Hindawi
International Journal of Clinical Practice
Volume 2024, Article ID 9916707, 13 pages
https://doi.org/10.1155/2024/9916707

*Review Article*

# The Efficacy and Safety of Hyperthermic Intravesical Chemotherapy Compared with Other Instillation Methods in Treating Intermediate- and High-Risk Non-Muscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis

**Yingying Yang,[1] Hongquan Liu,[1] Yongli Chu,[2] Jipeng Wang,[1] Jian Ma,[1] Guixin Ding,[1] Xingjun Bao,[1] Yuanshan Cui,[1] and Jitao Wu[1]**

[1]*Department of Urology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, No. 20 East Yuhuangding Road, Yantai 264000, Shandong, China*
[2]*Department of Gynecology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, No. 20 East Yuhuangding Road, Yantai 264000, Shandong, China*

Correspondence should be addressed to Yuanshan Cui; doctorcuiys@163.com and Jitao Wu; wjturology@163.com

Received 8 September 2023; Revised 7 April 2024; Accepted 23 April 2024; Published 9 May 2024

Academic Editor: Eirini Lidoriki



*Background*. In order to prevent the recurrence and progression of intermediate- and high-risk non-muscle invasive bladder cancer (NMIBC) after transurethral resection of bladder tumor (TURBT), various bladder instillation therapies have been developed in recent years. Among these, device-assisted Hyperthermic Intravesical Chemotherapy (HIVEC) has received a great deal of attention. *Objective*. To identify the efficacy and safety of HIVEC, we conducted this meta-analysis. *Methods*. We identified relevant articles from PubMed, Embase, and Cochrane Library databases. All published randomized controlled trials (RCTs) describing the role of bladder instillation for the treatment of intermediate- and high-risk NMIBC were involved. Outcomes included 1–3 years Recurrence-Free Survival (RFS), 1–3 years Progression-Free Survival (PFS), 5 years Overall Survival (OS), Adverse Events (AEs), and relevant subgroup analyses. *Result*. Our study involved a total of 10 RCTs and 1360 patients. In subgroup analysis, we found that compared to MMC instillation, HIVEC decreased the 1–3 years RFS (OR = 0.51; $p = 0.009$) while not increasing the incidence of AEs (OR = 0.86; $p = 0.30$). Compared with BCG instillation, HIVEC reduced the incidence of serious AEs (OR = 0.21; $p = 0.04$) while bringing the same efficacy (OR = 0.78; $p = 0.63$). *Conclusion*. HIVEC combined the advantages of efficacy and safety compared with the two recommended instillation modalities. As a potential alternative therapy, its widespread clinical effect remains to be further evaluated.

## 1. Introduction

As the commonest form of bladder cancer, non-muscle invasive bladder cancer (NMIBC) only affects the uroepithelium or subepithelial connective tissue and includes three stages (Tis, Ta, and T1) [1]. Its incidence rate in 60–69 years old is 0.96%, and 3.5% over 70 years old [2, 3]. TURBT is highly recommended for NMIBC due to its important role in diagnosis and treatment. But the high recurrence rate, 15–61% in 1 year and 31–78% in 5 years, limits its extensive application to some extent [4–6]. In order to prevent the recurrence and progression of NMIBC after TURBT, various bladder instillation therapies were developed in recent years.

For low-risk NMIBC, intravesical infusion chemotherapy within 24 hours after TURBT can reduce the recurrence rate by 30% and show an ideal effect to prevent the progression [7]. In addition, for intermediate- and high-risk NMIBC, immediate bladder instillation chemotherapy with follow-up instillation or bladder intravesical immunoinstillation is recommended [7, 8]. As a new method, chemotherapy hyperthermia (CHT) includes both hyperthermia and instillation chemotherapy, which has

attracted people's attention in recent years [9]. The application of CHT in bladder instillation is hyperthermic intravesical chemotherapy (HIVEC). HIVEC can be divided into various methods according to its different theories and equipment; among these, the "recirculation of heated chemotherapy" is the most commonly used [10, 11]. It requires the use of equipment in vitro to maintain the drug at 42-43°C before injecting it into the bladder [12, 13]. This method may affect the effectiveness of intravesical chemotherapy and also bring some changes in side effects [14, 15].

At this point, a thorough assessment of these approaches is still required. Several published RCTs' data were involved in this meta-analysis to evaluate the efficacy and safety of HIVEC and other instillation methods, to guide the selection of instillation methods in clinical practice. We present this article in accordance with the PRISMA reporting checklist.

## 2. Methods

*2.1. Information Sources and Search Strategy.* We performed a systematic search of RCTs in the following databases: MEDLINE (January 1, 1990–July 1, 2023), Embase (January 1, 1990–July 1, 2023), and the Cochrane Controlled Trials Register (January 1, 1990–July 1, 2023). The search terms were as follows: "Intravesical Chemohyperthermia," "Thermotherapy," "Immunoinstillation," "Chemoinstillation," and "randomized controlled trials." We further scanned the conference abstracts and proceedings in English language for candidate articles. Besides, we looked for the list of references of the included studies as well. Three authors participated independently in the literature search. Any disagreements about the screening results were discussed by two supervisors, and the final decision was based strictly on the inclusion and exclusion criteria. The statistical analysis follows "Guidelines for Reporting of Statistics for Clinical Research in Urology" [16].

*2.2. Inclusion Criteria, Exclusion Criteria, and Trial Selection.* The primary inclusion criteria are as follows: (1) the study compared the effect of HIVEC with other instillation methods in patients with intermediate- or high-risk NMIBC after TURBT; (2) the HIVEC treatment has specific requirements on drugs, temperature, course of treatment, and other factors; (3) the control group can be one of the conventional instillation methods—intravesical immunotherapy with BCG or chemotherapy instillation of MMC. (4) Restrict the hyperthermia methods: chemotherapy drugs are heated before instillation. Using other instillation methods besides HIVEC: RITE, EMDA, etc., should be excluded. Table 1 contains the details of the inclusion criteria. Editorials, commentaries, reviews, case reports, case series, and single-arm studies are excluded.

*2.3. Quality Assessment.* The Cochrane manual was used to assess the quality of all included studies [17]. The quality of these individual studies was determined by their evaluation methods, including patient allocation, concealment of allocation, and blinding. Each included study was evaluated by using the guidelines published in the Cochrane Intervention System Evaluation Manual, Version 5.1.0 [17]. Each study is evaluated and classified as "+" (meeting all quality standards, with low risk of bias), "?" according to its quality (it is not clear about one or more quality standards, with a moderate risk of bias), or "–" (it barely meets the quality standards, with a high risk of bias). The differences in this classification were resolved through discussions among researchers.

*2.4. Data Extraction.* We collected useful data from all involved articles, including the first author's name, publication date, study type, the suitability of study samples, patient treatment regimens, and data on research findings. The primary outcome is 1–3 years RFS, and the secondary outcomes are 1–3 years PFS and 5 years OS. RFS was defined by the proportion of patients with tumor recurrence, PFS was defined by the proportion of patients with tumor progression, and OS was defined by the survival proportion of patients during follow-up time. In order to assess the safety of different methods, we also analyzed the frequency of urination, dysuria, nocturia, hematuria, and other adverse events.

*2.5. Statistical Analysis and Meta-Analysis.* The data of this study were statistically analyzed by using the review manager software (version 5.4.0; Cochrane Collaboration, London, UK) [7]. 1–3 years RFS, 1–3 years PFS, 5 years OS, and AEs were analyzed to compare the therapeutic effect of HIVEC and other instillation methods on NMIBC after TURBT. Continuous data were analyzed with mean difference (MD), and dichotomous data were evaluated by odds ratio (OR) with 95% confidence interval (95% CI). Heterogeneity analysis: an individual study could be characterized as a fixed model if $p > 0.05$, otherwise a random-effects model was chosen for it. Statistical analysis: if $p < 0.05$, the result is considered to be statistically significant.

