RESEARCH COMMUNICATION

Risk of Malignancy Index in Preoperative Evaluation of Pelvic Masses

Tahereh Ashrafgangooei*, Mahdieh Rezaeezadeh

Abstract

Objective: The aim of this study was to evaluate the use of risk of malignancy index (RMI) based on a serum CA125 level, ultrasound findings and menopausal status in primary evaluation of patients with adnexal masses in daily clinical practice. Methods: One hundred and fifty one women with adnexal masses were enrolled. Ultrasound characteristics, menopausal status and serum CA125 level were documented preoperatively, and combined into the RMI afterwards. The sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of the RMI in prediction of ovarian cancer were calculated. Results: The RMI identified malignant cases more accurately than any individual criterion in diagnosing ovarian cancer. Using a cut-off level of 238 to indicate malignancy, the RMI showed a sensitivity of 89.5%, a specificity of 96.2%, a PPV of 77.3%, a NPV of 98.4% and an accuracy of 95.4%. Conclusion: RMI is a simple, easily applicable method in the primary evaluation of patients with adnexal masses of high risk of malignancy, resulting in timely referal to gynecological oncology centers for suitable surgical operations.

Keywords: Ovarian cancer - pelvic masses - preoperative evaluation - risk of malignancy index

Asian Pacific J Cancer Prev, 12, 1727-1730

Introduction

Ovarian cancer is the second most common gyncologic cancer in the developed countries; however, it is the fifth leading cause of mortality due to malignancies among women (Greenlee et al., 2001). An estimated 21,880 new cases of ovarian cancer are expected in the US in 2010. Ovarian cancer ranks second among gynecologic cancers, following cancer of the uterine corpus. An estimated 13,850 deaths are expected in 2010 (American Cancer Society, 2010). It is also the main cause of death due to gynecological cancer in the United States, with an estimate of 16,090 deaths and 25,580 new cases during the year 2004(American Cancer Society, 2004). As a result, mortality rate due to ovarian cancer is higher than all other gynecologic malignancies together (Landis et al., 1998). Besides, adnexal masses, however benign in 90% of cases, are the fourth most common gynecological causes for hospitalization (Grimes & Hughes, 1989). Five-year survival in patients with ovarian cancer varies, depending on being localized or accompanied by distant metastases from 93% to 28%, respectively; hence, screening, detection and treatment in earlier stages of the disease are of great importance (Bell et al., 1998).

One of the most common presentations of ovarian neoplasms is a pelvic mass (Enakpene et al., 2009). Considering the discrimination between benign and malignant tumors is a critical step in handling such cases clinically. It is estimated that in pre and postmenopausal women, ovarian tumors are malignant in 24% and 60% of patients, respectively (Manjunath et al., 2001; Yuen et al., 1997). Many women with advanced ovarian carcinoma undergo suboptimal primary surgeries at local hospitals. The amount of tumor left after the primary cytoreductive surgery is one of the most important prognostic factors in ovarian cancers (Engelen et al., 2006; Earle et al., 2006). The type of operation and the experience of the surgeon are other principal factors in prognosis (Engeland et al., 1995). Therefore, correct preoperative diagnosis is crucial and remains a challenging issue for gynecologists. This provisional diagnosis is useful in selective referral of relevant patients to specialized oncology centers and is thus helpful in planning for an appropriate surgical treatment (Vernooij et al., 2009). On the other hand, the increased morbidity and mortality due to unnecessary laparotomies performed to determine ovarian cancers at an early stage are a real clinical dilemma.

Jacob et al (Jacobs et al., 1990). originally developed a risk of malignancy index (RMI) with a sensitivity of 85.4% and a specificity of 96.9%, based on menopausal status, ultrasound morphologic features, and serum levels of CA-125. This algorithm has been tested on retro- and prospective studies with encouraging results (Davies et al., 1993). According to their results, determining adnexal masses as benign or malignant using RMI could be more sensitive and specific compared with ultrasound and serum CA-125 alone.

This study was designed to determine the effectiveness of the RMI algorithm in identifying cases of potential ovarian malignancy presenting at gynecologic cancer units in order

*Gynecologic Oncology, Kerman University of Medical Sciences, Keman, Iran. *For correspondence: dr_ganjooei@hotmail.com*

to make the right decision for subsequent referral of these patients to a cancer center, and also to reveal the most suitable cut-off value in benign-malignant determination.

