MR based electric properties imaging for hyperthermia treatment planning and MR safety purposes
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5 Hyperthermia Treatment Planning for cervical cancer patients based on electric conductivity tissue properties acquired \textit{in vivo} with EPT at 3T MRI

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Abstract

Introduction: The reliability of Hyperthermia Treatment Planning (HTP) is strongly dependent on the accuracy of the electric properties of each tissue. Currently used values are mostly based on ex vivo measurements. In this study, in vivo conductivity of human muscle, bladder content and cervical tumors, acquired with MR based Electric Properties Tomography (EPT), are exploited to investigate the effect on HTP for cervical cancer patients.

Methods: Temperature based optimization of five different patients was performed using literature based conductivity values yielding certain antenna settings, which are then used to compute the temperature distribution of the patient models with EPT based conductivity values. Furthermore, the effects of altered bladder and muscle conductivity were studied separately. Finally, the temperature based optimization was performed with patient models based on EPT conductivity values.

Results: The tumor temperatures for all EPT based dielectric patient models were lower compared to the optimal tumor temperatures based on literature values. The largest deviation was observed for patient 1 with $\Delta T_{90} = -1.37^\circ C$. A negative impact was also observed when the treatment was optimized based on the EPT values. For four patients $\Delta T_{90}$ was less than 0.6°C; for one patient it was 1.5°C.

Conclusions: Electric conductivity values acquired by EPT are higher than commonly used from literature. This difference has a substantial impact on cervical tumor temperatures achieved during hyperthermia. A higher conductivity in the bladder and in the muscle tissue surrounding the tumor leads to higher power dissipation in the bladder and muscle and, therefore, to lower tumor temperatures.

5.1 Introduction

Regional radiofrequency (RF) hyperthermia aims at heating the tumor to a temperature of 41°C to 43°C. Several randomized controlled trials [1-3] have shown an increased tumor response and overall survival for hyperthermia combined with radiotherapy or chemotherapy. However, tumor specific heating without inducing overheating in healthy tissue is technically challenging. Therefore, Hyperthermia Treatment Planning (HTP) is an essential step to improve the treatment quality. In HTP the optimal antenna settings (amplitudes and phases) are computed via electromagnetic (EM) field and thermal modeling. However, accurate tissue data acquisition, such as electric conductivity and permittivity, are critical for correct EM simulations and subsequent thermal dose computation in HTP. Currently used values in patient models are mostly based on ex vivo measurements of animal and human tissues [4,5]. Furthermore, as was shown in a review of the literature, there is a large variation in reported values between the different studies [6]. This variation can be explained by the use of tissues of various species and differences in measuring conditions (tissue temperature, in vivo, in vitro and ex vivo). Due to practical and ethical reasons, human in vivo electric property (EP) measurements are
scarce. Only easily accessible tissue types (e.g. skin, tongue) [4] and liver [7] have been measured in vivo.

Various deep HT studies [8–10] have investigated the impact of inaccurate input data on the accuracy of HTP in the cervical region. Van de Kamer et al. [8] found an error of 50% in the input data (the physical properties of fat, muscle and bone) resulting in an average error of <20% in power deposition (PD) and temperature distribution. They furthermore showed that in particular accurate knowledge of the conductivity values decreases this error [8]. We previously reported [9] that the sensitivity to uncertainty increases with increasing number of antennas and frequency; for all five tested clinical HTP-models it was shown that an input data uncertainty might lead to a lower tumor T90 (temperature achieved in at least 90% of the tumor volume) of up to 0.6°C and 1.4°C, for 4 and 12 channel systems, respectively. Canters et al. [10] investigated 20 patient models wherein they observed a maximum difference from the optimal T90 of around –3°C if uncertainties of input data (electric and thermal properties) were taken into account. Moreover, these studies showed that input uncertainties might lead to the occurrence of ‘hot spots’ in healthy tissue causing patient discomfort. In practice, the occurrence of hot spots limits the maximum achievable tumor temperatures, which is essential for the clinical outcome.

