



Original Article

Role of CD44 And MMP2 Marker in Diagnosis and Prognosis of Urinary Bladder Carcinoma

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Received: 12-10-2025

Accepted: 28-10-2025

Available online: 10-11-2025

ABSTRACT

Introduction: Lower urinary tract symptoms are caused by several factors. If a patient suffering from frequent urination associated with pain and blood in urine draws the attention of patients and brings them for consultations with the clinicians. Among serious causes for lower urinary tract symptoms is bladder carcinoma, affecting more men (3.67%) and comparatively fewer (0.83%) women. Clinicians, with the help of pathologists, confirm their diagnosis to decide on the choice of treatment options for better quality of life for the patients. Pathologists accomplish histopathology and subsequent use of CD44 and MMP2 antibodies as diagnostic and prognostic markers in urinary bladder carcinoma. Enables urologists to choose better treatment options to improve the quality of life of the sufferer.

Aim: This study was aimed at determining the sensitivity and specificity of CD44 and MMP2 for the diagnosis and prognosis of urinary bladder carcinoma.

Study Design: Prospective cross sectional analytical study design was chosen.

Material and Methods: Overall, 56 histopathological specimens were taken for study from men and women between the ages of 18 and 60 years. The tissue was received after transurethral resection of bladder tissue (TURBT) and radical cystectomy from the urology department. The tissues after fixation in 10% buffered formalin solution, grossing and sectioning were made. Thin sections of 4-to-6-micron thickness were prepared. Following standard tissue processing protocol, haematoxylin and eosin staining was done. The Dako immunohistochemistry protocol was followed for the positivity of the prepared and stained sections for liquid anti-CD44 antibody [ERP1013Y] ab51037 and anti-MMP2 antibody ab3750 reagents in 1:70 dilution. Then each section was examined under a microscope in high power at 100X.

Results and Observations: SPSS version 21 software was used for data analysis. Mean age $\pm$ SD of patients was 55.07 ± 11.99 years. Bladder carcinoma was found highest (46.4%) in patients of age group 60 years or more. Among study groups, males constituted 50 (89.3%) and females 6 (10.7%). The CD44 expression was significantly less in high grade than in low grade ($p < 0.001$). The highly significant association was found between MMP2 expression and tumour grades ($p = 0.006$). The MMP2 expression was significantly more in the high grade than the low grade ($p = 0.001$). In the present study, sensitivity was 89.2% (% accuracy of prediction of high grade. Specificity observed was 100% (% accuracy of prediction of low grades). Overall diagnostic accuracy reported 92.9% (% accuracy of true prediction).

Conclusion: CD44 expression is significantly more expressed in low grade non-invasive urothelial carcinoma (NMIBC) while MMP2 is significantly more expressed in high grade muscle invasive urothelial carcinoma (MIBC). Therefore, both CD44 and MMP2 is reliable and an excellent diagnostic biomarker marker.

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Keywords: MMP2 (matrix metalloproteinase), Anti-CD44 antibody [ERP1013Y] AB51037, Anti-MMP2 antibody AB37150 and Rotary Microtome, Radical cystectomy, Trans Urethral resection of bladder Tissue (TURBT).

INTRODUCTION

Urinary bladder is common site for cancer development in urinary tract. In India according to recent reports of National Cancer Registry Programme 2006, the overall incident rate of urinary bladder cancer is 2.25% (per 100000 annually) [1]. Gender wise prevalence is 3.67% among males and 0.83% for females [1]. Among all malignancies, urinary bladder carcinoma ranks eleventh, and its incidence is rising, according to GLOBOCAN 2020 world factsheet data. It has also been shown that the Indian population is on the rise. By 2040, there will be 79.6% more cases of urinary bladder cancer (UBC) in India, according to GLOBOCAN 2020[2]. In Western European nations and the United States, the lifetime risk for white males and females ranges from 1 in 80 and 1 in 25, respectively. Every year, about 145,000 individuals globally die out due to bladder cancer [3].

