

ORIGINAL PAPER

Introducing “HEDGE”: Sequential intravesical gemcitabine-based thermochemotherapy (HIVEC) plus docetaxel as a potential novel bladder-sparing strategy for BCG-unresponsive non-muscle-invasive bladder cancer

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Summary

Introduction: BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC) remains a major clinical challenge, with radical cystectomy recommended yet frequently declined or deferred. We introduce a regimen that combines hyperthermic intravesical chemotherapy (HIVEC) with gemcitabine immediately followed by intravesical docetaxel, which we named as “HEDGE” (HE = HIVEC, D = Docetaxel, GE = Gemcitabine). The rationale integrates: (i) the Guidelines of the European Association of Urology (EAU) construct of BCG-unresponsive disease as unlikely to benefit from further BCG; (ii) clinical experience supporting HIVEC-based chemotherapy; (iii) the growing evidence base for sequential gemcitabine/docetaxel; and (iv) experimental confirmation that gemcitabine remains stable at elevated temperatures, supporting its use within HIVEC circuits.

Materials and methods: BCG-unresponsive patients, according to the definition of the EAU on NMIBC, were prospectively selected to receive “HEDGE”. “HEDGE” consists of sequential intravesical gemcitabine-based thermochemotherapy (HIVEC) and intravesical docetaxel. It includes induction and maintenance scheme. Primary endpoints are recurrence and progression at 3, 6, 9, and 12 months. Secondary endpoints are feasibility and safety through documentation of adverse events (AE) based on The Common Terminology Criteria for Adverse Events (CTCAE) v6.0 (MedDRA) (National Cancer Institute/NCI, 2025).

We applied this treatment to 7 patients (5 men, 2 women).

Results: The included patients showed neither recurrence nor progression at 3 and 6 months. Finally, we documented Grade 2 AE in only 3 patients.

Conclusions: “HEDGE” looks feasible, safe, and showed no three- and six month recurrences in our first 7 BCG unresponsive NMIBC patients, supporting further clinical implementation and evaluation. This could be a therapeutic option for these patients.

KEY WORDS: BCG-unresponsive; Sequential; HIVEC; Gemcitabine; Docetaxel.

INTRODUCTION

Non-muscle-invasive bladder cancer (NMIBC), including stages Tis, Ta and T1 (1), represents about 75% of the primarily diagnosed bladder cancer cases (2). The fundamental first step of the therapy is the *transurethral resection of the tumor(s)* (TURBT). After TURBT, it is recommended, according to the Guidelines of the European Association of Urology (EAU) on NMIBC (GEAUN), that all patients are categorized, taking into account clinical and pathological data, in the following risk groups (for progression after TURBT without induction or maintenance BCG): low, intermediate, high and very high risk (2). Part of the intermediate-risk patients and all the high-, and very high-risk patients typically receive adjuvant, meaning after the initial TURBT, intravesical BCG-based therapy (induction and maintenance scheme). GEAUN recommend BCG as standard of care for the high and very-high risk patients (2). BCG-unresponsive disease includes all BCG refractory tumors and those who develop Ta/T1 high-grade (HG) recurrence within 6 months of completion of adequate BCG exposure or develop carcinoma *in situ* (CIS) within 12 months of completion of adequate BCG exposure (3). Adequate BCG is defined as the completion of at least five of six doses of an initial induction course plus at least two out of six doses of a second induction course or two out of three doses of maintenance therapy (2). These patients represent a population unlikely to benefit from further BCG and are at increased risk of progression, thereby prompting consideration of alternative bladder sparing strategies or early radical cystectomy (RC) (2). Clinical evidence established induction and maintenance BCG as effective for reducing recurrence and progression (2) in appropriate candidates, yet toxicity and the unresponsive subset are limitations (4). Within this context, there is a substantial need for alternative treatments in BCG-unresponsive cases.

