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Unveiling the ineffectiveness: Sox10's non participation in Ovarian Serous Carcinoma; retrospective clinicopathological analysis from National Cancer Institute

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Abstract

Background: The purpose of this study was to study the clinicopathological features of ovarian serous carcinoma in an Egyptian cohort as well as to uncover the potential role of Sox10 through evaluating immunohistochemical expression.

Methods: A retrospective study was carried out on sixty seven cases diagnosed as ovarian serous carcinoma at the Oncologic pathology Department – National Cancer Institute – Cairo University, during the period from 1st January 2015 to 31st December 2017. Automated staining for Sox10 was done on BenchMark ULTRA.

Results: The age of patients ranged from 26 to 76 years. The majority of cases had bilateral ovarian cancer; 43 cases (64%). Most of the cases; 30 cases (45%) were of FIGO stage III. Most of patients received adjuvant chemotherapy (69%). SOX10 expression in this research was completely negative in all studied case. Forty two cases (62.7%) had poor outcome; in the form of recurrence (32 cases; 47.8%), metastasis (7 cases; 10.5%), death (23 cases; 34.3%) or two events combined (18; cases; 26.9%). Median follow-up period was 38 months. A significant correlation was found between survival estimates and optimum debulking/minimal residual disease (p value= 0.001), FIGO stage (p value= 0.03), response to platinum based chemotherapy (p value = 0.004)

Conclusions: High grade and low grade serous carcinomas are heterogeneous diseases with the need of new effective therapeutic strategies. SOX10 is not expressed in ovarian serous carcinoma.

Keywords: Ovarian Cancer; SOX10; tumor grade; Median disease free survival

Introduction:

Ovarian cancer is the third most frequent type of gynecologic cancer, following cervical and uterine cancer. It has the poorest prognosis and the highest mortality rate. Ovarian cancer is three times more fatal than breast cancer, although having a lower prevalence. The tumor's hidden and silent growth, the delayed onset of symptoms, and poor screening lead to the detection of ovarian cancer in its advanced stages, which contributes to its high death rate. This cancer has been termed the silent killer as a result. *(Momenimovahed, 2019).* An estimated 21,400 new cases of ovarian carcinoma were reported in 2020, accounting for 1.2% of all cancer cases. That resulted in 13,700 incidences of death. A local stage constitutes 13.7% of cases, while a metastasized stage contributes to 52% of cases. Approximately 90% of ovarian tumors are epithelial, with the serous type being the most frequent (Zamwar et al, 2022). According to Sheta et al. (2021) ovarian cancer is Egypt's 11th leading cause of cancer, accounting for 2.1% of new cases and 2.3% of cancer-related fatalities. In December 2020, the Global Cancer Observatory (GLOBOCAN) estimated that there had been 2787 new cases. Numerous localized investigations carried out at various universities, including those by Helal et al. (2015) and Nassar et al. (2016) shown that the rising number of cases of serous ovarian cancer in Egypt's population is a serious health issue that needs further investigation. Poor survival and increased patient death are caused by the inability to diagnose the disease at an early stage (Narod, 2016).

Compared to high grade serous carcinoma (HGSC), low grade serous carcinoma (LGSC) is recognized as a separate cancer type with a different etiology. Both the pathophysiology and the clinical behavior of the two tumor subtypes are distinct. The clinical course of LGSC is slow, and it might originate from a serous borderline tumor (SBT) or denovo (Babaier et al., 2022). On the other hand, The presence of atypical tubal epithelial cells in women with BRCA1 (breast cancer gene 1) and BRCA2 (breast cancer gene 2) mutations has led to the identification of the distal Fallopian tube as a precursor location of HGSCs in a significant proportion of patients, (Matulonis et al, 2016).

During embryogenesis, the SRY-related HMG-box (Sox) family of transcription factors plays a crucial role in determining a cell's differentiation. Because these proteins' high-mobility-group (HMG) domains are more than or equal to 50% identical to the SRY gene, sox transcription factors gain their name. Twenty distinct Sox genes have been identified, and these genes are further divided into subclasses. The transcription factors Sox8, Sox9, and Sox10 are

members of the SoxE subclass of the Sox family. Neural crest migration and differentiation, chondrogenesis, gliogenesis, and sex determination are all attributed to the SoxE subclass collectively. (Hoang and Sy, 2023)**.** The development of the immunological, skeletal, and neurological systems is significantly influenced by the Sox genes. Initially, Sox10 staining by immunohistochemistry was mainly reported in salivary gland myoepitheliomas, peripheral nerve sheath cancers, and melanoma (Nelson et al 2017). The Sox10 gene, which codes for the Sox10 protein with an open reading frame that has 466 amino acids and a weight of 51 kDa, is found on chromosome 22q13. Within the SoxE subfamily, the protein has a highly conserved dimerization domain at its N-terminus. This 40 amino acid region helps the protein dimerize so that it can bind target genes (Bahmad et al., 2023). In melanomagenesis, Sox10 acts as an oncogene through cell cycle dysregulation, and in hepatocellular carcinoma, it activates the Wnt/β catenin cascade. On the other hand, it is downregulated or silenced in gastrointestinal and prostate cancer, indicating that it may have a tumor suppressor role in these diseases (Kwon et al, 2016)**.**

In this study, we aimed at studying the clinciopathological profile of primary ovarian serous carcinoma in a cohort of National Cancer Institute. Also, a trial to elucidate the possible role of Sox10 in ovarian serous carcinoma through its immunohistochemical expression was performed.

Ethical approval:

The study was approved by the Institutional Review Board (IRB) No.: IRB201920049.3 of National Cancer Institute (NCI) – Cairo University.

Material and methods

This retrospective study was conducted on 67 primary ovarian serous carcinoma diagnosed at the Department of Oncologic Pathology - NCI- Cairo university. Hematoxylin and Eosin (H&E) stained sections were verified for exact histologic typing following the classification of World Health Organization. Staging was done according to the International Federation of Gynecology and Obstetrics (FIGO) system. To obtain all relevant information on the initial tumor, type of surgery, adjuvant treatment, recurrence, and survival, retrospective reviews of patient files were carried out. Cases received neoadjuvant chemotherapy were excluded.

Immunohistochemistry

The study used immunohistochemical analyses on paraffin-embedded tissues and prepared one unstained section for the assessment of Sox10. Immunostaining was performed using BenchMark ULTRA autostainer, with steps including deparafanization, cell conditioning, antigen retrieval, monoclonal antibody application, Diaminobenzidine (DAB) as a chromogen, counterstaining with Hematoxylin II, and post-counterstaining with bluing reagent. The slides were cleared, cover slips applied, and the immunostaining was assessed using an Olympus light microscope.

