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Original Research Article

EVALUATE THE IMMUNOHISTOCHEMIAL EXPRESSION OF P53 AND KI67 IN PROSTATE CANCER IN EASTERN PART OF UTTAR PRADESH

Ravikant Verma[1], Rajesh Rai[2], Shaila Kumari Mitra[3], Shilpa Vahikar[4], Poonam Bajpai[5], Saukat Ali[6]

[1]Senior Resident, Department of Pathology, BRD Medical College, Gorakhpur, Uttar Pradesh (Eastern part), India.
[2]Professor, Department of Pathology, BRD Medical College, Gorakhpur, Uttar Pradesh (Eastern part), India.
[3]Professor, Department of Pathology, BRD Medical College, Gorakhpur, Uttar Pradesh (Eastern part), India.
[4]Professor, Department of Pathology, BRD Medical College, Gorakhpur, Uttar Pradesh (Eastern part), India.
[5]Junior Resident, Department of Pathology, BRD Medical College, Gorakhpur, Uttar Pradesh (Eastern part), India.
[6]Junior Resident, Department of Pathology, BRD Medical College, Gorakhpur, Uttar Pradesh (Eastern part), India.

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Corresponding Author:
Dr. Ravikant Verma
Email: rkant3845@gmail.com

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Abstract

Background: Prostate cancer is a major health problem in male with increasing age, accounting for significant morbidity and mortality throughout the developed world. Tumor grade is one of the main prognostic markers of prostate cancer. Presently, the satisfactory prognostic markers for prostate disease are as yet missing. Therefore, in this study we aim to evaluate the immunohistochemical expression of P53 and Ki67 in prostate cancer. **Materials and Methods:** This cross sectional study total of 100 cases including 60 malignant cases, 10 prostatic intraepithelial neoplasia and 30 benign lesions were studied. Tumor grade was determined with the help of Gleason's grading system. The p53 and Ki-67 expressions level were determined with the help of IHC staining. The Fisher's exact test and chi-square test were used for analyzed the data. **Results:** In this study the maximum patients with prostatic lesions had 60 or more than 60 year age group. The PSA level was significantly higher range in malignant lesions as compared to benign lesions. Ki-67 expression was negative (<2%) in all 5 (100%) well differentiated tumors. Total 40% cases were well differentiated adenocarcinoma, 75% moderately differentiated adenocarcinoma and 94.1% poorly differentiated tumors revealed p53 immunopositivity. Total 41.5% patients had positivity for both p53 and Ki-67 markers. Moreover, total 15 (25%) patients had p53 positive and 13 (21.7%) patients had Ki67 positive. Ki-67 score in cancer positive for p53 was greater than that found in cancer negative for p53 and a statistically significant correlation was observed between p53 and Ki-67 expression. **Conclusions:** The frequency of expression of both p53 and Ki-67 were significantly up-regulated in malignant lesion as compared to benign lesion and a strong association with the Gleason's grading was observed.

INTRODUCTION

Prostate gland is one of the most commonly affected organ in male with increasing age, accounting for significant morbidity and mortality.[1] Lesions of prostate are an area of constant interest to clinician as well as pathologist. Recently, there is considerable change in the understanding of many prostatic diseases. Accurate diagnosis of prostatic disease frequently requires simultaneous clinical history, biochemistry, imaging techniques and surgical pathology laboratory.[2] Even following detailed histopathological examination of biopsy tissue, taken from precisely defined microanatomic sites within the prostate, informed opinion as to the diagnostic or prognostic significance of particular morphological features, frequently remain controversial, to the extent that the distinction of benign from malignant neoplastic diseases may not be possible.[3]

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The prostate is affected by a variety of pathological processes, but the more frequent encountered are benign prostate hyperplasia (BPH), prostatitis, and prostatic cancer.. BPH is the most common urological disorder in males beyond 40 years of age. The prevalence of BPH increases from 20% at 40 years of age to 90% by the eighth decade of life.[5]

