Technical Quality of Deep Hyperthermia Using the BSD-2000

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Technical Quality of Deep Hyperthermia Using the BSD-2000

Technische Kwaliteit van Diepe Hyperthermie

Bij Gebruik de BSD-2000

Thesis

to obtain the degree of Doctor from the
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by command of the rector magnificus

Prof.dr. S.W.J. Lamberts

and in accordance with the decision of the Doctorate Board.

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by:

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born in Boroujen, Iran

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In the name of God
the compassionate, the merciful

to: my son,
my daughter,
and my wife.

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Chapter 1

General introduction

General introduction

In the introductory part of this thesis a brief background of hyperthermia, the performance of deep hyperthermia, thermometry in deep hyperthermia, an overview of the research, objectives, and outline of the thesis are presented.

1.1 Hyperthermia

Hyperthermia, *i.e.* raising the temperature of tumor tissue to 40-43 °C, is historically applied as an adjunctive therapy with established cancer treatments such as radiotherapy and chemotherapy (Wust *et al.*, 2002). In line with current trends for multimodality treatments, hyperthermia is also applied in a three modality option for cervical cancer, where the potential of radiotherapy + chemotherapy + hyperthermia is tested in phase III settings against radiotherapy + hyperthermia. Extensive biological research has shown that hyperthermia is one of the most, if not the most potent, modifiers of radiation known today (Kampinga and Dikomey, 2001). The main mechanism for cell death by hyperthermia is probably protein denaturation, observed at temperatures > 40 °C, which leads to among other things, alterations in multi-molecular structures like cytoskeleton and membranes, and changes in enzyme complexes for DNA synthesis and repair. Most normal tissues are undamaged by treatment for 1 hr at a temperature of up to 44 °C. Only nervous tissues appear more sensitive. Intratumor environmental factors like hypoxia and low pH, resulting from inadequate blood perfusion, make cells more sensitive to a

temperature increase (Gerweck *et al*., 1974; Kim *et al*., 1975; Freeman *et al*., 1977).

In tumor regions with insufficient blood flow cells are more thermosensitive than in regions with normal physiology, whereas in such regions a lower drug concentrations, and the resulting hypoxia decreases radiosensitivity. Hyperthermia may cause an increased blood flow, which results in improved drug delivery and better oxygenation. It can be hypothesized that hypoxic cells in the centre of a large tumor are relatively radioresistant but thermosensitive, whereas the well-vascularized peripheral portions of the tumor are more sensitive to irradiation (Endrich *et al*., 1979). This supports the use of combined radiation and heat; hyperthermia is especially effective against hypoxic cells, and irradiation eliminates the tumor cells in the periphery of the tumor, where heat would be less effective (Song *et al*., 1980; Kang *et al*., 1980). For the combination of chemotherapy and hyperthermia the effect is greatest for simultaneous application. The molecular-biological mechanisms of these effects are still under investigation.

The synergistic interaction between heat and radiation dose as well as various cytostatic treatments has been validated in clinical studies. In a review study van der Zee (2002) reported on all randomization trials performed until 2002. She found 19 positive trials and 8 trials with no significant difference following a combination of radiotherapy and chemotherapy or radiotherapy plus chemotherapy and hyperthermia compared with the same treatment without hyperthermia. Since then, two more positive phase III trials of chemotherapy + hyperthermia (Colombo *et al*., 2003; Verwaal *et al*., 2003), and one non-decisive trial of radiotherapy + hyperthermia (Vasanthan *et al.*, 2005) are published. Table 1.1 shows the results of all phase III trials, reported during 1991-2005, comparing radiotherapy alone *vs.* radiotherapy + hyperthermia, conducted by Western research groups. Earlier Falk and Issels (2001) reported on state of the art of hyperthermia and described beside phase III trials, also 17 selected phase I or II trials investigation, the effect of hyperthermia combined with radiotherapy, chemotherapy, or both in total of more than 2200 patients. All studies, except two, show a statistical significant higher (up to a doubling) tumor control and/or cure rate for the combined treatment modality.

Table 1.1: Comparison of the results of radiotherapy (RT) *vs.* radiotherapy plus hyperthermia (RT + HT) in randomized trials from Western research groups. Table copied from van Rhoon and van der Zee (2007) with permission.

Reference	Tumor	Endpoint	N[@]	RT	RT + HT
Jones *et al*. (2005)	Various superficial*				
	All tumors	Complete response rate	109	42%	66%
	Previously irradiated		39	24%	68%
Van der Zee *et al*. (2000)	All pelvic tumors*	3 years overall survival	358	24%	30%
	Bladder		143	22%	28%
	Rectum		101	22%	13%
	Cervix		114	27%	51%
Sneed *et al*. (1998a)	Glioblastoma multiforme*	2 years survival	112	15%	31%
Vernon *et al*. (1996)	Breast cancer*	Complete response rate	308	41%	59%
Emami *et al*. (1996)	Various	2 years survival	184	34%	35%
Overgaard *et al*. (1995)	Melanoma*	2 years local NED®	134	28%	48%
Valdagni *et al*. (1988; 1994)	Head & neck*	Complete response rate	44	41%	83%
		5 years survival		0%	53%
Perez *et al*. (1989; 1991)	Various	Complete response rate overall	236	30%	32%
		In small tumors (diam.<3 cm)	55	39%	52%
		In large tumors (diam.>3 cm)	181	27%	25%

[@]N= number of patients; *Statistical significant difference; ®NED= no evidence of disease.

Additionally, all studies report comparable acute and late toxicity in both treatment arms. The positive results of the most recent trials explain the renewed enthusiasm in hyperthermia, which is reflected in the growing number of institutes interested in the application of hyperthermia (van Rhoon and van der Zee, 2007).

1.1.1 Maturation of hyperthermia technology

Heating tissue for hyperthermia involves complex technology, physiology and biology. Since the early seventies, research has been directed at the development of techniques to apply and control hyperthermia. The majority of the hyperthermia treatments are applied using external devices; employing electromagnetic fields (EMF), radiofrequency (RF) or microwaves to transfer the energy to the tissue and to a lesser extend ultrasound technology (Statuffer, 2005). Clinical application of hyperthermia can be categorized in several areas,

whereby the name of the category reflects the type of application. The two most frequently used methods are: 1) superficial hyperthermia, and 2) loco-regional deep hyperthermia. Since in the present thesis the work was focused on the later procedure, a brief description is given.

1.1.2 Loco-regional deep hyperthermia

To obtain a sufficient penetration depth the radiative electromagnetic systems for loco-regional deep hyperthermia operate at frequencies ranging from 70 to 150 MHz. A physical consequence of this restriction is that the focal spot size in homogenous muscle or abdomen tissue will be large (10-15 cm in diameter) and the tissue is always located in the near field of the antenna.

Since 1970 strong effort have been directed at the design of optimal systems for loco-regional deep heating resulting at different generations of equipment. Therapeutic temperatures could be achieved in deep-seated tumors using the first generation equipment for loco-regional deep hyperthermia, but it appeared to be difficult to fulfil the temperature-time goals. To overcome these problems the second generation of the radiative deep heating devices, such as the BSD-2000 system (Turner and Schaefermeyer, 1989; Turner *et al*., 1989), the four-waveguide system (van Dijk *et al*., 1990), and the coaxial TEM (transverse electro magnetic) applicator (de Leeuw, 1993) provided the possibility of SAR (specific absorption rate)- steering by phase and amplitude control, or by re-positioning the patient. This generation provided longer therapeutic duration times, but new problems due to hot-spots appeared.

The third generation equipment has provided the possibility for three-dimensional (3D) SAR-steering and is characterized by an accurate control of phase and amplitude steering (*e.g.* solid state amplifiers with integrated phase-locked loop systems). This generation is also equipped with a treatment planning system and a cylinder-shaped applicator (the Sigma-60) or an elliptical-shaped (the Sigma-Eye) with 8 or 24 dipole elements, respectively, to improve hot-spot control (figure 1.1). The fourth generation consists of a hybrid system of the BSD-2000-3D together with an MRI (magnetic resonance imaging) system with the aim to solve the formidable challenge of accurately and non-invasively access the 3D temperature distribution during RF-heating.

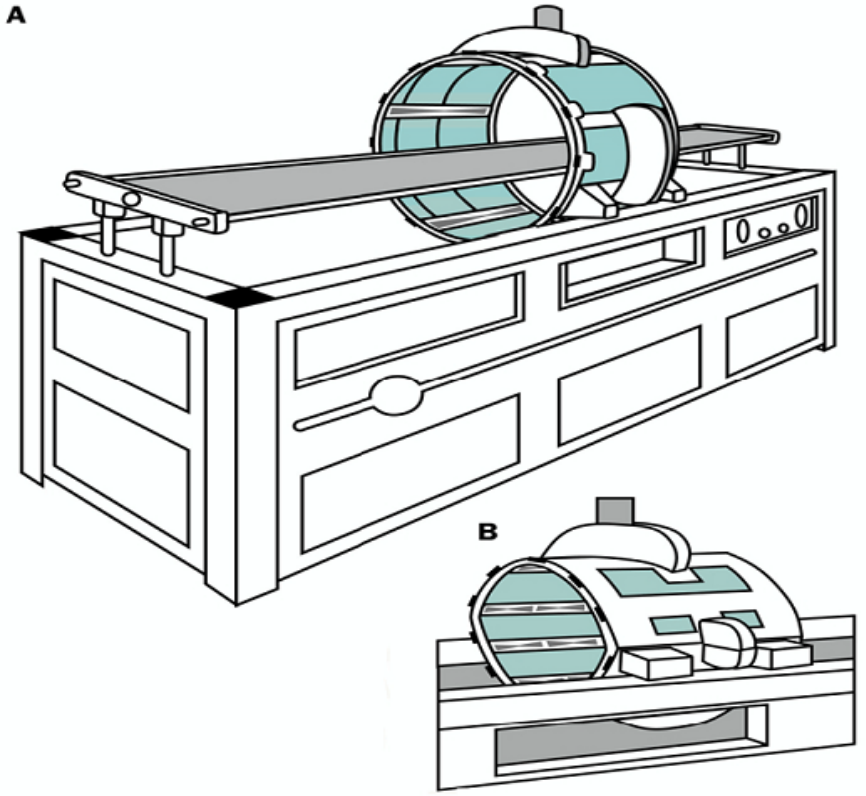

Figure 1.1: (a) Sigma-60 applicator (four dipole pairs) with treatment couch of the BSD-2000 system for loco-regional deep hyperthermia. Dipole antennae are schematically shown. (b) Sigma-Eye, a novel multi-antennae (12 dipole pairs) applicator, mounted on the same treatment unit as shown in (a). The elliptical form is more comfortable for the patient. Figure copied from Wust *et al*. (2002) with permission.

