Bone Hyperthermia Treatments: Temperature Monitoring

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Bone metastases and osteoid osteoma (OO) have a high incidence in patients facing primary lesions in many organs. In this arena, hyperthermia treatments (HTs) have gaining momentum as valuable alternatives to traditional therapies owing to their minimally invasive nature, the success rate in tumor control and the immediate effect in pain relief affecting the majority of patients. Temperature monitoring during HTs may significantly improve the clinical outcomes since the amount of thermal injury depends on the tissue temperature and the exposure time. This is particularly relevant in bone tumors due to the adjacent vulnerable structures (e.g., spinal cord and nerve roots).

Keywords: bone tumors ; CT thermometry ; fiber Bragg grating sensors ; fluoroptic sensors ; hyperthermia treatments ; MR thermometry ; thermocouples ; thermistors ; temperature monitoring ; ultrasound thermometry

1. Introduction

Hyperthermia treatments (hereafter HTs) have gaining momentum in the treatment of bone cancer. Such procedures have emerged as valuable alternatives to traditional therapies, owing to their minimally invasive nature [1][2][3][4]. Given the success rate in tumor control and the immediate effect of pain relief, HTs have been identified as a possible treatment in bone metastases by the National Comprehensive Cancer Network in its November 2020 guidelines [5]. The main principle of HTs is to achieve complete and effective cancer removal by raising cytotoxic temperatures (i.e., > 50 °C) [6]. Among HTs, radiofrequency ablation (RFA), laser ablation (LA), microwave ablation (MWA) and high focused ultrasound (HIFU) are well documented in the literature for bone malignancy management [7][8][9][10][11][12][13][14]. RFA, LA and MWA are performed via percutaneous access whereby a needlelike applicator is positioned within the tumor tissue under imaging guidance (e.g., computed tomography -CT-, magnetic resonance -MR-). Differently, HIFU is totally non-invasive and the treatment is carried out by means of a transducer placed on the external body surface corresponding to the area to be treated [15]. Working principles of these techniques differ according to the energy source employed, and cell necrosis is achieved by a localized increase in temperature because of energy-tissue interaction [6]. During HTs, the amount of thermal injury is strongly related to the temperature experienced by the tissue during the procedure and the exposure time, as outlined by the most popular models (e.g., Arrhenius' law, CEM 43 °C [16]). Therefore, keeping track of temperature changes over time accounts for valuable information to the clinician performing the procedure. Real-time temperature understanding allows adjusting treatment settings (e.g., input power and treatment time) to clearly identify the endpoint and ensure damage to the tumor portion plus a reasonable safety margin while preserving healthy surrounding anatomical structures [17][18][19][20][21]. Temperature tissue monitoring may be accomplished by many either contact or contactless techniques with different purposes. Among others, temperature map reconstruction resulting from tissue temperature measurements allows accurately estimating tissue damage, thus achieving a good match between the portion of tissue that should be damaged and the one that experiences cytotoxic temperatures during the procedure. Temperature knowledge gains further relevance in bone tumors growing adjacent to vulnerable structures such as the spinal cord and nerve roots [22]. The dealing of such lesions is characterized by the major challenge of preventing cytotoxic temperatures in susceptible areas [23]. Indeed, neural elements are not allowed experiencing temperatures higher than 45 °C since this would lead to permanent damage including in the worst cases paralysis or paresis that severely impact the patients' status [24][25][26][27]. Therefore, both thermal insulation techniques and/or temperature monitoring are mandatory in this scenario to improve the procedure's safety and efficacy [26][28][29]. While the firsts are carried out by injecting CO_2 or saline solution to create thermal dissection, temperature monitoring leads the way to correctly gather temperature information in the treated tissue without compromising sensitive elements [26][30][31]. Moreover, temperature measurement plays a key role in investigating the effectiveness of either available or novel ablation devices, thus affording optimization and understanding their performances, as well as gaining new findings on how various HT settings affect the treatment effects. In addition, single-point temperature measurements are broadly accepted in clinical settings to protect vulnerable anatomical areas from cytotoxic temperatures. In these cases, thermometers must be carefully inserted in the proximity of these structures by avoiding undesirable injuries. In spite of this potential impact, temperature monitoring is not well established in clinical settings since it presents several open challenges when performed during HTs.

