

Original Article

Current practices of urologists regarding intravesical therapy use for non-muscle-invasive bladder cancer patients.

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Doi: 10.29052/IJEHSR.v10.i1.2022.72-77

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Received 28/10/2021

Accepted 25/01/2022

First Published 26/02/2022



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Abstract

Background: Intravesical chemotherapy and immunotherapy is recommended as per the leading urology treatment guidelines of non-muscle invasive bladder cancer (NMIBC). These therapies also help in reducing the risk of progression and recurrence of NMIBC. The current study aims to assess the self-reported practices regarding intravesical therapy (IVT) used for NMIBC patients among urologists in Karachi.

Methodology: In this cross-sectional study, a proforma-based survey was conducted between January and March 2018, in which printed questionnaires regarding adjuvant treatment options for NMIBC were administered and collected by primary investigators by urologists in leading institutions of Karachi.

Results: It is observed that routine administration of single instillation of intravesical chemotherapy (SICA) after transurethral resection of bladder tumor (TURBT) was reported by 80% of the respondents, and almost one-third of them (37.3%) give SICA within 6 hours inward. A quarter of respondents practice induction therapy routinely in low-risk BC using Mitomycin, whereas Bacillus Calmette Geurin (BCG) as immunotherapy was used in 76.5% of high-risk cases. Regarding the time interval of intravesical therapy installation, most of the urologists reported for 45 mins (49%) followed by 30 mins (29.4%), 2 hrs (17.6%), and 3 hrs (3.9%). Maintenance therapy with BCG for high-risk BC was used by only 39% of urologists. While 76.5% of participants reported the use of radical cystectomy, as the failure of BCG.

Conclusion: Our survey results provide evidence of variation in practices by urologists and also highlight the poor guideline along with the risk of under-treatment of NMIBC patients. Therefore, joint efforts of all concerned individuals are needed who are involved in the treatment of NMIBC to improve the quality of care.

Keywords

Bladder Cancer, Chemotherapy, Immunotherapy, Noninvasive, Intravesical, Practices.



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Introduction

Cancer of the urinary bladder is one of the most common cancer globally, with more than 500,000 new reported cases in 2018. It is suggested to be more common in men as compared to women, with most cases in patients with age above 55 years¹. In Pakistan, it is the 9th most common cancer². Based on the degree of muscle involvement, bladder cancer is of four types and has five stages^{3,4}. The most common type of bladder cancer that accounts for up to 95% of cases is Urothelial cancer. While the remaining 5% of cases occur due to Squamous cell carcinoma, adenocarcinoma, and small cell carcinoma³. Up to 75% of the newly diagnosed bladder cancer are non-muscle invasive bladder cancer (NMIBC)⁴.

NMIBC, also known as Ta/T1/carcinoma in situ (CIS), is a diverse group of tumors with varied oncological outcomes. Because of the high risk of recurrence (60-70%) and advancement (10-25%), NMIBC must be diagnosed and treated as soon as possible⁵. Bladder cancer is among the most expensive cancers to manage on a per-patient basis because of its extended natural history, intense follow-up, and therapeutic options^{5,6}. Intravesical therapy (IVT) is considered as the backbone of organ-sparing NMIBC management, providing recurrence-free survival as shown in multiple randomized clinical trials^{6,7}.

As per European Association of Urology (EAU) guidelines, risk stratification of NMIBC, for the low-risk category, single instillation of intravesical chemotherapy, for intermediate-risk either one-year full dose of BCG or chemotherapy, for high risk one to three years full dose BCG and highest risk group cystectomy is recommended⁸. Patients with NMIBC benefit from following clinical practice guidelines since it minimizes morbidity and improves care. Patients with NMIBC who received at least half of the guideline-recommended care for assessment and management had a significant survival advantage, according to the Surveillance, Epidemiology, and End Results (SEER) research⁹. Despite various guidelines recommendations, studies have identified significant variation in

intensity of treatment, duration, and are mostly adherence to guidelines-recommended care^{10,11}.

