



Intravesical Gemcitabine Versus Distilled Water for Bladder Tumor Recurrence Prevention: A Clinical Trial

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Abstract

Background: Non-muscle-invasive bladder cancer (NMIBC) is associated with a high recurrence rate following transurethral resection of bladder tumor (TURBT). This clinical trial sought to compare the efficacy of intravesical gemcitabine versus distilled water in mitigating the recurrence of primary, low-grade urothelial neoplasms.

Materials and Methods: A randomized, double-blinded clinical trial was conducted at Urmia Imam Khomeini Hospital, Iran, from January 2022 to July 2023. Patients diagnosed with low-grade NMIBC via cystoscopy and undergoing TURBT were eligible for inclusion in this study. Participants were randomly assigned to one of two cohorts—receiving either intravesical gemcitabine or distilled water—using dedicated randomization software. Following treatment, patients underwent routine follow-up evaluations at three and six months, including cystoscopy and ultrasonography to assess for tumor recurrence.

Results: A total of 89 eligible patients were randomized to receive either gemcitabine or distilled water following TURBT, with a mean age of 57.80 ± 11.08 and 60.02 ± 11.16 years, respectively. Tumor recurrence within three months occurred in 4 cases (10%) in the gemcitabine group and 5 cases (12.5%) in the distilled water group. Fisher's exact test indicated no significant difference in tumor recurrence rates between the two groups ($P=0.5$). All nine recurrence cases involved low-grade tumors, which were subsequently treated with intravesical Bacillus Calmette-Guérin (BCG) following transurethral resection. Notably, no patients who remained recurrence-free after the first three months experienced recurrence during the second trimester.

Conclusion: In patients with suspected low-grade non-muscle-invasive urothelial neoplasms, intravesical administration of either gemcitabine or sterile distilled water immediately following TURBT led to a notable reduction in early tumor recurrence. These findings support the potential use of sterile distilled water as a viable intravesical prophylaxis due to its economic advantages and readily available nature.

Keywords: Gemcitabine, Urothelial cancer, Bladder, Non-muscle-invasive, Transurethral resection, Distilled water

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Introduction

Bladder cancer is the eleventh most prevalent malignancy worldwide and ranks seventh in terms of incidence among men (1). The majority of bladder cancers are of urothelial histology, with localized urothelial carcinoma of the bladder (UCB) broadly classified into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive disease (2). NMIBC encompasses approximately 75% of newly diagnosed cases and is characterized by a significant recurrence rate following initial treatment (3). Transurethral resection of bladder tumor (TURBT) remains the primary therapeutic approach for NMIBC management (4).

In light of the aforementioned challenges, and to mitigate recurrence risk, the 2020 Joint Guidelines on the Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer, jointly issued by the American Urological

Association (AUA) and the Society of Urologic Oncology (SUO), currently advocate for a solitary postoperative instillation of intravesical chemotherapeutic agents (e.g., gemcitabine, mitomycin C) within a 24-hour timeframe following TURBT in patient cohorts exhibiting suspected or confirmed low- or intermediate-risk bladder cancer (5). Notwithstanding these recommendations, nationwide cross-sectional analyses have indicated considerable variability in the implementation of intravesical chemotherapy, with the utilization rate of this therapeutic modality in NMIBC remaining comparatively low (6).

Various studies have demonstrated the positive effect of mitomycin in preventing the recurrence of primary and low-grade tumors (7, 8). Despite this favorable effect, the administration of mitomycin, especially in cases involving extensive transurethral resection (TUR) and bladder perforation, can be associated with severe complications

(9). In recent years, due to several factors, including the side effects of the drug and its high cost, the routine use of mitomycin has been discontinued in many centers across the country (10). In recent trials, a similar positive effect has been observed with gemcitabine compared to mitomycin (11). Gemcitabine is significantly less expensive than mitomycin and is associated with fewer side effects (12). Therefore, gemcitabine has recently been used instead of mitomycin in several urology centers (13).

