

Immunohistochemical Expression of HER2/Neu in Urothelial Carcinoma: A Cross-sectional Study

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ABSTRACT

Introduction: Urothelial Carcinoma (UC) is a disease with significant mortality, estimated to be the ninth most common cause of cancer worldwide and the thirteenth most common cause of death from cancer. It has a significant impact on public health and will continue to do so due to the high prevalence of smoking. To combat the growth of urothelial cancer, awareness regarding primary prevention must be underscored, and smoking cessation programs need to be encouraged and supported.

Aim: The aim of this study is to determine the expression of Human Epidermal Receptor 2 (HER2)/neu in UC and its association with age, size, type, grade, and invasion of the tumour.

Materials and Methods: This cross-sectional study was conducted at the Department of Pathology, Sri Guru Ram Das Institute of Medical Sciences and Research (a tertiary care centre) in Amritsar, Punjab, India, from January 1st, 2019, to December 31st, 2020. Fifty histopathologically proven cases of UC were examined. HER2/neu expression was studied using immunohistochemistry, and its correlation with age, size, type, grade, and invasion was analysed. The findings of the study were statistically analysed using Statistical Package for the Social Sciences (SPSS) software version 21.0, a statistical program for Microsoft Windows.

Results: A total of 50 patients were analysed for the study (40 males and 10 females, with a mean age of 60.4 years at presentation). Nineteen cases were low-grade, and 31 cases were high-grade, with high-grade cases being more invasive. Thirteen cases showed HER2/neu expression, of which 11 were high-grade, indicating a statistically significant relationship between grade and HER2/neu expression. Similarly, expression was higher in cases with lamina propria and muscularis propria invasion. Out of the 34 cases showing lamina propria invasion, 10 cases were positive for HER2/neu expression, constituting 29.4%. Among the 42 cases involving muscularis propria in the biopsy, 16 cases showed muscularis propria invasion by the tumour, with four cases (25%) being positive for HER2/neu expression.

Conclusion: The expression of HER2/neu increases with grade and shows more positive expression in high-grade invasive tumours involving lamina propria or muscularis propria. This indicates that HER2/neu protein overexpression is associated with aggressive disease and serves as a negative prognostic marker. Targeted therapy against HER2/neu may prove to be beneficial in such patients.

Keywords: Haematuria, Human epidermal receptor 2, Lamina propria, Muscularis, Prognostic

INTRODUCTION

UC is a disease that significantly contributes to the overall burden of human cancer. It is the fourth most common tumour after prostate cancer, lung cancer, and colorectal carcinoma, but it is the second most common urologic malignancy [1]. Approximately 90%-95% of UC cases arise from the lower urinary tract, including the bladder and urethra, while the remaining 5-10% of cases originate from the upper urinary tract, such as the renal pelvis and ureter [2]. In developed nations like the USA, the incidence of UC is 20.0 per 100,000, with a mortality rate of 4.3%. It predominantly affects men in the elderly age group, and an estimated 81,400 new cases and 17,980 deaths were projected for 2020 [3]. Various factors have been linked to the development of UC, including exposure to aromatic amines, smoking, environmental pollution, socio-economic status, analgesic abuse, fluid intake, genetic susceptibility, schistosomiasis, urinary tract disease, ionizing radiation, cyclophosphamide, and other drugs.

Painless gross haematuria is the most common complaint observed in these patients, and Transitional cell carcinoma is the most common subtype. These cancers can present as non-muscle-invasive, muscle-invasive, or metastatic malignancies. Mortality increases with the progression from superficial or locally invasive disease (pTa/pT1) to detrusor muscle-invasive disease (pT2). Immunohistochemical expression of HER2/neu in UC can aid in diagnosis and predicting prognosis. Human Epidermal Growth Factor Receptor-2 (HER2/neu) is a transmembrane glycoprotein

with intrinsic tyrosine kinase activity. It plays a role in the regulation of normal cellular proliferation; however, its overexpression may lead to neoplastic cell growth.

