Risk of malignancy index is not sensitive in detecting non-epithelial ovarian cancer and borderline ovarian tumor

Malignite risk endeksi borderline ve epitelyal olmayan over tümörlerinin tanısında duyarlı değildir

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Abstract

Objective: To determine the value of risk of malignancy index in detection of ovarian cancer and referral of adnexal masses.

Material and Method: Patients scheduled for surgery due to adnexal mass between May 2008 and August 2009 were prospectively included in the study. Risk of malignancy index (RMI) was calculated for each patient with a published formula (RMI=Ultrasonic score X menopausal status X Ca-125 (IU/ml) level). RMI >200 was accepted as positive for malignancy and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of RMI in detecting malignant cases were calculated.

Results: One hundred consecutive patients of whom 80 (80%) had benign ovarian cyst, 4 (4%) had borderline lesion and 16 (16%) had invasive ovarian cancer were included in the study. Forty-five percent (9/20) of malignant cases were epithelial ovarian cancer, 20% (4/20) were borderline ovarian tumor, 30% (6/20) were non-epithelial ovarian tumor and 5% (1/20) was a metastasis from the appendix. All the cases with epithelial ovarian cancer had positive RMI but only 1 of 4 borderline lesions, 2 of 6 non-epithelial ovarian cancers had positive RMI. The sensitivity of RMI was 60%, specificity was 88.8%, PPV was 57.1% and NPV was 89.9% for all cases. When the cancer cases other than epithelial ovarian cancers were excluded, the sensitivity, specificity, PPV and NPV of RMI was 76.92%, 88.75%, 52.63% and 95.95% respectively.

Conclusions: RMI is not adequate in detecting malignant cases in a population with high non-epithelial ovarian cancer and borderline ovarian tumor prevalence.

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Key words: Risk of malignancy index, Malignant, Benign, Ovarian cancer, Ultrasonography

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Özet

Amaç: Adneksiyal kitlelerin değerlendirilmesinde ve over kanserini tanımada malignite risk endeksinin değerini araştırmak.

Materyal ve Metod: Mayıs 2008 ve Ağustos 2009 tarihleri arasında adneksiyal kitle nedeniyle cerrahi uygulanması planlanan hastalar prospektif olarak çalışmaya dahil edildi. Malignite risk endeksi (MRE) daha önce yayınlanmış olan formül ile hesaplandı (MRE= ultrason puanı x menapozal durum x Ca-125 (IU/mL) seviyesi). MRE>200 olduğunda malignite pozitif olarak kabul edildi bu kestirim değerinin malign olguları saptamada ki duyarlılığı, özgüllüğü, pozitif öngörme değeri ve negatif öngörme değeri hesaplandı.

Bulgular: Çalışmaya alınan 100 hastanın 80 tanesinde (%80) benign over kisti saptanırken, 4 tanesinde (%4) borderline over kanseri ve 16 tanesinde de (%16) invaziv over kanseri saptandı. Malign hastaların %45'i epitelyal over kanseri iken, %20'si (4/20) borderline, %30'u (6/20) epitelyal olmayan over kanseri ve %5'i de (1/20) appendiksten metastazdı. Tüm epitelyal over kanseri olgularının MRE pozitif iken borderline olguların dörtte birinin ve epitelyal olmayan over kanserli olguların altıda ikisinin MRE'si pozitifti. MRE' nin tüm adneksiyal kitleler içinde over kanserini saptamadaki duyarlılığı %60, özgüllüğü %88.8, pozitif öngörme değeri %57.1 ve negatif öngörme değeri %89.9 idi. Epitelyal olmayan over kanserleri dışlandığında MRE'nin over kanserlerini tanımadaki duyarlılığı, özgüllüğü, negatif ve pozitif öngörme değerleri sırasıyla %76.9, %88.7, %52.6 ve %95.9 idi.

