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RESEARCH ARTICLE

TO COMPARE PERFORMANCE OF RISK OF MALIGNANCY INDEX 2, 3 AND 4 IN PREOPERATIVE DISCRIMINATION BETWEEN BENIGN AND MALIGNANT OVARIAN TUMOURS

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ABSTRACT

Ovarian tumours commonly present as adnexal masses which could be benign or malignant. To predict nature of ovarian tumours preoperatively is a great challenge for the gynaecologists preoperatively because of their bizarre and atypical behaviour. The present study was done to compare performance of Risk of malignancy Index 2, 3 and 4 in preoperative discrimination between benign and malignant ovarian tumours.

Methods: 175 women with ovarian tumours were included after obtaining informed written consent in the study. Risk of malignancy index 2,3 and 4 were calculated by their respective formulas using USG score, menopausal score and serum CA 125 level. Performance of these three indices were compared.

Results: The sensitivity of RMI 2, RMI 3 and RMI 4 was 58.06%, 54.84% and 61.3% respectively. The specificity of RMI 2, RMI 3 and RMI 4 was 98.61%, 98.61% and 99.31% respectively. The positive predictive value and negative predictive value of RMI 4 were more than RMI 2 and RMI 3. Diagnostic accuracy of RMI 4 was 92.6% and that of RMI 2 and RMI 3 were 91.43% and 90.86% respectively. There was no significant difference in the performance of these three indices (p-.98)

Conclusion: RMI is a simple, cost effective and easily applicable method to evaluate nature of ovarian tumours preoperatively. RMI 4 is slightly better than RMI 2 and RMI 3 in our study.

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INTRODUCTION

In India, ovarian cancer is third common cancer in women after cervical and breast cancer. As per the population based cancer registries in India, the age adjusted incidence rates of ovarian cancer vary between 5.4 to 8.0 per 100,000 population in different parts of the country (PBCR report). The 5 year survival rate of ovarian cancer is only 45% (Jemal *et al*., 2006; Stuart *et al*., 2011; Siegel *et al*., 2016) The worst prognosis of ovarian cancer is due to nonspecific symptoms and diagnosis of the disease in advanced stage. Up to 70% of the ovarian tumours are detected at advanced stages, with increased mortality rate (up to 70%) within two years and 90% within five years, which necessitate research into ovarian cancer screening methods (Menon *et al*., 2000). The commonest presentation of ovarian tumours is adnexal mass which could be benign or malignant. It is a great challenge for the gynaecologists to diagnose the nature of the ovarian tumours preoperatively because of their bizarre and atypical behaviour.

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Ultrasonography abdominal, transvaginal or three-dimensional, color Doppler study and tumour markers are frequently used to diagnose nature of the ovarian disease preoperatively. When used individually these methods have not shown better performance in detecting malignancy. Jacob *et al.* in 1990 developed a multi-parametric scoring index termed as risk of malignancy index 1 (RMI 1) using a mathematical formula obtained from the product of ultrasound score, menopausal status score and absolute value of CA 125 serum levels (Jacob *et al*., 1990). Later on RMI 2 was developed by Tingulstad *et al.* in 1996 and in 1999 they further modified it to RMI 3. The RMI 4 was developed by Yamamoto *et al*. in 2009. He incorporated tumour size in the existing formula. All these indices used different scorings of ultrasonography findings and menopausal status.

All these indices were better in differentiating malignant tumours from benign tumours than each parameter used individually. The present study was done to determine the ability of the three RMI indices (RMI 2, RMI 3 and RMI 4) in preoperative diagnosis of nature of ovarian tumour and to compare the performance of these indices.

MATERIAL AND METHODS

Patients with ovarian tumours who were appointed for laparotomy in the Department of Obstetrics and Gynaecology, S.M.S. Medical College, Jaipur were selected. 175 patients with ovarian tumours between April 2016 to March 2017, were included in the study after obtaining written informed consent. Ultrasonographic findings, menopausal status and serum CA 125 levels were recorded for each patient. On ultrasonographic examination, findings of ovary particularly multi locularity, solidity, bilaterality, ascites, and presence of metastasis were noted. Ultrasound scans were scored 1 point for each characteristics. Multilocular cyst, evidence of solid areas, evidence of metastasis, presence of ascites and bilateral lesions. Presence of character was scored as 1 and absence of character is scored as 0. USG score was obtained by summing each point. Minimum score = 0 and maximum score = 5. Postmenopausal status was defined as more than one year of amenorrhea or an age of more than 50 years in women who had a hysterectomy. All other women were considered premenopausal. Serum CA 125 was assayed by MEIA (micro particle enzyme immunoassay) technique for quantitative measurement. The optimal cut off value of serum CA 125 was 35 U/ml. RMI 2 and 3 were calculated using formula US x M x absolute value s.CA125 and RMI 4 was calculated using formula US x M x Tumour size (TS) x absolute value s.CA125. Where US is 1 for ultrasound score of 0 or 1 and US is 3 (RMI 3) or 4 (RMI 2 and 4) for ultrasound score of 2-5. M is 1 for premenopausal and 3 (RMI 3) or 4 (RMI 2 and 4) for post menopausal. Tumour size is measured on USG in cm. TS = 1 for tumor size (single greatest diameter) of <7 cm and TS = 2 for fortumor size (single greatest diameter) of ≥7 cm. For RMI 2 and 3, cut-off point was 200 and for RMI 4 it was 450. A RMI score above these were considered as high risk score. Surgical specimen was sent for histopathological examination. Histopathological diagnosis was considered as the gold standard for defining the outcome whether the tumour is benign or malignant. Prediction of risk of malignancy indices were correlated with histopathological diagnosis. Statistical analysis was done by standard statistical methods and a p value <0.05 was considered significant. Performance of RMI 3 and RMI 4 were analyzed in the form of sensitivity, specificity, Positive predictive value, Negative predictive value and diagnostic ability.

