Stellingen:

Het aantal invasieve temperatuursensoren is nooit genoeg en altijd teveel.

De combinatie van een korte broek en een doktersjas geeft aanleiding tot misverstanden.

27 MHz "ridged waveguides" zijn niet geschikt voor loco-regionale diepe hyperthermie in een plan-parallelle opstelling.

Het weer is net zo voorspelbaar als de minimale maximum temperatuur tijdens een hyperthermiebehandeling.

Stoorstraling dient niet verward te worden met strooistraling.

Diepe hyperthermie is alleen mogelijk met intensieve koeling.

Het huidige prototype van de ringapplicator vormt een goed basismodel voor verdere ontwikkeling van elektromagnetische applicatoren voor loco-regionale hyperthermie in het bekken.

Het bereiken van 'therapeutische' temperaturen (41-43 °C) in het bekken van een varken is geen garantie dat dit bij mensen ook lukt. Met andere woorden ook een varken is geen mens.

De goede resultaten van behandeling met radiotherapie in combinatie met hyperthermie bij zowel oppervlakkige thoraxwandrecidieven van borstkanker als bij inoperabele rectum-, blaas- en baarmoedertumoren rechtvaardigen de opname van deze behandelingssomaliteit in het gezondheidszorgpakket.

De modale Nederlandse patiënt is te adipeus om geschikt te zijn voor capacitiëve hyperthermie.

De tijd die een projectleider krijgt om te antwoorden op een verzoek van de projectbeoordelingscommissie is omgekeerd evenredig met de tijd die de commissie nodig heeft om het antwoord te beoordelen.

Gezien de frequentie waarmee openbare bestuurders misbruik maken van hun positie en het aantal politieke debatten over een paar tienden van procenten meer over minder is het ongepast de burger een verwijt te maken over het vervagen van zijn normen en zijn calculator gedrag.

De uitspraak "the burden of proof still lies on those who claim any biological action of high frequency currents other than heat production" van Christie en Loomis uit 1929 is nog steeds actueel.

G.C. van Rhoon, 3 mei 1994
RADIOFREQUENCY HYPERTHERMIA SYSTEMS

Experimental and clinical assessment of the feasibility of radiofrequency hyperthermia systems for loco-regional deep heating
RADIOFREQUENCY HYPERThERMia SYSTEMS

Experimental and clinical assessment of the feasibility of radiofrequency hyperthermia systems for loco-regional deep heating

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Technische Universiteit Delft,
op gezag van de Rector Magnificus Prof. Ir. K.F. Wakker,
in het openbaar te verdedigen ten overstaan van een commissie,
door het College van Dekanen aangewezen,
op dinsdag 3 mei 1994 te 10.30 uur
doors

GERARD CORNELIS VAN RHOON
natuurkundig ingenieur (HBO)

geboren te Hendrik Ido Ambacht
Dit proefschrift is goedgekeurd door de promotoren:
prof. dr. ir. P.M. van den Berg
prof. dr. H.S. Reinhold

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aan mijn ouders
aan Ien en Martijn
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6.1.1 The ring applicator system

6.2 Evaluation of the ring capacitor plate applicator for regional deep heating

6.3 Ring capacitor applicator: predicted energy distributions in a fat-muscle layered model for different ring electrode configurations

6.4 Radiative ring applicator: Energy distributions measured in the CDRH phantom

Chapter 7 Experimental assessment of electric impedance tomography integrated with the ring applicator

Chapter 8 Conclusions

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Summary

Samenvatting

Curriculum vitae
"Around the magnet Faraday
Was sure that Volta's lightnings play,
But how to draw them from the wire?
He drew a lesson from the heart:
'Tis when we meet, 'Tis when we part,
Breaks forth th' electric fire."

*Herbert Mayo, 1890.*
Chapter 1
Introduction

1.1 Thermobiology

Hyperthermia is defined as a temperature elevation by several degrees (3-7 °C) above the normal physiological level. Under normal physiological conditions no difference exists in the thermal sensitivity between normal cells and tumour cells. However, tumours are often characterized by an inadequate vascularization which results in a poor supply of blood and nutrients to some tumour areas. As a consequence, tumours contain hypoxic areas where the inherent low pH and nutrient deprived micro-environment sensitize the tumour cells to hyperthermia [Overgaard, 1977; Wike-Hooley et al., 1984].

The effectiveness of hyperthermia, i.e., the amount of cell kill, depends both on the temperature and the duration of temperature elevation. For temperatures above 42.5-43.0 °C the duration of the treatment can be decreased by a factor two per 1 °C increase of temperature to obtain similar cell kill. For temperatures below 42.5 °C this factor varies from four to six [Field, 1988]. Due to the heterogeneous blood flow in the tumour it will not be possible to increase the temperature of all tumour cells without overheating the normal tissue [Reinhold, 1987, 1988]. Thus, hyperthermia cannot be considered as an effective single modality for treatment of cancer.

The combination of hyperthermia with radiotherapy or chemotherapy appears to be ideal: the tumour cells in the inadequately perfused areas are more likely to survive after radiotherapy and chemotherapy, whereas such tumour cells can be killed selectively by hyperthermia. Moreover, as blood flow is an important part of the cooling mechanism, the less perfused areas may be heated more easily [Cater et al., 1964] when non-invasive heating techniques are used. Additionally, normal tissue responds to a heat load by a substantial increase of the local blood flow, whereas the blood flow increase of tumour tissue is limited or negative [Reinhold and Endrich, 1986; Reinhold, 1988; Reinhold and Van den Berg, 1990]. This would further increase the temperature gradient between tumour and normal tissues.

For more details about the underlying biology the reader is referred to extensive reviews published by Streffer and Van Beuningen [1987] and Overgaard [1989]. Recent summaries on several aspects of hyperthermia can be found in: An introduction to the practical aspects of clinical hyperthermia, edited by S.B. Field and J.W. Hand [1990].
1.2 Clinical hyperthermia studies

Clinical research in local hyperthermia has now been performed for two decades. It started with studies on patients with superficially located tumours who had failed to respond on a number of standard treatments. Table 1.1 shows the data of various non-randomized clinical "matched lesions" studies which indicate that hyperthermia in addition to a series of radiotherapy indeed does improve therapeutic results. Despite the fact that many of these studies will have suffered from a poor quality of heating due to the limitations of the first generation hyperthermia equipment, the clinical outcome shows a substantial and consistently increased complete response rate for the combined treatment modality.

Table 1.1. Comparison between radiotherapy (RT) and radiotherapy plus hyperthermia (RT + HT) in "matched lesions" [van der Zee et al., 1988].

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tumour histology</th>
<th>Complete response(^1) change following treatment with</th>
<th>Significant difference(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>RT + HT</td>
</tr>
<tr>
<td><em>Kim and Hahn [1979]</em></td>
<td>Various(^3)</td>
<td>7/28</td>
<td>25%</td>
</tr>
<tr>
<td><em>U et al. [1980]</em></td>
<td>Various</td>
<td>1/7</td>
<td>14%</td>
</tr>
<tr>
<td><em>Kim et al. [1982]</em></td>
<td>Malignant melanoma(^4)</td>
<td>25/54</td>
<td>46%</td>
</tr>
<tr>
<td><em>Scott et al. [1983]</em></td>
<td>Various(^4)</td>
<td>12/31</td>
<td>39%</td>
</tr>
<tr>
<td><em>Arcangeli et al. [1984]</em></td>
<td>Various</td>
<td>28/74</td>
<td>38%</td>
</tr>
<tr>
<td><em>Li et al. [1984]</em></td>
<td>Various(^4)</td>
<td>9/31</td>
<td>29%</td>
</tr>
<tr>
<td><em>Gonzalez Gonzalez et al.</em> [1986]*</td>
<td>Malignant melanoma</td>
<td>3/7</td>
<td>43%</td>
</tr>
<tr>
<td><em>Overgaard and Overgaard [1987]</em></td>
<td>Malignant melanoma</td>
<td>2/10</td>
<td>20%</td>
</tr>
<tr>
<td><em>Marchal and Bey [1987a]</em></td>
<td>Various</td>
<td>7/60</td>
<td>12%</td>
</tr>
<tr>
<td><em>Lindholm et al. [1987]</em></td>
<td>Various(^4)</td>
<td>7/28</td>
<td>25%</td>
</tr>
<tr>
<td><em>Howard et al. [1987]</em></td>
<td>Various</td>
<td>7/21</td>
<td>33%</td>
</tr>
<tr>
<td>All authors</td>
<td></td>
<td>108/351</td>
<td>31%</td>
</tr>
</tbody>
</table>

\(^1\) Complete response: tumour has totally disappeared; \(^2\) Difference significant according to Fisher's exact test with 2p<0.05; \(^3\) Malignant melanoma excluded; \(^4\) Large tumours combined treatment; small tumours radiotherapy alone.
The non-randomized character of these studies precludes, however, a definitive conclusion about the enhancement of tumour control by adding hyperthermia to radiation therapy. The first randomized trial for superficially located tumours was started in 1981 by the Radiation Therapy Oncology Group of the USA [Perez et al., 1989]. In 1985, this study was followed by three randomized trials on locally advanced unresectable breast cancer, neck nodes, and metastatic malignant melanoma, initiated and controlled by the European Society of Hyperthermic Oncology [Arcangeli et al., 1988]. In later years the encouraging higher response rates obtained with the combined treatment modality of radiation plus hyperthermia, together with the improved quality of heating offered by newly developed hyperthermia systems led to the start of several other randomized trials. A common problem associated with all randomized trials is the accrual of a sufficient number of patients. As a result several trials are still open for intake far beyond the estimated closing date. Some trials, however, have reached the required number of patients and have been analysed on the clinical outcome. Table 1.2 gives an overview of the results of the randomized trials which have been completed and analysed on the value of addition of local hyperthermia to a standard radiotherapy regimen. As with the "matched lesions" studies the results of the randomized studies point in the same direction: addition of hyperthermia to radiation therapy improves tumour control and/or cure rate. Additionally, all authors report comparable acute and late toxicity in both treatment arms, except for a higher incidence of thermal blisters in the patient group treated with hyperthermia.

The importance of adequate heating techniques is illustrated by the analysis of the randomized study of the Radiation Therapy Oncology Group. Perez et al. [1989; 1991] hypothesized that the complete response rate for patients with smaller chest wall tumours was higher than that for larger tumours, 62% versus 21%, because the smaller tumours were easier to heat adequately. Other authors [Myerson et al., 1990; Van der Zee et al., 1992] were also able to demonstrate a positive correlation between the quality of the hyperthermia technique and the treatment outcome. Perez et al. [1989; 1991] also found in their patient population a higher probability of sustained tumour control after induction of a complete regression. For patients with tumour lesions smaller than 3 cm the probability (p) to remain in complete response at 12 months after the start of treatment was significantly (p = 0.02) higher for patients treated by radiotherapy plus hyperthermia than for those treated by radiotherapy alone, 82% and 12%, respectively.

In conclusion, for a number of selected tumour sites hyperthermia can be considered to be a valuable supplement to the established treatment modalities, radiotherapy and chemotherapy, in cancer therapy if adequate techniques are available. For a definitive conclusion with regard to the site specific improvement of
tumour control to be expected from the addition of local or loco-regional hyperthermia to a standard series of radiotherapy, the available data are considered insufficient by the hyperthermia community. The common feeling is that only after a number of the presently still active randomized studies have been closed and properly analysed, definitive conclusions about the value of hyperthermia can be made. In the mean time, continuous development and evaluation of prototype heating systems is essential to obtain a range of 'site-specific' hyperthermia devices.

Table 1.2. Comparison of the results of radiotherapy (RT) versus radiotherapy plus hyperthermia (RT + HT) in randomized trials.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tumour</th>
<th>Endpoint</th>
<th>number of patients</th>
<th>RT</th>
<th>RT + HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berdov and Menteshashvili [1990]</td>
<td>Rectum carcinoma</td>
<td>local control</td>
<td>115</td>
<td>27%</td>
<td>55%</td>
</tr>
<tr>
<td>Datta et al. [1990]</td>
<td>Head &amp; Neck</td>
<td>complete response rate 18 months NED(^1) survival</td>
<td>65</td>
<td>32%</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19%</td>
<td>33%</td>
</tr>
<tr>
<td>Datta et al. [1987]</td>
<td>Uterine cervix</td>
<td>2 years NED(^1) survival</td>
<td>52</td>
<td>46%</td>
<td>67%</td>
</tr>
<tr>
<td>Overgaard et al. [1993]</td>
<td>Melanoma</td>
<td>1 year local NED(^1) 2 years local NED(^1)</td>
<td>134</td>
<td>28%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28%</td>
<td>48%</td>
</tr>
<tr>
<td>Perez et al. [1991]</td>
<td>Various</td>
<td>complete response rate overall small tumours(^2)  large tumours(^3)</td>
<td>236</td>
<td>30%</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55</td>
<td>39%</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>181</td>
<td>27%</td>
<td>25%</td>
</tr>
<tr>
<td>Savchenko [1987]</td>
<td>Advanced breast</td>
<td>stage II 2 years local NED(^1) stage III 2 years local NED(^1) 5 years survival</td>
<td>507</td>
<td>75%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>64%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>67%</td>
<td>73%</td>
</tr>
<tr>
<td>Sharma et al. [1989]</td>
<td>Uterine cervix</td>
<td>18 months local NED(^1)</td>
<td>50</td>
<td>50%</td>
<td>70%</td>
</tr>
<tr>
<td>Strotsky et al. [1991]</td>
<td>Urinary bladder</td>
<td>3 years survival</td>
<td>102</td>
<td>67%</td>
<td>94%</td>
</tr>
<tr>
<td>Valdagni et al. [1988]</td>
<td>Head &amp; neck</td>
<td>complete response rate 3 years local NED(^1) 3 years survival</td>
<td>44</td>
<td>41%</td>
<td>83%</td>
</tr>
<tr>
<td>Valdagni et al. [1990]</td>
<td></td>
<td></td>
<td></td>
<td>23%</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7%</td>
<td>41%</td>
</tr>
</tbody>
</table>

\(^1\) NED: no evidence of disease; \(^2\) tumour diameter <3 cm; \(^3\) tumour diameter \(\geq\)3 cm.
1.3 Methods to induce hyperthermia

Clinical application of hyperthermia can be categorized at three levels:

*Whole-body hyperthermia*

The core temperature of the patient is raised to 40.5-42.0 °C for a period of 1 to 2 hours. Presently, clinical use of whole-body hyperthermia is mainly limited to the combination with other systemic therapies, e.g., chemotherapy. Additionally, whole-body hyperthermia is considered to be used in combination with loco-regional deep hyperthermia. In the latter case, the objective is that a moderate whole-body hyperthermia of 40.0-40.5 °C will reduce the thermal gradients within the body, which will increase the minimum tumour temperature.

*Regional hyperthermia*

The organ or the extremity in which the tumour is located, is heated to 42.0-43.0 °C. Well known techniques are regional isolated perfusion of limb or arm and intraperitoneal irrigation. Clinical use is limited to the combination with chemotherapy.

*Local hyperthermia*

With local hyperthermia the aim is to heat the tumour to a temperature as high as possible (above 43 °C), while keeping the temperature of the normal tissue below 43 °C. Generally, local hyperthermia is divided in:

- local superficial hyperthermia: the heating of tumours located within 4 cm depth of the body surface, and
- loco-regional deep hyperthermia: the heating of large tumours located centrally in the body or extending to depths of more than 4 cm.

Local hyperthermia is most often applied in combination with radiotherapy, although there is a growing interest in the combination of local hyperthermia with chemotherapy. The variety in tumour location inside the body and the size and geometry of the tumour has resulted in the development of many techniques using either ultrasound or non-ionising electromagnetic radiation to induce heat within the human body. The fact that in the pioneering years electromagnetic systems could be built at relatively low costs, by using electromagnetic generators available from the physical therapy departments, explains the preferential use of electromagnetic hyperthermia systems by many institutes.

1.4 Progress of hyperthermia techniques at the Dr. Daniel den Hoed Cancer Center

In the Dr. Daniel den Hoed Cancer Center, clinical research on hyperthermia started in 1978. The original design was to induce whole-body hyperthermia up to a maximum tolerated level, and to administer additional local heating to the tumour by electromagnetic energy. This approach had to be abandoned after the first patient
treatment, during which it became apparent that unacceptable toxicity may occur. This is due to the fact that whole-body hyperthermia, induced by using the "Pomp-Siemens" cabin, requires general anaesthesia and that local heating in an anaesthetized patient is risky due to unnoticed local hot spots [Van der Zee et al., 1983]. In 1983, whole-body hyperthermia was abandoned in the Dr. Daniel den Hoed Cancer Center after 27 patients had been treated. From the clinical experience three conclusions can be drawn: 1) hyperthermia does induce tumour regression, 2) the patient received benefit from the treatment only if whole-body hyperthermia was combined with radiotherapy, and 3) the toxicity of whole-body hyperthermia could be unacceptably high. It was therefore decided to concentrate further on the development of local hyperthermia in combination with radiotherapy for tumour sites with unsatisfactory prognosis in terms of local control.

For superficial hyperthermia the research programme has resulted in the development of a multi-applicator multi-generator system, operating at 433 MHz, with which tumours at depths of maximally 4 cm over a surface area of maximally 400 cm² can be heated to therapeutic temperatures.

The development of systems for deep heating, however, progressed much slower, and was partially exceeded by developments elsewhere. From 1983, the RCA 27 MHz ridged waveguides have been tested on their feasibility to induce localized deep heating. In 1987, a 13.56 MHz capacitive hyperthermia system, HTM3000P, was added to the instrumentation. Parallel with the experimental and clinical evaluation of these two deep heating systems, which were available from the industry, the development of the ring applicator system was started. The results of this research, as described within this thesis, indicated that the best possibilities of achieving loco-regional deep heating with electromagnetic waves are to be expected from radiative devices, like the ring applicator, which are able to generate a circumferential electric field distribution around the patient.

In 1988, the BSD-2000 deep heating system with the Sigma-60 applicator was presented in Europe and offered promising perspectives for deep heating. At the same time, the Dutch government announced the possibility of funding Investigative Medicine programmes. As the BSD-2000 system was developed along the same interference principle as the ring applicator and as it was already available as a clinical hyperthermia system, it made sense to redirect a part of our research programme towards the clinical evaluation of this system. Early 1990, the BSD-2000 deep heating system was installed in the Dr. Daniel den Hoed Cancer Center. In June 1990, a randomized trial in patients with large tumours in the pelvic area was started to establish the value of loco-regional deep hyperthermia in addition to a standard series of radiotherapy. In this study, the BSD-2000 system is used to apply the loco-regional deep heating treatment. Since then, over 100 patients have been treated.
1.5 Objectives and outline of the thesis

Since the introduction of hyperthermia, research has been directed primarily at the development of techniques to apply and control hyperthermia. Nevertheless, the clinical application of local hyperthermia is still limited by the inability to deposit the energy selectively in the tumour.

As explained, the thermal dose is determined by the elevation of the temperature and the time at this elevated temperature. Hence, important demands to be fulfilled by a hyperthermia system are (a) it must be able to deposit energy selectively at depth and (b) the discomfort and stress caused by the system must be tolerable to the patient for a long period. In practice, a trade-off between these two considerations is unavoidable with each loco-regional deep hyperthermia system. As will be explained in Chapter 2, an applicator with a circumferential electric field distribution around the patient will give high energy absorption at depth. However, the water bolus around the patient, essential to couple the energy from the antenna to the patient, is very uncomfortable to the patient and decreases the treatment tolerance. On the other hand, the more 'patient friendly' hyperthermia systems like the capacitive devices, are known to have less favourable energy deposition at depth.

The purpose of the study reported in this thesis was to evaluate the deep heating characteristics of three electromagnetic hyperthermia systems:

(1) the RCA 27 MHz ridged waveguides system,
(2) the HTM3000P capacitive hyperthermia system, and
(3) a ring applicator system.

The course of the thesis is such that the reader is first informed about the general aspects involved with loco-regional deep heating. Chapter 2 provides an introduction to the different techniques available for loco-regional deep hyperthermia and includes an estimation to where the current level of art has progressed. Further, it gives the basic principles of electromagnetic heating and a description of the advantages and disadvantages of the various approaches used to induce loco-regional hyperthermia by electromagnetic devices. It will be explained that no ideal hyperthermia system exists. Chapter 3 describes practical methods, of which some have been used in this study, available to characterize a hyperthermia applicator. Additionally, knowledge about the energy and temperature distribution in dependence of body anatomy, blood flow, and the electromagnetic field applied can be obtained by theoretical modelling, which is reviewed in the second part of Chapter 3. This chapter ends with a summary about the relevance of thermometry and the problems involved with the measurement of temperature during a hyperthermia treatment.

Chapters 4-6 report results obtained during the last decade of the hyperthermia research programme within the Dr. Daniel den Hoed Cancer Center to study the clinical feasibility of deep heating.
Chapter 4 concerns the work on the RCA 27 MHz ridged waveguides. From 1983 until 1990 the ridged waveguides have been tested, either as a single waveguide or in a combination of two waveguides, on their feasibility of deep heating. At the low operating frequency (27 MHz) of this applicator the penetration depth of electromagnetic waves is large. The main advantage of this system is its simplicity: theoretically, deep heating could be achieved by the use of only two waveguides radiating in a parallel opposed arrangement and in phase. To reduce the size of the waveguide to clinically manageable dimensions it must be loaded with deionized water. However, reducing the aperture of a waveguide is known to affect the penetration depth. The objective of the study with this applicator was to investigate how much the penetration depth was reduced and whether the waveguides could be operated in a parallel opposed set-up in such a way that sufficient energy was deposited at depth.

Chapter 5 reports about the work performed with the HTM3000P capacitive hyperthermia system. Advantages of capacitive devices are their simplicity, easiness of handling, good access to the patient, and small and 'patient friendly' applicators. Well-known disadvantages are the excessive heating at the edges of the electrodes and the preferential heating of the fatty tissue. However, the use of salt water bolus in front of the electrodes and extensive pre-cooling can to some extent reduce the effect of these disadvantages. The aim of this study was to investigate the effect of these measures on the resulting deep heating capabilities of the commercial HTM3000P capacitive hyperthermia system for a selected group of patients.

Chapter 6 reports about the ring applicator, designed and developed at the department of Hyperthermia. The original purpose of this study was to develop a capacitive type of applicator, operating at low frequencies (27 MHz), but with the electric field directed primarily along the axis of the tissue cylinder enclosed by the ring electrodes. It was expected that in this way preferential fat heating could be avoided. Furthermore, as the electromagnetic energy is coupled capacitively, the electrodes do not need to be in contact with the tissue and patient discomfort might be avoided. From theoretical considerations it appeared that the principle of the ring electrodes should work also at higher frequencies and the objective was adapted to develop a ring applicator with (a) deep heating feasibilities based on the interference principle, (b) the ability to customize the energy distribution, (c) good access to the patient, (d) a broad frequency range and (e) the possibility to integrate additional measuring equipment in the gap between the ring electrodes, e.g. electric impedance tomography. The latter is demonstrated in Chapter 7.

The conclusions from the studies described in this thesis are given in Chapter 8, followed by a discussion on the current clinical status and present research to improve the quality of loco-regional deep hyperthermia.
Chapter 2
Loco-regional deep hyperthermia

2.1 Introduction

Ideally a hyperthermia system for treatment of deep-seated tumours would be able to deposit the majority of the power in the periphery of the tumour and around the major vessels. Moreover, the system should be simple and safe, cause no systemic stress and provide good access to the patient during treatment, preferably by not requiring contact with the body surface.

In reality, effective power deposition at depth with the aim to heat the entire tumour volume to therapeutic temperatures without overheating normal tissue appears to be quite difficult. In fact, for many hyperthermia systems there are fundamental reasons associated with the physics of these devices that renders such an objective not achievable for many tumour sites. With these challenging requirements in mind, a number of hyperthermia systems have been developed using either ultrasound or electromagnetic radiation to heat tumours located more than 4 cm from the body surface. Each system has specific characteristics that may greatly influence the tumour and normal tissue temperatures obtainable, and consequently the resulting tumour response and toxicity.

In Chapter 2.2 a summary will be given of the characteristics and problems involved with the various non-invasive electromagnetic techniques available for deep hyperthermia systems. The ultrasound and interstitial or intracavitary methods will be briefly summarized below to provide an impression of the deep heating feasibilities of these techniques.

Important physical advantages of ultrasound [Hunt, 1990; Hynynen et al., 1992] over electromagnetic heating techniques are the low absorption coefficient and the short wavelength in human tissues which enables highly focused energy deposition at depth. Thus, ultrasound penetrates deeper into the body than electromagnetic radiation and the highly localized power deposition makes that of all non-invasive hyperthermia systems developed for loco-regional deep heating only ultrasound has the potential to deposit the energy at selective locations within the tumour volume. The clinical use of ultrasound is, however, cumbersome due to two distinct physical
disadvantages: reflection of waves at interfaces between soft tissue and air or bone, and high absorption in bone. Especially with the early single, stationary, and planar ultrasound transducer designs these problems resulted in many of the clinical treatments in limiting normal tissue heating or pain [Corry et al., 1988; Hynynen et al., 1989; Kapp et al., 1988; Shimm et al., 1988]. Presently, the use of a well-focused ultrasound beam which is scanned rapidly, by mechanical or electrical means, across the tumour to generate an improved temperature distribution is investigated [Ibbini and Cain, 1990; Moros et al., 1990; Hand et al., 1992]. The premise is that if the ultrasound beam is scanned rapidly near the periphery of the tumour and the large vessels, thermal conductivity and blood flow will produce a homogeneous temperature distribution throughout the whole tumour volume.

The rationale to use interstitial hyperthermia is based on the fact that it has the ability to give highly localized and controllable heating. The disadvantage of the required invasive procedures with interstitial hyperthermia can be eliminated if interstitial hyperthermia is used as an adjuvant treatment modality in combination with interstitial brachytherapy. In this particular situation interstitial hyperthermia can be added without a fundamental change in application method: the catheters or needles implanted are utilized not only for positioning the radioactive sources but also for the introduction of hyperthermia applicators or - in the case of needle implants- directly as electrodes for resistive heating of the implanted volume. There are three general methods of interstitial hyperthermia used to produce well-localized heating of tumour volumes at depth in the body:

- radiofrequency localized current field technique, frequency range 0.5 to 27 MHz. Energy transfer is obtained either by direct galvanic contact between tissue and electrode (500 kHz) or through a capacitive coupling between the implanted wire electrode and the surrounding tissue (27 MHz).
- radiative techniques. Microwave antennas are used for their compatibility with brachytherapy procedures using plastic catheter. At frequencies above 300 MHz the radiative behaviour of the antenna becomes dominant and heating is obtained by the absorption of electromagnetic energy in the surrounding tissue.
- hot source technique. The tissue is heated by thermal redistribution of heat from implanted arrays of essentially equal temperature hot sources. Well-known hot source techniques are inductively heated ferromagnetic thermoseeds, hot-water tubes and resistance wires.

For more details on the underlying principles of interstitial and intracavitary hyperthermia the interested reader is referred to reviews on interstitial heating techniques by Stauffer [1990], Hand et al. [1991], and the Task Group Report of the ESHO "Interstitial and Intracavitary Hyperthermia" [Visser et al., 1993].

With respect to clinical treatments it should be realized that good hyperthermia
equipment does not guarantee a good hyperthermia treatment. Besides the obvious fact that the treatment should confirm to clinically realistic quality assurance and assessment demands, it should also be noted that a highly motivated and experienced staff is an absolute requirement to obtain the best clinical outcome for the patient.

Finally, for clinical use the merits of all deep heating methods currently used will depend strongly upon the precise location of the tumour. In absence of a universal heating system, continuation of development and clinical evaluation of new systems is mandatory in order to obtain a range of "site-specific" hyperthermia systems. Meanwhile, the limitations of each method should be kept well in mind.

2.2 Electromagnetic hyperthermia

2.2.1 Electromagnetic energy absorption

A good understanding of the basic principles of classical electromagnetics is essential for the design and implementation of hyperthermia systems. The purpose of this paragraph is to give a brief summary of the important electromagnetic principles and relationships pertinent to hyperthermia.

The interaction of the electromagnetic field with biological material is determined by the electric permittivity and magnetic permeability. Since the magnetic permeability of biological material is essentially equal to that of free space, the magnetic losses will be negligible. The electric permittivity of biological material, however, varies greatly with tissue type and with the frequency\(^1\) of the electromagnetic field and is expressed as:

\[
\varepsilon = \varepsilon_0 (\varepsilon' - j \frac{\sigma}{\omega \varepsilon_0}) = \varepsilon_0 (\varepsilon' - j \varepsilon'')
\]

where \(\varepsilon'\) and \(\varepsilon''\) are the real and imaginary parts of the complex relative permittivity \(\varepsilon_r\), respectively.

Electromagnetic energy is transferred to the material by polarization and rotation of dipolar molecules, and drift of electrons and ions. The amount of energy transferred by the electric field to a material can be derived from Poynting’s theorem and the average power transferred to the material is given by:

\[
P = \frac{1}{2} \sigma |E|^2
\]

where \(E\) is the complex electric field vector, and \(\sigma\) is the electric conductivity.

\(^1\) Considered are time harmonic fields with time factor \(\exp(j \omega t)\), in which \(\omega = 2\pi f\) is the angular frequency.
For hyperthermia the energy absorption in a material is often normalized to its mass density and is then called the specific absorption rate (SAR):

$$SAR = \frac{1}{2\rho} \sigma |E|^2.$$

The equation for the SAR shows that the energy absorption is directly proportional to $\sigma$ and thus indicates how lossy a material is. In general biological tissues can be divided in two groups: tissues with high water content like muscle, skin, and visceral organs, or tissues with low water content like fat and bone. The 'wetter' a tissue is, the more lossy it is. Table 2.1 shows typical values of $\varepsilon'$, $\varepsilon''$, $\sigma$, and $\tan \delta$, defined as $\varepsilon''/\varepsilon'$, at a number of frequencies for tissues with high and low water content. From Table 2.1 it can be seen that the values of $\varepsilon'$ and $\varepsilon''$ for the low water content tissues are one order of magnitude lower than those of the high water content tissues. With regard to the wide range of values for the low water content tissues it should be noted that relatively small variations in the water content of these materials will result in significant changes in $\varepsilon'$ and $\varepsilon''$. The quantity $\tan \delta$ is called the loss tangent and gives the -frequency dependent- relationship between the conduction currents and the dielectric displacement currents. For example, in tissues with high water content conduction currents give the major contribution to tissue heating when the frequency is below 400 MHz, whilst the role of displacement currents becomes dominant at higher frequencies.

Apart from the dielectric properties of the tissues, the conditions the electric

<table>
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<th>Table 2.1. Dielectric properties of tissue at various frequencies</th>
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<td><strong>Frequency (MHz)</strong></td>
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<tr>
<td><strong>Wavelength $\lambda$ (cm)</strong></td>
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<td>$\varepsilon'$</td>
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<tr>
<td>$\varepsilon''$</td>
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<tr>
<td>$\sigma$ (S/m)</td>
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<td>$\tan \delta$</td>
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<td><strong>Penetration depth (cm)</strong></td>
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Data after Johnson and Guy [1972]; for tissues with low water content the maximum value for $\varepsilon''$ is presented and used to calculate wavelength, $\sigma$, $\tan \delta$, and the penetration depth.
field has to satisfy at the boundary of two materials, media 1 and 2, are important factors for the resulting energy absorption. If the direction of the electric field is normal to the interface between the two materials, the boundary condition demands that the electric flux density $D$ is constant, thus

$$\varepsilon_1 E_1 = \varepsilon_2 E_2$$

In the case medium 1 is fat ($\varepsilon_i = \varepsilon_r$, $\sigma_i = \sigma_r$) and medium 2 is muscle ($\varepsilon_j = \varepsilon_m$, $\sigma_j = \sigma_m$), the ratio of the SAR becomes:

$$\frac{SAR_f}{SAR_m} = \frac{\sigma_r \rho_m |\varepsilon_m|^2}{\sigma_m \rho_f |\varepsilon_f|^2}$$

Using the values of $\varepsilon_r$, $\varepsilon_m$, and $\varepsilon_m$ from Table 2.1 and using $\rho_f = 940$ kg/m$^3$ and $\rho_m = 1070$ kg/m$^3$, it follows that

$$\frac{SAR_f}{SAR_m} = 12$$

and thus the SAR in fat is approximately one order of magnitude larger than that in muscle.

In the situation the direction of the electric field is parallel to the tissue interface between the two materials, the boundary condition demands that $E$ is continuous across the boundary, thus

$$E_1 = E_2$$

In this situation, again with medium 1 being fat and medium 2 being muscle, the ratio of the SAR is equal to the ratio of the electric conductivity of both tissues, i.e.,

$$\frac{SAR_f}{SAR_m} = \frac{\sigma_f}{\sigma_m}$$

Using the appropriate values for the electric conductivity it follows that

$$\frac{SAR_f}{SAR_m} = 0.07$$

and now the SAR in muscle is much larger than that in fat.

For the clinical application of hyperthermia the situation will not be as explicit as in the above-mentioned examples. Generally, with capacitive hyperthermia systems the main direction of the electric field will be perpendicular to the fat-muscle
transition and the ratio between fat and muscle SAR explains the preferential heating of fat tissue. With radiative hyperthermia systems, where the direction of the electric field is parallel to the body axis, the situation is more complex. In front of the aperture the direction of the electric field will be mainly parallel to the fat-muscle interfaces with associated high energy absorption in muscle. At depth, however, tissue transitions can have all directions and there both situations described above will occur!

2.2.2 Non-invasive electromagnetic hyperthermia systems

The frequency range of the electromagnetic radiation used for hyperthermia is rather small and it does not make sense to classify the various heating techniques by frequency, as is common within the field of communication. Instead, for medically used non-ionizing electromagnetic radiation it is more meaningful to classify the various applicators according to the physical principle involved in establishing the electric field.

Generally, applicators operating at low frequencies where the wavelength is large compared to the tissue dimensions \((L/\lambda < 1)\) are called quasi-static devices. With these devices the frequency is so low that the distribution of currents or fields is completely determined by Laplace’s equation and there is no propagation or a wave effect. The currents within the body tissue are produced by external metallic electrodes which are coupled inductively or capacitively. Characteristic for quasi-static devices is that the current distribution is more or less frequency independent, mainly determined by the geometrical arrangement of the applicators. For all capacitive and many inductive hyperthermia systems the power distribution is determined by the quasi-static electric field distribution.

The other major class of applicators is called the radiative devices and encompass radiating apertures, such as open-ended waveguides, horns, slots, etc. and some inductive applicators. Essential for this applicator class is that the size of the radiating aperture or the current loop with the inductive applicators is not negligible compared to the wavelength. In this case, the Maxwell equations have to be solved in order to obtain the electric field distribution. For these applicators the resulting field distributions are strongly affected by the frequency and usually cannot be calculated easily. However, by applying simplifying approximations some qualitative understanding can be obtained which may be valuable in guiding experimental design and interpretation of the experimental results.

To obtain a sufficient penetration depth the electromagnetic heating systems have to operate at low frequencies, range 10 to 120 MHz. A physical consequence of this restriction is that the "focal spot size" will be large. Therefore, in contrast to the ultrasound systems, selective tumour heating with electromagnetic deep heating
systems can only be obtained when the tumour blood flow is low compared to that of the surrounding normal tissue [Strohbehn et al., 1989; Wust et al., 1991]. Advantageous for electromagnetic systems is that the problems with air and bone are less severe than for ultrasound systems. However, depending on the electromagnetic applicator type used, the transition between tissues with low and high permittivity may cause significant changes in the local SAR. This in turn may result in localized hot spots in normal tissue which are often power limiting and thus result in a lower thermal dose within the tumour. The specific characteristics of these three classes of external electromagnetic applicators will be discussed in the next paragraphs.

**Inductive hyperthermia systems**

The inductive applicator in its simplest form is the single loop concentric coil, as illustrated in Figure 2.1. The RF current in the loop produces a primary magnetic field that is mostly axial and nearly uniform in the central part of the loop and secondary a concentric electric field which on its turn induces the currents necessary to heat the tissue. Since the body is essentially non-magnetic, it does not strongly perturb the magnetic field generated by the applicator, and as the electric field component is very weak, the permittivity does not affect the coupling very much. Hence, inductive applicators have the advantage that tuning and performance is not very sensitive to the body position. Other advantages of the inductive applicators are the direction of the electric field which is mostly parallel to the fat-muscle interface and, as no water bolus is required to improve energy coupling, the inductive applicator is rather easy to use. However, a disadvantage is that the magnitude of the electric field is proportional to the radial distance from the axis. As the power deposition is proportional to $|E|^2$, it will be clear that there is no power deposition at the centre of the tissue cylinder or patient and maximum power deposition at the surface.

The Magnetrode as developed by Storm et al. [1981] was the first clinical
hyperthermia system using the single current loop to induce heat. Although in the clinical situation the shape of the human body and its inhomogeneities will modify the power deposition pattern, the low power deposition at the centre of the body will remain. The latter has been demonstrated by several authors in both clinical [Oleson et al., 1983a; Oleson, 1984; Samulski, 1989; Sapozink et al., 1985] and theoretical [Strohbehn et al., 1986] studies. From these studies it appeared that use of the current loop applicator should be restricted for hyperthermia of eccentrically located tumours.