Evaluation of Immunohistochemical Staining

Expression of Sox10 was considered positive if nuclei of >25 % of tumor cells are stained, (Kwon et al 2016).

Statistical Methods

Excel and SPSS 24 were used for data analysis. Whereas qualitative data were described as number and percentage, numerical statistics were described as median. When appropriate, the relation between the qualitative variables was examined using the chi square test. The Kaplan-Meier method was used to analyze survival. The log rank test was used to compare the two survival curves. Overall survival (OS) was computed from the diagnosis date to the latest follow-up or death date. The period from the date of surgery to the date of relapse, death, or last follow-up was used to compute disease-free survival (DFS). Statistical significance was defined as a p-value of less than or equal to 0.05.

Results

I) Clinico-pathological data

This retrospective cohort study was conducted on sixty seven cases of ovarian serous adenocarcinoma collected from archived blocks of excision specimens (panhysterectomy and ovariectomy specimens) sent to the Pathology Department - National Cancer Institute, Cairo University, during the period from 1st January 2015 till 31st December 2017. Table 1 demonstrates different clinico-pathological data of the studied cases; the age ranged from 26 to 76 years with median value of 55 years. Thirty one out of sixty seven cases (46.3%) were ≤ 55 years. All cases were diagnosed as pure serous adenocarcinoma. Breast cancer ran in the family

in two of the cases. History of other malignancies were reported in three patients namely chronic myeloid leukemia, breast cancer & pleomorphic sarcoma. While a second primary follicular thyroid carcinoma was reported in two patients. The majority of cases had bilateral ovarian cancer; 43cases (64%). In unilateral ovarian cancer cases, (20%) were located in the left side & (16%) were located in the Rt side. Most of the cases; 30 cases (45%) were of FIGO stage III, (Figure 1&2). The majority of tumors; forty four were of high grade (66%) and the rest twenty three cases (34%) were of low grade, (Figure 3, 4). Stratification of CA-125 serum level was done as the following: <152 U/ml, 152-500 U/ml, 500-1000 U/ml, 1000-2000 U/ml and>2000 U/ml. Eighteen percent of cases presented by serum level <152 U/mL and 22% of cases presented by serum levels >2000 U/ml, as illustrated in Figure 5. The majority of cases received adjuvant chemotherapy 69% (Platinum-based agents) for 4-6 cycles. Forty cases received taxol/carboplatin, four cases received taxol/carbopblatin followed by Gemzar, one case received carboplatin only and another case received Hyperthermic intraperitoneal chemotherapy (HIPEC).

Table 1: Clinico-pathological data of the studied cases (n=67)

Clinicopathological variable		Frequency	Percentage (100%)
Age (years)	≤55	31	46.3
	>55	36	53.7
History of other malignancy	Yes	3	4
	No	64	96
Family history of breast cancer	Yes	2	3
	No	65	97
Tumor Grade	HGSC	44	66
	LGSC	23	34
FIGO Stage	I	23	35
	II	7	10
	III	30	45
	IV	7	10

Lymph node status	Positive	8	12
	Negative	14	21
	Not Available	45	67
Chemotherapy	Adjuvant	46	69
	Not received	21	31
Response to first line Platinum chemotherapy	Sensitive	39	85
	Resistant	6	15
CA125 level (U/ml)	< 152	12	18
	152-500	14	21
	500-1000	14	21
	1000-2000	12	18
	> 2000	15	22
Presenting symptoms	Pelviabdominal mass	50	75
	Others	17	25
Bilaterality	Bilateral	43	64
	Left	13	20
	Right	11	16
Distant metastases	Yes	7	10
	No	60	90
Residual disease	Yes	15	22.4
	No	52	77.6
Type of Operation	Ovariectomy	10	15
	Panhysterectomy	57	85

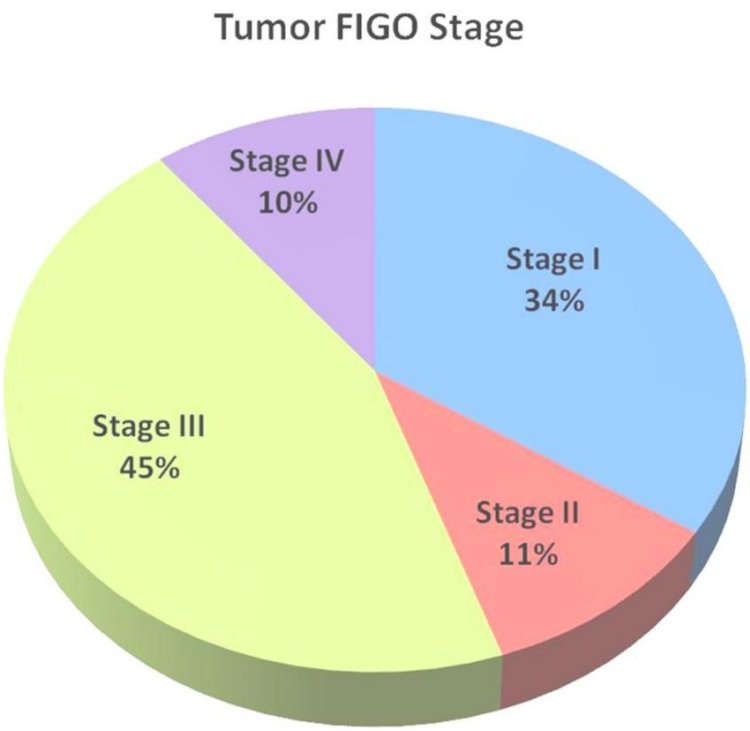

Figure 1: Distribution of tumor stage in the studied cases (n= 67).

