

**SINGLE CENTER AUDIT OF URINARY BLADDER MALIGNANCY: A 3-YEAR
RETROSPECTIVE ANALYSIS OF HOSPITAL DATA****Manjunath T.*, Puskal Kumar Bagchi, Mandeep Phukan, Debanga Sarma, Rajeev T. P. and
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ABSTRACT

Introduction: Urinary Bladder cancer (BC) is one of the most common urological malignancies. It accounts for a large case load in uro-oncology. As per the Indian cancer registry, bladder cancer constitutes the ninth most common malignancy and accounts for an overall 3.9% of all cancer cases. 70% to 85% have non-muscle-invasive bladder cancer (NMIBC) and 15% to 30% have muscle-invasive bladder cancer (MIBC). Transurethral resection is primarily employed treatment for NMIBC, whilst radical surgery either with neoadjuvant chemotherapy or adjuvant chemotherapy is used to treat MIBC. Clinical auditing is essential as it exposes the deficient areas of management. **Methods:** Cancer registry of the last 3 years at Dept. of Urology and Renal Transplant Gauhati Medical College Hospital was searched for demographic, clinical, pathological and prognostic data and results summarized using statistical parameters of univariate analysis. **Results:** There were a total of 97 patients in the NMIBC group with a majority in the 60-70- year age group. The most common grade was G2. Smoking was a constant phenomenon in all patients of NMIBC (n=97) and MIBC (n=40) population. Positive urine cytology was significantly associated with the MIBC population. **Conclusions:** Although TURBT is a standard of care for NMIBC, single modality treatment is not sufficient and high-grade tumors are dealt in aggressive manner and though induction and maintenance BCG immunotherapy deters progression and recurrence, it did not confer total immunity against the disease. Even radical cystoprostatectomy with pelvic lymphadenectomy / pelvic exenteration is the gold standard treatment for muscle-invasive urinary bladder cancer; some patients succumb to postoperative comorbidities.

KEYWORDS: irritative voiding, neoadjuvant chemotherapy, radical cystectomy, transurethral resection of bladder tumor.

INTRODUCTION

Urinary Bladder cancer is the sixth most common disease in men and the seventeenth most common disease in women globally.^[1] European association of urology (EAU) and American urological association (AUA) guidelines provide an evidence-based framework for the management of muscle-invasive bladder cancer (MIBC) and non-muscle invasive bladder cancer (NMIBC). It is challenging to implicate this policy in a vast subcontinent like India where the north-east part of this country is majorly affected by a heavy oncological catastrophe like urinary bladder carcinoma due to extensive use of tobacco and pesticide.^[2]

There is a wide spectrum of bladder cancer among them transitional cell urothelial tumors were most commonly manifested cancer nearly 90%.^[3] Age, gender, and racial factors all affect the survival and prognosis of patients with bladder cancer. Clinical auditing is essential as it exposes the deficient areas of management. It is essential to assess the risk factors which might define and predict

the future behavior of the tumor at an early stage.

After transurethral resection of the initial tumor patients with NMIBC showed a high risk of recurrence. The incidence of recurrence is in the range of 15-61% at 1 year and 31-78% at 5 years. These figures indicate the heterogeneous nature of NMIBC.^[4] Radical cystoprostatectomy (RC) along with pelvic lymph node dissection (PLND) with or without adjuvant chemotherapy (AC)/ neo-adjuvant chemotherapy (NAC) (level I evidence for NAC use in MIBC exists) remains the standard treatment for MIBC. Optimal management of MIBC is a multidisciplinary approach where the coordination between urologists, medical oncologists and in some cases radiation oncologists is required for staging, multimodality treatment, and follow-up.^[5]

An audit of the work of our department was conducted to review the management of all patients with carcinoma of the bladder over the past 3 years, which exposed the need for the accurate recording of information and the need

for a standardized protocol of management for this condition.

METHODS

This was a retrospective study conducted at the Department of Urology and renal transplant Gauhati medical college and Hospital between January 2017 and January 2020. All newly diagnosed cases were included in the audit. All prevalent and recurrent patients which were following up before 3 years were excluded from the study. A total of 137 patients with bladder cancer were reviewed for clinicopathological data (size, site, morphology, multiplicity, stage, and grade of tumor), epidemiological data (age, sex, occupation and smoking habit), investigations that included radiological findings and laboratory findings, treatment given and follow-up data. The collective patient's data were then entered into a large database facility and analyzed. The histopathology results were recorded just as they appeared in the notes as reported by different pathologists.

