Original Article

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To Study Clinicopathological and Immunohistochemical Expression of Estrogen Receptor, Progesterone Receptor and Her-2/Neu in Prostate Carcinoma

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ABSTRACT

Background: Prostate carcinoma is leading cause of cancer related deaths amongst men. This study evaluated expression of ER, PR, HER-2/neu in Prostatic carcinoma and its correlation with Gleason score and other clinical parameters.

Methods: 50 histopathologically proven PCa cases were subjected to IHC for ER, PR, HER-2/neu.

Result: Most common age group involved was 61-80years. Retention of urine was most frequent complaint. Most prominent Gleason score was (3+4) and group grade was 2. ER expression in tumor epithelial cells was 24% and in stromal cells was 36%. PR expression in stromal cells was 32%. HER-2/neu Cytoplasmic positivity was seen in 6% cases. It was seen that with increase in Gleason grade, ER, PR, HER-2/neu positivity was decreased.

Conclusion: ER, PR, HER-2/neu can be used as biomarkers in PCa management.

Keywords: *Prostate Carcinoma, ER, PR, HER-2/neu, Biomarkers*

Introduction

Prostate cancer (PCa) is continually a challenge as one of the leading causes of cancer-related death amongst men. In the developed countries PCa is one of the most common cancers. [1] Approximately 95% of PCa are adenocarcinomas. [2] Gleason grading is the most widely used and accepted histopathological method for providing information regarding PCa prognosis.

It is very essential to identify tumor markers which can act as targets for new therapeutic strategies and can act as prognostic indicators in Prostatic Cancer management and disease free or relapse-free survival. The estrogens play an important role in the male sex hormone secretion as well as growth, differentiation and homeostasis of normal prostate tissue. Estrogen Receptor (α and β) belong to family of ligand-modulated transcription factors (TCFs), also known as nuclear receptors which are often altered in PCa. [3]

Progesterone receptor (PR) belongs to steroid receptor superfamily. Stromal PR positivity may show an inhibitory effect on reactive stromal development and BPH but leads to PCa progression. So, it can be used as a potential therapeutic agent and a potential biomarker in PCa management. [4]

HER-2/neu is an oncoprotein. It is one of the four transmembrane receptors that belong to the erB family. It forms heterodimers by binding to specific ligands, enhancing cell signaling and assisting in cell growth and differentiation. [5] HER-2/neu overexpression in PCa might have a role in invasion of tumor, its aggressiveness and metastatic potentiality. This can also shed light on the role of Transutuzumab in the treatment of Patients with PCa. [6]

Materials and Methods

This study was conducted on 50 histopathologically proven cases of prostatic carcinoma. Blocks after cutting were stained with Hematoxylin and Eosin stain and were studied for classification and histopathological grading. Immunohistochemistry of the tumours was done for ER and PR and HER-2/neu. Positive and negative controls were run with every batch of the IHC. Test sections showed positivity in the form of specific color.

PR Scoring System: The degree of PR expression by IHC was calculated according to both dominant staining intensity and density in both TE and TS. [7]

Integrated score = (Staining intensity + Score of percentage of positive cells)/2

Negative result = 0

Low positivity = <1.75

High positivity = >1.75

HER-2/neu scoring system

1. Pattern of HER-2/neu expression: Membranous/ Cytoplasmic/ Cytoplasmic + Membranous
2. Intensity of staining: Mild/Moderate/Strong
3. % of cells stained:

1+	10-40% cells stained
2+	40-70% cells stained
3+	>70 % cells stained

Results

Majority of patients were in age group of 61-80 years of age constituting 76% of the total cases. Retention of urine was the most common chief complaint (34%) among the PCa patients followed by dysuria (20%). All the cases were of Adenocarcinoma. The most common Gleason score seen was (3+4) constituting 30% of the total.

Estrogen Receptor % in tumor epithelial cells was seen in 24% cases and stromal positivity was seen in 36% cases. Staining intensity varied from mild to strong with 7 cases showing mild, 3 cases showing moderate and 2 cases showing strong intensity. Out of 50 cases, 24% cases had an integrated score >2, which was considered positive. Majority of patients of Gleason score 7-8 showed ER positivity. As the grade increased, the ER positivity decreased. Correlation of ER with final Gleason score was found to have no statistical significance (p-value 0.835).

PR expression was negative in all cases in the epithelial cells. The stromal cells were positive for PR in 16 cases constituting 32%. The staining percentage varied from 4 to 56% and the staining intensity varied from mild, moderate to severe, with 2 cases (13%) showing mild, 9 cases (56%) showing moderate and 5 cases (31%) showing strong intensity respectively. Out of 16 PR positive cases, 13 cases (81%) had high score ≥1.75 and 3 cases (19%) had low score (<1.75). Out of 30 cases of M/c Gleason score 7-8, 10 cases were PR +ve and 20 cases were PR -ve. It was observed that PR stromal positivity decreased with increase in grade. However, no statistical significance was found (p-value 0.942).

