Hyperthermia Treatment Planning: Clinical Application and Ongoing Developments

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***Abstract*—Hyperthermia is a proven clinical anti-cancer treatment, used in combination with radiotherapy and/or chemotherapy. During hyperthermia, tumour tissue is heated to 40–43 °C using radiofrequency or microwave antennas, which strongly enhances effectiveness of radiotherapy and chemotherapy. Hyperthermia treatment quality depends on tumour temperatures achieved and treatment planning (i.e., simulation and optimization of absorbed power and temperature distributions) could be very useful to ensure and improve treatment quality. Hyperthermia treatment planning was mainly a research tool for decades, because of high computational costs and limited quantitative accuracy of treatment planning predictions due to a lack of patient-specific tissue properties. Thanks to developments over the past decade, treatment planning becomes increasingly important in the clinical workflow. Presently, main clinical applications of hyperthermia treatment planning are 1) applicator selection, 2) heating ability evaluation and 3) on-line treatment guidance. To improve the reliability and further increase applicability of treatment planning, ongoing developments focus on 1) dielectric imaging to derive patient-specific dielectric properties, 2) advanced thermal modelling including discrete vasculature and 3) biological modelling to predict the radiosensitizing effect of hyperthermia in terms of equivalent radiation dose. The increased clinical application and ongoing efforts will further improve treatment quality.**

***Index Terms*—Hyperthermia, RF heating, microwave heating, treatment planning.**

I. Introduction

HYPERTHERMIA is a clinically proven sensitizer to enhance the effectiveness of radiotherapy and chemotherapy in cancer treatments [1]. The aim during hyperthermia treatments is to raise the temperature in the tumour to 40–43 °C for 1 h [2]. Adding hyperthermia increases the tumour response rate typically with about 20% [3]. The effect of hyperthermia is tumour-selective, which means that radiation- and chemotherapy-related toxicity are not enhanced.

Hyperthermia thus allows for a lower radiation or chemotherapy dose, without reducing the effect on the tumour, but with a lower risk of treatment-related side-effects. In case of recurrence of a tumour after previous treatment, re-treatment is associated with a higher risk of side-effects and adding hyperthermia to a reduced dose allows a good tumour control, with an acceptable risk of side-effects. Low dose re-irradiation combined with hyperthermia is a proven effective treatment for example for recurrent breast cancer and recurrent malignant melanoma [4], [5].

For primary tumours hyperthermia can be added to the full dose radiotherapy or chemotherapy treatment schemes to increase the chance of tumour control. Effectivity has been proven by randomized trials for example for soft tissue sarcoma, cervical cancer, head&neck tumours and bladder cancer [6]–[9].

The heating equipment used depends on the tumour location. Microwave antennas operating at frequencies between 434 and 2450 MHz are usually applied for superficial tumours, i.e., up to 4 cm under the skin [10]–[12]. An array of multiple radiofrequency antennas operating at 60–150 MHz positioned around the patient can effectively heat more deep-seated tumours [13]–[16]. With this so-called loco-regional heating, phase-amplitude settings of the individual antennas should be selected such that adequate focusing to the target region is realized. A water bolus is used for electromagnetic coupling and skin cooling.

To ensure treatment quality, temperature monitoring is essential. According to the guidelines of the European Society for Hyperthermic Oncology (ESHO), treatment monitoring should be performed using thermometry probes [17], [18]. For superficial hyperthermia thermometry probes should be placed on the skin and when the tumour extends more than 1 cm deep, placement of one or more interstitial probes is highly recommended [17]. For loco-regional heating of pelvic tumours, minimally invasive endoluminal thermometry probes are often used [18], positioned in the vagina, rectum and bladder.

Although the effect of hyperthermia is tumour selective, excessive heating of normal tissue (hot spots) should be avoided. When hot spots occur the local tissue temperature is increased beyond 45 °C, which is a threshold at which the patient experiences a pain sensation [19]. Adaptations to the settings of the heating system are required to reduce the hot spot temperature and avoid thermal toxicity. These adaptations are based on the experience of the operator and temperature feedback by the (minimally) invasive thermometry probes.