Common irrigating solutions used in transurethral resection of the prostate (TURP) and TURBT include sterile distilled water, glycine solution, normal saline, and 5% dextrose in water (14). Research indicates that sterile distilled water is associated with an increased risk of intravascular hemolysis and acute renal failure when compared to other irrigating fluids during prostate TUR; however, it remains a safe option for TURBT (15). Historically, sterile distilled water has been used as an irrigating solution in TUR procedures, with its safety well-documented in surgical contexts (16). Numerous studies have investigated the impact of hypotonic shock on bladder cancer and hepatocellular carcinoma cells, revealing that malignant cells exposed to hypotonic solutions, including water, undergo membrane rupture and subsequent cell death (17, 18).

A key mechanism contributing to the recurrence of non-invasive bladder neoplasms is the detachment and subsequent implantation of tumor cells onto the bladder mucosa during TUR procedures (19). Given the potential for degradation of tumor cells released during TUR upon exposure to aqueous environments and the paucity of research exploring this phenomenon, this study aimed to compare the efficacy of gemcitabine – an established therapeutic modality – with that of distilled water in inhibiting the recurrence of primary, low-grade tumors. If gemcitabine and distilled water demonstrate comparable efficacy in reducing bladder tumor recurrence, distilled water may be preferred over gemcitabine due to its lower cost and wider availability.

Materials and Methods

This study was conducted as a randomized, double-blinded controlled clinical trial at Urmia Imam Khomeini Hospital, Iran, from January 2022 to July 2023. Patients diagnosed with bladder cancer who underwent TURBT were recruited for inclusion. The study protocol received ethical approval from the Ethics Committee of Urmia University of Medical Sciences (IR.UMSU.REC.1400.341) and adhered to the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study.

Eligibility criteria for study enrollment encompassed patients with a suspected diagnosis of low-grade urothelial neoplasia, as identified through the visual assessment

during office cystoscopy. This cystoscopic examination was undertaken due to the presence of symptoms suggestive of bladder cancer, such as hematuria, or conducted as part of routine surveillance for previously treated non-muscle-invasive urothelial neoplasms. Exclusion criteria included a history of non-urothelial or muscle-invasive bladder cancer within the preceding 18 months, more than two episodes of low-grade non-muscle-invasive urothelial neoplasia within 18 months, or the administration of intravesical therapy within six months prior to the index TURBT. Additional exclusion factors were a history of or concurrent upper urinary tract or prostatic urethral urothelial neoplasms, tumors exceeding 3 cm in maximum dimension, prior pelvic radiotherapy for any malignancy, or any malignancy treated within the preceding five years (excluding non-melanoma skin cancer or non-muscle-invasive bladder urothelial neoplasms).

Randomization

Participants were randomly assigned to either the gemcitabine or distilled water treatment group using a dedicated randomization software program. This simple randomization method was employed to assign unique identifiers to each participant, with the total sample size predetermined. After TURBT, participants were randomly allocated to receive either gemcitabine or distilled water for intravesical instillation. A double-blind approach was implemented throughout the study, ensuring that neither the participants nor the treating physicians were aware of the assigned treatment group.

- *Gemcitabine group:* Patients received a single intravesical dose of 2000 mg gemcitabine, dissolved in 100 mL of normal saline. The solution was instilled into the bladder via a Foley catheter and retained for three hours. Catheter clamping was employed to maintain the solution within the bladder throughout this period. To prevent rapid bladder filling, intravenous fluid administration was reduced. After the three-hour dwell time, the catheter was unclamped to facilitate urine flow and expel the drug.
- *Distilled water group:* Patients in this group received continuous bladder irrigation with sterile distilled water for three hours following TURBT. The drainage tube was positioned 40 cm above the bladder to maintain a near-constant volume of distilled water inside the bladder and ensure maximal contact between the bladder wall.

