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Research Article

CHALLENGES IN THE MANAGEMENT OF BLADDER TUMOUR

¹Hassan Mumtaz, ²Mumtaz Ahmad, ³Ayesha Zafar, ⁴Tehreem Fatima, ⁵Shamim Mumtaz.

¹House Surgeon, KRL Hospital Islamabad, Former Internee, Guys & St Thomas Hospital NHS Trust UK, Hassanmumtaz.dr@gmail.com, ²Professor of Urology, President: Pakistan Association of Urological Surgeons (PAUS), mumtazdr@hotmail.com, ³Department of Physiology, HITEC-IMS, ayeshazafar_30@hotmail.com, ⁴House Surgeon, Holy Family Hospital Rawalpindi, CIBNP, Fairfield USA, Tehreem94@outlook.com, ⁵Professor of Microbiology, shamimmicro@hotmail.com.

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Abstract:

Bladder cancer is a relatively common type of CA that most often arises in urothelial cells lining inside of bladder. Most bladder cancers can be detected at an early stage, where treatments might be highly effective, however early stage CA may recur even after successful treatment, therefore follow up is mandatory.

We present a 65 years old Female Presented on 22 June 2020 with Gross and painless hematuria since 4 days. An Ultrasound abdomen & pelvis was done revealing soft tissue mass, measuring 19x25x32 mm, directed inwards, arising from the left-posterior aspect of urinary bladder. A Cystoscopy/TURBT was done showing a solitary, papillary growth, more than 3 cm in size arising just above and lateral to the left ureteric orifice. Cold cup biopsy was taken from the base of the tumor during TURBT, which showed Papillary Urothelial Carcinoma, high grade pTa stage. There was a poor patient compliance as she was unwilling to undergo a repeat cystoscopy, so only a intravesical mitomycin could be given for 6 weeks.

Repeat TURBT is gaining widespread importance in evaluating the recurrence of bladder tumor. The primary reason for the recurrence is noncompliance of patients and an inability to follow-up after initial TURBT. There needs to be a strong doctor-patient relationship, responsible information sharing, mutual trust and a clear understanding of options in case of a recurrence for the disease to be properly managed. With appropriate doctor training and research upon the various modalities of treatment for BCA, the disease prognosis may be significantly improved.

Corresponding author:

Hassan Mumtaz,

House Surgeon, KRL Hospital Islamabad, Former Internee,

Guys & St Thomas Hospital NHS Trust UK, Hassanmumtaz.dr@gmail.com.

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INTRODUCTION:

Bladder cancer is a relatively common type of CA that most often arises in urothelial cells lining inside of bladder. The worldwide age standardized incidence rate (ASR) for bladder cancer is 10.1 per 100,000 for males and 2.5 per 100,000 in females. In Pakistan, bladder cancer is the 4th most common cancer with an age standardized rate of 6.8 per 100,000.[1-2]

The most common presenting symptom of BC is painless hematuria, however irritative voiding symptoms can often be present. Other symptoms include frequent urination, dysuria and back pain. Once it's spread, the CA may lead to anorexia, cachexia, malaise and other systemic manifestations.

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [3-4] (LE: 3). Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are excreted via kidneys and might contribute to the association between toxins and the CA. While family history seems to have little impact [5] on the incidence of BC, familial clustering of BC with an increased risk for first- and second-degree relatives has been suggested. [6] Other important risk factors include increasing age, male gender, chronic inflammation and exposure to various environmental and industrial chemicals.

Most bladder cancers can be detected at an early stage, where treatments might be highly effective, however early stage CA may recur even after successful treatment, therefore follow up is mandatory. The gold standard for diagnosing bladder cancer is biopsy obtained during cystoscopy. [7]. Other investigations

including urine cytology & upper tract imaging (primarily a CT scan of the abdomen and pelvis) are also useful. The various tests performed to assess the severity of disease may include MRI, PET scan, bone scan and X-rays.