The urothelium or transitional epithelium is the location where the majority of bladder cancers start. Based on epidemiological investigations, cancer primarily affects older men, and the presence of mucosal irritants could increase the excretion of carcinogenic chemicals and parasite infections in the urine. A number causative factors of factors are included that can be responsible for urinary bladder carcinoma. As most of the people in north India occupationally belonged to agriculture. Among these most of the people are smoker [4] and secondly, they are exposed to chemicals like anthranilic diamide, chlorpyrifos cypermethrin, lesenta, and tricyclazole were the pesticides/ insecticides commonly used in agriculture [5]. There is also evidence that parasitic infection specially schistosomiasis cause urinary bladder malignancy [6].

CD44 a complex trans-membrane glycoprotein, also called by multiple names like Hermes antigen, homing cell adhesion molecule, HUTCH-1, phagocytic glycoprotein-1, lymphocytes -homing receptor, and ECM III, is coded by the CD44 gene on chromosome 11[7], which consists of 20 exons [8]. Transcripts for CD44 gene undergo complex alternative splicing, which results in many functionally distinct isoforms, such as CD44 standard isoform (CD44s) and CD44 variant isoform (CD44v) [9]. CD44s are found in most of the human body cells [10], while CD44v is expressed primarily on cells during inflammation and on tumor cells. CD44 protein consist of a short C- terminal cytoplasmic domain, a trans- membrane domain, and seven extracellular domain which contain an N- terminal Hyaluronic acid binding link-homology module and stem region [11,112].

CD44 plays pivotal role in promoting tumor invasion and metastasis by contributing to adhesion of tumor cells to endothelium and fibronectin enriched matrices [13]. CD44v possessed selectin ligand activity. Expression of CD44 both in breast cancer and colon cancer cells enhanced adhesion to endothelial cells and fibronectin correlate its metastatic potential [14,15]. CD44 potentiated the adhesion of basal –breast cancer cell to endothelium and fibronectin in an alpha 5B1-integrin dependent manner, while CD44 knockdown attenuated adhesion ability [13].

Matrix metalloproteinases (MMPs) are a large family of Zinc dependent proteolytic enzyme, manly involved in the degradation of protein targets, that are component of the extracellular matrix. MMPs play a diverse and crucial role in normal physiological process such as tissue remodeling, embryonic development and reproduction. The MMPs family consists of at least 26 to 28 members and most MMPs are composed of several distinct domains, a catalytic domain (MMP7 and MMP26), N terminal prodomains (also termed propeptide) and a hemopexin-like C terminal domain connected by linker or hinge region, and others have additionally had fibronectin-like domain (MMP2 and MMP9) that are crucial for their activity, and substrate specificity. MMPs can degrade the extracellular matrix (ECM), and can control the formation of tumor blood vessels [10].

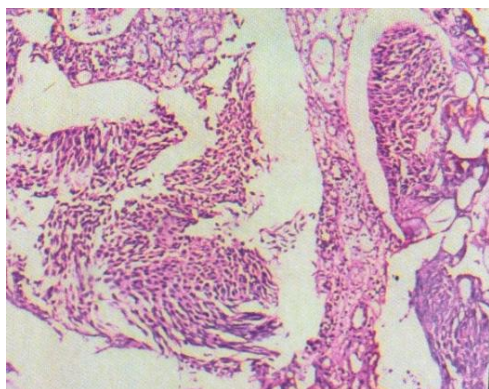


Image-2.1A: H/E Low Grade at 40X.

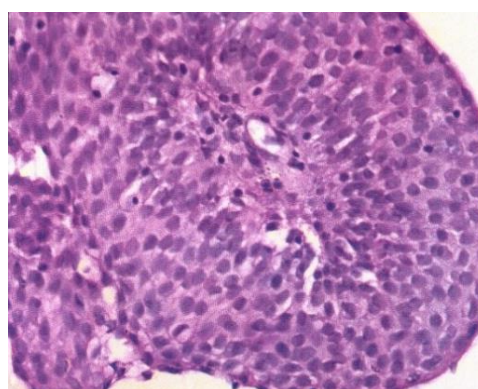


Image-2.1B: H/E low Grade at 100X

The present study was aimed at to determine the role of CD44 and MMP2 as a diagnostic and prognostic markers in urinary bladder carcinoma. The study was also primarily focused on primary outcome for its sensitivity and specificity in the expression pattern of CD44 and MMP2 in muscle invasive carcinoma with non-muscle invasive urinary bladder carcinoma.