HER-2/Neu cytoplasmic positivity was observed in 6% of total cases. Percentage positivity of HER-2/Neu ranged from 10-70% and all three cases showed moderate intensity. Two cases (67%) were having Gleason score 6 (3+3=6) and one case (33%) was having Gleason score 7 (4+3=7).

In the present study, it was seen that one case was Triple Positive (ER, PR, HER-2/neu Positive) which was of low grade. Whereas out of Triple Negative (ER, PR, HER-2/neu Negative) cases, 90% cases were of intermediate and high grade.

Discussion

Prostate cancer is the second most common cancer among men in the developed countries. Whereas in the developing countries, its incidence is on the rising trend. Average annual cancer incidence rate in India for PCa is 5-9.1 per 1,00,000 per year. [1]

In the present study, it was observed that all the patients were above 50 years of age. Maximum cases were in the age group of 61-80 years constituting 76% of the total. 10%

Table 1: Allred Score for Estrogen receptor evaluation.

Proportion Score	Positive Cells, %	Intensity	Intensity Score
0	0	None	0
1	<1	Weak	1
2	1 to 10	Intermediate	2
3	11 to 33	Strong	3
4	34 to 66		
5	≥67		

Total score = Proportion Score + Intensity Score

Table 2: On the basis of % of positive cells staining nuclei.

0	0%
1	≤5%
2	5-50%
3	>50%

Table 3: On the basis of staining intensity.

0	Negative
1	Weak
2	Moderate
3	Strong

Table 4: showing correlation of er with final Gleason score.

Final Gleason score	ER positive		ER negative		Total	
	No.	%	No.	%	No.	%
3-6 (Low grade)	1	8.33	3	7.89	4	8.00
7-8 (Intermediate grade)	8	66.67	22	57.89	30	60.00
9-10 (High grade)	3	25.00	13	34.21	16	32.00
Total	**12**	**100.00**	**38**	**100.00**	**50**	**100.00**

Table 5: Showing correlation of pr with final Gleason score.

Final Gleason score	PR positive		PR negative		Total	
	No.	%	No.	%	No.	%
3-6 (Low grade)	1	6.25	3	8.82	4	8.00
7-8 (Intermediate grade)	10	62.50	20	58.82	30	60.00
9-10 (High grade)	5	31.25	11	32.35	16	32.00
Total	**16**	**100.00**	**34**	**100.00**	**50**	**100.00**

Table 6: Showing correlation of HER-2/neu with final Gleason score.

Final Gleason score	HER-2/neu positive		HER-2/neu negative		Total	
	No.	%	No.	%	No.	%
3-6 (Low grade)	2	66.67	2	4.26	4	8.00
7-8 (Intermediate grade)	1	33.33	29	61.70	30	60.00
9-10 (High grade)	0	0.00	16	34.04	16	32.00

Table 7: Showing correlation of ER, PR and HER-2/neu with final Gleason score.

	Final Gleason score		
	3-6 (Low grade)	7-9 (Intermediate grade)	9-10 (High grade)
ER+ PR+ HER+	1	0	0
ER+ PR- HER-	0	6	3
ER+ PR+ HER-	0	1	0
ER- PR- HER+	1	0	0
ER- PR+ HER-	0	9	5
ER- PR- HER+	1	0	0
ER- PR+ HER+	0	0	0
ER+ PR- HER+	0	1	0
ER- PR- HER-	2	12	8

cases were above 80 years of age. In the study conducted by Naskar S et al, it was seen that most common age group having PCa was 71-80 years constituting 59% of the total cases. 8% cases were above 80 years of age. [8]

Gleason grading system is based on the architectural patterns of prostate adenocarcinoma seen on H&E sections. Five basic patterns which are scored from 1-5, are used to generate a histological sum score which is summed from scores of two most dominant pattern. This histologic sum score can range from 2 to 10. A score of 2-5 indicates the cancer is relatively slow growing and probably will not be very aggressive. A score of 5-7 indicates moderately aggressive cancer and score of 8 and higher indicates an aggressive cancer. [9]

In the present study, Most common score seen was (3+4) which constituted 30% of the total cases. The most prominent group grade was group grade 2, comprising 15 cases (30%). This was in concordance with the study conducted by Darnel AD et al which also showed that 39.3% of the PCa patients were having Gleason score of 7. The most common pattern observed was (3+4=7) seen in 40.7% cases. [10]

