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Diagnostic utility of the risk of malignancy index for borderline ovarian tumors

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Summary

Purpose of investigation: To determine the best cutoff value for the risk of malignancy index (RMI) by comparing the four malignancy risk indices (RMI 1, RMI 2, RMI 3, and RMI 4) in patients with borderline ovarian tumors (BOTs). *Materials and Methods:* The authors enrolled 510 patients in this retrospective study: 76 women with BOTs and 434 with benign adnexal masses. There were no restrictions in BOT histotypes. *Results:* The area under the curves for RMI 1, RMI 2, RMI 3, and RMI 4 were 0.742, 0.755, 0.765, and 0.787, respectively. RMI 4 performed better in diagnosing BOT preoperatively than RMI 1, RMI 2, and RMI 3, at a cutoff value of 190. *Conclusion:* RMI 4 at a cutoff value of 190 can be successfully used for identifying patients with suspected BOTs who require specialist referral.

Key words: Borderline ovarian tumor; Risk of malignancy index; Diagnosis.

Introduction

Borderline ovarian tumors (BOTs) are epithelial tumors of low malignant potential, and represent up to 15-20% of all ovarian malignancies [1]. These tumors are characterized by atypical proliferative epithelium with a stratified growth pattern but without destructive stromal invasion [1]. The majority of women with BOTs are diagnosed during their reproductive years; one-third are below 40 years at diagnosis and may be candidates for fertility-preserving treatments [2, 3]. Patients with BOTs usually have excellent prognoses; however, 11% relapse, of which 20-30% demonstrate malignant transformation [4].

Approximately 30% of patients with BOTs are asymptomatic, over 50% complain of non-specific symptoms such as abdominal bloating or discomfort, and 10% develop menstrual abnormalities [4, 5]. The majority of BOTs are detected on ultrasound scans. However, the lack of prominent ultrasonographic features means that BOTs are often misdiagnosed as benign or primary invasive ovarian tumors [6]. Therefore, several additional tests are used to differentiate BOT from pelvic masses, including CT, MRI, color Doppler ultrasonography, tumor markers, and patient menopause status.

The optimal treatment for BOTs is unilateral oophorectomy, but only in the hands of expert oncologic surgeons to limit the risk of surgical spill, residual in-situ disease, and inadequate staging associated with a higher risk of recurrence [7]. In cases of advanced disease or recurrence, adequate surgery with primary or secondary debulking is needed [7]. For these reasons, the preoperative discrimination of malignancy is especially important for BOTs. Accurate diagnosis and staging will facilitate optimal patient management, particularly in patients desiring to preserve their fertility. However, it is often difficult to differentiate BOT from other pelvic masses. Based on earlier studies, the preoperative diagnosis of BOTs remains challenging.

Jacobs *et al.* developed the Risk of Malignancy Index (RMI) in 1990 for identifying patients at high risk of ovarian malignancy who require referral to gynecological oncology centers [8]. The RMI is a scoring system based on a logistic regression model that combines ultrasonographic findings with menopausal status and serum cancer antigen (CA)-125 levels. Tingulstad *et al.* modified the RMI to develop RMI 2 and 3 [9, 10], and Yamamato *et al.* recently introduced RMI 4 [11]. However, previous studies have found that the RMI performs poorly in BOTs in young patients, and in pathologies with obscure ultrasonographic features. The test has also been reported to have a low sensitivity – it did not identify 73% (31/42 cases) of BOTs in one study [12]. Further studies are needed to address these concerns. At present, only one study has attempted to determine an adequate RMI cutoff value for preoperative assessment of BOTs. It compared the diagnostic performance of four malignancy risk indices. However, the study was confined to serous (n=30/50) and mucinous (n=20/50) BOTs [13].

The purpose of this study was to compare the four malignancy risk indices (RMI 1, RMI 2, RMI 3, and RMI 4) in patients with all BOT histotypes, and determine the best RMI index and an appropriate RMI cutoff value.