In recent years, pioneer systems for the implementation of hyperthermic intravesical chemotherapy (HIVEC) are developed. The basic principle is to increase to 43°C the temperature of the environment, in which the chemotherapeutic agent, most frequently Mitomycin C (MMC), is

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administered during the intravesical instillation. In a recent study, preclinical device data confirm that *gemcitabine* (GE) remains stable at clinically relevant hyperthermic temperatures, supporting its integration within HIVEC circuits (5). HIVEC enhances delivery and cytotoxicity of chemotherapy and has demonstrated clinically meaningful reductions in recurrence with acceptable tolerability across randomized and observational experiences (6, 7). Furthermore, sequential intravesical *gemcitabine/docetaxel* (SGED) has emerged as a leading second line strategy, showing encouraging recurrence free outcomes and, in some cohorts, favorable tolerability compared to BCG (8-10).

In our department we handle a large number of patients treated with BCG and therefore we also deal with an important number of BCG-unresponsive patients. Taking into account the increasing evidence for using HIVEC and SGED, the experimental confirmation that GE remains stable at elevated temperatures supporting its use within HIVEC circuits, and mostly the fact that RC is not “appealing” neither for physicians nor patients and that BCG-unresponsive patients will not benefit from further BCG, we introduce in clinical practice a regimen that combines HIVEC with GE immediately followed by intravesical *docetaxel* (D), which we named as “HEDGE” (HE = HIVEC, D = Docetaxel, GE = Gemcitabine).

MATERIALS AND METHODS

BCG-unresponsive patients, according to the definition of GEAUN, were selected for “HEDGE” therapy.

Exclusion criteria were: i) recurrent (non-primary) NMIBC at diagnosis, when BCG was decided, ii) active urinary tract infection (UTI), iii) active or prior tuberculosis, iv) discontinuation of induction, maintenance therapy, or follow-up, during the period of BCG-based therapy, for any reason other than death and v) history of pelvic surgery or radiotherapy.

We collected baseline epidemiological data; sex, age, body mass index (BMI), smoking status (active smoker, ex-smoker and non-smoker), alcohol consumption (yes or no), clinical and pathological data (number of tumors, tumor size, stage, WHO 2004/2022 grade, concomitant CIS). We stratify all patients in risk groups according to GEAUN.

The patients received an induction scheme (six weekly intravesical instillations) and a maintenance scheme (one monthly instillation for 12 months).

GE (1 gr in 40 ml normal saline/NS) is delivered via a HIVEC circuit under hyperthermic conditions at 43°C for 1 hour, followed immediately by intravesical D (37.5 mg in 50 ml NS) for 1 hour. Urine alkalinization 24 hours pre instillation was obtained as already described by other researchers (8).

Regarding follow-up and decision points, we performed cystoscopy and urine cytology every 3 months through 12 months and computed tomography/CT urography (CTU) at 12 months. Any cystoscopic recurrence was followed by TURBT for histologic confirmation. Non-high grade recurrence was not considered failure and therapy continued; any high grade recurrence or progression to muscle invasion were considered failure and led to dis-

continuation, aligning with the GEAUN and common intravesical trial endpoints (2, 3). We documented adverse events (AE) based on The Common Terminology Criteria for Adverse Events (CTCAE) v6.0 (MedDRA) (National Cancer Institute/NCI, 2025) (11). Serious adverse events (SAE) are of Grade ≥ 3 . In case of SAE, the treatment ends. Primary endpoints were considered recurrence and progression at 3, 6, 9, and 12 months. Secondary endpoints were feasibility and safety through documentation of AE and SAE.

The study followed the principles expressed in the Declaration of Helsinki (<https://www.wma.net/policies-post/wma-declaration-of-helsinki/>), and was reviewed and approved by the Institutional Review Board (IRB) of the University Hospital of Larissa, Larissa, Greece. All data generated or analyzed during this study are included in this published article and are fully available without restriction. Finally, all patients provided a written consent form for their treatment with “HEDGE” and reporting results.