## 3. Results

*3.1. Characteristics of the Individual Studies.* Our search strategy generated 211 articles. After browsing the abstract and title, 174 articles were deleted because the article content did not match. Among the remaining 37 articles, 18 articles were excluded because the experimental method is not random controlled trials. 10 were excluded due to the lack of complete and useful data. Finally, our study included 9 articles and 10 different RCTs [12, 18–25]. The study by Daniel A. in 2020 recorded two RCTs that have different control groups and are independent of each other. The details of the research selection process are shown in Figure 1, and the features and characteristics of the 10 RCTs are shown in Table 2.

*3.2. Quality Assessment of the Individual Studies.* Firstly, all of the included articles were RCTs. In addition, each study introduced the treatment scheme and calculated the sample

Table 1: Search strategy according to populations, interventions, comparators, outcomes, and study designs (PICOS).

| | Populations | Interventions | Comparisons | Outcomes | Study design |
|---|---|---|---|---|---|
| Inclusion criteria | Intermediate/high risk NMIBC after TURBT | Intravesical chemohyperthermia with strict conditions: MMC instillation for one year under 42–45°C, using the method of "recirculation of heated chemotherapy" | Chemotherapy instillation using MMC or immune instillation using BCG (body temperature) | Efficacy: 1–3 years RFS; 1–3 years PFS; 5 years OS. Safety: total AEs; severe AEs | Randomized controlled trials |
| Exclusion criteria | Non-intermediate/high risk NMIBC, or patients did not undergo the TURBT surgery | Not performed; using other instillation methods besides HIVEC: RITE, EMDA, etc. | Not performed; instillation methods using other drugs | Not including appropriate outcome indicators | Editorials, commentaries, reviews, case reports, case series, and single-arm studies |

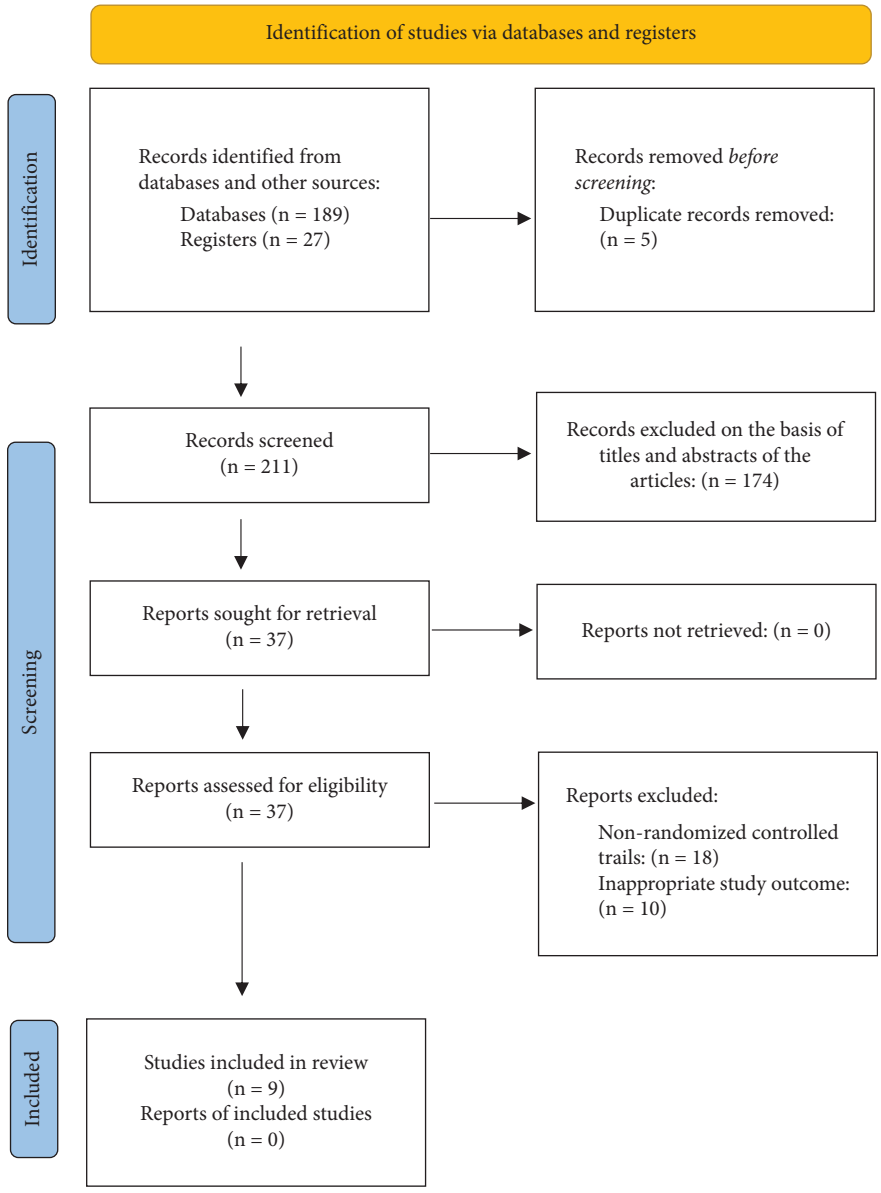


Figure 1: Flowchart of the study selection process.

size (Table 2). Guleria etc. did not introduce the randomization process in detail, so the blind method was rated as "?"; other studies were classified as "+." All details are shown in Figure 2.

### 3.3. *Efficacy*

*3.3.1. 1–3-Year RFS.* Eight RCTs [12, 18, 19, 21–25] and 1200 patients (599 in the HIVEC group and 601 in the other instillation group) were involved in collecting the number of relapses (Figure 3). All patients had intermediate to high-risk non-muscle invasive bladder cancer. A fixed effect model was used to evaluate these eight RCTs for significant heterogeneity between the two groups ($chi^2 = 2.86$, $p = 0.09$). The result showed that odds ratio (OR) was 0.55 and 95% CI was 0.41–0.74 ($p < 0.0001$). Hence, the 1–3 years RFS of HIVEC regimen was higher than that of other instillation methods. By subgroup analysis, there was no statistical significance between HIVEC and BCG group (OR: 0.90, 95% CI was 0.47–1.70, $p = 0.74$); compared with the MMC group, the 1–3 years RFS of HIVEC was significantly increased (OR: 0.48, 95% CI was 0.34–0.67, $p < 0.0001$). Therefore, for intermediate- and high-risk non-muscle invasive bladder cancer patients, HIVEC can reduce the recurrence rate of bladder chemotherapy instillation but cannot improve the recurrence rate of immune instillation.

