Loco-regional hyperthermia treatment planning: optimisation under uncertainty

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Citation for published version (APA):
Chapter 3

3D versus 2D steering in patient anatomies: a comparison using hyperthermia treatment planning

This chapter was published as:

Abstract

**Purpose:** In this study hyperthermia treatment planning is used to investigate whether the target temperature during hyperthermia treatment can be increased using the 3D AMC-8 instead of the 2D AMC-4 system (AMC: Academic Medical Center).

**Methods and Materials:** The heating ability of the AMC-4 and AMC-8 system was analyzed for five patients with cervix uteri carcinoma. Dielectric and thermal models were generated, based on a hyperthermia planning CT, at a resolution of $2.5 \times 2.5 \times 5.0 \text{ mm}^3$. Calculation of the electric fields with the finite-difference time-domain method was followed by SAR- and temperature-based optimization. The ability to correct for axial shifts of the patient by phase/amplitude steering was investigated for both systems. Finally, it was investigated whether adjusting the ring-to-ring distance of the AMC-8 system can be used for further optimization.

**Results:** An average increase in $T_{90}$ of $\approx 0.5^\circ \text{C} (0.2 – 0.8^\circ \text{C})$ was found for the AMC-8 system compared to the AMC-4 system. The gain in $T_{50}$ and $T_{10}$ was also $0.5^\circ \text{C}$ on average. The additional power required to achieve this gain was 36 to 71% of the power required for the AMC-4 system. The AMC-8 system has the capability of correcting changes in axial position ($-8$ cm, $+8$ cm), contrary to the AMC-4 system. For both systems the axial position should be known within $1–2$ cm.

**Conclusions:** Hyperthermia treatment with the AMC-8 system can lead to a clinically relevant increase of the target temperature compared to treatment with the AMC-4 system. The AMC-8 system provides large freedom in the axial positioning of the patient.
3.1 Introduction

Hyperthermia has proven its added value when combined with radiotherapy and/or chemotherapy in various randomized phase III trials for different tumor sites (12; 10; 52).

These good clinical results were achieved in spite of the fact that the temperature aimed for, 43°C during one hour of treatment, was seldomly achieved (3). The administered thermal dose to the target is generally lower because potential local overheating of normal tissue prevents applying sufficient power. Increasing the thermal dose is expected to lead to improved clinical results, given that the fraction of tumor cells surviving combined radiotherapy and hyperthermia was found to decrease significantly with increasing target temperature and treatment duration (2).

In most institutes, deep-seated tumors such as cervix uteri carcinoma are heated with loco-regional phased-array systems operating at frequencies in the range of 70 – 150 MHz (53; 54). The distribution of the absorbed power can be steered by varying the amplitude and the phase of the electric fields imposed by the individual antennas. In this way the thermal dose delivered to the tumor can be maximized within the limits of patient tolerance.

An important strategy to improve thermal dose delivery during hyperthermia treatment is the use and design of systems with a higher level of control on the power distribution in the patient. The level of control of a loco-regional hyperthermia device is determined by a number of system parameters. Frequency determines the wavelength and thus the scale of the interference pattern. With increasing frequency, electromagnetic waves penetrate with less depth into the patient; at the same time, constructive interference between multiple sources takes place on a smaller spatial scale resulting in a smaller focus as a result of the decreased wavelength. In addition, if the frequency becomes too large i.e. if the wavelength is much smaller than the typical dimension of the patient, it may not longer be possible to create a single focus.

The number of antennas and their geometrical configuration is another important design parameter. Different previous studies (47; 46; 55) investigated the effect of antenna number, configuration and applied frequency for different tumor sites on the achieved target temperature or power absorption. In these studies treatment quality was found to improve with an increasing number of antennas organized in multiple rings. The advantage of having a configuration with multiple rings of antennas is that the power or temperature distribution can be steered in 3D whereas...
Figure 3.1: The AMC-8 phased-array 70MHz waveguide system. The system consists of two rings of four waveguides. Every waveguide has a separate water bolus that provides superficial cooling of the patient and coupling of the incident electromagnetic field into the patient. The two bottom waveguides share the same water bolus. The distance between the two rings is adjustable.

A single ring system only allows for steering within a plane.