Materials and Methods

After obtaining the approval for the study by the hospital ethic committee on research affairs, all the women, consecutively undergoing surgery for a pelvic mass between October 2008 and November 2009 who were referred to our cancer center, were enrolled in the study. The aim of the study was explained appropriately and informed written consent was obtained.Pregnant patients and known cases of ovarian malignancy were excluded. Age, CA-125 serum levels, ultrasounds findings, and menopausal status of all the cases were recorded preoperatively. Currently, the network guidelines recommend calculation of the RMI (Obeidat et al., 2004) as modified by Tingulstad et al (Tingulstad et al., 1996). In all suspected patients of ovarian cancer. Hence, the modified RMI for each woman was calculated using the product of the ultrasound score (U), the menopausal score (M), and the absolute value of serum CA-125 inserted in the following formula:

RMI= U x M x serum CA-125

Five ultrasound features suggestive of malignancy were sought to derive U including multilocularity (more than bilocular), presence of solid areas, bilaterality, presence of ascites, and extraovarian tumors/evidence of metastases. U of 1 was given if none or one of these findings was detected and a score of 3 if two or more of these features were present(Bailey et al., 2006). Postmenopausal status was defined as more than one year of amenorrhea, or age older than 50 years for women who had undergone hysterectomy; they scored M=3. All other patients who did not meet these criteria were defined in a premenopausal status which scored M=1. The absolute values of serum CA-125 was entered directly into the mentioned equation.

The histopathological diagnosis was considered as the gold standard for defining the outcomes. Hence, the RMI was evaluated for sensitivity, specificity, positive (PPV) and negative (NPV) predictive values with reference to the actual presence of a malignant or benign pelvic tumor. Tumors were classified according to World Health Organization definitions (Andersen et al., 2003) and malignant tumors were staged according to the criteria of the international Federation of Gynecology and Obstetrics (Benedet et al., 2000).

All statistical analyses were done using SPSS version 15 (SPSS Inc., Chicago, IL) and Medcalc 7.4.4.1 for windows (Medcalc Software, Mariakerke, Belgium). A univariate statistical analysis was performed for all sonographic parameters and patient age. The Kologoromov-Smirnov test was used to evaluate the normal distribution of continuous data. According to their distribution, they were compared with the use of student's T and Mann-Whitney U tests. The proportion of malignant and benign cases with different sonographic parameters was compared with chi-square, Fisher's exact and Yates Corrected tests. To determine the best cut-off value to discriminate between benign and malignant adnexal masses, a receiver operating characteristics (ROC) curve was plotted. The best cut-off value was chosen according to the highest sensitivity with the lowest false-positive rate. A P-value <0.05 was considered to be significant.

Results

A total of 151 patients with a pelvic mass were referred to our center for surgery. Taking into account the histopathological reports, 132 (87.4%) had a benign tumor; while for 19 (12.6%) a malignant ovarian tumor was reported. Metastatic tumors included one primary carcinoma of the cervix and three gastric adenocarcinomas. The mean size of benign and malignant tumors was 77.92 ± 36.17 mm and 94.47 ± 36.62 mm, respectively, which was not significantly different between the two groups (p:0.05).

One hundred and thirty cases (86.1%) were premenopausal and 21 (13.9%) were postmenopausal. There were significantly more malignant tumors in the postmenopausal group (P=0.000) (Table 1). Considering ultrasound scores, 98% percent of patients with U score=1 had benign tumors; however, 65.4% of the patients who obtained U=3 were reported malignant in histopathology. There was a significant difference between the two groups (P=0.000).The median value of preoperative serum CA-125 level of the patients and the median values of the calculated RMI were also significantly different between benign and malignant cases (P=0.000). In ROC curve analysis, all the five evaluated parameters were found to be associated predictors of malignancy; however, RMI was the most impressive factor in prediction of malignancy (Figure 1).

The best performance obtained for the RMI was at the cut-off point 238 with a sensitivity of 89.5% (95% CI: 75.7 %-100%), a specificity of 96.2% (95% CI: 93%-99.5%), a PPV of 77.3% (95% CI: 59.8%-94.8%), an NPV of 98.4% (95% CI: 96.3%-100%), and an accuracy of 95.4%.

Taking into account the best obtained cut-off point for RMI, 5 cases were false and 127 true positive (RMI < 238, benign tumors) while 2 cases were false and 17 true negative (RMI ≥ 238, malignant tumors); one was a case