In both groups, urethral catheters were removed after a one-hour dwell time, or earlier if the patient experienced significant discomfort. According to the study protocol, intravesical drug administration could be omitted if the treating surgeon deemed it to pose a heightened risk such as in cases of potential bladder perforation, extensive resection, or significant postoperative hematuria. The majority of patients were discharged the following day.

Following pathology analysis, patients with confirmed muscle-invasive tumors, high-grade tumors, or any pathology other than low-grade urothelial cell carcinoma were excluded from the study.

A routine clinical examination was scheduled one month following the surgical procedure to assess for disease recurrence (20). Subsequent management of recurrent disease was left to the discretion of the treating physician. Similarly, for patients with no cancer detected during the index TURBT, or with high-grade urothelial cancer, non-urothelial bladder cancer, or muscle-invasive cancer, ongoing follow-up and treatment decisions were physician-directed, focusing on disease progression and overall survival. All control ultrasounds were performed at a single center by the same radiologist to ensure consistency.

Sample Size Calculation

The sample size for this study was determined based on the recurrence rates reported by Messing et al (12), which were 35% in the gemcitabine group and 59% in the normal saline group. Using these rates, a sample size of 67 individuals per group was calculated.

Statistical Analysis

Quantitative variables were summarized using means and standard deviations, while qualitative variables were presented as frequencies and percentages. Independent t-tests were employed to compare recurrence rates at three and six months between the two groups, assuming a normality distribution of quantitative variables. Fisher's exact test was used to assess associations between other qualitative variables. A *P* value of less than 0.05 was considered statistically significant. Data analysis was performed using SPSS version 21.

Results

This randomized clinical trial evaluated the efficacy of intravesical gemcitabine in patients with newly diagnosed, low-grade bladder tumors measuring ≤ 3 cm. A total of 89 eligible patients were randomized to receive either gemcitabine or distilled water following TURBT.

In the gemcitabine group ($n=44$), four patients were excluded due to pathological findings that were inconsistent with low-grade disease. These included one case of high-grade T1, one case of high-grade Ta, one case of inverted papilloma, and one case of cystic cystitis. In the distilled water group ($n=45$), five patients were excluded for similar reasons: three cases with high-grade T1 and two cases with inverted papilloma.

As presented in Table 1, the gemcitabine group consisted of 31 males (77.5%) and 9 females (22.5%), while the distilled water group contained 30 males (75%) and 10 females (25%). A chi-square test indicated no significant difference in gender distribution between the

two groups ($P=0.79$).

The mean age of patients was 57.80 ± 11.08 years in the gemcitabine group and 60.02 ± 11.16 years in the distilled water group. An independent t-test revealed no significant difference in age between the two groups ($P=0.19$). Tumor size was measured using ultrasound, cystoscopy, and pathology. The mean tumor size as measured by ultrasound was 18.10 ± 6.12 mm in the gemcitabine group and 19.50 ± 7.04 mm in the distilled water group. Independent t-test analysis indicated no significant difference in tumor size between the groups based on ultrasound ($P=0.34$).

Similar results were obtained using cystoscopy and pathology. The mean tumor size measured by cystoscopy was 16.92 ± 5.88 mm in the gemcitabine group and 18.10 ± 5.59 mm in the distilled water group ($P=0.36$). Pathological measurements yielded a mean tumor size of 15.75 ± 6.28 mm for the gemcitabine group and 18.10 ± 5.57 mm for the distilled water group ($P=0.08$). Overall, a t-test revealed no significant difference in tumor size between the gemcitabine and distilled water groups, regardless of the measurement method used (Table 1).

Tumor recurrence within the first three months was assessed using both ultrasound and cystoscopy. Recurrence was identified in 4 patients (10%) in the gemcitabine group and 5 patients (12.5%) in the distilled water group. Fisher's Exact Test indicated no significant difference in tumor recurrence between the two groups ($P=0.5$).

