I. Title

A Pilot Study Using Hyperthermic Irrigation Followed by Intravesical Chemotherapy in Patients with Low- to Intermediate-Risk Non-Muscle Invasive Bladder Cancer

Lay Summary

Bladder cancer is common. Most people with bladder cancer have a type called non-muscle invasive bladder cancer, or NMIBC. This cancer stays in the inner lining of the bladder. Even so, it often comes back after treatment. Because of this, patients need regular care and follow-up visits. Treatment usually starts with surgery to remove the tumor. After surgery, medicine is placed into the bladder to lower the risk of the cancer returning. One common medicine is Bacillus Calmette–Guérin (BCG). Many patients cannot receive BCG because of national shortages. This makes it important to find new treatment options. One possible treatment uses warm salt water in the bladder. Heat may help kill cancer cells. It may also help cancer drugs work better. This method has been used after surgery. It has not been tested during surgery. This study will test if heated salt water can be used safely during bladder tumor surgery. The study will include patients with low- or intermediate-risk NMIBC. Researchers will collect early information about recovery, side effects, and daily life. The results may help create new treatments and lower the chance that bladder cancer returns.

II. Study Focus

Abstract

Bladder cancer that has not grown into muscle is called non-muscle invasive bladder cancer, or NMIBC. The standard treatment for newly diagnosed bladder tumor is surgery to remove tumors called transurethral resection of bladder tumor (TURBT). However, many patients will suffer recurrence, even after adjuvant intravesical treatments. This means patients need many repeat treatments, which can be costly and lower their quality of life. Thus, researchers are looking for new ways to reduce the chance of recurrence. This study will test a new approach where heated saline is used during TURBT to help kill cancer cells. We will enroll 40 patients with low risk appearing bladder tumors to evaluate if this heated treatment is safe, practical, and well accepted. The results will help us understand if this method could improve treatment and reduce cancer returning in the future.

Background

Non-muscle invasive bladder cancer (NMIBC) represents approximately 75% of all bladder cancer diagnoses and carries a recurrence risk of up to 50% [1]. This high recurrence rate imposes a substantial economic burden related to ongoing treatment and surveillance, affecting both the physical well-being and financial health of patients [2]. Management strategies for NMIBC are guided by established clinical practice guidelines from the American Urological Association (AUA), European Association of Urology (EUA), and National Comprehensive Cancer Network (NCCN). These guidelines stratify NMIBC

into low-, intermediate-, and high-risk categories, with each level involving transurethral resection of the bladder tumor (TURBT) +/- adjuvant intravesical therapy. NMIBC is considered low risk if it is a papillary urothelial neoplasm of low malignant potential and low-grade urothelial carcinoma (stage Ta, ≤ 3 cm, and solitary tumor). Intermediate-risk NMIBC is if the tumor(s) are low grade urothelial carcinoma (T1 or > 3 cm or multifocal or recurrence within 1 year) and high-grade urothelial carcinoma (Ta and ≤ 3 cm and solitary tumor). The timing, maintenance schedules, and use of additional interventions vary according to risk classification.

Intravesical therapy was introduced to improve outcomes following TURBT, targeting residual microscopic tumor cells and floating cancer cells that may remain after surgery [3]. Delivered via a catheter directly into the bladder, these therapies, whether immunotherapy or chemotherapy, remain in situ for a set dwell time to maximize drug contact with the urothelium. This localized approach minimizes systemic toxicity compared to systemic and intravenous therapy.

Bacillus Calmette–Guérin (BCG) remains the gold standard intravesical immunotherapy which has a 5-year recurrence-free survival of 41% with a six-week induction course of BCG [4]. BCG reduces tumor recurrence and progression but cannot be given intravesically within two weeks of TURBT [5]. Intravesical BCG is administered once a week for six weeks. Six weeks after the last instillation of BCG, a cystoscopy is performed to evaluate recurrence or progression of NMIBC. Patients can be unresponsive to BCG which is recurrence of bladder cancer within six months of treatment. To enhance efficacy or treat BCG-unresponsive patients, agents such as interferon alpha-2b, mitomycin C (MMC), and gemcitabine have been combined with BCG. However, recurrence still occurs within two years in 24% to 55% of patients using these BCG combinations [6-8] Additionally, global BCG shortages driven by increased demand, limited manufacturing capacity, and reliance on a single strain approved in the United States have underscored the need to explore alternative agents and delivery strategies.

One such delivery strategy is hyperthermic intravesical chemotherapy (HIVEC), which administers warmed intravesical solutions at 41–45°C, sometimes with recirculation. Prior studies have shown that HIVEC can significantly reduce recurrence rates compared to normothermic intravesical chemotherapy without increasing adverse events [2]. Hyperthermia alone can sensitize tumor cells to chemotherapeutic agents, enhance drug penetration through increased bladder wall permeability, and improve intravesical drug solubility, reduce angiogenesis, and induce cell death through changes in cellular signaling and cellular structures [9-11]. Hyperthermia can have direct and indirect effects on cancer cells which have uncontrolled cellular signaling such as cell replication. DNA damage response. Directly hyperthermia can increase breaks in single- and double-stranded DNA, decrease DNA polymerase and topoisomerase activity [12]. The indirect effects of hyperthermia on DNA damage are the increased production of oxidative stress, cell cycle arrest, cell cycle checkpoint activation, deceleration of DNA replication, and cell death induction [12]. Using these effects to while bladder cancer is being resected from the bladder may stop residual cancer cell growth and spread after TURBT.

Significance

While standard-temperature TURBT and hyperthermic intravesical agent after TURBT have shown benefits, the benefit of using hyperthermic saline when delivered during TURBT for low- and intermediate-risk appearing bladder tumors is unknown. This leaves a promising therapy unexplored for patients with NMIBC. The pilot study will provide critical insight into clinical feasibility, safety, and logistical requirements for incorporating hyperthermic intravesical saline (HISA) into the treatment of NMIBC during tumor resection. It has the potential to shift the treatment paradigm and may lay the groundwork for future study that may lead to reducing recurrence risk in a disease with a high rate of relapse, while informing the design of future efficacy trials.

Specific Aims/Objectives

Aim 1: To assess the feasibility of implementing hyperthermic intravesical saline irrigation during transurethral resection of bladder tumor (TURBT) in patients with low- and intermediate-risk appearing non-muscle invasive bladder cancer (NMIBC). Hypothesis: Implementation of hyperthermic intravesical saline during transurethral resection of bladder tumors in patients will be feasible at our institution, as evidenced by achieving at least delivery of hyperthermic saline irrigation at 42 ±2°C during TURBT to 80% or 16 patients.

Aim 2: To generate preliminary data on 6-month oncologic outcomes and patient-reported outcomes following hyperthermic compared to normothermic intravesical saline irrigation use during TURBT in patients with low- to intermediate-risk NMIBC. Hypothesis: Hyperthermic saline irrigation during TURBT will have superior recurrence and recurrence-free survival, with comparable postoperative adverse events, and patient-reported quality-of-life scores compared to normothermic saline irrigation during TURBT.