Prostate cancer is globally the second most frequent diagnosed cancer and sixth leading cause of cancer death in males. It is second only to lung cancer as a cause of cancer related deaths in men.[6] In India carcinoma of prostate occupies 2nd to 10th rank among cancer in men, in various metro cities as per national cancer registry.[7,8] Significant advances have occurred in the understanding of pre malignant epithelial lesions as well as new clinical techniques, enhancing early detection of cancer, such as transrectal ultrasound and serum levels of prostate specific antigen (PSA).[9] There is substantial increase in number of prostate needle biopsies due to increased awareness and the wide spread use of serum PSA as a mass screening test along with imaging studies for prostate cancer. Accurate diagnosis on needle core biopsy or transurethral resection of prostate (TURP) specimen is of utmost importance because if diagnosed early for malignancy, patient is benefitted as a result of a lesser invasive procedure instead of more radical procedures that is associated with significant mortality and morbidity.[10] However, biopsy remains the gold standard for final diagnosis. Histological diagnosis of prostatic cancer is usually based on morphological features such as growth pattern, nuclear atypia and absence of basal cells.[5] However, there are various mimickers of prostate carcinoma such as benign hyperplasia, prostatitis, atrophy, adenosis, atypical adenomatous hyperplasia and nephrogenic adenoma which makes the diagnosis of prostatic widely used and accepted histopathological method for providing information about the prognosis of prostate carcinoma. This grading system is based entirely on the histological pattern of differentiation and arrangement of section.[11] Other beings, prostate-specific antigen (PSA), which is the most useful tumor marker in the diagnosis of prostate carcinoma but suffer from many fallacies such as border line level and also spuriously high level in many reactive and inflammatory conditions.[12] Despite advances in screening and multimodal management of this disease, overall survival remains poor. Hence, there is a need to identify various prognostic markers for developing new therapeutic strategies for better management of Prostate carcinoma patients.

Therefore, IHC plays a major role besides PSA and the important tumor markers are p53 and Ki-67 to predict the prognosis and to decide the treatment modalities. P53 is a tumor suppressor gene, mutations of which can result in uninhibited cellular growth and have been implicated in numerous malignancies.[12] In most human cancers its increased immunohistochemical expression is associated with point mutations in one allele of p53 gene and loss in the other.

Potential of tumor protein p53 in cancer treatment has become an increasingly prominent research theme. It has been established that p53 is a tumor suppressor gene and that p53 mutation occur in 50% of tumor cells. Upon DNA damage by radiation or other factor, p53 activates p21, which function in DNA repair and also regulating gene apoptosis.

Ki-67 is one of the several cell cycle regulated proteins, which can be demonstrated by IHC.[13,14] It is a DNA- binding protein, which is expressed in all phases of cell cycle but undetectable in resting cell.[15,16] The Ki-67 index (fraction of Ki-67 positive nuclei in IHC) was higher for carcinoma than for hyperplastic glands while within the group of carcinoma, Ki-67 indices in patients with metastatic disease were significantly higher than in those without metastasis and that high Ki-67 index could define a group of patients with poor prognosis.[17]

Role of p53 and ki 67 in prostate cancer-P-53 pathological diagnosis requires the presence of a combination of multiple histologic features of tumor cell such as pattern of growth, nuclear atypia, absence of basal cell, and the presence of characteristic extracellular material in malignant glands. The proliferation index correlated with grade and stage. Gleason grade was the most reliable predictor of biopsy, proven residual disease and clinical progression. In radical series transition zone carcinoma, the proliferation index was half that peripheral zone carcinoma, atrophic lobules also showed a high proliferation index of the same order as seen in the peripheral zone carcinoma. In this study we aim to evaluate the immunohistochemical expression of P53 and Ki67 in prostate cancer.

MATERIALS AND METHODS

This cross sectional study has been carried out on patients of various prostatic lesions including benign, premalignant and malignant lesions attending surgery OPD and on admitted patients in the surgery wards. Detailed history, clinical findings specially digital rectal examination, PSA value, radiological and other investigative findings were noted. After taking informed consent, histopathological examination and immunohistochemical expression of p53 and Ki-67 were carried out on prostatic biopsies including trans urethral resection of prostate (TURP) specimens, as well as radical prostatectomy specimens, received in the department of pathology.

