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Heated Intravesical Chemotherapy: Biology and Clinical Utility

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Synopsis

Non-muscle invasive bladder cancer (NMIBC) can be a challenging disease to manage. In recent years, hyperthermia therapy in conjunction with intravesical therapy has been gaining traction as a treatment option. Hyperthermic intravesical chemotherapy is an alternative method of managing NMIBC, especially if BCG might not be available. Trials of intravesical chemotherapy with heat are few and there has been considerable heterogeneity between studies. However, multiple new trials have accrued and high-quality data is on its way. In this review, we discuss the role of combined intravesical hyperthermia and chemotherapy as a novel approach for the treatment of bladder cancer.

Keywords

bladder hyperthermia; heated chemotherapy; heated mitomycin; intravesical chemotherapy; intravesical Mitomycin; HIVEC

INTRODUCTION

Bladder cancer (BC) is the 4th most commonly diagnosed cancer in men and more than 75% are non-muscle invasive (NMIBC) at diagnosis.^{1,2} NMIBC is generally treated with transurethral resection of the bladder tumor (TURBT) as a first step. In high-grade tumors, a repeat TURBT is often performed to ensure complete tumor removal and the absence of muscle-invasive cancer.³ Patients determined—based on grade, stage, number of tumors, size of tumors, etc.—to be at intermediate or high risk of recurrence are usually treated with adjuvant intravesical chemotherapy or Bacillus Calmette-Guerin (BCG). BCG-treated patients are generally offered maintenance therapy for 1 year if intermediate risk or 3 years if high-risk.⁴ Despite these years of active therapy, many (up to half) patients with NMIBC will experience a disease recurrence.⁵ For those patients whose tumors are BCG unresponsive, radical cystectomy is the standard of care salvage treatment but carries a significant morbidity and mortality risk.⁶ For this reason, most patients faced with the prospect of

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cystectomy inquire about bladder preserving alternatives and one such alternative is the combination of intravesical chemotherapy with heat.

Hyperthermia as a treatment for NMIBC

The application of mild fever-range heat (40-44°C) to the bladder is called hyperthermia (HT).⁷ HT is different from thermal ablation where temperatures reach 60-90°C. In general, HT can be used to 1) improve drug delivery to the bladder, 2) kill malignant urothelial cells directly, 3) improve bladder cancer sensitivity to chemotherapy, and 4) trigger anti-cancer immune responses.⁸⁻¹⁰

1) Drug delivery—When a tumor is heated between 38-42°C, several important vascular physiological effects occur. Local vasodilation occurs and results in increased blood flow to the tumor and adjacent tissue.¹¹ The warmer environment causes the lipid-protein membrane bilayer that contains cells to become more permeable, resulting in easier drug penetration into the cell through the cell membrane. These two mechanisms work synergistically to make an already leaky tumor vasculature even leakier, a phenomenon known as the *enhanced permeability and retention* (EPR) effect.¹² By increasing the EPR effect, HT improves drug delivery to bladder tumors which, in turn, leads to better tumor cell destruction.

2) Cytotoxicity—Since tumors are characterized by a constant state of a relatively inadequate resource supply, their microenvironment develops a hypoxic, acidotic, and energy-deprived character.¹³ HT to >42°C further alters blood flow to the tumor microenvironment, further depriving the tumor of the oxygen and nutrients that it needs to survive.¹³ Morphological changes observed when this occurs include an outflow of cytoplasm into the interstitial space, endothelial swelling, changes of the viscosity of blood cell membranes, and micro-thrombosis.^{11,14} Tumor cells are more sensitive to HT than normal urothelial cells and therefore suffer a lot more during mild heating.

3) Improving sensitivity to therapeutic agents—Multiple antineoplastic agents have been shown to be more efficacious when administered to a heated tumor,¹¹ and the thermal enhancement ratio (TER) quantifies the degree to which heat affects drug efficacy.¹⁵ The TER generally compares the ratio of cell kill at 43°C to that at 37°C, with drugs possessing a TER >1 working better with heat. Chemotherapeutic agents used to treat bladder cancer such as cisplatin, mitomycin C (MMC), gemcitabine, and doxorubicin all have a TER of >1.3.¹⁶ It is noteworthy that the timing of heating relative to chemotherapy exposure may be important. For example, gemcitabine appears to work better when administered 24 hours after HT.¹⁷

4) Anti-cancer immune responses—Temperature is a well-known regulator of immune function.¹⁸ Some relevant effects of HT on immunity include changes in number and phenotype of tumor-infiltrating leukocytes, improved tumor-infiltrating leukocyte function, and cytokine release.¹⁹ HT also causes heat-shock protein (HSP) release from tumor cells, particularly HSP70 and HSP90, resulting in cross priming of antigen-specific

cytotoxic T lymphocytes.²⁰ The consequence is that HT-treated tumors actively participate in their own demise by leading to a form of self-vaccination.

