Risk of Malignancy Index in the Pre-Operative Evaluation of Patients with Adnexal Masses

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Abstract

The aim of this study is to evaluate use of RISK of MALIGNANCY INDEX (RMI) in primary evaluation of adnexal masses without clear evidence of malignancy, by combining serum CA 125 levels, USG score and menopausal status. It is a cross sectional study conducted at Department of gynaec- oncology, Gujarat Cancer and Research Institute, Ahmedabad. A total of 40 women aged 20 to 65 years with ultrasound diagnosed adnexal masses, and serum measurement of cancer-associated antigen CA-125 levels, were studied. They all had surgical exploration (laparotomy) between May 2005 to July 2007 .The RMI was based on menopausal status, ultrasound morphology of adnexal masses and absolute level of serum CA-125. RMI cut-off of 200 was chosen. The various testing methods were evaluated for sensitivity, specificity, positive and negative predictive values. The best performance was with a RMI at a cut-off of 200 with a sensitivity of 66.66%, specificity of 63.15%, positive predictive value of 66.66% and negative predictive value of 65.15% to diagnose malignancy. When RMI was used, it is better in detecting benign tumour and malignant tumour rather than individual component. RMI to be a valuable, reliable and applicable method in primary evaluation of patients with adnexal masses, and a usable method for referral of advanced neoplasia to a more complex healthcare unit.

Keywords: Menopausal status, CA-125, ovarian cancer, risk of malignancy index

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Introduction

Ovarian cancer is third most common gynaecological malignancy with highest mortality [1]. Worse prognosis is correlated with late diagnosis. More than 75% patients have retroperitoneal and intra-abdominal spread at the time of diagnosis Up to 24% of ovarian tumours in premenopausal women are malignant and up to 60% are malignant in postmenopausal women [2-4]. Up to 70% cases are detected in advanced stages, with increased ovarian disease in which, mortality rate reaches 70 %, within 2 years and 90 %,within 5 years, which has encouraged cancer-screening programs. However, these are ineffective because of false positivity.

Ovarian cancer is difficult to manage since diagnosed mostly at an advanced stage, when survival chances are poor. Early detection increases long term survival, since effective treatments are available.

Several diagnostic methods for pelvic masses have been reported, such as tumour markers like CA-125, TAS and TVS, 3 – D USG, Colour Doppler USG. However none of these individually has shown to be of significantly better in detecting malignant tumours from clinically restricted ovarian masses

CA-125 is the most extensively studied ovarian cancer antigen – a high molecular weight glycoprotein. It is a useful pre-operative test for prediction of epithelial ovarian cancer and provides additional data, to discriminate between benign and malignant adnexal masses as well an adjunct screening modality. Normal levels are ≤ 35 IU / ml.

In 87 % patients doubling / halving time of CA 125 correlates with tumour progression or Regression. It correlates with stage of disease: stage 2, 3, 4 – 90, stage 1 – 50%. Increase in CA 125 and negative / equivocal Findings at CT / MRI may be suggestive of small lesion size. Serial levels can be used for follow up in cancer ovary and increase in levels at early stage is predictor of recurrence, regardless of imaging findings.

On the other hand it is a non specific tumour marker because in many benign conditions are associated with levels >100 U/ml. Malignancies especially stage I Cancer ovary, associated with normal or equivocal levels (35- 100U/ml).Negative CA 125 and negative imaging

findings, do not exclude recurrent tumour and there is no direct correlation between tumour size and CA 125 levels [5-8].

Ultrasonography is the study of choice for initial evaluation of suspected adnexal masses. It is relatively cheap, non-invasive and widely available. Trans abdominal sonography(TAS) is usually used for big ovarian tumour filling almost whole. Abdomen to see whole of the ovarian mass. Penetration of trans vaginal sonography(TVS) is more compared to TAS.

Findings commonly found on USG can be simple thin walled cyst (< 4 cm) indicating a low risk tumour, loculated cyst with thick septations with in a cystic area, papillary excrescence, localized overgrowth of epithelial lining of cyst. (If not protrude > 3 mm into a cyst cavity – not strongly malignant) indicate differential diagnosis between mucinous cystadenoma from cystadenocarcinoma. Focal solid areas (non fatty vascular), bilaterality, size and presence / absence of fluid in cul de sac (ascites) are other characteristics usually looked for.

TVS can detect minimal 8 ml of ascitic fluid. Moderate amount of fluid in post- menopausal woman increases suspicion but unfortunately in advanced cases. If no obvious stigmata of malignancy and size of lesion does not mandate surgery then follow up USG should be done in 6-8 weeks. It has sensitivity up to 85–97 % and specificity up to 56–97 % in postmenopausal patients. It has lower specificity in pre – menopausal females than post menopausal since cyclic menstrual changes found in USG that cause difficulty in interpretation.

Most reliable in predicting a lesion that is benign, but less accurate in detecting malignant. Most consistent finding s /o malignancy are papillary excrescence > 3 mm along the internal wall of mass and solid components with in mass [9-11].

