

# Is the Risk of Malignancy Index a predictive tool for preoperative differentiation between borderline ovarian tumor and ovarian cancer?

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## Summary

**Purpose:** To determine an appropriate Risk of Malignancy Index (RMI) cutoff value by comparative analysis of the four malignancy risk indices for distinguishing between borderline ovarian tumor (BOT) and ovarian cancer (OC). **Materials and Methods:** Retrospective analysis of the medical records of 339 patients (115 BOTs and 224 OCs). **Results:** There were no significant differences in the area under the ROC curve (AUC) for RMI 1, RMI 2, RMI 3, and RMI 4 (0.792, 0.791, 0.785, and 0.785, respectively). However, the diagnostic capability of the RMI was significantly greater than that of other factors. **Conclusion:** This study is the first to investigate the performance of the four Risk of Malignancy Indices for distinguishing between BOT and invasive OC. Although there were no significant differences between RMI scores, the RMIs were very effective at predicting an accurate preoperative diagnosis in patients with all BOT and OC histotypes.

**Key words:** Risk of Malignancy Index; Preoperative diagnosis; Borderline ovarian tumor; Ovarian cancer.

## Introduction

Ovarian cancer (OC) is the most aggressive gynecological malignancy in women, and centralization of primary surgery is recommended to optimize complete cytoreduction and survival. However, many patients with OC are treated by general surgeons [1-3] because it is difficult to know the precise nature of an ovarian tumor before surgery; this results in surgical spillage, residual carcinoma, and the subsequent need for additional surgeries.

Preoperative diagnostic accuracy is also important for borderline ovarian tumors (BOTs). These epithelial tumors of low malignant potential tend to have a favorable prognosis, but 11% recur, and 2-4% undergo permanent malignant transformation [4]. Moreover, most patients with BOTs are diagnosed during their reproductive years; approximately one-third (27-36% of cases) are < 40 years old at the time of diagnosis and may be candidates for fertility-preserving treatments [5, 6]. Therefore, although the optimal conservative treatment of BOTs is unilateral oophorectomy, the procedures should be performed by a gynecological oncologist. However, preoperative identification of ovarian malignancies is not always feasible with current diagnostic modalities. In particular, it is difficult to distinguish between BOT and OC, which would help to determine the scope of surgery; BOT can be managed less aggressively than invasive OCs, particularly in women who wish to preserve their fertility [7]. However, with a few exceptions, most previous studies have focused on preoperatively dis-

criminating between benign and malignant adnexal masses.

The Risk of Malignancy Index (RMI) was first developed by Jacobs *et al.* in 1990 for accurate preoperative diagnosis of OCs [8]. The RMI is a simple, reliable scoring system based on logistic regression that integrates ultrasonic features, menopause status, and cancer antigen (CA) 125 concentration. Tingulstad *et al.* revised the RMI to introduce RMI 2 and 3 [9, 10], and Yamamoto *et al.* newly introduced RMI 4 [11]. However, the RMI performs poorly in identifying BOTs, early invasive OCs (stage I), and non-epithelial OCs [12]. In addition, previous studies have usually included BOTs in the malignant disease group. Alanbay *et al.* evaluated the preoperative diagnostic values of RMI 4, ultrasound scores, menopausal status, and serum CA 125 and CA 19-9 levels in 2011 [13]. That study was the first to evaluate BOT separately. Meanwhile, to date, only one study has evaluated the optimal RMI cutoff for diagnosing BOT preoperatively. That study described the prognostic performance of RMI 1-4. However, it was limited to 30 serous (60%) and 20 mucinous (40%) BOTs [14]. Thus, very few studies have looked at BOTs separately. Additionally, no study has compared the preoperative utility of the four RMIs in distinguishing BOT from invasive OC.

This study aimed to evaluate the prognostic accuracy of the four Risk of Malignancy Indices (RMI 1, RMI 2, RMI 3, and RMI 4) in patients with BOT and invasive OC histotypes, and to define the best index and an optimal RMI cutoff value.

Table 1. — Distribution of diagnosis and stages in 339 patients presenting with a BOT and OC.