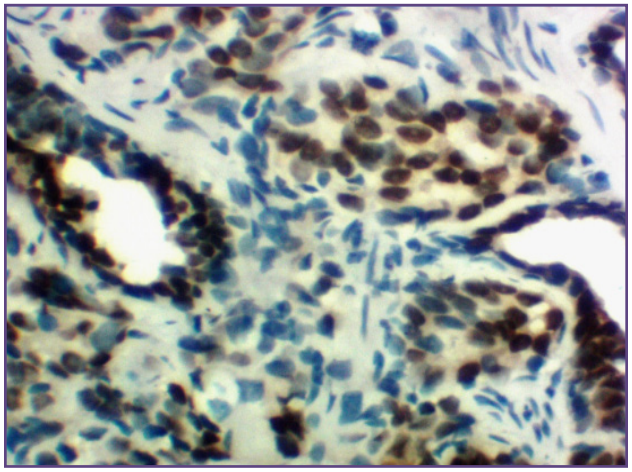

Fig. 1: Showing strong ER epithelial staining (nuclear) (IHC; 400x).

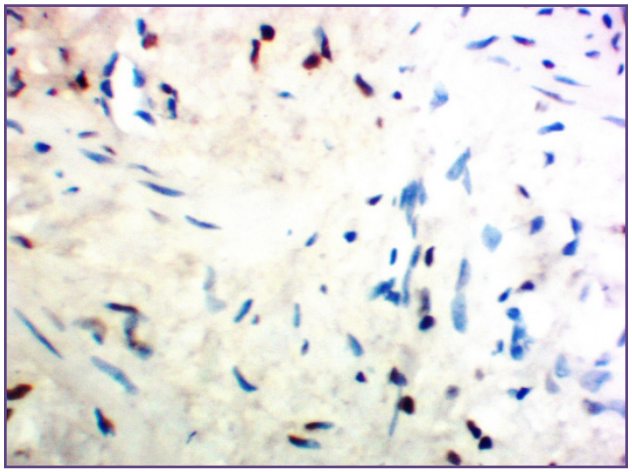

Fig. 2: Showing strong PR stromal staining (nuclear) (IHC;400X)

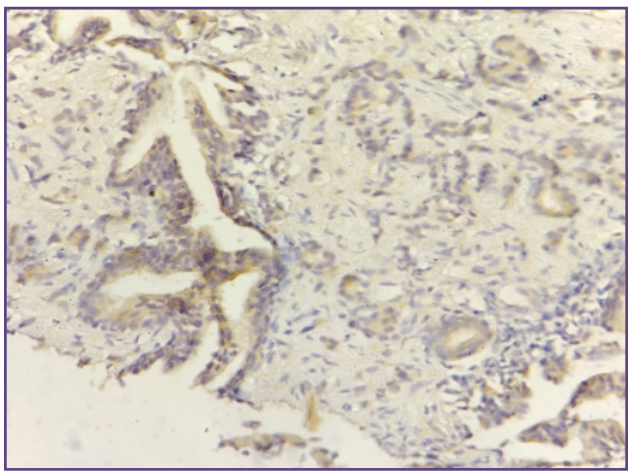

Fig. 3: Showing moderate HER-2/neu positivity (cytoplasmic) (IHC-400X).

ER expression % in tumour epithelial cells was seen in 12 cases constituting 24% and rest 38 cases (76%) showed no expression. Staining varied from mild to strong with 7 cases showing mild, 3 cases showing moderate and 2 cases showing strong intensity. % of ER expression in adjacent stroma was seen in 18 cases constituting 36%. Out of total, 8 ER +ve cases were in age group of 71-80 years. Majority of patients of Gleason score 7-8 showed ER positivity. As the grade increased, the ER positivity decreased.

This was in concordance with the study conducted by Horvath LG et al in which ER epithelial cell positivity was seen in 11.3% cases having PCa and adjacent stromal positivity was seen in 35% cases. It was observed that the ER positivity was also linked to relapse free survival. [11]

PR expression was negative in all cases in the epithelial cells while stromal cells showed PR positivity. Even 1% cell showing PR expression was taken as positive. Out of total 50 cases, PR in stromal cells was +ve in 16 cases constituting 32%. It was observed that PR stromal positivity decreased with increased in grade.

Whereas study done by Bonkhoff H et al, on 41 patients having PCa showed that PR positivity was observed in 36% patients having grade 3, 33% patients having grade 4 and 58% cases having grade 5 PCa. However, no correlation was found. Bankhoff H et al, conducted another study which revealed contrasting results. It was found that PR expression increased with the Gleason grade of the tumor in primary prostatic tumors. Its expression was high in androgen insensitive tumors (54%). [12]

HER-2/Neu staining was observed in 3 cases accounting for 6% positivity. Percentage positivity of HER-2/Neu ranged from 10-70% and all three cases showed moderate intensity. All showed Cytoplasmic HER-2/Neu positivity, 2 cases were having Gleason score (3+3) and 1 case was having score (4+3). It was seen that out of positive cases, maximum cases were low grade and HER-2/Neu positivity decreased as the grade increased.

