Comparison of risk of malignancy indices; RMI 1-4 in borderline ovarian tumor

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Summary

Purpose: The aim of this study was to evaluate prognostic values of the risk of malignancy index (RMI)/1-4 in patients with borderline ovarian tumors (BOTs). *Methods:* The study consisted of 50 patients with BOT diagnosed and treated between 2005-2010 and 50 patients with benign adnexal massses between 2009-2010 as a control comparison group in the retropsective study. Preoperative serum CA125, U score, tumor size (S), and menopausal status were recorded. The RMI 1-3 was calculated according to the formula; U×M×CA125 and RMI 4 formulation was; U×M×CA125×S. S equaled 1 for tumor size < 7 cm and was 2 when size ≥ 7 cm. The RMI 1-4 indices were calculated for all patients together with the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (DA). The performances of RMI indices were evaluated by McNemar's test and determined the best score cutoff value by the receiver operating characteristic (ROC) curve. *Results:* The mean age, median value of CA125, ultrasound score, menopausal status, median values of RMI 1-4 of BOTs were statistically higher than benign adnexal masses. The sensitivity of RMI 1-4 was 26, 36, 62, and 60% at cutoff 200 level, respectively. The areas under curve of RMI 1-4 were found to be 0.676, 0.665, 0.668 and 0.734, respectively. DA of RMI 1-4 was found to be 56, 59, 50, and 71, respectively. When RMI 1-4 indices were compared with each other RMI 4 was the best RMI for BOTs. *Conclusion:* RMI 4 was the best predictive RMI for preoperative discrimination of BOT at a cutoff level of 200.

Key words: Borderline ovarian tumor (BOT); Risk of malignany index (RMI).

Introduction

Borderline ovarian tumors (BOTs) were first described by Taylor in 1929 [1] and were introduced in 1971 by FIGO as a category of epithelial ovarian tumors [2]. BOTs account for 10-15% of all epithelial ovarian tumors. BOTs are accepted as malignant, although they are different from both benign epithelial ovarian tumors and invasive epithelial ovarian cancers. BOTs are diagnosed at clinically earlier stages, such as Stage I, and often affect young women who wish to preserve their fertility, have low potential for malignancy, have longer patient survival, and have later recurrence as compared with invasive epithelial ovarian tumors [3-7].

The preoperative evaluation of adnexal masses is rather complicated and the main purpose is to discriminate between benign and malignant lesions. Several parameters are used to assess the risk of malignancy, such as gray scale sonographic parameters, color Doppler ultrasonography, gynecologic examination, biochemical markers as tumor markers, and demographic characteristics i.e., menopausal status [8]. Instead of using these parameters alone, combined methods have been proposed for accuracy in differentiation of adnexal masses. Jacobs *et al*. in 1990 developed a risk of malignancy index (RMI) depending on serum CA125, menopausal state, and ultrasound findings [9]. Then RMI 2 was described by Tingulstad *et al*. in 1996 [10], RMI 3 was described by Tingulstad *et al*. in 1999 [11], and RMI 4 was described by Yamamoto *et al*. in 2009 [12].

BOTs have fewer scores of RMI characteristics; menopausal status, CA125 levels, and ultrasound scores. First, since the majority of women with BOTs are at reproductive age, absolute contribution of age at RMI is less [3, 5]. They are usually diagnosed at an early stage and only 50% early-stage ovarian cancers have elevated CA125 [13], and their tumor marker secretions are less than invasive ovarian cancers. Elevated serum tumor markers such as CA125, CEA and CA19-9 have been reported in only 25% to 60% of women with BOTs [14-18]. BOTs also have a borderline sonographic appearance and do not have a pathognomonic or typical sonographic pattern [19]. These factors may affect RMI calculation in BOTs. But when we searched the literature, we did not find any study that used RMI in BOTs separately from benign and malign adnexal masses. Usually BOTs are included in malignant groups, although BOTs are actually different from malignant groups.