The major feature of inductive applicators is that they do not require the use of a water bolus. Pressure of the water bolus is experienced by many patients as the most stressful part of the hyperthermia treatment. Therefore, more advanced inductive applicators have been designed by several research groups (see Figure 2.2). If a single loop current applicator is modified to a multi-loop applicator, it changes to the helical coil applicator as developed by Ruggera and Kantor [1984]. With the helical coil applicator multiple coils are formed cylindrically around the body to be heated (Figure 2.2a). The number of coils, the length of the helix, and the operating frequency is chosen such that resonance occurs. In this particular situation, the current through the coils induces a homogeneous longitudinal magnetic field in the body. Additionally, due to the potential difference between the first and last coil (resonance situation) a longitudinal electric field is created within the body. Heating occurs now by both the azimuthal and longitudinal component of the electric field which results in a more homogeneous energy distribution at the centre of the body, as found by several groups [Ellinger et al., 1989; Hagmann, 1985, 1987]. A different approach with a multi-loop applicator is to split the coil in two parts and to place the body to be heated in the gap [Oleson et al., 1983b]. With this so-called coaxial coil applicator a longitudinal magnetic field is induced perpendicular on the surface of the body of the patient (Figure 2.2b). As with the single loop applicator, a zero power deposition exists at the centre of the applicator. However, with this design the
applicator can be moved around the treatment volume and by an appropriate
scanning algorithm a homogeneous power deposition might be obtained. In clinical
studies, it appeared that this principle of heat induction performs well when applied
to deep-seated tumours in the thorax, but heating of tumours in the pelvis is poor
due to local pain [Corry et al., 1988; Corry and Jabbour, 1989]. The open-mode RF
toroid applicators as developed by Francozi [1987] operate similar to the coaxial coil
applicator; however the method used to create the necessary magnetic field is
different.

Capacitive hyperthermia systems

A capacitive hyperthermia system can be considered as composed by the
electrodes of a capacitor and is simply excited by applying an RF electric potential
across the electrodes. Figure 2.3 shows a schematic example of a set-up for a
capacitive hyperthermia system. Characteristic for this device is that the direction of
the electric field is nearly always perpendicular to the fat-muscle interface.
Therefore, as explained in the chapter on electromagnetic energy absorption, heating
of deep tissues by this system will be restricted by the preferential heating of the sub-
cutaneous fatty tissue. Additionally, excessive heating at the edges of the electrodes
will occur due to the high density of the electric field at this site. On the other hand,
features like simplicity, easy handling, good access to the patient, and absence of
systemic stress were convincing arguments for a number of research groups to
develop methods to oppose the treatment limiting effects of preferential fat heating
and edge effects.

Numerous solutions have been suggested to reduce the edge effects and
preferential fat heating. Sugaar and LeVeen [1979] were the first to suggest a
capacitive system with multiple (six) condenser plates. With their system, the
condenser plate pairs are energised crosswise, such that the central volume at depth
would be heated by three condenser plate pairs, while superficial tissues in front of
each plate would be heated only during one third of the time period. Insufficient
isolation between the condenser plates resulted in a large amount of cross-talk
between adjacent condenser plates with associated local hot spots and made the
principle fail. Sidi et al. [1982] have developed a more sophisticated system using a
similar principle. Their condenser system consists of three electrodes and by an
improved amplifier design they are able to control both phase and amplitude per
electrode. In this way, the group claims that their system possesses the ability of
SAR-steering. Experimental studies [Nussbaum et al., 1986] indicate the feasibility
to modify the vertical SAR distribution, but at the mid-depth little or no change of
the SAR distribution could be obtained. Furthermore, preferential heating of the
fatty tissue in front of the electrodes remains a limiting factor.
With regard to reduction of preferential fat heating and excessive heating at the edge of the electrodes in the clinical situation, the best results have been obtained with the following, simple measures:

1. The use of large electrodes. The diameter of the electrodes should be at least equal to the largest distance between the electrodes [I.A. Brezovich, personal communication, 1986].

2. The use of a chilled, salt water bolus. With extensive (pre-)cooling of the subcutaneous fatty tissue it will be possible to increase the temperature of the tumour located at depth to a higher level before the critical temperature of the fatty tissue (44-45°C) is reached. As thermal conduction is the driving force of cooling it will be clear that the depth to where the cooling is effective will be limited. In fact, the fat layer should not exceed a thickness of 2 cm [Hiraoka et al., 1987a; Kato et al., 1985]. The edge effects can be minimized by adding 1 gram NaCl per litre to the water bolus [Reddy et al., 1987].

Using these measures to oppose preferential fat heating and the edge effect, Japanese researchers [Abe et al., 1986; Hiraoka et al., 1984, 1987a,b; Nishimura et al., 1986; Song et al., 1986] have demonstrated that RF capacitive heating has the ability to obtain therapeutic temperatures in deep-seated tumours in clinical situations. Temperatures above 42 °C at the deepest spot of the tumour (>7 cm) were obtained in about 60% of the treatments, which is the same percentage as reported for the first radiative annular phased array system of BSD. In contrast with the annular phased array system, however, the RF capacitive system can be used also for the treatment of lung tumours. Tachibana et al. [1986] reported to obtain temperatures of 43 °C in lung tumours in 5 out of 6 patients.

At present, the clinical use and commercial production of the capacitive hyperthermia systems is concentrated in the Asiatic countries. This is mostly explained by the observation that the physique of the Asiatic patients is generally more suitable for a capacitive hyperthermia system than that of European or American patients.
Radiative hyperthermia systems

Based on the frequency dependent penetration depth, electromagnetic radiation at frequencies below 100 MHz seems to offer the best possibilities to achieve loco-regional deep heating in a non-invasive manner. The most simple approach is to use a waveguide or other radiating device operating at such a low frequency that the penetration depth of a single aperture is large enough to obtain sufficient energy deposition at the centre of the body. Examples of this approach are the 27 MHz ridged waveguide systems of RCA [Paglione et al., 1981] and of Sairem [Marchal et al., 1984, 1985]. At the operating frequency of these systems the plane wave penetration seems large enough to expect the ability to therapeutically heat a tumour in the pelvis. In order to obtain a clinically manageable applicator, the waveguides are dielectrically loaded with water. The reduction in aperture size, however, gives rise to the occurrence of fringing electric fields at the aperture of the applicator and consequently, a substantial reduction of the effective penetration is to be expected.

If, however, the energy deposition at depth of a single applicator is not large enough to obtain therapeutic heating, a logical and simple step is to increase the number of applicators around the body. For the incoherent case the energy deposition at the centre of the body is proportional to the sum of the squares of the electric fields of each applicator:

\[ P_{\text{incoherent}} = \sigma \left( \sum |E|^2 \right) \]

Maximum increase of energy deposition at depth is obtained if the applicators are operated coherently with the direction of the electric field parallel with the body axis. In this situation constructive interference between the electric field of the various
applicators exists and the energy deposition at the centre of the body will be proportional to the square of the sum of the electric fields of all applicators:

$$P_{\text{coherent}} = \sigma \left( \sum |E| \right)^2$$

Most of the radiative devices currently under consideration for clinical application of loco-regional deep hyperthermia generate a circumferential electric field distribution around the patient, directed parallel to the body axis and use the interference principle to achieve high power deposition at the centre of the body with minimal heating of the subcutaneous fat tissue (Figure 2.4). Well known among these systems are the BSD-1000 with 16 waveguides [Turner, 1982, 1984] and the BSD-2000 with 8 dipole applicators of BSD [Turner, 1988; Turner and Schaefermeyer, 1989], the coaxial TEM applicator [Lagendijk, 1983; De Leeuw and Lagendijk, 1987], and the "four-waveguide" system as developed by Van Dijk et al. [1989, 1990]. Differences between these devices exist in operating frequency (BSD-2000 variable frequency range 60-120 MHz versus single frequency 70MHz), the number of applicators used (16, 8, 1, and 4 respectively) and the "ability to control" the location of the focal volume.

The BSD-1000, also called the annular phased array system, was the first clinically available system using the interference principle. It consists of two adjacent circular arrays, with each array containing eight waveguide applicators. Important disadvantages of this first generation deep heating device were the lack of phase and amplitude control per applicator and the severe discomfort experienced by the patient from the integrated water bolus. In 1988 the BSD-1000 was succeeded by the BSD-2000 system. The BSD-2000 deep hyperthermia system uses the Sigma-60 applicator which consists of eight dipole antennas mounted in a transparent, Lucite shell of 60 cm diameter. In the design of the Sigma-60 applicator special attention has been given to reduce the discomfort of the patient and to incorporate the ability to perform SAR-steering. Per set of two dipole antennas the phase and amplitude can be changed by remote control.

The coaxial TEM applicator is unique concerning its open water bolus: due to the lack of water pressure on the skin of the patient a better treatment tolerance is expected. The coaxial applicator can be used over a broad frequency range. Unfortunately, with the coaxial TEM applicator the access to the patient during the hyperthermia treatment is very difficult and any visual inspection of the target area is impossible.

The four-waveguide system of Van Dijk et al. [1989, 1990] uses four-waveguides placed around the patient and is now commercially available through the Lund Science Company (Lund Variphase 5000 deep hyperthermia system). During the development special attention has been paid to the design of the waveguides and the
integrated water bolus. The system has been designed to operate at a single frequency, i.e., 70 MHz.

Schneider et al. [1994] have recently compared the deep heating characteristics of the coaxial TEM, the BSD-2000, and the four-waveguide system. They found that the three systems induced identical SAR-distributions within a homogeneous, elliptical phantom when the systems were operated at 70 MHz.

Besides the radiative systems for loco-regional deep hyperthermia mentioned above, several other systems, such as the CDRH helix [Shimm et al., 1989], the movable multi-applicator phased array [Raskmark and Andersen, 1984; Danish Hyperthermia Foundation, 1987], the ring applicator system [Franconi, 1987; Van Rhoon et al., 1988, 1990], and the DTS00 deep hyperthermia system [Borani et al., 1992] are presently under development or being evaluated on their clinical applicability.

The necessity and the feasibility of SAR-steering to customize the energy distribution, in order to optimize the temperature distribution have been demonstrated clinically and theoretically by several groups [Howard et al., 1986; Samulski et al., 1987; Sathiaselvan, 1986; Strohbehn et al., 1989; Wust et al., 1990, 1991]. Especially for the treatment of eccentrically located tumours the optimization techniques are of great value. For centrally located pelvic tumours high SAR gradients are present within the tumour, with maximum SAR induced in the flank and hip region, and less improvement may be expected from SAR steering. In this situation and in the case of rather thick patients heating at a low frequency (30-60 MHz) might be beneficial.
Chapter 3
Methods to evaluate the characteristics of hyperthermia applicators

3.1 Introduction
The energy distribution induced by an electromagnetic applicator is influenced by many parameters. As mentioned in Chapter 2, these parameters are amplitude, frequency, and polarization of the applied electric field together with the dielectric properties, size, and anatomy of the patient. Additionally, to limit the hyperthermia treatment to a localized region of the body it is required that the applicator is in close proximity to the body surface. The latter means that the body is often exposed to the near field of the applicator. In this area it is difficult to predict the complex electric field distribution of the applicator accurately and experimental assessment of the hyperthermia characteristics of an electromagnetic applicator will help to increase the knowledge about the feasibility to heat a specific tumour location. It will be clear that if the information obtained from the experimental phantom studies can be supplemented with theoretical modelling, a better choice can be made for the proper heating technique. Eventually, the combination of applicator characterization and theoretic modelling may lead to the so much wanted hyperthermia treatment modelling per individual patient. Until then control of the SAR steering and evaluation of the quality of the thermal dose delivered to the treatment volume will depend solely on the information obtained from the invasive thermometry used during each hyperthermia treatment. In this chapter each of these three fields is briefly summarized including an indication to where the field has progressed.

3.2 Characterization of the performance of electromagnetic applicators by phantom studies
The objective of phantom studies would be an accurate characterization of the complete vector field of an electromagnetic applicator, that is, the experiment must provide information about the amplitude, phase, and polarization of the electric field with a sufficient spatial resolution in the lossy media of the phantom. In practice, this
information is only partially obtained and there are two measuring methods available.

The first and most commonly used method of measuring the electric field is to determine the rate of change of temperature (dT/dt) after a short period of heating at high power, i.e., such that the temperature increase is determined only by the amount of absorbed energy. Under this condition, the SAR at any point in the phantom can be calculated from the temperature rise through:

$$\text{SAR} = c \frac{dT}{dt} = \frac{1}{2 \rho} \sigma |E|^2$$

where $c$ is the specific heat of the phantom material. As explained in Chapter 2.2 the SAR is also proportional to the square of the electric field and the local conductivity, and inversely proportional to the mass density. Essential for this method to measure the SAR distribution is that the experiments must be performed within a short time interval to minimize artifacts due to thermal conduction. A good estimate about the distance to where thermal conduction affects the temperature distribution can be obtained from the heat penetration depth into a uniform infinite half space:

$$x = \sqrt{\frac{\pi \lambda t}{\rho c}}$$

where $\lambda$ = thermal conductivity [W/m/°C]; $c$ = specific heat capacity [J/kg/°C]; $\rho$ = mass density [kg/m³], and $x$ = distance [m], that is, the depth at which the temperature differs by approximately 20% of the temperature increase from the initial temperature $T_0$. Clearly, the demands on the heating time will vary with the required spatial resolution for the measurement of the SAR distribution. For loco-regional deep heating a spatial resolution of 5 mm is often sufficient and heating times from 1 to 5 minutes are acceptable.

An old and accurate method is to measure the temperature distribution by infrared thermography using the split phantom technique [Guy, 1971]. This method requires the use of a solid, gelled phantom which can be split in two parts at the plane of interest. The exposed, two-dimensional temperature distribution can be measured quickly by an infrared-thermographic camera. Over the years several other methods have been introduced to replace the costly infrared-thermographic camera and to allow the SAR measurements in anatomically alike, non-homogeneous structures. Similar to infrared thermography, the use of liquid crystal sheets in combination with a colour photographic camera provides also two-dimensional information about the temperature distribution in a predetermined plane. The temperature distribution can be measured also by temperature sensors which are
scanned through the phantom. The disadvantage of this method is, however, that after each power pulse the temperature distribution in the phantom should be allowed to return to steady-state values. Consequently, the measurement of the SAR distribution over the whole plane of interest will be a time-consuming procedure. An advantage of the power-pulse technique using temperature probes is that it can also be used during the clinical treatment and thus provides a way to correlate measured SAR with predicted SAR at some selected sites in the body. Whether the temperature distribution is measured by infrared thermography, liquid crystal, or temperature sensors, caution should be exercised that the measuring technique does not disturb the SAR distribution [Hand, 1990; Schaubert, 1984]. The SAR distribution measured by temperature rise provides only information about the total intensity of the electromagnetic field per unit volume and not about the polarization of the electric field. By introducing layers of different phantom material in front of the applicator some information can be obtained about the relative strength of the tangential and perpendicular components of the electric field.

The second method to obtain information about the SAR distribution is to use miniature probes which measure the electric field directly. Typically, an electric field sensor can be divided in three sections: (1) the receiving antenna; (2) the cables to transport the measured signal; and (3) the instrument to analyse and present the information. Although many different antenna types [Bassen and Smith, 1983] are available, a miniature dipole antenna is most commonly used to measure the electric field. If the proper conditions for the phantom set-up are met (coaxial cable perpendicular on electric field to minimize perturbation), information can be obtained about amplitude and phase of the electric field. In this case the signal of the dipole antenna should be transmitted by a balanced coaxial cable to a vector voltmeter or a network analyser. In other situations the coaxial cable arrangement may cause significant disturbance of the electric field distribution. If no information about the phase of the electric field is needed, it is a common procedure to place a diode at the base of the dipole and to measure the resultant DC-voltage. Normally, carbon loaded Teflon leads are used to transport the DC-signal to the measuring unit [Bassen et al., 1975; Raskmark and Gross, 1987]. Alternatively, one may use a light-emitting diode (LED) and fibre-optic techniques to measure the signal [Bassen et al., 1977]. Both, carbon loaded Teflon leads as well as optic fibres have the advantage that they do not disturb the electric field distribution.

As the dipole antenna is predominantly sensitive to one polarization of the electric field, all three (x, y, and z) polarizations must be measured to obtain the entire electric field. Hereto, the dipole needs to be placed parallel to the direction of the electric field polarization of interest, which may not always be easy to achieve. If the dipole is, however, placed at an angle of 54.7 degrees to the axis of the probe
(corresponding to the angle of a line from the origin to the point (1,1,1) with any of the three axes x, y, z), three simple rotations of the probe over 120 degrees can resolve the entire electric field [Raskmark and Gross, 1987].

Until now only the BSD Medical Corporation [Turner, 1988] has been successful in developing an electric field probe with a diameter smaller than 1 mm, i.e., small enough to fit in standard thermometry catheters. In order to reduce the diameter of the electric field probe, insulation of the probe and the surrounding tissue consists only of a thin layer of shrinking tube material. Disadvantages of a thin insulation layer are that the sensitivity of the electric field probe is dependent upon the dielectric permittivity of the tissue surrounding the probe and that interaction errors due to the proximity of tissue boundaries [Bassen and Smith, 1983] are increased. Gopal et al. [1994] have recently developed an electric field probe capable to measure both the amplitude and phase of the electric field at frequencies of 434 and 915 MHz. They incorporated a thick insulating layer of low dielectric permittivity around the probe, resulting in a response error due to the surrounding media of less than 5%.

All electric field probe techniques mentioned so far only provide information about a single site in the phantom. Automated scanning techniques have been introduced to measure the SAR pattern of a whole plane but even then the experiment requires long periods of measurements. To overcome this problem Schneider and Van Dijk [1991] have developed a matrix of 137 light-emitting diodes (LED) to visualize the electric field distribution over a whole cross-section of an elliptical phantom. The leads of the LED’s form the dipole of the electric field probes as described above. The advantage of the LED matrix is that the effect of changing phase relation, amplitudes, or position of the applicators can be observed instantaneously.

Finally, to perform phantom studies, materials are needed to simulate human tissue. Several extensive reviews [Chou, 1987; Hand, 1990] have been published describing the many recipes available to construct liquid or solid phantoms in detail. The tissue equivalent materials used in the experiments of this study are described in the sections of materials and methods of Chapters 4, 5, and 6.

3.3 Treatment planning

Treatment planning for hyperthermia is still in its infancy when compared to radiation treatment planning [Hand, 1990; Paulsen, 1990; Roemer, 1990]. The growing ability of present hyperthermia systems to adapt the energy distribution, by phase and amplitude steering, to the individual patient situation forms an important reason for the increased interest in treatment planning during the last decade. To exploit the ability to customize the SAR distribution one needs to have a-priori knowledge of the SAR distributions which can be obtained with the different settings of phase and
amplitude. The problem of treatment planning for hyperthermia is conceptual, however, a very difficult task and requires powerful computer facilities. Traditionally it has been a two-step process: (1) to compute the heating rate or power deposition patterns produced in the body by the heating source, and (2) to compute the redistribution of energy due to thermal conduction and blood flow [Paulsen, 1990]. For the development of the theoretical models these two steps are decoupled, though it should be noted that for evaluation of predicted temperature distributions the two simulations must remain coupled. In an early review Roemer and Cetas [1984] identified four categories within the field of hyperthermia treatment planning: (1) comparative, (2) prospective, (3) concurrent, and (4) retrospective hyperthermic dosimetry. Comparative dosimetry is mainly used to compare the energy distribution induced by different heating devices using the same phantom and under similar conditions. The last three concepts refer to the prediction of temperature distributions in a specific patient using specific heating devices. These predictions have the purpose to evaluate the thermal dose delivered to the treatment volume with the aim to start with (prospective) or - if performed in real time - to maintain the optimal applicator configuration (concurrent). In the case of retrospective dosimetry the purpose is to improve the information about the thermal dose delivered within the tumour and to correlate this thermal dose with the clinical outcome. From extensive reviews [Lagendijk, 1990; Hand, 1990; Paulsen, 1990; Roemer, 1990] it is clear that major problems must still be solved before prospective, concurrent, or retrospective treatment planning can become routine practice.

With regard to thermal modelling no consensus exists on the best formulation of the equations describing the thermal problem. The conventional bioheat transfer equation has been used for most thermal modelling during the last 40 years. It neglects, however, (1) heat transport related to the mass transport of blood, (2) the actual temperature of the blood entering the local tissue volume, (3) the individual cooling of discrete large vessels, and (4) the venous vessel network by assuming an infinite thermal equilibrium length for all venous vessels. Several problems with regard to the complexity of tissue blood flow, the lack of information on vessel network properties of individual patients, and the considerable difficulties in designing the computational models, need to be solved before the actual thermal dose distributions applied in a clinical treatment can be predicted [Lagendijk, 1990].

For electromagnetic modelling the situation is more positive with regard to the comparative concept. At present, electromagnetic modelling is used in power absorption studies to compare the performance of different heating techniques. In an extensive review Paulsen [1990] has summarized the mathematical methods used to solve Maxwell’s equations. The current status of treatment modelling is such that it is clearly understood that the general problem to be solved is three-dimensional
and that the major limitation of the two-dimensional models is that they neglect the effects of the finite size of the radiating aperture. In numerical approaches [Hagmann and Levin, 1986; Hagmann, 1987; Lau and Sheppard, 1986; Van den Berg et al., 1983; Van Putten and Van den Berg, 1986; Visser et al., 1987] to predict the SAR distributions for an inhomogeneous medium it has been shown that ignoring the third (longitudinal) dimension introduces severe errors and tends to result in an optimistic prediction of the energy distribution. At present, several three-dimensional theoretical models are beginning to appear [Hornsleth et al., 1989; Sowinski and Van den Berg, 1990; Sullivan, 1991; Wust et al., 1989; Zwamborn and Van den Berg, 1992; Zwamborn et al., 1992] but their use is still limited to model studies. An important issue to address in the near future is the verification of the validity of the models used. As mentioned before, three-dimensional electromagnetic modelling requires powerful computer resources. In a recent publication Sullivan [1991] described two promising mathematical methods to facilitate three-dimensional modelling:

1. "superposition of electric fields". For each dipole quadrant of the Sigma-60 applicator the complex electric field distribution within the body is calculated separately and stored on disc. The total electric field within the body is obtained by superposition of the complex electric field of all four quadrants. To investigate the effect of phase and amplitude steering only the total electric field for each set of amplitudes and phases is calculated, simply by repeating the superposition procedure, a process that can be performed rapidly on a work-station.

2. "impulse response". This method is used to illuminate the body with a more complex wave-form than a single frequency sinusoid. A fast Fourier transform is used to extract the information on phase and amplitude for the frequencies of interest.

Finally, hyperthermia treatments are performed daily all over the world without three-dimensional treatment planning, indicating that the question to be addressed by treatment planning remains as formulated by Roemer [1987]: "Will it help to improve the quality of the hyperthermia treatment?" This question is difficult to answer. With regard to three-dimensional electromagnetic modelling it will be clear that optimization and parameter sensitivity studies will increase knowledge and understanding of the applicator characteristics. Ultimately, however, the question must be answered in relation to the results of clinical treatments. In this situation an adequate answer cannot be given before significant improvements in both the monitoring of the temperature distribution with high precision and spatial resolution in the whole treatment volume (tumour as well as normal tissue) and the ability to predict three-dimensional temperature distribution are obtained.

3.4 Thermometry and thermal dosimetry

Invasive thermometry is an essential part of each hyperthermia treatment. It pro-
vides the important clinical data necessary to control SAR-steering during the clinical treatment, to perform "thermal dose"-response studies, and to evaluate and compare the performance of heating systems. Under clinical circumstances the quality of the measured temperature distributions is critically dependent on the accuracy of the thermometry system and the distribution of the temperature measuring points over the treatment volume. Parameters with impact on the quality of measurement are the number of probes, their spacing, and their location. Temperatures measured at the periphery of the tumour specifically add to a better quality of measurement.

During the last decades good progress has been made with regard to thermometry. Unfortunately, all non-invasive thermometry methods, like electric impedance imaging, active microwave imaging, or microwave radiography are still in an experimental stage and used by a few research groups only [Conway et al., 1992; Bolomey and Hawley, 1990]. Therefore, invasive thermometry using electric or optic temperature probes is still a necessity. The principal errors due to electromagnetic and ultrasound interference or thermal conduction involved with these probes are well understood and described in detail in extensive thermometry reviews [Cetas, 1990; Samulski and Fessenden, 1990].

Commonly, thermocouple based thermometry systems are preferred because they are inexpensive (USD 50), while offering durability and very good specifications on accuracy, resolution and stability under laboratory conditions. Errors in temperature readings due to electromagnetic interference during clinical use is the main disadvantage of thermocouple systems. With the well-known power-pulse technique and placement of the thermocouple perpendicular to the direction of the electric field, these errors [Carnochan et al., 1986] can be minimized. The time interval between power off and temperature reading forms the critical part in the power-pulse technique. In situations where the probes cannot be placed perpendicular to the direction of the electric field, a small tissue cylinder surrounding the thermometry catheter might be heated preferentially, due to electromagnetic-interference. In these cases the generally used time interval of 3 seconds needs to be increased substantially before the measured temperature in the catheter is a good representative of the real tissue temperature [Chan et al., 1988].

Compared with thermocouple devices the important advantage of thermometry systems using fibre-optic or thermistors with high impedance leads is their immunity for strong electromagnetic fields. Bowman probes -thermistors using high impedance leads- [Bowman, 1976] are known for their accuracy and stability. Disadvantages of these probes are the limited length of the high impedance leads and the high costs per probe (USD 2000). To less extent, fibre-optic thermometry is also associated with high costs (USD 300). The important advantage of immunity to the electromagnetic radiation, the continuous improvement on accuracy, stability and time constant, and
the design of more cost effective read-out systems are convincing arguments for many hyperthermia groups to use fibre-optic thermometry.

As a consequence of the current tendency to use complex hyperthermia systems to heat large tumour volumes the demands on thermometry are growing continuously. One way to improve the information on the temperature distribution is to increase the density of temperature measuring points along the invasive catheter track by thermal mapping. This raises the question whether the sampling sites in the tumour tissue are sufficiently representative for the whole of the tumour mass. This problem has not yet really been solved. The number of thermometry probes within the treatment area is limited by the number of thermometry catheters which can be placed invasively within the treatment field. When using catheters which stay in place during a treatment series, the anatomy and movement patterns of adjacent body parts may restrict the localization of the catheters. The criteria for quality assurance guidelines as formulated by the Radiation Therapy Oncology Group [Dewhirst et al., 1990] and the European Society of Hyperthermic Oncology [Hand et al., 1989] can almost never be met. Furthermore, a tumour inevitably has a chaotic vessel network and the blood flows randomly through the tumour. Consequently, if multiple sampling sites for thermometry are employed, the apparent efficiency may decrease because the probability that one or more probes indicate the normal temperature of the inflowing blood, rather than that of the tumour tissue, increases with the number of sensors. It has been demonstrated from clinical data that the minimum temperature is strongly correlated with the number of temperature probes [Corry et al., 1988; Perez and Emami, 1989]. Therefore, present thermal dose studies address the question how to convert the crude indication of the temperature distribution into a single and valid descriptive parameter of the thermal dose delivered to the tumour. In practice this requires a method using various weight factors to integrate the large amount of information about temperature and probe distribution into a single thermal dose parameter [Edelstein et al., 1989; Engler et al., 1989; Clegg and Roemer, 1989; Corry et al., 1988; Dewhirst et al., 1987; Field, 1988; Oleson et al., 1989; Sim et al., 1984].

In summary, good progress has been made on thermometry methods and thermal dosimetry. However, during the clinical application of hyperthermia the operator must still rely on a coarse indication of the temperature distribution from a few temperature sampling sites and the sensitivity to feel warmth and pain by the patient.
Chapter 4
The RCA 27 MHz ridged waveguide system

4.1 Introduction

Since 1980 various techniques have been investigated to apply hyperthermia to deep-seated tumours (see Chapter 2). A straightforward and as it seemed at that time a technically simple approach was to use one or two radiative applicators with a large penetration depth. To obtain the required penetration depth it is necessary to choose the operating frequency of the waveguide as low as possible. For plane wave electromagnetic fields the penetration depth (i.e., the depth at which the electric field strength is reduced by a factor 1/e) decreases with increasing frequency and is given by [Townes and Schawlow, 1955]:

\[ d = \frac{1}{\omega \sqrt{\varepsilon \mu}} \left[ \frac{1}{2} \left( 1 + \left( \frac{\sigma}{\omega \varepsilon} \right)^2 - \frac{1}{2} \right) \right]^{-\frac{1}{2}} \]

where \( \omega \) is the angular frequency of the electromagnetic field, \( \mu \) is the magnetic permeability, \( \varepsilon \) is the electric permittivity, and \( \sigma \) the electric conductivity. Typical values for muscle are: \( d = 14.3 \) cm at 27 MHz and \( d = 1.3 \) cm at 2450 MHz. Apart from the frequency dependence of the penetration depth also the size of the radiating aperture is important: if the size of the aperture becomes small with respect to the wavelength in the irradiated medium, the penetration depth decreases with respect to the plane-wave penetration depth [Turner and Kumar, 1982]. This argues for a large aperture size, but on the other hand the dimensions should be such that the applicators can still be handled conveniently in a clinical setting.

With these considerations in mind a 27 MHz ridged waveguide was developed by Paglione et al. [1981]. Two-dimensional modelling by Van den Berg et al. [1983] demonstrated that two applicators operating at 27 MHz in a parallel opposing set-up, radiating in-phase, could deposit sufficient energy in a tumour located at the centre of the body to heat it to therapeutic levels (Figure 4.1). Based upon these encouraging results the ridged waveguides were selected for further evaluation.
Figure 4.1. Model of a cross-section of the human pelvis (a) and the computed temperature increase (b) with respect to 37 °C. Each number gives the temperature increase per square element (0.5 x 0.5 cm) of tissue; a dot indicates a temperature below 37 °C due to skin cooling. Total absorbed electromagnetic power per unit length in the axial direction of the body is 1600 W/m and time of irradiation is 24 minutes. The positions of the two parallel opposed waveguides at the ventral and dorsal side of the pelvis are indicated. The aperture fields are taken to be constant with equal amplitude and phase [Van den Berg et al., 1983, 1984].
From 1983 until 1989 the ridged waveguides have been tested, either as a single applicator or in a combination of two waveguides, regarding their feasibility for deep heating. As this study was performed over a long period, experimental work on phantoms progressed, after some time parallel with animal experiments and the clinical use of the waveguides. The experience of these latter activities was used to adapt the course of the experimental work. In the following chapters the results of the experimental and clinical studies will be reported. Firstly, the construction and the characteristics of the waveguides are described and secondly, the results of the study are described in a part concerning single waveguide applications and a part concerning the operation of the waveguides in a parallel opposed set-up.

4.2 RCA 27 MHz ridged waveguides

The main advantage of ridged waveguides is the lower cut-off wavelength for the TE_{10} mode with respect to conventional rectangular waveguides of the same internal dimensions. The properties and design criteria of ridged waveguides, as used outside the hyperthermia field, have been described by Chen [1957], Cohn [1947], Hopfer [1955], Mihran [1949], and Utsumi [1985]. The dimensions of the ridged waveguide applicator as developed by Paglione et al. [1981] are indicated in the lower part of Figure 4.2a. The waveguide has been manufactured by RCA Laboratories. It has a total surface area of 58.5 x 26.5 cm² with the area opposite the ridge measuring 29 x 13.7 cm² and a height of 86 cm. According to Paglione et al. [1981] most of the RF energy in the waveguide, 80%, is concentrated within the area opposite the ridge. In the original design of the RCA ridged waveguide a 5 cm thick bag for deionized water is integrated with the applicator to spread the high electric fields at the edge of the aperture. Additionally, a special, 2 cm thick, salt water bag is delivered with the waveguide. The purpose of this salt water bag is to limit energy absorption in the patient predominantly to the area opposite the ridge. The salt water in the bag should absorb most of the RF energy radiated by the aperture, except at the area opposite the ridge where a hole in the salt water bag exists.

Two different waveguides have been used in this study: a straight one and one with a 90 degree bend. The waveguides are shown in Figure 4.2b. The design of the bended waveguide should facilitate the use of two applicators in a parallel opposed or cross-fire arrangement. It was anticipated that the use of two waveguides, radiating in-phase, in a parallel opposed or cross-fire arrangement would produce a more advantageously absorbed power distribution for heating of deep-seated tumours. The waveguide is made from stainless steel and is constructed in three segments. The straight and 90 degree bended waveguide differ only in the top segment. Each waveguide segment is filled with deionized water. Power input is provided by either an ENI A-500 amplifier (500 W) or an adapted Curamed 419
Figure 4.2. The 27 MHz ridged waveguides: (a) schematic drawing with the dimensions of the waveguide; (b) a photograph showing both the straight and bended waveguide. Note the three tuning stubs for impedance matching.
generator (700 W; 50Ω; Enraf Nonius). Both forward and reflected power are measured with Bird Thruline Watt meters.

4.2.1 Waveguide characteristics

Each compartment of the waveguide is filled with deionized water and all air is removed; the total weight of a filled waveguide is 115 kg. At regular time intervals, the water in each compartment is filtered until an electric conductivity below 0.4 μS/m is measured. In the course of time the water becomes slowly polluted by metal-ions. In our situation, the electric conductivity increased from 0.4 μS/m to 0.8 μS/m in two months. An increase of the electric conductivity of the water to 2 μS/m results in a decrease of the efficiency of the waveguide by 10 per cent.

Three tuning stubs are provided for impedance matching. Before tuning each stub is maximally withdrawn and cleaned thoroughly with alcohol to provide a good electric contact between the stub and the waveguide. After a suitable load has been placed in front of the aperture, impedance tuning is obtained by slowly pushing the lower and upper stub into the waveguide. The lower and upper stub are used for coarse tuning and the stub in the middle is used to fine tune the impedance of the waveguide to obtain a reflected power below 10%. Large variations in reflected power occur with changes in the stub position of only a few millimetres. The optimal stub position is dependent on the load at the aperture. In general, better tuning is obtained with large phantoms. When the waveguides are operated at high power the temperature of the lower stub and the water in the lower compartment will increase due to a strong electric field around the tuning stub. With temperature changes the

<table>
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<tr>
<th>Tuning stub position 1 [cm]</th>
<th>Radiating efficiency [%]</th>
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<tr>
<td>A</td>
<td>B</td>
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<td>4.0-4.2</td>
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<td>3.7</td>
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<td>3.5-3.8</td>
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<tr>
<td>9.4-9.5</td>
<td>1.75-2.0</td>
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1 Length of the tuning stub outside the waveguide; measured from the nut to the top of the stub. During the experiment the water temperature in the waveguide increased causing a change in impedance which explains the range for the tuning stub position.
permittivity of the water will change and additional tuning of the waveguide impedance is required. This explains the rather unstable behaviour of the waveguide.

Impedance matching can be obtained with multiple combinations of the three tuning stub positions. Using the straight waveguide the effect of the stub positions upon the waveguide performance has been studied for three different combinations, as shown in Table 4.1. It appeared that the temperature distribution measured within the muscle equivalent phantom (distributions not shown but method described in Chapter 4.2) was not affected, although the maximum temperature increase varied between the experiments. The latter was in accordance with the results of calorimetric experiments in which a salt water phantom covering the whole aperture was heated at maximum power for 1 hour. The average temperature increase of the water volume is used to calculate the absorbed energy. The amount of energy coupled to the phantom varied between 66% and 83% of the net input energy at the coaxial connection measured by the Bird power meters. Pollution of the water was also found to have no effect on the temperature distribution in the phantom.
4.3 Single waveguide

The feasibility of the single waveguide to induce deep heating was evaluated using phantom and theoretical studies followed by an experimental testing of the waveguide on animals. Subsequently, the single waveguide has been used for clinical hyperthermia treatment of semi-deep tumours.

4.3.1 SAR distributions and temperature depth profiles measured in heterogenous phantoms

As mentioned before, the penetration depth in muscle equivalent tissue of a 27 MHz electromagnetic field radiated by a waveguide is affected by the size of the aperture. To obtain maximum penetration the size of the aperture should be comparable to the wavelength of the electromagnetic field in the irradiated medium. In the case of the ridged waveguides this condition is not met. For muscle tissue the wavelength of a 27 MHz electromagnetic field is about 68 cm compared to an effective aperture size of the ridged waveguide of 29 cm. The objective of the experimental study reported in this chapter was to investigate the influence of the shape and size of the aperture on the SAR patterns, to estimate how much the penetration in muscle-equivalent tissue is reduced, and to investigate, using inhomogeneous phantoms, whether the fringing fields will give rise to excessive heating in layers of fatty tissue.

Materials and methods

The phantom consisted of multiple rectangular sections, with the circumference of each section contained in a Lucite box measuring $63 \times 31.5 \times 20$ cm$^3$. During the experiments it was checked carefully that there was direct contact between material of adjacent sections of the phantom. Different phantom sizes could be constructed by varying the number of sections used.

The muscle-equivalent phantom was made according to the recipe of Ishida and Kato [1980] and was composed of 3 weight per cent agar, 0.33 weight per cent formaldehyde and 0.43 weight per cent NaCl in deionized water. The electric conductivity was measured to be 0.8 S/m at 27.12 MHz and 22 °C. The measurement was performed by means of a capacitive-plate probe coupled to a vector-impedance meter. For the inhomogeneous phantom configurations fresh pig fat was used to add a 2.5 cm thick layer of fatty tissue in front of the muscle-equivalent material. Additionally, in some phantoms a piece of foam, to simulate an air volume, was included to increase the complexity of the inhomogeneous phantom.

After the phantom was placed on the aperture the ridged waveguide was tuned to have less than 10% reflected power. Next, the phantom was heated for 5 minutes with an RF input power of approximately 500 W. Immediately following the heating
the phantom was split in two parts and the temperature profiles of the exposed surface were photographed using an infrared camera (Aga Thermovision 680). The whole temperature measurement procedure was normally performed within 45-60 s after the heating had been ended. The colour slides obtained from the infrared camera show the temperature distribution on a colour scale of 10 per cent width, i.e., 10 different colours between minimum and maximum.

