Ki67 as a prognostic marker in comparison with Gleason's grading system in prostatic carcinoma

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Abstract

Background & Objectives: Prostatic carcinoma is the most common malignancy in males in the western countries and it is also on the rise in the developing countries like India. There are many markers studied in prostatic cancers, but the most extensively studied one is Ki-67, the proliferative marker.[1,2] Prostatic cancers with Ki-67 over expression are generally aggressive.[3,4] The aim of the study was to assess the proliferative status of the prostatic adenocarcinoma with Ki67 immunostaining and to compare and analyze the association with Gleason's grading for the assessment of prognosis.

Materials & Methods: Forty six randomly selected patients who underwent transurethral resection of prostate, samples in the form of prostatic tru-cut biopsy and radical prostatectomy were studied. Gleason's grading and scoring were done on every case. The sections were also immunostained with monoclonal antibodies against Ki-67 and expression of Ki-67 was studied. The obtained results were statistically analyzed.

Results & Interpretation: A strong statistically significant correlation was found between Ki 67 expression and Gleason's score.

Conclusion: It is noteworthy that a significant correlation exists between the Gleason's score and the expression of Ki-67 in our study. We observed a high expression of Ki-67 for tumours with Gleason's score of 7 or above. Our results suggest that Ki-67 may be useful to serve as a prognostic predictor along with Gleason's grading in prostatic carcinoma.

Keywords: Gleason's grade, Ki-67, Prostatic cancer

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Introduction

Incidence of prostatic cancers is on the rise and researches are going on worldwide to find markers to predict prognosis. The most powerful histopathological predictor being Gleason's grading system which stratifies the prostatic carcinomas in to low grade and high grade, with the score of 7 and less being low grade tumours and a score of above 7 being high grade tumours.[5,6,7]

Ki-67 is the most studied of any immunochemical biomarker in prostate cancer. The Ki-67 protein functions as a nuclear antigen that is only expressed in proliferating cells. It is a marker of the growth fraction in malignant tissue.[8,9] It is determined by immunohistochemistry and expressed as a percentage of cells showing activity in a given tissue sample.

Most prostate cancers typically have very low percentage of growing cells and they grow slowly. Pollack and others have previously shown that, the greater the proportion of prostate tumor cells with Ki-67, the more aggressive the cancer.[10] Gleason's score, tumour volume, surgical margins and Ki-67 index are the most significant prognosticators. The most significant published survival-associated prognostica-tors of prostate cancer with extension outside prostate are microvessel density and total blood PSA. However, survival can potentially be predicted by other markers like androgen receptor, and Ki-67-positive cell fraction.[11,12,13] Studies have revealed the correlation between Ki-67 expression and Gleason's grade.[14,15]

The present study was undertaken to analyze the expression of Ki-67 in prostatic carcinomas and to categorize them in to low grade and high grade tumours according to their proliferative status, in comparison with Gleason's grade.

Materials & Methods

This study was a prospective study which included all types of prostatic specimen (Transurethral resection of the prostate, trucut biopsy and radical prostatectomy) reported as prostatic adenocarcinoma between the period 2006 and 2009 received in the Department of Pathology.

The tumors, after fixation with 10% neutral buffered formalin, were completely embedded in paraffin. The sections were cut with thickness of 3 – 4 microns and stained with hematoxylin-eosin stains for histopathological examination. All the cases were graded with Gleason's grading system and the most common score we observed was 6 (22%) and the

minimum score observed was 3 [*Figure 1A*] and the maximum score was 10. [*Figure 1B*]

The Gleason's score obtained for the cases is given in *table 1*. The sections were also immunostained, with monoclonal antibodies against Ki-67. Immunolocalization of Ki-67 was performed and Ki-67 labeling index was assessed for all the cases.