All nine recurrence cases involved low-grade tumors, which were treated with intravesical Bacillus Calmette-Guérin (BCG) following TUR. Notably, no patients who were recurrence-free after the first three

Table 1. Comparing Frequency and Mean Differences of Variables Between Study Groups

Variable	Gemcitabine Group	Distilled Water Group	<i>P</i> Value
Mean age	57.80 ± 11.08	60.02 ± 11.16	0.19
Sex			
Male	31 (77.5%)	30 (75%)	0.79
Female	9 (22.5%)	10 (25%)	
Tumor size based on ultrasound (mm)	18.10 ± 6.12	19.50 ± 7.04	0.34
Tumor size based on cystoscopy (mm)	16.92 ± 5.88	18.10 ± 5.59	0.36
Tumor size based on pathology (mm)	15.75 ± 6.28	18.10 ± 5.57	0.08
Tumor recurrence based on ultrasound			
Yes	4 (10%)	5 (12.5%)	0.5
No	36 (90%)	35 (37.5%)	
Tumor recurrence based on cystoscopy			
Yes	4 (10%)	5 (12.5%)	0.5
No	36 (90%)	35 (37.5%)	

months experienced new tumor recurrences during the second trimester.

Discussion

Bladder cancer represents a significant malignancy within the urogenital tract, characterized by a high incidence and a strong propensity for recurrence (21). While tumor progression is a potential concern across all non-invasive bladder tumors, recurrence is the primary issue in cases of low-grade NMIBC (22). The main therapeutic goals for NMIBC include the complete eradication of the primary lesion and a concerted effort to minimize the risk of recurrence or progression (23). It is widely acknowledged that within 6 to 12 months following TURBT without adjunctive therapy, a substantial proportion of NMIBC cases, estimated at 40%-80%, exhibit recurrence. Furthermore, a significant subset of patients (10%-25%), progress to muscle-invasive bladder cancer (MIBC) or develop regional or metastatic disease (24). This randomized controlled trial was designed to evaluate the short-term efficacy of intravesical gemcitabine compared to distilled water in patients diagnosed with NMIBC treated with TURBT.

Intravesical chemotherapy offers a potential therapeutic strategy for eradicating neoplastic cells potentially disseminated during TURBT, as well as for targeting residual tumor cells located at surgical margins and microscopic foci of disease (25). Consequently, the implementation of intravesical chemotherapy following TURBT is considered an effective strategy for reducing recurrence rates (26). However, the heterogeneous nature of bladder cancer, along with variations in individual patient characteristics, can influence the selection of intravesical chemotherapeutic drugs and their associated tumor clinical outcomes. Therefore, the careful selection of chemotherapeutic agents based on patient-specific disease profiles is crucial for optimal clinical outcomes (27). While numerous chemotherapeutic drugs have been employed for intravesical instillation, their effectiveness remains limited (25).

The optimal chemotherapeutic agents for intravesical administration should exhibit a high degree of selectivity for bladder tumor cells, achieve effective local drug concentrations, minimize systemic absorption, and possess a favorable adverse safety profile. Furthermore, these agents must effectively inhibit or reduce tumor recurrence (25). Gemcitabine, a pyrimidine antimetabolite widely employed in the systemic treatment of various malignancies, is a cell cycle-specific agent that primarily targets cells in S-phase (28). In vitro studies have demonstrated gemcitabine's capacity to inhibit the proliferation of multiple bladder cancer cell lines across different phases of the cell cycle, from the G1 to the S phase, ultimately inducing apoptosis in these neoplastic cells (24).

In the early 1990s, both in vitro and in vivo preclinical studies demonstrated gemcitabine's antitumor activity against transitional cell carcinoma (TCC) cells (29). These preclinical findings prompted further investigation into gemcitabine's therapeutic potential for bladder cancer, leading to a series of clinical trials. A significant proportion of these clinical trials have confirmed the efficacy of gemcitabine, either as a monotherapy or in combination with other chemotherapeutic agents (30, 31).