1.2 The BSD-2000

The BSD-2000 system is the most common deep hyperthermia system in clinical use. The BSD-2000 family of products includes the BSD-2000, the BSD-2000-3D, and the BSD-2000-3D-MR. These systems deliver non-invasively hyperthermic microwave energy to deep-seated tumors. The system includes a computer and software that control the delivery of microwave energy to the tumor, a microwave energy generator, multiple amplifiers that boost the microwave power, and a special applicator that delivers the microwave energy to the patient lying in a supine position on a specially designed support couch. The BSD-2000 system is able to direct, focus, and deliver microwave energy deep within the body by precisely steering the energy to the tumor from an array of cylindrical antennae. The basic BSD-2000 has eight microwave antennae enabling an electronic steering within the elliptical cross-section of the patient's body.

The BSD-2000-3D has 24 microwave antennae, which adds 3D steering of deep-focused energy, as opposed to the two-dimensional (2D) steering of energy available in the BSD-2000, enabling even more precise heating of the tumor (Wust *et al*., 2002). The 3D steering is particularly useful when implemented with a magnetic resonance system that is capable of non-invasive 3D imaging showing the temperature distribution in the heated regions. The later permits the 3D steering to more accurately target the energy to the tumor site. Using sophisticated microwave filtering and imaging software, the BSD-2000-3D-MR allows an MRI system to be interfaced with and operate simultaneously with a BSD-2000-3D (BSD Medical Corporation, 1998). The BSD-2000-3D-MR system is currently (2007) available only in two hyperthermia centers: Charité Virchow Klinikum in Berlin (Germany) and Duke University in Durham (USA).

1.3 Progress of loco-regional deep hyperthermia equipment in Rotterdam

In Hyperthermia Unit of Erasmus Medical Center in Rotterdam, where the present project has been performed, 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 tumor by electromagnetic energy. In 1983, whole body hyperthermia was abandoned after 27 patients had been treated. Since then, the RCA 27 MHz ridged waveguides have been tested on the feasibility to induce localized deep heating. In 1987, a 13.56 MHz capacitive hyperthermia system, HTM3000P, was tested and found to be inadequate. Since 1990 different configurations of the BSD-2000 system have been used for the application of loco-regional deep hyperthermia in Rotterdam. Early 1990, the BSD-2000 system with Quad amplifier tubes connected to the Sigma-60 applicator, was installed. In June 1998, the second configuration of the system, the BSD-2000-3D with Quad amplifier was replaced. Shortly, in June 1999 the next configuration of the system, the BSD-2000-3D using a Quad amplifier with 3D drawer which divides the four channels into 12 channels connected to the Sigma-60 or the Sigma-Eye applicator, was installed. In August 2000, the BSD-2000-3D with Dodek solid-state amplifiers upgraded. At present about 90 patients are treated yearly and in March 2007 the 1000th patient has been treated with the BSD-2000 hyperthermia system by the group.

1.3.1 How a patient is treated during a loco-regional deep hyperthermia session

Hyperthermia is carried out by the own institutional protocol, *i.e.* the Rotterdam treatment protocol for loco-regional deep hyperthermia. Closed-tip catheters are inserted intraluminally in the bladder, rectum, and vagina lumen (as relevant) at the beginning of each treatment session. For thermometry, thermistors with high impedance leads, *i.e.* the Bowman probes, as standard delivers by the BSD-2000 system are used to assess real time temperature reading. After catheter placement, the intraluminal depths are documented: using a standard caliper the hyperthermia technician measures manually the insertion length of the thermometry catheters. Temperature mapping is performed along the length of the thermometry catheter in 1 cm increments to a maximum mapping length of 14 cm. Thermal mapping starts just before the hyperthermia treatment and is repeated hereafter at 5-min intervals.

Usually, five loco-regional deep hyperthermia treatments are delivered to the whole pelvis volume once weekly during the period of radiotherapy. The frequencies used are in the range of 70-120 MHz. The initial RF-power is 400 W. Every 5 min the RF-power output to the applicator is increased, in steps of 100 W, (up to 1600 W), until the patient's tolerance threshold is reached. Hereafter, the SAR-steering is applied by changing phase and amplitude settings with the aim to reduce power-limiting hot-spots (*i.e.* normal tissue temperature > 43 °C or pain complaints of the patient) and to achieve intraluminal temperatures of 40-43 °C as homogeneously as possible.

The patient is carefully instructed to mention any unpleasant sensation that might be the result of a hot-spot, such as a burning sensation, a feeling of pressure, any pain, or bowel or bladder spasm. If the patient reports pain, which disappears within 1 min following power-decrease, it is considered to indicate a too high temperature, and then the treatment settings are adjusted to decrease power input at the specific location. Adjustments of treatment settings could be as follows: adaptation of phase settings, amplitude, and frequency, or by placing additional water boluses. For deep pain complaints phase steering is preferred, while for superficial pains amplitude steering is applied.

The hyperthermia treatment consists of a heating phase of 30 min followed by 60 min therapeutic time. The temperature of the applicator's water bolus is maintained at 20 °C. Systemic (oral) temperature is measured with regular intervals, *i.e.* just before start of treatment, at 15, 30, 60 min, and just before the end of the treatment session. Increase in systemic temperature is

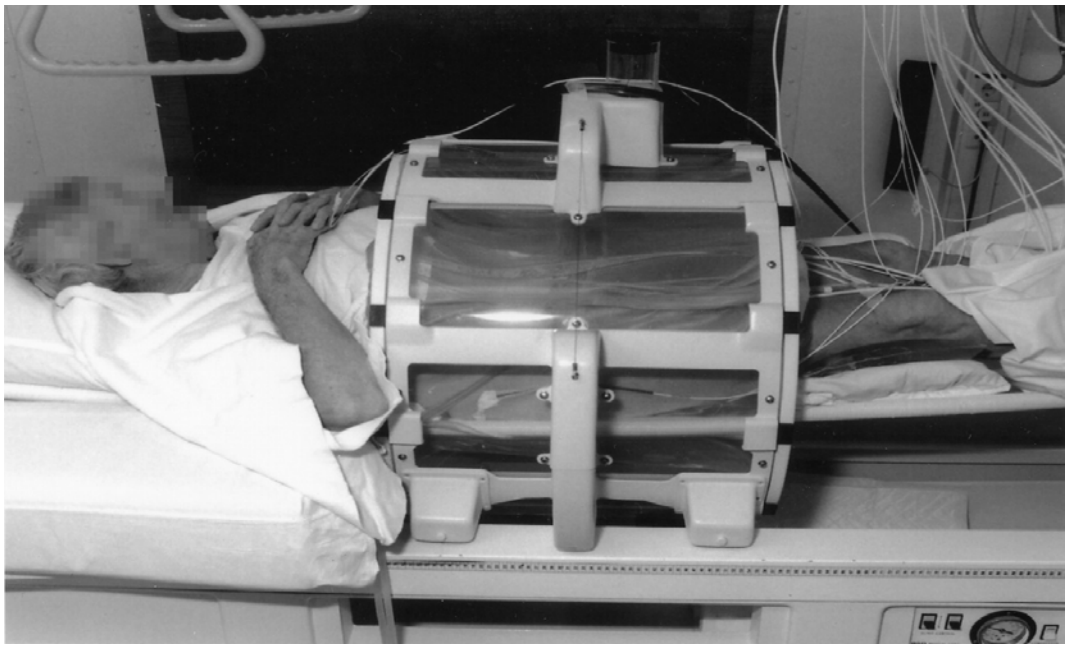

Figure 1.2: Example of a patient during loco-regional deep hyperthermia treatment with the BSD-2000 system and the Sigma-60 applicator. Figure copied from van der Zee (2002) with permission.

limited by cooling measures, *i.e.* undressing, air-conditioning, wet towels, ice packs, and cooling bolus placed in the neck. The bladder is kept empty with a Foley catheter. Figure 1.2 shows a patient during loco-regional deep hyperthermia treatment in the BSD-2000 system and the Sigma-60 applicator, surrounding the pelvic area of the patient. The space between applicator and skin is filled with water in a bolus bag (van der Zee, 2002).

1.4 Thermometry in hyperthermia

The basic premise underlying the need for thermal dosimetry is the ability to write a verifiable prescription for hyperthermia (Jones *et al*., 2006). As in any form of therapy, a sound dosimetric basis leads to unambiguous treatment, data reporting, and quality assurance (Dewhirst *et al*., 1993). Implementation of thermal dosimetry requires three steps. First, it is necessary to use accurate thermometers. Second, it is necessary to use a measure of treatment effect that has biological significance (*i.e.*, there is a quantitative relationship between the measure of treatment delivered and the cytotoxic effect of the treatment). The third step is to be able to prescribe and characterize the treatment to be delivered. Methods to accomplish this task are not straightforward, particularly as long as invasive thermometry is required that only a small part of the heated volume is sampled (Dewhirst, 1995).

