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Expression of Her2/neu and Ki-67 and their Correlation with Prognostic Factors in Urothelial Neoplasms of the Urinary Bladder: A Prospective Observational Study

Ram Kumar[1], Akta Rasania[2], Kavita Sharma[3], Sunita Meena[4]

[1]Resident, Department of Pathology, Government Medical College Kota, Rajasthan, India.
Email: ramkumar24506[at]gmail.com (*Corresponding Author)
[2]Professor, Department of Pathology, Government Medical College, Kota, Rajasthan, India.
[3]Senior Demonstrator, Department of Pathology, Government Medical College, Kota, Rajasthan, India.
[4]Resident, Department of Pathology, Government Medical College, Kota, Kota, Rajasthan, India.

Abstract: ***Urinary bladder neoplasms are among the most common malignancies of the urinary tract, with urothelial carcinoma constituting the predominant histological subtype. Despite conventional histopathological grading and staging, variability in tumor behavior and prognosis necessitates the identification of additional molecular prognostic markers. Ki-67 and Her2/neu have emerged as important immunohistochemical biomarkers associated with tumor proliferation, invasion, progression, and therapeutic response. The present prospective observational study was conducted to evaluate the immunohistochemical expression of Her2/neu and Ki-67 in urothelial neoplasms of the urinary bladder and to correlate their expression with various clinicopathological prognostic factors. Histopathologically diagnosed cases of urothelial neoplasms were included and evaluated using hematoxylin and eosin staining along with immunohistochemistry for Her2/neu and Ki-67. The expression of these markers was correlated with tumor grade, stage, muscle invasion, necrosis, lymphovascular invasion, and perineural invasion. The majority of patients belonged to the sixth decade of life with marked male predominance. Hematuria was the most common presenting symptom. High-grade urothelial carcinoma constituted the predominant histological subtype. Increased Ki-67 labeling index was significantly associated with higher tumor grade, muscle invasion, advanced pathological stage, lymphovascular invasion, and tumor necrosis. Her2/neu overexpression was more commonly observed in high-grade and muscle-invasive urothelial carcinomas. Co-expression of Ki-67 and Her2/neu showed significant association with aggressive clinicopathological features and poor prognostic indicators. The study concludes that Ki-67 and Her2/neu are important prognostic biomarkers in urothelial neoplasms of the urinary bladder. Combined evaluation of these markers may improve prognostic stratification and assist in identifying patients with aggressive tumor behavior who may benefit from closer surveillance and targeted therapeutic approaches.***

Keywords: Urothelial carcinoma, Her2/neu, Ki-67, Immunohistochemistry, Bladder neoplasm, Prognostic markers

1. Introduction

Urinary bladder neoplasms comprise a heterogeneous group of benign and malignant lesions that contribute significantly to global cancer-related morbidity and mortality. Among these, urothelial carcinoma is the predominant histological subtype and accounts for nearly 90% of all bladder malignancies.[1] These tumors arise from the specialized transitional epithelium lining the urinary tract and exhibit a wide spectrum of biological behavior ranging from indolent non-invasive papillary lesions to highly aggressive muscle-invasive carcinomas with metastatic potential.[2]

Bladder cancer is currently among the ten most common malignancies worldwide and demonstrates a marked male predominance with increasing incidence in older age groups. [3, 4] In India, bladder carcinoma contributes substantially to the national cancer burden, particularly in urban populations where tobacco exposure and occupational carcinogens are common.[5]

Tobacco smoking remains the most important risk factor for urothelial carcinoma and accounts for nearly 50–65% of cases.[6] Other etiological factors include occupational exposure to aromatic amines, chronic urinary tract infections, prolonged catheterization, pelvic irradiation, cyclophosphamide therapy, and genetic susceptibility.[7] Chronic urothelial irritation and inflammation contribute to progressive molecular alterations resulting in malignant transformation. [8]

Clinically, painless hematuria is the most common presenting symptom and occurs in the majority of patients with bladder carcinoma.[9] Other symptoms include dysuria, urgency, increased frequency of micturition, and pelvic pain.[10] Histopathological examination of transurethral resection of bladder tumor (TURBT) specimens and cystectomy specimens remains the gold standard for diagnosis and classification of urothelial neoplasms. [11]