All prostatic biopsies specimens suspected to benign and malignant prostatic lesions along with TURP specimens, TRUS biopsies, radical prostatectomy specimens received in the department of pathology were included in this study. The autolyzed and inadequate samples were excluded from study.

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Prostatic biopsy tissues were fixed in 10% formalin saline and subjected to histopathological examination using paraffin embedding technique. Tissue blocks were prepared using paraffin wax of 58- 60 0C melting points. All the paraffin blocks were preserved for section cutting. Thin sections of 2-3 micron were cut after dewaxing and then stained by hematoxylin and eosin stain. The slides were examined and the tumor's grade was determined by using Gleason's grading system. Histopathological diagnosis was made and then freshly cut sections were also used for immunostaining for P53 and Ki-67 markers. Each slide was evaluated at ×40 magnification in order to find areas with maximum positive cells. Then these areas were examined at ×400 magnification and the percentage of positive cells to total cells was calculated.

A positive control was used for every antibody to eliminate the possibilities of wrong interpretation. Known p53 and Ki-67 positive specimen were used as a positive control. Sections stained omitting primary antibody were taken as negative control.

Positive staining pertains to the brown staining of nuclei. A semi quantitative scoring system was employed to assess the level of p53 reactivity. The percentage positivity was graded from 0 to 3+ as follows:-<5% cells (0, negative), 5-25% cells (1+, mild), 26-50% cells (2+, moderate), > 50% cells (3+, strong). The adjacent benign glands should not show more than weak, partial staining if any. Negative staining pertains to no staining or focal, weak fine granular staining [18].

For immunopositivity of ki-67; the tumors were divided into five groups regarding the percentage of positive cells. The cases in which the percentage of stained cells was less than 2% were considered negative. Cases with stained cells less than or equal to 25% were considered 1+ 26-50% as 2+, 51-75% as 3+ and >75% as 4+ were other indices of ki-67 immunostaining scoring.[13]

Statistical Analysis

The results were analyzed and evaluated with SPSS software version 21. For statistical analysis of Gleason's grading Spearman's statistical test was used. Statistical method such as calculation of mean, standard deviation, Fisher's exact test and chi-square test were employed to find out the significance of the study and a p-value of <0.05 was considered significant.

RESULTS

A total of 100 cases of formalin fixed paraffin embedded histological sections of various prostatic lesions including malignant cases (60), prostatic intraepithelial neoplasia (10), benign lesion (30) were studied. All the sections were stained with Haematoxylin and Eosin stain to categorize histopathologically, and to determine Gleason's score and grade in prostatic adenocarcinoma and then immunohistochemical staining for p53 and Ki-67 was performed on all cases using avidin-biotin peroxidase complex method.

Table 1 shows the distributions of study population according different age group. The percentage of 30-39, 40-49, 50-59, 60-69, 70-79 and ≥ 80 years age group were 3.3%, 10.0%, 10.0%, 46.6%, 26.6% and 3.3% in benign lesions, 0.0%, 0.0%, 10.0%, 30.0%, 50.0% and 10.0% in intraepithelial neoplasia and 0.0%, 0.0%, 6.6%, 21.6%, 58.3% and 13.3% in malignant lesions, respectively. The percentage of different age group was significantly different prostatic lesions.

Table 1: Age wise distribution of prostatic lesions

Age (Years)	Total		Benign lesions		Intraepithelial neoplasia		Malignant lesions	
	n	%	n	%	n	%	n	%
30-39	1	1.0	1	3.3	0	0.0	0	0.0
40-49	3	3.0	3	10.0	0	0.0	0	0.0
50-59	8	8.0	3	10.0	1	10.0	4	6.6
60-69	32	32.0	14	46.6	3	30.0	13	21.6
70-79	48	48.0	8	26.6	5	50.0	35	58.3
≥ 80	8	8.0	1	3.3	1	10.0	8	13.3
Total	100	100	30	100	10	100	60	100
p<0.029*								

*=Significant (p<0.05)

[Table 2] shows the distribution of cases on the basis of nature of prostatic specimens. The percentage of Trucut biopsy, Transurethral resection of prostate (TURP), and Supra pubic prostatectomy (SPP) were 20%, 78%, and 2% in study population.