When deep-seated tumors are under treatment, hyperthermia departments apply invasive (intratumor) and/or minimally invasive (intraluminal) thermometry for temperature data acquisition. Some researchers believe that thermal dosimetry using intratumor thermometry is an absolute necessity to determine the temperature distributions achieved (Hand *et al*., 1989; Lagendijk *et al*., 1998; Lagendijk, 2000). However, strong variation exists in the opinions whether intratumor thermometry provides superior information over intraluminal thermometry. For instance, Sneed *et al*. (1998b) state that intratumor thermometry is critically important for deep-seated tumors. Whereas, van der Zee *et al*. (1998) suggest that if intraluminal thermometry is available, intratumor thermometry is neither an important requirement for prevention of toxicity, nor supportive for SAR-steering. This opinion is supported by Wust *et al*. (1998a; 2006) who also showed that if a tumor-related intraluminal temperature measurement point is available, additional intratumoral thermometry gives no further information that can improve the power-deposition pattern; and by Sreenivasa *et al*. (2006) who recently found that intraluminal temperatures are related to the response probability.

3D non-invasive thermometry systems by MRI may provide guidance for thermotherapy applications and become of future importance for hyperthermia applications in all hyperthermia centers (Hentschel *et al*., 1998; van Rhoon and Wust, 2005). At present clinical hyperthermia has to rely on intratumor or intraluminal thermometry in most of the practical situations (Sneed *et al*. 1998b; Wust *et al*. 2006). This invasive or minimally invasive thermometry is, besides the problems with the extremely limited information about highly inhomogeneous thermal dose distributions, a major clinical problem in the acceptance of hyperthermia (van der Zee *et al*., 1998).

In regional hyperthermia of the lesser pelvis, various intraluminal temperature-measuring tracks are available; these include bladder, urethra, vagina, cervix, and rectum. Based on the Rotterdam Hyperthermia Group's experiences (van der Zee *et al*., 1998) and following the ESHO guidelines (Lagendijk *et al*., 1998) in Rotterdam the thermometry for loco-regional deep hyperthermia of lesser pelvic tumors has restricted to intraluminal locations. Therefore, in the following chapters, in most of the cases, the temperature data used for the study have originated from the intraluminal thermometry. Exception is the data used in chapter 4 in which both intratumor and intraluminal temperatures are compared.

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. Hence, mandatory to allow the technical and clinical quality analysis of the hyperthermia treatment delivered is that the quality of the collected temperature data is without dispute (van Rhoon *et al*., 2005a). The later has been recognized years ago and extensive guidelines on the quality assurance demands for thermometry have been published by ESHO (Hand *et al.*, 1989), RTOG (Sapozink *et al*., 1991), and others (Visser and van Rhoon, 1995).

With regard to the so-called technical quality, *e.g.* the accuracy of the thermometry system, there exist no reason for concern. A closer look to the quality of the thermal data acquired during the deep hyperthermia treatment gives rise to a large number of questions for which a satisfactory answer is not easy to be formulated. For instance, a standard routine silently introduced over the years for thermal mapping is the assignment of a tissue type to each temperature measuring point along the intraluminal thermometry catheter. We may question the accuracy of this procedure or even further whether this represents a relevant operation? Which type of thermometry provides sufficient information during deep hyperthermia of lesser pelvic tumors: intratumor or intraluminal thermometry? Other important issues that need to be discussed are how to cope with movement of the thermometry catheter during treatment, the effect of tissue cooling by external cold-water bolus causing in non-representative minimum temperatures. In the light of the currently active trials performed by different institutes each with their own validated protocols and specific experience there exists a clear need to arrive at consensus on guidelines necessary to make a valid assessment and comparison of the quality of the hyperthermia treatments performed in the different clinical studies.

In this thesis the existing data from patients, who have been treated during the recent 15 years application of loco-regional deep hyperthermia by the Rotterdam Hyperthermia Group are used to search for variables that correlate with hyperthermia treatment quality to answer some of the above questions.

1.5 Overview: objectives and outline of the thesis

Chapter 1, the current chapter, presents a general introduction on the thesis providing a background, overview, and the objectives of the research.

Chapter 2 presents a specific tool that has been created to access the thermal data generated by the BSD-2000/3D. The hyperthermia treatment data produced by the BSD-2000/3D systems, which operate on a PDOS-based machine, are not easily accessible. Recently, the Rotterdam Hyperthermia Group has developed software called RHyThM (Rotterdam Hyperthermia Thermal Modulator). Detailed descriptions of RHyThM are shown in this chapter.

In *Chapter 3* RHyThM is used to investigate the temperature dynamics behavior of 22 patients with advanced cervical carcinoma treated with three-modality treatment, *i.e.* radiotherapy + hyperthermia + chemotherapy. When comparing our results with the data reported in other studies we were confronted with the question whether the difference among the temperatures reported in these studies is a real difference or merely a reflection of a difference in the equipment and the protocols used. Therefore, a discussion is initiated regarding the question: “Do we need a reference temperature point in order to compare the results obtained by different hyperthermia centers, which work on the same group of patients, using the same or nearly the same equipment?”

Chapter 4 discusses the challenging issue of intratumor *vs*. intraluminal thermometry. The basic questions of this part of the project were: 1) Is there a positive correlation between intratumor and intraluminal measured temperatures in the pelvis region? 2) What are the quantitative/qualitative differences between intratumor and intraluminal temperature measurements in the pelvis? 3) Can the intratumor temperature distribution be improved by SAR-steering?

Chapter 5 argues on another relevant question in deep hyperthermia treatment: is tissue type assignment a necessity for thermal analysis in intraluminal thermometry? Tissue type assignment, *i.e.* differentiation tumor from normal tissue, is a normal procedure for intratumor thermometry. As mentioned before, in Rotterdam Hyperthermia Unit, thermometry in patients with a tumor in the lesser pelvis is usually restricted to the intraluminal tracks. It was unknown whether discrimination between normal and tumor tissue is relevant for loco-regional deep hyperthermia thermal dosimetry using only

intraluminal tumor-contact and tumor-indicative thermometry. The hypothesis was that tissue type assignment does not provide more relevant information on intraluminal temperature distribution. In this chapter the acquired temperature data of 100 selected hyperthermia treatment datasets were analyzed to answer this question.

Chapter 6 assesses the prescribed RF-power and achieved temperatures data in 444 patients with primary cervical cancer. The objective was to evaluate the global behavior of the performance of loco-regional deep heating by the BSD-2000 and the Sigma-60 applicator driven with one of four different power drive systems during a 15-years time-period. The intention was to find a patient- or RF-power related parameter that correlates with average temperature in the clinical situation.

Chapter 7 shows the SAR-characteristics of the Sigma-60-Ellipse applicator, in which the E-field distributions were measured using the Schottky diode sheets and an abdomen-equivalent phantom. The objective was to characterize the energy distribution of the Sigma-60-Ellipse to find whether its SAR-characteristics are equivalent to those of the Sigma-60 and the Sigma-Eye applicators. Prior to replace the existing applicators, with their effectiveness demonstrated in the phase III trials, by a new applicator (Sigma-60-Ellipse) designed in order to improve comfort of the patient, it is an absolute requirement that such new applicator undergoes a rigorous quality assurance and control program. No doubt may exist that the new applicator, *i.e.* the Sigma-60-Ellipse, provides minimally the same technical performance, *i.e.* same SAR-distributions, as the old applicator. Therefore, the main issue was to find out whether the SAR-characteristics of the Sigma-60 (and or the Sigma-Eye) applicator match with the Sigma-60-Ellipse.

Chapter 8 presents discussion of the study and future perspectives, where the research presented in this thesis is discussed in the context of hyperthermia and thermometry in the near future.

Chapter 9 is a summary of the thesis and *Chapter 10* is ‘Sumenvatting’, *i.e*. the summary in Dutch. *Chapter 11* shows the list of articles, books, and publications, which are referred to in this thesis. Finally, *Chapter 12* is an appendix including abbreviations used in the present book, a personal word of thanks, curriculum vitae, and list of publications by the researcher.

Chapter 2

RHyThM, a tool for analysis of PDOS formatted hyperthermia treatment data generated by the BSD-2000/3D system

This chapter has been published as:

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Abstract

One of the systems used by hyperthermia groups for heating tumors in the pelvic region is the BSD-2000 system. Previous versions of the system operate on a PDOS machine and the majority of the currently installed systems are still running under PDOS. Availability of the PDOS formatted treatment data provided by the BSD-2000/3D has some difficulties. To facilitate analysis of the PDOS formatted treatment data generated by the BSD-2000/3D, a program called RHyThM (Rotterdam Hyperthermia Thermal Modulator) has been created. The purpose of RHyThM is first to read and check the integrity and validity of the treatment data for each measurement in position and time as provided by the BSD-2000/3D and secondly to register a tissue type, based on computer tomography information, for each temperature probe position. Prior to any analyses, RHyThM shows the temperature profiles enabling the user to check on probe movement and to correct for unrealistically high temperature gradients in position and time. Subsequently, this approved dataset is saved in a 'mother-file' for future on-demand thermal dose analyses. A unique feature of RHyThM is that it also shows all radiofrequency (RF) power signals for inspection. Finally, to make a quick assessment of the quality of the applied hyperthermia treatment, RHyThM reports several temperature indices for bladder, vagina, and rectum, as well as RF-power related quantities. In summary, RHyThM is considered a valuable tool as it quickly provides a quality index per treatment, which serves as input for the preparation of the next treatment. Further, it makes verified and improved primary datasets accessible for further analysis with advanced statistical programs.

2.1 Introduction

Temperature data acquisition for thermal dosimetry in hyperthermia has a long history. Several studies have shown that thermal data procurement, especially temperature data, is essential for investigation of thermal dose effect

relationships (Shrivastava *et al*., 1989; Dewhirst *et al*., 1990). The relation between temperature data and clinical results has been demonstrated in many researches through careful analysis (Oleson *et al*., 1989; Myerson *et al*., 1990; Leopold *et al*., 1992; Kaap and Cox, 1995). In order to perform the thermal dose effect relationship study, each of these groups had developed different procedures to make the available thermal data 'accessible'. It is noted that these early approaches were designed and built according to the computer facilities and data structures available in the late 1980s. The paper on thermal data analysis by Sapareto and Corry (1989) proposed a standardized database file format for hyperthermia treatments. This approach concerned mainly the recording of the data and of all events in a specific format during the treatment. It did not address the topic of the integrity validation of the data type as described further in the present paper. At this time the standardized hyperthermia database format program is not complemented in most commercial software. For instance, currently it is neither implemented in the PDOS version nor in the PC version of the operating software of the BSD-2000 deep hyperthermia system. Moreover, to the authors' knowledge the proposed database format has not found a wide implementation in the hyperthermia community. In ultrasound hyperthermia, specific software for storage and analysis of thermal data was developed by Straube *et al*. (1999). This attempt focuses on data entry and automatic analysis. No reference to a data integrity check is made in the paper.