Design

This study will be a prospective, single center, randomized controlled pilot study to enroll 40 adult patients diagnosed with low- to intermediate-risk appearing NMIBC admitted to Charleston Area Medical Center Memorial Hospital (CAMC). The duration of the study will be 18 months, which will include a 12-month enrollment period and a 6-month follow-up to evaluate short-term oncological outcomes. Patients included in this study will be separated into two treatment arms: The control arm (no HISA) will consist of standard intraoperative care that uses bladder irrigation with normothermic saline intraoperatively (n=20) and 1g of gemcitabine in the immediate postoperative setting. The intervention arm (HISA) will consist of administering hyperthermic intravesical saline intraoperatively (n=20) with 1g of gemcitabine delivered in the immediate postoperative setting. Gemcitabine will be allowed to dwell for 1 hour in both groups.

Sample

The study setting is the Charleston Area Medical Center (CAMC) Memorial Hospital. CAMC is a tertiary care facility in Charleston, WV serving patients in central and southern WV. It serves as a referral center for urologic oncology care, providing access to rural and underserved populations. The urology department at CAMC has a comprehensive oncology program and is staffed by three fellowship trained urologic oncologists.

Adult patients (≥ 18 years) with a visual diagnosis of low- to intermediate-risk appearing papillary tumor(s) at CAMC that meet the inclusion criteria will be the study sample.

Using previous clinic throughput, a total number of 40 patients (20 per treatment arm) will give ±12% uncertainty. This satisfies recommended range for pilot studies with recommendations of n=12 to 15 per arm for future main trials designed with 90% power and two-sided significance [13-15]. It is expected to review 1,000 charts.

Inclusion Criteria

- 18 to 89 years old
- Visual diagnosis of a papillary tumor(s) ≤ 3 cm
- Transurethral resection of bladder tumor (TURBT)
- ECOG performance status 0-2
- GFR ≥ 30 mL/min
- Informed consent of patient

Exclusion Criteria

- < 18 years of age
- Pregnancy
- Prisoners
- Evidence of distant metastasis
- Histologically confirmed high risk NMIBC prior to and after TURBT
- Prior carcinoma in situ
- Active infection or immunosuppression
- Intraoperative perforation
- Participation in another clinical trial with this urologic cancer diagnosis
- Postoperative bladder instillation failure

Active infection will be defined as documented urinary tract infection based on preoperative urine analysis or urine culture. Active immunosuppression will be defined as a patient with leukopenia or taking any active immunosuppressive medication.

Bladder instillation failure will be defined as the inability to successfully deliver and maintain the planned volume instilled fluid within the bladder for the intended dwell time of 60 minutes. Failure will be recorded if any of the following occur: the instillation cannot be completed due to catheter malfunctions, leakage, obstructions, or technical difficulty; premature loss of fluid from the bladder that prevents completion of the planned dwell period (minimum successful dwell time of 30 minutes); patient intolerance requiring early termination of the instillation; or

intraoperative or postoperative complications that require stopping the instillation for safety reasons, including but not limited to bladder perforation, uncontrolled bleeding, or hemodynamic instability. All instillation failures will be documented, along with the reason for failure and the volume and dwell time achieved prior termination.

The enrollment period will be 12 months with the goal of recruiting 40 patients (20 per treatment arm). It is expected to review 1,000 charts. The time period of study will be March 30, 2026, to May 31, 2030.

Procedures/Protocol

Research staff will review the investigator's census daily to identify new admissions who may be study candidates using a patient eligibility checklist (Appendix 1). All eligible patients (meeting preoperative inclusion criteria) will be informed about the study. Patients with capacity who agree to participate will be consented using the consent forms as written within 15 minutes prior to procedure. A note will be made in the patient's chart and in study binder detailing the consent. A patient educational handout (Appendix 2) will also be provided to patients during the consent process.

Patients will be enrolled only after a comprehensive informed consent process, which includes a detailed explanation of treatments, study objectives, potential risks, and benefits of hyperthermic intravesical saline, and the voluntary nature of participation. A consent form and the HIPAA authorization form will be signed and dated prior to enrollment. Each patient will be assigned a patient study number and randomized to a treatment arm after cystoscopy. The original signed consent will be kept and stored in a binder at the CAMC research office in the WVU building. After cystoscopy confirming the presence of a papillary tumor requiring resection, eligible patients will be randomized (1:1) by sealed envelope method to one of two treatment arms. Each allocation will be placed inside an opaque, sequentially numbered, sealed envelope. Envelopes will be identical in appearance to prevent unblinding. The envelopes will be stored securely and accessed only by authorized study personnel. After confirmation of the participant's eligibility, the next envelope in the numbered sequence will be opened in the presence of two staff members. The treatment assignment inside will be followed and documented. Once the pathology report is returned, the patients must remain in the low-intermediate risk category (low grade urothelial carcinoma, Ta or T1 stage) to remain in the study and will not be eligible to participate in any other study or induction course in the intravesical treatment regimen after enrollment.

The control arm (no HISA) will consist of standard intraoperative care including bladder irrigation with normothermic saline during TURBT. The intervention arm (HISA) will consist of bladder irrigation with hyperthermic intravesical saline intraoperatively during TURBT. Gemcitabine will be allowed to dwell for 1 hour in both groups in the immediate postoperative setting. Patients will have postoperative visits at 2- weeks (up to 1 month), 3- and 6-month (+/- two weeks) intervals post-treatment, then every 6 (+/- two weeks)

months thereafter for up to 3 years or until disease recurrence, progression, withdrawal, or death, whichever occurs first.

The following patient demographics will be collected:

- Age at procedure in years
- Sex – male, female, other
- Race – African American, Asian, White, other
- Ethnicity – Hispanic or non-Hispanic
- Body mass index at procedure
- Smoking history – yes or no
- Comorbidities (HTN, DM, Obesity, CAD, CHF, MI, COPD, CKD) - yes or no
- Date of bladder cancer diagnosis
- Prior bladder cancer history – yes or no
- Grade of previous bladder cancer
- Prior bladder cancer treatments – yes or no
- Type of previous bladder cancer treatment
- Glomerular filtration rate prior to surgery
- ECOG status prior to surgery
- Distant metastasis at time of procedure – yes or no
- Location of metastasis
- Size of bladder tumor
- Type of bladder cancer
- Active infection – yes or no
- Active immunosuppression – therapeutic use of drugs to suppress the immune system, yes or no
- Bladder capacity in mL
- Participation in clinical trial – yes or no
- Recruitment to study – yes or no
- Recruitment or denial date

The following data will be collected:

- Tumor size in cm
- Tumor location – dome, posterior wall, right lateral, left lateral, trigone, bladder neck, near ureteral orifice, diffuse/multifocal
- Number of each tumor
- Resection size in cm
- Complete or incomplete tumor resection
- HISA used – yes or no
- Estimated blood loss in mL
- Operative time in minutes
- Dates of initial and any sequential TURBT
- Dates of initial and any sequential cystoscopy
- Pathology reports of initial resection and all repeat resections
- Completion of HISA – yes or no
- 30- and 90-day readmissions

- 30-day and 90-day ER admissions
- Postoperative complications and adverse events
- Death of patient – yes or no
- Date of death
- Number of follow-up visits
- Dates of follow-up visits
- Cystoscopy findings
- TURBT findings
- Urine cytology findings
- Urinalysis findings
- Physical examination findings

Outcomes for Specific Aim 1: Patient recruitment and protocol adherence. Patient recruitment will be the number of patients recruited divided by the total number of eligible patients. Protocol adherence will be assessed per case. Full adherence is defined as: (1) assigned saline used; (2) temperature maintained at 42.0 ± 2.0°C for ≥80% of intended exposure; (3) delivery of hyperthermic saline occurred during the specified operative window, and (4) postoperative instillation of 1g gemcitabine for 60 minutes. Major deviations (including incorrect saline or temperature outside safety bounds >45°C) will be reported within 24 hours.

Outcomes for Specific Aim 2: 30-day and 90-day readmission rates, postoperative complications, adverse events, 3- and 6-month recurrence rates, location of recurrence, time to recurrence, disease-free survival, overall survival, hospital readmission rates, postoperative morbidity, EORTC QLQ-C30 and EORTC NMIBC24 scores for each follow-up visit

Age, sex, smoking status, comorbidities, prior bladder cancer, tumor size, tumor multiplicity, stage/grade, prior bladder cancer, prior intravesical therapy are potential confounding variables for this study. These variables will be collected for subgroup analyses, stratification, and covariate adjustment during data analysis.

Description of Procedure

The standard of care for low- to intermediate-risk non-muscle invasive bladder cancer is based on tumor characteristics as well as risk stratification systems [16]. Risk stratification for low-risk NMIBC is defined by National Comprehensive Cancer Network (NCCN) as a solitary, low-grade a Ta lesion < 3 cm, no carcinoma in situ or prior recurrence within the past year. Risk stratification for intermediate risk is defined by NCCN as multifocal or recurrent low-grade Ta tumors, low-grade Ta tumors with recurrence > 1 year from initial diagnosis, tumor ≥ 3cm, or multiple tumors [17].

Diagnosis of low- to intermediate- risk NMIBC is achieved through cystoscopy, urine cytology, and transurethral resection of bladder tumor (TURBT) with histological assessment. TURBT is the standard initial surgical procedure for diagnosing and treating visible bladder tumors, particularly non–muscle-invasive bladder cancer (NMIBC). It allows for both removal of the tumor and collection of tissue for histologic

diagnosis. TURBT procedure is expected to take 30 minutes for both intervention arms. The procedure steps for TURBT are listed below.

Procedure Steps:

1. **Anesthesia:** Performed under general or regional (spinal) anesthesia.
2. **Cystoscopic Access:** A rigid cystoscope is inserted through the urethra into the bladder.
3. **Visualization:** The bladder is inspected systematically to locate tumors and assess number, size, location, and morphology. Irrigation of the bladder with normothermic saline to fill and stretch the bladder to see inside clearly and safely remove any tumors if found during visualization.
4. **Tumor Resection:** Using an electrosurgical resection loop, the tumor is shaved off in fragments. Both superficial portions and deep tissue down to the muscularis propria are resected to ensure complete removal and accurate staging.
5. **Hemostasis:** Bleeding vessels are cauterized using electrocautery.
6. **Specimen Handling:** Resected tumor tissue and deep biopsies are sent separately to pathology for analysis (to distinguish Ta, T1, and muscle-invasive disease).
7. **Post-Resection Assessment:** Bladder is re-inspected to confirm complete resection; repeat resection may be performed if margins are uncertain.
8. **Immediate Intravesical Therapy:** A single postoperative instillation of chemotherapy.

Recovery & Follow-Up:

- Catheter may be left temporarily for bladder drainage.
- Patients are monitored for hematuria, infection, bladder perforation, or clot retention.
- Surveillance cystoscopy is scheduled per risk category due to high recurrence rates in NMIBC.

Standard of care for low-risk NMIBC is transurethral resection of bladder tumor, single immediate intravesical chemotherapy instillation (within 24 hours of TURBT). For surveillance, low-risk NMIBC will have a cystoscopy at 3-months (+/- 2 weeks). If negative, additional cystoscopy every 9- to 12-months (+/- 2 weeks) for up to 3 years.

Standard of care for intermediate-risk NMIBC is transurethral resection of bladder tumor followed by intravesical therapy. Either as an induction and maintenance intravesical chemotherapy or induction Bacillus Calmette-Guerin (BCG) with or without maintenance in select patients with higher risk features. Maintenance therapy is chemotherapy for up to one year and if used BCG for up to one year. Surveillance for intermediate-risk NMIBC will consist of cystoscopy and cytology at 3 months (+/- 2

weeks) and then every 3 to 6 months (+/- 2 weeks) for 2 years, then every 6 to 12 (+/- 3 weeks) months thereafter.

Intervention

Patients in the control arm (no HISA) will consist of standard intraoperative care for low- to intermediate-risk NMIBC including TURBT bladder irrigation with normothermic saline and instillation 1g of gemcitabine in the immediate postoperative setting. Tumor tissue will be sent to the department of pathology for review as per standard for histopathological evaluation.

The intervention arm (HISA) will be treated in the same way as the control arm with the addition of administering hyperthermic (42.0 ± 2°C) intravesical saline during the TURBT. Bladder irrigation with 1g of gemcitabine will be delivered in the immediate postoperative setting.

The Thermaclear FluidSmart Fluid management system (Stryker, MI) will be used to administer and irrigate the bladder with normothermic or hyperthermic intravesical saline during the TURBT.

General anesthesia will be administered, and the patient will be in the dorsal lithotomy position. With continuous irrigation with either the normothermic or hyperthermic saline (42.0 ± 2.0° C), using a 26 french resectoscope. Resection of the bladder tumor will be completed using a loop electrode with a monopolar/bipolar electrode. An Ellick evacuator will be used to remove resected tissue. In the immediate postoperative setting, a single dose of intravesical chemotherapy with 1g gemcitabine will be allowed to dwell for 1 hour in both groups. The patient will then recover in a post anesthesia care unit, with planned outpatient discharge.

Patients will have postoperative visits at 2- weeks (up to one month postoperative), 3- and 6-month (+/- two weeks) intervals post-treatment, then every 6 months (+/- two weeks) thereafter for up to 3 years or until disease recurrence, progression, withdrawal, or death, whichever occurs first.