Methods of delivering bladder hyperthermia

While there are many ways to categorize devices for hyperthermia, the most obvious category to both the patient and the clinician is how the heat is delivered – external versus internal. External devices use energy emitters to apply heat to a field within the body. They incorporate treatment planning systems to optimize the dose delivered and minimize damage to adjacent tissue, similar to the dose planning used in radiation therapy.

1) External devices—One type of external heating is deep regional radiofrequency, which uses an array of radiofrequency emitters to focus heat into the body. These devices require a medical physics team and a radiofrequency shielded room, which increases cost and decreases generalizability to office-based locations where NMIBC is typically treated. Furthermore, due to the risk of heating implanted metal, external radiofrequency-based heating is generally contraindicated in patients with implanted medical devices (e.g. pacemakers) and hip replacements.²¹ The BSD 2000 system is an example of an external deep regional radiofrequency device. It uses electromagnetic phased array applicators to deliver deep tissue hyperthermia and allows control of the 3D pattern of therapy specific to the patient's tumor.²²⁻²⁶ For bladder hyperthermia, the patient has temperature probes placed in the rectum, and bladder to monitor the internal temperature. A water filled applicator is then placed over the lower abdomen/pelvis and water is circulated to cool the skin during therapy. Another example is the AMC device, now sold as the Alba 4D system, which also uses radiofrequency arrayed systems to achieve deep tissue HT.^{22,27-29} As with the BSD system, it is coupled with a water bolus temperature control apparatus. Other electromagnetic systems include the Thermotron (only available in North Africa and the Middle East) and the Celsius 42 devices. A significant advantage of the Celsius 42 system is that it does not require a shielded room, though it has not been studied in NMIBC.

High intensity focused ultrasound (HIFU) is another form of external heating. As the name suggests, HIFU uses the focused soundwaves in an accurate and specific manner to increase the temperature of the tumor without harming adjacent tissue. The commercially available HIFU systems are large devices that externally deliver HIFU. There is a laparoscopic probe that uses a single transducer to image and deliver HIFU to the tumor in a more precise, albeit invasive manner.³⁰

2) Internal devices—Internal devices lack the depth of penetration of external devices but have the significant advantage of delivering heat almost exclusively to the bladder. There are 2 systems that use conductive hyperthermia the Combat Bladder Recirculating system (BRS) and Unithermia.^{31,32} Both devices externally heat fluid and the circulate it to the bladder via a 3-way irrigating Foley catheter. The recirculating fluid contains a chemotherapy agent chosen by the treating physician. Recirculating systems are the smallest, most portable, and least expensive bladder heaters. Synergo produces a third intravesical bladder heating system that also uses recirculating bladder irrigation but instead of a heat exchanger it employs a microwave radiofrequency emitting intravesical catheter to

heat the bladder.³³⁻³⁵ The Synergo device is presently the most well studied device amongst those mentioned, though several large trials of the Combat BRS device have accrued and will report results soon.

There are two additional devices worth mentioning, electromotive drug administration (EMDA) and nanoparticles. Although in the strict sense, these are not hyperthermia devices, they do share a similar therapeutic mechanism. EMDA uses a urethral catheter to deliver ionized drugs intravesically. Dispersive pads (similar to electrocautery) are placed on the lower abdomen and an electric current is applied intravesically to drive the drug into the urothelium at a rate proportional to the amount of current being applied. EMDA allows for greater depth of penetration than would be achievable by passive diffusion alone.³⁶ Nanoparticles can be administered intravenously or intravesically and they preferentially accumulate in tumors secondary to the enhanced permeability and retention effect.³⁷ Externally delivered light or alternating magnetic fields generates heat in the tissue hosting the nanoparticles.

Clinical experience with bladder hyperthermia

The combination of heat and intravesical chemotherapy has been utilized both in the neoadjuvant (pre-TURBT) and adjuvant settings (post-TURBT). For this review we use HIVEC as the acronym for hyperthermic intravesical chemotherapy. The large majority of HIVEC treatments done thus far have utilized MMC as the chemotherapy agent.

