THE RISK OF MALIGNANCY INDEX (RMI) IN PREOPERATIVE PREDICTION OF MALIGNANCY IN A CLINICALLY SUSPICIOUS OVARIAN MASS

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Summary

There is no satisfactory preoperative tools to differentiate a benign from malignant masses in pelvis. Serum CA125 level, pelvic ultrasonogram and menopausal status are used individually to predict malignancy with poor outcome but the use of three in association RMI can improve diagnostic performance. Objective :- To evaluate RMI scoring system as method of choice for predicting whether or not an ovarian mass is likely to be malignant. Design:- Cross sectional study. Settings:- Chi ttagong medical college hospital and Chittagong metropolitan hospital. Duration: January 2011 to October 2014. Sample size:-175 patients admitted in January 2011 to October 2014. The risk malignancy index was calculated as UXMXCA125 performed preoperatively. Ultrasound findings were scored depending on wall structure, wall thickness and echogenecity(1,4), Menopausal status pre and post menopausal scored as (1,4) and absolute level of CA 125 measured by radioimmunoassay. The individual performance were found in RMI (sen82%,spe 77%, +ve PV 81%, -vePV23, +veLR5.6,-veL. 53,accuracy 78%), USG(sen86%, spe23%,+vePV87%, vePV32%, +veLR6.5%, veLR.84, accuracy 82%), CA125 (sen72%, spe32%,+vePV87%,vePV32%, +veLR6.5, veLR.84,accuracy 67%), Manupausal status (sen84%,spe50%, +vePV21%,-vePV2.4%, +veLR, -veLR, accuracy78%).

The area under the ROC curve for risk malignancy index was (.8-.9), which was greater than the area for CA125(.6-.7), USG(.7-.8) score and menopausal status (.7-.8). The risk malignancy index using ultrasound morphological score, serum CA125 level and menopausal status might be of value in the preoperative assessment of ovarian carcinoma.

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Key words

Ovarian cancer; CA125; Ultrasound; Risk of malignancy.

Introduction

Ovarian cancer is the sixth(3.9%) female cancer in Bangladesh [1]. A worse prognosis is correlated with late diagnosis and 70% are detected at advanced stage with 70% mortality at 2 year & 90% at mortality at 5year [2]. In contrast the survival rate of women with early stage ovarian cancer is excellent. As a result there has been Increased interest in the development of methods that can detect ovarian cancer when it is curable. Ovarian tumour usually present as adenexal masses which gives rise to number of benign or malignant condition. The accurate diagnosis of adenexal mass is a challenge for gynaecologist, because of its bizarre and atypical behavior. Preoperative diagnostic procedure that are able to distinguish whether an ovarian tumour is benign or malignant could be useful in planning optimized treatment [3]. Untill now the standered strategy for differential diagnosis has been exploratory laperotomy. On the other hand detailed analysis of origin of pelvic mass has encouraged the use of minimal invasive surgery such as laparoscopy or mini leparotomy in selected cases [4]. A preoperative prediction of of malignancy can guide gynaecologist to refer women with suspected pelvic masses to an oncological unit for optimized debulking and appropriate therapy.

Several diagnostic methods for pelvic masses have been reported, such as abdominal & transvaginal ultrasonogram, three dimensional ultrasound ,color Doppler ultrasound and tumour marker [5]. However none of these methods used individually has shown significantly better performance in detecting malignancy from a clinically restricted ovarian masses suspiscious of malignancy [6]. CT,MRI are used for predicting peritoneal cancer index preoperatively in patient considered for peritonectomy/ cytoreductive surgery in advanced ovarian malignancies [7]. The development of a mathematical formula incorporating menopausal status, level of serum CA125 and ultrasound morphological score (Sessons score) has been described in literature in the form of different malignancy index [8]. These indexes were calculated using equation obtained from product of Ultrasound findings score, the menopausal status score and the absolute value of CA125 serum levels. Though there are three RMI index (1,2,3), the risk malignancy index(RMI) 2 preffered better for detecting ovarian malignancy and RMI 2 has increase sensitivity in most of the cases with out loss of major specificity at a cut off point off 200 [9]. Patient with RMI>200U/ml has an average 42 times the background risk of cancer and those with a lower value having 1.5 times the risk of ovarian cancer [10].

The purpose of the study was to evaluate the risk of malignancy index combining serum CA125 level, ultrasound score and menopausal status, in preoperative diagnosis for women with pelvic masses clinically restricted to ovaries and with out clear evidence of malignancy.

