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Correlation between Histopathological Type and Grade of Different Ovarian Tumors with Their Blood CA125 Levels

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Abstract

Introduction: *Women with ovarian carcinoma experience poor survival because symptoms are vague and diagnosis is unlikely at an early stage. Early detection is utmost important both for treatment and survival CA-125 is the most frequently used biomarker for ovarian cancer detection. In this study, the authors evaluated 60 distinct cases of benign and malignant primary ovarian tumors, of different cell lines and degrees of differentiation, aimed at assessing the relationship between serum levels of CA125 and the biological behavior and/or the histological degree of these neoplasms.*

Materials & Methods: *patients were selected for study after clinical suspicion fallowed by radiological evaluation .Serum sample for CA 125 sent preoperatively. Patients were operated and ovarian tissue sent for histopathological examination for typing and grading in pathology department. The study carried out with sixty patients for one year duration.*

Results: *After histopathological examination it was confirmed that 37 (61.6%) cases were suffering from benign ovarian tumor. 6 (10%) cases were suffering from borderline ovarian tumor and 17 (28.3%) cases from malignant ovarian tumor. Majority of patients with benign tumor (35/37, 94.59%) have their serum CA125 value <35 U/ml and most of patients with borderline & malignant tumors (18/23, 78.2%) have their serum CA125 value >35 U/ml. Again 7/17 (41.17%) of patients with malignant tumor have their serum*

CA125 value > 100 U/ml. 100% of patient with borderline tumors have their serum CA125 value in between 35-65 U/ml. The present study revealed that 100% of the patient having epithelial borderline/malignant tumors of grade I had their serum CA125 values within 35-65 U/ml. (6/7, 85.7%) of patients having epithelial borderline/ malignant tumor of grade III had their serum CA125 values >100 U/ml. Another important finding was that epithelial malignant tumor including Mucinous cystadenocarcinoma, Serous cystadenocarcinoma had their mean value more than 100 IU.

Conclusion: *Patients with borderline/malignant epithelial tumor had higher pre-operative serum CA125 value (>35U/ml) than benign ovarian tumors.CA125 had ascending relation with higher grade of tumor. With very high value of serum CA 125, one should think about serous or mucinous epithelial ovarian tumor.*

Keywords: *Benign Ovarian tumor, Borderline/Malignant Ovarian Tumor, Serum CA 125, Tumor grade*

Introduction

Ovarian carcinomas represent approximately 30% of malignant female genital tract tumors. Ovarian cancer the silent killer and the key is early detection. There are numerous types of ovarian tumors; overall they fall into benign, borderline and malignant category. The malignant ovarian tumors originated from the surface epithelium and/or stroma are graded as well differentiated (grade 1), moderately differentiated (grade 2) and poorly differentiated (grade 1); this classification is associated with prognostic factors and therapeutic modalities[1,2,3,4]. Symptoms of epithelial ovarian cancer are often nonspecific, especially in early stage cancer. Ultrasound is used to assess patients for ovarian cancer; ultrasound has a low specificity for determining if a mass is benign or malignant. The specificity is improved by using Doppler ultrasound and a morphology index but performance varies amongst different operators [5].

The use of tumor markers to further characterize the mass has come into clinical use. CA-125 is the most frequently used biomarker for ovarian cancer detection.[6] Around 90% of women with advanced ovarian cancer have elevated levels of CA-125 in their blood serum, making CA-125 a useful tool for detecting ovarian cancer after the onset of symptoms [7] Monitoring CA-125 blood serum levels is also useful for determining how ovarian cancer is responding to treatment [8] and for predicting a patient's prognosis after treatment.[9] This is because the persistence of high levels of CA-125 during therapy is associated with poor survival rates in patients.[10] Also, an increase in CA-125 levels within individuals in a remission is a strong predictor of the recurrence of ovarian cancer.[10] The estimated normal reference range is 0–35 U/ml, and its level increases in about 90% of women with advanced ovarian epithelial cancer, and in about 50% of patients in initial stages, in particular in tumors of a serous nature [11] The employment of the chemilumine-scence method for the assessment of serum CA 125 levels presents a sensitivity of 27%, a specificity of 97%, intra-and inter-assay coefficients of variation of 10%,and a linearity of up to 600 U/ml [12,13]

Materials and Methods

The study was carried out in the department of gynecology and obstetrics, Burdwan Medical College, a tertiary health care centre with sample size of sixty for one year duration with proper ethical clearance. Ovarian tumors are suspected clinically, sent for radiological confirmation and blood sample taken for CA-125 estimation. After operation ovarian specimen sent for histological typing and grading the in the department of pathology. The histologic grade of a tumor measures how abnormal or malignant its cells look under the microscope.[14] There are four grades indicating the likelihood of the cancer to spread and the higher the grade, the more likely for this to occur. Grade 0 is used to describe non-invasive tumors. Grade 0 cancers are also referred to as borderline tumors.[14] Grade 1 tumors have cells that are well differentiated (look very similar to the normal tissue) and are the ones with the best prognosis. Grade 2 tumors are also called moderately well differentiated and they are made up by cells that resemble the normal tissue. Grade 3 tumors have the worst prognosis and their cells are abnormal, referred to as poorly differentiated.