Initial Postoperative Follow-up (up to one month postoperative):

- Symptom review and physical examination as clinically indicated
- Urinalysis/urine culture if needed
- Patient counseling and education
- EORTC QLQ-C30 and NMIBC24 questionnaires

3-Month (+/- two weeks) Follow-Up:

- Cystoscopy for all patients
- Urine cytology for patients with intermediate-risk NMIBC
- Physical examination and symptom review
- Urinalysis and urine culture as clinically indicated
- Patient counseling and education regarding symptoms and surveillance
- EORTC QLQ-C30 and NMIBC24 questionnaires

6-Month (+/- two weeks) Follow-Up:

- Cystoscopy and urine cytology as indicated (particularly for intermediate-risk NMIBC)
- Physical examination and symptom assessment
- Urinalysis and urine culture if clinically warranted
- Patient counseling and reinforcement of surveillance plans
- EORTC QLQ-C30 and NMIBC24 questionnaires

If cystoscopy and cytology remain negative, subsequent cystoscopic surveillance will continue every 6 months (+/- two weeks) for up to 3 years per guidelines.

At each follow-up visit, quality-of-life will be assessed using the EORTC QLQ Core Questionnaire (EORTC QLQ-C30, version 3.0; Appendix 2) and the EORTC NMIBC24 module (Appendix 3) to evaluate general and bladder cancer-specific health domains [18]. The EORTC QLQ-C30 is a validated, cancer-specific, patient-reported outcome measure developed by the European Organization for Research and Treatment of Cancer (EORTC). It assesses the overall quality of life in cancer patients and is widely used across cancer types and treatment modalities. The questionnaire contains 30 items grouped into the following domains:

- Five functional scales: physical, role, emotional, cognitive, and social functioning
- Three symptom scales: fatigue, nausea and vomiting, and pain
- A global health status/quality of life scale
- Six single items: dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial difficulties

Most items are rated on a 4-point Likert scale from “not at all” to “very much,” while the global health status uses a 7-point scale. Responses are linearly transformed to a 0–100 scale, where higher scores indicate better functioning or, for symptom scales, greater symptom burden.

The EORTC QLQ-NMIBC24 module is designed specifically for patients with non-muscle invasive bladder cancer undergoing intravesical therapy or cystoscopic surveillance. It complements the QLQ-C30 by capturing disease-specific concerns through 24 items across these domains: urinary symptoms, intravesical treatment-related side effects, future worries and fear of recurrence or progression, sexual functioning and intimacy, and body image and gender-specific sexual issues. Items use the same 4-point Likert scale and are similarly transformed to a 0–100 scale, with higher scores reflecting increased symptom severity or concern. Both instruments have undergone extensive psychometric validation and cross-cultural translation, and are recognized internationally for their reliability, sensitivity, and clinical relevance.

Questionnaires will be administered at baseline (pre-treatment) and at predefined follow-up intervals to assess the impact of treatment and disease on patient-reported outcomes. They will be available in English and Spanish. Trained research staff will oversee questionnaire administration to maximize compliance and data completeness. The approximate completion time is 20 minutes. Completed forms will be collected and inserted into study binder. Any incomplete or missing questionnaires will be documented with reasons recorded.

Assessment Windows and Compliance

- Baseline: Questionnaires are considered for evaluation if completed prior to treatment initiation.
- End of Treatment: Questionnaires must be completed within 14 days of treatment completion.
- Follow-Up Visits: Questionnaires should be completed at scheduled visits up to 3 years post-treatment, within a window of ±1 month from the planned date.

In addition to the quality-of-life assessments, safety monitoring at follow-up visits will be used to monitor adverse events using the CTCAE v5.0 grading. Adverse events that will be monitored in this study for all participants are found below in Table 1. Research meetings and routine clinical oversight ensure timely detection of complications. The treatment setting includes immediate access to emergency care, trained urologists, and anesthesiologists.

All patients will receive standard of care which includes TURBT and immediate postoperative intravesical gemcitabine. The use of heated saline during TURBT is not the standard of care currently at CAMC. Alternatives include observation in select cases, induction/maintenance intravesical chemotherapy, or Bacillus Calmette-Guerin depending on risk category. Patients may decline participation and receive guideline-concordant NMIBC management without affecting their care. The rationale for the proposed study is to evaluate feasibility of delivery of hyperthermic intravesical saline administered during TURBT while maintaining an acceptable safety profile.

To further justify the rationale for this feasibility study, the safety profile of the use of heated solutions during hyperthermic intravesical saline with chemotherapy (HIVEC) have been reported in similar patient populations and procedural contexts. HIVEC is a bladder-sparing treatment for bladder cancer that combines chemotherapy with localized heat (40 – 43° C) that circulates in the bladder for an hour. HIVEC has also been used immediately after TURBT for the treatment of NMIBC. HIVEC when compared to bacillus Calmette-Guerin (BCG) instillation, American Urological Association guideline recommended treatment for high risk NMIBC, had no significant difference in adverse events; however, BCG instillation had higher incidence of dysuria as reported in a recent meta-analysis by Chai et al [19]. In a study comparing gemcitabine, HIVEC with mitomycin, and BCG intravesical therapy following TURBT, more treatment-related side effects were significantly more frequent in the BCG group, and the most common adverse events included lower urinary tract symptoms (LUTS),

dysuria, and urinary tract infections [20]. Gemcitabine intravesical instillation has shown a more favorable tolerance profile and no differences in adverse events when compared to mitomycin [21]. Gabriel et al reported that patients treated with 6 instillations compared to patients who had more than 6 cycles of (HIVEC) have less hematuria and urinary burning and that serious side effects (≥ grade 3) were rare and similar in both groups [22].

Under normothermic conditions, the bladder mucosa is near core body temperature. The hyperthermia component of this study introduces a controlled thermal component to the bladder environment. During the TURBT, the mucosal lining will be exposed to the irrigating fluid. As the heated saline circulates through the bladder, heat is transferred from the fluid to the bladder mucosa and superficial bladder walls through direct contact. This results in a gradual and localized increase in bladder temperature. Once irrigation is discontinued, the bladder temperature gradually returns to baseline through natural heat exchange with surrounding tissues and systemic circulation. The return to baseline temperature will be further increased during the one-hour postoperative bladder instillation with gemcitabine which uses normothermic solution.

Our study is not expected to change the safety or tolerability profile of using heated saline when compared to HIVEC procedures. In fact, the proposed use of heated saline during TURBT is anticipated to pose less risk than HIVEC due to several key differences: a shorter exposure duration (30 minutes vs 60 minutes) of using heated saline, the absence of chemotherapy agents in the irrigant, and a reduced number of instillation cycles. Unlike HIVEC, this study utilizes heated saline alone for a limited intraoperative period. As a result, the potential for local or systemic adverse effects is expected to be lower than that observed with HIVEC. Adverse events for the study in both arms are reported in (Table 1).