Treatment quality strongly depends on the achieved tumour temperatures [20]–[22], so it is very important to realize

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adequate tumour temperatures and maintain these temperatures in case of adjustments to the antenna settings. This can be quite challenging, especially when the heating system consists of multiple independent antennas, yielding a large number of degrees of freedom.

Hyperthermia treatment planning (HTP) can visualize the effect of different treatment strategies by simulation of absorbed power and temperature distributions in the patient. Using these predictions treatment quality can be improved [23]–[25]. HTP has been mainly a research tool for decades, because of high computational costs and limited quantitative accuracy caused by uncertainties in dielectric and thermal tissue properties. Thanks to substantial progress in computational power and computational techniques, integration of treatment planning in the clinical workflow is emerging. In this review we discuss the most important clinical applications of HTP and ongoing developments.

II. Hyperthermia Treatment Planning

In hyperthermia treatment planning simulations are based on a patient model, which is generated from CT or MR imaging in treatment position. This scan is manually or (semi-)automatically segmented into different tissue types. The patient model is then combined with the applicator model. The operating frequency is usually determined by the available clinically used hyperthermia applicator, but some devices allow a variable frequency, e.g., the BSD Sigma-60 system (60-120 MHz). A slightly better focusing can be achieved at higher frequencies [16]. Since the penetration depth of the electromagnetic field also decreases with increasing frequency, for loco-regional deep heating an operating frequency up to 90 MHz is usually preferred [15], [26] and frequency steering is not commonly applied in the clinic. Literature-based dielectric and thermal tissue properties [27]–[30] are assigned and electromagnetic field simulations and SAR/temperature calculations can be performed for specific system settings, and optimization of system settings. This process is illustrated in Fig. 1.

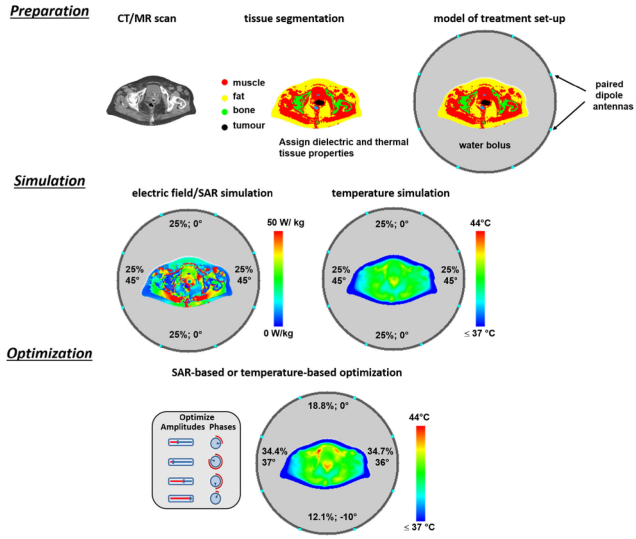

Fig. 1. Work flow of hyperthermia treatment planning. A CT or MR scan of the patient is segmented into different tissues and combined with the applicator model to generate a model of the treatment set-up. Next, SAR/temperature simulations and optimization can be performed.

A. Electromagnetic Field Simulations

Electromagnetic (EM) simulation techniques to solve Maxwell's equations are usually based on either finite difference (FD) techniques of finite element (FE) methods [23]. FD methods require discretization of the computational volume into rectangular voxels [31] and for EM simulations using the finite difference time domain method (FDTD) 10-20 voxels per wavelength are required. FE methods use tetrahedral or hexahedral meshes with variable element sizes [32], [33]. Absorbing boundary conditions are required to avoid reflections of the electromagnetic waves at the boundaries of the computational domain [34]–[36].

B. Thermal Simulations

Although the absorbed power is correlated with the achieved temperature, thermal simulations are required to account for relevant cooling mechanisms as tissue perfusion and water bolus cooling. Perfusion can increase significantly during hyperthermia, depending on the achieved temperature [37]. Therefore, thermal modelling is a challenging part of treatment planning.