Sonuç: Epitelyal olmayan kanser ve borderline over kanseri olgularının sıklığının yüksek olduğu bir toplulukta MRE, malign olguları tanımada yeterli değildir. (J Turkish-German Gynecol Assoc 2010; 11: 22-6)

Anahtar kelimeler: Malignite risk endeksi, malign, benign, over kanseri, ultrasonografi

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Introduction

Ovarian cysts are a common reason for admission to hospital (1). Due to the routine use of transvaginal ultrasonography as a part of gynecological examinations; even asymptomatic ovarian cysts in patients admitted for other complaints have been detected incidentally, increasing the incidence of ovarian cysts. However, differentiation of ovarian carcinomas from benign ovarian tumors is the major diagnostic problem. Preoperatively, the knowledge of the malignant nature of the adnexal mass would enable the optimum timing and conditions for the surgical treatment.

Malignant ovarian tumors, unlike other gynecologic cancers, are mostly asymptomatic and are diagnosed at advanced stages (2). These patients undergo extensive surgical debulking followed by combination chemotherapy and have high mortality rates. Appropriate primary surgery may greatly improve the prognosis of these patients (3-4). Therefore, the surgical intervention of malignant ovarian tumors should be done by gynecologic oncology surgeons who have special skill and experience.

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It is not practical for oncology surgeons to treat all adnexal masses to favor the prognosis, in case the mass is malignant. instead some referral criteria should be created to differentiate malignants from benigns. Individual diagnostic tools used to differentiate malignant cases are not adequate. The ultrasonographic findings such as multilocularity, presence of solid parts and irregularity of the cyst wall have been regarded in favor of malignancy (5). However, 1.6 to 9.6% and 0.73% of unilocular simple cysts were found to be malignant in postmenopausal and premenopausal women, respectively (6-7). Serum level of Ca-125 is a well recognized marker of epithelial ovarian cancer and it increases in >80% of epithelial ovarian cancer. However it increases in only 50% of stage I ovarian cancer and it can also increase in benign conditions like endometriosis, fibroma, pregnancy, menstruation, pelvic inflammatory disease, peritonitis and liver cirrhosis. Assesment of vasculature of the adnexal masses with Doppler ultrasonography was also investigated. Presence of central vessels and low vascular resistance was found to be in favor of malignancy (8). However, use of Doppler ultrasonography in the preoperative evaluation of the adnexal masses had a low sensitivity in detecting malignant ovarian tumors (9). Also, when combined to the gray scale morphologic evaluation, it did not increase the number of correct diagnosis (10, 11).

For the accurate preoperative diagnosis of ovarian cancers, Jacobs et al. (12) originally developed the risk of malignancy index (RMI) in 1990. They calculated the RMI based on menopausal status, ultrasonographic morphology of the adnexal mass and serum level of Ca-125. The sensitivity and specificity of RMI was found as 85% and 97%, respectively. They also found RMI to be more sensitive and specific from individual parameters used in calculation **o**f it, in detecting malignant cases. With this study we aimed to evaluate the value of RMI in the preoperative evaluation and referral of women with adnexal mass for optimal treatment.

Materials and Methods

The institutional ethical committee approved this study. We prospectively included the patients who were scheduled for surgery with the diagnosis of adnexal mass after they signed the written consent form, between May 2008 and August 2009. Age, parity, medical history, pelvic and physical examination findings were noted for all patients. Venous blood samples were taken from each patient and centrifuged in 4000 rpm for 3 minutes. The serum was taken to determine Ca-125 level. Ca-125 level was determined by using electrochemiluminescence technique (Immulite 2000 DPC®, Siemens, Los Angeles, CA, USA with Immunolyte 2000 kit, Medical Solutions Diagnostic, Los Angeles, CA, USA). Preoperatively, menopausal score (M), ultrasonographic score (U) and RMI were calculated for each patient, according to Tingulstad et al. (13).