Table 1: Adverse Events

Adverse Event	CTCAE Term	Expected Frequency	Typical CTCAE Grade
Injury to ureter or surrounding structures	Urinary Tract Injury	Rare	Grade 3-4; usually requires intervention
Urinary tract infection	Urinary tract infection	Common	Grade 1-2; Grade 3 if IV antibiotics or hospitalization required
Sepsis	Sepsis	Rare	Grade 3-5; usually secondary to infection or UTI; requires hospitalization and IV antibiotics
Acute kidney injury (AKI)	Acute kidney injury	Rare	Grade 1-3; may be transient or require intervention; usually associated with dehydration, infection, or anesthesia-related events
Bladder contracture/fibrosis	Bladder spasm/urinary retention	Rare	Grade 2-3; may require intervention

Urethral stricture	Urethral stricture	Rare	Grade 2-3; may require intervention
Burning with urination	Dysuria	Common	Grade 1-2 (mild-moderate)
Increased urinary frequency/urgency	Urinary frequency urinary urgency	Common	Grade 1-2
Blood in urine	Hematuria	Common	Grade 1 (microscopic), Grade 2 (visible)
Bladder pain/discomfort	Pain in urinary tract bladder spasm	Common	Grade 1-2
Bladder irritation/chemical cystitis	Cystitis	Uncommon	Grade 1-2 (mild); Grade 3 (severe, intervention indicated)
Fatigue	Fatigue	Uncommon	Grade 1-2
Bladder perforation	Bladder perforation	Rare	Grade 3-4 (requires hospitalization or surgery)
Severe chemical cystitis	Cystitis	Rare	Grade 3-4 (requires intervention)
Allergic reaction/hypersensitivity	Hypersensitivity	Rare	Grade 2-4 (rash to anaphylaxis)

Stopping Rules

Individual- Level

The hyperthermic saline during TURBT will be immediately discontinued for an individual subject if any of the following conditions occur during or immediately after TURBT.

- Inability to maintain the planned intravesical temperature within the predefined target range or an intravesical temperature exceeding 43°, despite corrective measures
- Sustained hypotension, hypertension, tachycardia, or bradycardia requiring anesthetic or pharmacologic intervention and judged by the operating surgeon or anesthesiologist to pose a safety risk
- Suspected or confirmed bladder perforation, uncontrolled intraoperative bleeding, and any anatomic or technical concern that in the judgement of the surgeon, makes continued TURBT unsafe
- Severe pain, autonomic instability, or other clinical signs suggesting intolerance of TURBT or any adverse event requiring early termination of the TURBT to protect patient safety

If the TURBT is terminated early, the subject will continue to receive standard postoperative care, and the event will be recorded as an instillation failure.

Study-Level

- Occurrence of Grade 3 or higher adverse events deemed related to the hyperthermic saline instillation ≥ 15% of enrolled subjects
- Failure to complete the planned TURBT in > 25% of cases, suggesting a lack of procedural feasibility
- Any pattern of serious or unexpected adverse events indicating that the intervention poses greater risk than anticipated

- Interim review demonstrating that continued enrollment is unlikely to establish feasibility or safety, based on predefined feasibility benchmarks or investigator and safety oversight consensus

Device Information

For this study, the control arm (no HISA) and the intervention arm (HISA) will be using the intravesical saline during the TURBT and bladder irrigation with 1g of gemcitabine will be delivered in the immediate postoperative setting. In order to irrigate the bladder with saline during the TURBT (30 minutes) and deliver chemotherapy after TURBT the X-FLO/Thermaclear FluidSmart Management System will be used. The Thermaclear device will also be used to warm the saline solution to 42.0 ± 2.0°C for the TURBT procedure only in the intervention arm (HISA).

Normal saline (0.9%) is an FDA-approved, lawfully marketed drug in the United States and is widely used for intravenous infusion, irrigation, and distention of body cavities. In this study, saline will be used solely as a bladder irrigation and distention fluid during TURBT, which is consistent with its labeled indications and clinical use. This study is not intended to promote or commercialize saline for a new use. This study also does not include the following: involve a change in the route of administration, dosage level, or subject population, the increase of risks of harm beyond those associated with standard clinical use. Heating the saline using the Thermaclear device does not alter its chemical composition, pharmacologic activity, or mechanism of action and is consistent with routine intraoperative irrigation practices.

The X-FLO/ Thermaclear FluidSmart Fluid Management System is a multifunctional surgical device designed to support fluid irrigation, distention, warming, and real-time monitoring of fluid input and output during endoscopic procedures in urology and gynecology. The system is ab FDA-cleared Class II medical device, cleared through the 510(k) pathway (K210628) under 21 CFR 884.1700. The system is intended to warm and pump fluids from IV bags to provide distention, fluid warming, and volume/deficit measurements in endoscopic procedures in gynecology and urology.

The X-FLO/Thermaclear FluidSmart Fluid Management System is a surgical fluid management platform designed to:

- Deliver pressurized irrigation fluid using a peristaltic pump
- Warm irrigation fluid using an integrated heating system
- Monitor fluid inflow and outflow volumes
- Calculate fluid deficit in real time
- Provide visual and audible safety alarms

The system consists of a touchscreen-controlled main unit, disposable sterile tubing sets, and optional modules for fluid deficit monitoring. The device warms irrigation fluid to near-body temperature prior to delivery and maintains user-defined pressure and flow parameters within established safety limits. The disposable tubing components are sterile and are designed for indirect tissue contact. All materials have undergone biocompatibility testing in accordance with ISO 10993 standards.

In this study the device will be used to warm and deliver saline for bladder irrigation during TURBT. The device will be used: according to its FDA-cleared labeling; without modification; without experimental software, hardware, or accessories; within standard pressure, temperature, and flow parameters; and by trained clinical personnel in the operating room. No investigational modifications will be made to the device. It is expected that using the Thermaclear FluidSmart Fluid management system which instantaneously warms the fluid will not add any additional procedure time for the intervention arm.

The use of the X-FLO/ThermaClear system in this study poses no greater risk than its routine clinical use. The device includes multiple safety features, including pressure limits, temperature monitoring, automatic shutoffs, and visual and audible alarms. Therefore, the device is FDA cleared, used on-label, unmodified, and poses no greater risk than routine clinical use.

All operating room personnel involved in procedures utilizing the X-FLO/ThermaClear Fluid Management System will receive standardized training prior to participation in the study. Training will be conducted by qualified clinical educators, manufacturer representatives, or users who have demonstrated competency with the device. Training minimizes the risk of user error and ensures that the device is used in accordance with its FDA-cleared labeling. Some staff have had prior experience with a similar device used in the past at CAMC. The device will be operated only by trained personnel, and no investigational modifications or experimental uses will be permitted.

Training will include:

Instruction: OR staff will receive an overview of the device's purpose, components, and FDA-cleared indications for use. They will also receive a review of the device setup and system components; disposable tubing sets and proper installation; fluid warming functionality; pressure and flow controls; fluid deficit monitoring features; and safety alarms and automated shutoff mechanisms.

Hands-On Demonstration and Simulation: Staff will participate in hands-on training sessions that simulate routine intraoperative use. These sessions will cover system startup and shutdown procedures; proper loading of saline bags and tubing sets; programming of temperature, pressure, and flow parameters; troubleshooting alarms and error messages; emergency procedures, including manual override and system discontinuation.