Phase 1 & 2 trials—To date, there are 5 clinical trials of neoadjuvant chemo ablative HIVEC for NMIBC and all used MMC. In these trials, 60-100% of patients had previously undergone some form of intravesical therapy (Table 1). The complete response rate of patients who underwent HIVEC ranged from 53% - 75% with a partial response rate of 20% - 47%. The recurrence rate ranged from 13% - 39% at a median follow up of 15 - 39 months.^{34,38-41}

The first trial of MMC HIVEC was conducted by Colombo *et al.* in 1995, where 44 patients underwent neoadjuvant administration of intravesical chemotherapy and simultaneous local bladder hyperthermia for eight 60-minute sessions done twice weekly, followed by TURBT 3 weeks later.³⁹ The complete response rate was 70%, partial response was 20% and no response in 9% of patients. After a mean follow-up of 24 months, 16% recurred.³⁹ In 2004, Gofrit *et al.* treated 52 patients with high-grade NMIBC with MMC HIVEC.³⁴ Of these, 28 men were treated with neoadjuvant HIVEC (MMC 80 mg) and 24 men adjuvant HIVEC (MMC 40 mg). More than 50% of both groups have been previously treated with BCG. Recurrence-free survival was 71% at a median follow up of 15 months. Surprisingly, in the neoadjuvant cohort, 75% of patients achieved complete response to therapy.³⁴ Subsequently, there were 2 randomized trials conducted by Colombo *et al.* where neoadjuvant HIVEC (MMC 40 mg) was compared to standard MMC, or to EMDA (MMC 40 mg) and standard MMC.^{40,41} HIVEC achieved a complete response in 66% of patients in both studies, compared to 22% for standard MMC and 40% for EMDA.^{40,41}

There are 3 phase 1 & 2 adjuvant trials reporting recurrence-free survival. In these 3 trials, the patient cohort consisted of intermediate and high-grade NMIBC. The 1 and 2-year recurrence-free survival ranges from 67% to 87% and 50% to 91%, respectively (Table 2).

Soria *et al.* utilized the Unithermia device which delivers heat via conducting heating. In this study, 34 patients with recurrent, intermediate risk NMIBC underwent a 6-week course of HIVEC (MMC 40 mg) for 45 min. The 1, 2 and 5-year RFS were 85%, 74% and 55% respectively.⁴² The other 2 trials utilized the Synergo system in high and intermediate risk NMIBC. Patients in both studies received two 30-minute sessions of HIVEC (MMC 20 mg) for 6-8 cycles. The 1 and 2-year RFS ranged from 67-87% and 61%-75%.^{34,43}

Phase 3—To date, there are no phase 3 trials utilizing neoadjuvant HIVEC for NMIBC but there are 3 adjuvant HIVEC trials. In 2003, Colombo *et al.* randomized 83 patients (>50% with high risk NMIBC) to HIVEC versus standard MMC. In both arms, patients received 20 mg/50 mL of MMC for two 30-minute sessions for 6 weeks. The 2-year RFS and 5-year RFS were 83% vs 38% and 62% vs 21% for HIVEC and standard MMC, respectively. The hazard ratio for HIVEC was 0.21.⁴⁴

Arends *et al.* subsequently reported a phase 3 randomized controlled trial where 190 patients with intermediate and high risk NMIBC were randomized HIVEC or BCG. Patients in the BCG arm received induction OncoTICE BCG (induction + maintenance at 3, 6 and 12 months). HIVEC patients received MMC (20mg/50mL) for two 30-minute sessions for 6 weeks, and maintenance course (3 cycles) at 3, 6 and 12 months. The 2-year RFS was better for HIVEC (82%) than BCG (65%).⁴⁵

More recently, in the HYMN trial 104 patients with BCG unresponsive NMIBC were randomized to HIVEC (MMC 20 mg/50mL) vs standard MMC. Patients received induction followed by three once-weekly maintenance instillations at 3, 6, 12, 18 and 24 months. There was no statistical difference in RFS between the arms at 2 years (HR 1.33; 95% CI 0.84-2.10, $p=0.23$).⁴⁶ At a median follow up of 35 months, the rate of disease progression was 8%.