The effect of different applicator loads has been studied with two phantom sizes mainly: one 'large' phantom (width 63 cm) covering the whole surface area of the waveguide and one 'small' phantom (width 31.5 cm) covering the area in front of the ridge of the waveguide. The experiments were performed with and without the salt water bag in front of the phantoms in order to investigate the 'shielding' effect of the special salt water bag delivered by RCA. The existence of fringing fields, e.g., strong electric field components directed perpendicular on the fat-muscle interface, has been studied with the inhomogeneous phantom experiments.

For most of the phantom configurations with a single waveguide set-up a temperature distribution has also been calculated using the theoretical model as described in detail in Chapter 4.3.2. The predicted temperature distributions are obtained by assuming a simple sinusoidal variation of the electric field strength along the major axis of the aperture as indicated in the inset of each figure. The values used in the model for the relative permittivity and for the electric conductivity are 109 and 0.8 S/m, respectively.

Results

In this chapter the results will be mainly discussed as measured temperature distribution rather than as SAR distribution. The reason for this is that the heating time of 5 minutes is about the upper limit at which the temperature distribution is determined by the absorbed power distribution. (This has been verified by using the theoretical model to compare a predicted SAR distribution with predicted temperature distributions after different times of heating.) However, with the additional time needed to perform the manual measurement of the temperature distribution, the overall time of the experiment becomes about 6 minutes.

Furthermore, for practical reasons most of the phantom experiments were performed with the straight ridged waveguide applicator. Experiments to compare the performance of both waveguides showed similar temperature distributions in the 'small' homogeneous phantom for both the bended and straight ridged waveguide. However, it was also found that the efficiency of the bended waveguide is approximately one third of the straight waveguide.

With regard to the accuracy of the temperature distribution measured by the infrared camera it must be noticed that the accuracy of the relative isotherms is not better than ±5 per cent. This means that for a penetration depth of 8 cm the
accuracy is ±1.5 cm. (Penetration depth is defined as $1/e$ of the amplitude of the electric field. As the temperature increase is proportional to $|E|^2$, the electric field penetration depth will be prescribed by the 13.5% isotherm.)

**Applicator loading**

The effect of applicator loading on the resulting temperature distribution in the phantom is shown in Figure 4.3. For three different applicator loadings the depth profile of the 13.5% isotherm (13.5% of the maximum temperature increase) is given. The three applicator loadings are:

(a) Central part of the aperture, including the ridge, covered by the 'small' muscle-equivalent phantom (width 31.5 cm). The other part of the aperture is radiating in air (Figure 4.3a).

(b) Central part of the aperture covered by the 'small' muscle-equivalent phantom. The other part of the aperture is covered with salt-free phantom material, i.e., representing a large water bolus (Figure 4.3b).

(c) The aperture is completely covered by the 'large' muscle-equivalent phantom (Figure 4.3c).

For all three applicator loadings the maximum temperature increase measured in the central cross-section was about 6 cm from the ridge. With regard to the penetration depth at this location a small variation is found as a function of the applicator

![diagram](image_url)

**Figure 4.3a.** 13.5% Isotherm as function of the aperture loading: (a) only the ridged area is covered by muscle-equivalent phantom.
Figure 4.3b, c. 13.5% Isotherm as function of the aperture loading: (b) the ridged area is covered by muscle-equivalent phantom, the sides are covered by 'gelled' deionized water; (c) the whole aperture is covered with muscle-equivalent phantom. The dots represent the 13.5% isotherm predicted by the theoretical model (see Chapter 4.3.2).
loadings, that is, 6.5, 7.5, and 7.5 cm, respectively. As the Figures 4.3a to 4.3c, show a large amount of energy is absorbed in the phantom outside the central area of the aperture. For the situation in which the whole aperture is covered by muscle-equivalent phantom large penetration depths, 10 and 12.5 cm respectively, are also measured at the short side, and at the lower and upper side of the aperture. Furthermore, a local minimum exists at the left and right of the area opposite the ridge.

**Shielding by the special salt water bag**

With the applicator loadings of Figure 4.3a and 4.3c the 'shielding' effect of the special, 2 cm thick, salt water bolus bag of RCA has been investigated. Figure 4.4 shows the result for the situation with the aperture completely covered by the 'large' muscle-equivalent phantom. The inset of Figure 4.4 indicates the position of line A-B and the dotted area gives the surface of the aperture with 'shielding' by the salt water bag. The points with temperature increases of 13.5, 50, and 90% of the maximum temperature increase along the line A-B of the aperture are shown. The values with the open symbols are obtained when the phantom material was placed directly on top of the aperture, while the closed symbols indicate the values obtained with the special salt water bag of RCA between the aperture and the phantom. During these experiments an extra water bolus containing deionized water was
Figure 4.5. Effect of shielding by the special salt water bag on the temperature distribution measured in the small phantom. The position of the phantom is indicated by the hatched area: (a) without salt shielding; (b) with salt shielding. Straight lines give measured and dashed lines give predicted relative isotherms at the 13.5, 50 and 90% level. A sinusoidal electric field distribution along the major axis of the aperture is assumed for the predicted distribution.
placed at the area opposite the ridge. The relative temperature distributions measured for both set-ups are comparable at the centre of the aperture. For the experiment without the salt water bag, only at the sides the 13.5% temperature increase is located deeper than for the experiment with the salt water bag. The penetration depth measured at the centre of the area opposite the ridge is about 7 cm for both experiments, i.e., with or without the salt water bag shielding. The maximum temperature increase was 3 and 2 °C, respectively. Similar for the 'small' phantom, Figures 4.5a and 4.5b show the temperature distribution for the 13.5, 50, and 90% isotherms measured along the line A-B without and with salt water bag, respectively. As shown in Figure 4.5b, due to the salt water bag in front of the aperture two hot spots occur at the left and right side of the phantom close to the salt water bag. In accordance with previous measurements, the penetration depth with the 'small' phantom is less than with the 'large' phantom, that is, 6 and 4.5 cm versus 7 cm.

Inhomogeneous phantoms

All experiments with inhomogeneous phantoms were performed using the 'small' applicator loading configuration and the phantom was placed directly on the rubber membrane of the deionized water bag in front of the aperture. No experiments with shielding by the salt water bag have been performed.

In Figure 4.6 the influence of a fat layer in front of the muscle-equivalent material on the temperature distribution is shown. Figure 4.6a shows the temperature distribution in a plane parallel with the major side of the waveguide and central in the area opposite the ridge (line a-b in the inset). Figure 4.6b shows the temperature distribution in the midplane through the ridge parallel with the minor side of the waveguide. The relative temperature increase in both Figures 4.6a and 4.6b is normalized to the maximum temperature increase measured in the plane through the ridge (Figure 4.6b). As shown, maximum heating occurs within the fat tissue close to the edge of the aperture opposite the ridge. Also, relatively high energy absorption occurs within the fatty tissue at the left and right side of the central plane in the area opposite the ridge (line a-b). The penetration depth in these experiments was 8.5 to 9.0 cm, including the 2.5 cm thick layer of fatty tissue.

Figure 4.7 shows how the temperature distribution is affected if an additional rectangular air gap of $8 \times 5 \times 31.5$ cm$^3$ is present within the phantom. Areas with maximum temperature increase ($dT \geq 90\% \text{ of } dT_{\text{max}}$) are present in the fat layer as well as in the muscle-equivalent tissue near the air-volume. The penetration depth, about 11 cm, is the largest measured in all experiments.

In a number of experiments the pig skin was not removed from the fat layer. Thus, the electromagnetic wave had to propagate through a ±5 mm thick skin layer
Figure 4.6. Relative isotherms in the small fat-muscle phantom located as indicated in the inset. (a) Distribution in a plane parallel with the major axis and located at 6 cm from the ridge (line a-b). (b) Distribution in the central plane parallel with the minor axis (line c-d). Straight lines give measured and dashed lines give predicted relative isotherms. A sinusoidal electric field distribution along the major axis of the aperture is assumed for the predicted distribution.
followed by the fat layer of 2.5 cm before it was absorbed in muscle-equivalent tissue. In these experiments a large heating of the skin tissue was observed.

**Discussion**

According to Paglione et al. [1981] 80% of the RF energy in the ridged waveguide would be concentrated in the area opposite the ridge. The results of the experiments performed with the 'large' phantom set-up (Figures 4.3b and 4.3c) demonstrate, however, that also a large amount of RF energy is present at the side walls of the waveguide. The irregular energy absorption pattern as obtained with the aperture completely covered with phantom material is disappointing. In the clinical situation the high energy levels at the side walls of the waveguide may cause hot spots, which will limit the possibility to increase the tumour temperature. The salt water 'shielding' bag as provided by RCA did only marginally enhance the concentration of the RF energy to the area opposite the ridge. An adverse effect of the salt water bag is that it induces hot spots at the edges of the bag. Only with the 'small' phantom the maximum energy absorption was measured in the centre of the aperture, that is, in the area opposite the ridge as claimed by Paglione et al. [1981].
Figure 4.8. Transverse electric field profile of a ridged waveguide. (a) $\text{TE}_{10}$ mode. (b) $\text{TE}_{10}$ mode [Utsumi, 1985].

In this situation, however, the depth of 6 cm for the 13.5% isotherm level is about 1-2 cm smaller than with the large phantom. The penetration depth of 7.5 cm as measured for large phantoms is in good agreement with the 8 cm as reported by Marchal et al. [1985], who are investigating the deep heating feasibility of the Sairem 27 MHz ridged waveguide. They do not report the existence of the high SAR levels at the minor sides of the waveguide aperture. Although their ridged waveguide is designed according to the same principles, the latter may indicate that the Sairem ridged waveguide differs from the RCA ridged waveguide.

The low energy absorption as found in the 'large' phantom above the aperture area at the sides of the waveguide next to the ridge are somewhat surprising. In a standard rectangular waveguide the electric field lines will run from top to bottom plate over the whole aperture, whereby the electric field intensity along the major axis varies with a sinusoidal profile. For the ridged waveguide the electric field lines will run top to bottom at the aperture area opposite the ridge, but for the aperture area outside the ridge the electric field lines must also be perpendicular to the sides of the ridge. In general, the local electric field intensity at the edge of the ridge is, due to converging of the electric field lines at the edge, approximately 1.5 to 2.5 times the electric field intensity at the centre of the ridge [Hopfer, 1955]. This ratio is depending on the curvature of the edge. Utsumi [1985] has demonstrated that the electric field profile in the aperture of the waveguide depends on the ratio of the gap of the ridge to the minor axis of the waveguide. If this ratio is about 0.5, then areas with a low intensity of the electric field exist in the corners of the waveguide for a $\text{TE}_{10}$ mode (Figure 4.8). The low energy absorption found at the centre of the aperture areas at the sides of the waveguide cannot be explained by the standard
TE_{10} mode electric field distribution. In fact, the measured profile corresponds better to the electric field profile of the TE_{10} mode. However, with the dimensions of the waveguide the cutoff frequency for this mode of operation is above 60 MHz. On the other hand, the measured temperature distribution might be caused by a deformation of the TE_{10} mode electric field profile due to the third tuning stub which is placed at \( \pm 10 \) cm distance from the aperture. In order to obtain good impedance tuning this stub must be pushed far into the waveguide. As each stub has a circular disc of 5 cm diameter at the end of the tuning rod, the deformation of the electric field distribution will be substantial and the short distance to the radiating aperture may prohibit the restoration of the expected sinusoidal electric field distribution.

As can be derived from the experiments with the inhomogeneous phantoms, fringing electric fields exist close to the aperture. The results given in figure 4.6b indicate that especially at the upper edge of the waveguide a strong electric field component in the z-direction exists. This latter electric field component is directed perpendicular on the fat-muscle interface and will cause excessive heating of the fatty tissue as explained in Chapter 2.2. Similar hot spots have been reported by Marchal et al. [1985]. Furthermore, the fringing electric field components cause high energy absorption close to the aperture. As a result the penetration depth of 7-8 cm found for the 27 MHz ridged waveguides is substantially smaller than that of a plane electromagnetic wave at similar frequency (14.3 cm).

The predicted temperature distributions shown in Figures 4.3a to 4.3c, 4.5a, 4.6a, and 4.7 indicate that the theoretical model predicts a too large penetration depth and does not predict the heating in the fatty tissue layer. This difference between the measured and predicted distributions is due to neglecting of the third dimension and the assumption that the electric field is polarized in one direction only. Additionally, the accuracy of the predicted temperature distributions will depend strongly on the description of the electric field distribution over the aperture. These aspects will be discussed in Chapter 4.3.2.

4.3.2 Evaluation of temperature depth profiles predicted by a two-dimensional model²

The model used has been developed at the Delft University of Technology and has been described elsewhere in detail [Van den Berg, 1984; Van den Berg et al., 1983, 1984]. The model has been implemented in Fortran-77 on a PDP 11-44 and on a personal computer. For the present specific application only the main features of the

---

calculation are described.

The approach used is essentially two-dimensional and applies to structures which vary less rapidly in the axial direction than in a transverse plane perpendicular to the axis. The programme calculates the temperature distribution in a plane with an arbitrary distribution of electric permittivity and conductivity, while the aperture electric field is directed perpendicular to this plane. The spatial distribution of the aperture electric field, both in amplitude and phase, can be chosen arbitrarily around the object. The calculation is performed in two steps: first, the electromagnetic problem is solved, namely, the calculation of the volume density of generated heat; next, the heat conduction problem is solved, taking into account the thermal properties of the tissue configuration and, if applicable, the effects of skin cooling and blood flow.

As discussed in Chapter 3.2, it should be reminded that the real problem is of three-dimensional nature. At the time this study was performed, the handling of three-dimensional structures of realistic size and anatomical complexity was beyond the reach of the clinically available computer system. Therefore, with the known limitations, two-dimensional computational modelling was the best available tool to investigate the influence of tissue parameters and the applicator set-up on the resulting temperature distribution. With respect to clinical applications two-dimensional modelling has been used to evaluate the feasibility of a specific heating method beforehand and to find ways for optimization the hyperthermia heating techniques. An example of a predicted temperature distribution by the model for a computed tomography derived tissue configuration is given in Figure 4.1. The results should be regarded as a best case solution, due to ignoring the third dimension.

In order to use the computer model for planning purposes its reliability should be investigated carefully. In this chapter the results of the two-dimensional computer simulations are compared to the measured temperature distribution in the different homogeneous muscle-equivalent phantoms as described in Chapter 4.3.1. The optimal choice of input parameters for the simulations might be derived from this comparison.

**Computational model**

**Electromagnetic problem**

The electric field to be calculated can be written as the sum of the incident field \( E^i \) and the scattered field \( E^s \); accounting for the response of the tissue configuration:

\[
E = E^i + E^s
\]

The incident field is emerging from an aperture, which is modelled as a radiating slit in a perfectly conducting screen. This field can be found from an integral represen-
A representation contains the aperture electric field distribution $E^a$ (as specified in the input) and a two-dimensional free space Green's function [Jones, 1964]. The scattered field is calculated through a domain-integral representation, taking into account that the irradiated body is present in free space and that it manifests itself through the presence of secondary sources of contrast currents which in their turn are related to the contrast in electromagnetic properties over the tissue configuration:

$$E^s(r) = \int_{D} G(|r-r'|)C(r')dA(r')$$

where $G(|r-r'|)$ is Green's function; $|r-r'|$ denotes the distance between a point of the aperture, $r$, and a point of the object, $r'$; $C(r')$ is the contrast source density, which is a function of the permittivity and the conductivity over the subject and the electric field $E$; $D$ is the domain occupied by the body. The yet unknown contrast source $C(r')$ can be obtained from an integral equation:

$$E(r) = E^i(r) + \int_{D} G(|r-r'|)C(r')dA(r')$$

where $r \in D$. The integral equation is solved by an iterative technique in which the integrated square error is minimized [Van den Berg et al., 1983]. The convergence of the iterative scheme can be improved by the use of a conjugate gradient version [Van den Berg, 1984]. For these numerical calculations the domain, i.e., the body cross-section is divided into a number of subsquares, usually $72 \times 44$. Each subsquare is ascribed to a specific tissue type, for which the information from a computer tomography (CT) scan is used. The $256 \times 256$ matrix with CT numbers is converted to a $64 \times 64$ matrix with different characters for the various tissue types. As a first step an automatic conversion from CT numbers to tissue types is performed using a table with CT number ranges versus tissue types, for bone, muscle, lymph node, fat, lung and air. Next, this matrix of tissue characters is corrected (by means of a digitizer) during a visual examination of the CT-scan by a clinician. This manual correction of the matrix appears necessary mainly for tissues for which the specificity of the CT-scan is low, such as muscle, lymph node, and tumour. If an accurate tissue configuration has been obtained, a table of tissue types and respective electromagnetic properties is used as input to the programme. After calculation of the electric field the volume density of generated heat power is calculated for each pixel from:

$$\dot{w}_h = \frac{1}{2} \sigma |E|^2$$
Heat conduction problem

The matrix of power densities for each pixel serves as input for the second part of the simulation in which temperature distributions after chosen times of heating are calculated. This is performed by solving the two-dimensional bio-heat problem through a suitable numerical spatial discretization of the equation of heat flow in integral form (for the domain $S$ inside a simply closed contour $C$ with outward normal vector $\nu$),

$$
\int_S \rho c \frac{\partial T}{\partial t} dA + \int_C \mathbf{v} \cdot \mathbf{q} ds = \int_S (\dot{w}_e - \dot{w}^c_e(T)) dA
$$

and the thermal conduction equation in integral form (along a path of integration from a point $P$ to a point $Q$ with tangent vector $\tau$)

$$
\int_P^Q \kappa^{-1} \tau \cdot \mathbf{q} ds = T_P(t) - T_Q(t)
$$

where the following physical quantities with their appropriate units are used: $t$, time(s); $T$, temperature ($^\circ$C); $\mathbf{q}$, heat flow density (W/m$^2$); $\rho$, volume density of mass (kg/m$^3$); $c$, specific heat capacity (J/kg/$^\circ$C); $\kappa$, thermal conductivity (W/m/$^\circ$C); $\Phi_e$, volume density of extracted heat power (cooling; W/m$^3$), and $\Phi_e$, volume density of generated heat power (W/m$^3$). The term $\Phi_e$ denotes the cooling due to blood circulation which is a function of the blood flow rate $F$ (m$^3$/kg/s) and the local temperature of the blood. The cooling function is simply chosen to be:

$$
\dot{w}_e = (F \rho)_{\text{dose}} (\rho c)_{\text{blood}} (T - 37)
$$

A table with thermal properties ($\kappa$, $\rho$, $c$), blood flow rates, and initial temperatures for the whole configuration is used as input. As boundary conditions either an isothermal surface or a heat-insulating surface can be chosen, dependent on the value chosen for the thermal conductivity of the surrounding air.

Using the same subdivision as in the electromagnetic problem and a finite-difference method in time [Van den Berg, 1984], an explicit iterative scheme has been arrived at. The temperature distributions are calculated after a chosen number of time steps. The magnitude of the time step should be chosen not too large to ensure stability of the calculation. Typical values of the time step are 10 or 20 s. The overall heating time is usually chosen between 5 and 15 min.

It should be mentioned that the intention of the present simulations was primarily to study the influence of the choice of the electromagnetic parameters and the aperture field distribution. As generally recognized, also blood flow effects play an essential role in the resulting temperature distribution, both through an increase
of the effective thermal conductivity by means of the small vessels and through strong cooling effects by the larger vessels. The present theoretical method represent the integrated counterpart of the differential equations known as the bioheat transfer equation [Pennes, 1948]. It is now well known [Lagendijk, 1984, 1990] that the validity of this approach is limited, as heat transport through mass transport of blood is not taken into account and also the effects of the venous blood vessels are ignored. Before, however, blood flow effects and other thermal effects can be studied effectively, the optimal choice of electromagnetic parameters should be understood.

Results

The input parameters for the calculations are listed in Table 4.2. For the electromagnetic problem values for the permittivity and the electric conductivity are needed as well as the amplitude and phase distribution of the aperture electric field. The reliability of the computer model is investigated by comparison of predicted and measured temperature distributions for the different homogeneous muscle-equivalent phantoms as described in Chapter 4.3.1.

The influence of the parameters permittivity ($\varepsilon$) and electric conductivity ($\sigma$) has been studied by varying both parameters in calculations of the temperature distributions for homogeneous phantoms after a short time of heating (5 min.). The relative temperature distribution in this case is not influenced by the power output of the waveguide. It appears that $\varepsilon$ has only a minor influence on the temperature distribution, at least in these homogeneous configurations. Variation of $\sigma$ has a more significant effect: the penetration depth decreases strongly over a range of values studied from 0.4 to 2.4 S/m. This is to be expected: at 27 MHz the quantity $\varepsilon\omega/\sigma$ (which determines the conductor-or-isolator properties of a material) is rather small, less than 0.2; therefore, the agar (and hence muscle tissue) can be considered a fairly good conductor. In the extreme case of a perfect conductor the penetration depth becomes independent of the value of the permittivity $\varepsilon$ and inversely proportional to the square root of the electric conductivity $\sigma$.

In general, the simulated temperature distributions for a single applicator show a too deep penetration, if the true value for $\sigma = 0.8$ S/m is used, as is demonstrated in some of the figures of Chapter 4.3.1. Good agreement could be obtained for the penetration depth at the central axis for both the small and the large phantoms by choosing artificially the value $\sigma = 2.0$ S/m. The effect of overestimating the penetration depth may be caused by the necessarily two-dimensional approach of the simulation, in which the divergence of the electric field in the third dimension is not taken into account.
Table 4.2 Electric and thermal parameters used for the simulation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>27.0 MHz</td>
</tr>
<tr>
<td>Electric conductivity</td>
<td></td>
</tr>
<tr>
<td>(measured)</td>
<td>0.8 S/m</td>
</tr>
<tr>
<td>(used in simulation)</td>
<td>2.0 S/m</td>
</tr>
<tr>
<td>Relative permittivity</td>
<td>109.0</td>
</tr>
<tr>
<td>Power per unit length in the axial direction</td>
<td>800.0 W/m</td>
</tr>
<tr>
<td>Mass density</td>
<td>1000.0 kg/m³</td>
</tr>
<tr>
<td>Specific heat capacity</td>
<td>3.5 kJ/kg/°C</td>
</tr>
<tr>
<td>Thermal conductivity</td>
<td>0.63 W/m/°C</td>
</tr>
<tr>
<td>Blood flow rate</td>
<td>0.0 m³/kg/s</td>
</tr>
<tr>
<td>Time step</td>
<td>10.0 s</td>
</tr>
<tr>
<td>Overall time</td>
<td>300.0 s</td>
</tr>
<tr>
<td>Configuration: homogeneous agar/saline phantom matrix 72 x 44 elements</td>
<td></td>
</tr>
</tbody>
</table>

It should be noted that this effect is, naturally, not modelled properly by a change in the electric conductivity. The application of a larger value for $\sigma$ is just an ad hoc measure to attain good agreement between measurement and simulation for these homogeneous phantoms. A three-dimensional model is required to take into account the effects of an electric small aperture in a physically correct manner.

Regarding the choice of the aperture electric field, an ideal distribution would be a single line segment, of constant amplitude and phase, extending over the width of the area across the ridge of the waveguide, as shown in Figure 4.9. Cohn [1947] and Chen [1957] have found, however, that the aperture electric field distributions are of cosine type for ridged waveguides: the field strength decreases slowly going outward from the centre and reaching zero at the side of the aperture (see also Figure 4.9). Utsumi [1985] has taken into account near-field effects at the ridge of the waveguide and has applied a variational analysis to derive the electric field profiles for the $TE_{10}$ dominant mode and other transverse electric and magnetic field modes. These results show a significant effect of the ridge, leading to a curvature in the electric field lines, especially over the wide part of the waveguides, that is, in the aperture area outside the ridge. It is therefore to be expected that this more complicated electric field distribution will influence the temperature distribution in the case of waveguide loads extending outside the ridge area. Hence, a qualitative difference may be expected for the temperature distributions in the large and the
small phantom.

Simulated temperature distributions in comparison with phantom thermography data are shown in Figure 4.10 for the small phantom and in Figures 4.11 and 4.12 for the large phantom. The calculated isotherms are given as solid lines and the measured isotherms are indicated as dashed lines. Both distributions are expressed as percentages of the maximum temperature increase. A qualitative difference is noticeable: for the small phantom the temperature increase is concentrated in the centre of the phantom, while for the large phantom also temperature elevations at the lateral sides of the aperture are visible. The aperture electric field distribution for the small phantom could simply be chosen as a single line segment of 20 cm length. With this length (and the artificial choice of \( \sigma = 2.0 \text{ S/m} \)) a reasonable agreement of the 13.5 (1/\( e \)) and 50% isotherms is attained. The measured isotherms for the large phantom could not be reasonably approximated in the simulation with a single aperture electric field segment (Figure 4.11) or with cosine-type distributions as shown in Figure 4.9. To reasonably describe both lateral and central temperature increases a distribution with five line segments as shown in Figure 4.12 had to be adopted. Furthermore, it should be mentioned that the curvature of the electric field lines outside the ridge area, if present, can be expected to influence the accuracy of the simulation: the programme does assume that the electric field is always polarized perpendicular to the plane of calculation. If the electric field lines show a curvature outside the ridge area (Figure 4.8), as derived by Utsumi [1985], this effect cannot be taken into account in a physically correct manner. With the electric field in the
Figure 4.10. Calculated (solid lines) and measured (dashed lines) relative temperature distributions for the small phantom covering the aperture area across the ridge of the waveguide. The aperture electric field distribution is a single line segment of 20 cm width as indicated in the upper part. To reach acceptable agreement the artificial value \( \sigma = 2.0 \text{ S/m} \) had to be used.

aperture assumed as consisting of five line segments, a reasonable agreement is obtained, again with \( \sigma = 2.0 \text{ S/m} \), as shown in Figure 4.12.

Discussion

The reasonable overall agreement, eventually obtained between the results of computer simulations and measured temperature distributions in homogeneous phantoms, as shown in Figures 4.10 and 4.12, suggests that the limitations of a two-dimensional approach can to a certain extent be compensated by assuming a larger value of the electric conductivity of the medium. Also an accurate approximation of the aperture electric field distribution over the aperture of the ridged waveguide is an absolute requirement.
E(aperture) distr.

![Image of temperature distribution]

Large phantom
w×h=61×20 [cm]  
T(min)=37°C  
T(max)=37°C + 8.08°C

Solid lines: calculated isotherms (100%, 90%, 50%, 13.5%)
Dashed line: measured isotherms (90%, 50%, 13.5%)

Figure 4.11. Calculated (solid lines) and measured (dashed lines) relative temperature distributions for the large phantom covering the whole aperture area of the waveguide. The assumed aperture electric field distribution is a single line segment as indicated. Again, the artificial value of $\sigma = 2.0$ S/m is used to correct for the penetration depth at the central axis. Using this aperture electric field distribution the measured temperature increases at the sides of the waveguide are not predicted.

For realistic inhomogeneous tissue configurations, e.g., as shown in Figure 4.1, the ad hoc choice of a larger electric conductivity cannot be expected to give accurate results due to the marked differences in the electromagnetic parameters of the tissues present. Furthermore, as the programme does assume that the electric field is always polarized perpendicular to the plane of calculation it will not predict preferential heating in fatty tissue. As explained earlier, the fringing electric fields present at the edges of the aperture will contain an electric field component directed perpendicular to the fat-muscle interface. For these complex inhomogeneous configurations three-dimensional calculations are necessary to reach a satisfactory degree of accuracy. Although three-dimensional modelling techniques are available.
for heterogeneous tissue configurations, the fine mesh dimensions that are needed in hyperthermia modelling result in a large number of pixels. Even with the presently available powerful work stations considerable computer time is needed to accurately predict a three-dimensional energy distribution. Until fast simulation techniques are available, the present model might be used to estimate the feasibility of a particular heating method beforehand, but the limitations as outlined above should be kept in mind. Of course the validity of this two-dimensional computational model has to be verified for each hyperthermia applicator separately.

For the 27 MHz ridged waveguides the outcome of the two-dimensional predictions of this model should be viewed as a 'best-case' result. If the result of the simulation is negative, i.e., if heating in a part of the target volume is insufficient, it is improbable that the actual heating results will be better than the simulated data.
If the results of the simulation are positive, however, the clinical results can still be disappointing, due to an overestimation of the penetration depth. Therefore, the simulation results shown in Figure 4.1 for a case of cervix carcinoma as a clinical example may be too optimistic.

For higher frequencies the differences between measurements and model calculations (using measured tissue parameters as input) may be expected to be smaller as, with the smaller ratio of wavelength to applicator size, the limitations of the two-dimensional model may be less important. Preliminary calculations for differently sized waveguides at 433 MHz both in this institute and by Van Dijk et al. [1985] seem to confirm this expectation.

4.3.3 Animal and clinical studies with a single 27 MHz ridged waveguide

During the period of phantom experiments the demand for a hyperthermia treatment of large tumours with depths extending to approximately 7 cm was growing steadily. Therefore, animal experiments with a single ridged waveguide were performed to study the in-vivo temperature distribution and to investigate the performance of the applicator set-up under clinical conditions. Hereafter, the first clinical treatment was performed using the bended ridged waveguide in July 1984 and the last treatment, using the straight waveguide, was performed in June 1989. In this period a total of 18 patients, of whom 10 had a tumour located in the pelvic region, were treated. The results of the preclinical animal experiments and the ability of the bended and straight ridged waveguide to induce deep heating in patients with a tumour located in the pelvic region are reported in this chapter.

Materials and methods

For both the animal experiments as well as the patient treatments RF power input to either the bended or straight ridged waveguide was obtained from the Curamed generator. This generator was preferred for its high power output.
(maximum 700 W). Forward and reflected power were measured by Bird Thruline Watt meters with a sensitivity of 1000 and 500 W, respectively.

To improve energy transfer from the waveguide to the treatment area for both animal or patient a water bolus was placed between the tissue and the aperture of the ridged waveguide. Two circulating water bolus systems were available. In the case that the aperture plane was orientated in the vertical direction (heating of a tumour in the perineum) an open water bolus was used. In the situations in which the aperture was in the horizontal plane (heating of a tumour in the back) a closed water bag was used. In both water bolus systems the temperature of the circulating water could be set between 14 to 45°C. In addition, non-circulating water bags were used as additional loading of the waveguide aperture. The different applicator positions are shown schematically in Figure 4.13.

**Animal experiments**

Two times the buttocks of a large male pig (weight 80-100 kg) were heated with the bended ridged waveguide. The animal laid on its back. The open water bolus, thickness approximately 5 cm, was placed between the bended waveguide and the buttocks of the animal. During the experiment the animal was under general anaesthesia using Ethrane within a standard mixture of N₂O/O₂ inhalation gases. Thermometry was performed in nine catheters, eight invasive in muscle tissue and one in the rectum. In Figure 4.14 the experimental set-up and a schematic representation of the location of the temperature probes in each experiment are shown. Temperatures were measured by home-made multi-sensor thermocouples connected to an Ellab DU-3 read-out unit. The heating procedure consisted of 15 minutes of RF on, starting at a power level of 200 W which was increased to 700 W at the end of the experiment. During the RF on period the thermocouples were removed from the catheters. After the RF was switched off they were quickly re-inserted and the temperature was measured after three seconds of equilibration time. The overall time of each experiment was about 2½ hours.

**Patient treatments**

From July 1984 to June 1989, 10 patients (two male and eight female) with large tumours were included in this feasibility study and heated with the ridged waveguide applicator. Clinical selection criteria included Karnofsky ≥70, no heart complaints and normal blood pressure. A large metallic implant and/or pacemaker were absolute exclusion criteria. A detailed description regarding sex, age, and tumour location and depth of the patients treated in this study is given in Table 4.3.

For temperature measurements during the clinical treatments three different thermometry systems were used. In the first five patients (#177 to #262) a four-channel fibre-optic thermometry system (TP4, Clinitherm Corporation, USA) with
Figure 4.14. (a) Experimental set-up during heating of the buttocks of the pig. Schematic representation of the location of the thermometry catheters for the first (b) and the second (c) experiment.
single sensor probes was used together with the, earlier mentioned, multi-sensor thermocouple system. In the last five patients (#301 to #351) thermometry was improved greatly and with these patients a 24-channel fibre-optic temperature measuring system (FT1210, Takaoka, Japan) was used. With the FT1210 fibre-optic system single sensor probes as well as four-sensor probes were available. All three thermometry systems were calibrated against a standard mercury thermometer (±0.02°C accuracy) using a water bath of ±0.05 °C stability. The overall accuracy of the FT1210 system was ±0.2°C. The TP4 system needed to be recalibrated at the end of each treatment in order to correct the temperature measurements for drift of the instrumentation. After correction for drift the accuracy of the TP4 was also ±0.2 °C. The Ellab DU-3 thermocouple system had an accuracy of ±0.1 °C. However, during the time needed to insert the thermocouple probe in the thermometry catheter and to obtain thermal equilibration, the temperature of the surrounding tissue will decrease. Thus, although the calibration accuracy of the thermocouple system is better than that of the fibre-optic systems, the tissue temperatures measured with the thermocouple system will be less accurate.

Before the first hyperthermia treatment all patients had thermometry catheters inserted transcutaneously into tumour and normal tissue. If necessary this was performed under guidance of computed tomography. The thermometry catheters were made of Polyethylene tubing (800/100/260/100, Portex Ltd, UK) with an inner diameter of 0.75 mm (Ellab and TP4) or 0.86 mm (FT1210) depending upon the thermometry system used. Each catheter remained in place until the end of the whole treatment series, unless it had to be removed for clinical reasons (such as infection). If possible, thermal mapping was performed at regular intervals by manually moving the temperature probe in 1 cm steps along the thermometry catheter in case the TP4 fibre-optic thermometry system was used. However, in many treatments the water bolus prohibited access to the thermometry catheters and temperatures could be measured only at a single point in each catheter.

Hyperthermia was applied twice per week immediately after irradiation. The treatment consisted of a heating period of 15 min and a hyperthermia treatment period of 1 h. During the hyperthermia treatment period the goal was to obtain a minimum tumour temperature of 43 °C. If this goal could not be obtained hyperthermia was administered at maximum tolerable RF power or until normal tissue temperatures reached 44 °C. Evaluation of the hyperthermic treatment was performed using the percentage of all measured temperatures above 40 °C (both in space and in time) and the maximum temperature achieved during the hyperthermic treatment period.
Table 4.3 Patient characteristics.

<table>
<thead>
<tr>
<th>patient number</th>
<th>sex</th>
<th>age</th>
<th>tumour type</th>
<th>location</th>
</tr>
</thead>
<tbody>
<tr>
<td>177</td>
<td>m</td>
<td>61</td>
<td>bladder carcinoma</td>
<td>perineal</td>
</tr>
<tr>
<td>178</td>
<td>f</td>
<td>51</td>
<td>recurrent ovarian carcinoma</td>
<td>labia and vagina</td>
</tr>
<tr>
<td>180</td>
<td>f</td>
<td>38</td>
<td>recurrent rectum carcinoma</td>
<td>presacral</td>
</tr>
<tr>
<td>196</td>
<td>m</td>
<td>71</td>
<td>prostate carcinoma</td>
<td>prostate</td>
</tr>
<tr>
<td>262</td>
<td>f</td>
<td>49</td>
<td>recurrent anal carcinoma</td>
<td>vagina</td>
</tr>
<tr>
<td>301</td>
<td>f</td>
<td>77</td>
<td>recurrent rectum carcinoma</td>
<td>presacral</td>
</tr>
<tr>
<td>303</td>
<td>f</td>
<td>41</td>
<td>recurrent cervix carcinoma</td>
<td>vagina and presacral</td>
</tr>
<tr>
<td>346</td>
<td>f</td>
<td>62</td>
<td>recurrent rectum carcinoma</td>
<td>presacral</td>
</tr>
<tr>
<td>348</td>
<td>f</td>
<td>74</td>
<td>recurrent rectum carcinoma</td>
<td>presacral</td>
</tr>
<tr>
<td>351</td>
<td>f</td>
<td>76</td>
<td>recurrent rectum carcinoma</td>
<td>presacral</td>
</tr>
</tbody>
</table>

Results

Animal experiments

In one animal two deep heating experiments were performed. With the first experiment the majority of the temperature probes were placed in the left buttock. The second experiment was a repetition of the first experiment but with the majority of the temperature probes placed in the right buttock.

For the first animal deep heating experiment the temperature-time profiles at some selected sites along three thermometry catheters (2, 5, and 6) are shown in Figure 4.15. From the temperature profile it follows that an RF power input of at least 400 W is needed to induce heating at depth. Furthermore, the temperature increase appears to level off from 80 minutes onwards. As indicated by the RF power level bars at the bottom of Figure 4.15, the RF on/off pulse period was about 15 minutes 'on' and 3 to 6 minutes 'off'. During the RF off period the waveguide and water bolus were removed; the thermocouple probes were inserted in the thermometry catheters and the temperature at all 21 sites was measured; and finally, the water bolus and waveguide were replaced.

The temperature distribution measured for both animal experiments is summarized in Table 4.4. For the first experiment the temperatures measured at the end of the heating experiment which lasted 138 minutes, are given as function of depth in Table 4.4a. For the second experiment the temperature distribution is given
Figure 4.15. First animal deep heating experiment: temperature-time profiles at some selected sites along three thermometry catheters (2, 5, and 6). The bars at the bottom indicate periods with RF power.

in Table 4.4b at the time the temperatures were stabilized, i.e., 78 minutes. In the first experiment temperatures from 41.0 to 42.0 °C are measured at a depth of 6 to 8 cm, with a maximum temperature of 43.8 °C at 2 cm depth. In the second experiment the maximum temperature measured is lower, i.e., 42.1 °C, but is located at 5 cm depth. Furthermore, the temperatures measured at a depth of 7 and 8 cm are higher for the first experiment, 41.0 - 42.0 °C, than for the second experiment, 39.7 - 41.5 °C. The low temperature of the water bolus in the second experiment, 16 °C, results in a good cooling of the subcutaneous tissue of the buttocks as the temperatures measured at depths to 2 cm tissue remain below 40 °C. Finally, increase of core temperature was limited in both experiments, i.e., 0.8 and 1.5 °C, respectively.

