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To study the expression of ki-67 and p53 on TURP specimens to identify prostate carcinoma – A Meta – Analysis

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Abstract:
Prostate cancer is a major health problem throughout the developed world. Tumor grade is one of the most important prognostic factors of prostate cancer. At present, adequate prognostic markers for prostate cancer progression are still lacking, in spite of intensive investigation. Accordingly, we studied the role of immunohistochemical (IHC) expression of p53 and Ki-67 as a prognostic factor in carcinoma prostate and correlated their expression with Gleason's grade.
Considering that most cases of prostate cancer are diagnosed microscopically before metastatic spread and among these, few cases have rapid and life-threatening outcome. Therefore, if these groups can be differentiated from each other we can help patients remarkably. The immunohistochemical expression of Ki-67 and p53 should be assessed in all the cases of prostate carcinoma as these markers allow identification of tumors with a higher rate of cell growth. They also permit development of prognostic factors as their expression increases with increase in the grade and these patients can be benefited with the appropriate targeted treatment leading to increase in the survival time.

Keywords: *ki67, p53, TURP prostatic & carcinoma.*
Study Design: *Review Article*

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I. Introduction:

Prostate cancer is the second most frequently diagnosed cancer and the fifth leading cause of cancer death in males.[1] Incidence increases from 20% in men in their fifties to approximately 70% in men between the age of 70 and 80 years.[2] Prostate cancer is not only significant for its lethality but also for the extremely high morbidity associated with it. The etiology of prostate cancer is unknown but clinical and experimental observations suggest that hormonal, genetic, and environmental factors influence its pathogenesis. Specific molecular mechanisms are involved in the development and progression of prostate cancer. More than 95% of prostate cancers are adenocarcinoma.[2]

Nowadays, more patients are diagnosed at earlier stages, due to increased availability of prostatic-specific antigen (PSA) measurement and other diagnostic methods. With delay in diagnosis of the low-grade tumor, the quality or length of patient's life is not significantly changed, but a high-grade tumor in a young person might spread quickly and lead to the patient's death within 2 years. [3]

Prognostic factors are divided into two clinical and biological groups. Clinical factors are obtained using blood tests and radiological and microscopic evaluation of biopsies. Tumor grading is one of these important factors. Several grading systems have been introduced for prostate cancer. One of these methods, which is very acceptable, is Gleason's grading. This method is based on the patterns of tumor cell differentiation. Range of grading is from one to five. Total Gleason's grading (score) is obtained by sum of total grades of primary and secondary patterns together. Therefore, Gleason's grading will vary from 2 to 10. Gleason's grade is 2–4 in well differentiated tumors, 5–7 in moderately differentiated tumors, and 8-10 in poorly differentiated tumors. Regarding Gleason's grading, probability of patients' mortality is determined.[4] Biological factors are other categories of prognostic factors. Among these P53, P27, and Ki-67 can be noted.

p53 is a tumor suppressor gene, mutations of which can result in uninhibited cellular growth and have been implicated in numerous malignancies.[5]. In most human cancers, its increased immunohistochemical

expression is associated with point mutations in one allele of p53 gene and loss in the other. Thomas et al and Shurbaji et al evaluated the immunohistochemical detection of p53 protein in prostate cancer and its utility as a prognostic indicator. They concluded that mutations of p53 gene, which have long half-life, are involved in carcinogenesis of prostate cancer, and that p53 reactivity marks an aggressive subset of prostate cancer.[6,7].

Ki-67 is one of several cell-cycle-regulating proteins, which can be demonstrated by IHC.[8,9] It is a DNA-binding protein, which is expressed in all phases of cell cycle but undetectable in resting cells.[10,11]

METHODOLOGY :

We conducted a thorough literature search in the PubMed and Google Scholar databases using the following keywords: Ki-67, p53, TURP, Prostatic carcinoma. Case reports and case series were not considered cross references in the chosen article were also checked for additional studies. Publications with available histopathological and IHC correlation were considered for meta-analysis.

In published studies, most commonly routine histopathological processing was done followed by staining with H &E stain. The slides were observed under light microscope and Gleason scoring was done using modified Gleason scoring system. IHC marker (Ki-67, p53) was done on formalin fixed paraffin blocks of each tumor and were mounted on polylysine coated slides. Ki -67 protein is a cellular proliferation marker expressed in nuclei of proliferating cells. p53 is tumor suppressor gene . According to our assessment, the studies used for this review contained a sufficient amount of raw and processed data.

Table No. 01: SCORING of p53:

PERCENTAGE POSITIVITY	SCORE	STAINING INTENSITY	SCORE
<5%	0	NIL	0
5 – 25%	1	MILD	1
25 -50%	2	MODERATE	2
>50%	3	SEVERE / STRONG	3

INDEX for Ki-67:

+1=Index less than equal to 25%
+2=Index between 26-50%
+3=Index between 51-75%
+4=Index between 76-100%

TABLE 02: Showing Ki 67 and p53 expression in prostate carcinoma

No.	STUDY	No. of CASE	Ki-67 EXPRESSION	P53 EXPRESSION
01	Madani et al	49	71.4%	42.9%
02	Moul et al	162	38.3% -100%	69%
03	Harjot kaur et al	50	48%	48%
04	Renuka verma et al[21]	60	61-100%	76%
05	Thompson et al	29	76%	-
06	Zhong et al	202	67.76%	-
07	Makarewicz et al	82	93%	-

II. Discussion:

Prostate cancer is a major health problem throughout the developed world. Tumor grade is one of the most important prognostic factors of prostate cancer. Now-a-days more patients are diagnosed at earlier stages. Increased early detection of the disease is due to increased availability of PSA measurement and also because of using other diagnostic methods such as cystoscopy, transurethral ultrasonography, biopsy and tumor markers. Various markers such as p53 and Ki-67 are expressed immunohistochemically in prostate cancer.

Madani et al high Ki-67 expression was observed in 71 % cases of prostate cancer while p53 expression was noted in 42.9 % cases, also observed that Ki-67 expression increased from 62.2% to 88% as the grade increased.[12] **Moul et al** showed Ki-67 expression in 38.3% of cases and p53 expression in 69% of

cases.[13] also recommended the clinical use of Ki-67 and p53 immunohistochemical protein expression in the primary tumor as combined predictors of disease progression.[13]

Thompson et al and **Zhong et al**showed Ki-67 in 76.0% and 67.76% of cases respectively whereas a very high Ki-67 expression of 93% was observed by **Makarewicz et al.Marian Sulik et al** had also stated significant correlation between immunopositivity of Ki-67 and higher Gleason grade.[14,15,16,17]

Moul et al showed Ki-67 expression in 38.3% of cases and p53 expression in 69% of cases.**Borce et al** have also showed that accumulation of p53 had a special correlation with patients survival. The presence and activity of p53 was greatly associated with the cell proliferation marker Ki-67 and the level of p53 activity was an important independent prognostic factor that was inversely associated with patient survival.[18]

Harjot kaur et al showed48% cases exhibiting positivity for both of these markers.**Rashed et al** demonstrated a positive relationship between the expressions of Ki-67 and p53 in patients with low grade prostate cancer.[19,20]

III. Conclusion :

Considering that most cases of prostate cancer are diagnosed microscopically before metastatic spread and among these, few cases have rapid and life-threatening outcome. The immunohistochemical expression of Ki-67 and p53 should be assessed in all the cases of prostate carcinoma as these markers allow identification of tumors with a higher rate of cell growth. They also permit development of prognostic factors as their expression increases with increase in the grade and these patients can be benefited with the appropriate targeted treatment leading to increase in the survival time.

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