Several thermal models with varying complexity have been developed [38], [39]. The Pennes bioheat model [40] is most commonly used in HTP. This model is computationally efficient and describes the impact of perfusion by a heat sink, proportional to the perfusion rate and the local temperature rise. This does not account for the direction of blood flow or heat exchange between large thermally significant blood vessels and tissue.

C. Optimization Techniques

The phase and amplitude settings of a phased-array heating system determine the heating pattern and thereby treatment quality. Optimization strategies to determine the best phase-amplitude settings for individual patients can be subdivided into SAR-based and temperature-based optimization methods.

SAR-based optimization methods aim to maximize the SAR in the tumour target, since SAR is correlated with temperature. Quality indicators suitable for use as objective function should therefore have a good correlation with predicted temperatures. Commonly used objective functions that satisfy this criterion are the hot spot-target SAR quotient (HTQ) and the SAR target coverage (TC) [41]–[44]. The HTQ is defined as the ratio between the average SAR in a small normal tissue volume representing hot spots, e.g., the 50 ml, 1% or 0.1% normal tissue volume with the highest SAR, and the volume averaged SAR in the target [41], [42]. The TC can be defined as the tumour volume percentage covered by the 25% (TC25) or 50% (TC50) iso-SAR [42]–[44]. However, a disadvantage of SAR-based optimization remains that important cooling mechanisms as perfusion and bolus cooling are difficult to account for.

Temperature-based optimization aims to maximize the target temperature with constraints to normal tissue temperatures. Since a large number of temperature calculations are performed during the optimization process, efficient superposition techniques have been developed [45]–[48]. Temperature-based optimization introduces additional uncertainties in perfusion compared to SAR-based optimization. However, a study evaluating the impact of tissue perfusion uncertainty demonstrated that temperature-based optimization is preferable, despite these uncertainties [49].

D. Accuracy

The accuracy of hyperthermia treatment planning depends on the reliability of the dielectric and thermal tissue parameters used. As mentioned above, usually average literature values are assumed in simulations, but there is a large intra and inter-patient variation in these parameter values. The uncertainty in dielectric tissue properties (up to 50%) yields an inaccuracy of $\sim$20% in both specific absorption rate (SAR) and temperature predictions [50]. Both dielectric and thermal tissue properties are temperature-dependent. However, in the hyperthermic temperature range the temperature-dependency of these tissue properties is very limited, with exception of blood perfusion [51]. Perfusion levels significantly increase up to a factor 10, depending on the temperature [37]. This also depends on e.g., age and condition of the patient and the inaccuracy in temperature predictions due to uncertainties in enhanced perfusion values at hyperthermic temperatures further affects the quantitative reliability of simulations.

E. Software Packages

Dedicated treatment planning software packages for hyperthermia are HyperPlan (Dr. Sennewald Medizintechnik. GmbH) [52] and Plan2Heat (Amsterdam UMC, Amsterdam, The Netherlands) [53]. HyperPlan has been developed for use in combination with the locoregional BSD-2000 hyperthermia systems [54], [55]. Plan2Heat is a more flexible treatment planning system, allowing modelling of different applicators for superficial and locoregional hyperthermia. Plan2Heat is mainly used in combination with the AMC-4/ALBA-4D system and the ALBA ON 4000 system [56]–[58].

EM and thermal simulations for HTP can also be performed using more general simulation software packages, such as Sim4Life (https://zmt.swiss/sim4life), COMSOL (www.comsol.com), Ansys High Frequency Structural Simulator (HFSS; www.ansys.com) and CST STUDIO SUITE (www.cst.com). When using these general simulation software packages, functionality for optimization is usually not available and additional software tools should be developed; an example of this is VEDO [59].

III. Clinical Applications

Integration of hyperthermia treatment planning in the clinical workflow is emerging and quality assurance guidelines start recommending the use of treatment planning for locoregional hyperthermia [18]. Treatment planning can be instrumental in pre-treatment evaluations, such as applicator selection and analysis of the heating ability, but also during treatment HTP can be applied for on-line treatment guidance. These main clinical applications are summarized in Fig. 1, and discussed below.