Ki-67 labeling index: The number of cells with nuclear positivity for Ki-67 were counted and expressed as percentage. The index was noted as low or high with the cutoff of Ki-67 labeling index being kept as 7, according to the earlier studies.[15] This was then compared with the Gleason's score of the corresponding histopathological sections.[*Figure 1C,D*]

The comparison between Gleason's grade and Ki-67 in the samples tested is shown in *table2*. The observed values were compared and analyzed using SPSS-17.0.

Results

The total number of biopsies selected for the test was 46. The age group of patients diagnosed with prostatic adenocarcinoma was 42 – 89 years. Number of samples according to the sample type were trucut biopsy -39 (85%), TURP – 5 (11%) and prostatectomy - 2 (4%).

The comparison between Gleason's grade and Ki-67 labeling index clearly states that, there exists a linear relationship between Gleason's grading system and Ki-67 labeling index, as they both show an increasing trend in carcinomas, which is statistically significant with the p value being less than 0.05.

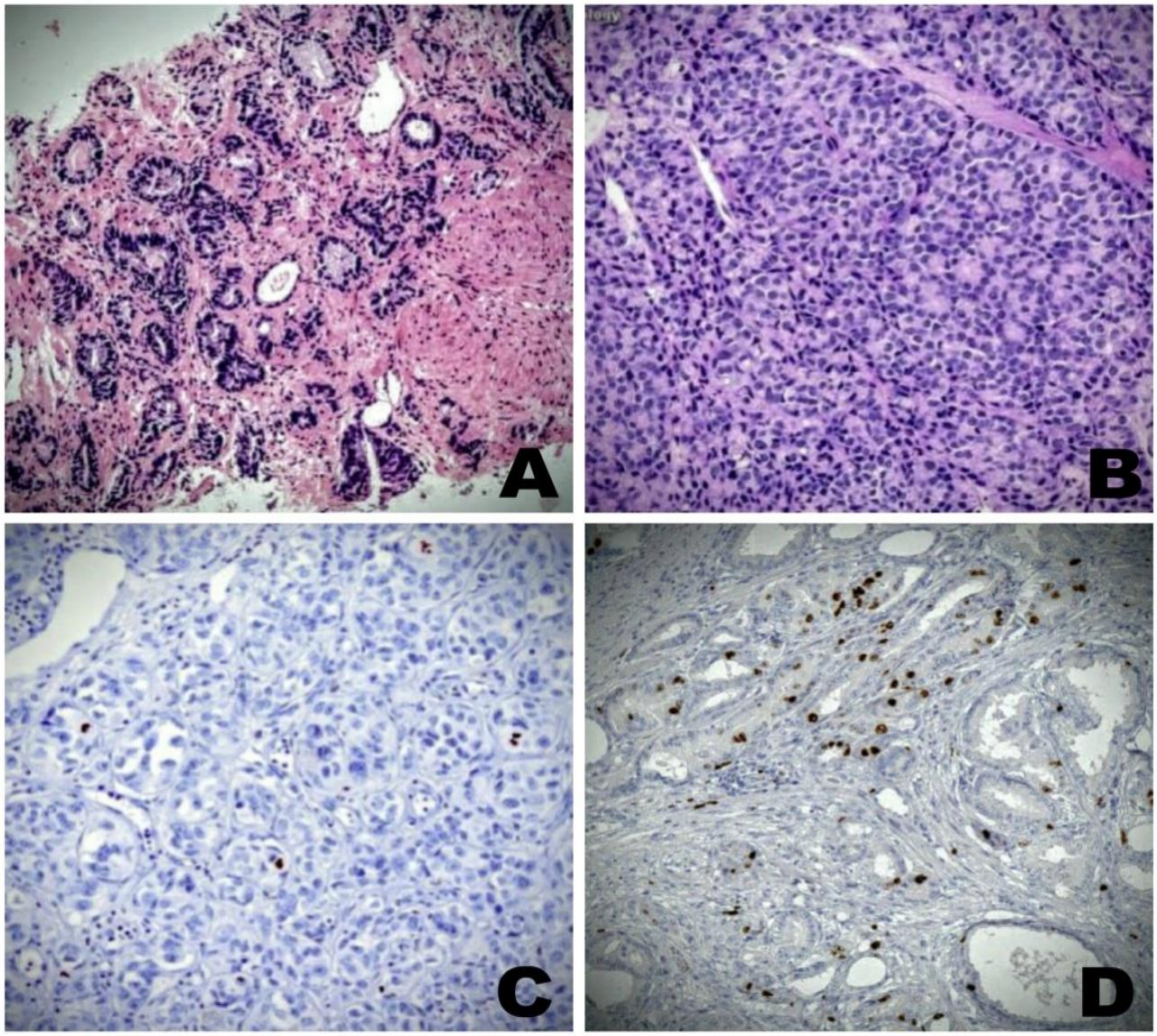

Fig. 1:(A) - Photomicrograph of prostatic carcinoma, Gleason's grade low, H& E, X 100. **(B):** Photomicrograph of prostatic carcinoma, Gleason's grade high, H & E, X 100**. (C):** Photomicrograph of prostatic carcinoma, Ki-67 labeling index low, X 100. (**D):** Photomicrograph of prostatic carcinoma, Ki-67 labeling index high, X 100.

Table 1: Table Showing the Gleason's Score Obtained for the Cases

Gleason's score	No of cases	Percentage(%)
3	5	11
4	7	15
5	8	18
6	10	22
7	5	11
8	8	17
9	2	4
10	1	2

Table 2: Comparison between Gleason's Score and Ki-67 Labeling Index

	Ki-67 labeling index- Low	Ki-67 labeling index- High	Total no of cases: 46
No of cases	36	10	**P value**
	Gleason's score – Low	Gleason's score - High	**<0.05**
No of cases	35	11	

Discussion