Materials & methods

Women with pelvic masses apparently restricted to ovary who were planned for laperotomy in CMCH and CMPH from January 2010 to October 2014 were selected. Total 175 patients were included in the study who met the following criteria (a) age 20 years or older(b) ovarian masses diagnosed clinically and sonologically having preoperative measurement of CA125 (c)planned for laperotomy. The CA125 serum level, ultrasound findings and menopausal status were registered preoperatively.

The exclusion criteria were the patient with (a) incomplete medical record (b) clinically and radiologically (CT,USG) advanced malignancy and /or who had histological diagnosis of malignant ovarian cancer. Serum CA125 sample were assessed by radioimmunoassay. Ultrasound examination was preffered using 3.75 MH abdominal convex transducer and morphological evaluation was done by observation of different echogenecity, wall thickness, septa and papillae (Sessons score). A score was attributed to each ultrasound findings termed the ultrasound score according to sessons score. Postmenopausal status was defined as more than one year of amenorrhea or a age of 50 years in women who had hysterectomy. All other women were considered premanupausal. Laperotomy was done and the excised tissue was sent for histopathological analysis. Histological diagnosis was considered as the gold standered for defining the outcome and it was classified as benign and boarderline or malignant. Patients participation in the study was concluded once the histopathological report were obtained after surgery.

We used cut off level 200 to indicate malignancy .In RMI 2 U-M-serumCA125 where total USG Score of 0 give U=O, score1 give U=1 & score >2, U= 4,manupausal status gave M. The risk malignancy index was calculated with attribution of 1 for pre-manupausal status & 4 for post menupausal status(M) versus ultrasound score(4) and the obsolute values of CA 125 serum level ie; USG X M X CA125.

Sensitivity & specificity, +ve & -ve predictive value ,+ve and-ve likelyhood ratio individually of CA125,USG, menopausal status with reference to the presence of a benign & boarderline or malignant pelvic masses were calculated. Sensitivity was defined as % of patients with boarderline or malignant disease having a +ve test result ,specificity the % of patient with a benign disease having a –ve test result while +ve predictive value was defined as % of patient with a +ve test result having boarderline or malignant disease. The -ve predictive value was defined as the % of patient with a –ve test result having benign disease. The likelyhood ratio indicates the value of the test for increasing certainity about a positive diagnosis.

A high likelyhood ratio may show that the test is useful but not a good indicator of the presence of disease. The histological diagnosis was considered as gold standard. In the receiver Operative characteristics curve evaluation CA125, USG, menopausal status and RMI 2 and the area under the curve also evaluated.ROC curve is a fundamental tool for diagnostic test evaluation. True +ve (sensitivity) is plotted in function false+ve rate.(100-specificity) of different cut points of different parameter. The area under ROC curve is a measure of how well a parameter can distinguish between benign and malignant and the area is interpreted as .90-1=Excellent, .80-.90=good,.70-.80=Fair,.60-.70= poor,.50-.60=Fall. With increase sensitivity the curve steep to the left with modest decrease in specificity which is very favourable.

Results

Total 175 patients were included in the study. Median age were 43yrs (20-65yrs). Among them 121 patient are premanupausal. The median preoperative CA125 was 108.8IU/L and ranged from 05 to 5500U/ml. The most USG score was 2-5. Table I shows the patients characteristics. Among the 175 hisltology confirmed 145 patients as malignant, 2 being boarderline malignancy and 30 were benign. The distribution of histological diagnosis are shown in Table II. In table IV shows the rate false+ve (23) and false –ve (15). Statistically difference between benign, boarderline and malignant group were present in the following factors age, USG score ,menopausal status and serum CA125.

Majority of malignant disease had ovarian malignancy (143), Krukenburge tumour (2). The ovarian carcinoma include 80 at FIGO stage 1,50at stage II,15 at stage III with lymph node invasion and omental deposit .The sensitivity, specificity, positive and negative predictive value, positive and negative likely hood ratio of serum CA 125, USG score and menopausal status are reported. The performance status obtained for CA125 at a cut off point of 35IU/L were sensitivity (72%), specificity (40%), +ve predictive value (85%), -ve predictive value (77%)+ve likelyhood ratio (5.8),-ve likelyhood ratio (.3), accuracy (67%).