Similarly N Ady et al, conducted a study on 31 patients having PCa. In this study HER-2/Neu positivity was seen in 9% cases. However, patients having Gleason score 6 showed 33% HER-2/Neu positivity while patients having Gleason score 7 or 8-10 showed 67% HER-2/Neu positivity. [13]

Study done by SA Daoud et al, showed that among 60 PCa patients, HER-2/neu positivity was seen in 31.7% cases. In this study, positive correlation was found between HER-2/neu expression and stage of tumor. [14] But this was not in

concordance with the present study. In the present study, it was seen that one case was Triple Positive (ER, PR, HER-2/neu Positive) which was of low grade. Whereas out of Triple Negative (ER, PR, HER-2/neu Negative) cases, 90% cases were of intermediate and high grade. This correlation was statistically significant.

Conclusion

It is concluded that PCa is more common in elderly population in the age group of 61-80 yrs. It is also seen that with increase in Gleason score and grade, the expression of ER, PR and HER-2/neu decreases in Prostatic carcinoma. All the cases of prostate cancer should be subjected to ER, PR, HER-2/neu expression. It is very essential to identify tumor markers which can act as targets for new therapeutic strategies and can act as prognostic indicators in Prostatic Cancer management and disease free or relapse-free survival.

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Competing Interests

Nil

Reference

1. Jain S, Saxena S, Kumar A. Epidemiology of prostate cancer in India. Meta Gene. 2014;596-605.
2. Randolph TL, Amin MB, Ro JY, Ayala AG. Histologic variants of adenocarcinoma and other carcinomas of prostate cancer: pathologic criteria and clinical significance. Mod Pathol.1997;10:612-19.
3. Leach DA, Powell SM, Bevan CL. Women in cancer thematic review: new roles for nuclear receptors in prostate cancer. Endocrine-Related Cancer. 2016;23(11):T85-108.
4. Grimm, Hartig SM, Edwards DP. Progesterone receptor signaling mechanisms. J MolBiol.2016;428:3831–49.
5. Siampanopoulou A,Galaktidou G, Dimasis N, Gotzamani-Psarrakou A. Profiling serum HER-2/neu in prostate cancer. Hippokratia. 2013;17(2):108–12.
6. Domingo-Domenech J, Fernandez PL, Filella X, Martinez-Fernandez A, Molina R, Fernandez E et al. Serum HER2 extracellular domain predicts an aggressive clinical outcome and biological PSA response in hormone-independent prostate cancer patients treated with docetaxel. Ann Oncol. 2008; 19:269-75.
7. Naskar S, Kundu SK, Bhattacharya NK. A study to correlate histopathology, biochemical marker and immune–histochemical expression of sex steroid receptors in prostatic growth. Indian J PaediatrOncol.2014;35(1):40-3.
8. Naskar S, Kundu SK, Bhattacharya NK, Bhattacharya PK, Kundu AK. A study to correlate histopathology, biochemical marker and immune-histochemical expression of sex steroid receptors in prostatic growth. Indian J PaediatrOncol. 2014;35(1):40-3.
9. Chen N, Zhou Q.The evolving Gleason grading system. Chin J Cancer Res. 2016;28(1):58–64.
10. Darnel AD, Lafargue CJ, Vollmer RT, Corcos J,Bismar TA. TMPRSS2-ERG fusion is frequently observed in Gleason pattern 3 prostate cancer in a Canadian cohort. Cancer BiolTher. 2009;8(2):125-30.
11. Horvath LG, Henshall SM, Lee CS, Head DR, Quinn DI, Makela S et al. Frequent loss of estrogen receptor-beta expression in prostate cancer. Cancer Res. 2001; 61: 5331-5.
12. Bonkhoff H. Progesterone receptor expression in human prostate cancer: correlation with tumor progression. Prostate. 2001;48(4):285–91.
13. Ady N, Morat L, Fizazi K, Soria JC, Mathieu MC, Prapotnich D et al. Detection of HER-2/neu-positive circulating epithelial cells in prostate cancer patients. British Journal of Cancer. 2004;90(2):443-8.
14. Sahar Aly Daoud, Mohamed Faisal, Rehab Mohamed Sharaf. HER-2/neu immunostaining overexpression in Prostatic adenocarcinomas in relation to tumor pathological behavior. Middle East Journal of Scientific Research. 2016;24(2):459-64.

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