In addition to the trials noted above, there are 6 observational studies of neoadjuvant HIVEC and 10 of adjuvant HIVEC and these are summarized in Tables 1 and 2.^{31,35,47-59}

Recurrence-free survival curves from the various studies utilizing the Synergo, Combat BRS and Unithermia devices are pooled and shown in Figure 1.

Clinical experience with EMDA

The combination of MMC and EMDA has been utilized both in the neoadjuvant (pre-TURBT) and adjuvant settings (post-TURBT). Intravesical EMDA MMC is administered using a controlled electric current of up to 30 mA using a battery-powered generator. A specialized 16 Fr catheter is inserted and urine drained. MMC is then instilled with an operating current of 15-20 mA pulsed electrical current for 20 to 30 minutes per session. To date, 2 small clinical trials have utilized EMDA in the neoadjuvant setting (Table 3) and 4 studies have used EMDA in the adjuvant setting (Table 4). EMDA was found to have a complete response rate of 40% in the neoadjuvant setting.^{41,60} In the adjuvant setting,

EMDA was found to have a 1-year RFS, 2-year RFS and 5-year RFS rate of 86-100%, 49-80%, 38-40% respectively.⁶¹⁻⁶⁴ One study evaluated TURBT, TURBT with immediate postoperative MMC and neoadjuvant MMC with EMDA followed by TURBT. Patients with intermediate-risk and high-risk disease in all three groups were then placed on maintenance MMC and BCG, respectively. The group that received neoadjuvant MMC with EMDA followed by TURBT had the highest 5-year RFS of 62% compared to 37% in the TURBT only arm.⁶⁵

Safety

The first bladder hyperthermia treatment was attempted in 1972 where Thio-Tepa was used in conjunction with HT up to 44°C for low stage bladder tumors.⁶⁶ Since then, multiple adverse events that include hematuria, UTI, sepsis, stricture, allergic reaction to chemotherapy agent, dysuria, frequency, urgency and incontinence have been reported (Table 3). There was insufficient data to pool for grade 3 or higher adverse events, UTI, sepsis and allergic reaction. The rate of grade 3 or higher adverse event rate ranges from 10-12% across all sources of energy in patients receiving HT in clinical trials published.^{31,67} UTI and sepsis occurred in 0-23% of patients, and strictures in 0-10%.⁶⁷ Allergic reaction occurred in 0-15% of patients.⁶⁷ Pooling data for randomized controlled trials showed that the relative risk of hematuria in the HT arm is 1.28 (95% CI 0.89-1.83, I²=0).

Future perspective & other novel agents

For intermediate risk NMIBC, HIVEC-I (EudraCT 2013-002628-18) and HIVEC-II (ISRCTN 23639415) are multi-institutional randomized controlled trials comparing HIVEC with standard MMC in patients with intermediate-risk NMIBC. Both trials have completed accrual (N = 598 subjects combined). HIVEC-HR (EudraCT 2016-001186-85) is assessing HIVEC in high-risk NMIBC and HIVEC-R (EudraCT 2014-005001-20) is assessing HIVEC as neoadjuvant chemoablation. All of these trials are using the Combat BRS device. Lastly, the RITE-USA trial () is assessing HT with the Synergo device for BCG-unresponsive NMIBC.

A novel temperature-sensitive liposome drug delivery system is worth highlighting here. The first drug, called ThermoDox and developed at Duke, is loaded with doxorubicin and is administered systemically to releases free drug when it arrives in tissues heated to 41°C. When combined with bladder HT, this technology allows for organ-specific targeting of systemic agents. In a swine model, ThermoDox is able to achieve doxorubicin levels far exceeding free doxorubicin while minimizing toxicity in other organs.⁶⁸

CONCLUSIONS

Intravesical chemotherapy and hyperthermia therapy is safe and able to augment the efficacy of intravesical chemotherapy for the treatment of BCG refractory NMIBC, especially in a time of BCG shortage. Further prospective randomized controlled trials combining other forms of chemotherapy with hyperthermia therapy is warranted to determine if improved efficacy is obtained in those drugs. Other combinations of therapy such as combining

hyperthermia and intravesical chemotherapy therapies such as PD-1/PD-L1 blockade is warranted.

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Key points

1. Heat can improve drug delivery, increase cancer cell sensitivity to therapeutic agents, and trigger anti-cancer immune responses.
2. Three methods of bladder heating are available clinically: external deep regional radiofrequency heating, intravesical catheter radiofrequency heating, and recirculating conductive heating.
3. Administering intravesical chemotherapy with heat is safe and appears to improve treatment efficacy.