Table 1. Results of Univariate Statistical Analysis

Criteria	Benign	Malignant	P-value
Age (mean±SD)	37.0±8.79	50.8±12.9	0.000
Menopausal status (M)			
Premenopausal	123 (93.2%)	7 (36.8%)	0.000
Post menopausal	9 (6.8%)	12 (63.2%)	
Sonographic morphology			
Multilocularity	9 (6.8%)	9 (47.4%)	0.000
Presence of solid area	86 (65.1%)	18 (94.7%)	0.005
Presence of ascites	5 (3.8%)	15 (78.9%)	0.000
Bilaterally	7 (5.3%)	2 (10.5%)	0.322
Evidence of metastases	2 (1.5%)	3 (15.8%)	0.015
Ultrasound score (U)			
1	123 (98.4%)	2 (1.6%)	0.000
3	9 (34.6%)	17 (65.4%)	
Serum CA-125 (u/ml) *	19.1 (4-400)	126.4 (3-700)	0.000
RMI *	21.7 (5-1200)	1062 (53-2889)	0.000

* reported as median (min-max)

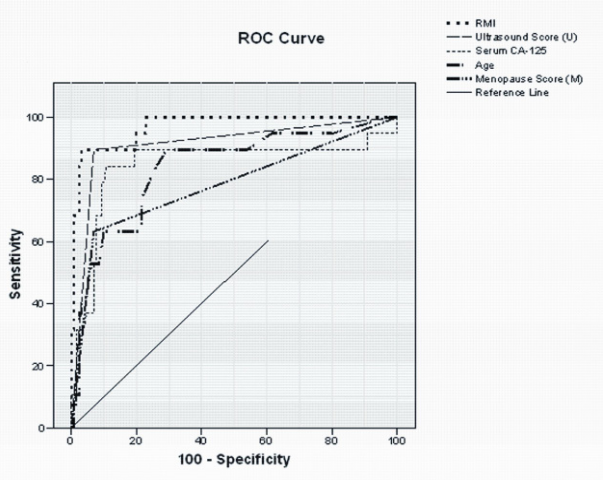

Figure 1. Receiver Operating Characteristics (ROC) curves of individual predictors showing the relationship between sensitivity and specificity of RMI, U score, M score, Serum CA-125 and age in the discrimination between benign and malignant masses

of dysgerminoma and one a case of Yolk tumor.

Multivariate analysis model showed that RMI, Ultrasound score (U=3) and CA-125 serum levels were the independent predictors of malignancy. However, none of the ultrasound morphologic features were the independent predictors.

Discussion

The prevalence of ovarian neoplasms has been rising during last decades. Silent occurrence and slow progression, besides few effective methods for early diagnosis makes its mortality rate the highest among gynecologic malignancies (Guidozzi, 1996). If patients with ovarian cancers are diagnosed at stage I, the cure rate could be as high as 80-90% and the mortality rate could decrease up to 50% (Zalel et al., 1996). Hence, a new method of early diagnosis is of great importance for prediction of the prognosis and medical management of the ovarian neoplasm. Selective referral of patients with high risk of malignancy to specialized oncology centers is substantial since the primary cytoreductive surgery has a great role in predicting the prognosis of ovarian cancers.

Table 2. Comparison of our Results with Previous Studies*

Study	No.	Sens	Spec	PPV	NPV
Jacobs et al.1990	143	85.4	96.9		
Davies et al.1993	124	87.0	89.0		
Tingulstad et al.1996	173	71.0	96.0	89	88
Tingulstad et al.1999	365	71.0	92.0	69	92
Morgante et al.1999	124	58.0	95.0	78	87
Manjunath et al. 2001	152	73.0	91.0	93	67
orres et al. 2002	158	73.0	86.0		
Ma et al.2003	140	87.3	84.4	82	89
Andersen et al.2003	180	70.6	87.7	66	90
Obeidat et al.2004	100	90.0	89.0	96	78
Ulusoy et al.2006	296	71.7	80.5	67	84
Our study (RMI=238)	151	89.5	94.7	71	98

*Values were % given for RMI=200; Sens, Sensitivity; Spec, Specificity; PPV, positive predictive value; NPV, negative

Table 2 summarizes the results of past related studies. The best cut-off value for RMI in several publications was 200 (Jacobs et al., 1990; Tingulstad et al., 1996; Tingulstad et al., 1999).

If the cut-off value of RMI is set 238 instead of 200, the sensitivity, specificity, PPV and NPV will improve dramatically comparing to most of previous studies.

Although we used the Ultrasound scoring system of Bailey et al.(2006) our results for RMI were in agreement with the results from other studies in which RMI was suggested to be better than other single parameters, with the highest area under the curve. In our study, RMI of <238 yielded high sensitivity and specificity of 89.5% and 96.2%, respectively, which were higher compared with other studies. Endometriosis contributed to the highest numbers of false positive (80%) whilst the false negative cases included dysgerminoma and Yolk tumor, which seems to be of importance in clinical practice.