The incidence of HER2/neu overexpression in bladder cancer ranges from 9% to 34%, one of the highest rates among all human malignancies. The correlation between HER2/neu expression and tumour grade and stage, as well as their prognostic value, has been variably reported [4]. The current study aimed to assess the expression of HER2/neu in UC and establish its correlation with age, size, type, grade, and invasion of the tumour.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Pathology, Sri Guru Ram Das Institute of Medical Sciences and Research (a tertiary care centre) in Amritsar, Punjab, India, from January 1st, 2019, to December 31st, 2020, on 50 histopathologically proven cases of UC. Ethical clearance was obtained from the Institutional Ethical Committee (Ref. No. Patho 175/19).

Inclusion criteria: All urinary bladder biopsies and cystectomy specimens received in the pathology department were included in the study.

Exclusion criteria: All other histopathology specimens, except urinary bladder biopsies and cystectomy specimens, autolyzed specimens, or tiny inadequate urinary bladder biopsy specimens, were excluded from the study.

Study Procedure

The histopathological sections from bladder biopsy tumours were obtained. The samples were fixed in 10% neutral buffered formalin for a duration of 12-24 hours. Paraffin wax blocks were made, and 3-5 µm sections were taken on poly-L-lysine coated slides. Two sections were taken; one was processed for Haematoxylin and Eosin (H&E) staining, while the other was processed for immunohistochemical staining for HER2/neu using a Primary antibody-Rabbit Monoclonal antibody (Biocare Medical) after antigen retrieval by heat method in Decloaker. A 3'3 Diaminobenzene was used as the chromogen. Positive and negative controls were run with every batch of the IHC. HER2/neu positive breast carcinoma cases were taken as positive control.

The urothelial tumours were classified according to the 2016 World Health Organisation-International Society of Urological Pathology (WHO-ISUP) Consensus classification [5]. Gross and histomorphological features of all UC cases were studied. HER2/neu expression and staining patterns were analysed, and the expression of HER2/neu with age, size, type, grade, and invasion of the tumour was established. For HER2/neu, only membranous staining was taken into consideration. Staining intensity was defined as mild, moderate, or strong, and patterns were finally scored. Scores 2 and 3 were considered positive for HER2/neu, as used by Jimenez RE et al., and Nadoushan MR et al., in their respective research [6,7].

The interpretation of IHC scoring was done in the following manner in the present study:

- **Negative (Score 0):** No staining observed or incomplete, faint, or barely perceptible membrane staining in less than or equal to 10% of invasive tumour cells.
- **Negative (Score 1+):** Incomplete, faint, or barely perceptible membrane staining in more than 10% of invasive tumour cells.
- **Equivocal (Score 2+):** Incomplete and/or weak to moderate circumferential membrane staining in more than 10% of invasive tumour cells or complete, intense, circumferential membrane staining in less than or equal to 10% of invasive tumour cells.
- **Positive (Score 3+):** Complete, intense, circumferential membrane staining in more than 10% of invasive tumour cells.

STATISTICAL ANALYSIS

The data were described in terms of frequencies (number of cases), relative frequencies (percentages), and p-values. The chi-square test was applied to calculate the p-value. All statistical calculations were performed using SPSS software version 21.0, a statistical program for Microsoft Windows.

RESULTS

A total of 50 patients were diagnosed over a period of two years, with a mean age at presentation of 60.4 years. There were 40 males and 10 females in the study. The oldest patient was 80 years old, while the youngest was 31 years old [Table/Fig-1].

Age group (years)	Males, n	Females, n	n (%)
30-50	8	2	10 (20)
51-70	27	6	33 (66)
71-90	5	2	7 (14)
Total, n (%)	40 (80)	10 (20)	50 (100)

[Table/Fig-1]: Showing age and sex distribution.