Diagnosis	N (%)		Stage				N (%)
	Premenopausal (n = 174)	Postmenopausal (n = 165)	I	II	III	IV	Total (n = 339)
BOT <sup>†</sup>							
Mucinous	58 (71.6)	26 (76.5)	84	0	0	0	84 (73.1)
Serous	21 (26.0)	4 (11.8)	24	0	0	1	25 (21.7)
Seromucinous	1 (1.2)	1 (2.9)	2	0	0	0	2 (1.7)
Clear cell	0 (0.0)	2 (5.9)	2	0	0	0	2 (1.7)
Endometrioid	1 (1.2)	0 (0.0)	1	0	0	0	1 (0.9)
Brener	0 (0.0)	1 (2.9)	1	0	0	0	1 (0.9)
Total BOT cases	81 (100)	34 (100)	114	0	0	1	115 (100)
OC <sup>‡</sup>							
Serous	49 (52.6)	73 (55.7)	26	7	82	7	122 (54.5)
Mucinous	15 (16.1)	15 (11.5)	20	3	7	0	30 (13.4)
Endometrioid	14 (15.1)	10 (7.6)	9	6	9	0	24 (10.7)
Clear cell	11 (11.8)	11 (8.4)	14	2	6	0	22 (9.7)
Malignant mixed müllerian tumor	2 (2.2)	5 (3.8)	2	0	4	1	7 (3.2)
Transitional cell carcinoma	1 (1.1)	6 (4.6)	2	2	3	0	7 (3.2)
Squamous cell carcinoma	1 (1.1)	3 (2.2)	2	2	0	0	4 (1.8)
Undifferentiated	0 (0.0)	3 (2.2)	2	0	1	0	3 (1.3)
Seromucinous	0 (0.0)	1 (0.8)	1	0	0	0	1 (0.4)
Peritoneal carcinoma	0 (0.0)	1 (0.8)	0	0	1	0	1 (0.4)
Small cell carcinoma	0 (0.0)	1 (0.8)	1	0	0	0	1 (0.4)
Papillary adenocarcinoma	0 (0.0)	1 (0.8)	0	0	1	0	1 (0.4)
X-müllerian adenosarcoma	0 (0.0)	1 (0.8)	0	1	0	0	1 (0.4)
Total OC cases	93 (100)	131 (100)	79	23	114	8	224 (100)

†: Borderline ovarian tumor, ‡: Ovarian cancer

## Matweials and Methods

This retrospective study was conducted at the Department of Obstetrics and Gynecology of Dong-A University Medical Center. Clinical data were obtained from 115 women with BOTs and 224 with OCs, all of whom were admitted to the hospital between January 7, 2000 and September 30, 2016 for scheduled laparoscopy or laparotomy. Definite histopathologic diagnosis was classified according to World Health Organization definitions, and staging was determined using International Federation of Gynecology and Obstetrics (FIGO) criteria [15]. RMI performance was determined by ultrasound features, menopausal status, serum CA 125 concentration, and tumor size.

All patients underwent transvaginal ultrasound examination; when indicated (usually by the presence of a huge mass), abdominal ultrasound was also conducted. Five ultrasonic findings highly suggestive of cancer (multilocularity, solid components, bilateral masses, intraperitoneal fluid, and evidence of metastases) were used to determine the ultrasound score (U). For bilateral complex adnexal tumors, more morphologically complicated tumors were included; if both masses had similar ultrasonic morphology, the larger one was used in the analysis. Menopausal status (M) was divided into postmenopausal (amenorrhea > 1 year, or age > 50 in women with hysterectomy for any

reason) or premenopausal. Tumor size (S) was classified as the diameter of the tumor at its largest as determined by ultrasound. The following formulas were used:

(1)  $RMI\ 1 = U \times M \times CA\ 125$ . U = 0, 1, or 3 indicates a total ultrasound score of 0, 1, or 2, respectively. M = 1 or 3 indicates premenopausal or postmenopausal status, respectively. Preoperative CA 125 serum concentration is applied directly to the formula [8].