Patients who had amenorrhea for at least 1 year and hysterectomized patients aged 50 years or older were accepted as menopausal. Premenopausal cases got 1 and postmenopausal cases got 3 points as menopausal score (13).

Sonographic examination was undertaken by the same physician, who is the first author (O.M.). Five-10 Mhz trans-vaginal and trans-abdominal probes (PVT-375AT, Toshiba Xario®, Toshiba Medical Systems, Tokyo, Japan) were used for evaluation. Ultrasonographic scoring system evaluating multilocularity, bilateralism, presence of solid area, findings supporting intra-abdominal metastasis and presence of ascites was used (13). Each criterion got 1 point if present or got 0 point if not present. The scores of each criterion were added to find out the total score. U was determined as 3 if the total score was ≥2 or as 1 if the total score was ≤1 (13).

RMI was calculated as: RMI= (M)x(U)x(Ca-125 IU/ml). Cut off value for RMI was taken as 200 which was originally used by Jacobs et al (12) and later confirmed by others as the optimal cut off point (14-15).

Intra-operative findings were noted for all patients. Surgical specimens were evaluated with frozen section intra-operatively. Because 20-25% of borderline ovarian tumors have the final diagnosis of malignant ovarian tumor after the evaluation of paraffin embedded sections (16), cases that had borderline and malign ovarian tumor diagnosis in frozen sections underwent comprehensive surgical staging. Surgical procedure of all the borderline and malignant ovarian tumors was accomplished by a specialized gynecologic oncology surgeon, who is the third author (M.M.M). Histopathologic examination of the specimens was then carried out in paraffin embedded sections and the diagnosis was accepted as the final histopathology diagnosis. All the findings were evaluated in respect of the final histopathology diagnosis.

Statistical analysis

Statistical Packages for Social Sciences (SPSS) 13.0 for Windows and Medcalc version 7.4.4.1 for Windows were used for statistical analysis. Measurable variables were given as mean±standard deviation (SD) and un-measurable variables were given as number and percentage (%). RMI and final histopathology diagnosis were compared with chi-square test. Menopausal scores and ultrasonographic morphological findings were compared with Pearson chi-square and Fisher's Exact chi-square tests. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of RMI and U was determined. Sensitivity was calculated as the ratio of true positives to true positives + false negatives, specificity was calculated as the ratio of true negatives to true negatives + false positives, PPV was calculated as the ratio of true positives to true positives + false positives and NPV was calculated as the ratio of true negatives to true negatives + false negatives. The level of significance was set at $P<0.05$.

Results

Between May 2008 and August 2009, a total number of 100 consecutive patients were included in the study. Final histopathologic diagnosis was benign in 80 cases (80%), borderline in 4 cases (4%) and malignant in 16 cases (16%). The mean ages of cases were 40.2±14 years (range 16-79) and

46.7±15.8 years (range 16-77) in benign and malignant groups respectively (p=0.073).

Cases with benign adnexal mass had the diagnosis of endometrioma most frequently (n=24, 30%). The second most frequent diagnosis was mature teratoma (n=15, 18.5%). Histopathologic diagnosis of benign cases is given in Table 1.

Borderline ovarian tumors (BOT) accounted for 20% (4/20) of malignant ovarian tumors.

Among malignant tumors, epithelia originated tumors were the most frequent (13/20, 65% including the BOT). Germ cell tumors (3/20, 15%) and sex cord stromal tumors (3/20, 15%) were the second most frequently diagnosed tumors. In one case (1/20, 5%) a metastatic ovarian tumor which originated primarily from appendix was diagnosed. Characteristics of malignant cases are given in Table 2.