Patient treatments

In total 57 hyperthermia treatments have been applied using a single bended or straight ridged waveguide. 54 and 49 of these treatments could be used to evaluate the feasibility of a single ridged waveguide to induce deep heating in pelvic tumours with regard to the measured temperature distribution or the treatment limiting factor, respectively.
Table 4.4a. Temperatures measured after 138 minutes of heating as function of depth for the first animal experiment.

<table>
<thead>
<tr>
<th>depth [cm]</th>
<th>location of temperature measurement</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>rectum</th>
<th>core</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31.7</td>
<td>40.0</td>
<td>42.0</td>
<td>39.9</td>
<td></td>
<td>39.2&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>43.8</td>
<td>37.4</td>
<td>40.3</td>
<td>43.2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>42.2</td>
<td>42.5</td>
<td>43.0</td>
<td>42.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>42.8</td>
<td>42.0</td>
<td></td>
<td>41.1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>41.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>41.0</td>
<td></td>
<td>41.9</td>
<td>41.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>42.0</td>
<td>41.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> temperature measured by Schwan-Ganz catheter in the heart.

Table 4.4b. Temperatures measured after 78 minutes of heating<sup>1</sup> as function of depth for the second animal experiment.

<table>
<thead>
<tr>
<th>depth [cm]</th>
<th>location of temperature measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>1</sup> time of stabilized temperature distribution; <sup>2</sup> temperature measured in the nose of the pig.
The bended ridged waveguide has been used only in the beginning of the patient treatments, that is, for patients #177, #178, #196 and for the first treatment of patient #262. In these patients the best set-up to heat the tumour area was by placing the bended waveguide in front of the perineum or above the lower abdomen. At that time, such a set-up (see Figure 4.13) could be realized only with the bended ridged waveguide. From the third treatment of patient #262 onwards the straight waveguide was mounted on a mobile support system with the possibility to place the aperture of the straight waveguide in both a horizontal and a vertical position. The reason for this change was the low efficiency of the bended waveguide. As can be seen in Table 4.5 the only limitation to further increase the tumour temperature was shortage of available RF power in 70% of the treatments applied with the bended waveguide. For the straight waveguide available RF power was the limiting factor in only 31% (11 of 35, see Table 4.5) of the treatments. However, ten of these eleven treatments concerned the first two patients (#180 and #262) treated with the original straight waveguide as delivered by RCA. From patient #301 onwards the straight waveguide was adapted: the 3 mm thick rubber membrane at the aperture of the waveguide was replaced by an 0.05 mm thick PVC membrane. The flexibility of the very thin membrane made adaption of the water bolus to the body contour much easier. Hence, a good electromagnetic contact, i.e., without dielectric discontinuities between the waveguide and the patient could be obtained. Additionally, the membrane provided a good thermal contact between the skin and the water bolus. By connecting an external circulation pump to the water bolus it was easily possible to control the skin temperature. For the last five patients (#301 to #351) treated with the improved straight waveguide, shortage of RF power was the limiting factor only once. However, for these patients pain in the hyperthermia field was now becoming the limiting factor in 70% of the treatments. In less than 10% (3 of 35) a treatment was limited by a too high (>43 °C) temperature of the normal tissue.

Table 4.5. Incidence of treatment limiting factors for the two types of ridged waveguide applicator.

<table>
<thead>
<tr>
<th>type of ridged waveguide</th>
<th>number of hyperthermia fields</th>
<th>pain in hyperthermia field</th>
<th>normal tissue temperature &gt;43 °C</th>
<th>available RF power too low</th>
<th>toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>bended</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>one small blister</td>
</tr>
<tr>
<td>straight</td>
<td>35</td>
<td>15</td>
<td>3</td>
<td>11</td>
<td>one subcutaneous burn</td>
</tr>
</tbody>
</table>
Table 4.6. Summary of the temperature distributions measured during the hyperthermia treatments applied by a 27 MHz ridged waveguide per patient.

<table>
<thead>
<tr>
<th>patient number</th>
<th>number of treatments</th>
<th>treatments with tumour temperatures</th>
<th>median maximum temperature$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>40-41</td>
<td>41-42</td>
</tr>
<tr>
<td>various tumour types</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>177</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>178 A$^2$</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>178 B$^2$</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>196</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>262</td>
<td>7$^3$</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>303</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>recurrent rectum carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 A</td>
<td>6$^4$</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>180 B</td>
<td>5$^4$</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>301</td>
<td>5$^5$</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>346</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>348</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>351</td>
<td>9</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

$^1$ between brackets the cumulative number of maximum temperatures evaluated for all treatments; 
$^2$ the treatment area was divided in two hyperthermia fields, A and B, which were treated in turns; 
$^3$ one treatment was interrupted due to problems with the bended ridged waveguide and one treatment was without invasive thermometry; 
$^4$ after the first hyperthermia treatment, the treatment area was divided in two hyperthermia fields giving a total of 11 hyperthermia treatments; 
$^5$ one treatment not evaluable.

In Table 4.6 a summary of the temperature distributions measured during the hyperthermia treatments applied with a single ridged waveguide for each patient is given. The ability of a single ridged waveguide to induce deep heating is evaluated using (a) the number of treatments with at least one tumour temperature measured in the specified temperature range (40-41; 41-42; >42 °C), and (b) using the median
Figure 4.16. Frequency distribution in space and time of all measured tumour temperatures. The value represents the average of the temperature measurements for all treatments performed with a single 27 MHz ridged waveguide.

of all maximum temperatures measured in tumour and normal tissues. As shown in Table 4.6, the percentage of treatments with at least one temperature measurement of 42 °C or higher is very low, i.e., 9% (5/54). For a threshold temperature of 41 or 40 °C this percentage is 30% (17/54) and 55% (31/54), respectively. If the median maximum temperature as presented in Table 4.6 is used as an indicator for the success of the treatment with a threshold temperature of 40 °C, then in only two patients with four treatments this criterion is met. In Figure 4.16 the frequency distribution of the measured tumour temperatures during all treatments is shown for five temperature intervals. As can be seen in this figure, 84.9% of all measured tumour temperatures are below 40 °C and a temperature above 40, 41, 42 or 43 °C was obtained only in a small fraction of all measurements, i.e., in 15.1, 6.1, 1.1, and 0.4 per cent, respectively.

During the clinical treatments a number of practical problems was found, which become important when the ridged waveguides are operated over longer periods, that is, 1-2 hours. For instance, the tuning becomes unstable which results in a lower efficiency. Also the tuning stub can become too hot to handle which makes it difficult to perform additional tuning. Furthermore, the large dimensions of the treatment field and the great weight of the waveguide make it more or less impossible to
customize the SAR distribution during treatment if the patient complains about pain or a local hot spot.

Discussion

In both animal experiments good heating at depth is obtained: temperatures above 42 °C at 5 cm depth. In the first experiment the maximum temperature, 43.8 °C, is measured at 2 cm depth; in the second experiment the maximum temperature, 42.1 °C, is measured at 5 cm depth. This finding can be explained by the difference in the temperature of the water bolus used in each experiment. In the first experiment the water bolus temperature was 35 °C and thus the subcutaneous tissue temperature increased rapidly. In the second experiment the water bolus temperature was 16 °C and thus the skin of the pig was actively cooled. As a result, the temperatures of the subcutaneous tissue remain much lower and the maximum temperature will be localized deeper in the tissue. Additionally, in the first experiment higher temperatures at depths around 7 cm are measured than in the second experiment. The latter is a consequence of the fact that in the first experiment the temperature at 5 cm depth is also higher (0.7 °C) than in the second experiment. At this depth the influence of the water bolus temperature is negligible and, besides individual variations, the temperature profile in both experiments is expected to be similar.

The deep heating performance of the single ridged waveguide as found in these animal experiments is in good agreement with the findings reported by Paglione et al. [1981] and by Marchal et al. [1985, 1987a]. They heated the gluteal region of a pig, which was positioned on its back on top of a straight ridged waveguide, and measured maximum temperature increase at a depth of 5 cm in muscle tissue and between 6 to 9 cm in the vagina. Both groups used active cooling during the animal experiments. Furthermore, their experimental and theoretical work showed that passive cooling at the surface resulted in a temperature profile with a maximum at 2 cm depth, while with active cooling the maximum temperature was located at 4.5 cm depth.

The tumour temperatures measured during the patient treatments are, especially when compared to the temperatures measured in the animal experiments, disappointingly low. Although in 31 of the 54 (55%) hyperthermia treatments of all 10 patients a maximum temperature above 40 °C was reached, the frequency distribution shows that only 15% of all measured tumour temperatures were above 40 °C. The latter fact indicates that only in small tumour volumes and for short duration the tumour temperature could be increased above 40 °C. For the first five patients treated, see Table 4.5, it was anticipated that the temperatures remained low because of the shortage in available RF power. For the last five patients, #301 to #351, the
improved straight waveguide was used and for this group of patients the treatment was limited by a too low RF power level only once. However, temperature analysis of this subgroup did not show a better heating of the tumour. On the contrary, for this group only 8% of the measured temperatures were above 40 °C. On the other hand, the incidence of the treatment limiting factors pain and overheating of normal tissue all occurred, except in one case, within the subgroup of the last five patients. The latter finding may indicate that at higher RF power levels the incidence of local hot spots due to the fringing fields at the edges of the ridged area, as found in the phantom experiments, are increasing rapidly. Hence, based upon these clinical findings it must be concluded that the ridged waveguide has a limited deep heating feasibility for tumours located in the pelvic region.

Unfortunately, no published literature concerning the performance of the 27 MHz ridged waveguide of RCA under clinical conditions has been found. A questionnaire among the various groups who have been using these waveguides showed that those who responded [Cunningham; A. Lipton; A. Yerushalmi, personal communication, 1990] have terminated the use of the ridged waveguide. Only the hyperthermia group in Nancy [Marchal et al., 1985, 1987a, 1991], using ridged waveguides designed to similar principles but built by Sairem, has reported on the temperature distribution in patients measured during hyperthermia treatment for deep-seated tumours. On the basis of their clinical experience with 73 patients [Marchal et al., 1991] they conclude that it is feasible to heat tumours at a depth of 5 cm to 42 °C or higher. Regrettably, the temperature data in their publications cannot be used for comparison as they do not distinguish between temperatures measured invasively in the tumour and within the natural cavities. Regarding the SAR patterns in gelatine/salt phantoms induced by the Sairem ridged waveguides, 

Marchal et al. [1985, 1987a] report a similar penetration depth, e.g., 8 cm. However, they did not report the existence of the high SAR levels at the sides of the waveguide as found for the RCA ridged waveguides. Hence, the two ridged waveguide applicators may be different. If so, this could explain the different conclusions about the feasibility to perform clinical deep heating of pelvic tumours using a ridged waveguide applicator.

Apart from evaluating the deep heating feasibility of the ridged waveguide from the achieved temperature distributions, other factors not mentioned before may influence the clinical applicability of the ridged waveguides. For instance, it was experienced that a strong stray radiation field was present around the body of the patient outside the treatment area (especially at the head) and around the total waveguide set-up. This stray radiation field became inconveniently perceptible when taking care of the patient. Every time the patient was touched by the treatment personnel a small shock was perceived due to localized high RF field intensities. Besides these personal inconveniences, the stray radiation also caused disturbances
of the electronic equipment used to monitor temperatures, vital signs, and also on forward- and reflected-powermeters. Additionally, the large amount of energy outside the target area caused an increase of the core temperature of the patient. With the new water bolus system these problems were reduced to a certain extent due to the better coupling of energy from the waveguide to the patient.

In summary, heating of semi deep-seated tumours in the pelvic region by a single ridged waveguide of RCA resulted in disappointingly low temperatures. Even if a threshold temperature as low as 40 or 41 °C is chosen only 15% and 7%, respectively, of the temperatures measured during all hyperthermia treatments are above this threshold value.
4.4 Two-waveguides set-up

4.4.1 Experimental and animal studies using two ridged waveguides in a parallel opposed arrangement

Although the design of the bended waveguide facilitates the use of two applicators in a parallel opposed or cross-fire arrangement, the experiments have been limited to the use of two waveguides, radiating in-phase, in a parallel opposed arrangement. The purpose of the phantom experiments was to gain insight in the feasibility of the parallel opposed arrangement to induce high energy absorption at depth. After the first series of phantom experiments a number of animal experiments have been performed to study the behaviour of the two-waveguides set-up under clinical conditions. Based upon the experience from the animal study, additional phantom experiments have been performed.

The experiments performed with a single 27 MHz ridged waveguide (Chapter 4.3.1) showed that the penetration depth in muscle-equivalent tissue is 7 to 8 cm if the whole aperture is covered by phantom material; a value larger than of any other single waveguide applicator [Hand, 1990]. Extrapolating the exponential decay of the SAR profile to a depth of 10 cm, e.g., the centre of the 20 cm thick phantom, gives a relative value of 6 to 8%. For the case of two waveguides in a parallel opposed arrangement, radiating coherently and in phase, this means that a relative SAR between 24 and 32% can be expected at the centre of the phantom. Although the accuracy of the infrared camera at low SAR values is less than at higher SAR values it was decided not to adjust the thickness of the phantom, as only few patients will have an anterior-posterior distance smaller than 20 cm. Alternatively, the electric conductivity of the muscle-equivalent tissue could have been reduced. However, at the time these experiments were performed, no consensus existed about the average value for the electric conductivity of pelvic tissue. Therefore, it was preferred to continue the experiments with the same phantom composition as used for the single waveguide experiments. At present, it is common practice to consider phantom material with an electric conductivity of 2/3 of that of muscle tissue as equivalent to pelvic tissue. As a consequence, the SAR distributions measured in this study within the muscle-equivalent phantoms should be regarded as providing an indication of the lower limit of the deep heating feasibility of the ridged waveguides in a parallel opposed arrangement.

Materials and methods
Waveguide arrangement

The parallel opposed arrangement of the waveguides is shown schematically in Figure 4.17. The straight waveguide was standing on the floor, while the bended
waveguide was positioned above the phantom or the animal with the use of a lift truck. As the lift truck was made of metal, it was inevitable that large metal parts were located in the proximity of the radiating aperture. These experiments were performed with the original waveguides, i.e., the water bolus of the straight waveguide had not been modified yet.

The waveguides could be used in a non-coherent and a coherent mode. For the non-coherent mode two separate RF generators were used. For the coherent mode the Enraf Nonius generator was modified to provide an additional low level signal output which was used, through an electronic attenuator, as input signal for the ENI amplifier. The straight applicator was connected to the ENI amplifier and the bended waveguide to the Enraf Nonius RF generator. The RF output level of the straight waveguide could be controlled by the attenuator. The phase difference between the waveguides was controlled at high power levels by adapting the total length of coaxial cable between RF source and waveguide. The 'electric length' of each waveguide was obtained by dividing the physical length of the waveguide from the coaxial cable connection to the aperture by the waveguide wavelength ($\lambda$). These values were 0.66$\lambda$ for the straight waveguide and 1.0$\lambda$ for the bended waveguide. In the phantom experiments of the first series and in the animal experiments the RF power input to the straight waveguide was set at one third of the bended waveguide
to correct for the difference in radiating efficiency between both waveguides. In the second series of phantom experiments the power ratio between both waveguides was varied.

**Phantom experiments**

The phantom composition and construction as well as the procedure to measure the temperature distribution at the surface of the phantom, using the AGA infrared camera, have been described in Chapter 4.3.1 'Material and methods'. From this series of phantom experiments onwards the technique to measure the temperature distribution of the exposed surface was improved: the AGA infrared camera was interfaced to a personal computer [Van Deursen and Van Rhoon, 1988]. In this way, the temperature distribution was measured within 30 seconds after termination of the heating and hereafter the results will be discussed as SAR distribution. In this chapter, relative SAR means that the SAR distribution is normalized to maximum SAR measured in the plane of interest. Furthermore, the data became available in digitized form and the measured temperature distribution could be corrected for background signals and for errors introduced by the infrared lens.

To investigate whether the presence of the second waveguide affected the SAR distribution as obtained in the single waveguide set-up, experiments were performed with one waveguide active, while the other waveguide was placed in position but was connected to a 50 Ohm dummy load. Hence, RF energy coupled via cross-talk to the second waveguide could be measured and, as it was absorbed in the load, would not be re-radiated by the second waveguide. In the first series of experiments the 'large' phantom, covering the whole aperture, was used to measure the SAR distribution at the central cross-section plane. The plane of measurement was parallel with the direction of the electric field in the aperture for all reported experiments.

After the experience with the animal experiments, a second series of phantom experiments using the 'small' phantom, i.e., covering only the aperture area of the ridge, was performed. The method used to obtain maximum penetration depth has been described in detail in Chapter 4.3.1. To obtain sufficient 'applicator loading', additional water bolí were placed above the aperture area at the sides of the waveguide, comparable to the situation during the animal experiments. This set-up was used to investigate the reproducibility of the SAR distributions and whether the water bolí gave rise to the occurrence of (unexpected) hot-spots.

**Animal experiments**

The in-vivo deep heating feasibility of the ridged waveguides in a parallel opposed arrangement was tested on the hindquarters of pigs. During the experiment the animal was lying on a wooden table in which an opening provided access to the aperture of the straight waveguide to the treatment area. The aperture of the bended
waveguide, carried by the lift truck, was positioned above the straight waveguide on the opposite side of the animal. To increase the penetration depth the areas at the sides of the aperture, which were not covered by the pig, were loaded with phantom material or bags containing deionized water (see Chapter 4.3.1, 'Applicator loading'). Additionally, water bolus were placed in front of each aperture to improve energy transfer between the waveguides and the animal. In some experiments these water bolus were circulated with cold water to cool the subcutaneous tissues to further improve deep heating.

A total of five experiments using three pigs have been performed. The weight of the animals varied between 35 and 55 kilograms and they were under general anaesthesia using Ethrane within a standard mixture of N₂O/O₂ inhalation gases for the duration of the experiment.

The temperature distribution was measured at the central cross-section between both waveguides using multi-point thermocouples connected to an Ellab DU-3 readout unit extended with a ten-channel switchboard. For this purpose five closed-end catheters, Polyethylene tubing (800/100/260/100, Portex Ltd, UK), were inserted over a length of 8 to 15 cm spaced at different distances over the total thickness of the hindquarters of the animal. The thermocouples used were custom-made from copper and constantan wire, with three or four measuring points separated by 2 cm.

RF energy was applied using a power-pulse technique to avoid selective heating of the thermocouples: during the RF on period the thermocouples were removed and they were quickly re-inserted after RF energy was switched off. Temperatures were measured 3 seconds after insertion to allow thermal equilibration of the thermocouple with the surrounding tissue. To further increase the density of thermometry the multi-point thermocouples were pulled back 6 or 8 cm to perform a second series of temperature measurements within the thermometry catheter. The overall time necessary to measure a complete set of temperatures took 2-3 minutes. Generally, the heating time, i.e., the RF on period, was 15 minutes in most experiments and thus the overall pulse period was 17 to 18 minutes.

At the end of each experiment the animal was inspected for acute toxicity and if toxicity was absent, returned to the animal house for a follow-up of at least two weeks to monitor late development of burns.

Results

First series of phantom experiments

Figure 4.18 shows, for both the bended and straight waveguide, the SAR-depth profile through the site of maximum SAR for the situation of the parallel opposed arrangement and for the single waveguide set-up. No influence of the passive second waveguide or the large metal parts of the lift truck is seen on the absorption depth
Figure 4.18. SAR-depth profiles for the bended (a) and straight (b) waveguide at the central cross-section plane through the site of maximum SAR. The SAR-depth profile measured for the single waveguide set-up and for a parallel opposed arrangement with the opposite waveguide connected to a 50 Ohm dummy load are shown.
Figure 4.19. SAR distribution at the central cross-section plane of the aperture obtained with the bended and straight waveguide in the parallel opposed arrangement and radiating in phase. The direction of the electric field is parallel with the plane of measurement. The net power input applied to the straight waveguide is one third of that to the bended waveguide.

profile or the SAR distribution at the central plane of the aperture. The penetration depth measured for the bended or straight waveguide was 6-8 cm and independent of the waveguide arrangement. Generally, the temperature measurement with the bended waveguide had a large signal noise as it was difficult to obtain a sufficient temperature increase due to the low efficiency of the bended waveguide. Furthermore, a large amount (10-20%) of cross-talk between the two waveguides in the parallel opposed arrangement was measured during the experiments.

Figure 4.19 shows the SAR distribution at the central cross-section plane of the aperture obtained with the bended and straight waveguide in the parallel opposed arrangement and operated in phase. The direction of the electric field is parallel with
the plane of measurement. The distribution shows two SAR maxima directly in front of the waveguides and a rapid decrease of the SAR with increasing depth due to diverging of the electromagnetic energy. At the centre of phantom, e.g., at 10 cm depth, the SAR is between 20 and 30% of the maximum SAR in this plane.

An impression of the SAR distribution over the complete aperture is given in Figure 4.20. The distribution in each of the five planes was obtained from five successive experiments using an identical applicator set-up and similar power settings. The normalization has been performed to the maximum SAR measured in the cross-section plane at the minor side of the waveguide. In all experiments the highest SAR was found consistently at the left or right minor side of the aperture. If the SAR distribution at the central cross-section plane is normalized to the maximum SAR at the side plane, then the relative SAR at the centre of the phantom is only 20%.

The effect of coherency and a 180 degrees phase difference on the SAR-depth profiles at the central cross-section plane through the site of maximum SAR is shown in Figure 4.21. As expected, the highest SAR level at the centre of the phantom is obtained when both waveguides are operated coherently and in phase. The SAR depth profile obtained when the waveguides are operated non-coherently is around 10% of the maximum SAR. The third SAR depth profile shown is for the situation in which both waveguides are operated 180 degrees out of phase. In this case, the SAR at the centre does not reach zero, which might be caused by an unbalanced RF power input to the waveguides. The relatively low maximum SAR measured in front of the straight waveguide is indicative for a lower net RF power input to the straight waveguide compared to the bended waveguide.

**Animal experiments**

**First experiment**

The purpose of this experiment was to obtain general experience with the performance and specific characteristics of the waveguide set-up during deep heating of the hindquarters of pigs. Muscle-equivalent phantom material was used to obtain additional loading of the aperture at the side areas.

For the first heat pulse a low RF power setting was used: forward and reflected RF power for the straight waveguide were 80 and 15 W, and 200 and 15 W for the bended waveguide, respectively. A temperature decrease varying from 0.4 to 1.8 °C was measured in the target volume as well as for the core temperature. Apparently, the heat loss under influence of the anaesthesia was larger than the heating due to the absorbed RF energy. For the second heat pulse the forward energy to the waveguides was increased to 170 and 400 W, respectively. The temperature increase measured along the central cross-section line in the midplane is given in Table 4.7. Oral temperature increased only 0.4 °C (32.9 to 33.3 °C) during this period indicating
Figure 4.20. The SAR distribution in a cross-section plane at five different locations of the aperture shown for the waveguides in a parallel opposed arrangement and radiating in phase. The net input power to the straight waveguide is one third of that to the bended waveguide. Normalization of the SAR is performed to the maximum SAR measured in the plane at the side of the waveguide.
Figure 4.21. SAR-depth profiles at the central cross-section plane through the site of maximum SAR for both waveguides radiating (a) coherently and in phase, (b) non-coherently, and (c) coherently and 180 degrees out of phase.
Table 4.7. Forward and reflected power of the waveguides and the temperature increase along the central cross-section line of the midplane for the first animal experiment.

<table>
<thead>
<tr>
<th>Heating time [min]</th>
<th>Forward/reflected power per waveguide</th>
<th>Temperature increase in the central plane¹ at a depth of [mm]</th>
<th>Rectal</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bended</td>
<td>Straight</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>15</td>
<td>400/20</td>
<td>170/10</td>
<td>-0.5</td>
<td>1.6</td>
</tr>
<tr>
<td>15</td>
<td>400/15</td>
<td>180/5</td>
<td>0.5</td>
<td>1.3</td>
</tr>
</tbody>
</table>

¹Total thickness of the hindquarters of the pig was 165 mm. The bended waveguide was at "depth" 0 mm; the straight waveguide 165 mm.

a selective heating of the hindquarters. When the RF power was turned on again an electric discharge destroyed a thermocouple which was not removed from the thermometry catheter. After replacement of the thermocouple and thermometry catheter the experiment was continued with a third and final heating period. For this heat pulse forward and reflected power for the straight and bended waveguide were 180 versus 5 W and 400 versus 15 W, respectively and again selective heating of the hindquarters was obtained. The temperature increase along the central cross-section line is also given in Table 4.7; oral temperature increase was limited to 0.4 °C.

At the end of the experiment a large and severe (third degree) burn was noticed at the "knee" joint of the left hind leg. The severity of the burn was such that the animal was euthanased at the end of the experiment. Two explanations were considered for the occurrence of the burn: (a) the leg had been in front of the aperture of the bended waveguide with the area of the burn located below the edge of the ridge where high intensity fringing fields exist; (b) the area of the burn was in contact with the phantom material at the sides of the aperture, which may have caused a local increase in SAR.

Second experiment

In the previous experiment the muscle-equivalent phantom material might have added to the development of a burn. It was therefore decided to use, from this experiment onwards, deionized water bolli to load the areas at the side of the aperture. Furthermore, in this experiment maximum RF power output, varying between 600 to 700 W, was given to the bended waveguide. At the start of each heat pulse the ratio of the net power input between the straight and bended waveguide was set at approximately 0.33. During the 15 minutes of heating this ratio appeared to vary from 0.37 to 0.22 due to instability of the waveguide impedances. In Table 4.8
Table 4.8. Forward and reflected power of the waveguides and the cumulative temperature increase along the central cross-section line of the midplane for the second animal experiment.

<table>
<thead>
<tr>
<th>Effective heating time (^1) [min]</th>
<th>Forward/reflected power per waveguide</th>
<th>Cumulative temperature increase in the central plane(^2) at a depth of [mm]</th>
<th>Rectal</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bended</td>
<td>Straight</td>
<td>37</td>
<td>57</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>15</td>
<td>620/10</td>
<td>320/90</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>30</td>
<td>600/30</td>
<td>280/70</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>45</td>
<td>620/0</td>
<td>280/120</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>60</td>
<td>700/10</td>
<td>300/150</td>
<td>1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>75</td>
<td>660/10</td>
<td>280/130</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
<td>90</td>
<td>660/10</td>
<td>300/150</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) The table gives the cumulative time of all heat pulses. The time after each heat pulse necessary to perform the temperature measurements (2-3 minutes) is not included.

\(^2\) Total thickness of the hindquarters of the pig was 170 mm. The bended waveguide was at "depth" 0 mm; the straight waveguide 170 mm.

A summary of the temperature increase measured along the central cross-section line of the midplane is given, together with the oral and rectal temperature and the power settings for each waveguide. At the start of the experiment the temperatures at the central cross-section line varied from 29.7 to 30.5 °C. As can be seen from Table 4.8 a selective heating of the hindquarters of the animal was obtained after 90 minutes. However, the temperature increase over the hindquarters is not symmetric and maximum temperature increase, 4.9 °C, occurs at the side in front of the straight waveguide. At the end of the experiment no acute or late toxicity was seen.

**Third experiment**

The animal used in this experiment was the same as used in the second experiment. In the time interval between both experiments of 6 weeks, the animal had recovered and grown to 55 kg. The thickness of the hindquarters was 200 mm. The aim for the ratio between the power of the straight and bended waveguide was 0.33, but variations of ±0.05 had to be accepted. In general, the RF settings for the bended and straight waveguide are similar to those used in the second experiment.

In Figure 4.22 the temperature profiles after six heat pulses, overall time 102
minutes, at four cross-section lines in the midplane are shown. In this experiment skin cooling, at 10-15 °C, was used for the first time. As can be seen in Figure 4.22 a maximum temperature of 41.6 °C is measured at a depth of 110 mm and all profiles show maximum temperature increase at the centre and are relatively symmetric. Furthermore, no increase of the oral temperature was measured and no acute or late (within two weeks) toxicity was noticed.

Fourth experiment

A new animal with a weight of 30 kg and a thickness of the hindquarters of 150 mm was used in this experiment. The waveguide arrangement was identical to the one as used in the third experiment. After the first heat pulse with a net power input ratio of 0.37 the maximum temperature increase measured was located close to the aperture of the straight waveguide. Therefore, the power ratio for the following heat pulses was decreased to a value varying between 0.20 to 0.26 with the aim to homogenize the temperature increase. The cumulative temperature increase after the first five heat pulses, overall heating time 75 minutes, along three cross-section lines in the midplane are shown (see inset) in Figure 4.23a. As can be seen the temperature increase remains higher in front of the straight waveguide, despite the adapted power ratio. Additionally, in this experiment no selective heating of the hindquarters could be achieved as is shown in Figure 4.23b. This figure shows the temperature measured orally, rectally, and close to the centre of the hindquarters (depth 55 mm at line c in Figure 4.23a) versus time. Finally, again no toxicity was seen after this experiment.

Fifth experiment

In this experiment the animal of the fourth experiment was heated for the second time. The interval between both experiments was 4 weeks. The thickness of the hindquarters was now 190 mm. The objective in this experiment was to mimic the clinical treatment, that is, to start with low power output, to slowly increase power output, and to continue the experiment until the temperatures at the hindquarters were above 40 °C. In Figure 4.24 the course of oral, rectal, and hindquarter (at three central sites) temperature is shown. As can be seen, the effectiveness of the cooling from the water bolus is such that the amount of heat withdrawn from the hindquarters is larger than the heat induced by absorption of electromagnetic energy radiated by the waveguides. Only after 90 minutes, when the power input to the waveguides was set at the maximum and the skin cooling was stopped, the temperature started to increase. However, the core temperature represented by the oral temperature showed an increase equal to that measured at the rectum or centre of the hindquarters.
Figure 4.22. Temperature profiles during the third animal experiment as function of depth at four locations A, B, C, and D, as indicated. Time of measurement is 102 minutes after the sixth heat pulse.
Figure 4.23. Temperatures measured during the fourth animal experiment. (a) temperature increase after five heat pulses, time 75 minutes, along three different cross-section lines through the hindquarters of the animal (see inset). (b) Temperature versus time measured orally, rectally and at the centre of the hindquarters.
Table 4.9. Forward and reflected RF power, and temperatures measured orally, rectally and in the central plane at five depth locations during the fifth animal experiment.

<table>
<thead>
<tr>
<th>Effective heating time(^1) [min]</th>
<th>Forward/reflected power per waveguide</th>
<th>Cumulative temperature increase in the central plane(^2) at a depth of [mm]</th>
<th>Rectal</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bended</td>
<td>Straight</td>
<td>10</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>36.4</td>
<td>36.8</td>
<td>36.6</td>
</tr>
<tr>
<td>36</td>
<td>400/15</td>
<td>33.1</td>
<td>33.8</td>
<td>35.0</td>
</tr>
<tr>
<td>90</td>
<td>500/40</td>
<td>35.6</td>
<td>34.8</td>
<td>35.2</td>
</tr>
<tr>
<td>119</td>
<td>600/10</td>
<td>36.6</td>
<td>36.2</td>
<td>36.0</td>
</tr>
<tr>
<td>159</td>
<td>660/45</td>
<td>38.9</td>
<td>38.0</td>
<td>38.0</td>
</tr>
<tr>
<td>213</td>
<td>630/110</td>
<td>41.4</td>
<td>40.9</td>
<td>40.9</td>
</tr>
</tbody>
</table>

\(^1\) Time after the start of the first heat pulse including the time needed to measure the temperatures after each heat pulse; \(^2\) Total thickness of the hindquarters of the pig was 190 mm. The bended waveguide was at "depth" 0 mm; the straight waveguide 190 mm.

Figure 4.24. Time-temperature profile measured orally, rectally and at three sites located centrally in the hindquarters during the fifth animal experiment.
Thus, no selective heating of the hindquarters is obtained. The cumulative temperature change in the central plane at five depth locations is shown in Table 4.9 and a homogeneous heating is obtained throughout this plane.

Unfortunately, when the animal was removed from the waveguide set-up a third degree burn with a diameter of 8 cm and a depth of 3.5 cm (extending to the hip bone) was noticed in the left leg. During the experiment this leg was in front of the straight waveguide with the burn located in the area opposite the ridge and above the exterior edge along the major axis of the waveguide aperture. No thermometry probes were present at this location.

**Second series of phantom experiments**

Figure 4.25 shows the SAR-depth profiles at the location of maximum SAR in the central cross-section plane, i.e., at the centre of the area opposite the ridge, for three successive measurements. In all three experiments the waveguides were loaded with the 'small' phantom and additional water bolus at the sides of the aperture. For the first and second experiment the ratio of net power input between the straight and bended waveguide was about 0.30. For the third experiment this ratio was reduced
in accordance with the outcome of the previous experiments, in order to increase the SAR in front of the bended waveguide. Except for the manipulations concerning the exposure of the plane of interest to the infrared camera for measuring the temperature distribution, the waveguide set-up was left untouched in order to improve reproducibility. Nevertheless, as shown in Figure 4.25, large variations in the resulting SAR distribution were found. On the basis of the SAR-depth profile obtained with the first experiment it appears that only the straight waveguide is radiating energy (Figure 4.25a). In the second experiment (Figure 4.25b) with approximately a similar ratio of net power input to the waveguides, the maximum SAR is still measured in front of the straight waveguide, but now a relative SAR of 50% is measured in front of the bended waveguide. In the third experiment the ratio of the power input of the straight waveguide to the bended waveguide has been reduced to 0.18. In this situation the maximum SAR is measured in front of the bended waveguide (Figure 4.25c), while the SAR in front of the straight waveguide reaches 55%.

The SAR-depth profile obtained in the 'small' phantom, using the same waveguide set-up, but without the additional water bolus at the sides of the aperture is shown in Figure 4.26a. For this experiment again a power ratio of 0.30 was used and, as is shown, a nearly symmetric SAR-depth profile is found for a line through the SAR maximum in front of both apertures. A summary of the forward and reflected power settings for these four experiments is given in Table 4.10. In Figure 4.26b the complete SAR distribution for the central cross-section obtained with the last set-up is shown. The figure illustrates that the area with a SAR of more than 50% of the maximum SAR in front of the bended waveguide is much smaller than the area in front of the straight waveguide.

Table 4.10. Forward and reflected power setting per experiment to investigate the reproducibility of the SAR distribution for the parallel opposed arrangement.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Straight waveguide</th>
<th>Bended waveguide</th>
<th>Ratio of net power input</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>forward power</td>
<td>reflected power</td>
<td>forward power</td>
<td>reflected power</td>
</tr>
<tr>
<td>1</td>
<td>235</td>
<td>95</td>
<td>540</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>240</td>
<td>90</td>
<td>540</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>100</td>
<td>620</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>60</td>
<td>560</td>
<td>20</td>
</tr>
</tbody>
</table>
Discussion

The results obtained in the first series of phantom experiments showed that the SAR distribution induced in a large muscle-equivalent phantom is not affected by the applicator set-up. For both the bended and straight waveguide similar SAR distributions were measured using either a single applicator set-up or the parallel opposed set-up with one applicator connected to a load. In addition, these experiments showed that a large amount of cross-talk existed. Hence, in the parallel opposed arrangement tuning of a waveguide is no longer an independent procedure, but due to the cross-talk proper tuning of one waveguide will also affect the performance of the second waveguide.

The relative SAR values (20-30%) measured at the centre of the midplane in the muscle-equivalent phantom, obtained with both waveguides radiating in phase (Figures 4.19 and 4.21), are in acceptable agreement with the range of relative SAR, 24 to 32% as expected from the SAR-depth profile for a single applicator. Reasonable agreement between extrapolated (12 to 16%) and measured (10%) relative SAR at the centre in the midplane was found for the situation in which both waveguides are operated incoherently. If the waveguides are operated coherently but
180 degrees out of phase then, as expected because of destructive interference, low SAR values are measured at the centre of the midplane. The SAR measurements outside the central cross-section showed that also in the parallel opposed arrangement the highest SAR values were found in the planes located at the left and right minor side of the aperture. In general, the width of the pelvic will be less than 45 cm for most patients. Therefore, during clinical treatments the high SAR values at the side of the aperture are not expected to cause great problems as they are located outside the patient. However, this will not be the case for the small spots with high SAR levels found at the edges of the ridge, which may result in pain or in too high temperatures in normal tissue.

In contrast to the encouraging results obtained in the first series of phantom
Table 4.10. Summary of the animal experiments.

