RESEARCH ARTICLE

Comparative Evaluation of the Risk of Malignancy Index Scoring Systems (1-4) Used in Differential Diagnosis of Adnexal Masses

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Abstract

Background: To determine the cut-off values of the preoperative risk of malignancy index (RMI) used in differentiating benign or malignant adnexal masses and to determine their significance in differential diagnosis by comparison of different systems. Materials and Methods: 191 operated women were assessed retrospectively. RMI of 1, 2, 3 and 4; cut-off values for an effective benign or malignant differentiation together with sensitivity, specificity, negative and positive predictive values were calculated. Results: Cut-off value for RMI 1 was found to be 250; there was significant (p<0.001) compatibility at this level with sensitivity of 60%, positive predictive value (PPV) of 75%, specificity of 93%, negative predictive value (NPV) of 88% and an overall compliance rate of 85%. When RMI 2 and 3 was obtained with a cut-off value of 200, there was significant (p<0.001) compatibility at this level for RMI 2 with sensitivity of 67%, PPV of 67%, specificity of 89%, NPV of 89%, histopathologic correlation of 84% while RMI 3 had significant (p<0.001) compatibility at the same level with sensitivity of 63%, PPV of 69%, specificity of 91%, NPV of 88% and a histopathologic correlation of 84%. Significant (p<0.001) compatibility for RMI 4 with a sensitivity of 67%, PPV of 73%, specificity of 92%, NPV of 89% and a histopathologic correlation of 86% was obtained at the cut-off level 400. Conclusions: RMI have a significant predictability in differentiating benign and malignant adnexal masses, thus can effectively be used in clinical practice.

Keywords: Risk of malignancy index - adnexal mass - differential diagnosis

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Introduction

Ovarian cancer ranks the sixth among cancer-related deaths in women. In western countries, it is the fourth most common cause of cancer-related deaths (Yavuzcan et al., 2009). In addition to the imaging challenges of the ovaries and the fallopian tubes arising from their anatomic locations, late presentation of the symptoms in malignant events of these organs leads to a diagnosis at advanced stages. The 5-year survival rate at stage 1 is above 90% but unfortunately the majority of patients diagnosed are at an advanced stage whose 5-year survival rate is only 30-73%. Adnexal masses are a common clinical phenomenon in outpatient gynecology clinics (Landis et al., 1999; Iyer et al., 2010).

Although patient age, serum CA-125 values, ultrasonographic morphology, computerized tomography, magnetic resonance or methods such as positron emission tomography are being used in the differential diagnosis of adnexal masses, an agreed appropriate standard preoperative method is yet to be introduced (Rossi et al., 2011). Therefore, several scoring systems have been developed for the purpose of differentiating benign or malignant adnexal masses. The Risk of Malignant Index (RMI) scoring system for preoperative diagnosis of pelvic masses was first developed by Jacob et al. (1990). This system was further revised by Tingulstad et al. as RMI 2 and RMI 3 (Tingulstad et al.,1996). By inclusion of tumor size among these criteria RMI 4 was formed (Yamamoto et al., 2009). Nevertheless, data indicating that RMI indexes are not sensitive enough for some populations and that cut-off values of these scoring systems should be changed is also available (Ashrafgangooei et al., 2011; Ong et al., 2013).

Our aim in this study is to evaluate the significance of RMI indexes used in differentiating benign or malignant adnexal masses by comparing them with each other. Cut-off values, sensitivity, specificity, negative and positive predictive values of RMI 1, 2, 3 and 4 for every woman in our study population who was operated

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after a preoperative diagnosis of an adnexal mass were retrospectively calculated and compared with each other.

Materials and Methods

Study population

One hundred and nineteen patients admitted and operated in second Obstetrics and Gynecology Clinic of Izmir Ataturk Training and Research Hospital between 2007 and 2011 were assessed retrospectively. Every patient was evaluated with ultrasonography two weeks before the surgery. All of the excised adnexal masses were subjected to intraoperative frozen section evaluation; in case of a malignant result, surgical staging was performed according to International Federation of Gynecology and Obstetrics (Benedet et al., 2000). Furthermore, malignant adnexal masses were definitely identified by expert pathologists as ovarian carcinomas, borderline ovarian tumors and tubal carcinomas whereas other adnexal masses were classified as benign adnexal masses during the histopathologic evaluation following the intraoperative frozen sections.

RMI scoring systems

RMI 1, RMI 2 and 3, and RMI 4 as described by Jacobs, Tingulastad and Yamamato et al., respectively, were calculated for every patient. Menopausal status, ultrasound score of the adnexal mass and serum CA 125 levels of the patients were used for these calculations (Jacobs et al., 1990; Tingulstad et al., 1996; Tingulstad et al., 1999; Yamamoto et al., 2009).

