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ORIGINAL PAPER

Hyperthermic *vs* normothermic mitomycin C for intermediate-risk NMIBC: A real-world retrospective cohort study

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Summary

Introduction: *Hyperthermic intravesical chemotherapy (HIVEC) with mitomycin C (MMC) is an emerging strategy in the management of intermediate-risk non-muscle-invasive bladder cancer (IR-NMIBC). By combining chemotherapy with controlled hyperthermia (43°C), this approach aims to enhance drug absorption, increase cytotoxicity, and stimulate immune activation, potentially improving efficacy compared to standard MMC. The aim of this study was to compare oncologic efficacy, adverse effects, and safety between HIVEC and standard normothermic MMC in patients with IR-NMIBC.*

Patients and methods: *We conducted a retrospective cohort study including 76 patients with IR-NMIBC treated between January 2020 and December 2023. Patients received HIVEC (n = 36) or standard MMC (n = 40) following complete transurethral resection of bladder tumor (TURBT). The instillation schedule consisted of four weekly induction instillations followed by three monthly maintenance instillations. The primary endpoint was recurrence-free survival (RFS); secondary endpoints included progression-free survival (PFS), adverse events (AEs), and treatment compliance.*

Results: *A total of 76 patients were included: 36 received HIVEC and 40 received standard MMC. Baseline characteristics were balanced across groups, with a median age of 68 years and 86.8% male. Most tumors were unifocal (85.5%), stage pTa (88.2%), and low-grade (61.8%). At a median follow-up of 36 months (IQR 24-36), recurrence occurred in 38.9% of HIVEC patients versus 30.0% in the MMC group. Median time to recurrence was longer with HIVEC (15.0 vs 10.5 months). The 24-months recurrence-free survival was 62.2% for HIVEC and 69.4% for MMC (p = 0.365). Progression to muscle-invasive disease occurred in one MMC patient (2.5%); none progressed in the HIVEC arm (PFS at 24 months: 100% vs 97.5%, p = 0.343). Compliance was high in both arms (HIVEC 88.9%, MMC 87.5%). Adverse events were mild (grade 1-2) and evenly distributed; no grade ≥ 3 events were observed. Treatment discontinuation due to toxicity occurred in 13% of HIVEC and 7% of MMC patients (p = 0.47).*

Conclusions: *HIVEC with MMC demonstrated comparable oncologic outcomes to normothermic MMC in IR-NMIBC, with a longer time to recurrence and similar tolerability. These findings suggest its potential use in selected patients, but should be interpreted with caution due to the retrospective design and limited sample size. Prospective studies are needed to confirm these results.*

KEY WORDS: *Urinary bladder neoplasms; Mitomycin; Hyperthermia, Induced; Administration, Intravesical; Treatment outcome.*

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INTRODUCTION

Bladder cancer is the ninth most commonly diagnosed malignancy globally, with over 600,000 new cases reported in 2022, and remains an important source of morbidity and healthcare burden (1).

Urothelial carcinoma is the predominant histological subtype, accounting for over 90% of cases in Western countries. At diagnosis, approximately 75% of patients present with *non-muscle-invasive bladder cancer* (NMIBC), which, despite its lower cancer specific mortality compared to muscle-invasive disease, poses significant clinical challenges due to its high recurrence rates and the need for long-term surveillance and treatment (2, 3).

Intermediate-risk NMIBC (IR-NMIBC) comprises a heterogeneous group of tumors, including recurrent or multifocal low-grade tumors, large solitary tumors (> 3 cm), and some T1 lesions with limited risk factors (4, 5). In this group, adjuvant therapy following *transurethral resection of bladder tumor* (TURBT) is recommended to reduce recurrence and progression rates (2).

MMC is one of the most widely used agents in this setting. Multiple instillations have demonstrated efficacy in reducing recurrence and are recommended by guidelines as an adjuvant treatment. (6) Although *Bacillus Calmette-Guérin* (BCG) may be used in selected cases, its broader use is limited by toxicity and persistent supply issues, highlighting the need for alternatives (7, 8).

