RESEARCH ARTICLE

Pre-Operative Evaluation of Ovarian Tumors by Risk of Malignancy Index, CA125 and Ultrasound

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Abstract

Purpose: To evaluate the diagnostic performances of risk of malignancy index (RMI), CA-125 and ultrasound score in differentiating between benign and borderline or malignant ovarian tumors and find the best diagnostic test for referral of suspected malignant ovarian cases to gynaecologic oncologists. Materials and Methods: This prospective study covered 467 women with pelvic tumors scheduled for surgery at our hospital between July 2011 and July 2013. The RMI was obtained from ultrasound score, CA125 and menopausal status. The diagnostic values of each parameter and the RMI were determined and compared using Statistical Packages for Social Sciences Version 14.0.1. Results: In our study, 61% of ovarian tumors were malignant in the post-menopausal age group. RMI with a cut-off 150 had sensitivity of 84% and specificity of 97% in detecting ovarian cancer. CA-125>30 had a sensitivity of 84% and a specificity of 83%. An ultrasound score more than 2 had a sensitivity of 96% and specificity of 81%. RMI had the least false malignant cases thus avoiding unnecessary laparotomies. Ultrasound when used individually had the best sensitivity but poor specificity. Conclusions: Our study has demonstrated the RMI to be an easy, simple and applicable method in the primary evaluation of patients with pelvic masses. It can be used to refer suspected malignant patients to be operated by a gynaecologic oncologist. Other models of preoperative evaluation should be developed to improve the detection of early stage invasive, borderline and non-epithelial ovarian cancers.

Keywords: Ovarian tumours - RMI - CA125 - ultrasound - malignancy - staging

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Introduction

Ovarian cancer is the most deadly gynecological cancer as 70% of the women are diagnosed only in advanced stage (Rafii et al., 2012). Ovarian malignancy is the fifth leading cause of cancer deaths (CDC statistics). Quality of primary cyto reductive surgery is one of the most important factor for survival of the patient (Vergote et al., 2011; Jelovac et al., 2012). Many women with advanced ovarian carcinoma undergo suboptimal surgery by a gynaecologist (Stashwick et al., 2011). Ideally patients with ovarian malignancy should be operated by a gynecologic oncologist or referred to a cancer center. However in practice, preoperative diagnosis of malignancy is not so easy (Tingulstad et al., 1996).

In order to refer a patient to an oncologist or cancer center, a diagnostic test which can identify malignant ovarian tumor with good sensitivity and specificity is required. Presentation of ovarian cancer in advanced stages is straightforward (Webb et al., 2004). However in cases of early stages, diagnosis is difficult as they present with vague complaints. Ultrasound or CA-125 when used alone had many limitations (Jacobs et al., 1990; Kawai et al., 1992; Menon et al., 2009; Jacob et al., 2011; Bruchim et al., 2013; Van et al., 2013). Hence we have tried combining these tests together to yield a better diagnostic performance. In this study, we compare RMI, CA-125, menopausal status and ultrasound in pre-operative evaluation of ovarian tumors.

To evaluate the diagnostic performance of risk of malignancy index (RMI) and its components like menopausal status, CA-125 and ultrasound score in differentiating between benign and borderline or malignant ovarian tumors pre-operatively. To compare the 3 modalities included in RMI scoring with each other. To find the best diagnostic test for referral of suspected malignant ovarian cases to gynaecologic-oncologists.

Materials and Methods

This is a prospective study conducted in a tertiary care hospital from consecutive 467 women with pelvic tumors scheduled for surgery at Gynaec-oncology department between July 2011 and July 2013. Preoperative ultrasound findings, serum CA 125 levels and menopausal status were collected.

As proposed by Jacobs et al. (1990), the RMI is defined as the multiplied result of the menopausal status (M),

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ultrasound score (U) and serum CA 125 level.

RMI=USG×M×CA 125

Ultrasound scoring

In all cases, Ultrasound scoring was performed using a 3.5-MHz abdominal convex transducer or 7.5-MHz vaginal probe (GE Medical). Serum CA 125 was determined by radioimmunoassay (Roche, Pennsylvania, USA). The ultrasounds were performed by Sonologists specially trained in Obstetrical and Gynaecological ultrasonography. Ultrasound findings are scored with one point for each of the following: Multi-locular cyst, Evidence of solid areas, metastases, Presence of ascites, Bilateral Lesions.

Menopausal status

Pre-menopausal age group is scored as 1 and Post-menopausal as 2. Women with more than an year of amenorrhea or Age 50 years or older among women who had hysterectomy. CA-125 (C) will be considered in absolute values. (U/mL) and entered directly into the formula.