Ongoing support and refresher training: Staff will demonstrate competency through supervised practice. Refresher training will be provided as needed throughout the study period, particularly for new staff or if protocol changes occur. Manufacturer-provided materials, quick-reference guides, and on-call technical support will be available.

Data Collection/Instrumentation

All personnel involved in data collection will undergo protocol-specific training, periodic reviews, and retraining sessions for consistency. Training will

include instruction on standardized data definitions, data collection form usage, source documentation, and query resolution processes. Retraining will occur at regular intervals and when protocol amendments are implemented.

A password protected excel file will be used to create a standardized data collection form to insert collected data (pre-screening, operative, and follow-up) from medical chart review as a quality control measure to do real-time logic checks, and to prevent missing data. The EORTC QLQ-C30 Core Questionnaire and EORTC QLQ-NMIBC24 supplement module responses will be collected from patients in person during medical visits. Data will be inserted into a password protected excel file. Patient eligibility checklists, consent documents, and patient completed EORTC QLQ-C30 Core Questionnaires and EORTC QLQ-NMIBC24 supplement modules will be stored in a study binder in the locked office at the facility.

Regular data monitoring and periodic audits by the research staff will be completed to confirm adherence to protocol, compare source documents to entered data, and validate key clinical events. Missing data, errors, and protocol deviations will be tracked and reported. Personnel with high error rates will receive targeted retraining. Data discrepancies will be resolved within seven days.

Prior to analysis of data, a final comprehensive data cleaning will be conducted. All outstanding queries will be resolved, and final source document verification will be completed. After completion of all quality checks, data will be saved and analyzed.

Data will be collected via patient chart review for pre-screening data/variables, and for operative and follow-up data/variables.

Data Analysis

The Center for Health Services and Outcomes Research will be responsible for data analysis. SAS version 9.4 (SAS Institute, NC) or SPSS version 29 (IBM, NY) will be used to analyze the data. Categorical variables will be reported as the number and percentage. Continuous variables will be reported as standard deviation or median with interquartile range. Feasibility data will be analyzed using descriptive statistics and confidence intervals.

Preliminary comparative statistics between both arms will be determined although the study is expected to be underpowered. Descriptive statistics will be compared between both arms using Chi-square and Fisher's exact tests where appropriate.

All scales and single-item measures of the EORTC QLQ-C30 and QLQ-NMIBC24 will be scored following standard EORTC guidelines. Analysis of using the EORTC QLQ Core Questionnaire (EORTC QLQ-C30, version 3.0; see Appendix 2) and the EORTC NMIBC24 module (Appendix 3) will use items are that are rated on a 4-point Likert scale from "not at all" to "very much," or while the global health status uses a 7-point scale. Responses will be linearly transformed to a 0–100 scale, where higher scores indicate better functioning or, for symptom scales, greater symptom burden. Research staff will monitor questionnaire completion and follow-up on missing responses. For multi-item scales, if ≤50% of items are missing, prorated

scoring (“half-scale rule”) will be applied. If >50% are missing, the scale score will be considered missing. Single-item missing data will be treated as missing for analysis purposes. Compliance rates between study arms will be compared at each time point. The overall score for each questionnaire will be reported as mean with standard deviation or median with interquartile range. An independent t-test or Mann-Whitney U test if non-parametric will be used to compare overall scores for the HISA and no HISA arms. For comparing categorical domain scores within the questionnaires between the HISA and no HISA arms, an independent t-test or Mann-Whitney U test if non-parametric will be used. Multivariable analysis will be performed to adjust for confounders.

Interim feasibility data will be reviewed by the study investigators and institutional oversight bodies as appropriate. Decisions to stop or modify data analysis will prioritize participant safety and scientific validity. This study is designed as a feasibility study with exploratory secondary outcomes. Accordingly, stopping rules for data analysis will focus on feasibility failure, excess harm, or futility rather than early efficacy. No formal early stopping for superiority is planned. Enrollment and data analysis for Aim 1 may be stopped early for futility if interim review demonstrates that achieving the feasibility threshold is unlikely. Specifically: If ≥ 5 of the first 10 patients fail to achieve the target temperature due to technical, safety, or procedural limitations, the study team will pause enrollment and review feasibility; and if after 15 enrolled patients, fewer than 12 patients have successfully received hyperthermic saline at the target temperature, the probability of reaching the predefined feasibility benchmark will be considered low, and the study may be terminated for infeasibility. Data collection and analysis for Aim 2 may be halted early if: the rate of grade 3 or higher adverse events attributable to hyperthermic saline exceeds that of normothermic comparator group by ≥ 15% absolute difference; and a pattern of unexpected or serious adverse outcomes emerges that suggests excess harm associated with hyperthermic saline. If these conditions are met, comparative analyses will be limited to descriptive statistics and formal outcome comparisons may be suspended.

Because this study is not powered for oncological efficacy, formal statistical futility boundaries for recurrence outcomes will not be applied. However, if interim descriptive analyses demonstrate substantially worse recurrence, recurrence-free survival or patient-reported outcomes in the hyperthermic group compared to normothermic controls, further comparative analyses may be discontinued.

If the study is stopped early for feasibility failure, safety concerns, or futility all enrolled patients will be included in intent-to-treat descriptive analyses and feasibility outcomes, adverse events, and available follow-up data will be summarized.

III. Human Participants

Participant Population/Recruitment Method(s)

Potential participants will be prospectively identified at Charleston Area Medical Center Memorial Hospital through review of urology clinic schedules, pathology reports, cystoscopy procedure logs, and transurethral resection of bladder tumor (TURBT) operative reports. Initial pre-screening will be conducted by trained research staff in collaboration with the treating physicians. Review of electronic medical records, clinic

logs, and tumor board lists will be used to identify participants using a pre-screening checklist (Appendix 1) to assess basic eligibility. Pre-screening information will be recorded in a pre-screening log. Screening will be conducted by phone call or by an in-person discussion to confirm eligibility. If eligible, the patient will be invited for an informed consent discussion.

The rationale, design, and purpose of the study will be explained to each participant with information on both treatment arms. The patient will be informed that after giving consent, they will be randomly selected to have either heated or room temperature saline during the procedure and they will not know which treatment they will receive but the physician will. It will be explained to the patient that this is known as single blinded randomization and means that the patient will be randomly assigned to one of the two treatments based on chance, like a flip of a coin. Neither the patient nor the researcher will choose your assigned group. They will have an equal chance of being in either group. All patients will be informed that the study includes a comparison between standard of care alone and standard of care plus an investigational procedure. They will be informed there is a chance that they will receive only standard of care. Their group assignment will not affect their ability to withdraw or receive care.

The patient will receive written patient information and will have the opportunity to ask questions. The patient will have until 15 minutes prior to the procedure to consider participating in the study. Written informed and signed consent from the patient is required before the start of treatment.