Hyperthermic intravesical chemotherapy (HIVEC) has emerged as a promising alternative. This approach involves the delivery of MMC heated up to 43°C, enhancing cytotoxicity through multiple mechanisms: increased urothelial permeability, inhibition of DNA repair, improved tissue

penetration, and immunomodulation. At elevated temperatures, *heat shock proteins* (HSPs) are released from cancer cells, triggering activation of dendritic cells, cytotoxic T lymphocytes, and *natural killer* (NK) cells, further potentiating the antitumor immune response. Additionally, hyperthermia improves MMC solubility at therapeutic concentrations, overcoming a known limitation (9, 10).

Recirculating systems such as the *COMBined Antineoplastic Thermotherapy* (COMBAT) BRS system offers a controlled intravesical heating and drug delivery. Randomized trials including HIVEC-1 and HIVEC-II have compared HIVEC to standard normothermic MMC. These studies suggest that hyperthermic MMC offers comparable oncologic outcomes, with acceptable tolerability (11, 12).

Our study aimed to compare the oncological outcomes, adverse effects, and treatment adherence of HIVEC versus standard MMC in patients with IR-NMIBC.

Patients and methods

A retrospective cohort study was conducted between January 2020 and December 2023 to compare HIVEC with standard intravesical MMC in the adjuvant treatment of IR-NMIBC, as defined by the *European Association of Urology* (EAU) risk stratification. The study adhered to Good Clinical Practice guidelines, the 2007 Declaration of Helsinki, and applicable local regulations.

Patient selection

We included patients with IR-NMIBC as defined by the EAU risk stratification, using either the *World Health Organization* (WHO) 1973 or the 2004 WHO/*International Society of Urological Pathology* (ISUP) urothelial carcinoma grading systems. Visually complete TURBT was required before treatment.

Patients were classified as intermediate-risk according to the EAU Guidelines, which define this group as patients without *carcinoma in situ* (CIS) who do not meet the criteria for low-, high-, or very high-risk categories. Specifically, high-grade Ta tumours were included when unifocal, < 3 cm, and without CIS or additional high-risk features, as they do not fulfil the requirements for high- or very high-risk classification. No patients with CIS, variant histology, upper tract or urethral involvement, or prior muscle-invasive disease were included.

Treatment allocation was determined through multidisciplinary team discussion, primarily based on institutional availability of the HIVEC system and patient preference. Both treatment arms were considered acceptable options within the intermediate-risk setting. No formal clinical algorithm was used to guide assignment, reflecting real-world decision-making in the absence of strict recommendations or head-to-head comparative evidence.

Treatment schedules

Patients received either standard MMC (40 mg in 50 mL at room temperature) or hyperthermic MMC via the COMBAT BRS system (*Combat Medical, Wheathampstead, UK*). HIVEC was administered at a target temperature of 43°C (±1°C) with continuous recirculation through a three-way Foley catheter.

Treatment assignment was determined following discussion in a multidisciplinary team meeting. All patients followed the same instillation schedule: four weekly instillations (induction) followed by six monthly instillations (maintenance), with treatment initiated between 8 and 12 weeks after TURBT.

Follow-up and treatment evaluation

Patients were followed every 3 months during the first two years. Flexible cystoscopy and urine cytology were performed at every visit. Upper tract imaging was performed at baseline and thereafter only if clinically indicated.

Efficacy endpoints

The primary endpoint was *recurrence-free survival* (RFS), defined as the time from TURBT to histologically confirmed bladder tumor recurrence. Secondary endpoints included *progression-free survival* (PFS), defined as time from TURBT to progression to muscle-invasive disease (≥ T2).

Safety analysis

Adverse events (AEs) were assessed at each instillation and follow-up visit. *Serious adverse events* (SAEs) were defined as any event resulting in death, life-threatening complications, hospitalization, or permanent disability. AE severity was graded according to the *Common Terminology Criteria for Adverse Events* (CTCAE v4.0), ranging from grade 1 (mild) to grade 5 (death).

