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Bio functional evaluation of CA 125 levels as a non invasive diagnostic and prognostic marker in ovarian tumors

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Abstract
Introduction: CA 125, a 200 kilo-Dalton glycoprotein has been advocated as a prognostic marker in epithelial ovarian cancers and its role as a screening tool, particularly in cases of familial ovarian cancers is being evaluated. Since its development, measurement of serum level of CA125 antigen has become a standard component of routine management of women with advanced ovarian cancer and levels less than 35 U/mL are now accepted as normal.
Objective: To assess the diagnostic and prognostic significance of serum CA 125 levels by correlating the pre-operative levels with the histological type, biological behaviour and post-operative levels.
Material and methods: 60 cases of ovarian tumors diagnosed between July 2012 to June 2014 were studied to evaluate the association of pre-operative CA 125 levels with age, presenting symptoms, histological grade, presence of necrosis, capsular breach, ascites and extra-ovarian extension. The post-operative CA 125 levels were followed up in cases of malignant ovarian tumors to note its prognostic significance.
Results: Epithelial tumors were the most common ovarian tumors and were associated with elevated levels of CA125 which correlated with their grade, presence of necrosis, capsular breach, extra-ovarian extension and ascites. The significant elevation and association of CA125 levels with the known prognostic markers along with the post operative reduction, supports its prognostic significance in cases of epithelial ovarian tumors.
Conclusion: CA 125 levels are non invasive, diagnostic and prognostic serum markers in epithelial ovarian tumors.

Keywords: Ovarian carcinoma, CA 125, prognostic marker, histological type, histological grade

1. Introduction
CA 125, a 200 kilo-Dalton cell membrane glycoprotein recognized by the murine monoclonal antibody was first discovered by Bast and colleagues in 1981 and is considered to have extensive utility as a diagnostic and prognostic marker in epithelial ovarian carcinomas [1]. Though it is expressed by a variety of epithelial cells, and is present in the circulation of patients with a variety of cancers, the levels are more relevant with ovarian cancers. Since its development, measurement of serum level of CA125 antigen has become a standard component of routine management of women with ovarian cancer [1]. CA125 levels of less than 35 U/mL are now accepted as normal [2]. Approximately one-half of the patients who have localized (Stage 1) ovarian cancer and 90% of patients with advanced disease (Stages 2–4) have increased serum concentrations of CA 125 [3].
Several studies have evaluated CA125 as a potential screening tool to assess its feasibility, sensitivity and specificity. [4] The level of CA125 taken in conjunction with pelvic ultrasound and menopausal status may help to distinguish benign from malignant disease [5]. Its role as a prognostic marker in epithelial ovarian cancers and as a screening tool, particularly in cases of familial ovarian cancers is being evaluated and has shown extensive utility. The levels also correlate well with response and can be used to define relapse [6].
The aim of the present study was to assess the diagnostic and prognostic value of serum CA 125 levels by associating the pre-operative levels with the clinic pathological parameters including the histological type of tumor, the biological behaviour and the known prognostic factors like the age of the patient, histological grade, capsular breach, necrosis and extra-ovarian extension. Pre-operative CA 125 levels were also compared with post-operative levels in malignant ovarian tumors to note its significance.

2. Materials and methods
A total of 60 cases with a histopathological diagnosis of ovarian neoplasm, over a period of 24 months, from July 2012 to June 2014 have been included in the present study. A brief clinical history with age, presenting symptoms and signs were noted. Blood samples were collected in plain vacutainers pre-operatively from all patients with ovarian tumors and post-operatively in patients with malignant ovarian tumors. CA 125 levels were recorded by chemiluminescence method using a Siemens hormone analyzer.
Post operatively the salient gross features such as size of the tumor, presence of solid areas, necrosis, capsular breach and extra-ovarian extension were noted and further the specimens were routinely fixed in 10 per cent formalin, embedded in paraffin and sections were stained with haematoxylin and eosin (H & E) for study of microscopic details. The epithelial tumors were graded based on MD Anderson Cancer Centre Grading System. The pre-operative serum CA 125 levels were associated with clinical and morphological variables to note its significance as a

prognostic marker.