<table>
<thead>
<tr>
<th>Animal experiment</th>
<th>Result</th>
<th>Core heating</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>selective heating at hindquarters asymmetric temperature profile</td>
<td>no</td>
<td>3rd degree burn</td>
</tr>
<tr>
<td>2</td>
<td>selective heating at hindquarters asymmetric temperature profile</td>
<td>no</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>selective heating at hindquarters symmetric temperature profile maximum temperature 41.6 °C</td>
<td>no</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>nonselective heating at hindquarters asymmetric temperature profile</td>
<td>yes</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>nonselective heating at hindquarters homogeneous temperature increase</td>
<td>yes</td>
<td>3rd degree burn</td>
</tr>
</tbody>
</table>

experiments, the results of the animal experiments showed a much lower feasibility of deep heating with the parallel opposed ridged waveguide set-up. A summary of the animal results is given in Table 4.10. In two of the five animal experiments severe third degree burns occurred at sites outside the centre of the field and in places thermometry was not performed. In both experiments the site of the burn was near an edge of the waveguide aperture. The fringing fields present at these edges are expected to be the cause of the burns. Regarding the burn occurring during the first experiment the contact of the leg with the muscle-equivalent phantom material may have enhanced the severity of the burn. Commonly, if such strong local heating occurs in the clinical situation, the patient would complain about pain or too high local temperatures. In such a situation the output of RF power would be decreased to a level tolerated by the patient and generally this will prevent the development of tissue damage. Additionally, in two of the five experiments the core temperature of the animal increased as much as the temperature in the target volume. For the three experiments in which selective heating of the hindquarters could be achieved, it was difficult to obtain a large temperature increase with the available RF power. For only two animals selective heating at the hindquarters could be obtained without toxicity. In one animal the temperature distribution in the central plane was asymmetric, with the maximum temperature increase in front of the straight waveguide. In the other animal (third experiment, Figure 4.22) the maximum temperature increase was measured at the centre of the hindquarters.

The second series of phantom experiments to investigate the unpredictable behaviour of the ridged waveguides in the parallel opposed set-up showed that it is
difficult to obtain a symmetric SAR-depth profile in the central plane. The difference in efficiency between the bended and the straight waveguide increases the sensitivity of the SAR distribution for variations in the amplitude ratio. However, the large variation found in the SAR values directly in front of the bended applicator cannot be explained only by variation in the input RF power. In the first and second experiment the difference in input RF power to both waveguides is negligible. Nevertheless, the relative SAR value in front of the bended waveguide changes from 10-20% in the first experiment to 50% in the second experiment. Furthermore, in the fourth experiment with a similar ratio of the input RF power a symmetric SAR depth-profile is measured. Moreover, comparing the SAR distribution in front of the bended waveguide in this last experiment (Figure 4.26) with the first measured SAR distribution in front of the bended waveguide (Figure 4.19), a large difference can be noted. In the first measurement (Figure 4.19) the SAR distribution in front of the bended waveguide is comparable to the one of the straight waveguide. In the last experiment (Figure 4.26) this is not the case. In fact, the SAR distribution in front of the bended waveguide has a much smaller width compared to the straight waveguide. This difference indicates that the performance of the bended waveguide has changed over the period of the animal experiments. Therefore, at the end of the second series of phantom experiments it was decided to modify the bended waveguide to a straight waveguide.

As with the single waveguide, literature reporting the performance of ridged waveguides used in a parallel opposed arrangement are rather scarce. Again the only data available are from the hyperthermia group in Nancy [Marchal et al., 1991]. They investigated the deep heating performance of parallel opposed ridged waveguides in a cylindrical tissue equivalent phantom of 20 cm diameter. For both waveguides radiating in phase and with approximately equal power they measured a relative electric field strength of 98% at the centre of the phantom. As no details about the experimental set-up are supplied it is difficult to explain the difference in their results compared to the results of this study. One explanation might be that for a cylindrical phantom the RF waves from the sides of the aperture will add to increase the SAR at the centre of the phantom. In the rectangular phantoms used in this study the RF waves from the sides of the aperture will be attenuated strongly by the time they reach the centre of the phantom.

To summarize, the first series of phantom experiments indicated that it is possible to obtain a relative SAR of around 30% at the centre of a 200 mm thick muscle-equivalent phantom using the 27 MHz ridged waveguides of RCA in a parallel opposed arrangement and operating in phase. In subsequent animal experiments it was not possible to reproduce the deep heating feasibility of the ridged waveguides in a parallel opposed arrangement. Hereafter, additional phantom experiments using the ridged waveguides in a parallel opposed arrangement but
under similar conditions showed large variations in the SAR distributions measured.

Especially the unstable performance of the bended waveguide in the parallel opposed set-up caused unpredictable SAR distributions. This fact and, to a lesser extent, the high intensity fringing electric fields at the edges of the waveguide aperture, make the original 27 MHz ridged waveguides of RCA unsuitable for clinical use in a parallel opposed set-up to induce loco-regional deep heating. On the other hand, the relative SAR level of 30 to 40%, as measured at the centre of the muscle-equivalent phantom, was within the range anticipated at the start of the study. Therefore, it was decided to adapt the bended waveguide to a straight waveguide in order to improve the stability. Additionally, improvement of the reproducibility was expected if phase and amplitude measuring equipment would be installed at the aperture of each waveguide. However, at the time the bended waveguide was modified to a straight waveguide (autumn 1988) progress made in the development of the radiative applicators using a circumferential electric field distribution was such that it was decided to stop further research on the ridged waveguide system.
Chapter 5
The HTM3000P capacitive hyperthermia system

5.1 Introduction

At the start of this study in 1987, several devices using electromagnetic energy, e.g., the annular phased array system [Turner, 1984], the Thermotron RF-8 [Kato et al., 1985; Song et al., 1986], the concentric coil [Storm et al., 1981], the ridged waveguide [Paglione et al., 1981], and the coaxial TEM applicator [Lagendijk, 1983] were under investigation to determine their feasibility to induce loco-regional deep hyperthermia. These investigations had not yet resulted in clinical data showing improved response rates, but rather the reports were mostly confined to the evaluation of the efficiency of a system for regional deep heating [Emami et al., 1984; Gibbs et al., 1984; Marchal et al., 1985; Oleson et al., 1983a; Stewart et al., 1984] or to the comparison of two systems [Sapozink et al., 1985]. Although technical progress was made, the interpretation of the clinical experience with the various devices was complicated and it was difficult to decide whether a particular technique was to be preferred. On the one hand, based on principles of physics, some researchers anticipated more favourable deep heating feasibilities of those devices, which generate a radiative, circumferential electric field distribution around the patient, than from the radiofrequency (RF) capacitive systems [Franconi, 1987; Hand, 1987; Turner, 1984]. On the other hand, clinical experience with both the radiative and the RF capacitive systems did not support this assumption.

For a number of cases it was shown to be possible to heat lower pelvic tumours with either the annular phased array system [Gibbs et al., 1984; Sapozink et al., 1985] or a single 27 MHz ridged waveguide [Marchal et al., 1985], but the majority of the loco-regional deep hyperthermia treatments were characterized by a low and moreover unpredictable thermal dose. Subjective and objective local problems such as pain in various organs and in bone [Emami et al., 1984], but also tissue necrosis or thrombosis [Marchal et al., 1985] were reported to limit the temperature increase. In addition, patient intolerance to the treatment due to general symptoms like anxiety and a rise in core temperature were serious practical problems at that time, which resulted in the application of a very moderate heat dose with the radiative
hyperthermia systems.

At the same time, several researchers [Abe et al., 1986; Hiraoka et al., 1987a,b; Kato et al., 1985; Nishimura et al., 1986; Song et al., 1986] demonstrated the ability of RF capacitive hyperthermia systems to achieve regional deep heating in Japanese patients with acceptable treatment times (1 hour). A clear advantage of the RF capacitive systems over other deep heating systems is their simplicity and ease of handling. Due to the relatively small applicators used, good access to the patient during treatment is provided and the applicator set-up causes no systemic stress. Well-known disadvantages of RF capacitive systems are excessive heating at the edges of the electrodes and preferential heating of the subcutaneous fat tissue. However, measures were introduced which should partly eliminate these problems. Excessive heating at the edge of the electrodes can be adequately reduced by the use of a salt-water bolus in front of the electrode [Brezovich et al., 1981; Hand and Hind, 1986; Reddy et al., 1987]. To oppose the preferential heating of the subcutaneous fat tissue it is essential to perfuse the bolus in front of the electrodes with cold water at a temperature of 5-10 °C. In a theoretical study using a one-dimensional bioheat equation, Kato et al. [1985] predicted that cooling of the skin surface at 10 °C can prevent preferential fat heating if the thickness of the fat tissue is less than 1.4 cm. In an experimental study using RF capacitive heating with cooling of the subcutaneous tissue Kato et al. [1985] demonstrated that good deep heating of the lower abdomen of pigs could be obtained without overheating the fat tissue.

Clinically, Hiraoka et al. [1987a] demonstrated that preferential heating of the fat layer could be adequately counteracted with efficient cooling, provided that the fat layer does not exceed a thickness of 2.0 cm. Additionally, Kato et al. [1985] and A. Yerushalmi (personal communication, 1986) suggested using extensive pre-cooling of the subcutaneous fatty tissues to further reduce the limiting effects of preferential fat heating.

Most studies showing adequate heating with an RF capacitive hyperthermia system have been performed on Japanese patients, as they generally are less obese than European or American patients. The aim of the present study was to investigate the capability of a particular RF capacitive hyperthermia system, including extensive pre-cooling of the subcutaneous tissue, to induce loco-regional heating in deep pelvic tumours for a selected group of Dutch patients. The commercially available RF capacitive system HTM3000P was used, of which the heating characteristics were -prior to the clinical application- verified on phantoms and animals. This system will be described in the following sections.

5.2 HTM3000P capacitive hyperthermia system

The HTM3000P system (MME, Israel and Tecnomatix, Belgium) operates at a
frequency of 13.56 MHz and is equipped with standard rigid rectangular capacitor plate electrodes of $10 \times 10 \text{ cm}^2$ and $15 \times 20 \text{ cm}^2$. For cooling purposes a water circuit is integrated within each capacitor plate and connected to the cooling unit of the HTM3000P system (minimum water temperature 5 °C). Impedance matching is performed automatically by the system and maximum RF power output is 1400 W. For thermometry the HTM3000P system is equipped with five thin (diameter 0.6 mm) Teflon-coated copper-constantan thermocouples. Each thermocouple is RF filtered and at the beginning of an experiment or treatment an RF interference test with the thermocouples in place was performed to check for self-heating. In this way, continuous temperature monitoring could be performed during clinical treatment without RF interference. Furthermore, the system is computer controlled to facilitate the clinical treatment, to automatically verify whether all subsystems (cooling, matching, thermometry, etc.) are properly working and to display this information including the measured temperature distribution. If a subsystem fails RF power is automatically switched off. Transfer of RF power to the patient can be set continuous or pulsed with variable on-off intervals in steps of 5 seconds. A schematic representation of the HTM3000P is given in Figure 5.1.

Figure 5.1. Schematic representation of the HTM3000P capacitive system.
5.3 Phantom and animal experiments with the HTM3000P capacitive hyperthermia system

5.3.1 Materials and methods

Phantom experiments

For each applicator configuration the SAR distribution was measured in a homogeneous muscle-equivalent phantom with an area of 40 × 30 cm². The thickness of the phantom was 10 cm with the small capacitor plate electrodes (HTM100, size 10 × 10 cm²) and 20 cm with the large capacitor plate electrodes (HTM300, size 15 × 20 cm²). For these experiments the capacitor plates were placed directly on the phantom material; no water cooling of the capacitor plate was used. The muscle material used was composed of 3 weight per cent agar, 0.33 weight per cent formaldehyde and 0.32 weight per cent NaCl in de-ionized water. The electric conductivity was estimated to be 0.6 S/m at 13.56 MHz [Ishida and Kato, 1980]. The SAR distribution was derived from the temperature distribution, which was measured after 3 minutes of heating with an RF input power of 500-900 W. After removing the capacitor plates and splitting the phantom, the temperature distribution of the exposed surface was measured within 30 seconds after termination of the heating by means of an AGA infrared camera interfaced to a personal computer [Van Deursen and Van Rhoo, 1988].

Animal experiments

To test the in-vivo deep heating feasibility of this system the hindquarters of pigs were first cooled for 30 minutes. The subcutaneous tissues were cooled by the water circuit integrated within each capacitor plate with the water temperature at 5 °C. No additional water bolus between the capacitor plates and the skin was used in these experiments. As the animal was lying on the lower capacitor plate, good contact between the capacitor plate and the skin of the animal was easily obtained. For the upper capacitor plate tape had to be used in order to improve the thermal contact by applying some pressure on the capacitor plate. After 30 minutes of pre-cooling, RF heating was administered for 1.5 - 2 hours with the large (15 × 20 cm²) capacitor plates. Four deep heating experiments, using two animals, were performed: three with the first - and one with the second animal. The first time an animal was used in a deep heating experiment, it was 3 months old and weighed ±35 kilo. The

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animals were under general anaesthesia using Ethrane within a standard mixture of \( \text{N}_2\text{O}/\text{O}_2 \) inhalation gases for the complete duration of the experiment. Temperatures were measured with the thermocouple system of the HTM3000P system and additionally with a fibre-optic thermometry system: the TP4 Clinitherm and the ASEA fibre-optic thermometry system (FT1110, only used in the fourth experiment). The Clinitherm TP4 fibre-optic thermometry system does not display temperatures below 20 °C. In each experiment 9 to 12 catheters, insertion length 8 to 15 cm, were used to acquire the temperature information of the surface tissues as well as of the tissues at a relative depth of approximately 1/4, 1/2, and 3/4 of the total thickness of the hindquarters. The insertion depth of the thermometry catheters was chosen such that the tip of all catheters was in the central cross-section between the capacitor plates. The thermometry catheters were made of Polyethylene tubing (800/100/260/100, Portex Ltd, UK) with an outer diameter of 1.27 mm and an inner diameter of 0.86 mm. A schematic representation of the experimental set-up is given in Figure 5.2. In the third and fourth experiment the thermometry probes were pulled back manually through the catheters with intervals of 1 cm ("thermal mapping") to obtain information about the temperature distribution along the catheters.
Figure 5.3. Relative SAR distribution in the vertical cross-section plane at the centre of the HTM300 capacitor plate electrode along the major axis (20 cm). Frequency 13.56 MHz; net input power 900 W for 3 minutes; phantom size $20 \times 30 \times 40 \text{ cm}^3$.

5.3.2 Results

Phantom experiments

For the small capacitor plate electrodes the effective treatment area (relative SAR $\geq 50$ per cent of the maximum SAR measured) directly below the electrodes equals the plate size ($100 \text{ cm}^2$). Although the heating is inhomogeneous with the highest SAR-values located at the side opposite the cable connection, there is no edge effect noticeable. The effective treatment area decreased to $75 \text{ cm}^2$ and $\pm 35 \text{ cm}^2$ at a depth of 2.5 cm and 5 cm, respectively; the total phantom thickness was 10 cm. The SAR measurement for the large applicator ($15 \times 20 \text{ cm}^2$) with a phantom thickness of 20 cm did not show any edge effect either, and maximum SAR values opposite the cable connection. However, for this applicator the effective treatment area at the phantom surface is smaller ($225 \text{ cm}^2$) than the plate size ($300 \text{ cm}^2$). Figure 5.3 shows the SAR distribution in the vertical cross-section at the centre of these large capacitor plates. The distribution shows that the SAR drops rapidly with increasing depth and is decreased at the centre of the phantom to a relative SAR of 30 per cent of the maximum SAR at the surface. If there was only partial contact between the electrode and the phantom surface, the effective treatment area at the surface of the phantom was reduced to $90 \text{ cm}^2$. 
Figure 5.4. Temperature-time profile for the first animal experiment. (a) Catheters 1, 2, 3 and 4. (b) Catheters 5, 6, 7, 8 and 9.
Animal experiments

The temperature-time profiles for the different locations in the central plane of the first experiment are shown in Figures 5.4a and 5.4b. In this experiment the pig weighed 35 kg and the distance between the electrode at the left and the right thigh of the pig was 19 cm. The fat thickness varied between 8 and 17 mm within the area below the capacitor plates. The temperature profiles measured at the side on which the animal was lying during heating are labelled with "low side" and the accompanying number indicates the approximate distance of the temperature probe to the lower capacitor plate. Likewise, the temperature profiles in the upper thigh are labelled with "high side" and the accompanying number indicates the distance of the temperature probe to the upper capacitor plate. The label with the highest number, in this experiment temperature profile "high side 95 mm" (Figure 5.4b), was located centrally between the electrodes. Pre-cooling for 30 minutes gave, as shown in Figures 5.4a and 5.4b, a maximum temperature reduction, about 20 °C, of the subcutaneous tissues at 5 mm depth. Less, but still substantial cooling, 5-15 °C, was measured in the subcutaneous tissues at a depth of 25 mm and, as expected no or minimal cooling occurred at the deeper locations. The steep temperature increase for the subcutaneous temperature locations after the RF power had been turned on indicated that a large amount of energy was deposited in the fatty tissue. Once a temperature of 43 °C was reached at depth the RF power could be reduced from 600 W to 130 W and the temperature could be easily maintained at a constant level by small power variations. Although a rather small pig was used, the increase of core temperature, measured orally, was negligible. At the end of the treatment a small, second degree burn was observed in the subcutaneous tissue between both hind legs.

In the second experiment with this animal, weight 39 kg and a distance between the capacitor plates of 20 cm, again deep heating could be easily obtained and controlled, as during the first experiment. The time period between both experiments was 2 weeks. In Table 5.1 the temperature distribution across the central plane is given after 30 minutes of heating. At the end of this treatment no new burns had developed.

The third experiment with the same animal, weight 65 kg, fat thickness 8 to 25 mm and with a distance between the capacitor plates of 22.5 cm, lasted 2 hours (30 minutes cooling and 90 minutes heating). This experiment was performed 5 weeks after the second experiment. The temperature-time profiles at the different locations in the central plane are shown in Figures 5.5a and 5.5b. Again, these figures show the effectiveness of pre-cooling and rapid heating of the superficial tissue layers. The latter effect was also noticeable if RF power was switched on each time after a short period of zero RF power for temperature regulation purposes. Additionally, the temperature at the central location remained lower than the temperature at the 1/4 ("high side" 40 mm) and 3/4 depth ("low side" 60 mm)
Figure 5.5. Temperature-time profile for the third animal experiment. (a) Catheters 1, 2, 3 and 4. (b) Catheters 5, 6, 7, 8, and 9.
Figure 5.6a,b. Temperature profiles as function of position along the thermometry catheter at different times during the third animal experiment: at the start of the experiment, after 25 minutes of cooling, and after 30 and 90 minutes of heating. (a) superficial catheter 1. (b) superficial catheter 9.
Figure 5.6c,d. Temperature profiles as function of position along the thermometry catheter at different times during the third animal experiment: at the start of the experiment, after 25 minutes of cooling, and after 30 and 90 minutes of heating. (c) superficial catheter 6. (d) intramuscular catheter 5.
location. In catheters 1, 9, 6, and 5 thermal mapping was performed at different times during this treatment: at the start of the experiment, after 25 minutes of cooling, and after 30 and 90 minutes of heating; the results are shown in Figures 5.6a to d. For the superficial catheters (1, 9, and 6) the effect of cooling was noticeable along the whole catheter length. For the superficial tissue the temperature increase during heating appeared to be dependent on the effectiveness of (pre)cooling, i.e., the temperature profile during heating followed the temperature profile after 25 minutes of cooling. For the temperature profile at 40 mm depth, Figure 5.6d, there was no effect of cooling and the temperature increase during heating was higher for the locations closer to the central cross-section. At the end of the treatment again a second degree burn was noticed between the hind legs of the pig.

The fourth experiment was performed with the second animal; weight 32 kg, distance between the electrodes 16.5 cm and fat thickness from 8 to 15 mm. A salt water bag (9 g NaCl per litre water) was placed between the hind legs of the animal to prevent the occurrence of burns at this site. Additionally, three catheters (10, 11, and 12) were inserted subcutaneously below the upper capacitor plate in a plane perpendicular on the central plane, directed from the hip towards the foot. Depth of insertion was 4, 3, and 6 mm, respectively. The temperatures in these catheters were measured with the ASEA fibre-optic thermometry system. The temperature-time profiles at the central plane for this experiment are shown in Figures 5.7a and 5.7b. Maximum heating occurred at the "high side" of the animal. It was not possible to change this distribution. In this experiment thermal mapping was performed at different times during the period (time interval 20 to 60 minutes) the temperatures at depth, i.e., catheters 5, 6 and 7, were stabilized. The result is shown in Figures 5.8a - 5.8d. Figure 5.8a gives the temperature profile along the catheter for the three additional subcutaneous locations (catheters 10, 11, and 12) after 20 minutes of heating. Compared to the temperature profiles measured along the catheters at the "standard" subcutaneous locations, Figures 5.8b and 5.8d, it can be seen that the temperatures along catheters 11 and 12 (Figure 5.8a) are much higher (range 41 to 44 °C). For the deeper locations, catheters 5, 6, and 7, the temperature along catheter 5 is above 45 °C over a length of 2 cm, which is 2-3 °C higher than the maximum temperatures measured along catheters 6 and 7 which were located more towards the lower electrode. No burns could be detected at the end of the treatment. However, during the follow-up period a deep intramuscular burn developed in the right hind leg below the upper capacitor plate for which the animal had to be euthanasized after one week. At the autopsy that followed a large intramuscular burn, diameter 10 cm, was observed extending from the fat-muscle transition to the region where catheter 5 had been located, that is, at a depth of 3 to 4 cm.
Figure 5.7. Temperature-time profile, for the fourth animal experiment. (a) catheters 1, 2, 3, 4 and 5. (b) catheters 6, 7, 8, 9 and 10.
Figure 5.8a, b. Temperature profiles as function of position along the thermometry catheter at different times during the fourth animal experiment. (a) Subcutaneous catheters 10, 11, and 12, time 20 minutes. (b) Subcutaneous catheters 1, 2, and 3, time 50 minutes.
Figure 5.8c,d. Temperature profiles as function of position along the thermometry catheter at different times during the fourth animal experiment. (c) Intramuscular catheters 5, 6, and 7, time 55 minutes. (d) Subcutaneous catheters 4, 8, and 9, time 40 minutes.
Table 5.1. Temperature profile along the main axis of the central plane between the upper and lower capacitor plate electrode for all animal experiments after 30 minutes of heating.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Distance between electrodes [mm]</th>
<th>High side [mm]</th>
<th>Centre</th>
<th>Low side [mm]</th>
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<tr>
<td></td>
<td>5-10 7-25 40-55</td>
<td>High side</td>
<td>Low side</td>
<td>45-60</td>
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<td>1</td>
<td>190</td>
<td>29.4</td>
<td>41.7</td>
<td>44.1</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
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<td>42.9</td>
<td>41.2</td>
</tr>
<tr>
<td>3</td>
<td>225</td>
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</tr>
<tr>
<td>4</td>
<td>165</td>
<td>27.2</td>
<td>32.6</td>
<td>44.6</td>
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5.3.3 Discussion

In the experiments performed with the homogeneous muscle-equivalent phantoms no edge-effect could be measured. This can be explained by two factors. First, the capacitor plate electrode is covered by a 3-5 mm thick rubber insulator. Because of this insulator the high concentration of RF currents at the edges of the electrode will be already diverged to some extent when they reach the phantom tissue. Secondly, the applicator has been designed with holes in the metal electrode. In this way additional edges are created which may add to a homogenization of the SAR distribution. The experiments showed also that immediately below the applicator the effective field size for the small applicator equalled the applicator size, that is, 100 cm², while for the large applicator the effective field size, 225 cm², was smaller than the applicator size, 300 cm². For both applicators the maximum SAR was always measured at the side opposite the cable connection. As expected, a rapid decrease of the SAR with depth was found. For the large electrode the relative SAR-value at the centre of the 20 cm thick muscle-equivalent phantom dropped to 30% of the maximum value. Furthermore, the effective field size depended on the contact between the electrode and the phantom.

The animal experiments performed show that deep heating can be obtained with the HTM3000P capacitive hyperthermia system. In Table 5.1 the temperature profiles along the main axis of the central plane between the electrodes are given for all four experiments during steady state conditions.

Pre-cooling for 30 minutes using the cooling system integrated in the capacitor plate electrodes with a water temperature of 5 °C lowered the temperature of the superficial tissues (depth 5-10 mm) to around 15 °C. The temperature increased with depth but for the subcutaneous tissues at a depth of 10-25 mm pre-cooling could still
lower the temperature to 20-30 °C. From Table 5.1 and the data presented in the various temperature-time graphs (Figures 5.4 - 5.8) it is clear that more efficient cooling was obtained at the side on which the animal was lying during heating. Due to this difference in cooling efficiency the temperature profile along the main axis of the central plane is asymmetric in all experiments, with the higher temperatures located at the upper side. The inability of a capacitive system to customize the power input per capacitor plate electrode, and thus the inability to adjust asymmetry of the temperature distribution, is inherent to a two-plate capacitive hyperthermia system.

The differences in the locally absorbed energy were illustrated by the large variation in temperature increase at the time RF power was turned on. The rate of temperature monitoring in these experiments was, unfortunately, too low to allow the calculation of the local SAR on the basis of the power-pulse technique. During the initial heating period the temperature of the subcutaneous tissues could increase to 40-44 °C. Once a stable temperature at depth was reached the RF power was reduced and the temperature of the subcutaneous tissues decreased at most sites to acceptable levels. As can be seen in Table 5.1 it became more difficult to raise the temperature at the centre of the treatment field when the distance between the electrodes increased. In general, a stable temperature at depth could easily be maintained by small power variations. In all animal experiments the increase of core temperature, measured orally, was less than 1 °C. At the end of each experiment the colour of the skin below the capacitor plate electrode was white, indicating vasoconstriction due to the effectiveness of cooling. Shortly after removal of the electrodes, the skin blood flow recovered and the colour changed to healthy pink.

Minimal toxicity was seen at the superficial tissues directly below the capacitive plate electrodes, again illustrating the effectiveness of the cooling. With regard to the burns that developed in the subcutaneous tissue between both hind legs during the first and third treatment, it is expected that these can be prevented by placement of a salt water bag between the legs. The severe burn observed after the fourth experiment can be explained by the high temperatures of 44-46 °C that were measured at this location for long periods. Compared to the temperature profiles measured at the "standard" subcutaneous locations in the central plane, Figures 5.8b and 5.8d, it is conspicuous that two of the three temperature profiles in Figure 5.8a are in the range from 41 to 44 °C, while for all other profiles at the subcutaneous locations the temperatures remain below 39 °C. At autopsy it was observed that the burn extended along the tracks of the additionally placed subcutaneous thermometry catheters towards the intramuscularly located thermometry catheter "high side 32 mm". One reason might be that the - better conducting - cylinder of interstitial fluid around the catheter tracks may have formed a shunt for the RF energy through the fat tissue, resulting in a higher energy deposition around these catheters. This also
explains the high temperatures measured by two of the three additional subcutaneous thermometry catheters.

In summary, the experiments performed indicate that the HTM3000P is able to heat large volumes at depth to therapeutic temperatures in pigs with a fat layer of 1-2 cm. The efficiency of pre-cooling of the subcutaneous tissues depends strongly on the thermal contact between the cooling device and the skin. In the clinical situation an additional salt water bolus bag needs to be attached to the capacitor plate electrodes to improve the cooling of the subcutaneous tissues. Furthermore, the risk of severe burns will be less during patient treatments, as the patient will not be anaesthetized and thus will warn for high temperatures at sites were no thermometry is performed.

5.4 Radiofrequency capacitive heating with the HTM3000P of deep-seated tumours using pre-cooling of the subcutaneous tissues: results on thermometry in Dutch patients

5.4.1 Materials and methods

Patient population

From September 1987 to March 1990, 11 patients (10 male and one female), with large pelvic tumours were included in this feasibility study. Ten patients had a recurrent rectal carcinoma and one patient had a recurrent sigmoid carcinoma. Tumour dimensions ranged from $5 \times 5 \times 6$ to $15 \times 16 \times 14$ cm$^3$. Tumour location was presacral in nine patients and eccentric to the lateral side of the pelvis in two patients. Clinical selection criteria included Karnofsky $\geq 70$, no heart complaints, and normal blood pressure. A thickness of the subcutaneous fat $\geq 2$ cm at the centre of the field at the dorsal side of the patient or metallic implants were exclusion criteria. A detailed description regarding sex, age, fat thickness, and pelvic size of patients accepted for this study is given in Table 5.2. One patient (#301) was included in the study despite the fact that the anterior fat thickness exceeded 2 cm. For all patients the thickness of the fat tissue increased going from the centre towards the more lateral measurement sites.

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### Table 5.2. Patient characteristics

<table>
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<th>Patient number</th>
<th>Sex</th>
<th>Age yr</th>
<th>Fat thickness [cm]</th>
<th>Pelvis size [cm]</th>
<th>Number thermometry catheters</th>
<th>HT treatments standard set-up</th>
<th>adapted set-up</th>
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<td></td>
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*patient 0301 excluded in calculation of mean and standard deviation (sd).*

### Heating methods

All treatments were performed with the HTM3000P RF capacitive system as described in Chapter 5.2. During the clinical treatments an additional flexible water bolus was used in front of each capacitor plate to obtain good coupling between the ridged plate and the tissue, and to provide good cooling of the subcutaneous tissues. These water bolus, size 15 × 15 cm² and 20 × 25 cm², were perfused with saline water, 1 g/l NaCl, with a temperature of 5-10 °C measured at the bolus site. For the eccentric tumour locations with tumour growth extending to the subcutis the temperature of the additional water bolus was increased to 30-40 °C. In general, a pair of the largest capacitor plates with the largest water bolus were used. In many treatments the transfer of RF power to the patient was set from continuous to pulsed with variable on-off intervals in steps of 5 seconds when the maximum tolerance of the patient was achieved.

### Thermometry

For thermometry the five thin (diameter 0.6 mm) Teflon-coated copper-constantan thermocouples of the HTM3000P system were used. Each thermocouple is RF filtered and at the beginning of each treatment an RF interference test with
the thermocouples in place was performed to check for self-heating. In this way continuous temperature monitoring could be performed during clinical treatment without RF interference. Additionally, a 24-channel fibre-optic thermometry system (FT1210, Takaoka, Japan) was used for deep and superficial temperature measurement. Both systems were calibrated against a standard mercury thermometer and showed an accuracy of ±0.2 °C. Before the first hyperthermia treatment all patients had thermometry catheters inserted transcutaneously and under guidance of computed tomography into tumour and normal tissues (see Table 5.2). The thermometry catheters were made of Polyethylene tubing (800/100/260/100, Portex Ltd, UK) with an outer diameter of 1.27 mm and an inner diameter of 0.86 mm. Each catheter remained in place until the end of the whole treatment series, unless it had to be removed for clinical reasons (infection). For the patients with a presacral tumour location the objective was to insert two deep thermometry catheters through the buttocks into the tumour. Additionally a third superficial thermometry catheter was inserted at 1-2 cm depth in the subcutis at the back of the patient. For eccentric tumours two or more thermometry catheters were inserted through the skin closest to the tumour volume. If possible, thermal mapping was performed at 15 min intervals during each hyperthermia treatment by manually moving the temperature probe in 1 cm steps along the thermometry catheter. In practice, at least one thermal mapping during the cooling period and two thermal mappings during the heating period were obtained. Location and tissue type of each temperature measuring point was obtained from the computed tomography scan obtained during placement of the thermometry catheters.

**Hyperthermia**

Hyperthermia was applied twice weekly immediately after irradiation, except for one patient (0385) who had only one hyperthermia treatment in combination with

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**Figure 5.9.** Schematic example of the standard and the adapted applicator set-up used.
Table 5.3. Number of temperature measuring points per treatment.

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Range</th>
<th>Mean</th>
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<tr>
<td>Tumour</td>
<td>1-16</td>
<td>9.4</td>
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<tr>
<td>Muscle</td>
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<td>Connective tissue</td>
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intra-arterial chemotherapy. The hyperthermia treatment consisted of 30 minutes pre-cooling using the flexible bolus with a water temperature of 5-10 °C, a heating period until the tumour temperature reached 42 °C but with a maximum of 15 minutes, and a hyperthermia treatment period of 1 hour. During the hyperthermia treatment period the goal was to obtain a minimum tumour temperature of 43 °C. If this goal could not be obtained hyperthermia was administered at maximum tolerable RF power or until normal tissue temperatures reached 44 °C. Two types of applicator set-up were used. At the start of the study the "standard" set-up with a capacitor plate at the anterior and posterior side of the patient was used. From the third patient onwards, an adapted set-up with a capacitor plate at the lateral sides of the patient was also used. In Figure 5.9 both the standard and adapted set-up are illustrated.

Evaluation of the hyperthermia treatment is performed using the percentage of all measured temperatures above 40 °C (both in space and time) and the mean and maximum temperature calculated over the 1 hour hyperthermia treatment period.

5.4.2 Results

A total of 53 out of 57 hyperthermia treatments performed were available for evaluation of the capability of the RF capacitive system to induce deep heating in pelvic tumours. In four hyperthermia treatments the temperature data were insufficient for analysis. Table 5.3 gives the number of individual temperature measuring points per treatment for each tissue type within the hyperthermia treatment volume.

Effect of pre-cooling

Generally, the extensive skin cooling with water at 5-10 °C for 30 minutes was very well tolerated by the patients. Only the initial contact with the cold water bolus caused some discomfort which diminished rapidly.
Figure 5.10. Mean temperature profile along the catheter track measured after 20 minutes of cooling with water at 5-10 °C and after 30 and 60 minutes of heating. Data are given only for the subcutaneous tissues. (a) Standard applicator set-up, average over 11 treatments. (b) Adapted applicator set-up average over 13 treatments. The bar indicates one standard deviation. S = skin; F = fat; M = muscle.

In Figure 5.10a and 5.10b the mean temperature distribution along the deep thermometry catheters is shown for both the standard (11 treatments) and adapted (13 treatments) applicator set-up after 20 minutes of pre-cooling and after 30 and 60 minutes of RF heating. As shown in Figure 5.10a and 5.10b, 20 minutes of pre-cooling reduces the temperature of the subcutaneous fatty tissue at the skin to below 15 °C. In contrast, the blood flow and good thermal conductivity of the muscle tissue oppose a large temperature decrease at the fat-muscle interface and therefore the temperature during cooling does not decrease below 25 °C at this location. Note that the thermometry catheters are not crossing the fat layer perpendicular, and therefore the catheter length within the fat tissue is not equal to the measured fat thickness.
Table 5.4. Normal tissue and tumour temperatures during the different applicator set-ups used for patient no. 0311.

<table>
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<td>$T_{\text{max}}$</td>
<td>$T_{\text{mean}}$</td>
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<tr>
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<td>44.4</td>
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<tr>
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<td>41.8</td>
<td>38.1</td>
<td>42.6</td>
<td></td>
</tr>
</tbody>
</table>

as reported in Table 5.2! The difference in thermal conductivity of the fat and muscle tissue is very well illustrated by the difference in the slope of the temperature profile in both tissues and the effect of cooling disappears rapidly with increasing muscle tissue depth.

The temperature profiles obtained after 30 and 60 minutes of RF heating illustrate the feasibility of the cold water cooling technique to effectively remove the RF energy from most of the fat layer and to protect it from overheating. However, at the interface from fat to muscle tissue the cooling is, as mentioned above, less effective and at this place preferential fat heating, with maximum temperatures exceeding 44 °C, range 41.1 to 45.7 °C, cannot be prevented!

Effect of applicator set-up

At the start of this study only the standard set-up for the capacitive plate applicators was used, that is, anterior and posterior applicators for the presacral tumour location. However, the temperatures obtained during the first hyperthermia treatment of the third patient using the standard applicator set-up were very disappointing, i.e., the maximum tumour temperature was only 38.8 °C. Therefore, it was decided to investigate the effect of different applicator placements. As demonstrated in Table 5.4, the best result with respect to mean and maximum tumour temperature was obtained during the fifth treatment using the adapted applicator set-up. By placing the applicator under an angle of approximately 45° at the left and right side of the patient the maximum tumour temperature obtained was
Table 5.5. Paired comparison of tumour temperature of the best treatment with each applicator set-up.

<table>
<thead>
<tr>
<th>Patient</th>
<th>% temperatures above 40 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>311</td>
<td>0</td>
</tr>
<tr>
<td>321</td>
<td>100</td>
</tr>
<tr>
<td>324</td>
<td>71</td>
</tr>
<tr>
<td>370</td>
<td>4</td>
</tr>
<tr>
<td>371</td>
<td>67</td>
</tr>
<tr>
<td>383</td>
<td>17</td>
</tr>
</tbody>
</table>

nearly 2 °C higher than with the more conventional standard applicator set-up.

From the 11 patients in this study, six have been treated with both the standard and adapted applicator set-up and could be evaluated for the effect of the applicator configuration upon temperatures achieved. A comparison of the percentage of the measured tumour temperatures above 40 °C for the best treatment with each set-up is given in Table 5.5. As shown, the temperature data of this group of six patients do not show a clear advantage for the standard or adapted applicator set-up. Both the adapted and the standard set-up performed better in two patients, while no difference in performance was obtained in the other two patients. However, if the temperature data are judged per patient a clear benefit for the individual patient can be recognized! If the appropriate applicator set-up is used the percentage of tumour temperatures above 40 °C can increase from 0-20 to as high as 80-100. A comparison of the percentage of tumour temperatures above 40 °C for the first treatment with each applicator set-up showed similar results.

Overall temperature distribution

As a result of the extensive placement of thermometry catheters (mean 2.7 per patient) a large number of temperature measuring points were available to evaluate the overall temperature distribution. The tissue type of each temperature measuring point was identified per treatment. Hereafter, a frequency table of the measured temperatures during the 1 hour treatment period was calculated per tissue type. The
Figure 5.11. Frequency distribution of the temperature measured in the various tissue types for all treatments performed with RF capacitive heating using 30 minutes of pre-cooling with water at 5-10 °C. No distinction is made for the applicator set-up.