In the authors' view, hyperthermia data acquisition is the first of a three-step process to establish thermal dose effect relationships. The essential steps are: 1) availability of reliable and verified temperature data, 2) to perform short-term minimum thermal dose analysis to allow modification of the succeeding treatment session, 3) to perform long-term extensive and scientific retrospective temperature data analysis. As reported above, the available software solutions have not found general application nor they do provide the feasibility as required from the three-step philosophy. Consequently, the software was developed specifically for the BSD-2000 system.

In deep hyperthermia treatment, the BSD-2000 system (BSD Medical Corporation, Salt Lake City, Utah, USA) is one of the systems used for heating tumors in the pelvic region (Turner *et al*., 1989). The latest version of the system uses an MS-Windows PC; nonetheless, the majority of the currently installed systems are still running under PDOS. In the past, the PDOS

environment appeared to be advantageous for equipment control; nevertheless, it also presented a drawback for data analysis as an easy transfer of the data was obstructed due to the different disk formats of the PDOS and MS-Windows. For years the only option to acquire the temperature data was to redirect the data via the printer port to the RS-232 port of a PC and catch the ASCII data. Only after the introduction of the PDOS real time multi-tasking software as installed on the BSD-2000-3D system it is possible to copy PDOS-disk formatted data to an MS-Windows disk format, allowing the development of PC-based data access and analysis tools.

This paper presents the approach towards improvement of the accessibility of the treatment data generated by the BSD-2000/3D system. Stimulated by the availability of the PDOS-disk formatted data, RHyThM (Rotterdam Hyperthermia Thermal Modulator) was developed as a thermal analysis tool. Essential in the development of RHyThM is that two demands are met. The first demand is that the program should provide a quality index per treatment, which serves as input for the preparation of the next treatment. These quality indices per treatment must be easily obtained as the conclusive step of each treatment. Further, the criteria for these quality indices are made by each hyperthermia group to reflect their experiences. The second demand is that the program should make available a complete and verified dataset for on demand thermal dose analysis for scientific purposes. Considering the fact that at present a standardized and reliable thermal dosimetry system is still lacking (Dewhirst *et al*., 1993; Dewhirst and Sneed, 2003) each approach for thermal data analysis should be characterized by flexibility. Hence, each automatic tool used to check the integrity and to correct the measured temperature data must leave the improved original data easily accessible for any future analyses with different evaluation parameters using standard statistical programs, *e.g.* STATA, for data analysis. The most prominent reason to develop the tool was the need to check the integrity of the data available from more than 800 patients, who have received over 3500 treatments from our group with the BSD-2000/3D system since 1990. In this paper, an overview of the program is given and the different steps of RHyThM are introduced in detail.

2.2 Description of RHyThM; features of the tool

The steps of RHyThM are illustrated in the flowchart as presented in figure 2.1 and are explained hereafter. RHyThM has been created in and operates under

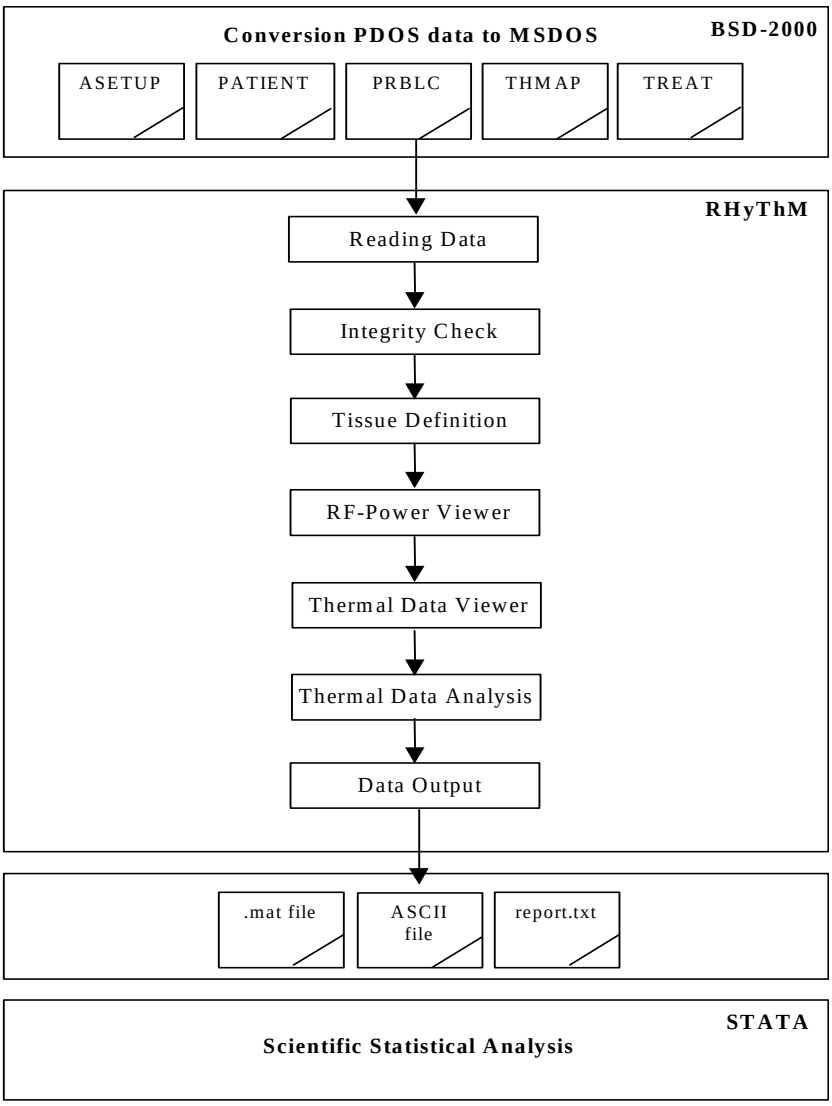

Figure 2.1: Steps of the Rotterdam Hyperthermia Thermal Modulator (RHyThM).

the MATLAB environment. Prior to the use of RHyThM, all data recorded by the BSD-2000/3D system software has to be transferred from the PDOS environment to the MSDOS using a PDOS command.

2.2.1 First and second steps: Reading data and Integrity check

RHyThM reads all MSDOS formatted data files and checks the integrity of both the RF-power and thermal data. The integrity check values are defined in a settings-file. The results are shown in the Report-Window (figure 2.2). For the RF-power integrity check RHyThM counts the number of records and verifies which amplifier system is used by checking the length of the power array. If the power array contains data for only four channels, it is concluded that a 4-channel amplifier system (*i.e.* BSD-2000) was used. Alternatively, if

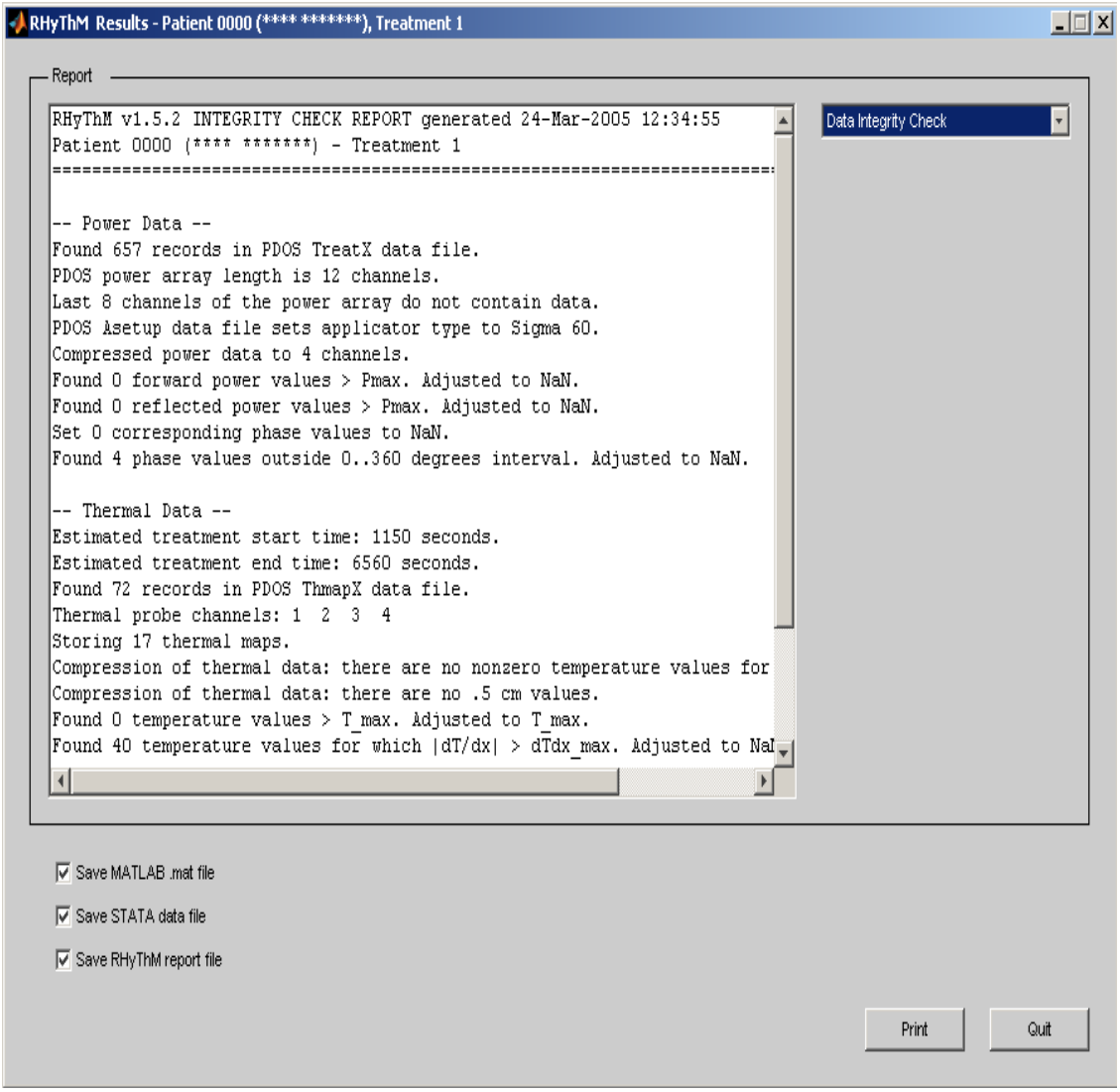

Figure 2.2: Example of a BSD-2000/3D treatment data import and integrity check by RHyThM.