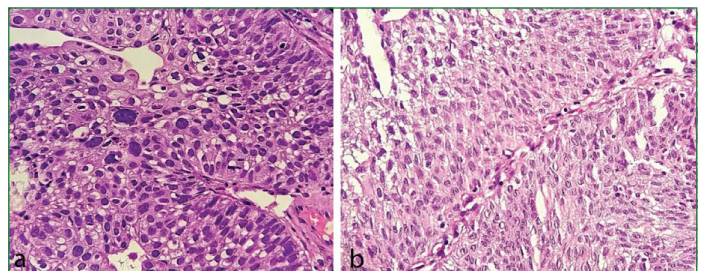
The patients presented with a variety of complaints, with painless haematuria being the most common (n=25) [Table/Fig-2]. The size of the tumours varied from 0.76 to 8 cm, with 44 (88%) cases falling within the range of up to 6 cm [Table/Fig-3]. Out of the total 50 cases, 31 (62%) were classified as high-grade UC, while 19 (38%) were classified as low-grade [Table/Fig-4a,b].

Chief complaint	n (%)
Painless haematuria	25 (50)
Burning micturition	6 (12)
Painless haematuria+burning micturition	7 (14)
Painless haematuria+increased frequency	5 (10)
Increased frequency+burning micturition	3 (6)
Painless haematuria+increased frequency+burning micturition	4 (8)

[Table/Fig-2]: Chief complaints of the cases.

Tumour size (cm)	n (%)
0.76-3.0	21 (42)
3.1-6.0	23 (46)
≥6.1	6 (12)
Total	50 (100)

[Table/Fig-3]: Showing size of the tumour radiologically.



[Table/Fig-4]: a) Photograph showing high-grade papillary Urothelial Carcinoma (UC) (H&E, 400X); b) Photograph showing low-grade papillary Urothelial Carcinoma (UC) (H&E, 400X).

In high-grade papillary UC cases, 29 cases showed lamina propria invasion, with a highly statistically significant difference (p-value <0.001), indicating that the tendency of tumours to invade the lamina propria increases with increasing grade of the tumour. In low-grade papillary UC cases, only five showed lamina propria invasion [Table/Fig-5].

Histological grade	Total no. of cases	Lamina propria		Muscularis propria	
		Invasive	Non invasive	Invasive	Non invasive
Low-grade, n	19	5	14	0	15
High-grade, n	31	29	2	16	11
p-value	-	<0.001		-	-

[Table/Fig-5]: Showing relationship between histological grade and invasion. The p-value in bold font indicates statistically significant value

Out of the 42 biopsy specimens that included the muscularis propria, invasion was seen in 16 (100%) cases, all of which were high-grade papillary UCs of the invasive type. None of the cases were of the low-grade type, indicating that muscularis propria invasion was mainly observed in high-grade invasive cases [Table/Fig-6].

HER2/neu expression: Cases showing incomplete or complete HER2/neu membranous staining in ≥10% of cells were considered positive. HER2/neu expression was seen in 13 (26%) cases out of the total 50 cases, of which two belonged to the low-grade category and 11 belonged to the high-grade category [Table/Fig-6].

Histological type	HER2/neu positive cases	HER2/neu negative cases	Total
Low-grade papillary Urothelial Carcinoma (UC) cases, n (%)	2 (15.38)	17 (45.94)	19 (38)
High-grade papillary Urothelial Carcinoma (UC) cases, n (%)	11 (84.61)	20 (54.05)	31 (62)
Total, n	13	37	50
p-value	<0.05		

[Table/Fig-6]: Relationship between HER2/neu positive cases and histological grade of tumour. The p-value in bold font indicates statistically significant value

Out of the total 13 cases showing positive HER2/neu expression, 10 cases (76.95%) were above 50 years of age, and only 3 (23.07%) cases belonged to the less than 50-year age group. The median age in HER2/neu positive cases was found to be 57 years. Although HER2/neu expression was seen to increase with age, the relationship between HER2/neu expression and the patient's age was found to be statistically insignificant, with a p-value of 0.74. Similarly, 12 cases were males, with only one female showing positive HER2/neu expression. However, this gender difference was also statistically insignificant, with a p-value of 0.19 [Table/Fig-7]. The highest HER2/neu positivity was observed in cases measuring 0.76-6.0 cm in size, with a statistically insignificant p-value of 0.66 [Table/Fig-8].

