A Systematic Review of Regional Hyperthermia Therapy in Bladder Cancer

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Abstract

Context—Bladder cancer therapy remains suboptimal as the morbidity and mortality remains high amongst those with non-muscle invasive and muscle-invasive disease. Regional hyperthermia therapy (RHT) is a promising adjunctive therapy being tested in multiple clinical contexts.

Objective—To systematically review the literature on the efficacy and toxicity of RHT.

Evidence Acquisition—The systematic review was registered with the PROSPERO database (Registration number: CRD42015025780) and was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We queried PubMed, EMBASE, and Cochrane libraries. Two reviewers reviewed abstracts independently and a third reviewer arbitrated disagreements. The last search was performed on August 28, 2015. A descriptive analysis was performed and quality assessment was conducted using the Newcastle-Ottawa Quality Assessment Scale for observational studies, and the Cochrane Risk of Bias Assessment Tool for trials.

Evidence Synthesis—We identified 859 publications in the initial search, of which 24 met inclusion criteria for full-text review. Of these, we were able to obtain data on the outcomes of interest for 15 publications.

Conclusions—The review underscores the limited nature of the evidence; definitive conclusions are elusive. However, the promising results of RHT in the setting of intravesical chemotherapy, chemotherapy and radiotherapy show a trend towards legitimate efficacy.

Keywords

Bladder cancer; urothelial carcinoma; regional hyperthermia therapy; radiohyperthermia; chemohyperthermia

1. Introduction

There will be an estimated 74,000 new cases of bladder cancer and 16,000 deaths in the United States in 2015. This represents 4.5% of all new cancers in the US and it remains the 5th most common [1]. Over 75% are non-muscle invasive bladder cancer (NMIBC) and of these, 50% will recur after the transurethral resection of bladder tumor (TURBT) [2]. Caring for NMIBC involves continued surveillance and frequently, intravesical therapy. Intravesical therapy with chemotherapy and/or immunotherapy has suboptimal efficacy and some toxicity. Especially the patients that are at high risk for a recurrence are found to be refractory to this form of therapy and often proceed to radical cystectomy [3]. Muscle invasive bladder cancer (MIBC) often leads to a cystectomy per guidelines and the associated significant morbidity and mortality [4, 5]. Patients are faced with the anxiety and physical burden, not to mention that bladder cancer is the most expensive malignancy per patient [6]. Novel therapies are being sought as ways to reduce the morbidities and costs of the disease, and potentially preserve that patient's native bladder.

Pre-clinical data provide strong evidence that hyperthermia has the potential to induce anti-tumour immunity [7]. There are at least five proposed mechanisms for the activation of the immune response by hyperthermia. 1) Tumor cells increase surface expression of several markers (e.g., MHC class I) when exposed to heat. 2) Heat causes the tumor to release HSPs, which in turn activates the host immune response. 3) Heated tumor cells release exosomes that carry tumor antigens to the immune system. 4) Heat alone directly activates the immune system. 5) Heat renders the tumor vasculature more permeable which allows for better trafficking of immune cells [8].

Additionally, hyperthermia is an interesting topic of research because of the sensitizing effect with chemotherapy and/ or radiotherapy. Hyperthermia has been shown to enhance drug delivery and thermosensitizes cancer cells to certain antineoplastic drugs [9, 10]. In bladder cancer, it leads to chemosensitization by impairing the repair of damaged DNA and has synergistic action with cytotoxic agents, such as Mitomycin C [11, 12].

Broadly, hyperthermia of the bladder can be achieved via different methods: radiofrequency emitting intravesical catheters (e.g. Synergo, operating at a frequency of 915 MHz [10, 13, 14], externally heated chemotherapy fluid circulation in the bladder [15], intravesical magnetic nanoparticles [16], and external deep regional radiofrequency transmission with 70–110 MHz [17]. While the intravesical heating methods are more commonly used and produce uniform temperatures across the urothelial lining of the bladder, there is a significant temperature gradient measured through increasing depth of the bladder wall. This temperature gradient is unlikely to be important for the treatment of NMIBC (which is confined to the urothelium and suburothelial lamina propria), but may have important consequences for the treatment of muscle invasive bladder tumors. Clinical evidence for the positive effect of radiofrequency-induced hyperthermia (operating at 915 MHz) was published in a meta-analysis in Ta-1 G1-3 NMIBC. After the combination of heat and intravesical therapy with Mitomycin C (MMC), a 59% relative reduction in NMIBC recurrence was seen compared to MMC alone [18]. According to progression, lower rates were seen in case of chemohyperthermia although in most studies an adequate follow up was

lacking [19]. Regional hyperthermia therapy (RHT) results in a more uniform temperature distribution across the bladder wall and the field can be directed beyond the bladder itself to the lymphatic drainage. There are severally commercially available RHT devices including the AMC device, BSD devices, and Thermotron device.