RMI score was calculated as,

RMI score=Ultrasound score (U)×Menopausal score (M) ×CA-125 (C)

The diagnostic values of each parameter and the RMI were determined and compared. The histopathologic diagnosis was of course ultimately the gold standard. Statistical analyses were performed using SPSS version 14.0.1

Identification of subjects

Inclusion Criteria-Women of all ages admitted with ovarian mass in SRMC Hospital. Exclusion Criteria-Women not operated for any reasons or those who did not have an ultrasound or CA-125 done pre-operatively. Women whose histopathology report turned out to be leiomyoma.

Results

During the study period, a total of 467 cases of ovarian tumors were evaluated pre-operatively after applying exclusion criteria. 22.5% of the cases were Malignant and 77.5% of the cases were Benign. 94% of the ovarian tumors in age group <40 years were Benign, while 61% of the ovarian tumors in age group >50 years were Malignant. 11.5% of ovarian tumors in pre-menopausal age group were malignant while 61% of ovarian tumors were malignant in post-menopausal age group.

Among the histopathological diagnosis, Epithelial ovarian masses were the majority in both Benign as well as Malignant group. Borderline tumors constituted just 3.4% of the total cases. Malignancy rate increased as the age increased.

RMI >200 had 21 false benign and 6 false malignant cases. Out of the 21 false Benign cases, 10 were Borderline ovarian tumors and 7 were non-epithelial ovarian tumors. These 7 non-epithelial tumors were picked up by other tumor markers. RMI had the least false positive cases and hence avoided unnecessary Staging Laparotomies. Significant number of Borderline tumors were not diagnosed.

When RMI Score >150 was used, it resulted in only 17 False negative cases and and 12 False positive cases. 17 False negative cases were mostly non-epithelial tumours which were diagnosed with other tumor markers. Majority of those 12 false positive cases were Dermoid

Table 1. Distribution of Cases by Diagnosis

Benign	
Serous cystadenoma	73
Mucinous cystadenoma	42
Endometriomas	34
Functional cysts	26
Simple cysts	76
Hydrosalpinges, Para-ovarian, Tubal cysts	39
Dermoid cysts	37
Tubo-ovarian abscess	10
Chronic Ectopic/Ectopic pregnancy	12
Brenner tumor	1
Fibroma	12
Malignant	
Borderline Serous cystadenoma	8
Borderline Mucinous cystadenoma	8
Serous cystadenocarcinoma	46
Mucinous cystadenocarcinoma	2
Endometrioid carcinoma	6
Clear cell carcinoma	1
Mixed epithelial cell carcinoma	6
Brenner tumor	1
Germ cell tumor	5
Sex cord stromal tumor	2
Metastatic tumor	7
Undifferentiated/poorly differentiated carcinoma	13

Table 2. Case Distribution by Age, Menopausal Status, Ultrasound Score and CA-125

Variables	Benign n=362	Malignant n=105	Total	Comments
Age Group				
<20 years	30	3	33	Youngest-14 years.
21-40 years	220	12	232	Oldest-89 years.
41-50 years	80	39	119	Mean age-39 years.
>51 years	32	51	83	
Menopausal Status				
Premenopausal	322	42	364	22% of the cases were
Postmenopausal	40	63	103	post-menopausal.
Ultrasound Score				
0	104	1	105	Poor positivepredictive value and good negative
1	188	4	192	predictive value.
2-5	69	101	170	
CA-125 (IU/mL)				
<30	301	17	318	Poorpositive predictive value
>30	61	88	149	

Table 3. Comparison of RMI, CA-125 & Ultrasound

	HPE	RMI) (>200	USG (>2)	CA-125 (>30)
Total Benign	362	377	297	326
Total Malignant	105	90	170	141
False Benign		21	4	17
False Malignant		6	69	61

and Endometriotic cysts which were diagnosed with Ultrasonography and clinical examination and thus not increasing the laparotomies. RMI had poor sensitivity in Germ cell and Sex-cord stromal tumors. RMI Score >150 was better than RMI Score >200 in our study (Table 4)

Most malignant ovarian tumors had more than two findings in Ultrasound. Ultrasound score-3 was found in both Benign and Malignant ovarian tumors. Ultrasound score - 0 was found only in Benign ovarian tumors. Benign ovarian tumors had all three Ultrasound scoring present. Malignant ovarian tumors had an Ultrasound score-3 in 96% of the cases. Among the ultrasound parameters, presence of Ascites and solid areas had the maximum malignant cases. Multi-loculations was found in both Benign as well as Malignant ovarian tumors.