A. Applicator Selection

Treatment planning can be very useful to improve treatment quality by investigating treatment options when different applicators are available and to determine an optimal heating strategy in non-standard cases. This was demonstrated by a summary of case studies for superficial hyperthermia [60]. It was shown that treatment planning could troubleshoot treatment limiting hot spots by selection of the most effective type of superficial applicator (Lucite, Lucite cone or conventional waveguide applicator). Not only the type of antenna, but also the orientation of the antenna (i.e., E-field polarization) can substantially affect the heating pattern. Treatment planning can thus also be used to optimize target coverage and minimize hot spots resulting from e.g., sternum cerclage wires or a thick fat layer covering the tumour, by positioning the antenna such that the E-field direction yields the lowest risk of hot spots [60]. Furthermore, treatment planning was demonstrated to be useful for analysis of the SAR coverage resulting from an array with multiple applicators to treat a large tumour area.

Sub-superficial head and neck tumours, i.e., extending up to 6 cm from the surface, can be treated using standard superficial Lucite cone or current sheet applicators, but also with the HYPERcollar, a dedicated phased-array system for head and neck tumours. Treatment planning can be used to predict treatment efficacy and a simulation study in 24 patients retrospectively analysed the predicted treatment quality achievable by the different applicators [61]. This analysis showed that in general a better target coverage is achieved with the HYPERcollar. However, adequate target coverage can also be achieved with a Lucite cone applicator for tumours extending up to 5 cm from the patient surface, provided that the aperture fully covers the target [61].

While usually a macroscopic tumour is defined as target of the hyperthermia treatment, locoregional peritoneal hyperthermia aims at heating the whole peritoneum to treat peritoneal micrometastases as an alternative to hyperthermic intraperitoneal chemotherapy (HIPEC). Treatment planning was applied to investigate the coverage that can be achieved with five different clinically available locoregional heating systems [62]. Results showed that a fairly good coverage of the peritoneum can be achieved with the AMC-4/ALBA-4D, Sigma-60, and Sigma-Eye systems, but the best and most homogeneous coverage was observed for the AMC-8 system [62].

The applications mentioned above considered radiofrequency and microwave heating, using radiative electromagnetic fields. A fundamentally different heating technique is capacitive heating, using two electrodes. An electric field is applied between the electrodes and power is deposited in the tissue as a result of the alternating voltage field. Capacitive and radiative techniques yield a different orientation of the dominant E-field component, which substantially influences the heating patterns. Treatment

planning can be very helpful to evaluate the heating characteristics of such different techniques [63], [64]. Simulation studies for both superficial and deep heating showed that a thick superficial fat layer can be more treatment limiting for capacitive heating since more severe hot spots can occur in the fat layer [63], [64]. Capacitive heating can realize therapeutic temperatures in patients with very little fat. However, in general, radiative heating yields more favorable temperature distributions, without excessive heating of normal tissue.

B. Heating Ability Analysis

In clinical practice, situations can occur where the physician is not sure about the feasibility of heating a specific target. In those cases, treatment planning can be very useful to perform a heating ability analysis. Simulations can demonstrate whether a specific target is expected to be heated adequately without significant problems or not.

A study performed in 30 patients with cervical, rectal, and prostate carcinoma demonstrated a good correlation between treatment planning predictions and the reported clinical data during locoregional hyperthermia regarding acute toxicity (i.e., hot spots) and prediction of easy-to-heat or difficult-to-heat patients [55].

This qualitative predictive value can also be used to predict whether hyperthermia can be safely applied when for example an implant is present in the hyperthermia treatment field. A simulation study evaluated the impact of the presence of metal and silicone port-a-cath implants [65]. Different arrangements were simulated, evaluating the port-a-cath located centrally below the applicator or at an edge, and with various different translations and orientations of the applicator. Results were compared to a control situation without a port-a-cath and showed that a metal port-a-cath located anywhere in the hyperthermia treatment field tremendously affects SAR coverage and yields high local SAR hot spots. In a worst-case scenario this might result in an effective treatment volume of only $\sim$12% of the total volume for the control model. A silicone port-a-cath only significantly affects the SAR coverage when located centrally below the applicator. The predicted effective treatment volume for that case was 64% of the control set-up without a port-a-cath.

