Department of Radiation Oncology Faculty Papers

Department of Radiation Oncology

6-1-2016

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Thermal dosimetry for bladder hyperthermia treatment. An overview

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Abstract

The urinary bladder is a fluid filled organ. This makes, on the one hand, the internal surface of the bladder wall relatively easy to heat and ensures in most cases a relatively homogeneous temperature distribution; on the other hand, the variable volume, organ motion, and moving fluid cause artefacts for most non-invasive thermometry methods, and require additional efforts in planning accurate thermal treatment of bladder cancer.

We give an overview of the currently used and investigated thermometry methods for hyperthermia treatments of bladder cancer, and discuss their advantages and disadvantages within the context of the specific disease (muscle invasive or non-muscle invasive bladder cancer) and the heating technique used. The role of treatment simulation to determine the delivered thermal dose is also discussed. Generally speaking, invasive measurement methods are more accurate than non-invasive methods, but provide more limited spatial information; therefore, a combination of both is desirable, preferably supplemented by simulations. Current efforts at research and clinical centres continue to improve non-invasive thermometry methods and the reliability of treatment planning and control software.

Due to the challenges in measuring temperature across the non-stationary bladder wall and surrounding tissues, more research is needed to increase our knowledge about the penetration depth and typical heating pattern of the various hyperthermia devices, in order to further improve treatments. The ability to better determine the delivered thermal dose will enable clinicians to investigate the optimal treatment parameters, and consequentially, to give

better controlled thus even more reliable and effective thermal treatments.

1. Introduction

Bladder cancer is the fourth most common malignancy among Western men. [1] About 75 % of patients present with non-muscle invasive bladder cancer (NMIBC); NMIBC is confined to the mucosa and lamina propria (stages Ta, T1) and includes carcinoma in situ (CIS). [2] The other 25 % present with cancer invading the bladder musculature up to the perivesicular fatty tissue (muscle-invasive bladder cancer, MIBC). As detailed in section 2, these are distinct diseases with very different outlook, treatment modalities, and hyperthermia requirements. Hyperthermia (HT) has been investigated for decades as a method to improve the results of bladder cancer treatments. Most trials have focussed on the treatment of NMIBC. In order to reduce recurrences, HT is used to enhance the efficacy of chemotherapeutic instillations. For about two decades, HT in NMIBC was performed mostly with the Synergo-system, an intracavitary radio-frequency (RF) device. The last few years, other heating approaches, introduced briefly in section 3, have been increasingly used to deliver a controlled thermal dose to the target bladder region.

There have been far less trials using HT for MIBC treatment. In this case, the heat has to penetrate the entire bladder wall and part of the surrounding tissue, reducing the number of suitable HT devices, and increasing the complexity of both the treatment and the determination of the delivered thermal dose. Since bladder and tissue properties are patient-dependent, heterogeneous and time-varying, some form of thermometry during treatment is mandatory. As outlined in section 4, which thermometry technique is most suitable depends on both the tumour type and the heating device. The current standard is to use minimally invasive, local thermometry, but non-invasive regional thermometry methods are receiving increasing attention. Whereas hyperthermia treatment planning (HTP) and treatment simulation are not usually performed in intracavitary heating methods with shallow heat penetration —which may limit our options to optimize these treatments—, multi-physics simulations are paramount to apply reliably deep HT treatments. An introduction to the available HTP systems is given in section 5, with special attention to the particular anatomical and physiological properties of the bladder.

The pros and cons of several options to heat the tumour, measure the temperature, and simulate the treatment are discussed in more general terms in section 6. We then summarize the unique properties of the bladder, in particular its accessibility, and its similarity, in physical terms, to a fluid-filled bag with internal convective flow and no significant heat loss due to blood perfusion. Finally, we present recommendations for implementing good thermal dosimetry practices and interesting future research

topics.

2. Bladder Cancer

NMIBC and MIBC are clearly different tumour identities from both clinical, therapeutic, and thermal points of view. Whereas superficial tumours have an infiltration depth of less than about 20 cell layers (approximately 0.2 mm) and a very small risk of regional or distant disease, muscle invasive tumours can infiltrate up to 2 cm from the bladder lumen, and have a high risk of metastasising. Therefore, MIBC generally needs a much more aggressive treatment, and a much greater penetration depth of the HT treatment than NMIBC.

2.1 Non-muscle Invasive Bladder Cancer

Standard treatment for NMIBC is transurethral resection (TUR) of all visible lesions. Progression into a muscle-invasive cancer (section 2.2) is seen in 20–30 %, and recurrence even in 50–75 % depending on the risk group of the tumour [3].

To prevent tumour recurrence following TUR, immunotherapy or intravesical chemotherapy (CH) is given. In many cases, standard of care is immunotherapy with bacillus Calmette-Guérin (BCG), which can also influence the progression rate when given as maintenance therapy. [4,5] Unfortunately BCG is not without severe side effects, both local and systemic, which can even be life threatening. [6] The most commonly used CH agent is mitomycin C (MMC), followed by epirubicin and doxorubicin, which are instilled into the bladder in single, multiple weekly and/or maintenance dose regimens.

To improve this, combination therapies with local HT have been introduced. A synergistic effect is seen in vitro when combining HT and MMC in different bladder cell lines. [7] Phase I and II trials have been conducted with intracavitary RF hyperthermia (section 3.2b). Toxicity seems to be acceptable although a thermal reaction of the mucosa frequently occurs. [8] Only one randomised trial in intermediate/high risk patients has been conducted. After a follow up of 10 years the disease free survival was 53 % vs 15 % in favour of the combined arm with HT. [9] Other local heating techniques have since been explored, such as intravesical conductive heating (section 3.2a) [10] and loco-regional phased array HT systems (section 3.2d); so far only case reports and pilot studies have been published, but all showed promising results with acceptable toxicity. [11,12]

2.2 Muscle Invasive Bladder Cancer

Standard therapy for MIBC is a radical cystectomy. [13–15] Survival and loco-regional recurrence rates are however strongly dependent on tumour stage and general patient condition. [16]

At present, the most common bladder-preserving treatment for MIBC is combined radiotherapy (RT) and CH, which is generally only applied for unresectable tumours or patients medically unfit for cystectomy. However, long-term data show that overall survival is comparable when modern radiation techniques are used. [17–19] The addition of sensitizing CH (cisplatin, MMC and/or 5-FU) to RT in MIBC treatment has improved 5-year survival (from 35 % to 48 %) and reduced 2-year loco-regional recurrence rates (from 32 % to 18 %). [20] However, considering the toxicity of CH for this generally older patient group, HT is an attractive alternative as RT sensitizing agent for patients not eligible for CH. Only one randomized trial evaluated the additive effect of HT to RT in MIBC. Although the addition of deep regional HT increased the complete response rate with no increase of late toxicity, it did not significantly prolong the duration of local control and survival. [21] Achieved intracavitary temperatures, which are not representative of temperatures in the deep infiltrating parts of MIBC, were recorded but not reported.