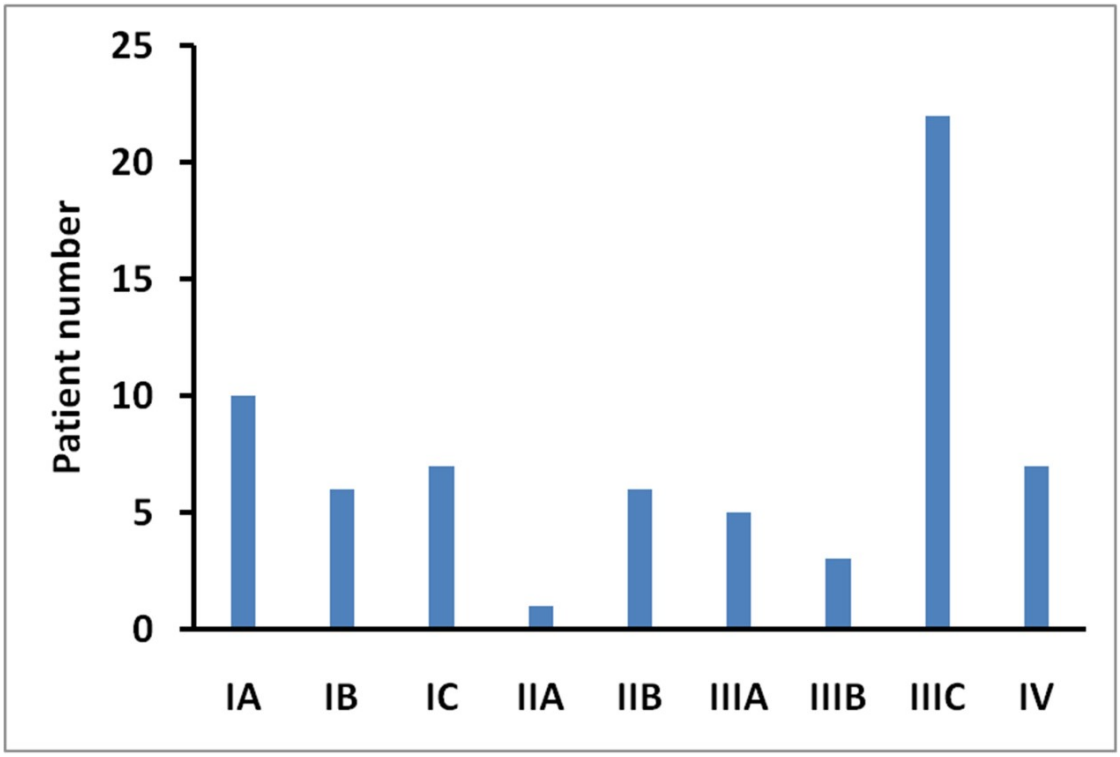

Figure 2: Detailed distribution of the studied cases in relation to FIGO stages

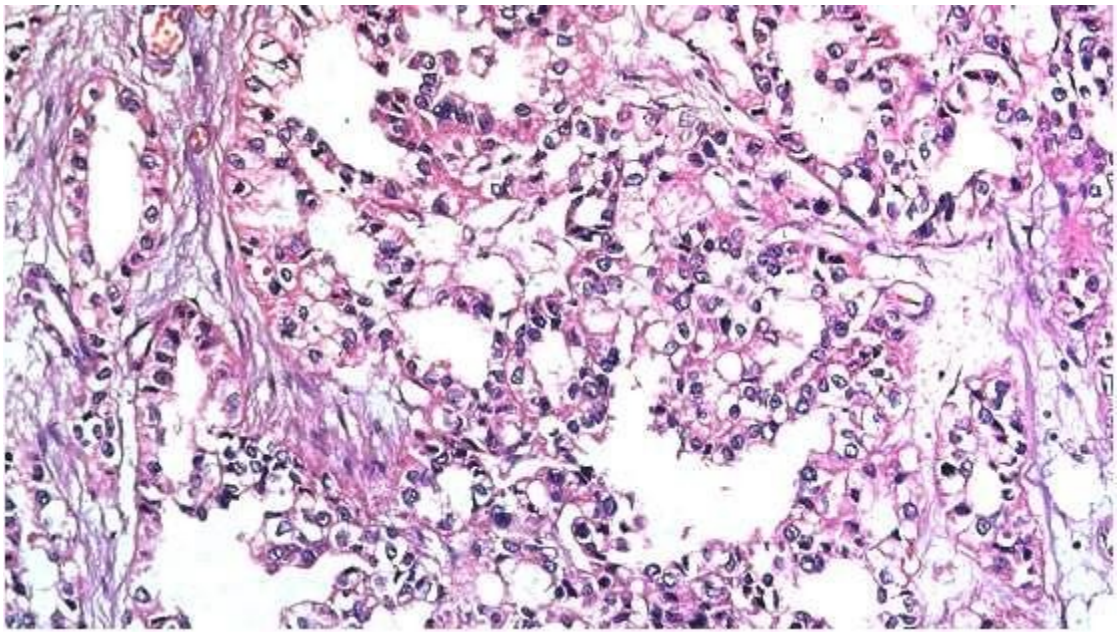

Figure 3: Low grade serous carcinoma, FIGO stage I (H&E, original magnification x200).

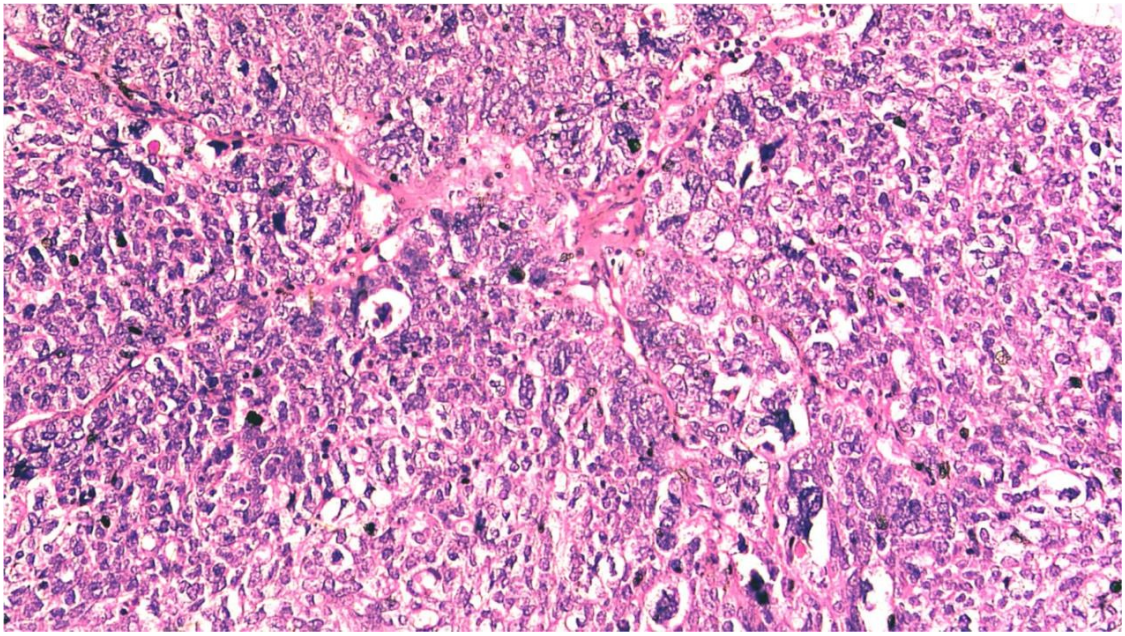

Figure 4: High grade serous carcinoma, FIGO stage IV, (H&E, original magnification x200