STATISTICAL ANALYSIS

All the data (n=137) including the number of patients with different T stages and grades were calculated. The data analysis was centered at 2 years overall survival (OS), 2 years disease-free survival (DFS), 2 years progression-free survival (PFS). The management protocol and guidelines for NMIBC/MIBC were evaluated and compared with the recent advancement of the bladder cancer treatment protocol.

RESULTS

Non-muscle invasive bladder cancer

A total of 97 patients with NMIBC were included in this study. The median age of the patients was 63.6 years at surgery and the majority of them (n=28, 28.90%) belonged to the age group of 60-69 years.

According to grade-wise distribution, the maximum number of patients were categorized into G2 NMIBC (45.6%, n=47). A total of 26.9% (n=7) and 34% (n=16) patients amongst different grades of G1 and G2 following TURBT fell in the age group of 60-69 years, respectively (Grade, 1973 WHO definition). However, the majority of patients 20.6% (n=20) from the G3 category belonged to the age group of 50-59 years (Figure 1A). The distribution of patients according to the WHO TNM stage was based on the individual tumor T stage following surgery (TURBT) and histopathological typing. Out of 97, 79 (81.5%) patients had T1 stage and the remaining 18 (18.5%) patients had Ta stage category. The majority of patients from the Ta stage (27.8%, n=5) category and T1 (29.1%, n=23) stage category were in the age group of 60-69 years (Figure 1B).

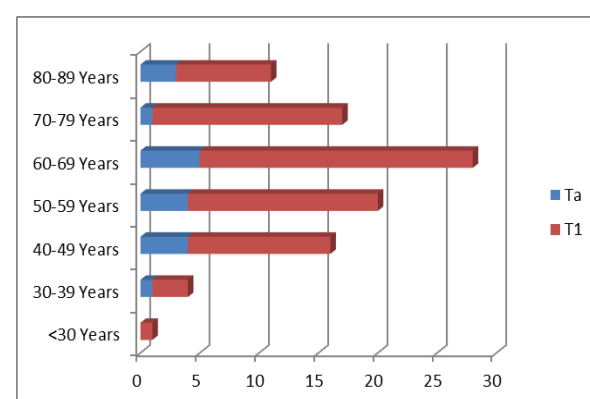
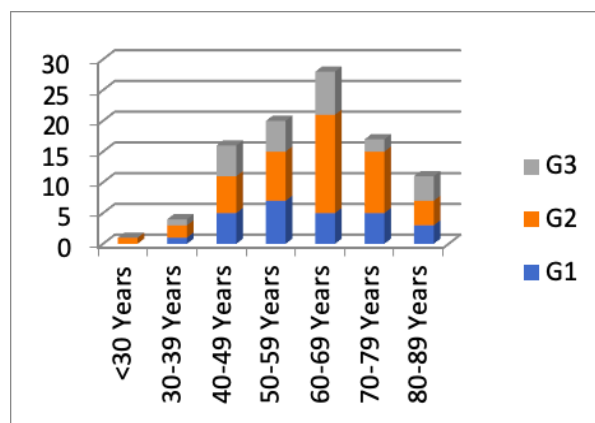


Figure 1 A and B: Grade and T stage distribution following surgery among various age categories in NMIBC population.

Majority of patients were male (77.6% [n=80]). The maximum numbers of male (51.21%, n=41) and female patients (47.10%, n=8) were observed with G2 and G1 categories, respectively. T1 stage was more common in both male (82.5%, n=66) and female (76.5%, n=13) patients (Figure 2).

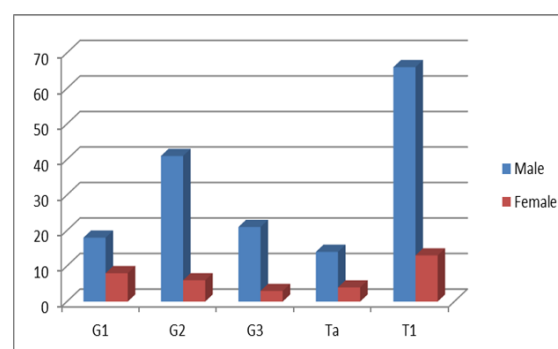


Figure 2: Grade and T stage distribution following surgery among gender categories in NMIBC population.