A previous study investigated the efficacy of immediate postoperative intravesical gemcitabine administration in a patient cohort similar to the present study. Although the findings indicated gemcitabine's safety and tolerability, the study did not establish conclusive evidence of clinical efficacy in reducing tumor recurrence (32). Recent research has highlighted sterile water as a potential alternative for intravesical therapy (33, 34). Many investigations have demonstrated that sterile water can induce tumor cell lysis, primarily through the mechanism of osmotic cytolysis (35, 36). The concept of utilizing sterile water for therapeutic purposes was initially introduced by Price who proposed its application for peritoneal cavity irrigation to eliminate disseminated cancer cells following surgical intervention for various neoplastic conditions (37). Subsequent in vitro investigations provided further support for this approach, demonstrating the capacity of sterile water to induce significant tumor cell death within just 10 minutes across a spectrum of cell lines (38).

The results of this study indicated no significant difference in efficacy between gemcitabine and sterile distilled water in preventing tumor recurrence following TURBT in patients with NMIBC. The observed recurrence rate at the three-month follow-up interval was 10% in the gemcitabine group and 12.5% in the distilled water group. These findings suggest that the continuous postoperative intravesical administration of sterile water may offer comparable efficacy to single intravesical administration of gemcitabine in the management of NMIBC. A retrospective study conducted by Grivas et al reported comparable recurrence-free rates between patient cohorts with both single and multiple bladder tumors who underwent sterile water bladder irrigation and those who received a single immediate dose of mitomycin C (MMC) (33). In another investigation by Onishi et al, patients with intermediate-risk NMIBC who underwent TURBT were randomized to receive either continuous saline bladder irrigation (n=123) or intravesical MMC instillation (n=115). At the one-year follow-up, recurrence-free rates were 76.7% and 81%, respectively, with no statistically significant differences observed between the two groups regarding recurrence-free rate, time to first recurrence, or recurrence frequency (34).

The findings of this investigation demonstrate the efficacy of distilled water as an irrigant solution during and immediately following TUR of superficial TCC.

Distilled water functioned as a destructive agent against free-floating neoplastic cells within the bladder cavity, potentially preventing re-implantation and subsequently reducing recurrence rates. This observation is consistent with the previous research (39), which suggested that distilled water, due to its lower mucosal irritation compared to other irrigants, may mitigate the inflammatory response that can contribute to increased recurrence rates within predisposed tissues. Notably, no adverse events or complications such as hemolysis or severe anemia were observed during the study period.

The present study also revealed a marked male predominance in the sex-wise distribution of NMIBC, which exceeds the rates reported in Western literature. This discrepancy may be attributed to lower exposure to industrial carcinogens among women who work outside the home in Western societies. In this study, among 80 patients with bladder tumors, initially suspected of having NMIBC based on cystoscopy, 71 were confirmed to have NMIBC upon final biopsy. Furthermore, no statistically significant differences were observed between the study groups regarding tumor size as assessed through ultrasonography, cystoscopy, or histopathological examination. These findings are consistent with the findings of previous research (40), which have suggested that a combination of negative urine cytology and expert cystoscopic evaluation can accurately identify histologically confirmed low-grade and low-stage tumors in more than 90% of cases.

Limitations

This study has several limitations, including a relatively small sample size, the inherently high recurrence rate characteristic of bladder tumors, and a relatively brief follow-up period. Despite these constraints, and acknowledging the critical need for alternative first-line therapeutic strategies in the management of intermediate- and high-risk NMIBC, the findings of this investigation demonstrate acceptable oncologic outcomes and a favorable safety profile within the short-term follow-up period for this cohort of patients with low-risk NMIBC.

Conclusion

In individuals with suspected low-grade non-muscle-invasive urothelial neoplasms, immediate post-resection intravesical administration of both gemcitabine and distilled water resulted in a statistically significant reduction in tumor recurrence risk. Although no statistically significant difference was observed between the two groups, the findings support the use of sterile distilled water due to its lower cost and greater availability.

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Competing Interests

The authors declare competing interests relevant to the content of this article.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Urmia University of Medical Sciences (No. IR.UMSU.REC.1400.341).

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