RESULTS

Out of 175 patients included in our study, 144 patients (82.3%) were diagnosed to have benign tumours and 31 patients (17.7%) had malignant tumours. Table 1 shows distribution of the patients according to Age, menopausal status, USG score and serum levels of CA 125. 80.6% patients with malignant tumours were above 30 years of age in contrast to 50.7% patients with benign tumours. 35.5% patients with malignant tumours were postmenopausal in contrast to14.6% patients with benign tumours. 81% patients with malignant tumours had a USG score of 2 -5 in contrast to 4.8% patients with benign tumours.

Table 1. Distribution of patients according to age, menopausal status, USG score and S.CA125 levels

Variables	Benign (n= 144)		Malignant (n=31)		X^2	p value
	No	%	No	%		
Age						
<30	71	49.3	6	19.4	9.29	.002
>30	73	50.7	25	80.6		
Menopause status						
Premenopausal	123	85.4	20	64.5	7.46	.006
Postmenopausal	21	14.6	11	35.5		
USG score						
0-1	137	95.1	9	29.0	80.63	.0
2-5	7	04.8	22	81.0		
S. CA 125(U/ml)						
<35	133	92.4	10	32.3	61.67	.0
>35	11	07.6	21	67.7		

Table 2. Comparison of performance of CA 125, USG score, menopausal status with RMI

	Sensitivity %	Specificity %	PPV %	NPV %	Diagnostic accuracy %
S. CA 125	67.7	92.4	65.6	93.1	88.0
USG score	70.9	95.1	75.9	93.8	90.8
Menopausal status	35.5	85.4	34.4	86.0	76.6
RMI 2	58.06	98.61	90.0	91.61	91.43
RMI 3	54.84	98.61	89.47	91.03	90.86
RMI 4	61.3	99.31	95.0	92.3	92.6

Table 3. Performance of RMI 2, RMI 3 and RMI 4

	Benign (n=144)		Malignant (n=31		Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI	Diagnostic accuracy 95% CI	P value
	No	%	No	%						
RMI 2										X^2= 0.04
<200	142	98.6	14	45.2	58.06	98.61	90.0	91.61	91.43	
>200	2	2.4	17	54.8	39.6 - 75.5	95.1 – 99.8	68.7 – 97.4	87.8 –94.3	86.3 – 95.1	P = .98
RMI 3										Not
<200	142	98.6	15	48.4	54.84	98.61	89.47	91.03	90.86	significant
>200	2	2.4	16	51.6	36.0 – 72.7	95.1 – 99.8	67.4 – 97.2	86.8 – 93.2	85.6 -94.7	
RMI 4										
<450	143	99.3	13	41.9	61.3	99.31	95.0	92.3	92.6	
>450	1	0.7	18	58.1	42.2 – 78.2	96.2 – 99.9	72.5 – 99.3	88.4 – 94.9	87.6-95.9	

67.7% patients with malignant tumours had serum level of CA 125>35U/ml as compared to 7.6% patients with benign tumours. On univariate analysis, there was statistically significant difference in patients with benign and malignant tumours on the basis of age (p-.002), menopausal status (p-.006), USG score (p-.0) and serum CA 125 levels (p- .0). Mean levels of serum CA 125 was significantly more in patients with malignant tumours (52.7±48.68U/ml) than with benign tumours (19.18±17.14U/ml) with a p value of 0.0000. Table 2 compares performance of CA 125, menopausal status, USG score with RMI. Sensitivity of CA 125 and USG score was better than all RMI. Specificity and positive predictive value of all RMI were better than CA 125, menopausal status, USG score. Evaluation of RMI 2, RMI 3 and RMI 4 is shown in Table 3. For RMI 2 and RMI 3 a cut-off of 200 and for RMI 4 a cut –off of 450 was used. The sensitivity of RMI 2, RMI 3 and RMI 4 was 58.06%, 54.84% and 61.3% respectively. The specificity of RMI 2, RMI 3 and RMI 4 was 98.61%, 98.61% and 99.31% respectively. The positive predictive value and negative predictive value of RMI 4 were more than RMI 2 and RMI 3. Diagnostic accuracy of RMI 4 was 92.6% and that of RMI 2 and RMI 3 were 91.43% and 90.86% respectively.