Age group (years)	HER2/neu positive cases, n (%)		HER2/neu negative cases, n (%)		Total, n (%)
	Males	Females	Males	Females	
30-50	3 (25)	0 (0)	5 (17.85)	2 (22.22)	10 (20)
51-70	5 (41.66)	1 (100)	22 (78.57)	5 (55.55)	33 (66)
71-90	4 (33.33)	0 (0)	1 (3.57)	2 (22.22)	7 (14)
Total	12 (24)	1 (2)	28 (56)	9 (18)	50 (100)
p-value for age=0.74					
p-value for sex=0.19					

[Table/Fig-7]: Showing relationship between HER2/neu positive cases with age and sex distribution.

Size (cm)	HER2/neu positive cases, n (%)	HER2/neu negative cases, n (%)	Total, n (%)
0.76-3.0	5 (38.46)	16 (43.24)	21 (42)
3.1-6.0	6 (46.15)	17 (45.94)	23 (46)
≥6.1	2 (15.38)	4 (10.81)	6 (12)
Total, n	13	37	50
p-value 0.66			

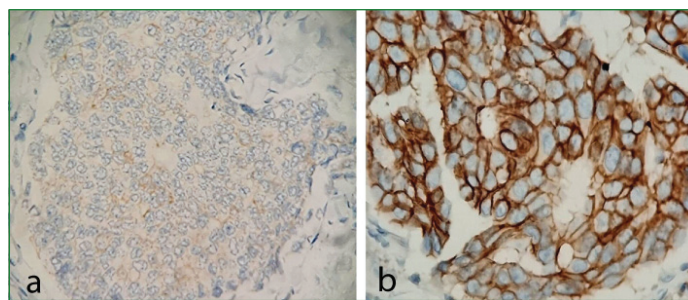
[Table/Fig-8]: Showing relationship between HER2/neu positive cases and size of tumour.

Out of the total 50 cases, 13 cases showed positive HER2/neu expression. Among these 13 cases, 2 (15.38%) were low-grade and 11 (84.61%) were high-grade papillary UC, indicating that HER2/neu was expressed more in high-grade tumours. A statistically significant correlation was observed between high-grade tumours and HER2/neu positivity, with a p-value of <0.05 [Table/Fig-6]. HER2/neu expression was seen in two cases of low-grade papillary UC, both of which were non-invasive. Ten out of eleven cases of high-grade papillary UC showed superficial invasion into the lamina propria. Although HER2/neu expression was more prominent in high-grade tumour cases with superficial invasion, no statistically significant relationship was found between HER2/neu expression and invasion. Only four out of 11 cases showed invasion into the muscularis propria [Table/Fig-9].

Histological grade	HER2/neu positive cases	Lamina propria		Muscularis propria	
		Invasive	Non invasive	Invasive	Non invasive
Low-grade, n	2	0	2	0	2
High-grade, n	11	10	1	4	7
p-value 0.42 (Lamina propria), 0.89 (Muscularis propria)					

[Table/Fig-9]: Showing relationship between HER2/neu and invasion.

High-grade cases mainly showed strong intensity of staining, while low-grade cases presented with moderate staining intensity. Both low-grade papillary UC cases showing HER2/neu positivity had moderate intensity of staining. Out of the 11 HER2/neu positive high-grade papillary UC cases, one showed mild, three showed moderate, and seven showed strong HER2/neu immunostaining. Thus, strong staining intensity was seen in the majority of high-grade papillary UC cases [Table/Fig-10a,b,11].