The BSD-2000 (BSD Medical, Salt Lake City, UT, USA) (and its predecessor, the BSD-1000) has been one of the most widely studied devices for RHT. It has been used in trials alone, and as an adjunct to surgery, radiation, and chemotherapy [17,20–23]. This system delivers RHT emitting electromagnetic radiofrequency radiation using a 100±2 MHz radiofrequency Sigma Eye twenty-four array of dipole antennas that surround the patient as the applicator. Applicator selection is based on patient size. Proprietary software pre-plans treatment sessions. The bladder temperature can then be measured through the Foley catheter to assure that the target temperature of 40–45°C is achieved [24]. The patient is then treated for a duration of 45–60 minutes once the therapeutic temperature is met. System power, frequency, relative antenna power, and phase were adjusted frequently during treatment to optimize bladder heating and patient tolerance based on measured temperatures, blood pressure, and patient verbal feedback.

The AMC 70 MHz phased array system consists of one or two rings, each with 4 wave guide antennas (aperture 33×21 cm) positioned around the pelvis of the patient and connected to a phase and amplitude controlled RF Generator (SSB Electronic). Patients are treated in supine position, using cooled water pillows to connect the antenna power to the patient. Phase settings are first optimized to create a focus at the rectum guided by an E-field probe in the rectum, followed by a phase shift of the dorsal and ventral antenna to move the focus from rectum to bladder [25].

Final settings are validated by performing ΔT pulses for three phase settings with 40° phase shifts between the dorsal and ventral antenna [26].

Thermometry is performed with 14-sensor thermocouple probes (Ella CS, Czech Republic) inserted in catheters in bladder, rectum (and vagina, if applicable). Temperature data are recorded using a 196-channel thermometry unit. Treatment continued for 60 min after bladder temperatures reached 41°C, or for a maximum total duration of 90 min, whichever was shortest [17, 27, 28].

The Thermotron (Yamamoto Vinita, Co., Osaka, Japan) is an 8 MHz radiofrequency capacitive heading device. The output ranges from 271–965 (578 ±86.2) Watt. Large, deep seated tumors require large electrodes, and conversely small, superficial tumors respond to smaller electrodes. Pairs of electrodes with a cooling bolus are placed on the front and back of the patient. Patients with subcutaneous fat tissue > 2 cm thickness had superficial tissue was cooled for 15–20 min prior to and during heating with 10–15°C saline. For heating deep areas of the body, an overlay bolus sheet in addition to the regular bolus was applied and the body surface was cooled continuously during heating [29, 30].

This collaborative review provides a critical overview of current literature concerning the role of deep regional hyperthermia for the treatment of NMIBC and MIBC.

2. Evidence Acquisition

The systematic review was registered with the PROSPERO database (Registration number: CRD42015025780) and was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. A search of Medline, Embase, Cochrane Library, CancerLit and ClinicalTrials.gov databases was undertaken for candidate manuscripts from 1966 through August 2015 and was not limited by language.

Candidate manuscripts were reviewed according to the Cochrane Collaboration criteria and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Two reviewers (TL and AG) independently performed database searches, assessed candidate manuscripts for inclusion criteria, and extracted primary data. A detailed description of the search strategy is given in Appendix A. Authors and experts in the field were asked for additional studies. In order to address a paucity of data on this topic, this systematic review followed the best-available-evidence approach and included several single group studies, a decision made a priori [31]. Reviewed studies consist of prospective and retrospective cohorts in which all subjects received a single intervention and the outcome was assessed over time, but lacks an internal comparison.

2.1 Eligibility criteria

Studies were eligible if they met the following inclusion criteria: 1) Adult patients with diagnosis of bladder cancer, 2) intervention with regional hyperthermia.