*3.3.2. 1–3-Year PFS.* Six RCTs [18, 19, 21–23, 25] and 1096 patients (549 in the HIVEC group and 547 in the other instillation group) were involved to collect the number of progress (Figure 4). All patients had intermediate to high-risk non-muscle invasive bladder cancer. A fixed effect model was used to evaluate these six RCTs for no significant

Table 2: Study and patient characteristics.

| Study (year) | Country of study | Study design | Recruitment period | Duration of follow-up (months) | Number of patients (HIVEC/ standard instillations) | Age (HIVEC/ standard instillations) | Sex (M/F) | Risk stratification (intermediate/ high risk) | Agent for HIVEC | Agent for standard instillations | Statistical analysis | ITT analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Padilla 2020 | Spain | RCT | 2016-2017 | 24 | 14/27 (BCG)/15 (MMC) | Mean 74/76 (BCG)/ 69 (MMC) | 49/7 | 0/41 (BCG) 15/27 (MMC) | MMC | BCG/MMC | ANCOVA | No |
| Thyavihally 2021 | India | RCT | 2017–2020 | 22 | 22/29 | Mean 62/61 | 45/6 | 29/22 | MMC | BCG | ANCOVA | Yes |
| Ramos 2022 | Spain | RCT | 2016–2021 | 33.7 | 25/25 | Mean (SD) 74.1 (10.4)/73.0 (8.65) | 43/7 | 1/49 | MMC | BCG | ANCOVA | Yes |
| Tan 2022 | UK | RCT | 2014–2017 | 24 | 127/125 | Mean 70/69 | 178/ 74 | 39/213 | MMC | MMC | Kaplan–Meier | No |
| Guleria 2022 | India | RCT | 2019–2021 | 12 | 70/70 | NA | NA | NA | MMC | BCG | ANCOVA | No |
| Angulo 2023 | Spain | RCT | 2014–2020 | 24 | 106/106 | Mean 66/68 | 174/ 38 | 77/135 | MMC | MMC | Kaplan–Meier | Yes |
| Ekin 2015 | Turkey | Retrospective Cohort Study | 2004/ 01–2014/01 | 33 | 40/142 | Mean (SD) 68.2 (9.26)/ 64.0 (10.61) | 167/ 15 | 65/117 | MMC | BCG | Kaplan–Meier | No |
| Ba 2017 | China | RCT | 2006/ 12–2014/12 | 47 | 28/25 | Mean (SD) 50.7 (1.9)/51.6 (2.3) | 49/4 | 7/46 | MMC | MMC | t-Test, Kaplan–Meier | No |
| Ruan 2021 | China | RCT | 2009–2015 | 63 | 182/182 | Mean 117 (≤65) + 65 (>65)/108 (≤65) + 74 (>65) | 290/ 74 | 220/144 | MMC | MMC | ANCOVA | No |

RCT, randomized controlled trial; ANCOVA, analysis of covariance; ITT, intention-to-treat; NA, not available.

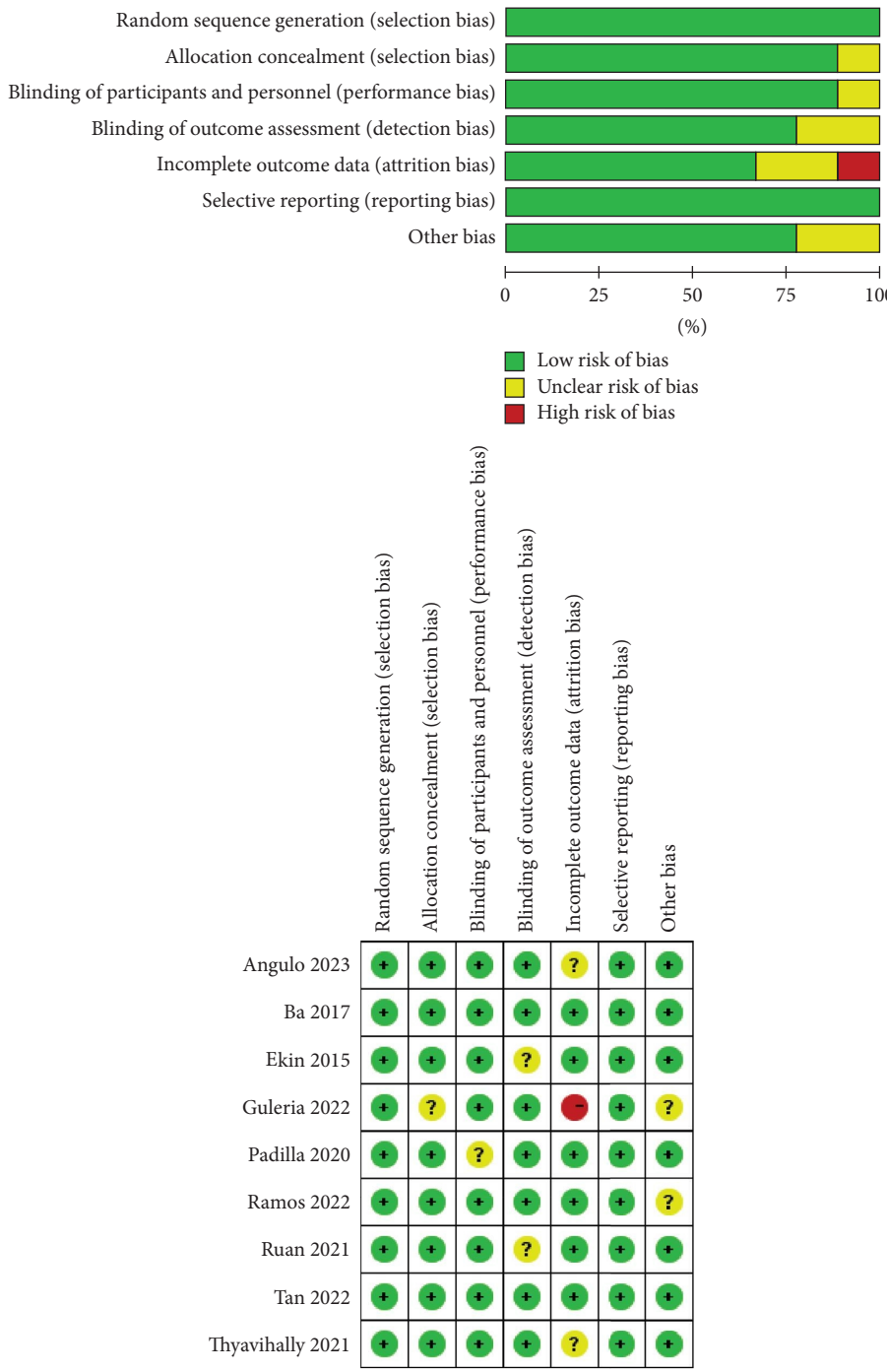


Figure 2: The risk of bias summary and graph.

heterogeneity between the two groups ($chi^2 = 0.01$, $p = 0.92$). The result showed that OR was 0.67 and 95% CI was 0.34–1.31 ($p = 0.08$). Therefore, for intermediate- and high-risk non-muscle invasive bladder cancer patients, there was no statistically significant difference between the 1–3 years PFS of the HIVEC regimen and other instillation methods. In subgroup analysis, there was no significant improvement in the efficacy of HIVEC for both immune instillation and chemotherapy instillation methods.