[Table/Fig-10]: a) HER2/neu positivity with mild intensity (partial or complete membranous staining) (H&E, 400X). b) HER2/neu positivity with strong intensity (partial or complete membranous staining) (H&E, 400X).

HER2/neu staining intensity	HER2/neu positive cases in low-grade type (>10% cells positive)	HER2/neu positive cases in high-grade type (>10% cells positive)	Total, n
Mild, n (%)	0 (0)	1 (9.09)	1
Moderate, n (%)	2 (100)	3 (27.27)	5
Strong, n (%)	0 (0)	7 (63.63)	7
Total, n	2	11	13

[Table/Fig-11]: Showing staining intensity with histological grade of tumour.

Two positive cases of low-grade papillary UC showed percentage positivity varying from >50% to ≤75%. Meanwhile, 11 cases of high-grade papillary UC showed HER2/neu positivity with the percentage of positive cells varying from 15% to 89%. Six cases of high-grade showed positive cells in the range of >25% to ≤50%, three cases in the range of >50% to ≤75%, and one case each in the range of ≤25% and >75% [Table/Fig-12].

Percentage of HER2/neu positive cells	Low-grade papillary Urothelial Carcinoma (UC) cases, n (%)	High-grade Papillary Urothelial Carcinoma (UC) cases, n (%)
>10 to ≤25%	0	1 (9.09)
>25 to ≤50%	0	6 (54.54)
>50% to ≤75%	2 (100)	3 (27.27)
>75%	0	1 (9.09)
Total, n	2	11

[Table/Fig-12]: Percentage of HER2/neu positive cells in low-grade and high-grade papillary UC.

By multiplying the percentage positivity and intensity, a final score of ≥2 was considered positive and ≤1 as negative. According to this, a total of 13 cases were positive with a score of ≥2. Both cases of low-grade papillary UC were positive with a score of 2, and 4 out of 11 cases of high-grade papillary UC were positive with a score of 2. Additionally, 7 out of 11 cases were positive with a score of 3, suggesting that high-grade tumours presented with a higher score [Table/Fig-13].

Final score	Low-grade papillary Urothelial Carcinoma (UC) cases, n	High-grade Papillary Urothelial Carcinoma (UC) cases, n
0	–	–
1	–	–
2	2	4
3	–	7
Total	2	11

[Table/Fig-13]: Final score on considering percentage positivity and intensity.

DISCUSSION

UC is a devastating disease and is the fourth most common tumour after prostate cancer, lung cancer, and colorectal carcinoma. The expression of HER2/neu protein in UC has been studied by various authors due to its involvement in the pathogenesis of these tumours and its potential therapeutic or prognostic significance [7]. In our study, the mean age of the cases was found to be 60.4 years. Gupta P et al., conducted a study on a cohort of 561 bladder cancer

patients and reported similar results with a mean age of 60.2 ± 4.4 years [8]. Prakash G et al., conducted a study on 419 patients with bladder carcinoma at Tata Memorial Hospital and concluded that the median age at presentation was 59 years, with a range of 18-88 years [9].

Regarding the distribution of sexes, only 10 (20%) cases were females, while the remaining 40 (80%) were males, resulting in a male to female ratio of 4:1. Other studies conducted by different authors reported male to female ratios ranging from 4.4:1 to 4.7:1 [10,11].

Most of the patients presented with painless haematuria, followed by painless haematuria and burning micturition as the second most common complaint. These findings are similar to the study conducted by Chinnasamy R et al., where painless haematuria was also the most common complaint observed in 111 out of 156 patients [10]. The size of the tumours ranged from 0.76 to 8.0 cm on radiology/cystoscopy, with the majority (88%) of the cases being up to 6 cm. All the lesions had a papillary configuration. These findings were similar to a study done by El Ochi MR et al., which reported that 58.3% of cases were 3 cm or larger in size [12].