all 12 channels of the power array contain valid data, it is concluded that the Dodek amplifier system (*i.e.* BSD-2000-3D) is used. Secondly, it reads from the 'ASETUP' file which applicator type (Sigma-60 or Sigma-Eye) is used. If the Sigma-60 is used with the 12-channel Dodek amplifier, it automatically compresses the RF-power data to four channels. To rule out unrealistically high RF-powers all readings are verified against limited maximum forward and reflected power values. These maximum values are user-defined in the settings-file. Similarly, RHyThM checks whether all recorded phase values are within a 0-360° interval. From the power data history, RHyThM estimates the treatment start and treatment end time.

Next, RHyThM allocates from the 'ThmapX'-file which temperature measurement probes are used, how many thermal maps are performed, and

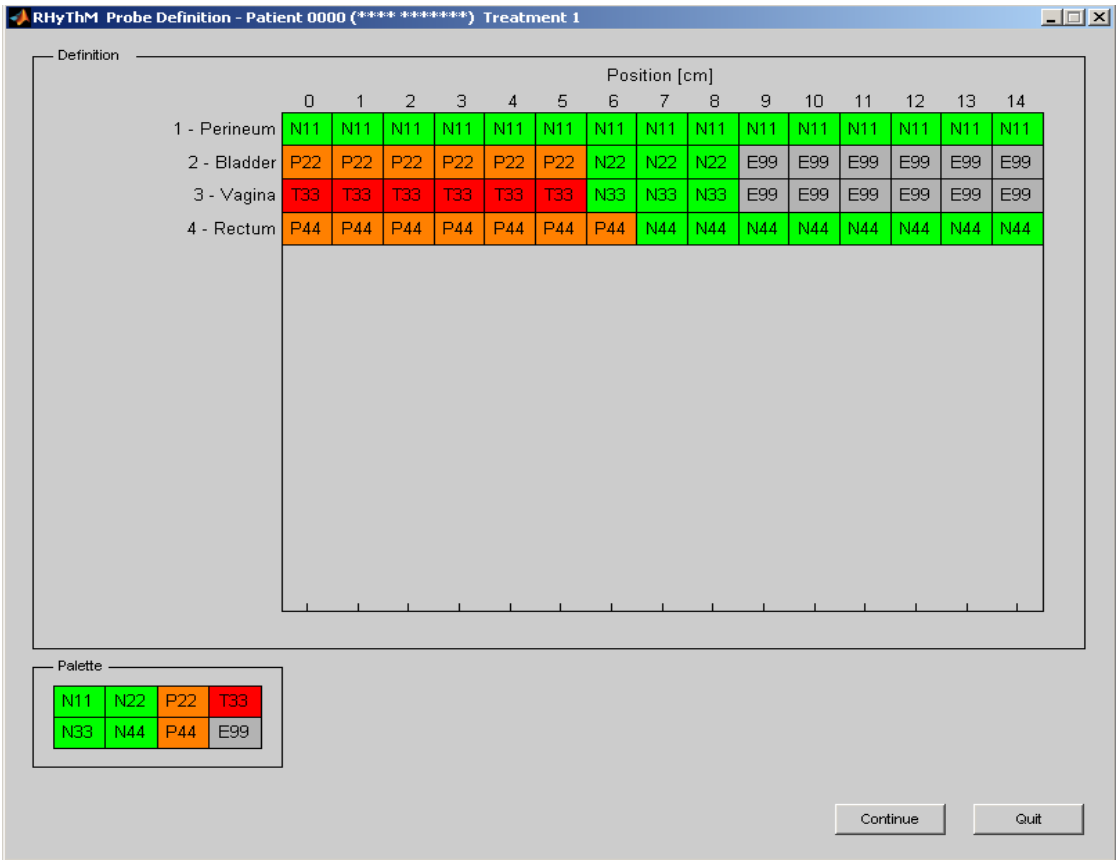

Figure 2.3: Probe definition window. Based on the CT-scan information all temperature probe positions are assigned the related tissue type. N11, N22, N33, and N44 are codes for normal tissue in perineum, bladder, vagina, and rectum, respectively. P22 and P44 are codes for tumor-indicative in bladder and rectum, respectively. T33 is a code for tumor-contact in vagina. E99 shows that the measurement is outside the tissue.

assesses the thermal map step size, *i.e.* 0.5 or 1.0 cm. As the temperature measurement with the Bowman probes is sensitive to sudden movements of the patients, RHyThM also checks (and counts) all temperature values on a gradient criterion in position and time, *i.e.* |dT/dx| should be smaller than dT/dx_{max} as default defined in the settings-file. If |dT/dx| values larger than dT/dx_{max} are found, then these values are adjusted to not-a-number (NaN). Moreover, RHyThM Integrity Check logs which thermal analysis mode is used. If the user manually specifies a time-horizon for the thermal analysis, the analysis horizon and the number of thermal maps within the selected time-horizon are given. This selection is performed in the RF-power viewer.

2.2.2 Third step: Tissue definition

In this stage, the temperature probe position for each thermometry catheter is translated into a tissue type, such as normal tissue, tumor-contact, or tumor-indicative, based on the CT-scan information obtained in radiotherapy position.

If the temperature probe position is located outside the tissue, it is labeled as an error (E99). In the settings-file default names are available to identify the location of the thermometry catheter, for instance bladder, vagina, and rectum lumen. Based on the probe definition file, RHyThM comes up with the default tissue coding. The probe definition window (figure 2.3) allows the user to assign interactively a tissue definition to each position, using the identification code.

2.2.3 Fourth step: RF-power viewer

The BSD-2000/3D system records forward and reflected power output and phase at 10 s intervals for all 12 RF-channels. In the RF-power viewer window (figure 2.4) the operator can inspect the details of the total power or for individual applicator. In addition, the edit mode allows correction of erroneous

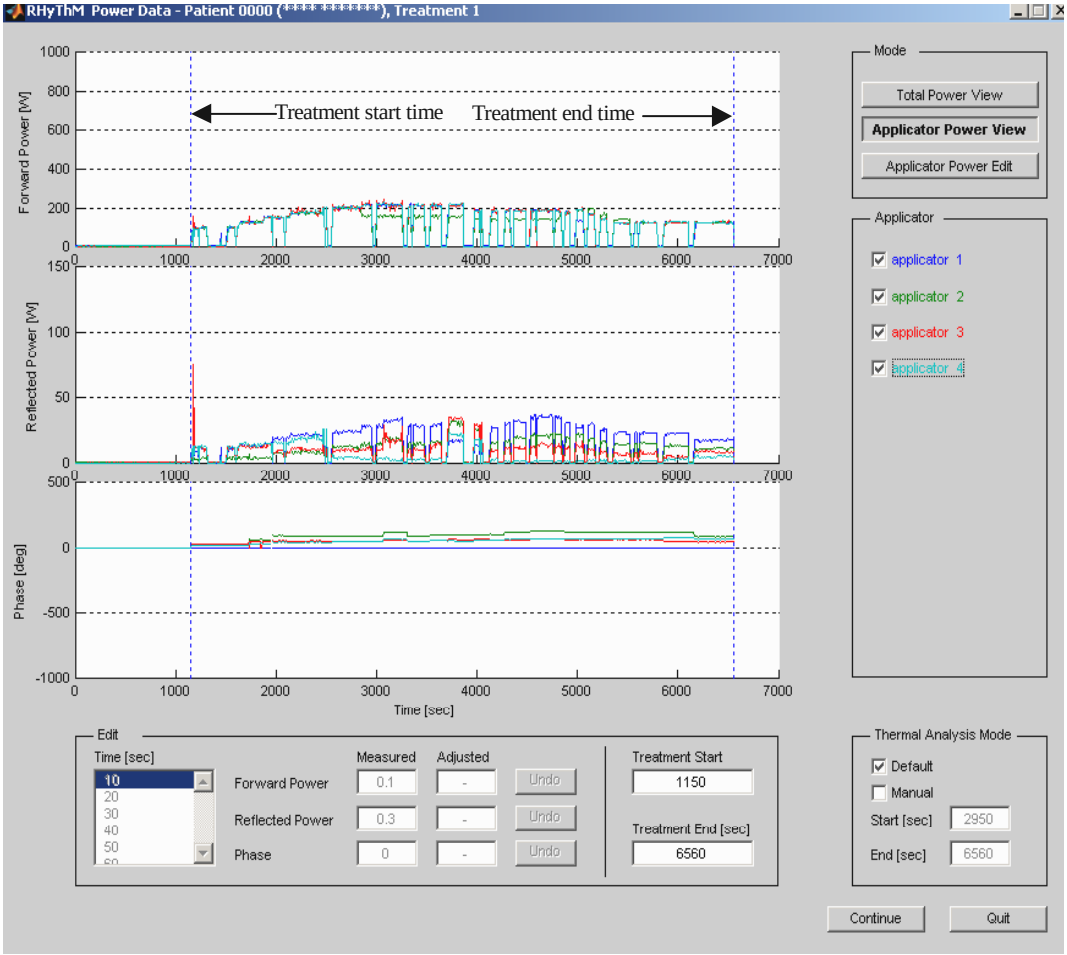

Figure 2.4: RF-power viewer: total power view, applicator power view, and applicator power edit panels of RHyThM. Forward power, reflected power, and phase are shown in the upper, middle, and lower graphs, respectively. The left lower panel enables the user to adjust erroneous RF-power data. The right lower panel enables the user to select a time-horizon for thermal analysis.

power data. Three separate graphs show profiles of total forward power, total reflected power, as well as phase *vs*. time. The effect of an on/off switch during the treatment is visible in the forward and reflected power graphs. The applicator panel indicates the number of each channel that is 1-4 for the Sigma-60 and 1-12 for the Sigma-Eye. If the user identifies an irregularity in the graph such as spikes in forward and reflected power or phase measurements that is out of bound, the user is able to zoom and edit the erroneous data point. Two more parameters, *i.e.* treatment start and end time as indicated on the profiles can be adjusted to represent the real treatment start and end time to provide a representative analysis. The user may manually specify a time-horizon for the thermal analysis, which is of course used for RF-power analyses.

