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Expression Of BCL2 and P53 in Ovarian Epithelial Tumors

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ABSTRACT

Ovarian cancer is the sixth most common cancer among women worldwide and the second most common gynecological malignancy. It has the worst prognosis and the highest mortality rate. The overall 5-year survival rate of patients with ovarian cancer is only about 30%, mainly due to absence of symptoms at early stages and its poor prognosis. It has been demonstrated that dysregulation of the genes involved in apoptosis, such as Bcl2 and p53, plays an important role in tumor formation. Bcl2 is capable of inhibiting apoptosis. p53 functions as a tumor suppressor by arresting cell cycle at G1 phase and by triggering apoptosis. Mutation of p53 gene is one of the most common changes associated with many cancers including ovarian cancers. This prospective study was conducted over a one and half year period from January 2021- August 2022 on 32 specimens of surface epithelial tumor of ovary received in 10% neutral buffered formalin at the Department of Pathology, at a tertiary care center. The tissues were stained with Haematoxylon and Eosin. Representative sections were taken for immunohistochemistry using antibodies against Bcl2 and p53 proteins were performed. 32 cases of surface epithelial tumors comprising 19 benign, 6 borderline and 7 malignant epithelial tumors were studied. Serous cystadenoma was the most commonly observed epithelial ovarian tumour. Majority of the malignant and borderline cases occurred in the age group of 41-60 years. Most of the cases were unilateral with right sided predominance. Bcl2 expression was seen in 15 out of 19 (78%) of benign, 5 out of 6 (83.3%) of borderline and 4 out of 7 (57%) of malignant tumors with a p value 0.6 (>0.05). Wild type p53 expression was observed in all cases of benign and borderline surface epithelial ovarian tumors. Mutant p53 expression was seen in all malignant tumors. The p value for p53 expression in benign, borderline and malignant surface epithelial tumors was 0.00 (<0.05). High grade serous carcinomas in contrast to other epithelial ovarian tumors showed a strong intense over expression pattern of mutant p53 expression, hence can be useful in detecting cell type in ovarian high grade malignancies. p53 appears to be a marker with better significance in distinguishing benign, borderline and malignant tumors in comparison to Bcl2 protein. p53 expression though positive in all the malignant epithelial ovarian tumors, it was noted that >80% of the malignant cells showed intense nuclear positivity in high grade serous carcinomas, as against <50% cell nuclear positivity in mucinous and clear cell carcinomas. This could be useful in detecting cell type in high grade ovarian malignancies.

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Key Words

Epithelial serous ovarian tumor, p53, Bcl2, gynecology malignancy

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INTRODUCTION

Ovarian cancer is the fifth most common cause of death due to cancer in women and accounts for three percentages of all cancers in females[1]. There are three main categories of primary ovarian tumours. These include surface epithelial tumours, sex cord stromal tumours and germ cell tumours[1]. The epithelial tumours comprise about more than ninety percentage of malignant tumours and sixty percentage of all ovarian neoplasms. p53 protein is responsible for maintaining the integrity of the genome via the induction of cellular apoptosis by mitochondrial pathways. Mutations in p53 interfere with its ability to arrest the cell cycle. Bcl2 is an oncoprotein which inhibits apoptosis[1]. Immuno histochemical studies with epithelial ovarian carcinoma indicate the presence of strong Bcl2 expression in tumours with low grade, whereas p53 accumulation was associated with advanced stage ovarian tumours and high grade tumours in various studies[2]. In the search for the best available prognostic factors, immunohistochemistry plays a valid and an important role. Two of the markers which are used for immunohistochemical evaluation of ovarian tumours worldwide are p53 and Bcl2. The present study evaluates the role of immuno histochemical markers p53 and Bcl2 in various surface epithelial ovarian tumors. Histopathological study and immuno histochemical markers aid in individualization of treatment strategies in various epithelial ovarian tumours.

