



Original Article

Evaluation of surface epithelial ovarian tumors and its correlation with preoperative serum CA125 levels in a tertiary care centre

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Abstract

Introduction: Ovarian cancer is ranked third most frequent female cancer in India. The incidence varies between 2.2 to 7.8 per lakh population in various parts of India and there is steady increase in age standardized incidence rate of ovarian carcinoma.¹ The present study was aimed to evaluate the histomorphology of epithelial ovarian tumors and to find the relationship between serum CA-125 levels with histopathology and staging of these neoplasms.

Material & Methods: 105 cases of surface epithelial ovarian tumors were evaluated over a period of one year from July 2018 to June 2019 in the Department of Pathology I.G.M.C Shimla. Preoperative serum CA125 levels were noted. Malignant tumors were staged using FIGO staging.

Results: Serous tumors were the most common tumors reported in the study constituting 67 cases (63.8%). Benign tumors (64.76%) comprised the major group followed by malignant tumors (29.52%) and borderline tumors (5.7%). Serum CA125 concentration in benign, borderline and malignant tumors were compared and statistically significant difference was found ($p=0.000$). CA125 showed positive correlation with the stage ($p=0.024$) of ovarian cancer. However no significant correlation was found between subtype of benign, borderline and malignant tumors with serum CA125 levels.

Conclusion: Patients with borderline /malignant epithelial tumors had higher preoperative serum CA125 value as compared to benign ovarian tumors.

Keywords: surface epithelial ovarian tumors, serum CA125, age distribution, FIGO staging.

Introduction

Ovarian cancer poses a great challenge to the healthcare system as it accounts for the significant number of deaths from the malignancies of female genital tract. According to the national cancer registry data, it is ranked third most frequent female cancer in India following carcinoma cervix

and breast. The incidence varies between 2.2 to 7.8 per lakh population in various parts of India and there is steady increase in age standardized incidence rate of ovarian carcinoma.¹ About 80% of tumors are benign occurring in the young women between the ages of 20 to 45 years whereas borderline tumors occurs in slightly

older age group. Incidence of malignant tumors increase with age, occurring predominantly in premenopausal and peri-menopausal women.

Cancer Antigen-125 (CA125) is the most frequently used biomarker for ovarian cancer detection. Its level increases in about 90% of the women with advanced ovarian epithelial tumors and in 50% of patients in the early stages particularly in tumors of serous nature. Response to the treatment and prognosis can also be determined by monitoring CA 125 levels^{2,3}

Material and Methods

Present cross sectional study was conducted in department of pathology over a period of one year from July 2018 to June 2019. A total of 105 ovarian tumor samples obtained through cystectomy, oophorectomy and pan hysterectomy specimens received in the department were evaluated. Relevant clinical details were retrieved from the records. All the lesions diagnosed as surface epithelial ovarian tumors on histopathological examination with pre-operative assessment of serum CA125 levels were included in the study.

The specimens received were adequately fixed in 10 % neutral buffered formalin. Gross findings were noted and adequate representative sections were taken .The tissue sections were processed, paraffin embedded, 2-4 micron thin section were cut and stained with haematoxylin and eosin stain using standard protocol. The tumors were categorized according to WHO classification. The sensitivity, specificity and diagnostic accuracy of serum CA125 was calculated in percentage with reference to histomorphology of specimens. p value <0.05 was considered to be statistically significant.

