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REVIEW

Should continuous bladder irrigation be recommended when single instillation of intravesical chemotherapy cannot be used after transurethral resection in low-risk non-muscle invasive bladder cancer?

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Abbreviation used: BC, bladder cancer; LR, low risk; NMIBC, Non-muscle invasive bladder cancer; TURBT, transurethral resection bladder tumor; IR, intermediate risk; SI, single instillation; MMC, CBI, Continuous bladder irrigation

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ABSTRACT

Reducing the recurrence rate in patients with low-risk non-muscle invasive bladder cancer patients is a critical concern in the urologic community. The gold standard treatment is single instillation (SI) of intravesical chemotherapy after transurethral resection of bladder tumor (TURBT), but unfortunately, it is underused. Continuous bladder irrigation (CBI) after TURBT is an alternative strategy to SI for the prevention of bladder tumor implantation and recurrence. The aim of this review was to present the evidence that supports CBI after TURBT when SI is not possible.

Keywords: low-risk, non-muscle invasive bladder cancer, continuous bladder irrigation, recurrence

Approximately 70% of new non-muscle invasive bladder cancer (BC) are classified as low risk (LR-NMIBC) [1]. These tumors are associated with a significant risk of recurrence requiring invasive procedures during follow-up and further treatment.

One of the possible mechanisms underlying early recurrence might be the dissemination and implantation of floating cancer cells during and after transurethral resection of bladder tumor (TURBT) [2]. Four large meta-analyses have consistently shown that single instillation (SI) after TURBT reduces the recurrence rate compared to TURBT alone not just in LR but also in intermediate risk (IR) NMIBC (Level 1a evidence) [3,4]. One randomized Phase III clinical trial, SWOG 0337, compared SI of Gemcitabine versus saline post TURBT. The study demonstrated a 34% decrease in the risk of recurrence in the gemcitabine arm (4-year estimated recurrence rate 35% versus 47%, HR 0.66, 95%CI 0.48 – 0.90) [5]. Based on those results AUA and EAU guidelines recommend instillation of chemotherapy immediately after TURBT [6,7]. Despite these recommendations, SI is not universally utilized in clinical practice. Recent studies have shown that there was a marked underuse of SI of chemotherapy among urologists. Only 18% and 2% of urologists always used a single instillation of chemotherapy after TURBT, while 28% and 66% never employed it in European countries and the United States respectively [8]. Possible reasons for the lack of wide adoption of SI could be related with urologist issues (Some believe that decreasing low-grade bladder cancer recurrences is not clinically important) or health system issues (such as increase in costs, insufficient training and inexperience in handling chemotherapeutic agents among nursing staff), pharmacy logistics, uncertainty of malignancy and tumor invasion at the time of TURBT, suspected bladder perforation with possible serious side effects [9]. Even most complications related to Mitomycin C (MMC) extravasation are local and mild, bladder necrosis, pudendal neuritis or ureterohydronephrosis could potentially occur [10].

Continuous bladder irrigation (CBI) is rarely used even with full awareness of its oncological benefit, but is commonly adopted to prevent blood clotting and catheter obstruction after TURBT. In fact, TURBT is performed in several countries in an inpatient setting, and a great many patients received CBI after surgery. Two questions present themselves: Is CBI able to prevent hematuria as effectively as described by Onishi *et al*. [9] in avoiding cancer cell implantation? Should we assume that both strategies are equally to effective in the absence of a clinical trial?

Hypothetically, CBI can be effective in preventing exfoliated

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tumor cells from implantation into the bladder wall, and can lower tumor recurrence rate. However, it is important to perform complete tumor resection covering sufficient surrounding and depth, including muscle tissue, since CBI has no ablative effect on residual tumor cells at the resection site.

Sylvester *et al*. [3] carried out a systematic review and reported that postoperative irrigation reduced the risk of recurrence in a non-randomized comparative study involving 1592 NMIBC patients, and adjusting for the European Organisation for Research and Treatment of Cancer (EORTC) recurrence risk score, and found that postoperative irrigation reduced the relative risk of recurrence by 21%.

In 2017, Onishi *et al*. [9] published a non-inferiority single institution clinical trial comparing CBI with saline for 18 hours versus SI with Mitomycin C in low and intermediate risk NMIBC patients. After 5 years of follow-up, CBI was not inferior to SI in terms of recurrence and progression, with a lower adverse event rate (6% in the CBI arm versus 27% in MMC arm, $P < 0.05$). Another study conducted by Böhle *et al*. have shown that single instillation of gemcitabine followed by CBI immediately after TURBT was not superior to CBI alone after TURBT in terms of recurrence-free survival. In the study, gemcitabine and placebo were instilled immediately after TURBT, and then continuous irrigation with saline was performed for 20 hours in both arms. The authors concluded that CBI in both arms could have diluted the benefit of SI with Gemcitabine [11].

