RESEARCH ARTICLE

Role of a Risk of Malignancy Index in Clinical Approaches to Adnexal Masses

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Abstract

Objective: The aim of this study was to evaluate predictive role of risk of malignancy index in discriminating between benign and malignant adnexal masses preoperatively. Methods: This retrospective study was conducted with a total of 569 patients with adnexal masses/ovarian cysts managed surgically at our clinic between January 2006 and January 2012. Obtained data from patient files were age, gravidity, parity, menopause status, ultrasound findings and CA125 levels. For all patients ultrasound scans were performed. For the assessment of risk of malignancy index (RMI) Jacobs' model was used. Histopathologic results of all patients were recorded postoperatively. Malignancy status of the surgically removed adnexal mass was the gold standard. Results: Of the total masses, 245 (43.1%) were malignant, 316 (55.5%) were benign and 8 (1.4%) were borderline. The mean age of benign cases was lower than malign cases (35.2±10.9 versus 50.8±13.4, p<0.001). Four hundred and five of them (71.2%) were in premenopausal period. Malignant tumors were more frequent in postmenopausal women (81% versus 29%, p<0.001). All ultrasound parameters of RMI were statistically significantly favorable for malignant masses. In our study ROC curve analysis for RMI provided maximum Youden index at level of 163.85. When we based on cutoff level for RMI as 163.85 sensitivity, specificity , PPV, NPV was calculated 74.7%, 96.2%, 94% and 82.6%, respectively. Conclusions: RMI was found to be a significant marker in preoperative evaluation and management of patients with an adnexal mass, and was useful for referring patients to tertiary care centers. Although utilization of RMI provides increased diagnostic accuracy in preoperative evaluation of patient with an adnexal mass, new diagnostic tools with higher sensitivity and specificity are needed to discriminate ovarian cancer from benign masses.

Keywords: Adnexal mass - risk of malignancy index - CA125 - ovarian cancer - ultrasonography

Asian Pac J Cancer Prev, **15 (18)**, 7793-7797

Introduction

Adnexal masses are common gynecological conditions and might be encountered at every stage of a woman life. Ovarian malignancy a common cause of adnexal mass is the most common second gynecological malignancy and the most lethal gynecologic cancer (Wanapirak et al., 2006; Arun-Muthuvel et al., 2014). In preoperative assessment prediction of the benign or malignant character of an adnexal mass is important and an accurate diagnosis is required for choosing appropriate management method. Many women with ovarian cancer are presented in late stages. The reason is that the lack of effective screening methods to detect the disease at early stages (Tongsong et al., 2009).

The most efficient and well known screening method includes evaluation of CA125 and then ultrasound in case of abnormal results of CA125. The survival rate is related to the stage of the disease at the diagnosis (Ashrafgangooei et al., 2011). In patients diagnosed with advanced stage III-IV ovarian cancer, the 5-year survival rate is about 30%, whereas in those diagnosed at an early stage the 5-year survival rate is about 90% (Su et al., 2013). Therefore it seems worthwhile to detect ovarian cancer at an early stage (Mathevet et al., 2013). Patients who have their initial diagnostic surgery performed by a gynecologic oncology surgeon in a tertiary center are more likely to be optimally cytoreduced.

Previously palpable ovary and postmenopausal adnexal mass were the major indication for surgery (Bell et al., 1998). Widespread use of ultrasonography has increased the number of women with adnexal masses, and different ultrasound features provided to follow up these patients without performing any surgical interventions due to low malignancy potential. It is estimated that 5-10% of women in The US will undergo a surgical procedure

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for a suspected ovarian neoplasm during their lifetime, and 13-21% of these women will be found to have an ovarian malignant neoplasm (Disaia et al., 2012). In many cases diagnosis is made during surgery or after histopathologic evaluation. The inadequacy of current preoperative diagnostic tools is resulting in unnecessary surgical procedures.

In recent years different laboratory markers, imagination methods and clinical parameters were presented for identifying malignancy potential of an adnexal mass. In this study we aimed to evaluate the role of RMI in discriminating between benign and malignant in women with adnexal masses preoperatively.

