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Correlation of Immunohistochemical Expression of p53 in Benign and Malignant Prostate Lesions

Deepti Agarwal[1], Anu Sharan[2*], Swaran Kaur[3], Ruchi Agarwal[4], Atul Khandelwal[5]
[1]Professor [2]Post graduate student [3]Professor and Head [4]Professor Department of Pathology
[5]Associate Professor Department of Surgery BPS GMC (W) Khanpur Kalan Sonepat, Haryana, India 131305

***Corresponding Author:**
Dr. Anu Sharan
Department of Pathology, BPS GMC (W), Khanpur Kalan, Sonepat, Haryana, India 131305

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ABSTRACT

Introduction: Inflammation, benign prostatic hyperplasia and tumors are the pathological processes which affect prostate frequently. In India, prostate cancer is the fifth most common cancer among men. The expression of p53 corresponds with the progression of prostate cancer and has thus been regarded as a prostate marker for prostate carcinoma.

Material and methods: The study design was cross-sectional and total numbers of 70 cases of prostate specimens were included. H&E stained sections were studied and classified into benign and malignant lesions. Carcinoma cases were histologically graded according to the modified Gleason grading system. Immunohistochemical staining for p53 nuclear protein was performed in all the cases and a semi-quantitative assessment was done to assess the level of reactivity.

Results: Of the total 70 cases, 49 (70%) were categorised as benign prostatic hyperplasia and 21 (30%) were categorised as prostate carcinoma. p53 was expressed in 12 cases (57.1 %) of carcinoma prostate and none of the cases of BPH were positive. This difference was statistical significant (p value = 0.001). It was observed that lower the Gleason grade, the IHC scores was also low and it increased with increasing Gleason grade. However, this finding was not statistically significant (p value > 0.05).

Conclusion: The expression of p53 is significantly upregulated in malignant prostate lesions as compared to benign lesions. It is likely that p53 positive tumors detected at biopsy display aggressive biological feature, hence p53 might be a prognostic indicator among metastatic risk cases.

Keywords: prostate, BPH, prostate carcinoma, p53, Gleason grading

INTRODUCTION

The human prostate is a walnut sized fibromusculoglandular organ which weighs up to 20 gm in normal adults. It is a retroperitoneal organ that encircles the neck of the bladder and urethra.[1] Inflammation, benign prostatic hyperplasia (BPH) and tumours are the pathological processes which affect the prostate frequently. BPH is a benign enlargement of the prostate gland and refers to stromal and/or glandular epithelial hyperplasia.[2] Its histological prevalence at autopsy was found to be 50% in men aged 50–60 years and 90% in those over 80 years.[3]

Prostate cancer is the second most common cause of cancer and the fifth leading cause of cancer deaths among men worldwide.[4] In India, it is the fifth most common cancer among men.[5] The histological Gleason score of the adenocarcinoma of the prostate is a good and an established prognostic indicator. Recently, a modified Gleason grading system has been introduced by the International Society of

Urological Pathology (ISUP) and is recommended by the World Health Organization (WHO).[6]

There are a number of mutated genes, as well as several genes that are up or down regulated in prostate cancer. The most consistently observed site of mutation is the p53 gene and these mutations are common in advanced prostate cancer.[7] Protein p53 is a nuclear phosphoprotein that produces growth arrest at the G1–S checkpoint, allowing DNA repair and growth suppression. Loss of this activity through mutation produces genetic instability and allows metastatic progression. The expression of p53 corresponds with the progression of prostate cancer and has thus been regarded as a prognostic marker for prostate cancer.[8]

The present study is intended to find the correlation between expression of p53 on immunohistochemistry in benign and malignant prostate lesions.

