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Overview of bladder heating technology: matching capabilities with clinical requirements.

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1 **Overview of bladder heating technology: matching capabilities with clinical requirements**

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14 **Running Head:**

15 Heating Technology for Bladder Cancer

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19 **Key Words:**

20 bladder cancer, hyperthermia, intravesical heating, electromagnetic heating,

21 thermochemotherapy

22 **Abstract**

23 Moderate temperature hyperthermia (40-45°C for one hour) is emerging as an effective
24 treatment to enhance best available chemotherapy strategies for bladder cancer. A rapidly
25 increasing number of clinical trials have investigated the feasibility and efficacy of treating
26 bladder cancer with combined intravesical chemotherapy and moderate temperature
27 hyperthermia. To date, most studies have concerned treatment of non-muscle invasive bladder
28 cancer (NMIBC) limited to the interior wall of the bladder. Following the promising results of
29 initial clinical trials, investigators are now considering protocols for treatment of muscle invasive
30 bladder cancer (MIBC). This paper provides a brief overview of the devices and techniques
31 used for heating bladder cancer. Systems are described for thermal conduction heating of
32 bladder wall via circulation of hot fluid, intravesical microwave antenna heating, capacitively
33 coupled RF current heating, and radiofrequency phased array deep regional heating of the
34 pelvis. Relative heating characteristics of the available technologies are compared based on
35 published feasibility studies, and the systems correlated with clinical requirements for effective
36 treatment of MIBC and NMIBC.

37

38 **Introduction**

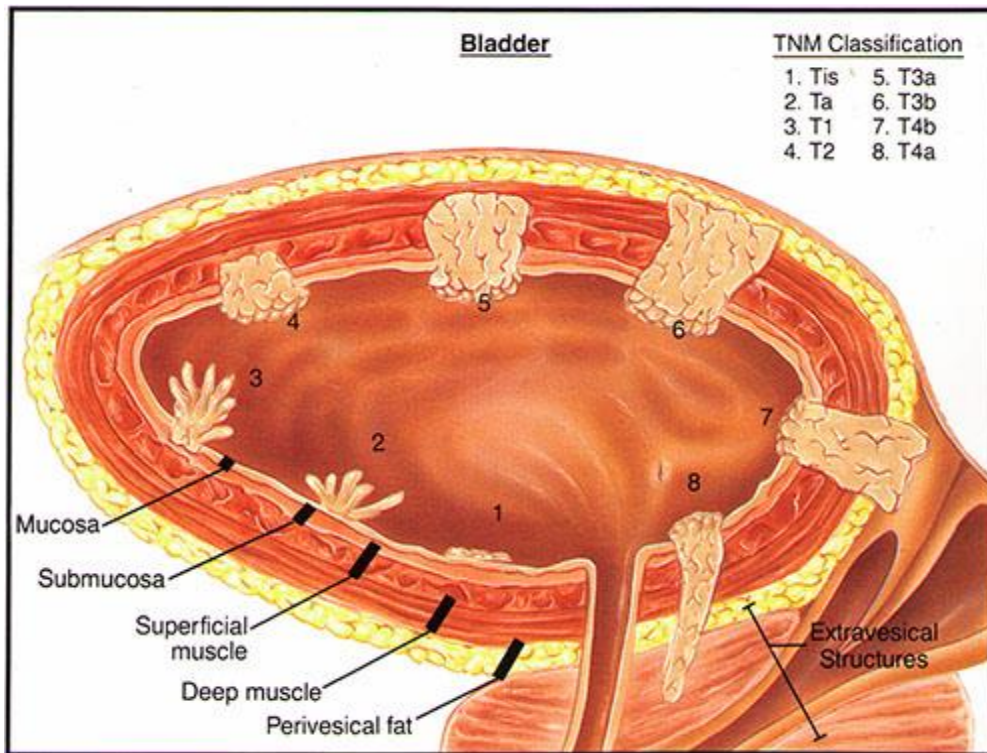
39 The purpose of this paper is to review the capabilities of various heating technologies available
40 for treatment of bladder cancer, with an eye toward correlating typical performance
41 characteristics of each approach with the clinical requirements. Bladder tumors present either
42 as non-muscle invasive (NMIBC), 70%, or as muscle invasive (MIBC), 30%, carcinomas.(1)
43 While most clinical studies to date have concerned treatment of NMIBC superficial disease
44 limited to the interior wall of bladder,(2-7) future clinical trials must address the more aggressive
45 MIBC that extends beyond the bladder wall out into surrounding pelvic tissues. Thus depending
46 on the extent of disease, heating systems are required to accomplish different clinical goals of
47 treatment.

48

49 For healthy persons, the mean bladder wall thickness is 3.0 ± 1 mm and 3.3 ± 1.1 mm for female
50 and male respectively with a weak positive correlation between wall thickness and age.(8)
51 According to current staging criteria, NMIBC cancers encompass all Tis, Ta, and T1 bladder
52 tumors that are limited to the mucosa and submucosa, i.e. involving less than 1 mm penetration
53 into the bladder wall. Hence, if adequate transurethral resection of the intrabladder tumor growth
54 has taken place prior to treatment, the therapeutic temperatures (40-43°C) of the hyperthermia
55 treatment should target a depth of about 1 mm in order to produce heat activation of intravesical

66 chemotherapy. For MIBC, i.e. tumor stages T2-T4a, the hyperthermia target extends to much
67 greater depths and a heating system for MIBC must be able to deposit significant power
68 throughout the bladder wall and for some patients out into extravascular pelvic tissues to enhance
69 the delivery and activation of systemically administered chemotherapeutic throughout the
60 muscle invasive component of disease.