Currently, no available diagnostic tests are perfect with 100 % sensitivity and specificity. USG often fails to differentiate between benign and malignant conditions. CA 125 although raised in 80 % Ca. ovary, only in 50 % of these cases raised CA-125 values can be seen in stage I and increased levels are found in other non malignant conditions also.

The development of a mathematical formula, using a logistic model incorporating menopausal status, CA 125 and USG findings, in a score system, has been described in literature, in lite, in form of different malignancy indices.

These indices were calculated using a simplified regression equation obtained from product of USG finding score, menopausal status score and absolute value of CA 125 level. Originally in 1990, Jacobs et al RMI # 1, then in 1996, Tingulstad et al RMI #2 and in 1999, modified RMI # 3 came in light.

Differences between three indices were different scorings of USG and menopausal status [12-17]. All indices presented a significantly better performances, in diagnosing malignancy then did each of predictor separately.

So, there is no definitive preoperative method for differentiating between benign and malignant adnexal masses. Evaluations of CA 125 serum levels, USG findings and menstrual status, have been tested in isolation as diagnostic methods. The evaluation of these three methods in association with each otherwould improves diagnostic performance.

Materials and Methods

This It is a cross sectional study conducted at department of Gynaec- oncology, Gujarat Cancer and Research Institute, Ahmedabad. 40 women between May 2005 to July 2007 aged 20 to 65 years were selected who were diagnosed as adnexal masses.

Serum CA 125 samples assayed by (RIA, Gamma Camera) entered model as continuous variable.

Ultrasound (U) examination was performed using 3.75 M Hz abdominal convex transducer (WIPRO GE). The lesions were evaluated according to at least one of morphologic features; multilocularity, solid areas, bilaterality, ascites, extra-ovarian tumours. Using logistic regression a score was attributed to each USG finding termed as Ultrasound score (U). Each finding is given one point.

A total of > 2 points gave U = 4 $\leq$ 2 points gave U = 1

Menopausal status, Post menopausal status was defined as $\geq$ 1 year of amenorrhea or age >50 years in post – hysterectomy women. All other women were considered pre menopausal.

Post- menopausal M = 4 Pre -menopausal M = 1

Exclusion criteria were obvious clinical features of malignant ovarian diseases and/or ultrasound confirmed diagnosis of metastatic diseases.

$$RMI = U \times M \times CA\ 125$$

Women were submitted to laparotomy and the tissue was excised, sent for HPE, which was considered as gold standard for defining outcome it being classified as benign or malignant.

Statistical Analysis

RMI was evaluated for sensitivity, specificity and positive and negative predictive value (PPV&NPV),with reference to actual presence of benign or malignant pelvic tumour. Cut off level of 200 decided. Chi square test was applied to see the significance of the results of data of the study according to P value and DF.

Results

Table 1 shows that from May 2005 to July 2007,40 patients with palpable /ultrasonographically demonstrated adenexal masses were evaluated with RMI. all these patients underwent surgery. According to histopathological examination of surgical specimen of 40 women. 21(52.5%) were malignant and 19 were found (47.5%) benign. Epithelial 16(76.2%) cases, non-epithelial 5 (23.8%) and metastatic nil.

Table 2 shows that out of 40 tumours 15 tumours were found in the age group of after 50. Just as there is increased chance of tumour being malignant at older age ,so is after menopause. In postmenopausal stage 57.14% tumour are malignant. In premenopausal stage incidence of malignant tumours and benign tumours are 42.86% (9) and 52.63 %(10) respectively. The mean serum CA-125 level was 429.6 U/ml and 90.98 U/ml for the benign and malignant groups, respectively. Significant differences were found regarding age, menopausal status and serum CA-125 level.

Table 3 shows that at cut off level of more then 200 RMI, 14 tumours are diagnosed Malignant and 6 tumours are Benign. At less then 200 RMI 7 tumours are diagnosed malignant and 13 tumours are benign. Chi sqaure test was applied. P value was found to be <.05. There is statistically significant difference seen when cutt off of RMI considered 200 for distinguishing malignant and benign tumour.

Table 4 shows that at cut of level of 200, RMI has sensitivity of 66.66%, specificity 63.66%, positive predictive value 66.66% and negative predictive value is 65.15% .Combinedly all four show significantly high values at cut off of 200 compared to any other given cut off level of RMI, indicating most appropriate cut off level to consider for diagnosing malignancy.

Table 5 shows that the sensitivity, specificity, positive predictive and negative predictive values of RMI at a cut-off level of 200, at a serum level of CA-125 35 U/ml, menopausal status and ultrasound morphology are shown in below table. RMI with a sensitivity of 66.66%, specificity of 63.5%, and positive predictive value of 66.66 % and negative predictive value of 65.15 %.It has the highest PPV, NPV and specificity value as compared with individual screening modalities which shows that RMI has highest ability to diagnose malignancy in individuals who actually found to have malignancy in histopathological examination, similarly it has highest ability to find out individuals who were actually free of malignancy.