Studies were excluded if they involved: 1) pediatric patients, 2) animal studies, or 3) review papers 4) case reports, or 5) ablative temperatures > 45C. The review was not restricted to the English language. Duplicate publications were also excluded and only manuscripts where the full-text publication was retrievable were included.

2.2 Quality assessment

Study quality assessment was conducted using the Newcastle-Ottawa Quality Assessment Scale, which is used to evaluate studies based on three criteria: (i) patient selection, (ii) comparability of groups, and (iii) ascertainment of outcome or the Cochrane Risk of Bias Tool for clinical trials. Studies were assessed on a star scoring scale, with higher scores given for higher quality studies. Studies were not excluded in the review based on the perceived quality of the study. The primary end point was response. The secondary end points were recurrence, time to progression and adverse event (AE) rate.

3. Evidence synthesis

3.1 Search results

We identified 859 publications in the initial search, of which 24 met inclusion criteria for full-text review. Of these, we were able to obtain data on the outcomes of interest for 15 publications. A total of 346 patients who underwent RHT treatment for bladder cancer were included. Characteristics of the studies which were included can be found in Table 1.

3.2 Non-muscle invasive bladder cancer

There were two pilot studies using RHT with intravesical mitomycin C (MMC) in NMIBC [21, 27], and a third trial using intravesical doxorubicin [32]. Geijsen *et al.* employed the AMC 70 MHz device and involved 6 weekly courses of RHT combined with intravesical chemotherapy with MMC in 18 patients with intermediate and high risk NMIBC after trans urethral resection of the bladder tumor; it was then followed with a maintenance period over the next 12 months. During maintenance, the patients received a single course of RHT with MMC at 3, 6, 9, and 12 months [27]. The primary endpoint of this trial was feasibility and toxicity. No grade 3 toxicity or higher was seen and the temperatures achieved in the bladder were satisfactory. They reported a recurrence free survival rate of 78% at 24 months. However, 3/9 patients who had completed induction showed recurrent or progressive disease and one developed distant metastasis. 83% of the patients completed induction and 50% completed maintenance, or a 17% and 50% dropout rate, respectively.

Inman *et al.* assessed 15 NMIBC, in patients who were BCG refractory. The treatment protocol consisted of 6 weekly courses of RHT combined with intravesical MMC. A maintenance schedule involved monthly RHT with intravesical MMC for 4 additional months. 73% of patients completed induction and maintenance for a dropout rate of 27%. Recurrence-free survival at 24 months was 33%, but this was maintained beyond 3 years. None of the recurrences progressed to muscle invasive disease. Six of the ten patients who experienced recurrence underwent a cystectomy and all were node negative with no greater than T1 disease [21]. The difference in length of the treatment period may have influenced the lower dropout rate and lower recurrence free survival compared to Geijsen *et al.*

Ueda *et al.* performed a nonrandomized trial comparing intravesical HPC-doxorubicin in 20 patients to intravesical HPC-doxorubicin combined with RHT using the Thermotron device in 11 patients with NMIBC. A complete response was noted in 6/11 (54.5%) patients with combination therapy versus 7/20 (35%) in intravesical therapy alone. A partial response was seen in 27.3% versus 30% in combination versus intravesical alone [32]. The manuscript did not include results analyzed by grade, a mean follow up, or a recurrence rate.

Additionally, there were three studies that looked at both NIMBC and MIBC [20, 33, 34]. The efficacy and toxicity of these trials will be discussed below in the MIBC section.

Toxicity—Geijsen *et al.* determined toxicity would be a primary endpoint and used CTC 3.0 [35]. Over 10% of patients experienced a grade 2 toxicity comprised of bladder complaints and lower back pain. No grade 3 or 4 toxicities were seen, but 6/18 patients discontinued therapy because of physical complaints, including MMC allergy. No damage was observed cystoscopically. The secondary objective was bladder cancer recurrence and progression. Similarly, Inman *et al.* did not report any grade 3 or higher toxicities. The most common adverse event was grade 1 urethral discomfort (40%) followed by abdominal discomfort from the device (33%) [21]. Ueda *et al.* reported adverse events including dysuria and frequency. The intravesical alone group reported adverse effect rate of 25% and the cohort with RHT reported 27% [32].