Majority of the patients having smoking (n=70, 72.2%) and tobacco chewing (n=72, 74.2%) as their etiological history. Industrial workers (dye and rubber industry) constituted the next common etiology for bladder cancer. Majority of the patients (n=90, 92.8%) presented with painless hematuria (Table 1).

Table 1: Grade and T stage distribution (NMIBC) with etiological characteristics.

Variable	Grade			T Stage		Total (N=97)
	G1 (N=56)	G2 (N=33)	G3 (N=21)	Ta (N=26)	T1 (N=71)	
Smoking	10 (38.5)	39 (83.0)	21 (87.5)	11 (61.1)	59 (74.7)	70 (72.2)
Tobacco	15 (57.7)	36 (76.6)	21 (87.5)	11 (61.1)	61 (77.2)	72 (74.2)
Dye workers	5 (19.2)	16 (34.0)	15 (62.5)	5 (27.8)	31 (39.2)	36 (37.1)
Rubber industry workers	2 (7.7)	13 (27.7)	14 (58.3)	5 (27.8)	24 (30.4)	29 (29.9)

Data represented as n (%).

Ultrasonography was done as a primary investigation. Median dimensions of the UB mass lesion on USG examination was 2.8X2.4 [SD (L)-1.14, (B)-1.49] and on CECT Abdomen with Pelvis was 3.9X3X2.2 [SD (L)-2.36, (B)-1.93, (H)-1.68]. About 70.1%, (n=68) in the NMIBC group presented with a single mass in the preliminary radiological investigation (USG/CECT Abdomen with Pelvis). Urine cytology was positive in 50.5% (n=49) patients.

All 97 patients with NMIBC who were physically fit to undergo surgery with diagnostic and or curative intent were initially subjected to TURBT. Histopathological findings revealed that 71 patients had pT1 stage and the remaining 26 had pTa stage. Grade wise distribution, depicted in Table 2.

Table 2: Grade wise distribution of TUBT biopsy.

Variable	N=97
Stage	
Ta	26 (26.8)
T1	71 (73.2)
Grade	
G1	43 (55.8)
G2	33 (42.8)
G3	21 (27.3)

Data shown as n (%).

Repeat TURBT was done in high-grade tumors. In our study 54 patients (G2=33+G3=21) are subjected to re-TURBT which showed residual tumors in 40% (n=20) patients. Grade up- gradation from G3 occurred in 6 patients. The detrusor muscle was not identified in 15 TURBT samples for which Re-TURBT was done.

Patients with high-grade T1 (G2, G3) received induction (once weekly for 6 weeks) and maintenance (once monthly for 12 months) BCG immunotherapy (73.2%, n=71). Concomitant CIS was present in 36.9% (n=26) of the T1 sub-population and among them male smokers more than 60 years of age were predominant. Adjuvant chemotherapy (AC) in the form of GC [Gemcitabine (1000 mg/m² I/V on day 1, 8, 15) and cisplatin (70mg/m² on day 2)] for a total of 4 cycles, 28 days apart were received by 6.4% of patients with NMIBC. Only two patients had derangement in kidney function and who deteriorated post first cycle of GC were shunted for Carboplatin instead of cisplatin.

Maximum early recurrences (at 6 months of follow up)

were seen with T1 G2 (16.1%, n=13,) and G3 (18.1%, n=9,) population groups which were treated with re-TURBT.

A total of 130 TURBTs and 7 cold cup biopsies were performed by residents and consultants at our hospital. There were Twelve (8.8%) complications, including eight (4.2%) cases of hematuria that required blood transfusion because six patients were taking antiplatelet and two patients had incomplete coagulation of the resected surface. Four (3.4%) patients were observed with bladder perforation. Of these, three (2.7%) perforations were small extraperitoneal perforations requiring only prolonged catheter drainage. These perforations were caused by residents in their second or third year of urology training. One (0.7%) perforation was intraperitoneal, which required abdominal exploration to control bleeding.

