

Diagnostic efficacy of risk of malignancy index in adnexal mass: a prospective study

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ABSTRACT

Objectives: The purpose of this study was to determine if the risk of malignancy index (RMI 2) can distinguish between benign and malignant adnexal masses in the women with adnexal masses. **Methods:** This is a prospective observational study conducted over a period of two years from 2012 to 2014. A total of 100 cases of adnexal mass were selected using purposive sampling technique. Information regarding age, parity, menstrual status, history of previous surgery and symptoms were noted. RMI 2 was calculated for each patient. Statistical analysis was done using SPSS software version 21. **Results:** Majority (60%) of the women were in the perimenopausal or menopausal age group (40-60 years). Majority of the patients ie 62% had levels of CA-125 above 100U/l, 16% had levels between 35-100U/l and 22% had levels <35 U/l. RMI was greater than 200 in 72% patients indicating malignancy and was less than 200 in 28% of the patients suggesting benign disease. The sensitivity of the RMI for diagnosing malignant lesions was 84% while the specificity was 67%. The PPV was 89% and the NPV was 57%. **Conclusion:** RMI appears to be a valuable, reliable and applicable method in the primary evaluation of patients with pelvic masses and a usable method in referral of relevant patients for centralised surgical treatment.

Keywords: RMI, ovarian cancer, referral.

Ovarian cancer is the fourth most common malignancy in females and the second most common gynaecological malignancy after cervical cancer¹. Epithelial ovarian cancer has the highest fatality to case ratio of all the gynaecological malignancies because more than two-thirds of patients have advanced disease at diagnosis². It presents a major surgical challenge, requires intensive and often complex therapies, and is extremely demanding of the patient's psychological and physical energy.

Ovarian cancer most commonly presents as adnexal mass. Adnexal abnormalities may be discovered as a result of screening, be an incidental finding, or be recognized as a result of investigations performed specifically for a

suspected pelvic mass³. The only definitive way of determining whether a mass is benign or malignant is removal at surgery. However, the majority of women with adnexal masses will not have malignant disease and many do not require surgery. Those women who are likely to have ovarian cancer should be referred to specialized oncology centres with ability to perform optimal surgical staging and cytoreduction^{4,5}.

The discrimination between benign and malignant adnexal masses is central to decisions regarding clinical management and surgical planning in such patients. Patients with malignant tumors should be referred to a gynecological oncologist, as the quality of cytoreductive surgery and

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surgical staging/lymph node dissection are important prognostic factors in ovarian cancer ^{4,5}. The extent of cytoreductive surgery is associated with the specific skills and experience of well-trained gynaecologic oncologists hence, improving the prognosis and five year survival ⁶. Furthermore, appropriate and timely referral to a gynecological oncologist has been proven to increase survival in patients with ovarian cancer⁷. Streamlining of referrals in oncology has always been a clinical challenge in attempting to create a satisfactory safety net.

Pelvic assessment, tumor markers, and radiological investigations have been proposed in this regard, but all of the parameters when considered separately, are inadequately sensitive or specific. Various methods of evaluating ovarian mass have also been proposed ⁸. Risk of malignancy index (RMI) is a combined parameter, which is simple, practical and highly sensitive, and more specific. RMI is calculated with a simplified regression equation obtained from the product of menopausal status score (M), ultrasonography score (U), and absolute value of serum CA-125 ⁹. Jacobs et al (1990) was first to devise RMI 1 which utilized the ultrasound findings, menopausal status and serum CA 125 levels to predict the risk of malignancy with greater sensitivity and specificity than any one factor alone. Later, it was adjusted by Tingulstad et al in 1996 as RMI 2 and again modified in 1998 as RMI 3. Yamamoto et al created their own model of a malignancy risk index. They added the parameter of the tumour size (S) to the RMI and have termed it the RMI 4 ¹⁰⁻¹². Some of the potential advantages of RMI include rapid triage of patients through the referral system. Early identification of ovarian carcinomas and referral to a gynecologic oncologist can facilitate accurate staging of the disease and optimal cytoreductive treatment, enhancing patient survival¹³. The purpose of this study was to determine if the RMI (RMI 2) can distinguish between benign and malignant adnexal masses in the population of women referred to the Gujarat Cancer and Research Institute.