Statistical analysis

Continuous variables were tested for normality using the Shapiro-Wilk test. Non-normally distributed variables were compared using the Mann-Whitney U test. Categorical variables were compared using the Chi-square test or Fisher's exact test as appropriate.

Recurrence-free survival (RFS) and *progression-free survival* (PFS) were estimated using the Kaplan-Meier method and compared using the log-rank test. A p-value of < 0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 25 (*IBM Corp., Armonk, NY, USA*).

Results

Baseline characteristics

Seventy-six patients with IR-NMIBC were included in the study. Of these, 36 received HIVEC with mitomycin C and 40 were treated with standard normothermic MMC. Baseline demographic and tumor characteristics were comparable between groups (Table 1). The median age was 68 years (*interquartile range* [IQR] 60-75.75), and the majority were male (86.8%). Most tumors were unifocal (85.5%) and classified as stage pTa (88.2%). Regarding grade, 90.8% of tumors were classified as G2. When grouped according to WHO classification, 61.8% were low-grade and 38.2% high-grade. Tumor size was less than 3 cm in 69.7% of patients. A primary diagnosis was present in 61.8% of cases, while 38.2% were recurrent tumors. No statistically significant differences were observed between groups for any of the baseline variables (all $p > 0.05$).

Table 1.
Baseline clinical and demographic characteristics by treatment group.

	HIVEC	Normo MMC	p-value
Age, median (IQR)	63.5 (56.0-76.0)	69.5 (61.0-75.0)	0.122
Sex, n (%)			0.391
· Male	30 (83.3%)	36 (90.0%)	
· Female	6 (16.7%)	4 (10.0%)	
Stage, n (%)			0.728
· pTa	31 (86.1%)	36 (90.0%)	
· pT1	5 (13.9%)	4 (10.0%)	
Grade (1973), n (%)			0.271
· G1	5 (13.9%)	2 (5.0%)	
· G2	31 (86.1%)	38 (95.0%)	
Grade (2004), n (%)			0.284
· Low Grade	20 (55.6%)	27 (67.5%)	
· High Grade	16 (44.4%)	13 (32.5%)	
Focality, n (%)			0.891
· Unifocal	31 (86.1%)	34 (85.0%)	
· Multifocal	5 (13.9%)	6 (15.0%)	
Size, n (%)			0.120
· < 3 cm	22 (61.1%)	21 (52.5%)	
· ≥ 3 cm	14 (38.9%)	19 (47.5%)	
Primary/Recurrent, n (%)			0.077
· Primary	26 (72.2%)	21 (52.5%)	
· Recurrent	10 (27.8%)	19 (47.5%)	
Immediate postoperative MMC, n (%)			0.858
· Yes	31 (86.1%)	35 (87.5%)	
· No	5 (13.9%)	5 (12.5%)	
ECOG, n (%)			0.774
· 0	30 (83.3%)	32 (80.0%)	
· 1	6 (16.7%)	8 (20.0%)	

Oncologic outcomes

Follow-up
The median follow-up for the entire cohort was 36 months (IQR 24-36). Patients in the HIVEC group had a median follow-up of 28 months (IQR 24-36), compared to 36 months (IQR 30-42) in the MMC group.

Recurrence-free survival
Twenty-six patients (34.2%) experienced tumor recurrence during follow-up: 14 in the HIVEC group (38.9%) and 12 in the MMC group (30.0%). While recurrence occurred more frequently in the HIVEC group, the median time to recurrence was longer: 15.0 months (IQR 12.0-18.0) *versus* 10.5 months (IQR 6.0-17.25) in the MMC group. These differences were not statistically significant.
The estimated recurrence-free survival (RFS) at 12 months was 80.6% (95% CI, 64.0-90.4) in the HIVEC group and 82.5% (95% CI, 67.2-91.6) in the MMC group. At 24 months, RFS was 62.2% (95%, CI 44.2-76.6) and 69.4% (95%, CI 53.1-81.9), respectively. Kaplan-Meier analysis revealed no significant difference in RFS between the two groups (log-rank p = 0.365) (Figure 1).