Measurement of serum CA 125

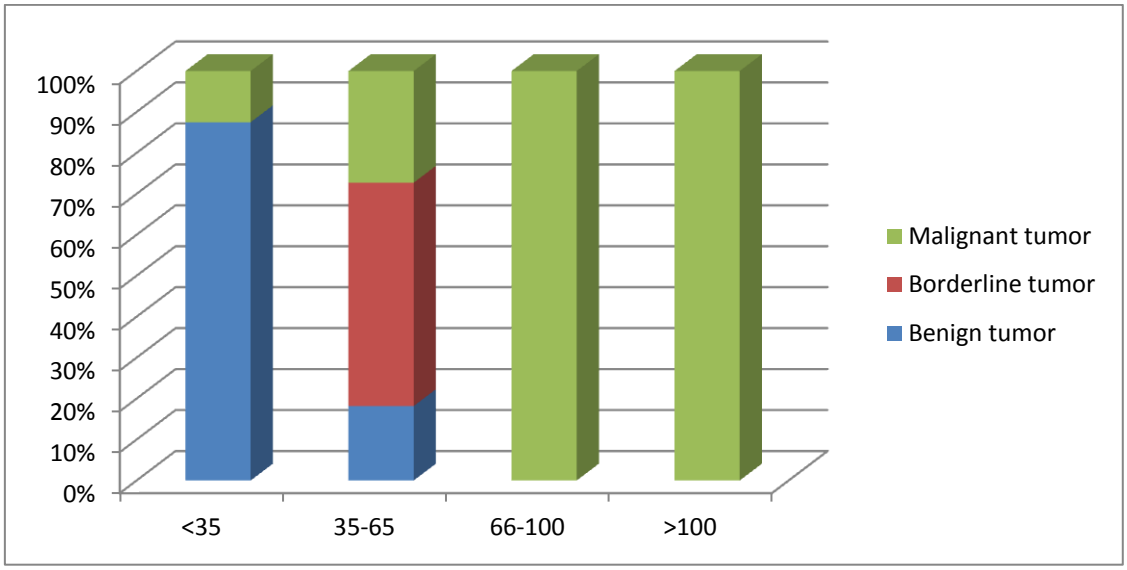
For measurement of serum CA 125, after a four-hour fast patients' sera were used as biological samples, with no hemolysis, collected in red-top tubes, minimum volume: 2 ml, without anticoagulant, centrifuged, refrigerated and sent to laboratory, where 0.5 ml was added to cuvettes for the use of chemiluminescence in an immunology system. The method is based on the detection of light emitted by a chemical reaction between the glycoprotein antigen molecule and the chemiluminescent substrate, that is, the emission of visible light is proportional to the investigated reagent.

Result and Analysis

For the present study 60 cases of ovarian tumor were selected. Among the study population 49 cases were in premenopausal age group and 11 cases were in postmenopausal age group.After histopathological examination it was confirmed that 37 (61.6%) cases were suffering from benign ovarian tumor. 6 (10%) cases were suffering from borderline ovarian tumor and 17 (28.3%) cases from malignant ovarian tumor.

Table -1 Value of CA125 level in different type of tumor (Benign/Borderline/Malignant)

Value of CA125 in U/ml	<35	35-65	66-100	>100	Significance
Benign tumor(37)	5	2	0	0	P value is <0.001 significant
Borderline tumor(6)	0	6	0	0	
Malignant tumor(17)	5	3	2	7	



Bar diagram shows distribution of different ovarian tumor in relation with different CA-125 level

In the present study majority of patients with benign tumor (35/37, 94.59%) have their serum CA125 value <35 U/ml and majority of patients with borderline & malignant tumors (18/23, 78.2%) have their serum CA125 value >35 U/ml. Again 7/17 (41.17%) of patients with malignant tumor have their serum CA125 value > 100 U/ml. 100% of patient with borderline tumors have their serum CA125 value in between 35-65 U/ml.

The finding had a significant statistical association of serum CA125 value among benign, borderline & malignant ovarian tumors, more the malignant potentiality of the tumor have higher value of serum CA-125.