RESULTS

Seven BCG-unresponsive patients (5 male, 2 female) completed the six week induction plus three monthly maintenance instillations, resulting in a total of 63 sessions of “HEDGE” treatment. Their mean age was 71.6 years (60-84). All patients were either obese or overweight. All of them had a smoking history and 2 of them remained active smokers. Only 2/7 did not drink alcohol. All patients suffered from high-grade (HG) disease. Only 1/7 was diagnosed with Ta stage and only 1/7 had concomitant carcinoma in situ (CIS). The rest (5/7) had T1 disease. In all cases, tumor size was ≤ 3 cm. Single tumors were found in 5/7 cases and multiple tumors in 2/7 patients. Taking into account risk classification proposed by GEAUN, we had 5 high-risk (HR) patients, one very high-risk (VHR) patient and one intermediate risk (IR) patient.

Regarding primary endpoints, at 3 and 6 months, no recurrences were detected by cystoscopy and urine cytology. Consequently, no disease progression was also documented. In relation to secondary endpoints, our patients experienced only moderate AE (Grade 2). Supportive medication included oral paracetamol 500 mg in 2/7 patients and solifenacin 5 mg per os was administered 24 hours pre instillation in one patient. No SAE (Grade ≥ 3) was recorded.

All patients' characteristics as well as the above mentioned results are presented comprehensively in Table 1.

DISCUSSION

BCG-unresponsive patients represent a clinical challenge. Unfortunately, in the recent past we were unable to offer these patients an alternative and effective bladder-sparing treatment. RC stood as the only option. Thankfully, the therapeutic field changed dramatically, bringing new therapies for this group of NMIBC patients.

An approach for patients who do not respond to BCG aims to enhance the effectiveness of intravesical chemotherapy. Several methods have been investigated, including the use of devices that create a more favorable

Table 1.
Comprehensive presentation of the patients' characteristics and results.

Patient/Parameter of characteristics	1	2	3	4	5	6	7
Gender	Male	Female	Male	Male	Female	Male	Male
Age	74	77	68	84	60	71	67
Body Mass Index (BMI)	27.4	30	31.8	37	25.4	25.2	27.1
Class	Overweight	Overweight	Obese	Obese	Overweight	Overweight	Overweight
Smoking	Ex	Yes	Ex	Ex	Ex	Ex	Yes
Alcohol	Yes	No	Yes	No	Yes	Yes	Yes
Stage	T1	T1	T1	T1,Tis	T1	Ta	T1
Grade	HG	HG	HG	HG	HG	HG	HG
Number of tumors	Single	Multiple	Single	Single	Multiple	Single	Single
Tumor size	≤ 3 cm	≤ 3 cm	≤ 3 cm	≤ 3 cm	≤ 3 cm	≤ 3 cm	≤ 3 cm
Risk Group	High	High	High	Very High	High	Intermediate	High
Induction (Doses)	6	6	6	6	6	6	6
Recurrence ± Progression after induction	No	No	No	No	No	No	No
3-month Maintenance (Doses)	3	3	3	3	3	3	3
Recurrence ± Progression after 3-month maintenance	No	No	No	No	No	No	No
Adverse Events (AEs)	No	No	Yes	No	Yes	No	No
Serious Adverse Events (SAEs, Grade ≥ 3)	No	No	No	No	No	No	No

microenvironment for tumor eradication. One of the most commonly used modalities is *chemo hyperthermia* (CHT), which was initially known as the *radiofrequency induced thermo chemotherapy effect* (RITE). Historically, RITE was used in NMIBC (12), but technological advances and improved mechanistic understanding led to a newer form of therapy, termed *hyperthermic intravesical chemotherapy* (HIVEC). Both methods are based on the principle of hyperthermia. CHT is generally applied either as neoadjuvant therapy before TURBT or as adjuvant, prophylactic, or ablative treatment.

Although different devices and protocols are available, the core concept is to increase the temperature of the intravesical environment to 43°C during drug instillation, most commonly with MMC (6, 13). A recent study demonstrated and substantiated the feasibility of administering GE using a CHT device as well (5). Elevated temperature has been observed to increase tumor perfusion and alter cell membrane characteristics, thereby enhancing intracellular concentrations of the chemotherapeutic agent (14).