3. Results

Distribution of ovarian tumors

Majority of the tumors were epithelial (75 %) while there were 13 % germ cell tumors and 12 % sex cord stromal tumors.[Fig: 1] Majority (66.6 %) of the epithelial tumors were benign and among them, the most common was serous cystadenoma (70%) while others included mucinous cystadenoma (27 %) and mixed epithelial tumor (3%). Malignant epithelial tumor constituted 28.8 % of epithelial tumors and included serous cyst adenocarcinoma (38%), mucinous cyst adenocarcinoma (31%), poorly differentiated carcinoma (15%), clear cell carcinoma (8 %) and transitional cell carcinoma (8%). Borderline tumors formed 4.4 % of epithelial tumors and included one case each of serous and mucinous tumors. Of the germ cell tumors, majority were benign cystic teratomas (89%) while there was a single case of malignant mixed germ cell tumor. Of the sex cord stromal tumors, majority were malignant and included granulosa cell tumors and there was a single case of fibroma that accounted for the benign counterpart.

The serum CA 125 levels were significantly increased in epithelial tumors with the mean value being 101U/ml, while the mean levels were much lower being 18U/ml in both sex cord stromal tumors and germ cell tumors.

Distribution of ovarian tumors based on biological behaviour and their association with CA125 levels: Majority of the ovarian tumors were benign (63.3%), while the malignant tumors formed 33.3% and borderline tumors constituted 4.4 %.[Fig:2]

Correlating the serum CA 125 levels with the biological behaviour of ovarian tumors, a linear increase was noted as the biological behaviour moved through the spectrum of benign to malignant with borderline cases lying intermediate between the two. The mean CA 125 levels in malignant and borderline epithelial tumors were 206.55U/ml and 106.5U/ml respectively while the levels were much lower in benign tumors being 13U/ml. [Fig: 3]

Grading of epithelial tumors and their association with CA125 levels: The epithelial tumors were histologically graded based on MD Anderson Cancer Centre Grading System which is a two-tier grading system. Tumors with high degree of nuclear atypia and > 12 mitotic figures /10 high per field (HPF) were graded as high-grade tumors while tumors with mild to moderate degree of nuclear atypia and mitotic figures < 12/ HPF were grouped as low grade tumors. Based on this system, it was seen that 76% of the epithelial tumors were of low grade and the remaining 24 % were of high grade. A significant association was noted between the serum CA 125 and the grade of epithelial tumors. The mean CA 125 level in low grade tumors was 22.25U/ml while it was 319.6 U/ml in cases of high grade tumors. [Table: 1]

CA 125 levels in non epithelial ovarian tumors: Of the 15 cases of non-epithelial ovarian tumors, only one case of granulosa cell tumor and the only case of malignant mixed germ cell tumor had elevated CA 125 levels.[Table : 2]

Association of CA125 levels with age: A higher number of ovarian tumors were seen in patients above 45 years of age. The mean CA 125 levels were higher in this age group of patients (108.79 U/ml) compared to patients < 45 years of age. However, no statistical association was found between age, biological behaviour and CA 125 levels. [Table: 3]

Association of CA125 levels with menstrual disturbances: Of the 60 cases, 12 cases presented with menorrhagia. Granulosa cell tumor was most frequently associated with menstrual disturbances (4/7 cases). Statistically there was no significant association between CA 125 levels and menstrual disturbances. [Table-4])

Association of ca 125 with known prognostic factors: A significant association was found between serum CA 125 levels and presence of necrosis, capsular breach, extraovarian extension and ascites. [Table: 5]

Necrosis: Out of the 14 tumors that showed necrosis, 10 were high grade malignant epithelial tumors and the remaining 4 cases were malignant non epithelial tumors. The mean CA 125 level of these tumors with necrosis was 274.14 U/ml while the remaining tumors without necrosis had a much lower mean CA 125 level of 21.68U/ml.

Capsular breach: 9/11 high grade tumors showed invasion of tunica albuginea. The mean CA 125 level of tumors with capsular breach was found to be 342.24 U/ml while tumors with intact capsules had a much lower mean CA 125 level of 21.84 U/ml

Extraovarian extension: 6/11 high grade tumors showed extraovarian extension. Tumors deposits were seen in the omental fat in 4 cases while the external surface of uterus showed nodular tumor deposits in 2 cases.The mean CA 125 levels in tumors with extraovarian extension was 374.5 U/ml while the mean CA 125 levels in tumors without extraovarian extension was 41.67 U/ml.

Ascites: 8 cases of high grade epithelial tumors and the only case of malignant mixed germ cell tumor presented with ascites. The mean CA 125 level in tumors with ascites was 362.42 U/ml and was significantly higher than the mean CA 125 levels in the remaining tumors without ascites which was found to be 30.85 U/ml.

