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Original Research Article

Study of significance of p53 expression in primary ovarian tumour

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ABSTRACT

Background: The purpose of the study was to understand the molecular changes that happen in human cancer, P53 gene mutation. Here, with respect to P53 immunohistochemical staining were taken into consideration as the surrogate for the mutational analysis. This was used for the diagnosis of ovarian cancer.
Aim: The main aim of the study was to evaluate the immunohistochemical frequency of the P53 and to correlate its expression with the prognosis.
Materials and Methods: In the current study 107 cases associated with ovarian cancer were studied. The samples received were hysterectomy as well as unilateral and bilateral salpingo-oophorectomy specimens, which were fixed in 10% neutral buffer formalin and processed routinely.
Results: 68.7% of the patients showed P53 malignant ovarian tumours. In the benign, it was considered as negative or in the position of borderline tumour. No statistically significant correlation was shown between the age and P53 expression. There was statistically significant difference between borderline, benign and the malignant tumors. It was also assessed that there was a statistically significant difference between P53 expression and serous carcinoma in the current study.
Conclusion: The present study concludes that P53 tumor gene was found to be mutated in more than the 50% of the human cancer and was expressed as the aberrant form of protein. The study also concludes that in borderline tumor, P53 rarely mutates and is results in poor prognosis.

1. Introduction

Ovarian cancer represents 25% of the malignancy with respect to the genital tract.[1,2] Worldwide, it is the 7^{th} leading cause of death among the women[3,4] due to cancer, and is the 6^{th} most common form of cancer diagnosed among women.[5] In a developing nation like India, it is third leading kind of cancer diagnosed among women after cervix cancer and breast cancer. Further P53 tumour is mutated in more than 50% of the human cancer[6] cases. This is the reason why it has gained attention of many scholars.[7] The P53 has mutated and is over expressed in 50%-60% cases of ovarian cancer.[8] Moreover, P53 is rarely mutated into borderline tumours[9] and is often related with the poor prognosis.[10] P53 is often associated with the spontaneous mutation instead of the chemical carcinogen[11] activity. The main aim of the present study was to evaluate the P53 expression frequency in the various forms of tumours. The study also correlates P53 with the prognosis.

2. Materials and Methods

Our study included 107 specimens of ovarian tumour patients admitted to the Department of Pathology M.K.C.G. Medical College and Hospital for histopathological examination during the study period from September 2018 to September 2020. The samples received were hysterectomy as well as unilateral and bilateral salpingo-

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oophorectomy specimens, which were fixed in 10% neutral buffer formalin and processed routinely.

2.1. Inclusion criteria

Patients included in the present study were the ones who had undergone surgery for ovarian tumors in the Department of Gynecology irrespective of age. They were all diagnosed with ovarian tumors by histopathology.

2.2. Exclusion criteria

1. Those patients who did not give consent for IHC
2. Lesions having inflammatory etiology on histopathology
3. Metastatic cancers from non-ovarian primary and inadequate biopsies.

Out of 107 cases 74 cases were epithelial tumours, 23 were germ cell tumours, 08 were sex cord stromal tumours and 02 were teratomas.

In this study, the expression of P53 protein with respect to immunohistochemical staining were studied. This was compared with the age of patients, grade of tumours as well as histopathological forms.

Here, haematoxylin as well as eosin-stained slides related to the formalin fixed paraffin embedded biopsy blocks was examined. The effort was made with an aim to assess expression of P53 immunohistochemical. It was assessed on the formalin fixed paraffin embedded tissue with the help of P53.

2.3. Immunohistochemical Staining Interpretation

In order to record the P53 nuclear staining[12] result, a semi-quantitative histochemical score was taken into consideration. For the purpose to examine the percentage, more than 1000 tumour cells in a multiple high-power field were taken into consideration. The effort was also made in order to examine the intensity of the staining. With an aim to exclude the subjectivity efforts were taken with an aim to check the slides for more than once.

The guidelines for P53 scoring are given below:

Table 1: To assess the positive reaction intensity in most of the cell tumours

Intensity score (IS)	Intensity score observation by staining
1	Weakly positive +
2	Moderately positive ++
3	Strongly positive +++

Positive control slides were included in each run of staining. Positive control slides were prepared from a case known to be positive for P53.