For adjuvant therapy after TURBT, the regimen mirrors MMC monotherapy, typically comprising an induction course followed by a maintenance schedule, depending on the protocol (7, 15). Colombo et al. investigated this in a randomized trial (2011) comparing MMC with CHT. They found that, over 24 months, the recurrence rate among patients who received MMC was significantly higher than among those who received CHT; specifically, they reported a relative reduction of 59% in NMIBC recurrences when CHT was used compared with MMC alone (6). Observational studies have examined *progression free survival* (PFS) in patients treated with HIVEC.

Some reported better outcomes than with BCG, whereas others did not find significant differences (15). Plata et al. conducted a multicenter study in Spain (16). It was shown that at 5 years the *recurrence-free survival* (RFS) was 50.37% (53.3% for intermediate risk and 47.14% for high risk NMIBC) and the PFS was 89.83% (94.02% for IR and 84.23% for HR NMIBC). Multivariable analysis indicated that recurrent tumors, HIVEC adjuvant therapy duration < 4 months, and HR disease increased the risk of recurrence (16). Independent risk factors for progression were HR disease, the use of induction only HIVEC (ie, without maintenance), and the recurrent tumors (16).

Because research in this field spans decades, data about AE are difficult to compare owing to the use of non-validated questionnaires. Nevertheless, a 2011 systematic review quantified several AE reported in earlier studies. The most frequent on treatment AE were bladder spasms and pain, occurring in 21.6% and 17.5% of patients, respectively. Post treatment, the most common symptoms were mild lower urinary tract complaints such as dysuria, urgency, nocturia, frequency, and hematuria (17). A 2021 study evaluated AE of HIVEC in patients who either failed BCG or had contraindications for BCG, finding that the most common AE were dysuria, frequency, and incontinence (18). That study also assessed per instillation symptoms and recorded additional systemic AE. As with MMC alone (ie, without CHT), myelosuppression is a potential AE if MMC is systemically absorbed; however, the risk of this effect is considered negligible (19). Moreover, 8.1% of patients reported mild flu like symptoms, 7.3% had abdominal pain, and 5.7% experienced nausea. Multiple studies have also reported nonspecific

rashes at frequencies similar to those observed with MMC monotherapy (up to 6%). In certain HIVEC modalities, there is a risk of a thermal reaction at the posterior bladder wall, with focal hyperemia at the device contact site. These reactions are often mild and resolve within a few months (20, 21). Finally, there is a risk of reduced bladder capacity, which also exists with MMC therapy alone (without CHT). However, the literature does not conclude that this effect is attributable exclusively to the hyperthermic component (17). In summary, the vast majority of the common AE associated with HIVEC are considered mild and tolerable for the majority of patients. An increasing body of evidence describes SGED as an alternative to BCG therapy. This approach initially emerged in response to BCG shortages (22). SGED has shown encouraging effectiveness for NMIBC across risk groups. The mechanism of action derives from the distinct pharmacology of each agent (i.e., no direct synergism is presumed): D inhibits cell proliferation by disrupting microtubule function, while GE, a deoxycytidine nucleoside analog, halts DNA synthesis (23). Standard practice begins with a six-week induction course mirroring BCG schedules, followed by monthly maintenance for at least 12 months; when the initial disease assessment confirms a complete response, maintenance may be extended up to 24 months, as this prolonged schedule has been associated with durable RFS in HR NMIBC (8,10). Urine alkalinization prior to each instillation is recommended specifically for the docetaxel step, as an alkaline urinary pH enhances drug stability and optimizes intravesical drug-tissue contact; the most widely used regimen consists of oral sodium bicarbonate 1,300 mg administered the evening before and again on the morning of each instillation (8). At present, protocols for SGED are not fully standardized. The most common GE dose is 1g (some studies report 2 g) and the D dose is 37.5mg (9, 10). Administration typically involves intravesical GE via a single use urethral catheter. The patient does not void for 1 hour. After bladder emptying, D is instilled via a new single use urethral catheter and retained for another hour, followed by voiding to evacuate the drug (22).