2. Temperature Monitoring: Main Techniques and Applications in Bone HTs

Extensive investigations have been devoted to providing suitable solutions for continuous temperature monitoring during HT since the knowledge of temperature may be beneficial to ensure the procedure's safety. Basically, thermometric techniques employed in this scenario can be classified as either contact-based or contactless methods [18]. Contact-based techniques involve the insertion of the sensing element within the treated tissue. This category includes thermocouples, thermistors, fluoroptic sensors, and fiber Bragg grating (FBG) sensors. Contactless techniques do not require direct contact with the measurement site. This category involves diagnostic imaging techniques (i.e., magnetic resonance imaging, MRI, computed tomography, CT, and ultrasound thermometry), allowing a temperature mapping reconstruction during the procedure.

The main benefits and drawbacks of thermometric techniques employed during HTs are summarized in **Table 1**.

Thermometric Techniques	Benefits	Drawbacks
Thermocouples	Low cost; small size; robustness; wide measurement range; and short response time	Invasive; single point measurement; metallic composition; potential measurement artifacts
Thermistors	Low cost; small size; robustness; high sensitivity; short response time; good accuracy	Invasive; single point measurement; potential measurement artifacts
Fluoroptic sensors	Biocompatibility; small size, immunity to electromagnetic fields; wide measuring range; high accuracy	Invasive; single point measurement; fragility; potential measurement artifacts
FBGs	Biocompatibility; small size; immunity to electromagnetic fields; high accuracy; short response time; multi-point temperature measurements;	Invasive; fragility; cross-sensitivity to strain; high-cost
CT-thermometry	Non-invasive; thermal map reconstruction; good spatial resolution; fast acquisition time; temperature precision around 3 °C	Ionizing radiation dose; potential measurement artifacts; quite expensive
US-thermometry	Non-invasive; thermal map reconstruction; absence of ionizing radiation; quite inexpensive	Potential measurement artifacts

MR-thermometry	Non-invasive; thermal map reconstruction; absence of ionizing radiation; linear relationship between T1 and temperature variations in the range of 30 °C and 70 °C; no tissue type dependence for PRF method	Potential measurement artifacts; lack of MR signal in cortical bone; expensive

The first application of bone RFA in a clinical trial dates back to 1992, as reported in a scientific article published by Rosenthal et al. [32]. Among a huge number of studies focused on bone RFA, many of them have also investigated temperature. During RFA in bone cancer, temperature monitoring was mainly accomplished by thermocouples and thermistors as evidenced by studies reported in the literature [22][33][34][35][36][37][38][39][40][41][42]. The aim of these studies was to highlight the key role of temperature knowledge in preventing acute complications in lesions involving vulnerable structures (e.g., nerve roots and spinal cord) close to tumor mass and to evaluate the influence of specific anatomical parameters or the design of ablation devices on temperature distribution.

On the other hand, LA found application in bone a few years later by Gangi et al. [43] for the treatment of OO. Only few studies investigated temperature monitoring during LA [44][45][46][47][48][49]. All these studies carried out MR-thermometry to evaluate temperature distribution during HT. This technique allows displaying in real-time temperature map and keeping track of thermal injuries in the vertebral bodies and spinal canal.

The first scientific investigations on MWA in bone go back to 1996 [50][51]. Studies concerning temperature monitoring during MWA in bone are lacking in the literature and the few research articles found are quite recent [52][53][54][55][56]. The main thermometric techniques used in this scenario to monitor temperature were thermocouples and FBGs. While some of the studies mentioned performed temperature monitoring to preserve nearby structures from irreversible injuries, others have demonstrated the usefulness of multipoint temperature measurements by FBGs to gain information regarding the heat distribution not only near the treated area but also in the surrounding ones.