(2)  $RMI\ 2 = U \times M \times CA\ 125$ . U = 1 indicates a total ultrasound score of 0 or 1, and U = 4 indicates a score of 2. M = 1 or 4 indicates premenopausal or postmenopausal status, respectively. Preoperative serum CA 125 concentration is applied directly to the formula [9].

(3)  $RMI\ 3 = U \times M \times CA\ 125$ . U = 1 indicates a total ultrasound score of 0 or 1, and U = 3 indicates a score of 2. M = 1 or 3 indicates premenopausal or postmenopausal status, respectively. Preoperative CA 125 serum concentration is applied directly to the formula [10].

(4)  $RMI\ 4 = U \times M \times S \times CA\ 125$ . U = 1 indicates a total ultrasound score of 0 or 1, and U = 4 indicates a score of 2. M = 1 or 4 indicates premenopausal and postmenopausal status, respectively. S = 1 or 2 indicates a tumor size of 7 cm and 7 cm, respectively. Preoperative CA 125 serum concentration is applied directly to the formula [11].

Sensitivity is a measure of the proportion of patients with OC who had positive test results. Specificity is a measure

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

Variables	BOT	OC	Significance level	
	N = 115 (33.9%)	N = 224 (66.1%)	Test	p
Age (years)	41.37 ± 17.64	52.22 ± 14.64	$\chi^2$	< 0.001
Menopausal status				
Premenopausal	81 (70.4%)	93 (41.5%)	$\chi^2$	< 0.001
Postmenopausal	34 (29.6%)	131 (58.5%)		
Ultrasound score			$\chi^2$	< 0.001
0	7 (6.1%)	0 (0%)		
1	41 (35.7%)	49 (21.9%)		
2	51 (44.3%)	96 (42.9%)		
3	11 (9.6%)	54 (24.1%)		
4	5 (4.3%)	23 (10.3%)		
5	0 (0%)	2 (0.9%)		
Tumor size	16.46 ± 8.65	11.49 ± 5.95	$\chi^2$	< 0.001
CA 125 (IU/ml)	95.41 ± 185.12	659.98 ± 831.67	U-test	< 0.001

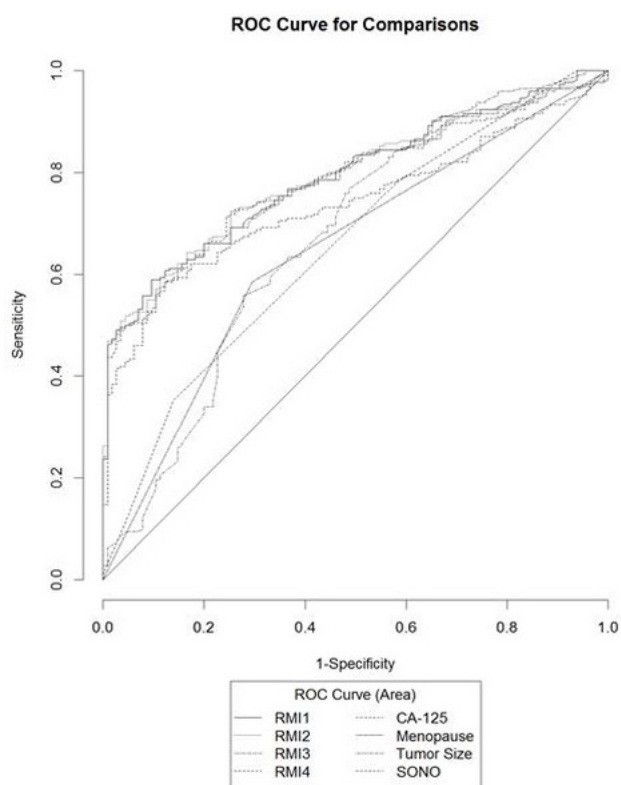


Figure 1. — Receiver operating characteristic (ROC) curves of the individual predictors showing the relationship between sensitivity and specificity of serum CA 125 level, menopause score, tumor size, ultrasound score, and RMI in the discrimination between BOTs and OCs.

of the proportion of patients with BOT who had positive test results. Predictive value of positive (PPV) gives the proportion of patients with positive tests and verified OC, and predictive value of negative (NPV) represents the propor-

tion of patients with negative tests and verified BOT. This study received the approval of the hospital ethics committee, and appropriate written informed consent was obtained from individual patients.