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Materials and Methods

This was a retrospective study conducted at the Department of Obstetrics and Gynecology of Dong-A University Medical Center between January 7, 2007 and August 25, 2015. Clinical data were obtained from 76 women with BOTs scheduled for laparoscopy or laparotomy, as well as a control group of 434 women with benign adnexal masses. Ultrasound findings, menopausal status, preoperative serum CA125 levels, and tumor sizes were checked.

A total ultrasound score (U) was calculated for each patient. If there were bilateral adnexal tumors, the more morphologically complicated tumor was evaluated; if both masses were morphologically similar, the larger one was utilized in the statistical analysis. An ultrasound score of 1 point was given for each of the following ultrasonographic features suggestive of malignancy: a multi-loculated cystic lesion containing papillary projections and solid areas, bilateral lesions, intraperitoneal fluid, and intra-abdominal metastases.

Postmenopausal status (M) was defined as more than one year of amenorrhea, or being 50 years of age in women who had undergone a hysterectomy. All other women were considered premenopausal. The tumor size (single greatest diameter) (S) was measured using ultrasound. The serum CA125 level was applied directly to the formula.

Based on the data obtained, the RMI 1, RMI 2, RMI 3, and RMI 4 scores were calculated for each patient. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (DA) of each of the four indices were also calculated. The formulae are as follows:

(1) RMI 1 = U × M × CA 125; a total ultrasound score of 0 yielded U = 0, a score of 1 yielded U = 1, and a score of ≥ 2 yielded U = 3. Premenopausal status yielded M = 1 and postmenopausal status yielded M = 3. The serum CA125 level was applied directly to the calculation [8].

(2) RMI 2 = U × M × CA125; a total ultrasound score of 0 or 1 yielded U = 1, and a score of ≥ 2 yielded U = 4. Premenopausal status yielded M = 1 and postmenopausal status yielded M = 4. The serum CA125 level was applied directly to the calculation [9].

(3) RMI 3 = U × M × CA125; a total ultrasound score of 0 or 1 yielded U = 1, and a score of ≥ 2 yielded U = 3. Premenopausal status yielded M = 1 and postmenopausal status yielded M = 3. The serum CA125 level was applied directly to the calculation [10].

(4) RMI 4 = U × M × S × CA125, where a total ultrasound score of 0 or 1 yielded U = 1, and a score of ≥ 2 yielded U = 4. Premenopausal status yielded M = 1 and postmenopausal status yielded M = 4. A tumor size of < 7 cm yielded S = 1, and ≥ 7 cm yielded S = 2. The serum CA125 level was applied directly to the calculation [11].

In this study, the definitive diagnoses for included patients were based on the histopathologic examination of surgical specimens. Tumors were classified according to World Health Organization definition, and BOTs were staged in accordance with the International Federation of Gynecology and Obstetrics (FIGO) criteria [14]. Sensitivity was defined as the proportion of patients with BOT who had positive test results. Specificity was defined as the proportion of patients with benign disease who had positive test results. PPV was defined as the proportion of patients with positive tests who had BOT, and NPV was defined as the proportion of patients with negative tests who had benign disease. DA was defined as the proportion of all BOT patients with positive tests and patients with benign disease with negative tests combined. This study was approved by the hospital ethics committee, and written informed consent was obtained from all participants.

All statistical analyses were carried out with SPSS 15.0. The chi-square (χ^2) test was used to interpret the differences in the ultrasound score, age, menopausal status, and tumor size distribution. The Mann–Whitney U test was used to compare the differences in the distribution of CA125 among patients with BOTs and benign tumors. The Kolmogorov–Smirnov test was used to assess the normality of the continuous distribution for data. Continuous data were compared with the Student *t*-test or Mann–Whitney U test, according to their distribution. To determine the best cut-off value for differentiating malignant and benign adnexal masses, a receiver operating characteristic (ROC) curve was plotted. An ROC curve was plotted to demonstrate the tradeoff between sensitivity and specificity in distinguishing between BOTs and benign tumors. A *p*-value of less than 0.05 was considered statistically significant.