Heating ability analysis using treatment planning can thus be supportive in the decision whether hyperthermia will or will not be part of a treatment strategy for non-standard cases.

C. On-line treatment guidance

Although pre-treatment planning has some limitations because of the uncertainties in tissue properties, it can still be very useful in on-line treatment guidance to suppress treatment limiting hot spots and improve tumour heating. A cross-over trial comparing treatment planning-guided steering and steering based on empirical steering guidelines demonstrated that treatment planning-guided steering is feasible [66].

However, predictions are not quantitatively reliable so hot spots and sub-optimal tumour heating can still occur. A study evaluating the predictive value of simulated SAR and temperature for changes in measured temperature after phase-amplitude steering during locoregional demonstrated a correlation between measured and simulated changes in SAR and temperature [67]. This allows adaptive treatment planning to be used on-line to determine alternative antenna settings to improve treatment quality, as demonstrated in several studies [57]–[59], [68], [69].

A study in 8 patients treated for pelvic tumours showed that treatment planning can help to determine alternative phase-amplitude settings to suppress treatment limiting hot spots, without affecting tumour heating [57]. All patient-reported hot spots were resolved with assistance of on-line treatment planning and the tumour temperature change measured using standard thermometry probes was on average only -0.02 °C (range, -0.26 °C to 0.31 °C).

Subsequently, it was demonstrated that improvement of pelvic tumour temperatures is feasible [58]. For three patients yielding a representative selection from daily clinical practice regarding both tumour location (eccentric vs. central) and patient sizes (slender/thin vs. obese; BMI <25 kg/m^2 vs. BMI >30 kg/m^2) an improvement in tumour temperatures with more than 0.5 °C was realized by the assistance of treatment planning [58].

The feasibility of using treatment planning to improve tumour heating was also demonstrated for head and neck cancer [59]. Evaluation of two cases showed that either the predicted SAR distribution was already optimal, or could be further improved with alternative settings increasing the target SAR from 96 to 178 W/kg.

Treatment planning-guided steering can also be helpful in combination with non-invasive MR-thermometry feedback to optimize focusing. This has been demonstrated for extremity soft-tissue sarcomas, with effective re-optimization of antenna settings based on MR-thermometry feedback [68]. Another study showed that treatment planning allowed improved localization of heat in the tumour earlier in treatment, compared to MR-thermometry feedback alone [69].

IV. Education and Training

Applications of simulations as discussed in the previous sections also provide a very practical instrument for education and training for hyperthermia technicians and physicians. Treatment planning simulations in a simplified phantom set-up provide a unique and detailed insight in the heating patterns generated by a hyperthermia applicator or array of applicators, and also help to understand basic steering strategies. As a next step in training, realistic treatment scenarios can be evaluated to obtain insight in treatment optimization using treatment planning. Well-trained personnel is essential to ensure treatment quality.

V. Ongoing developments

Ongoing developments aim to improve the quantitative reliability of (pre-)treatment planning. Important research topics to realize this are dielectric imaging and advanced thermal modelling. Moreover, a further integration of hyperthermia treatment planning into clinical workflow is aimed for by providing insight in the radiosensitizing effect of hyperthermia. Therefore, biological modelling is explored to quantify this sensitizing effect by predicting an equivalent enhanced radiation dose (Fig. 2).

