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ORIGINAL ARTICLE

Her-2 Expression Status in Different Histopathological Grades of Urothelial Carcinoma

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ABSTRACT

Introduction: Urothelial carcinoma is the predominant histological sub-type and accounts for 90% of human urinary bladder cancers. It is among the ten common malignancies of adults in Pakistan. Her-2 receptor modifications including mutations have been previously evaluated as one of the major players in carcinogenesis of urinary bladder's carcinoma arising from urothelium. The increase in expression of Her-2 receptor is seen in higher grade carcinomas along with muscle infiltration in comparison to tumors of lesser grade and not invading muscle layer.

Aims and Objectives: To compare epidermal growth factor (Her-2) receptor expression status between high and low grade, infiltrative and non-infiltrating carcinoma of urinary bladder's urothelium.

Materials and Methods: 50 cases with diagnosis of primary papillary urothelial carcinoma with variable stages and grades, from both genders and different ages, were selected using convenience sampling for current cross sectional study. Routined protocols opted for immunohistochemical staining to observe Her-2 expression in urothelial cancer trans-urethral resection specimen. If more than 10 percent of cells with positive circumferential complete, and intense membrane staining for Her-2 were taken as positive as assessed semi-quantitatively by using immuno-reactive scoring system designated by ASCO/CAP guidelines.

Results: Patients having ages ranging from 42 to 95 years including 37 males and 13 females were selected for current study. Her-2 immunostaining revealed, positivity in 27 (54%) patients. Results interpreted showed more number of cases having higher grade ($p= 0.0006$) and infiltration ($p = 0.0001$) with Her-2 positivity.

Conclusions: The current study showed significant amount of Her-2 positivity in greater grade and carcinomas possessing muscle invasion as compared to tumors of lower grade and those not invading muscle wall.

Key words: Her-2 receptor, Low grade urothelial carcinoma, Invasive papillary urothelial carcinoma

INTRODUCTION

Malignant carcinoma of urinary bladder urothelium comprises major proportion and among top ten mostly observed malignancies in world. Rate of incidence as per documentation are much high Europian countries, Northern America and Africa.[1] In Pakistan, urothelial carcinoma registered cases prevalence is increasing.[2,3] Out of all types of urinary bladder tumors carcinoma of urothelial type is predominant one and also frequent sub-type from microscopic point of view. Urothelial tumor represents up to 95 % of all tumors involving bladder in Pakistan population.[4]

Her-2 is an oncogene and a member of an epidermal growth receptor family having tyrosine-kinase activity. The detection of amplification of this oncogene resulting in over-expression of Her-2/neu protein signifies its integral part in modulating landscape of various invasive carcinomas in the body including breast, urinary bladder, etc.[5] The expression status of Her-2 receptor is required for the stratification of patients most likely to be benefited from targeted hormonal therapy i.e. epidermal growth factor receptor inhibitors like Trastuzumab.[6]

Expression of Her-2 receptor is being reported in various malignancies like carcinoma affecting transitional epithelium of bladder, ovarian carcinomas, endometrial malignant tumors, tumors of salivary gland and pancreas, as well as, lung cancers.[7] Association of Her-2 with urinary bladder oncogenesis is proved and mentioned by evidences.[8]

Two factor i.e. cancer infiltration into detrusor muscle/muscularis propria and grading on histopathological examination has clinically significance in urothelial bladder cancers.[9] The grade and stage of urinary bladder's carcinoma originating from urothelium act as important tools in current evaluation for making therapeutic strategies.[4,9] However, histological basis alone are not adequate to assess biological behavior in transitional cell cancers. For predicting aggressiveness and prognosis and effectiveness of management, improved criteria and adjuvant methods for detection are required to be studied and explored.[10]

Her-2 positive status of receptors is correlated with aggressiveness of primary infiltrating carcinoma of urothelial origin. More commonly Her-2 receptor is observed in high grade urothelial cancer.[11] The Her-2 has been shown more pronounced in urothelial carcinoma of higher stage and grade meaning having tumor with muscle invasion while cancers of lower grade with no invasion into detrusor muscle have been lesser Her-2 expression.[12] Transitional cell malignant tumors of urinary bladder reveal decreased or absent Her-2 receptor expression.[9,12]

The present study was planned to compare Her-2 receptor expression in various grades of urothelial cancers and also in infiltrative and non-invading carcinomas of urinary bladder urothelial tumors.

METHODS AND MATERIALS

The current study is cross-sectional conducted at Niazi Medical and Dental college, Sargodha. Total 50 specimens were collected after opting convenience method of sampling. Patients including both males and females belonging to every age groups were studied. Urothelial carcinoma of urinary bladder with muscle invasion and no invasion plus low and high grades were part of this study. Patients having recurrent tumor or non-primary urinary bladder urothelium cancer and also with history of taking hormonal therapy, radiotherapy or chemo-therapy were not included. Trans-urethral resection samples from malignant urinary bladder tumor (TUR-BT) processed with routine procedure for histological examination were seen for grading and staging based on World Health Organization (W.H.O.) histopathological classification of tumors of urinary tract. Immunostaining for Her-2 according to instructions of manufacturer was done. Results of staining were analyzed and based on Fisher's exact test, results were taken as significant statistically at $p < 0.05$.