At our department, loco-regional hyperthermia treatments were carried out using a single ring, four waveguide system operating at 70 MHz: the 2D AMC-4 system (56). Recently a new version of the system operating at the same frequency of 70 MHz with an extra ring of four waveguides was introduced in the clinic: the AMC-8 system (figure 3.1) (53). Simulations and measurements in phantoms showed that the full-width-half-maximum of the heating pattern was found to be prolonged with at least 50% in the axial direction, depending on the aperture size and the ring-ring distance (57). At equal superficial power deposition, the power in a target located at the center of the phantom was found to increase when moving from four to eight waveguides with up to 30% (53).

All these pre-implementation studies involved homogeneous phantoms; in this study hyperthermia treatment planning will be used to address the question whether the target temperature during loco-regional hyperthermia treatment can be increased using the AMC-8 instead of the AMC-4 system. To this end, for both systems, the heating efficacy under standard positioning is investigated as well as its sensitivity with respect to changes in patient position. Furthermore the ability of both systems to correct for those changes in position by adjustment of phases and amplitudes is investigated. Finally it is investigated whether the variable ring-ring distance pro-
Table 3.1: Data are taken from Gabriel et al. (22) and the ESHO Taskgroup Committee (58). $\sigma$ is the electric conductivity, $\epsilon_r$ the relative electric permittivity, $\rho$ the density of the tissue, $c_p$ the heat capacity, $k$ the thermal conductivity and $W_b$ the volumetric tissue perfusion rate. *The heat capacity of air is increased by a factor of 10 to allow a larger time step during simulation. The effect on the temperature distribution is negligible.

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>$\sigma$ (S/m)</th>
<th>$\epsilon_r$ (-)</th>
<th>$\rho$ (kg/m$^3$)</th>
<th>$c_p$ (J/(kg K))</th>
<th>$k$ (W/(m K))</th>
<th>$W_b$ (kg/(m$^3$ s))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner-air</td>
<td>0.0</td>
<td>1.0</td>
<td>1.29</td>
<td>10000$^*$</td>
<td>0.024</td>
<td>0.0</td>
</tr>
<tr>
<td>Bone</td>
<td>0.05</td>
<td>10</td>
<td>1595</td>
<td>1420</td>
<td>0.65</td>
<td>0.12</td>
</tr>
<tr>
<td>Fat-like</td>
<td>0.06</td>
<td>10</td>
<td>888</td>
<td>2387</td>
<td>0.217</td>
<td>1.1</td>
</tr>
<tr>
<td>Muscle-like</td>
<td>0.75</td>
<td>75</td>
<td>1050</td>
<td>3639</td>
<td>0.56</td>
<td>3.6</td>
</tr>
<tr>
<td>Tumour</td>
<td>0.74</td>
<td>65</td>
<td>1050</td>
<td>3639</td>
<td>0.56</td>
<td>1.8</td>
</tr>
</tbody>
</table>

vides a useful additional degree-of-freedom to optimize heating with the AMC-8 system.

### 3.2 Materials and Methods

#### 3.2.1 Definition of the patient model

For a group of five patients with a cervix uteri carcinoma, a data-set was acquired with computerized tomography (CT) ($0.9 \times 0.9 \times 5.0$ mm$^3$) and was automatically segmented into inner-air, fat, bone and muscle tissue, based on the Hounsfield units (23). The axial extent of the scans was approximately 60 cm. This is not sufficient for simulation of heating with the AMC-8 system and for this reason the scans were extended by copying the top and bottom slices. Appropriate dielectric and thermal parameters were assigned as reported in table 3.1 (22; 58). A radiation oncologist delineated the gross-target-volume (GTV) as the target volume for optimization. Table 3.2 gives an overview of a number of patient characteristics. To reduce the computational costs, the data-set was re-sampled on a $2.5 \times 2.5 \times 5.0$ mm$^3$ grid. The technique used for re-sampling is referred to as the winner-takes-all technique: a low-resolution voxel is assigned the properties of the tissue type that takes up to largest fraction of its volume.
Table 3.2: $V_{\text{fat}}$ and $V_{\text{muscle}}$ are the volume of fat- and muscle-like tissues respectively. $D_{\text{LR}}$ and $D_{\text{AP}}$ are the largest distance measured for each patient in the left-right and the anterior-posterior direction, respectively.