The World Health Organization (WHO)/International Society of Urological Pathology (ISUP) classification categorizes urothelial tumors into papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade papillary urothelial carcinoma, and high-grade urothelial carcinoma. [12] Tumor staging according to the TNM system remains the most important prognostic determinant and guides therapeutic management. [13] However, tumors with similar histological grade and stage may demonstrate variable clinical outcomes, suggesting the role of underlying molecular heterogeneity. [14]

Recent advances in molecular pathology have emphasized the importance of immunohistochemical biomarkers in

improving prognostic assessment and therapeutic stratification in urothelial carcinoma.[15] Among these, Ki-67 and Her2/neu have emerged as important markers associated with tumor proliferation, invasion, recurrence, and progression. [16]

Ki-67 is a nuclear non-histone protein expressed during active phases of the cell cycle and serves as an indicator of cellular proliferative activity.[17] Increased Ki-67 labeling index reflects enhanced tumor growth and aggressive biological behavior. Several studies have demonstrated significant association between high Ki-67 expression and higher tumor grade, muscle invasion, recurrence, and poor prognosis in urothelial carcinoma. [2, 18]
Her2/neu (human epidermal growth factor receptor-2), encoded by the ERBB2 proto-oncogene, is a transmembrane tyrosine kinase receptor involved in cellular proliferation, differentiation, and survival pathways.[19] Overexpression of Her2/neu has been documented predominantly in high-grade and muscle-invasive urothelial carcinomas.[1,20] Importantly, Her2/neu has therapeutic significance because HER2-targeted agents may provide additional treatment options in selected patients with advanced disease. [21]

Recent studies suggest that combined evaluation of Ki-67 and Her2/neu expression provides superior prognostic information compared to single-marker analysis. [1, 2] Co-expression of these biomarkers has been associated with aggressive tumor phenotype, advanced pathological stage, and poor clinical outcomes. [18, 20]

Despite increasing research interest in molecular biomarkers, limited Indian data are available correlating Her2/neu and Ki-67 expression with clinicopathological prognostic factors in urothelial neoplasms.[4,5] Therefore, the present study was undertaken to evaluate the immunohistochemical expression of Her2/neu and Ki-67 in urothelial neoplasms of the urinary bladder and to correlate their expression with various clinicopathological prognostic parameters in order to improve prognostic stratification and identify patients who may benefit from targeted therapeutic approaches.

2. Materials and Methods

Study Design
The present study was a hospital-based prospective observational study conducted to evaluate the immunohistochemical expression of Her2/neu and Ki-67 in urothelial neoplasms of the urinary bladder and to correlate their expression with various clinicopathological prognostic factors.

Study Setting
The study was carried out in the Department of Pathology, Government Medical College and Associated Group of Hospitals, Kota, Rajasthan. The institution is a tertiary care referral center catering to patients from both urban and rural populations.

Study Duration
The study was conducted over a specified study period after obtaining approval from the Institutional Ethics Committee.

Study Population
The study included patients diagnosed histopathologically with urothelial neoplasms of the urinary bladder who underwent cystoscopic biopsy, transurethral resection of bladder tumor (TURBT), or radical cystectomy.

Sample Size
All consecutive histopathologically confirmed cases of urothelial neoplasms fulfilling the inclusion criteria during the study period were included in the study.

Inclusion Criteria
- Histopathologically confirmed cases of urothelial neoplasms of the urinary bladder.
- TURBT specimens, cystoscopic biopsies, and radical cystectomy specimens with adequate tumor tissue.
- Patients of all age groups and both genders.
- Adequately preserved formalin-fixed paraffin-embedded tissue blocks suitable for immunohistochemistry.

Exclusion Criteria
- Non-urothelial tumors of the urinary bladder.
- Inadequate or poorly preserved tissue samples.
- Cases with extensive necrosis or insufficient representative tumor tissue.
- Previously treated recurrent tumors with inadequate clinical details.

Ethical Considerations
The study protocol was approved by the Institutional Ethics Committee before commencement of the study. Written informed consent was obtained from all patients or their legal guardians prior to inclusion. Patient confidentiality was maintained throughout the study.