MATERIAL AND METHODS

Before conducting study institutional ethical clearance (IEC) was taken from King George's Medical University Lucknow, Uttar Pradesh. A cross sectional analytical prospective study design was chosen in hospital setting. The study was conducted in collaboration with Department of Pathology and the Department of Urology of the King George's Medical University between 2018 to 2019 over a period of one year.

A total of 56 male and female patients were included in the study after taking written informed consent. Among 56 patients 50 were males and 6 were females. The age of participants was 18 years to more than 60 years. These study group participants were selected based on clinical history for suspicion of urinary bladder carcinoma diagnosed by cystoscopy, per-abdominal ultrasonography (USG) and contrast enhanced computed tomography abdomen (CECT).

Inclusion criteria were biopsy of the tissue obtained from patient who were operated upon transurethral resection of bladder tissue (TURBT) and radical cystectomy with clinical suspicion of urinary bladder carcinoma. The surgical procedure was performed by Urologist in Urology Department. Exclusion criteria were inadequate sample tissue and patients who were not given written informed consent.

As soon as bladder tissue resected followed by surgical procedure TURBT or radical cystectomy, specimens were kept in 10% buffered formalin solution for 24 hours for fixation. Smaller core biopsies were grossed on same day of receiving. While bigger biopsies specimens were allowed to fix overnight in 10% neutral buffered formalin. Thin section of 4-to-6-micron thickness were prepared using manual rotary microtome. These were stained routinely with hematoxylin and eosin. Using Carousal type of tissue processor standard steps of tissue processing (i) fixation, (ii) dehydration, (iii) clearing, (iv) infiltration and (v) embedding were adopted. Histopathological examination was done. Grading the lesion was into muscle invasive carcinoma (MIBC) and non-invasive bladder carcinoma (NMIBC) based on AJCC 8th edition [16] guidelines was made.

Pathologic Stage classification (pTNM, AJCC 8th Edition) [16]

pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour
pTa	No invasive papillary carcinoma
pTis	Urothelial carcinoma in situ: (flat tumour)
pT1	Tumour invade lamina propria (subepithelial connective tissue)
pT2	Tumour invades muscularis propria
pT2a	Tumour invades superficial muscularis propria (inner half)
pT2b	Tumour invades deep muscularis propria (outer half)
pT3:	Tumour invades peri-vesical soft tissue
pT3a	Tumour invades peri-vesical soft tissue microscopically
pT3b	Tumour invades peri-vesical soft tissue macroscopically (extravesical mass)
pT4	Extravesical tumour directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
pT4a	Extravesical tumour directly invades any of the following: prostatic stroma, seminal vesicles, uterus or vagina.
pT4b	Extravesical tumour directly invades pelvic wall, abdominal wall

Regional lymph nodes (pN) [16]

pNX	Lymph nodes cannot be assessed
pN0	No lymph node metastasis
pN1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac or sacral lymph node)
pN2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac or sacral lymph node metastasis)
pN3	metastasis to the common iliac lymph nodes.

Distant Metastasis (pM)[16]

pM1	pM1: Distant metastasis
pM1a	metastasis limited to lymph nodes beyond the Common iliacs.
pM1b	Non-lymph node distant metastases