Correlation of pre-operative and post operative levels of CA 125 levels: The post-operative serum CA125 levels were noted in the 20 malignant ovarian tumors and the 2 borderline epithelial tumors.There was a significant reduction in CA 125 levels post-operatively (p value <0.01). The mean pre-operative levels were 207.6U/ml and mean post –operative values were found to be 134.5U/ml. Thus a mean reduction of 73.1U/ml (35.1 %) was noted. [Fig: 4]

Table 1

Histological Grade	number of Cases	Mean CA 125 (U/ml)	STD. Deviation	Std. Error Mean	P Value
Low	34	22.258	40.93121	6.82187	**< 0.01**
High	11	319.60	225.95985	65.22899	

Table 2

Tumor Category	Number	Mean CA 125 Levels	CA 125 (>35 U/ML)
Sex Cord Stromal tumors			
Granulosa Cell tumor	06	11.5 (n = 5)	56 (n=1)
fibroma	01	12.5	
germ Cell tumors			
Mature Cystic Teratoma	07	13	
malignant Mixed germ cell tumor	01		48.6 (n =1)

Table 3: Association of ca 125 with age

Age	Number	CA 125 Mean	CA 125 std deviation	Std Error Mean	P Value
< 45	22	31.86	50.77	10.823	0.84
>45	38	108.79	190.52	30.91	

Table 4: Association of ca 125 with menstrual disturbances

Menstrual Disturbances	NO.	Ca 125 Mean (U/ml)	Std. Deviation	Std. Error Mean	P value
YES	12	19.52	17.05	4.923	0.137
NO	48	95.85	173.844	25.092	

Table 5: Association of CA 125 with prognostic factors

Variable	No.with positive findings	Mean CA 125 levels in positive cases (U/ml)	Mean CA 125 levels in Cases without positive findings	P value
Capsular breach	11	342.24	21.84	< 0.01
Necrosis	14	274.14	21.68	< 0.01
Extraovarian extension	6	374.51	41.76	< 0.01
Ascites	9	362.42	30.85	< 0.01