MATERIALS AND METHODS

This cross sectional study was conducted over a period of one year on all types of prostate specimens received in the Department of Pathology at Bhagat Phool Singh Government Medical College for Women, Khanpur Kalan, Sonepat. The sample size was 70 cases. Labelled prostate tissue specimens including TURP chips and needle biopsy specimens were received in our department along with requisition form. Specimens were grossed, processed, sectioned and stained accordingly. H&E stained sections were studied under light microscope and classified into benign and malignant lesions. Carcinoma cases were histologically graded according to ISUP 2014/ WHO 4th edition Gleason grading system. Immunohistochemical staining for p53 nuclear protein was performed in all the cases and a semi-quantitative assessment was done to assess the level of p53 reactivity.[9]

Grade	Features
0	when no staining is observed
1	when less than 10% of tumor cell nuclei are positive
2	when more than 10%, but less than 33% of the nuclei are positive
3	If more than 33% of nuclei are positive

RESULTS

Patients of prostatic lesions range from 40-86 years. 4 ,cases 70Of the total 9)70 were (%categorisedas Benign ProstaticHyperplasia2 and 1) 30 (%were categorised as prostate carcinoma on the basis of histomorphological features. Patients of BPH were in the age range of 40-85 years with a mean age of 66 years and those of carcinoma prostate were in the age range of 54-86 years with a mean age of 70 years. Patients of carcinoma prostate were in higher age group as compared to patients of BPH, with a peak incidence at and above 7th decade. All carcinoma prostate cases were histologically adenocarcinomas. Each case was further graded using modified Gleason grade group system.

Amongst the 21 cases of carcinoma prostate, m.(%61.9) 4 aximum cases belonged to grade group Two cases (9.5%) were found to be of ,1 grade group three cases (14.3%) of gthirteen ,2 rade group cases 61.9)%) of and 4 grade group 3 cases (14.3%) of g5 rade group. There was no case belonging to grade (1 Figure ,1 Table) .3 group

The p53 expression was assessed in all the cases of carcinoma prostate and BPH by immunohistochemical staining. Cells with strong brown nuclear immunoreactivity were considered as positive and scored semi-quantitatively. p53 was expressed in the 12 cases (57.1%) of carcinoma prostate and none of the cases of BPH were positive. This difference was stastically significant as compared to negative IHC stain in all BPH patients (p value =0.001). (Table 2)

The p53 immunostaining expression was scored depending on the number of nuclei stained brown. IHC score 1 (< 10% nuclei stained) was seen in 6 cases (28.6 %) of carcinoma prostate, IHC score 2 (10-33% nuclei stained) in 4 cases (19%), IHC score 3 (> 33% nuclei stained) was seen in 2 cases (9.5%) and9) cases42.9(2 Figure) .showed no staining (%

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Comparison of p53 IHC score with Gleason grading was done. It was observed that lower the Gleason grade, the IHC score was also low and it increased with increasing Gleason grade. this ,Howeverfinding was notstatistically significant (p value >0.05). (Figure 3)

DISCUSSION

Prostatic enlargement is a major health problem throughout the world. Three pathological processes which affect the prostate frequently are: inflammation, benign prostatic hyperplasia and tumours. Of these three, the benign prostatic hyperplasia is most common, with increasing incidence as age advances. The disease is rare before the age of 50 years and the incidence increases with age.[1] More patients are diagnosed at earlier stages, due to increased availability of PSA measurement. PSA rise among men with either normal or abnormal digital rectal examination (DRE) findings suggests malignancy, but histology remains the gold standard in reaching a conclusive diagnosis.[10]

In the routine pathological examination of carcinoma prostate, the Gleason grading is a great help to predict the aggressiveness of the tumor. It is being widely used as a prognostic marker and to guide the therapeutic approach. Five basic patterns (scored 1–5) are used to generate a histological sum score (summed from scores of two most dominant patterns), which can range from 2 to 10.[11]

The tumour suppressor gene p53 links cell damage with DNA (deoxyribonucleic acid) repair, cell cycle arrest and apoptosis. With loss of function of p53, DNA damage goes unrepaired, and leads to malignant transformation. The ability of p53 to control apoptosis in response to DNA damage has important therapeutic implications. As the common modalities of cancer treatment, irradiation and chemotherapy, mediate their effects by inducing DNA damage and subsequent apoptosis. Tumors that retain normal p53 are more likely to respond to such therapy than tumors that carry mutated alleles of the gene. The normal p53 gene is short-lived and is not stained by routine immunohistochemical staining. It has been recognized that nonsynonymous *TP53* missense mutations result in nuclear accumulation of p53 protein that can be detected as overexpression by immunohistochemistry.[12]

It plays an important role in prostate cancer progression because abnormal p53 expression is associated with bone metastases and development of androgen independent disease. It correlates with high histological grade, advanced stage and clinical disease progression.[13] With the knowledge of the recent molecular aspects, the over-expressed p53 in prostatic carcinoma could be used as a marker to assess the prognosis and management of the cases.