Furthermore, considering synergistic effects of HT with both ionizing radiation and CH agents, a tri-modality treatment could further increase the local response rate of chemoradiation in MIBC. First results of a phase I–II study combining radiochemotherapy with deep regional HT in T1 and T2 bladder carcinoma showed encouraging results with a 3-year local recurrence free survival of 85 %. [22,23] This group uses non-invasive magnetic resonance imaging (MRI) based temperature measurements (*cf.* section 4.2.d), but results of the temperature data have not been published.

3. Hyperthermia

Hyperthermia works in myriad ways, which depend on temperature and treatment duration (thermal dose), combination of treatment modalities, and tumour site. Mechanisms of HT include increased blood perfusion, [24–26] altered cell metabolism, activated apoptotic pathways, [27] increased drug uptake, inhibited DNA damage repair, [28–30] and activation of the immune system. [31,32] Each mechanism has a different thermal dose-effect relation, making thermal dosimetry a complicated parameter.

In some cases, concomitant HT may actually lower drug efficacy, as heating may degrade the drug. Fortunately, this appears not to be the case for MMC [33].

3.1 Thermal Dose

Thermal dose is a measure of the cumulative exposure of tissue to a specific time and temperature combination. The commonly used measure for thermal dose is *Cumulative Equivalent Minutes at 43 °C*, or CEM_{43}, [34,35] which is based on an Arrhenius relationship:

$$CEM_{43} = \int R^{43-T} \, dt \; [\min] \tag{1}$$

with dt [min] the time spent at temperature T [°C], and the breakpoint R a constant usually taken to be ¼ for $T < 43$ °C and ½ for $T > 43$ °C. There are also indications that the actual values for R may be closer to ⅛ and ¾, respectively, and that the breakpoint may be 47 °C rather than 43 °C. [36] Also, it is uncertain over which temperature range this relation holds. Hyperthermia treatment temperatures are typically in the range 39–45 °C, as temperatures lower than 39 °C are mostly ineffective and temperatures higher than 45 °C may cause unwanted toxicities including immediately evident patient pain. [37,38] Note that dose effect relationships differ for different tissue types: 10 CEM_{43} for the skin has a very different effect than 10 CEM_{43} for muscle. [39] Lastly, and most importantly, the dose definition in equation (1) is based on direct cell kill, which is generally not the main therapeutic action of HT. For example, blood perfusion appears to initially increase with temperature up till about 43.5 °C, above which perfusion will decrease because of vascular collapse [24,40,41]; this affects reoxygenation and drug delivery, complicating the empirical formulation of a thermal dose. Nevertheless, there is a fair body of evidence that CEM_{43} works reasonably well as a measure for thermal dose, [35] there is substantial clinical experience with CEM_{43} and no better substitute is available. [42].

Another point to note is that temperature is a local quantity, *i.e.*, a value at a single point, while physiological effects are associated with a regional volumetric scale. To describe temperature throughout a treatment volume, temperatures are typically given as T_{90}, T_{50}, T_{10}, or a combination thereof, which are the temperatures reached in at least 90 %, 50 %, and 10 % of the target volume during treatment, respectively. This implies that tumour temperatures should be known with reasonable accuracy and sampling density throughout the targeted volume; this is currently challenging for both invasive and non-invasive thermometry techniques and consequently T_{50} can generally be established with more certainty than T_{90}. These measures can be combined with CEM_{43} to give corresponding thermal dose measures within the tumour volume. The minimal or average T_{90} or T_{50} over the treatment or even all treatment sessions may also be given. Other measures for thermal dose have been suggested but such alternatives

have not been widely adopted. For instance, [43] used T_{rise}, defined as the realised T_{50} over both tumour and surrounding healthy tissues, time averaged over the intended treatment duration. For cervical cancer T_{rise}, performed comparably to $CEM_{43} T_{90}$ in predicting disease specific survival.

On a final note, also the timing of the HT treatment —before, after or concomitant with the primary treatment modality— and the time interval between HT treatments, have noticeable impact on treatment effectiveness and safety. As there is no widely accepted way to include HT timing in the thermal dose definition due to the complex synergy with the primary modalities; it will not be discussed in this paper. [44,45]

3.1.a   *Quality Control*

Since even a mild temperature change has significant effect on physiology, temperature control during HT treatments is paramount to assure therapeutic quality, independent of target region. [38,46,47] This is especially true for bladder treatments, where the device used and the tumour type above all determine thermal distributions. On the one hand the bladder fluid can be heated relatively easily (using a variety of techniques described in section 3.2) and its temperature will be relatively uniform due to convective mixing. This generally causes the bladder wall to be heated also fairly homogeneously, due to conduction (unless the heating pattern is highly heterogeneous, *cf.* section 3.2.b). On the other hand the ion concentration inside the urine can vary greatly between patients, or even treatments, leading to a high uncertainty in dielectric properties —for RF heating highly relevant—, and hence to large inter-treatment and inter-patient variability. Moreover, the flow inlet and outlet of the bladder, and in some cases of the chemotherapeutic solution, can cause local temperature changes.

Hyperthermia treatments usually last for 45–90 min (with invasive treatments typically lasting shorter than non-invasive ones), and during this time the volume of the bladder increases linearly [48] or varies due to the constant drain through a urinary catheter. This is in particular an important point for simulations of bladder HT treatments and, consequently, for heating methods that require treatment planning. When bladder volume is not controlled through a urinary catheter, treatment parameters as power, phase and amplitude have to be adjusted during treatment to ensure a homogeneous temperature rise in the bladder. Since a change in bladder filling may also cause significant changes to the neighbouring anatomy, [49,50] this is also relevant for adjacent hyperthermia treatment sites, such as the cervix. [21,43]

The bladder has the advantage that intracavitary temperature measurements are feasible. However, it

is quite difficult to position temperature probes in the bladder precisely and stationary. In contrast to other treatment sites, during bladder treatments temperature mapping by moving probes through catheters is usually not performed due to the need to clamp the urinary catheter. [51] The temperature probe measures either the temperature of the bladder fluid or of the bladder wall. Therefore temperature measurement methods, which measure both bladder wall and bladder fluid, are recommended. [52,53] Phantom measurements showed that the temperature of the bladder filling and the bladder wall may differ more than 1 °C, this has yet to be verified *in vivo*.