Dako Immunohistochemistry Protocol was followed

- I. **DEPARAFFINIZATION:** was done by keeping in xylene of previously 3-5-micron thick cut section which were fixed at 56⁰ C for 20 minutes. These sections were rehydrated through graded alcohols followed by distilled water for 5 minutes in each.
- II. **UNMASKING OF ANTIGENIC SITES BY PRESSURE COOKER ANTIGEN RETRIEVAL METHOD:** deparaffinized sections were placed in TRIS-EDTA (TRIS-1.121gm, EDTA0.37gm and tween 20-500µl) buffer for antigen retrieval at 98⁰ C for 25 minutes and then cooled at room temperature. It was followed by 3 gentle washes in tris for 5 minutes each.
- III. **PEROXIDASE TREATMENT:** Sections were treated with 3% hydrogen peroxide for 10 minutes to block endogenous peroxidase activity. It was followed by 3 gentle washes in TRIS buffered saline (ph. 7.4) for 5 minutes each.
- IV. **PRIMARY ANTIBODY:** Slides were wiped off and incubated for 90 minutes with primary antibody at 4⁰ C in a moist chamber. Slides were rinsed with TRIS EDTA buffer (ph. 9) thrice.
- V. **BIOTINYLATED LINK ANTIBODY (DacoEnVisionFlex™):** Excess buffer was wiped of and sections were covered with link antibody(secondary) for 30 minutes at room temperature.
- VI. **ENZYME CONJUGATE:** Enzyme conjugate (streptavidin horse Redish peroxidase) was applied for 30 minutes followed by 3 washes in TBS for 5 minutes each.
- VII. **SUBSTRATE CHROMOGEN SOLUTION:** Concentrated Diaminobenzene (DAB) solution was diluted with substrate buffer (500µl substrate buffer + 2 drops DAB)
- VIII. **COUNTERSTAINING:** Sections were dipped in 10% haematoxylin 2-5 times and washed in distilled water for 5 minutes followed by mounting of section in DPX. Presence of brown coloured end product at the site of target antigen was indicative of positive reactivity.

Utilized antibody in the present study was 1. Anti- MMP2 antibody ab37150 in liquid form. Dilution used was 1:70 and incubated over a period of 90 minutes. It stains at cytoplasm level on positive reactivity. This antibody is species specific to rat, mouse, chicken and Human. 2. Anti-CD44 antibody [ERP1013Y] ab51037 was also used in liquid form. Dilution used was 1:70 and incubated for 90 minutes. CD44 antibody stains at plasma membrane level on positive reactivity. CD44 antibody was considered positive control for human breast carcinoma tissue and human urinary bladder. While MMP2 antibody was considered positive control for human neurofibroma.

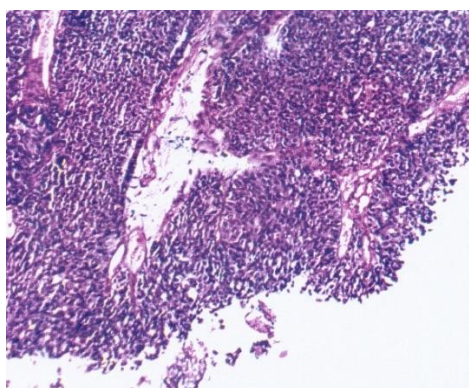


Image-2.1C: H/E High Grade at 40X.

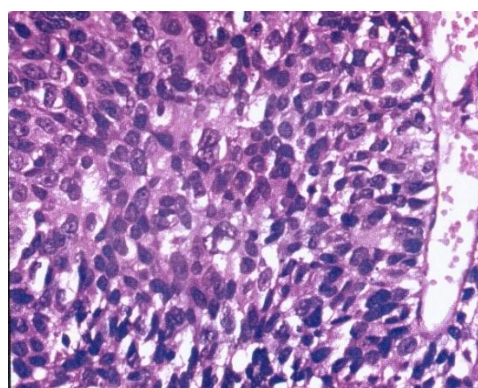


Image-2.1D: H/E High Grade at 100X

RESULTS AND OBSERVATIONS

The statistical analysis was done by using SPSS version 21. Mean and standard deviation were calculated. Chi square test and student 't' test was employed. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy was calculated. To minimize bias study groups were stratified in 18-29 years, 30-39 years, 40-49 years, 50-59 years and more than 60 years, The overall mean age was 55.07±SD11.99 years (18-75) including male and female patients. Most of the case belonged to age 60 years or more which constituted 46.4% (26 out of 56). Only 3.6% (2 out of 56) cases were aged below 30 (age group 18-29) years.