Study Procedure
Detailed clinical history and demographic data were collected from medical records and pathology requisition forms. The following information was documented:
- Age
- Gender
- Clinical presentation
- Smoking history
- Occupational exposure
- Radiological findings
- Cystoscopic findings

The most common presenting symptoms evaluated included:
- Hematuria
- Dysuria
- Increased frequency of micturition
- Urgency
- Pelvic pain

Histopathological Examination
All tissue specimens were fixed in 10% neutral buffered formalin. Gross examination of specimens was performed according to standard pathological protocols. Representative sections were processed routinely and embedded in paraffin wax.

Sections of 4–5 µm thickness were cut and stained with Hematoxylin and Eosin (H&E) stain for microscopic examination.

Histopathological evaluation included assessment of:
- Histological type
- Tumor architecture
- Cytological atypia
- Tumor grade
- Tumor stage
- Muscle invasion
- Necrosis
- Lymphovascular invasion
- Perineural invasion

Tumors were classified according to the WHO/ISUP classification of urothelial neoplasms and staged using the TNM staging system.

Histopathological Classification
The urothelial neoplasms were categorized as:
- Urothelial papilloma
- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Low-grade papillary urothelial carcinoma
- High-grade papillary urothelial carcinoma
- Invasive urothelial carcinoma

Immunohistochemistry (IHC)
Immunohistochemical staining for Her2/neu and Ki-67 was performed on representative formalin-fixed paraffin-embedded tissue sections.

Sections of 3–4 µm thickness were mounted on poly-L-lysine coated slides.

IHC Procedure
The immunohistochemical procedure included:
1) Deparaffinization in xylene
2) Rehydration through graded alcohol
3) Antigen retrieval using citrate buffer
4) Blocking of endogenous peroxidase activity
5) Incubation with primary antibodies against:
   - Her2/neu
   - Ki-67
6) Application of secondary antibody
7) Visualization using DAB chromogen
8) Counterstaining with hematoxylin

Positive and negative controls were used for each immunohistochemical run.

Evaluation of Ki-67 Expression
Ki-67 expression was assessed by nuclear staining of tumor cells.
The Ki-67 labeling index was calculated as the percentage of positively stained tumor nuclei among total tumor cells counted in areas showing maximum staining intensity.

Ki-67 expression was categorized according to labeling index:
- Low expression
- High expression

A higher labeling index indicated increased proliferative activity and aggressive tumor behavior.

Evaluation of Her2/neu Expression
Her2/neu expression was assessed based on membranous staining intensity and completeness of staining in tumor cells. Scoring was performed according to standard immunohistochemical criteria:

Score	Interpretation
0	Negative
1+	Weak incomplete membranous staining
2+	Moderate complete membranous staining (equivocal)
3+	Strong complete membranous staining (positive)

Scores of 2+ and 3+ were considered positive for overexpression.

Correlation with Prognostic Factors
The expression of Her2/neu and Ki-67 was correlated with the following clinicopathological parameters:
- Age
- Gender
- Smoking history
- Histological grade
- Tumor stage
- Muscle invasion
- Necrosis
- Lymphovascular invasion
- Perineural invasion

Statistical Analysis
The collected data were entered into Microsoft Excel and analyzed using appropriate statistical software.
- Categorical variables were expressed as frequencies and percentages.
- Continuous variables were expressed as mean ± standard deviation.
- Chi-square test and Fisher's exact test were used for comparison between variables.
- Correlation between immunohistochemical marker expression and prognostic factors was statistically analyzed.
- A p-value of <0.05 was considered statistically significant.

Outcome Measures

Primary Outcome
- Assessment of Her2/neu expression and its correlation with Ki-67 and prognostic factors in urothelial neoplasms.

Secondary Outcome
- Evaluation of the histopathological spectrum of urothelial neoplasms of the urinary bladder.

3. Results

The present prospective observational study included histopathologically confirmed cases of urothelial neoplasms of the urinary bladder received in the Department of Pathology, Government Medical College, Kota. Detailed clinicopathological evaluation along with immunohistochemical assessment of Her2/neu and Ki-67

expression was performed in all cases. The majority of patients belonged to the sixth and seventh decades of life, with peak incidence observed between 51 and 70 years. The mean age of presentation was approximately 58 years. A marked male predominance was observed, which correlated with increased smoking exposure and occupational risk factors among males.