There is a paucity of local data in Pakistan regarding practices of intravesical therapy and its adherence to the guideline. In order to describe patterns of treatment and further highlight particular areas where consensus is missing, we performed a survey on practices relevant to the management of NMIBC. The aim of this study was to assess urologists in Karachi's self-reported practices regarding intravesical treatment utilization for non-muscle-invasive bladder cancer patient.

Methodology

In this cross-sectional study, a proforma-based survey was done between January and March 2018. A total of 60 printed multiple-choice questionnaires were delivered to the Aga Khan Hospital, Liaquat National Hospital, Kidney Centre, Indus Hospital, Jinnah Postgraduate Medical Centre, Abbasi Shaheed Hospital, and Tabba Kidney Institute, all of which provide urological services. Because all of the responses were anonymous, the survey did not need to be reviewed by the Institutional Review Board.

The questionnaire, which was confidential, self-administered, and unvalidated, was sent to consultant urologists and residents from affiliated hospitals. The proforma consisted of age, gender, designation, practice settings, workload experience (no. of TURBT per year), and ten questions regarding intravesical therapy. In these questions of IVT, they were asked about single instillation, induction, maintenance, and failure after intravesical therapy.

The data was analyzed using SPSS version 24.0 and presented as descriptive statistics of the significant determinants. To show the management preferences, a frequency table was created. Cross tabulation was done for specific questions regarding intravesical therapy between EAU recommended answers and variables like designation (consultant Vs. resident) and workload experience (number of TURBT per year). The Chi-

square test was applied to compare the different of opinion between consultant and residence, a $p < 0.05$ was considered significance.

Results

Out of 60 distributed proformas, overall, 51 (85%) respondents completed the survey. The majority were consultants (39%), followed by junior residents (35%) and chief residents (26%). Among the survey group, most urologists perform 10-20 TURBT per year (67%).

80% of the hospitals surveyed responders reported standard single intravenous chemotherapy (SICA) after TURBT (Table 1), and all institutions (100 %) chose mitomycin C as the chemotherapeutic drug of choice. Regarding the time of SICA administration, 37.3% gave within 6 hrs of TURBT in recovery room, 29.4% gave after 6 hrs of TURBT in recovery room, 27.5% within 24 hrs of surgery in ward and 5.9% in the operating room immediately

after surgery. In comparison to new cases of high-grade (HG) NMIBC, where 76% of responders frequently utilized induction IVT, just 23% of new cases of LG disease used induction IVT. The number of respondents who said they used IVT on a regular basis in recurrent LG cases was higher than those who said they used it on a regular basis in fresh LG instances (31.4% vs. 23% , respectively). Among the responders of routine induction intravesical BCG at a new diagnosis of HG NMIBC, only 39% endorse routine maintenance intravesical BCG in this setting (Table 1).

When asked about the duration of IVT, the majority of responders keep IVT in place for 45 mins (49%), followed by 30 mins (29.4%), 2 hrs (17.6%), and 3hrs (3.9%). In terms of posture change during intravesical therapy, 65% of patients change their posture, whereas 35% do not. When it came to BCG failure, 76.5% of subjects said they had to have a radical cystectomy.

Table 1: Urologist's response in relation to current practices of IVT in NMIBC.

Variables	Responses N (%)	
SICA after TURBT	Never	1(2)
	1/2 the time	4(8)
	2/3 of times	5(10)
	Always unless contraindicated	41(80)
Low Risk NMIBC	Never	31(61)
	1/3 the time	3(6)
	1/2 of times	5(10)
	Always unless contraindicated	12(23)
IVT	Never	5(10)
	1/3 the time	5(10)
	1/2 of times	2(4)
	Always unless contraindicated	39(76)
Induction in high risk NMIBC	Never	4(8)
	1/3 the time	4(8)
	1/2 of times	4(8)
	2/3 of times	5(10)
BCG	Always unless contraindicated	34(66)
	Never	12(23.5)
	1/3 the time	2(4)
	1/2 of times	12(23.5)
Maintenance in high risk NMIBC	2/3 of times	5(10)
	Always unless contraindicated	20(39)

Interestingly, residents responded with more positive answers according to the current recommendation compared to the consultants, but none of the factors were statistically significant. On the other hand, those who perform 10-20 TURBT per year were found to respond much better-recommended answers as compared to others but again, here it was not statistically significant (Table 2).