61



62
63 Figure 1. Pictorial of bladder cancer staging classification as regards penetration of disease into the
64 bladder wall. Reprinted with permission from Katelaris Urology, [http://www.katelarisurology.com.au/about-](http://www.katelarisurology.com.au/about-bladder-cancer/)
65 [bladder-cancer/](http://www.katelarisurology.com.au/about-bladder-cancer/).

66

67 The different tumor pathology of NMIBC and MIBC must be reflected in the clinical practice of
68 applying adjuvant hyperthermia and thus the requirements on technology for heating these two
69 diseases are quite different. For NMIBC with Tis, Ta, and T1 tumors, the target to be heated is
70 well defined (~1 mm deep) and the technological demands for adequate heating of such shallow
71 depth tumors are relatively easily met with uncomplicated thermal conduction heating solutions.
72 For MIBC however, the tumor is ill-defined and variable in depth, size, shape and location
73 (especially the advanced cases) demanding much higher flexibility in power deposition
74 capabilities of the hyperthermia system to adequately heat the desired target volume. For this
75 situation, effective use of heating technology is critically dependent on treatment planning,

76 temperature measurement, and feedback control strategies. The modeling and thermal
77 dosimetry approaches used to monitor and guide these complex treatments will be addressed in
78 another paper of this special issue. Similarly, the clinical requirements for treating NMIBC and
79 MIBC will be described in accompanying papers that summarize specific procedures and clinical
80 results of the most common bladder treatment approaches. This special issue also includes
81 specific coverage of the biological effects of hyperthermia, the pharmacologic effects of heat
82 activated drug therapy, and the immunological effects of adjuvant hyperthermia.

83
84 In this overview, we describe the currently available methods for heating both NMIBC and MIBC
85 disease, as well as their basic physical principles. Based on the available literature, we compile
86 a semi-quantitative table to compare performance attributes of each technology. Finally, this
87 summary information is organized to provide clinicians with an overview of pros and cons of the
88 alternative approaches to heat NMIBC and MIBC, to aid the selection of hyperthermia method
89 that best matches the tumor target.

90
91 **Devices and Techniques for Clinical Heating of Bladder Cancer**

92 The available technology for heating bladder cancer differs greatly in principle of heating,
93 technological complexity, labor resources, preparation time, quality assurance demands, and
94 cost. Transfer of energy may occur by direct thermal conduction, electromagnetic (EM) fields, or
95 ultrasound (US) waves. Each of these technologies requires quite specific clinical and technical
96 procedures that produce unique depth of penetration and uniformity of temperature.(9-12) The
97 following paragraphs briefly describe the general characteristics, limitations and benefits of each
98 heating method. To our belief, we have included all currently available clinical approaches. In
99 our attempt to provide meaningful data for comparison of heating techniques in Table 2, we tried
100 carefully to avoid inclusion of duplicate patient data from published feasibility studies. A
101 common challenge is to accurately monitor the temperature distribution of the entire tumor as it
102 invades different depths into the bladder wall, especially in the case of more extensive MIBC
103 disease. Temperature gradients in the target volume occur due to variable local blood perfusion
104 and to heterogeneity of absorbed energy from the heat source. Appropriate thermal dosimetry
105 procedures are covered in another paper of this special issue.

106
107 ***Radiative EM energy based external heating***
108 *Principles:*

109 Typical radiofrequency (RF) phased array applicators operating between 70 and 120 MHz
110 produce a large hot spot at the phase focus but also heat skin and a significant portion of pelvic
111 tissue outside the focus. Heating patterns possible with electromagnetic phased array
112 applicators have been studied extensively.(13-17) Located centrally in the pelvis and filled with
113 a mixture of lossy urine and drug that has no blood perfusion cooling, the bladder heats
114 preferentially using an appropriately phased array of RF antennas around the torso to focus
115 power deposition in and around the bladder. A 14-patient Phase I clinical trial was conducted to
116 study the feasibility of treating NMIBC with intravesical Mitomycin C (MMC) combined with
117 external radiofrequency phased array deep hyperthermia.(6) The thermal dosimetry of that 14
118 patient trial showed that adequate heating, defined as a bladder temperature above 40°C for
119 more than 40 min, was achieved in 96% of the treatments, and 73% of the patients completed
120 the course of 10 treatments per protocol.(18) A subsequent 18 patient trial using the
121 Amsterdam AMC-4 or AMC-8 waveguide system (17) produced similar results, demonstrating
122 feasibility of heating NMIBC with low toxicity using an external electromagnetic phased array.(3)
123 Excellent bladder temperatures were achieved (i.e. an average bladder temperature of 41.6°C
124 for 60-90 min each treatment) with 83% completing the six induction treatments and 50%
125 completing all 10 treatments. Since the diffuse focus produced by 70-120 MHz phased array
126 systems is larger than the bladder dimensions, this heating approach deposits power not only in
127 the bladder contents but also directly in the bladder wall and tissues surrounding the bladder.
128 Thus, these electromagnetic heating approaches can be expected to heat the entire bladder
129 wall and potentially muscle invasive disease extending outside the bladder. To date, no large
130 trials of MIBC have been reported, but the feasibility of heating locally advanced MIBC has been
131 demonstrated in a small study of 5 patients.(19) This study showed that interstitially measured
132 tumor temperatures correlated with intraluminal measured temperatures (average tumor
133 temperature 40.9±1.1°C vs tumor indicative bladder lumen temperature 40.7±1.3°C). These
134 feasibility studies suggest that the RF deep heating approach is suitable for heating bladder
135 cancers extending into the pelvis, especially when combined with MR thermal monitoring to
136 define the 3D temperature distribution throughout the pelvis in real time during treatment.(20-22)
137 Since most centers do not have MR thermal monitoring capability yet, control of the treatment
138 relies more heavily on careful treatment planning whenever the tumor target extends 1 cm or
139 more from the typical bladder and rectal temperature monitoring sites. Software is available for
140 patient specific treatment planning of deep heat treatments, such as Sigma HyperPlan (Dr
141 Sennewald Medizintechnik GmbH, Munich, Germany), a program that was optimized
142 specifically for the BSD2000 Sigma applicators. The utility of this comprehensive planning