A major weakness of the evidence available regarding CBI is the long duration of the infusion. Contrariwise, at least two retrospective studies on CBI for over 2 – 3 hours have shown no reduction in recurrence compared to no CBI and a significantly shorter recurrence-free survival rate compared to SI [12,13]. A large proportion of studies demonstrated the benefit of CBI with 18–24 hours of saline infusion. However, this duration of CBI may limit its cost-effectiveness and applicability, as many bladder tumors are currently treated by outpatient procedures and long-time irrigation would end up requiring hospital admission [13]. Further trials are needed to elucidate if 6–8 hours of CBI could provide a prophylactic effect on bladder cancer recurrence.

Limited evidence exists regarding the use of other irrigants rather than normal saline, which is widely used in clinical practice. Reports involving distilled water may have additional benefit by causing osmotic lysis due to hypotonic effect and preventing subsequent attachment of exfoliated cancer cells to the bladder wall [14]. Furthermore, *in vitro* studies have shown that distilled water may have a cytotoxic effect equivalent to Mitomycin C on bladder cancer cells [15–16]. Nonetheless, several complications have been reported, involving acute hyponatremia, massive intravascular hemolysis and death after bladder irrigation with distilled water [17]. Therefore, irrigation with saline may be superior in terms of safety especially in the case of unrecognized perforation.

Finally, two recent meta-analyses comparing CBI versus SI after TURBT concluded that CBI stands as an alternative to SI and provided a better balance between the prevention of BC recurrence and the rate of adverse events than SI [18–19].

It has been known that bladder cancer poses a financial burden on the public health system. Because of long-term survival and the need for lifelong routine monitoring and treatment, it represents one of the most expensive cancers [20]. In this sense, using strategies to reduce the rate of recurrence will have a positive impact in economic terms. Many authors assessed the cost-effectiveness of Mitomycin C after surgery, suggesting that the strategy of SI after TURBT lowers cost by reducing tumor recurrence [21]. The main hurdles to use of Mitomycin C is the high cost and significant drug shortage. Conversely, other drugs like gemcitabine are readily available and considerably less expensive (average sales price for 2 g of gemcitabine is $55.70 and for 40 mg of mitomycin is $1062.72) making them an interesting alternative [5]. To our knowledge, to date, there are no face-to-face comparison between SI and CBI in terms of economic costs but we presume that CBI will be a cheaper option than SI as an adjuvant treatment after TURBT. Further clinical studies focusing on the financial cost of the aforementioned techniques will be warranted to evaluate the real cost of both strategies.

We believe that given the scarce implementation of SI in the daily practice and in view of the evidence presented, urologic societies should promote the notion that LR-NMIBC patients should receive adjuvant treatment after TURBT to reduce bladder cancer recurrence.

Urological community should be aware that the treatment alternative for low-risk tumors can never be TURBT alone, and SI or CBI must always be an option for the prevention of not only bleeding but also the implantation of neoplastic cells, as described by Onishi *et al*. [9].

REFERENCES

1. Kirkali Z, Chan T, Manoharan M, Algaba F, Busch C, Cheng L, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology. 2005 Dec;66(6 Suppl 1):4–34. https://doi.org/10.1016/j.urology.2005.07.062 PMID:16399414
2. Soloway MS, Masters S. Urothelial susceptibility to tumor cell implantation: influence of cauterization. Cancer. 1980 Sep;46(5):1158–63. https://doi.org/10.1002/1097-0142(19800901)46:53.0.CO;2-E PMID:7214299
3. Sylvester RJ, Oosterlinck W, Holmang S, Sydes MR, Birtle A, Gudjonsson S, 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 Feb;69(2):231–44. https://doi.org/10.1016/j.eururo.2015.05.050 PMID:26091833
4. 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 Urol. 2013 Sep;64(3):421–30.