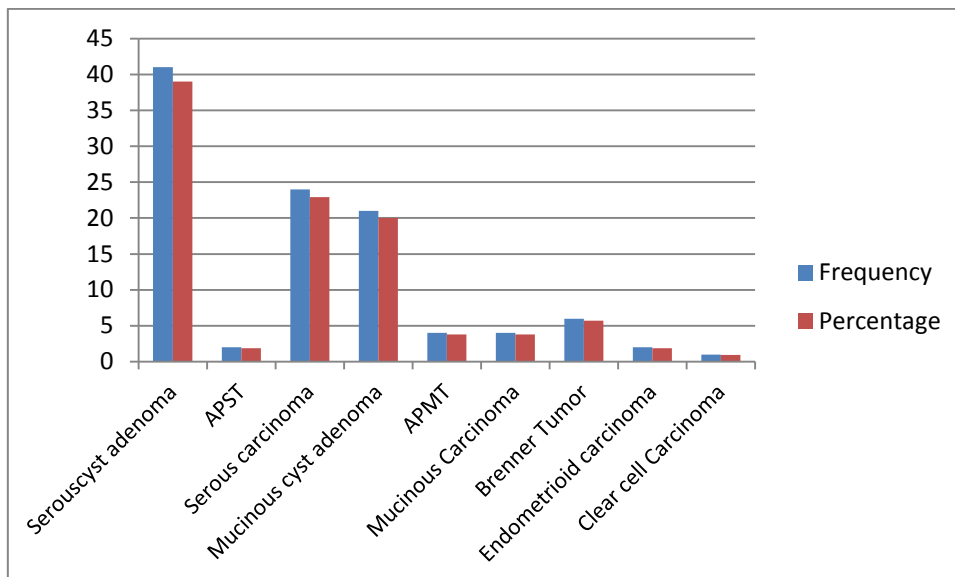
Observation and Results

Age of all patients ranged from 18-90 years, with mean age being 47.56±14.88 years. Majority of the patients i.e 57 out of 105 (44.76%) were seen in 40-60years age group.

Histological classification was performed in accordance with the WHO classification of ovarian tumors. Serous tumors were the most common tumors encountered in the study constituting 67 cases (63.8%), mucinous tumors 29 cases (27.6%), transitional cell tumor 6 cases (5.7%), endometrioid tumor 2 cases (1.9%) and clear cell carcinoma 1 case(0.9%) (**Table 1 Fig 1**)

Table 1: Spectrum of ovarian tumors (n=105)

TYPE OF TUMOR	NO. OF CASES	PERCENTAGE
SEROUS TUMORS	67	63.8
a. Benign		
Serous cyst adenoma	41	39
b. Borderline		
Atypical proliferative Serous tumors	2	1.9
c. Malignant		
Serous carcinoma	24	22.9
MUCINOUS TUMORS	29	27.6
a. Benign		
Mucinous cyst adenoma	21	20
b. Borderline		
Atypical proliferative mucinous tumor	4	3.8
c. Malignant		
Mucinous carcinoma	4	3.8
TRANSITIONAL	6	5.7
a. Benign		
Brenner	6	5.7
b. Borderline	0	0
c. Malignant	0	0
CLEAR CELL	1	0.9
a. Benign	0	0
b. Borderline	0	0
c. Malignant		
Clear cell carcinoma	1	0.9
ENDOMETRIOID	2	1.9
a. Benign	0	0
b. Borderline	0	0
c. Malignant		
Endometrioid	2	1.9
SEROMUCINOUS TUMORS	0	0
UNDIFFERENTIATED	0	0



Tumors were further categorized as benign, borderline, & malignant based on their biological behaviour. Benign tumors (64.76%) constituted the major group followed by malignant tumors (29.52%) and borderline tumors (5.7%). Mean age for Benign, Borderline and Malignant tumours were found to be 43.8, 45.5, and 56.1

years respectively. Statistically significant difference was observed between biological behaviour and age of presentation of ovarian tumors (p=0.0004). Incidence of malignant neoplasms increases as the age progresses. **Table 2**

Table 2: Age wise distribution of surface epithelial ovarian tumors (n=105)

	Total	<40 years	40-60 years	>60 years	Mean age(years)	p-value
Benign	68	27	33	8	43.8	0.0004
Borderline	6	2	3	1	45.5	
Malignant	31	1	21	9	56.1	
Total	105	30	57	18		

Serum CA125 correlation with ovarian tumors

Preoperative serum CA125 levels were recorded in all the patients. Value less than 35 U/ml were

taken as normal. 44 out of total 105 cases showed increased serum CA125 values. **Table 3**

Table 3: Distribution of serum CA 125 levels in surface epithelial ovarian tumors (n=105)

CA125 levels	<35U/ml		>35U/ml		Mean CA125 U/ml	p-value
	No of cases	%age	No of cases	%age		
Ovarian lesion						0.0000
Benign	59	86.7	9	13.2	31.2	
Borderline	2	33.3	4	66.6	110.80	
Malignant	0	0	31	100	1258.26	
Total	61		44			

Majority of benign cases, 59 (86.7%) had serum CA125 levels within normal limits. Values >35U/ml were seen in all the malignant cases with majority having markedly raised levels above 500U/ml. These cases were associated with stage III and stage IV tumors. 4 out of total 6 borderline tumors showed serum CA125 levels above

35U/ml with range varying from 45.2U/ml to 372.6U/ml.