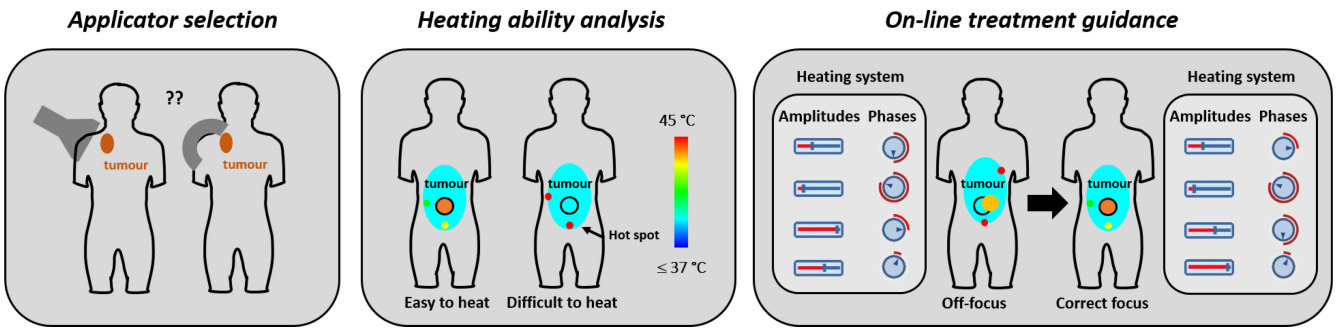

Fig. 2. Summary of the three most important clinical applications of hyperthermia treatment planning: applicator selection, heating ability analysis and on-line treatment guidance.

A. *Dielectric Imaging*

The quantitative reliability of E-field and SAR simulations depends largely on the dielectric tissue properties, i.e., electrical conductivity (σ (S/m)) and permittivity (ε(-)). These properties are frequency-dependent and can vary largely per tissue type, per tumour, and per patient [27]–[29], [70]–[73]. Therefore, ideally a patient-specific 3D map of the dielectric properties would be used as input to realize quantitatively reliable SAR predictions by treatment planning.

Several MRI techniques to image local permittivity and conductivity are investigated. Initially, two-step dielectric imaging methods were explored, which determine the water and fat content using standard MRI techniques. In the second step these water contents are converted to complex permittivity maps [74], [75], assuming a fixed relationship between water content and electrical properties. A drawback of these methods is that the reconstruction accuracy varies strongly per tissue type.

Direct methods such as MR-based electrical property tomography (MR-EPT) aim to map the conductivity using MRI, using the B_1^+ amplitude and phase. This yields a reconstructed conductivity at the Lamor frequency (e.g., 128 MHz @ 3T). A small correction is required when the heating device operates at a different frequency (e.g., -3% for 70 MHz) [76]. Phantom models demonstrated a good quantitative agreement for MR-EPT with direct probe measurements (mean deviation $<$10%) [77]. First *in vivo* applications suggested considerable deviations for the reconstructed electrical conductivity in patients compared to commonly used literature values. For example, the average *in vivo* conductivity of muscle tissue was 14% higher [78]. This had a substantial impact on predicted tumour temperatures by treatment planning, with a difference in optimized T90 (i.e., the temperature at least achieved in 90% of the tumour) varying between 0.6 and 1.5 °C [76].

Some literature also suggests that the electric conductivity of tumour tissue could be about 10% higher than for normal tissues [70], [73], [78]. Simulation results showed a limited effect of this increased tumour conductivity on predicted tumour temperatures for loco-regional hyperthermia [64]. For superficially located tumours, increased tumour conductivity might affect the absorbed power in the tumour and thereby the output power needed to realize the desired temperature level [70].

For accurate prediction of hot spots, the reconstruction accuracy at tissue interfaces is important. MR-EPT methods assume piece-wise constant media and yield reconstruction errors occur near tissue boundaries. To overcome this problem, methods have been developed to reconstruct the conductivity in an iterative fashion based on a contrast source inversion approach (CSI-EPT; contrast source inversion-electric properties tomography) [79], [80]. Results showed improved reconstruction near tissue boundaries and the ability to reconstruct small tissue structures, but CSI-EPT is computationally expensive [79].

Recently, efficient deep-learning based methods were investigated, in which a convolutional neural network (CNN) is trained to learn the mapping relation between B_1^+ and electric properties [81], [82]. In silico validation and *in vivo* comparison with a conventional EPT technique demonstrated that deep-learning EPT in the pelvis yields anatomically-detailed and noise-robust 3D conductivity maps with good sensitivity to tissue conductivity variations [82].