The aim of this study was to evaluate the diagnostic performance of RMI 1-4 for BOTs and determine the best RMI index and cutoff level for preoperative evaluation of BOTs. To the best of our knowledge, this is the first study evaluating and comparing RMI indices of BOTs.

Materials and Methods

The clinical data were obtained from 50 women with BOTs diagnosed and treated between 2005-2010, and 50 women with benign adnexal masses between 2009-2010 as a control comparison group in this retrospective study. Only serous and mucinous BOTs with complete laboratory and clinical data were

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included in this study; all others were excluded. Preoperative serum CA125, ultrasound findings, tumor size (single greatest diameter; S), menopausal status, and histopathologic results were recorded. If the adnexal masses were bilateral, the more morphologically complex the tumor was considered, and if both masses were morphologically similar, the largest one was considered in the statistical analysis. An ultrasound score of 1 was assigned for each of the following ultrasound features suggesting malignancy: a multilocular cystic lesion, solid areas, bilateral lesions, ascites, and intraabdominal metastases findings [9]. A total ultrasound score was calculated for each patient. Postmenopausal status was defined as more than one year of amenorrhea, or being 50 years or older among women who had undergone hysterectomy. All other women were considered premenopausal. Final diagnoses of the participants were based on the histopathologic examination of surgical specimens.

The RMI was calculated according to the formula: the ultrasound scores (U), the menopausal score (M), and the serum CA125 level: RMI: U x M x CA 125 for RM1-3. RMI 4 formulation was: Ux M x CA125 x S. S equaled 1 for tumor size < 7 cm, was taken as 2 when tumor size was ≥ 7 cm. The scoring system of menopausal status and total ultrasound score were based on originaly described RMI indices, for example menopausal status was scored as 3 at RMI 1, while it was scored as 4 at RMI 4. The scoring system of RMI 1-4 is shown in Table 1.

The RMI 1, RMI 2, RMI 3, and RMI 4 indices were calculated for all patients together with the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of the four methods.

Tumors were classified according to World Health Organization definitions and borderline ovarian tumors were staged according to the criteria of the International Federation of Gynecology and Obstetrics [20]. Pathologically, BOTs were characterized by features of malignant epithelial ovarian tumors, including stratification of epithelial lining of the papillae, formation of microscopic papillary projections, epithelial pleomorphism, atypicality, and mitotic activity, without invasion of stroma [21].

All statistical analyses were done using the Statistical Package for Social Sciences 12.0 (SPSS Inc., Chicago, IL). With all sonographic parameters and patient age, a univariate statistical analysis was performed. The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous data. Continuous data were compared with the use of the Student's t and Mann-Whitney U tests according to their distribution. The chi-square test was used to test the differences in distribution of menopausal status and U score. The Mann-Whitney U-test was applied for differences in distribution of CA125 and tumor size among women with benign and BOTs. McNemar's test was used when testing differences in performance between RMI 1, RMI 2, RMI 3, and RMI 4.

To determine the best score cutoff value to discriminate between BOTs and benign adnexal masses, a receiver operating characteristic (ROC) curve was plotted. The best cutoff value was chosen according to the highest sensitivity with the lowest false-positive rate. A probability value $p < 0.05$, was considered to be statistically significant.

Results

A total of 100 patients were included in the study. Fifty patients had benign adnexal masses, whereas 50 patients had BOTs. Histopathological diagnoses of the study are shown in Table 2. Histopathological results revealed 30 (60%) serous and 20 (40%) mucinous BOTs. The rates of benign lesions were simple serous cysts 10%, endometriomas 24%, dermoid cyst 14%, serous cystadenomas 26%, mucinous cystadenomas 22%, paratubal cyst 1% and tuboovarian complex 2%.