143 program looks very promising but overall accuracy in complex tissue regions like the pelvis is
144 still under evaluation.(23-26) Other multi-physics software is available commercially that is
145 flexible for modeling power deposition and corresponding thermal heat transfer in the body from
146 any applicator, such as SEMCAD X (SPEAG, Zurich Switzerland), HFSS (Ansys Corp,
147 Canonsburg PA, USA), COMSOL Multi-Physics (Comsol Inc., Burlington MA, USA), CST Studio
148 Suite (CST, Framingham MA, USA), and others. The value of these powerful electromagnetic
149 and thermal modeling programs is currently under evaluation. See accompanying article in this
150 special issue on thermal dosimetry and treatment planning.(27)

151 Temperature measurement during radiative electromagnetic heating of bladder cancer is often
152 performed by a single catheter using multiple sensor temperature sensors or by thermal
153 mapping.(3, 6, 18, 19) Recently, Cordeiro et al. (28) introduced a special catheter to improve
154 the quality of temperature measurement during NMIBC hyperthermia. Once in the bladder, the
155 catheter unfolds like an umbrella and places three temperature sensors against the bladder wall
156 equally distributed around the circumference.

157 *Typical EM deep heating systems*

158 The BSD2000 RF Phased Array Hyperthermia System (Pyrexar Corp., Salt Lake City UT, USA)
159 powers 1-3 annular rings of dipole antennas with phase adjustable signals in the range of 80-
160 120 MHz. Several applicator configurations are available for treatment of pelvic disease. A four
161 channel system powers four twin dipole antennas spaced around either a 60 cm diameter
162 annular array (Sigma 60 applicator), or a smaller 57 x 40 cm elliptical array (Sigma Ellipse).(14-
163 16) The BSD2000 3D and 3D/MR Hyperthermia Systems include an elliptically shaped Sigma
164 Eye applicator that is MR compatible to fit inside a 60 cm dia MR magnet.(21, 22) The Sigma
165 Eye applicator includes three coaxial rings of four twin dipole radiators, for a total of 24
166 antennas driven with the 12 power channels at a frequency of 100 MHz. The system takes
167 advantage of custom software that obtains 3D thermal image data during treatment to provide
168 realtime feedback to the 12 independent phase and amplitude controls.(20, 22, 29, 30) All
169 Sigma applicators have a flexible silicone membrane inside the applicator that inflates like an
170 annular doughnut shape around the torso and fills with circulating temperature controlled
171 deionized water to cool the skin and couple electric field into the patient.

172

173 Deep regional heating of large regions in the pelvis may be accomplished similarly with a 70
174 MHz radiofrequency phased array system (AMC-4 or -8) using either 1 or 2 rings of 4
175 waveguide antennas, each with an aperture size of 33 x 21 cm and temperature controlled

176 waterbolus coupling to the patient.(3, 17, 31). While the single ring 4 antenna system has been
177 used successfully in a clinical trial to heat bladder disease,(3) recent studies indicate that the 3D
178 SAR steering of the AMC-8 system promises an enlarged SAR focal region as well as improved
179 control and localization of heating.(17, 32) The 70 MHz four antenna system is now available
180 commercially as the Alba 4D (Alba Hyperthermia Systems, Roma Italy).

181

182 ***Capacitively coupled external electric current heating***

183 *Principles:*

184 Using lower frequency RF such as 8 - 13.56 MHz, electromagnetic energy may be delivered to
185 tissue via electric current that flows between capacitively coupled electrodes on the skin
186 surface. All currently available systems have two electrodes that are generally coupled to the
187 skin with electrically conductive temperature controlled saline pads to conduct and spread
188 electric current into tissue and cool the skin surface.(33-35) Electrical current must flow through
189 the high resistance fat tissue layer before splitting into multiple current paths through the
190 intervening tissue between electrodes. Thus, maximal power deposition normally occurs in the
191 superficial fat layer which must be cooled with temperature regulated saline bolus.(36, 37) At
192 depth, electrical currents distribute such that more current flows through low resistance tissues
193 like muscle and tumor, and less current flows in parallel through high resistance tissues like fat,
194 bone and aerated lung.(33, 38) With power deposition proportional to the current squared,
195 more power is deposited in tissues along the higher current pathways in low resistance tissues.
196 Thus power deposition is possible in low resistance urine filled bladder even though maximum
197 heating rate likely occurs in the high resistance superficial fat layer just under the electrodes.
198 Using different size electrodes, RF currents and tissue heating may be concentrated under the
199 smaller electrode. Ongoing clinical use primarily in Asia has demonstrated the ability to heat into
200 the hyperthermic range in patients with sufficiently thin layers of high resistance fat tissue
201 overlying tumor, using aggressive skin cooling.(5, 37, 39)