Figure 1:
Combined Kaplan Meier Graph of recurrence free survival for all studies on chemothermia therapy.

Table 1: Phase 1 & 2 trials and observational studies on neoadjuvant intravesical chemotherapy therapy

Author & year	Study design	Sample size	Treatment	Heat Source	Induction Schedule	Maintenance schedule for CR group	% of patients with previous intravesical treatment	f/u	CR	PR	NR	Recurrence Rate
Colombo 1995 ³⁹	Phase 1	44	30mg MMC in 60ml water for 40 minutes	Synergo (42.5-44.5°C)	Twice-weekly within 6 weeks (Total of 8 sessions)	-	63.6%	24 months (mean)	70.4	20.4	9.1	15.9%
Gofrit 2004 ³⁴	Phase 1	28	(40mg MMC dissolved in 50ml of distilled water for 20 minutes) × 2	Synergo (42 ± 2°C)	Once-weekly × 8	Once-monthly × 4	60.1%	15.2 months	75%	-	-	19%
Sousa 2014 ³⁸	Phase 1	15	80mg MMC dissolved in 50ml of distilled water for 60 minutes	Combat BRS (42 ± 1°C)	Once-weekly × 8	Partial responder once-weekly × 4, then once-monthly × 11. CR did not received maintenance	74%	29 months	53%	47%	0%	13.3%
Colombo 1996 ⁴⁰	Phase 2	29	(40mg MMC in 50 ml distilled water for 30 minutes) × 2	Synergo (42.5-46°C for 60 minutes)	Once/twice-weekly × 6-8	-	100%	38 months	66%	34%	0%	27%
		23	40mg MMC in 50 ml sterile water for 60 minutes	-	Once/twice-weekly × 6-8	-	100%	36 months	22%	26%	52%	39%
Colombo 2001 ⁶³	Phase 2	36	40mg MMC in 50 ml of saline for 60 minutes	-	Once-weekly × 4	-	-	-	27.7%	-	-	-
		29	40mg MMC diluted in 50ml of distilled water for 60 minutes	Synergo (mean of 42.5°C)	Once-weekly × 4	-	-	-	66%	-	-	-
		15	40mg MMC dissolved in 150ml of distilled water & EMDA for 20 minutes	Physionizer 30	Once-weekly × 4	-	-	-	40%	-	-	-
Rigatti 1991 ³⁵	Observational	12	30mg MMC dissolved in 60ml of	SB-TS 100 (41.5-43.5°C)	Once/twice-weekly × 6-8	-	-	16 months	41.7%	33.3%	25%	8.3%

Author & year	Study design	Sample size	Treatment	Heat Source	Induction Schedule	Maintenance schedule for CR group	% of patients with previous intravesical treatment	f/u	CR	PR	NR	Recurrence Rate
			distilled water for 60 minutes									
Moskovitz 2005 ⁴⁹	Observational	10	(40mg MMC dissolved in 50ml of distilled water for 30 minutes) × 2	Synergo (42 ± 2°C)	Once-weekly × 8	Once-monthly × 4	80%	5.6 months (mean)	80%	-	-	-
Witjes 2009 ⁶³	Observational	26 (100% CIS)	(40mg MMC dissolved in 50ml of distilled water for 30 minutes) × 2	Synergo (41-44 °C for 60 minutes)	Once-weekly × 6	Once every 6 weeks × 6 (total of 6 sessions)	66.7%	22 months	92%	-	-	22%
Moskovitz 2012 ⁵¹	Observational	26	(40mg MMC dissolved in 50ml of distilled water for 30 minutes) × 2	Synergo (approximately 42°C)	Once-weekly × 8	Once every 6 weeks for 1 st year (20mg MMC)	76.9%	9 months	79%	8%	13%	16%
Volpe 2012 ⁵²	Observational	14	(40mg MMC dissolved in 50ml of distilled water for 30 minutes) × 2	Synergo (42 ± 2°C)	Once-weekly × 8	Once-monthly × 6	100%	14 months (mean)	42.9%	9.9%	47.2%	46.3%
Sousa 2016 ³¹	Observational	24	80mg MMC dissolved in 50ml of distilled water for 60 minutes	Combat (43 ± 0.5 °C)	Once-weekly × 8	Once-monthly × 6	33%	37 months	62.5%	33.3%	4.2%	31.3%

Dose in the maintenance group is similar to treatment unless stated otherwise. HT: hyperthermia therapy; MMC: Mitomycin C; EMDA: Electromotive drug administration; CR: Complete response

Table 2: Phase 1, 2 & 3 trials and observational studies on adjuvant intravesical chemothermia therapy.