<table>
<thead>
<tr>
<th>Patient</th>
<th>GTV (cc)</th>
<th>$V_{\text{fat}}$ (cc)</th>
<th>$V_{\text{muscle}}$ (cc)</th>
<th>$D_{\text{LR}}$ (cm)</th>
<th>$D_{\text{AP}}$ (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>139.3</td>
<td>9797</td>
<td>18135</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>88.9</td>
<td>15417</td>
<td>11048</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>26.9</td>
<td>17012</td>
<td>12087</td>
<td>38</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>52.5</td>
<td>24682</td>
<td>10309</td>
<td>48</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>75.1</td>
<td>24042</td>
<td>14245</td>
<td>44</td>
<td>29</td>
</tr>
</tbody>
</table>

3.2.2 Definition of the phased-array wave guide system and patient positioning

The AMC-4 and AMC-8 system consist of four and eight 70 MHz waveguides (aperture size $20.2 \times 34.3 \text{cm}^2$) organized in one and two rings, respectively (figure 3.2). Each waveguide can be translated independently in the direction normal to its aperture. In the clinic, the position of the waveguides is chosen such that a gap of five centimeters exists between the waveguides and the patient. Water boluses are placed between these gaps to assure adequate coupling of the incident electromagnetic field. Furthermore these water boluses, circulated with distilled water kept at approximately $12^\circ \text{C}$, provide superficial cooling that is essential to prevent overheating. For the AMC-8 system the distance between the two rings can be varied. Unless mentioned otherwise, this distance was set to 1.5cm (figure 3.2).

By default, the patient model was positioned in the AMC-4 model such that the center-of-gravity (COG) of the target volume coincides with center of the applicator ring. For the AMC-8 system, the COG of the target volume coincided with the center of the two rings. This means that the axial position of the COG is in between the two rings.

3.2.3 Calculation of the electric field distribution

The electric field distribution in the patient was determined by superposition of the fields imposed by the different antennas. Therefore, in the simulations, all waveguides were excited separately with unit amplitude and phase zero to calculate the
3D versus 2D steering in patient anatomies

Figure 3.2: Coronal cross-section of the waveguide configuration of the AMC-4 (left) and AMC-8 (right) phased-array system and the water boluses. Waveguide aperture size equals $20.2 \times 34.3 \text{cm}^2$. The distance between the two rings of the AMC-8 system (ring – ring distance (RRD)) can be varied and is in this study by default 1.5 cm.

individual fields.

To compute the electric field distribution, the finite-difference time-domain (FDTD) method was used (37). The computational domain was truncated using a perfectly matched layer (59). By discrete Fourier transformation the complex electric field was stored after 35000 steps in time ($\Delta t = 0.95\Delta t_{\text{Courant}}$). To accelerate the FDTD algorithm, a graphical processing unit (GPU) implementation was used (60). The computation time for a single field was 30 - 45 minutes for a simulation volume of typically 15 million cells.

3.2.4 Optimization

To evaluate the performance of the two systems for a series of five patients, two optimization procedures were followed: SAR- and temperature-based optimization.

SAR-based optimization

An optimization procedure based on the specific absorption rate (SAR) was used to investigate the ability to focus the power absorption on the target region for varying axial positions of the patient for the AMC-8 and AMC-4 system. The patient was shifted in the caudal – cranial direction from $-8 \text{cm}$ to $+8 \text{cm}$ with 2 cm steps. For each position, the ratio of SAR delivered to the target and delivered to the patient in total was optimized (61). The optimization procedure was constrained by requiring
that the power delivered by a single antenna is within 10 and 40% and 5 and 25% of
the total power for the AMC-4 and the AMC-8 system, respectively.

A drawback of this SAR-based optimization procedure is that phase and ampli-
tude settings that give optimal coverage of the target region may lead to unaccept-
ably high SAR levels elsewhere. This problem could potentially be solved if there
was a rational basis to constrain SAR to specific levels. However, in an (off-line)
optimization procedure, such constraints are hard to define since the corresponding
temperature levels are largely dependent on variables such as tissue perfusion and
other forms of cooling e.g. water bolus cooling. Although SAR-based methods can
be tailored to suppress overheating with certain efficiency (45), temperature-based
optimization suppresses overheating naturally by setting the maximum tolerable
normal tissue temperature as a constraint (62).