202

203 Two clinical studies report on the performance of capacitively coupled hyperthermia to heat
204 locally advanced MIBC. Masunaga et al. (40) reports that an average intravesical bladder
205 temperature of $41.5 \pm 1.1^\circ\text{C}$ was obtained in their group of 28 patients. They also indicate that
206 significantly higher bladder temperatures were achieved in patients with a subcutaneous fat
207 layer less than 2 cm thickness. The average duration of the heat treatment was 44.4 ± 8 min for
208 patients with an average bladder temperature $>41.5^\circ\text{C}$, and 40.5 ± 5.9 min for patients with
209 bladder $T_{\text{avg}} < 41.5^\circ\text{C}$. Uchibayashi et al (41) analyzed the ability to heat locally advanced

210 muscle invasive bladder tumors in 46 patients. They report similar findings: intravesical and
211 tumor temperatures could be raised to 42.5°C or higher for patients with subcutaneous fat
212 layers less than 2 cm thickness. In obese patients, it was more difficult to heat the bladder tumor
213 to the required level. Thermometry was performed using Teflon coated thermocouples placed in
214 the ureter, rectum and tumor. Patient complaints concerned pain at the edge of the electrodes in
215 nearly half of the patients, and was the limiting factor for power elevation in these patients.

216

217 *Typical heating systems:*

218 Capacitively coupled RF heating systems are available with two moveable capacitive plate
219 electrodes around a treatment bed such as the 13.56 MHz 600 W Celsius TCS system (Celsius
220 42+ GmbH, Cologne Germany), and two electrodes mounted on a parallel opposed rotating arm
221 as in the 8 MHz Thermotron RF-8 (Yamamoto Vinyter, Japan).(35, 36)

222

223 ***Ultrasound energy based external heating***

224 *Principles:*

225 Several ultrasound array devices have been designed for hyperthermia treatment of large deep
226 tissue targets.(42-44) However the majority of focused ultrasound applications involve smaller
227 target volumes that take advantage of the short wavelength to produce tightly focused hot spots
228 for rapid thermal ablation without effecting surrounding normal tissues.(45, 46) With care to
229 manage reflections and absorption of ultrasound near air and bone, the small hot spot can be
230 shifted to produce successive overlapping regions to treat larger volumes such as human
231 bladder. While ultrasound travels through urine without much loss, power can be focused on
232 the bladder wall itself to produce effective localization of heat in specific tumor target regions.
233 The challenge of this technique is in designing the scanning algorithm that provides
234 homogenous bladder wall heating. Although the feasibility of heating bladder with ultrasound
235 has been demonstrated,(47) large tissue targets in the pelvis are generally heated using
236 electromagnetic phased array sources having longer wavelengths that both penetrate and
237 produce larger bladder-sized focal zones. At present no commercial systems are available that
238 are optimized for bladder treatment and no clinical studies have been reported.

239

240

241 ***Radiative EM energy based internal heating: Intravesical Microwave Antenna***

242 *Principles:*

243 As an alternative to localizing heat in bladder from external sources, one can radiate energy
244 from a small diameter intraluminal microwave antenna inserted into the bladder through a
245 special multilumen urethral catheter. The advantage of this method is that energy does not
246 travel through a large volume of normal tissue before impinging on the bladder target, but is
247 instead aimed directly at the adjacent tumor target from inside the bladder. In addition, well
248 localized heating around the intravesical antenna can be achieved with rather simple equipment
249 compared to external phased array sources. Further, the use of microwave radiation increases
250 the penetration of effective heating in perfused tissue of the bladder wall in comparison to
251 thermal conduction only heat sources. Microwave antennas that can be placed inside 1-2 mm
252 diameter catheters have been investigated by many groups and the principles and typical
253 radiation patterns have been reviewed previously.(48) The first system optimized for use inside
254 the bladder applies power to a 915 MHz coaxial cable antenna that is introduced into the
255 bladder inside a special Foley catheter and radiates an EMF into tissue around the antenna tip.
256 Because fluid inside the bladder is circulated around the antenna and through an external
257 temperature controlling heat exchanger, heat is removed from the fluid during treatment
258 enabling use of higher antenna power levels without overheating the fluid. This allows the
259 microwave field to penetrate further through the electrically lossy urine/drug filled bladder to
260 deposit energy directly in the bladder wall.

261
262 Of all hyperthermia systems used for heating NMIBC, intravesical microwave heating has the
263 highest number of clinical studies performed. The eight studies reported in Table 1 are not
264 exhaustive; however they cover 287 patients treated by four different institutions and hence
265 provide strong endorsement for the clinical viability of intravesical microwave antenna
266 heating.(2, 49-54) The largest reported study of this approach by Nativ et al. (55) is a
267 retrospective analysis of 111 NMIBC patients. Overall the clinical experience with intravesical
268 microwave heating demonstrates that therapeutic temperatures ($42\pm 2^{\circ}\text{C}$) are routinely achieved
269 inside the bladder, though the median temperature and temperature range vary substantially
270 between institutes. In general, the studies indicate that heat treatments are well-tolerated with a
271 high proportion of patients completing the entire treatment course. Reported adverse events are
272 mostly local and transient such as pain and bladder spasm during treatment sessions, followed
273 by hematuria, dysuria and transient incontinence. It should be noted that typical intravesical
274 microwave systems measure temperature at three different points along the inner wall of
275 bladder, providing a small but representative sampling of achieved intra-bladder
276 temperatures.(28, 51) The relatively large temperature range reported can be explained by the

277 non-uniform irradiation pattern of an interstitial microwave antenna in an irregular shaped fluid-
278 filled bladder. This non-uniform power deposition pattern is also associated with the relatively
279 high incidence of thermal reactions seen in the posterior bladder wall.