The total number of temperature measuring points evaluated was 496 for tumour, 290 for muscle, 381 for fat and 116 for connective tissue. In Figure 5.11 the temperature distribution is shown for all tissue types and indicates that at most sites low temperatures were measured. As shown in Figure 5.11, 58% of all measured tumour temperatures were below 40 °C and a temperature above 41 or 42 °C was obtained in only a small fraction of the tumour measuring points, that is, 7% and 3%, respectively. Similar temperature distributions were found for muscle, connective, and fat tissue. The highest frequency (10%) of measurements with a temperature above 43 °C is found within the fat layer.

Table 5.6 reports for the nine patients with presacral tumour locations the tissue type where the maximum temperature was measured during each hyperthermia treatment. Overall the maximum temperature was measured more frequently in normal (fat, muscle and connective) tissue (67%) than in tumour tissue (33%). Differentiating the results shows that this ratio is better with the standard applicator set-up than with the adapted applicator set-up: 47 versus 53% and 81 versus 19%, respectively. In general, as shown in Table 5.6, the maximum temperature measured within the normal tissue was, besides local pain, often limiting the increase of RF power.
Table 5.6. Frequency (N) of tissue type where the maximum temperature (T_max) was measured during each treatment.

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Overall</th>
<th>Standard set-up</th>
<th>Adapted set-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>&lt;T_max&gt;</td>
<td>sd</td>
</tr>
<tr>
<td>Tumour</td>
<td>12</td>
<td>41.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Muscle</td>
<td>3</td>
<td>42.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Subcutaneous fat</td>
<td>19</td>
<td>43.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>2</td>
<td>42.1</td>
<td>-</td>
</tr>
</tbody>
</table>

<T_max> = average of all T_max measured within that tissue type; sd = standard deviation.

5.4.3 Discussion

Tolerance of the patient to the hyperthermia treatment with the HTM3000P was very good. Some initial discomfort was caused by the pre-cooling, but the patients became rapidly accustomed to the cold water bolus. During treatment the patients were provided with additional cooling (wet washcloths, fan etc.) on request.

From Table 5.6 the standard set-up appears to be more favourable regarding the percentage of treatments with the maximum temperature at the tumour. This difference should, however, be carefully interpreted, as for all patients the average of the maximum tumour temperatures (41.8 °C) was relatively low, and increase of tumour temperature (i.e., RF power) was often limited by local pain. Furthermore, most patients experienced the adapted applicator set-up as being more comfortable.

Clinical studies reporting on the effect of surface cooling before and during RF heating are rather scarce. Hiraoka et al. [1987a] reported in detail on their thermometry results during RF heating. In agreement with the theoretical work of Kato et al. [1985] they reported, for their clinical application using cooling only during RF heating, a greater heating efficacy when the fat thickness measured less than 1.5 cm. Recently, Rhee et al. [1991] reported their results using pre-cooling with RF heating. They found that pre-cooling at 10 °C for 20 minutes could successfully prevent overheating of the subcutaneous fat tissue as thick as 2.0-2.5 cm. Unfortunately, the results of the present study are less favourable regarding the effect of pre-cooling. As shown in Figure 5.11 and Table 5.6, even after 30 minutes of pre-cooling with water at 5-10 °C, preferential heating of the fat could not be avoided in 19 of the 36 hyperthermia treatments (53%). When the results of this study are compared to the data of Rhee et al. [1991] or to the theoretical data of Kato et al. [1985] it should,
however, be realized that within clinical studies the reported fat thickness is very
dependent upon the precise location of the measurement. As is demonstrated in
Table 5.2, the anterior and posterior fat thickness can differ by as much as 1.8 cm.

Independent of the exact fat thickness a qualitative comparison of the
temperature profile measured along the thermometry catheter (Figures 5.10a and
5.10b) shows good agreement with the temperature profiles predicted by Kato et al.
[1985]. As is shown in Figures 5.10a and 5.10b, a steep thermal gradient exists in the
subcutis and the maximum temperature is found only in a small volume at the
transition of fat to muscle tissue. The latter indicates that thermal mapping along a
thermometry catheter crossing the subcutaneous tissues is essential to measure the
maximum temperature of the fat tissue. Thus one must realize that it is highly
probable that the maximum temperature is not measured if the temperature of the
fat tissue is obtained only at a single location. Multipoint temperature measurements
within the subcutaneous tissues are therefore advisable in order to prevent possible
normal tissue damage. In this study patients could tolerate temperatures within the
fat tissue at 2 cm depth as high as 45.5 °C without complaining of pain. This finding
has also been reported by Rhee et al. [1991]. If this limiting temperature is not
adequately measured, RF power will not be reduced and, consequently, subcutaneous
burns may occur.

As mentioned before, in 53% of the hyperthermia treatments preferential fat
heating could not be avoided. For the remaining 47% of the hyperthermia treatments
the limiting factor was local pain. The latter indicates the existence of high normal
tissue temperatures at places where thermometry is absent. This means that the
statement about 53% fat heating only relates to the observed temperatures and
obviously not to all the fatty tissue present within the hyperthermia treatment field.
Furthermore, the inability to customize the SAR distribution to obtain a more
favourable temperature distribution, or to reduce local pain other than by changing
the electrode configuration, was a severe disadvantage. This limitation is even more
enhanced in view of the disappointingly low fraction of the measured tumour
temperatures above 40 °C, as demonstrated in Figure 5.11. Unfortunately, this
problem exists for all presently available two-electrode capacitive RF heating devices.
It should be added, however, that present experience with the second-generation
radiative deep heating devices also indicates a limited feasibility to adapt the SAR
distribution, and a strong dependence of the SAR distribution on tissue anatomy.

In Table 5.7 an attempt to compare the thermometry results of the present study
to the thermometry data given by other groups using RF capacitive heating systems
has been made. Of the literature only the papers of Egawa et al. [1988] and Hiraoka
et al. [1987a] provided sufficient details regarding the thermometry data to enable
a comparison. As can be noticed from Table 5.7, the thermal dose in this study
Table 5.7. Comparisons of thermal dose reported by other groups.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Median maximum tumour temperature</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T&lt;41 °C</td>
<td>41-42 °C</td>
<td>42-43 °C</td>
<td>&gt;43 °C</td>
</tr>
<tr>
<td>Hiraoka et al. [1987a]</td>
<td>15</td>
<td>13%</td>
<td>27%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>11</td>
<td>13%</td>
<td>64%</td>
<td>18%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>N</th>
<th>Treatments with tumour temperatures &gt; 42 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egawa et al. [1988]</td>
<td>8</td>
<td>36</td>
<td>64%</td>
</tr>
<tr>
<td>Present study</td>
<td>11</td>
<td>56</td>
<td>32%</td>
</tr>
</tbody>
</table>

expressed as a frequency table for median maximum tumour temperature, or as the percentage of treatments with at least one tumour temperature ≥42 °C, is lower than reported by both Japanese groups. It should be noted that in this study a different hyperthermia system (HTM3000P) was used than in the other Japanese studies (Thermotron RF-8). However, the difference might also be caused by the fact that for this study a higher probability existed of measuring power-limiting subcutaneous tissue temperatures, as obtained from the extensive thermometry in the fat-muscle interface region. Consequently, lower tumour temperatures can be expected as the RF power was reduced when subcutaneous tissue temperatures exceeded 44.0 °C.

In summary, the present study indicates that pre-cooling with saline water boli at 10 °C is well tolerated by the patient, and can effectively reduce the temperature of the subcutaneous fat tissue. However, pre-cooling cannot avoid preferential heating at the interface from fat to muscle tissue: in 53% of the treatments maximum temperatures were measured in the fat tissue. In this study it is also demonstrated that within this Dutch patient population the quality of the hyperthermia treatment that can be achieved with this type of equipment, is rather poor: 60% of the measured tumour temperatures was below 40 °C. For the individual patient a substantial gain in thermal dose could be obtained when the conventional anterior-posterior applicator set-up was changed to the adapted set-up with lateral applicator positions.
Chapter 6
A ring applicator system for loco-regional deep hyperthermia

6.1 Introduction

Based on the frequency dependent penetration depth, electromagnetic radiation at frequencies below 100 MHz offer the best possibilities to achieve loco-regional deep heating in a noninvasive manner. Currently, several devices using the interference principle to achieve maximum energy deposition at depth have been developed. Each system has its own specific advantages and disadvantages. Essential differences exist in the ability to control the SAR distribution, the construction of the water bolus, the frequency range over which the antenna can be operated, and the overall size of the applicator set-up.

At the time (1985) the development of the ring applicator was started only the annular phased array -BSD 1000- [Turner, 1984] was available for clinical loco-regional deep heating. Disadvantages of this applicator were the large overall size of the applicator set-up and the limited access to the patient during treatment. Therefore, the objectives for the ring applicator were to design an applicator which should:
(a) possess deep heating feasibilities based on the interference principle, characteristic for a radiative applicator;
(b) provide good access to the patient;
(c) cause no anxiety or stress to the patient;
(d) operate over a broad frequency range;
(e) provide the ability to customize the SAR distribution to the patients’ anatomy in order to reduce hot spots; and
(f) be easy to construct.

In the following paragraphs the development of the ring applicator will be reported. First, the experimental results of the ring applicator operating at a low frequency, 13.56 and 27.12 MHz, and with relatively small diameter electrodes are reported. Secondly, for the same ring applicator configuration a parameter study has been performed using a three-dimensional model developed by Sowinski et al. [1989]
to investigate how preferential fat heating due to the radial component of the electric field in front of the ring electrodes can be avoided. Thirdly, the performance of the ring applicator for loco-regional deep heating has been verified experimentally on a phantom of realistic size. Finally, the results of the first attempt to integrate a non-invasive thermometry system with the ring applicator are presented.

6.1.1 The ring applicator system

Basically, the ring applicator used in all experiments consists of two ring shaped electrodes which are placed around the tissue cylinder to be heated. The ring electrodes are made of aluminum or copper and need to be covered by an insulator for safety reasons. Due to the positioning of the plates along the enclosed tissue cylinder the electric field is mainly parallel to the body axis. This means that the direction of the electric field is parallel to the fat-muscle transition and therefore preferential heating of the subcutaneous fatty tissue will be avoided. Only at the site of the ring electrodes a small area exists where the electric field has a radial direction and at these sites preferential heating of fatty tissue (or other low conductivity tissue) may occur. A schematic representation of the applicator is shown in Figure 6.1. Variables influencing the resulting absorbed energy distribution are tissue cylinder radius \(a\), ring width \(b\), electrode to phantom gap \(c\), gap width \(d\), and the operating frequency.
For small ring diameters the ring applicator will introduce a quasi-static electromagnetic field, as a consequence of the low operating frequencies; in these cases the ring applicator is referred to as ring capacitor plates or ring capacitor applicator. When the diameter of the ring applicator is comparable to the wavelength in the tissue or phantom material, the electromagnetic field will have a radiative behaviour [Andersen, 1987; Durney, 1987]. In that situation a circumferential electric field with constant phase and amplitude is created around the phantom and constructive interference may occur, as with all other radiative hyperthermia devices. Although the results presented here are obtained at 13.56, 27.12, 33, and 70 MHz, the applicator principle works over a broad frequency range as has been reported by Raskmark and Andersen [1984] and Sminia et al. [1985].

The design is not new. Patents have been allowed already in 1932 [Rosenthal, 1932] and 1938 [Dorr, 1938] for similar applicator designs intended to be used for physical therapy. Brown et al. [1947] described a related industrial system with a much smaller diameter of the ring electrodes which he suggested to use for heat sterilization of milk. Furthermore in 1965, Scott [1965] referred to the ring electrode applicator from Dorr [1938] as "cuff electrodes". He anticipated that the cuff electrodes would become popular among physical therapists and would replace the inductive coil applicator on account of their ease of use and efficacy. His discussion of the possible energy distribution in tissue is debatable. As will be shown in the following paragraphs the energy distribution in the extremities will be more or less homogeneous and not, as Scott mentioned, in the outer layers of the muscle tissue. On the other hand, the good heating at depth obtained with the ring applicator is, according to some of the present physical therapists, also its biggest problem: the reduced sensibility of the patient to sense heat at depth increases the risk of burns. It may be questioned whether the latter concern is real or has its origin in the unfamiliarity with the energy distribution of the ring applicator.
6.2 Evaluation of the ring capacitor plate applicator for regional deep heating

In this chapter the results from the initiating study to investigate the feasibility of the ring applicator to induce loco-regional deep heating are reported. Because of the small ring diameters and the low operating frequencies the ring applicator will behave as a capacitive, quasi-static device. For these configurations the ring applicator is referred to as ring capacitor plates.

The first prototype consisted of two capacitive plates with a cylindrical aperture at the centre of each plate in which a cylindrically shaped tissue volume can be placed. Phantom measurements showed that the second prototype, consisting of the two narrow rings (Figure 6.1), gave identical results. Therefore, detailed information on these measurements is omitted and the results reported here are all obtained by using ring electrodes of 5 cm width and 0.02 cm thickness.

6.2.1 Approximate theoretical solution within a homogeneous tissue cylinder

Assume a radiofrequency (RF) voltage $V$ (time dependence $\exp(j\omega t)$, $\omega =$ angular frequency) applied over two highly conducting metallic plates situated at the opposite ends of a very long homogeneous tissue cylinder. For a small cylindrical section far from the RF feeding points no fringing effects will be present and RF currents will flow axially through the cylinder. Hence the current density, as well as the electric and magnetic field intensities, will have axial symmetry and only variation of these quantities as a function of radial distance will occur. By using a cylindrical polar coordinate system $r, \phi, z$, the following differential equation in terms of the electric field intensity $E=E_r$, inside the tissue cylinder is obtained [Brown et al., 1947]:

$$\frac{\partial^2 E}{\partial r^2} + r^{-1} \frac{\partial E}{\partial r} + (\omega^2 \mu \epsilon - j\omega \mu \sigma) E = 0$$

The general solution of this equation is a Bessel function of the first kind and zero order. By using the normalization $E(r)=E_0$ for $r=0$ the final solution is obtained:

$$E(r) = E_0 J_0(kr)$$

with: $k=(\omega^2 \mu \epsilon - j\omega \mu \sigma)^{1/2}$; $\mu, \sigma$ and $\epsilon$ are the magnetic permeability, the electric conductivity, and the electric permittivity, respectively.

---

Figure 6.2. Predicted relative energy distribution as function of the radial distance $r$ in a muscle-equivalent tissue cylinder. The electric field has only a $z$-component and the energy is normalized to the energy at the centre ($E^2/E_0^2$). The dots indicate the ratio at $r=3$ and 6 cm, respectively, as measured in a 7.7 and 13.5 cm diameter muscle-equivalent phantom heated with a 27 MHz electric field.

In Figure 6.2 the relative energy distribution $E^2/E_0^2$, predicted by the derived formula for this particular electromagnetic field within the muscle-equivalent tissue cylinder is given. For the three frequencies 13.5, 27.1, and 40.6 MHz the value of the electric conductivity used was 0.625, 0.612, and 0.693 S/m and of the electric permittivity 160, 113, and 97, respectively. It clearly shows that the lowest frequency has a better penetration depth, i.e., a better ratio of central to superficial heating. Furthermore, it shows that at the commonly used frequency of 27.12 MHz a homogeneously muscle cylinder with a diameter of 26 cm is preferentially heated at the centre ($[E(r=13)]^2/E_0^2=0.86$). If an absorbed energy ratio of unity between centre and surface is accepted, then the diameter of the muscle cylinder can be increased to 36 cm, which is about the same size as the largest dimension of a human cross-section at the pelvis. The present approximate solution is also valid in the case of a microwave cavity [Brezovich et al., 1982], to which the annular phased array and the TEM applicator show good similarity. A more rigorous model of the TEM applicator has been reported by Van Putten and Van den Berg [1986].
For the modified applicator, as presented here, the resulting normalized radial energy distribution at the centre of the gap between the two rings will closely resemble the situation with a metallic plate on the top and bottom of the muscle cylinder.

6.2.2 Materials and methods

The dependence of the SAR distribution upon width \((b)\) of the plates, electrode to phantom gap \((c)\), gap length \((d)\) between the plates, radius \((a)\) of the tissue cylinder, and distance between plate and tissue surface has been studied experimentally for a ring capacitor plate applicator using muscle-equivalent phantoms. The muscle-equivalent phantom material used was composed of 3 weight per cent agar, 0.33 weight per cent formaldehyde, and 0.32 weight per cent NaCl in deionized water. The electric conductivity is estimated to be 0.6 S/m at 27.12 MHz [Ishida and Kato, 1980]. The cylindrical phantom could be split along an axial separation plane into two equal sections, each contained in a half PVC tube. The copper electrodes of the ring capacitor plate applicator were placed directly on the phantom's PVC-cover without isolation. During heating the adjacent phantom surfaces were in contact through a very thin polyethylene film. Phantom diameters (including PVC-cover) were 7.7, 13.5, and 24 cm, thickness of the PVC-cover was 0.2, 0.3, and 0.7 cm, respectively and all had a length of 50±1 cm. For each experiment the temperature distribution was measured after 3 to 5 minutes of heating, the shorter periods being used for the smaller phantoms. The short heating time limits the thermal conductivity effects; hence, for a homogeneous phantom the measured temperature distribution effectively represents the SAR distribution. After removing the rings and splitting the phantom the temperature distribution of the exposed surface was measured within 30 s by an AGA-680 infrared camera interfaced to a personal computer [Van Deursen and Van Rhoon, 1988]. Analysis of the data was performed on the same computer.

As an RF source, an oscillator connected to a 500 W RF power amplifier (ENI, A500) at 13.56 MHz or at 27.12 MHz, a 650 W generator (Enraf Nonius, Curamed) was used. In order to tune the ring capacitor plate applicator to an impedance of 50 Ohm a broad-band tuner (Drake MN2700) was connected between these sources and the applicator. Forward and reflected power were measured by Bird Thruline Wattmeters.

6.2.3 Results

Matching of the applicator system to the power source by the low budget Drake tuner could be easily obtained for small diameter phantoms with standard width and gap of the ring of 5 and 15 cm, respectively. However, increasing the gap size, the electrode to phantom distance, and the cylinder diameter, as well as decreasing the ring width, made matching more difficult. For some applicator set-ups with the large
Figure 6.3. Relative SAR distributions (\$ > 25, \# > 50, \% > 75, and \$ > 90\%) obtained with the ring capacitor plate applicator in a muscle-equivalent tissue cylinder of 7.7 cm diameter and 50 cm length. (a) gap width 10 cm, f = 27.12 MHz; (b) gap width 15 cm, f = 27.12 MHz; (c) gap width 15 cm, f = 13.56 MHz.

diameter phantom it was even not possible to obtain good matching. In these situations a tuner with a wider impedance range than the one used is needed.

Figures 6.3a to 6.3c give the SAR distributions as 25, 50, 75, and 90 percentage isocurves with respect to the maximum measured SAR, obtained in the 7.7 cm diameter phantom for three different applicator configurations. The distributions shown in Figures 6.3a and 6.3b are both obtained at 27.12 MHz and they illustrate that the length (d) of the gap, 10 versus 15 cm, has no significant influence for this small diameter phantom. Comparing Figures 6.3b and 6.3c shows that identical SAR distributions are obtained for equal gap lengths (15 cm) when the operating frequency is decreased from 27.12 to 13.56 MHz. In all three situations good central heating (SAR > 75\%) is obtained in the tissue volume enclosed by the two rings. Furthermore, it is of importance to notice that there is no preferential heating at the edges of the rings, even though the non-isolated rings were placed directly onto the PVC cover.

The results for a similar set of measurements for the 13.5 cm diameter phantom
Figure 6.4. Relative SAR distributions (\( \geq 25 \), \( \geq 50 \), \( \geq 75 \), and \( \geq 90\% \)) obtained in the 13.5 cm diameter muscle-equivalent phantom are given. (a) gap width 10 cm, \( f = 27.12 \) MHz; (b) gap width 25 cm, \( f = 27.12 \) MHz; (c) gap width 25 cm; \( f = 13.56 \) MHz.

are given in Figures 6.4a to 6.4c. Although the small hot spot at the edge of the ring with the 25 cm gap decreases the relative SAR distribution over the rest of the volume, the influence of the gap length is again negligible. In both cases, gap length 10 and 25 cm (Figures 6.4a and 6.4b), there is good central heating with SAR-values over 75%. However, at this phantom diameter both distributions show a small but definite preferential heating at the edge of the rings. The experiment with the 10 cm gap length (Figure 6.4a) indicates that the rings can be operated closely to each other, which provides an easy method to restrict the heated volume. Also, lowering
Figure 6.5 Relative SAR distributions (\(\text{\(\%\)} > 25\), \(\text{\(\%\)} > 50\), \(\text{\(\%\)} > 75\), and \(\text{\(\%\)} > 90\%\)) obtained in the 13.5 cm diameter phantom with different distances between the ring electrode and the PVC-tube, gap width 15 cm, \(f=27.12\) MHz. Distance between the ring electrodes and the PVC-tube is 0.2 cm (a) and 1 cm (b), respectively.

the operating frequency for a phantom of this size shows some influence upon the SAR distribution as compared with the 7.7 cm diameter phantom (Figure 6.4c). Comparison of the SAR distributions obtained at 27.12 MHz (Figure 6.4b) and 13.56 MHz (Figure 6.4c) indicates that the latter distribution has a somewhat more homogeneous central heating; the volume with SAR-values between 75 to 100\% is larger at 13.56 MHz than at 27.12 MHz. However, hot spots at the edge of the rings also occurred at the lower frequency. The SAR distributions presented in Figure 6.5a and 6.5b show that the hot spots at the edge of the rings disappear if the ring to surface distance is increased to 1 cm (Figure 6.5b). The effectively heated volume in this specific applicator positioning is, however, somewhat smaller; the 75\% isocurve is now located approximately 1 cm from the inner boundary of the rings. A SAR determination (Figure 6.5a) performed for a 0.2 cm ring to surface distance results in a decrease of the edge effect, but it does not disappear completely.

The ultimate purpose of this applicator development was, however, to demonstrate its feasibility for deep heating. Therefore, SAR measurements were performed on a muscle-equivalent phantom with a diameter of 24 cm. With a zero
ring to phantom surface distance heating at the edge of the rings dominated and no substantial central heating could be obtained. Again, increasing the ring to phantom surface distance to 1 cm results in a decreased intensity of the hot spots directly below the rings. Additionally, a large part of the central tissue volume between the rings shows heating up to 30 to 40% of the maximum SAR value as is illustrated in Figure 6.6. However, the high temperature gradient present below the rings may have caused some thermal conduction, resulting in an overestimation of the heating rate at the centre. It can be seen that the hot spots at the edges only extend to a superficial layer of 1 cm thickness.

Finally, the ratio of the SAR at 4/5 of the phantom radius to the SAR at zero radius is plotted in Figure 6.2 for the 7.7 and 13.5 cm diameter phantoms heated at 27 MHz. From this it can be seen that the radial energy distribution is reasonably predicted by the limited model used. For the 24 cm diameter phantom this ratio has not been plotted, as for this particular measurement the inaccuracy of the relative SAR values below 40 is about 5 to 10 and therefore the ratio will have no valuable meaning.

6.2.4 Discussion

Due to the low frequencies used, the ring capacitor plates may be viewed as a quasi-static applicator, similar to a capacitive plate system [Andersen, 1987; Durney, 1987]. However, the direction of the induced electric field, mainly parallel to the body axis instead of perpendicular, is the major difference between the ring applica-
tor and conventional capacitive systems. Only at the location of each ring a radially directed electric field exists within a local and small volume of the phantom, which extends to approximately 1 cm depth. This radial component of the electric field converges to the edge of the rings and causes the hot spots as measured in the phantom experiments. A similar finding has been predicted by the three-dimensional model as developed by Van Putten and Van den Berg [1986] for the 'coaxial TEM' applicator. As the results of the experiments show, these hot spots do not occur, or are of no concern as long as the tissue diameter does not exceed 8 cm. For large-diameter tissue cylinders a way to reduce these hot spots is to place the rings at a small distance of the tissue surface. In the phantom experiments (Figures 6.4 and 6.5) presented, a good reduction in the intensity of the hot spots was obtained with a 1 cm air gap between the electrode and the PVC-cover.

Especially with regard to the feasibility of the ring capacitor plates for deep heating, the reduction of these high-intensity radial electric field components in front of the rings is of great importance. Although no experiments with a fat layer in front of the rings have been performed, the problem of these hot spots will be even more accentuated when deep heating is attempted in large-diameter tissue volumes with a thick superficial fat layer. However, by increasing the air gap between the ring and the tissue surface, or by replacing the air gap by a water bolus which can be used simultaneously for skin cooling, and by adaption of the rings, it may be possible to reduce the intensity of the hot spots to an acceptable level.

The choice of a low operating frequency results in a larger volume with maximum SAR and therefore, a loss of focusing ability (steering of the SAR maximum). However, the advantage of steering the heating pattern is still unclear [Gibbs, 1984; Halac et al., 1983; Sathiaseelan, 1986]. And as focusing at higher frequencies appears still to be technically difficult and sensitive to tissue geometry [Charny et al., 1986] it is questionable whether this is a real loss, especially in view of the gain in penetration depth. Of the presently available deep heating systems the ring capacitor plates show resemblance to the RF Helical Coil applicator reported by Ruggera and Kantor [1984]. Due to the design of the helical coil homogeneous heating is induced by both the azimuthal and longitudinal component of the electric field. No preferential heating or hot spots in the fatty tissue surrounding the muscle layer occurred in their experiments. However, in contrast to the ring capacitor plates the length of the Helical Coil applicator is approximately two times the length of the effectively (SAR > 50%) heated volume. The mini-annular phased array, as manufactured by BSD Medical Corporation, is another applicator system with resemblance to the ring capacitor plates. With this system good central heating in an amputated human leg could be obtained, without overheating of bone and fatty tissue, as was reported by Charny et al. [1986].
Comparison of the mini-annular phased array and the Helical Coil applicators with the ring capacitor plates show that an advantage of the latter might be that access to the treatment field is not obstructed by the antenna or the water bolus. Furthermore, the size of the ring applicator is not fixed; therefore, adaption of the gap width to the treatment volume can be easily obtained. The length of the effectively heated volume (SAR > 50%) equals the gap width for phantom diameters up to 13.5 cm, even for gap widths as small as 10 cm. This may be especially important in the treatment of head and neck cancer.

Other similar applicator systems, derived independently via different theories and principles, have been reported by Raskmark and Andersen [1984] and Sminia et al. [1985]. These authors also use ring-type systems, but they operate at the higher frequencies of 70 and 434 MHz, respectively. This shows that the principle of the ring applicator may be used over a large frequency band. With their system Raskmark and Anderson [1984] also showed the possibility of steering the focus by dividing the ring into four sections.

The results on the temperature distributions obtained with the ring capacitor plates presented here cannot be used for comparison with the results of the annular phased array or the coaxial TEM applicator. The agreement between the predicted radial distribution, as calculated with the limited mathematical model and the measured radial distribution, supports our expectations of the deep heating feasibility of the ring capacitor plates. In addition to this simple model a three-dimensional computer programme has been developed by Sowinski et al. [1989]. Calculations performed with this model also indicate the deep heating possibilities of the ring capacitor plates if the hot spots at the edges of the rings are absorbed in the bolus material.

A reason, not discussed so far, for changing the applicator system might be the level of stray radiation. As this has not been measured yet, it is too early to tell whether this will be of great importance.

In conclusion: the ring capacitor plate applicator is a simple and compact construction with good heating capabilities for the treatment of the extremities (arms and lower leg). For these parts of the body, with a relative small diameter, the hot spots at the edges of the rings do not appear. When these hot spots are absorbed in bolus material the ring capacitor plate applicator may also show deep heating capabilities.
6.3 Ring capacitor applicator: predicted energy distributions in a fat-muscle layered model for different ring electrode configurations

In Chapter 6.2 the SAR distributions obtained with the ring capacitor applicator in homogeneous muscle-equivalent phantoms show that a small area exists at the position of the ring electrodes in which the electric field has a radial direction. In this chapter the relevance of this radial component of the electric field is studied for an inhomogeneous fat-muscle model. The results, based on measured and predicted SAR-distributions, show that preferential fat heating can be adequately controlled by proper adjustment of the electrode configuration. This latter makes the ring capacitor applicator a valuable supplement to existing applicators, especially for those hyperthermia centres that already possess a radiofrequency heating system.

6.3.1 Materials and methods

Phantom experiments

During the phantom experiments the electrodes were connected to a 13.56 MHz generator (Tecnomatix, HTM3000P) of 1200 W output power equipped with an automatic tuning device. Temperature distributions were measured through infrared thermography for a homogeneous muscle-equivalent phantom or a layered, inhomogeneous fat and muscle-equivalent phantom. The muscle-equivalent material used was composed of 3 weight per cent agar, 0.33 weight per cent formaldehyde, 0.32 weight per cent NaCl, and 96.35 weight per cent deionized water. The electric conductivity (σ) is estimated to be 0.6 S/m at 27.12 MHz [Ishida and Kato, 1980]. The fat-equivalent material [Bini et al., 1984] was made in three phases. For 100 cm\(^3\) fatty tissue phantom it was comprised in the first phase of: 40 g Acrylamide, 0.267 g MBA (N, N'-Methylene-Bis-Acrylamide), 1.33 cm\(^3\) TMEDA (N, N, N', N'-Tetra-Methyl-Ethylene-Diamine), 0.01 mole NaCl and 90 cm\(^3\) Ethanediol. In the second phase it was comprised of: 0.65 weight per cent AP (Ammonium Persulfate) in 10 cm\(^3\) Ethanediol. In phase 3 degassing and mixing of phase 1 and 2 was performed.

The electric properties [Bini et al., 1984] of the resulting fat material at room temperature and at 27.12 MHz are $\sigma = 0.01$ S/m and $\varepsilon_r = 22$. The exact conductivity of the fat material is dependent upon the temperature of the material and the frequency used. After correction for the frequency of 13.56 MHz used in the experiments and a mean temperature of the material during the experiment of $\pm 30$ °C, these properties are estimated to be: $\sigma = 7-8$ mS/m and $\varepsilon_r = 25$.

The cylindrical phantom was split along a plane through the axis into two equal

---

sections. During heating the adjacent phantom surfaces were in contact through a very thin (0.03 mm) polyethylene film. The phantom diameter in all experiments was 135 mm; the length of the phantom was 500 mm. The homogeneous muscle-equivalent phantom had a diameter of 127 mm and the ring electrodes were placed directly on the phantom surface. The electrodes were insulated with the 0.03 mm thick polyethylene foil. The inhomogeneous phantom consisted of a muscle-equivalent tissue cylinder of 105-109 mm diameter covered by a 9-11 mm thick layer of fat-equivalent tissue and was contained in a 4 mm thick Poly Vinyl Chloride (PVC) tube.

The temperature distribution was measured after 3 minutes of heating with an RF input power of 500 W. After removing the rings and splitting the phantom the temperature distribution of the exposed surface was measured within 30 seconds after cessation of the heating by means of an infrared camera (AGA-680) interfaced to a personal computer [Van Deursen and Van Rhoon, 1988]. Analysis of the data was performed on the same personal computer.

**Theoretical model**

The theoretical model computes the electromagnetic field induced by the ring capacitor applicator in radially layered tissue configurations. The model assumes that the pair of coaxially-mounted ring electrodes are perfect conductors and infinitely thin. All other variables as electrode diameter \(2a\), ring width \(b\), distance between the electrodes \(d\), and radial tissue configuration are inputs to the programme; the tissue configuration is located between \(r=r_n\) and \(r=r_{n+1}\), with \(1 \leq n \leq N-1\) \((N = \text{number of tissues})\). An RF voltage difference \(V\) (time dependence \(\exp(\jmath \omega t)\), \(\omega = \text{angular frequency}\)) is present between the two electrodes. As the set-up has cylindrical symmetry, the electric field needs only to be solved in the \(z\)- and \(r\)-direction. The electromagnetic properties of each tissue are characterized by its permittivity \((\varepsilon)\), its electric conductivity \((\sigma)\), and its permeability \((\mu)\). In the domain where the field quantities are continuously differentiable, they satisfy the first and the second Maxwell field equations: \(\text{curl } H = (j \omega \varepsilon + \sigma) E\) and \(\text{curl } E = - j \omega \mu H\), respectively. The continuity conditions at the interfaces and the conditions at the boundary of the phantom need to be supplemented. The second Maxwell field equation is solved by putting \(E = -\text{grad } V\); substituting this term in the first Maxwell field equation and after applying the div operator to this equation, the following partial differential equation for the electric potential in each homogeneous layer is obtained:

\[
\nabla^2 V = \varepsilon \nabla \eta \nabla^2 r + r^{-1} \nabla \eta \nabla r + \nabla \eta \nabla z^2 = 0
\]

with the boundary conditions:
(1) the potential $V$ and the radial component of the electric current density are continuous across all interfaces;
(2) across the part of the outer tissue interface ($r = a$), where no electrodes are present, the radial component of the electric current density is 0;
(3) at the outer tissue interface ($r = a$) the potential $V$ is continuous and at the position of the electrodes equal to the prescribed potential.

The method of computation uses the spatial Fourier transform of all field quantities with respect to the axial $z$-coordinate. The solution of these field quantities is a superposition of the modified Bessel functions of the first and second kind, each of zero order. To obtain the field quantities at each tissue interface a transfer-matrix is used to compute the transformed field for different values of the radial coordinate. In this way only the potential distribution at the interface $r = a$, where the electrodes are located, needs to be solved. The problem is thus reduced to a dual boundary value problem for the electric potential and the jump of the $r$-component of the generalized electric current density at the interface where the ring electrodes are located. An iterative scheme is used to solve this problem and an inverse Fourier transform is used to calculate the interior electric field in the radially layered model. Finally, the volume density of the total dissipated electromagnetic power is obtained by superposition of the dissipated power due to the radial and axial components of the electric field. For a detailed description of the model see Sowinski et al. [1989].

The programme runs on a personal computer (IBM PC/AT or higher). Normally a root-mean-square error of less than $10^{-3}$ for the potential $V$ at the outer boundary is obtained after five iterations. The number of iterations is slightly dependent upon the size of the electrodes. As a consequence of the assumed quasi-static behaviour of the set-up, the most important restriction is the size of the ring applicator, which must be small in comparison to the wavelength of the electromagnetic field used. The programme needs two other prescriptions:
(1) the rim points of the electrodes should be positioned exactly between two adjacent sample points in the $z$-direction;
(2) the FFT-period, for the calculation of the Fourier transform, should be large to obtain negligible electric potentials at the boundary of this period.

In this study, the model has been used to predict SAR-distributions for tissue configurations similar to those of the phantoms, thus using conductivity and relative permittivity values of the respective phantom materials. Secondly, the model has been used to perform a study on the dependence of the energy distribution upon the applicator configuration. This includes the width of the ring electrodes, the distance between the ring electrodes, and the gap between the electrode and the tissue surface. Additionally, the influence of air or distilled water as a medium between electrode and phantom surface has been studied. In the latter studies the values used
for conductivity and permittivity are those reported in the literature for human muscle and fat tissue [Johnson and Guy, 1972] and are given in Table 6.1.

6.3.2 Results
Comparison of measured and predicted SAR distributions

To allow a direct comparison between the measured and the predicted SAR-distributions, they are normalized to the average absorbed energy within the muscle tissue cylinder enclosed by the inner margins of the ring electrodes (for more details see Sowinski et al. [1989]).

Two examples of measured relative SAR-distributions for the inhomogeneous fat-muscle equivalent phantom configuration are given in Figures 6.7a and 6.7b. Each distribution is obtained using a ring width of 50 mm, a distance of 250 mm between the ring electrodes, an electrode to phantom gap of 0 mm (Figure 6.7a) or 10 mm (Figure 6.7b), respectively, and a frequency of 13.56 MHz. Figures 6.8a and 6.8b show, for the same phantom and electrode configurations, the relative SAR-distributions predicted by the theoretical model. Both the measured (Figure 6.7a) and the predicted (Figure 6.8a) SAR-distribution indicate that the maximum energy absorption is obtained within the 10 mm thick fat layer near the edges of the ring electrodes when the electrodes are placed directly on the PVC tube. By introducing a distance of 10 mm between the ring electrode and the phantom surface the preferential heating of the fatty tissue near the edges of the ring electrodes disappears (Figures 6.7b and 6.8b).

Table 6.1. Electromagnetic parameters [Johnson and Guy, 1972] of tissues used in the theoretical model.

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Frequency</th>
<th>13.56 MHz</th>
<th>27.12 MHz</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\epsilon$</td>
<td>$\sigma$ [S/m]</td>
<td>$\epsilon$</td>
</tr>
<tr>
<td>Muscle</td>
<td>150</td>
<td>0.62</td>
<td>113</td>
</tr>
<tr>
<td>Fat</td>
<td>25</td>
<td>0.009</td>
<td>20</td>
</tr>
<tr>
<td>PVC</td>
<td>4.5</td>
<td>0.000005</td>
<td>4.5</td>
</tr>
<tr>
<td>Air</td>
<td>1</td>
<td>0.0000002</td>
<td>1</td>
</tr>
<tr>
<td>Water</td>
<td>80</td>
<td>0.0002</td>
<td>80</td>
</tr>
</tbody>
</table>
Table 6.2. Comparison between measured and predicted relative SAR-distrib-
utions.¹

<table>
<thead>
<tr>
<th>Electrode configuration</th>
<th>Predicted SAR-distribution</th>
<th>Measured SAR-distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Max SAR fatty tissue</td>
<td>Muscle SAR centre border</td>
</tr>
<tr>
<td>El-Ph gap (mm)</td>
<td>Distance between rings (mm)</td>
<td>2.02</td>
</tr>
<tr>
<td>0</td>
<td>250</td>
<td>1.27</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>1.98</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>@</td>
</tr>
</tbody>
</table>

¹ Width of the ring electrodes: 50 mm; frequency 13.56 MHz; relative SAR normalized to average absorbed energy in muscle tissue cylinder.
² Percentage of the total volume of the muscle tissue enclosed by the inner margins of the ring electrodes which obtained a relative SAR between 0.75 and 1.25.
@ This experiment was performed with a homogeneous muscle-equivalent phantom configuration.