The treatment of bladder cancer depends upon the depth of invasion into the bladder wall. Some modalities of treatment include surgery, localized and systemic chemotherapy, radiation therapy, immunotherapy and target therapy. Transurethral Resection Of Bladder Tumor (TURBT), Laser Therapy, Immunotherapy (in form of BCG) and Intravesical Chemotherapy are used to treat superficial tumors [8]. Patients at high risk for progression should be considered for cystectomy and urinary diversion [9]. The treatment of Bladder cancer is expensive and associated with certain taboos in our society. People at various stages of CA require different sets of investigations. It's very important to address the issue of repeated investigations and its effect on patients so that prognosis of BC can be improved.

Case Presentation:

A 65 years old Female Presented on 22 June 2020 with Gross and painless hematuria since 4 days. She had Diabetes Mellitus type II since six years and she had an appendectomy done 20 years back. Her BP was 180/100 mm Hg, otherwise her examination was unremarkable. Routine investigation (Table 1) were done which showed Ultrasound abdomen & pelvis revealed a soft tissue mass, measuring 19x25x32 mm, directed inwards, arising from the left-posterior aspect of urinary bladder. However the upper urinary tract appeared normal.

Urine Examination:	
Colour	Light reddish
Blood	++++
RBC's	Field Full
Blood Complete Picture:	
HB	11.3 g/dl
TLC	9000 c/mm
PLT	285,000 c/mm
Renal Function Tests:	
Urea	24 mg/dl
Creatinine	0.9 mg/dl

(Table 1)

A Cystoscopy/TURBT was planned which involved the administration of spinal anesthesia with bilateral obturator block. A solitary, papillary growth, more than 3 cm in size arising just above and lateral to the left ureteric orifice was found. The bladder mucosa was unremarkable. (Fig 3 Post TURBT)

A complete resection was performed, using white light and mono polar diathermy. Cold cup biopsy was taken from the base of the tumor during TURBT. A dose of intravesical mitomycin was instilled within 24 hours of post TURBT.

(Fig 3 Post TURBT)



Histological Type	Papillary Urothelial CA
Lamina Propria	Identified
Lamina Propria Invasion	Not identified
Muscularis Propria	Not identified
Lympho Vascular Invasion	Not identified
Provisional/ISUP grade	High Grade
Pathological Staging	pTa

Histopathological report revealed (Table 2)

A final diagnosis of Papillary Urothelial Carcinoma, high grade pTa stage was made.

The patient compliance was poor, as she was unwilling to undergo a repeat TURBT. Therefore, a weekly course of intravesical mitomycin was started for 6 weeks & Cystoscopy was planned at 3 months.

DISCUSSION:

Bladder cancer is heterogenous with respect to its presentation and outcomes. Mutations, genomic deletions or amplifications that affect cell cycle can influence the clinical outcomes, therefore the presentation of disease may vary among individuals. Despite advances in recent years, treatment of bladder cancer has not advanced beyond cisplatin-based combination therapies and surgery. Many novel targeted agents have been investigated in animal models during multiple studies. These studies have

limitations of using cell lines with mutations in the downstream targets. Molecular studies have uncovered oncogenic roles of fibroblast growth factor receptor 1 and 3 (FGFR1 and FGFR3) in bladder carcinoma. MIBC show many chromosomal rearrangements, however, recurrent gene fusions are only reported in FGFR3-TACC3 [10,11].

The initial treatment of choice for bladder cancer is TURBT (Transurethral Resection of Bladder Tumor). A number of studies have demonstrated a significant risk of residual tumors after initial TURB of Ta/T1 lesions and hence a second TURB is recommended. A Systematic Review analyzing 8,409 patients with Ta or T1 HG BC has demonstrated a 51% risk of disease persistence and an 8% risk of under staging in T1 tumors with initial TURB. Another meta-analysis with T1 tumors demonstrated that the prevalence rate of residual tumors and upstaging to invasive disease after

TURB remained high in a subgroup with detrusor muscle in the resected specimen. [12]]. A second TURB can increase recurrence-free survival (RFS) [13-14]], and provide prognostic information [15]]. In Pakistan, one of the biggest challenges is to convince patients for a follow-up. Most of the patients are lost to follow-up and do not present for secondary evaluation and hence lead to a poor prognosis of the disease.