Table 1. Histopathology diagnosis of benign adnexal masses

Histopathology diagnosis	N (%)
Endometrioma	24 (30%)
Mature teratoma	15 (18.75%)
Serous cystadenoma	13 (16.25%)
Corpus luteum/corpus hemorrhagicum/ follicular cyst	12 (15%)
Paratubal cyst	6 (7.50%)
Mucinous cystadenoma	5 (6.25%)
Tubo-ovarian abcess	4 (5%)
Fibroadenoma	1 (1.25%)
Total	80 (100%)

Seventy five percent of the cases were premenopausal (75/100), whereas 25% (25/100) were postmenopausal. Eighty-eight percent of premenopausal cases (66/75) were diagnosed with benign adnexal mass, whereas 12% (9/75) was diagnosed with malignant adnexal mass. For postmenopausal cases, 40% (10/25) was diagnosed with benign adnexal mass and 60% was diagnosed with malignant adnexal mass. Malignant cases were significantly more frequent in postmenopausal cases (p<0.001).

Among the morphologic criteria used for sonographic scoring, the presence of solid area (17/20, 89.4% vs 35/80, 43,2%; p<0.001), ascites (7/20, 36.8% vs 1/80, 1.2%; p<0.001), findings supporting intraabdominal metastasis (6/20, 31.57% vs 1/80, 1.2%; p<0.001) were found significantly more frequently in malignant cases compared to benign cases. However, sonografically, the rate of multilocularity (9/20, 47.3% vs 27/80, 33.3%; p=0.3485) and bilaterality (2/20, 10% vs 10/80, 12.3%; p=1) were found to be similar in malignant and benign cases, respectively (Table 3).

Sonographically, out of 100 cases 22 cases had a simple adnexal mass (total score=0, U=1), 51 cases had a semicomplex

Table 2. Characteristics of cases with malignant adnexal tumors

Patient No:	Age	U	CA-125(IU/ml)	M	RMI	Histopathology Diagnosis
1	55	3	52,6	3	473	Serous Cyst Adenocarcinoma
2	60	3	49,7	3	447,3	Serous Cyst Adenocarcinoma
3	39	3	500	1	1500	Serous Cyst Adenocarcinoma
4	68	3	50,1	3	450,9	Serous Cyst Adenocarcinoma
5	48	3	43,3	3	389,7	Serous Cyst Adenocarcinoma
6	55	3	347	3	3123	Serous Cyst Adenocarcinoma
7	43	3	179	1	537	Serous Cyst Adenocarcinoma
8	50	3	500	1	1500	Serous Cyst Adenocarcinoma
9	38	1	17,1	1	17,1	Granulosa Cell Tumor
10	52	1	5,8	3	17,4	Granulosa Cell Tumor
11	77	3	23,1	3	207,9	Granulosa Cell Tumor
12	62	3	255	3	2295	Clear Cell Adenocarcinoma
13	17	3	77,3	1	695,7	İmmature Teratoma
14	16	3	46,5	1	139,5	Endodermal Sinus Tumor
15	51	3	19	3	171	Carsinoid Tumor
16	36	3	26	1	78	Metastasis from Appendix
17	28	3	77,9	1	233,7	Serous Borderline Tumor
18	44	1	7,6	1	7,6	Serous Borderline Tumor
19	34	1	37	1	37	Serous Borderline Tumor
20	60	1	30	3	90	Serous Borderline Tumor

adnexal mass (total score=1, U=1) and 27cases had a complex adnexal mass (total score=2-5, U=3). Malignant adnexal mass was diagnosed in 10.1%, 5.9% and 51.8% and benign adnexal mass was diagnosed in 90.9%, 94.1% and 48.1% of simple, semicomplex and complex adnexal masses respectively. Sensitivity, specificity, PPV and NPV of finding a complex adnexal mass sonographically in the detection of malignant cases was 75%, 83.75%, 53.57% and 93.06%, respectively.