The characteristics of the study group according to age, menopausal status, tumor markers, tumor size, and U scores are shown in Table 3. The mean age of the patients

Table 1. — *Scoring system of menopausal and ultrasound score of RMI 1-4.*

Ultrasound characteristics	RMI 1(9)	RMI 2(10)	RMI 3(11)	RMI 4(12)
0	0	1	1	1
1	1	1	1	1
2-5	3	4	3	4
Menopausal status				
Premenopausal	1	1	1	1
Postmenopausal	3	4	3	4

RMI: Risk of malignancy index.

Table 2. — *Histopathological diagnoses of the study.*

BOTs	N(%)
Serous	30 (60%)
Mucinous	20 (40%)
Benign adnexal masses	
Simple serous cyst	5 (10%)
Endometrioma	12 (24%)
Dermoid cyst	7 (14%)
Serous adenoma	13 (26%)
Mucinous adenoma	11 (22%)
Paratubal cyst	1 (2%)
Tuboovarian complex	1 (2%)

BOT: Borderline ovarian tumor.

Table 3. — *Characteristics of the study group according to age, menopausal status, tumor markers, tumor size, and ultrasound scores.*

Characteristics	Benign (n; 50)	BOTs (n; 50)	*p* value
Median age (years)*	35.2 ± 12.3	42.1 ± 14.0	0.014
Menopausal status**			
Premenopausal rate	44 (88%)	36 (72%)	0.046
Postmenopausal rate	6 (12%)	14 (28%)	
Median CA125 levels (IU/l)&	34.18 ± 24.98	152 ± 355.47	0.031
Tumor size (cm)&	5.66 ± 1	12.12 ± 7.88	< 0.001
Ultrasound score**			
0	31 (62%)	12 (24%)	0.002
1	10 (20%)	20 (40%)	
2-5	9 (18%)	18 (36%)	

*Student's t-test, **Chi-square, &Mann-Whitney U.

Table 4. — *Median RMI 1-4 values of BOTs and benign adnexal masses.*

	RMI 1	RMI 2	RMI 3	RMI 4
Median total	190.43 ± 646.3	360.46 ± 1158.33	258.99 ± 813.63	670.1 ± 2323.86
Benign group	59.58 ± 104	93.44 ± 131.9	74.7 ± 96.9	116.1 ± 207.64
Borderline group	321.28 ± 893.4	627.48 ± 1596.2	443.28 ± 1121.9	1224.1 ± 3200.2

Table 5. — *Sensitivity, specificity, PPV, NPV, and DA for predicting borderline tumors at different cutoff levels of RMI 1-4.*

Cutoff	Sensitivity				Specificity				PPV (%)				NPV (%)				DA (%)			
	RMI1	RMI2	RMI3	RMI4	RMI1	RMI2	RMI3	RMI4	RMI1	RMI2	RMI3	RMI4	RMI1	RMI2	RMI3	RMI4	RMI1	RMI2	RMI3	RMI4
50	54	62	62	74	70	64	64	64	64	63	63	67	60	63	63	71	62	63	63	69
100	40	62	48	64	78	76	78	76	65	72	69	73	57	67	60	68	62	69	63	70
150	30	48	38	62	82	80	82	80	63	71	68	76	54	61	57	68	56	64	60	71
200	26	36	32	60	86	82	86	80	65	67	70	75	53	56	56	67	56	59	59	70
250	22	32	26	48	92	82	90	80	73	64	72	71	54	55	55	61	57	57	58	64
300	22	28	26	46	94	90	94	88	79	74	81	79	55	56	56	62	58	59	60	67
350	20	26	22	44	98	92	98	94	91	76	92	88	55	55	56	63	59	59	60	69
400	18	24	20	38	98	94	98	94	90	80	91	86	54	55	55	60	58	59	59	66

PPV: Positive predictive value, NPV: Negative predictive value, DA: Diagnostic accuracy.