*3.3.3. 5-Year OS.* Two RCTs [22, 23] and 414 patients (207 in the HIVEC group and 207 in the other instillation group) were involved (Figure 5). The two RCTs in the control group were all treated with chemotherapy instillation, so we did not conduct the subgroup analysis. A fixed effect model was used to evaluate these two RCTs for no significant heterogeneity between the two groups ($chi^2 = 3.73$, $p = 0.05$). The result showed that OR was 0.71 and 95% CI was 0.45–1.09 ($p = 0.12$). Therefore, for intermediate- and high-risk

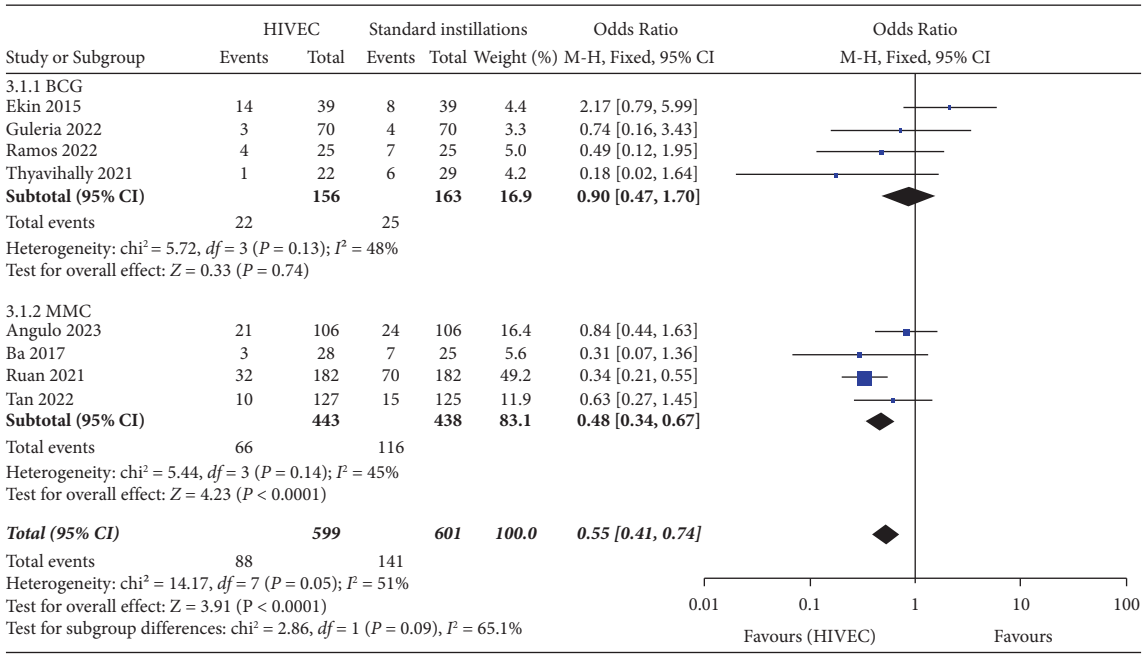


Figure 3: Forest plots showing the result of the efficacy: 1–3 years RFS. RFS, recurrence-free survival; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

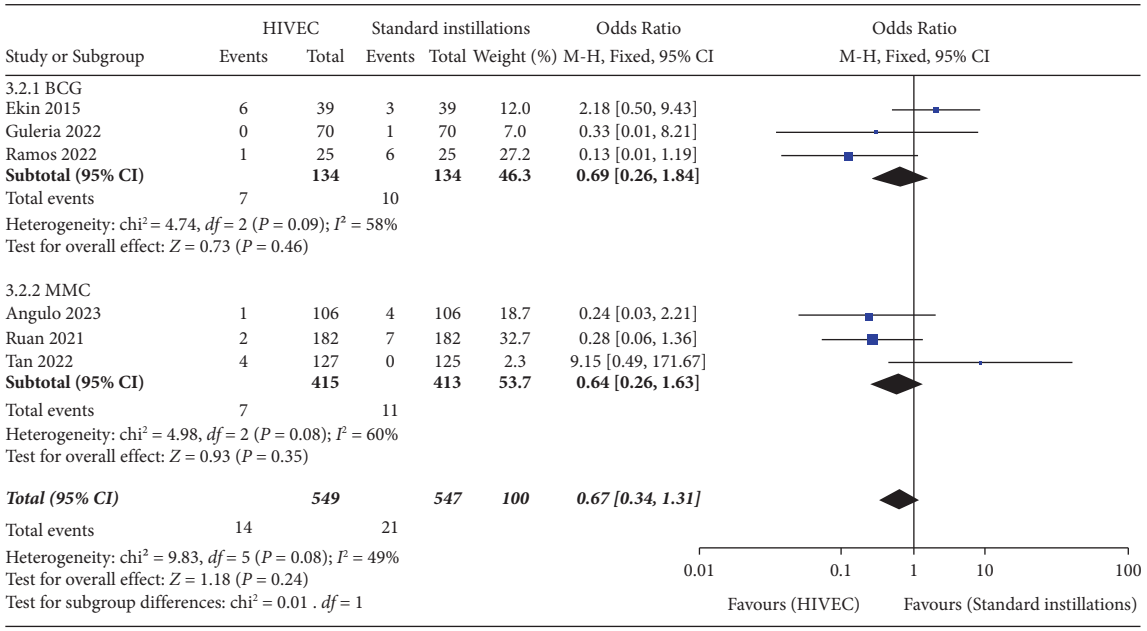


Figure 4: Forest plots showing the result of the efficacy: 1–3 years PFS. PFS, progression-free survival; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

non-muscle invasive bladder cancer patients, there was no significant improvement in the 5-year OS of HIVEC compared with other instillation groups.

*3.4. Safety.* Adverse events (AEs) were routinely assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [26]. A total of 999 patients were included in 7 RCTs [18, 20–25]. A fixed effect model was used for the significant heterogeneity between the two groups ($chi^2 = 0.22$, $p = 0.64$) (Figure 6). For the total number of AES occurrences, there was no significant difference between the HIVEC group and the normal temperature instillation group (OR = 0.84, 95% CI: 0.64–1.10, $p = 0.20$). According to the CTCAE, we also evaluated the number of severe AES occurrences; a total of 594 patients were included in 5 RCTs [18, 20, 21, 23, 24]. A fixed effect model was used for the significant heterogeneity between the

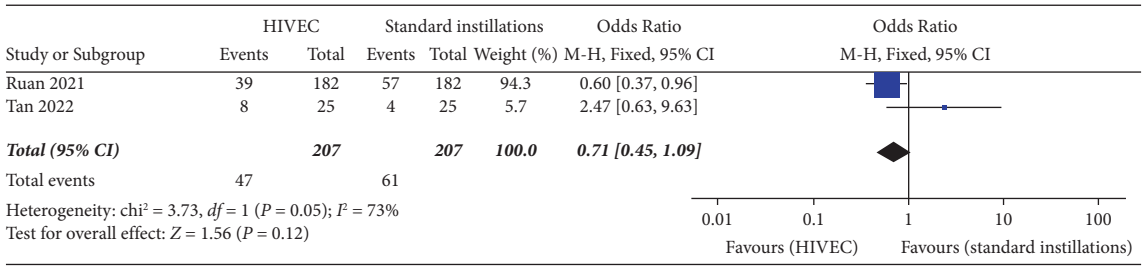


Figure 5: Forest plots showing the result of the efficacy: 5 years OS. OS, overall survival; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