Temperature-based optimization

To investigate the ability of the two systems to heat the target while respecting nor-
mal tissue constraints, temperature-based optimization was performed for varying
axial patient positions. As for the SAR-based optimization, the patient was shifted
in caudal-cranial direction from \(-8\) to \(+8\) cm in 2cm steps. This shows which patient
position leads to optimal heating and, by shifting the patient without changing the
phase/amplitude settings, how sensitive the thermal dose is for positioning errors.
Das et al. showed, by using Pennes bio-heat equation (27), how phase and ampli-
tude can be related to the local temperature \(T(x, y, z)\) using the previously calculated
electric fields (28). This method was used in this study. The relevant steady-state
temperature fields (28) were calculated using a GPU accelerated finite-difference
method. The relevant parameters for the temperature calculations are presented in
table 3.1. We defined the following object function for optimization (63)

\[
\Pi(\vec{v}) = \sum_{V_{\text{target}}} \max(0, T_{\text{threshold}} - T(\vec{x}; \vec{v}))
\]

(3.1)

where \(V_{\text{target}}\) is the target volume and is a complex-valued vector holding the am-
plitudes and phases of the different sources. This function is minimized under the
constraint that the temperature in normal tissue does not exceed a constraint tem-
perature here chosen to be 45°C (64). The value of was set to 43°C. Additional con-
straints were specified for the contribution to the total power of a single antenna.
For the AMC-4 system this contribution should be within 10 and 40%, for the AMC-
8 system within 5 and 25%. Solutions to this non-linear constrained optimization problem were computed using the CFSQP package (eps = 1e-5, epseqn = 1e-5, miter = 35/50 (AMC-4/AMC-8)) \(^{(65)}\). Since the optimization process might halt on a local minimum, 20 runs with random starting points in phase/amplitude space were performed for the AMC-4 system and 10 runs for the AMC-8 system (to limit the computation time).

In order to determine the potential gain in tumor temperature when treating with the eight antenna system instead of treating with four antennas, \(T_{90}\), (for 90 percent of the tumor volume \(T \geq T_{90}\), \(T_{50}\) and \(T_{10}\) of the target volume were compared. Furthermore the total power absorbed in the patient was calculated. Cumulative temperature - volume histograms (TVH) were made to analyze the differences in the overall temperature distribution.

### 3.2.5 Variation of the ring-to-ring distance

Since the distance between the two rings of the AMC-8 system can be varied, it was investigated whether this is a relevant degree-of-freedom in the optimization procedure. Hence, temperature-based optimization was performed setting the ring-to-ring distance (RRD) to 1.5, 3.5, 5.5 and 7.5cm. In addition, the sensitivity of the thermal dose to the RRD was investigated. This was done by applying the settings resulting from optimization at 1.5cm RRD and evaluating the thermal dose at larger distances.

### 3.3 Results

#### 3.3.1 SAR-based optimization

Figure 3.3 shows the relative SAR ratio (SAR in the target divided by SAR in the total volume) as a function of axial position for both systems for all five patients after optimization of this ratio. As a scaling factor, the SAR ratio under optimal positioning for the AMC-4 system is used. This figure shows that for the AMC-8 system the SAR ratio increases moving the patient to off-center positions, whereas for the AMC-4 system, the SAR ratio decreases.
Figure 3.3: The normalized ratio of target- and normal tissue SAR for the AMC-4 and the AMC-8 system for different axial positions after optimization for patients 1 to 5. The SAR ratios are normalized by the SAR ratio found for the AMC-4 system under optimal positioning. Antennas were not allowed to contribute more to the total delivered power than 40% or less than 10% for the AMC-4 system and no more than 25% or less than 5% for the AMC-8 system.
Figure 3.4: The temperature gain for $T_{10}$, $T_{50}$ and $T_{90}$ when moving from the AMC-4 to the AMC-8 system for patient 1 to 5. The applied settings resulted from temperature-based optimization. For the AMC-8 system a 1.5cm ring–ring distance was applied.