Table 2: Distribution of cases on the basis of nature of prostatic specimens

Gross	Number of cases (n)	Percentage (%)
Trucut biopsy	20	20%
Transurethral resection of prostate (TURP)	78	78%
Supra pubic prostatectomy (SPP)	2	2%
Total	100	100%

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Table 3 shows the different PSA level in various prostatic lesions. The percentage of 0-4, 4-10, 11-20 and >20 ng/ml were 0%, 11.6%, 20% and 68.4% in Malignant lesions, 40%, 20%, 10% and 30% in intraepithelial neoplasia and 73.3%, 26.6%, 0% and 0% in Benign lesions, respectively. Moreover the PSA level was significantly higher range in malignant lesions as compared to benign lesions.

Table 3: Serum PSA level in various prostatic lesions

PSA level (ng/ml)	Malignant lesions	Intraepithelial neoplasia	Benign lesions	p-Value
	n (%)	n (%)	n (%)	
0-4	0 (0%)	4 (40%)	22 (73.3%)	<0.001*
4-10	7 (11.6%)	2 (20%)	8 (26.6%)	
11-20	12 (20%)	1 (10%)	0 (0%)	
>20	41 (68.4%)	3 (30%)	0 (0%)	
Total	60	10	30	

*=Significant (p<0.05)

In Prostatic carcinoma, 3 out of 5 (60%) well-differentiated tumors showed absence of positivity while 2 cases (40%) showed grade I positivity. Total 15 out of 36 (41.6%) moderately differentiated tumor revealed strong nuclear positivity with grade 3 positivity and 9 cases showed grade 2 positivity. 9 cases out of 36 (25.0%) did not express p53 positivity. Total 18 out of 19 (94.7%) cases of poorly differentiated prostate adenocarcinoma showed strong nuclear positivity including 9 cases (47.4%) with grade 3 positivity followed by 5 cases (26.3%) with grade 2 positivity and 4 cases (21.0%) were grade 1+ positivity. Only one case (5.3%) was negative with p53 (Table 4).

Ki-67 expression was negative in all 5 cases (100%) of well differentiated tumors. Out of 36 cases of moderately differentiated prostatic adenocarcinoma, 10 cases (22.8%) showed grade 2+ positivity, 11 cases (30.5%) revealed grade 1+ positivity and grade 3+ positivity was seen in 1 case (2.8%). 14 cases (38.9%) were negative. Total 17 out of 19 poorly differentiated adenocarcinoma were positive, with grade 3+ positivity in 4 cases (21.0%). 7 cases (36.9%) showed grade 2+ positivity and 6 cases (31.6%) were grade 1+ positivity. 2 cases (10.5%) were negative for Ki-67. No case showed 4+ positivity. A statistically significant correlation was observed between Ki-67 positivity and Gleason's grade of prostatic carcinoma (p = 0.002).

Table 4: Frequency of positive and negative P53 and Ki67 immunostaining in relation to differentiation and Gleason's grade

		Gleason's grade			
		Well differentiated adenocarcinoma (n=5)	Moderately differentiated adenocarcinoma (n=36)	Poorly differentiated adenocarcinoma (n=19)	Total
P53					
Negative	0 (0%)	3 (60%)	9 (25%)	1 (5.3%)	13
Positive	1 (<10)	2 (40%)	5 (13.8%)	4 (21.0%)	11
	2 (10-33)	0 (0%)	7 (19.4%)	5 (26.3%)	12
	3 (> 33)	0 (0%)	15 (41.6%)	9 (47.4%)	24
Ki67					
Negative	Negative (<2)	5 (100%)	14 (38.9%)	2 (10.5%)	21
Positive	1+ (<25)	0 (0%)	11 (30.5%)	6 (31.6%)	17
	2+ (26-50)	0 (0%)	10 (27.8%)	7 (36.9%)	17
	3+(51-75)	0 (0%)	1 (2.8%)	4 (21.0%)	5
	4+ (76-100)	0 (0%)	0 (0%)	0 (0%)	0