280

281 *Typical intravesical microwave antenna system:*

282 The Synergo SB-TS 101 System (Medical Enterprises Europe B.V., Amstelveen, The
283 Netherlands) consists of a 915 MHz microwave applicator that is inserted into the bladder via a
284 special multilumen 19.5F or 20F catheter. A peristaltic pump slowly circulates MMC through the
285 catheter into the bladder through a temperature controlled heat exchanger that cools the drug
286 and helps homogenize intrabladder temperature during application of microwave power.
287 Temperatures are measured in the urethra and with three thermocouples pressed against the
288 bladder wall by the inflated catheter balloon.(4, 51)

289

290 ***Intravesical Thermal Conduction Heating***

291 *Principles:*

292 The most straightforward approach to heating tissue is to apply a heated surface in intimate
293 contact with the target tissue to enable heat transfer across a thermal gradient. To uniformly
294 heat the interior wall of a complex shaped bladder cavity, this simple heat transfer approach is
295 best accomplished by vigorously circulating externally heated fluid (and drug) at a controlled
296 temperature throughout the bladder. Due to the dynamics of turbulent flow, there is a non-
297 uniform velocity profile across the inner bladder surface but with sufficient circulation the entire
298 target tissue on the inner wall of bladder will come in contact with rapidly moving near equi-
299 temperature fluid. With no power deposition directly in tissue, the resulting temperature
300 distribution is dependent only on bladder tissue thermal parameters rather than heterogeneous
301 electrical or acoustic tissue properties. Using thermal conduction only heating, maximum tissue
302 temperature is readily determined with confidence to be the measured input temperature of the
303 circulating fluid, and thus thermal toxicity is easily avoided. The constant temperature interface
304 should provide relatively uniform heating of the inner surface of bladder even with
305 heterogeneous thermal properties that effect heat penetration into the wall. While temperature
306 of the bladder lumen may be nearly constant, there is a steep temperature gradient within the
307 bladder wall as heat dissipates rapidly into surrounding cooler tissues. Especially because of
308 heat losses to normothermic blood perfusing the bladder wall tissues, the penetration depth of
309 effective heating is limited when the driving thermal gradient is only 7°C (44 - 37°C). The
310 accompanying modeling and thermal dosimetry paper in this special issue specifically

311 addresses penetration of heat into the bladder wall with various heating technologies. Previous
312 studies of temperature gradients in perfused tissue adjacent to a hot (or cold) surface show that
313 the effective heating potential of a 7°C thermal gradient extend no more than 2-3 mm deep.(56,
314 57). For NMIBC cancers that extend <2mm into the bladder wall, this thermal gradient induced
315 heating should be sufficient for effective treatment. Clinical experience at three institutes using
316 two different intravesical thermal conduction heating systems indicates excellent performance
317 with a very high percentage of patients completing the prescribed treatment course (see Table
318 1).

319

320 Alternatively, thermal conduction heating from inside the bladder may be accomplished without
321 the need to circulate expensive chemotherapeutic through multi-lumen connecting tubes to an
322 external temperature regulating heat exchanger. Efforts are underway to investigate the use of
323 ferromagnetic nanoparticle (MNP) solutions that can be mixed with drug and injected into the
324 bladder through a standard Foley catheter. With this approach, the MNP are heated via
325 magnetic induction coupling from an externally applied alternating magnetic field, usually at a
326 frequency of 50-100 kHz to minimize direct eddy current heating in the pelvis. As demonstrated
327 in preclinical studies, the MNP can produce sufficient heating to raise the temperature of the
328 chemotherapeutic mixture in bladder to the desired treatment temperature.(58) Inductively
329 coupled heating is distributed throughout the MNP solution producing relatively homogeneous
330 internal bladder temperature, and convection current mixing of bladder contents further
331 minimizes temperature gradients during treatment. For magnetic coupled nanoparticle solutions,
332 temperature must be monitored with a probe inserted into the bladder through the Foley
333 catheter. Unlike the rapidly circulated heated fluid approach, the maximum bladder temperature
334 is not known precisely as the intraluminal probe will generally underestimate the peak
335 temperature due to small gradients within the unstirred magnetic fluid/chemotherapeutic
336 mixture.

337

338 *Typical intravesical thermal conduction systems:*

339 There are two commercial systems that heat bladder by circulating heated drug through the
340 bladder. The Combat BRS System (Combat Medical Ltd – Wheathampstead, Herts UK) heats
341 chemotherapeutic (e.g. MMC) to the desired intrabladder temperature in the range of 40-44°C
342 and circulates the heated drug through the bladder via a soft and flexible 16F 3-way catheter
343 with coude tip to facilitate insertion into the bladder.(59) The device consists of a temperature
344 controlled waterbath heat source and peristaltic pump to circulate drug through the bladder via a

345 low volume high efficiency heat exchanger. Temperature of the circulating fluid is monitored with
346 an inline probe and all treatment parameters are controlled via a simple touch screen user
347 interface with graphical temperature display and safety alarms for high and low temperature,
348 and overpressure.

349 The Unithermia System (Elmedical Ltd, Hod-Hasharon Israel) for Bladder Wall Thermo-
350 chemotherapy uses a similar design concept to heat chemotherapeutic to about 46.5°C in order
351 to obtain 44-44.5°C drug temperature inside the bladder using a circulation rate that achieves
352 approximately 4 exchanges of bladder fluid contents per minute.(60, 61) This rapid circulation
353 of drug within the bladder improves the uniformity of drug temperature contacting the inner
354 surface of bladder and provides fresh drug to the bladder wall surface continuously for the
355 typical 50 min thermochemotherapy treatment.