Materials and Methods

This retrospective study evaluated the data of women with adnexal masses operated at Dr.Zekai Tahir Burak Women's Health Research and Education Hospital, Department of Gynecology and Oncology which is a referral medical center located in the middle region of Turkey. A total of 569 patients with adnexal mass/ ovarian cyst managed surgically at our clinic between January 2006 and January 2012 were subjected to the current study. Obtained data from patients' file were; age, gravidity, parity, menopause status, ultrasound findings and CA125 levels. For all patients ultrasound scan was performed by expert radiologists of our institution using Aloca Prosound a7, Aloca Prosound 5500, Toshiba Aplio 500, and Hitachi Avius, Tokyo, Japan, with abdominal probe (3.5-5 MHz) and endovaginal probe (5-6.5 MHz). On ultrasound examination multilocularity, solid areas, bilaterality, presence of ascites and evidence of metastases were recorded for each patient. Patients with absence of these detailed ultrasound findings on files were excluded. All blood samples were centrifugated at 4000 rpm for 3 minutes and CA125 was measured using commercially available immunoassay kits (Immulite 2000 Immunoassay System by Siemens). Histopathologic results of all patients were recorded postoperatively. Malignancy status was the gold standard of the surgically removed adnexal mass. Stage of malignant tumor was determined according to FIGO (International Federation of Gynecology and Obstetrics). For the assessment of RMI Jacobs' model was used.

Risk of malignancy index

RMI is a formula which was firstly described by Jacob et al. (1990) in discriminating malignant adnexal masses. RMI for all the patients was calculated, using the formula; RMI=(U)x(M)x(CA125). In the formula, "U" represents the ultrasonographic index, "M" is menopausal status, while CA125 is calculated directly into the equation. In our study menopause was accepted as 1 year amenorrhea for natural menopause and >50 year-old for surgical menopause. If premenopausal status is present 1 point was given and if postmenopausal status is present 3 points were given. The ultrasound scan result expressed as a score of 0, 1 or 3. If none of the ultrasound findings were detected 0 point was given, for one finding 1 point and two or more findings 3 points were given. Cutoff level was taken for RMI as 200. Optimal value of RMI for our study population was calculated by ROC curve analysis.

Statistical analysis

All the data analyses were performed with IBM® SPSS® Statistics 20 for Mac (IBM Corp, Los Angeles, California, USA) and tables of results were done by Microsoft® Excel® for Mac 2011 (Microsoft Corp, Santa Rosa. California, USA). Data were presented as mean±standard deviation and median (minimum-maximum). The Shapiro-Wilk test of normality was done. When there was a homogeneous distribution the Student's t-test was used for independent groups and if not the Mann-Whitney U-test was used to determine the statistical significance of differences. The Chi-square test is used to compare frequencies between groups. Diagnostic performance of different parameters in predicting malignity and benignity was evaluated by using the receiver-operating characteristics (ROC). Sensitivity, specificity, positive and negative predictive values were calculated for meaningful cuttoff values. In 95% confidence interval and $p<0.05$ was considered statistically significant.

Results

Pathology reports of the 569 patients 245 (43.1%) were malignant, 316 (55.5%) were benign and 8 (1.4%) were borderline. Borderline was included in malignant group. The mean age of patients with benign disease was 35.23±10.87 and in those with malignant disease, it was 50.78±13.39 ($p<0.001$). The histopathology

Table 1. The Histopathologic Results of Benign and Malignant Cases

Group Pathology	Number of Cases (n)	Percentage (%)
Benign		
Endometrioma	124	39.2
Serous cystadenoma	74	23.4
Mucinous cystadenoma	22	7
Mature cystic teratoma	40	12.7
Haemorrahagic cyst	27	8.5
Folliculer cyst	20	6.3
Fibroma	9	2.8
Total	316	100
Malignant		
Serous epithelial	100	39.5
Mucinous epithelial	13	5.1
Endometrioid	42	16.6
Clear cell	15	5.9
Mixt epithelial	26	10.3
Carsinosarcom	3	1.2
Disgerminom	2	0.8
Embryoner	2	0.8
Choriocarsinoma	1	0.4
Granulosa cell	32	12.6
Sertoly cell	1	0.4
Methastatic	7	2.8
Borderline serous	5	2
Borderline mucinous	3	1.2
Malign mixt mullerian tumor	1	0.4
Total	253	100