Results

A total of 510 patients were included in the study; 76 patients had BOTs and 434 patients had benign adnexal masses. Histopathological assessment of the BOTs included 52 mucinous, 18 serous, two seromucinous, two clear cell, one endometrioid, and one Brenner. The majority of BOTs belonged to Stage IA (93%); 3% were Stage IB, 3% Stage IC, and 1% Stage II–III. Regarding the benign lesions, 42.4% were mature cystic teratomas, 21.4% were serous cystadenomas, 18.9% were mucinous cystadenomas, and 6.0% were endometriomas. The FIGO stages [14] of the borderline cases and the histopathological classification of the benign cases are detailed in Table 1.

The mean age was 42.1 ± 17.5 years in patients with BOTs, and 40.0 ± 15.2 years in patients with benign lesions. The two groups were similar in terms of age ($p = 0.279$). The proportion of premenopausal patients in the BOT group and benign disease group were 71.1% and 75.3%, respectively, and the difference was not statistically significant ($p > 0.05$). The median value of CA125 levels was 81.0 ± 90.3 U/mL in the BOT group and 34.8 ± 61.6 U/mL in the benign disease group; the difference was statistically significant ($p < 0.001$). The mean tumor size was 15.8 ± 8.4 mm in the BOT group and 7.6 ± 4.0 mm in the benign disease group, and the difference was statistically significant ($p < 0.001$). In terms of the ultrasound scores, in the BOT group, 9.2% (seven cases) were U = 0, 27.6% (21 cases) were U = 1, 52.3% (39 cases) were U = 2, 6.6% (five cases) were U = 3, and 5.3% (four cases) were U = 4. For the benign disease group, this was 27.4% (119 cases), 34.8% (151 cases), 36.6% (159 cases), 1.2% (5 cases), and 0% (0 cases), respectively. The difference between the groups was statistically significant ($p< 0.001$). The study findings regarding age, menopausal status, tumor markers, tumor size, and ultrasound score are shown in Table 2.

The achievements of RMI 1, RMI 2, RMI 3, and RMI 4 at different cutoff levels are presented in Table 3. The area under the curve (AUC) for RMI 1, RMI 2, RMI 3, and RMI 4 was 0.742, 0.755, 0.765 and 0.787, respectively. RMI 4 had a higher accuracy than RMI 1, RMI 2, and RMI 3. A direct comparison of the four indices showed that RMI 4 at a

Table 1. — *Distribution of diagnosis and stages in 510 patients presenting with a BOT and benign mass.*

Diagnosis	N (%)		Stage				N (%)
	Premenopausal (n=383)	Postmenopausal (n=127)	IA	IB	IC	II-IV	Total (n=510)
BOT							
Mucinous	38 (70.4)	14 (63.6)	52	0	0	0	52 (68.5)
Serous	14 (25.8)	4 (18.0)	13	2	2	1	18 (23.7)
Seromucinous	1 (1.9)	1 (4.6)	2	0	0	0	2 (2.6)
Clear cell	0 (0.0)	2 (9.2)	2	0	0	0	2 (2.6)
Endometrioid	1 (1.9)	0 (0.0)	1	0	0	0	1 (1.3)
Brenner	0 (0.0)	1 (4.6)	1	0	0	0	1 (1.3)
Total BOT cases	54 (100)	22 (100)	71	2	2	1	76 (100)
Benign							
Mature cystic teratoma	155 (47.2)	29 (27.7)					184 (42.4)
Serous cystadenoma	58 (17.6)	35 (33.4)					93 (21.4)
Mucinous cystadenoma	61 (18.6)	21 (20.1)					82 (18.9)
Endometriosis	25 (7.6)	2 (1.8)					27 (6.0)
Fibroma	6 (1.2)	7 (6.3)					13 (3.0)
Tubo-ovarian abscess	5 (1.5)	0 (0.0)					5 (1.2)
Corpus luteal cyst	5 (1.5)	1 (0.9)					6 (1.4)
Paratubal cyst	4 (1.2)	2 (1.9)					6 (1.4)
Fibrothecoma	1 (0.3)	4 (3.6)					5 (1.2)
Mucinous cystadenofibroma	2 (0.6)	1 (0.9)					3 (0.7)
Struma ovarii	2 (0.6)	1 (0.9)					3 (0.7)
Actinomycosis	2 (0.6)	0 (0.0)					2 (0.5)
Brenner tumor	2 (0.6)	0 (0.0)					2 (0.5)
Serous cystadenofibroma	0 (0.0)	2 (1.9)					2 (0.5)
Sclerosing stromal tumor	1 (0.3)	0 (0.0)					1 (0.2)
Total benign cases	329 (100)	105 (100)					434 (100)