Muscle Invasive Bladder Cancer

There were a total of 40 patients in the MIBC group with a majority (32.8 %) in the 50-59 years age group. The mean age of the male and female population was 57.9 years and 53.4 years, respectively. Early age migration was clearly observed in the MIBC group. The majority of patients (45.45%, n=28) diagnosed with T2 stage followed by T3 stage (36.36%, n=9) and T4 stage (18.18%, n=3).

Tobacco (87.5%) and smoking (82.5%) were the most common etiological factors associated with the MIBC population. The presence of hematuria was found in 92.5% of patients with MIBC. The incidence of hemorrhage and irritative voiding was present among all T4subpopulations (Table 3).

Table 3: T Stage (MIBC) distribution according to etiological characteristics and clinical symptoms.

Characteristics	T2 (N=28)	T3 (N=9)	T4 (N=3)	Total (N=40)
Etiological characteristics				
Tobacco	24 (85.7)	8 (88.9)	3 (100)	35 (87.5)
Smoking	23 (82.1)	8 (88.9)	2 (66.7)	33 (82.5)
Dye workers	22 (78.6)	6 (66.7)	3 (100)	31 (77.5)
Rubber industry	22 (78.6)	5 (55.6)	2 (66.7)	29 (72.5)
Clinical symptoms				
Hemorrhage	26 (92.9)	8 (88.9)	3 (100)	37 (92.5)
Irritative voiding	25 (89.3)	7 (77.8)	3 (100)	35 (87.5)
Hemorrhage and Irritative voiding	23 (82.1)	6 (66.7)	3 (100)	32 (80)
Positive urine cytology	22 (78.6)	8 (88.9)	2 (66.7)	32 (80)
Data shown as n (%).				

Median dimensions of the UB mass lesion on USG examination was 3.6X2.9 cm [SD (L)-1.34, (B)-1.29] and on CECT Abdomen with Pelvis was 6.6X5.4X4.2 cm [SD (L)- 2.57, (B)-1.79, (H)-1.59].

After confirmation of muscle-invasive biopsy report, 19 (47.2%) patients underwent RC with the diversion with curative intent along with adjuvant GC chemotherapy. A total of 13 (32.1%) patients underwent radical TURBT with the intent of organ preservation along with follow-up GC chemotherapy. Cystoscopic biopsy was performed in 8 (22.9%) patients with MIBC under local anesthesia and follow-up chemotherapy. Nine patients developed recurrences of lung and liver metastasis

during the first 3 years of follow-up.

Out of 19 radical cystoprostatectomy /pelvic exenteration and ileal conduit, nine (47.3%) patients had mild surgical site infections, six (31.5%) patients had severe postoperative complications in the form of urinoma, stoma necrosis and enteric anastomotic leak requiring reparative surgeries. The 3-month mortality rate was 5% (n=2).

A total of 18 patients succumbed to death over the period of 3 years of follow-up due to various reasons summarized in Table 4.

Table 4: Outcome of the study.

Outcomes	Total number of patients (N=137)
Patients alive	119 (86.9)
Death due to various co-morbid conditions	6 (4.4)
Death due to advanced stage of the disease	4 (2.9)
Death due to disease progression and cancer cachexia	8 (5.8)
Data shown as n (%).	

The OS, DFS, and PFS were estimated during 3 years of follow-up and summarized in Table 5.

Table 5: Grade wise and stage wise survival analysis for NMIBC and MIBC population

Variables	Overall survival	Diseasefree survival	Progression free survival
NMIBC			
Grade			
G2	36 (77.3)	31 (67.1)	34 (72.8)
G3	17 (65.2)	14 (58.2)	16 (65.6)
MIBC			
Stage			
pT2	20 (72.1)	17 (61.9)	17 (61.2)
pT3	6 (63.9)	5 (51.0)	6 (63.0)
Data shown as n (%).			