Data were analyzed with SPSS (version 17). The  $\chi^2$  (chi-square) test was used to investigate differences in the distribution of age, menopausal score, tumor size, and ultrasound score between groups. The Mann-Whitney U test was used to evaluate differences in the distribution of CA 125 concentration among patients with BOTs and OCs. Continuous variables were analyzed with the Mann-Whitney U test and Student's t-test, according to their distribution. Normality of continuously distributed data was assessed with the Kolmogorov-Smirnov test. To indicate the tradeoff between sensitivity and specificity of the four RMI scores, CA 125 concentration, menopause score, tumor size, and ultrasound score in differentiating between BOTs and OCs, a receiver operating characteristic (ROC) curve was plotted; it also determined the best cutoff value for RMI 1-4 scores. A  $p$ -value < 0.05 was regarded as statistically significant.

## Results

In total, 339 patients were enrolled in this study: 115 (33.9%) with BOTs and 224 (66.1%) with OCs. The BOT lesions included 84 mucinous, 25 serous, 2 seromucinous, 2 clear cell, 1 endometrioid, and 1 Brenner. The majority of BOTs were stage IA (93%); 1.8% were stage IB, 4.3% stage IC, and 0.9% stage II-III. The OCs were almost all epithelial tumors, of which serous (54.5%) was the predominant type. Mucinous tumor (13.4%) was the second most common malignant type, followed by endometrioid tumor (10.7%). More than half of the OCs were stage III (50.9%); 35.3% were stage I, 10.2% stage II, and 3.6% stage IV. Table 1 shows the histopathology and FIGO classification [15] of the tumors.

Table 3. — Sensitivity, Specificity, and Positive (PPV) and Negative (NPV) Predictive Values 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 (%)
RMI 1	170	59.1	77.2	57.1	78.6
	200	65.2	75.5	57.7	80.9
	230	70.4	71.4	55.9	82.5
	260	73.9	69.2	55.2	83.8
	290	74.8	67	53.8	83.8
RMI 2	280	74.8	67.9	54.4	84
	310	74.8	66.5	53.4	83.7
	340	80	66.1	54.8	86.6
	370	80	65.2	54.1	86.4
	400	80	63.4	52.9	86.1
RMI 3	170	59.1	77.2	57.1	78.7
	200	65.2	75.5	57.7	80.9
	230	70.4	71.4	55.9	82.5
	260	73.9	69.2	55.2	83.8
	290	74.8	67	53.8	83.8
RMI 4	530	84.4	61.2	52.7	88.4
	580	86.1	61.2	53.2	89.6
	630	87.8	60.7	53.4	90.7
	680	88.7	58.9	52.6	91
	730	90.4	58	52.5	92.2

Mean age, proportion of premenopausal patients, CA 125 concentration, and tumor size were significantly different between the BOT and OC groups (age:  $41.37 \pm 17.64$  vs.  $52.22 \pm 14.64$  years, respectively; premenopausal percentage: 70.4% vs. 41.5%, respectively; CA125 concentration:  $95.41 \pm 185.12$  U/mL vs.  $659.98 \pm 831.67$  U/mL, respectively; mean tumor size:  $16.46 \pm 8.65$  mm vs.  $11.49 \pm 5.95$  mm, respectively; all  $p < 0.001$ ). In the BOT group, 6.1% (7/115), 35.7% (41/115), 44.3% (51/115), 9.6% (11/115), 4.3% (5/115) and 0% were U = 0, 1, 2, 3, 4, and 5, respectively. In the OC group, these numbers were 0% (0/224), 21.9% (49/224), 42.9% (96/224), 24.1% (54/224), 10.3% (23/224), and 0.9% (2/224), respectively. Each U value was significantly different between the BOT and OC groups ( $p < 0.001$  for each). The data for age, menopausal status, serum tumor markers, tumor size, and ultrasound scores are given in Table 2.