Table 1. Distribution of tumour according to histopathological report

Type		**Number**	**%**
Malignant tumours		21	52.5
A)Epithelial tumour		16	76.2
	Stage 1(borderline)	3	14.2
	Stage 1(invasive)	4	19.04
	Stage 2	4	19.04
	Stage 3 & 4	5	23.8
B)Non Epithelial tumour		5	23.8%
	Granulosa cell tumour	3	
	Immature teratoma	2	
	Sarcoma	0	
Metastatic tumour		0	
Benign tumour		19	47.5
	Ovarian serous epithelialcysts	4	
	Ovarian mucinousepithelialcysts	7	
	Ovarian fibroma	2	
	Dermoid cysts	2	
	PID (Inflammatory / T-O mass)	2	
	Endometriotic cysts	1	
	Hemorrhagic Ovarian cysts	2	

Table 2. Distribution of patients with adenexal masses according to different criteria

AGE (yrs)	TOTAL NO.	MALIGNANT(n)(%)	BENIGN(n)(%)
<20	1	0	1(5.3)
21-30	4	1(4.8)	3(15.8)
31-40	10	7(33.33)	3(15)
41-50	10	4(19.05)	6(31.6)
>51	15	9(42.9)	6(31.6)
Total	40	21	19
Menopausal state			
Premenopausal	19	9(42.86%)	10(52.63%)
Postmenopasal	21	12(57.14%)	9(47.37%)
CA-125			
Mean(average)		429.6	90.98
More than 35(u/ml)	30	17	13
Upto 35(u/ml)	10	4	6
Ultrasound score(U)			
Malignant(2-5)	19	11	8
Benign(0-1)	21	10	11

Table 3. Risk of Malignancy Index (Cut of 200)

RMI	Malignancy	Benign
>200 (M)	14	6
<200 (B)	7	13
Chi Square: 4.91, DF: 1, P = 0.026 (P<0.05)		

Table 4. RMI according to different cut offs

RMI (cut off)	Sensitivity (%)	Specificity (%)	PPV(Malignant) (%)	NPV(Benign) (%)
50	85.71	15.78	52.99	50
100	77.27	44.44	62.96	61.53
150	73.91	52.94	68	60
200	**66.66**	**63.15**	**66.66**	**65.15**
250	63.63	61.11	66.66	57.89
>300	61.9	61.11	65	55

Table 5. Comparative results

	SENSITIVITY %	SPECIFICITY %	PPV %	NPV %
CA 125 Overall Premenopausal postmenopausal	 80.95 66.66 91.66	 31.75 20 44.44	 56.66 42.85 68.75	 60 40 80
USG Overall Premenopausal postmenopausal	 50 33.33 58.33	 57.89 70 55.55	 57.89 33.33 63.63	 52.38 53.84 50
RMI at Cut off value of 200	66.66	63.15	66.66	65.15

Discussion

In women without evidence of advanced ovarian cancer, current Risk of Malignancy index is useful in clinical practice for differentiating malignant from benign adnexal masses, as compared to each individual component measured separately. This occurs because RMI system translates morphological description of adnexal masses into objective numerical data,

reducing bias attributable to examiner's subjectivity. RMI also facilitates selection of cases for referral to an oncological unit and also helps Surgeon to choose surgical approach.

For e.g.: In Premenopausal (35 yrs) : Solid well defined tumour

CA 125 - 45 U / ml : - RMI 45

At cut off 150, Benign with FN: 21 %

At cut off 100, Benign with FN: 16 %

In Postmenopausal (65 yrs): Similar tumour

CA 125- 97 U/ml : - RMI 291

At cut off 150, Malignant with FP: 25 %

At cut off 200: Malignant with FP: 14 %

RMI should be used as the primary evaluation Of patients with adnexal masses, because of the simplicity of method. RMI can be used in daily clinical in non – specialized Gynaecological departments and by all gynaecologists. RMI has resulted in better planning of time of surgery, surgical approach, laparotomy Vs laparoscopy, transverse abdominal Vs median longitudinal abdominal incision.

Other models of pre-operative should be developed to detection of non-epithelial ovarian cancers, borderline ovarian cancers and early stage invasive cancer. The combined PET/CT is used as a supplementary image modality prior to surgery in primary ovarian cancer patients whenever accurate and comprehensive preoperative evaluation of primary tumour and metastasis is desired. PET/CT has also been found to be more effective means of identifying patients with recurrent ovarian/Fallopian tube cancer as compared with PET, CT, MRI and ultrasound alone. Although combined PET/CT may be superior to RMI, their lack of clear evidence of benefit, the relative expense and limited availability of these modalities, and the delay in referral and surgery that can result, make their routine use not recommended [18-20].

Thus RMI is apparently able to identify, the probability of Malignant adnexal masses by incorporating serum CA125 levels USG morphology, menopausal status performed

individually in woman with adnexal masses. The present study has demonstrated the RMI to be a valuable, reliable and applicable complex healthcare unit, although it does not seem to show prognostic value.

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Disclosure

The authors of this manuscript have no conflicts of interest.

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