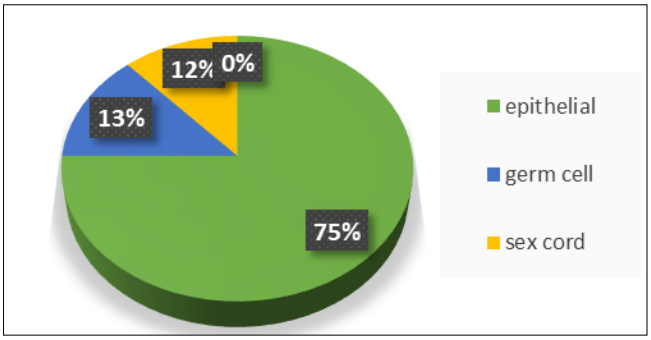

Fig 1: Distribution of ovarian tumors

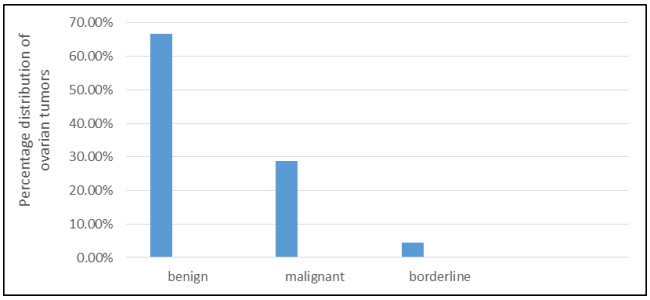

Fig 2: Distribution of epithelial tumors

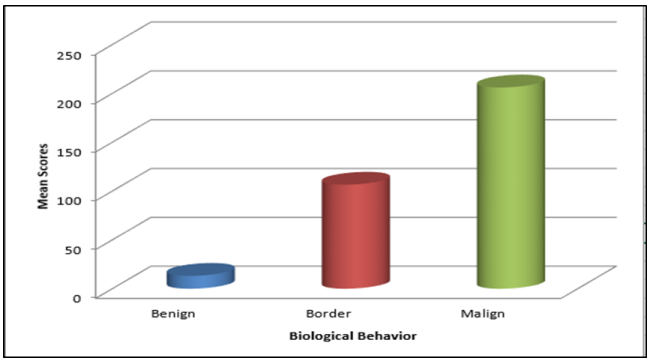

Fig 3: Association of ca 125 levels with biological behaviour of ovarian tumors

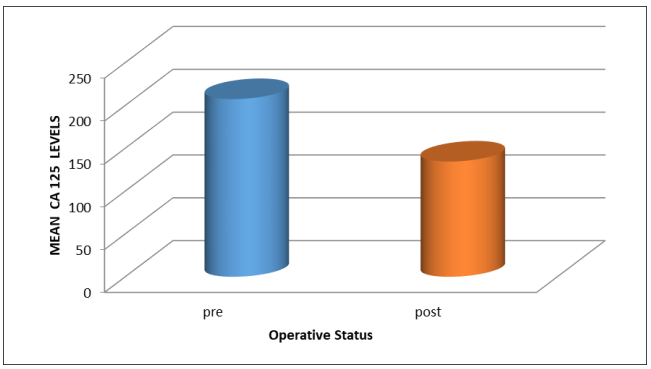

Fig 4: Association of pre-operative ca 125 levels with post-operative levels

4. Discussion

Ovarian neoplasm exhibit great diversity in terms of histogenesis, clinical behaviour and malignant potential and thus necessitates a detail evaluation of clinical behaviour and the various prognostic markers. CA 125 is one of the most useful prognostic markers that helps to note the disease progression, individualize treatment within subgroups of patients and are used to monitor responses to chemotherapy and or relapse.

Epithelial ovarian tumors were the most common ovarian tumors and they constituted 75 % in the present study, this is close to the observations of 77% by Badge *et al.*, while Sarkar *et al.* (66.8%), Sethi *et al.* (60%) and Gupta *et al.* (54.7%) have noted a slightly lower percentages. [7, 8, 9, 10] Among the epithelial tumors, benign tumors were more common and serous cystadenoma and serous cyst adenocarcinomas were the most common benign and malignant epithelial tumors. These findings are similar to that of Badge *et al.*, Kanthikar *et al.* and Cruikshank *et al.* [7, 11, 12]

Age and CA125 levels

In the present study 17 cases had significant elevation of CA125 levels (> 30 u/ml), of these 64.7 % of cases were

above 45 years while 35.2 % of cases were below 45 years of age. These results are in comparison to the findings of Paramsivam *et al.* who have noted that 61.7 % of cases with elevated CA 125 (> 30 U/ml) were above 50 years while the rest (38.3%) were below 50 years of age. However, no significant association was found between age and CA 125 levels in both the studies. [13]

CA 125 levels in epithelial tumors

Hogdall *et al.* has stated that CA125 is a serum marker, reported to be elevated in more than 80% of epithelial ovarian tumors. [14] Substantiating the above statement in the present study the mean CA 125 levels in epithelial tumors was 101 U/ml while it was 18U/ml in both sex cord and germ cell tumors.

Among the malignant epithelial tumors, the highest levels of CA 125 were seen with serous cystadenocarcinomas, with the mean CA 125 levels being 407.6 U/ml, while the lowest value was found in mucinous cystadenocarcinomas (57.1 U/ml). Cruikshank *et al.* has found highest levels of CA125 in serous cystadenocarcinomas, with the mean CA 125 levels being 616 U/ml and lowest values in clear cell carcinoma, with the mean value being 116 U/ml. [12] [Table: 6]

CA 125 levels in non-epithelial tumors

CA 125 levels are generally not elevated in non epithelial tumors, however in the present study the values were elevated in one case of granulosa cell tumor and the only case of malignant mixed germ cell tumor. Cruikshank *et al.* have also noted elevated values in two cases of sex cord stromal tumors (mean values being 195 U/ml) and one case of sarcoma (CA 125 level 122 U/ml) [12].

Association of CA125 levels with grading and staging of epithelial tumors

The importance of FIGO stage and residual disease status as prognostic factors in ovarian carcinoma is universally accepted. However the significance of histological grade as a prognostic indicator has been questioned with several studies having shown it as an important factor while others have failed to do so. Major contributing factor to this controversy is the absence of a uniform grading system for these tumors. Current grading systems typically analyze architectural pattern, nuclear/cytological atypia, mitotic index or a combination of these features [15].

Malpica *et al.* on comparing the two tier grading system of MD Anderson Cancer Centre Grading system (MDACC) with the three tier-grading system of Shimizu Silverberg grading system, have found that the MDACC grading which incorporated two well defined criteria, easier to follow and provided better reproducibility [15]. The prognostic utility of the MDACC grading system was also statistically supported in the study by Malpica and was the choice in the present study [15].