Materials and methods

This is a prospective observational study conducted over a period of two years from 2012 to 2014. A total of 100 cases of adnexal mass were selected using purposive sampling technique. All the patients were admitted to the Department of Gynaec-oncology at G.C.R.I., Ahmedabad. Approval was obtained from the ethics committee of the institution.

All women presenting with adnexal masses scheduled for surgery were recruited for the study. Women already

diagnosed cases with ovarian malignancy receiving chemotherapy, masses arising from urinary tract and gastrointestinal tract and pregnancy with its complications like ectopic, molar and post abortive were excluded from the study. Apart from the demographic information, information regarding age, parity, menstrual status, history of previous surgery and symptoms were noted. All patients underwent routine physical examination.

Apart from the routine pre-operative investigations, menopausal status, abdominal ultrasound findings and preoperative serum CA 125 levels were recorded. Serum levels of CA-125 were measured by Electrochemiluminescence immunoassay (ECLIA) method. An ultrasonographic evaluation of their pelvic mass for each of the following characteristics: multilocularity (more than bilocular), presence of solid areas, bilaterality, presence of ascites, and extra ovarian tumors or evidence of metastases. For each ultrasonographic characteristic a score of one was assigned and a total ultrasound score (U) was calculated. Postmenopausal status (M) was defined as more than one year of amenorrhea or an age of more than 50 years in women who have had a hysterectomy. The modified RMI (RMI 2) 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:

$$\text{RMI} = \text{U} \times \text{M} \times \text{Serum CA-125}$$

For analysis purposes, tumours of low malignant potential were classified as malignant because it was considered ideal for these tumours to be surgically managed by a gynaecologic oncologist and the final histopathology was regarded as the true definite outcome. Staging laparotomy was performed for all patients. The type of surgical procedure done were either unilateral salpingo-oophorectomy, unilateral salpingo-oophorectomy with biopsy of the contralateral ovary, total abdominal hysterectomy and unilateral salpingo-oophorectomy, total abdominal hysterectomy with bilateral salpingo-oophorectomy, with omentectomy, with bilateral pelvic lymph node dissection and debulking surgery. Surgical staging was carried out in suspected malignant ovarian tumors. The pelvic and para-aortic lymph nodes were evaluated and all enlarged lymph node were resected. Infracolic omentectomy was performed. The other operative findings recorded were gross appearance and cut surface, ascites, site of extra ovarian involvement and tumor size.

Specialist gynaecological oncology surgeons at GCRI performed all surgical procedures. Histopathological examination of all specimens were done in the department of pathology at GCRI by a specialist in gynaecological pathology. The tumours were classified according to the WHO classification. Malignant tumours were staged according to the FIGO staging system. Statistical analysis was done using SPSS software version 21. A univariate statistical analysis was performed for all sonographic parameters and patient age.

Results

During the two year period, 100 women who met the inclusion criteria were enrolled in the study. Majority (60%) of the women were in the perimenopausal or menopausal age group (40-60 years). Only 7% are under the age of 20 years and 13% above the age of 60 years (table 1). Twenty percent of the women were in the age group of 21-40 years.

Table 1: Age distribution

Age in years	Number of patient (N=100)	
	Benign	Malignant
<20	04	03
20-40	14	06
40-60	17	43
>60	05	08

The median age was 48 years. A large proportion (62%) of the women were menopausal, 36 % were menstruating and only 2 were premenarchal. Parity is an important etiological factor and greater parity affords greater protection against ovarian cancer. In our study, 1% were nulliparous, 75% were multiparous and 9% were unmarried. In nulliparous patients and patients with one child, future child bearing was given due consideration and fertility preserving surgery was carried out wherever possible.