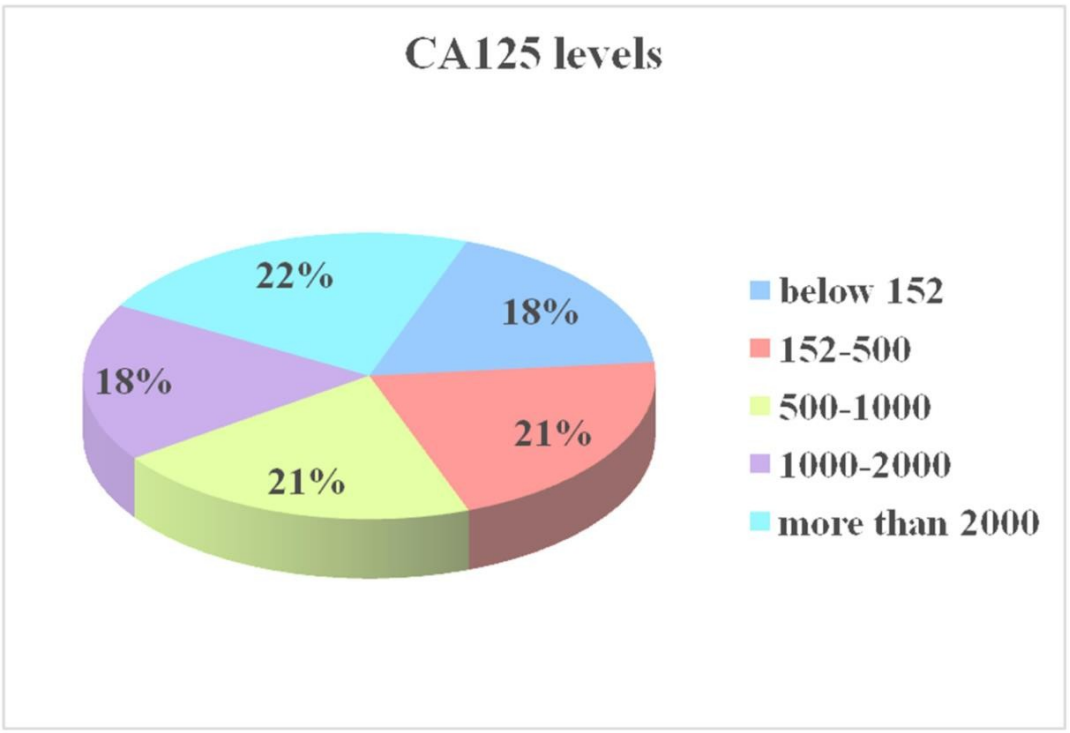

Figure 5: Stratification of CA125 (U/ml) in the studied cases (n= 67).

II) Immunohistochemical results of Sox10:

All the studied cases showed complete negative immunostaining reaction to Sox10 immunohistochemical marker despite various attempts at increasing incubation times of the primary antibody and applying different modifications in the staining protocol (Figures 6 and 7).

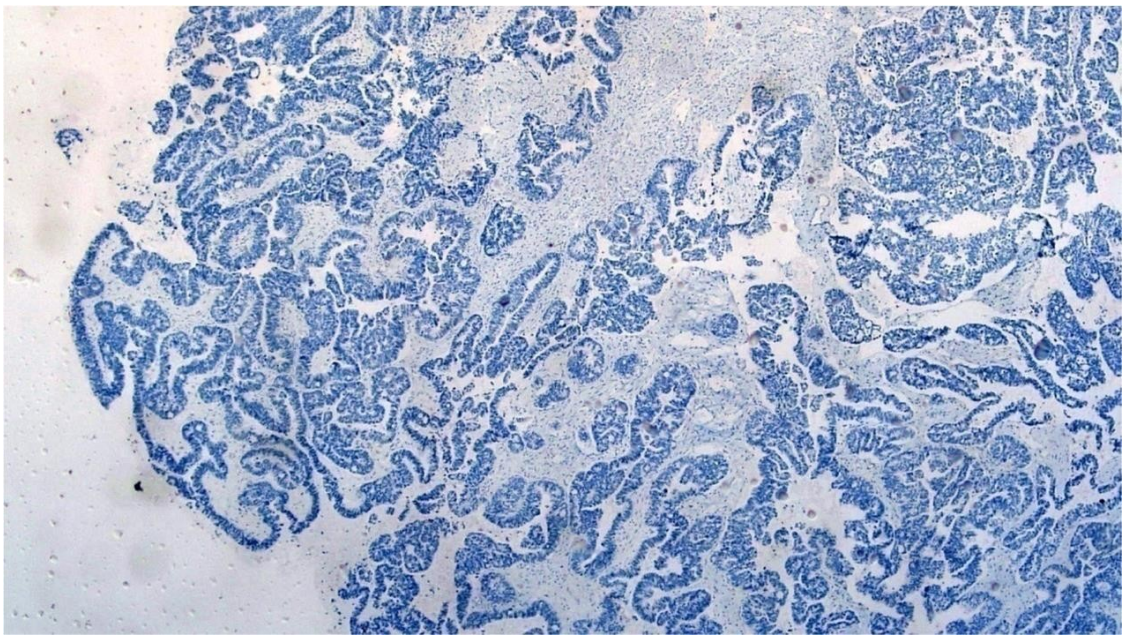

Figure 6: Immunostained slide for a case of low grade serous carcinoma showing complete negative reaction to Sox10, (DAB), original magnification × 200).