In the present study, there were 19 (38%) cases of low-grade and 31 (62%) cases of high-grade papillary UC. Lamina propria invasion was seen in 68% of cases, i.e., 34 cases, out of which 85.3% were high-grade and 14.7% were low-grade, with a highly significant p-value of <0.001 between the histological grade of the tumour and lamina propria invasion. This shows that the tendency of tumours to invade the lamina propria increases with increasing grade of the tumour. Similar findings were seen in a study conducted by Selhi PK et al., on a cohort of 321 patients with 166 cases of UC, where lamina propria invasion was seen in 56 out of 166 cases, i.e., 33.73%, out of which 18 (32%) were low-grade and 37 (66%) were high-grade, and two cases were adenocarcinoma [11]. It has been emphasised by both Lopez-Beltran A and Cheng L, and Paner GP et al., in their studies that superficial bladder tumours should be separated by pathologists into non-invasive (pTa) and lamina propria invasive (pT1), as the latter have a significantly poorer prognosis [13,14]. Although Kobayashi H et al., in his study, mentioned that patients with low-grade Ta bladder cancer should be followed-up for up to 10 years from the initial diagnosis for tumour recurrence and worsening prognosis [15].

Muscularis propria was included in 42 cases, of which 16 showed invasion. All of them were high-grade invasive papillary UC cases, and none of the low-grade cases showed muscularis propria invasion, indicating that muscularis propria invasion increases with an increase in the histological grade of the tumour. These findings correlate well with the observations made in another study that reported muscularis propria invasion in 42% of cases, all of which were high-grade tumours [11]. Lopez-Beltran A and Cheng L, and Paner GP et al., have both emphasised the importance of including muscularis propria in the biopsy, as invasion into it is associated with a significantly poorer prognosis, and failure to include it may lead to the understanding of the tumour [13,14].

HER2/neu expression is involved in cellular processes such as cell growth, survival, and migration, and its abnormal activation can lead to oncogenic transformation. Amplification or overexpression of HER2 is observed in various cancers, including breast, gastric/gastroesophageal, ovary, endometrium, bladder, lung, colon, and head and neck. In invasive urothelial bladder carcinomas, the range of HER2 amplification and/or overexpression is reported to be 23% to 80% for overexpression and 0% to 32% for amplification [16]. Targeted therapy against HER2 has shown the most benefit in cases with gene amplification, and immunohistochemical analysis of the HER2 protein is used as an initial screening tool to determine cases for further analysis of HER2 gene status using Fluorescent In Situ Hybridization (FISH) [16].

In our study, HER2/neu positivity was observed in 13 cases, with 2 being low-grade and 11 being high-grade papillary UC cases.

Out of the 40 male patients, 12 (30%) showed positive HER2/neu expression, while only 1 (10%) out of the 10 female patients showed positive HER2/neu expression, resulting in a male to female ratio of 12:1. However, there was no statistically significant correlation found between HER2/neu expression and sex, with a p-value of 0.19. Similar findings were reported by El Ochi MR et al., where the male to female ratio of HER2/neu expression was 11:1 [12]. El Gehani K et al., also found HER2/neu expression in 23 out of 39 cases, with no significant correlation between HER2/neu expression and sex [17]. Abdelwahab MM and Elbasateeny SS found HER2/neu positivity in 24 out of 60 cases of UC, with no significant correlation between age, sex, and HER2/neu expression [18].

In our study, the median age of HER2/neu positive cases was 57 years, which is similar to the findings of El Ochi MR et al., where the median age was 60 years [12]. The majority of the cases in our study ranged in size from 0.76 to 6.0 cm, and a high proportion of HER2/neu positive cases were observed within this size range (84.61%). However, there was no statistically significant association between tumour size and HER2/neu expression, with a p-value of 0.66. Another study showed that out of 12 HER2/neu positive cases, 9 had a size range of ≥ 3 cm [12].