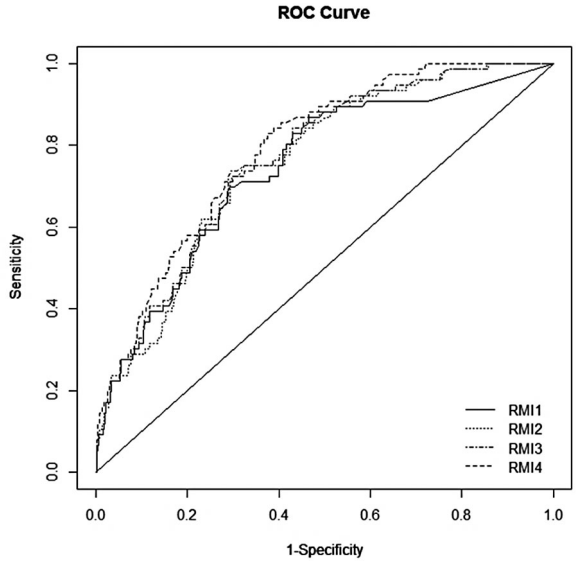

Figure 1. Receiver operator characteristic curve showing the achievements of RMI 1, RMI 2, RMI 3, and RMI 4.

cutoff level of 190 was significantly better at predicting malignancy than RMI 1 at a cutoff level of 80 (p = 0.0048), RMI 2 at a cutoff level of 110 (p = 0.0000), and RMI 3 at a cutoff level of 80 (p = 0.0021) (Table 4). RMI 4 at a cutoff level of 190 had a sensitivity of 71.1%, a specificity of 70.7%, a PPV of 29.8%, a NPV of 93.3%, and a DA of 70.8%. The achievements of RMI 1, RMI 2, RMI 3, and RMI 4 are presented as ROC curves in Figure 1.

Discussion

BOTs are a distinct subtype of epithelial ovarian tumors identified by FIGO in 1961 and adopted by the World Health Organization (WHO) in 1973 [7]. Pathologically, BOTs are characterized by stratification of epithelial lining of the papillae, formation of microscopic papillary projections, epithelial pleomorphism, atypicality, and mitotic activity, without invasion of stroma [15]. Although these features are similar to those of malignant epithelial ovarian tumors, they are very different from ovarian carcinomas in terms of the younger age at diagnosis (45 *vs.* 55 years), higher infertility rate (observed in up to 35% patients with BOTs), lower frequency of *BRCA* gene mutations, distribution of tumor histotypes, lower FIGO stage (75% *vs.* 25% at FIGO Stage I), and better overall prognosis [3, 7, 16]. However, it is difficult to differentiate BOT from benign tumors and ovarian carcinomas preoperatively – a multicenter survey found that only 8.4% of cases had a

Table 2. — *The distribution of benign and malignant cases by age, menopausal status, ultrasound score, tumor size, and serum CA 125.*

Variables	Benign	BOT	Significance level	
	n=434 (85.1%)	n=76 (14.9%)	Test	*p*
Age (years)	40.0 ± 15.2	42.1 ± 17.5	χ^2	0.279
Menopausal status				
Premenopausal	327 (75.3%)	54 (71.1%)	χ^2	0.515
Postmenopausal	107 (24.7%)	22 (28.9%)		
Ultrasound score				
0	119 (27.4%)	7 (9.2%)	χ^2	0.000
1	151(34.8%)	21 (27.6%)		
2	159 (36.6%)	39 (51.3%)		
3	5 (1.2%)	5 (6.6%)		
4	0 (0.0%)	4 (5.3%)		
Tumor size	7.6 ± 4.0	15.8 ± 8.4	χ^2	0.000
CA 125 (IU/ml)	34.8 ± 61.6	81.0 ± 90.3	U-test	0.000

preoperative diagnosis of BOT [17].

