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Multimodal approach to predict ovarian malignancy prior to laparoscopy

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Abstract

Objective: To assess the performance of Ca-125, transvaginal sonography and RMI in prediction of ovarian cancer.

Methods: This is a prospective study of 60 women conducted at Dr. D.Y Patil Medical College and Hospital, Pimpri. Patients underwent Serum Ca-125 level, transvaginal sonography and risk of malignancy index (RMI) was calculated as per formula devised by Jacobs *et al* into high risk, moderate risk and low risk.

Results: The mean age of patients detected as malignant was 49.33 years. Using multimodal approach, achieved sensitivity of 100%, 33.33% and 66.67% and specificity of 52.94%, 58.82% and 94.12% in low, moderate and high risk group as per RMI categorization.

Conclusion: Multimodal approach using Ca-125, TVS and RMI calculation helps in predicting women with ovarian cancer prior to laparoscopy or laparotomy. The methodology is simple and can be used in gynecology clinics and less-specialised centres.

Keywords: Ovarian cancer, risk of malignancy index, TVS, Ca-125

1. Introduction

Ovarian cancer though, is considered as the disease of western world [1] but it has been estimated to be the third most common cause in India [2]. Age standardised incidence rates (ASR) for ovarian cancer varied from 0.9 to 8.4 per 100,000 person years in various registries and the highest incidence was noted in Pune and Delhi registries [3].

The age specific incidence rate (ASIR) for ovarian cancer revealed that the disease increases from 35 years of age and reaches its peak between ages 55-64 years [3]. The poor prognosis is attributed to the fact that ovarian cancer is the "cancer that whispers" because it often occurs at menopause when ovaries have no physiological role and therefore abnormal ovarian function shows no clear cut symptoms [4]. Survival for ovarian cancer is the poorest of all gynaecological cancer sites, with a five year relative survival rates of 44% for all stages [5]. The main reasons for this poor survival are the lack of early detection strategies and an unfavourable anatomical situation.

Reduction in mortality rates could be gained from progress in surgery and medical treatments and finding the correct role of an organised screening programme.

Number of tests specific and non- specific are available to detect ovarian cancer such as tumour marker, transabdominal sonography (TAS), transvaginal sonography (TVS), MRI, CT, PET. However, none of these tests have a high specificity and positive predictive value.

The problem of early detection of ovarian cancer is intensified by lack of detection of any one single screening tool which is specific, sensitive, non-invasive, easy to use and cost effective. Randomised controlled trials do not support routine screening for ovarian cancer in general population. Screening asymptomatic women for ovarian cancer using ultrasonography, serum tumour markers or pelvic examination is not recommended. To add to the difficulty a screening tool for the general population does not exist as is for cervical cancer.

The Risk of Malignancy Index (RMI) was originally developed by Jacobs *et al* in 1990 [6]. This RMI is a simple scoring method which can be used in less specialised centres [6].

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This index involves a multimodal screening approach which involves level of serum cancer antigen 125(Ca-125), pelvic ultrasound (TVS) and calculation of RMI (risk of malignancy index = ultrasound findings x menopausal status x CA-125 value) prior to laparoscopy and/or laparotomy. It will help us to predict with high accuracy, the probability of ovarian malignancy in women with an ovarian mass particularly in postmenopausal age group.

2. Aims and objectives
1. To assess the performance of combination of Ca-125, transvaginalsonography and RMI (risk of malignancy index) in prediction of ovarian cancer in women presenting with a clinical or ultrasound feature suggesting of an ovarian mass.
2. To see the sensitivity and specificity of Ca-125 level alone as well as transvaginalsonography alone in prediction of ovarian cancer.

3. Materials and methods
Type of study: Prospective
Period of study: July 2011 To September 2013
Sample size: 60 cases

Inclusion criteria: All women diagnosed with a clinical impression or an ultrasonographic feature suggestive of an ovarian mass. These women underwent serum Ca 125 level and transvaginal ultrasound and then on the basis of Ca 125 level, the ultrasound features (U) and the menopausal status (M).
Prospective clinical study of 60 cases was conducted at D.Y Patil Medical College, Hospital and Research Centre, Pimpri, Pune from period of April 2011 to November 2013.
All the patients were evaluated as per the proforma.
Institutional Ethical Committee approval was taken prior to commencement of study.
A written and informed consent was taken from the patient.

Ultrasound findings: scored with one point for each
- Multi-locular cyst
- Evidence of solid areas
- Evidence of metastasis Presence of ascites
- Bilateral lesions

U = 0 (ultrasound score of 0)
U = 1 (ultrasound score of 1)
U = 3 (ultrasound score of 2-5)

Menopausal status is scored as:
Postmenopausal status is graded M = 3.
Premenopausal status is graded M = 1.
The risk of malignancy index shall be calculated as follows using Jacobs *et al* formula:

RMI = U x M x CA-125
Ultrasound features (U)
Menopausal status (M)

RISK	RMI	Women (%)	Risk of cancer (%)
Low	<25	40	<3%
Moderate	25-250	30	20%
High	>250	30	75%

Jacobs *et al*

General Rules
1. Women with high risk of malignancy (>75%) - refer to cancer centre.
2. Moderate risk of malignancy (20%) - refer to cancer unit / gynae oncologist.
3. Low risk (<3%) - refer to gynae unit / oncologist.

