# Relation Between *HER-2* Gene Expression and Gleason Score in Patients with Prostate Cancer

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**Introduction:** *HER-2* is a proto-oncogene of the tyrosine kinase receptor family on chromosome 17. Overexpression of this gene affects the growth and prognosis of some tumors. This study was performed to evaluate the expression of the *HER-2* gene in patients with prostate cancer and its relation with the Gleason score.

**Materials and Methods:** Pathology specimens of all men with prostate cancer who had undergone radical prostatectomy without any supportive treatment were studied. The Gleason scores of the specimens and the expression of *HER-2* gene were examined. The expression of *HER-2* was scored between zero and 3+ in accordance with the HercepTest method. Patients with scores of 2+ and 3+ were considered to be positive for *HER-2* overexpression.

**Results:** Of 150 cancerous prostate specimens evaluated, 20 (13.3%) were positive for *HER-2* gene overexpression. A weakly positive *HER-2* overexpression (2+) was seen in 15 of them (75%) and the remaining 5 (25%) were strongly positive. The Gleason score was not different between the *HER-2*-postitive and *HER-2*-negative patients ($P = .08$). Fourteen out of 97 patients (14.4%) with a Gleason score less than 7 and 6 out of 53 (11.3%) with scores of 7 or greater were positive for *HER-2* overexpression.

**Conclusion:** The frequency of *HER-2* gene overexpression is not very high in our patients with prostate cancer, and we failed to show any association of *HER-2* expression and the Gleason score.

*Keywords: prostate cancer, HER-2 gene, Gleason score, immunohistochemistry*

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## INTRODUCTION

Prostate cancer is the most common malignancy in men and the second cause of death due to cancer.[1] Surgery and radiotherapy are promising for tumors limited to the prostate; however, it is seldom useful in advanced tumors, and in such cases, hormone therapy is the only kind of treatment that may result in improvement. Many studies have been performed to evaluate factors affecting the prognosis of prostate cancer in order to find treatment options that can improve life expectancy in the patients. One of the newly introduced treatments is the use of a monoclonal antibody named *trastuzumab*, the effect of which on progressive breast cancer with a positive hairy-related 2 (*HER-2*) proto-oncogene has been proved.[2] *HER-2* is a proto-oncogene of the tyrosine kinase receptor family on chromosome 17.[3] This protein acts as the site of growth factor; however, its complete structure has not been understood.

Overexpression of this gene affects the growth and prognosis of some tumors.[3] The studies performed

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in this regard have shown different results. In an investigation on 150 patients with prostate cancer, 66% of the patients were positive for *HER-2* and its expression had no relation with the Gleason score and the stage of the disease.[4] In another study in Spain, 44% of the patients were positive for *HER-2* and the level of expression was significantly related to the Gleason score.[5] The prevalence of this gene had been reported to be very low (8%) in another study.[6] An increase in the prevalence of this cancer is predicted in Iran due to the increase in life expectancy. We designed this study to evaluate the frequency of *HER-2* in the patients with prostate cancer and its relation with the prognosis of the tumor.

## MATERIALS AND METHODS

Patients with prostate cancer at Shohada-e-Tajrish Hospital and Shaheed Labbafinejad Medical Center between 2002 and 2004 were evaluated in this cross-sectional study. Pathology specimens of all men with prostate cancer who had undergone radical prostatectomy without any supportive treatment were studied. Diagnosis had been made according to their clinical course, ultrasonography, and biopsy. A single pathologist examined the archival paraffin-embedded tumor tissue of these patients, confirmed the diagnoses of adenocarcinoma of the prostate, and determined the Gleason scores using light microscopy.

For examination of *HER-2*, 4-µm thick sections were taken and stained using the immunohistochemical methods for the *HER-2* oncoprotein according to the Histostain-Plus Kit instructions (Zymed Laboratories, Pasching, Austria). The pathologist who performed the immunohistochemistry was blind to the Gleason scores. The expression of *HER-2* was scored between zero and 3+ in accordance with the HercepTest method.[6] Patients with scores of 2+ and 3+ were considered to be positive for *HER-2* overexpression (Table 1).[6]

Overall, of 165 patients with prostate cancer, 150 were studied. In 6 cases, the patients had received chemotherapy or radiotherapy, and therefore, were excluded. In addition, 9 patients were excluded due to technical problems in immunohistochemical staining of their specimens. Data including the Gleason scores and immunohistochemistry results were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). Comparison of the Gleason scores between the 2 groups with and without *HER-2* overexpression was done by the Mann-Whitney *U* test. A *P* value less than .05 was considered significant.