A significant association was noted between the serum CA 125 and the grade of epithelial tumors. The serum levels of CA125 increased with increasing grade of tumor, as was noted by Nagele F *et al.* and Paramasivam *et al.* [13, 16] Cooper *et al.* have also recorded similar results with grade 3 tumors having a mean Ca125 levels of 928 U/ml while the grade 1 -2 tumors had a significant lower CA 125 level of 323 U/ml [17]. Tamakoshi *et al.*, Gotlieb *et al.* and Ayhan *et al.* have reported that majority of advanced stage lesions have CA 125 levels > 35 U/ml [18, 19, 20] [Table: 7].

Association of ca 125 with known prognostic factors

A significant positive association was found in the present study between the pre-operative CA 125 levels and presence of capsular breach and extra-ovarian extension and ascitis. These findings are consistent with the findings of Cambruzzi *et al.* wherein the CA 125 levels were correlated with degree of differentiation, invasion of tunica albuginea with invasion of pelvic structures [Table: 8] and those of Cooper *et al.* who has noted a significant elevation of CA125 levels in cases associated with ascites.[17, 21] Petri *et al.* and Geisler JP have stated that high preoperative serum levels of CA125 predict decreased length of survival and Nagele *et al.* have commended it as the most powerful prognostic factor for survival [16, 22, 23]. [Table: 9]

Table 6: Comparative studies on ca 125 levels in malignant epithelial tumors

Histological type of malignant epithelial ovarian tumors	Mean Ca 125 Levels (U/ ml)	
	Study by Cruikshank *et al.* [15]	Present study
Serous	616	407.6
Mucinous	211	57.1
Endometrioid	243	-
Clear cell	116	300
Transitional	-	350
Undifferentiated	530	246.2

Table 7: Various studies associating ca 125 with tumor stage

Reference	No.of patients	Stage 1 >35u/ML	Stage II/ III/ IV >35 U/ml	Total >35U/ ml
Tamakoshi *et al.* [21]	93	41/73(56%)	14/20(70%)	55/93 (59%)
Gotlieb *et al.* [22]	54	19/36 (53%)	11/13 (85%)	30/49 (61%)
Ayhan *et al*, [23]	60	20/50 (40%)	9/10 (90%)	29/60 (48%)

Table 8: Studies comparing ca 125 levels with capsular breach and extraovarian extension

1)Invasion of tunica Albuginea	Study By Cambruzzi *et al.* [20]		Present Study	
	%	P value	%	P value
Present	28.6%	< 0.01	18.3	< 0.01
Absent	71.4 %		81.6	
2) Invasion of pelvic structures /peritoneal implants				
Present	14.3 %	< 0.01	10	< 0.01
Absent	85.7 %		90	

Table 9: Studies denoting prognostic significance of pre-operative ca 125 levels

Author	*Result*	*Variables Adjusted For*
1)Cooper [18]	Significant association of CA 125 levels and Disease specific survival	Age, histology FIGO stage, ascites and optimal cytoreduction
2)Petri [24]	Patients with stage 1 EOC and pre-operative CA 125 levels <65U/ml had a significantly longer survival compared to those with serum CA 125 levels >65U/ml	Age, histology, FIGO, substage, grade, chemotherapy
3) Geisler JP [6]	In epithelial ovarian carcinoma, high preoperative serum levels of CA125 predict decreased length of survival	Histology FIGO substage, grade
4) Nagele F, [8]	Preoperative CA125 was the most powerful prognostic factor for survival	Age, FIGO substage, grade

5. Conclusion

Pre-operative CA 125 levels were significantly raised in advanced and histologically high grade malignant epithelial tumors which had features of capsular breach, necrosis, extra-ovarian extension and ascites. There was also a significant reduction in the post-operative levels, thus signifying CA 125 levels as non invasive, diagnostic and prognostic serum markers in epithelial ovarian tumors.

Ethical approval: The study has been approved by the institutional research ethics committee and has been performed in accordance to the ethical standards.