356

357 **Devices and Techniques for Pre-Clinical Bladder Heating**

358 Preclinical studies are often used in the development and optimization of new cancer treatment
359 strategies. Rodent studies are most common though larger animals are also used to model the
360 human treatment situation more closely. Since human bladder capacity is approximately 500
361 ml,(62) the small size of bladder in mice (~ 0.15 ml) and rats (~ 1 - 1.5 ml) requires different
362 heating systems(58, 63). Farm pigs are also used for preclinical studies, with bladder volumes
363 ranging from 250 ml to larger than human bladders. Thus preclinical studies require unique
364 heating technology that can localize heat within the desired bladder target which may be buried
365 over 3 to 12 mm from the skin surface. Hyperthermia studies are often performed in mice using
366 simple thermal conduction heating via waterbath, but that approach generally produces regional
367 if not systemic temperature rise that would complicate interpretation of biologic response to
368 specific bladder therapy. In recent years, a number of approaches have been reported for
369 improved localization of heat in animal bladders.

370

371 ***Radiative external microwave antenna heating***

372 In order to elevate temperature in a urine filled bladder at depths of 3-8 mm below the skin of
373 small animals like mice and rats, microwave antenna systems have been developed at 915 MHz
374 and 2450 MHz. These antennas are generally 1-2 cm in diameter and coupled to tissue with a
375 temperature controlled waterbolus to cool the superficial tissues and allow localization of heat in
376 underlying bladder. Salah et al. describe the heating performance of a 1 cm diameter water
377 filled circular waveguide microwave antenna designed specifically for heating small rodent
378 bladders.(63) Another microwave antenna designed for small volume heat treatments has been

379 reported previously (64, 65) with heating patterns that demonstrate feasibility of treating small
380 animal bladders. Snow et al. report the feasibility of heating *in vivo* pig bladder with no acute
381 toxicity using a small array of 915 MHz square slot dual concentric conductor antennas.(66, 67)

382

383 ***Inductively coupled ferromagnetic nanoparticle heating***

384 An increasing body of literature describes the use of ferromagnetic nanoparticles (MNP) injected
385 into a tumor directly or administered systemically with the goal of concentrating sufficient
386 magnetic material in the target to heat tissue from coupling to an externally applied magnetic
387 field. For NMIBC disease where the target tissue is located ≤ 2 mm deep into the bladder wall,
388 the injection of magnetic fluid into the bladder intermixed with chemotherapeutic and
389 subsequent heating of bladder via external magnetic field seems straightforward. Oliveira et al.
390 (58) report a feasibility study of introducing a concentrated magnetic fluid into rat bladder via
391 urethral catheter and heating the bladder by magnetic field coupling to the ferrofluid. With no
392 forced stirring, thermal gradients will occur inside the bladder. However, homogenization of
393 intrabladder temperatures is anticipated due to natural convective stirring of bladder contents
394 driven by the small thermal gradients.

395

396 ***Gold nanoparticle enhanced photothermal ablation***

397 Another area of development involves laser or electric field coupled heating of gold
398 nanoparticles.(68) Cho et al.(69) describe a treatment approach involving photothermal
399 ablation of superficial bladder cancer. They propose to fill the bladder with a solution of gold
400 nanorods conjugated to anti-EGFR antibodies that will bind to EGFR-expressing bladder cancer
401 cells. Then by introducing near infrared radiation to the interior of the bladder via a modified
402 cystoscope, power may be deposited preferentially in the gold nanorods sufficient to thermally
403 ablate adjacent tumor cells.

404

405 **Correlation of Heating Technologies with Clinical Requirements**

406 ***General characteristics of the clinical problem***

407 As explained earlier, there are primarily two types of disease to be addressed in this review:
408 NMIBC and MIBC. These two diseases are quite different biologically and anatomically, and
409 require significantly different treatment approaches. The corresponding requirements for heating
410 these two diseases are also quite different. Superficial bladder cancers involve only the mucosa
411 and sub-mucosa layers along the inner bladder surface, generally with a thickness ≤ 2 mm. On
412 the other hand, MIBC by definition extends into the muscle layers of the bladder wall and even

413 into extravescical structures outside the bladder; this deeper disease presents a wide range of
414 technical challenges to effective heating. Thus optimal heating of NMIBC requires
415 homogeneous heating of the bladder interior extending < 2-3 mm into the bladder wall, and
416 ideally there would be minimal heating of normal tissues outside the bladder. Optimal treatment
417 of MIBC requires heating not only the bladder wall but also a variable amount of tissue outside
418 the bladder. Of all the available heating technology, some systems are better suited to limiting
419 the extent of heating to just a thin rim of target disease on the interior of the bladder, and other
420 devices are better suited to heating large regions of pelvis including bladder and surrounding
421 tissues.

422 Criteria for determining effectiveness of treatment include:

- 423 Homogeneity of heating around the interior surface of bladder
- 424 Depth of penetration of heating through bladder tissue
- 425 Circulation/mixing of drug in contact with inner surface of bladder wall
- 426 Heating of normal tissue outside the bladder
- 427 Heating of tumor tissue outside the bladder
- 428 Ease of heating
- 429 Patient tolerance

430

431 ***Clinical infrastructure requirements***

432 In addition to comparing technological performance of the above mentioned systems by
433 characterizing their ability to localize and uniformly heat tumor, other important considerations
434 for selecting a hyperthermia system include the initial capital investment, space, supplies, and
435 personnel and time required to prepare for and apply each treatment.