In conclusion: In NMIBC only limited phase I/II studies have been performed using regional hyperthermia in combination with different schedules of intravesical chemotherapy and different therapy regimens making a real comparison difficult.

3.3 Muscle invasive bladder cancer

RHT has been used to treat MIBC alone and in combination with chemotherapy and radiation therapy. Early reports examined heterogeneous treatment protocols and vaguely defined categories of bladder cancer [34, 36]. More dedicated trials examined each individual combination.

3.4 Radiohyperthermia (RH)

There has only been one prospective, randomized controlled trial of RHT in MIBC as an adjunct to radiation therapy. Van der Zee *et al.* enrolled 358 patients with pelvic tumors of which 101 had MIBC. The patients were then randomized to radiotherapy alone (n= 49) or radiotherapy with hyperthermia (n=52). A CR was noted in 25/49 (51%) vs 38/52 (73%) in the radiotherapy versus combination groups respectively. The overall survival was 22% for radiotherapy and 28% for combination therapy at 3 year follow up; this difference was not significant [17].

There have been several observational cohorts examining a similar protocol of RH for a total of 63 patients. Masunaga *et al* performed a clinical trial comparing radiotherapy in 21 patients to RH in 28 patients (6 NMIBC 22 MIBC) using the Thermotron device prior to planned cystectomy [37]. All patients received 24 Gy of radiation (4 Gy/day on 3 days/ week) either alone, or in combination with hyperthermia. They then underwent a surgical resection within a week of completed this preoperative therapy. There were no local recurrences in the group treated with hyperthermia, while there was one instance in the radiotherapy alone group. Both groups experienced distant metastasis without a significant difference in numbers (2 in radiotherapy alone, 4 in RH). Although the survival rate was higher in the RH group, they were unable to show statistical significance, probably due to the small number of patients. In another study in Japan, Uchibayashi *et al.* performed a trial with a cohort involving RH (mean 49 ± 3 Gy) in 19 patients. There was a CR in 3/19 patients and a PR of 8/19 patients. The survival period was 65, 31.5 and 11.6 months for T2, T3, T4 disease respectively [38]. Sapozink *et al.* performed a pilot study with the BSD device on 5 bladder cancers [23], and Nishimura *et al.* had a retrospective case series that applied RHT and radiation (40–50 Gy) to 4 bladder tumors [39]. There were 5 complete responses among these patients without mention of the tumor stage. Noguchi *et al.* compared a cohort of patients with RH to another cohort of RH (40 Gy) plus chemotherapy (RH+MVAC). The response rates between the groups were similar; a CR of 4/17 and 4/18 and a PR of 5/17 and 7/18 for RH and RH+MVAC respectively [33]. Petrovich *et al.* examined 20 patients with urothelial cell that are described as advanced tumors. All patients received hyperthermia and this may have been alone or with chemotherapy or with radiotherapy. A complete response was not seen in any of the patients and only 2 partial responses were noted. Both of the PR had received radiation in addition to hyperthermia [22].

Toxicity—In Noguchi *et al.* both the RH and RH+MVAC groups two-thirds experienced tenesmus and frequency. Fewer than 20% experienced fatty necrosis [33]. They did report one case of a contracted bladder thought to be related to the hyperthermia but did not distinguish side effects by tumor type. Sapozink *et al.* did not distinguish amongst histology, but did note that the most common toxicities were pain and bladder spasm [23]. The RCT listed adverse events without a grade or distinction to tumor, but included subcutaneous burns in 20 patients, skin burns in 5 patients, and urinary tract infection [17].

3.5 Chemohyperthermia (CH)

There have been two publications looking specifically at RHT with intravenous chemotherapy. Rietbroek *et al.* employed the AMC 70 MHz device at weekly intervals with cisplatin for 4 patients with T3 or T4 disease for a minimum of 4 cycles. Two patients had partial response with a duration of 5 and 7 months [28]. Uchibayashi *et al.* performed a trial with two cohorts of MIBC; the CH cohort consisted of 19 patients receiving THP-adriamycin and 9 patients received platinum based chemotherapy. The other cohort involved RH and will be discussed below. There was a CR in 2/27 patients and a PR of 7/27 patients. The survival period in those treated with THP was 45.2, 15.4, and 13.5 months for T2, T3, T4 disease respectively, and for cisplatin 24, 36, and 8.5 months [38].