RMI was calculated using the formula "RMI= M x US x serum CA 125". M and US represent the menopausal status and ultrasound score, respectively, which were combined with serum CA 125 levels. M values for RMI 1, RMI 3, RMI 2 and RMI 4 in pre-and postmenopausal patients were 1, 3, 1 and 4 respectively. Premenopausal M value for RMI 4 was 1 and postmenopausal M value was 4. Postmenopausal status was defined as being amenorrheic for more than one year or being over 50 years of age in the presence of a hysterectomy history (Jacobs et al., 1990; Tingulstad et al., 1996; Tingulstad et al., 1999; Yamamoto et al., 2009).

Features that constituted the ultrasonographic scoring system were multilocularity, bilaterality, solid areas, ascites and the presence of an extraovarian tumor (Ekerhovd et al., 2001). US score for RMI 1 in the absence of any ultrasonographic feature was calculated as 0.2, in the presence of 1 feature as 1 and in the presence of ≥2 features as 3. US scores for RMI 2 with none or 1 of the features indicated earlier and ≥2 features were 1 and 4, respectively; for RMI 3 with none or 1 of the features and ≥2 features were 1 and 3, respectively; for RMI 4 with none or 1 of the features and ≥2 features were 1 and 4, respectively. In RMI 4 tumor size (S) is also included in the calculation. If the tumor size is <7cm S is equal to 1 and if the tumor is >7 S is equal to 2 (Jacobs et al., 1990; Tingulstad et al., 1996; Tingulstad et al., 1999; Yamamoto et al., 2009).

Statistical analysis

Descriptive statistics of the data included mean, standard deviation, median, minimum and maximum values, proportion and frequency. The level of impact was measured using the ROC curve analysis. Agreement was assessed by Kappa analysis. SPSS 21.0 statistical software was used for statistical analyses. The p values<0.05 were considered statistically significant.

Results

Adnexal masses belonging to 191 patients in total were retrospectively evaluated. According to the definite histopathologic diagnoses 145 of these masses were benign (75.9%) and 46 were malignant (24.1%); all of the malignant masses originated from the ovaries, no malignancies of tubal origin were detected. The mean age of the participants was 45±15.87 years. The mean size of the adnexal masses was 8.5±4.3 cm. Serum CA-125 levels in patients with malignant masses were significantly higher compared to patients in the benign group. Histological subtypes of the benign and malignant masses are presented in Table 1. The RMI analysis of the adnexal masses and data of the Kappa agreement analysis for each RMI score are listed in Table 2, respectively.

In our study Kappa value for RMI 1 was 0.574 when the cut-off value was set at 200 which yielded 60.9% sensitivity, 73.7% positive predictive value, 93.1% specificity, 88.2% negative predictive value and 85.3% histopathologic correlation. While evaluating an adnexal mass preoperatively based on RMI 1 with a cut-off value of 250, there has been a significant ($p<0.001$) compatibility at RMI 1 ≤250 and 250< cut-off values between benign and malignant with a sensitivity of 60.9%, a positive predictive value of 75.7%, a specificity of 93.8%, a negative predictive value of 88.3% and a total correlation of 85.9%. The best performance cut-off value for RMI 1 in differential diagnosis of adnexal masses was defined as 250; with a cut-off value of 250 the specificity has risen from 93.1% to 93.8% while histopathologic correlation has risen from 85.8% to 85.9% (Table 2). In this study we showed that RMI 1 has a significant [A.U.C: 0.87 (0.81-0.94); $p<0.001$] predictive power in differentiation of benign and malignant patients (Table 2).

When the cut-off value for RMI 2 was set at 200 the Kappa value was 0.57. A specificity of 67.4%, a negative predictive value of 89.7%, a positive predictive value of 67.4% and a histopathologic correlation of 84.3% was yielded with the cut-off value of 200. The best performance for RMI 2 was obtained with a cut-off value of 200 during preoperative evaluation of adnexal masses. In this study we showed that RMI 2 has a significant [A.U.C: 0.89 (0.83-0.94); $p\leq0.001$] predictive power in differentiation of benign and malignant patients (Table 2).