This study has compared four malignancy risk indices (RMI 1, RMI 2, RMI 3, and RMI 4) in patients with BOTs, so as to establish the best RMI index and an optimal RMI cutoff value for improving preoperative diagnostic accuracy. This is especially important for BOTs. Fertility preservation is crucial in patients with suspected BOTs, particularly since many are still of childbearing age. In addition, although BOTs tend to have good prognoses, 11% recur, and 2-4% demonstrate malignant transformation [4]. Moreover, there is still no proven benefit for adjuvant chemotherapy [5, 18-20]. As such, an accurate preoperative diagnosis will aid adequate staging by experienced oncologic surgeons, which is the all-important determinant of prognosis in patients with suspected BOTs.

The RMI was designed to help identify patients with high risk of malignancy, such that appropriate referral to gynecological oncology centers can be made [8]. However, it is most effective at predicting invasive malignancy in postmenopausal patients who have a higher incidence of ovarian carcinomas. It performs poorly as a diagnostic tool for patients with BOTs, and very few studies have addressed this issue. The RMI calculations are affected by the fact that patients with BOTs are mainly premenopausal, and tend to have low serum CA125 levels. These features are similar to those of benign tumors. Therefore, the present authors studied these RMI parameters in BOTs and benign lesions.

In 2011, Alanbay *et al.* [21] assessed the prognostic values of RMI 4, the ultrasound score, menopausal status, serum CA125, and CA19-9 levels in patients with BOTs. Their study was the first in the literature to evaluate BOT patients separately. They found that a RMI 4 cutoff value of 200 was suitable for differentiating between benign tumors and BOTs. Yenen *et al.* [13], meanwhile, compared the diagnostic performance of RMI 1-4 for BOTs directly. In their study, RMI 4 performed better than RMI 1-3 at the cutoff level of 200, with a sensitivity of 60%, a specificity of 80%, a PPV of 75%, a NPV of 67%, and a DA of 70%. However, this study was limited to only serous and mucinous BOTs, to the exclusion of all other histotypes. To the best of the present authors' knowledge, this study is the first to compare the RMIs in patients with all histotypes of BOTs. They found that RMI 4 was the best RMI for predicting BOTs. An RMI 4 score of 190 achieved a sensitivity of 71.1% and a specificity of 70.7%.

Ultrasonography represents the best diagnostic modality for detecting BOTs [22]. However, its use is limited by its subjective nature even in the hands of experts. Bailey *et al.* [23], recognizing the ultrasound subjective 'pattern recognition' method, examined the RMI in a diverse patient population. They accounted for variation in ultrasound and differences in automated CA125 assays and validated the RMI in a typical clinical setting. They found that at a RMI cutoff value of 200, the RMI had a sensitivity of 87.4%, a specificity of 56.8%, a PPV of 86.8%, and an NPV of 58.1%. In 2010, Moore *et al.* [24] reported the RMI score by using pelvic ultrasound, CT, MRI, or any combination of the three imaging modalities; the sensitivities reported for the RMI in this study were similar to those reported by Bailey *et al.*; however, these studies were confined to ovarian malignancies alone.

Several recent studies have examined the grayscale and color Doppler sonographic features of BOTs. Emoto *et al.* [25] reported that BOTs showed significantly higher intratumoral vascularity and lower vascular resistance in tumor vessels, as compared to those of benign tumors. However, subsequent studies were unable to establish any specific Doppler flow indices for diagnosing BOTs [6, 26]. Another new ultrasound technology, the three-dimensional (3D) ultrasound, does not offer any additional benefit in diagnosing BOTs specifically [27]. The 3D grayscale images are helpful in detecting irregularities of the inner or outer wall of the mass, or papillary projections into a cyst cavity from the cyst wall. However, previous studies comparing the utility of 3D and conventional two-dimensional ultrasound in predicting BOTs found that they were largely comparable.

Several studies have reported the utility of modern imaging techniques such as CT and MRI in diagnosing BOTs. While CT can identify the complex architectural patterns of BOTs, the contrast between the cystic and solid components of the tumors are best appreciated on T2-weighted MRI [28, 29]. The soft tissue contrast on CT scans is also relatively poor, which limits the specific diagnosis of BOTs.