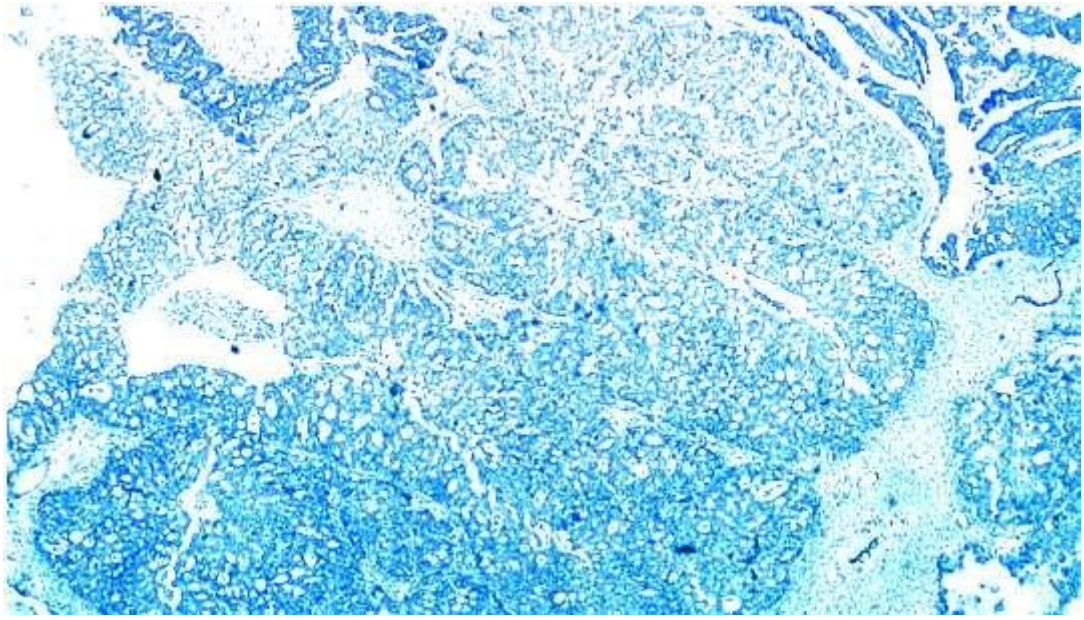

Figure 7: Immunostained slide for a case of high grade serous carcinoma showing complete negative reaction to Sox10 (DAB), original magnification × 200).

III) Survival analysis

Disease outcome after follow up

Median follow-up period was 38 months ranging from 4 month up to 69 months. Forty two cases (62.7%) had poor outcome; in the form of local recurrence (32 cases; 47.8%), distant metastasis (7 cases; 10.5%), death (23 cases; 34.3%) or two events combined (18; cases; 26.87%).

Overall survival (OS):

Table (2) illustrates different values for cumulative OS rate at 12 and 36 months in relation to clinicopathological parameters. Significant p value was observed with patients' age (p value = 0.03) and residual disease (p value = 0.001) in relation to survival data (figures 8 & 9).

Table 2: Overall survival rate in relation to clinicopathological data.

Clinicopathologic variable	Subgroups	NO	NO of events	Median survival estimate(months)	Cummulative survival at 12 months (%)	Cummulative survival at 36 months (%)	p value
Whole group		**67**	**23**	**NR**	**88**	**72.1**	
Age (years)	≤55 yrs	31	6	NR	90.1	78.5	**0.03**
	>55 yrs	36	17	42	86.1	66.6	
Laterality	Right	11	4	52	81.8	68.2	
	Left	13	4	NR	92.3	80.8	0.95
	Bilateral	43	15	NR	88.4	70.8	
CA-125 (U/ml)	<152	12	2	NR	90.9	90.9	
	152-500	13	2	NR	92.3	83.9	0.17
	500-1000	15	7	52	86.7	64.2	
	1000-2000	11	4	42	90.9	75.8	

	>2000	16	8	39	81.3	53.0	
Operation	Ovariectomy	10	5	52	80	53.3	0.33
	Panhysterectomy	57	18	NR	89.4	75.1	
Lymph node metastases	Yes	8	6	41	78.5	69.8	0.79
	No	14	3	42	100.0	75.0	
FIGO stage	I	23	4	NR	91.1	85.0	0.14
	II	7	3	NR	85.7	53.6	
	III	30	12	45	90.0	74.5	
	IV	7	4	19	71.4	42.8	
Grade	LGSC	23	8	NR	95.5	74.2	0.7
	HGSC	44	15	NR	84.1	71.3	
Residual disease	No	52	13	NR	100.0	33.0	**0.001**
	Yes	15	10	12	44.0	8	
Chemotherapy response	Sensitive	55	17	NR	89.0	74.2	0.23
	Resistent	12	6	42	83.3	61.7	
Metastases	Positive	7	4	42	85.7	71.4	0.44
	Negative	60	19	NR	88.2	72.0	

NR: not reached.