Therefore, much effort has been focused on acquiring more accurate electric properties for HTP as well as for other applications such as evaluation of safety in telecommunications [11] and magnetic resonance imaging (MRI) [12–14]. Some non-invasive studies focused on acquiring these values based on MRI grayscale intensity [15,16] which mainly relates the electric properties to tissue water content. These techniques are sensitive to RF field inhomogeneities that influence the grayscale intensity. Furthermore, these techniques do not account for other factors that determine electric properties, such as blood content, ionic concentrations [17] and tumor specific physiological changes. Recently, other non-invasive MR based methods have received an increased attention as they reconstruct EP values by exploiting the interaction of tissue with the EM fields generated by the RF MR coils. One such technique is Electric Property Tomography (EPT) [18–22] which reconstructs electric properties using $B_1^+$ field measurements acquired by standard MR systems.

Studies wherein the impact of uncertainty of electric property values were investigated [8–10] assumed the conductivity of tumor to be equal to muscle tissue. However, various studies have shown that conductivity values of tumors of the breast [23–25], liver [7,26,27], bladder [28] and gliomas of the brain [29] are elevated compared to healthy tissues. Furthermore, these studies did not take into account the high conductivity of urine as shown in [30–32]. Therefore, in a previous study, we used EPT to determine the conductivity values of muscle, bladder content and cervical tumor in vivo [32]. Large discrepancies between the literature values were reported in that study.

The aim of this study is to evaluate the effect of these discrepancies for HTP. For this purpose, we first evaluated the effect of measured conductivity on T50 and T90 for a HTP plan optimized using literature conductivity values. Secondly, we evaluated the difference between optimized plans based on literature or EPT-based conductivity values.
5.2 Methods & Materials

5.2.1 Patient models

To study the effect of EPT based conductivity values on HTP, real life models were derived from CT-scans (voxel size: 0.9375×0.9375×5.00 mm\(^3\)) from five patients with cervical cancer who received regional hyperthermia as part of their treatment. These scans were made under same treatment set-up, regarding mattresses and water bolus, as during a hyperthermia treatment. Tissue segmentation for bone, fat, inner-air and muscle was based on thresholding by Hounsfield units [33], with manual delineation of the bladder and the cervical tumor by a radiation oncologist. Finally, the patient models were down sampled based on the winner-takes-all principle [34] to 2.5×2.5×5.0 mm voxel size and Finite Difference Time Domain (FDTD) simulations [35] were conducted using the 70 MHz AMC-4 and AMC-8 system configurations as described in [36] and [37], respectively. These two systems are similar except for using 4 and 8 antennas, respectively. This difference in number of antennas affects the steering capabilities and was shown to affect the impact of deviations in conductivity input data [9].

5.2.2 Temperature optimization

Temperature based optimization was performed to determine patient-specific phase-amplitude settings leading to optimal tumor heating [38–40]. Temperature based optimization is preferred over Specific Absorption Rate (SAR) optimization as the former takes the relevant heating and cooling mechanisms in the human anatomy into account. The tumor temperatures are in the end the determining factor for clinical outcome.

The tissue temperature computations were based on the conventional Pennes’ bio-heat transfer equation [41]:

\[
c \rho \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) - c_b W_b (T - T_{\text{art}}) + P
\]

where \( c \) is the specific heat capacity, \( \rho \) the tissue density [kg/m\(^3\)], \( k \) the thermal conductivity [W m\(^{-1}\) K\(^{-1}\)], \( c_b \) the specific heat of blood [J kg\(^{-1}\) K\(^{-1}\)], \( W_b \) the volumetric perfusion rate [kg m\(^{-3}\) s\(^{-1}\)], \( T_{\text{art}} \) the local arterial or body core temperature (37°C) and \( P \) the power density [W m\(^{-3}\)] added by the heating system. The latter one is directly affected by the varied conductivity values in this study as \( P = \sigma \| E(\sigma, \varepsilon_r) \|^2 / 2 \). The term \( \nabla \cdot (k \nabla T) \) represents the heat conduction in tissue and \( c_b W_b (T - T_{\text{art}}) \) models the perfusion. Thermal properties shown in Table 1 are taken from literature [42,43]. The blood perfusion reported in the literature, however, is in general based on measurements conducted in resting conditions. Therefore, we have used elevated perfusion values to account for the thermal stress under hyperthermic conditions [44].
The optimization process aimed at a tumor temperature of 43°C by minimizing the following objective function:

$$\sum_{Tumor} (\max(43 - T(x, y, z), 0))^2, \quad (x, y, z) \in \text{tumor tissue},$$

which minimizes the tumor volume with a temperature below 43°C. To avoid excessive normal tissue heating a maximum tolerable normal tissue temperature of 45°C was imposed. Constraints were further imposed on the antenna contributions to the total delivered power such that for the AMC–4 a single antenna contribution was set to at least 10% and a maximum of 40% to the total power. For the AMC–8 the constraints were set to 5% and 25%, respectively. This procedure was optimized using CFSQP (C routines for Feasible Sequential Quadratic Programming) [45]. The temperature based optimization exploited in this manuscript is described in more detail in [40].

Tumor temperatures of the optimized temperature distributions were expressed as T50 and T90, representing the temperatures at least achieved in 50% and 90% of the tumor volume, respectively. Moreover, the SAR corresponding to the optimal antenna settings was analyzed as well.

### Table 1. Thermal properties assigned to different tissue types used for hyperthermia treatment planning. Values are based on [42,43].

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Density $\rho$ [kg m$^{-3}$]</th>
<th>Perfusion $W_b$ [kg m$^{-3}$ s$^{-1}$]</th>
<th>Thermal conductivity $k$ [W m$^{-1}$ K$^{-1}$]</th>
<th>Specific heat capacity $c$ [J kg$^{-1}$ K$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>1.29</td>
<td>0</td>
<td>0.024</td>
<td>10000*</td>
</tr>
<tr>
<td>Bone</td>
<td>1595</td>
<td>0.12</td>
<td>0.65</td>
<td>1420</td>
</tr>
<tr>
<td>Muscle</td>
<td>1050</td>
<td>3.6</td>
<td>0.56</td>
<td>3639</td>
</tr>
<tr>
<td>Fat</td>
<td>888</td>
<td>1.1</td>
<td>0.22</td>
<td>2387</td>
</tr>
<tr>
<td>Cervical tumor</td>
<td>1050</td>
<td>1.8</td>
<td>0.56</td>
<td>3639</td>
</tr>
<tr>
<td>Bladder</td>
<td>1050</td>
<td>3.6</td>
<td>0.56</td>
<td>3639</td>
</tr>
</tbody>
</table>

*The value of $c$ used for air was ten times too high in order to allow larger time steps in thermal computations. This has a negligible effect on the steady-state temperature ($<2 \times 10^{-5}$°C).

### 5.2.3 Impact of EPT based conductivity values

To assess the effect on tumor temperature, electromagnetic field simulations were conducted for each patient for five different combinations of dielectric properties. We first established the tumor T90 and T50 after optimization with literature values and then recalculated T50 and T90 with the same antenna settings but now using EPT-based data for one or more tissue types.
Chapter 5

The EPT reconstructions were performed using $B_1^+$ amplitude measurements and the transceive phase approximation ($\varphi^+ \approx \varphi^{\pm}/2$) was applied as described in literature [19,21,46,47]. The central equation of the EPT method is the homogenous Helmholtz equation

$$\frac{\nabla^2 B_1^+}{B_1^+} = -\mu_0 \varepsilon_0 \varepsilon_r \omega^2 - i \mu_0 \sigma \omega \quad (3)$$

where $B_1^+$ is the complex transmit field ($B_1^+ = |B_1^+| e^{i\varphi^+}$), $\omega$ is the Larmor angular frequency, $\mu_0$ and $\varepsilon_0$ are the permeability and permittivity of vacuum, respectively, and $\varepsilon_r$ and $\sigma$ are the unknown relative permittivity and conductivity of the object of interest, respectively. Using the measured $|B_1^+|$ and the $\varphi^\pm$ distribution the conductivity can be reconstructed by

$$\sigma = \text{Im} \left( \frac{\nabla^2 (|B_1^+| e^{i\varphi^+})}{|B_1^+| e^{i\varphi^+}} \right) \frac{1}{-\mu_0 \omega} \quad (4)$$

and the relative permittivity by

$$\varepsilon_r = \text{Re} \left( \frac{\nabla^2 (|B_1^+| e^{i\varphi^+})}{|B_1^+| e^{i\varphi^+}} \right) \frac{1}{-\mu_0 \varepsilon_0 \omega^2} . \quad (5)$$