### 3.3.2 Temperature-based optimization

Figure 3.4 shows the increase in target $T_{10}$, $T_{50}$ and $T_{90}$ for the AMC-8 compared to the AMC-4 system after temperature-based optimization applying standard positioning. $T_{90}$ shows an average increase of $\approx 0.5^\circ C$ (range $0.2 – 0.8^\circ C$). $T_{50}$ and $T_{10}$ show a similar increase.

Figure 3.5 shows the additional power needed to achieve the higher target temperatures for the AMC-8 system. The increase in total power is found to be between 36 – 71% of the power that was required for heating with the AMC-4 system.

As illustrated in figure 3.6, a gain in target temperature is associated with an increase of the volume with a temperature close to the constraint level. As an example, for patient 1 the volume with a temperature of 44°C is ten times larger when treating with the AMC-8 compared to the volume when treating with the AMC-4 system.

An example of the temperature distribution after temperature-based optimization for the AMC-4 and the AMC-8 system for one of the five patients (patient 1) is shown in figure 3.7. It can be seen that the temperature distribution extends over a larger length in the axial direction (here particularly clear for the legs). Higher tumor temperatures are achieved however for the same maximum normal tissue temperature.
Figure 3.5: Total absorbed power for the AMC-4 and the AMC-8 system for patients 1 to 5. The applied settings result from temperature-based optimization. For the AMC-8 system a 1.5cm ring – ring distance was applied.

3.3.3 Patient positioning

Figure 3.8 compares the $T_{90}$ and $T_{50}$ found using settings from temperature-based optimization for varying axial patient positions. For every shift $T_{90}$ and $T_{50}$ are evaluated using settings that result from I) optimization with the patient model at the correct/actual position (unconnected markers in figure 3.8) and II) optimization without a shift of the patient (connected markers). It shows the ability of the two systems to correct for axial shifts of the patient. For the AMC-8 system, both the $T_{90}$ and $T_{50}$ are found to be relatively stable for all patients over a range of $-8$cm to $+8$cm. Without correction for axial patient shifts, the thermal dose is found to be equally sensitive for both systems (power was scaled to the highest tolerable level, i.e. such that the maximum temperature equals the constraint temperature). The ability of the AMC-4 system to correct for patient position variations is clearly very limited.

3.3.4 Ring-to-ring distance

Figure 3.9 shows the $T_{90}$ heating with the AMC-8 system using different distances between the two rings relative to the results found using a default 1.5cm ring – ring distance. The left figure shows the effect of increasing the distance without adjustment of phase/amplitude settings (total power is set to the highest tolerable level).
Figure 3.6: Cumulative temperature - volume histograms of the temperature distribution resulting from temperature-based optimization for the five patients. The inserts zoom in to the 43 - 45°C range of the histogram. Indicated in the lower-left corner of each plot is the patient number.
Figure 3.7: An example of the resulting temperature distribution (right) after temperature-based optimization with the corresponding coronal slices (left) for the AMC-4 system (top) and the AMC-8 system (bottom).
Figure 3.8: \( T_{90} \) and \( T_{50} \) for different axial shifts (z-axis) of patients 1 to 5. For every shift the \( T_{90} \) and \( T_{50} \) were evaluated for two sets of amplitudes and phases. The first is the result of optimization with the patient modelled at the correct/actual position (unconnected markers). The second results from optimization without shifting the patient (connected markers). The figure shows that the AMC-8 system has the capability of correcting for changes in axial position of the patient, contrary to the AMC-4 system.
Minor deviations (<2cm) in the RRD lead to a decrease of the $T_{90}$ below 0.3°C (with exception of patient 3). The figure on the right shows the difference in $T_{90}$ after optimizing for 3.5, 5.5 and 7.5cm distance compared to the $T_{90}$ found using the ‘standard distance of 1.5cm. The optimal RRD is 5.5 cm for patient 1, 3.5cm for patient 2, 1.5cm for patient 3, 7.5cm for patient 4 and 1.5cm for patient 5, but in general adjusting the RRD does not lead to a profound improvement in thermal dose delivery.