Mean values of serum CA125 in benign (31.2U/ml), borderline (110.80U/ml) and malignant (1258.26 U/ml) tumors were compared and statistically significant association was found. (p=0.000), more the malignant potentiality of the

tumor have higher values of CA125.

Benign tumors

Serous cyst adenoma constituted the predominant group 41 (60.3%) among benign neoplasms followed by mucinous cyst adenomas 21(30.9%) and Brenner tumor 6(8.8%). Mean age of presentation in benign tumors was 43.8 years. Benign serous tumours are usually small and the mucinous tumours present as huge masses. The

smallest tumour in our study was a serous cystadenoma measuring (3x2x1) cm and the largest tumour was mucinous cystadenoma measuring (38x30x4) cm. Grossly serous cyst adenoma were predominantly unilocular cystic structures in 38 out of 41 cases. Three cases had both cystic and solid components.

In the present study majority of serous and mucinous cyst adenomas revealed normal levels of tumor marker. **TABLE 4**

Table 4: Serum CA125 in benign tumors (n=68)

Serum CA125	<35U/ml		>35U/ml	
	No of cases	Percentage	No of cases	Percentage
Ovarian tumor				
Serous cyst adenoma	34	50	7	10.1
Mucinous cyst adenoma	19	27.9	2	3
Brenner tumor	6	8.8	-	-
Total	59		9	

Only 7 cases of serous cyst adenomas and 2 cases of mucinous cyst adenoma showed CA125 value more than 35U/ml. Serum levels were found to be within normal limits in all 6 cases of Brenner tumor.

Mean Serum levels in serous cyst adenoma, mucinous cyst adenoma and Brenner tumor was 28.1U/ml, 44.3U/ml and 8.2U/ml respectively. No significant correlation was found between subtype of benign tumors and serum CA125 levels (p=0.725)

Borderline tumors

Borderline tumors accounted for 6(5.7 %) out of total 105 cases and included 4 cases of Atypical proliferative mucinous tumors (APMT) and 2 cases of Atypical proliferative serous tumors (APST).. Mean age of presentation was 45.50 years. All of these showed unilateral involvement of ovaries. Tumor size ranged between 3-20cm, cystic predominantly with focal solid areas.

4 out of 6 tumors showing borderline differentiation had serum CA125 levels above 35 U/ml with range between 45.2U/ml to 372.6U/ml. **(Table 5)**

Table 5: Distribution of preoperative serum CA 125 levels in borderline tumor (n=6)

Serum CA125	<35U/ml		>35U/ml	
	No of cases	Percentage	No of cases	Percentage
Serous(APST)	1	16.7	1	16.7
Mucinous(APMT)	1	16.7	3	49.1
Total	2		4	

In APST mean CA125 concentration was 195.5U/ml and in APMT was 68.4 U/ml. No statistically significant association was found between CA125 and subtype of borderline tumors (p=0.331).

Malignant tumors

Comprised 31 out of total 105 (29.52%) cases. Majority of malignant neoplasms were of serous

carcinoma 24(77.4%) followed by mucinous carcinoma 4(12.9%), endometrioid carcinoma 2 (6.5%) and clear cell carcinoma1(3.2%).

Most of the serous carcinomas were bilateral and had mixed solid and cystic consistency.23 out of 24 serous carcinomas were high grade tumors. Mean age of presentation of malignant tumors was 56.2 years. Majority of serous and all mucinous

carcinoma were seen in 5 th decade or later age group. Single case of clear cell carcinoma presented in 62 years of age. Oldest patient (90 years) in our study was of endometrioid carcinoma.

All the malignant neoplasms revealed raised serum levels of CA125 ranging from 69.3U/ml to 6809U/ml (**Table 6**)

Table 6: Serum CA125 in malignant surface epithelial ovarian tumors (n=31)

Serum CA125	<35U/ml		>35U/ml		Mean Serum CA125 Levels
	No of cases	percentage	No of cases	Percentage	
Ovarian tumor					
Serous carcinoma	-	-	24	77.4	1427.30
Mucinous carcinoma	-	-	4	12.9	465.2
Clear cell carcinoma	-	-	1	3.2	1804.8
Endometrioid carcinoma	-	-	2	6.5	542.6
Total			31	100	

In 15 of 24 cases (48.4%) of Serous carcinoma and in clear cell carcinoma preoperative serum CA125 levels were markedly raised above 500U/ml. No association was found between CA125 level and histologic subtype among malignant tumors (p=0.615)

Serum CA125 correlation with FIGO staging

Malignant tumors were staged according to FIGO criteria into stage I, II, III & IV. Maximum number of patients 21(67.8%) were seen in stage III and IV followed by stage I in 7 (22.5%) patients and stage II in 3(9.7%).