Table 2: Based on positive cells in percentage:

Proportion score (PS)	Proportion score observation
0	<5% positive cells
1	5%-25% positive cells
2	26%-50% positive cells
3	51%-75% positive cells
4	76%-100% positive cells

2.4. Statistical analysis

In the present study, descriptive analysis was used. The arrangement of data was performed in the categorical order. For the given purpose, various tests were applied such as ANOVA, Fisher exact test and the Chi-square test. The SPSS 23.0 version of the software was used. The significance value was taken as the less than 0.05.

3. Results

Table 3: Distribution of ovarian tumours according to histological classification

Histomorphological types	Number	Percentage
Epithelial tumours	74	68.23%
Sex cord stromal tumours	08	7.48%
Germ cell tumours	23	22.43%
Monodermal teratoma	02	1.86%
Total	107	100

Table 3 shows that out of the 107 ovarian tumours surface epithelial tumours predominate followed by germ cell tumour, sex cord stromal tumours and struma ovary.

Table 4: Age distribution of surface epithelial tumours

S.No.	Age groups	Benign	Borderline	Malignant	Total
1	11-20	0	0	0	0
2	21-30	9	0	0	9
3	31-40	14	2	0	16
4	41-50	23	3	5	31
5	51-60	5	0	6	11
6	61-70	1	0	4	5
7	71-80	0	0	2	2
	Total	52	5	17	74

Table 4 shows that maximum benign tumors were seen in the age group of 41-50 years. All the malignant tumors were found in the age group above 40 years.

Table 5 shows that amongst entire spectrum of the surface epithelial ovarian tumors, serous tumors predominate followed by mucinous tumors.

As evident from the above Table 6, most of the malignant tumors were of size more than 10cm and solid in texture on cut surface showing necrotic areas, hemorrhage and, papillary excrescences. Borderline and benign tumors were mostly size more than 10 cm and cystic on cut section.

Table 5: Distribution of surface epithelial ovarian tumours

Histotype	Total no	%	Average percentage (n=Total cases)
Serous cystadenoma	32	43.24	62.16
Borderline serous tumour	2	2.7	(n=46)
Serous carcinoma	12	16.21	
Mucinous cystadenomas	19	24.75	35.14
Borderline mucinous tumours	5	6.7	(n=26)
Mucinous carcinoma	2	2.7	
Clear cell carcinoma	1	1.35	1.35(n=1)
Malignant brenner tumours	1	1.35	1.35(n=1)
Total epithelial tumours	74	100	100

Table 6: Distribution of epithelial ovarian tumours based on size, gross morphology, and laterality

Features	Size		Gross			Laterality	
Lesions	</=10cm	>10 cm	Solid	Cystic	Both	Unilateral	Bilateral
Benign	17	36	0	53	0	51	2
Borderline	1	4	0	4	1	5	0
Malignant	1	15	8	0	8	10	6

Table 7: Overall corelation of P53 with various clinicopathological factors

S.No.	Variables	Total no	Positive cases (%)	Negative cases (%)	P-value
1	Age groups				
	</=40 Years	24	2(8.33)	22(91.67)	P=0.14
	> 40 Years	50	13(26)	37(74)	
2	Differentiation				
	Benign	52	1(1.92)	52(99.08)	
	Borderline	5	3(60)	2(20)	P<0.00001
	Malignant	17	11(70.59)	5(29.41)	
	Serous carcinoma grades				
3	Low grade	4	2(50)	2(50)	P<0.05
	High grade	8	8(100)	0(0)	
	Types based on histology				
	Serous	10	7(70)	3(20)	
4	Mucinous	4	4(100)	0	P=0.06
	Malignant brenner	1	0	1(100)	
	Clear cell	1	0	1(100)	
	Figo stages				
	Figo stage I	7	3(42.86)	4(57.14)	
5	Figo stage II	7	5(71.43)	2(28.57)	P=0.18
	Figo stage III	1	1(100)	0	
	Figo stage IV	1	1(100)	0	

On the basis of Table 7, it can be stated that there are 26% people in which P53 expression was found positive and were more than the age of 40. On the other hand, patients whose age was less than or equal to 40 years the P53 expression was recorded as 8.33%. In addition, it was also examined that the P53 expression was found positive in the patients that were above the age of 40. However, the difference examined was not statistically significant.

From Table 7 it was examined that only 1 case out of the 52 cases were positive for P53. Additionally, with respect to the borderline ovarian tumour 3 out of the 5 cases were positive. Moreover, with regard to the malignant ovarian tumor 11 out of 17 cases were positive. However, there was statistically significant difference between borderline, benign and malignant with respect to the P53 examines was less than 0.00001.