2.2.4 Fifth and sixth steps: Thermal data viewer and Thermal data analysis

For thermal data verification RHyThM assembles a 3D interactive graph of temperature output *vs*. position and time (figure 2.5a). The user can also switch to a 2D graph, which is convenient to check whether the insertion depth of the thermal mapping catheter remained constant during the whole treatment. By clicking on the 3D-graph the user can manipulate the view-angle of the graph in order to easily recognize erroneous temperature data points (figure 2.5b). As it can be seen in the lower panel of figure 2.5, RHyThM provides an editor mode for individual evaluation of each data point by selecting position and time. RHyThM already automatically detects unrealistically high temperature gradients in position and time. In the edit mode the user can correct these temperature values. The thresholds for too high temporal and spatial temperature gradients are defined in the settings-file.

2.2.5 Seventh step: Data output

At this time all available data is valid and is used for the thermal and power analysis. In the ‘default’ mode RHyThM calculates the following general temperature-related dose parameters:

- T_{min}, T_{mean}, T_{20}, T_{50}, and T_{90} between start of the therapeutic heating period and end of the treatment.
- T_{max} between start of treatment and end of the treatment.

In the ‘manual’ mode the output depends on the time-horizon selected by the user for the analysis. Next, RHyThM reports these temperature-related dose parameters per individual thermal map location including the tissue type.

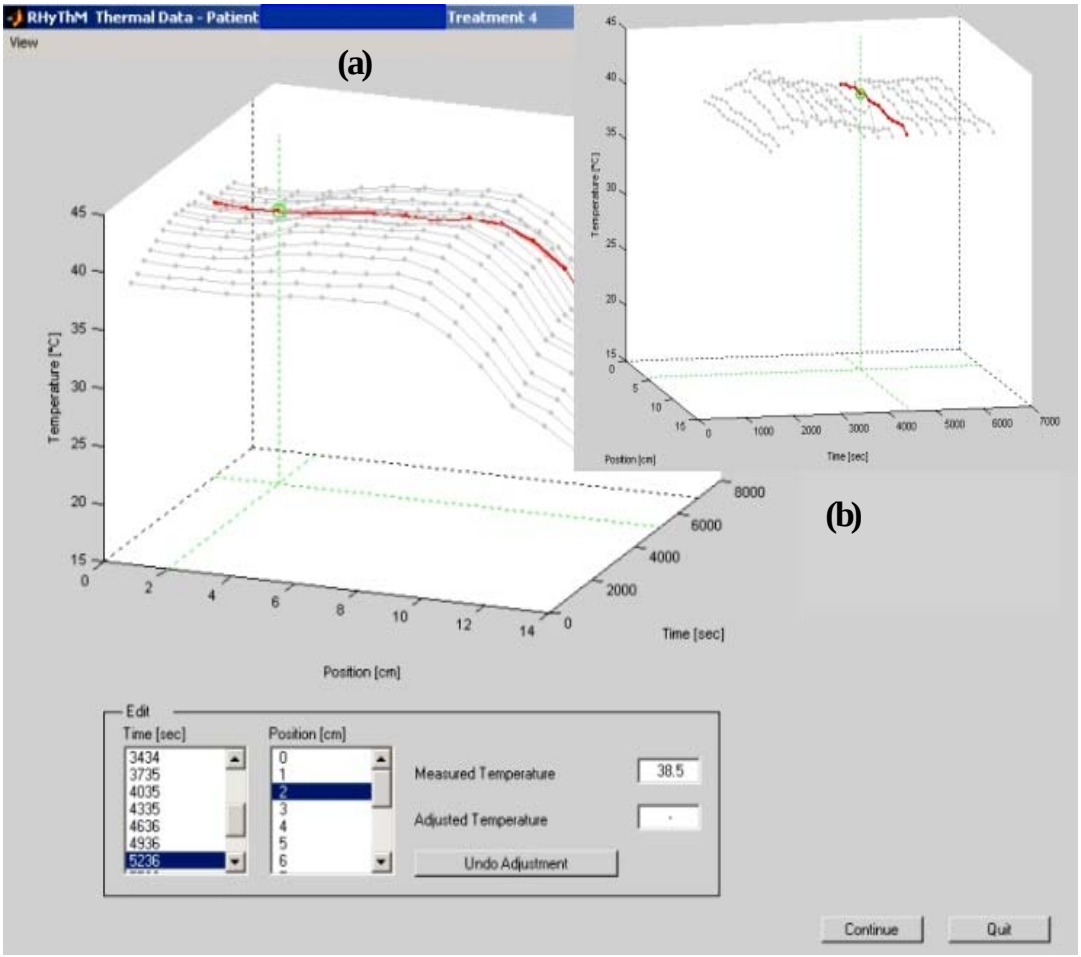

Figure 2.5: (a) Thermal data validation to check for probe movement and for unrealistically high temperature gradients in position and time. (b) Right upper legend, which is an inset, shows a sample of indefinite views of the graphical outputs (useful to recognise erroneous temperature data points). The lower panel enables the user to adjust erroneous temperature data.

Additionally, a more integrated evaluation is obtained from the temperature data analyses per tissue type, *i.e.* normal, tumor-contact, tumor-indicative, and all. For each main thermometry location, *e.g.* for hyperthermia in the pelvic region these are bladder, vagina, and rectum, a separate report is printed and saved as a text-file. As an example, figure 2.6 shows the results for a thermometry catheter in the vagina.

Furthermore, the thermal analysis includes overall tumor statistics, which are based on the measurements from all tumor points from all probes. They are listed on a separate page in the report. Furthermore, RHyThM performs an analysis on the recorded RF-power data of the whole treatment and provides several RF-power-related treatment evaluation parameters. For instance, maximum and average of forward and reflected power, as well as integrated power (kJ). Further, it records number of RF-power off-switches and

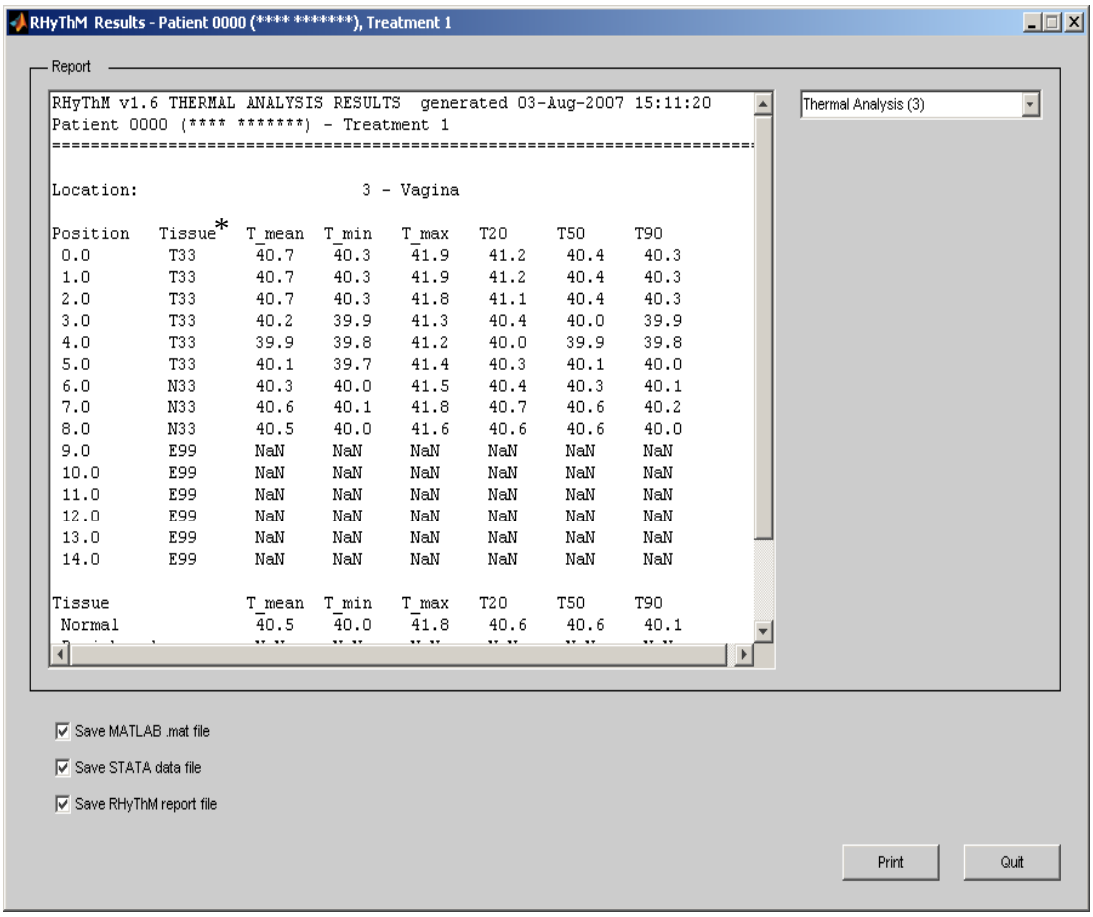

Figure 2.6: RHyThM Results: analyzed temperature data reported for vagina. * T33 and N33 are two codes for tumor-contact and normal tissue in vagina, respectively. E99 shows the measurement is outside the tissue and NaN means not-a-number.

calculates the total and maximum of switches off time (figure 2.7). In order to make the complete verified set of data available for future scientific thermal dose analysis, RHyThM stores the data as an original MATLAB data file and in ASCII format accessible for standard statistical packages. The ASCII format file provides temperature measurement data available per patient, per treatment number, per probe number, per mapping position, and per time point.