Author & Year published	Trial	Sample size	Treatment per session	Heat Source	Induction schedule	Maintenance schedule for CR group	Risk Group (% patients)	Hx of intravesical therapy (% patients)	Follow up, Median (IQR)	1-year RFS	2-year RFS	5-year RFS
Gofrit 2004 ³⁴	Phase 1	24	(20mg MMC in 50ml of distilled water for 20 minutes) × 2	Synergio (42 ± 2°C)	Once-weekly × 8	Once-monthly × 4	High grade (100%)	87.5%	35.3 months (mean)	66.5%	60.6%	52.1%
Soria 2016 ⁴²	Phase 1 & 2	34	(40mg MMC in 50ml saline for 22 minutes) × 2	Unithermia (42.5 ± 1°C)	Once-weekly × 6	Once-monthly × 4	High grade (53%) Low grade (47%)	100%	41 (–)	85.4%	73.5%	55.2%
vanderHeijden 2004 ⁴³	Phase 2	90	(20mg MMC in 50ml of distilled water for 30/60 minutes) × 2/1	Synergio (41 – 44°C)	Once-weekly × 6-8	Once-monthly × 4-6	High risk (41%) Intermediate risk (59%)	66.1%	18 (4-24)	86.7%	75.4%	-
Colombo et al 2003 ⁴⁴	Phase 3	42	(20mg MMC in 50ml of distilled water for 30 minutes) × 2	Synergio (42 ± 2°C)	Once-weekly × 8	Once-monthly × 4	High grade (90.5%)	-	24 months (–)	88.7%	82.8%	61.7%
		41	20mg MMC in 50ml of distilled water for 60 minutes	-	Once-weekly × 8	Once-monthly × 4	High grade (97.6%)	-		50.3%	38.4%	21.3%
Arends 2016 ⁴⁵	Phase 3	92	(20mg MMC in 50ml of distilled water for 30 minutes) × 2	Synergio (42 ± 2°C)	Once-weekly × 6	Once every 6 weeks for the 1 st year	High grade (81.6%) Low grade (18.4%)	52%	24 months (–)	90.5%	80.2%	-
		98	BCG (Oncoice) full dose for 120 minutes	-	Once-weekly × 6	Three weekly doses at 3, 6 & 12 months	Intermediate risk (67.4%) High risk (32.6%)		75.8%	66.5%	-	
Tan 2019 ⁴⁶	Phase 3	48	(20mg MMC in 50ml of distilled water for 30 minutes) × 2	Synergio (42 ± 2°C)	Once-weekly × 6	Once every 6 weeks for the 1 st year, once every 8 weeks for the 2 nd year	High grade (100%)	100%	36 months (23.1-44.5)	49.8%	35%	-
		56	BCG or standard of	-	Once-weekly × 6	Three weekly instillations at 3,	High grade (100%)	100%		56.7%	42.1%	-