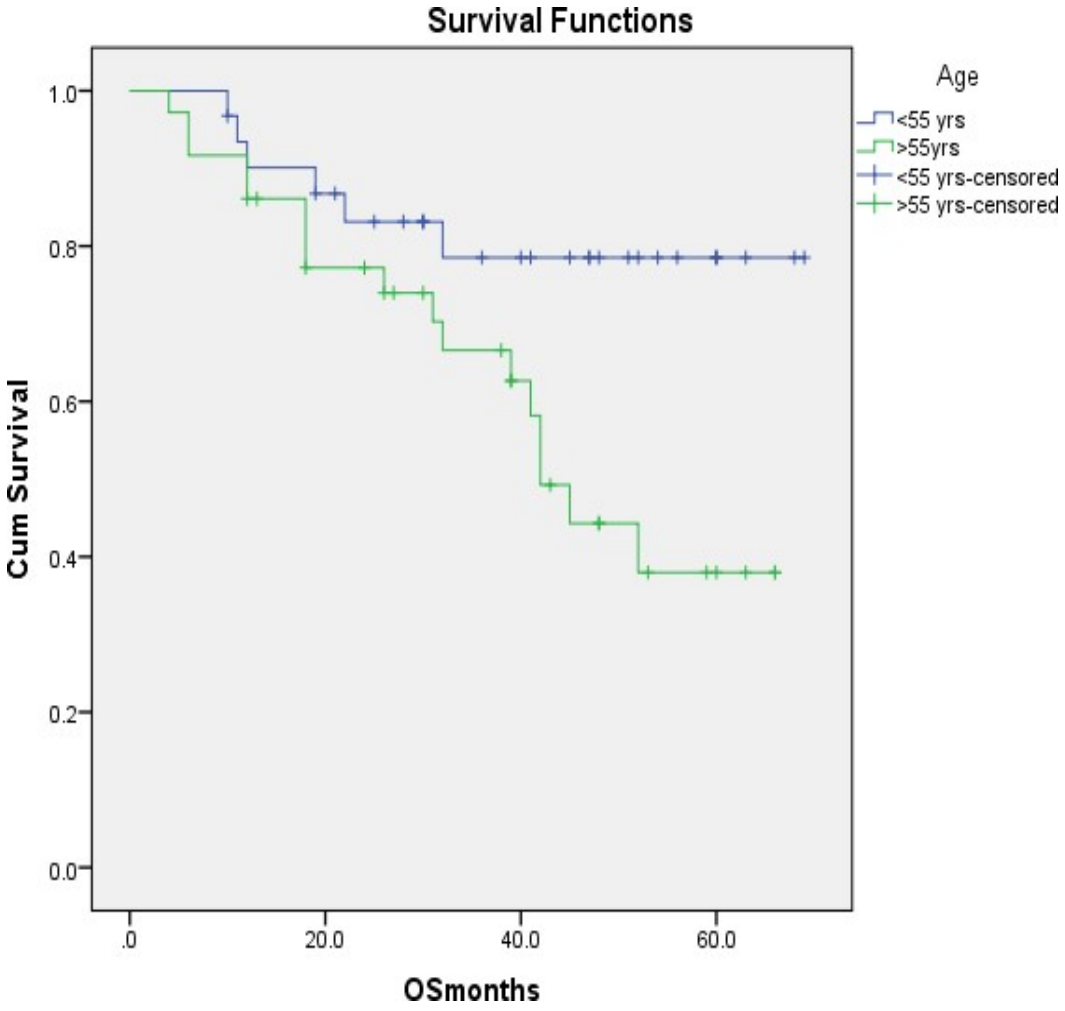

Figure 8: Overall survival in relation to patient's age, p = 0.03

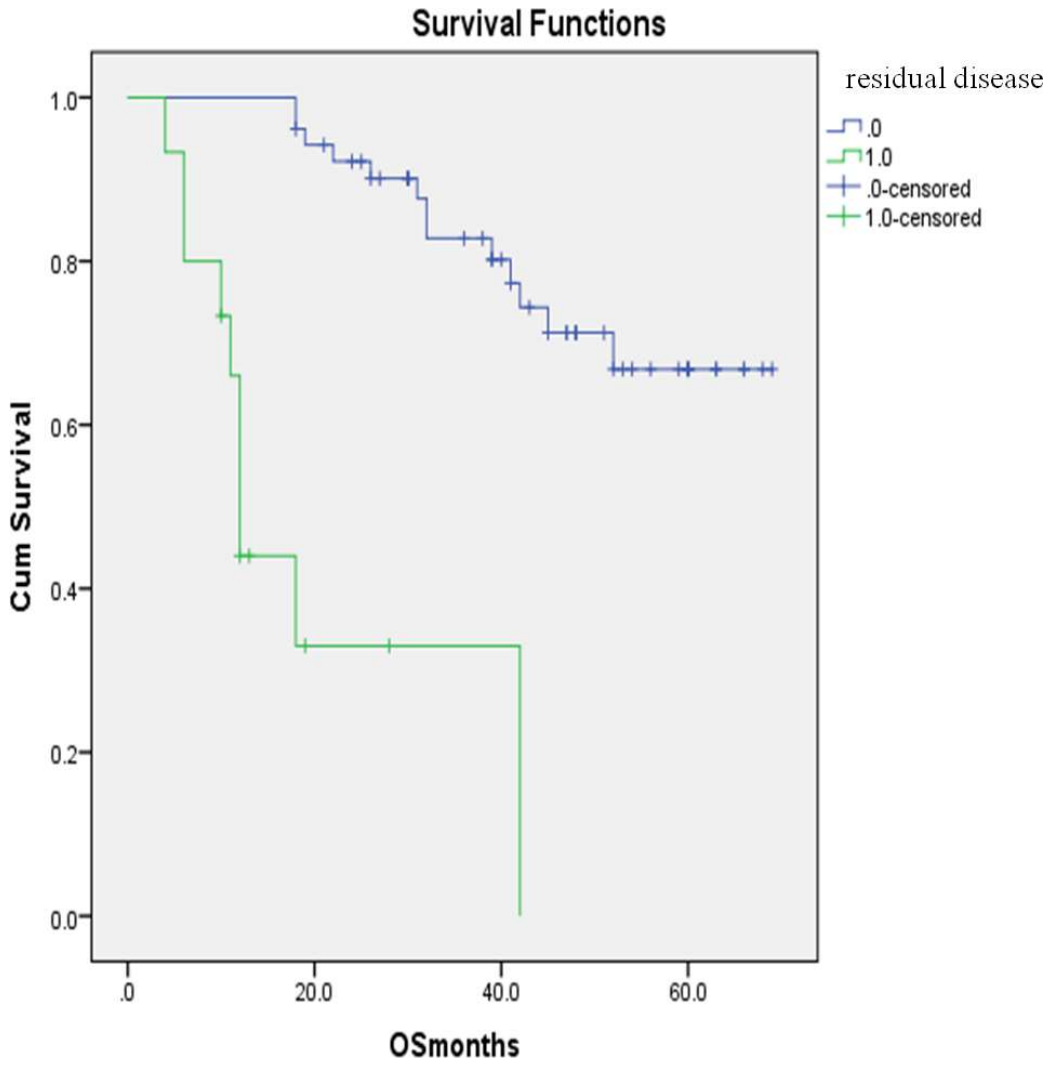

Figure 9: Overall survival in relation to residual disease, 1= residual disease after operation and debulking, 0= no residual disease/optimal debulking, p=0.001.

Disease free survival (DFS):

Median disease free survival estimate was 42 months. A significant correlation was observed between longer DFS with low FIGO stage (p value= 0.03, Figure 10), in patients whose tumors showed good response to platinum-based chemotherapy (p value = 0.004, Figure 11) and in patient who received optimal debulking or with minimal residual disease (p value= 0.001, Figure 12). A non significant correlation was obtained between disease free survival and other clinicopathological factors **(Table 3).**

Table 3: Disease free survival in relation to clinicopathological data in the studied cases.

Clinicopathologic variable	Subgroups	NO	NO of events	Median survival estimate (months)	Cummulative survival at 12 months (%)	Cummulative survival at 36 months (%)	p value
Whole group		**67**	**32**	**42**	**83.1**	**50.5**	
Age (Years)	≤55 yrs	31	16	31	80.5	45.4	0.88
	>55 yrs	36	16	42	85.4	55.4	
Laterality	Right	11	7	24	81.8	47.7	0.39
	Left	13	4	NR	83.3	64.8	
	Bilateral	43	21	36	83.5	47.7	
CA-125 (U/ml)	<152	12	3	NR	91.7	82.5	0.1
	152-500	13	7	36	69.2	46.2	
	500-1000	15	9	24	71.4	34	
	1000-2000	11	4	35	100	46.7	
	>2000	16	9	24	87.5	38.9	
Operation	Ovariectomy	10	5	42	90.0	51.4	0.65

	Pan-hysterectomy	57	27	51	81.9	50.2	
Lymph node metastases	Positive	8	7	25	83.3	40.0	0.47
	Negative	14	6	18	62.5	33.3	
FIGO stage	I	23	6	NR	91.3	75.4	**0.03**
	II	7	5	24	85.7	28.6	
	III	30	16	35	79.5	42.7	
	IV	7	5	33	68.6	25.7	
Grade	LGSC	23	11	51	91.3	60.3	0.66
	HGSC	44	21	33	78.9	45.1	
Residual disease	No	52	24	51	92.3	57.5	**0.001**
	Yes	15	8	11	46.1	NR	
Chemotherapy response	Sensitive	55	22	51	86.9	59.6	**0.004**
	Resistent	12	10	16	66.7	16.7	
Metastases	Positive	7	5	25	83.3	16.7	0.23
	Negative	60	27	51	83.1	54.8	

NR: not reached.