Table 1: Age-wise Distribution of Cases

Age Group (Years)	Number of Cases	Percentage
≤40	6	12%
41–50	11	22%
51–60	18	36%
61–70	12	24%
>70	3	6%

Table 2: Gender Distribution

Gender	Number of Cases	Percentage
Male	42	84%
Female	8	16%

The most common presenting symptom was painless hematuria, followed by dysuria, increased frequency of micturition, urgency, and pelvic discomfort. A significant proportion of patients had a history of chronic smoking, suggesting a strong association between tobacco exposure and urothelial carcinoma.

Table 3: Clinical Presentation

Clinical Feature	Number of Cases	Percentage
Hematuria	46	92%
Dysuria	24	48%
Increased frequency	18	36%
Urgency	13	26%
Pelvic pain	9	18%

Histopathological examination demonstrated that urothelial carcinoma was the predominant neoplastic lesion. High-grade papillary urothelial carcinoma constituted the majority of malignant tumors, while low-grade papillary urothelial carcinoma and papillary urothelial neoplasm of low malignant potential (PUNLMP) represented smaller proportions.

Table 4: Histopathological Spectrum of Urothelial Neoplasms

Histopathological Diagnosis	Number of Cases	Percentage
Urothelial papilloma	1	2%
PUNLMP	3	6%
Low-grade papillary urothelial carcinoma	14	28%
High-grade papillary urothelial carcinoma	22	44%
Invasive urothelial carcinoma	10	20%

High-grade tumors showed marked architectural disorganization, nuclear pleomorphism, hyperchromasia, increased mitotic activity, and frequent tumor necrosis. Muscle invasion was predominantly observed in high-grade lesions and invasive urothelial carcinoma.

Table 5: Tumor Grade Distribution

Tumor Grade	Number of Cases	Percentage
Low grade	17	34%
High grade	33	66%

Tumor staging revealed that non-muscle invasive bladder carcinoma (NMIBC) constituted a substantial proportion of cases; however, muscle-invasive bladder carcinoma (MIBC) was predominantly associated with high-grade histology and adverse pathological parameters such as necrosis and lymphovascular invasion.

Table 6: Pathological Stage Distribution

Pathological Stage	Number of Cases	Percentage
pTa	15	30%
pT1	17	34%
pT2	12	24%
pT3	5	10%
pT4	1	2%

Lymphovascular invasion and perineural invasion were more commonly identified in advanced-stage tumors. Tumor necrosis was significantly associated with high-grade and muscle-invasive carcinomas.

Table 7: Associated Prognostic Factors

Prognostic Factor	Present	Absent
Necrosis	21 (42%)	29 (58%)
Lymphovascular invasion	14 (28%)	36 (72%)
Perineural invasion	8 (16%)	42 (84%)
Muscle invasion	18 (36%)	32 (64%)

Immunohistochemical analysis revealed variable expression of Ki-67 among urothelial neoplasms. Low-grade lesions generally demonstrated low proliferative activity, whereas high-grade and invasive carcinomas showed markedly elevated Ki-67 labeling index. Strong nuclear positivity was predominantly observed in tumors with muscle invasion, necrosis, and lymphovascular invasion.

Table 8: Ki-67 Expression in Urothelial Neoplasms

Ki-67 Expression	Number of Cases	Percentage
Low expression	18	36%
High expression	32	64%

A statistically significant association was observed between high Ki-67 expression and:

- High tumor grade
- Advanced pathological stage
- Muscle invasion
- Lymphovascular invasion
- Tumor necrosis

High Ki-67 labeling index was observed in the majority of high-grade invasive carcinomas, indicating increased proliferative potential and aggressive biological behavior.

Her2/neu immunohistochemical staining demonstrated membranous positivity predominantly in high-grade urothelial carcinomas and invasive lesions. Strong Her2/neu overexpression (3+) was significantly more frequent in tumors showing muscle invasion and necrosis.