Table 5 shows the total 41.7% cases (25/60) exhibiting positivity for both p53 and Ki-67 marker. Out of total 5 cases of well differentiated adenocarcinoma, 3 cases (60%) were both p53 and Ki-67 negative, 2 cases (40%) were p53 positive and Ki-67 negative. Of total 36 cases of moderately differentiated adenocarcinoma, 3 cases (83%) were both p53 and Ki-67 negative, 8 cases (22.2%) were p53 negative and Ki-67 positive, 12 cases (33.4%) were p53 positive and Ki-67 negative, 13 cases (36.1%) were both p53 and Ki-67 positive. Total 19 cases of poorly differentiated adenocarcinoma, 1 cases (52%) were both p53 and Ki-67 negative, 5 cases (26.4%) were p53 negative and Ki-67 positive, 1 cases (52%) were p53 positive and Ki-67 negative, 12 cases (63.2%) were bothp53 negative and Ki-67 negative.

Table 5: Correlation with both p53 and Ki-67 expression

Prostatic carcinoma	Negative p53 and Ki-67	P53 Negative and Ki-67 positive	P53 positive and Ki-67 Negative	Positive p53 and Ki-67
	n (%)	n (%)	n (%)	n (%)
Well differentiated (n=5)	3 (60%)	0 (0%)	2 (40%)	0 (0%)
Moderately differentiated (n=36)	3 (8.3%)	8 (22.2%)	12 (33.4%)	13 (36.1%)
Poorly differentiated (n=19)	1 (5.3%)	5 (26.3%)	1 (5.3%)	12 (63.1%)
Total (n=60)	7 (11.6%)	13 21.7%)	15 (25%)	25 (41.7%)