Table no -1.1 Distribution of procedures along with cases among study subjects

Procedures	Cases	Frequency (%)
Procedure Done	Cystoscopy	19 (33.9%)
	Per-abdominal USG	24 (42.9%)
	CECT	13 (23.2%)
Tissue	Radical Cystectomy	3 (5.4%)
	TURBT	53 (94.6%)
Histology	High grade Lamina Invasive	11 (19.6%)
	High grade Muscle Invasive	22 (39.3%)
	Low grade Lamina Invasive	11 (19.6%)
	Low grade Superficial	12 (21.4%)

Grade	Low Grade	23 (41.1%)
	High Grade	33 (58.9%)

Distribution of cases according to tissue removal procedure the radical cystectomy was 5.4% (3/56) and the TURBT 94% (53/56). The maximum cases were of the high-grade muscle invasive 39.4% (22/56) followed by 21.4% (12/56) low grade superficial. While Low grade lamina invasive and high-grade lamina invasive urothelial carcinoma were in equal proportion 19.6% (11/56) each respectively. Low grade carcinoma was found in 41.1% (23/56) cases. High grade carcinoma was found in 58.9% (33/56).

Table 1.1a Showing Distribution of cases according to CD44 expression

CD44 Expression	Total	Low Grade		High grade		Significance	
	No.	No.	%	No.	%	Chi Sq	p- value
Score 1	15	0	0%	15	100%	42.47	<0.001
Score 2	22	4	18.2%	18	81%		
Score 3	19	19	100%	0	0%		

Table 1.1a shows Score 1 of CD44 expression was seen in 15 cases with all the high grades. Score 2 was seen in 22 cases with 18.2% low and 81.8% high grades. While score 3 was seen in 19 cases with all low grades. The highly significant association was found between CD44 expression and tumour grades ($p < 0.001$). When comparison of expression between high and low grades carcinoma was made then the mean CD44 expression value among low grade tumour was $2.83 \pm SD0.388$ while for high grade carcinoma it was $1.55 \pm SD0.506$. The CD44 expression was significantly less in high grade than the low grade ($p < 0.001$).

Table 1.1b Showing Distribution of cases according to MMP2 expression

MMP2 Expression	Total	Low Grade		High grade		Significance	
	No.	No.	%	No.	%	Chi Sq	p- value
Score 1	12	9	75.0%	3	25.0%	10.39	0.006
Score 2	33	13	39.4%	20	60.6%		
Score 3	11	1	9.1%	10	90.9%		

Table 1.1b shows Score 1 of MMP2 was seen in 12 cases with 25% high grades and 75% low grades. Score 2 was seen in 33 cases with 39.4% low and 60.6% high grades. While Score 3 was seen in 11 cases with 9.1% low grades and 90.9% high grades. The highly significant association was found between MMP2 expression and tumour grades ($p = 0.006$). when comparison of MMP2 expression between high grade and low grades carcinoma was made the mean expression value among low grade was $1.65 \pm SD0.57$ while for high grade carcinoma it was $2.21 \pm SD0.60$. The MMP2 expression was significantly more in high grade than the low grade ($p = 0.001$).

To show correlation between CD44 and MMP2 expression spearman correlation coefficient (ρ) test was done. This showed significant negative correlation ($\rho = -0.426$, $p = 0.001$) between CD44 and MMP2 expression. It means when the value of CD44 increases, the value of MMP2 decreases. When logistic regression analysis to predict tumour grade on the basis of CD44 and MMP2 expression it generated equation $PG = -22 \cdot 13(CD44) + 1.56(MMP2) + 43.01$. High grade will be predicted when $PG > 0$, else low grade will be predicted. A significant high agreement ($k = 0.848$, < 0.001) was found between predicted grade and actual grade as found in histopathology.

Table 1.1c Showing validity summary of logistic regression analysis

Sensitivity	89.2%
Specificity	100%
Positive Predictive value (PPV)	100%
Negative Predictive value (PPV)	82.6%
Diagnostic Accuracy	92.9%

Clear from table 1.1c that this predictive model has sensitivity 89.2 (% accuracy of the prediction of high grade), specificity 100 (% accuracy of the prediction low grade) and diagnostic accuracy 92.9% (% accuracy of true prediction).