Table 2: Difference of opinion regarding the use of IVT in NMIBC between consultants and senior residents.

Variables	Consultant N(%)	Resident N(%)	p-value
SICA	17(41)	24(59)	0.38
IVC in low-risk NMIBC	13(42)	18(58)	0.52
IVC in high-risk NMIBC	16(42)	22(58)	0.52
BCG induction in high risk NMIBC	11(32)	23(68)	0.13
BCG maintenance in high risk NMIBC	8(40)	12(60)	0.58

Discussion

Long-term treatments and follow-up techniques are the most expensive ways to treat cancer, and their practice patterns and adherence to guidelines vary widely⁵. Pakistani urologists widely adopt international guidelines recommended by American Urology Association (AUA), European Association of Urology (EAU), and National Comprehensive Cancer Network (NCCN).

When compared to TURB alone, prompt instillation of intravesical therapy after TURB considerably reduces the recurrence rate, according to four comprehensive meta-analyses involving nearly 1,476 to 3,103 individuals¹²⁻¹⁵. Our study reflected that the Pakistani urologists had shown excellent compliance of 80% with immediate intravesical chemotherapy in managing NMIBC patients.

After TURBT for intermediate or high-risk NMIBC, intravenous instillation of BCG is routine therapy, as there is indications that it prevents bladder tumour recurrence or development⁴. An induction course accompanied by maintenance therapy is advised for maximum efficacy, but the length of maintenance therapy is debatable. A meta-analysis of 20 trials, however, was unable to identify which BCG maintenance protocol was the most efficacious¹⁶.

Considering HG disease, it is reported that the grade-specific patterns of IVT, with significant

consensus for routine induction and maintenance therapy, mostly with BCG. Except in recurring cases or cases with multiple and/or big volume tumour, respondents were less inclined to employ induction IVT in LG condition. According to the findings of this study, this method is used at a low rate in HG disease. The spread of this method has yet to be investigated in administrative claims, therefore it remains a viable area of investigation for future researchers.

This is also observed in current study that the number of correct responses in the practice pattern of IVT was higher among residents than consultants. This could be due to the fact that consultants do not keep themselves abreast of the latest practice guidelines, or they do not get themselves involved in the practical care and follow-up of NMIBC patients.

Although the current study's findings include descriptive data to help us better understand current care trends in NMIBC, still the study's flaws needed to be acknowledged. The survey's multiple-choice format has one significant flaw: where the respondents were not given the option of entering free text or alternative responses to the questions. Prospective data collecting in actual clinical practice should be included in future research. This data could be useful for practicing physicians and policymakers, and it builds on previous successful examples of surgeon-led

efforts to reduce variability in care processes and outcomes¹⁷. We also identify that many providers have experienced MMC and BCG shortages recently. The current survey did not capture such data as shortages of needed intravesical therapeutics and other logistic support that intrude deliverance of guidelines-recommended care by healthcare providers and may portray another variability between intentions and actual care provided.

Conclusion

It can be said that the 2019 EAU Non-muscle-invasive Bladder Cancer management Guidelines are generally in line with self-reported IVT use in NMIBC. Respondents reported considerably greater rates of perioperative chemotherapy (single-dose) than claims-based research from previous eras, as well as grade-specific patterns of use for induction and maintenance IVT. Future research is needed to see if these self-reported habits are consistent with real clinical practice. Finally, following these guidelines can be linked to better clinical results in real-world patient populations. These findings highlight the importance of prospective registry studies in filling evidence gaps and laying the groundwork for quality improvement programs in this field.

Conflicts of Interest

The authors have declared that no competing interests exist.

Acknowledgment

We would like to acknowledge hospital staff and doctors for their immense contribution and support.