The most common complaint was abdominal pain (63%) followed by abdominal distension (40%), abdominal mass (38%) and nonspecific complaints of vomiting and anorexia (25%). Majority of the patients ie 62% had levels of CA-125 above 100U/l, 16% had levels between 35-100U/l and 22% had levels <35 U/l. Upon analysing, out of 24 benign cases 18 had serum CA-125 values well within the normal limits whereas 6 had levels more than 35. Among the 76 malignant cases, only five had levels below 35 that they were false negative whereas majority of the cases (71) had elevated levels. RMI was greater than 200 in 72% patients indicating malignancy and was less than 200 in 28% of the patients

suggesting benign disease. Majority (65%) had ultrasound scoring of more than 2 suggesting that the mass is malignant

Table 2: Histopathological co-relation of malignant adnexal mass with RMI

HPE type		RMI<200	RMI>200
Serous	Borderline	-	1
	Malignant	5	46
Mucinous	Borderline	2	2
	Malignant	1	5
Germ cell tumour		1	1
Sertoli cell tumour		-	1
Transitional cell carcinoma		-	1
Granulosa cell tumour		1	3
Adenofibrocarcinoma		-	1
Seromucinous tumour		-	2
Metastatic carcinoma	Sigmoid	1	2
	Breast	-	1
Total		12	64

in nature. The histopathological co-relation of malignant masses with RMI is shown table 2. It shows that majority of the cases were serous adenocarcinoma (81%), 1 borderline and 51 malignant. Ten were of mucinous variety out of which 4 were borderline and 6 were malignant. Four were metastatic from other sites, 3 being from sigmoid and 1 from

Table 3: False positive cases in benign cases

Histopathological diagnosis	Number
Mucinous tumour	2
Teratoma	2
Benign cyst	2
Infective Tuberculosis	1
Salpingo-oophoritis	1

breast. Among benign cases, majority were teratoma (29%) of which 5 had RMI < 200 and 2 had RMI more than 200. 5 were of mucinous variety out of which 3 had RMI <200. Five were hemorrhagic cysts and 4 were infective in nature.

Table 4: False negative cases in malignant cases

Histopathological diagnosis	Number
Borderline mucinous tumour	2
Malignant mucinous tumour	1
Germ cell tumour	1
Metastatic tumour from sigmoid	1
Granulosa cell tumour	1

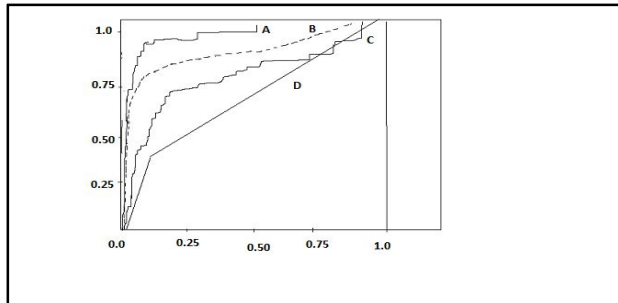
Among the infective cases, 3 were of tuberculosis and 1 was of salpingo-oophoritis. Out of eight false positive cases, 2 were mucinous tumour, 2 were teratoma, 2 were benign cyst and 2 were of infective type (table 3). Solid parts found in dermoid cysts and multilocular cystic lesions found in mucinous cystadenomas may attribute to the false positive cases. Out of the six false negative cases shown in table 4, 2 were of borderline mucinous variety, 1 was malignant

mucinous, 1 was germ cell tumour and 1 each were metastatic tumour from sigmoid and granulosa cell tumour.

Table 5: RMI in adnexal masses

RMI	Benign	Malignant
<200	16 (57%)	12 (43%)
>200	8 (11%)	64 (89%)

There may be limitation of RMI in detecting borderline cases. In patients with RMI >200, 89% were malignant and 11% were benign whereas in those with RMI <200, 43% were malignant and 57% were benign (table 5). The



- A- Risk of Malignancy Index
- B- Ultrasound Score
- C- CA-125
- D- Menopausal status

Figure 1: Receiver operating curves (ROC) showing the diagnostic performances of CA-125, ultrasonographic scores and the risk of malignancy index.

sensitivity of the RMI for diagnosing malignant lesions was 84% while the specificity was 67%. The PPV was 89% and the NPV was 57%. The figure-1 shows receiver operating curves showing the diagnostic performances of CA-125, ultrasonographic scores and the risk of malignancy index of the patients. The ROC curves were constructed to determine the appropriate cut-off value for discriminating benign from borderline and malignant tumors.

