IOTA

Table 3. Diagnostic Indices of IOTA Simple Rules in Predicting Malignant Adnexal Masses

IOTA Simple Rules	Pathologic Diagnoses		Total
	Malignant Masses (Number)	Benign Masses (Number)	
Malignant	88	10	98
Benign	19	202	221
Total	107	212	319
Sensitivity	= 82.2% (88/107)	95% CI: 75.0%; 89.5%	
Specificity	= 95.3% (202/212)	95% CI: 92.4%; 98.1%	
Positive predictive value	= 89.8% (88/98)	95% CI: 83.8%; 95.8%	
Negative predictive value	= 91.4% (202/221)	95% CI: 85.9%; 97.0%	
Positive likelihood ratio	= 17.2	95% CI: 9.5; 32.1	
Negative likelihood ratio	= 0.19	95% CI: 0.12; 0.28	

simple rules could be applied, sensitivity was 82.9% (95% CI, 75.0%-89.5%), specificity 95.3% (95% CI, 92.4%-98.1%), positive likelihood ratio 17.2 (95% CI, 9.5-32.1) and negative likelihood ratio 0.19 (95% CI, 0.12-0.28) (Table 3).

In the 79 cases in which the simple rules yielded inconclusive results, 50 (63.3%) masses did not exhibit B-rule or M-rule e.g. cases of some regular solid tumors with scanty color flow mapping or smooth multilocular tumors >10 cm with scanty color flow mapping and 29 (36.7%) masses exhibited at least one B-feature and one M-feature, e.g. irregular solid tumors with poor vascularization acoustic shadowing or unilocular cysts with more than four papillary projections and no flow.

Discussion

This study performed external validation of the IOTA simple rules in differentiating between benign and malignant adnexal masses. Our results show that application of the rules yielded high diagnostic performance but approximately 20% of the tests were inconclusive.

Differentiation of benign from malignant tumors can be achieved by several techniques such as clinical assessment, serum CA 125 (Erdogan et al., 2005; Mousavi et al., 2006), sonographic morphology (Sassone et al., 1991; Timmerman et al., 1999), or spectral Doppler evaluation (Kurjak et al., 1993; Tongsong et al., 2009). However, most proposed sonographic assessments need high expertise, limiting them from widely use in clinical practice. Therefore, Timmerman et al. (2010a), the IOTA group, developed the ultrasound simple rules and validated for diagnostic performance. The simple rules seem to be more attractive and practical because they are uncomplicated and user-friendly in categorizing an adnexal mass as benign or malignant. Nevertheless, only few studies from other groups in the world have been conducted to test the accuracy and reproducibility of the simple rules. Fathallah et al. (2011) performed a prospective study using the IOTA simple rules in a series of 122 masses. The malignancy rate was 11.5% (14 malignancies). The IOTA simple rules were applicable in 89.3% of masses. The sensitivity of the rules was 73% (95% CI: 45-100%) and the specificity was 97% (95% CI: 94-100%). Sensitivity was relatively low, when compared to our results whereas the applicable rate was very high.

The difference may partly be due to the low malignancy rate (only 14 cases) in the study reported by Fathallah et al. (2011). More recently, Hartman et al. (2012) reported a prospective study in a series of 103 women and 110 adnexal tumors. They demonstrated that the majority of tumors were correctly classified using the IOTA simple rules. CA 125 alone performed worse than did ultrasound in discriminating malignant from benign adnexal tumors. Recently, Kaijser et al. (2013) demonstrated that an ultrasound based prediction model (developed by IOTA) shows a better diagnostic performance than ROMA for the characterization of a pelvic mass in both pre- and postmenopausal women.

The weakness of this study may include the followings:

1) The authors had some experience on gynecologic ultrasound. Thus, sonographic evaluation of the tumor was not a blind method. As a consequence, the some characteristic features of the mass could have been anticipated, such as tip of the ice berg sign relatively specific for dermoid cyst or ground-glass appearance for endometriotic cysts, etc. However, the assessment of adnexal masses using IOTA simple rules was objective, therefore such a bias should be only minimal; 2) A potential weakness of this study was that only adnexal masses undergoing operation were included. This is indispensable, as pathological examinations or operative findings as a gold standard was required in a study determining diagnostic performance with regard to malignancy. However, this bias may be unlikely to affect the conclusion, since masses not requiring surgery are likely to be less complex and easier to categorize.

Our results as external validation suggest that the IOTA simple rules are robust. Together with its simplicity, thus this study indicates that the rule is likely to make generalizable, and we believe that it should be possible for any qualified ultrasound practitioner to obtain information on the ultrasound variables required for the rules.

One limitation of this technique should be mentioned is that the test had a significant number of inconclusive results, approximately 20%, which need further evaluation by the sonographic experts.

In conclusion, the IOTA simple rules have high diagnostic performance in differentiating between benign and malignant adnexal masses. Application of the IOTA simple rules yielded acceptable results in terms of sensitivity and specificity. However, the inconclusive result is relatively high and this group must be referred to expert sonographers.