McElree et al. reported in HR, BCG naïve NMIBC that recurrence rates were similar between SGED and BCG (8). In a subsequent, larger cohort, the same group of authors showed that SGED achieved superior RFS for any recurrence (HR = 0.56, $p = 0.02$) and for HG recurrences (HR = 0.57, $p = 0.04$) versus BCG (9). Another multicenter study, compared SGED with BCG in IR NMIBC; at a median follow up of 48.6 months, RFS was similar between regimens. Notably, most patients had TaLG disease (primary or recurrent) rather than TaHG (10) and the SGED maintenance schedule consisted of monthly instillations for one year. However, given the lack of standardized maintenance, extending maintenance to 2-3 years is supposed to provide additional benefit (22). In the BCG unresponsive setting, Yim et al. retrospectively analyzed 102 patients who received SGED with induction and maintenance for up to two years; 12 and 24 month RFS were 65% and 49%, respectively (24). The SGED AE profile resembles that of intravesical GE and appears more favorable than BCG in comparative series. McElree observed lower treatment discontinuation with SGED

than with BCG (2.9% vs 9.2%, $p = 0.02$). The most frequent AE with SGED were bladder spasms (21%), UTI (8.7%), and urgency/frequency (8.7%). In contrast, 49.4% of BCG treated patients experienced AE, including urgency (11.5%), dysuria symptoms (12.6%), hematuria (10.9%), UTI (6.9%), and three cases of Grade ≥ 3 events, one of which was grade 5, meaning fatal (11). Of note, prophylactic oxybutynin was administered in the McElree SGED cohort (9). This remains an active and evolving research area. The BRIDGE trial, a prospective phase III study, is comparing SGED with BCG in patients with HR NMIBC and is currently ongoing (25).

Our department handles an important number of BCG-unresponsive patients. Therefore, we want to offer them alternatives other than RC. The therapeutic rationale underlying "HEDGE" rests on the convergence of two independently validated intravesical modalities. HIVEC has demonstrated clinically meaningful recurrence reduction relative to chemotherapy alone, with an acceptable tolerability profile across both randomized and large observational cohorts. The feasibility of delivering GE within a HIVEC circuit has been substantiated at the device level, with experimental data confirming GE's molecular stability under hyperthermic conditions. Concurrently, SGED has accrued a growing evidence base supporting its use as an alternative or salvage strategy in BCG-unresponsive NMIBC, with RFS data and a tolerability profile that compare favorably with BCG in several cohorts. Given that each component has independently demonstrated sufficient clinical activity to justify routine clinical use, it is biologically and clinically reasonable to hypothesize that their sequential combination - HIVEC-enhanced GE followed by D ("HEDGE") may yield at least additive benefit. The present early experience, while limited in sample size, is directionally consistent with this hypothesis.

Regarding efficacy, the absence of recurrence at 6 months in all 7 treated patients, each of whom completed full induction plus three monthly maintenance instillations, represents an encouraging early signal. We acknowledge that 7 patients constitute a small series, and definitive conclusions regarding RFS or PFS cannot be drawn at this stage. Nevertheless, it is worth noting that the favorable direction of this early outcome, interpreted alongside the established evidence for HIVEC and SGED, lends biological plausibility to the expectation of meaningful disease control with continued accrual and longer follow-up.

With respect to safety and tolerability, the present dataset acquires particular relevance when considered in terms of total treatment exposures rather than patient number alone. Across 7 patients, a cumulative total of 63 individual "HEDGE" administrations were completed, with no AE exceeding Grade 2. This observation warrants contextual framing: early-phase clinical trials - whether Phase I dose-escalation or Phase II feasibility studies - are specifically designed to establish the safety profile of novel therapeutic interventions in human subjects, and cohort sizes in such settings are frequently of comparable or only modestly larger magnitude. In that context, 63 administrations with exclusively low-grade toxicity constitute a more robust safety signal than patient count alone might suggest, and supports the tolerability of the "HEDGE" regimen in this population.

The principal strengths of the present work are threefold. First, “HEDGE” introduces, for the first time, a prospective sequential combination of two established and guideline-contextualized intravesical modalities (HIVEC with GE and intravesical D) in a BCG-unresponsive NMIBC population. Second, data are collected prospectively with predefined endpoints (RFS, PFS, CTCAE-graded AE), which enhances the interpretability and reproducibility of future findings. Third, the initial efficacy and safety signals are encouraging and directionally consistent with the mechanistic rationale. The primary limitation is the small number of patients reported here.