Figure 1.
Recurrence Free Survival by treatment group.

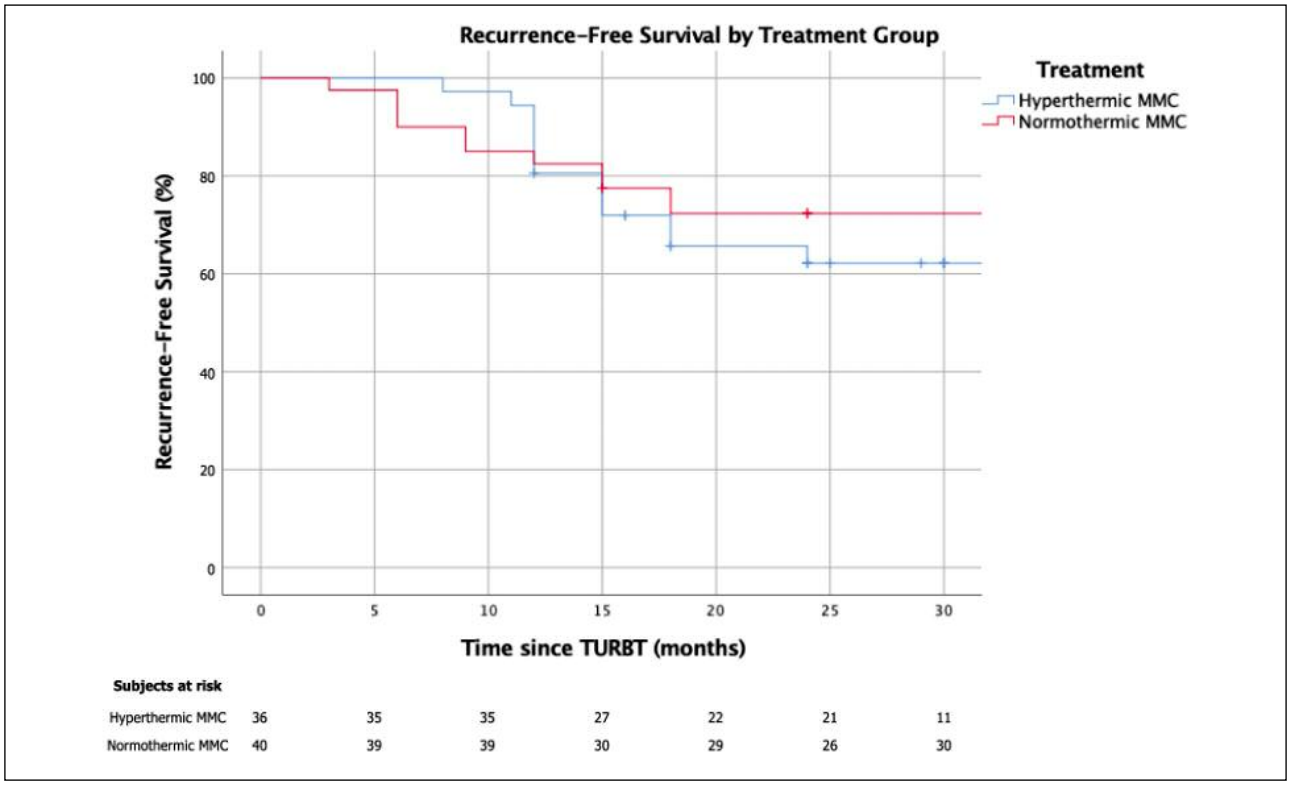
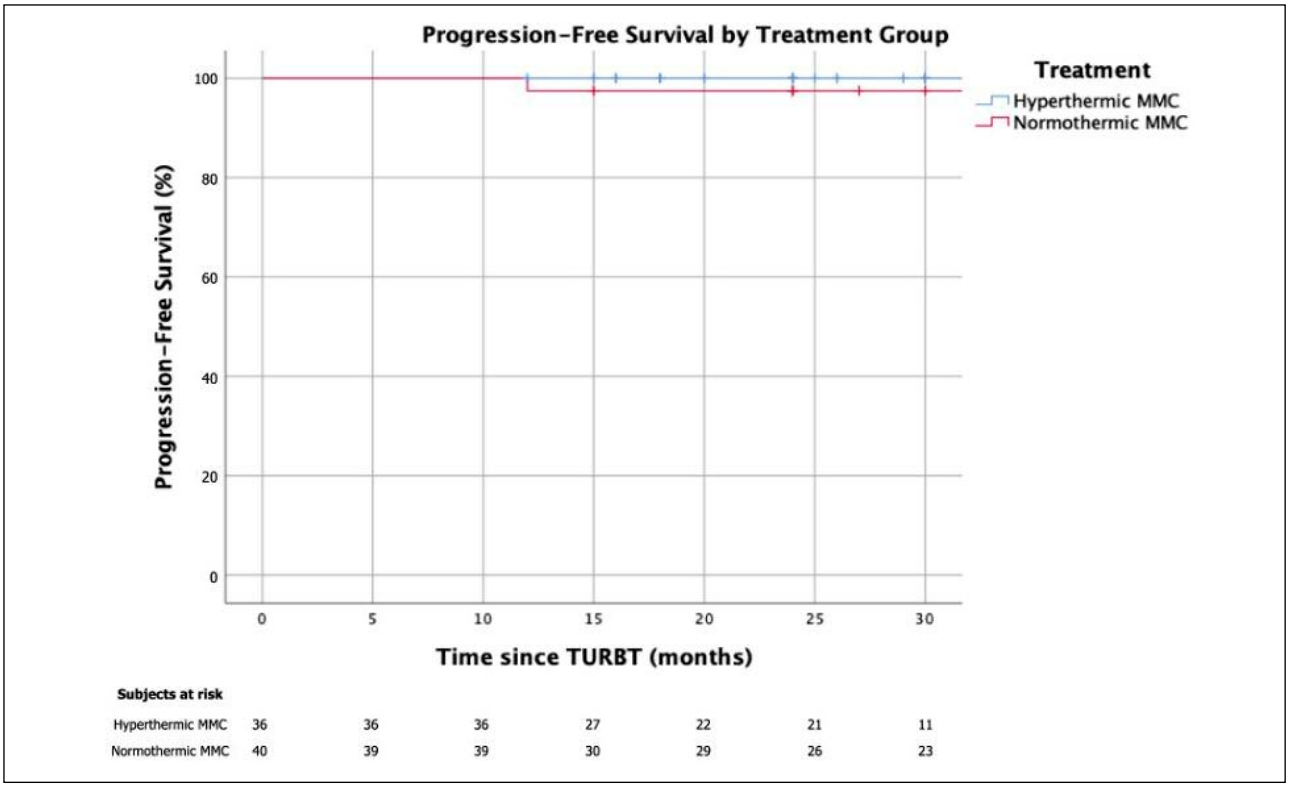