https://doi.org/10.1016/j.eururo.2013.06.009 PMID:23830475

5. Messing EM, Tangen CM, Lerner SP, Sahasrabudhe DM, Koppie TM, Wood DP Jr, et al. Effect of Intravesical Instillation of Gemcitabine vs Saline Immediately Following Resection of Suspected Low-Grade Non-Muscle-Invasive Bladder Cancer on Tumor Recurrence: SWOG S0337 Randomized Clinical Trial. JAMA. 2018 May;319(18):1880–8. https://doi.org/10.1001/jama.2018.4657 PMID:29801011
6. Babjuk M, Böhle A, Burger M, Capoun O, Cohen D, Compérat EM, et al. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol. 2017 Mar;71(3):447–61. https://doi.org/10.1016/j.eururo.2016.05.041 PMID:27324428
7. Witjes JA. Topic issue on new treatments in bladder cancer. World J Urol. 2009 Jun;27(3):285–7. https://doi.org/10.1007/s00345-009-0390-4 PMID:19229539
8. 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 May;187(5):1571–6. https://doi.org/10.1016/j.juro.2011.12.056 PMID:22425105
9. Onishi T, Sugino Y, Shibahara T, Masui S, Yabana T, Sasaki T. Randomized controlled study of the efficacy and safety of continuous saline bladder irrigation after transurethral resection for the treatment of non-muscle-invasive bladder cancer. BJU Int. 2017 Feb;119(2):276–82. https://doi.org/10.1111/bju.13599 PMID:27444991
10. Chemi J, Jaunarena JH, Camean J, Azuri W, Villaronga A, Villoldo GM. Post-Transurethral Resection of Bladder Tumor Bladder Perforation Resulting in Mitomycin C Extravasation, Pudendal Neuralgia, and Ureterohydronephrosis. J Endourol Case Rep. 2020 Dec;6(4):315–8. https://doi.org/10.1089/cren.2020.0117 PMID:33457662
11. Böhle A, Leyh H, Frei C, Kühn M, Tschada R, Pottek T, et al.; S274 Study Group. Single postoperative instillation of gemcitabine in patients with non-muscle-invasive transitional cell carcinoma of the bladder: a randomised, double-blind, placebo-controlled phase III multicentre study. Eur Urol. 2009 Sep;56(3):495–503. https://doi.org/10.1016/j.eururo.2009.06.010 PMID:19560257
12. Do J, Lee SW, Jeh SU, Hwa JS, Hyun JS, Choi SM. Overnight continuous saline irrigation after transurethral resection for non-muscle-invasive bladder cancer is helpful in prevention of early recurrence. Can Urol Assoc J. 2018 Nov;12(11):E480–3. https://doi.org/10.5489/cuaj.5122 PMID:29989883
13. Lenis AT, Asanad K, Blaibel M, Donin NM, Chamie K. Continuous saline bladder irrigation for two hours following transurethral resection of bladder tumors in patients with non-muscle invasive bladder cancer does not prevent recurrence or progression compared with intravesical Mitomycin-C. BMC Urol. 2018 Oct;18(1):93. https://doi.org/10.1186/s12894-018-0408-6 PMID:30355350
14. Pode D, Alon Y, Horowitz AT, Vlodavsky I, Biran S. The mechanism of human bladder tumor implantation in an in vitro model. J Urol. 1986 Aug;136(2):482–6. https://doi.org/10.1016/S0022-5347(17)44926-3 PMID:3525861
15. Levin DR, Moskovitz B. Distilled water versus chemotherapeutic agents for transitional bladder carcinoma. Eur Urol. 1986;12(6):418–21. https://doi.org/10.1159/000472671 PMID:3102241
16. Fechner G, Pocha K, Schmidt D, Müller SC. Reducing recurrence and costs in superficial bladder cancer: preclinical evaluation of osmotic cytolysis by distilled water vs. mitomycin. Int J Clin Pract. 2006 Oct;60(10):1178–80. https://doi.org/10.1111/j.1742-1241.2006.00847.x PMID:16669821
17. Bell MD. Sudden death due to intravascular hemolysis after bladder irrigation with distilled water. J Forensic Sci. 1992 Sep;37(5):1401–6. https://doi.org/10.1520/JFS13331J PMID:1402764
18. Zhou Z, Zhao S, Lu Y, Wu J, Li Y, Gao Z, et al. Meta-analysis of efficacy and safety of continuous saline bladder irrigation compared with intravesical chemotherapy after transurethral resection of bladder tumors. World J Urol. 2019 Jun;37(6):1075–84. https://doi.org/10.1007/s00345-019-02628-7 PMID:30612154
19. Mahran A, Bukavina L, Mishra K, Buzzy C, Fish ML, Bobrow A, et al. Bladder irrigation after transurethral resection of superficial bladder cancer: a systematic review of the literature. Can J Urol. 2018 Dec;25(6):9579–84. PMID:30553282
20. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer: a comprehensive review of the published literature. PharmacoEconomics. 2003;21(18):1315–30. https://doi.org/10.1007/BF03262330 PMID:14750899
21. Hentschel AE, Blankvoort CJ, Bosschieter J, Vis AN, van Moorselaar RJ, Bosmans JE, et al. Trial-based cost-effectiveness analysis of an immediate postoperative mitomycin C instillation in patients with non-muscle-invasive bladder cancer. Eur Urol Open Sci. 2022 Jan;37:7–13. https://doi.org/10.1016/j.euros.2021.12.008 PMID:35243387