Lastly, a feasibility assessment about the efficacy of HIFU treatment for the treatment of primary and secondary bone tumors appears in 2001 [57]. Other relevant studies have also explored temperature monitoring using MR-thermometry [58][59][60][61][62][63][64]. Temperature measurements were carried out to ensure the safety of the procedure and thermal map of bone tissue was also derived to obtain temperature information about bone and soft tissue. Also, one of these studies proposed a predictive temperature model to tune the acoustical energy deposition automatically with the aim of controlling temperature rise at the focal point.

In view of the above, pre-clinical and clinical studies were found to explore the applicability of specific thermometric techniques tailored to this specific scenario. Among contact-based and contactless techniques used to record temperature during HTs, only some of them were adopted in this specific context. Thermocouples, thermistors, and MR-thermometry play a leading role during HTs in bone. Very few studies addressed the potential of FBGs for temperature measurements purposes during bone ablation, despite their popularity in other hyperthermia applications. Otherwise, fluoroptic sensors were only used in the validation of MR-thermometry during bone HIFU procedures. To the best of our knowledge, to date, literature lacks investigations regarding CT and ultrasound thermometry in bone ablation. From non-exhaustive inferences, contactless techniques could be expected preferably in bone ablation context where preserving vulnerable structures is a priority. Unfortunately, despite this category of techniques is capable of reconstructing temperature tissue map, it is not immune to drawbacks which severely limits its use. Of course, the use of sophisticated algorithms to estimate temperature and the high costs of diagnostic imaging techniques are two of the negative issues to noteworthy. In case of CT-thermometry the radiation dose is another aspect to be kept in mind. Furthermore, contactless thermometry is affected by measurement artefacts due to patients' movements, especially those due to breathing, hence the need to implement alternative solutions to overcome this concern (e.g., signal acquisition during breathing holding, algorithms devoted to artifact removal). Unexpected, contact-based techniques are so far well suited to the context. The broad implementation of transducers such as thermocouples and thermistors are mainly due to their low cost, small size, robustness, wide measuring range, short response time and ease to use which make them preferable to other techniques involving a high level of expertise. Despite their invasiveness, many studies exploring temperature monitoring in bone employed such kind of solution offering the right balance between affordability and reliability. Also, the use of these techniques overcomes the issue of breathing-related artifacts. On the other hand, thermocouples and thermistors provide a single-point measurement, thus it is not feasible to obtain temperature map for estimating thermal tissue damage.

Moreover, owing to their metallic composition, these thermometers cannot work in presence of high electromagnetic fields (e.g., MR). Although FBGs are currently lacking special attention in the field of bone ablation, they appear very promising in this arena because of their countless features, among others biocompatibility, small size, immunity to electromagnetic fields, wide measuring range and high sensitivity. A special mention deserves their multiplexing capability which allows temperature measurements in several point with high resolution (even less than 1 mm) and an accuracy around 0.1 °C (but strongly dependent to the quality of the interrogator system). Thus, it is possible to obtain reliable temperature map which is the key aspect especially in this specific context where incorrect estimation could lead to irreversible injuries in healthy susceptible areas.

Summing up, the literature and the clinical practice corroborated the importance of this key aspect during bone HTs. Most of the studies aimed at assessing tissue thermal response (e.g., in cortical bone, epidural space, bone marrow) and preventing permanent damage in vulnerable structures, which represents the most challenging aspect of this scenario. Other works investigated the suitability of specific thermometric techniques in monitoring and predicting temperature under particular settings. Only some explored the performances of specific devices in terms of enhancement in safety and clinical outcomes improvement. However, despite many investigations were performed during clinical trials, nowadays, temperature monitoring during bone ablation is still severely restricted in this scenario. In our view, substantial research efforts are still necessary for making practical some technologies in medical scenarios where clinicians may benefit of being led by real-time temperature knowledge during the procedures without being forced to alter their clinical practice.

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