Table 7 also showed that the positive cases of P53 in serous carcinoma were examined as 10 out 12. Thus, it can be said that all 4 cases related to the mucinous carcinoma showed positivity for P53. But this is not the case in malignant Brenner tumor and cell carcinoma. The expression of P53 was not statistically significant with the historical type of tumor. Here p-value was equal to 6.

Table 8: A comparative analysis of P53 Immuno study with other study

	Present study	Naik et al	Sylnia et al	Giurgea et al	Hariozinska et al
Age </=40 years	2/25	13/55	7/34*		
Age>40 years	12/49	12/55	14/26*		
Benign	1/52	5/82	0/17	0/11	0/15
Borderline	3/5	9/12	2/10	1/15	1/1
Malignant	11/17	13/16	19/33	10/26	24/45
Stage I	3/7			1/7	3/14
Stage II	5/6			3/8	3/14
Stage III	1/1			4/8	
Stage IV	1/1			2/3	21/31
Low grade	2/4	$\frac{1}{2}$		1/8	
High grade	8/8	7/7		9/16	
Serous	9/12	5/7	11/18	10/24	
Mucinous	2/2	$\frac{1}{2}$	0/14	0/2	16/28
Endomrtroid					3/7
Clear cell	0/1	1/1	0/1		5/10
Malignant brenner	0/1	1/1			