Vulnerable Populations

This study is not specifically recruiting or excluding vulnerable populations outside of the stated inclusion/exclusion criteria. Children, < 17 years of age, and pregnant people are not eligible for participation due to risks to the fetus, thus eliminating the vulnerable populations of children, fetuses, and neonates. The medical record review will not specifically include any information to identify the participants as a vulnerable population such as economically or educationally disadvantaged persons, or employees or students.

Benefits

Although direct benefits are not guaranteed for participants, the participants will have access to a new potential therapy that may improve control or reduce recurrence, delayed progression, or improved bladder preservation beyond standard intravesical therapy. The participants will be managed by a multidisciplinary research team, which may offer a higher level of attention or coordinated care. The indirect benefits to participants will include contributions to medical knowledge by helping the research team gather essential information for safety, feasibility, and preliminary efficacy data.

Risks and Discomforts

Patients in this study (both arms) will experience some burden of participation by filling out questionnaires (minimum of 4 questionnaires) during routine medical visits.

Risks of participating include treatment-related risks (both intervention arms):

- Dysuria
- Urgency
- Hematuria

- Chemical cystitis
- Suprapubic pain/pressure

Systemic absorption of gemcitabine is minimal and can occur if the bladder is perforated. Systemic absorption, although rare, has been reported for the following effects:

- flu-like symptoms
- nausea
- vomiting
- myelosuppression

Contraindications for instillation treatment consist of bladder perforation, gross hematuria, active urinary tract infection, and known gemcitabine hypersensitivity. Procedural risks include anesthesia or sedation risks during TURBT and hyperthermic/normothermic saline delivery. All treatment is delivered in a setting with immediate access to emergency care, including training urologists and anesthesiologists.

Patient might experience the following psychological risks:

- anxiety or emotional distress from uncertainty in receiving experimental treatment
- disappointment, or regret if the treatment is not effective or must discontinue
- therapeutic misconception in which the belief of the trial guarantees benefits rather than understanding of its experimental nature.

Study documents and informed consent conversations will use clear, understandable language to explain the experimental nature of the treatment and ensure participants understand risks, benefits, and alternatives. These documents and informed conversations will have information to reinforce that the study is investigational, and that benefits are not guaranteed.

The patient could also be at legal risk for the loss of confidentiality. Mitigation efforts to prevent the loss of confidentiality by research staff can be found in the privacy and confidentiality section below.

Consent Process

The research coordinator or other research team members will obtain informed consent. All eligible patients will be informed about the study. Patients will be informed that their participation is completely voluntary and whether they decide to pate or not will in no way affect their current or future relationship with their attending physicians, residents, or staff at Charleston Area Medical Center. Furthermore, they will also be informed that they have the right to withdraw from the research at any time without penalty.

Patients with capacity who agree to participate will be consented using the consent forms as written within 15 minutes of procedure. A note will be made in the patient's chart detailing the consent. The patient will sign and date the consent and the HIPAA authorization form attached to it. Each patient will be assigned a patient study number and randomized as described in the protocol section. The original signed consent will be kept

and stored in a binder at the CAMC research office in the WVU building. A copy of the consent form will be placed in the patient's chart, and another will be given to the participant.

For this study, there is no request for the use of an LAR.

To minimize the possibility of coercion or undue influence the following strategies will be implemented:

- Neutral, non-authoritative language will be used during the consent process
- Patient will have 15 minutes prior to TURBT procedure to decide to participate with the option to call office
- No financial compensation will be offered for procedure
- Voluntariness will be emphasized

English is the language used by those obtaining consent. English is most common language understood by the prospective patient population. Patients will be presented with consent forms and with patient education brochure .

Waiver of Documentation of Consent:

No waiver of documentation of consent is required for this study due to obtaining written informed consent from participants.

Waiver or Alteration of HIPAA Authorization

We request a waiver of HIPAA authorization to permit access to protected health information (PHI) for the purpose of identifying and pre-screening potential participants prior to obtaining informed consent and written HIPAA authorization. This pre-screening will involve review of medical records, clinic schedules, pathology reports, imaging, and procedure logs to assess preliminary eligibility based on study inclusion and exclusion criteria.

This activity is necessary to determine whether individuals may be appropriate candidates for the study and to avoid unnecessary contact with patients who clearly do not meet eligibility requirements. It would be impracticable to conduct this screening without access to PHI, as eligibility cannot be determined without reviewing clinical information.

Only the minimum necessary PHI will be accessed for this purpose, and data will be limited to information directly relevant to eligibility determination. All accessed information will be handled confidentially, stored securely, and accessed only by authorized study personnel. No PHI obtained during pre-screening will be used for research analyses unless the individual subsequently provides informed consent and HIPAA authorization.

This waiver poses no more than minimal risk to participant privacy, and appropriate safeguards will be implemented to protect confidentiality in accordance with institutional policies and HIPAA regulations.

Privacy and Confidentiality

The investigators, study coordinator, and additional research personnel will collect and manage patient information/data confidentially to the extent permitted by law. The

database containing study information shall be protected and stored on a HIPAA-compliant, secure server. During data collection, the medical record or patient account number will be linked to an anonymous number that will be destroyed after data collection to ensure full data extraction without compromising the patients' privacy. The primary researcher will keep data in a password-protected database. This data will be locked, and only IRB-approved personnel involved in this investigation will have access to it. Any documents with study information will be kept in a locked office. Patient FIN will be linked to the study number so that research staff can ensure full data extraction without compromising the patients' privacy. Any electronic data will contain minimal PHI or no PHI. All results will be reported with no identifiers. Upon completion of the study, all patient information and data collection documents associated with this research will be deleted and shredded.

Costs to Participants

The patient will be responsible for all co-pays and deductibles associated with routine care billable to insurance and/or them.

Payments/Gifts to Participants

Patients will not be paid or receive gifts for their participation.

Debriefing

A debriefing will be given at the end of the study by secure written communication at the end of the study (Appendix 4).

Intervention

All participants will receive standard perioperative and postoperative clinical care at CAMC, and any adverse effects occurring during or after TURBT will be managed following established institutional and urologic practice guidelines. Because the study intervention, hyperthermic intravesical saline at 42.0 ± 2.0°C, is delivered intraoperatively in a controlled surgical environment, continuous monitoring of vital signs and bladder status will occur throughout the procedure. The operating surgeon and anesthesia team will immediately address any intraoperative complication, including bladder perforation, thermal injury, bleeding, or hemodynamic instability using standard and established clinical protocols.

Postoperatively, participants will be evaluated at routine follow-up visits at 2 weeks, 3- and 6- months with interim assessment if symptoms develop. Any adverse event reported by the participant or detected during follow-up will be triaged by clinical research team and promptly referred to a CAMC urologist for medical evaluation and treatment. Serious or unexpected adverse events will be reported to the institution review board per institutional policy. Participants who experience clinically significant adverse effects related to the intervention may be withdrawn from the study at the discretion of the treating clinician to ensure patient safety. Medical interventions including additional imaging, laboratory testing, urgent clinic visits, or hospital evaluation will be arranged as clinically indicated.