Permittivity reconstructions are more challenging due to higher noise levels in experimental B_1^+ maps [83]. Permittivity reconstruction techniques have been developed for the brain [83], [84]. Reconstruction of the permittivity in the pelvic region is even more challenging, since this also requires techniques to compensate for artefacts from e.g., bowel motion and blood flow, which is subject of ongoing research [85].

B. *Advanced Thermal Modelling*

Thermal modelling in hyperthermia treatment planning is normally based on the Pennes' bioheat equation [40], which describes the thermal influence of blood flow by a 'heat sink'. This can result in significant inaccuracies in temperature predictions of $\sim$1–2 °C [86], because this simplified model does not account for the local cooling effect of large blood vessels and the direction of the blood flow. This can have an impact on both predicted tumour temperatures as well as on the prediction of hot spots.

To improve temperature predictions by treatment planning, advanced thermal models including large discrete vasculature have been developed [39]. Models evolved from straight vessel structures [87] to realistic 3D vasculature models with vessel trees reconstructed from angiograms [47], [88], [89]. Accurate

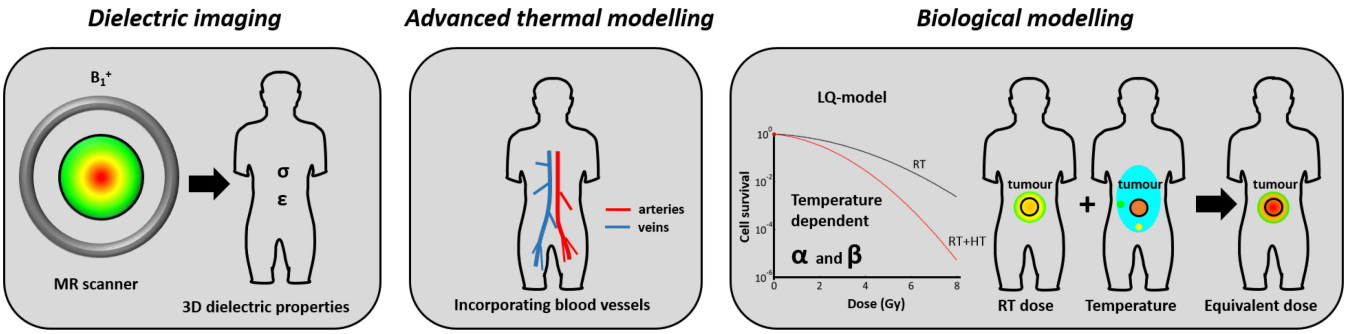

Fig. 3. Summary of the three most important research topics in hyperthermia treatment planning: dielectric imaging to reconstruct patient specific dielectric tissue properties, advanced thermal modelling including discrete vasculature and biological modelling to quantify the radiosensitizing effect of hyperthermia (HT) in terms of equivalent radiation (RT) dose.

modelling of vessels down to 0.5 mm diameter is realized by numerical separation between the tissue grid and the vessel tree [90]. Initially, this model was computationally expensive, but recently developed GPU-based algorithms make it sufficiently fast for clinical use, since steady-state temperature distributions can be calculated within about a minute [47]. Detailed vessel tree information needed for these advanced thermal simulations can be reconstructed automatically from contrast enhanced MR angiograms [89], which enables routine (on-line) clinical use.

Models suitable for clinical use are thus available, but the blood flow rate is an important input parameter, which remains uncertain and greatly affects the predicted temperatures. Non-invasive blood flow measurements can be performed using MRI techniques, but values before or after hyperthermia may differ significantly from values during hyperthermia. At hyperthermic temperature levels the blood flow rate can increase significantly up to a factor 10 [37], but the increase is *a priori* unknown and depends on several factors such as the temperature achieved, age and condition of the patient etc. Thermal decay measurements after switching power off can be used to estimate the perfusion level at the location of standard clinical thermometry probes [91]. This provides information only at specific locations. Therefore, achieving detailed and adequate blood flow estimates during hyperthermia remains challenging and subject of further research.