Conflict of interest: "We declare that we have no conflict of interest"

6. References

1. Bast R, Feeney M, Lazarus H, Nadler L, Coloin R, Knapp R. Reactivity of a monoclonal antibody with human ovarian carcinoma. J Clin Invest. 1981; 68:1331-7.
2. Bast R, Klug T, St John E, Jenison E, Niloff JM, Lazarus H, *et al.* A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med. 1983; 309:169-71.
3. Nustad K, Bast RC, Obrien T, Nilszson O, Seguin P, Suresh M, *et al.* Specificity and affinity of 26 monoclonal antibodies against the CA 125antigen: first report from the ISOBM TD-1 workshop. Tumor Biol. 1996; 17:176-219.
4. Meyer T, Rustin GJS. Role of tumour markers in monitoring epithelial ovarian cancer. British Journal of Cancer. 2000; 82:1535-38.
5. Eagle K, Ledermann J. Tumor Markers in Ovarian Malignancies. The Oncologist. 1997; 2:324-29.
6. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas J. A risk of malignancy index incorporating CA125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol. 1990; 97:922-29.
7. Badge S, Gosavi A, Sullhya K. Histopathological study of ovarian tumors. Indian Medical Gazette. 2013; 32:345-51.
8. Sarkar R. Ovarian neoplasms – A 14 years study. J Obstet Gynecol India. 1996; 46:156-160.
9. Sethi D, Ahluvalia C, Sharma U, Khetarpal S. A synchronous presentation of two different ovarian tumors: A rare occurrence. Ann Med Health Sci Res. 2013; 3(2):268-70.
10. Gupta S, Singh P, Mehrotra T, *et al.* A Clinicopathologic study of ovarian tumors. Ind J Pathol Microbiol. 1986; 29:354-62.
11. Kanthikar SN, Dravid NV, Deore PN, Nikumbh DB, Suryavanshi K. Clinicohistopathological analysis of neoplastic and non-neoplastic lesions of the ovary- A3 year prospective study in Dhule, North Maharashtra, India. Journal of Clinical and Diagnostic Research. 2014; 8(8):04-07.
12. Cruikshank, Fullerton, Klopper. The clinical significance of Pre-operative CA 125 in ovarian cancer. British Journal of Obstetrics and Gynaecology. 1997; 94:692-95.
13. Paramasivam, Tripcony, Crandon, *et al.* Prognostic importance of pre-operative CA125 in International Federation of Gynaecology and obstetrics Stage 1 epithelial cancer: An australian multicentre study. J Clin Oncol. 2005; 23: 5938-42.
14. Hogdall CK, Mogensen O, Tabor A, Mogensen B, Jakobsen AK, NorgaardPedersen B, *et al.* The role of serum tetranectin, CA 125, and a combinedindex as tumor markers in women with pelvic tumors. Gynecol Oncol. 1995; 56:22-8.
15. Malpica A, Deavers MT, Lu K, *et al.* Grading ovarian serous carcinoma using a two-tier system. Am J Surg Pathol. 2004; 28:496-504.
16. Nagele F, Petru E, Medl M, Kainz C, Graf AH, Sevelda P: Preoperative CA. An independent prognostic factor in patients with stage I epithelial ovarian cancer. Obstet Gynecol. 1995; 86:259-64.
17. Cooper BC, Sood AK, Davis CS, Ritchie JM, Sorosky JI, Anderson B, Buller RE. Preoperative CA 125 levels: an independent prognostic factor for epithelial ovarian cancer. Obstet Gynecol. 2002; 100:59-64.
18. Tamakoshi K, Kikkawa F, Shibata K, *et al.* Clinical value of CA125, CA19-9, CEA, CA72-4, and TPA in borderline ovarian tumor. Gynecol Oncol. 1996; 62:67-72.
19. Gotlieb WH, Soriano D, Achiron R, *et al.* CA 125 measurement and ultrasonography in borderline tumors of the ovary. Am J Obstet Gynecol. 2000; 183:541-46.
20. Ayhan A, Guven S, Guven ES, *et al.* Is there a correlation between tumor marker panel and tumor size and histopathology in well stagedpatients with borderline ovarian tumors? Acta Obstet Gynecol Scand. 2007; 86:484-90.
21. Cambruzzi1 E, Rosane de Lima. Simone Luís Teixeira, Karla Lais Pêgas. The relationship between serum levels of CA 125 and the degree of differentiation in ovarian neoplasms. Bras Pathol Med Lab. 2014; 50:20-25.
22. Petri AL, Hogdall E, Christensen IJ, Kjaer SK, Blaakaer J, Hogdall CK. Preoperative CA125 as a prognostic factor in stage I epithelialovarian cancer. APMIS. 2006; 114:359-63.
23. Geisler JP, Miller GA, Lee TH, Harwood RM, Wiemann MC, Geisler HE. Relationship of preoperative serum CA-125 to survival in epithelial ovarian carcinoma. J Reprod Med. 1996; 41:140-142.