In our study, ultrasound had a sensitivity of 96.1% and a specificity of 80.9%. There were 69 false positive cases and 4 false negative cases. Among the 69 false positive cases, 66 cases had RMI <200. There were 22 Dermoid cysts in the false positive group. 17 cases of these 22 Dermoid cysts had characteristic features of a Dermoid in Ultrasound and hence Laparotomies were not performed. There were 14 Serous and 14 Mucinous cystadenomas among the false positives. Serous and Mucinous cystadenomas had the most negative Laparotomies.

CA-125 had 17 false benign cases and 61 false malignant cases. Among the 17 false benign cases, majority were Borderline ovarian tumors. CA-125 was not significant in these cases and even ultrasound could pick up only 10 out of these 17 cases. Even RMI could pick up only 7 out of these 17 cases. Out of these 61 false malignant cases, 55 cases were correctly diagnosed by RMI. 18 cases out of 61 had been wrongly diagnosed as malignant by ultrasound. CA-125 and Ultrasound used individually had good sensitivity however the specificity was poor. These results are similar to those of a previous study by Jacobs et al in 1990.

Discussion

We have used the RMI developed by Jacobs et al in our study. In Pre-menopausal patients, CA125 was not accurate enough to predict malignancy and conditions like hemorrhagic cysts, endometriosis, Pelvic inflammatory disease had false elevations in CA-125 levels. But studies have proven that CA-125 is the tumor marker with highest specificity for epithelial ovarian cancer (Jing et al., 2013). Menopausal status was no where near the performance of RMI, while CA 125 and the ultrasound had similar performances.

Table 4. Performance of Diagnostic Tests

Variables		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
RMI Cut-Off	50	94	82	60	98
	75	90	88	69	96
	100	88	92	76	96
	150	84	97	88	95
	200	79	98	92	94
	250	77	98.6	94	93.7
CA 125 (U/mL)	20	87	72	47	95
	30	84	83	59	94.6
	50	75	92	72	93
	70	71	94	77	92
	90	67	96	84	91
	150	61	98	91	89
Ultrasound score	≥1	99	71	49	99
	≥2	96	81	59	98.6
Menopausal status					
Postmenopausal		60	89	61	88

The absence of all components of ultrasound were associated with benign ovarian tumors and when these features were present, they were more likely to be a malignant tumor. Although an ultrasound score of 2 was associated with a high risk of malignancy, the clinical value of ultrasound as an individual test was limited by the observation of features of malignancy in 69 patients with benign disease.

Previous studies have shown that an RMI with a cut-off of 200 gives the most optimal result (Tingulstad et al., 2014). However, an RMI of 150 had an optimal performance in our study. This could be due to different study populations. Performance of RMI, CA-125 were poor in Borderline and in early stage ovarian cancers as they had poor scores both on ultrasound and CA 125 levels. Our main reason for developing the RMI is the referral of patients with suspected ovarian cancer to gynecologic oncologists (Geomini et al., 2009; Dodge et al., 2012).

RMI had the best specificity and Ultrasound had the best sensitivity. RMI had the least false malignant cases among all individual criteria. Ultrasound had the least false benign ovarian tumors and also the maximum number of false malignant cases. Application of USG and CA-125 individually would have resulted in a lot of unnecessary Laparotomies (Dodge et al., 2012).

This study has shown that, the RMI with cut-off value of 150, is a better tool for differentiating benign and malignant ovarian tumors. The RMI has outperformed CA125 and Ultrasound in diagnosing ovarian cancer pre-operatively. RMI is a good predictor of malignancy with good sensitivity and it had the least false malignant cases thus avoiding unnecessary laparotomies. Ultrasound when used individually had the best sensitivity but poor specificity. CA 125 when used individually resulted in a number of false positive and false negative malignant ovarian cancers. Among the RMI scoring system, level more than 150 had good sensitivity and specificity compared to 200. RMI had poor sensitivity in detecting borderline ovarian tumor and non-epithelial ovarian tumors. Ultrasound detected most of the cases which were missed by RMI. Our study has demonstrated RMI to be an easy, simple and applicable method in the primary evaluation of patients with pelvic masses. It can be used to refer suspected malignant patients to operated be by a gynaecologic oncologist.

Other models of preoperative evaluation should be developed to improve the detection of non-epithelial ovarian cancers, borderline ovarian tumors, and early stage invasive disease (Bast et al., 2005; Yurkovetsky et al., 2010; Li et al., 2013). Ultrasound morphological scoring system should be developed further to improve the detection rate of malignant ovarian tumors (Menon et al., 2010). Considering the fact that ovarian cancers are

detected mostly at an advanced stage further research and investment is needed in developing a screening tool as the mortality is very high (Bast et al., 2005; Yurkovetsky et al., 2010; Bian et al., 2013; Li et al., 2013).

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