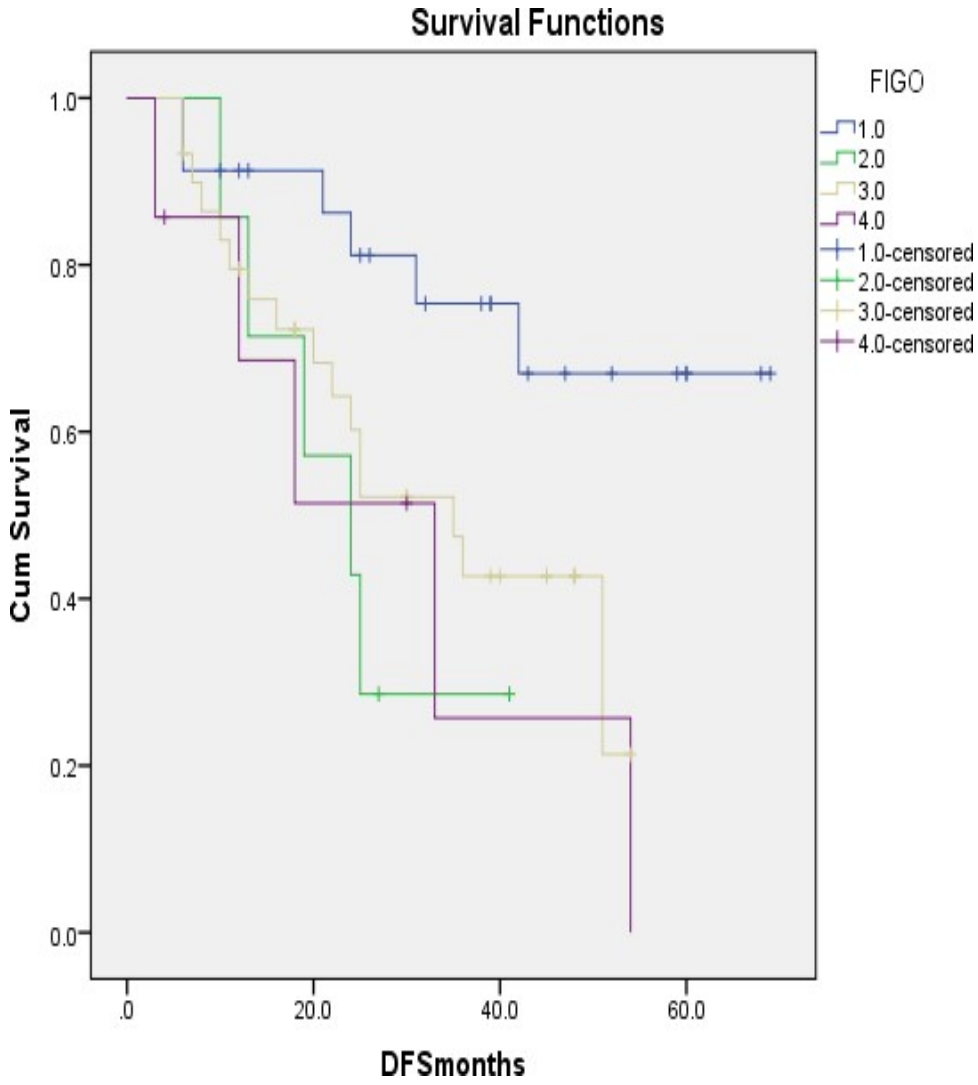

Figure 10: Disease free survival in relation to FIGO stage, p=0.03.