Patients underwent surgery and histopathological diagnosis of ovarian mass was regarded as the definitive outcome. Ovarian cancer was staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification [7].

4. Observations and results
The data was collected, analysed and the following observations were made and results were drawn.

1. Age distribution
Of 60 patients, 9 (15%) patients had malignant disease. The mean age of the patients with ovarian mass in our study was 42.55 years (range, 16 to 64 years).

Table 1: Value of Ca 125 used alone to predict possibility of malignancy.

N=60	Raised CA-125 (>35 U/ml)	Malignant	Non Malignant	Sensitivity	Specificity	Positive Predictive value	Negative Predictive value
60	15 (25%)	6 (40%)	9 (60%)	66.67%	82.35%	40%	93.33%

In table 1, Ca 125 level when done alone was raised in 25% of patients. Sensitivity of 66.67% was seen when Ca 125 was used to predict the possibility of malignancy alone.

Table 2: Value of Transvaginal sonography in diagnosis of ovarian cancer.

N=60	TVS Findings s/o malignancy	Malignant	Non Malignant	Sensitivity	Specificity	Positive predictive value	Negative predictive value
60	9(15%)	3(33.33%)	6(66.67%)	33.33%	88.23%	33.33%	88.23%

The above table 2 shows the importance of transvaginalsonography in detecting malignant ovarian mass. A morphological index which scores the findings giving a risk of malignancy estimation has been devised. These include criteria like thickness of internal borders, type of cysts, presence of septa, papillary projections and ovarian tissue echogenicity.
In our study, 15% of ovarian masses had findings suggestive of malignancy, thus increasing the specificity to 88.23%.

Table 3: Malignancies in low, moderate and high RMI

	Category	Total number of cases	Malignant	Non malignant	Risk of cancer
Risk of malignancy index(RMI)	Low risk (0- 25)	27	0	27	0%
	Moderate risk (25-250)	24	3	21	12.5%
	High risk (250 above)	9	6	3	66.67%
	Total	60	9	51	

Table 3 shows multimodal approach to predict ovarian malignancy in ovarian mass calculated by the algorithm US x M x CA 125

The RMI was calculated in 60 patients with ovarian mass and we found out that women who were identified as high risk had an overall risk of cancer of 66.67%

Table 4: Value of RMI in diagnosis of ovarian malignancy in 60 patients.

RMI range	Number of patients	Malignant	Non malignant	Sensitivity	Specificity	Positive Predictive value	Negative predictiv e value
Low (0-25)	27 (45%)	0	27	100%	52.94%	27.27%	100%
Moderate (25-250)	24 (40%)	3 (12.5%)	21 (87.5%)	33.33%	58.82%	12.5%	83.33%
High (250 above)	9 (15%)	6 (66.67%)	3 (33.33%)	66.67%	94.12%	66.67%	94.12%

A multimodal approach involves a combination of tests and increases the sensitivity for early detection of ovarian cancer. Using multimodal approach, a specificity of 94.1% and positive predictive value of 66.67% for the detection of ovarian cancers was achieved.

6. Discussion
About 10% of women undergo exploratory surgery for evaluation of ovarian masses during their lifetime [8]. Early detection and prompt referral to gynae oncologist definitely improves the survival rate. However, the difficulty lies in predicting ovarian malignancy.

Here, we report, how a multimodal approach using the RMI score helps us in predicting malignant ovarian disease.

1. Age distribution
The mean age of the patients with ovarian mass in our study was 42.55 years (range, 16 to 64 years). The mean age of the patients with malignant disease was 49.33 years. The mean age of the patients with benign disease was 41.33 years. This is slightly higher than that reported in a similar study by Akdeniz et al. in 2009 [9].
The incidence of ovarian cancer increases with age [10]. The ASIR increases from 35 years of age and peaks to 55-60 years [3].

Table 5: Value of Ca 125 used alone to predict possibility of malignancy.

N=60	Raised CA- 125 (>35U/ml)	Malignant	Non Malignant	Sensitivity	Specificity	Positive Predictive value	Negative Predictive value
60	15(25%)	6(40%)	9(60%)	66.67%	82.35%	40%	93.33%

Out of 60, 15 (20%) women studied had an increased Ca 125.
In a UK study, CA-125 achieved a specificity of 99.9% and a sensitivity of 78% and a positive predictive value of 26.8% at one-year follow up [11].
The JANUS study showed raised CA-125 only in 105 cases (0.26%) out of 39,300 healthy women [12].
CA-125 alone is neither sensitive nor specific to detect early ovarian cancer as it is also elevated in conditions like

fibroids, endometriosis, pregnancy, pancreatitis and cirrhosis of liver, therefore Ca-125 is not recommended for use in screening asymptomatic women by the NACB panel as well as other authoritative organisations [13, 14] but may be of great significance in women with a history of hereditary ovarian cancer, nulliparity, HRT therapy etc. Ca-125 measurements may be used to monitor response to chemotherapeutic response.