MATERIALS AND METHODS

Prospective study of 32 ovarian surface epithelial tumours from January 2021- August 2022 received in the Department of Pathology at a tertiary care center was included in the study. Methods of grossing given in Ackerman's Surgical Pathology, Appendix E, were followed for surface epithelial tumours of ovary. All tissues were collected in 10% buffered formalin[5]. micron thickness tissue sections were cut for paraffin blocks and stained with haematoxylin and eosin to classify them into benign, borderline and malignant. All cases were stained with p53 and Bcl2 immuno histochemical markers. All the surface epithelial tumours of the ovary were included in the present study. Non neoplastic lesions and other non epithelial tumours of the ovary were excluded from the study.

RESULTS AND DISCUSSIONS

Histopathology and immunohistochemistry of 32 cases of surface epithelial ovarian tumours were studied. The study included 19 benign, 6 borderline and 7 malignant surface epithelial ovarian tumours.

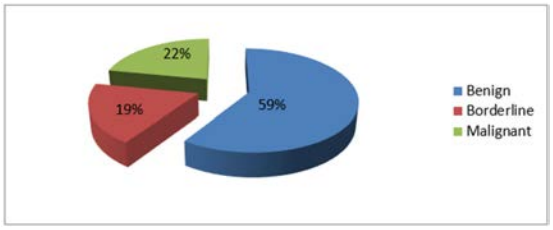

Fig.1: Frequency of Benign, Borderline and Malignant Surface Epithelial Tumours (n=32)

In the present study a total of 32 cases were considered. Among them 19 (59.4%) were benign, 6 (18.8%) borderline and 7 (21.9%) malignant tumours of the ovary respectively.

Table 1: Histological Types of Benign Ovarian Epithelial Tumours (n=19)

Benign epithelial Ovarian Tumours	Number of cases included in the study
Serous cystadenoma	11
Mucinous cystadenoma	6
Endometriosis cystadenoma	2

19 benign surface epithelial ovarian tumours were studied. Majority of the cases were serous cystadenoma (11), followed by mucinous cystadenoma (6) and endometriosis cystadenoma (2) cases respectively.

Table 2: Histological Types of Malignant Ovarian Epithelial Tumours (n=7).

Malignant epithelial Ovarian Tumours	Number of cases included in the study
Low grade serous carcinoma	1
High grade serous carcinoma	2
Clear cell carcinoma	2
Mucinous carcinoma	2

From the above table frequency of serous carcinoma was higher compared to other epithelial ovarian carcinoma.

Table 3: Histological Types of Borderline Ovarian Epithelial Tumours (n=6)

Borderline epithelial Ovarian Tumours	Number of cases included in the study
Borderline mucinous tumour	4
Borderline serous tumour	2

6 borderline epithelial ovarian tumours were included in the study. Majority of cases were of borderline mucinous ovarian tumours followed by serous ovarian tumour.

Table 4: Age Wise Distribution of the Cases (n=32)

	Ovarian epithelial tumours				
Age (in years)	Benign (n=19)	Borderline (n=6)	Malignant (n=7)	Total	P-value
40 and below	8	1	2	11	
41-60	8	5	5	18	
Above 60	3	0	0	3	0.486
Total	19	6	7	32	

Among the 7 malignant cases, majority of the cases belong to 41-60 years. A similar observation was seen in case of borderline epithelial ovarian tumours. On

using Chi square test, no statistically significant difference was observed in the age wise distribution of the cases.

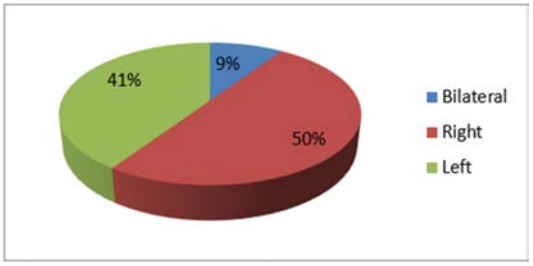

Fig. 2: Location of Benign, Borderline and Malignant Surface Epithelial Tumours (n=32)

Majority of the epithelial ovarian tumours studied were right sided in laterality.

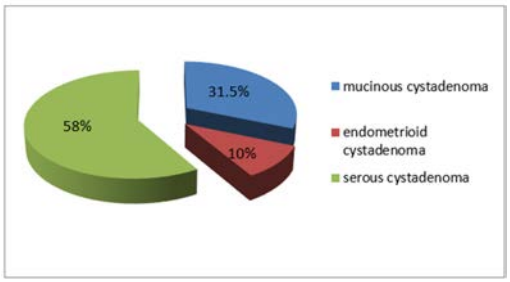

Fig. 3: Histological Types of Benign Surface Epithelial Tumours (n=19)

Majority of the cases included in the study were serous cystadenoma ovary.