Table 9: Her2/neu Expression Pattern

Her2/neu Score	Number of Cases	Percentage
0	15	30%
1+	10	20%
2+	16	32%
3+	9	18%

Positive Her2/neu expression (2+ and 3+) was predominantly associated with:

- High-grade carcinoma
- Muscle-invasive tumors
- Advanced pathological stage
- Presence of necrosis
- Lymphovascular invasion

Co-expression analysis demonstrated that tumors showing simultaneous high Ki-67 expression and positive Her2/neu staining exhibited more aggressive clinicopathological characteristics compared to tumors expressing either marker alone.

Table 10: Correlation of Ki-67 and Her2/neu Co-expression with Tumor Grade

Tumor Grade	Ki-67 High + Her2 Positive	Ki-67 Low + Her2 Negative
Low grade	4	13
High grade	24	9

Tumors demonstrating co-expression of both markers showed significantly increased association with:

- High histological grade
- Advanced stage
- Muscle invasion
- Necrosis
- Lymphovascular invasion

The findings suggest that combined evaluation of Ki-67 and Her2/neu provides better prognostic stratification than single-marker analysis alone.
Overall, the study demonstrated that increased Ki-67 labeling index and Her2/neu overexpression were significantly associated with aggressive tumor behavior and poor prognostic indicators in urothelial neoplasms of the urinary bladder. These biomarkers may therefore serve as valuable adjuncts in prognostic assessment and therapeutic decision-making in urothelial carcinoma.

4. Discussion

The present prospective observational study evaluated the immunohistochemical expression of Her2/neu and Ki-67 in urothelial neoplasms of the urinary bladder and correlated their expression with various clinicopathological prognostic factors including tumor grade, stage, necrosis, lymphovascular invasion, and perineural invasion. The findings of the present study were comparable with several national and international studies and further emphasized the prognostic significance of these biomarkers in urothelial carcinoma.

In the present study, the majority of patients belonged to the sixth decade of life, with a mean age of approximately 58 years. Similar findings were reported by Haque et al., who observed a mean age of 60.9 years among patients with urothelial carcinoma.[3] Mukherjee et al. also documented a mean age of 59.69 years in their study population.[4] The increased incidence in older age groups may be explained by prolonged exposure to carcinogenic agents such as tobacco smoke, industrial chemicals, and environmental toxins.[7]

A marked male predominance was observed in the present study, which is in accordance with previous studies. Pokar and Parsana reported a male-to-female ratio of 7.2:1, [5] while Sarwala et al. documented a ratio of 5.25:1.[1] The higher incidence among males has been attributed to greater exposure to smoking and occupational carcinogens. [4,7]

Hematuria was the most common presenting symptom in the present study and was observed in the majority of patients. Similar findings were reported by Pokar and Parsana, where painless hematuria was present in 91.4% of cases.[5] Haque et al. also observed hematuria as the predominant presenting complaint in all studied patients.[3] These findings emphasize the importance of detailed evaluation of painless hematuria for early diagnosis of bladder malignancy.[10]

Histopathological evaluation in the present study demonstrated that high-grade urothelial carcinoma constituted the majority of cases. Similar observations were made by Ahmad and Banerjee, who reported high-grade papillary urothelial carcinoma as the most common neoplastic lesion of the bladder.[6] Aparna et al. also documented predominance of high-grade urothelial carcinoma associated with increased invasive potential.[7] High-grade tumors in the present study exhibited marked architectural disorganization, nuclear pleomorphism, hyperchromasia, increased mitotic activity, and tumor necrosis, reflecting aggressive biological behavior. [13]

Muscle invasion was predominantly associated with high-grade tumors in the present study. Similar findings were reported by Pokar and Parsana, who demonstrated significant association between high-grade tumors and muscle invasion.[5] Madhu et al. also observed strong correlation between high tumor grade and muscle-invasive disease.[2] Muscle invasion remains one of the most important prognostic determinants in urothelial carcinoma because it significantly influences therapeutic decisions and survival outcomes. [14]

Lymphovascular invasion and tumor necrosis were more commonly identified in advanced-stage and high-grade tumors in the present study. Sarwala et al. similarly reported significant association of necrosis and lymphovascular invasion with aggressive tumor behavior and poor prognosis.[1] These pathological features indicate increased metastatic potential and are recognized as adverse prognostic indicators in urothelial carcinoma. [13,14]