Another determinant of prognosis is the involvement of detrusor muscle; if its NMBIC vs MBIC. In a cohort of 2,451 patients with BCG-treated T1G3/HG tumors (a second resection was performed in 935 patients), the second resection improved RFS, progression-free survival (PFS) and overall survival (OS) only in patients without detrusor muscle in the specimen of the initial resection [16]. Hence, second TURB is more effective in patients without involvement of the muscle. The results of the second resection (residual tumors and under staging) reflect the quality of the initial TURB. Four large meta-analyses comprising 1,476 to 3,103 patients have consistently shown that repeated TURB significantly reduces the recurrence rate compared to TURB alone [17—20]. A meta-analysis of 2,278 eligible patients shows that the 5-year recurrence rate is reduced by 14% - from 59% to 45%, when a repeat TURBT/cystoscopy is done [16]. Rizvi *et al* 1981 revealed that a delay in diagnosis and patient resistance to radical surgery are two important impediments in the treatment of bladder CA[21].

Another hindrance is tumor recurrence despite successful treatment. Assessment of circulating tumor DNA in combination with improved imaging modalities may improve the prediction of micro-metastatic disease. Different genetic subtypes of MIBC show varying degrees of chemosensitivity. Further progress needs to be made in order to develop a common molecular classifier that can be used easily for daily clinical decision making. With the advent on immuno-oncology, bladder-sparing protocols are on the rise as an alternative to surgery. The extent of transurethral bladder tumor resection has a marked impact on the response rates to TMT and neoadjuvant chemotherapy [22]

As in elderly patients, radical cystectomy is the curative intervention for patients with MIBC, recurrent high grade superficial BCA, and high-grade T1 disease. However, certain aspects of treatment are of significant importance in successful treatment of young BCA patients. Young male patients undergoing RC may suffer from post-operative infertility and impotence. Prostate and seminal vesicles sparing RC

in addition to nerve sparing procedure can be a valuable option for people who still want to preserve fertility. Preservation of urinary continence by performing a nerve sparing procedure and orthotopic neobladder urinary diversion is preferred to attain a proper quality of life and body image [23].

The overall rate of recurrence for NMIBC is 60% to 70%, and the overall rate of progression is 20% to 30%. Ta tumors (which are mostly low grade) rarely progress to a higher stage, but they tend to recur. High-grade Ta tumors account for only 2% to 9% of all cases of NMIBC [24].

CONCLUSION:

Non-muscle invasive bladder cancer remains an important urologic oncologic challenge and a cumbersome economic burden on the health-care system. Repeat TURBT is gaining widespread importance in evaluating the recurrence of bladder tumor. The primary reason for the recurrence is noncompliance of patients and an inability to follow-up after initial TURBT. With proper discussion about treatment options and shared decision-making, patient compliance may be increased. There needs to be a strong doctor-patient relationship, responsible information sharing, mutual trust and a clear understanding of options in case of a recurrence for the disease to be properly managed. With appropriate doctor training and research upon the various modalities of treatment for BCA, the disease prognosis may be significantly improved.

REFERENCES:

1. <https://biocoreopen.org/ijcc/Clinicopathological-Features-of-Bladder-Tumors-in-a-Single-Institution-in-Hyderabad-Sindh-Pakistan.php#:~:text=Bladder%20cancer%20is%20primarily%20a,of%206.8%20per%20100%2C000%204>
2. <https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Non-muscle-Invasive-Bladder-Cancer-2020.pdf>
3. Burger, M., *et al*. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol*, 2013. 63: 234. <https://www.ncbi.nlm.nih.gov/pubmed/22877502>
4. van Osch, F.H., *et al*. Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies. *Int J Epidemiol*, 2016. 45: 857. <https://www.ncbi.nlm.nih.gov/pubmed/27097748>
5. Egbers, L., *et al*. The prognostic value of family history among patients with urinary bladder