## RESULTS

One hundred and fifty specimens positive for prostate cancer were evaluated. The mean age of the patients was 70.3 ± 8.9 years (range, 32 to 90 years). *HER-2* expression was increased in 20 patients (13.3%). A weakly positive result (2+) was seen in 15 patients (10.0%) and a 3+ score in 5 (3.3%). The Gleason scores and *HER-2* expressions are demonstrated in Table 2. The Gleason score was not different between the *HER-2*-postitive and *HER-2*-negative patients ($P = .08$). Fourteen out of 97 patients (14.4%) with Gleason scores less than 7 and 6 out of 53 (11.3%) with scores of 7 or greater were positive for *HER-2* overexpression.

**Table 2.** *HER-2* Overexpression in Patients With Prostate Cancer Categorized by Their Gleason Scores

| Gleason Score | Number of Patients | *HER-2* 2+ | *HER-2* 3+ |
|---|---|---|---|
| 2 | 11 | 4 | 0 |
| 3 | 15 | 1 | 2 |
| 4 | 14 | 1 | 1 |
| 5 | 29 | 2 | 1 |
| 6 | 28 | 2 | 0 |
| 7 | 35 | 4 | 1 |
| 8 | 11 | 1 | 0 |
| 9 | 5 | 0 | 0 |
| 10 | 2 | 0 | 0 |
| Total | 150 | 15 | 5 |

**Table 1.** *HER-2* Scoring by Immunohistochemical Staining[6]

| *HER-2* Overexpression | Scoring | Staining |
|---|---|---|
| Negative | 0 | Less than 10% staining |
| Negative | 1 | Weak staining in more than 10% of the cells only in the cell wall |
| Weakly positive | 2 | Weak to moderate staining in all parts of the cell wall in more than 10% of the cells |
| Strongly positive | 3 | Staining in all parts of the cell wall in more than 10% of the cells |

## DISCUSSION

In our study, only 13.3% of the patients with prostate cancer had overexpression of *HER-2*, which is in accordance with the findings of a study by Jorda and associates who had shown a 15% overexpression of *HER-2* in 220 pathologic blocks.[7] In a similar study performed by Lara and colleagues, only 8% of the patients had *HER-2* overexpression.[6] However, our results completely disagree with the results of 2 other studies that reported a 66% and 44% frequency of *HER-2* overexpression in their patients.[4,5] Also, we found out that overexpression of this gene was not significantly related to the Gleason score. Fonseca and colleagues had the same result, but their sample size was small.[4] Lara and colleagues reported no correlation between *HER-2* overexpression and the Gleason score of 62 patients.[6] In contrast to our findings, San Miguel Fraile reported a significant association between these 2 factor.[5] In a study on 216 patients, 97% of the *HER-2*-positive tumors had a Gleason score of 7 or higher.[7]

The differences in the prevalence of *HER-2* overexpression reported by the above studies might be due to the technical variations in the evaluation methods of the gene expression such as the antigen preservation, antigen retrieval techniques, antibody selection, and sampling for immunohistochemical staining.[8] A standard method of immunochemical staining approved by Food and Drug Administration (FDA) was first used by Sanchez and colleagues at Indiana University.[9] They used 2 different antigen-retrieval techniques for evaluation of *HER-2* expression: the standard FDA-approved HercepTest assay and a modified HercepTest—which employed an alkaline citrate buffer (pH 9.0)—for antigen retrieval and a 1-hour primary antibody incubation time. They found a statistically significant relation between the *HER-2* expression and the Gleason score. It was also noticed that *HER-2* was positive only in 1 patient with the standard method, but in 19 with the modified technique.[9] Lara and colleagues used 2 methods of immunohistochemical staining and evaluation of shed *HER-2* antigen levels in serum by enzyme-linked immunosorbent assay and discovered that no relation existed between these 2 methods.[6] Signoretti and colleagues believed that the differences in the results of *HER-2* gene studies was due to the different locations of biopsy.[10] Biopsy may be taken from the androgen-sensitive cells and a positive *HER-2* overexpression is reported to be more frequent in these cases. The prevalence of *HER-2* overexpression in cases with prostate cancer resistant to the hormone therapy was much higher than the localized cancer (78% versus 25%).[10] However, some studies do not confirm such a difference.[6] Some researchers have attempted to determine the prevalence of *HER-2* overexpression in patients with resistant cancer to phase 2 hormone therapy (docetaxel plus trastuzumab). A higher *HER-2* overexpression rate in the patients resistant to hormone therapy in comparison with the patients with hormone-dependent prostate cancers (40% versus 14%) was reported.[11]

## CONCLUSION

We concluded that the frequency of *HER-2* gene overexpression in our patients with prostate cancer seemed to be quite low and there was no significant relation between the expression of *HER-2* and the Gleason score. However, our findings might be biased by the small number of patients and research on large samples might lead to different conclusions.

## CONFLICT OF INTEREST

None declared.

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