The available procedures to adjust treatment settings to correct for too low or too high temperatures and ensure a high quality treatment, differ drastically between the heating devices.

3.2 Delivering Thermal Dose to the Bladder

There are various technologies to deliver HT to the bladder. They differ in the way they heat the bladder wall, and consequently they have different heating patterns and different requirements regarding thermal modelling, thermal dosimetry, and treatment control. We briefly introduce the most widely used methods as well as methods currently under investigation. A comprehensive review of heating technology is given elsewhere in this Special Issue. [54]

Heating methods can be divided between invasive (section 3.2a,b) and non-invasive (section 3.2c,d,e) methods. Invasive systems heat only a shallow depth into the bladder wall, limiting their use to non-muscle invasive disease. Non-invasive RF heating systems extend heating deeper into the bladder wall and surrounding tissues, potentially enabling MIBC treatment, and providing an additional challenge for adequate thermometry, but also offering more options for intracavitary thermometry. A combination of two systems, *e.g.* external phased array RF heating with recirculating warm fluid, may combine some advantages of both systems.

3.2.a *Recirculating Heated Fluids*

The simplest method to deliver heat to the bladder is based on closed circuit recirculation of an externally heated chemotherapeutic solution. The high flow rates (200–300 ml/min) of these systems ensure good mixing of the bladder contents resulting in a very homogeneous temperature in the lumen and at the bladder wall surface. [55] Since the temperature of the fluid and the bladder inner surface is well-known, there is no real need for treatment planning. However, with this thermal conduction heating approach, there is no direct measurement of the bladder wall temperature, and the estimated penetration depth across the wall is less than 4 mm, limiting its use to NMIBC. A recent porcine trial using the COMBAT

system measured the temperature on both the internal and external surfaces of the bladder wall, employing thermistors (section 4.2b). The results demonstrate that spatial distribution of the temperature on the bladder surface is relatively uniform (<0.4 °C), but the thermal gradient across the wall can reach 2–3 °C.

3.2.b   *Intravesical Microwave Antenna*

The Synergo system (Medical Enterprises BV, Amsterdam, the Netherlands), in use since 1991, [57] has the longest track record with respect to HT enhanced MMC treatments for NMIBC. The system heats the bladder wall via 915 MHz microwave radiation from an intracavitary antenna with recirculating cooled chemotherapeutic solution, cooling the urethra around the hot microwave antenna feedline to prevent thermal toxicities.

Positive results have been shown in both ablative and prophylactic treatments for intermediate and high-risk NMIBC patients. [9] Non-thermal side effects have been reported to be similar to standard MMC. [8] Continuous operator control is required to keep the temperature at the desired level of 42±2 °C. [58] Since the radiation pattern produced by the antenna is non-uniform, [57,59] the system may cause "hot spots" and superficial burns in about 40 % of cases, [8] or potentially ineffective "cold spots". These may not be detected by the limited integrated thermometry which consists of 3-5 thermocouple sensors (0.2 °C accuracy), pressed against the bladder wall. The reported temperature is usually the average of the three sensors, and variations per sensor during treatment are typically not more than 1.0–1.5 °C. Patient specific HTP would be extremely challenging and is not applied. Heat penetration into the bladder wall is expected to be deeper than that of recirculation systems, but insufficient for MIBC; a study that investigated the temperature gradient over the bladder wall in a sheep model revealed that the difference between inside and outside temperature was 3.3–5.3 °C. [60]

For a more extensive introduction and an overview of all recent trials with this system, the reader is referred to Van Valenberg *et al.*, elsewhere in this Special Issue. [58]

3.2.c   *Capacitive Deep Hyperthermia*

Capacitive heating works at relatively low RF frequencies of 5–30 MHz; all reported studies in treating bladder cancer used 8 MHz. Capacitive systems consist of two electrodes, placed on the anterior and posterior side of the patient. Heating occurs primarily because of dielectric loss. Due to its high resistivity, a subcutaneous fat layer of more than about 2 cm is a contra-indication for treatment. [61]

Using electrodes of different size localizes heating near the smaller electrode, but this form of power steering is very limited. Treatment simulation is still advisable because of the large influence of patient anatomy and bladder filling, and to evaluate possible temperature distributions. Although it is in general not possible to preferentially heat a deep tumour using a capacitive system, preferential heating of the bladder will occur naturally and can be further enhanced by increasing the salinity of the bladder contents to steer electric current through the lossy urine. Published studies show good obtained temperatures and good clinical results; an overview is given elsewhere in this Special Issue. [62]

3.2.d   Phased Array Deep Hyperthermia

There are two commercially available phased array RF hyperthermia systems, operating at 70–120 MHz. These systems use either one or three rings of antennae around the patient. Phased-array systems generate a steerable heat focus, which can be shifted towards the target volume by adjusting power and phase of the signals. Patient specific HTP is an important tool for steering of phased array systems, particularly for the more complex multi-ring heating systems. [38,63,64]

In treatment planning, the power and phase of each channel are optimized to maximize the heat delivery to the target and minimize hotspots above 45 °C in healthy tissue, [63,65,66] requiring not only accurate simulations and a treatment planning quality assurance, but also rigorous system characterization. [63] Power control during HT treatment with these systems is generally based on intraluminal temperature measurements. [67] The BSD2000/3D/MR system uses 3D non-invasive MR-based temperature measurements during therapy. [68,69]

Phased array deep HT devices have been used clinically for various treatment sites in the pelvic and abdominal area; recently, the feasibility of using these systems for NMIBC bladder HT has been proven. [11,12] This method has the potential to realize a more homogeneous thermal dose distribution than the intracavitary RF system, which should result in lower heat-related toxicity. Additionally, phased array systems have a much greater penetration depth, depositing energy in the entire bladder wall and the surrounding pelvic tissues, making it possible to induce better quality HT particularly in MIBC cases. An overview of clinical results is given elsewhere in this Special Issue. [62]