DECLARATIONS

Ethical approval and consent for participate: This work was conducted in accordance with the principles of the Declaration of Helsinki (<https://www.wma.net/policies-post/wma-declaration-of-helsinki/>) and was reviewed and approved by the Institutional Review Board (IRB) of the University Hospital of Larissa. Informed consent was obtained from all individual participants included in the study.

Use of Artificial Intelligence: The authors declare that no generative AI or AI-assisted technologies (including large language models, chatbots, or image creators) were employed in the production of the submitted work, including the writing process, data analysis, or image generation. The manuscript has been solely revised by a professional linguistic reviewer for language accuracy.

Availability of data and material: All data underlying the findings of this study are fully available within the manuscript without restriction. Further inquiries can be directed to the corresponding author.

Competing interests: The authors declare that there are no potential conflicts of interest regarding the research, authorship, or publication of this paper.

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Authors' contributions: L. Mitrakas: Conception and design, acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; A. Zisopoulos: Acquisition of data, or analysis and interpretation of data; final approval of the version to be published; K. Dimitropoulos: Analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the version to be published; S. Siafakas: Acquisition of data, or analysis and interpretation of data; final approval of the version to be published; K. Gkouletsa: Acquisition of data, or analysis and interpretation of data; final approval of the version to be published; V. Tzortzis: Drafting the article or revising it critically for important intellectual content; final approval of the version to be published; Author Contributions: All authors have contributed significantly to the work, have approved the final version of the manuscript, and agree with its submission. A detailed description of the contribution of each author is provided.

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This series represents the earliest phase of an ongoing prospective implementation, and robust time-to-event analyses will require substantially larger cohorts with extended follow-up. Accordingly, the present findings should be interpreted as hypothesis-generating and feasibility-supporting rather than confirmatory. Finally, we hope that “HEDGE” will be considered interesting and feasible and maybe in the future will have a role in the clinical practice.

CONCLUSIONS

“HEDGE”, HIVEC with gemcitabine immediately followed by intravesical docetaxel, looks feasible, safe, and showed no three- and six month recurrences in our first 7 BCG unresponsive NMIBC patients, supporting further clinical implementation and evaluation. This could be a therapeutic option for this challenging group of patients.

REFERENCES

1. Brierley JD, Giuliani M, O' Sullivan B, et al. *Union International Contre le Cancer/UICC, TNM Classification of Malignant Tumours*, 9th Edition, ISBN: 978-1-394-21687-1, Wiley; 2025.
2. EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3. EAU Guidelines Office, Arnhem, The Netherlands.
3. Kamat AM, Sylvester RJ, Böhle A, et al. *Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group*. *J Clin Oncol*. 2016; 34:1935-44.
4. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance BCG immunotherapy for recurrent Ta, T1 and CIS bladder tumors. *J Urol*. 2000; 163:1124-1129.
5. Jing L, Wenjian C, Meimei Z, et al. Novel device with gemcitabine for hyperthermic intravesical chemotherapy: development and investigation. *Int J Hyperthermia*. 2023; 40:2129103.
6. Lammers RJ, Witjes JA, Inman BA, et al. Intravesical chemotherapy with hyperthermia in NMIBC: a systematic review. *Eur Urol*. 2011; 60:81-93.
7. Kastner L, Rieger C, Pfister D, et al. HIVEC as an alternative option in non-muscle invasive bladder cancer: Experiences from a high volume center. *Urol Oncol*. 2024; 42:245.e19-245.e26.
8. McElree IM, Steinberg RL, Martin AC, et al. Sequential intravesical gemcitabine and docetaxel for BCG naive high risk NMIBC. *J Urol*. 2022; 208:589-599.
9. McElree IM, Steinberg RL, Mott SL, et al. Gemcitabine/docetaxel versus BCG for high risk NMIBC. *JAMA Netw Open*. 2023; 6:e230849.
10. Tan WS, McElree IM, Davaro F, et al. Sequential intravesical gemcitabine and docetaxel as an alternative to BCG in intermediate risk NMIBC. *Eur Urol Oncol*. 2023; 6:531-534.
11. National Cancer Institute, U.S. Department of Health and Human Services. *Common Terminology Criteria for Adverse Events (CTCAE)*, Version 6.0, 2025, NCI CTCAE and AE Reporting Site.
12. Tan WS, Panchal A, Buckley L, et al. Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guérin or Institutional Standard in Patients with Recurrence of Non-muscle-invasive Bladder Cancer Following