436

437 Of the intravesical systems, the circulating fluid thermal conduction method is the most
438 straightforward to apply. Due to the known maximum temperature of the circulating fluid, this
439 approach has the lowest risk of side effects from uncontrolled excessive temperature. It also is
440 the least demanding of resources for calibration and quality assurance validation. The
441 intravesical microwave antenna system is similarly compact, but includes a power generator
442 that produces non-uniform power deposition around the antenna and unknown temperature
443 peaks in tissue. Thus this technology requires stepwise more quality assurance and personnel
444 training to obtain safe and reproducible performance. In either case, the intravesical systems
445 should be applied only for heating superficial NMIBC.

446

447 External RF hyperthermia systems require a more substantial infrastructure to purchase and
448 maintain the equipment, and to provide appropriate RF shielding for non-ISM band EMF. The
449 technology for capacitively coupled electric current systems is relatively straight forward and
450 maintenance with minimal QA verification measurements should be sufficient for safe
451 operational use. A consequence of the relatively simple capacitive plate technology is a lack of
452 flexibility to adjust power deposition pattern for optimal tumor heating and to effectively
453 accommodate patient complaints with minor adjustments of heating parameters. In comparison,
454 the external RF radiative systems use the most complex technology and require the most
455 extensive support structure. The advantage is that they are the only systems that can heat both
456 NMIBC and MIBC disease. And with carefully designed treatment protocols, heating of NMIBC
457 has been demonstrated with acceptable personnel resources, i.e. with only one person to
458 operate the system. If the bladder is filled with a high absorbing liquid, preferential heating can
459 be obtained with predefined antenna settings and without extensive hyperthermia treatment
460 planning. Investing in a radiative EMF method should be considered when there is a need to
461 apply hyperthermia to locally advanced muscle invasive bladder tumors. In that application,
462 heating of MIBC should be performed using optimal antenna settings obtained by patient
463 specific hyperthermia treatment planning, and with the deep hyperthermia system operated
464 following appropriate quality assurance guidelines.(70-73)

465

466 ***Pros and Cons of Bladder Heating Technologies***

467 A summary of advantages and disadvantages is provided in Table 2 for each of the heating
468 technologies described above. For treatment of NMIBC limited to the interior of bladder,
469 intravesical heating approaches appear most appropriate. As illustrated before, the simplest
470 way to heat bladder wall tumors is via the circulating, heated fluid approach. This has the
471 advantage of knowing both the maximum temperature anywhere in tissue and effective extent of
472 heating is limited to about 2-3 mm maximum penetration through the bladder wall, which is
473 sufficient for NMIBC. Thus, circulating fluid thermal conduction heating may be expected to
474 produce fewer toxicities compared to more complicated microwave heating approach that is
475 known to produce non-homogeneous power deposition with "hot spots" and potentially burns in
476 the posterior bladder wall and "cold spots" or places of ineffective heating at the dome and near
477 the trigone. Potential advantages of the intravesical microwave thermo-chemotherapy approach
478 stem from the increased penetration of microwave energy into somewhat thicker tumors (3-6
479 mm) and the use of circulating cooled drug to limit indiscriminant heating particularly in the
480 bladder neck and urethra. This claim may be overstated however, as the precooled drug

481 solution is heated during circulation both in the multilumen catheter where drug flows slowly
482 through the same catheter with a hot radiating microwave antenna and in the bladder where the
483 drug surrounds the radiating antenna. Thus, although improved penetration of heating may be
484 possible using the intravesical microwave antenna, significant thermal gradients are produced
485 within the bladder as well as the tumor due to non-uniform power deposition from the antenna
486 and slow circulation of fluid in the multilumen catheter.

487
488 Although external electromagnetic heating systems are more complex than intravesical devices,
489 there are potential advantages that result from the more complete heating of bladder, bladder
490 wall, and tissues surrounding the bladder, which may prove important for long term clinical
491 response. Obvious weaknesses of external regional heating approaches stem from the lack of
492 knowledge of peak temperatures and hot spots in tissue, and inclusion of significant volumes of
493 normal tissue within the heated region. Current pilot studies have demonstrated the feasibility of
494 using external RF systems to effectively heat NMIBC with minimal toxicity,(3, 6, 18) but the
495 determination of any advantage in terms of clinical outcome awaits larger clinical trials.

496

497 **Summary**

498 This review outlines the clinical requirements for heating bladder as a component of
499 thermochemotherapy for bladder cancer. Devices and techniques currently available to heat
500 bladder are described briefly and the equipment correlated with most appropriate clinical
501 disease, either muscle invasive bladder cancer or non-muscle invasive bladder cancer.
502 Representative commercially available clinical equipment systems are identified for each type of
503 energy delivery. And several systems are described within the context of pre-clinical heating
504 equipment currently available for use in animal studies. This article is intended to supplement
505 the detailed descriptions of clinical disease, biological goals of treatment, clinical trial results,
506 thermal dosimetry and treatment planning descriptions that are contained in other articles of this
507 special issue on bladder cancer.

508

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512

513 **Declaration of Interest**

514 The authors report no conflicts of interest. The authors alone are responsible for the content
515 and writing of the paper.