Author & Year published	Trial	Sample size	Treatment per session	Heat Source	Induction schedule	Maintenance schedule for CR group	Risk Group (% patients)	Hx of intravesical therapy (% patients)	Follow up, Median (IQR)	1-year RFS	2-year RFS	5-year RFS
			care at institution			6, 12, 18 & 24 months						
Moskovitz 2005 ⁴⁹	Observational	22	(20mg MMC dissolved in 50ml of distilled water for 30 minutes) ×2	Synergio (42 ± 2°C)	Once-weekly × 6-8	Once-monthly × 4-6	High grade (68.2%) Low grade (31.8%)	63.5%	9.6 months (mean)	100%	70%	-
Nativ 2009 ⁵³	Observational	111	(20mg MMC in 50ml solution for 30 minutes) ×2	Synergio (42 ± 2°C)	Once-weekly × 6	Once every 4-6 weeks ×6	High grade (61%) Low grade (39%)	100%	16 months (range 2-74)	85%	56%	-
Halachmi 2011 ⁵⁴	Observational	56	(20mg MMC for 30 minutes) ×2	Synergio (42 ± 2°C)	Once-weekly × 6	Once every 4-6 weeks × 6	High grade (100%)	54%	18 months (range 2-49)	77%	42.9%	-
Moskovitz 2012 ⁵¹	Observational	66	(20mg MMC in 50ml solution for 30 minutes) ×2	Synergio (approximately 42°C)	Once-weekly × 6	Once every 6 weeks for 1 st year	High grade (45.5%) Low grade (51.5%) Not reported (1.5%)	74.2%	23 months (range 3-84)	86.5%	67.2%	-
Volpe 2012 ⁵²	Observational	16	(20mg MMC dissolved in 50ml of distilled water for 30 minutes) ×2	Synergio (42 ± 2°C)	Once-weekly × 6	Once-monthly × 6	High grade (100%)	100%	14 months (mean)	87.5%	58.6%	-
Maffezzini 2014 ⁵⁵	Observational	42	40mg MMC dissolved in 50ml of distilled water for 60 minutes	Synergio (42.5 ± 1.5°C)	Once-weekly × 4	Once every 2 weeks ×6, then once-monthly ×4	High grade (100%)	64.3%	38 months (range 4-73)	88.1%	80.2%	63.5%
Ekin 2015 (APICP) ⁵⁶	Observational	43	40mg MMC dissolved in 50ml of distilled water for 60 minutes	UniThermia (42.5-45°C)	Once-weekly ×6	Three weekly instillations at month 3 & 6	High grade (58.1%) Low grade (41.9%)	-	30 months (range 9-39)	82%	61%	-
Ekin 2015 (CIU) ⁵⁷	Observational	40	40mg MMC in 50 ml saline solution for 60 minutes	UniThermia (42.5-45°C)	Once-weekly ×6	Three-weekly instillations at month 3 & 6	High grade (60%) Low grade (40%)	-	33 months (24-39)	92.2%	73.6%	-

Author & Year published	Trial	Sample size	Treatment per session	Heat Source	Induction schedule	Maintenance schedule for CR group	Risk Group (% patients)	Hx of intravesical therapy (% patients)	Follow up, Median (IQR)	1-year RFS	2-year RFS	5-year RFS
Sooriakumaran 2016 ⁵⁹	Observational	97	40mg MMC dissolved in 50ml of normal saline for 60 minutes	Synergo (41 - 44°C)	Once-weekly × 6-8	Once every 6 weeks for the 1 st year, one every 8 weeks for the 2 nd year (20mg MMC)	High grade (100%)	90.7%	27 months (16-47)	82.7%	66.0%	48.6%
Sousa 2016 ⁴²	Observational	16	40mg MMC dissolved in 50ml of distilled water for 60 minutes	Combat (43 ± 0.5°C)	Once-weekly × 4	No	High risk (71%) Intermediate risk (29%)	81.3%	24 months	100%	88.1%	-

Dose in the maintenance group is similar to treatment unless stated otherwise. HT: hyperthermia therapy; MMC: Mitomycin C; BCG: Bacillus Calmette-Guerin; RFS: Recurrence Free Survival; Hx: History; CR: Complete Response

Table 3: Adverse events from phase 1, 2 & 3 trials and observational studies on intravesical chemothermia.

Author	Year	Study Type	N	Energy	Complete treatment (%)	Grade 3 adverse events (%)	Hematuria (%)	UTI or sepsis (%)	Stricture (%)	Allergic reaction (%)
Colombo	1995	Phase 1	44	RITE	-	-	-	-	2	2
Gofrit	2004	Phase 1	52	RITE	96	-	2	10	2	10
Sousa	2014	Phase 1	15	Conduction	-	0	20	13	0	7
Soria	2016	Phase 1/2	34	Conduction	88	12	-	4	-	-
Colombo	1996	Phase 2	29	RITE	93	-	-	-	0	-
Colombo	2001	Phase 2	29	RITE	100	0	-	-	-	-
vanderHeijden	2004	Phase 2	90	RITE	100	-	9	0	4	9
Colombo	2003	Phase 3	42	RITE	69	-	7	0	7	12
Arends	2016	Phase 3	184	RITE	-	-	-	-	-	-
Tan	2018	Phase 3	48	RITE	90	10	48	23	6	15
Moskovitz	2005	Observational	47	RITE	-	4	17	0	6	4
Nativ	2009	Observational	111	RITE	95	8	19	2	5	8
Witjes	2009	Observational	26	RITE	92	-	3%	-	-	-
Halachmi	2009	Observational	56	RITE	91	-	4	0	2	12.5
Moskovitz	2012	Observational	92	RITE	96	4	7	1	5	1
Volpe	2012	Observational	30	RITE	100	-	27	7	0	13
Maffezzini	2014	Observational	42	RITE	88	0	62	0	0	0
Ekin (APICP)	2015	Observational	43	Conductive	93	12	9	0	0	7
Ekin (CJU)	2015	Observational	40	Conductive	95	-	-	-	-	-
Sooriakumaran	2015	Observational	97	RITE	93	7	14	23	0	0
Kiss	2015	Observational	21	RITE	62	52	24	0	10	10
Sousa	2016	Observational	40	Conductive	98	8	23	23	3	3