At a USG score of 4 sensitivity (86%), specificity (23%), +ve predictive value (87%), -ve predictive value (32%), +ve likelyhood ratio (6.5), -ve likelyhood ratio (.84)accuracy (82%). In post manupasal patients at score of 4 sensitivity (84%), specificity (50%),+ve predictive value (95%), -ve predictive value (80%), +ve likelyhood ratio (21) and –ve likely hood ratio(4), accuracy81%. The performance status obtained for RMI at a cut off point of 200 were sensitivity (82%), specificity (77%), +ve predictive value (81%), -ve predictive value (23%), +ve likelyhood ratio (5.6),-ve likelyhood ratio (2.1), accuracy78%. In the receiver operative characteristics curve evaluation, for CA125,USG score and menopausal status were found to be relevant predictor of malignancy to the left of diagonal line.The area under the receiver operative characteristics curve for CA125 was (.6-.7)-, USG (.7-.8), menopausal status (.7-.8) and that of RMI (.8-.9). The area under ROC curve for menopausal status is more on the left than other two individual parameter like USG and CA125.The area under ROC curve for the the risk of malignancy is far left and is more than that of menopausal status. Table IV shows the rate of False +ve and false –ve. In total cut off level of 200 the false +ve cases were23 and false –ve 15.

Table 1 : Different variables in relation to pelvic masses

Variable	Benign	Boarderline	Malignant
Age(year)			
20-29 yr	10	0	16
30-39yr	11	1	28
40 49yr	5	0	50
>- 50yr	4	1	49
Manupausal status			
Pre-manupausal	40	1	80
Post manupausal	4	1	49
USG score			
0	0	0	0
1	23	0	6
2-5	7	2	137
Ca125 IU/L			
Mean	65.9	46.4	950
Minimum	5	15	10
Maximum	1000	220	5500

Table II : Distribution of hitological findings

Benign	no(30)	Boarderline	Malignant (143)
Endometrioma	9	Serous 1	Serouscarcinoma 60
Mucinous cystadenoma	8	Mucinous1	Mucinous carcinoma 50
Dermoid cyst	4		Edometroid carcinoma 4
Leiomyoma	1		Granulosa cell tumour 5
Fibroma	2		Dysgerminoma 12
			Endodemal Sinus tumour 4
Pelvic tuberculosis	3		Metastatic carcinoma 2
Tubo-ovarian abscess	2		
Chronic ectopic	1		

Table III : RMI at a cut off point of 200

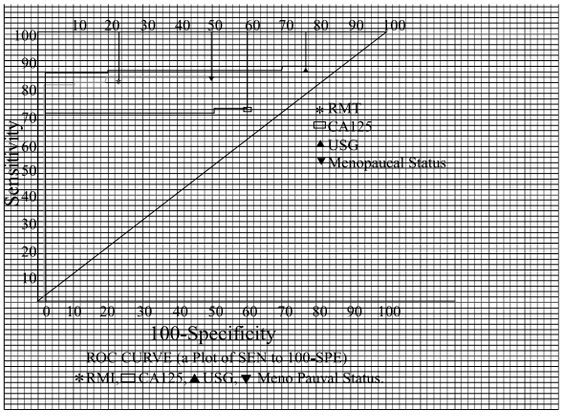
RMI	Benign	Boarderline	Malignant
<200	23	2	15
>200	7	128	

Table IV : Number of False Positive and false negative

False positive (23)	False negative(15).
Dermoid cyst -5	Boarderline tumour -2
Mucious cystadenoma-5	
Chronic ectopic -1	Granulosa cell tumour -4
Leiomyoma -1	
Endometrima -4	Dysgerminoma -5
Pelvic tuberculosis -3	Metastatic Ca -2
Tubo ovarian abscess -2	Endometrial carcinoma -2
Fibroma of ovary -2	

Table V : Diagnostic performance SEN, SP, PV, LR to predict malignancy

- Variable	Sensitivity	Specificity	+vePV	-vePV	+ve LR	-veLR	Accuracy
CA-125(35%)	72%	40%	85%	77%	5.8	.3	67%
USG (4)	86%	23%	87%	32%	6.5	.84	82%
Postmeno-							
Pausal status (4)	84%	50%	95%	80%	21	4	81%
RMI(200)	82%	77%	81%	23%	5.6	.53	78%



ROC CURVE (a Plot of SEN to 100-SPE)
*RMI, □CA125, ▲USG, ▼ Meno Pauval Status.