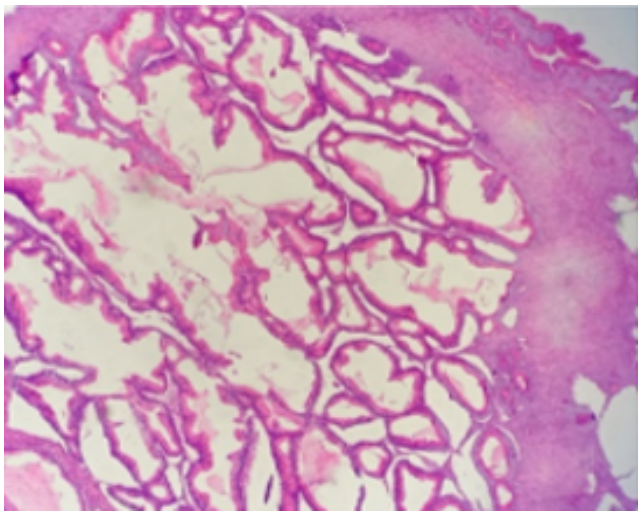

Fig. 1: H&E stain (100X) mucinous cystadenoma

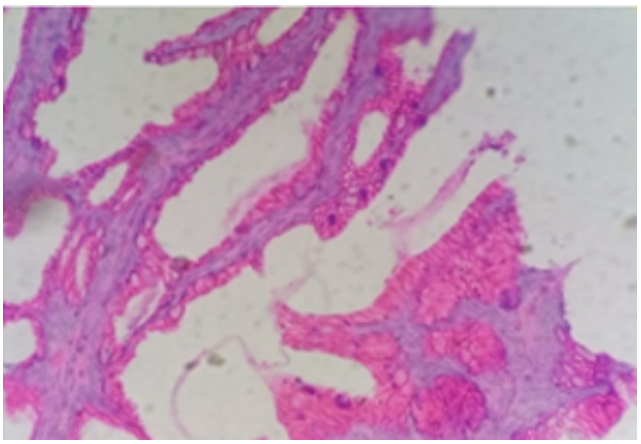

Fig. 3: H&E stain (400X) Mucinous cystadenoma

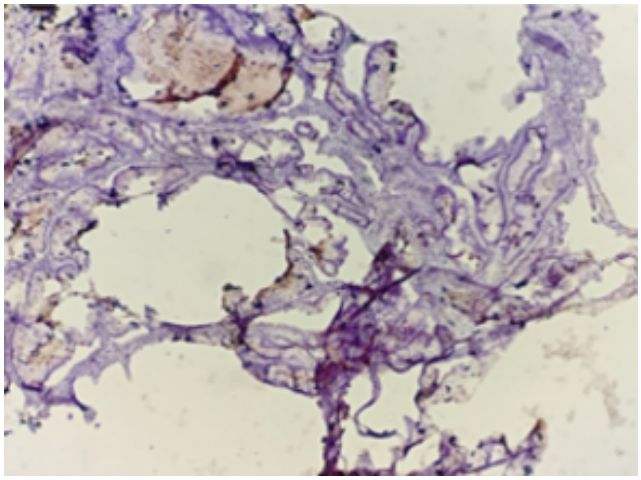

Fig. 2: IHC-p53 (100X) mucinous cystadenoma

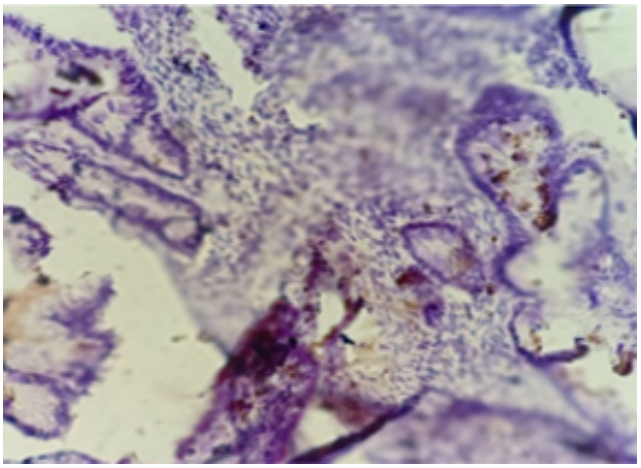

Fig. 4: IHC-p53 (400X) mucinous cystadenoma

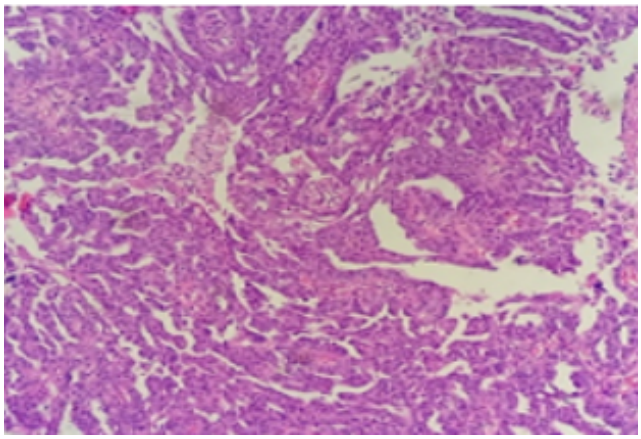

Fig. 5: H&E stain (100X) high grade serous carcinoma

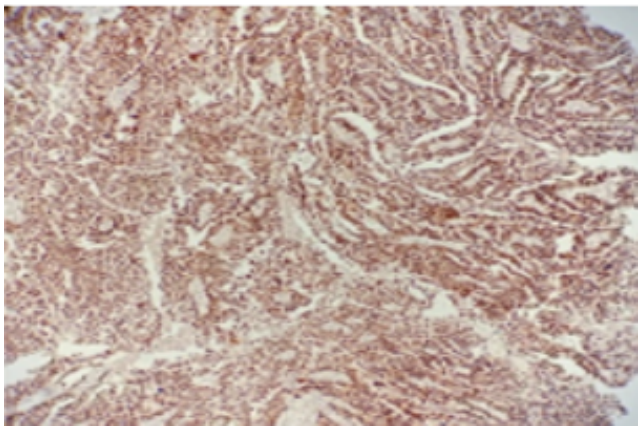

Fig. 6: IHC-p53 (100X) high grade serous carcinoma

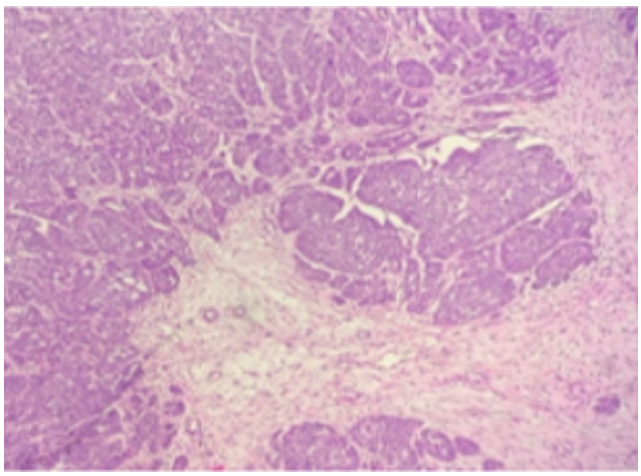

Fig. 7: H7E stain (100X) high grade serous carcinoma

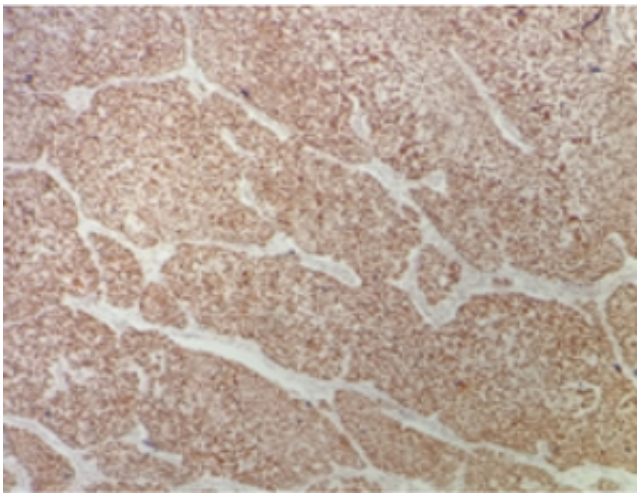

Fig. 8: IHC-p53 (100X) high grade serous carcinoma

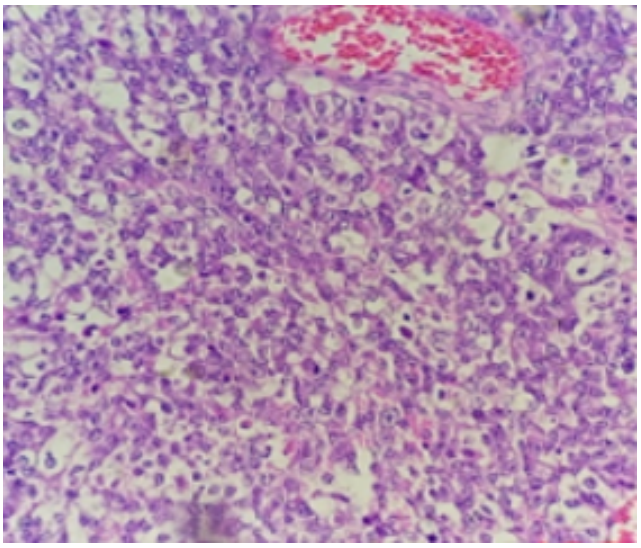

Fig. 9: H&E stain (400X) high grade serous

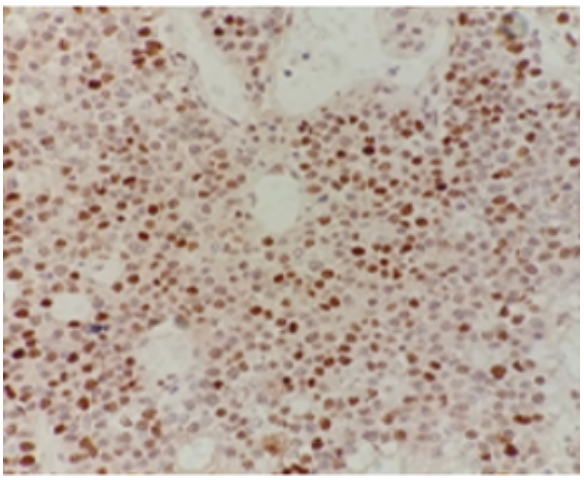

Fig. 10: IHC-p53 (400X) high grade serous carcinoma

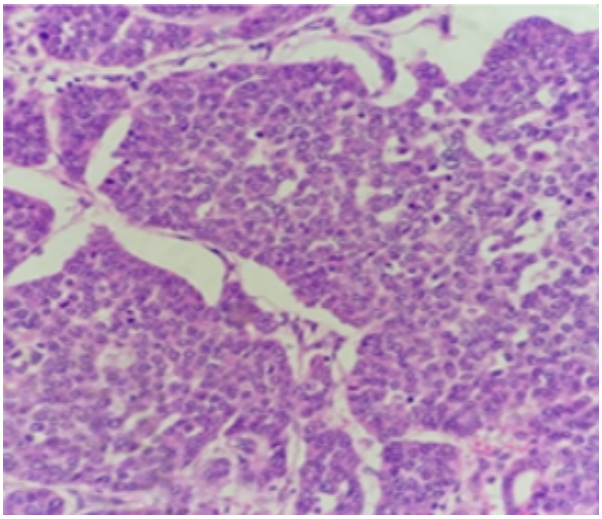

Fig. 11: H&E stain (400X) high grade serous carcinoma

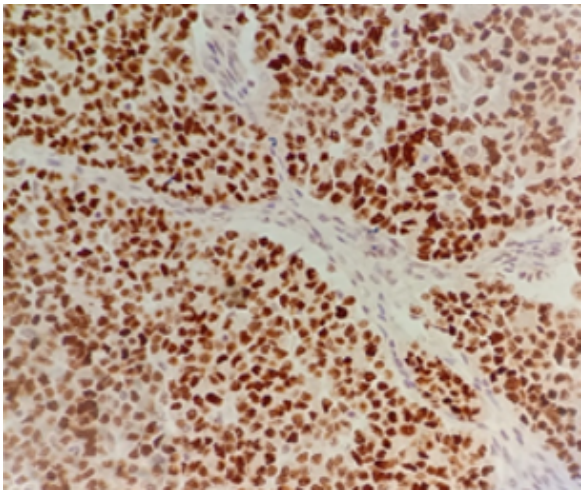

Fig. 12: IHC-p53 (400X) high grade serous carcinoma

The positivity related to the P53 in a low-grade carcinoma was 50%. But in case of high-grade carcinoma was recorded as 100%. Thus, it was correct to say that there was a statistically significant between grade of serous carcinoma and P53 expression ($p<0.05$).

As per the FIGO staging system, the positive rate for the P53 in the stage 1 was 3 out of the 7. The positivity rate was 5 out of 7 in the stage 2. But all the cases of stage 1 as well as stage 4 were 100% positive. On the other hand, the difference was also not the statistically significant as the p-value was recorded as p=0.18. It was also examined that increased number of P53 positivity cases were also seen in the increasing phase of the tumour. It was also evident from Table 7 that there was positive correlation between the P53 immunostaining and high-grade tumor.