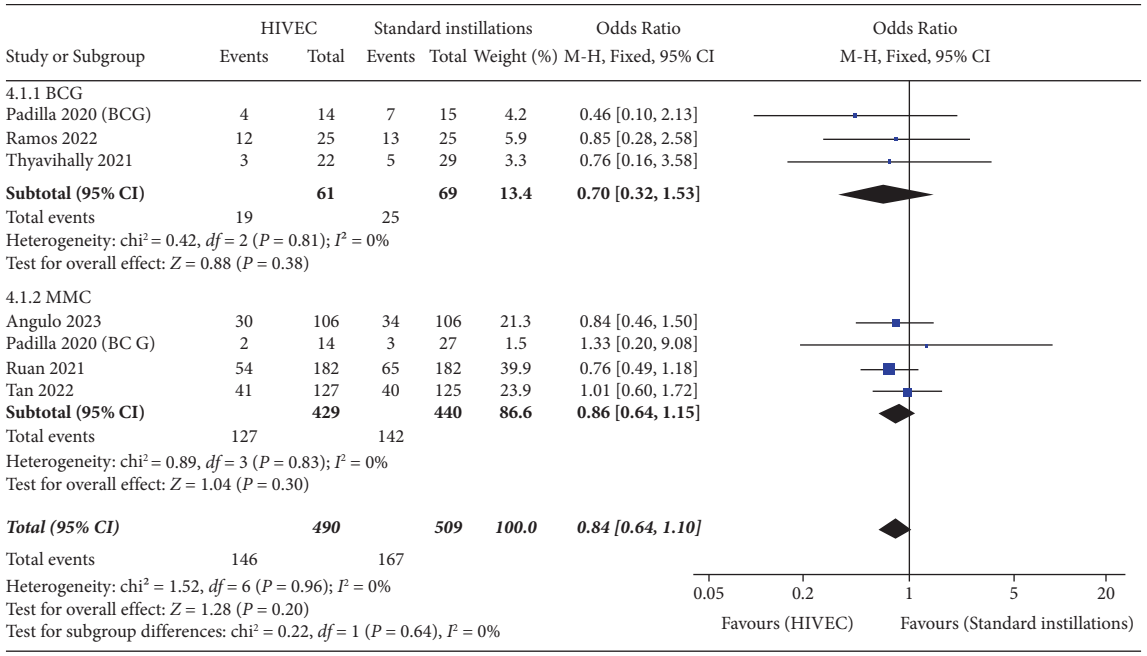


Figure 6: Forest plots showing the result of the safety: AEs. AE, adverse event; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

two groups ($chi^2 = 4.90$, $p = 0.03$) (Figure 7). In subgroup analysis compared to BCG, HIVEC can reduce the severe AES incidence (OR = 0.21, 95% CI: 0.04–0.99, $p = 0.05$). The incidence rate is not statistically significant between HIVEC and MMC groups. These results indicated that HIVEC can improve the efficacy of BCG instillation, which is the same as MMC instillation.

## 4. Discussion

The preferred treatment for intermediate- and high-risk NMIBC is intravesical treatment after TURBT, but it is associated with high recurrence rates, high progression rates, and frequent (often lifelong) invasive monitoring and intravesical treatment [27–29]. To increase the patients' postoperative living quality, it is vital to lower the rate of disease recurrence and progression. Intravesical instillation therapy is commonly used for NMIBC, and the European Association of Urology (EAU) guidelines strongly recommend immediate postoperative single instillation chemotherapy such as mitomycin C (MMC), epirubicin (EPI), or pirarubicin and/or maintenance MMC or BCG according to risk classification [30]. Despite intravesical therapy, approximately 30%–50% patients eventually relapse within 1 year.

Intravesical therapy is a common guideline practice for postoperative NMIBC. According to the European Association of Urology (EAU) guidelines, a single instillation should be performed immediately after surgery [26]. MMC is an antitumor medication that was discovered in actinomycetes' culture solution. It is one of the nonspecific medications that are frequently utilized in the cycle. EPI belongs to antibiotic antitumor drugs. Pirarubicin is an anthracyclic antibiotic. The three all can be embedded directly between the DNA nucleobases, interferingthe process of replication and transcription. While preventing tumor recurrence, controlling tumor progression, and improving the prognosis of patients, it may bring chemical cystitis symptoms like frequent urination, urgency, pain in urination, and hematuria as well as systemic reactions like bone marrow suppression and gastrointestinal discomfort. Besides that, between 30% and 50% of patients eventually experience a recurrence within a year even with instillation therapy [31]. BCG is the most

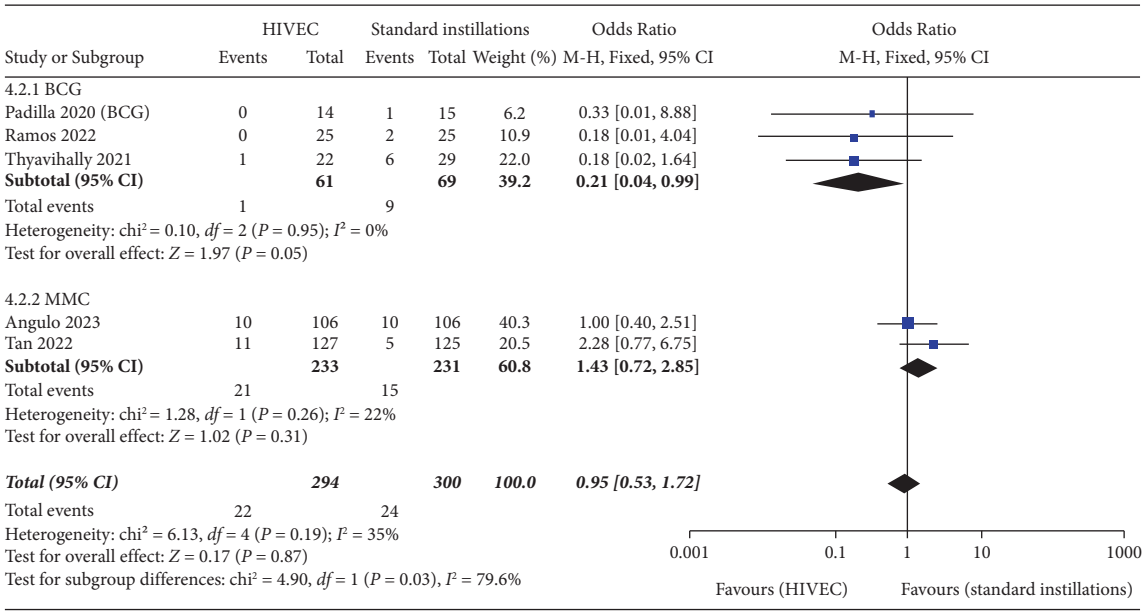


Figure 7: Forest plots showing the result of the safety: severe AEs. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

commonly used immunoinstillation medication. As an immune agent, it can induce local specific immune response to kill tumor cells. BCG immunoinstillation is the gold adjuvant treatment for medium to high-risk NMIBC patients after TURBT; it can bring better efficacy compared to chemotherapy instillation. But it also increases the incidence of negative events. In recent years, HIVEC has received increasing attention. Our study focuses on reperfusion after heating chemotherapy drugs and compares its efficacy and safety with traditional instillation methods.

The effectiveness was assessed by using the 1–3 years RFS as the primary outcome observation. Cancer recurrence refers to the recurrence or spread of cancer cells that were previously thought to have been eliminated or controlled after surgical treatment to other areas within a period. Recurrence is closely related to residual tumor cells that have not been detected after surgery [32, 33]. After restricting tumor types and treatment methods, it can effectively evaluate the efficacy of postoperative instillation methods. In this study, the 1–3 years RFS of the HIVEC group was lower. The residual tumor cells were the main origin of tumor recurrence, especially for some subclinical lesions, which were difficult to detect by medical images [31]. In addition, the persistence of high predisposing factors for tumorigenesis also led to a high risk of tumor reoccurrence and further development. Some experimental studies have shown that 42°C temperature led to denaturation of cytoplasmic structures and enzymatic proteins, inducing apoptosis and necrosis [34, 35]. Besides, heat shock proteins (HSP), especially HSP70, can be released by high temperature as well, which stimulates adaptive T cell responses during cell necrosis and induces activation of the innate and adaptive immune system [34]. In addition, hyperthermia enhances cell membrane permeability , increasing the uptake of drugs by cells. The alteration of HSP activity in hyperthermic environments can chemosensitize tumors to alkylating agents (e.g., MMC) [36, 37]. The above mechanism increased the efficacy of the infused drug. So we hypothesized that HIVEC might have a more potent ability to induce the apoptosis and necrosis of residual cells; the decrease of residual malignant cells greatly reduces the possibility of recurrence. MMC, cisplatin, gemcitabine, Adriamycin, and EPI are all available for intravesical treatment of NMIBC, but in the subgroup analysis compared with general chemotherapy instillation, the drug used in all studies was MMC, which just fit the current clinical situation that MMC had long been the preferred drug for chemotherapy instillation [38]. RFS was lower in the HIVEC group under the control of chemotherapeutic agents, showing that the device-assisted thermotherapy approach can optimize the efficacy of instillation chemotherapy. Furthermore, the subgroup analysis compared with immunoinstillation is warranted because the intravesical BCG is the gold adjuvant therapy for patients with intermediate- and high-risk NMIBC after TURBT [39, 40]. The results showed that the HIVEC group had a lower RFS, indicating that the device-adjuvant heat therapy can greatly improve the efficacy of instillation, and even had more desirable efficacy than immune instillation.