In the first case (I) the tissue properties for muscle, air, bone and fat are based on literature [5,42,43,48] and the tumor and bladder are assigned muscle electric property values. In the second case (II) the conductivity values were based on EPT [32]. In [32] only the conductivity values of muscle, bladder filling and cervical tumor were acquired, therefore, other tissue parameters were kept the same as in the first case. In the third case (III) the bladder conductivity was higher than in the second case, while other properties were the same as in II. Based on [32] the inter-patient variation of bladder content conductivity was higher and the maximum observed bladder conductivity was approximately 2.50 S/m; similar values were also observed in [49–51]. Case IV and V, consisted of dielectric patient models where the conductivity of bladder or muscle only, respectively, was assigned based on EPT [32], while the other values were kept the same as in the first case. We have investigated the effect of bladder and muscle separately to gain more insights on tissue and organ specific contributions. In [32] the conductivity values at 128 MHz (3T field strength) were measured, therefore, 3% lower values were used for 70 MHz frequency which is in accordance with the deviation found in this frequency range for various tissue types [5]. An overview of all tissue parameters used for EM field computations is given in Table 2.

Temperature based optimization was conducted for the literature based model (case I) for all patients resulting in optimized antenna settings for each patient valid for literature data. Those antenna settings were then applied to patient models with different conductivity values as in case II–V. The T50, T90 and SAR were then compared to case I, the model using literature based conductivity values.
Table 2. Electrical properties assigned to different tissue types at 70MHz used for Hyperthermia Treatment Planning. The values are based \[5,42,43,48\], whereas, in bold are shown the electrical conductivity values based on EPT \[32\].

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Electrical conductivity σ [S/m]</th>
<th>Relative permittivity ε_r</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Air</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bone</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.75</td>
<td>0.93 (±0.14)</td>
</tr>
<tr>
<td>Fat</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Cervical tumor</td>
<td>0.75</td>
<td>1.00 (±0.15)</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.93</td>
<td>1.80 (±0.54)</td>
</tr>
</tbody>
</table>

The uncertainty of EPT based conductivity values is around 15% for muscle and cervical tumor as reported in \[22,32\]. The variation of bladder content conductivity was larger (30%) as there is also a large variation of sodium content in urine between different individuals \[30,50\]. Therefore, to evaluate the effect of uncertainty of EPT values, we have conducted additional simulations for the minimal and maximal conductivity values of muscle, cervical tumor, and bladder content, respectively, as shown between the brackets in case II (Table 2).

### 5.2.4 Impact of muscle permittivity variation

Based on the equation for Specific Absorption Rate \(\text{SAR} = \sigma \| E(\sigma, \varepsilon_r) \|^2 / 2\rho\) [W/kg] one would expect a determinative effect on HTP due to uncertainties in tissue conductivity values. However, the electric field is also influenced to some extent by the tissue permittivity. As we have previously reported \[32\] only conductivity values, the effect of permittivity uncertainties was investigated by considering the uncertainty of muscle permittivity only, as it constitutes of a large volume that has the largest relative permittivity value in the pelvic region. Therefore, the largest effect on the temperature distribution would be caused by deviations from the literature value for muscle tissue.