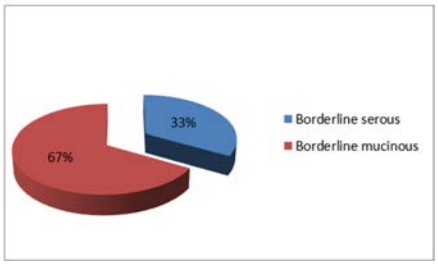

Fig. 4: Histological Types of Borderline Surface Epithelial Tumours (n=6)

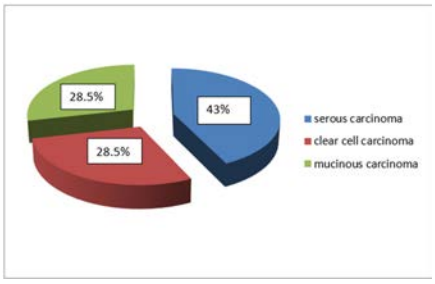

Fig. 5: Histological Types of Malignant Surface Epithelial Tumours (n=7)

Serous carcinoma was observed in higher frequency compared to other malignant surface epithelial ovarian tumours.

Table 5: Comparison and Significance of p53 IHC Staining in Various Epithelial Ovarian Tumours (n=32)

	p53 staining in ovarian tumours				
Staining	Benign (n=19)	Borderline (n=6)	Malignant (n=7)	Total	p value
Wild type	19	6	0	25	
Mutant type	0	0	7	7	
Total	19	6	7	32	0.00

All the 7 malignant cases showed to be mutant type of p53 expression. All benign and borderline cases showed p53 wild type expression ($p<0.001$).

Table 6: Comparison and significance of Bcl2 IHC staining in various epithelial ovarian tumours (n=32)

	Bcl2 staining in ovarian tumours				
Staining	Benign (n=19)	Borderline (n=6)	Malignant (n=7)	Total	p value
Intense	16	5	4	25	
Weak	3	1	3	8	
Total	19	6	7	32	0.628

Bcl2 expression was seen in 15 out of 19 (78%) of benign, 5 out of 6 (83.3%) of borderline and 4 out of 7 (57%) of malignant tumours with a p value 0.6 (>0.05).

Table 7: Bcl2 and p53 Expression in Benign Epithelial Ovarian Tumours (n=19)

	Bcl2		p53	
Benign(n=19)	Strong	Weak	Wild	Mutant
Serous cystadenoma (n=11)	10	1	11	0
Mucinous cystadenoma (n=6)	5	1	6	0
Endometrioid cystadenoma (n=2)	1	1	2	0

Majority of benign surface epithelial ovarian tumours show epithelial and stromal strong Bcl2 positivity with wild type patchy p53 expression.

Table 8: Bcl2 and p53 Expression in Borderline Epithelial Ovarian Tumours (n=6)

	Bcl2		p53	
Borderline tumour (n=6)	Strong	Weak	Wild	Mutant
Borderline Serous tumours (n=3)	2	1	3	0
Borderline Mucinous tumours (n=4)	4	0	4	0

Few of the cases show weak epithelial and stromal Bcl2 positivity but none of the case shows mutant p53 expression. None of the borderline cases in the study showed mutant p53 expression while majority of the cases showed epithelial and stromal strong Bcl2 positivity. A similar observation was noted in benign epithelial ovarian tumours.

Table 9: p53 Expression in Malignant Epithelial Ovarian Tumours (n=7)

Malignant Tumour (n=7)	p53			
	Wild	Mutant Aberrant	Over Expression	Null
Low grade serous carcinoma (n=1)	0	1	0	0
High grade serous carcinoma (n=2)	0	0	2	0
Clear cell carcinoma (n=2)	0	2	0	0
Mucinous carcinoma (n=2)	0	0	2	0

Both the high grade serous surface epithelial ovarian tumour included in the study showed predominantly overexpression pattern of mutant p53 expression with characteristically >80 % of tumour cells showing intense nuclear positivity. A case of low grade serous carcinoma included in the study showed aberrant cytoplasmic expression. Clear cell carcinoma showed aberrant cytoplasmic expression.