Table 3 shows the performance of the four indices (RMI 1, RMI 2, RMI 3, and RMI 4) at different cutoff points. There were no significant differences in the area under the curve (AUC) among the four malignancy risk indices (the AUC of RMI 1, RMI 2, RMI 3, and RMI 4 were 0.792, 0.791, 0.785, and 0.785, respectively). However, there was a statistically significant difference in the diagnostic performance of the RMI compared to that of the other factors (serum CA 125 concentration, menopause score, tumor size, and ultrasound score) (Table 4). The diagnostic performance of these factors with the RMI is shown in ROC curves (Figure 1).

## Discussion

The RMI effectively identifies women with a high risk of ovarian malignancy, facilitating referral to a gynecologic oncology center and adequate staging by expert oncologic surgeons. It performs best in invasive epithelial OC, especially in postmenopausal women, who have a higher incidence of ovarian malignancies. Meanwhile, the RMI has significant limitations in diagnosing BOTs in young women and when pathologies have obscure ultrasound features; only a few studies have attempted to address this issue.

This study was conducted to define the best RMI for patients with all histotypes of BOT and OC. To our knowledge, this is the first study to compare the four Risk of Malignancy Indices for distinguishing between BOT and OC. The results could contribute greatly to adequate staging by gynecologic oncologists, which is of major prognostic importance in patients with suspected ovarian malignancies. Accurate preoperative diagnosis of BOTs and OCs using the RMI may aid in defining the scope of surgery. This is especially important for fertility preservation in patients with BOTs, many of whom are still of childbearing age. Although over the past decades, the optimal treatment for BOTs has changed in favor of radical surgery, fertility-sparing surgery remains an adequate treatment option for fertile women with early-stage BOT. Some reports indicate that radical surgery including lymphadenectomy is not superior in terms of relapse-free survival [16, 17]. Therefore, for the vast majority of BOT patients, radical operative treatment may represent overtreatment and be associated with increased surgical risk. Of course, frozen sections are

Table 4. — The predictive performance of serum CA 125, menopausal status, tumor size, ultrasound score, and RMIs in AUROC for discrimination between BOT and OC groups.

Variables	AUROC <sup>†</sup>	Asymptomatic 95% Confidence Interval		p-value
		Lower bound	Upper bound	
RMI 1	0.792	0.745	0.838	< 0.001
RMI 2	0.791	0.744	0.838	< 0.001
RMI 3	0.785	0.738	0.832	< 0.001
RMI 4	0.785	0.737	0.832	< 0.001
CA 125	0.739	0.689	0.785	< 0.001
Menopause	0.645	0.591	0.696	< 0.001
Tumor size	0.672	0.62	0.722	< 0.001
Ultrasound	0.655	0.601	0.705	< 0.001

<sup>†</sup> Area under Receiver Operating Characteristic

also helpful in determining comprehensive surgical staging intraoperatively. However, frozen sections had high sensitivity, specificity, and predictive values only in the identification of benign versus malignant ovarian tumors [18]. Previous studies have reported suboptimal performance of frozen section diagnosis for BOTs; the overall accuracy of this method was 60% in terms of agreement between permanent histological diagnosis and frozen section results [19]. Frozen sections were more useful for excluding benign tumors [18].

Ultrasonography is a highly specific modality for BOT diagnosis [20]. However, its use is limited by its subjective nature, even in expert hands. In addition, because of the lack of definitive sonographic variables for BOTs versus invasive tumors, BOTs are often overdiagnosed as primary invasive tumors, particularly as early-stage OC [21, 22]. Doppler ultrasonography, which is well known for examination of tumor vascular patterns, made correct, specific predictions in only 5% of cases [23, 24]. A new ultrasound technology, three-dimensional (3D) ultrasound, is useful in detecting wall irregularities of the mass or papillary projections [25]. However, the utility of 3D ultrasonography in predicting BOTs was not clinically significant compared with conventional two-dimensional ultrasound.