Acknowledgements

We wish to thank the Faculty of Medicine Research Fund of Chiang Mai University and the National Research University Project under Thailand's Office of the Higher Education Commission for financial support.

References

- Alcazar JL, Guerriero S, Laparte C, Ajossa S, Jurado M (2011). Contribution of power Doppler blood flow mapping to gray-scale ultrasound for predicting malignancy of adnexal

- masses in symptomatic and asymptomatic women. *Eur J Obstet Gynecol Reprod Biol*, **155**, 99-105.
- Alcazar JL, Pascual MA, Olartecoechea B, et al (2013). IOTA simple rules for discriminating between benign and malignant adnexal masses: prospective external validation. *Ultrasound Obstet Gynecol*, **42**, 467-71.
- Arab M, Yaseri M, Ashrafganjoi T, et al (2012). Comparison of two ovarian malignancy prediction models based on age sonographic findings and serum CA125 measurement. *Asian Pac J Cancer Prev*, **13**, 4199-202.
- Erdogan N, Ozcelik B, Serin IS, Akgun M, Ozturk F (2005). Doppler ultrasound assessment and serum cancer antigen 125 in the diagnosis of ovarian tumors. *Int J Gynaecol Obstet*, **91**, 146-50.
- Fathallah K, Huchon C, Bats AS, et al (2011). External validation of simple ultrasound rules of Timmerman on 122 ovarian tumors. *Gynecol Obstet Fertil*, **39**, 477-81.
- Guerriero S, Alcazar JL, Pascual MA, et al (2011). The diagnosis of ovarian cancer: is color Doppler imaging reproducible and accurate in examiners with different degrees of experience? *J Womens Health*, **20**, 273-7.
- Hafeez S, Sufian S, Beg M, et al (2013). Role of ultrasound in characterization of ovarian masses. *Asian Pac J Cancer Prev*, **14**, 603-6.
- Hartman CA, Juliato CR, Sarian LO, et al (2012). Ultrasound criteria and CA 125 as predictive variables of ovarian cancer in women with adnexal tumors. *Ultrasound Obstet Gynecol*, **40**, 360-6.
- Kaijser J, Van GT, Van HK, et al (2013). A comparison between an ultrasound based prediction model (LR2) and the risk of ovarian malignancy algorithm (ROMA) to assess the risk of malignancy in women with an adnexal mass. *Gynecol Oncol*, **129**, 377-83.
- Kurjak A, Predanic M, Kupesic-Urek S, Jukic S (1993). Transvaginal color and pulsed Doppler assessment of adnexal tumor vascularity. *Gynecol Oncol*, **50**, 3-9.
- Lerner JP, Timor-Tritsch IE, Federman A, Abramovich G (1994). Transvaginal ultrasonographic characterization of ovarian masses with an improved, weighted scoring system. *Am J Obstet Gynecol*, **170**, 81-5.
- Mousavi AS, Borna S, Moenoddini S (2006). Estimation of probability of malignancy using a logistic model combining color Doppler ultrasonography, serum CA125 level in women with a pelvic mass. *Int J Gynecol Cancer*, **16**, 92-8.
- Sassone AM, Timor-Tritsch IE, Artner A, Westhoff C, Warren WB (1991). Transvaginal sonographic characterization of ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. *Obstet Gynecol*, **78**, 70-6.
- Timmerman D, Ameye L, Fischerova D, et al (2010a). Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. *BMJ*, **341**, 6839.
- Timmerman D, Schwarzler P, Collins WP, et al (1999). Subjective assessment of adnexal masses with the use of ultrasonography: an analysis of interobserver variability and experience. *Ultrasound Obstet Gynecol*, **13**, 11-6.
- Timmerman D, Testa AC, Bourne T, et al (2008). Simple ultrasound-based rules for the diagnosis of ovarian cancer. *Ultrasound Obstet Gynecol*, **31**, 681-90.
- Timmerman D, Van CB, Testa AC, et al (2010b). Ovarian cancer prediction in adnexal masses using ultrasound-based logistic regression models: a temporal and external validation study by the IOTA group. *Ultrasound Obstet Gynecol*, **36**, 226-34.
- Tongsong T, Wanapirak C, Neeyalavira V, Khunamornpong S, Sukpan K (2009). E-flow Doppler indices for prediction of benign and malignant ovarian tumors. *Asian Pac J Cancer Prev*, **10**, 139-42.
- Tongsong T, Wanapirak C, Sukpan K, Khunamornpong S, Pathumbal A (2007). Subjective sonographic assessment for differentiation between malignant and benign adnexal masses. *Asian Pac J Cancer Prev*, **8**, 124-6.
- Yavuzcan A, Caglar M, Ozgu E, et al (2013). Should cut-off values of the risk of malignancy index be changed for evaluation of adnexal masses in Asian and Pacific populations? *Asian Pac J Cancer Prev*, **14**, 5455-9.