In present study, all cases were subjected to IHC staining for p53. Among 49 cases of BPH, p53 was expressed in none (0%) cases, while in 17 prostate carcinoma cases (80.1%) it was positively expressed. The expression of p53 was significantly up-regulated in prostatic cancer as compared with benign prostatic hyperplasia (BPH).

T heobservation s made in our studyare in agreement with Sasor et al and Singh et al who revealed lack of p53 immunoreactivity in BPH.[14&17] Stattin et al observed that patients with p53-positive tumors had a significantly shorter survival and were resistant to radiotherapy than the p53-negative group. Thus, p53 status could play a role in the evaluation of patients prior to radiotherapy, since p53 inactivation may produce radio-resistant tumors.[18] Similarly Scherr et al suggested that determination of p53 expression in pre-treatment stage may be helpful for predicting response to definitive radiotherapy.[19] (Table 3)

CONCLUSION

Although prostate cancer is prevalent among men, relatively little is known about the molecular mechanisms involved in the development and progression of the disease. Specific molecular mechanisms are involved in the development and progression of prostate cancer. Therefore, much research has been orientated in identifying prognostic factors that distinguish indolent versus aggressive form of prostate cancer. The present study concludes that the p53 immunoexpression is upregulated in prostate carcinoma cases as compared to BPH. p53 may be an effective anti-cancer target for suppression of the malignant proliferation of PC cells, and for prostate cancer gene therapy.

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LEGENDS

Gleason Grade group	No. of cases (n=21)	Percentage
1	2	9.5
2	3	14.3
3	0	0
4	13	61.9
5	3	14.3

Table 1 :**Distribution of carcinoma prostate cases according to Gleason's grade group**

Lesion	p53 expression		p value	Result
	Absent	Present		
BPH	49	NIL	0.001	Highly significant
Carcinoma Prostate	9	12		

Table 2: p53 expression in various prostate lesions

Studies	of cases .No		positivity 53p	
	BPH	PCa	BPH	PCa
Sas(2000) or et al[14]	15	37	%0	%62.2
Pet(2006) rescue et al[9]	-	30	-	%36.6
[15](2010) Chakravarthi et al	-	80	-	%76.3
(2011) Madani et al[16]	-	49	-	%42.9
[17](2017) Singh et al	58	12	%0	%100
Present study	49	21	%0	%80.1

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Table3: Comparative analysis of p53 positivity in BPH and carcinoma prostate cases with previous studies.