In our study, out of the total 50 cases of UC, 13 (26%) showed positive HER2/neu expression. Among these 13 cases, 2 (15.38%) were low-grade and 11 (84.61%) were high-grade papillary UC. This suggests that HER2/neu expression is more common in high-grade tumours than in low-grade tumours, and there is a statistically significant correlation between HER2/neu expression and the histological grade of the tumour (p-value <0.05). Similar findings were observed in a study by Abdelwahab MM and Elbasateeny SS, where 24 out of 60 (40%) cases showed HER2/neu positive expression, with 8 out of 24 (33.3%) being low-grade and 16 out of 36 (33.3%) being high-grade, and a statistically significant correlation was found between HER2/neu expression and histological grade (p-value 0.023) [18].

Another study by Atis G et al., also found a statistically significant correlation between HER2/neu expression and histological grade, with Grade-3 tumours showing higher expression compared to Grade-1 and 2 tumours (p-value 0.012) [4]. Similarly, a study by Hammam O et al., found a significant correlation between HER2/neu protein expression and increasing grade of the tumour (p-value <0.01) [16].

When correlating HER2/neu positive cases with staining intensity, we observed that both low-grade HER2/neu positive cases had moderate staining intensity, while the majority of high-grade cases (7 out of 11; 63.63%) showed strong intensity of staining. This finding is consistent with a study by Kumar S et al., which also found a higher staining intensity associated with high-grade tumours [19]. Furthermore, when correlating HER2/neu positive cases with the final score, all 13 HER2/neu positive cases showed a final score of ≥ 2 . Both low-grade cases were positive with a score of 2, and out of the 11 high-grade HER2/neu positive cases, 4 had a score of 2 and 7 had a score of 3. This indicates that as the histological grade of the tumour increases, the final score for HER2/neu expression also tends to increase.

Out of the 50 cases examined in our study, lamina propria invasion was observed in 34 cases, with 10 of these cases (29.4%) showing positive HER2/neu expression. Additionally, muscularis propria invasion was seen in 42 cases, with 16 cases (25%) showing HER2/neu expression. These findings are consistent with a study by Atis G et al., where HER2/neu expression was found in 5 out of 28 superficial tumour specimens (17.8%) and 7 out of 18 invasive tumour specimens (38.8%) [4]. Another study by Kumar S et al., reported HER2/neu expression in 70% of both superficial and muscle-invasive urothelial tumours, although no statistical significance was found between HER2/neu expression in superficial

versus invasive bladder tumours (p-value 1.00) [19]. Shawky AE et al., concluded that HER2/neu expression was more frequent in carcinomas invading the perivesical fat (pT3), constituting 81.8% [20]. HER2/neu, a member of the Epidermal Growth Factor Receptor family, is known to play a role in the pathogenesis of several cancers. Its abnormal activation can lead to cellular effects such as cell growth, survival, migration, and oncogenic transformation. Targeting the HER2 gene product with the monoclonal antibody Trastuzumab has led to advances in the treatment of cancers, particularly in cases with gene amplification, as seen in UC [20].

Limitation(s)

The main limitation of the present study was the small sample size. Conducting further studies with a larger sample size may provide more accurate results.

CONCLUSION(S)

In conclusion, it can be inferred that HER2/neu expression increases with the grade of the tumour, particularly in high-grade invasive tumours involving the lamina propria or muscularis propria. This indicates that HER2/neu protein overexpression is associated with aggressive disease and serves as a poor prognostic marker. Previous studies have suggested that targeted therapy against HER2/neu may be beneficial in such patients and could potentially help prevent recurrence. This treatment approach may hold value for patients undergoing treatment for metastatic UC, as current therapy options are limited.

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PLAGIARISM CHECKING METHODS: [Jan H et al.]

- Plagiarism X-checker: Jul 30, 2022
- Manual Googling: Apr 22, 2023
- iThenticate Software: Apr 29, 2023 (9%)

ETYMOLOGY: Author Origin

EMENDATIONS: 9

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jul 26, 2022**
Date of Peer Review: **Sep 09, 2022**
Date of Acceptance: **May 01, 2023**
Date of Publishing: **Jan 01, 2024**