Although the contrast between the solid and cystic components of ovarian tumors is best perceived on T2-weighted magnetic resonance imaging (MRI), MRI cannot be used to properly distinguish between borderline and invasive tumors [26, 27]. Positron emission tomography-computed tomography (PET-CT) also carries a potential risk of false-negative interpretation of BOTs due to the tumor's cystic nature [28, 29]. As such, modern imaging techniques have no proven added benefit for diagnosis of BOTs.

The RMI was created to predict ovarian malignancies preoperatively. However, the RMI calculations in BOTs are affected by premenopausal status and relatively low serum CA 125 levels. Yenen *et al.* first assessed the diagnostic values of RMI 1-4 for BOTs in 2012 [14]. The authors showed that RMI 4 was the best malignancy risk index in patients with BOTs with a cutoff point of 200. The sensi-

tivity, specificity, PPV, NPV, and diagnostic accuracy in differentiating BOTs from other tumors were 60%, 80%, 75%, 67%, and 70%, respectively. However, the study was limited in its focus on serous and mucinous BOTs to the exclusion of all other histotypes.

The present study attempted to identify the best RMI for patients with all BOT and OC histotypes. Unlike previous studies, this study found no significant differences in the AUC between RMI 1, RMI 2, RMI 3, and RMI 4. However, RMI performed significantly better than other factors (serum CA 125 concentration, menopause score, tumor size, and ultrasound score). In past studies, RMI 4 was found to be the best of the four indices. Yamamoto *et al.*, who newly introduced RMI 4, also showed that RMI 4 was more reliable than RMI 1-3 in distinguishing between benign tumors and invasive OCs [11]. However, in this study, RMI 4 was not superior to RMI 1, RMI 2, and RMI 3. We can speculate that the larger size of BOTs compared to OCs ( $16.46 \pm 8.65$  mm vs.  $11.49 \pm 5.95$  mm) was a significant factor that contributed to the lack of superiority of RMI 4 in distinguishing BOTs from OCs.

Moore *et al.* reported increased sensitivity and specificity in the detection of preoperative ovarian carcinoma when integrating human epididymis protein 4 (HE4) and CA 125, and then developed a simple biomarker-based risk of ovarian malignancy algorithm (ROMA) in 2009; unlike RMI, ROMA does not require ultrasonography [30]. Remarkably, their later study showed that ROMA was far better than RMI (AUC 0.909 vs. 0.762) at detecting stage I invasive OCs [31]. Also, ROMA showed improved detection of BOTs. However, further improvements of HE4 and ROMA as differential tools are still required, especially regarding premenopausal women; furthermore, larger studies are needed.

Recently, Van Calster *et al.* introduced the assessment of different neoplasias in the adnexa (ADNEX) model, which is able to discriminate between five types of adnexal tumors (benign, borderline tumor, stage I cancer, stage II-IV cancer, and secondary ovarian cancer) [32]. It is convenient to use online or in mobile applications. The polytomous diag-



nostic approach to adnexal tumors is novel. It was also able to distinguish well between benign tumors and each of the four malignancy types (with AUCs between 0.85 and 0.99). However, as in previous studies, it did not discriminate between BOTs and OCs.

This study is the first to confirm the effectiveness of RMIs in predicting an accurate preoperative diagnosis in patients with all BOTs and invasive OCs. These results could increase preoperative diagnostic accuracy and aid in defining the extent of surgery. Still, further studies are required to examine the potential and limitations of RMI for distinguishing between BOTs and OCs. Further prospective multicenter studies to verify our findings are also warranted.

## Conclusion

RMI is a simple and cost-effective method that can be used in primary healthcare centers for identifying patients at high risk of ovarian malignancy who should be referred to gynecologic oncologists. A properly planned surgery would not only improve disease prognosis, but would also allow fertility-sparing surgery to be offered to women of childbearing age with early stage BOTs.

## Author contributions

All authors contributed to the manuscript at all stages including design, planning, data abstraction, and manuscript writing.

## Acknowledgements

This work was supported by the Dong-A University research fund.

## Conflicts of interest

We have no conflicts of interest to declare.

Submitted: February 27, 2019

Accepted: June 03, 2019

Published: June 15, 2020

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