Toxicity—Rietbroek *et al.* evaluated toxicity using the WHO grading system, but did not report toxicities by tumor type. They did not report any grade 4 toxicities, and felt that the only hyperthermia related toxicities were fat necrosis (11%), 2 cases of skin burns, and most commonly, mild pain (31%) [28]. Uchibayashi *et al.* reported burns in 13/46 patients and anorexia in 11 patients [38]. Measured bladder temperatures were not given in relation to these toxicities.

3.6 Quadrimodal therapy

Several studies have looked at the combination termed quadrimodal therapy, defined as surgery (trans urethral resection of the bladder tumor, chemotherapy, radiation therapy, and RHT. Ohguri *et al.* used this therapy in order to preserve the bladders of three patients with MIBC (all T2 disease, one N0, 2 N1) [40]. This protocol involved higher temperatures (average from 44.5, 47, 47.4) than is typically achieved in the majority of trials, but was chosen for better local response. The hyperthermia was given immediately following radiotherapy (total dose 66–70 Gy) during the course of chemotherapy. All three patients achieved a complete response without any recorded recurrence or metastasis (16, 18, and 40 months).

As mentioned earlier, Wittlinger *et al.* examined quadrimodal therapy in MIBC. Their protocol was more defined than the cases described by Ohguri *et al.* and involved 19 patients with T2 MIBC in addition to 26 high risk NMIBC patients. All patients underwent a TURB. In the entire trial 15/45 patients completed less than the minimum number of RHT sessions [20]. At the initial re-TURBT, 96% of patients had a complete response and recurrence free survival was 81% at three years. There were 5 disease specific deaths, all of which involved distant metastases with complete local control. Disease specific survival was 88% at 3 years and overall survival as 80% at 3 years while disease free survival and metastasis free

survival were 71% and 89% respectively. The 3 year bladder preservation rate was 97% for those alive, and 96% overall.

Toxicity—In Ohguri *et al.* no grade 3 or greater toxicity was reported, but all patients experienced cystitis [40]. Wittlinger *et al.* recorded toxicity using National Cancer Institute Common Terminology Criteria (CTCAE), version 3.0 [20, 35]. Grade 3 and 4 sequelae were reported in 24% of patients. Specifically, 1 salvage cystectomy for hematuria, 1 contracted bladder (<100), a reduced bladder capacity (100–200 mL) was seen in 13% of patients, and 2 bowel obstructions [20].

4. Limitations

This systematic review represents a comprehensive summary of a clinically relevant topic. The inclusion of single group studies suffers from several drawbacks. The lack of internal comparisons limits the role for inference of the comparative effectiveness, and alternative explanations should be considered for the effects seen other than the intervention being studied. However, single arm reviews are appropriate for the identification and possible quantification of harms. They are common in the evaluation of novel technology and compose the majority of available data. The inclusion of such studies is common amongst systematic reviews and criteria for inclusion have been proposed by Ip *et al* [41]. The choice of a proxy comparison is open to bias because it depends upon assumptions. For many of the studies without an internal control, the unlikelihood of spontaneous regression of disease coupled with the documented response rates is informative. Comparisons of adverse events are difficult because the older studies used non-validated questionnaires, whereas more recent studies used Common Toxicity Criteria for Adverse Events. There is also inconsistent analysis amongst the trials. The populations examined have heterogeneity in demographic factors (particularly race and functional status), and span a large period of time. Similarly, there was no standardized methodology.

5. Conclusions

Our systematic review suggests that with regional hyperthermia high bladder temperatures can be achieved with acceptable toxicity. It may be effective in both the NMIBC and MIBC setting regardless of adjunctive therapies. It offers improved efficacy at tumor eradication, reduced recurrences, and the potential to spare the native bladder. This systematic review serves as a call to action for better designed clinical trials, and indeed, there are 109 ongoing clinical trials involving some form of hyperthermia [42]. The promise of deep regional hyperthermia seen by the effect size has been largely ignored secondary to the disparate and small body of evidence. This nascent technology has been smoldering for years, and is now ready to be delivered to the forefront of therapy, particularly for high risk NMIBC, and for those patients not suitable for a cystectomy.