This study does not include research-only imaging or genetic testing; however, incidental findings may occur during routine clinical procedures performed as part of standard of care. Any incident found detected during these procedures will be handled

according to standard clinical practice: clinical review and documentation, participant communication, and referral for appropriate care. Incidental findings requiring treatment will not automatically remove the participant from the study unless continued participation poses additional risk or interferes with safety monitoring. Decisions will be made collaboratively by the clinical investigator and treating urologists.

Investigator Qualifications

Michael Stencel, DO, is a urologist at Charleston Area Medical Center in Charleston, WV.

- Staniorski CJ, Yu M, Sharbaugh D, Stencel MG, Myrga JM, Davies BJ, Yabes JG, Jacobs B. Predictors of persistent opioid use in bladder cancer patients undergoing radical cystectomy: A SEER-Medicare analysis. Urol Oncol. 2024 Jul;42(7):220.e21-220.e29. doi: 10.1016/j.urolonc.2024.03.010. Epub 2024 Apr 1. PMID: 38565428.

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Project Mentor

Samuel Deem, DO, is the program director for the department of Urology at Charleson Area Medical Center in Charleston, WV.

Residents

Jared Zopp, DO, is a fourth year urology resident for the department of Urology at Charleston Area Medical Center in Charleston, WV.

Zachary Meyer, DO, is a first year urology resident for the department of Urology at Charleston Area Medical Center in Charleston, WV.

Other Study Personnel

Jacqueline Fannin, PhD, is a research scientist at Charleston Area Medical Center Institute for Academic Medicine in Charleston, WV.

Scott Dean, PhD, is a senior statistician at Charleston Area Medical Center Institute for Academic Medicine in Charleston, WV.

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Appendix 1 Patient Eligibility Checklist

Patient Eligibility Checklist

Study Title: Hyperthermic Irrigation Followed by Intravesical Chemotherapy in Patients with Low- to Intermediate-Risk Non-Muscle Bladder Cancer

Site: CAMC Memorial Hospital

Study Population: Adult patients (>18 years) with a diagnosis of low- or intermediate-risk NMIBC

Patient ID: _____ **Date:** _____ **Reviewer:** _____

Inclusion Criteria

Check all that apply.

#	Criterion	Yes	No	Comments
1	Age ≥ 18 years	☐	☐	
2	Visual diagnosis of a papillary tumor ≤ 3 cm	☐	☐	
3	Histologically confirmed low- or intermediate-risk NMIBC (stage Ta or T1)	☐	☐	
4	Undergoing transurethral resection of bladder tumor (TURBT)	☐	☐	
5	ECOG performance status 0–2	☐	☐	
6	GFR ≥ 30 mL/min	☐	☐	
7	Informed consent obtained	☐	☐	

Additional comments:

Exclusion Criteria

Check all that apply.

#	Criterion	Yes	No	Comments
1	Age < 18 years	☐	☐	
2	Pregnant	☐	☐	
3	Evidence of distant metastasis	☐	☐	
4	Histologically confirmed high-risk NMIBC	☐	☐	
5	Prior carcinoma in situ (CIS)	☐	☐	
6	Active infection or immunosuppression	☐	☐	
7	Intraoperative bladder perforation	☐	☐	
8	Poor bladder capacity	☐	☐	
9	Participation in another clinical trial	☐	☐	

Additional comments:

Eligibility Determination

☐ Eligible ☐ Not Eligible

Reviewer Signature: _____ **Date:** _____

Appendix 2 EORTC Q30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): __ __ __ __ __ __ __ __
Today's date (Day, Month, Year): 31 __ __ __ __ __ __ __ __

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

SPECIMEN

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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SPECIMEN

Appendix 3 EORTC NMIBC24

EORTC QLQ–NMIBC24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently during the day?	1	2	3	4
32. Have you had to urinate frequently at night?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house, because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Have you had pain or a burning feeling when urinating?	1	2	3	4
38. Did you have a fever?	1	2	3	4
39. Did you feel ill or unwell?	1	2	3	4
40. Did you have trouble arranging your life around the repeated bladder treatment appointments (cystoscopies or instillations)?	1	2	3	4
41. Did you worry about having repeated bladder treatments (cystoscopies or instillations)?	1	2	3	4
42. Were you worried about your health in the future?	1	2	3	4
43. Did you worry about the results of examinations and tests?	1	2	3	4
44. Did you worry about possible future treatments?	1	2	3	4
45. Did you have a bloated feeling in your abdomen?	1	2	3	4
46. Have you had flatulence or gas?	1	2	3	4
47. To what extent were you interested in sex?	1	2	3	4
48. To what extent were you sexually active (with or without sexual intercourse)?	1	2	3	4
49. For men only: Did you have difficulty gaining or maintaining an erection?	1	2	3	4
50. For men only: Did you have ejaculation problems (e.g. dry ejaculation)?	1	2	3	4
51. Have you felt uncomfortable about being sexually intimate?	1	2	3	4
52. Have you worried that you may contaminate your partner during sexual contact with the bladder treatment you have been receiving?	1	2	3	4
53. To what extent was sex enjoyable for you?	1	2	3	4
54. For Women only: did you have a dry vagina or other problems during intercourse?	1	2	3	4

Questionnaires are available from the EORTC Quality of Life Group (www.EORTC.be/qol/). Copy right EORTC Quality of Life Group

Appendix 4 Debrief Participant Letter

Study Title: A Pilot Study of Hyperthermic Intravesical Saline During Transurethral Resection of Bladder Tumor in Patients with Non-Muscle Invasive Bladder Cancer

Dear [Participant Name],

Thank you for taking part in our clinical research study. Now that you have finished your involvement, we want to share more information about the study and your part in it.

This pilot study looked at how safe and tolerable it is to use hyperthermic intravesical saline (HISA) with gemcitabine as an added treatment for non-muscle invasive bladder cancer (NMIBC). We also wanted to see if this approach is practical to use. To do this, we compared two groups of participants:

- One group received the standard treatment, which includes removing the bladder tumor with a procedure called transurethral resection of the bladder tumor (TURBT) and any follow-up care recommended by the clinical team.
- The second group received the standard treatment plus HISA during the TURBT procedure. HISA is an investigational therapy that delivers warmed saline directly into the bladder.

You were randomly assigned to: **[INSERT: "Arm A – Standard of Care" OR "Arm B – Standard of Care + HISA]**.

We waited to tell you which group you were in during the study to avoid influencing your experience and to make sure your symptom reports were as accurate as possible. Now that you have finished the study, we can share this full information with you.

If you have any questions about your group assignment, your participation, or how this may impact your future care, please don't hesitate to contact the study team at:

[Study Coordinator Name]
Phone: [XXX-XXX-XXXX]
Email: [email@example.edu]