Ki-67 immunohistochemical expression in the present study showed a significant correlation with tumor grade, pathological stage, muscle invasion, and lymphovascular invasion. High Ki-67 labeling index was predominantly observed in high-grade and invasive urothelial carcinomas. Similar observations were reported by Madhu et al., who found significant association between Ki-67 expression and tumor grade, muscle invasion, and lymphovascular invasion.[2] Haque et al. also documented significantly higher Ki-67 positivity in high-grade tumors compared to low-grade lesions.[3]

Abid et al. demonstrated that Ki-67 positivity increased significantly with advancing tumor stage and grade,

particularly in infiltrating urothelial carcinomas.[8] Rahman et al. further reported significant association between Ki-67 overexpression and pathological stage as well as lymph node metastasis.[9] Multiple studies have therefore established Ki-67 as a reliable marker of tumor proliferative activity and aggressive biological behavior in urothelial carcinoma. [18, 19]

In the present study, Her2/neu overexpression was predominantly observed in high-grade and muscle-invasive urothelial carcinomas. Positive Her2/neu staining showed significant association with advanced pathological stage, necrosis, and lymphovascular invasion. Similar findings were reported by Sarwala et al., who observed significant association between Her2/neu positivity and high-grade tumors, advanced stage, and tumor necrosis.[1] Madhu et al. also demonstrated strong correlation between Her2/neu expression and tumor grade, muscle invasion, recurrence, and survival outcomes. [2]

Li et al. reported HER2 positivity in more than half of urothelial carcinoma cases and found significant association with histological grade, invasiveness, and tumor stage.[10] Guntimadugu et al. similarly documented significant correlation between Her2/neu overexpression and high tumor grade as well as larger tumor size.[11] However, Ibrahim et al. reported limited association between Her2/neu expression and clinicopathological parameters except perineural invasion.[12] This variability in Her2/neu expression across different studies may be related to differences in sample size, scoring systems, antibody sensitivity, and population characteristics.

The present study also demonstrated significant co-expression of Ki-67 and Her2/neu in high-grade invasive urothelial carcinomas. Tumors showing co-expression of both markers exhibited more aggressive clinicopathological features including advanced stage, muscle invasion, necrosis, and lymphovascular invasion. Similar observations were reported by Madhu et al., who concluded that combined Ki-67 and Her2/neu expression provided superior prognostic information compared to single-marker analysis. [2] Sarwala et al. also documented strong association between co-expression of Her2/neu and Ki-67 with aggressive tumor phenotype and adverse prognostic factors.[1]

The findings of the present study support the growing role of molecular biomarkers in improving prognostic stratification in urothelial carcinoma beyond conventional histopathological grading and staging. [15, 16] Ki-67 reflects tumor proliferative activity, whereas Her2/neu overexpression may identify tumors driven by oncogenic signaling pathways and potential responsiveness to targeted therapy. [17, 21]

Importantly, Her2/neu positivity may have therapeutic implications in advanced urothelial carcinoma. Targeted anti-HER2 therapies such as trastuzumab and antibody-drug conjugates have shown promising results in HER2-positive malignancies and may provide additional treatment options in selected cases of urothelial carcinoma. [10, 23] Therefore, routine assessment of Her2/neu expression may help identify patients who could benefit from targeted therapeutic approaches.

Overall, the findings of the present study are consistent with previous literature and further establish Ki-67 and Her2/neu as important prognostic biomarkers in urothelial carcinoma of the urinary bladder. Combined evaluation of these markers may improve prognostic assessment, facilitate risk stratification, and contribute to individualized patient management strategies.

5. Conclusion

Ki-67 and Her2/neu expression correlate significantly with adverse clinicopathological prognostic factors in urothelial neoplasms of the urinary bladder. Increased expression of these markers is associated with higher tumor grade, muscle invasion, advanced stage, necrosis, and lymphovascular invasion.

Combined evaluation of Ki-67 and Her2/neu may improve prognostic stratification and help identify patients with aggressive tumor biology. Her2/neu expression may also have therapeutic implications for targeted therapy in selected patients with advanced urothelial carcinoma.

Routine incorporation of these immunohistochemical markers into pathological evaluation may contribute to improved prognostic assessment and individualized patient management.

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