Induction or Maintenance Bacillus Calmette-Guérin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial. *Eur. Urol.* 2019; 75:63-71.

13. Stauffer PR, Van Rhoon GC. Overview of bladder heating technology: Matching capabilities with clinical requirements. *Int. J. Hyperth.* 2016; 32:407-416.

14. Van Hattum JW, Scutigliani EM, Helderma RCPA, et al. A scalable hyperthermic intravesical chemotherapy (HIVEC) setup for rat models of bladder cancer. *Sci. Rep.* 2022; 12:7017.

15. Bahouth Z, Halachmi S, Moskovitz B, Nativ O. The role of hyperthermia as a treatment for non-muscle invasive bladder cancer. *Expert Rev. Anticancer Ther.* 2016; 16:189-198.

16. Plata A, Guerrero-Ramos F, Garcia C, et al. Long-Term Experience with Hyperthermic Chemotherapy (HIVEC) Using Mitomycin-C in Patients with Non-Muscle Invasive Bladder Cancer in Spain. *J. Clin. Med.* 2021; 10:5105.

17. Colombo R, Da Pozzo LF, Lev A, et al. Local Microwave Hyperthermia and Intravesical Chemotherapy as Bladder Sparing Treatment for Select Multifocal and Unresectable Superficial Bladder Tumors. *J. Urol.* 1998; 159:783-787.

18. Thomsen JA, Nielsen Dominiak H, Lindgren MS, Jensen JB. Adverse events of hyperthermic intravesical chemotherapy for non-muscle invasive bladder cancer patients. *Scand. J. Urol.* 2021; 55:281-286.

19. Paroni R, Salonia A, Lev A, et al. Effect of local hyperthermia of the bladder on mitomycin C pharmacokinetics during intravesical

chemotherapy for the treatment of superficial transitional cell carcinoma. *Br. J. Clin. Pharmacol.* 2001; 52:273-278.

20. Colombo R, Da Pozzo LF, Salonia A, et al. Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. *J. Clin. Oncol.* 2003; 21:4270-4276.

21. González-Padilla DA, González-Díaz A, Guerrero-Ramos F, et al. Quality of life and adverse events in patients with nonmuscle invasive bladder cancer receiving adjuvant treatment with BCG, MMC, or chemohyperthermia. *Urol. Oncol.* 2021; 39:76.e9-76.e14.

22. Lidagoster S, Ben-David R, De Leon B, Sfakianos JP. BCG and Alternative Therapies to BCG Therapy for Non-Muscle-Invasive Bladder Cancer. *Curr Oncol.* 2024; 31:1063-1078.

23. Roumiguié M, Black PC. Sequential Gemcitabine plus Docetaxel Is the Standard Second-line Intravesical Therapy for BCG unresponsive Non-muscle-invasive bladder cancer: *Pro. Eur. Urol. Focus* 2022; 8:1117-1120.

24. Yim K, Melnick K, Mott SL, et al. Sequential intravesical gemcitabine/docetaxel provides a durable remission in recurrent high-risk NMIBC following BCG therapy. *Urol. Oncol. Semin. Orig. Investig.* 2023; 41:458.e1-458.e7.

25. A Randomized Phase III Trial of Intravesical BCG versus Intravesical Docetaxel and Gemcitabine Treatment in BCG Naive Non-Muscle Invasive Bladder Cancer (The BRIDGE Trial)—NCI. Available online: <https://www.cancer.gov/research/participate/clinical-trials-search/v?id=NCI-2022-04864&r=1> (accessed on 2 December 2023).

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