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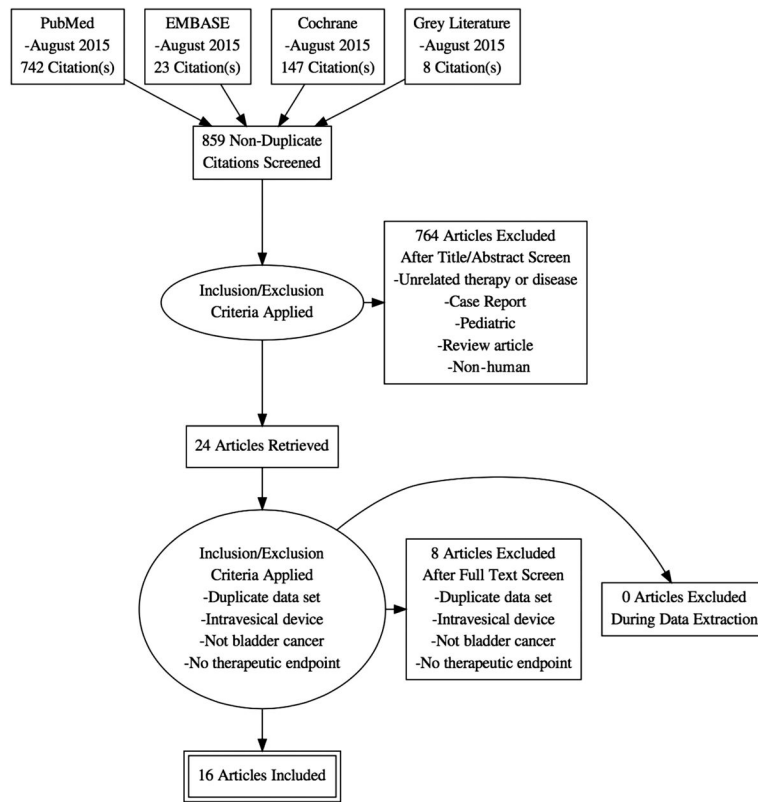
Figure 1.
Flow diagram of evidence acquisition

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Table 1

Overview of all trials concerning regional hyperthermia therapy for bladder cancer

Reference	Study Type (retro vs. pro)	Number of patients	Patient Population (NMIBC, MIBC)	Study Description	Type	Device	Temperature °C	CR	PR
Geijsen et al.[26]	Prospective	18	NMIBC	Pilot: Phase I/II	HT plus intravesical MMC	AMC	40.6–42.1		
Hisazumi et al.[33]	Retrospective	39	MIBC, NMIBC	Case Series		Eight-MHZ RF		9 (23%)	6 (15%)
			13 NMIBC		HT	Thermotron		0	0
					Radiohyperthermia			2 (15%)	0
					Chemohyperthermia			4 (31%)	0
			26 MIBC		HT	Thermotron		0	0
					Radiohyperthermia			3 (12%)	5 (19%)
					Chemohyperthermia			0	1 (4%)
Inman et al.[20]	Prospective	15	NMIBC	pilot	HT plus intravesical MMC	BSD 2000	Goal 42±2		
Masunaga et al.[36]	Prospective	28	MIBC, NMIBC	Phase I and II Trial	Radiohyperthermia vs radiation	Thermotron	39.4–44.0		
Naito et al.[35]	Retrospective	21	MIBC	Case Series	Chemohyperthermia, radiohyperthermia			0	10 (48%)
Nishimura et al.[38]	Retrospective	4	MIBC	Case Series	Radiohyperthermia	Thermotron	Average 38–43	2 (50%)	1 (25%)
Noguchi et al.[32]	Prospective	35	MIBC, NMIBC	Pilot	Quadrimodal vs radiohyperthermia	Radiofrequency apparatus	Goal 42	8 (23%)	12 (34%)
			18 MIBC, NMIBC		Radiohyperthermia			4 (22%)	7 (39%)
			17 MIBC, NMIBC		Chemoradiohyperthermia			4 (23%)	5 (29%)
Ohguri et al.[39]	Retrospective	3	MIBC	Case Series	Chemoradiohyperthermia	Thermotron	Average/patient 43.7–45.5	3 (100%)	0
Petrovich et al.[21]	Prospective	20		Phase I	Hyperthermia plus radiation	BSD 1000	Goal 42.5	0	2 (10%)
Rietbroek et al.[27]	Prospective	4	MIBC	Pilot	Chemohyperthermia	AMC	Goal 41.0	0	2 (50%)
Sapozink et al.[22]	Prospective	5	MIBC	Pilot	Radiohyperthermia	BSD 1000	Goal 42.0	2 (40%)	0
Uchibayashi et al.[37]	Prospective	46	MIBC	cohort	Chemohyperthermia or radiohyperthermia	Radiofrequency apparatus	Goal 42.5	5 (11%)	15 (33%)
			27 MIBC		Chemohyperthermia			3 (11%)	8 (30%)
			19 MIBC		Radiohyperthermia			2 (11%)	7 (37%)
Ueda et al.[31]	Prospective	11	NMIBC	cohort	HT plus intravesical doxorubicin	Thermotron	Goal 42.0	6 (54%)	3 (27%)
Van der Zee et al.[18]	Prospective	52	MIBC	Randomized	Radiohyperthermia vs radiation	BSD, and others	Goal 42.0	38 (73%)	
Wittlinger et al.[19]	Prospective	45	MIBC, NMIBC	Phase II	Quadrimodal	BSD 2000	Goal 41.5	36 (80%)	45 (96%)