3.2.e   Magnetic Nanoparticle Fluids

Investigation has begun on the use of ferromagnetic nanoparticle (MNP) solutions that, mixed with CH, can be instilled in the bladder. The MNPs are heated via magnetic induction coupling to an externally applied alternating magnetic field, usually at a frequency between 50–100 kHz to minimize direct heating

of the pelvis. Pre-clinical studies have demonstrated that MNPs can produce sufficient heating inside the bladder. [70] However, investigations continue to optimize nanoparticle and surfactant formulations to minimize toxicity of MNP solutions. [71]

Heat generation is distributed throughout the fluid, which combined with convective mixing helps to homogenize the internal bladder temperature. For magnetic coupled MNP solutions, temperature must be monitored with an intracavitary non-metallic or EM interference (EMI) shielded probe. Unlike the circulating externally heated fluid approach, the maximum bladder temperature is not precisely known as the intracavitary probe may underestimate a localized peak temperature in the unstirred magnetic fluid.

MNP will distribute well within the bladder producing relatively homogeneous temperatures throughout the bladder interior, though temperatures are not as uniform as for circulated fluid systems. Introduction of this technology into clinical practice awaits demonstration of lack of toxicity of the magnetic fluid when delivered into the bladder at a clinically effective concentration.

4. Temperature Measurement

4.1 Precision and Accuracy

Treatment outcome correlates to thermal dose in the target area for a variety of tumour types. [43,72–84] However, when temperatures exceed 44 °C, heat related toxicity can occur. [37] Thus, it is important to measure temperature accurately, reliably and in real-time throughout and around the target area, *i.e.* the bladder wall and lumen. An accuracy of 0.2 °C and precision of 0.1 °C is preferable. Temperature should be recorded in real-time to be able to adjust the power settings and optimize the temperature distribution during treatment.

It is important to have (invasive) temperature measurements not only in the bladder, but also in neighbouring tissues that receive heat, such as the urethra, and, for capacitive and phased array deep HT, the cervix and rectum. These measurements give more information about the temperature distribution in the pelvic area and provide feedback for steering the power focus into the bladder to maximize target dose and avoid excessive heating of normal tissues. [51] It is important to provide feedback identifying the exact position of the heat focus within the patient [51]; therefore, it is preferable to use either probes with multiple measurement points, multiple single point probes in the target area, to perform thermal mapping along the invasive catheter, or to use high resolution 3D thermal imaging. [38,69,85,86]

If microwave or RF heating devices are used, temperature probes that do not interfere with EM fields

are preferred (fibre-optic or high resistance lead thermistor probes). For sensors interfering with EM fields (*i.e.* thermistors and thermocouple probes), the power should be turned off during the temperature measurement. [47] Accurate invasive probes are still required along with MR thermometry in hybrid MR-HT systems (*cf.* section 4.2.d).

4.2 Thermometry Methods

Numerous methods are available to measure temperatures. Recently, a review was published for thermometry during thermal ablation [87]; here, we focus on mild HT with special attention to the bladder. Generally, temperature is recorded most accurately with invasive probes such as thermistors, thermocouples, or fibre-optic sensors inserted into the bladder. For circulating heated fluids, the temperature in the bladder is mostly homogeneous and readily determined by any internal probe. The rapid falloff of temperature within the bladder wall needs to be predicted by treatment planning or determined experimentally. For heating with an intravesical microwave antenna, the temperature distribution is more complex; thus, three thermocouple sensors are placed at the bladder wall at points of expected high and low field strength, providing a better definition of the heating pattern. [88–91] Since the microwave antenna will deposit power non-uniformly directly in bladder wall tissue as well as the internal fluid, improved dosimetry would include volumetric thermometry techniques to characterize the 3D temperature distribution in a wider volume around the bladder. For heating with external RF systems, significant heating occurs regionally within the pelvis. Such treatments may be monitored with minimally invasive (intracavitary or intraluminal) probes in bladder, vagina and rectum, [12,51] but non-invasive thermometry supplemented by patient specific simulations would provide more complete feedback on heating in and around the bladder and facilitate better treatment control.

To provide reliable feedback, invasive temperature probes (section 4.2a,b,c) must be placed securely at the point of interest, which may be challenging. The bladder is easily accessible via the urethra, however, the exact location of the probe remains difficult to determine. Spatial resolution of either technology may be better than 1 mm in the radial direction in the presence of steep gradients stretching up to about 5 mm in relatively homogeneous configurations, thus providing a point measurement that does not reflect the volumetric temperature pattern. If intravesical heating methods are used, the sensor needs to be incorporated into the (disposable) treatment set, as is the case with the Synergo system and the recirculating fluid external heat exchanger systems. The temperature of fluid inside the bladder is not

necessarily the same as that of the bladder wall, and new approaches have been reported to characterize these temperatures. Using an "umbrella probe" that presses sensors against the bladder wall, somewhat similar to the Synergo thermometry system, it has been shown in phantom studies that these indeed measured the bladder wall temperature, which was lower than the temperature of fluid filling the bladder lumen. [52] Although it would be ideal from a dosimetric point of view, especially when treating MIBC, it is impossible to have temperature probes on each side of the bladder wall to ensure accurate characterization of the thermal distribution, except in animal studies.

Table 1 summarises the most important properties of each thermometry technique; below, they are discussed in more detail.

4.2.a   Thermocouples

Thermocouples are based on the Seebeck effect. A temperature gradient over a conductor results in a material specific electric potential. Joining two different conductors results in a measurable voltage or current from which a temperature difference between both ends of the measurement wire can be deduced. The sensitivity and accuracy depend mostly on the materials used. For HT applications, type T (copper-constantan) thermocouples are widely used, as they have good precision in the HT temperature range. They generally are rugged, reliable, fast, and long term stable, with a precision of 0.01–0.1 °C and, assuming proper calibration, an accuracy of better than 0.1 °C. [60,92,93] Thermocouples have a fast response time and are generally thinner and less fragile than fibre-optic probes (section 4.2.c), important in a clinical environment. Spatial resolution along the wire can be a problem, [94] especially when several thermocouples are combined in one probe; *e.g.* multi-sensor thermocouples with up to 14 sensors, spaced 0.5–1 cm apart. [12,52,93] This can be improved by using manganin-constantan probes, as they exhibit the same thermal sensitivity, but less thermal smearing than copper-constantan probes [94]; however, they are less readily available.