We also compared 1–3 years PFS to evaluate the efficacy. Cancer progression refers to the presence of residual tumor tissue confirmed by examination results after surgery and the progression of the condition over time, including grading, staging, lymph node metastasis, and distant metastasis. The residual tumor tissue plays a crucial role in cancer progression [41, 42]. Therefore, PFS can also effectively evaluate the killing effect of postoperative instillation methods on residual cells. For intermediate- and high-risk NMIBC, PFS presented as the early micrometastasis, which occurred via the invasion of residual tumor cells into the lamina propria [42]. After its progression to muscle invasive bladder cancer (MIBC), it might likely further progress to lymph nodes or other organs, leading to distant metastases.

In the overall analysis, there was no significant difference in PFS between the HIVEC group and the normothermic instillation group for 1–3 years. We speculate that although hyperthermia instillation can induce apoptosis and necrosis of residual cells after surgery [34, 35], it does not significantly improve the micrometastasis of residual tumor cells to the lamina propria. We also analyzed the 5 years OS and found no significant difference between the two groups. This result may also require further RCTs to participate in the evaluation due to the insufficient number of studies included.

While evaluating the efficacy of thermal instillation therapy, we also considered safety. Instillation treatment will bring cystitis, dysuria, gross hematuria, influenza-like symptoms, fever, and other adverse reactions. We evaluated the total number of AE and found that HIVEC was not significantly different from other instillation methods. According to the CTCAE standard, we classified Grade IV and Grade V adverse events as serious adverse events, such as urinary blood and urinary fistula, which need involuntary commitment, and further evaluated the incidence of serious AEs. In the subgroup analysis compared with BCG, HIVEC could well reduce the incidence of serious AEs, but there was no statistically significant difference compared with the MMC group. This confirms the safety of HIVEC. Although BCG instillation has always been the gold standard for efficacy and brings better efficacy than MMC instillation, it also has a higher incidence of AEs, and a considerable number of patients cannot tolerate this regimen. Through subgroups, we found that HIVEC can reduce the incidence of adverse events and bring similar therapeutic effects to BCG. Compared to immune instillation and chemotherapy instillation, HIVEC can have both therapeutic and safety advantages. At present, intravesical maintenance chemotherapy (MMC) is still the main treatment method for intermediate- and high-risk NMIBC in many regions of the world [36], and device-assisted hyperthermia effectively compensates for its insufficient efficacy without increasing the incidence of adverse events; Although BCG intravesical instillation has been proved to be more effective than conventional chemotherapy instillation, there are still treatment failures and strongly related toxicity problems, especially cystitis and systemic BCG infection, which limit its general clinical application [36, 37]. Especially for patients who have failed BCG treatment, HIVEC is a recommended mode that maintains high safety while achieving good efficacy [38, 39]. Moreover, there is no need to consider the shortage of BCG supply, as it is more suitable for clinical expansion [40]. We recommend the expanded application of HIVEC in clinical practice. However, the efficacy and safety of instillation therapy also depended on a variety of other factors, such as the dose and concentration of the drug and the duration of instillation maintenance [43, 44]. Through screening and quality assessment, the ten RCTs we included were all well-controlled for these confounding factors. The treatment dose of infusion chemotherapy drug MMC is 20–60 mg/time, soluble in normal saline to ensure the concentration is 1-2 mg/ml then once a week for 6 times. Following that,once every 6 weeks for a total of 6 times. BCG instillation dose is 120 mg/time, dissolved in 50 ml normal saline and retained for 2 hours for the first time. Started with once a week infusion for 6 times. Then once every 2 weeks for a total of 3 times. Following that, once a month until 1 year. The control temperature of hyperthermia is at $42 \pm 2^{\circ}C$. Other confounding factors such as individual patient differences, surgical operation for TURBT, and patient's postoperative lifestyle should also be taken into account simultaneously. To reduce the influence of confounding factors by expanding the sample size, a total of 1360 participants, 614 in the experimental group and 746 in the control group, were included in this study after screening.

The equipment model also affects the evaluation of the results. Among the ten RCTs we included, 7 of them used "The Combat Blade Recirculating System (BRS)" [18, 20, 21, 23, 24, 45], 2 of them used the "BR-TRG-I type high precision hyperthermic intrauterine fusion treatment system (Guangzhou Bright Medical Technology Co., Ltd. Guangzhou, China)" [12, 22], and 1 of them used the "Unithermia system (Elmedical, Hod Hasharon, Israel)" [19]. These three devices all follow the principle of heating and recirculation, heating the drug to reach the target temperature externally and then performing the instillation circulation at a constant rate [46, 47]. Restricting this condition controls the selection bias. In addition to this pattern, there are many other methods for bladder hyperthermia instillation: radiofrequency-induced thermochemotherapy effect (RITE), electromotive drug administration (EMDA), etc. [48, 49]. These methods work according to different principles and are promising tools.

Compared with the previous research on this topic, our study added the studies of intravesical immune therapy (BCG), complemented by depicting a subgroup comparison of the efficacy and safety of HIVEC versus BCG instillation after TURBT. In addition, to reduce confounding bias, the studies we included were all RCTs. We also expanded the sample size to increase credibility and clinical practicability. Meanwhile, there are some limitations that need to be considered in our study. The quality of the included studies was heterogeneous: (1) different randomization processes and blinding methods were used; (2) to improve the clinical application guidance, further evaluation for other intravesical hyperthermia methods is still needed. EMDA and RITE belong to deep thermotherapy, which uses physical energy to produce thermal effects in local tissues, heating tumor tissues for immediate metabolic reactions and killing tumor cells [48, 50–52]. However, they cause local bladder mucosal burns and cauterization, and the possibility of postoperative secondary infection and bladder stress is increased. HIVEC is a thermostatic instillation of drugs, which focuses on the heat brought by the drugs [47, 53]. Considering that different principles of heat generation bring about different efficacy and adverse reactions, this paper selects the therapy of heating followed by instillation as the inclusion criterion.

## 5. Conclusion

Our study analyzed the role of HIVEC in patients with intermediate- and high-risk NMIBC. Compared with traditional methods of immunotherapy and chemotherapy,

HIVEC has both effective and tolerable advantages. We recommend expanding the clinical application of HIVEC. At the same time, we also need more long-term clinical research studies.