Figure 2.
Progression Free Survival by treatment group.



Progression-free Survival
Progression to muscle-invasive disease occurred in one patient (1.3%) in the MMC group. No cases of progression were observed in the HIVEC group. At 24 months, progression-free survival (PFS) was 100% in the HIVEC group and 97.5% in the MMC group (log-rank p = 0.343) (Figure 2).

Treatment compliance and safety

Treatment compliance
Compliance with treatment was high in both groups. In the HIVEC group, 32 out of 36 patients (88.9%) completed at least four of the seven planned instillations, compared to 35 out of 40 patients (87.5%) in the MMC group (p = 0.867). The median number of instillations completed was 7 (IQR 6-7) in both groups.

Adverse events
A total of 18 patients in each group experienced at least one adverse event (HIVEC 50.0%, MMC 45.0%; p = 0.82). No grade ≥ 3 adverse events were reported in either group. In the HIVEC group the most common adverse events were dysuria (19.4%), bladder spasms (13.9%), hematuria (11.1%), and urinary tract infection (8.3%). Less frequent events included urgency/frequency (5.6%) and fever (5.6%).
In the MMC group, dysuria was also the most frequently reported symptom (20.0%), followed by urgency/frequency (7.5%), bladder spasms (7.5%), hematuria (5.0%), and urinary tract infection (5.0%). There were no statistically significant differences in the incidence of individual adverse events between groups.
Treatment discontinuation due to adverse events occurred in 13% of patients of the HIVEC group and 7% in the MMC group (p = 0.47) (Table 2).

Discussion

Hyperthermic intravesical chemotherapy (HIVEC) with *mitomycin C* (MMC) is an increasingly explored adjuvant treatment for patients with IR-NMIBC. The rationale for com-

Table 2.
Distribution of adverse effects according to treatment group.

Adverse efects	HIVEC (36)	Normo MMC (40)	p-value
Any AE, n (%)	18 (50%)	18 (45%)	0.82
Grade ≥ 3 AE, n (%)	0 (0%)	0 (0%)	1.00
Bladder spasms, n (%)	5 (13.9%)	3 (7.5%)	0.47
Urinary frequency/urgency, n (%)	2 (5.6%)	3 (7.5%)	1.00
Dysuria, n (%)	7 (19.4%)	8 (20.0%)	1.00
Hematuria, n (%)	4 (11.1%)	2 (5.0%)	0.41
Fever, n (%)	2 (5.6%)	0 (0%)	0.22
Rash, n (%)	1 (2.8%)	2 (5.0%)	1.00
Urinary tract infection, n (%)	3 (8.3%)	1 (2.5%)	0.34
Treatment discontinuation, n (%)	5 (13.9%)	3 (7.5%)	0.47

bining chemotherapy with thermal energy lies in enhanced urothelial permeability, increased cytotoxicity, and stimulation of immunogenic mechanisms such as heat shock protein release and local immune activation (13).

In our cohort, HIVEC demonstrated comparable oncologic outcomes to standard MMC. While recurrences were more frequent with HIVEC, the longer median time to recurrence may point to a delayed tumor regrowth. These findings are in line with the HIVEC-II trial, which reported no significant difference in 24-month disease-free survival between HIVEC and MMC (61% *vs* 60%) and the HIVEC-I trial, which found similar recurrence-free survival across different hyperthermia durations (11, 12). A recent systematic review by *Ghodoussipour et al.* reinforced these observations, reporting similar 2-year recurrence-free survival across randomized trials and no significant differences in safety or patient-reported outcomes (14).

However, considering the biological rationale behind hyperthermia, it is somewhat surprising that we did not find a clear clinical benefit. We expected a more favorable outcome with HIVEC, particularly in improving recurrence-free survival. This raises an important question: should HIVEC be routinely recommended in the adjuvant setting in IR-NMIBC, or is its best reserved for selected clinical scenarios?

From a safety perspective, our findings reinforce the favourable tolerability of HIVEC. No grade ≥ 3 adverse events were observed, and most patients reported only mild lower urinary tract symptoms. These findings mirror multicenter real-world experiences, including the Spanish cohort by *Plata et al.* and the HIVEC-HR randomized trial, both of which demonstrated acceptable tolerability and low rates of severe adverse events in patients treated with HIVEC (15, 16).

Nonetheless, these comparable outcomes and tolerability must be weighed against the additional complexity and cost of HIVEC compared to standard MMC. While both regimens demonstrated similar efficacy and safety in our cohort, HIVEC involves specialized equipment, longer instillation durations, and greater resource allocation. Its cost – estimated at nearly €2,000 for an induction cycle – far exceeds that of standard MMC, which is simpler to administer and more widely available (9, 17).