Table-2 Value of CA125 level in different type of benign tumor (Epithelial/Non-epithelial)

Value of CA125 in U/ml	<35	35-65	66-100	>100	P value
Benign epithelial tumor	17	1	0	0	0.5-0.1 (not-significant)
Benign non-epithelial tumor	18	1	0	0	

Table-3 Value of CA125 level in different type of borderline/malignant tumor (Epithelial/Non-epithelial)

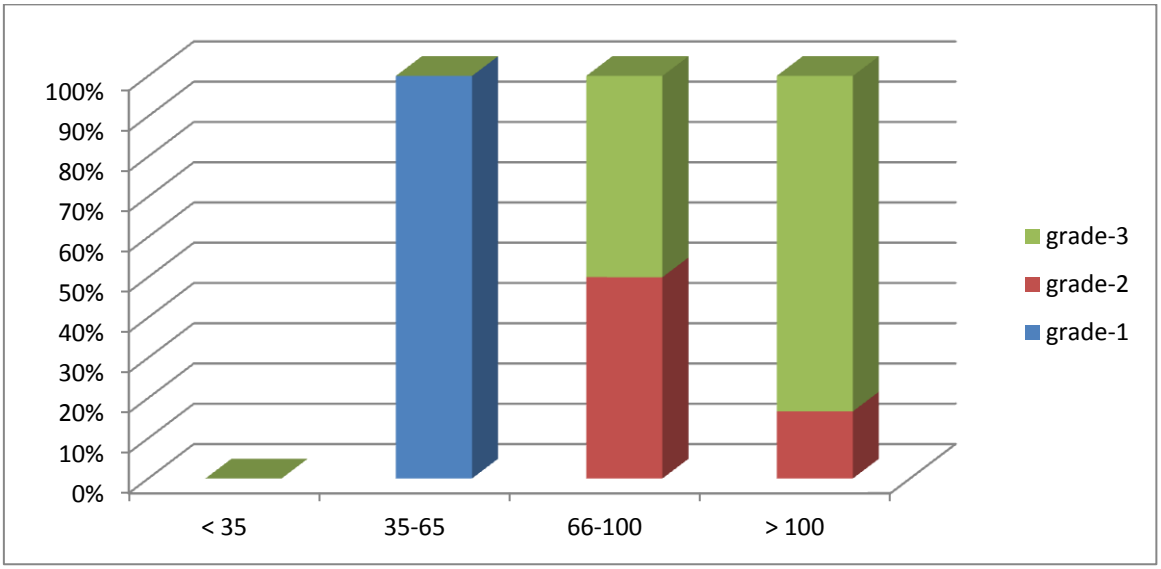
Value of CA125 in U/ml	< 35	35-65	66-100	>100	P value
Borderline/malignant epithelial tumor	0	6	2	7	<0.05 significant
Borderline/malignant non epithelial tumor	5	3	0	0	

100% of the patients having borderline/malignant epithelial ovarian tumors had their serum CA125 value >35 U/ml and 46.6% (7/15) of them had value >100 U/ml . On the other hand 62.5% (5/8) of the patient having non epithelial borderline

/malignant tumor had their serum CA125 value <35 U/ml and none of them had value >65 U/ml. The result suggests that serum CA125 level is highly elevated in cases of borderline/ malignant epithelial tumors but not in cases of other malignant varieties. The finding is statistically significant; thereby serum CA125 value is significantly high in epithelial borderline/malignant tumor than their non –epithelial counterpart.

Table -4 Value of CA-125 in different grade of tumor

Value of CA125 in U/ml	<35	35-65	66-100	>100	p value
Grade- I(6)	0	6	0	0	<0.001
Grade- II(2)	0	0	1	1	significant
Grade-III(7)	0	0	1	6	



Bar diagram shows distribution of different grades borderline and malignant of ovarian tumor in relation with different CA-125 level

The present study revealed that 100% of the patient having epithelial borderline/malignant tumors of grade I had their serum CA125 values within 35-65 U/ml. (6/7,85.7%) of patients having epithelial borderline/ malignant tumor of grade III had their serum CA125 values >100 U/ml. So the result suggests higher the grade of epithelial malignant ovarian tumor greater is the level of serum CA125.

Table -5 Mean values of CA125 in different benign tumor

Histopathological types of Benign tumor	Mean value of CA125
Serous cystadenoma	11.127
Mature teratoma	13.139
Mucinous cystadenoma	27.48
Fibroma	26.65
Mixed epithelial tumor	22.83
Brenner	12.22

Table -6 Mean values of CA125 in different Borderline/ malignant tumor tumor

Histopathological types of Borderline/ malignant tumor	Mean value of CA125
Borderline mucinous cystadenoma	53.8175
Mixed germ cell tumor	18.41
Immature teratoma	56.145
Borderline serous cystadenoma	54.075
Mucinous cystadenocarcinoma	299.773
Serous cystadenocarcinoma	339.103
Dysgerminoma	19.225
Yolk sac tumor	47.15

While considering different histopathological variety of tumor,all benign ovarian tumor, Dysgerminoma and Mixed germ cell tumor have mean serum CA-125 value below 35 IU. Other borderline/ malignant tumor including Borderline mucinous cystadenoma, Immature teratoma, Borderline serous cystadenoma, Yolk sac tumor had mean serum CA-125 value within 35-65 IU. The interesting finding was that epithelial malignant tumor including Mucinous cystadenocarcinoma ,Serous cystadenocarcinoma had their mean value more than 100 IU.