When used in RF systems, thermocouples will interact with the EM field. [93] Significant self-heating may occur; therefore, the power needs to be switched off for 5 s so that self-heating artefacts can dissipate before each temperature measurement.

4.2.b   Thermistors

Thermistors are resistors whose resistance changes with temperature. The thermistor's two terminations can be connected in several ways to readout circuitry: the most accurate has 4-wire configuration, two for

driving the current and two for measuring the voltage thus compensating for non-negligible wire resistance. Negative temperature coefficient (NTC) thermistors are widely used in medical applications since they are inexpensive, accurate and robust. Thermistors are generally made of a ceramic or polymer compound, which exhibit a resistance with non-linear temperature dependence. The Steinhart–Hart equation is a widely used third-order approximation [95] valid over a very large range of temperatures (hundreds of °C) and for traditional ceramic sensors. When operated over a small temperature range (*i.e.* hyperthermia, 34–44 °C), thermistors offer a linear temperature behaviour.

Recent NTC thermistors are silicon (Si) or germanium (Ge) based and have significantly improved performance versus conventional ceramic NTC thermistors. Although Si/Ge thermistors have a logarithmic temperature-resistance curve, they have higher thermo-sensitivity and do not need individual calibration in the working temperature range (0.2 % interchangeability). Additionally, smaller form factor Si thermistors can have resistance at room temperature of few MΩ, so self-heating is negligible and the sensor is resilient to negative environmental conditions. A very high resistance wire (*e.g.* Kanthal 35 AWG, ~1 Ω/cm) could be added to reduce interference from long wires without shielding or affecting performance. Conventional ceramic/polymer thermistors which suffer from poor interchangeability, and self-heating.

4.2.c   *Fibre-optic Probes*

Fibre-optic temperature sensors are based mainly on one of two technologies: fluoroptic and semiconductor band gap (SCBG) technologies. Fluoroptic technology takes advantage of optical properties inherent in phosphorescent materials. The instrument determines the temperature of the sensor by measuring the decay time of its emitted light. This decay time is a persistent sensor property and it varies precisely with temperature. Although fibres are typically reinforced with coating and can bend without affecting measurements significantly, the fluorescence material is often damaged with usage and time, limiting the life of the sensor. Alternatively, SCBG technology provides accurate measurements using the temperature-dependent bandgap shift of a Gallium Arsenide (GaAs) crystal.

Although fibre-optic sensors are expensive and fragile, they have a fast response and are immune to interference from RF and microwave sources. They are also electrically safe and resistant to chemicals and corrosion. Because of their ease of use (single point calibration) and good accuracy (0.2 °C), they are used for a variety of thermal medicine applications. In bladder cancer therapy, fixed or moving fibre sensors

are utilized for intracavitary monitoring of temperature (rectum, urethra/vagina) mostly in animal studies [96] and as references for MR guided treatments. [97]

4.2.d Magnetic Resonance Imaging

Several non-invasive thermometry techniques for HT applications are under investigation, but the only method in clinical use is MR thermometry. [86,98] There are a number of temperature-sensitive MR parameters, [99] but MR thermometry in clinical HT is based on the proton resonance frequency shift (PRFS) method because of its wide temperature range, high linearity, good sensitivity and spatio-temporal resolution. [100] The PRFS technique is based on comparing phase maps made during treatment with a baseline made before treatment. [101] PRFS can be used in tissues with high water content (*e.g.* muscle), not in low water content tissues (*e.g.* fat and bone). [102] PRFS measurements have been shown to be an excellent tool to guide HT treatments in the pelvic region [68] and extremities. [85]

MR thermometry requires the non-trivial design and installation of RF heating devices in an MR scanner. The first commercial solution, developed at Charité University Medical Center, showed the feasibility to integrate BSD Medical's Sigma-Eye applicator into a 1.5 T MR scanner (Symphony; Siemens Healthcare GmbH, Erlangen, Germany) for treatments of tumours in the pelvis. They showed that quantitative MR measurements during heating are feasible for the pelvic region but also that susceptibility artefacts and the distortions by the applicator must be carefully taken into account for accurate MR measurements. [86,103]

Although a very attractive option for dosimetry in the clinic, especially for MIBC, there are no reports concerning MR thermometry monitoring of bladder cancer treatments. There are a number of motion related challenges to overcome, caused by *e.g.* filling of the bladder and bowel movements. First, misalignment of mid-treatment from initial baseline images causes artefacts in the thermometry maps, which is not easily corrected in post-processing. Second, movement of tissue interfaces lead to changes in the main magnetic (B_0) field of the scanner, invalidating some underlying assumptions of the reconstruction algorithm. For slow changes in the B_0 field, techniques are under development to filter artefacts [104,105] or use a silicon [106] or fat [107] reference, but fast changes require dedicated motion robust approaches. Finally, there are motion artefacts from convective currents or externally recirculated fluids inside the bladder that induce image distortion and temperature rise calculation errors. These distortions and errors may be overcome by masking signals from these locations, provided that the (moving) bladder volume is accurately located at all times. For MIBC treatment with RF devices, practical

solutions may include catheter based emptying of the bladder and means that restrict convection in the bladder.

To date, MR thermometry is the only technique that provides clinically proven 3D non-invasive temperature monitoring, but obtaining an accuracy of 0.1 °C requires additional technologies. Still, MR guidance has the added benefit of monitoring not only temperature, but also the tumour.

4.2.e   *Microwave Radiometry*

Every object radiates energy proportional to its absolute temperature with frequency distributed across the EM spectrum. [108] Thermal radiation emitted at 0.5–5 GHz microwave frequencies can travel several cm through biological tissue. [109] A microwave radiometer collects safely, painlessly and passively, through an antenna, a number of these photons proportional to the tissue composition and absolute temperature. By collecting photons at different frequencies, it is thus possible to reconstruct the thermal profile across several cm of tissue below a sensing antenna placed on the skin. [110] This skin contact requirement is a major drawback when the technique is to be combined with deep hyperthermia methods that require a water bolus between antenna and patient (*cf*, section 3.2c,d).