Table 6. — *Comparison of RMI 1-4 values with each other by using MacNemar's test.*

Cutoff level	50	100	150	200	250	300	350	400	450
RMI 1-2	0.125	0.001	0.008	0.063	0.063	0.25	0.125	0.125	0.125
RMI 1-3	0.125	0.125	0.25	0.25	0.5	0.5	0.5	1	1
RMI 1-4	0.002	0.001	< 0.001	< 0.001	< 0.001	0.001	< 0.001	0.002	< 0.001
RMI 2-3	1	0.016	0.063	0.5	0.25	1	0.5	0.25	0.25
RMI 2-4	0.031	1	0.008	< 0.001	0.008	0.008	0.004	0.031	0.008
RMI 3-4	0.031	0.016	< 0.001	< 0.001	0.001	0.004	0.001	0.004	0.001

with benign lesions was 35.2 ± 12.3, and BOTs was 42.1 ± 14.4 years, and there was a significant difference in ages of the groups ($p < 0.05$). The premenopausal rate of benign and borderline were 44 (88%) vs 36 (72%), respectively. There was a significant difference between the two groups according to their menopausal status ($p < 0.05$). The median value of CA125 serum levels of the patients with benign cases were 34.18 ± 24.98 mIU/ml, and BOTs were 152 ± 355. 47 mIU/ml, and the difference was statistically significant ($p < 0.05$). The ultrasound scores obtained from sonographic morphologic findings were U= 0: 31 (62%) cases; U=1: ten (20%) and U=2-5: nine (18%) were found to be benign and 12 (24%), 20 (40%), and 18 (36%) were BOTs, respectively. There was a significant difference between the two groups ($p < 0.05$).

The median RMI 1-4 values of BOTs and benign adnexal masses are shown in Table 4. The median values of the calculated RMI 1-4 for BOTs were higher than benign adnexal masses, and there was a significant difference between the two groups ($p < 0.001$).

When we compared the ROC curve evaluation of RMI 1-4 according to the area under curve (AUC), RMI 4 was found to be significantly superior to other RMIs. The AUC of RMI 1-4 was found as 0.676, 0.665, 0.668, and 0.734, respectively. The ROC curve analyses of RMI 1-4 are shown in Figure 1.

The performance of RMI 1-4 with respect to different cutoff levels is shown in Table 5. When a cutoff level was set at 200, diagnostic accuracy of RMI 1-4 was found to be 56, 59, 50, and 71, respectively.

When RMI scores 1-4 were compared with each other, e.g, RMI 1 vs RMI 4, by using MacNemar's test, RMI 4 was found to be the best RMI for BOTs ($p < 0.05$) (Table 6).

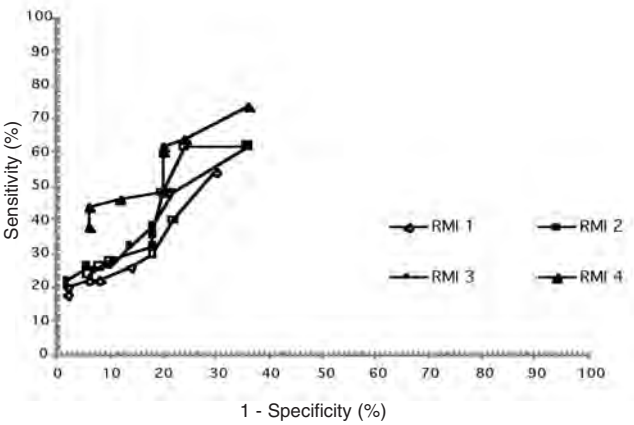

Figure 1. — Receiver operator characteristic curve showing the performance of RMI 1, RMI 2, RMI 3 and RMI 4.

Discussion

A pelvic mass is one of the most frequent indications for referral to a gynecologist [12] and differentiating between benign and malignant is the most important step for both appropriate preoperative assessment and optimal surgical choice [8]. Jacobs *et al*. in 1990, developed a RMI depending on serum CA125, menopausal state, and ultrasound findings, and recommended its use in benign-malignant determination of adnexal masses [9]. Then, RMI was modified by Tingulstad *et al*. as RMI 2 and RMI 3 [10, 11], and later modified by Yamamato *et al*. as RMI 4 [12], who added the parameter of the tumor size score (S) to the RMI formulation.