Although our study did not include BCG-treated patients, the relevance of HIVEC as an alternative therapy has grown in recent years, particularly in the context of BCG shortage. *Fankhauser et al.* suggests the use chemohyperthemia or electromotive drug administration in case of complete absence of BCG (8). Supporting this position, a randomized trial by *Arends et al.* reported non-inferiority of HIVEC compared to BCG in terms of recurrence-free survival, with fewer adverse events in the HIVEC group (18).

Beyond clinical efficacy, hyperthermia may exert antitumor effects at the molecular level, such as downregulation of Ki-67 and activation of immune pathways (9). We did not assess tumor biology directly, but the longer time to recurrence with HIVEC might reflect some of these mechanisms. However, future studies integrating translational endpoints are needed to validate this hypothesis.

Treatment protocols for HIVEC remain heterogeneous across the literature. In our study, patients received an induction course of one weekly HIVEC instillation for four consecutive weeks, followed by a maintenance phase consisting of one monthly instillation for six months. A systematic review of randomized trials suggests that more prolonged treatment schedules with standard MMC may improve efficacy but may also increase toxicity (6). Standardization of HIVEC protocols is essential to enable comparisons and optimize possible therapeutic benefit.

Another evolving domain is the role of molecular biomarkers in NMIBC management. Mutations in FGFR3 and TERT promoter are frequent in intermediate-risk tumors and have been linked to recurrence risk. Likewise, immune markers such as PD-L1 expression may influence response to intravesical therapy. Incorporating such biomarkers into future HIVEC trials could enable personalized treatment strategies, guiding intensity and duration of therapy (19).

Our study has several limitations. As a retrospective analysis with a small sample, there is an inherent risk of selection bias – particularly because treatment allocation was not randomized but based on multidisciplinary team decision. We did not perform a predefined sample size calculation, and the shorter follow-up in the HIVEC group may have influenced recurrence estimates. Although likely sufficient to capture early recurrences, it may not reflect longer-term outcomes. The absence of patient-reported outcomes also limits assessment of tolerability, and as a single-centre study, generalizability may be limited.

In contrast, prospective randomized trials such as HIVEC-II included predefined power calculations to detect meaningful differences (12). Similarly, the study by *Arends et al.*, which enrolled both intermediate- and high-risk patients, incorporated a formal power analysis but closed prematurely and remained underpowered. (18) These examples reinforce the need for adequately powered trials to define the clinical role of HIVEC.

Nonetheless, our standardized treatment protocol and structured follow-up support the internal validity of our

Declarations

Ethical approval and consent for participate: *Not applicable.*

Consent for publication: *Not applicable.*

Availability of data and material: *The datasets used and analyzed during the current study are available upon reasonable request from the corresponding author.*

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Authors' contributions: *JAP, study concept, data analysis and interpretation, manuscript original drafting; DVB, data collection and interpretation, manuscript drafting; AMF, data collection and manuscript reviewing; RM, data collection and manuscript reviewing; APM, data collection and manuscript reviewing; ML, study concept, data analysis and manuscript reviewing; PC, data interpretation and manuscript reviewing; RG, data interpretation and manuscript reviewing; BJP, manuscript drafting and reviewing; PP, data collection and interpretation, manuscript drafting; CR, study conception and design, data analysis and manuscript reviewing; All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.*

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findings. While HIVEC showed comparable oncologic outcomes to standard MMC, the lack of a clear efficacy advantage – alongside a slightly higher recurrence rate – calls for a cautious interpretation. Further prospective studies are warranted to identify which patients may benefit most from this approach.

Conclusions

HIVEC with MMC showed oncologic outcomes comparable to standard MMC in patients with IR-NMIBC. Although recurrence was more frequent in the HIVEC group, the longer time to recurrence and favourable safety profile suggest its potential use in selected cases. Still, in the absence of a clear oncologic advantage and considering its increased logistic demands and cost, its widespread use may be difficult to justify.

Moreover, the retrospective design and limited sample size of our study preclude definitive conclusions, and the findings should be interpreted with caution. Prospective, adequately powered studies are needed to better define the role of HIVEC in clinical practice.

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