## Disclosure

No direct or indirect commercial incentive is associated with publishing this article.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Jitao Wu was responsible for conceptualization. Yingying Yang, Hongquan Liu, and Yongli Chu were responsible for data curation and resources. Yingying Yang and Hongquan Liu were responsible for formal analysis, original draft preparation, and software. Jitao Wu and Yuanshan Cui were responsible for funding acquisition and review and editing. Yingying Yang, Jipeng Wang, and Jian Ma were responsible for investigation. Yingying Yang, Guixin Ding, and Xingjun Bao were responsible for methodology. Yuanshan Cui was responsible for project administration. Yongli Chu and Jitao Wu were responsible for supervision. Yingying Yang and Hongquan Liu are the co-first authors.

## Acknowledgments

This work was supported by the National Natural Science Foundation of China (nos. 82370690 and 82303813), Shandong Science and Technology Program (nos. ZR2023MH241 and ZR2023QH271), Joint Fund of Shandong Natural Science Foundation (ZR2021LSW019) Taishan Scholars Program of Shandong Province (nos. tsqn201909199 and tsqn202306403).

## References

[1] Z. Kirkali, T. Chan, M. Manoharan et al., "- bladder cancer: epidemiology, staging and grading, and diagnosis," *Urology*, vol. 66, no. 6, pp. 4–34, 2005.

[2] R. Jj and F. P. Secin, "Epidemiology, etiology and prevention of bladder cancer," *Archivos Españoles de Urología*, vol. 73, no. 10, pp. 872–878, 2020.

[3] B.. Sk, "Bladder cancer survivorship," *Current Urology Reports*, vol. 19, no. 12, pp. 018–0860, 2018.

[4] J. Dobruch and M. Oszczudłowski, "- bladder cancer: current challenges and future directions," *Medicina*, vol. 57, no. 8, p. 749, 2021.

[5] K. B. Farling, "Bladder cancer: risk factors, diagnosis, and management," *The Nurse Practitioner*, vol. 42, no. 3, pp. 26–33, 2017.

[6] W. Oosterlinck, K. Decaestecker, and X. Id- Orcid, "Update on early instillation of chemotherapy after transurethral resection of non-muscle-invasive bladder cancer," *Expert Review of Anticancer Therapy*, vol. 18, no. 5, pp. 437–443, 2018.

[7] R. L. Steinberg, L. J. Thomas, and M. A. O' Donnell, "Combination intravesical chemotherapy for non-muscle-invasive bladder cancer," *European Urology Focus*, vol. 4, no. 4, pp. 503–505, 2018.

[8] F. Boccardo and L. Palmeri, "Adjuvant chemotherapy of bladder cancer," *Annals of Oncology*, vol. 129, p. 17, 2006.

[9] A. Sousa Escandón, J. León Mata, D. Sousa González, M. Alvarez Casal, S. Rodríguez, and S. Piñeiro Vazquez, "Neoadjuvant Chemohyperthermia: our experience after 10 years," *Archivos Españoles de Urología*, vol. 71, no. 4, pp. 438–446, 2018.

[10] F. Soria, M. Allasia, M. Oderda, and P. Gontero, "Hyperthermia for non-muscle invasive bladder cancer," *Expert Review of Anticancer Therapy*, vol. 16, no. 3, pp. 313–321, 2016.

[11] K. Hendricksen, "Device-assisted intravesical therapy for non-muscle invasive bladder cancer," *Translational Andrology and Urology*, vol. 8, no. 1, pp. 94–100, 2019.

[12] M. Ba, S. Cui, B. Wang et al., "Bladder intracavitary hyperthermic perfusion chemotherapy for the prevention of recurrence of non-muscle invasive bladder cancer after transurethral resection," *Oncology Reports*, vol. 37, no. 5, pp. 2761–2770, 2017.

[13] O. Ra, M. R. Abern, and B. A. Inman, "- hyperthermia as adjunct to intravesical chemotherapy for bladder cancer," *BioMed Research International*, vol. 262313, no. 10, p. 1, 2013.

[14] R. En, Z. Vujaskovic, and B. A. Inman, "Hyperthermia as a treatment for bladder cancer," *Oncology*, vol. 24, no. 12, pp. 1149–1155, 2010.

[15] J. W. Snider 3rd, N. R. Datta, and Z. Vujaskovic, "Hyperthermia and radiotherapy in bladder cancer," *International Journal of Hyperthermia*, vol. 32, no. 4, pp. 398–406, 2016.

[16] M. Assel, D. Sjoberg, A. Elders et al., "Guidelines for reporting of Statistics for clinical research in Urology," *The Journal of Urology*, vol. 201, no. 3, pp. 595–604, 2019.

[17] J. Higgins, S. G. Thompson, J. J. Deeks, and D. G. Altman, "Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane collaboration," *Naunyn-schmiedebergs Archiv für Experimentelle Pathologie und Pharmakologie*, vol. 5, no. 2, p. S38, 2008.

[18] J. C. Angulo, J. L. Álvarez-Ossorio, J. L. Domínguez-Escrig et al., "Hyperthermic mitomycin C in intermediate-risk non-muscle-invasive bladder cancer: results of the hivec-1 trial," *European Urology Oncology*, vol. 6, no. 1, pp. 58–66, 2023.

[19] R. G. Ekin, I. Akarken, F. Zorlu et al., "Intravesical Bacillus calmette-guerin versus Chemohyperthermia for high-risk non-muscle-invasive bladder cancer," *Canadian Urological Association Journal*, vol. 9, no. 5-6, pp. E278–E283, 2015.

[20] D. A. Gonzalez-Padilla, A. Gonzalez-Diaz, F. Guerrero-Ramos et al., "Quality of life and adverse events in patients with nonmuscle invasive bladder cancer receiving adjuvant treatment with bcg, mmc, or Chemohyperthermia," *Urologic Oncology: Seminars and Original Investigations*, vol. 39, no. 1, pp. 76 e9–e76 e14, 2021.

[21] F. Guerrero-Ramos, D. A. Gonzalez-Padilla, A. Gonzalez-Diaz et al., "Recirculating hyperthermic intravesical chemotherapy with mitomycin C (hivec) versus bcg in high-risk non-muscle-invasive bladder cancer: results of the hivec-hr randomized clinical trial," *World Journal of Urology*, vol. 40, no. 4, pp. 999–1004, 2022.

[22] Q. Ruan, D. Ding, B. Wang et al., "A multi-institutional retrospective study of hyperthermic plus intravesical chemotherapy versus intravesical chemotherapy treatment alone in intermediate and high risk nonmuscle-invasive bladder cancer," *Cancer Biol Med*, vol. 18, no. 1, pp. 308–317, 2021.

[23] W. S. Tan, A. Prendergast, C. Ackerman et al., "Adjuvant intravesical Chemohyperthermia versus passive

chemotherapy in patients with intermediate-risk non-muscle-invasive bladder cancer (Hivec-Ii): a phase 2, open-label, randomised controlled trial," *European Urology*, vol. 83, no. 6, pp. 497–504, 2023.

[24] Y. B. Thyavihally, S. S. Waigankar, P. Dev et al., "Comparing adverse effects, short term outcomes, and cost implications of hyperthermic intravesical chemotherapy with mitomycin-C and intravesical Bacillus calmette-guerin instillation (moscow-I strain) in the management of intermediate and high-risk nonmuscle invasive bladder cancer," *Urology Annals*, vol. 13, no. 4, pp. 424–430, 2021.

[25] K. Guleria, R. Sood, H. Goel, U. Sharma, and A. Singla, "PD26-04 A randomized study to compare outcomes of intravesical chemohyperthermia with mitomycin C vs intravesical BCG for intermediate and high risk NON-muscle invasive bladder cancer (NMIBC)," *The Journal of Urology*, vol. 207, no. Supplement 5, Article ID e488, 2022.