results of benign and malign cases are shown in Table 1. The distribution of benign and malignant cases by age, tumor size, parity, CA125 level and RMI value are described in Table 1. And ultrasound score, ultrasound features, menopausal status are also shown in the same table. Significantly more postmenopausal women had malignant disease than premenopausal women (p<0.001). All ultrasound parameters of RMI were statistically significantly favorable for malignant masses (p<0.001). The mean serum level of CA125 was significantly higher among women with malignant masses when compared with women who had a benign adnexal mass (270.8 IU/mL versus 41.5 IU/mL, p<0.05). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for CA125 after setting at a level of 35 IU/mL. Optimal results were found at level of 79.9 IU/mL from ROC curve analysis. RMI score was calculated by using (U)x(M)x(CA125) formula. Based on the data obtained from RMI score sensitivity, specificity, PPV and NPV were calculated as considering cutoff level of RMI for 200. ROC curve analysis gave maximum Youden index at level of 163.5 in our study. The RMI at the cutoff level of 163.5 had a sensitivity 74.7%, specificity 96.2%, PPV 94%, NPV 82.6%. The comparative diagnostic performance of RMI score of our study is shown in Table 3. Receiver operating characteristic curves of RMI, menopause status, ultrasound score and CA125 level are shown in Figure 1.

Table 2. Demographic, Ultrasound and Laboratory Features of the Cases

		Benign (n:316)	Malignant (n:253)	p value
Age		35.2±10.8	50.8±13.4	<0.001
Tumor size (mm)		97.2±46.9	59.9±26.3	<0.001
CA125(IU/mL)		41.5±48.0	270.8±236.5	<0.001
RMI		50.0±68.8	1291.3±1659.8	<0.001
Parity	Multipara	179	218	<0.001
	Nullipara	137	35	
US Score	1	302	118	<0.001
	3	14	135	
Bilaterality	(-)	276	166	<0.001
	(+)	40	87	
Metastasis	(-)	0	244	<0.001
	(+)	0	9	
Ascit	(-)	315	231	<0.001
	(+)	1	22	
Solid area	(-)	65	49	<0.001
	(+)	251	204	
Multilocularity	(-)	267	162	<0.001
	(+)	49	91	
Menaopause score	1	286	119	<0.001
	3	30	134	

*The difference between groups is statistically significant p<0.05

Table 3. Sensitivity, Specificity, PPV and NPV for RMI (around 200) in The Literature

	n	Sensitivity	Spesificity	PPV	NPV
Arun-Muthuvel et al., 2014	467	79	98	92	94
Terzic et al., 2013	540	83.8	77.2	47	95.1
Sayasneh et al., 2013	255	72	94		
Van Gorp et al., 2012	432	76	92	87	85
Ashrafgangooei et al., 2011	151	89.5	94.7	71	98
Akker et al., 2010	548	81	85	48	96
Yamamoto et al., 2009	253	80	86.4	52.5	95.8
Obeidat et al., 2004	100	90	89	96	78
Andersen et al., 2003	180	70.6	87.7	66.1	89.8
Ma et al., 2003	140	87.3	84.4	82.1	89
Manjunath et al., 2000	152	73	91	93	67
Tingulstad et al., 1999	365	71	92	69	92
Davies et al., 1993	124	87	89		
Jacobs et al., 1990	143	85.4	96.9		
Our study	569	73.5	97.1	95.3	82

*PPV and NPV values which were not given in studies are not included in the table. Data presented as (%)

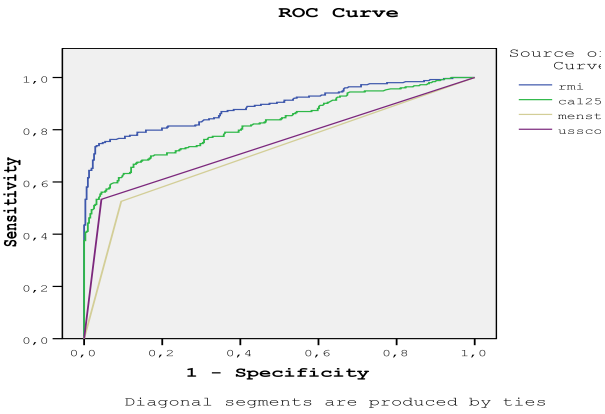

Figure 1. The Comparison of ROC of RMI, CA125, Menopause Score and US Score in Evaluation of The Adnexal Masses

Discussion

CA125 was first described by Bast et al (1981) and found elevated levels in 80% of epithelial ovarian cancers. They stated that 35 IU/mL was a threshold value for CA125 in their following study (Klug et al., 1984) and afterwards many studies related CA125 were made in preoperative diagnosis of an adnexal mass. In our study when 35 IU/mL was taken as a cutoff level for CA125, sensitivity and specificity was 78.6% and 63.5% respectively. ROC curve analysis for CA125 provided maximum Youden index at level of 79.97. And sensitivity, specificity, PPV and NPV were calculated in order of 66.7%, 87.2%, 80.8%, 76.4% for this value. But serum CA125 can be elevated in various conditions including benign diseases not only malignancies (Bian et al., 2013) and its predictive role in malignancies was singly limited.