2.3 Experiences when entering and analyzing the treatment data

To evaluate the performance of RHyThM regarding the data integrity check a test run of RHyThM on a selected group of 22 patients with advanced cervical cancer was performed. The patients were treated by radiotherapy + hyperthermia + chemotherapy. Details respecting temperature data are presented in Fatehi *et al*. (2006b). Data transfer from PDOS to MSDOS was successful for 21 patients. For one patient the data of all four treatments was lost due to a reading failure of the floppy under PDOS. Additionally, it was not

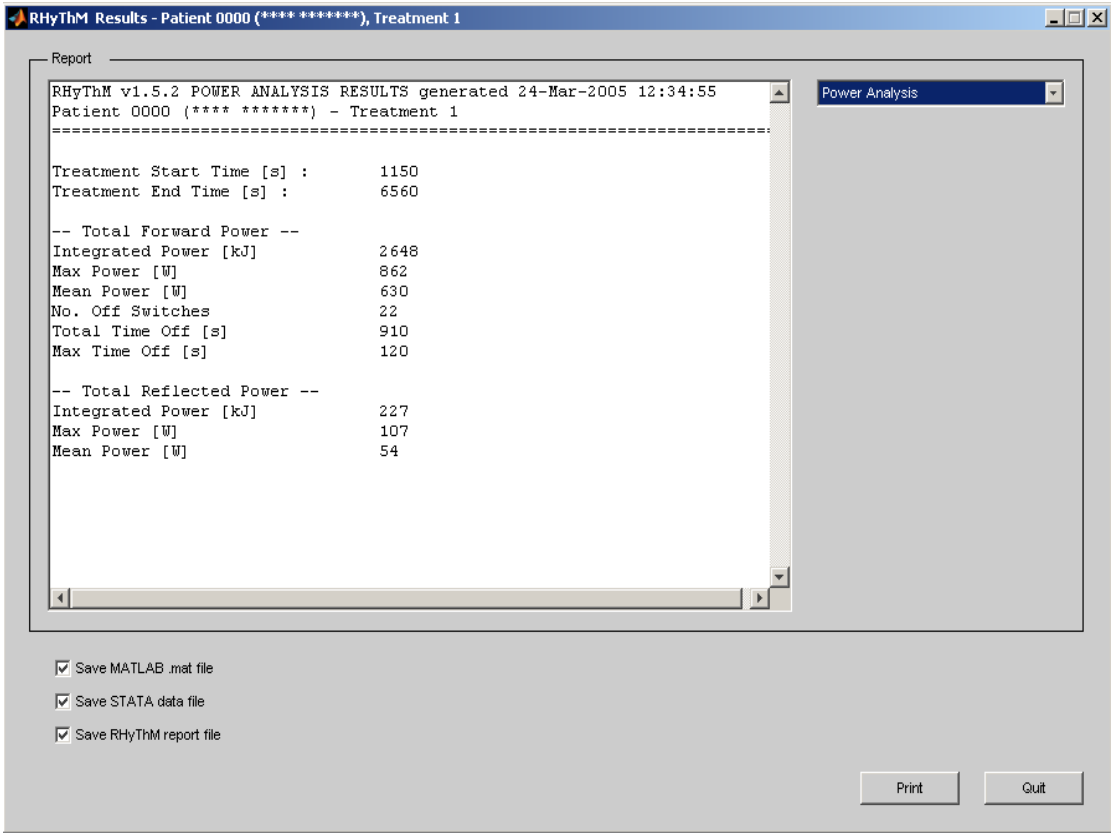

Figure 2.7: The results of analyzed RF-power quantities as reported by RHyThM.

possible to transfer a single treatment for three other patients. Hence, of the 104 treatments performed 97 treatment records could be made available for analysis and seven treatment data records were inaccessible. Hereafter, the MSDOS data was imported in RHyThM to perform the data analysis.

For each single treatment, tissue type assignment was done according to the tissue map trajectory per thermometry catheter as provided by the hyperthermia physician and for the insertion length as measured by the hyperthermia technician. A step change in the slope of the profile of the first temperature map was used to verify the precise location of the transition between in- and outside the body, as reported by the hyperthermia technician. If necessary the location of the transition of the body was corrected to much better with the steep temperature gradient.

Overall, RHyThM performed satisfactorily, was able to check integrity and validate the temperature data and performed the tissue type assignment and thermal analysis for all remaining 97 treatments. Two minor problems were experienced:

- *Defining tissue type and insertion length.* Overall, it was necessary to adapt the insertion length for 53 out of 291 thermal map trajectories (18%) or in 39 out of the 97 treatments (40%). Initially, a dislocation of the thermal probe could only be recognized in the fifth step of RHyThM, *i.e.* thermal data viewer. For more convenience an additional tool, *i.e.* 'First Thermal Map' was added. This part of the program shows the first temperature map of a treatment next to the probe definition window and helps to identify the correct insertion length. Without the additional tool correction is only possible when the user quits RHyThM and starting all over again.
- *Detection of temperature gradients in position and time.* The temperature profile is checked for too large gradients in position and time. In the current implementation a single jump or fall in the temperature causes two temperature points to be identified as NaN: the temperature point itself and the point following it. At first a sudden movement causes a steep gradient, which is correctly identified as an erroneous temperature value. However, as the movement is transient, the next measurement will be at a correct temperature, hence causing an inverse temperature gradient compared to the previous one. RHyThM, incorrectly, identifies this value as an error.

2.4 Discussion

In the authors' opinion RHyThM is a valuable tool greatly enhancing the possibilities for analysis of temperature data obtained during hyperthermia treatments with the BSD-2000/3D system. The RHyThM program enables easy access to the PDOS data files, performs an important integrity check of the data, connects the tissue assignment with the thermal data, and includes the correction of unrealistic temperature values due to mechanical stress on the Bowman temperature probes. In comparison to earlier programs (mostly based on eavesdropping the ASCII codes on the RS232 cable to the printer) it provides besides the thermal mapping temperature data also all other data stored by the BSD-2000 control program. A striking feature is the availability of the forward and reflected RF-power values and the phase for each channel. Further, the current version of RHyThM provides a minimum of data analysis required to make a fast assessment of the quality of the hyperthermia treatment delivered. In this situation this information is used as input for our weekly multi-disciplinary discussion reviewing the quality of the hyperthermia treatments delivered as a preparation for the next treatment of each patient.

In an exploratory study (Fatehi *et al*., 2006b) with the intention to evaluate the performance of RHyThM, it was found that for seven out of 104 treatments, *i.e.* ~7%, it was not possible to recover the data, due to a reading failure or a failure to transfer the data from PDOS to MSDOS. During the application of the hyperthermia treatments (currently > 3500) using the BSD-2000/3D, one has regularly noticed that the data recording with the PDOS floppy disk unit is sensitive to RF-interference. Such an accident is indicated by the BSD system with the warning 'disk error, data might be lost'. It is anticipated that when one started analyzing the data of treatments performed years ago, the percentage of lost data files will grow as the reliability of the current BSD-2000-3D software system has been improved significantly since 1990.

During the period of the development of RHyThM, the BSD Corporation has upgraded the PDOS control of the BSD-2000-3D to a newly designed MS-Windows based platform. Major advantages of this upgrade are a better exchangeability of the hardware and, in the authors' view even more important, a highly improved access to the treatment data. According to Turner (2004), the current PC-software of the BSD-2000-3D solves most of the difficulties experienced with the older PDOS software. The files are now in comma separated value file format (.csv) allowing processing of the data for tissue assignment and mapping length validation. Integrity and quality data check are, as far as is known, not yet incorporated. Although this new MS-Windows based platform provides an important improvement, the need for RHyThM remains as the majority of the deep hyperthermia centers are still using the BSD-2000/3D systems running under PDOS.

Independent of the software used to analyze the data (RHyThM or the new MS-Windows platform of the BSD-2000 system) the correction of mechanical-based errors in the thermal mapping data, *i.e.* curling, sticking, and slip of thermometry catheter, remains to be manual and specific for each occurrence. In the data analysis of the exploratory study (Fatehi *et al*., 2006b), one had to correct the insertion depth of the thermal catheters for 53 of 291 thermal map trajectories. Hence, in 82% the tissue assignment used in the data analysis was valid for the entire treatment duration and for the remaining 18% the tissue assignment used resembles only the tissue distribution valid at the end of the treatment.

As explained in the experiences, the way that RHyThM checks on short and too steep temperature gradient in position or time has a high potential of

assigning two instead of one temperature measurement as an invalid value. These limitations of RHyThM will be addressed in a future version. The design of RHyThM does not provide functionality to calculate thermal dose expressed as equivalent minutes at 43 °C. The reason for this choice is simple, RHyThM is considered only as a tool to prepare the thermal data for further analysis with more advanced statistical packages.

The availability of the full details of the RF-power applied to the patient provides the opportunity for new interesting analysis between RF-power or temperatures achieved and (indirect) pain complaints. Accurate information about the applied RF-power during the entire deep hyperthermia treatment as provided by RHyThM might add relevant and welcome extra input in finding the proper answer to the posed problem.

2.5 Conclusion

RHyThM is a valuable tool enabling easy access to the temperature and power data recorded during deep hyperthermia treatments performed with the BSD-2000 system. A critical demand is the ability to transfer the PDOS formatted disks to MSDOS formatted disks. RHyThM performs an important integrity and validation check of the data, it connects the tissue assignment with the thermal data, and it includes the correction of unrealistic temperature values. A unique feature is the availability of the forward and reflected RF-power values and the phase for each channel. RHyThM provides a minimum of data analysis required to make a fast assessment of the quality of the hyperthermia treatment. Although the newest BSD-2000 operating systems run under MS-Windows, the availability of RHyThM is of interest for many hyperthermia groups as the majority of the currently installed BSD-2000 systems are still running under PDOS.