In our study Kappa value for RMI 3 was 0.557 when the cut-off value was set at 200. The best performance for RMI 3 was obtained with a cut-off value of 200. With RMI 3≤200 and 200< cut-off values there was a significant ($p<0.001$) correlation with a sensitivity of 63%, a positive predictive value of 69%, a specificity of 91%, a negative predictive value of 88% and a total correlation of 84% between benign and malignant. The histopathologic

Table 1. Histologic Subtypes of the Adnexal Masses

Noninvasive benign lesions	N (%)	Invasive malignant lesions	N (%)
Corpus Hemorhagicum	6	Borderline musinous tumor	5
Corpus luteum cyst	8	Borderline serous tumor	4
Endometrioma	26	Clear cell carcinoma	3
Fibroma	3	Dysgerminoma	2
Fibrothecoma	3	Granulosa cell tumor	1
Follicular cyst	8	Endometrioid type carcinoma	4
Mature cystic teratoma	24	Immature teratoma	1
Musinous cyst	3	Undifferentiated carcinoma	2
Musinous cystadenoma	12	Mixed epithelial carcinoma	1
Myoma uteri	7	Malignant cystadenofibroma	1
Paraovarian cyst	3	Malignant mesenchymal tumor	1
Paratubal cyst	4	Malignant mixed Müllerian tumor	1
Serous cyst	11	Malignant musinous carcinoma	2
Serous cystadenoma	16	Serous cystadenocarcinoma	16
Tubo-ovarian abscess	11	Transitional cell carcinoma	1

Table 2. RMI 1-4 Scores of Cut-off Values with the Best Performance

		Tumor		Compatibility	Specificity	NPV	Sensitivity	PPV	Kappa	p
		Benign	Malignant							
RMI 1	≤250	136	18	85.9%	93.8%	88.3%	60.9%	75.7%	0.586	<0.001
	250<	9	28							
RMI 2	≤200	130	15	84.3%	89.7%	89.7%	67.4%	67.4%	0.57	<0.001
	200<	15	31							
RMI 3	≤200	132	17	84.3%	91.0%	88.6%	63.0%	69.0%	0.557	<0.001
	200<	13	29							
RMI 4	£400	134	15	86.4%	92.4%	89.9%	67.4%	73.8%	0.616	<0.001
	400<	11	31							

*Kappa agreement analysis was used. NPV: Negative predictive value. PPV: Positive predictive value

correlation was found to be 84.3%. RMI 3 has a significant [A.U.C: 0.89 (0.83-0.94); p≤0.001] predictive power in differentiating benign and malignant patients (Table 2).

Kappa value for RMI 4 was 0.58 when the cut-off value was set at 450. This value yielded 92.4% sensitivity, 72.5% positive predictive value, 64% negative predictive value, 88.7% sensitivity and 85.3% histopathologic correlation. When the cut-off value was set as 400, Kappa value was noted as 0.616. The best performance for RMI 4 was obtained with a cut-off value of 400. With RMI 4 ≤400 and 400< cut-off values there was a significant (p≤0.001) correlation with a sensitivity of 67.4%, a positive predictive value of 73.8%, a specificity of 92.4%, a negative predictive value of 89.9% and a total correlation of 86.4% between benign and malignant. RMI 4 has a significant [A.U.C: 0.87 (0.81-0.94)/ p≤0.001] predictive power in differentiation of benign and malignant patients (Table 2).

Discussion

Our data demonstrates that with the determined cut-off values RMI 1, 2, 3 and 4 scoring systems which are non invasive and easily accessible in the outpatient gynecology clinic, could be included among methods used in differentiating benign and malignant adnexal masses preoperatively.

Adnexal masses are one the most common gynecologic hospital admissions. In the outpatient clinics, ultrasonography and serum CA-125 levels are fundamental in evaluation of the masses. Ultrasonographic features such as multilocularity, presence of solid areas, irregularities in the cyst wall favor malignancy (Valentin et al., 2004). However, 1.6-1.9% of simple (anechoic) unilocular cysts in the pre-menopausal period may be malignant while in the post-menopausal period this probabality is 0.73% (Ekerhovd et al., 2001). CA-125, a marker used in epithelial ovary malignancies, is elevated in more than 80% of the cases. However, it's elevated only in 50% of stage 1 ovarian tumors; benign conditions such as pregnancy, PID and endometriosis may also cause elevation in the serum levels (Osmers et al., 1998).

While 30% of the post-menopausal ovarian tumors are malignant, this rate is only 7% during the pre-menopausal period (Fiorca et al., 1996). Prevalence of malignancy in our study was 37% in total; 27% in the post-menopausal and 10% in the pre-menopausal periods. In the literature this rate is reported to be 30-43% (Davies et al., 1993; Finkler et al., 1998; Obeidat et al., 2004; Geomini et al., 2009).