3.4 Discussion

This study applied hyperthermia treatment planning to investigate whether the use of the eight antenna, double ring, 3D AMC-8 system is expected to result in higher target temperatures relative to treatment with the single ring, 2D AMC-4 system. A similar comparison is relevant for the 2D BSD Sigma 60 and the 3D BSD Sigma Eye applicator.

Figure 3.3 showed that the position of the patient in either the AMC-4 or the AMC-8 system plays an important role in the fraction of the total power that can be delivered to the target. This analysis did not take hot-spots into account. Consequently, no statements can be made about the tolerable power level which is to be determined by the maximum temperature in the patient. For the AMC-4 system, moving the patient away from the mid-plane reduces the fraction of power that can be delivered to the target. For the AMC-8 system, moving the patient away from the transversal mid-plane in between the two rings is beneficial for the power delivered to the target. However, superficial levels of power absorption will increase leading to a lower tolerable power level in clinical practice. Different behavior is expected to occur when comparing the BSD Sigma 60 (2D, 1 ring) and the BSD Sigma Eye applicator (3D, 3 rings). Under standard positioning, in a three ring set-up the target is in the center of the middle ring, while for the two ring AMC-8 system the target is in between the rings.

Temperature-based optimization can be constrained more straightforwardly by setting a maximum normal tissue temperature and is therefore preferred over SAR-based optimization. However, a disadvantage of temperature-based optimization is the uncertainty in the perfusion distribution under hyperthermic conditions. With the present-day lack of perfusion data, accurate clinical patient-specific temperature-based optimization is not feasible. The gain found in this study is therefore expected to be dependent on thermal modeling parameters. Our estimates are assumed to represent the correct average but will deviate for the individual patients. However,
Figure 3.9: Differences in T<sub>90</sub> after temperature optimization for the AMC-8 system using varying RRDs. Results are relative to the results for a RRD of 1.5 cm. The figure on the left shows the change in T<sub>90</sub> applying optimized settings for a 1.5cm RRD at larger distances without adjustment of settings. The figure on the right shows the T<sub>90</sub> optimizing for the actual distances relative to the optimal T<sub>90</sub> for a RRD of 1.5cm.
temperature-based optimization is clinically the most relevant method to evaluate the heating of the same patient with different apparatus by means of simulation. Temperature-based optimization of the target temperature showed an average increase of the target $T_{90}$ with $0.5^\circ C$ with large inter-patient variability ($0.2 - 0.8^\circ C$) for the AMC-8 system compared to the AMC-4 system. $T_{50}$ and $T_{10}$ increased typically with $0.5^\circ C$ as well (figure 3.4). This increase is clinically relevant since the cumulative minutes at $43^\circ C$, a parameter commonly used to describe thermal dose, approximately doubles with every $0.5^\circ C$ increase in temperature (for temperatures below $42.5^\circ C$) (66).

As shown in figure 3.8, for the AMC-8 system the tumor temperature expressed as $T_{90}$ and $T_{50}$ is relatively insensitive to changes in the axial position of the patient when the optimization takes the actual position into account. These results are comparable to those of Gellermann et al. for the 3D BSD Sigma Eye applicator (35). Altering the axial position of the patient might prove to be a strategy to relieve complaints reported in earlier treatment sessions. The absorption at a specific hot-spot can be diminished while the tumor temperature is maintained at the desired level. The impact on the temperature distribution of shifting the patient in axial direction differs from changing phases and amplitudes. By shifting the patient the electric field distribution of the individual fields is changed while those under phase/amplitude steering obviously remain unchanged. In addition shifting the patient in axial direction can be a way to treat patients that under standard positioning have insufficient length to be treated with two rings. The results of figure 3.3 and figure 3.8 show that positioning accuracy in the axial direction should be within 1 – 2cm for both the AMC-4 and AMC-8 system. If this accuracy is achieved differences in target temperature remain within $0.25 - 0.5^\circ C$. These are substantial differences compared to the increase in target temperature heating with the AMC-8 instead of the AMC-4 system. Canters et al. (36) found that for the 2D BSD-2000 Sigma 60 system, shifting the patient in the positive $z$-direction (equivalent to the shifting of the applicator in negative $z$-direction) and applying optimized settings for standard positioning reduced the hot-spot target quotient (HTQ) for which they presented a strong correlation with the target $T_{50}$. Similar behaviour is not observed in our study since, by optimizing directly for temperature, changing the position while not adjusting the settings is expected to make tumor heating less effective. However, it is observed for the AMC-4 system that if the temperature distribution is optimized for varying axial positions, for patients 1, 2, 4 and 5 (figure 3.8) a shift in caudal direction of 2cm (4cm is optimal for patient 5) causes an increase in $T_{50}$. This shift corresponds
to an applicator shift of 2cm as discussed in (36).