RESULTS

During this study, 50 transurethral resection urothelial carcinoma specimens from urinary bladder were underwent histological and immunohistochemical marker assessment.

29 (58%) patients revealed high grade of urothelial cancer and lower grades were seen in 21 patients (42%). After applying muscular proper layer's infiltration criteria of urothelial carcinoma, 31 cases (62%) were diagnosed as non-invading tumors while 19 cases (38%) were invasive carcinomas.

The results of Her-2 immuno-staining were given scores according to intensity of color, circumferential staining pattern and cells' percentage that were stained positive. Score of 2+ were not included as these are equivocal cases requiring FISH confirmation.[5]

Her-2 staining distribution among high and low graded urothelial carcinomas revealed score 1, i.e. out of 15, 12(80%) were of lower grade tumors (Figure - 1) and out of 11, 9 (81.1%) having score of 3 had been higher graded carcinomas (Figure - 1).

Figure 1: Distribution of Her-2 staining scores in different grades of urothelial carcinoma.

The distribution of Her-2 staining scores in non-invading and infiltrating urothelial cancers showed 81.1% of cancers with score 3 as invasive cancers whereas 12 neoplasms out of 15 (80%) had score 1 were non-invasive carcinomas (Figure - 2).

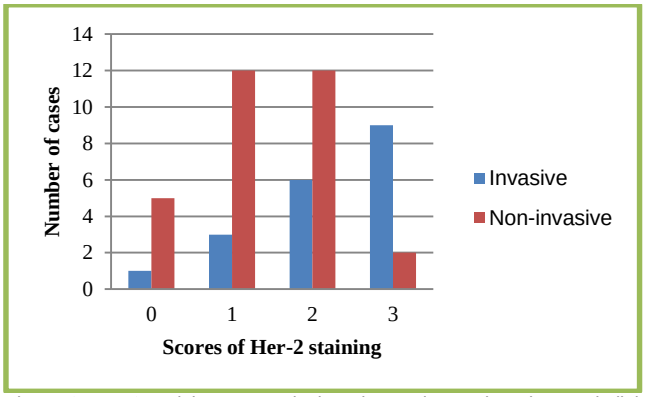

Figure 2: Her-2 staining scores in invasive and non- invasive urothelial carcinoma

The comparison of Her-2 expression status in high and lower grades of tumors was significantly high (*p value* = 0.0006) (Table - 1).

Table 1: Comparison of her-2 expression in different grades of urothelial carcinoma

Histological Grades	Her-2 expression		Total
	Positive	Negative	
Low	05	16	21
High	22	07	29
Total	27	23	50

In similar manner, correlation of Her-2 expression among non-infiltrative and invading urothelial cancers showed 17 (89.47%) invading tumors with positive Her-2, while, 21(67.74%) non-invasive carcinomas had negative Her-2 staining (*p value* = 0.0001) (Table - 2).

Table 2: Expression of Her-2 in invasive and non-invasive urothelial carcinoma

Urothelial Carcinoma	Her-2 expression		Total
	Positive	Negative	
Invasive	17	02	19
Non-Invasive	10	21	31
Total	27	23	50

DISCUSSION

Urothelial carcinoma is one of prominent causes of mortality and morbidity world-widely. Urothelial cancer is out of commonest malignancies observed in Pakistan.[1,2]

At initial diagnosis about 70% are low grade urothelial tumors and up to 70% of urothelial carcinomas belong to non-invasive category. Frequency of various grades of malignant urothelial tumor as mentioned in this study is not in concordance with a few other studies.[2,13] Patients in our population make delay in presentation and hence the above mentioned discrimination is seen in this study.

The assessment of Her-2 expression can help in segregating patients having more risk and poses susceptibility for an aggressive and high staged malignancies having increased chances of recurrence.[4,7,8]

Similarity of observing significant correlation of higher grade of urothelial carcinoma with stronger Her-2 expression status has been also revealed by current study. The observation in present study is in terms of intensity of staining, pattern and number of cells having positive staining.[7,8,11,12] In certain studies higher graded urothelial tumor showing Her-2 expression is more in number.[6,8,9] The observations of this study are corresponding to findings of many studies both mentioning significant number of cases (75.86%) having high grade carcinomas reveal Her-2 positivity and Her-2 negativity is identified in tumors belonging to lower grade.

The correlation of scores of Her-2 staining expression among non-invasive and invading urothelial carcinomas were reported in a few studies. Such studies declared that invasive carcinomas have higher scores of staining scores as compared to non-invasive carcinomas.[10,11,12,13] In concordance to these studies, the current study also indicated higher percentage of cells and stronger Her-2 positivity in more number of muscle invasive cancers as compared to the non-invasive tumors.

Her-2 expression status proves to be a helpful therapeutic and diagnostic tool also possessing relation with advanced clinical outcome and with aggressive features in urothelial carcinoma.[7,14]

This study can guide as a clue to elucidate the clinical and therapeutic benefits of Her-2 as targeted therapy in urothelial carcinomas of urinary bladder in human.

Further studies, regarding the Her-2 expression status in urothelial carcinoma of urinary bladder are needed to determine the role of anti-Her-2 therapy as an adjuvant tool.

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