Table 10: Mutant p53 Over expression in High Grade Serous Carcinoma and Mucinous Carcinoma Based on Percentage of Tumour Cells Showing Nuclear Positivity.

Malignant tumour (n=4)	Mutant p53 over expression <50 % tumour cells positivity	>80% tumour cells positivity
High grade serous carcinoma (n=2)	0	2
Mucinous carcinoma (n=2)	2	0

Mucinous carcinoma also showed over expression pattern of mutant p53 expression however the percentage of cells showing nuclear positivity was <50%.None of the cases included in the study showed null type pattern of mutant p53 expression. Malignant high grade serous carcinoma included in the study showed p53 overexpression with more than 80% of the tumour cells showing strong nuclear staining. Mucinous carcinoma also showed overexpression pattern but with <50% of tumour cells showing nuclear positivity.

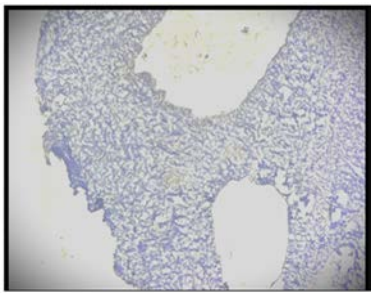

Fig. 6: Photomicrograph: Immunohistochemistry Stained Section Showing Patchy p53 Wild Type Expression (IHC:p53, 40x)

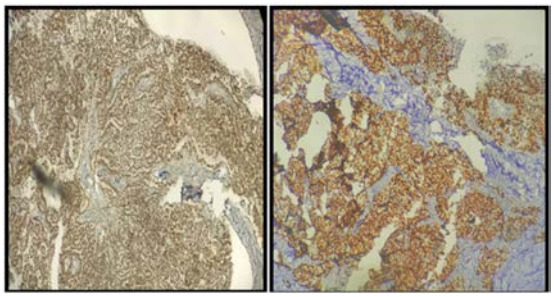

Fig. 7: Photomicrograph: Immunohistochemistry Stained Section Showing p53 Over Expression in High Grade Serous Carcinoma (IHC:p53, 40x) in >80% of Tumour Cells

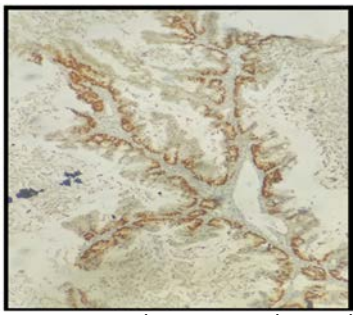

Fig. 8: Photomicrograph: Immunohistochemistry Stained Section Showing p53 Expression in Mucinous Carcinoma (IHC:p53, 40x) Seen in <50% of Tumour Cells

Fig. 9: Photomicrograph: Immunohistochemistry Stained Section Showing p53 Cytoplasmic Expression in Clear Cell Carcinoma (IHC:p53, 40x

Ovarian cancer is the fifth most common cause of death due to cancer in women and accounts for three percentages of all cancers in females[1]. Three main categories of primary ovarian tumors include surface epithelial tumors, sex cord stromal tumors and germ cell tumours[1]. The epithelial tumors comprise about more than ninety percentage of malignant tumors and sixty percentage of all ovarian neoplasms.

Age Distribution: Recent studies on role of growth factors in ovarian cancers have been carried out in various institutions. Hence two growth factor receptors of prognostic value have been found which appears to be involved in ovarian tumour development, most important of these markers being p53 and Bcl2[3]. The use of histopathological study and immuno histochemical markers aid in individualization of treatment strategies in various epithelial ovarian tumours. In the present study majority of patients with malignant and borderline epithelial ovarian tumors belong to 41-60 years of age. This observation was similar to studies done by Chandra[4] in an Indian cancer set up. In malignant epithelial ovarian tumours majority of cases belonged to 41-60 years which was comparable to the study done by Chandra[4] which was done in an Indian set up but against the study done by Bogger-Meggido[5] which showed a preponderance of age group above 60 years . This was a study done in a western set up. This variation could probably be due to the topographical and ethnic variation.