516 Table 1: Comparison chart of clinical studies of bladder hyperthermia

Equipment	Reference	Frequency (MHz)	Study Size	Prescribed # Tx	Treatment Schedule	Ave Power [W] or Temp [°C]	Goal/Achieved Temperature	HT Duration	Goal Treatment Completed	Max Toxicity (CTCAE score)	Most Common Toxicity
External Deep Regional RF											
BSD-2000 RF Phased Array HT System	Inman 2014 (6) Juang 2014 (24)	80-120	14	10	6 x 1/wk + 4 x 1/mon	740 ± 162W	96% > 40 min at T ₉₀ > 40°C	Ave Time >40°C 53.1 ± 8.8 min	73%	Grade 2	40% Foley Cath Pain 33% Abdominal Discomfort
BSD-2000 RF Phased Array HT System	Fatehi 2007 (25)	75-90	5	NR	1/wk	NR	40.9°C tumor 40.7°C lumen	60-90 min	NR	NR	NR
AMC-4, AMC-8 Waveguide Phased Array System	Geijsen 2015 (3)	70	18	10	6 x 1/wk + 4 x 1/mon	553W	T ₉₀ = 41.6°C	60-90 min	83% Induction 50% Full	Grade 2	38% Local Pain and Bladder Spasms
Capacitive Plate Electrodes											
Yamamoto Vinyter - RF-8 Capacitive Heating System	Masunaga 1994 (41)	8	28	4	2/wk + RT	578 ± 86W	42.1 + 8.0°C	35-60 min			43% Pain Under Electrodes
Yamamoto Vinyter - RF-8 Capacitive Heating System	Uchibayashi 1995 (42)	8	46	6-10	2/wk + RT		42.5°C	60		Grade 2	28% Burn, 24% Anorexia 20% Sub-Q Induration
Intravesical Microwave Antenna											
Synergo SB-TS 101 Transurethral MW System	Colombo 1995 (44)	915	44	8	2/wk in <6 wks	< 60 W	42.5 - 44.5°C	60 min Goal >40 min Minimum	97%	NR	Mild Urge and Urethral Burning
Synergo SB-TS 101 Transurethral MW System	Colombo 1996 (45)	915	29	6-8	1-2/wk in <6 wks	NR	42.5 - 46°C	60 min (2 x 30 min to Refresh Drug)	93%	Grade 3	Mild Urgency
Synergo SB-TS 101 Transurethral MW System	Colombo 1998 (46)	915	19	8	1/wk	NR	42.5 - 46°C	60 min Goal >40 min Minimum	96%	NR	Moderate/Severe Urgency, Mild Urethral Burning
Synergo SB-TS 101 Transurethral MW System	Colombo 2003 (2)	915	42	12	8 x 1/wk + 4 x 1/mon	NR	42 ± 2°C	60 min (2 x 30 min to Refresh Drug)	88%	NR	Pelvic Pain and Posterior Wall Thermal Reaction
Synergo SB-TS 101 Transurethral MW System	Kiss 2015 (47)	915	21	6-12		NR	42 ± 2°C	60 min (2 x 30 min to Refresh Drug)	62%	Grade 4 CTC Score - NCIC	57% Pain and Bladder Spasms
Synergo SB-TS 101 Transurethral MW System	Maffezzini 2014 (48)	915	42	14	4 x 1/wk + 6 x 2/mon + 4 x 1/mon	NR	42.5 ± 1.5°C	60 min Goal >40 min Minimum	76%	Grade 2	100% Thermal Reaction Posterior Bladder Wall
Synergo SB-TS 101 Transurethral MW System	van der Heijden 2004 (49)	915	90	10-14	6-8 x 1/wk + 4-6 x 1/mon	NR	41 - 44°C	60 min (2 x 30 min to Refresh Drug)	10 ± 2	Toxicity All Local Healed Spontaneously	72% ± 1 Toxicity 100% Thermal Reaction Posterior Bladder Wall
Synergo SB-TS 101 Transurethral MW System	Nativ 2009 (50)	915	111	12	6 x 1/wk + 6 every 4-6 wks	NR	42 ± 2°C	60 min (2 x 30 min to Refresh Drug)	95%	Grade 3	31% Pain and Bladder Spasms
Intravesical Thermal Conduction											
Combat Medical Ltd - Combat BRS System	Sousa 2014 (54)	-	15	8	8 x 1/wk	43 ± 1°C	Bladder Temp Not Measured	96% - 60 min 99% > 40 min	99%	Grade 2	33% Irritative Lower Urinary Tract
Elmedical Ltd - Unithermia System	Ekin 2015 (55)	-	43	12	6 x 1/wk + 3 x 1/wk in months 3 and 6	NR	Bladder Temp Not Measured	60 min	93%	Grade 5 Institutional CTC Score	37% Noninfective Cystitis
Elmedical Ltd - Unithermia System	Soria 2015 (56)	-	34	6	6 x 1/wk	42.5 ± 1°C 44.5°C Peak	Bladder Temp Not Measured	45 min	88%	Grade 3	24% Bladder Spasms

517

518

519 Table 2: Relative heating characteristics of clinical bladder hyperthermia systems

Heating Criterion	External			Intravesical	
	Deep Regional Electromagnetic	Deep Focused Ultrasound	Capacitive Current	Microwave	Circulating Heated Fluid
Homogeneity of heating around interior wall of bladder	+	--	-	--	++
Depth of penetration of heating through tissue	++	++	++	-	--
Control of maximum temperature	--	-	--	-	++
Circulation/mixing of drug in contact with bladder wall	-	-	-	+	++
Heating of tumor tissue outside the bladder	++	+	+	-	--
Heating of normal tissue outside the bladder	--	-	--	+	++
Ease of Heating	-	--	-	-	++
Patient Tolerance	-	-	-	-	+

520

521 ++ Major Advantage, + Moderate Advantage, - Moderate Shortcoming, -- Major

522 Shortcoming

523

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