Table 2

Overview of toxicity associated with regional hyperthermia therapy

Study	General	Fatigue	Myalgia	Anxiety	Genitourinary	Urethral pain	Cystitis	Dysuria	Hematuria	Bladder spasm	Weak urinary stream	Vaginitis	Frequency	Contracted bladder	Incontinence
Geijsen et al										10 (7%)					
Hisazumi et al															
Inman et al		2 (13%)	1 (7%)	1 (7%)		6 (40%)	4 (27%)		3 (20%)	2 (13%)	1 (7%)	1 (7%)			
Masunaga et al															
Nishimura et al *														1 (3%)	
Noguchi et al													24 (69%)		
Ohguri et al							3 (100%)								
Petrovich et al *															
Rietbroek et al															
Sapozink et al		11 (26%)		6 (14%)						11 (26%)					
Uchibayashi et al															
Ueda et al								3 (27%)							
van der Zee et al *															
Wittlinger et al.														7 (16%)	1 (2%)

Study	Dermatologic	Burns/blister	Induration/ swelling	Pruitis	Rash	Bruising	Flushing	Fat necrosis	Neurologic	Dizziness	Confusion	Extrapyramidal sympoms	Infectious	Urinary tract infection
Geijsen et al														
Hisazumi et al		21/39 (54%)	10/39 (26%)											
Inman et al		4 (27%)		3 (20%)	2 (13%)	1 (7%)	1 (7%)			2 (13%)	1 (7%)	1 (7%)		2 (13%)
Masunaga et al														
Nishimura et al *				3 (10%)				2 (6%)						
Noguchi et al														
Ohguri et al														
Petrovich et al *		4 (8%)												
Rietbroek et al		2 (14%)						5 (36%)						
Sapozink et al				2 (5%)										
Uchibayashi et al		15 (33%)	9 (20%)											

	Dermatologic	Burns/blister	Induration/ swelling	Pruitis	Rash	Bruising	Flushing	Fat necrosis	Neurologic	Dizziness	Confusion	Extrapyramidal sympoms	Infectious	Urinary tract infection
Ueda et al														
van der Zee et al *		5 (3%)	20 (11%)											
Witlinger et al.														

	Cardiovascular	Hypertension	Gastrointestinal	Nausea or vomiting	Anorexia	Constipation	Ileus	Diarrhea	Abdominal pain	Procedure related	Positional discomfort	Heat intolerance/pain with applicator
Geijsen et al											22 (16%)	29 (20%)
Hisazumi et al												
Inman et al		3 (20%)		2 (13%)		1 (7%)			5 (33%)			1 (7%)
Masunaga et al		0 (0%)						1 (4%)				12 (43%)
Nishimura et al *												18 (55%)
Noguchi et al				17 (49%)				4 (11%)				
Ohguri et al								1 (33%)				
Petrovich et al *		4 (8%)										25 (47%)
Rietbroek et al												31% of treat-ments
Sapozink et al				8 (19%)	11 (24%)							32 (74%)
Uchibayashi et al												
Ueda et al												
van der Zee et al *												
Witlinger et al.							1 (2%)	1 (2%)				