In conclusion, the present study demonstrated that RMI was a better estimate in diagnosing adnexal masses with high risk of malignancy and sudsequently guiding the patients to gynecological oncology centers for suitable and effective surgical interventions compared with individual parameters of Ultrasound score, CA-125 or menopausal score. Simplicity and applicability of the method in the primary evaluation of patients with pelvic masses makes it a good option in daily clinical practice in non-specialized gynecologic departments.

Acknowledgements

The author would like to thank Farzan Institute for Research and Technology for technical assistance. Authors have no conflicts of interests.

References

American Cancer Society. Cancer facts and figures 2004. Available from: http://209.135.47.118/downloads/STT/CAFF_finalPWSecured.pdf. Access: 20 Jul 2010

American Cancer Society. Cancer Facts & Figures 2010. Available from: http://www.cancer.org/acs/groups/content/@nho/documents/document/acspc-024113.pdf. Access: 20 Jul 2010.

Andersen ES, Knudsen A, Rix P, et al (2003). Risk of malignancy index in the preoperative evaluation of patients with adnexal masses. *Gynecol Oncol* , **90**, 109-112.

Bailey J, Tailor A, Naik R, et al(2006). A risk of malignancy index for referral of ovarian cancer cases to tertiary center: does it identify the correct cases. *Int J Gynecol Cancer*, **166**, 30-34.

Bell R, Petticrew M, Sheldon T (1998). The performance of screening tests for ovarian cancer: results of a systematic review. *Br J Obstet Gynaecol*, **105**, 1136-1147.

Benedet JL, Hacker NF, Ngan HYS (2000). Staging classifications and clinical practice guidelines of gynaecologic cancers. *Int J Gynecol Obstet*, **70**, 207-312.

Davies AP, Jacobs I, Woolas R, Fish A, Oram D (1993). The adnexal mass: benign or malignant? Evaluation of a risk of malignancy index. *Br J Obstet Gynaecol*, **100**, 927-931.

Earle CC, Schrag D, Neville BA et al. (2006). Effect of surgeon

specialty on processes of care and outcomes for ovarian cancer patients. *J Natl Cancer Inst*, **98**, 172-180.

Enakpene CA, Omigbodun AO, Goecke TW, et al(2009). Preoperative evaluation and triage of women with suspicious adnexal masses using risk of malignancy index. *J Obstet Gynaecol Res,* **35**, 131-8.

Engeland A, Haldorsen T, Tretli S, et al (1995). Prediction of cancer mortality in the Nordic countries up to the years 2000 and 2010. *APMIS,* **49**, 1-161.

Engelen MJ, Kos HE, Willemse PH, et al (2006). Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. *Cancer*, **106**, 589-98.

Greenlee RT, Hill-Harmon MB, Murray T, et al(2001). Cancer statistics, 2001. *CA Cancer J Clin*, **51**, 15-36.

Grimes DA, Hughes JM (1989). Use of multiphasic oral contraceptives and hospitalizations of women with functional ovarian cysts in the United States. *Obstet Gynecol*, **73**,1037-1039.

Guidozzi F (1996). Screening for ovarian cancer. *Obstet Gynecol Surv*, **51**,696-701.

Landis SH, Murray T, Bolden S, et al(1998). Cancer Statistics, 1998. *CA Cancer J Clin*, **48**, 6-29.

Jacobs I, Oram D, Fairbanks J, et al (1990). A risk of malignancy index incorporating CA125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol*, **97**, 922-9.

Manjunath AP, Pratapkumar AP, Sujatha K, et al (2001). Comparison of three risk-of-malignancy indices in evaluation of pelvic masses. *Gynecol Oncol*, **81**, 225-9.

Obeidat BR, Amarin A, Latimer JA, et al (2004). Risk of malignancy index in the preoperative evaluation of pelvic masses. *Int J Gynecol*, **85**, 255-8.

Tingulstad S, Hagen B, Skjeldestad FE, et al (1999). The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. *Obstet Gynecol*, **93**, 448-52.

Tingulstad S, Hagen B, Skjeldestad FE, et al(1996). Evaluation of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. *Br J Obstet Gynaecol*, **103**, 826-31.

Vernooij F, Heintz AP, Coebergh JW, et al (2009). Specialized and high-volume care leads to better outcomes of ovarian cancer treatment in the Netherlands. *Gynecol Oncol*, **112**, 455-61.

Yuen PM, Yu KM, Yip SK, et al (1997). A randomized prospective study of laparoscopy and laparotomy in the management of benign ovarian masses. *Am J Obstet Gynecol,* **177**, 109-14.

Zalel Y, Tepper R, Altaras M, et al(1996). Transvaginal sonographic measurements of postmenopausal ovarian volumes as a possible detection of ovarian neoplasia. *Acta Obstet Gynecol Scand,* **75**, 668-71.