In general, EPT is able to reconstruct the permittivity value as well, however, the reliability of the permittivity reconstruction at 3T is less reliable as shown in \[21\]. EM field and thermal modeling were performed for two patients using muscle permittivity values deviating 20% from the literature value. More specifically, EM simulations were conducted for patient 1 and 5 with conductivity values as described in case II (Table 1) while muscle permittivity was fixed for each simulation at 60, 70, 75, 80 and 90. Patient 1 and 5 were chosen because the effect of muscle conductivity on T90 was lowest and highest, respectively, for these patients. We denote these cases as \(\text{II}_{\varepsilon_r,m=60-90}\). All other permittivity values remained unchanged. Antenna settings optimized for the literature based model (case I) were used to compute the temperature distributions for different permittivity values.
5.2.5 EPT based versus literature data based temperature optimization

Temperature based optimization was also performed for the patient model using EPT based conductivity values (case II) of all patients to compute the tumor temperature achievable for EPT conductivity values. These results were then compared to the tumor temperature achieved when optimization was conducted using the literature based dielectric models (case I). We compared the tumor T90 between optimization with literature values (I) and optimization with EPT values (II).

In Table 3 an overview is given which shows the dielectric case on which the temperature optimization was performed (Data set optimization) and for which dielectric case these antenna settings were applied (Actual parameters). For example label I→II means that antenna settings optimized for case I were applied to dielectric case II.

Table 3. An overview of the dielectric data sets used for optimization (2nd row) and the dielectric data set on which the optimized antenna setting was applied (3rd row). Data sets are listed in Table 2. The results are depicted in figures 1–4.

<table>
<thead>
<tr>
<th>Label</th>
<th>I→I</th>
<th>I→II</th>
<th>I→III</th>
<th>I→IV</th>
<th>I→V</th>
<th>I→VI</th>
<th>I → II_{ε_r,m=60–90}</th>
<th>II→II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimization dataset</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Actual parameters</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
<td>V</td>
<td>VI</td>
<td>II_{ε_r,m=60–90}</td>
<td>II</td>
</tr>
<tr>
<td>Figure</td>
<td>1,2,3,4</td>
<td>1,2</td>
<td>1,2</td>
<td>1,2</td>
<td>1,2</td>
<td>1,2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

5.3 Results

5.3.1 Impact of EPT based conductivity values

The tumor T90 and T50 for the dielectric cases I–V are shown in Figure 1. The tumor temperatures for all EPT based dielectric patient models (cases II–V) are lower compared to the literature based model of the corresponding patients 1–5. The largest deviation is observed in patient 1 where ΔT90 = −1.37°C (AMC–8) is observed for the EPT based dielectric model (II) and a ΔT90 = −1.81°C (AMC–8) in combination with an elevated bladder conductivity value (III). The impact of different dielectric models on tumor T90 in patients 2–5 was relatively low (ΔT90 ≤ −0.57°C). The lowest impact on T90 is observed when EPT conductivity values were assigned only to the bladder (IV). This was the case for patients 2–5, however, in patient 1 the T90 was substantially influenced by the conductivity of bladder (IV). In Figure 2 the tumor SAR is shown for all patient models as presented in Figure 1. A similar trend regarding tumor SAR is observed for all dielectric cases.

Since the conductivity of bladder content, based on [32], is higher than the currently used value based on literature, the absorbed power in the bladder is higher and, therefore, the average SAR in the tumor is lower, as observed in Figure 2. An even
stronger impact on T50 and T90 is observed when assigning an even higher bladder conductivity (case III) that might occur as reported in [32] and [49–51]. The same trend is observed for the cervical tumor SAR, as more power is dissipated in the bladder. The impact of varying only the bladder conductivity was also investigated (case IV) and the observed difference in T50 and T90 for patients 2–5 was less than 0.5°C, whereas in patient 1 the T90 deviation was 1.32°C. This difference in effect can be compared with the difference in bladder volume for patients 1–5 plotted in Figure 2A, an insert in Figure 2, where we can see that bladder volume varies between 33 mL for patient 4 and 5 and 497 mL for patient 1.