Mean serum CA125 concentration in Stage I, II, III, IV was 464.05, 218.13, 1397.40 and 3316.76 U/ml respectively and showed significant positive correlation with stage (p=0.024).

Discussion

Ovarian tumors are heterogenous group of neoplasms of epithelial, stromal & germ cell origin. Even in a single group of tumors inherent heterogeneity exists with biological behaviour

ranging from benign to highly aggressive malignant tumor. Cancer Antigen-125(CA125) is the most frequently used biomarker for ovarian cancer detection. It has an established role in monitoring treatment, detecting recurrence of ovarian cancer and as a prognostic marker for advanced ovarian cancer.

Most of the studies published on ovarian tumors also observed serous tumors to be the predominant group among ovarian tumors followed by mucinous type . Percent incidence of these tumors (63.8% & 27.6%) in the present study are comparable to that reported by Jha et al⁴ and Nalini⁵ et al. Endometrioid tumor and Clear cell tumor constituted 1.9 & 0.9% cases respectively in comparison to the studies conducted by Nalini⁵ & Rao NK⁶ et al. (**Table 7**)

Most of the tumors in this study showed benign morphology followed by malignant & borderline tumors correlating well with other published studies. Percent incidence of these tumors in our study was consistent with the observation by Mankar 7 et al 2015.

Table 7: Spectrum of surface epithelial ovarian tumors

	Year	No of cases	Serous tumors %age	Mucinous tumors %age	Transitional Tumors %age	Endometrioid Tumors %age	Clear cell Tumors %age
Jha et al	2008	84	67.5	32.5	-	-	-
Pradhan et al	2012	39	46.1	38.4	5.2	-	-
Nalini et al	2016	141	61.7	32.6	2.1	0.7	0.7
Rao NK et al	2017	244	55.7	38.5	1.6	2.5	0.8
Present study	2019	105	63.8	27.6	5.7	1.9	0.9

Age of the patients in present study ranged from 18-90 years, with a mean of 47.56 ± 14.88 years. This is comparable to the study conducted by Nalini⁵ et al in which the age ranged between 14 to 76 years with mean age being 42 years. Jha et al⁴ reported mean age of 53.35 years in their study of 86 patients with ovarian tumors.

Benign tumors

Total 68 benign tumors were reported in our study. 41 cases (60.3%) were of Serous cyst adenoma, 21 cases (30.9%) of mucinous cystadenoma & 6 cases (8.8%) of Brenner tumor were reported. These results were in concordance with study carried out by Nalini et al and Tiwari et al⁸. In their study of 117 cases, Nalini et al (2016) found 60.6% of serous cyst adenoma, 34.1% mucinous cyst adenoma, 2.5% Brenner tumour and 2.5% seromucinous cystadenoma. Tiwari et al⁸ (2016) also found similar results with serous cyst adenoma (61.2%) being the most common benign tumor followed by mucinous cyst adenoma (35.4%).

In the present study 86.9% of benign tumors showed serum CA125 levels within normal limits and increased in rest 13.1% cases. Elevated preoperative levels were found in 7 patients of serous cyst adenoma and 2 patients of mucinous cyst adenoma. Roy et al⁹ 2015 reported increase in Serum levels in 5.41% benign cases whereas Verma et al¹⁰ reported increase in 10% cases, similar to our study.

Borderline tumors

In this study, 6 out of a total of 105 cases were borderline tumors which included APMT 66.6% and APST 33.3% and correlated well with the studies conducted by Nalini et al and Tiwari et al. They both reported high percent incidence of APMT (57.1% & 60%). In comparison Rao NK et al showed higher percent incidence of APST (6.6%) among six study cases of borderline tumors.