Funding

The author(s) received no specific funding for this work.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin.* 2018;68(6):394-424.
2. Badar F, Mahmood S. Cancer in Lahore, Pakistan, 2010–2019: an incidence study. *BMJ open.* 2021;11(8):e047049.
3. Martin JW, Carballido EM, Ahmed A, Farhan B, Dutta R, Smith C, Youssef RF. Squamous cell carcinoma of the urinary bladder: Systematic review of clinical characteristics and therapeutic approaches. *Arab J Urol.* 2016;14(3):183-191.
4. Lee LJ, Kwon CS, Forsythe A, Mamolo CM, Masters ET, Jacobs IA. Humanistic and economic burden of non-muscle invasive bladder cancer: results of two systematic literature reviews. *CEOR.* 2020;12:693.
5. Muhammad Farhan, Syed Muhammad Nazim, Jibrán Ahmed, Hammad Ather. Frequency and predictors of recurrence of bladder tumour on first check cystoscopy - a tertiary care hospital experience *J Pak Med Assoc.* 2016(Suppl 3)(10):S125-S130.
6. Avritscher EB, Cooksley CD, Grossman HB, Sabichi AL, Hamblin L, Dinney CP, Elting LS. Clinical model of lifetime cost of treating bladder cancer and associated complications. *Urology.* 2006;68(3):549-553.
7. Aziz PA, Raja RA, Khimani V, Nasir Z, Aziz PAA, Qureshi N, Pathan S, Ahmed A. Isolated intracranial Rosai Dorfman Disease without nodal involvement. *Int. j. endorsing health sci. res.* 7(4):188-191.
8. Witjes JA, Bruins M, Cathomas R, Compérat E, Cowan NC, Gakis G, Hernández V, Lorch A, MJ R, Thalmann G, van der Heijden A. EAU guidelines on muscle-invasive and metastatic bladder cancer. *EAU Guidelines.* 2019.
9. Chamie K, Saigal CS, Lai J, Hanley JM, Setodji CM, Konety BR, Litwin MS. Urologic Diseases in America Project. Quality of care in patients with bladder cancer: a case report?. *Cancer.* 2012;118(5):1412-1421.
10. Snyder C, Harlan L, Knopf K, Potosky A, Kaplan R. Patterns of care for the treatment of bladder cancer. *Urol J.* 2003;169(5):1697-1701.
11. Madeb R, Golijanin D, Noyes K, Fisher S, Stephenson JJ, Long SR, Knopf J, Lyman GH, Messing EM. Treatment of nonmuscle invading bladder cancer: do physicians in the United States practice evidence based medicine? The use and economic implications of intravesical chemotherapy after transurethral resection of bladder tumors. *Cancer.* 2009;115(12):2660-2670.

12. Sylvester RJ, Oosterlinck W, Holmang S, Sydes MR, Birtle A, Gudjonsson S, De Nunzio C, Okamura K, Kaasinen E, Solsona E, Ali-El-Dein B. 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. J. Urol.* 2016;69(2):231-244.
13. Jung K, Lein M, Ringsdorf M, Roigas J. Renal and urological problems. *Radiother Oncol.* 2007;82:185-190.
14. Abern MR, Owusu RA, Anderson MR, Rampersaud EN, Inman BA. Perioperative intravesical chemotherapy in non-muscle-invasive bladder cancer: a systematic review and meta-analysis. *J Natl Compr Cancer Netw.* 2013;11(4):477-484.
15. Perlis N, Zlotta AR, Beyene J, Finelli A, Fleshner NE, Kulkarni GS. 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. J. Urol.* 2013;64(3):421-430.
16. Cookson MS, Chang SS, Oefelein MG, Gallagher JR, Schwartz B, Heap K. National practice patterns for immediate postoperative instillation of chemotherapy in nonmuscle invasive bladder cancer. *J urol.* 2012;187(5):1571-1576.
17. Herr HW. Is maintenance bacillus Calmette-Guérin really necessary?. *Eur Urol.* 2008;54:971-973.