In general terms, a microwave radiometer consists of three basic modules: 1) a skin contacting sensor composed of a calibration switch system and a first stage amplifier, 2) a processing unit with high gain amplification, signal filtering, and conversion to a digital signal, and 3) calibration, control and temperature reconstruction software. [111,112] The software provides signal processing with temporal averaging, drift compensation, and a signal-to-temperature conversion. Technological advances have resulted in radiometers able to track temperature 5 cm deep in the brain with a sensitivity of 0.4 °C. The same technology was used to demonstrate feasibility of simultaneous warming and temperature monitoring of porcine bladder. [113,114]

For a single band radiometer, there is just one signal and the specific tissue volume being sensed depends on the radiation pattern of the receive antenna and the selected frequency band, allowing to accurately estimate temperature of a tissue volume at depth [110,115–117]. A temperature depth profile can be reconstructed if radiometer signals are collected over multiple carefully chosen frequency bands [118,119]. An array of radiometric sensors could then provide lateral information and, combined with depth profiles, produce 3D thermal mapping.

However, several challenges are limiting the use of this technology to lab research and preclinical models. Accuracy of the radiometric readings is highly dependent on antenna calibration, tissue

properties, and patient anatomy. The calibrations generally involve a combination of both theoretical modelling and experimental confirmation in known heterogeneous tissue models. [110,114,120,121] Other critical factors for accurate radiometry are the contact reliability between sensor and tissue, motion artefacts, and EMI shielding. When combined with EM heating, accurate readings require turning off the power sources during the measurement period (*e.g.* 2–5 s power off intervals) potentially introducing a 'cooling' error. Figure 1 compares microwave and fibre-optic temperature measurements, showing a large delay for the radiometer.

Although it ultimately could be a cost effective technology, the thermal profile reconstruction is quite complex. Despite the challenges, radiometry has made significant advances in recent years. It may therefore soon play a role by complimenting invasive measurements for thermal dosimetry during bladder HT, especially in those clinics where MR or ultrasound systems are not readily available.

4.2.f Ultrasound

Ultrasound (US) imaging is capable of tissue thermometry using a variety of methods, covered comprehensively in a recent review article by Lewis *et al.* [122] US is real-time and offers a spatial resolution of 1–2 mm. Challenges with US thermometry include the non-linear response to temperature changes, and a limited range of measurement from body temperature to less than 50°C. Furthermore, compatibility of US devices with specific HT systems must be considered, both in terms of RF and acoustic interference, and the potential of US probes to disrupt energy transmission into the body. Patient movements and the fluid convection may also contribute to artefacts in the temperature measurements. To date, there are no reports in the literature of using US thermometry to monitor bladder heating, and the few reports of using the method *in vivo* have been limited to preclinical rodent studies. [123–125]

There are two US thermometry techniques with potential suitability for monitoring bladder treatments. The first is the use of speckle tracking or thermal strain imaging to detect speed of sound changes during heating. [126,127] This technique offers a temperature resolution of approximately 1 °C and is amenable to 2D B-scan imaging. Unaddressed issues include the robustness of the temperature calculations on a layered structure such as the bladder. Further, thermal strain methods are sensitive to bulk motion, requiring motion compensation or efforts to keep the bladder volume constant. The other promising approach is shear wave thermometry, [128] which measures the speed of propagation of a shear wave generated in the target tissue. Shear stiffness changes could be used to identify thermal dose levels

as estimation of tissue damage. [129] Moreover, this technique does not have the motion sensitivity of thermal strain imaging, making it more practical for bladder treatments.

Reliable clinical US systems are available in most of the urology clinics that perform cancer treatments. Advantages of US thermometry are portability, accessibility of the bladder to US, and ability to image the bladder wall clearly from outside the body or from transurethral systems. The fluid in the bladder is not likely to cause major artefacts, however, temperature measurements within the fluid are not feasible with US. Moreover, the motion of the bladder as it fills needs to be taken into account. Finally, depending on the heating method, the placement of the probe may be problematic. US thermometry is not yet standard on clinical systems, therefore applications in the near future are limited to research studies with prototype devices.

5. Temperature Simulation

No HT treatment planning system currently in use accurately models the urinary bladder including convective flow, although some steps have been made to correct for this. [48] Instead, the entire bladder, including contents, is typically modelled as a solid muscle. Thus two errors are introduced regarding the bladder content, since it is neither a solid, nor does it have muscle-like tissue properties. The resulting errors do not only affect the bladder itself, but may also have an impact on surrounding tissues. The presence of an air bubble within the bladder also appears to affect bladder wall temperature homogeneity. [130]

5.1 Clinical Simulation Methods

Hyperthermia treatment planning (HTP) for bladder treatments is used clinically almost exclusively for phased array systems (section 3.2d). For many years, HTP has been used mainly retrospectively, [131–133] but nowadays HTP is used more often before and during clinical HT to improve treatment quality. [51,64,134,135] The clinical relevance of HTP is emphasized in the recent Quality Assurance Guidelines for clinical application of loco-regional HT, specifying the requirements for HTP. [47] The need for adequate treatment planning has led to a number of dedicated treatment planning software packages that can be used for clinical applications. [63,66,135]

All systems follow the same basic principle. Based on a segmented patient model, they first compute the EM field, based on a catalogue of dielectric and thermal tissue properties, and calculate the resulting energy absorption, or SAR (Specific Absorption Rate). Using this SAR distribution, they may compute a temperature distribution based on Pennes' bio-heat equation, [136] which relates temperature change to

energy uptake, thermal diffusion, and heat loss due to blood perfusion. The chosen modelled perfusion rate usually reflects the increased level expected at elevated temperatures. Many systems support temperature dependent perfusion rates to reflect increases in perfusion during treatments, but these are not commonly used as they do not substantially improve the steady state solution and negatively impact calculation times. Phase/amplitude optimization can be done based on SAR or temperature objectives.