The majority of prostate carcinomas may not progress to clinically significant disease. A minor fraction of the clinical cases remains confined to the prostate for many years and other carcinomas progress rapidly to a life threatening disease. How to distinguish these three biologically different types, is a question of great importance.[16] Pathologists play an important role in preoperative diagnosis and in the postoperative prognostic evaluation. Histological grading is a very important factor for the assessment of prognosis. Although the reproducibility is not perfect, still the Gleason's grading system is the most favoured prognostic factor, and highly significantly associated with survival and/or progression. In the Gleason's grading system, the widely accepted cutoff value to stratify carcinomas as low grade and high grade is 7. Prostatic carcinomas with Gleason's score of 7 and below are called low grade carcinomas and are associated with better prognosis. On the other hand, carcinomas with Gleason's score of above 7 are called as high grade tumours and are often associated with worse clinical outcome with rapid disease progression and early mortality.[17]

In addition to Gleason's grading, assessment of proliferative status by Ki-67 is a widely accepted fact. Ki-67 is one of the several cell-cycle-regulating proteins, which can be demonstrated by immunohistochemistry. It is a DNA-binding protein, which is expressed in all phases of cell cycle but undetectable in resting cells. Similar studies by Pollack et al and others state that, Ki-67 index was higher for prostatic carcinomas than for hyperplastic glands.[17,18] Other studies have proved that within the group of carcinomas, Ki-67 indices in patients with metastatic disease were significantly higher than in those without metastasis.[19,20]

In our study, we observed a statistically significant relationship between Gleason's grading system and Ki-67 labeling index, both of which maintain a linear and significantly increasing trend from lower grade to higher grade prostatic carcinomas.

Conclusion

Gleason's grading system is the most powerful prognostic predictor of prostatic carcinoma and assessment of proliferative status by Ki-67 adds value to the grading system by categorizing the tumours in to low grade and high grade and there by having a strong impact in the assessment of prognosis. Hence, combination of Gleason's grading system and Ki-67 labeling index will strengthen the prognostic assessment of prostatic carcinoma.

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