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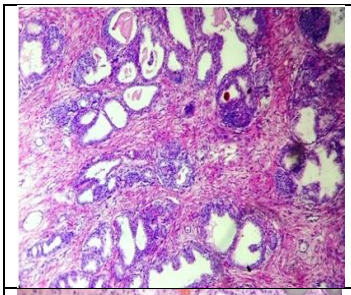
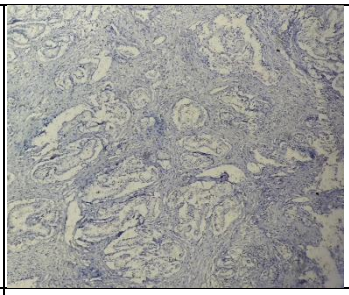
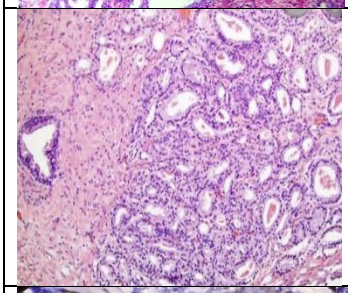
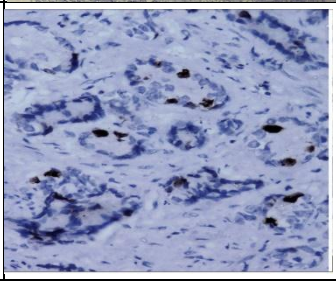
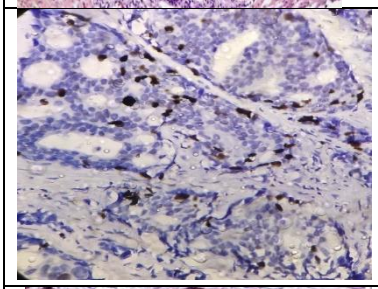
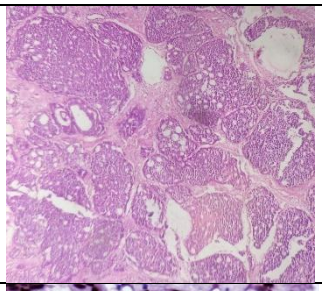
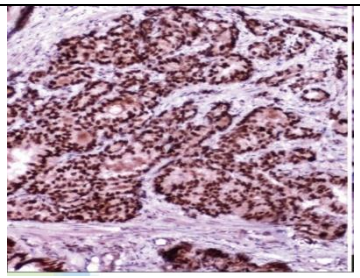
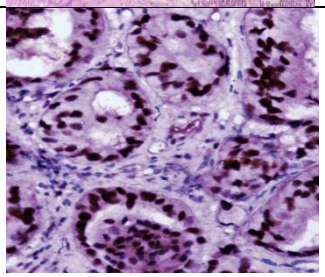
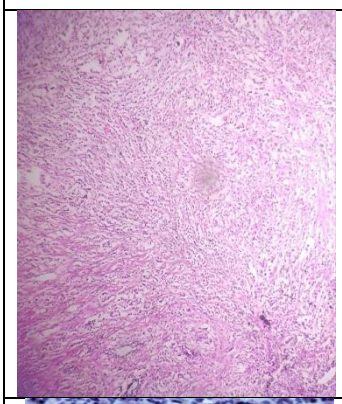
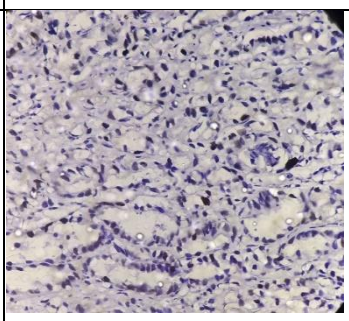
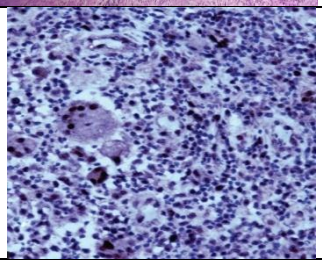
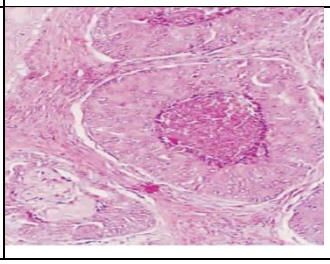
 **Microphotograph 1- Benign prostatic hyperplasia showing benign proliferation of glands along with stromal hyperplasia(H&EX100)**	 **Microphotograph 2 Benign prostatic hyperplasia showing negative with P 53**
 **Microphotograph 5 - Well differentiated adenocarcinoma of prostate showing proliferation of well formed neoplastic glands with central lumina. The glands are arranged back to back with little intervening stroma (H&EX100).**	 **Microphotograph 6 Well differentiated adenocarcinoma of prostate showing positivity with P-53**
 **Microphotograph 7 Well differentiated adenocarcinoma of prostate showing positivity with ki-67**	 **Microphotograph 8 - Moderately differentiated adenocarcinoma of prostate showing distinct neoplastic, variably sized glands along with poorly formed glands infiltrating into the stroma (H&EX100).**
 **Microphotograph 9 - Moderately differentiated adenocarcinoma of prostate showing positivity with P-53**	 **Microphotograph 10 - Moderately differentiated adenocarcinoma of prostate showing positivity with Ki-67**
 **Microphotograph 11 - Poorly differentiated adenocarcinoma of prostate showing diffusely infiltrating relatively uniform tumor cells in stroma with minimal gland formation, cells having high N:C ratio, pleomorphism, hyperchromatic nuclei, with coarse chromatin and prominent nucleoli (H&EX100).**	 **Microphotograph 12 Poorly differentiated adenocarcinoma of prostate showing positivity with P-53**
 **Microphotograph 13 Poorly differentiated adenocarcinoma of prostate showing positivity with Ki-67**	 **Microphotograph 14 Poorly differentiated adenocarcinoma of prostate with comedonecrosis**

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DISCUSSION

In context to the cases selected for study, the age of patients ranged from 39 to 86 years with mean age of 67.3+ 8.9 years. Youngest patient was 39 years old and oldest patient was 86 years old. Out of 100 cases, maximum cases (78%) were 60-79 years age group Our finding was supported by various previous studies, they who reported 70.3%, 81.39%, 56.44%, in 60-79 years of age group. Various other studies reported the more cases in 8th decade, while Natapuskar et al., 2014 found higher incidence in 6th decade.[19-20].