The impact of a higher muscle conductivity was also observed in the case (V) where the EPT based conductivity value was assigned only to muscle (Figures 1 and 2). The impact due to correction limited to the conductivity values for muscle, differs from patient to patient. Because of the high volume of muscle and tumor tissue, the highest impact was observed in patient 5 (ΔT90 = −0.46°C for AMC–4). The impact of higher tumor conductivity (case VI) on tumor temperature was very limited as can be observed in Figures 1 and 2. Tumor T90s are very similar to the case I, however, a slight increase of T50 by 0.20°C and 0.16°C (for AMC–4) is observed for patients 4 and 5, respectively, which have the largest tumor size in this patient population. For AMC–8 the T50 increase for patients 4 and 5 is slightly higher, 0.25°C and 0.21°C, respectively. An increase of tumor SAR is also observed in these two patient models (Figure 2).

The impact of uncertainty of EPT data on tumor T90 is shown in Figure 3. The lowest conductivity values for muscle, cervical tumor, and bladder content lead to a higher tumor temperature compared to the mean values in case II. The difference between planned (I) and lowest conductivity values is then 0.80°C for patient 1, and less than 0.18°C for all other patients. On the other hand, the highest conductivity values obviously have an even higher negative impact on tumor temperature as indicated by the corresponding lower part of the error bars in Figure 3.

5.3.2 Impact of muscle permittivity variation

In Figure 4 the impact of muscle permittivity variation (case IIεr,m=60–90) on tumor T90 for patients 1 and 5 is shown. For easy comparison, the T90 for case I and II as depicted in Figure 1, are repeated in this graph. It is observed that the impact of permittivity variation on the tumor T90 is relatively low for patient 1. The maximum error in tumor T90 does not exceed 0.11°C (AMC–4) between highest and lowest
possible permittivity, whereas the application of EPT values (case II) on this patient lead to a \( \Delta T_{90} \) of \(-1.26^\circ C\) (AMC–4). The variation of permittivity in patient 5 resulted in a relatively larger (but still small) error of \( 0.16^\circ C\) (AMC–8) whereas the T90 deviation due to EPT values (II) was \( 0.34^\circ C\) (AMC–8).

5.3.3 Impact of EPT based patient model on optimized temperature distribution

In Figure 5 the tumor T90s for a literature based dielectric model are presented by white bars for patient 1–5 as also shown in Figure 1. The gray bars in Figure 5 represent the tumor T90 when temperature based optimization is performed using the EPT based patient models. It is observed that the tumor T90 is lower for all patients when optimized using EPT conductivity values. The difference in T90 varied between \(-1.50^\circ C\) (patient 1; AMC–8) and \(-0.33^\circ C\) (patient 5; AMC–8).

In Figure 6 an example of a transversal slice of patient #1 is shown and the resulting temperature distribution for the cases (I→I), (I→II) and (II→II). Hot spots arise due to application of antenna settings optimized for literature values to EPT based model (I→II, Fig. 6c), these are not visible in the slice shown as they occurred on transversal slices outside tumor volume. The corresponding SAR distributions are shown in the second row of Figure 6.
Figure 1. Tumor T90 (top) and T50 (bottom) in patients 1–5 for AMC–4 and AMC–8 system. The white bar represents the optimized case for properties based on literature values. Using the same antenna settings, the tumor temperature for different cases are computed and represented by other bars.
Figure 2. Tumor SAR in patients 1–5 for AMC–4 and AMC–8 system. The white bar represents the optimized case for properties based on literature values. Using the same antenna settings, the tumor temperature for different cases are computed and represented by other bars.

Figure 3. Tumor T90 in patients 1–5 for AMC–4 and AMC–8 system. The white bar represents the optimized case for properties based on literature values. The error bars represent the minimum and maximum tumor T90s when using highest and lowest conductivity values, respectively, as presented in case II (Table 2).
Figure 4. Tumor T90 for patient 1 (top) and 5 (bottom) for optimized cases with literature value (white) and for EPT based conductivity values of muscle, cervical tumor and bladder filling (black). The other bars represent tumor T90 values for different values of muscle permittivity.
Figure 5. Tumor T90 for patient 1–5 based on literature values (white) and on EPT based conductivity values (gray). The applied antenna settings were computed for both cases separately by temperature based optimization.