Discussion

Risk malignancy index RMI 2 is useful in clinical practice for differentiating malignant from benign Pelvic masses, as compared to each individual component measured separately .The cut of value of RMI 200 had found to be have in the literature the best discrimination between benign and malignant masses [11]. The RMI is a simple and effective system to apply in clinical practice and it uses inexpensive commonly available technique and tests to predict malignancy. The role of other imaging modalities such as MRI,CT and PET in the diagnosis and to differentiate benign from malignant yet to be clearly estabilished [12]. The index was more accurate in comparison with the best individual predictor and absolute serum CA125 level. ln our study individual USG sensitivity, specificity, +vepredictive and-ve predictive value were 86%, 23%, 87%and 32% .Very low specipicity may be due to inclusion criteria and in part bylevel of training and experience of different sinologist. Serum CA125 rises 85% cases of epithelial ovarian cancer (benjapibal et al 2007, leeelahakorn et al 2005) with a sensitivity83. 1% but a specificity of39.3%. In our study serum CA125 sensitivity and specificity were also 72% and 40%respectively [13]. Serum CA125 between 400 to 500 IU/ml automatically is greater tha200 but would not be a deciscion making process [14].

The validity of index depends on the proportion of malignant neoplasm and benign process, the proportion of limited and advanced stages. Age is major factor in dertermining the likely hood of cancer

with age adjusted rates increasing as age advances [15]. In our study 54 patient were more than 50 yrs or post manupausal ,50 of them (92%)had malignancy. On an average women with malignant pathology were older (65 vs 20),had a higher CA125 (5500 vs10)were most likely to be postmanupausal(49vs 4) and had a higher score (2-5) in USG (139 vs 6). In the present study malignancy was 82% more than to those (Jacob,s et al, Tangs et al 2007, 29-35%) [16]. In our study increase sensitivity (82%) RMI2 was reported than those by other previous studiesJacob,s sensitivity 73% and specificity 93%.

This increase in sensitivity (82%) with out much loss of specificity (77%) is mainly due to inclusion of pelvic masses only suspiscious of malignancy and restricted to ovary.But in others non selscted population only with pelvic mass were included in those study. For the same reason Tengelstat et al sensitivity 76% & specificity 82% in 2006 [13]. Increase sensitivity is also important because a low sensitivity leads to an increase number of benign cases managed in oncology unit. In Thiland ,Leelahakom et al.(2005) including a higher USG score sensitivity, specificity._+ve predictive and -ve predictive value were 88.6%, 90.7%, 70.5%, 97% respectively [17].Inclusion of suspicious but without any clinical evidence leads to higher rate of early stageI (80,55%), stage II(50,35%) and boarderline ovarian tumour (2) found in our study. In Jacobs(1990) the prevalence of stage I was 26% while the prevalence 36% in our study. Selection of suspiscious and restrited pelvic mass also leads to the difference.

In our study majority false negative cases (15,9%) were mucinous boarderline tumour and early stage (sageI) serous malignant tumour and granulosa cell tumour. Low level serum CA125 and low USG score were likely to explain the false -ve.

False positive cases (23,13%) were dermoid cyst and mucinous cystadenoma. Solid parts found in dermoid cyst and multiloculer cystic lesion found in mucinous cyst adenoma, chronic ectopic, CA125 elevation due to peritoneal irritation in pelvic tuberculosis, tubiovarian abscess,, endometrima, ovarian fibroma,chronic ectopic producing high RMI may attribute to the false positive rate. Causes of false +veity and -veity were more or less same like other studes (Wat,fFrazi [18]. Ascites associated with pelvic masses Is a recognized sign of malignancy [16]. Sonologically detected ascites were found in 3 patients with raised CA125 (pelvic tuberculosis) and 2 clinically diagnosed but with very low CA125 (ovarian fibroma) gave false+ve results .Among the advance tumour 15 were in stage III, so classed due to lymph nodeinvasion and omental deposit but none presented clear preoperative evidence of malignancy.

The RMI2 index itself useful in reffering in patient with advanced neoplasm to a more complex health care unit.In the present study the malignant ovarian tumour consisted mainly of early invasive or boarderline tumour (82%). Boarderline tumour and benign process can be treated in regional hospital by gynaecologist, although invasive neoplasia particularly advancea cases demands appropriate therapy by skilled surgical team in a equipped centre. The risk of malignancy index facilitates the selection of cases for referral to an oncology unit and also helps the surgeon to choose a surgical approach. RMI index is direcly related to structural complexity not the tumour measurement and bilterility [19]. A 62 yrs post menopausal old patient with solid well defined tumour 100cc USG 4 & a CA125 level of10 IU/ml present a malignancy index of160 and hitologically was found malignant, granulosa cell tumour (Fig 1, 2) a false –ve result. Again a postmenupausal lady with big clinically suspiscious sonolucent ovarian tumour more than about3000cc, USG score1 and CA125400/IU present a risk malignancy index of1600 at a cut off point 200 and was found benign (serous cell tumour)histology confirmed the diagnosis(fig 3) a false +ve result.