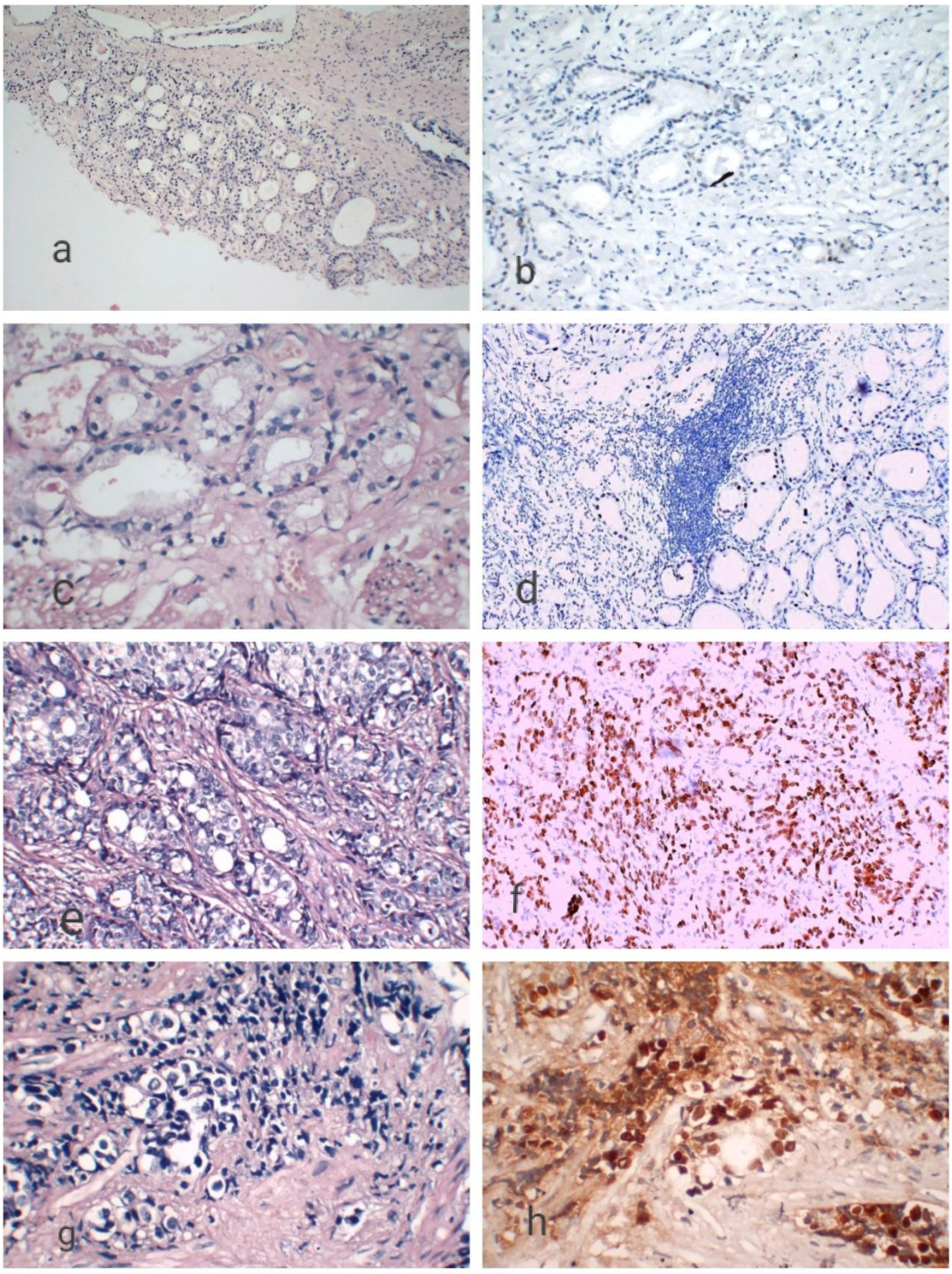

Figure 1: Prostate adenocarcinoma a. H&E 200x- Gleason grade 1 showing back to back arrangement of malignant glands b. IHC 200x- p53 positivity is seen in <10% cells c. H&E 100x- Gleason grade 2 showing predominantly well-formed glands with lesser component of poorly formed glands d. IHC 200x- p53 positivity is seen in <33% cells e. H&E 100x- Gleason grade 4 showing only poorly formed and fused glands f. IHC

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200x- p53 positivity is seen in >33% cells g. H&E 200x- Gleason grade 5 showing malignant cells arranged singly and in sheets h. IHC 200x- p53 positivity is seen in <33% cells.