Figure 6. An example of the resulting temperature distribution of patient #1 corresponding to transverse slice (a) for the case; (b) planned with literature values (I→I) and (c) the case where the same antenna settings are applied on the EPT based model (I→II). In (d) is shown the distribution resulting for temperature based optimization based on EPT model (II→II). The corresponding SAR distributions are shown in (e)–(g).
5.4 Discussion

In this study we investigated the difference in planned hyperthermia temperatures between electric conductivity values from the literature and values assessed *in vivo* by MRI-based EPT in cervical cancer patients [32]. The impact of EPT values for muscle, bladder and tumor values was investigated in CT-datasets of five patients and for both the AMC–4 and the AMC–8 system operating at 70 MHz. A lower tumor temperature was observed when using EPT based conductivity values both when phase and amplitude were optimized for literature values and when they were optimized for the actual EPT based values (Figures 1 and 5).

As cervical tumors are surrounded by muscle tissue, of which the *in vivo* conductivity value is higher [32], more power is dissipated in the muscle, and therefore, the tumor SAR is lower, as is shown in Figure 2. This subsequently results in a lower tumor T50 and T90 (Figure 1). Based on the used patient models, a large bladder volume has a negative impact on the maximum tumor SAR and, hence, on the tumor T50 and T90. The negative impact of ‘bladder only’ on T50 and T90 might seem slightly counterintuitive as one would expect a bladder with a higher conductivity to reach higher temperatures and subsequently, through heat transfer, to lead to a higher tumor temperature; but this was not the case for patient models used in this study. However, it should be noted that the fluid inside the bladder is modeled as a solid, so that the effects of convection are ignored, and the amount of heat transferred is probably underestimated [52]. The T90 and the SAR in the bladder (not shown here) were slightly lower in most patients. A higher local maximum temperature was, however, observed in the bladder in most patients due to elevated bladder conductivity. Finally, in dielectric cases (I→II, I→III, I→V) the temperature constraint of 45°C for normal tissues was violated for all patients.

As observed in Figure 5 the tumor T90 is lower in all cases of electric conductivity values, even though the temperature optimization is based on EPT conductivity values (II→II). The worst case is observed in patient 1 (ΔT90 = −1.50°C, for AMC–8), whereas for other patients the maximum tumor T90 was less than 0.6°C lower compared to literature based model. This indicates that the higher conductivity value of muscle limits the maximum tumor temperature that can be achieved. As tissue conductivity increases with temperature (for muscle about 2% °C−1) [53] and since the EPT measurements were performed at non-hyperthermic temperatures, the power dissipation in the muscle may be even higher during hyperthermia. However, the additional effect on tumor T90 due to the tissue temperature increase is expected to be relatively low since a 24% muscle conductivity increase (case V) leads to ΔT90 ≤ −0.46°C (see Figure 1). Future studies should, furthermore, focus on the benefit of EPT based treatment planning in a clinical setting.

EPT can be easily incorporated in the current clinical practice as in general all cervical cancer patients undergo an MR examination for diagnostic purposes. An MR provides higher soft tissue contrast allowing for more accurate definition of tumor region and, in addition, MR-only based radiotherapy is feasible [54–56]. Due to the
increased utilization of MR in the clinic, acquisition of B1 maps for EPT can be efficiently included in the clinical workflow.

Various studies have demonstrated that the tissue electric conductivity is determinative for SAR \([8,57]\), nevertheless, the electric permittivity affects the EM behavior inside the human anatomy as well. We have limited the permittivity uncertainty to muscle only as it has a relatively high permittivity compared to other tissue in the pelvic region, and represents a high tissue volume. Therefore, its uncertainty was expected to have the largest impact. As observed in Figure 4, the variation of electric permittivity of muscle by 20% around the literature value has a relatively low impact on the tumor T90 compared to the impact of conductivity values (Figure 4). The uncertainty of 20% for permittivity is quite high, and in practice a lower uncertainty is expected. Based on \([58]\) the permittivity of porcine brain tissue drops by 3% after animal death (at 900 MHz and 1800 MHz) while the same study reported a 15% drop of conductivity value after death. Furthermore, Kraszewski et al. \([59]\) reported an approximately 5% higher permittivity value for skeletal cat muscle when measured \textit{in vivo} at 100MHz. Therefore, the lower permittivity uncertainty compared to conductivity and its low impact on tumor T90 (Figure 4), indicate that in particular the measurement of \textit{in vivo} conductivity values contributes strongly to a reliable HTP. In contrast to conductivity, a slightly higher muscle permittivity seems to have a positive effect on tumor T90 (Figure 4) probably due to the higher penetration depth of EM fields at higher tissue permittivity \([60]\).