Figure 3.9 addresses the question whether the variable ring-to-ring distance (RRD) provides a useful extra degree-of-freedom in the optimization of the thermal dose. As the figure illustrates small, patient specific, differences are found when changing this distance. For patients 1 and 4 relevant improvements were found while for patients 2, 3 and 5 the standard RRD was either the best choice or improvements were very small (< 0.1°C). Given the computational costs associated with including this parameter in the optimization procedure (those increase with a factor of 4), a standard RRD of 1.5cm was considered to be acceptable. Moreover, the uncertainties currently present in HTP render it questionable whether relative small improvements can be predicted accurately for individual patients.

The variable ring-to-ring distance is a unique feature of the AMC-8 system. However, when designing multi-ring systems a choice has to be made as well for the axial spacing of the antennas. Extrapolating our results, in general the impact on heating efficacy will be minor and other requirements such as limiting applicator coupling might have priority.

In our study the patient model is based on the automated segmentation of a CT scan resulting in only a limited number of tissue types. The accuracy of the segmentation in terms of dielectric and thermally alike tissues/tissue types is however expected to influence the predicted temperature distribution. However, hot-spots are dominantly located at interfaces of bone, fat, and muscle tissue i.e. high dielectric contrast, in the superficial fat layers (sufficiently deep for cooling to be ineffective) and in the proximity of bony structures due to resonance effects. These hot-spots are expected to dominate the optimization result. The purpose of our study is to compare two different systems based on patient models that are representative for the population and hence the used level of detail in our study is considered appropriate.

The volume of the patient that is heated with both the AMC-4 as well the AMC-8 system is relatively large compared to the target volume since these systems are loco-regional hyperthermia devices. The consequences for thermal modeling when large volumes are heated are presently unclear. All thermal modeling done was based on Pennes’ bio-heat equation that is particularly suited for the modeling of small scale heating problems where arterial pre-heating is expected to be absent. Whether heating of such large volumes can still modeled accurately is unclear. Van den Berg et al. (34) studied the modeling of vascular heat transfer for prostate hyperthermia. They concluded that pre-heating in the arteries feeding the prostate vasculature can be neglected whereas accurate thermal modeling requires including the prostate vas-
culature. Based on the equilibration length, increasing the heated volume by heating with eight versus four antennas is not expected to cause important differences.

Another effect, not covered in the simulations is the increase in systemic temperature (67). As shown, a major increase of power is required, and moreover feasible, when heating with eight antennas. As shown in figure 3.5, the total power absorbed in the patient to realize the optimized temperature distribution for the AMC-8 system was in the range of 752 – 927W as compared to 468 – 607W for the AMC-4 system. This is also reflected in figures 3.6 and 3.7, showing that the heated volume is significantly larger for the AMC-8 system. This may result in an extra increase of the systemic temperature that has an important impact on the heat transfer via the vasculature and for example lead to an additional increase in $T_{90}$. To relate the increase of power to an increase in systemic temperature further clinical data has to be acquired.

3.5 Conclusions

Loco-regional hyperthermia treatment with the 3D AMC-8 system can lead to a clinically relevant increase of the target temperature compared to treatment with the 2D AMC-4 system. The $T_{90}$ and $T_{50}$ of the target increased with $0.5^\circ$C but with large patient variability. The additional power required to realize this increase ranged from 36 to 71% of the power required for the AMC-4 system. Ring-to-ring distance is of minor importance but should be known for proper optimization within 2cm. For the AMC-8 system, the achievable thermal dose is stable over a range of $-8$cm to $+8$cm shifting the patient in caudal – cranial direction. Axial position should be known within 1 – 2cm both for the AMC-4 and the AMC-8 system.

Acknowledgements The work described in this article was financially supported by the Dutch Cancer Society (grant UVA 2004 3834).