When loco-regional heating is performed using one of the BSD Sigma systems, [137] the commercially available HTP system Sigma-HyperPlan (Dr Sennewald Medizintechnik GmbH, Munich, Germany) can be used. Besides the standard segmentation method various other methods are available to generate a patient model based on a CT scan. [138] E-field and temperature calculations can be performed using either the finite element method with tetrahedral grids or the Finite Difference Time Domain (FDTD) method. [139] The FDTD method can be applied on a tetrahedral grid generated using segmented regions as well as on a voxel grid generated using the CT Hounsfield Units. [131]

SEMCAD X and Sim4life (SPEAG, Zurich, Switzerland) are commercially available multi-physics simulation platforms that are more flexible and allow modelling of various applicator configurations as well as MRI guidance and interactions. Add-on segmentation tool iSEG, which contains several fully automatic and interactive segmentation techniques, can be used to create patient models. Specific work-flows are available for standardized HTP. Calculations are based on finite difference and finite element methods. Some extensions to the Pennes model are available, including user-defined anisotropic thermal conductivity, temperature dependent parameters and pseudo-1D boundary conditions to model the impact of vasculature and blood flow.

The AMC hyperthermia treatment planning system (Academisch Medisch Centrum, Amsterdam, the Netherlands) is a flexible in-house developed FDTD based HTP system that allows for various applicator systems. [140–142] Tissue segmentation is based on Hounsfield Units, which can be combined with manual delineations and corrections. A unique feature of this planning system is the DIscrete VAsculature (DIVA) thermal model, which allows realistic modelling of blood flow. [143,144] The DIVA model subdivides the model geometry into a voxelized tissue space and a grid-independent vessel space describing vasculature by 3D curves compatible with CT/MRI angiography software.

In addition to these dedicated planning software platforms, COMSOL, Ansys High Frequency Structural Simulator (HFSS) or CST STUDIO SUITE also allow for E-field calculations and basic thermal

simulations for HTP. These packages provide flexibility in applicator modelling, but require linking to other software for tissue segmentation, advanced thermal modelling and optimization of SAR or temperature distributions.

The software packages used to perform clinical HTP for bladder treatments differ between institutions and the choice may depend on individual preferences. Nevertheless, additional software tools will be required for specific or relatively new applications, such as adaptive treatment optimization.

5.2   Dielectric Tissue Properties

The accuracy of SAR and subsequent thermal modelling is dependent on the accuracy of the dielectric and thermal patient model, and thus on the quality of the tissue segmentation. In current HTP systems, the liquid contents of the bladder are assigned the same electrical and thermal properties as the bladder wall. The investigation of human autopsy samples of Gabriel *et al.* [145,146] resulted in a low permittivity of bladder wall tissue ($\varepsilon_{r,wall}$ = 20) as well as a very low conductivity (σ_{wall} = 0.27 S/m) at 37 °C. This is much lower than the values typically used for muscle, to which the bladder wall is generally assumed to be similar. For instance, the database of Sigma HyperPlan lists a permittivity of $\varepsilon_{r,filled}$ = 78 for bladder and a conductivity of σ_{filled} = 0.6 S/m (both wall and contents) at a frequency of 90 MHz.

However, the dielectric properties of the fluids inside the bladder differ strongly from those of the bladder wall. Yuan *et al.* [48] measured the dielectric properties of the treated bladder fluid (urine and MMC) at a frequency of 90 MHz and reported a permittivity equal to HyperPlan ($\varepsilon_{r,fluid}$ = 78) but a much higher conductivity (σ_{fluid} = 1.81 S/m), similar to results in a porcine study. [147] Given the ease of procedure, this type of measurement should be done more often to obtain a clearer insight in conductivity and permittivity value and variation. For tissues, however, human *in vivo* electric property measurements are scarce, due to practical and ethical reasons, and therefore MR based methods such as Electric Properties Tomography (EPT) for non-invasive measurement have received increased attention. [148–152] The resolution of such methods is currently inadequate to distinguish the bladder wall, but the bladder contents can be measured. A recent study using EPT in cervical cancer patients found a large interpatient variation: σ_{fluid} = 1.80 ± 0.54 S/m, [152] which had a major impact on HTP. [153] The impact on the bladder is shown in Figure 2b,d.

Moreover, electrical conductivity is temperature dependent; in a study with various freshly harvested tissues, the conductivity of bladder wall increased from 0.95 to 1.01 S/m and that of muscle from 1.03 to 1.13 S/m when the temperature was increased from 37 to 45 °C. [154] Additionally, it has been shown that

the electrical impedance increase of bladder wall tissue is affected by the presence of tumour tissue, an effect that does not occur in certain other tissues such as cervical tissue. [155]

There have been very few studies concerning the impact of using different dielectric values for bladder HTP. One group studied the combined effect on HTP accuracy of updated values of both dielectric and thermal parameters. [48] A treatment planning study on cervical cancer patients found a large impact on HTP outcome using *in vivo* dielectric properties and bladder volume. [153] In one patient model with a full bladder, the difference between optimization with literature values and EPT values for the T_{90} was 1.37 °C; for patient models with practically empty bladder the temperature decrease was less than 0.57 °C. [153] Although results for the cervix cannot be directly translated to the bladder, it suggests treatment with a full bladder may be beneficial.

5.3 Thermophysical Bladder Properties

Apart from the dielectric properties mentioned in the previous section, there are two principal differences between a bladder properly modelled as a fluid filled organ, and a bladder modelled as a solid muscle: the absence of perfusion, and the presence of convection. In local or loco-regional HT, blood perfusion of tissues is a very important factor for temperature simulations, [156] and it is typically modelled as a heat sink. In the bladder interior, there is no perfusion, and therefore, no heat sink; instead, the only heat removal is through conduction to the (perfused) bladder wall.

Secondly, in an unevenly heated fluid, convection will occur under the influence of gravity. This is a much more effective heat transport mechanism than thermal conduction, and consequently, it tends to homogenize temperature throughout the fluid. Additionally, there will be a nett heat transport against the gravitational pull.

A first step to mimic the effects of convection is a model with highly increased effective heat transfer. [48] This large effective heat transfer property should preferably be anisotropic, but not all HTP systems allow for that. A drawback of this approach is that the effective value for heat transfer depends on many factors and is not easily derived. Thus it is necessary to fit the effective conductivity to measured temperatures, making the method empirical and available only from the second treatment session onwards.