RITE: Radiofrequency-Induced Thermo-chemotherapeutic Effect; UTI: Urinary Tract Infection

Table 4:

Clinical trials and observational studies on adjuvant intravesical MMC and EMDA.

Author & Year published	Trial	Sample size	Treatment per session	EMDA device/curr ent	Induction schedule	Maintenance schedule for CR group	Risk Group (% patients)	Hx of intravesical therapy (% patients)	Follow up, Median (IQR)	1- year RFS	2- year RFS	5- year RFS
DiStasi 2003 ⁶¹	Phase 3	36	40mg MMC in 100ml of distilled water for 60 minutes & EMDA	20mA for 30 minutes	Once-weekly ×6	Non-responders: 2 nd induction course Responders: Once-monthly ×10	High grade (100%)	-	43 months	100%	66%	38%
		36	40mg MMC in 100ml of distilled water for 60 minutes	-	Once-weekly ×6	Non-responders: 2 nd induction course Responders: Once-monthly ×10	High grade (100%)	-		100%	62%	34%
		36	81mg BCG in 50ml saline for 120 minutes	-	Once-weekly ×6	Non-responders: 2 nd induction course Responders: Once-monthly ×10	High grade (100%)	-		100%	39%	21%
		105	81mg BCG for 120 minutes	-	Once-weekly ×6	Once-monthly × 10	High grade (100%)	41%	88 months (63-110)	73%	77%	56%
DiStasi 201 ⁶⁵	Phase 3	107	(Week 1 & 2: 81mg BCG for 120 minutes Week 3: 40mg MMC in 100ml of distilled water & EMDA) ×3	20mA for 30 minutes	3 cycles (9 weeks total)	Month 1, 2, 4, 5, 7 & 8: MMC + EMDA Month 3, 6 & 9: BCG	High grade (100%)	42%		100%	49%	40%
		124	TURBT	-	Once	Low-risk: none Intermediate risk: 40mg MMC dissolved in 50ml of sterile water for 60 minutes weekly ×6 High risk: 81mg BCG dissolved in 50ml of saline for 120 minutes weekly ×6	High grade (82%)	No previous intravesical treatment	92 months (61-126)	62%	42%	37%
		126	TURBT + immediate postoperative 40mg MMC in 50ml water for 60 minutes		Once		High grade (81%)		82 months (50-125)	65%	47%	43%
Riedl 1998 ⁶³	Observational	124	Neoadjuvant 40mg MMC in 100ml water for 30 minutes & EMDA +TURBT	20mA for 30 minutes	Once		High grade (82%)		85 months (57-126)	87%	70%	62%
		22	40mg MMC in 100ml saline	15mA for 20 minutes	Once-weekly × 4	-	High grade (95%)	-	7.3 months (mean)	-	-	-

Author & Year published	Trial	Sample size	Treatment per session	EMDA device/current	Induction schedule	Maintenance schedule for CR group	Risk Group (% patients)	Hx of intravesical therapy (% patients)	Follow up, Median (IQR)	1-year RFS	2-year RFS	5-year RFS
Gan 2016 ⁶⁴	Observational	22	(Week 1 & 2: BCG Week 3: 40mg MMC & EMDA) ×3	Physionizer @ 30: 20mA for 30 minutes	3 cycles (9 weeks total)	(Once-weekly BCG) ×3 on month 3 and every 6 months for 3 years	High grade (100%)	-	24 months	86%	80%	-

Dose in the maintenance group is similar to treatment unless stated otherwise. MMC: Mitomycin C; BCG: Bacillus Calmette-Guerin; RFS: Recurrence Free Survival; Hx: History; CR: Complete Response