Table 6: Value of transvaginal sonography in diagnosis of ovarian cancer.

N=60	TVS Findings s/o malignancy	Malignant	Non Malignant	Sensitivity	Specificity	Positive predictive value	Negative predictive value
60	9 (15%)	3 (33.33%)	6 (66.67%)	33.33%	88.23%	33.33%	88.23%

TVS offers better resolution.In our study 15% of malignant ovarian masses show higher specificity of 88.23%.

Table 7: Value of transvaginal ultrasound in diagnosis of malignancy in adnexal masses.

Authors	Patients (n)	Malignant	specificity	Senstivity
Granberg et al[(.28)]	50	16	82	100
Sassone et al[129]	143	13	83	100
Kurjak etal[130]	83	29	98	48
Hata et al[13I]	63	27	69	85
Weiner etal[132]	53	17	69	94
Kawai et al[133]	109	40	65	90
Total	501	142	79	83

TVS alone had a specificity varying from 65-98% and sensitivity ranged from 48-100% which is comparable to our study but it is directly related to the operator's experience and therefore has a definite degree of error and exactitude

and therefore TVS alone is not recommended as a single test for detection of ovarian cancer and should be combined with Ca 125 measurements for promising results.

Table 8: Malignancies in low, moderate and high RMI

	Category	Total number of cases	Malignant	Non malignant	Risk of cancer
Risk of malignancy index(RMI)	Low risk (0- 25)	27	0	27	0%
	Moderate risk (25-250)	24	3	21	12.5%
	High risk (250 above)	9	6	3	66.67%
	Total	60	9	51	

In our study, women were in the high risk group, where RMI was 66.67%.

Table 9: Risk of cancer in low, moderate and high risk of malignancy index.

Risk	Rmi	Risk of cancer (%)	Women (%)
Low	<25	<3	40
Moderate	25-250	20	30
High	>250	75	30

According to Jacob *et al*, possibility of malignancy in moderate and high risk of malignancy index is 20% and 75% respectively which is comparable with our study which has malignancy index of 12.5% and 66.67% respectively.

Table 10: Value of RMI in diagnosis of ovarian malignancy in 60 patients.

RMI range	Number of patients	Malignant	Non Malignant	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Low (0- 25)	27 (45%)	0	27	100%	52.94%	27.27%	100%
Moderate(25-250)	24 (40%)	3 (12.5%)	21 (87.5%)	33.33%	58.82%	12.5%	83.33%
High(250 above)	9 (15%)	6 (66.67%)	3 (33.33%)	66.67%	94.12%	66.67%	94.12%

Using multimodal approach, a specificity of 94.1% and positive predictive value of 66.67% for the detection of ovarian cancers was achieved.

Table 11: Trials using multimodal approach for diagnosis of ovarian cancer.

Study	Features & screening strategy	Patients Screened (n)	Positive Screens (n)	Operations for cancer (n)
Jacobs *et al* [120,94]	Age >= 45 years, postmenopausal serum CA-125 TAS if CA-125 increase	22,000	41	3.7
Jacobs *et al* [121]	Age >= 45 years, postmenopausal RCT, Serum CA-125 TAS/TVS if CA-125 increase	10,958 (3 annual screens)	29	4.8
Grover *et al* [122]	Age >= 40 years or with family history Serum CA-125 TAS/TVS if CA-125 increase	2550	16	16
Adonakis *et al* [,23]	Age> 45 years Serum CA-125 TVS, if CA-125 increase	2000	15	15

Jacob *et al* achieved a specificity of 99.9% and positive predictive value of 26.8% for the detection of ovarian and fallopian tube cancers in 22000 post-menopausal women. Similar studies were done by Grover *et al* and Adonakis *et al* which is comparable with our study.
Multimodal approach in triaging women is more promising in detection of ovarian cancer as specificity increases with application of this method.

7. Conclusion
Screening for ovarian malignancy in general population is difficult as there is no premalignant state. One single investigate modality does not help in detecting ovarian malignancy with accuracy but multimodal approach achieved a very high specificity of 94.12% and positive predictive value of 66.67% in our study. Multimodal approach using Ca-125, TVS and age of the patient helps to identify women who are at low, moderate and high risk of cancer. Ca-125 should be considered as the only tumour

marker in combination with TVS for early detection of ovarian cancer especially in women who are at high risk, with history of hereditary syndromes, detection of recurrence and monitoring of therapy and prognosis. Awareness programmes regarding ovarian cancer in women will help in promoting early referral and detection of ovarian cancer.

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