More recently, a physically more sophisticated and computationally more intensive approach was reported in a study investigating the effects on the temperatures of convection in the bladder, using a thermophysical fluid model extension to the AMC HTP system, the results of which are shown in Figure

2c,d. [130] However, for good precision such a model requires the measurement of physical properties that are not routinely determined at this time, such as the viscosity of urine. [157] While modelling convection is particularly important for HT treatments of the bladder (both for MIBC and NMIBC), it is also relevant for treatments of nearby organs such as the cervix, rectum and prostate, as significant temperature differences may occur in tissues up to 1.5 cm distance from the bladder. [48,130]

6. Discussion

An increasing number of clinical studies using HT in the treatment of bladder cancer are being performed and results demonstrate very promising improvement in clinical outcomes. Thermal dosimetry is important to safeguard these treatments and to determine dose-effect relations. In this paper, we describe the methods that are currently employed or that are being studied to determine thermal dose.

The urinary bladder is unique in the human body in that natural convection can occur in a large volume that affects temperature distribution in the surrounding pelvic region. In the context of HT treatment for bladder cancer, this has a number of advantages and disadvantages. Convection enhances homogenization of temperature in the bladder contents and results in a similarly homogeneous thermal dose to the inner bladder wall. Treatment simulations, [130] phantom measurements, [52] and clinical experience [158] all demonstrate a temperature variation of less than 0.5 °C along the bladder wall. This supports the concept that measuring a limited number of points inside the bladder is sufficient to obtain a good impression of temperature of the entire bladder wall surface. An exception occurs when air is present in the bladder, shielding part of the bladder wall from contact with the bladder fluid, altering the local EM field, and potentially affecting the accuracy of non-invasive thermometry.

Another exception occurs during treatments with an intravesical antenna, in which the heterogeneous power deposition produces definite hot and cold spots within the bladder with temperature differences of several °C. [60,91,159,160] In the case of thermal conduction based intravesical heating methods (*e.g.* recirculating heated fluids or MNPs), a steep temperature gradient occurs across the bladder wall. External heating methods have the potential to produce the most homogeneous temperature distribution and deepest heat penetration of the bladder wall, but may not produce equally high temperatures, [11,12] especially when the patient anatomy is unfavourable. [51] An interesting option is to combine an internal and external heating method, *e.g.* combining phased array RF heating with closed circuit recirculation, especially in the context of MIBC where effective heat penetration and high thermal dose are essential.

However, convection currents or forced circulation of the bladder fluids have some important drawbacks for certain thermometry techniques, especially since the most promising non-invasive volumetric thermometry method, MRI, is very sensitive to motion. While restricting convection or emptying the bladder is, of course, impossible for NMIBC treatments with chemotherapeutic solutions, it could be an option for MIBC treatments that are combined with RT alone. However, in that case, one would also lose the preferential heating of the bladder and its homogenizing effect on temperatures in the region.

Generally speaking, invasive thermometry technologies are more accurate and further developed than non-invasive methods. The accuracy and stability of thermocouple, thermistor, and fibre-optic based probes is well-established and the techniques are fully tested in a wide range of clinical applications. There are reports of promising clinical applications for emerging microwave radiometry, [110,118,120,161] but most of the literature to date involves system development and feasibility testing. MR thermometry is more mature and is in clinical use, but accuracy is still insufficient for use as a stand-alone technique. For characterization of bladder temperature during clinical HT, it is currently more logical to combine invasive sensors inside the bladder with external volumetric monitoring to improve knowledge of the temperature distribution extending through the bladder wall and potentially invading surrounding pelvic tissue. Given the current lack of knowledge of the temperature outside the bladder lumen, such combinations of accurate invasive methods, and more spatially informative non-invasive methods are essential.

Given recent progress in thermal modelling, [48] one can imagine further improved characterization of pelvic temperature distribution using a combination of local thermometry, volumetric thermometry and patient specific simulations, as demonstrated for *e.g.* head and neck cancer [162] where measurements and simulations are combined into estimated temperature maps. [163] One example of a hybrid simulation/optical probe approach recently demonstrated accurate assessment of the T_{50}, based on sparse invasive probe measurements, [164] but the fusion of MRI and invasive measurements in the same coordinate space is still challenging. [165] For bladder cancer, this technique might provide a good option to reconstruct the temperature within the bladder wall. Moreover, MR could potentially be used to map changes in tissue perfusion and dielectric properties, to be used as input for real-time treatment simulation, but this cannot currently be combined with MR thermometry.

Naturally, thermometry options are often limited by the specific heating technique used. In the case of recirculated fluids or intravesical microwave heating, the invasive thermometry options are determined by the manufacturer. In these cases, ultrasound or radiometric thermometry may provide additional information on the temperature distribution throughout the bladder wall. In the case of external heating methods, outside access to the patient may be limited by the presence of the HT device; but there is unrestricted access to the bladder through the urethra. In many cases, interference between the HT device and thermometry system may be an issue, but for most thermometry techniques this can be relatively easily solved by proper shielding or by temporarily turning the power deposition off during measurements. The exception is MRI thermometry, which typically requires a redesign of the devices with which it is combined.

Notwithstanding the technological challenges, accurate thermal dosimetry is highly relevant, both scientifically to gain insight into the heating properties of various HT devices and to study thermal dose-effect relations, and clinically to ensure good treatment quality.

7. Conclusion

For NMIBC treatment using thermal conduction HT devices, simple measurement of the fluid temperature is likely to be sufficient to control the delivered thermal dose, provided the penetration depth is well-known and clinical efficacy has been proven in randomised controlled trials. For more complex treatment techniques, and for MIBC treatment, more elaborate methods are required to determine and control the thermal dose. Currently, none of the thermometry methods can by itself offer the required accuracy and spatial information. Although invasive probes are reliable and accurate, they deliver very limited spatial information; on the other hand non-invasive regional measurements provide volumetric thermal distribution data but suffer from various artefacts while failing to obtain the required accuracy. Finally, while multi-physics simulations provide important insight into possible temperature distributions from the various heating approaches, they need more accurate input in order to deal with inter-patient and inter-treatment variability. Therefore, combinations of at least two, but preferably all three dosimetry approaches are essential.

The fact that the urinary bladder is a fluid filled organ, is both a boon and a bane. On the one hand, it makes the inside bladder wall relatively easy to heat and ensures in most cases a relatively homogeneous internal wall temperature distribution; on the other hand, the variable volume, organ motion, and

moving fluid cause artefacts for most non-invasive thermometry methods, and necessitates additional physics considerations for accurate treatment planning.

8. Acknowledgements

9. Declaration of Interest

Dr Alejandro Sousa Escandon is a clinical advisor of Combat Medical Ltd. Dr Margarethus M. Paulides is consultant and has financial interest in Sensius BV.

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