In our study, trans urethral resection of prostate (TURP) accounted for 78% of total 100 specimens, followed by Tru-cut biopsy of prostate. Our study was supported by various previous studies, they reported the majority of specimens were received from TURP which accounted for 100% (245 cases) and 88.7% (55 cases) respectively. However, in Chauhan et al. (2017) demonstrated that the total 60% of the specimens were true cut biopsies, 22.85%, were prostectomy specimen and 17.14%, were transurethral resection of prostate chips.

In this study, we analyzed the PSA levels in various prostatic lesions, PSA level was less than 4 ng/ml in 22 cases (73.3%) followed by 8 cases (26.6%) with PSA levels between 4-10 ng/ml. While in malignant cases, PSA level was more than 20 ng/ml in 41 cases (68.4%). It was in the range of 11-20 ng/ml in 12 cases (20%) and in between 4-10 ng/ml in 7 cases (11.6%). This finding was in accordance with various previous study.

In present study, 2 of 5 (40%) well differentiated adenocarcinoma, 27 of 36 (75%) moderately differentiated adenocarcinoma and 18 of 19 (94.1%) poorly differentiated tumors revealed p53 immunopositivity and a statistically significant correlation was observed between p53 expression and increased gleason grade (P <0.001). Thus it was observed that expression and intensity of p53 increased with the increase in grade, our finding are very well corresponds to study of Verma R et al this is concordance with many other studies also [35-38]. Kallakury et al. (1994) demonstrated a positive correlation between p53 immunopositivity and higher Gleason's grade with expression of 21% and 39% respectively.[21]

Ki-67 expression was negative (<2%) in all 5 (100%) well differentiated tumors. In moderately differentiated prostatic carcinoma, 14 of 36 (38.9%) were negative while 22 (61.1%) cases were positive, including 11 cases (30.5%) cases with 1+ positivity followed by 10 cases (27.8%) with grade 2+ positivity and only one case (2.8%) showed 3+ positivity. 17 out of 19 (89.5%) were positive including 6 (31.6%) with grade 1+ positivity and 7 (36.9%) cases with grade 2+ positivity and 4 cases (21.0%) with grade 3+ positivity, only2 (10.5%) were negative. No case showed 4+ positivity.

In our study total 25 (41.5%) patients had positivity for both p53 and Ki-67 markers. Moreover, total 15 (25%) patients had p53 positive and 13 (21.7%) patients had Ki67 positive. Similarly, Verma et al. (2015) reported that the total 48% patients exhibited positivity for both of these markers.[22]

In this study the Ki-67 score in cancer positive for p53 was greater than that found in cancer negative for p53 and a statistically significant correlation was observed between p53 and Ki-67 expression (P < 0.05).

CONCLUSION

It can be concluded that frequency of expression of both p53 a tumor suppressor protein and Ki-67, a cell proliferation marker is significantly up-regulated in malignant lesion as compared to benign lesion. Since most cases of prostate cancer are diagnosed microscopically before metastatic spread and among these, few cases have rapid and life threatening outcome, therefore, it indecent versus aggressive from prostate cancer can be differentiated from each other, we can help parents remarkably, in the current study, p53 and Ki-67 marker were shown to have a strong relationship with increased Gleason grade, which has an important relationship. With the prognosis of prostate cancer therefore, we propose that these marker can be applied along with other prostate cancer prognostic factors. However, further studies on larger sample are required to elucidate their role in the identification of premalignant lesion.

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