APMT were more common in 40-60 years age group and was in concordance with study done by Pradhan et al¹¹ & Rao NK et al. Mean age of

presentation in BOTs was 45.50 years close to the mean age of 48.6 years reported by Tiwari et al. In present study elevated CA125 levels were observed in 1/2 (50%) case of APST and 3/4 (75%) cases of APMT. In comparison Kolwijck et al¹² found elevated serum levels of CA125 in 70% of serous borderline tumors and 34% of mucinous borderline tumors. They also stated that the preoperative serum CA125 levels are significantly higher in advanced lesions & in serous tumors.

Malignant ovarian tumors

Serous carcinoma was the most frequent (24/31, 77.4%) histological type of malignancy reported in this study. Nalini et al, Rao NK et al and Mankar et al⁷ also reported 76.47%, 81.8% and 64.6% of serous carcinoma, being the most common malignancy observed in their study. Mucinous carcinoma (12.9%) was the second common tumour reported by our study and consistent with the observation conducted by Nalini et al and Rao NK et al. Two cases of endometrioid carcinoma and one case of clear cell carcinoma were encountered in present study and by Nalini et al. Rao NK et al also found 2 cases of transitional cell tumour in their study. However we did not find any case of transitional cell carcinoma.

Mean age of malignant tumors was 56.2 years comparable to that reported by Tiwari et al 2016 (59.3 years). Majority of serous and all mucinous carcinoma were seen in 5th decade and later age consistent with the study carried out by Pradhan et al. Single case of clear cell carcinoma was reported in 62 years of age whereas Rao NK et al reported this in 4th decade. In our study all the malignant tumors (100%) were associated with markedly raised serum CA125 levels & was in confirmation with the study conducted by Cambuzzi et al¹³ on 60 study cases. Studies carried out by Roy et al, and Verma et al also observed serum levels >35 U/ml in 70.6% and 71.43% cases respectively.

Serum CA125 concentration in benign, borderline

and malignant tumors were compared and statistically significant association was found ($p=0.000$). Cambruzzi et al 2014 also described a significant association between serum level of CA125 and biological behavior of ovarian tumors ($p=0.0002$), suggesting that high levels of tumor marker are associated with malignant neoplasms and lesions having more aggressive biological behaviour.

FIGO stage

FIGO stage is one of the universally accepted prognostic factors for patients with ovarian carcinoma. Early stage of ovarian tumors is associated with good prognosis because surgical treatment is enough for patients in stages I and II. Patients with advanced-stage disease often require debulking, or cytoreductive surgery, as well.⁷

Most of the similar studies observed the clinical presentation of ovarian cancers in advanced stages and only few studies found the patients in early stage of disease. In our study also, majority of the patients presented in FIGO stage III & IV followed by stage I which is in conformity with the observation made by Atla B¹⁴ et al & Vasquez FM¹⁵ et al. Stage I tumours were reported to be more common in the study carried out by Cambruzzi E¹³ et al (2014) on 60 cases.

This study showed significant correlation of serum CA125 with FIGO staging ($p=0.024$) in concordance with the observation by Igor But¹⁶ et al. In contrast Osman¹⁷ et al did not find any statistical significant relationship between CA125 and FIGO Stage ($p=0.08$).

Table 8: Comparison of diagnostic accuracy of Preoperative Serum CA 125 levels

Authors	Year	No of cases	Sensitivity %	Specificity %	Diagnostic Accuracy %
Rama mani et al	2007	75	90.66	81.48	-
Tiwari et al	2016	58	94.7	49.3	59.3
Present study	2019	105	100	82.43	87.62

In this study the sensitivity and specificity of CA125 to predict malignant behaviour of ovarian neoplasm was 100% and 82.43% respectively. Rama mani & Tiwari et al in their study group observed sensitivity to be 90.6% & 94.7% respectively. However specificity (81.48%) in the study performed by Rama mani et al is correlating well with our study. (Table 8)

Conclusion

Higher value of preoperative serum CA125 levels were associated with borderline / malignant surface epithelial ovarian tumors especially serous type and high grade tumors. Serum CA125 levels correlated well with biological behaviour of tumors and ovarian cancer staging (FIGO). Proper recognition and classification of ovarian tumors is essential for appropriate management as malignant tumors are usually picked up at an advanced stage owing to their asymptomatic

nature and inaccessible site for aspiration cytology and biopsy. Early screening is necessary especially in developing countries to increase the survival rate.

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