Being a simple scoring system and being applied directly into clinical practice without the introduction of

expensive or complicated methods are the main advantages of RMI compared with other diagnostic tests [22]. In comparison with age, menopause score, the ultrasound score and serum CA125 level, the RMI was significantly superior to all of them [23]. Although the RMI index has been used to differentiate benign and malignant ovarian masses, there is not yet a study in the literature using a RMI index in BOTs as a separate group. Usually, studies of RMI consisted of malignancy and benign subjects and BOTs were included in the malignant group. Morever, the number of BOTs were small and even their numbers were not described separately.

An appropriate triage of BOTs is important since like ovarian invasive malignancies, especially BOTs with invasive implants do require proper staging (still recommended) and need fertility sparing surgery for women desiring future fertility [3-5]. However, BOTs and malignant ovarian cases have different characteristics. Considerable numbers of BOTs are premenopausal, have low CA125 level, and exhibit simple cyst characteristics. These differences may influence RMI values in BOTs, and low values for RMI characteristics result in low RMI scores in BOT groups [3-7]. BOTs have low scores both on ultrasound scores and CA125 levels [24]. RMI performance is different in premenopausal and postmenopausal groups [21]. The RMI predicts invasive malignancy best in the postmenopausal group; also there is a higher incidence of ovarian cancer in postmenopausal women compared with premenopausal women [22]. Ovarian enlargements and ovarian masses are more frequently detected in premenopausal age [25, 26]. The other factor is the lower diagnostic accuracy of serum CA125 in premenopausal patients because CA125 levels fluctuate during the menstrual cycle, being the highest during menstruation. Also, diseases such as endometriosis and pelvic inflammatory disease are more frequent in premenopause. These diseases are known to cause elevated CA125 [23]. BOTs have low CA125 levels compared to invasive ovarian cancer. Elevation of CA125 depends mainly on ovarian cancer stage [27]. CA125 levels were increased in 50% of patients with ovarian cancer in FIGO Stage I, in 90% of those in Stage II, in 92% of those in Stage III, and in 94% of those in Stage IV disease [28].

BOTs are usually diagnosed at an early stage and also mucinous BOTs tend to have lower tumor stages compared with serous BOTs. Therefore serum tumor markers are different for both serous and mucinous tumors at related stages [6, 29]. Also, elevated CA125 levels of serous BOTs are higher than for mucinous BOTs [30].

In our opinion, BOTs need to be studied as separate groups from both benign and malignant adnexal lesions. Similar to our proposed theory, a study indicated that borderline malignancies were allocated to a non-invasive group when calculating the sensitivity and specificity levels, leaving only invasive malignancies to be detected for referral to a gynecologic oncologist [22]. A study using RMI 1/2 and Tailor's regression model, found that the sensitivity of RMI 1/2 for BOTs was only 25% and indicated that RMI performed best in diagnosing invasive epithelial ovarian malignancies and not nonepithelial and borderline tumors [31]. Therefore, we used the RMI 1-4 index for BOTs to study them as a separate group.

In our study, when the cutoff level was set at 200, the sensitivity of RMI 1-4 was 26, 36, 32 and 60% (extremely lower than the literature) and specificity was defined as 86, 82, 86 and 80%, respectively, which was similar to the literature. Also when the cutoff was set at 200, the sensitivity of RMI 4 was better than RMI 1-3; (60% vs 26, 36, 32. The DA of RMI 4 was found higher than RMI 1-3, at a cutoff of 200 (71% vs 56, 59, and 50%, respectively. The specificity of RMI at a cutoff of 200 was found similar to RMI 1-3; 80% vs 86, 82 and 86%, respectively. The PPV of RMI 4 was found to be higher than RMI 1-3 (75% vs 65, 67, and 70%, respectively (Table 5). This predominance of RMI 4 markedly continued at different cutoff levels of RMI (Table 4). For example, when the cutoff level was set at 50, the sensitivity of RMI 1-4 was 54, 62, 62, and 74, respectively (lower than the literature). The DA, PPV, and NPV of RMI 4 were higher than the other RMI 1-3 values.