- cancer. *nt J Cancer*, 2015. 136: 1117. <https://www.ncbi.nlm.nih.gov/pubmed/24978702>
6. Martin, C., *et al.* Familial Cancer Clustering in Urothelial Cancer: A Population-Based Case-Control Study. *J Natl Cancer Inst*, 2018. 110: 527. <https://www.ncbi.nlm.nih.gov/pubmed/29228305>
 7. Walid MS, Heaton RL. [Can posthysterectomy cystoscopy be utilized as a screening test for bladder cancer?](https://www.ncbi.nlm.nih.gov/pubmed/29228305). *German Med Sci*. 2008;6:56-61.
 8. Hall MC, Chang SS, Dalbagni G, Pruthi RS, Seigne JD, Skinner EC. [Guideline for the management of nonmuscle invasive bladder cancer \(stages Ta, T1, and Tis\):2007 update.](https://www.ncbi.nlm.nih.gov/pubmed/178231430) *American J Urol*. 2007;178:2314-30.
 9. Shalhoub PJ, Quek ML. [Clinical decision-making and guideline recommendations, management of bladder cancer in the elderly.](https://www.ncbi.nlm.nih.gov/pubmed/2010660710) *Aging Health*. 2010;6:607-10.
 10. Williams SV, Hurst CD, Knowles MA (2013) Oncogenic FGFR3 gene fusions in bladder cancer. *Hum Mol Genet* 22: 795-803.
 11. Sharma J, Gondkar K, Deb B, Kumar P (2018) Targeting Gene Fusion Events in Bladder Carcinoma. *J Mol Genet Med* 12: 361.
 12. Naselli, A., *et al.* Role of Restaging Transurethral Resection for T1 Non-muscle invasive Bladder Cancer: A Systematic Review and Meta-analysis. *Eur Urol Focus*, 2018. 4: 558. <https://www.ncbi.nlm.nih.gov/pubmed/28753839>
 13. Grimm, M.O., *et al.* Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol*, 2003. 170: 433. <https://www.ncbi.nlm.nih.gov/pubmed/12853793>
 14. Divrik, R.T., *et al.* The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. *J Urol*, 2006. 175: 1641. <https://www.ncbi.nlm.nih.gov/pubmed/16600720>
 15. Sfakianos, J.P., *et al.* The effect of restaging transurethral resection on recurrence and progression rates in patients with nonmuscle invasive bladder cancer treated with intravesical bacillus Calmette- Guerin. *J Urol*, 2014. 191: 341. <https://www.ncbi.nlm.nih.gov/pubmed/23973518>
 16. Hashine, K., *et al.* Results of second transurethral resection for high-grade T1 bladder cancer. *Urol Ann*, 2016. 8: 10. <https://www.ncbi.nlm.nih.gov/pubmed/26834394>
 17. Sylvester, R.J., *et al.* Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation? *Eur Urol*, 2016. 69: 231. <https://www.ncbi.nlm.nih.gov/pubmed/26091833>
 18. Sylvester, R.J., *et al.* A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol*, 2004. 171: 2186. <https://www.ncbi.nlm.nih.gov/pubmed/15126782>
 19. Abern, M.R., *et al.* Perioperative intravesical chemotherapy in non-muscle-invasive bladder cancer: a systematic review and meta-analysis. *J Natl Compr Canc Netw*, 2013. 11: 477. <https://www.ncbi.nlm.nih.gov/pubmed/23584348>
 20. Perlis, N., *et al.* Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non-muscle-invasive bladder cancer recurrences: an updated meta-analysis on 2548 patients and quality-of-evidence review. *Eur Urol*, 2013. 64: 421. <https://www.ncbi.nlm.nih.gov/pubmed/23830475>
 21. <https://webcache.googleusercontent.com/search?q=cache:FWqagYC5iaUJ:https://jpma.org.pk/article/details/6621+&cd=2&hl=en&ct=clnk&gl=pk&client=safari>
 22. GeorgiosGakis. Management of Muscle-invasive Bladder Cancer in the 2020s: Challenges and Perspectives. *European Urology Focus Volume 6, Issue 4, 15 July 2020.* <https://www.sciencedirect.com/science/article/abs/pii/S2405456920300237>
 23. Nabbout P, Eldefrawy A, Engles CD, Culkin DJ, Slobodov G. Muscle-invasive bladder cancer in a young adult: a case report and a review of the literature. *Cent European J Urol*. 2013;66(2):185-187. doi:10.5173/ceju.2013.02.art18
 24. Aldousari S, Kassouf W. Update on the management of non-muscle invasive bladder cancer. *Can Urol Assoc J*. 2010;4(1):56-64.doi:10.5489/cuaj.777.