DISCUSSION

In present study histological biopsies were taken as control. Among the included 56 patients with urinary bladder carcinoma, we observed maximum of 22 cases high grade muscle invasive urothelial carcinoma. High grade lamina invasive urothelial carcinoma and low-grade lamina invasive cases were reported 11 for each. While 12 cases with low grade superficial non-invasive carcinoma histologically. The cell surface glycoprotein CD44 plays a central role in cell to cell and cell to matrix adhesion [13]. CD44 promotes fixation and maintenance of the tissue integrity and participates in microenvironmental signal transduction [17]. CD44 gene exons can be combined by alternative splicing to form several

isoforms [9]. The CD44 acts as a metastatic tumour suppressor gene for urinary bladder carcinoma [18]. The expression of CD44 both at mRNA and protein level is down regulated during bladder cancer progression, with down regulating high tumour grade [18].

In present study based on the extent and intensity of the staining they are divided in three categories shown in table 1.1d

Table 1.1d CD44 Staining pattern (membranous)

Extent and intensity of intensity	Score
Focally positive/Slightly heterogenous staining	1(Negative)
Strong heterogenous staining	2 (Positive)
Strong homogenous staining	3 (Positive)

MMP2 is a type of collagenase, 72 kD, which is also known as gelatinase and is a member of of group of secreted varying in size from 110 to 901bp metalloproteases. T MMP2 gene is 17 kb long with 12 introns ranging from 175 to 4350bp located within the region of chromosome 16p13.9 [19, 20, 21].

The extent of staining was scored as % of tumour cells positive stained shown in table 1.1e

Table 1.1e MMP2 staining pattern (Cytoplasmic)

Proportion of the tumour cell positive (%)	Score
≤ 25%	1 (Negative)
25% - 75%	2(Positive)
>75%	3 (Positive)

Maximum patients in the present study were in their 50 -80 years of age. Bladder carcinoma was reported more in male. Most of the patients were presented haematuria (blood in urine). Male/Female ratio was reported 89.3:10.7. Major proportion of the patients were diagnosed as high grade 58.9% (33/56) and 41.1% (23/56) low grade urothelial carcinoma histologically.

In our study CD44 expression was positive in 68.18% (15/22) for high grade muscle invasive urinary bladder carcinoma which was higher as compared to Erdogan G. et al [22] and Sugino et al [23]. They reported 45% and 33% respectively. Our study reported 27% (3/11) high grade lamina invasive this finding was significantly low as compared to Endogen et al (45%) and Sugino et al (100%). However, our study reported 100% (23/23) positivity in in low grade urothelial carcinoma (invasive or non-invasive). In this respect finding of our study was exactly same as compared to Endogen et al [22] and Sugino et. al. [23].

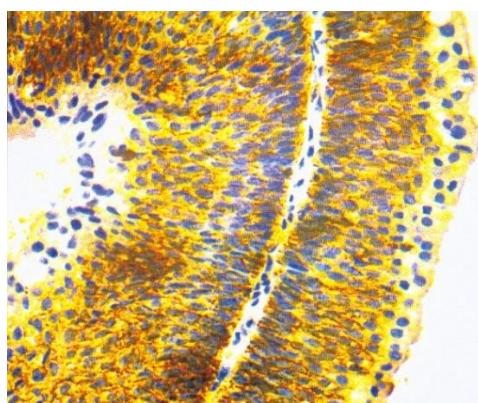


Image-2.1E: CD44 in Low Grade at 100X (Score-3).