There are several studies for RMI in the evaluation of adnexal masses. Sensitivity, specificity and cutoff values of RMI studies vary largely, and most studies evaluated a range of cutoff levels varying between 25 and 250, although many authors suggest that the best cutoff value for RMI is 200 [9-11, 32]. Contrary to others, one study recommends the use of a RMI cutoff level of 153 [23]. Sensitivity of RMI 1 at a cutoff level of 200 was reported to be 85, 71.7, 90, and 88.5%, respectively [9, 23, 33, 34]. In a review of 109 studies comparing risk scores to predict differentiation of benign from malignant lesions; the pooled estimate for sensitivity was 78% and specificity was 87% when 200 was used as a cutoff level [8]. Our results are lower then the above-mentioned studies.

In a study where BOTs were included in invasive malignant groups, sensitivity was especially low (25%), similar to our study [30]. In different studies, sensitivity of RMIs in BOTs had a large range of sensitivity of 25%, 40% and 75%, respectively [31, 10, 34]. According to a systematic review, the pooled estimate for sensitivity of RMI 2 at a cutoff of 200 was 79%, and specificity was 81% [8]. In our results, the sensitivity and specificity of RMI 2 were 36% (lower than the literature), and 82% (similar to the literature), respectively.

In a study evaluating RMI 3 the sensitivity and specificity were found to be 74% and 91%, respectively [8]. In our study the sensitivity of RMI 3 was lower than the literature, and the 200 cutoff level sensitivity was 32%.

When we analyzed AUC of RMI 1-4 by ROC analysis, we found that AUC of RMI 4 was the highest of all (0.734 RMI 4 vs 0.676, 0.665, 0.668 RMI 1-3, respectively). In one study, the AUC of RMI was found to be 0.893 for the whole study, where it was 0.839 for the premenopausal and 0.911 for the postmenopausal group. Our results were lower compared to the results of this study [22].

When RMIs were compared with each other by Mac-

Nemar's test, different cutoff levels were determined such as RMI 4 vs RMI 1-3; RMI 4 was the best RMI in all different cutoff levels, $p < 0.001$ (Table 6). Our results showed that RMI 4 is the best predictive RMI model for differentiating benign and BOTs.

There are few studies in the literature comparing RMI with each other. In one study, a direct comparison of the RMI 1-3 indices at a cutoff level of 200 showed that there is no statistically significant difference in performance of the three methods in identifying malignancy, according to sensitivity, specificity, NPV, PPV and DA. For example, the specificities of RMI 1, RMI 2, and RMI 3 were shown as 91, 82, and 91%, respectively [32]. In another study RMI 1-3 in patients with abnormal pelvic masses were compared and RMI 2 was indicated as better than others (sensitivity 79% vs 71 and 71) but the specificities were similar [35]. A direct comparison of the RMI 1-4 showed that RMI 4 at a cutoff level of 450 was significantly better at predicting malignancy than RMI 1, 2 and RMI 3 at a cutoff level of 200 [12].

The differences between our results and the literature may also result from the numbers of BOT studies, because generally BOTs take place in small groups in RMI studies, and RMI usually differentiates benign and malignant disease and usually BOTs are not included as separate groups.

Consequently, borderline malignancies tend to have lower RMI values compared to invasive malignancies and are therefore less detectable. Thus, low score results in low RMI values, and most BOTs may have lower values than 200 as a cutoff level. Using RMI 4, which adds the tumor size to RMI formulation, may be more useful with increased sensitivity for the detection of BOTs.

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