Discussion

Despite the development of new treatments and therapies designed to improve the five year survival rate, ovarian cancer still remains the deadliest cancer of the female reproductive tract. Five-year survival rate is 90% when disease is confined to the ovaries but overall survival is poor because only 25% of cases are found in this early stage. Unfortunately, most cases are diagnosed in the late stages of the disease, when the five-year survival rates fall below 20%, with most patients having metastatic disease at presentation. This further contributes to worsening the prognosis. The lack of precise early warning signs is one of the factors that further contribute to the fact that

only 25% of ovarian tumors are identified at stage I [15].

In the present study majority of patients with benign tumor (94.59%) have their serum CA125 value <35 U/ml and majority of patients with borderline & malignant tumors (78.2%) have their serum CA125 value >35 U/ml. While comparing the value of serum CA125 in between benign epithelial & non epithelial ovarian tumors, it was noted that values of serum CA125 of majority of patients with epithelial (94.4%) & non epithelial (94.73%) ovarian tumors are <35 U/ml.Again (41.17%) of patients with malignant tumor have their serum CA125 values > 100 U/ml. 100% of patient with borderline tumors have their serum CA125 value in between 35-65 U/ml.The finding had a significant statistical relation,as the malignant potentiality increases value of Serum CA-125 also go up.

100% of the patients having borderline/malignant epithelial ovarian tumors had their serum CA125 value >35 U/ml and (46.6%) of them had value >100 U/ml. on the other hand (62.5%) of the patient having non epithelial malignant tumor had their serum CA125 value <35 U/ml and none of them had value >65 U/ml. The result suggests that serum CA125 level is highly elevated in cases of borderline/ malignant epithelial tumors but not in cases of other malignant varieties. Thereby Duffy *et al*. describe that CA 125 measurement must be employed in postmenopausal patients, for its serum concentration is associated with the distinction between benign and malignant tumor processes, although it is not related to diseases in initial stage or restricted to the ovary[12]

Eduardo Cambruzzi et al [16] described a significant association between serum levels of tumor marker CA 125 and the degree of differentiation in malignant ovarian neoplasms with epithelial differentiation, suggesting that high levels of serum CA-125 are associated not only with malignant neoplasms, but also with lesions with more aggressive biological behavior. n. osman et al [17] did not found Preoperative CA125 level with stage, tumor grade or OS (p=0.08. p=0.113 and p=0.847 respectively) a strong correlation was seen however between postoperative CA125 level (recorded prior to commencement of chemotherapy) and stage, tumor grade and OS (p<0.0001, p<0.0001 and p<0.01respectively) Rosai described that the histologic grade and the disease stage are associated with serum CA 125 levels and the disease-free survival rate [18].

Our study did not show any association in benign tumor with CA-125, However we found strong association between grading and level of CA-125 in borderline/malignant tumor, indicated by increment of CA-125 value with higher grade of tumor. Sellva Paramasivam et al [19] found CA-125 levels more than 30 U/mL were associated with higher grade, sub stage 1B and 1C, nonmucinous histological type, and older age. Igor But et al [20] found tumor grade bears a strong influence on the preoperative CA 125 level; the correlation is high and statistically significant (r= 0.74,P< 0.01). The influence of FIGO stage on preoperative CA 125 level is also significant (r= 0.51,P< 0.01), but the results of the multivariate analysis show that the influence of tumor grade on

preoperative CA 125 level is stronger ($P< 0.01$). Another finding of our study was two malignant epithelial tumor, Mucinous cystadenocarcinoma and Serous cystadenocarcinoma showed disproportionate higher value of CA-125 in comparrision to other malignant tumor. Alonso et al. [21] cite that serum CA 125 values in cases of serous ovarian cystadenoma may be so high as those found in malignant tumors of this anatomic site. Kolwijck *et al*. describe that the pre-operative serum CA 125 levels are significantly higher in advanced lesions and in serous tumors ($p < 0,001$) [13]

Conclusion

Patients with benign ovarian tumors had their serum CA125 level <35U/ml, like that of normal healthy women. Patient with borderline/malignant epithelial tumor had higher pre-operative serum CA125 value (>35U/ml).CA125 had ascending relation with higher grade of tumor. With very high value of serum CA 125, one should think about serous or mucinous epithelial ovarian tumor.

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