Moore *et al.* [30] developed a simple biomarker-based risk of ovarian malignancy algorithm (ROMA). Unlike RMI, this does not require ultrasonography. A later study found that ROMA was far better (AUC 0.909) than RMI (AUC 0.762) in detecting early stage ovarian carcinoma

Table 3. — *Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and diagnostic accuracy (DA) for predicting malignancy at different cutoff levels of four malignancy risk indices (RMI 1, RMI 2, RMI 3, and RMI 4).*

	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)
RMI 1	60	71.1	62.0	24.7	92.4	63.3
	70	71.1	66.6	27.1	92.9	67.3
	80	69.7	70.3	29.1	93.0	70.2
	90	65.8	71.2	28.6	92.2	70.4
	100	61.8	73.3	28.8	91.6	71.6
RMI 2	70	75.0	60.4	24.9	93.2	62.5
	90	75.0	65.4	27.5	93.7	66.9
	110	72.4	70.0	29.7	93.5	70.4
	130	64.5	72.8	29.3	92.1	71.6
	150	61.8	76.0	31.3	91.9	73.9
RMI 3	60	75.0	61.3	25.3	93.3	63.3
	70	75.0	66.1	27.9	93.8	67.5
	80	73.7	70.0	30.1	93.8	70.6
	90	67.1	71.0	28.8	92.5	70.4
	100	63.2	73.3	29.3	91.9	71.8
RMI 4	90	82.9	61.1	27.2	95.3	64.3
	140	73.7	66.8	28.0	93.5	67.8
	190	71.1	70.7	29.8	93.3	70.8
	240	60.5	74.7	29.5	91.5	72.5
	290	57.9	79.7	33.3	91.5	76.5

Table 4. — *Comparison of RMI 1, RMI 2, RMI 3 and RMI 4 values with each other.*

Cutoff-value	*p*-value
RMI 1-2	0.3835
RMI 1-3	0.1293
RMI 1-4	0.0048
RMI 2-3	0.0005
RMI 2-4	0.0000
RMI 3-4	0.0021

[24]. However, although ROMA improved the differentiation between BOTs and ovarian cancer, it was not helpful in distinguishing between BOTs and benign tumors.

Patients with BOTs have a good overall survival rate (FIGO Stage I: 95%, Stage II-IV: 70%-85%), with a 11% relapse rate, and a 2-4% absolute risk of developing invasive disease (i.e. 33.3% of all recurrences) [7]. Nevertheless, to enhance the prognosis, the preoperative evaluation and treatment of patients with suspected BOT should take place at a tertiary gynecologic oncology center. The RMI is a simple scoring test for predicting ovarian malignancy. However, several studies have reported that it has significant limitations in identifying BOTs (low malignant potential), Stage 1 invasive ovarian cancers and non-epithelial ovarian cancers [31]. Moreover, previous studies tended to include BOTs in the malignant disease group. Therefore, the present authors evaluated the best RMI cutoff value by comparing four malignancy risk indices in patients with all histotypes of BOTs.

Of the four indices, RMI 4 was the most impressive in predicting BOTs. The cutoff value of 190 had a relatively good NPV (93.3%), such that only a small number (22 of 510 people tested) of individuals with false negative tests would have a false sense of security. However, it also had a lower PPV (29.8%), which meant that only 29.8% of the people with a positive test actually had BOT. It incorrectly assigned a suspicion of BOT to a great number (127 of 510 people tested) of individuals. The present authors believe that this resulted from the larger number of patients in the control group compared to the BOT group. However, RMI 4 at a cutoff value of 190 showed good overall predictive ability in this present study; this was corroborated by the other diagnostic performance parameters (sensitivity, specificity, DA, and NPV). Further studies are needed to investigate the potential and limitations of RMI in the detection of BOTs. In addition, the present study has certain limitations, such as being a retrospective analysis with inherent biases. As such, further prospective multicenter studies to validate the present findings are also warranted.

Conclusion

RMI is a simple and cost-effective test for identifying patients who should be referred to specialistic services from primary care. In patients with suspected BOTs, a RMI 4 cutoff value of 190 may be used to aid differential diagnosis.

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