In Table 6.2 some relevant parameters, obtained from the measured and predicted SAR-distribution, are given for 4 different phantom and electrode configurations. The parameters used are: maximum relative SAR in the fatty tissue; relative SAR at the centre and at the border of the muscle tissue cylinder in the midplane (z=0); and the volume of the muscle tissue receiving a relative SAR between 0.75 to 1.25. The table shows that the measured and predicted data, for the relative SAR in the muscle tissue at both locations and for the volume of muscle tissue with a relative SAR between 0.75 and 1.25, only once have a difference larger than 6 per cent. The lower intensity of the maximum relative SAR in the fatty tissue in the measured distributions (Figures 6.7a, 6.7b and Table 6.2) reported, can be explained by heat conduction during the 3 minute heating time. Additionally, comparison of Figures 6.7a and 6.8a, and Figures 6.7b and 6.8b, respectively, illustrates that in the measured SAR-distributions some radial heat flow occurred from the muscle tissue towards the fatty tissue for the phantom tissue cylinder between the electrodes. Similarly, some outward heat flow along the cylinder axis can be seen. Furthermore, note that for the latter configuration of a fat-muscle phantom with the electrodes at 10 mm from the phantom surface, the “Estimated Treatment Volume” [Sim et al., 1984], defined as the volume receiving a SAR > 50% of the
Figure 6.7. Measured relative energy distributions within the fat-muscle model. Fat-equivalent tissue: $\varepsilon_r=25$, $\sigma=0.007$ S/m; muscle-equivalent tissue: $\varepsilon_r=80$, $\sigma=0.6$ S/m; frequency: 13.56 MHz; RF power 500 W during 3 minutes. The ring electrodes had a width of 50 mm and the distance between the ring electrodes was 250 mm. (a) Ring electrodes placed directly on the phantom surface. (b) Ring electrodes placed at 1 cm distance of the phantom surface, gap medium: air.

maximum SAR, equals the muscle tissue volume enclosed by the inner margins of the electrodes (Figures 6.7b and 6.8b), that is, 4.3 and 4.5 dm$^3$, respectively.

Model study on the ring electrode configuration

For this model study all predicted SAR-distributions are normalized to the maximum SAR within the entire heated volume, regardless of tissue type. The dependence of the predicted relative SAR-distribution for the electrode configuration is demonstrated by Figures 6.9-6.11.
Figure 6.8. Predicted relative energy distributions within the fat-muscle model. Fat equivalent tissue: $\varepsilon_r=25$, $\sigma=0.007$ S/m; muscle-equivalent tissue: $\varepsilon_r=80$, $\sigma=0.6$ S/m; frequency: 13.56 MHz. The ring electrodes had a width of 50 mm and the distance between the ring electrodes was 250 mm. (a) Ring electrodes placed directly on the phantom surface. (b) Ring electrodes placed at 1 cm distance of the phantom surface, gap medium: air.

Figure 6.9 shows the maximum relative SAR within the fatty tissue below the electrodes and the relative SAR at the centre of the muscle tissue as function of the gap between electrode and phantom surface (El-Ph gap). Additionally, the estimated treatment volume (ETV) as fraction of the total volume enclosed by the inner margins of the ring electrode is plotted. All relative SAR-distributions were calculated using a ring width of 50 mm, a distance between the electrodes of 250 mm, and air or distilled water as medium between the electrode and the
Figure 6.9. Predicted relative SAR in the muscle tissue at the centre of the model; maximum relative SAR in the fatty tissue near the ring electrode and the estimated treatment volume (ETV) as percentage of the tissue volume enclosed by the inner margins of the ring electrodes. All variables are given as function of the electrode to the phantom surface gap. Ring width: 50 mm; distance between rings: 250 mm.

Frequency 13.56 MHz: (a) gap medium: air; (b) gap medium: distilled water.

Frequency 27.12 MHz: (c) gap medium: air; (d) gap medium: distilled water.
Figure 6.10. Predicted relative SAR in the muscle tissue at the centre of the model; maximum relative SAR in the fatty tissue near the ring electrode and the estimated treatment volume (ETV) as percentage of the tissue volume enclosed by the inner margins of the ring electrodes. All variables are given as function of the ring width. Electrode to phantom surface gap: 10 mm; distance between rings: 250 mm. Frequency 27.12 MHz: (a) gap medium: air; (b) gap medium: distilled water.

phantom surface. It can be seen from these graphs (Figures 6.9a - 6.9d) that for both operating frequencies, that is, 13.56 and 27.12 MHz, the maximum relative SAR within the fatty tissue is decreasing with increasing El-Ph gap. Generally, the ratio between the relative SAR in the fatty tissue and the relative SAR at the centre of the muscle tissue is lower, thus better, at 27.12 MHz than at 13.56 MHz. From the relative ETV values it can be derived that at 13.56 MHz with air or water as gap medium and an El-Ph gap of less than 10 mm or 5 mm, respectively, no substantial heating (relative SAR in muscle < 0.5) at depth is obtained (Figures 6.9a and 6.9b). The ETV values of less than 10 per cent (Figures 6.9a and 6.9b) are indicative for dominating hot spots near the edges of the electrodes, caused by the high relative SAR predicted within the fatty tissue. For most other electrode configurations the relative ETV is between 62 and 76 per cent and is slightly decreasing for increasing EL-Ph gap distances (Figures 6.9a - 6.9d).

Figures 6.10a and 6.10b show the influence of the ring width on the relative ETV and the relative SAR in fat and muscle tissue only for a frequency of 27.12 MHz. El-Ph gap and distance between the electrodes were kept constant at 10 mm and 250 mm, respectively; air or distilled water were used as gap medium. Increasing the
Figure 6.11. Predicted relative SAR in the muscle tissue at the centre of the model; maximum relative SAR in the fatty tissue near the ring electrode and the estimated treatment volume (ETV) as percentage of the tissue volume enclosed by the inner margins of the ring electrodes. All variables are given as function of the distance between the ring electrodes. Ring width: 50 mm; electrode to phantom surface gap: 10 mm. Frequency 27.12 MHz: (a) gap medium: air; (b) gap medium: distilled water.

ring width from 20 mm to 100 mm causes the relative SAR at the centre of the muscle tissue cylinder to increase from 0.6 to 1.0 in the configuration with air as gap medium (Figure 6.10a). A large decrease (60 to 70%) of the relative SAR within the fatty tissue is obtained when the ring width is increased from 20 to 100 mm (Figures 6.10a and 6.10b). Again, distilled water as gap medium gives better SAR ratios between fat and muscle tissue. Also a small increase of the relative ETV, from 62 to 74%, can be noticed with increasing ring width.

Finally, the variation of these quantities (fat and muscle relative SAR, and relative ETV) as function of the distance between the electrodes is shown in Figures 6.11a and 6.11b. In this case, ring width and El-Ph gap were kept constant at 50 mm and 10 mm, respectively, with either air or water as gap medium. The calculations were again limited to the frequency of 27.12 MHz. In comparison to the previous distributions (Figures 6.9b - 6.9d, 6.10a and 6.10b), the relative SAR within the fatty tissue now shows a smaller change with increasing distance between the electrodes and varies between 80 to 100% and 40 to 50%, respectively, for the gap media used, that is, air or water. The maximum SAR is always located within the muscle tissue, irrespective of the distance between the electrodes. However, it should be noted that with increasing electrode distance the relative SAR at the centre of the muscle
cylinder increases, which indicates that the radial distribution within the muscle tissue becomes more homogeneous. The relative ETV shows a decrease with increasing distance between the electrodes: with air as gap medium the relative ETV is reduced from 83 to 72%; for distilled water as gap medium a larger reduction, 87 to 68%, is found. The non-monotonic behaviour of the maximum relative SAR in the fatty tissue (Figures 6.10c, 6.11a and 6.11b) is caused by variations in the size and number of the sample points in the \( r \) and \( z \)-direction.

6.3.3 Discussion

Both the qualitative (Figures 6.7a - 6.8a and 6.7b - 6.8b) and quantitative (Table 6.2) comparison of predicted and measured relative SAR distributions for the phantom configurations show good to excellent agreement. With regard to the relative SAR at the centre and at the border of the muscle tissue cylinder for \( z = 0 \), and for the volume of muscle tissue with a relative SAR between 0.75 and 1.25, the differences are generally less than 6 per cent. The larger differences of 30-72 per cent observed at the locations of hot spots in the fatty tissue below the electrodes may well be caused by thermal conduction during the 3 minute heating time. Hence, from these comparisons it can be concluded that the numerical model is accurate and very suitable to perform theoretical studies on the influence of the electrode configuration upon the SAR-distribution in inhomogeneous layered tissue models.

Due to its design, the ring capacitor applicator creates an electric field distribution within a cylindrical body, which is mainly directed parallel to the body axis. In this sense it is comparable to radiative systems operating at higher frequencies [Andersen, 1987; Durney, 1987; Franconi, 1987]. Only at the location of the ring electrodes where the electric field diverges from the edge of the ring electrodes a radial component of the electric field exists and consequently preferential heating of the fatty tissue below the ring electrodes may be expected [Van Rhoon et al, 1988; Raganella et al., 1989]. The results of both measured and predicted relative SAR distributions (Figures 6.7a and 6.8a) show indeed that preferential heating of the fatty tissue in front of the ring electrodes occurs when the electrodes are placed directly on the phantom. However, a significant reduction of the SAR at these locations is obtained when a 1 cm air gap between the electrode and phantom surface is introduced (Figures 6.7b and 6.8b). Analysing the theoretical prediction at 27.12 MHz for the latter electrode configuration (El-Ph gap 10 mm, ring width 50 mm, distance between the electrodes 250 mm, air as gap medium, and realistic \( \sigma \), \( \varepsilon \) values for muscle and fat) indicates that the radial component of the electric field contributes for more than 90 per cent to the energy absorption at the hot spot in the fatty tissue in front of the ring electrode. Furthermore, the analysis showed that the intensity of the radial component of the electric field decreases rapidly with
Table 6.3. Minimum values, necessary to obtain a ratio of the fat SAR to the
centre muscle SAR lower than 0.8, for the various parameters studied in the fat-
muscle layered phantom model.

<table>
<thead>
<tr>
<th>Gap medium</th>
<th>Frequency (MHz)</th>
<th>El-Ph gap (mm)</th>
<th>Ring width (mm)</th>
<th>Distance between electrodes (mm)</th>
<th>Fat thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>13.56</td>
<td>&gt;30°</td>
<td>50</td>
<td>250</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>27.12</td>
<td>&gt;10°</td>
<td>50</td>
<td>250</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>&gt;50°</td>
<td>250</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>50</td>
<td>250&lt;1&lt;400°</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>50</td>
<td>250</td>
<td>≥11°</td>
</tr>
<tr>
<td>Water</td>
<td>13.56</td>
<td>&gt;10°</td>
<td>50</td>
<td>250</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>27.12</td>
<td>≥5°</td>
<td>50</td>
<td>250</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>≥20°</td>
<td>250</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>50</td>
<td>≥50°</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>50</td>
<td>250</td>
<td>≥1°</td>
</tr>
</tbody>
</table>

° variable parameter.

Increasing distance to the ring electrode. A steeper decay of the radial component
of the electric field is obtained when water, instead of air, is used as gap medium.
A consequence of the rapid decay of the radial component of the electric field is that
preferential fat heating at the transition of fat to muscle tissue is reduced with
increasing fat thickness. This has been confirmed by the theoretical model for the
standard electrode configuration used, that is, frequency 27.12 MHz, El-Ph gap 10
mm, ring width 50 mm, distance between the electrodes 250 mm, and fat thicknesses
of 5, 10, 15, and 20 mm. From the predicted distributions the minimum thickness of
fatty tissue needed to obtain a ratio of fat SAR to muscle SAR lower than 0.8, are
estimated as 11 mm with air and 1 mm with water as gap medium (Table 6.3).

A summary of the results of the electrode configuration study is given in
Table 6.3. This table gives the minimum or maximum value for each single
parameter necessary to obtain a ratio of fat SAR to muscle SAR lower than 0.8, with
all other parameters of the electrode or phantom configuration kept constant. For
example, if for muscle and fat tissue the values of the relative permittivity (150 and
25) and the conductivity (0.62 and 0.009 S/m) are used as reported in the literature
[Johnson and Guy, 1972], the theoretical model predicts that at a frequency of 13.56 MHz the introduction of a 1 cm air gap between the electrode and the phantom surface will be insufficient to reduce the maximum SAR in the fatty tissue (Figure 6.9a). Hence, as is shown in Figure 6.9a the El-Ph air gap has to be increased up to 30 mm before a substantial decrease, that is 0.8, of the relative SAR within the fatty tissue can be expected. For the model calculations performed with respect to the El-Ph gap (Figures 6.9a-d), the best ratio of fat to muscle SAR is obtained at 27.12 MHz with distilled water as gap medium and an El-Ph gap of 20 mm (Figure 6.9d). Independent of the El-Ph distance the relative SAR values predicted in the fat and muscle model show a more favourable distribution at a frequency of 27.12 MHz (Figures 6.9c and 6.9d) than at 13.56 MHz (Figures 6.9a and 6.9b). The relative SAR within the fatty tissue is approximately two times lower at 27.12 MHz than at 13.56 MHz for an El-Ph gap larger than 5 mm and water as gap medium.

Another efficient method to decrease the SAR within the fatty tissue is to increase the ring width as demonstrated in Figures 6.10a and 6.10b. However, the disadvantage of this method is that the total length of the applicator increases by 2 cm for each cm added to the ring width. Hence, this method can only be used if the space at the treatment volume to be heated is large enough to cope with the additional applicator length.

Increasing the distance between the electrodes (Figures 6.11a and 6.11b) is a simple way to adapt the axial length of the heated volume to the treatment volume. Even for a distance between the electrodes as short as 5 cm, a relative SAR higher than 0.6 is obtained at the centre of the muscle cylinder (Figures 6.11a and 6.11b).

As reported earlier, the ring capacitor applicator shows good resemblance to the RF helical coil applicator and to the mini-annular phased array. Although differences exist between the operating frequencies all three applicator types are able to induce homogeneous energy deposition patterns, within cylindrical phantom models [Ruggera and Kantor, 1984; Guerquin-Kern et al., 1987; Charney et al., 1988; Van Rhoon et al., 1988]. An advantage of the ring applicator over the other two heating systems is that the distance between the ring electrodes, and thus the size of the applicator, can be chosen freely. Therefore, the length of the effectively heated volume can be easily adapted to the length of the required treatment volume.

In the present investigations only cylindrical models have been studied and no information can be presented yet on the behaviour of the energy distribution for differently shaped, for example, tapered phantom models. However, the maximum of the energy distribution is anticipated to shift towards the smaller cross-section region, similar as reported for the mini-annular phased array [Guerquin-Kern et al., 1987; Charney et al., 1988].

In conclusion, at 27.12 MHz both the measured and the predicted energy
deposition patterns within multilayered models demonstrate that the ring capacitor applicator may be well suited for hyperthermic treatment of the extremities. The most simple applicator configuration, with a ring width of 50-100 mm and placed in air at a distance of 20-30 mm from the tissue surface, can be used if there is no limitation to the length of the applicator. In the case of a hyperthermic treatment at a location where the size of the applicator is limited, a more complicated electrode configuration may be required. In such a case good results may be expected from the use of ring electrodes of 20 mm width placed on a 10 mm thick water bolus.

6.4 Radiative ring applicator: Energy distributions measured in the CDRH phantom

In the previous chapters it has been have demonstrated both experimentally and theoretically, that it is feasible to adapt the SAR-distribution in small cylindrical phantoms (diameter ≤ 13.5 cm) by changing the ring applicator configuration. This chapter reports on the feasibility of the ring applicator to obtain deep heating in a phantom of realistic human size, that is, the well known CDRH phantom as developed by the "Center for Devices and Radiological Health" (CDRH). Experiments have been performed at two frequencies (33 and 70 MHz) to investigate the ability to focus the SAR at depth and to perform SAR steering by amplitude control. The results demonstrate that the ring applicator with large diameter electrodes and operating at frequencies above 20 MHz can create a radiative circumferential electric field distribution around the phantom. As with other radiative systems, like the coaxial TEM applicator [De Leeuw et al., 1990], the Sigma applicator [Turner and Schaefermeyer, 1989] or the four-waveguide system [Van Dijk et al., 1990], constructive interference will occur and results in maximum energy deposition at the centre of the phantom.

6.4.1 Materials and methods

The applicator consisted of a PVC tube, length 58 cm and inner diameter 48 cm, in which the ring electrodes of tin-plated copper (thickness 0.2 mm) were cemented to the inner surface. The electrodes had a diameter of 48 cm, a width of 10 cm, and the gap width between the upper and lower ring electrode was 31.6 cm. Radiofrequency (RF) energy was fed to the ring applicator at one, four or eight different points to investigate the effects of potential distribution over the electrode surface.

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(Figure 6.12). A custom built (Institute for Electronic Systems) four-channel (50 W per channel) broadband RF power generator was used to drive each feeding point. Amplitude and phase of each channel could be controlled independently. RF power per channel was measured by Bird inline power meters, phase per channel was measured through a bidirectional coupler with a Hewlett Packard vector-voltmeter (HP 8405A). Open line transformers were used to match the impedance at each feeding point of the ring applicator. Experiments were performed at frequencies of 33 and 70 MHz.

The CDRH phantom consists of a 1 cm thick, solid fat-equivalent shell filled with pelvic-equivalent liquid and has an elliptical cross-section of $22 \times 32$ cm² and is 57 cm long. Various electric conductivities ($\sigma = 0.4-1.0$ S/m at 20 °C) of the pelvic-equivalent liquid were obtained by solving different amounts of NaCl (2, 3 or 5 g/l) in tap water based on Stogryn's [1971] formula. This gave the possibility to investigate the focusing ability of the ring applicator as function of electric conductivity. The SAR distribution was determined with a three-dimensional electric field measuring system developed at the Institute of Electronic Systems [Raskmark and Gross, 1987]. The system uses a single Schottky diode (HP 5082-2774) electric field dipole probe.
(length 8 mm) connected to a high impedance DC voltmeter via a pair of twisted high resistance leads (Flurosint 819, 250 kOhm/ft). The three orthogonal electric field components are measured by orienting the dipole at an angle of 54.7 degrees to the axis of the probe. Three rotations of the probe over 120 degrees can resolve the entire electric field. A relative calibration on the probe is performed in the media of interest and the magnitude of all three field components is measured. Scanning is performed only in the inner elliptical compartment filled with liquid muscle-equivalent tissue and is accomplished in three dimensions with a Hewlett Packard (HP) plotter mounted on a stepper motor controlled platform. Spatial accuracy within a horizontal plane \((x, y)\) is better than \(\pm 0.03\) mm and for the \(z\)-direction \(\pm 1\) mm. The overall accuracy for the electric field measurements is \(\pm 5\%\) for signals over a 20 dB range. The time to perform a scan over half the CDRH phantom with a 20 mm resolution (>5000 pixels) is approximately 4 hours.

Additionally, the theoretical model was used to compute the electromagnetic field distribution induced by the ring applicator in radially layered cylindrical tissue configurations. The pelvic-equivalent tissue cylinder (radius 15 cm) was, analogue to the CDRH phantom, enclosed by a fat layer of 1 cm thickness and assumed indefinitely long. Furthermore, the model assumes that the pair of coaxially mounted ring electrodes are perfect conductors, infinitely thin, and that the potential is constant over the perimeter of the ring electrodes. For a detailed description see Sowinski et al. [1989]. At the time this study was performed the present three-dimensional theoretical model [Zwamborn et al., 1992], which is capable to predict the energy distribution in any inhomogeneous structure, was still under development.

### 6.4.2 Results

### RF feeding points

Several experiments were performed to investigate the influence of the frequency and the number and location of the energy feeding points on the resulting SAR distribution. Figure 6.13 shows the SAR distribution measured at the cross-section midplane between the electrodes when the ring applicator is operated at 33 MHz, using a single RF feeding point. The relative SAR distribution shows high energy absorption at the side of the RF feeding point, zero energy absorption at the centre of the phantom, and a second, mirror image alike, high energy absorption area at the side opposite the RF feeding point. Maximum energy absorption with this set-up was measured in front of the inner edge of the upper ring electrode at the side opposite the RF feeding point. The mirror image alike high SAR area can be explained by the induced potential distribution over the perimeter of the electrode. At 33 MHz the half wavelength of the electromagnetic field in water (30 °C) is \(\pm 53\) cm and the half perimeter of the electrode is 75 cm. This means that the electromagnetic field at the side opposite the RF feeding point will be out of phase with the electro-
Figure 6.13. Relative SAR distribution measured at the cross-sectional midplane of the phantom and the ring electrodes. The ring applicator is operated at 33 MHz and only one RF feeding point at the right side is used.

magnetic field at the RF feeding point. As a consequence, the circumferential electric field distribution induces a destructive interference at the centre of the phantom.

Operating the applicator with four RF feeding points resulted in some improvement at 33 MHz but not at 70 MHz. With regard to constructive interference at the centre of the phantom, stray-radiation, and control of the RF power to each channel satisfactory results were obtained when eight RF feeding points were used. The increase to eight RF feeding points was realized by splitting the RF signal of a single amplifier over two RF feeding points. In addition, the experiments performed at 70 MHz demonstrated a better operating of the ring applicator system when the RF feeding points were located symmetrically to the phantom (see Figure 6.12). In all experiments reported hereafter eight RF feeding points have been used.

33 MHz SAR experiments

The ability of the ring applicator to produce heat at depth within the CDRH phantom is illustrated in Figures 6.14a - 6.14c. Figure 6.14a shows the SAR distribution at the central cross-section with $\sigma = 0.6$ S/m for the inner phantom part. The SAR distribution in the yz and xz plane is shown in Figures 6.14b and 6.14c. As can be seen from Figure 6.14a the SAR distribution at the central cross-section is more
Figure 6.14a,b. Relative SAR distribution measured at the cross-sectional midplane of the phantom and the electrodes (a), and in the yz planes (b). Eight RF feeding points; frequency 33 MHz; $\sigma = 0.6$ S/m.
or less uniform. The latter is in good agreement with the predicted SAR distribution for the cylindrical model with an overall diameter of 32 cm (see Figure 6.15). The small hot spots, including the maximum SAR value, in the lower right hand corner of the SAR distribution are caused by an imperfection of the experimental set-up.

The SAR distribution measured with \( \sigma = 0.4 \) S/m for the inner phantom part did not differ significantly from the SAR distribution measured with \( \sigma = 0.6 \) S/m. Figure 6.15a shows the measured SAR profile along the major axis of the phantom at the central cross-section for both conductivities. For comparison, the SAR profile along the axis at the central cross-section as predicted for the cylindrical model is shown in Figure 6.15b. Reasonable agreement exists, although the measured SAR profiles do not show the degree of focusing ability which might have been expected from the predicted SAR profiles.

Figure 6.16a shows the SAR distribution measured at the central cross-section with power output from only two of the four amplifiers. Equal power was applied to the left and upper RF feeding points and zero power was applied to the right and lower RF feeding points. Note, however, that these RF feeding points remained connected to the amplifiers, which resembled a 50 Ohm load. As shown in Figure 6.16a this amplitude steering resulted in maximum SAR values in the upper-left quadrant. Applying energy to the same two RF feeding points, but now disconnecting the other two RF feeding points from the amplifiers, which act as an open line, results in a much less favourable SAR distribution as shown in Figure 6.16b. Here again, the electromagnetic fields originating from the left and upper RF feeding points are reflected 180 degrees out of phase at the open RF feeding points. As a
Figure 6.15. Comparison of the measured (a) and predicted (b) SAR profile along the major axis of the phantom at the central cross-section. Frequency 33 MHz; $\sigma = 0.4$ and 0.6 S/m.
Figure 6.16. SAR distribution measured at the central cross-section with power output from the upper and left RF feeding point, while the lower and right RF feeding points are connected to a 50 Ohm load (a) or are left as an open line (b).
result, a destructive interference exists at the centre and high SAR values are measured at the periphery of the phantom.

**70 MHz SAR experiments**

At this frequency the work was concentrated on SAR experiments to demonstrate the focusing ability of the ring applicator. In all experiments equal power was applied to each RF feeding point. The SAR distributions measured at the central cross-section for $\sigma = 0.4$, 0.6, and 1.0 S/m are shown in Figures 6.17a - 6.17c, respectively. No focusing effect was found with $\sigma = 1.0$ S/m. Lowering the electric conductivity to 0.6 S/m, a value often quoted as being equivalent to the average electric conductivity of all abdominal tissues at this frequency, results in a small but definitive maximum at the centre. If the electric conductivity of the water is further decreased to a value of 0.4 S/m, the resulting SAR distribution shows, as expected, a more pronounced focusing with the maximum SAR at the centre of the phantom. Here again, the small hot spots, including the maximum SAR value, in the lower right hand corner of the SAR distributions are caused by an imperfection of the experimental set-up.

![SAR distributions measured at the central cross-section for $\sigma = 0.4$ S/m. Frequency 70 MHz.](image)

**Figure 6.17a.** SAR distributions measured at the central cross-section for $\sigma = 0.4$ S/m. Frequency 70 MHz.
Figure 6.17. SAR distributions measured at the central cross-section for $\sigma = 0.6$ (b) 1.0 S/m (c). Frequency 70 MHz.
Figure 6.18. Comparison of the measured (a) and predicted (b) SAR profile along the major axis of the phantom at the central cross-section. Frequency 70 MHz; $\sigma = 0.4, 0.6,$ and $1.0$ S/m.
Finally, Figures 6.18a and 6.18b show that good agreement exists between the measured SAR profile along the major axis at the central cross-section of the elliptical phantom and the SAR profile along the axis at the central cross-section predicted for the cylindrical model.

6.4.3 Discussion

To obtain maximum constructive interference at the centre of the phantom it is essential to create a circumferential electric field distribution with constant phase and amplitude around the phantom. Whether such a circumferential electric field distribution can indeed be obtained will strongly depend on the diameter of the ring applicator, the operating frequency, and the number and location of RF feeding points. For the ring applicator configuration, as used in this study, it was found that eight RF feeding points were sufficient to create a circumferential electric field distribution with good constructive interference at the centre of the phantom. No experiments with more than eight RF feeding points were performed. This finding is in agreement with the Sigma-60 applicator of the BSD Corporation, which uses the same number of dipole applicators.

The hot spots, including the maximum SAR value, as measured in the lower right hand corner of several SAR distributions (Figures 6.14a, 6.17b and 6.17c) are caused by an imperfection of the experimental set-up. This was experimentally confirmed at 70 MHz with three different set-up combinations of the phantom and the applicator. The standard applicator and phantom set-up, with power settings per channel such that a good symmetrical SAR distribution (Figure 6.17a) was obtained, served as a reference for this experiment. Turning only the CDRH phantom by 180 degrees and using the same amplitude settings, no difference in the measured SAR distribution was found. Turning, however, the whole applicator set-up (including the phantom) by 180 degrees resulted in a SAR distribution with hot spots and a maximum SAR in the lower right hand corner. The latter indicates that part of the electromagnetic field from the applicator is coupled to the nearby experimental set-up, whereby especially the platform (large metallic parts) to support the HP plotter is suspected to have an influence on the electromagnetic field.

The SAR distribution measured for the ring applicator at 70 MHz with the lower values of electric conductivity (0.4 and 0.6 S/m) are in good agreement with those reported for the Sigma-60 dipole applicator [Tumer and Schaefermeyer, 1989] and the Coaxial TEM applicator [De Leeuw et al., 1991]. For all three systems the SAR distribution is characterized by a broad maximum at the centre of the phantom and minimum SAR values at a distance of approximately 10 cm from the centre. The SAR distribution measured for $\sigma = 1.0$ S/m, muscle-equivalent at 70 MHz, demonstrated the effect of the reduced penetration depth with increasing electric
conductivities. As expected, the radiative electromagnetic fields are rapidly absorbed, showing maximum SAR values at the periphery of the phantom, and the constructive interference is no longer able to create a local maximum.

With the lower frequency of 33 MHz a better penetration depth exists, however, now the long wavelength prohibits focusing to a small volume. As expected, the measured SAR profile is indeed characterized by a more or less uniform distribution which is in reasonable agreement with theoretical predictions. The non-symmetrical distribution is, next to the experimental set-up, also a consequence of the sampling method and the normalization to the maximum value measured. The ability of the ring applicator to perform SAR steering by amplitude control has been demonstrated experimentally. However, as there is no focus at a frequency of 33 MHz it will be obvious that SAR steering is limited and can only result in directing the major energy absorption to one quadrant of the phantom. Nevertheless, the results are encouraging with regard to the capability of the ring applicator to perform SAR steering at the higher frequencies (70-100 MHz).

The solid material used for the fat-equivalent tissue prohibited SAR measurement within the fat layer. As the direction of the electric field induced by the ring applicator is mainly parallel to the body-axis, thus parallel to the fat-muscle interface, low energy absorption in the fatty tissue will occur. In this respect, the ring applicator does not differ from the other existing radiative systems for loco-regional deep hyperthermia. The theoretical modelling performed does indeed predict a low SAR in the fatty tissue for all experimental set-ups. At 33 MHz the ratio of the maximum SAR in the fatty tissue, located below the inner edge of the ring electrodes, to the maximum SAR in the pelvic-equivalent tissue was 0.7 and 0.85 for $\sigma = 0.4$ and 0.6 S/m, respectively. At 70 MHz these ratios were 0.35, 0.40, and 0.35 for $\sigma = 0.4$, 0.6, and 1.0 S/m, respectively. Furthermore, by adapting the configuration of the ring applicator (see Chapter 6.3) it is possible to optimize the SAR distribution such that a minimal heating of the fat tissue in front of the ring electrodes exists.

With regard to the ability to obtain heating at depth there seems to be no difference between the various radiative hyperthermia systems for loco-regional deep heating. This has also been confirmed by a study of Schneider et al. [1994]. They used the LED matrix [Schneider and van Dijk, 1991] to compare the SAR distribution at the central cross-section plane of three loco-regional deep heating systems and found no difference in the SAR characteristics. The latter does not exclude that a specific design of the deep heating system might offer particular advantages for clinical application of loco-regional hyperthermia. With the Coaxial TEM applicator, for instance, the open water bolus results in a significant reduction of water pressure on the abdomen of the patient. An advantage of the ring applicator, besides the earlier mentioned feasibility to perform longitudinal SAR control, might be that the gap between the ring electrodes allows the installation of additional equipment.
In conclusion, it has been demonstrated that the ring applicator is capable to induce a radiative circumferential electromagnetic field with a constructive interference pattern at the centre of the phantom. Experimentally, encouraging results with respect to the ability to perform deep heating and SAR steering in a phantom of realistic size have been obtained. Of course, in the clinical situation tissue anatomy will greatly affect the SAR distribution and may cause the local maximum and the smooth profile as measured in the CDRH phantom to disappear. Presently, clinical experience with the second-generation radiative devices indicates a limited feasibility to adapt the SAR and temperature distribution due to tissue anatomy and blood flow.
Chapter 7
Experimental assessment of electric impedance tomography integrated with the ring applicator\textsuperscript{8}

7.1 Introduction
With the current clinical application of hyperthermia the operator must still rely on the limited information from a few temperature sampling sites and the feeling of warmth and pain by the patient. If the operator could be informed more extensively about the temperature distribution at depth a much better control of the energy application is expected. Several methods -X-ray computer tomography, ultrasound, magnetic resonance imaging, active and passive microwave imaging, and electric impedance tomography [Bolomey and Hawley, 1990]- are considered for non-invasive thermometry. All methods measure temperature indirectly through a parameter which is to a greater or lesser extent temperature dependent. Most of the methods are still in their infancy and substantial improvements are needed with regard to electromagnetic compatibility, spatial resolution, accuracy, time to collect and process the data, and costs. It is expected that, eventually, non-invasive thermometry systems will be a valuable tool to indicate the location of hot spots and cold spots within the treatment volume.

This chapter reports on the results of a study to assess the clinical potential of electric impedance imaging for non-invasive temperature monitoring. The ability of the Sheffield electric impedance tomography system [Brown and Seager, 1987] to monitor impedance changes under conditions of high radiofrequency field intensities was tested and additionally the induced temperature distributions measured by electric impedance tomography and invasive thermal probes were compared. Experiments were performed on a heterogeneous tissue-equivalent phantom and the leg of a healthy volunteer, both heated by the ring applicator.

Electric impedance imaging reconstructs the internal resistivity distribution of

an object from electric measurements on the periphery. As tissue resistivity varies as a function of temperature by around 2%/°C [Zheng and Shao, 1984], it is possible to relate impedance changes measured by electric impedance tomography with temperature changes. Particular advantages of electric impedance tomography systems compared to other non-invasive thermometry systems are compatibility with heating devices, sensitivity, relatively low costs, and simplicity.

7.2 Materials and Methods

The Sheffield electric impedance tomography (EIT) system [Barber and Seager, 1987; Brown and Seager, 1987] employs a ring of 16 electrodes in galvanic contact to the body or phantom. The measuring principle is well known: a current (frequency 50 KHz) is injected between two adjacent electrodes and the potential difference is measured between all other adjacent electrode pairs. The current injection is then moved to the next pair. This procedure is repeated until a current has been injected to all electrode pairs [Barber and Brown, 1984]. Electric impedance tomography is a differential method: measurements are carried out for a reference condition and then again after heating of the object. In this way the measured potential distributions are indicative for the impedance changes in the structure. As a second step

![Diagram of the EIT system](image)

Figure 7.1. A schematic representation of the ring applicator heating a cylindrical phantom during electric impedance imaging at the central plane.
these impedance changes can be converted by a mathematical algorithm to a change in temperature distribution. In the present system the reconstruction algorithm provides only the relative change of the EIT signal for each pixel and the signal is reported in relative EIT units. The electronic procedure of the measurement is controlled by a personal computer which may also convert impedance to temperature changes. Time resolution of the system is 40 ms to collect a full set of data. Averaging over 100 data sets (i.e., measurement time 4 s) gives a temperature resolution of about 0.5 °C. Spatial resolution is dependent on the number of electrodes; for this 16-electrode system it is about 10% of the diameter of the measuring ring, although theoretically it may be enhanced to 5%. A schematic representation of the experimental set-up is shown in Figure 7.1.

The ring applicator set-up used in the phantom experiments consisted of two copper ring electrodes of 12.5 mm width placed directly onto the PVC-tube at a distance of 100 mm from each other. During the experiments heating the leg of the volunteer (GvR) clinical electrodes (the copper rings are insulated by a teflon cover) were used in a similar set-up. In all experiments the electrodes were connected to a 27.12 MHz RF generator (Enraf Nonius, Curamed 419); the forward power used was 250 W and approximately 80 W was reflected.

The phantom diameter including the Poly Vinyl Chloride (PVC) tube was 135 mm; the length of the phantom was 500 mm. The homogeneous muscle-equivalent phantom had a diameter of 127 mm and was contained in a 4 mm thick PVC-tube. The heterogeneous phantom consisted of a muscle-equivalent tissue cylinder of 105-109 mm diameter covered by a 9-11 mm thick layer of fat-equivalent tissue. The muscle-equivalent material used was composed according to Ishida and Kato [1980]. The fat-equivalent material was made according to the recipe of Bini et al. [1984]. The estimated electric properties of the fat material at room temperature are: conductivity (\(\sigma\)) = 0.01 S/m and relative permittivity (\(\varepsilon\)) = 22 at 27.12 MHz. The electrodes for the electric impedance tomography system were placed through the PVC-tube and had direct galvanic contact with the phantom material.

To measure the temperature increase at fixed locations in the phantom a multi-channel fibre-optic thermometry system was used (FT1210, Takaoka, Japan).

7.3 Results

The effect of RF interference could be discerned to affect the proper functioning of either the electric impedance tomography measuring system or the personal computer used to control the process of measurement. At low RF power no interference occurred but the RF power was also too low to induce significant heating in the phantom. At higher RF power levels (>50 W) the electronic circuits performing the electric impedance tomography voltage measurements were not
Figure 7.2. Measured EIT signal (a) and temperature profile (b) along the x-axis at the central cross-section of the phantom as function of time. For comparison the predicted SAR distribution is also shown.
functioning due to RF interference. By using a power-pulse technique with heating periods of 60 s followed by 15 s to restore the electronic circuits of the electric impedance tomography system and 15 s for electric impedance tomography measurement. Occasionally, RF interference occurred directly on the PC which caused the loss of the collected data of the experiment.

Unfortunately, no experiments with a fat-muscle layered phantom could be performed. The fatty tissue material was composed such that the dielectric properties matched those of human fat at 27 MHz. At the frequency of electric impedance tomography measurement (50 KHz) the conductivity of the fatty material was too low to obtain reliable measurements. The problem of matching the dielectric properties of phantom material at two, largely separated, frequencies will be difficult to solve. Only freshly slaughtered pig fat might be a good substitute.

In the experiments performed with the homogeneous muscle-equivalent phantom the set-up of the ring electrodes was chosen to provide a small radial temperature decay towards the centre of the cylindrical phantom. Even though a power-pulse technique was used, the data obtained of only two experiments (homogeneous muscle and homogeneous muscle with two foam inserts) were sufficient to perform detailed
Figure 7.4. Locations of temperature measurement for the phantom configuration of a homogeneous muscle equivalent tissue cylinder containing two foam inserts.
analysis.