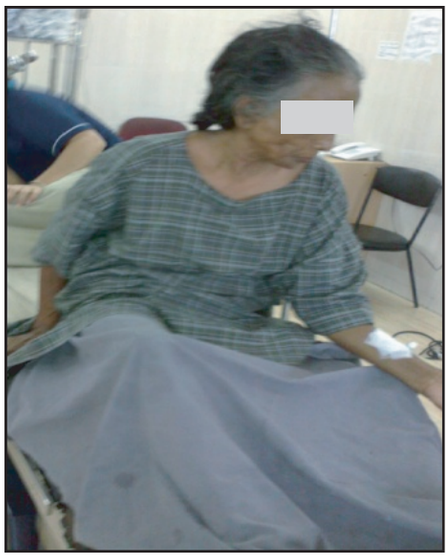


Fig 1 : A 63yrs lady with G.cell tumour

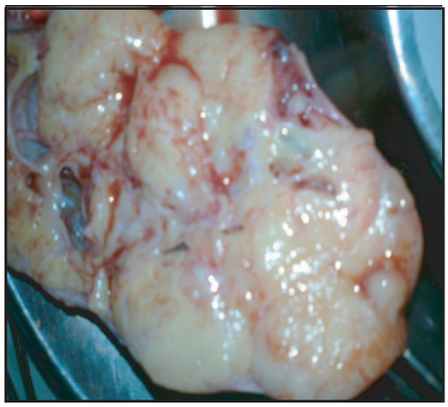


Fig 2 : G.Cell tumour On cut section

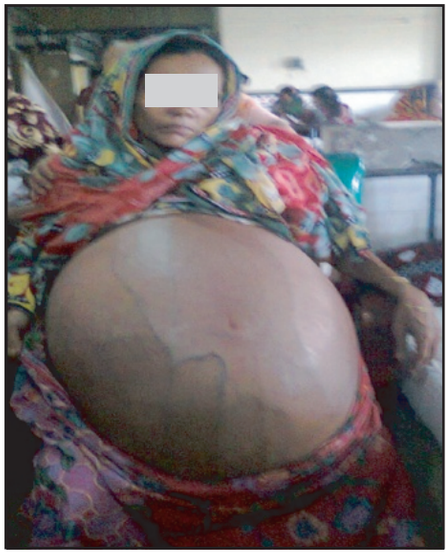


Fig 3 : A 55 yrs lady with serous cell tumour

Surgica staging and cytoreductive surgery before the adminis tration of chemotherapy remains an important component in the management of patients with ovarian cancer. Aggressive cytoreduction demands highly specialized skills and the amount of residual tumour volume after surgery is an important prognostic factor for survival and quality of life [3]. The use of RMI will clearly benefit patients with early ovarian cancer if their primary surgery is performed by a gynaecology oncologist as this could potentially avoid further surgery or chemotherapy. Many gynaecological oncology units have already been using one of these malignant risk indices to facilitate distinguish benign from malignant tumour [4]. An Australian study using RMI to identify high risk ovarian cancer patients preoperatively used CT scan feature instead of USG to calculate RMI. We used USG like others considering cost effectiveness but of use any one is justifiable and not to delay the treatment of these patients [6]. The use of RMI also helps to reduced the number of operations performed on benign cases as small size >_5-8cm [19]. In our study all patients needed surgery as we included patients with palpable pelvic masses suspiscious of malignancy and restricted to ovary.

The studies in the literature to date have not shown any difference between these imaging modalities in distinguishing between benign and malignant disease [9]. In our population RMI revealed a bitstatistical difference between sensitivities and specifities of these tests mainly due to selection criteria. The RMI2 can be chosen as a tool for triage referral for suitable surgical treatment laparoscopy or laperotomy, locally or in oncology center [20].

Women reffered to oncology unit with suspected ovarian cancer the dilemma for gynaecologist is in deciding whether the pelvic mass is likely to be malignant and who would operate on the patients. Prognosis in ovarian cancer correlates strongly with the ability to achieve optimal cytoreduction which is more feasible in oncology centre with greatest surgical experience [21].

Conclusion

RMI scoring system is the method of choice for predicting whether or not an ovarian mass is likely to be malignant. With an RMI score more than 200 should be reffered to a centre with surgeon experienced in ovarian cancer surgery.

Disclosure

All the authors declared no competing interest.

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