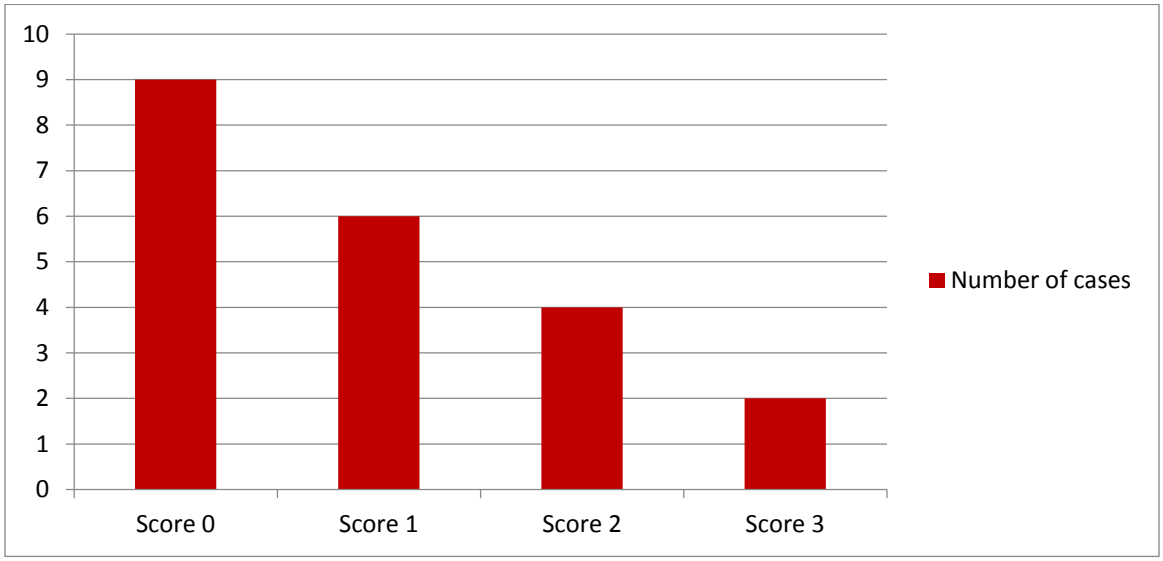

Figure 2: Bar diagramexpression showing of p53 in carcinoma prostate cases (n=21)

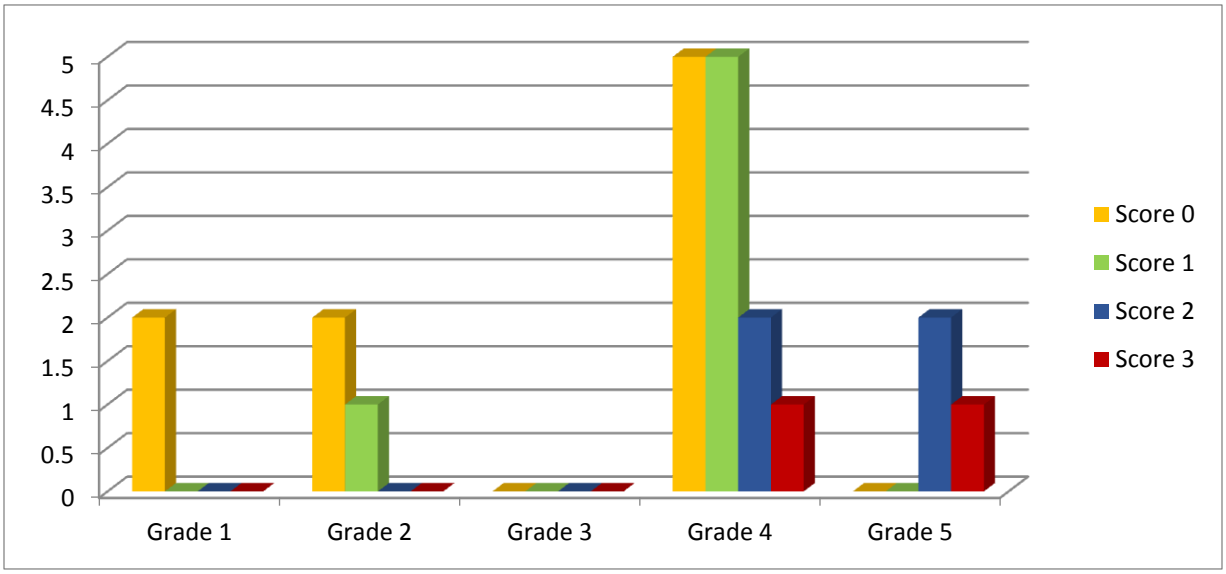

Figure 3: Bardiagrq32am showing correlation between modified Gleason grading and p53 IHC score.

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