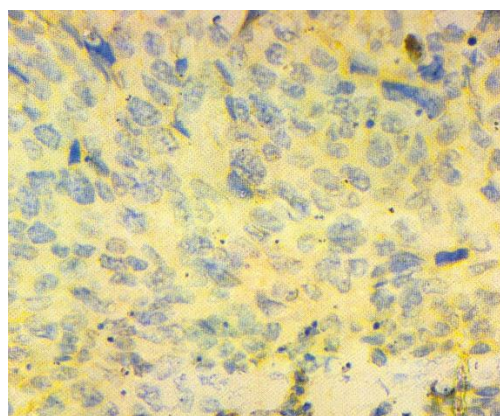


Image-2.1F: CD44 in High Grade at 100X (Score-1)

Positivity pattern of MMP2 expression (cytoplasmic) in this study was reported 83.36% (19/22) for high grade muscle invasive carcinoma it was higher as compared to 63% reported by Erdogan G. et. al. Likewise we found 100% (11/11) high grade lamina invasive carcinoma again higher in percentage as compared to 71% (20/28) reported by Erdogan G. et. al. Reason for this difference may be a smaller number of samples. Low grade invasive MMP2 positive carcinoma was found 36.36% (4/11) which was lower as compared 79% (15/19) reported by Erdogan G. et. al, again possibility of a smaller number of samples. However, we reported low grade superficial MMP2 positive carcinoma 75% (9/12) this value was higher in comparison of 55% (5/9) as reported by Erdogan G. et. al. Reason of the difference may be larger number of samples.

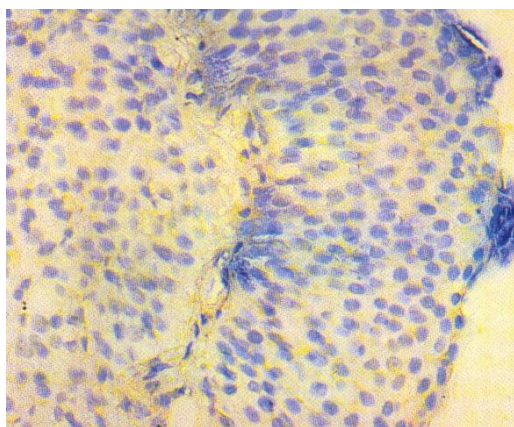


Image-2.1G: MMP2 Low Grade at 100X (Score-1).

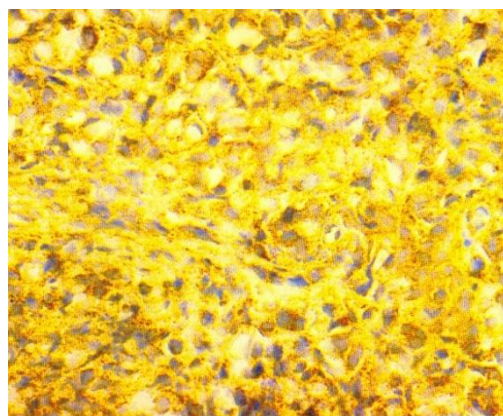


Image-2.1H: MMP2 Low Grade at 100X (Score-3)

Our study results obtain in Indian cohort of patient is concordance with similar such study done western world of cohort study. CD44 expression is significantly more in low grade non-invasive urothelial carcinoma. While MMP2 is significantly more expressed in high grade muscle invasive urothelial carcinoma.

LIMITATIONS:

Limitation of study the present study was surgical procedure TURBT through which possibly inadequate tissues were obtained from bladder tissue, as it may not have all layers of bladder wall. While Radicle cystectomy specimens were may be performed in advance stage and these specimens were lesser in number as compared to samples obtained throughout TURBT. Duration of study was shorter and lesser number of samples were processed.

CONCLUSION

The CD44 expression is significantly more in low grade urothelial non muscle invasive carcinoma (NMIBC) was found. While MMP2 is significantly more expressed in high grade muscle invasive urothelial carcinoma (MIBC). The predictive model as depicted from our study from the validity summary of logistic regression analysis has shown sensitivity 89.2%, specificity 100% and diagnostic accuracy 92.9% (ref table no. 1.1c). It is therefore, CD44 and MMP2 antibody have a definite role in the diagnosis and prognosis of the urinary bladder carcinoma as a biomarker.

For definite diagnosis and prognosis, a greater number of patients with long duration of follow up should be done and also these finding need to be correlated with recently described molecular biomarkers of urothelial carcinoma.

CONFLICT OF INTEREST

We declare no conflict of interest.

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