Discussion

Currently, it appears that the best way to detect early ovarian cancer for both the patient and her clinician to have a high index of suspicion of the diagnosis in the symptomatic woman⁵. The discrimination between benign and malignant adnexal masses is central to decisions regarding clinical management and surgical planning in such patients. Several studies have shown that ovarian cancer patients who underwent surgery by a gynecologist had better survival

compared with patients who underwent surgery by general surgeons^{14,15}. Subsequently, it was suggested that surgery by a gynecologic oncologist would improve survival further¹⁶⁻¹⁸. A standardized method for preoperative identification of probable malignant masses would allow optimization of first-line treatment for women with ovarian cancer¹⁹. Unfortunately, no single method accurately predicts ovarian malignancy at present. A scoring system that would help to predict malignancy would aid in proper counseling and timely referral to a specialized centre.

In this study, we aim to determine if the RMI (RMI 2) can distinguish between benign and malignant adnexal masses. In our study, 100 cases of adnexal masses were analysed and risk of malignancy was calculated and various parameters were studied. All the patients underwent treatment as per standards of care given by NCCN and FIGO. We found that the mean age of the patients was 48 years which is higher than that of the study by Tahereh et al. Ovarian cancer was most common in the age group of 41-60 years²⁰. The US score appeared to be the most useful in discriminating benign and malignant ovarian tumours^{21,22}. A score of more than 7 yielded the maximal area under the curve and would be the best indicator of malignant nature of the ovarian mass with the highest sensitivity and specificity. Several retrospective and prospective studies have reported RMI to be the best available tool for triage and referral of ovarian malignancies^{23,24}.

In our study, out of the 76 patients, only 12 had RMI less than 200 with a positive predictive value of nearly 90%. 62% of the patients in our study were menopausal which is similar to incidence rates reported in other studies²⁵⁻²⁷. Among the 76 malignant cases, only five had levels below 35 that is they were false negative whereas majority of the cases (71) had elevated levels. This corroborates with the findings of the study published in J Med Assoc Thai Vol. 88 Suppl 2 2005 in which the level was >35 U/ml in 23% and 89% of benign and malignant ovarian tumours respectively²⁸. Most studies reported an increased diagnostic accuracy and performance with an RMI cut-off of 200^{9-12, 24, 26}. A recent study reported a sensitivity of 89.5%, specificity of 96.2%, positive predictive value of 77.3%, and negative predictive value of 98.4% when a higher RMI cut-off of 238 was used for the screening²⁰. Yamamoto et al. (2009) reported a sensitivity and specificity of 75% and 91%, respectively, using a cut-off of 450²⁹. There also seems to be limitation of RMI in detecting borderline cases but more studies are required to establish the relation³⁰. The sensitivity of RMI as calculated

by this study is 84%, specificity being 67% and the positive and negative predictive value 89% and 57% respectively.

As opposed to this, the study by Jacobs et al gave a sensitivity of 85.4% with a specificity of 96.9%¹¹ whereas Tahereh et al 89.5% and 94.7%²⁰ respectively. Previous studies (Tingulstad's et al) showed a reduced sensitivity of RMI for lesions of borderline malignancy¹². Comparable results are seen in our study. However, in all studies, the number of borderline tumors has been small.

Conclusion

In conclusion, the present study has demonstrated RMI to be a valuable, reliable and applicable method in the primary evaluation of patients with pelvic masses and a usable method in referral of relevant patients for centralised surgical treatment. A very strong argument for the use of RMI in the primary evaluation of patients with pelvic masses is the simplicity of the method and its easy applicability. This study confirms its accuracy in detecting malignancy but also highlights its limitations in excluding benign diseases.

Conflict of interest: None. **Disclaimer:** Nil.

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