DISCUSSION

In our study malignant ovarian tumours were diagnosed in 17.7% patients on histopathological examination. Our results were similar to that observed by Jung-Woo-Park *et al* in 2012.[10]A higher prevalence was reported in previous studies (Ulusoy *et al*., 2007; Watcharada Moolthiya and Pissamai Yuenyao 2009, Abdulrahman Jr *et al*., 2014 and Zarchi *et al* 2015) ranging from 29-35%. On univariate analysis, there was statistically significant difference in patients with benign and malignant tumours on the basis of age (p-.002), menopausal status (p-.006), USG score (p-.0) and serum CA 125 levels (p-.0). Mean levels of serum CA 125 was significantly more in patients with malignant tumours (52.7±48.68U/ml) than with benign tumours (19.18±17.14U/ml) with a p value of 0.0000. Our results were in accordance with the results observed by Jung-Woo Park *et al.,* 2012, ABF Mohammed *et al.,* 2014, Yamamoto *et al.,* 2015. Sensitivity, specificity, positive predictive value and negative predictive value for s. CA 125 at a cut-off of 35 U/ml, was 67.7%, 92.4%, 65.6% and 93.1% respectively. USG score had a sensitivity, specificity, positive predictive value and negative predictive value of 70.9%, 95.1%, 65.6% and 93.1% respectively. Menopausal status had a sensitivity, specificity, positive predictive value and negative predictive value of 35.5%, 85.4%, 34.4% and 86% respectively. Jung-Woo Park *et al* 2012[10] observed sensitivity, specificity, positive predictive value and negative predictive value of CA 125 at 40 U/ml as 73.4%, 83.1%, 53.2% and 92.3% respectively. The sensitivity, specificity positive predictive value and negative predictive value of menopausal status and USG score observed in our study were comparable with that observed by Jung-Woo Park *et al.,* 2012. At a cut-off of point of 200, the sensitivity, specificity, positive predictive value and negative predictive value of RMI 2 were 58.06%, 98.61%, 90% and 91.6% respectively. At a cut-off of point of 200, the sensitivity, specificity, positive predictive value and negative predictive value of RMI3 were 54.84%, 98.61%, 89.47% and 91.03% respectively and at a cut-off of 450 RMI 4 had a sensitivity, specificity, positive predictive value and negative predictive value of 61.3%, 99.31%, 95% and 92.3% respectively. Sensitivity of various RMI ranged from 73-90%, specificity ranged from 78-90%, PPV and NPV ranged from 60- 96% in the previous studies. (Yamamoto *et al*., 2009; Ulusoy *et al*., 2007; MojganKarimi-Zarchi *et al*., 2015; Obeidat *et al*., 2004; Van den Akker *et al*., 1995; Manjunath *et al*., 2001). Out of three RMI, RMI 4 has better sensitivity, specificity, positive predictive value and negative predictive value. Our results were in accordance with results observed by Yamamoto *et al.,* 2009 who reported that, at a cut-off level of 450, sensitivity, specificity, positive predictive value and negative predictive value of RMI were 86.8%, 91.0%, 63.5% and97.5% respectively. In our study, no statistical difference was found between RMI 2, RMI 3 and RMI 4 in their performance to identify malignant ovarian tumours. The previous studies done by Manjunath *et al*., 2001, Akturk *et al*., 2011 and Jung-Woo Park *et al*., 2012 also did not observe any statistically significant difference in identification of malignancy between different RMI. RMI 4 had a highest diagnostic accuracy of 92.6% out of all RMI in our study. Our results were similar to that observed by Yamamoto *et al* 2009 they found diagnostic value of RMI to be 90.4%. Diagnostic accuracy of all RMI in our study was better than CA 125, USG score and menopausal status when used alone. Our findings were in agreement with findings of Jung-Woo Park *et al* 2012.

It is very essential to differentiate malignant ovarian tumours from benign ovarian tumours preoperatively so as to plan an effective and optimum surgical treatment.RMI with a diagnostic accuracy of 90% will help in planning the effective management.

Conclusion

RMI is a simple, cost effective and easily applicable method to evaluate nature of ovarian tumours preoperatively. RMI 4 is slightly better than RMI 2 and RMI 3 in our study. The RMI score can be used even at peripheral setup and will help in selective referral of the patients at higher centre.

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