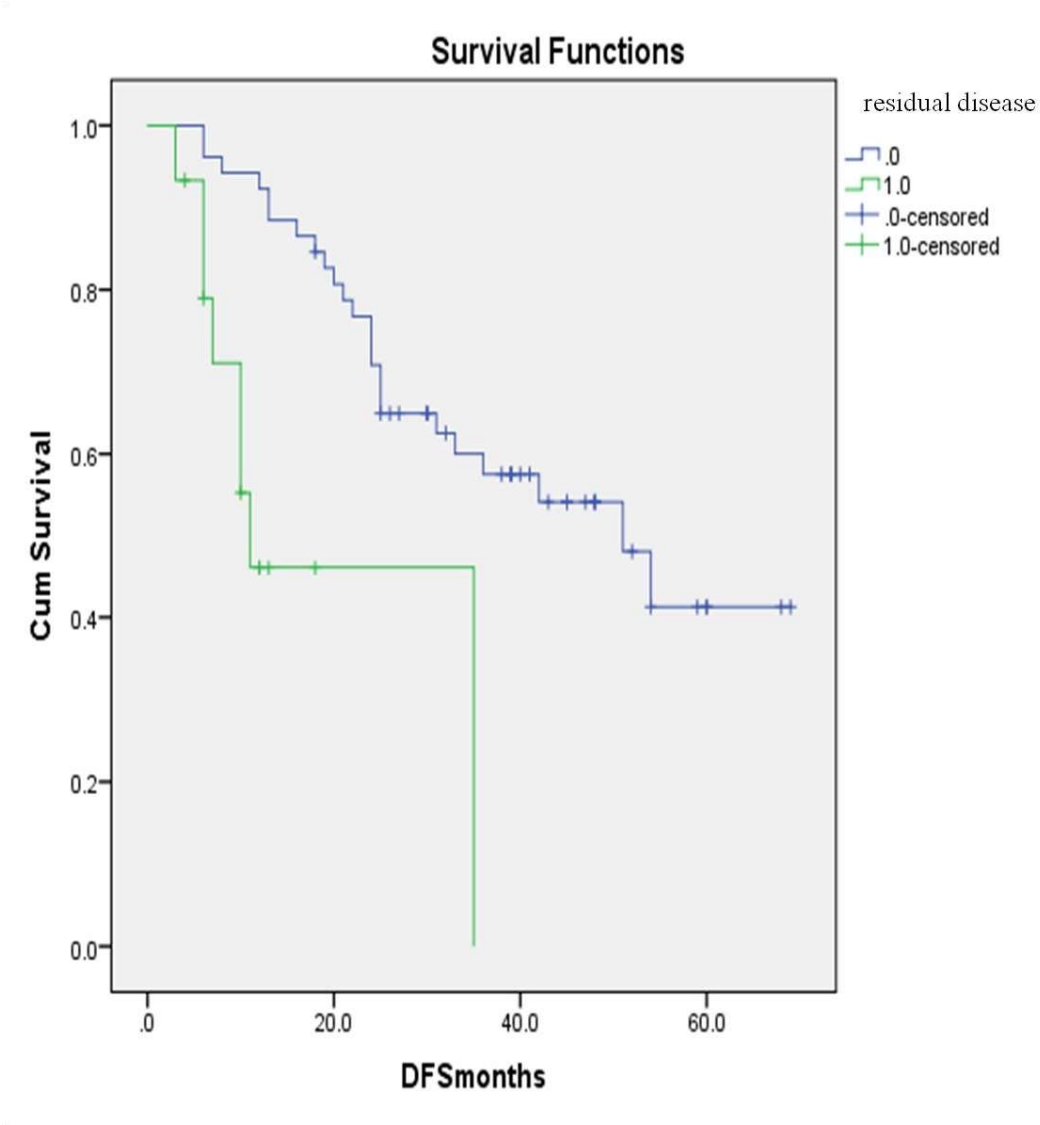

Figure 11: Disease free survival in relation to residual disease, showing highly significant p value=0.001.

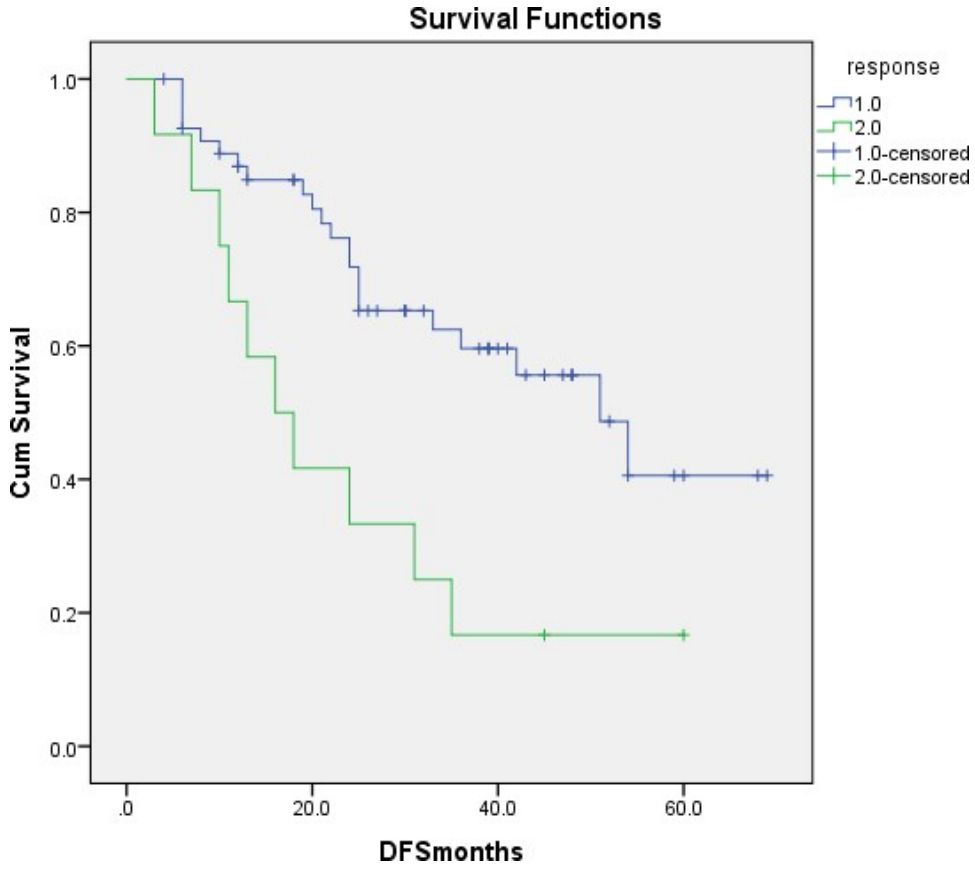

Figure 12: Disease free survival in relation to response to platinum-based chemotherapy, exhibiting highly significant p value=0.004, with DFS curve for patients whose EOC are chemosensitive was better than those with chemoresistent tumors.

Discussion

Regarding grade of tumor, we found that 44 cases were of high grade (66%) and the remaining twenty three cases (34%) were of low grade. This is in concordance with what *Hatano et al 2019* stated in their review, that epidemiologically, the vast majority of serous carcinoma are cases of high grade. Regarding other clinicopathological features, in our study we found that the age of patients ranged from 26 to 76 years with median value of 55 years, 3% had family history of breast cancer. Most patients (75%) presented with pelvi-abdominal mass, which comes in line with what *Kalachand et al 2020* had reported in their series. The highest percentage of our cases was staged as of FIGO stage III (45%), this is in concordance with what Torre et al 2018 stated that most of their cases of serous carcinomas were at stage III (51%), reflecting the aggressive nature of prevailing high-grade serous carcinomas. Most of the studied cases in our series (69%) received adjuvant Taxol/carboplatin chemotherapy. This is in partial agreement with what *Kalachand et al 2020 stated* in their study that 78.9% of their patients received adjuvant platinum based-therapy. As regards to other clinicopathological features, no significant correlation was found in relation to age, laterality, FIGO stage, CA125 serum level, lymph node status.

In our study, Median follow-up period was 38 months ranging from 4 month to 69 months. Highly significant correlation between longer overall survival and optimal debulking was observed. This is in similar with what Wohlmuth *et al 2022* concluded that women with full cytoreduction and no macroscopic residual disease had better results..

SOX10 expression in this research was completely negative in all studied cases, despite trials for antigen retrieval from more recent tumor tissues processed in our department in less than one month, increasing incubation period of the antibody above recommended time from 32 minutes to 60 minutes and doubling volume of the antibody used.

Conclusion

High grade and low grade serous carcinomas are heterogeneuos diseases with the need of new effective therapeutic strategies. A significant correlation was observed between longer overall survival /disease free survival and optimal debulking/minimal residual disease. SOX10 is not expressed in ovarian serous carcinoma.

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