Laterality: In the present study an overwhelming majority of cases of in both benign and borderline epithelial ovarian tumors were unilateral. These findings were in concordance with the studies done by Chandra[4] In the malignant epithelial ovarian tumors majority of cases were unilateral. This observation was similar to the studies done by Chandra[4], in a study

done in and Indian set up but was against the study done by Boger-Megiddo[5] and Dane[6]. Both of these studies were done in western setup. Hence variation in laterality of malignant epithelial ovarian tumors could be due to the topographical and ethnic variation.

Histological Types of Benign Epithelial Ovarian Tumors: In the present study majority of cases of benign epithelial ovarian tumor were of serous cystadenoma of ovary which was similar to observations in the study done by Chandra[4], in a study done in India and two other studies done by Anderson[7] and Torre[8]. This was followed by mucinous cystadenoma ovary.

Histological Types of Malignant Epithelial Ovarian Tumours: In the present study majority of the cases of malignant epithelial ovarian tumor were of serous carcinoma of ovary which was similar to observations in the study done by Boger-Megiddo[5] and Havrilesky[9].

Bcl2 Expression in Benign, Borderline and Malignant Surface Epithelial Tumors: The present study showed Bcl2 expression benign 78%, 83.3% and 57% in benign, borderline and malignant surface epithelial ovarian cancers respectively. This was similar to observation done by Chan[10] where he reported the Bcl-2 expression positivity rate in normal ovary tissue and benign, borderline and malignant ovarian tumours as 79%, 100%, 78% and 33%, respectively. A significant decrease in Bcl-2 expression from benign to malignant tumours was reported. This was in concordance with the present study with respect to benign and borderline cases but malignant ovarian tumours showed 57% positivity, which was against other studies with <50% positivity. Henriksen[11] in his study on 55 cases of epithelial ovarian tumours, showed 83.3% positivity in benign tumours, 90% intense positivity in borderline tumours and 80% of malignant tumours, which was similar to our study. Herod[12] in his study on seventy malignant ovarian epithelial tumours, 24% were positive for Bcl2. In comparison the present study present study showed 57% positivity.

P53 Expression in Benign, Borderline and Malignant Surface Epithelial Tumours: The present study showed 100% p53 expression in all malignant epithelial ovarian tumours and none of the benign and borderline cases expressing p53. Herod[12] in his study on seventy malignant ovarian epithelial tumours found that (61%) 43/70 were positive for expression of p53 immunohistochemistry. Arik[13] in his study on a total of 71 tumours including 29 benign, 14 borderline and 28 malignant ovarian serous tumours, p53 expression was not observed in benign or borderline serous tumours. The p53 expression rate in serous carcinomas was 42.9%. In comparison our study showed 100% p 53 expression in all malignant epithelial ovarian tumours. In the present study p53 expression in benign epithelial ovarian tumors was zero which is concordance with the study by Marks[14]. In their study on immuno histochemical study on p53 expression in 107 epithelial ovarian cancers, 54/107 cases (50%) showed p53 positivity and nil expression of p53 in benign surface epithelial tumours.

P53 Expression in Malignant Epithelial Ovarian Tumours: In the present study p53 mutant expression though positive in all the malignant epithelial ovarian tumours, it was noted that >80% of the malignant cells showed intense positivity in serous carcinomas, as against <50% cell positivity in mucinous and clear cell carcinomas. This could be useful in detecting cell type in high grade ovarian malignancies. This was correlating with studies done by Amanullah[15] and Cole[16].

Limitation: The study is limited due to small sample size.

CONCLUSION

p53 mutant expression though positive in all the malignant epithelial ovarian tumors, it was noted that >80% of the malignant cells showed intense positivity in serous carcinomas, as against <50% cell positivity in mucinous and clear cell carcinomas. This could be useful in detecting cell type in high grade ovarian malignancies. The results indicate that p53 is a good marker for the diagnosis of malignant surface epithelial ovarian tumors, thus able to differentiate benign and malignant tumors. Bcl2 mutation is not a reliable criterion for differentiating benign, borderline and malignant surface epithelial tumors of the ovary.

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