[26] A. Freites-Martinez, N. Santana, S. Arias-Santiago, and A. Viera, "Using the common Terminology criteria for adverse events (ctcae- version 5.0) to evaluate the severity of adverse events of anticancer therapies," *Actas Dermo-Sifiliográficas*, vol. 112, no. 1, pp. 90–92, 2021.

[27] D. Oswald, M. Pallauf, T. R. W. Herrmann et al., "- [transurethral resection of bladder tumors (turbt)]," *Urologe Ausgabe A*, vol. 61, no. 1, pp. 71–82, 2022.

[28] L. Martínez-Piñeiro, "Checklist for transurethral resection of bladder tumor (TURBT): a step forward in the standardization for TURBT reporting," *European Urology Open Science*, vol. 48, pp. 22-23, 2023.

[29] B. V, Id Orcid, and S. Hoshi, "Prostatic urethra recurrence after transurethral resection of bladder tumor," *Clinical Case Reports*, vol. 10, no. 1, 2022.

[30] M. Babjuk, M. Burger, R. Zigeuner et al., "Eau guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update," *European Urology*, vol. 64, no. 4, pp. 639–653, 2013.

[31] M. Babjuk, M. Burger, O. Capoun et al., "European association of Urology guidelines on non–muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ)," *European Urology*, vol. 81, no. 1, pp. 75–94, 2022.

[32] B. Ucpinar, A. Erbin, A. Ayranci et al., "Prediction of recurrence in non-muscle invasive bladder cancer patients. Do patient characteristics matter?" *J buon*, vol. 24, no. 4, pp. 1659–1665, 2019.

[33] Y. Waseda, S. Kobayashi, E. Kanda et al., "Impact of bladder neck involvement on recurrence in patients with non-muscle-invasive bladder cancer: an analysis based on a time-dependent model," *Clinical Genitourinary Cancer*, vol. 18, no. 2, pp. e62–e70, 2020.

[34] H. H. Kampinga, "Cell biological effects of hyperthermia alone or combined with radiation or drugs: a short introduction to newcomers in the field," *International Journal of Hyperthermia*, vol. 22, no. 3, pp. 191–196, 2006.

[35] C. W. Song, J. G. Rhee, and S. H. Levitt, "- blood flow in normal tissues and tumors during hyperthermia," *Journal of the National Cancer Institute*, vol. 64, no. 1, pp. 119–124, 1980.

[36] B. Emami and C. W. Song, "Physiological mechanisms in hyperthermia: a review," ***Physics*, vol. 10, no. 2, pp. 289–295, 1984.

[37] C. W. Song, M. S. Kang, J. G. Rhee, and S. H. Levitt, "- the effect of hyperthermia on vascular function, ph, and cell survival," *Radiology*, vol. 137, no. 3, pp. 795–803, 1980.

[38] J. Zhang, M. Li, Z. Chen, J. OuYang, Z. Ling, and X. Id- Orcid, "Efficacy of bladder intravesical chemotherapy with three drugs for preventing," *Journal of Healthcare Engineering*, vol. 30, Article ID 2360717, 2021.

[39] J. Han, X. Gu, Y. Li, and Q. Wu, "Mechanisms of BCG in the treatment of bladder cancer-current understanding and the prospect," *Biomedicine and Pharmacotherapy*, vol. 129, Article ID 110393, 2020.

[40] M. Vasekar, D. Degraff, and M. Joshi, "Immunotherapy in bladder cancer," *Current Molecular Pharmacology*, vol. 9, no. 3, pp. 242–251, 2016.

[41] Y. Fujii, "Prediction models for progression of non-muscle-invasive bladder cancer: a review," *International Journal of Urology*, vol. 25, no. 3, pp. 212–218, 2018.

[42] D. Lamm, R. Persad, M. Brausi et al., "Defining progression in nonmuscle invasive bladder cancer: it is time for a new, standard definition," *The Journal of Urology*, vol. 191, no. 1, pp. 20–27, 2014.

[43] R. Carando, B. Pradere, L. Afferi et al., "The role of device-assisted therapies in the management of non-muscle invasive bladder cancer: a systematic review," *Progrès en Urologie*, vol. 30, no. 6, pp. 322–331, 2020.

[44] W. S. Tan and J. D. Kelly, "Intravesical device-assisted therapies for non-muscle-invasive bladder cancer," *Nature Reviews Urology*, vol. 15, no. 11, pp. 667–685, 2018.

[45] K. Guleria, R. Sood, H. Goel, U. Sharma, and A. Singla, "PD26-04 A randomized study to compare outcomes of intravesical chemohyperthermia with mitomycin C vs intravesical BCG for intermediate and high risk NON-muscle invasive bladder cancer (NMIBC)," *The Journal of Urology*, vol. 207, no. Supplement 5, Article ID e488, 2022.

[46] M. A. Arrabal Polo, M. T. Melgarejo Segura, Y. Yanez Castillo, A. Morales Martinez, M. Pareja Vilchez, and M. Arrabal Martin, "Adjuvant intravesical treatment in patients with intermediate and high-risk non-muscle-invasive bladder cancer with bcg versus mmc applied with Combat or emda. Results of a prospective study," *Journal of Cancer Research and Clinical Oncology*, vol. 149, no. 10, pp. 7453–7459, 2023.

[47] A. Sousa, I. Piñeiro, S. Rodríguez et al., "Recirculant hyperthermic intravesical chemotherapy (hivec) in intermediate-high-risk non-muscle-invasive bladder cancer," *International Journal of Hyperthermia*, vol. 32, no. 4, pp. 374–380, 2016.

[48] R. Colombo, H. van Valenberg, M. Moschini, and J. A. Witjes, "Radiofrequency-induced thermo-chemotherapy effect (rite) for non muscle invasive bladder cancer treatment: current role and perspectives," *Urologia*, vol. 83, no. 2_suppl, pp. 7–17, 2016.

[49] R. R. Weichselbaum, H. Liang, L. Deng, and Y. X. Fu, "Radiotherapy and immunotherapy: a beneficial liaison?" *Nature Reviews Clinical Oncology*, vol. 14, no. 6, pp. 365–379, 2017.

[50] F. Pierconti, P. Straccia, S. Emilio et al., "Cytological and histological changes in the urothelium produced by electromotive drug administration (emda) and by the combination of intravescical hyperthermia and chemotherapy (thermochemotherapy)," *Pathology, Research and Practice*, vol. 213, no. 9, pp. 1078–1081, 2017.

[51] M. Racioppi, L. Di Gianfrancesco, M. Ragonese, G. Palermo, E. Sacco, and P. F. Bassi, "Electromotive drug administration (emda) of mitomycin C as first-line salvage therapy in high risk bcg failure non muscle invasive bladder cancer: 3 Years follow-up outcomes," *BMC Cancer*, vol. 18, no. 1, p. 1224, 2018.

[52] M. Zazzara, A. Nazaraj, M. Scarcia, G. Cardo, R. Carando, and G. M. Ludovico, "Electromotive drug administration of mitomycin C (Emda/Mmc) versus intravesical immunotherapy with Bacillus calmette-guérin (bcg) in intermediate and high risk non muscle invasive bladder cancer," *Urologia Internationalis*, vol. 107, no. 1, pp. 64–71, 2023.

[53] L. Doisy, A. Cimier, A. Adypagavane et al., "Efficacy of hivec in patients with high-risk non-muscle invasive bladder cancer who are contraindicated to bcg and in patients who fail bcg therapy," *International Journal of Hyperthermia*, vol. 38, no. 1, pp. 1633–1638, 2021.