For the experiment with the homogeneous muscle phantom temperatures were measured at six locations along one main axis of the central plane, that is, at positions L65, L55, L45, L35, C00, and R25. L65 is located at 65 mm towards the left of the centre (C00; see Figure 7.4). For the EIT signal and the temperature figures 7.2a and 7.2b show the measured profiles along the x-axis, left to right, at the central plane as function of time. For comparison the predicted SAR profile, as calculated by the model described in Chapter 6.3.1 is also plotted in each graph. Good correlation between temperature increase and EIT signal exists for the measuring points R25, L35, L45, and L55. In Figure 7.3 the temperature increase is correlated to the increase of the EIT signal at all sensor sites for the various time intervals. It can be deducted that the sensitivity of the electric impedance tomography measuring system is approximately 69 EIT units per degree Celsius. The figures also show a clear difference between electric impedance tomography and temperature readings at location L65 and at the centre of the phantom. The temperature increases measured at these locations are in good agreement with the expected SAR distribution if heat loss at the surface of the phantom is taken into account.

The second experiment had two artificial inhomogeneities, small pieces of foam (size 4 x 1 x 1 cm³) inserted into the homogeneous muscle-equivalent tissue cylinder; temperature increase within the phantom was now measured at 8 locations (see Figure 7.4). Again good correlation between temperature increase and increase of EIT signal was obtained at all measuring points except at the centre location. Figures 7.5a-h show the increase of EIT signal and temperature versus time for each measuring point. The correlation between temperature and EIT signal increase for all sensor sites and time intervals is summarized in Figure 7.6. An electric impedance tomography sensitivity of 72 EIT units/°C was found.

The purpose of the experiment to heat the leg of the volunteer was twofold. First, it was investigated whether the metal electrodes of the electric impedance tomography system would be heated selectively, which would increase the risk of burns, and secondly, whether the electric impedance tomography system would function properly under clinical conditions. Therefore, no attempt was made to insert temperature sensors into the leg and consequently, no correlation between temperature and EIT signal could be made. During this experiment no selective heating of the electric impedance tomography metal electrodes was experienced by the volunteer. However, the problem of RF interference was found to be more pronounced. For clinical applications the ring electrodes need to be covered with an insulator to protect the patient against the high RF potentials. This causes the ring applicator set-up to produce more stray-radiation. By using the power-pulse technique the effect of this RF interference could be limited to some extent.
Figure 7.5. Increase of temperature and EIT signal as function of time for all measuring sites for the inhomogeneous phantom. (a) R25, (b) C00, (c) L30, (d) L40, (e) L50, (f) L60, (g) A45 and (h) A60.
Figure 7.5. Increase of temperature and EIT signal as function of time for all measuring sites for the inhomogeneous phantom. (a) R25, (b) C00, (c) L30, (d) L40, (e) L50, (f) L60, (g) A45 and (h) A60.
Figure 7.6. Correlation of temperature increase and increase of the EIT signal at the temperature sensor sites for the inhomogeneous phantom.

7.4 Discussion

The information obtained from the experiments performed successfully, demonstrates that the electric impedance tomography system is capable of detecting temperature changes during hyperthermia applied with the Ring applicator system.

The difference found between the EIT signal and the measured temperature increase at location L65 is caused by the position of the temperature probe: it is located at the transition from muscle-equivalent phantom material to the PVC-shell. This means that the temperature sensor is located in an area in which a large temperature gradient exists and therefore indicates a value between the high temperature of the muscle tissue and the low temperature of the PVC-shell. Due to the large difference in the electric conductivity of muscle tissue and PVC the electric impedance tomography will only record the resistivity changes of the muscle tissue. Hence, this explains the higher sensitivity at this location and it can be regarded as an error due to the experimental set-up. The poor correlation between EIT signal and temperature at the centre (C00) of the phantom is explained by the low sensitivity of the electric impedance tomography system for changes in the resistivity at the centre of the phantom [Seagar et al., 1987; Amasha et al., 1988]. The good
correlation found between temperature and resistivity changes for the other measuring sites show that under these very controlled experimental conditions and after calibration, electric impedance tomography could measure temperature rise during hyperthermic heating with a temperature resolution of around 0.75°C. Similar findings between electric impedance tomography measurements and temperature during electromagnetic heating of a phantom leg have been reported by Griffiths and Ahmed [1987].

For future clinical applications an encouraging observation during the experiment on the leg of the volunteer is that no selective heating of the electric impedance tomography metal electrodes occurred. Additionally, the good correlation between the radial profile of the temperature distribution (Figure 7.2b) and the predicted SAR distribution indicates that the metal electric impedance tomography electrodes do not affect the heating pattern of the ring applicator.

The experiments reported here have highlighted some problems associated with electric impedance tomography monitoring of temperatures limiting its imaging capability during RF heating. These problems need to be overcome to enable implementation of non-invasive temperature monitoring by electric impedance tomography during clinical hyperthermia treatments. Some possible solutions are discussed below.

The problem of electromagnetic compatibility between the electric impedance tomography system and the heating equipment is mainly due to the many leads to the electrodes coupling electromagnetic radiation efficiently into the electronic circuits. One solution is to adopt the power-off protocol, in which electric impedance tomography data are collected during the power-off periods, as has been done in the present study. However, the time needed for transients to decay (>15 s) may lead to too long power-off periods and therefore result in inefficient hyperthermia treatments. Replacing the normal leads with leads with low metal content and ensuring that the leads are perpendicular to the electric field may reduce the coupling of electromagnetic radiation. Employing sophisticated electronic RF filtering in conjunction with the before mentioned precautions and placement of the electronic circuits within a Faraday cage should reduce the problems to acceptable levels. The RF filter must be designed such that the leads to the electrodes effectively represent a high impedance for the RF energy. If the RF filter would represent a short to ground for the RF energy excessive heating at the electric impedance tomography electrodes may occur with associated burns to the patient.

To increase the sensitivity of the electric impedance tomography system for resistivity changes at the centre of the body it will be necessary to implement improved algorithms to reconstruct the conductivity. For the Barber-Brown [1984] reconstruction algorithm, as used in this study, the sensitivity depends on the area of the
resistivity change (large areas are more sensitive than small areas). For a circular configuration of the electric impedance tomography electrodes this means that the sensitivity at the periphery of the ring is better than at the centre. To a certain extent the application of weighing functions can be used to correct for this non-uniform sensitivity [Seager et al., 1987; Amasha et al., 1988]. Clearly, a trade-off has to be made between spatial resolution and accuracy. Alternatively, an iterative reconstruction algorithm can be used which is more accurate but may suffer from instability related to noisy data and uncertainty in electrode position [Hawley, 1990].

Additionally, other problems not investigated in this study, like deterioration of electrode contact, resistivity changes due to blood flow changes, and real time presentation of the measured resistivity distribution also need to be addressed prior to clinical implementation of electric impedance tomography during hyperthermia treatments. Furthermore, all present reconstruction algorithms are limited to a two-dimensional case. In reality, the current will also flow out of the plane of measurement which may have, especially for the heterogeneous human anatomy a disturbing effect on the measured resistivity distribution.
Chapter 8
Conclusions

The application of loco-regional deep hyperthermia with the aim to heat the entire tumour volume to therapeutic temperatures is not an easy task. The thermal dose applied to the tumour is determined by both the height of the temperature and the time during which this elevated temperature is maintained. The temperature which can be achieved in the tumour depends on the energy deposition at depth and on the local blood flow. At present it is, however, not yet possible to manipulate the tumour blood flow, specifically in a well controlled manner. The duration of the elevated temperature depends on the ability of the patient to tolerate the treatment. Energy deposition and treatment tolerance are to a certain extent affected by the hyperthermia system used and therefore, a trade-off between patient comfort and the ability to deposit energy at depth has to be made. For the three radiofrequency hyperthermia systems discussed in this thesis different trade-off criteria have been used (Chapter 2). Whether these different approaches have resulted in the desired loco-regional deep heating feasibility has been the subject of this thesis. The outcome of the experimental and clinical studies can be summarized as follows:

(1) the RCA 27 MHz ridged waveguides system

The phantom experiments performed with this system show that the RF energy is not concentrated to the area opposite the ridge as was assumed by Paglione et al. [1981]. On the contrary, high-intensity electric fields are present at the side walls of the waveguide as can be concluded from the irregular SAR pattern obtained if the aperture is completely covered with phantom material. Furthermore, the experiments with inhomogeneous phantoms show that, especially at the upper edge of the waveguide, strong fringing electric fields exist close to the aperture. As a result, the penetration depth of 7-8 cm found for these waveguides is substantially smaller than that of a plane electromagnetic wave at the same frequency (14.3 cm).

With regard to the clinical application it was found that semi-deep heating could be obtained with the single straight waveguide. Tumour temperatures measured during the patient treatments remained, however, relatively low due to local pain caused by the irregular SAR pattern. The finding that only 15% of all measured
tumour temperatures were above 40 °C indicates that heating was limited to small parts of the tumour volume and short periods only.

When both waveguides were used in the parallel opposed arrangement the strong electric field intensities outside the ridged area gave rise to complicated and unpredictable SAR patterns. Also, the animal experiments performed with the parallel opposed arrangement of both waveguides showed a large variation in the ability to induce deep heating. In three of the five animal experiments core heating and/or a severe third degree burn occurred, which could only be partly explained by the poor performance of the bended waveguide or the strong fringing electric fields at the edges of the aperture. Therefore, it is concluded that the original 27 MHz ridged waveguides of RCA are not suited for clinical use in a parallel opposed arrangement to induce loco-regional deep heating.

(2) the HTM3000P capacitive hyperthermia system

The experiments performed on the buttocks of pigs with a fat layer of 1-2 cm showed that this system is able to heat large volumes at depth to temperatures above 42 °C. Despite these encouraging experimental results, the clinical data obtained during the hyperthermia treatment of tumours in the pelvis are rather disappointing. This is even more pronounced considering the fact that the patients were selected on the criterion of a fat thickness less than 2 cm. Although pre-cooling with saline water bolus at 10 °C was well tolerated by the patient, the increase of tumour temperature was limited in most treatments by unacceptably high temperatures at the interface of the subcutaneous fat tissue to the deeper muscle tissue. At this interface the effect of (pre-)cooling is negligible and in 53% of the treatments the maximum temperature was measured at this location. For individual patients a substantial gain in thermal dose could be obtained by changing the conventional anterior-posterior applicator set-up to the adapted set-up with lateral applicator positions. The overall quality of the hyperthermia treatment is poor: 60% of the measured tumour temperatures are below 40 °C. In conclusion, the HTM3000P capacitive hyperthermia system including extensive pre-cooling of the subcutaneous tissues cannot induce adequate hyperthermia in pelvic tumours of Dutch patients, even if these patients are selected on the criterion of a fat thickness less than 2 cm.

(3) the Ring applicator

The experiments and theoretical modelling show that within a cylindrical tissue volume enclosed by the ring electrodes the direction of the electric field is indeed parallel to the body axis. Only at the edges of the ring electrodes a radial component of the electric field exists. Experiments using homogeneous muscle-equivalent phantoms with diameters up to 14 cm show that the maximum SAR is always located at the centre of the phantom as long as the separation of the ring electrodes is equal to or larger than the phantom diameter. For inhomogeneous phantoms preferential heating of the fatty tissue may occur at the edges of the ring electrode due to the
radial component of the electric field. Measured and predicted SAR distributions demonstrate, however, that preferential heating at this location can be adequately controlled by proper adjustment of the ring electrode configuration, e.g., by increasing the gap between electrode and phantom surface. In general, water instead of air as a gap medium is advantageous with respect to avoiding preferential fat heating and the voltage over the ring electrodes. A simple way to adjust the axial length of the heated volume to the desired treatment volume is to adapt the distance between the electrodes.

The experiments performed at 33 and 70 MHz show that a ring applicator with a diameter of 48 cm is able to induce a radiative circumferential electromagnetic field with a constructive interference pattern at the centre of the CDRH phantom. At 33 MHz, RF power of equal amplitudes and phase applied to all eight feeding points result in a more or less uniform SAR distribution in the central cross-section. With RF power supplied to four adjacent feeding points and the other feeding points connected to a 50 Ω load, higher SAR values were measured in front of the active feeding points, illustrating the feasibility of SAR steering by amplitude control. Experiments at 70 MHz and electric conductivities of 0.4 and 0.6 S/m show the focusing ability with the maximum SAR located at the centre of the phantom.

In conclusion, measured and predicted SAR patterns within multi-layered models demonstrate that a ring applicator of small diameter and operating at 27 MHz is well suited for hyperthermia treatment of the extremities. With regard to deep heating, i.e. using ring electrodes of a large diameter and frequencies around 70 MHz, further research is needed to fully characterize the advantages and disadvantages of the ring applicator compared to existing deep hyperthermia systems. Especially, the feasibility to perform longitudinal SAR control needs to be investigated. An advantage of the ring applicator demonstrated in this thesis, is that the gap between the electrodes allows the installation of additional equipment. The experiments with the electric impedance tomography system for non-invasive monitoring of temperatures have highlighted some problems associated this system which currently limit its imaging ability during RF heating. The problems of electromagnetic compatibility and low sensitivity for resistivity changes at the centre of the body must be overcome to enable further research towards the feasibility of non-invasive thermometry by electric impedance tomography during clinical hyperthermia.

**CURRENT CLINICAL STATUS**

Clinical experience with the first generation equipment for deep loco-regional hyperthermia showed that therapeutic temperatures could be achieved in deep-seated tumours, but also indicated the difficulty to fulfil the temperature-time goals. In approximately 90% of the clinical treatments with the former annular phased array
system (BSD-1000) local pain, general discomfort, and rise of normal tissue temperature was power limiting. To overcome these problems the second generation of the radiative deep heating devices, such as the Sigma-60 applicator, the four-waveguide system, and the coaxial TEM applicator, provide the possibility of SAR-steering by phase and amplitude control or by re-positioning the patient. Additionally, to reduce anxiety and discomfort of the patient special attention has been paid to the design of the integrated water bolus for the Sigma-60 applicator and the four-waveguide system. Due to the open water bolus of the coaxial TEM applicator complaints of discomfort caused by water pressure are not encountered with this system.

Clinical experience with these devices indicate that these improvements indeed lead to higher temperatures for longer periods, i.e., a better quality of the hyperthermia treatment. On the other hand, old problems might be replaced by new problems. For the Sigma-60 applicator Feldman et al. [1991] found that preferential heating of the perineal fat can be treatment limiting. Oleson [personal communication, 1991] reported that hot spots are produced in bony prominences of the pelvis, particularly over the sacrum, the hip joint, the superior iliac crest, and the pubic bone. Additionally, for systems using a closed water bolus the fringing fields at the area where the bolus bag contacts the skin result in hot spots in the anterio-lateral thighs. These findings emphasize the need for continuing applicator development with the aim to improve the flexibility to adapt the SAR distribution to the patients' anatomy. Therefore, current research is concentrating in general on the use of advanced three-dimensional modelling to provide the optimum settings of frequency, amplitude, and phase for radiative array systems. More specifically with respect to array applicators, the research concentrates on implementation of quality assurance procedures to ensure that the actually delivered treatment matches the optimized treatment plan, better control of the location of the "focal spot" by introducing independent phase control for each array element, and longitudinal control of the SAR distribution. With regard to the longitudinal control of the SAR distribution the ability of the ring applicator to adapt the axial length of the effective electric field may be a particular advantage.

For the clinician the ultimate proof of the efficacy of adding loco-regional deep heating to a standard treatment is, of course, a substantial increase in tumour control rate. For this purpose, three Dutch institutes (Academic Medical Center, Amsterdam; Dr. Daniel den Hoed Cancer Center, Rotterdam; Academic Hospital Utrecht) are participating in a national randomized comparative trial in which the addition of hyperthermia to standard radiotherapy is investigated in inoperable tumours in the pelvis (rectum, uterine cervix and bladder). It is very encouraging that the preliminary results, which had to be reported to the Ministry of Welfare, Health and Cultural Affairs, show a 21% increase in local control rate by adding hyperthermia, for the total group of patients.
List of abbreviations

CDRH  centre for devices and radiological health  
CT computer tomography  
DC direct current  
EIT electric impedance tomography  
El-Ph electrode to phantom  
ESHO European society of hyperthermic oncology  
ETV estimated treatment volume  
FFT fast fourier transform  
HP Hewlett Packard  
HT hyperthermia  
HTM hyperthermia machine  
LED light emitting diode  
max maximum  
min minimum  
NED no evidence of disease  
p probability  
PVC poly vinyl chloride  
RF radiofrequency  
RT radiotherapy  
SAR specific absorption rate  
TE transverse electric  
TEM transverse electromagnetic  
UK United Kingdom  
USD United States dollar
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Summary

Hyperthermia is defined as a temperature elevation by several degrees (3-8 °C) above the normal physiological level. Experimental data show that adding hyperthermia to radiotherapy or chemotherapy can have a complementary effect: the tumour cells in the insufficiently perfused areas are more likely to survive after radiotherapy and chemotherapy, whereas these hypoxic tumour cells can be killed preferentially by hyperthermia. The thermal dose applied to the tumour is determined by both the height of the temperature and the duration of this elevated temperature. The temperature that can be achieved in the tumour depends on the energy deposition within the tissues at depth and on the local blood flow, whereas the duration of the elevated temperature depends on the ability of the patient to tolerate the treatment.

Since the introduction of hyperthermia, research has been directed primarily at the development of techniques to apply and control hyperthermia. Nevertheless, the clinical application of loco-regional deep hyperthermia is still a difficult task, as local blood flow is an uncontrolled parameter with high impact on the resulting temperature distribution. On the other hand, energy deposition and treatment tolerance are affected by the hyperthermia system used. For the presently available hyperthermia systems different trade-offs between patient comfort and the ability to deposit energy at depth were made. The three radiofrequency hyperthermia systems discussed in this thesis represent some of the approaches to apply a maximum thermal dose to the whole tumour volume.

The introduction (Chapter 1) briefly explains the biological rationale of hyperthermia and summarizes the results of numerous clinical hyperthermia studies. The clinical outcome of non-randomized matched lesions studies, as well as the results of randomized trials demonstrate that addition of hyperthermia to radiation therapy indeed does improve tumour control and/or cure rate. Furthermore, there is a clear indication that in combined treatments a high quality of the hyperthermia treatment is essential to obtain an enhancement of the clinical outcome. Consequently, continuation of development and clinical evaluation of new systems is mandatory to obtain a range of "site-specific" hyperthermia systems.

Chapter 2 provides an introduction to the different techniques available for loco-regional deep hyperthermia and explains the basic principles of electromagnetic heating. This chapter also describes the advantages and disadvantages of the various electromagnetic devices used to apply loco-regional hyperthermia.

Chapter 3 describes several methods to characterize the SAR distribution induced by an electromagnetic hyperthermia applicator. Additionally, knowledge about the energy or temperature distribution in dependence of body anatomy, blood flow, and the electromagnetic field applied can be obtained from theoretical modelling. This chapter ends with a summary about the relevance of and the
problems encountered with thermometry during a hyperthermia treatment.

The results obtained from the hyperthermia research programme in the Dr. Daniel den Hoed Cancer Center on the clinical feasibility of deep heating are reported in Chapters 4-6.

Chapter 4 describes the studies performed to test the 27 MHz ridged waveguides of RCA, either as a single waveguide or as a combination of two waveguides. The results of these studies show that an irregular energy pattern exists over the aperture of the waveguide: a large amount of RF energy is present at the side walls and also strong fringing electric fields exist at the upper edge of the waveguide. The penetration depth of 7-8 cm as measured in a large phantom, i.e. covering the whole aperture, is substantially smaller than that of plane electromagnetic waves at this frequency (14.3 cm). For small phantoms, i.e., covering only the ridge area of the aperture, the penetration depth decreased to 6 cm. The two-dimensional theoretical model used in this study is too optimistic on penetration depth and does not predict heating in the fatty tissue layer. In animal experiments it was possible to heat the buttocks of a pig to a temperature of 41 °C at a depth of 7 to 8 cm using a single ridged waveguide. The clinical results were, however, disappointing. Although in 31 of the 54 patient treatments a tumour temperature above 40 °C was reached, temperature analysis showed that only 15% of all measured tumour temperatures were above 40 °C. This indicates that temperatures above 40 °C were limited to small parts of the tumour volume and during short periods. The second part of this chapter concerns the use of two ridged waveguides in a parallel opposed arrangement. In phantom experiments a relative SAR of 30% was measured at the centre of a 200 mm thick muscle-equivalent phantom. Unfortunately, the unstable performance of the bended ridged waveguide in the parallel opposed set-up gave often rise to the occurrence of unpredictable SAR distributions. Also the animal experiments were rather unsuccessful: in three of the five experiments core heating and/or a severe third degree burn could not be prevented. The latter and, to a lesser degree, the high intensity fringing electric fields at the edges of the waveguide aperture, make the original 27 MHz ridged waveguides of RCA not suitable for clinical use in a parallel opposed arrangement to induce loco-regional deep heating.

Chapter 5 reports about the investigations with the HTM3000P capacitive hyperthermia system. The experiments performed on the buttocks of pigs with subcutaneous fat tissue of 1-2 cm thickness show that the system is able to heat large volumes at depth to temperatures above 42 °C. The clinical treatments performed within this study indicate that pre-cooling with saline water bolus at 10 °C is well tolerated by the patient, and can effectively reduce the temperature of the subcutaneous fat tissue. However, pre-cooling cannot avoid preferential heating at the interface from fat to muscle tissue: in 53% of the treatments the maximum temperature was measured at this location. The data also demonstrate that for this population of Dutch patients the quality of the hyperthermia treatment is rather poor: 60% of the measured tumour temperatures was below 40 °C. Finally, for the individual patient a substantial gain in thermal dose could be obtained when the conventional anterior-posterior applicator set-up was changed to the adapted set-up with lateral applicator positions.

Chapter 6 reports about the ring applicator which has been designed and developed at the department of Hyperthermia of the Dr. Daniel den Hoed Cancer Center. Due to its design, the ring applicator creates an electric field distribution
within a cylindrical body, which is mainly directed parallel to the body axis. The advantage of such an electric field direction is that preferential fat heating can be avoided.

Sections 6.2 and 6.3 describe the different investigations performed with a ring applicator of relatively small diameters (<25 cm) and operating at low frequencies (<30 MHz). Under these conditions the ring applicator can be viewed as a quasi-static applicator. The experiments and theoretical modelling show that within the tissue volume enclosed by the ring electrodes the direction of the electric field is indeed parallel to the body axis. Only at the edges of the ring electrodes a radial component of the electric field exists and consequently, preferential heating of the fatty tissue may occur at this location. Measured and predicted SAR distributions demonstrate, however, that preferential heating at the edges of the ring electrodes can be adequately controlled by proper adjustment of the ring electrode configuration, e.g., by increasing the gap between electrode and phantom surface or by using water instead of air as a gap medium. Furthermore, a simple way to adjust the axial length of the heated volume to the desired treatment volume is to adapt the distance between the electrodes. In conclusion, measured and predicted SAR patterns within multi-layered models demonstrate that a ring applicator with a small diameter and operating at 27 MHz is well suited for a hyperthermia treatment of the extremities.

The results in Section 6.4 demonstrate that a ring applicator with a diameter of 48 cm is able to induce a radiative circumferential electromagnetic field with a constructive interference pattern at the centre of the CDRH phantom. For this ring diameter eight RF feeding points were necessary to obtain a circumferential electric field distribution with constant phase and amplitude. The SAR distributions measured at 70 MHz with electric conductivities of 0.4 and 0.6 S/m are in good agreement with those reported for the Sigma-60 dipole applicator and the coaxial TEM applicator. The SAR distribution measured at 70 MHz with an electric conductivity of 1.0 S/m demonstrates the effect of the reduced penetration depth with increasing electric conductivities. At 33 MHz a better penetration depth exists, but now the long wavelength prohibits focusing to a small volume. Finally, it is demonstrated that this system allows some SAR steering by amplitude control.

In Chapter 7 the possibility to place additional equipment in the gap between the ring electrodes is demonstrated. The experiments on non-invasive thermometry highlighted some of the problems associated with electric impedance tomography monitoring of temperatures limiting its imaging capability during RF heating. The problems of electromagnetic compatibility and low sensitivity for resistivity changes at the centre of the body must be overcome to enable application non-invasive thermometry by electric impedance tomography during clinical hyperthermia treatments.

Chapter 8 gives the conclusions concerning the feasibility to induce loco-regional deep heating of each of the three systems investigated. Additionally, the current clinical status and present research programmes on loco-regional deep hyperthermia are briefly reported.

In conclusion: the results of the studies described in this thesis indicate that the best possibilities for achieving loco-regional deep heating with electromagnetic waves are to be expected from radiative devices, which are able to generate a circumferential electric field distribution around the patient.
Samenvatting

Hyperthermie, een verhoging van de lokale weefseltemperatuur met 3 à 8 °C, heeft een celdodend effect. De combinatie van hyperthermie met radiotherapie of chemotherapie lijkt ideaal. Cellen in onvoldoende geperfundeerde gebieden van de tumor zijn relatief ongevoelig voor radiotherapie of chemotherapie, terwijl hyperthermie juist deze celpopulatie uitschakelt. De grootte van het celdodend effect van hyperthermie is afhankelijk van de hoogte van de temperatuur en de duur van de behandeling. De balans van de hoeveelheid geabsorbeerde energie en de hoeveelheid energie afgevoerd door het langsstromende bloed bepaalt de temperatuurstijging van het weefsel. De duur van de behandeling wordt bepaald door de mate waarin de patiënt de behandeling kan verdragen. Ondanks het feit dat vanaf het begin van de hyperthermiebehandeling zeer veel tijd is besteed aan de ontwikkeling van verwarmingsapparatuur, blijft de temperatuurstijging in het weefsel nog in belangrijke mate onvoorspelbaar als gevolg van de wisselende doorbloeding van het weefsel. Het toedienen van een goede hyperthermiebehandeling is dan ook niet eenvoudig. De hoeveelheid geabsorbeerde energie en de tolerantie van de hyperthermiebehandeling hangen af van de gebruikte hyperthermie-apparatuur. In het algemeen geldt dat de behandeling met hyperthermie-apparatuur waarmee een groot volume verwarmd wordt, minder goed verdragen wordt dan met hyperthermie-apparatuur waarmee een klein volume verwarmd wordt. De drie electromagnetische hyperthermiesystemen (werkend in het frequentiegebied van 10 tot 100 MHz) die in dit proefschrift besproken worden, vertegenwoordigen verschillende methoden die zijn voorgesteld om een maximale thermische dosis aan een tumorvolume toe te dienen.

Hoofdstuk 1 geeft een korte toelichting op de biologische basis van hyperthermie en een samenvatting van de diverse klinische studies naar de waarde van hyperthermie. De resultaten van zowel niet-gerandomiseerde als gerandomiseerde studies lijken de experimentele resultaten te bevestigen: door toevoeging van hyperthermie aan radiotherapie kunnen de resultaten van lokale behandeling van tumoren aanzienlijk verbeterd worden. Uit deze studies is tevens gebleken dat de kwaliteit van de hyperthermiebehandeling een belangrijke factor is voor het eindresultaat. Voor het bereiken van een optimaal klinisch resultaat bij de diverse voor behandeling in aanmerking komende tumoren, is een continuering van ontwikkeling en klinische evaluatie van hyperthermie-apparatuur noodzakelijk.

Hoofdstuk 2 geeft een overzicht van de beschikbare technieken voor diepe hyperthermie. De principes en de voor- en nadelen van de verschillende elektromagnetische verwarmingstechnieken worden in detail beschreven.

Verschillende methoden voor het bepalen van de energieverdeling in een fantoom zijn beschreven in paragraaf 3.1. Bij de klinische toepassing zal, ten gevolge van de anatomie van de patiënt en de doorbloeding, de temperatuurverdeling sterk
afwijken van de energieverdeling in het fantoom. Met behulp van theoretische modellen is het mogelijk inzicht te verkrijgen in de grootte van deze effecten. Paragraaf 3.2 geeft een samenvatting van de theoretische modellen. Tot slot geeft paragraaf 3.3 een toelichting op de noodzaak van uitgebreide temperatuurmetingen tijdens een diepe hyperthermiebehandeling.

De resultaten van het hyperthermie-onderzoekprogramma binnen de Dr. Daniël den Hoed Kliniek naar de klinische toepassing van diepe hyperthermie worden besproken in Hoofdstuk 4 tot en met 6.

Hoofdstuk 4 beschrijft het onderzoek aan de 27 MHz "ridged waveguides" van RCA. De energieverdeling over de stralende opening van de golfpijp heeft een zeer onregelmatig patroon. Met name aan weerszijden van de stralende opening werd een sterke concentratie van de energie gemeten. Uit de metingen met inhomogene fantomen bleek tevens dat aan de bovenzijde van de opening sterke, zogenaamde "fringing fields" bestaan. Typerend voor deze elektrische velden in de nabijheid van de rand van de stralende opening is dat zij een richting loodrecht op de stralende opening hebben en daardoor lokaal een ongewenste verwarming van het vetweefsel kunnen geven. Indien de gehele stralende opening bedekt wordt met spier-equivalent fantoom materiaal wordt een indringdiepte gemeten van 7-8 cm. In geval alleen het "ridged"-deel van de stralende opening is bedekt, neemt de indringdiepte af tot 6 cm. Dit is aanzienlijk minder dan de indringdiepte (14.3 cm) voor een vlakke golf bij een frequentie van 27 MHz. In alle berekeningen voorspelde het gebruikte theoretische model een te optimistische waarde voor de indringdiepte. Door het twee-dimensionale karakter van dit model wordt tevens de verwarming van het vetweefsel niet voorspeld. Uit het dierexperimenteel onderzoek blijkt dat met een enkele golfpijp in de billen van een varken temperaturen tot 41 °C op een diepte van 7-8 cm bereikt kunnen worden. De bereikte temperaturen tijdens de klinische behandelingen met een enkele golfpijp zijn echter teleurstellend. Hoewel bij 31 van de 54 behandelingen een temperatuur boven 40 °C werd gemeten, blijkt uit de analyse van de temperatuurgegevens dat slechts 15% van alle gemeten tumortemperaturen hoger dan 40 °C is. Dit betekent dat temperaturen >40 °C beperkt zijn tot kleine tumorvolumina en slechts gedurende een korte periode gehandhaafd blijven. In het tweede deel van Hoofdstuk 4 worden de resultaten van het onderzoek aan twee golf pijpen in een plan-parallelle opstelling geraapporteerd. In het centrum van het 200 mm dikke, spier-equivalente fantoom werd een relatieve SAR van 30% bereikt. De werking van de beide golfpijpen in deze opstelling was echter instabiel en de geëxduceerde energieverdeling in het weefsel/fantoom was onvoorspelbaar. Ook de resultaten bij de verwarming van varkens waren teleurstellend: bij drie van de vijf dierexperimenten was sprake van een aanzienlijke totale lichaamsverwarming en/of ontstond een ernstige, derdegraads brandwond. Op basis van deze resultaten moet geconcludeerd worden dat de originele "RCA ridged waveguides" in een plan-parallelle opstelling ongeschikt zijn voor verwarming van diepgelegen tumoren in het bekken.

Hoofdstuk 5 beschrijft het onderzoek verricht met het HTM3000P capacitive hyperthermiesysteem. Uit het dierexperimenteel onderzoek volgt dat met dit apparaat grote delen centraal in het bekken van varkens tot 42 °C verwarmd kunnen worden. Uit het klinische deel van dit onderzoek blijkt dat patiënten het 30 minuten durende voor-koelen van het onderhuidse oppervlakkige vetweefsel met een zoutwater bolus van 10 °C goed verdragen. Zoals verwacht, resulteert het voorkoelen in een grote verlaging van de temperatuur in het vetweefsel. Echter, het voorkoelen
kan niet voorkomen dat op de overgang van vet- naar spierweefsel een selectieve verwarming van het vetweefsel ontstaat. In 53% van de behandelingen werd de maximum temperatuur gemeten op deze overgang. In het algemeen viel de kwaliteit van de hyperthermiebehandeling tegen: 60% van de gemeten tumortemperaturen bleef beneden de 40 °C. Wel werd geconstateerd dat een aanzienlijke winst in de kwaliteit van de hyperthermiebehandeling bereikt werd indien per individuele patiënt de optimale applicator opstelling werd gebruikt: conventioneel met een elektrode op buik en rug of "aangepast", dat wil zeggen onder elke bil een, onder 45 graden geplaatste, elektrode.

Hoofdstuk 6 beschrijft de resultaten verkregen met de ring-applicator, die is ontwikkeld binnen de afdeling Hyperthermie van de Dr. Daniël den Hoed Kliniek. Bij de ring-applicator worden twee cirkelvormige elektroden om een cilindervormig lichaam geplaatst. Afhankelijk van de diameter van de ring-elektrode in relatie tot de golflengte van het elektromagnetische veld, zal een ring-applicator zich quasi-statisch dan wel radiatief gedragen.

De resultaten van het experimentele en theoretische onderzoek, beschreven in de paragrafen 6.2 en 6.3 tonen aan dat de richting van het elektrisch veld voornamelijk parallel is met de as van de cilinder. Alleen bij de randen van de ring-elektroden is een radiale component van het elektrisch veld aanwezig, waardoor op deze lokatie selectieve verwarming van het vetweefsel kan optreden. Uit de metingen en de theoretische berekeningen volgt dat selectieve verwarming aan de rand van de ring-elektrode effectief gecontroleerd kan worden door een juiste keuze van de afmetingen van de ring-elektroden, de positie van de elektroden ten opzichte van het weefsel, en het gebruik van water als koppelingsmedium tussen de elektroden en het weefsel. Door de afstand tussen de ring-elektroden te variëren kan op eenvoudige wijze de lengte van het verwarmingsveld aangepast worden aan de lengte van het te behandelen weefselvolume. Concluderend kan gesteld worden dat een ring-applicator met kleine diameter en werkend bij lage frequenties zeer geschikt lijkt voor hyperthermiebehandelingen van tumoren in armen of benen.

In paragraaf 6.4 wordt aangetoond dat een ring-applicator met een diameter van 48 cm een radiatief, circumferentiële elektrisch veld kan induceren. Bij deze diameter van de ring-applicator zijn acht aansluitpunten voor de RF energie nodig om een constante amplitude- en fase-verdeling over de ring-elektrode te verkrijgen. In deze configuratie ontstaat ten gevolge van additive interferentie het gewenste maximum in de energieverdeling in het centrum van de applicator. De SAR verdelingen in het CDRH fantoom gemeten bij 70 MHz en met elektrische geleidingen van 0.4 en 0.6 S/m zijn in goede overeenstemming met de SAR verdelingen gerapporteerd voor de Sigma-60 en coassiale TEM applicatoren. WORDT DE ELEKTRISCHE GELEIDING VAN HET FANTOOM MATERIAAL VERHOOGD TOT 1.0 S/m, DAN OVERHEERST BIJ 70 MHz HET EXPONENTIËLE AFVAL VAN HET ELEKTROMAGNETISCH VELD EN DE RELATIEVE SAR IN HET CENTRUM VAN HET FANTOOM VERMINDERT TOT ONGEVEER 45%. Bij 33 MHz is de indringdiepte van het elektromagnetisch veld beter, maar door de grotere golflengte is focusering niet mogelijk en ontstaat een homogene verwarming in het centrale vlak van het fantoom. Tenslotte werd aangetoond dat met de ring-applicator de SAR verdeling in zekere mate gestuurd kan worden door amplitude-controle.

In Hoofdstuk 7 wordt de mogelijkheid om additionele apparatuur te installeren in de ruimte tussen de ring-elektroden aangetoond. De experimenten met niet-
invasieve thermometrie tonen een aantal specifieke problemen bij het meten van temperatures met "electric impedance tomography" (EIT) wanneer deze techniek gebruikt wordt tijdens RF verwarming. Voordat verder onderzoek naar de waarde van niet-invasieve thermometrie via EIT mogelijk is dienen adequate oplossingen gevonden te worden voor het probleem van elektromagnetische compatibiliteit en de lage gevoeligheid van het EIT systeem voor weerstandsverandering centraal in het te meten object.

Hoofdstuk 8 geeft voor elk apparaat een conclusie over de mogelijkheden voor het toedienen van een diepe hyperthermiebehandeling. Daarna volgt een algemene discussie over de huidige klinische resultaten van diepe hyperthermie en onderzoek-programma's naar de verbetering van diepe hyperthermie-apparatuur.

Concluderend: uit de studies beschreven in dit proefschrift volgt dat voor de Nederlandse patiënt voor het toedienen van een diepe hyperthermiebehandeling met elektromagnetische straling de beste resultaten verwacht mogen worden van radiatieve applicatoren waarmee een elektrisch veld gericht langs de lichaamsas en rondom de patiënt kan worden aangelegd.
Dankwoord

 Dit proefschrift zou er niet gekomen zijn zonder Huib Reinhold. In 1977 durfde hij het aan om mij in dienst te nemen voor een NKB onderzoeksproject naar de klinische toepassing van hyperthermie voor de behandeling van kanker. Naast de vele praktische zaken die ik van hem heb geleerd, ben ik hem ook dankbaar voor zijn stimulering en begeleiding in mijn ontwikkeling tot wetenschappelijk onderzoeker. De ruimte die hij aan zijn medewerkers gaf voor hun wetenschappelijke ontplooiing, heb ik altijd zeer gewaardeerd.

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hockeyen...).

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maar, helaas, ik heb nog steeds geen ijzeren geheugen.
Curriculum vitae


In 1987 heeft hij de Lund Science Award gekregen als erkenning voor originaliteit en kwaliteit van een publikatie in het International Journal of Hyperthermia. Van 1989 tot 1993 was hij medeprojectleider van een ontwikkelingsgeneeskundeproject met als doel het vaststellen van de waarde van hyperthermie als aanvulling bij radiotherapie voor de behandeling van bekken tumoren.