DISCUSSION

This audit highlights the need for precise and proper documentation in preliminary assessment and follow-up of patients with bladder cancer. Taking biopsies from the deep resection margin of the tumor should be done accurately. In this study, 15 patients underwent a biopsy which was negative for Detrusor muscle during initial resection. Repeat biopsy was done after 3 weeks showed four more patients of MIBC. A regular audit should be conducted in order to improve the management of bladder tumors and to enlighten the drawbacks of management. The present retrospective analysis revealed that urinary bladder cancer was highly heterogeneous. The characteristic of urinary bladder cancer patients included in this study was in accordance with many clinical trials. The single-institutional study showed that bladder cancer management at our setup encompasses a well-defined and robust diagnostic and therapeutic protocol along with timely intervention to decrease the risk of progression of NMIBC cases to MIBC and MIBC to metastatic cases.

In India, the prevalence of urinary bladder cancer is estimated to be 5.6% in men and 1.8% in women while an actual crude rate is about 1 in 174 men and 1 in 561 women.^[6] Bladder cancer is more common in men with men to women ratio of 3: 1, indicating sex-linked etiological factors.^[7] The present study revealed a similar men-to-women ratio (4.7:1). The reason for men's predominance was due to risk factors like smoking and occupation exposures. Smoking in men and tobacco chewing in women under the scanner was an important aspect in this study. Occupational exposure including dye and rubber industry, leather worker, painter, machinist, and aluminum worker in men may be the reason for the higher prevalence of bladder cancer in men.^[8-11]

The most common presentation is painless hematuria, which is seen in more than 90% of patients with bladder cancer.^[12] In this study, 92.5% of patients had painless hematuria. This high incidence may be due to a lack of screening for microscopic hematuria in the form of the dipstick or flexible cystoscopy, even in high-volume

centers.

TCC is the most common variant accounted for 90% of bladder cancer in the western countries and India similarly noted in the current study.^[13, 14] However, adenocarcinoma (AC) accounts for less than 2% of bladder cancer.

Urine cytology also helps in the diagnosis of high-grade bladder tumors; this study had 65.25% positivity. A cytologic diagnosis of "positive for malignancy" has a high specificity and positive predictive value of greater than 90% for the diagnosis of high-grade urothelial carcinoma (HGUC).^[15] Urine cytology is also useful for surveillance in patients with known urothelial carcinoma.^[16]

The main objectives of the analysis were to calculate the DFS for patients with completely resected tumors and to determine the PFS for patients with post-operative residual disease and patients who did not receive a surgical treatment upfront, OS of all patients, a complication of the surgery and the management and the 3-year mortality rate. Our 36 monthly follow up of NMIBC and MIBC study population showed encouraging result.

In the present study, OS, DFS and PFS for 3 years were mentioned which was in accordance with the previous study of 432 patients who underwent RC with PLND and TURBT as their treatment schemes.^[17] Another study reported 74% and 80% OS for pT2 and pTa stage, respectively.^[2] Slightly higher rates were achieved in the present series. Moreover, 3 years PFS for pT2 and pT3 stage in the present study was similar to the 5 years PFS for pT2 and pT3 in the previous study.^[2]

While analyzing the data of 3 years OS for grade 3 patients in NMIBC group was 65.2% indicating regular RC with PLND and diversion was a primary goal for the treatment of grade 3 tumors. However, RC with PLND is considered as gold standard treatment for MIBC.^[18] RC provides excellent local cancer control with the lowest pelvic recurrence rates and 50% to 70% 5-year cancer-specific survival.^[4] Nonetheless, RC is one of the most

complex urological surgical procedures with reported early complication and perioperative mortality rates of 20% to 57%.^[8-10, 19-24] and 0.3% to 5.7%, respectively.^[8-10, 19, 22, 24]

The present study has few limitations. Apart from the fact it was a single-center study, the audit was retrospective in character.

CONCLUSION

The present study findings showed that though TURBT is a standard of care for NMIBC, single modality treatment is not sufficient and high-grade tumors are dealt with in an aggressive manner, and induction and maintenance BCG immunotherapy did not confer total immunity against disease progression and recurrence. Even RC with pelvic lymphadenectomy / pelvic exenteration is the gold standard treatment for MIBC; some patients succumb to postoperative comorbidities. Clinical auditing is essential as it exposes the deficient areas of management. An accurate initial assessment should include an assessment of factors that might define and predict the future behavior of the tumor at an early stage.

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