When sonographic findings were combined with the menopausal status and Ca-125 value (RMI), sensitivity, specificity, PPV and NPV in the detection of malignant cases were found as 60%, 88.8%, 57.1% and 89.9% respectively, when the cut off value of RMI was set as 200. (Table 4)

When epithelial ovarian tumors only were taken into consideration (8 serous cystadenocarcinoma, 1 clear cell carcinoma and 4 serous borderline tumor) sensitivity, specificity, PPV and NPV of RMI score in detecting malignant cases were found as 76.92%, 88.75%, 52.63% and 95.95% respectively, with the cut off value of 200 (Table 5).

Discussion

In the current study, the overall prevalence of malignancy was 20%, including the borderline ovarian tumors (60% and 12% in post and premenopausal patients, respectively), reflecting the unselected nature of the study population. However, although the non-epithelial ovarian cancer constitutes 10% of ovarian cancers in the general population, its prevalence is 30% in our study population.

We found RMI to be successful in identifying the benign cases (specificity=88.8%). This finding was in accordance with the findings of other studies (specificity ranged between 77 to 97%) (12-15, 17-19). However, apart from other studies we found the sensitivity of RMI as 60% which was similar to the findings of Tanriverdi et al (20). RMI was positive in all invasive epithelial ovarian cancers, however it was positive in only 1 out of 3 germ cell tumors, 1 out of 3 endodermal sinus tumors and 1 out of 4 borderline ovarian tumors. Others also found RMI negative in most of non-epithelial ovarian cancers and borderline ovarian tumors (19). Therefore the low sensitivity of RMI for our population can be attributed to the high prevalence of non-epithelial ovarian cancers and borderline ovarian tumors. When we excluded the non-epithelial ovarian cancers, the sensitivity of RMI increased to 76.92%, which is in accordance with the other studies (sensitivity ranged between 70.6 to 90%) (12-15, 17-19, 21).

We found the PPV of RMI as 57.1%. However, others found the PPV between 66.1 and 96% (14, 15, 17-19, 21). In our study population, endometrioma was the most common diagnosis among benign adnexal masses comprising 30% (24/80). Fifteen out of 24 endometrioma cases (62.5%) had a Ca-125 level more than 30 IU/ml and 25% of cases (6/24) had a false positive RMI. Yamamoto et al (22) also found the PPV of RMI as 52.5% in a population in which 40% of benign adnexal masses was diagnosed with endometrioma and 20% of endometrioma cases had false positive RMI.

RMI, after originally being developed by Jacobs et al (12) and modified as RMI-2 (17) and RMI-3 (13) by Tingulstat et al, has been tested in prospective and retrospective studies (14, 15, 18, 19). Studies found the sensitivity of RMI as 70.6 to 90% and the specificity as 77 to 97%. It is found to be more sensitive and specific from individual parameters used in calculation of RMI in detecting malignant cases. With these findings, RMI is currently being used as a referral criterion of adnexal masses to oncology centers by some gynecology units (19, 21). However we found it inadequate in detecting ovarian cancers in a population which has a high prevalence of non-epithelial ovarian cancer and borderline ovarian tumors.

Table 3. Frequency of morphologic findings in malignant and benign adnexal masses

	Malignant	Benign	p
Solid Area	89.4%	43.2%	<0.001
Ascites	36.8%	1.2%	<0.001
Findings supporting intraabdominal metastasis	31.57%	1.2%	<0.001
Multilocularity	47.3%	33.3%	0.3485
Bilaterality	10%	12.3%	1

Table 4. RMI scores according to the final histopathology diagnosis

RMI Score	Final Histopathology Diagnosis		Total
	Benign	Malignant	
<200	71	8	79
>=200	9	12	21
Total	80	20	100

Table 5. RMI scores when malignant tumors other than epithelial ovarian tumors were excluded

RMI Score	Final Histopathology Diagnosis		Total
	Benign	Malignant	
<200	71	3	74
>=200	9	10	19
Total	80	13	94

Conclusion

Although RMI has high sensitivity in detecting epithelial ovarian cancers, it is not adequate in detecting non-epithelial ovarian cancers and borderline ovarian tumors.

Conflict of interest
None declared

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