C. Biological Modelling

Hyperthermia is always combined with radiotherapy or chemotherapy and a next step in treatment planning is therefore to evaluate and plan the combined treatment. Biological modelling to predict the hyperthermic radiosensitization in terms of effective enhanced radiation dose uses models based on the linear-quadratic (LQ) model, with temperature-dependent values of the LQ-parameters α and β derived from experimental data [92]. Using such a temperature-dependent LQ-model, the full 3D equivalent dose can be calculated voxel-by-voxel [93], [94].

Since hyperthermia treatment planning, as well as the exact α and β parameters, still yield some uncertainties, equivalent dose predictions are also not quantitatively reliable. Nevertheless, biological modelling can provide an estimate of the clinical effect of hyperthermia in terms of additional radiation dose, which was demonstrated to be very useful to answer clinical research questions [94]–[96].

Biological modelling has shown that the radiosensitization effect of hyperthermia is typically comparable to an extra 10Gy dose escalation to the tumour, while not enhancing the normal tissue dose [94], [97]. A numerical study in prostate cancer patients suggested that this can substantially increase the local control rate, especially for high-risk patients [94]. According to clinical dose-response curves, the predicted extra 10Gy (from 76 to 86Gy) would increase the local control probability from approximately 85/90% to almost 100% for intermediate-risk and low risk patients. For high-risk patients the local control would increase from $\sim$ 50% to $\sim$ 90% [94].

Another biological modelling study evaluated the theoretical feasibility of re-irradiation combined with hyperthermia for infield recurrent pediatric sarcoma in the pelvic region and the extremities [95]. Results showed that low dose re-irradiation plus hyperthermia could effectively realize a possibly curative equivalent dose distribution [95]. Despite the modelling uncertainties, these two studies demonstrate that hyperthermia can significantly improve treatment outcome, and clinical pilot studies could be considered.

Biological modelling also provides an excellent tool to answer clinical research questions that are ethically difficult to investigate in a clinical trial. An example of this is the impact of the time interval between radiotherapy and hyperthermia treatments. A planning study in cervical cancer patients showed that application of hyperthermia immediately before or after radiotherapy yields the largest therapeutic gain [96]. A retrospective analysis of clinical data confirmed these results [98].

As demonstrated above, biological modelling provides a very useful tool to obtain more insight in the effect of combined treatments with hyperthermia. Clinical data show a hyperthermia-induced reduction of the α/β ratio for recurrent breast cancer, cervical cancer and head and neck cancer [99]. This can be used to effectively optimize clinical dose-fractionation schedules. The hyperthermic enhancement of the parameters α and β can vary per tumour type and is strongly temperature-dependent [92], [100]. Thus, reliable data about the temperature-dependency of these parameters for specific tumours treated with hyperthermia and radiotherapy are important for adequate

prediction of the equivalent radiation dose and treatment optimization [92], [96], [100]. Further research therefore focuses on derivation of temperature-dependent LQ-parameters for various tumours and normal tissues, as well as direct optimization of the equivalent dose instead of optimization of radiotherapy and hyperthermia treatments separately. Prediction of chemotherapy-enhancement by hyperthermia is also explored [62].

VI. Conclusion

Hyperthermia treatment planning has been mainly used as a research tool for many years, but integration in the routine clinical workflow is emerging. Treatment planning simulations have a qualitative predictive value, that can be utilized in clinical practice. Several clinical applications show that treatment planning is very useful to ensure and improve treatment quality. Uncertainties in tissue properties and perfusion still limit the quantitative accuracy and research on these topics is ongoing to improve the quantitative reliability. Furthermore, biological modelling is developed to obtain insight in the effectiveness of combined treatments. Using this concept, the radiosensitization effect of hyperthermia can be quantified in terms of an enhanced equivalent radiation dose.

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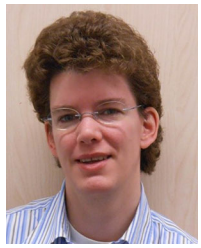

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