In our study sensitivity, specificity, PPV and NPV was 52.9%, 90.5%, 81.7% and 70.6%, respectively for menopause score (M)=3. Specificity and PPV for M were higher than the values reported in the literature (Jacobs et al., 1990; Tingulstad et al., 1999; Manjunath et al., 2001; Ma et al., 2003).

Ultrasound score (U) was obtained from data of morphologic findings on ultrasound. Sensitivity, specificity, PPV and NPV for U=3 (positive morphologic findings 2-5) was 53.3%, 95.5%, 90.6%, 71.9%, respectively. Specificity and PPV for U were higher than the values reported in the literature like menopause score (Jacobs et al., 1990; Tingulstad et al., 1999; Manjunath et al., 2001; Ma et al., 2003).

Combination of different markers to increase diagnostic performance became a current issue and novel parameters and indexes were produced. RMI is one of the most important and was first described by Jacobs et al in 1990. They designed a study using patients' age,

ultrasound score, menopausal status and serum CA125 to assess how they could best distinguish between 141 patients with pelvic masses. This index was statistically virtually as effective a discriminant between cancer and benign lesions as more formal methods. Using a RMI cutoff level of 200, the sensitivity was 85.4% and the specificity was 96.9%. In our study we found sensitivity 73.5%, specificity 97.1%, PPV 95.3% and NPV 82% by using RMI of more than 200. In the literature different values were defined for RMI and our results confirmed these studies (Jacobs et al., 1990; Davies et al., 1993; Tingulstad et al., 1999; Manjunath et al., 2001; Anderson et al., 2003; Ma et al., 2003; Obeidat et al., 2004; Yamamoto et al., 2009; Van der Akker et al., 2010; Ashrafgangooei et al., 2011; Van Gorp et al., 2012; Sayasneh et al., 2013; Terzic et al., 2013; Arun-Muthuvel et al., 2014).

Afterward many modified methods and new scoring systems have been defined (Yavuzcan et al., 2013; Winarto et al., 2014). Also different tumor markers such as human epididymis protein 4 are suggested in differentiating ovarian cancer from other benign gynecologic diseases (Lin et al., 2012). Although different methods were defined for preoperative assessment of adnexal mass, RMI is still recommended in both the UK and USA (Geomini et al., 2009).

In a systematic review of 109 studies including 21750 women with adnexal masses consisted of 83 different prediction models. RMI was the best predictor and when 200 were used as the cutoff level, the pooled estimate for sensitivity was 78% for a specificity of 87% (Geomini et al., 2009).

To assess the diagnostic performance of a method and its usefulness and validation in a population first of all participants should be selected randomly. Usefulness of RMI is related to its malignancy prevalence. In our study real malignancy prevalence was found 44.5%. Our malignancy prevalence was a bit higher than the other studies (30%-43%) (Jacobs et al., 1990; Davies et al., 1993; Ma et al., 2003). The reasons for this could be; our hospital is one of the biggest tertiary center in the region, number of patients who were referred to our hospital with suspicion of malignancy is large and as well as exclusion of benign cases because of restricted data about ultrasound findings on their files.

In different studies different sensitivity, specificity, PPV and NPV were found and our results were compatible with the literature. In our study RMI was also best predictor for discriminating between benign and malignant in women with adnexal masses preoperatively. Differences between results in different researches are arising from the variations in study populations. And subjectiveness of ultrasound scoring is poor side of RMI. In our study ROC curve analysis for RMI provided maximum Youden index at level of 163.85. The strength of our study is its number of patients. Our study is one of the few studies which is one centered study that have maximum number of patients. And the limitation is its retrospective design.

In conclusion, we researched the predictive role of RMI in clinical approach to adnexal masses. We found that RMI alone is better predictor than separately from menopause status, ultrasound score and CA125 level. Although utilization of RMI provides increased diagnostic accuracy in preoperative evaluation of patient with an adnexal mass, new diagnostic tools with higher sensitivity and specificity are needed to discriminate ovarian cancer from benign masses.

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