In this study we have not considered the uncertainty of thermal properties \([61]\), however, it has been investigated in other studies \([9,62]\). We previously studied the impact of ±25% uncertainty in perfusion parameters alone (of muscle and fat) \([9]\). The difference between optimal and realized T90 for five patients was on average 0.2°C and 0.3°C lower, for the AMC–4 and AMC–8 system, respectively. The present paper shows that the tissue properties have a profound impact on the amount of energy one is able to get into the tumor. This impact remains important, even when the role of perfusion is taken into account. Other uncertainties that were not considered include the patient position, organ deformation and manual versus automatic tissue segmentation \([12,63–68]\). Furthermore, the temperature distributions in this study were based on the Pennes bioheat model which is commonly used in the literature. A more accurate but also more complex way to compute temperature distributions is by modeling discrete blood vessels \([69]\) which requires additional data of the vasculature in the heated region and information regarding the blood flow during hyperthermia treatment. Therefore, in absence of the additional data we have used the standard thermal model. Regardless, the SAR computations are only influenced by electric properties and showed a decrease of tumor SAR due to EPT conductivity values.

In this study we have limited the impact of EPT based conductivity values on cervical tumor which is generally located in the central pelvic region. However, the impact on pelvic tumors located in the periphery would suffer less from higher muscle or bladder conductivity compared to cervical tumors. For instance, if the bladder would be the target region \([70–72]\) then it would likely be less affected by the higher muscle conductivity. In addition, a full bladder might be more beneficial for the treatment of
bladder tumors than an empty bladder, however, additional simulations are required to confirm this effect. For the treatment of cervical tumors, however, an empty bladder seems to be beneficial as more power is deposited in the tumor. Only patient 1 had a completely full bladder, having the largest negative impact on tumor temperature, whereas patient 4 and 5 with practically an empty bladder showed the lowest impact.

We have investigated the impact of EPT values on heating with the AMC–4 and AMC–8 systems. However, the impact on tumor temperatures when using a configuration with more than 8 channels and/or systems operating at higher frequencies is expected to be even higher, as also shown in [9] for a 12 and 18 channel system. Since the penetration depth of EM fields decreases with increasing frequency, it should be investigated to which extent the EPT based values impede tumor heating. As the conductivity of urine is much higher [42,43,48] than currently considered in models it should be explored if an empty bladder would be beneficial for the tumor temperature. Results in this study suggested that a small bladder volume has a positive impact on the tumor T90, but this should be investigated in a larger population and verified by measurement during hyperthermia. Finally, as a higher muscle conductivity had a determinative effect on tumor T90 for four out of five patients (Figures 1 and 2), research should also be focused on how to circumvent the higher power dissipation outside the target region.

5.5 Conclusion

Electric conductivity values acquired by EPT are higher than the literature values used until now, which has a substantial impact on cervical tumor temperatures achieved during hyperthermia. A higher muscle conductivity value surrounding the tumor leads to higher power dissipation in the muscle and, therefore, lower tumor temperatures. This effect is observed when the treatment is performed using the optimized antenna settings for a literature based dielectric model, as well as for the case where the treatment is optimized based on the EPT values. For four patients the difference between the optimal tumor T90 and realized with EPT values (II→II) was less than 0.6°C; for one patient it was 1.5°C. A large bladder volume also leads to a lower tumor SAR and T90, therefore, an empty bladder is beneficial for treatment of cervical tumors. Application of amplitude/phase settings optimized for the literature based model lead in most cases to treatment limiting hotspots, confirming the necessity for optimization based on correct input data.

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Chapter 5


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