When Jacob et al. (1990) used the RMI formula for the first time in differentiating benign and malignant adnexal masses, a specificity of 97% and a sensitivity of 85% was obtained with the cut-off value set to 200. Moreover, the cut-off value is evaluated between 25 and 250 in numerous studies. In the systematic review of Geomini et al. (2009) assessing 109 studies including 21,750 adnexal masses, the RMI sensitivity and specificity were 87% and 78%, respectively, when the cut-off value was accepted as Jacob et al. (1990). When the cut-off level was considered 50, specificity and sensitivity were calculated as 74% and 91%, respectively. In our study, specificity and sensitivity for RMI 1 at the cut-off value of 200 were 93.1% and 60.9%, respectively. With the cut-off value set

at 200, specificity has been found to be compatible with the literature (a range of 77-97%) (Jacobs et al., 1990; Tingulstad et al., 1996; Tingulstad et al., 1999; Manjunath et al., 2001; Andersen et al., 2003; Ma et al., 2003; Obeidat et al., 2004; Chia et al., 2008). However, sensitivity is found to be lower (53-60%) similar to studies conducted in Turkey (Tanriverdi et al., 2007; Meray et al., 2010).

Although there is no statistically significant difference in our study, the best performance in the differential diagnosis of adnexal masses was obtained with the cut-off value set at 250. With the cut-off value of 250, histopathologic correlation has risen from 85.3% to 85.9% and specificity has risen from 93.1% to 93.8%. Similarly, in the study of Yavuzcan et al. conducted in Turkey the best performance for RMI 1 was obtained at the cut-off value of 250 (95.9% sensitivity and 75% specificity) (Yavuzcan et al., 2013). In the study of Engelen et al. (2006) performed on 302 women, cut-off value yielding the best performance for RMI with 88.2% specificity and 74.3% sensitivity was found to be 250. In their study of 182 patients, Bouzari et al. reported that the best performance cut-off value for RMI 1 and 3 is 265 and for RMI 2 it's 355 (96% specificity, 92% sensitivity) (Bouzari et al., 2011).

Ashrafgangooei et al. have found the best performance cut-off value for RMI 1 on 151 patients to be 238 (96% specificity, 89.5% sensitivity) (Ashrafgangooei et al., 2011). In the study of Tingulastad et al. (1996) using the RMI 2 for the first time, 92% specifity and 80% sensitivity were obtained with a cut-off value of 200. We have found the best cut-off value to be 200 with 89.7% specificity and 67.4% sensitivity in differentiation of benign and malignant adnexal masses. Although the best performance cut-off obtained was 200, sensitivity and specificity were lower compared to Tingulastad et al. (1999). In a comprehensive review RMI 2 has been evaluated in seven studies. With the cut-off value set at 200, the pooled estimate of sensitivity was 79% (71-78%) and specifity was 81% (72-90%) (Geomini et al., 2009). Considering the review, sensitivity of our study was lower.

In the study of Tingulastad et al. (1996b) with the cut-off value set at 200 specificity and sensitivity were 93% and 71%, respectively. Manjueth et al. (2001) reported a specificity of 91% and a sensitivity of a 74% in their study on RMI 3. Similar to Tingulastad et al. (1999a) the best cut-off value defined for RMI 3 in differentiating adnexal masses preoperatively in our study with 91% specificity and 63% sensitivity was 200; despite the similarity, specificity and sensitivity were lower. The best cut-off value for RMI 3 has been found to be 200 in similar studies (van den Akker et al., 2011).

Yamamoto et al. (2009) reported 91% specificity and 75% sensitivity with the cut-off value set at 450 in their first study on RMI 4 index. In our study these values were 92.4% and 63%, respectively. However, with the cut-off value set at 400, sensitivity rises from 63% to 67.4% giving the best performance. In a similar study of Yavuzcan et al. conducted in Turkey the best performance for RMI 4 has been reported as 400 (with 91% specificity and 75% sensitivity) (Yavuzcan et al., 2013). Similar to previous studies Van den Akker et al. have found the best cut-off value to be 450 for RMI 4 in the differential diagnosis of adnexal masses (van den Akker et al., 2011).

The RMI scoring system is shown to be efficient in out study population. Cut-off values used in previous studies testing the RMI scoring system could efficiently differentiate benign and malignant adnexal masses. Although cut-off values discovered in our study have yielded better performances for RMI 1 and 4, no statistical significance was found.

In conclusion, RMI is a noninvasive, easily accessible and applicable, inexpensive and beneficial method in preoperatively classifying adnexal masses as low and high grade.

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