4. Discussion

In the current study, P53 was found in 68.75% of malignant ovarian tumours. Other similar studies have shown variable ratios (38.46%- 81.25%).[13,14] The reasons for this variation were unknown. However, possible causes for this variation may be the following:

1. The different antibody properties.
2. The scoring system applied for P53 immunoreactivity.
3. The tissue fixation procedure.

4.1. P53 expression in relation to age

In the current study, no statistically significant correlation was shown between the age and P53 expression. The finding is similar to the study that is conducted by Naik et al (2015)[15] as well as Sylvivia et al[16] (2012). The significance found for the same is p=0.912 and p>0.05. On the other hand, the P53 expression found among the patients with age more than 40 years. The results were related to the somatic mutation accumulation. Li Fraumeni patients with P53 mutation develop tumours earlier and with a higher frequency.

4.2. P53 Immunoexpression and nature of the lesion

In the current study, there was statistically significant difference between borderline, benign and the malignant tumors. The study performed by Harlozinsk et al (1996)[17] with the significance of <0.05, Sylvivia et al (2012)[16] with the significance of <0.05, Giurgea et al (2012)[18] with the significance of <0.05 and Naik et al (2015)[15] with a significance of <0.05.

4.3. P53 Immunoexpression and histotype of carcinoma

The serous carcinoma was considered P53 positive as the study has been conducted by the different individuals that are seen in the 6^{th} table. The results are not at par with the study conducted by Naik et al (2015).[15]

4.4. P53 expression and grade of serous carcinoma

Based on the conducted analysis, it was also assessed that there was a statistically significant difference between P53 expression and serous carcinoma in the current study. But Giurgea et al (2012)[18] had not found any correlation.

4.5. P53 expression and FIGO staging

With respect to the table number 5 in the current study, the positive rate of P53 increases with the stage. This is very much similar to the study that was conducted by Giurgea et al (2012).[18] But the given result was not statistically significant with the p=0.18.

5. Conclusion

The present study concludes that P53 tumor gene was found to be mutated in more than the 50% of the human cancer.[19] The given form of cancer was mutated in between 50 to 75% ovarian carcinoma which was expressed as the aberrant form of protein. This was examined by the IHC.[20] The study also concludes that in borderline tumor, P53 rarely mutates and is results in poor prognosis. The P53 abnormality pattern was consistent with the spontaneous mutation rather than activity of chemical carcinogens. The P53 expression has a role in pathogenesis of these tumors as evident from malignant tumors, especially in high grade serous ovarian carcinoma.[21] Higher expression of p53 in malignant tumours compared to borderline tumours helps in distinguishing between borderline and malignant and in diagnosis in case of dilemma**.**

6. Conflict of Interest

There are no conflicts of interest in this article.

7. Source of Funding

None.

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