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Chapter 3

Temperature data analysis for 22 patients with advanced cervical carcinoma treated in Rotterdam using radiotherapy, hyperthermia, and chemotherapy: A reference point is needed.

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Abstract

Introduction: The growing interest and participation in multi-institutional trials involving deep hyperthermia treatment is an important step towards the further consolidation of hyperthermia as an oncological treatment modality. However, the differences in the clinical procedures of hyperthermia application also raises questions as how to compare the reported temperatures data obtained by the different institutes. In this study our recent developed approach, RHyThM (Rotterdam Hyperthermia Thermal Modulator), has been used for thermal data analysis to investigate the temperature dynamics behavior of a series of deep hyperthermia treatments. ***Patients and methods:*** All 22 patients (104 hyperthermia treatments) with locally advanced cervical carcinoma who participated in a feasibility study for treatment with a three-modality therapy were selected. The patients received mega-voltage external beam radiotherapy to the pelvis in daily fractions of 2 Gy five times a week to a total dose of 46 Gy and additional brachytherapy, at least 4 courses of weekly cisplatin (40 mgm^{-2}) and five sessions of weekly loco-regional deep hyperthermia treatments with the BSD-2000-3D and the Sigma-60 or the Sigma-Eye applicators at frequencies of 70-120 MHz. Using RHyThM tissue type was defined along the insertion length, based on the CT scan information in radiotherapy position, for each single treatment. A step change in the slope of the profile of the first temperature map was identified to verify the insertion length of the thermometry catheter and precise location of the transition between in- and outside the body. Data analysis was performed based on the temperature readout provided by RHyThM. ***Results:*** The temperature and RF-power data of 97 treatments could be analyzed. The intra-vaginal temperature indices were slightly lower than those for bladder and rectum. The average T_{50} (median temperature) in all lumina, *i.e.* bladder, vagina, and rectum, was 40.4±0.6 °C. The average vagina lumen T_{50} was 40.0±0.8 °C. The average bladder and rectum lumen T_{50} was 40.6±0.7 °C and 40.5±0.6 °C, respectively. When the analysis was restricted to the deepest 5 cm of the vagina lumen, the average T_{50} was 39.8±0.9 °C. Good correlation exists between the various temperature indices like T_{20}, $T_{50,}$ and T_{90}, for all lumen measurements in bladder, vagina, and rectum. No correlation was found between temperature indices and treatment number. For the complete patient population, no relationship was found between T_{50} and net integrated RF-power applied. In an explorative analysis on individual patient level, a positive correlation coefficient or trend was found in 14 patients between normalized net integrated RF-power and vagina T_{50}. ***Conclusion:*** Average overall lumen T_{50} for bladder, vagina, and rectum differ less than 1 °C, indicating that a large volume was heated relatively homogeneously. The vagina T_{50} value depends on how many measurement points are included for the analysis. In this group of patients the vagina T_{50} of the first treatment is not a good measure to discriminate between patients with '*heatable*' and '*non-heatable*' tumors. In order to compare temperature data reported by different institutes dealing with the same group of patients, one needs a strict and clear agreement on which temperature measurements or reference point(s) that should be included in the analysis.

3.1 Introduction

Well-controlled Phase III clinical trials have shown that hyperthermia in combination with radiotherapy results in better tumor response than radiotherapy alone (Overgaard *et al*., 1996; Valdagni *et al*., 1988; Valdagni and Amichetti, 1994; Vernon *et al*., 1996; Sneed *et al*., 1998a). For advanced cervical cancer, van der Zee *et al*. (2000) and Harima *et al*. (2001) have

demonstrated a significant benefit of adding hyperthermia to radiotherapy, *i.e.* an increase of the 3-year overall survival from 27% for radiotherapy-alone to 51% for radiotherapy plus hyperthermia and an increase in complete response rate from 50 to 80%, respectively; whereas Vasanthan *et al*. (2005) failed to demonstrate a benefit of the combined treatment. Van der Zee *et al*. (2005) indicate several reasons, which may explain why Vasanthan *et al*. were not able to demonstrate the benefit of a combination of radiotherapy and hyperthermia for their patients. For instance, the observed temperature distribution may not reflect the quality of the hyperthermia treatment due to a too low number of temperature probes (van der Zee *et al*., 2005). Although the observed temperature increase appears adequate, the data from limited thermometry is not representative for the whole target volume. The comment of van der Zee *et al*. (2005) addresses a major issue concerning the interpretation of hyperthermia results, that is 'can one use thermometry or thermal dose data to compare clinical studies and/or explain strong variations in treatment outcome?'

From a biological point of view, the introduction of a thermal dose parameter is of great importance to predict treatment outcome. Reported data from human clinical trials illustrate that the temperature exceeded by 50% (T_{50}) and 90% (T_{90}) of monitored sites within the tumors may have prognostic significance and predictive values for response (Leopold, *et al*., 1992; 1993). Moreover, the concept of cumulative equivalent minutes at 43 °C (*i.e.* CEM43°C), which was introduced by Sapareto and Dewey (1984) based on cell culture data, indicates the relation between different heating times and temperatures to one another. The study of Maguire *et al*. (2001) was a first attempt to test the concept of CEM43°CT_{90} as a prognostic and prescriptive thermal dose parameter. In this phase II trial study patients were first selected on the '*heatability*' of their tumor and if the tumor was '*heatable*' they received additional ($n \geq 10$) hyperthermia treatments. Based on the thermal dose effect relationship for soft tissue sarcoma, as has been established by Oleson *et al*. (1993), a minimum thermal dose (CEM43°CT_{90} =10 min) was prescribed. Unfortunately, the complete response rate achieved (56%) was significantly below the projected complete response rate of 76%. The later illustrates that translation of the thermal dose concept to a clinical prescriptive parameter is still complicated and hampered by limited knowledge of the biological processes involved in hyperthermia. In a recent letter to the editor, Dewhirst and Sneed (2003) elucidated on the rather complex and multi-functional character of the

process involved in enhancing tumor cell kill by radiotherapy or chemotherapy in combination with hyperthermia, demonstrating the still un-mature state of this topic and the need for more research.

In the authors' opinion, the above does not mean that one cannot exploit temperature data to improve treatment quality. If one limits the question to only address the day-to-day technical quality of a hyperthermia treatment within a single institute, the current thermometry can provide already valuable information. In case one wants to compare hyperthermia quality among various equipment, one needs to arrive at more uniform procedures of thermometry. For a technical evaluation of the hyperthermia treatment it was anticipated that it would suffice to focus the temperature analysis on T_{20}, T_{50}, and T_{90}.

The current study concentrates on temperature dynamics of the treatment instead of a thermal dose effect analysis. In this study the most important reason to investigate treatment temperature dynamics is to evaluate reproducibility of the hyperthermia treatment, to compare the hyperthermia quality in various institutes, and to compare the different equipment utilized for heating the same tumor area. This paper presents a temperature data analysis that is performed using a recently developed program, RHyThM (Rotterdam Hyperthermia Thermal Modulator) (Fatehi *et al*., 2006a). The thermal analyses of the data obtained for the patients with locally advanced cervical cancer, which were treated with radiotherapy plus hyperthermia and chemotherapy, has been primarily chosen with the intention to evaluate the performance of RHyThM.

During this analysis it was noticed, however, that the analysis of the thermal data is also of high interest to identify potential discrepancies in analysis and reported 'thermal dose' among institutes participating in phase II/III clinical trials. When comparing the results with the data reported in other studies, we are confronted with the question whether the difference among the temperatures reported in these studies is a real difference or merely a reflection of a difference in the equipment and the protocols used.

In the light of the currently active trials performed by different institutes, each with their own validated protocols and specific experience, we believe that there exist a clear need to arrive at consensus on new and tight guidelines to make a valid assessment and comparison of the quality of the hyperthermia treatments performed in the various clinical studies and among the different institutes (van Rhoon *et al*., 2005b).

3.2 Patients and methods

3.2.1 Patients

The temperature data of all 22 patients (104 treatments) with advanced cervical carcinoma referred between May 2000 and June 2002 for hyperthermia treatment as part of a phase II study on the feasibility of three-modality cancer treatment, *i.e.* radiotherapy plus hyperthermia and chemotherapy, was used in this thermal data analysis. These patients are also included in the combined analysis of the three prospective phase II trials as were carried out in Norway, the USA, and the Netherlands, of which the clinical results were recently published by Westermann *et al*. (2005). Eligible patients were aged >18 years with previously untreated, histologically confirmed invasive cancer of the uterine cervix. Loco-regional deep hyperthermia had to be technically feasible. Serious concomitant disease or active infection was not allowed and neither was previous malignancy that conceivably still could be active. Patients were aged 31-75 years (mean 44), all had a good general condition (WHO 0-1), squamous cell carcinoma FIGO (International Federation of Gynecology and Obstetrics) stage IIB (n=19), IIIA (n=1) or IIIB (n=2).

3.2.2 Radiotherapy and chemotherapy

All patients received megavoltage (≥ 10 MV) external-beam radiotherapy to the whole pelvis to a total of 46 Gy in five fractions of 2 Gy a week using a four-field box technique. Brachytherapy was administrated with high-dose rate brachytherapy (17 Gy, two fractions of 8.5 Gy). Radiotherapy was performed at different institutes, *i.e.* Rotterdam, Arnhem, and Enschede, in the Netherlands. Chemotherapy consisted of at least four and maximum five courses of weekly cisplatin (40 mgm^{-2}, i.v.) with standard hydration and anti-emetic pre-medication.

3.2.3 Hyperthermia

Regional whole pelvis hyperthermia was delivered once weekly during the period (5-6 weeks) of radiotherapy and chemotherapy administration, starting 1 to maximally 6 hrs after radiotherapy. Hyperthermia was delivered with the BSD-2000-3D annular phased array system (BSD Medical Corporation, Salt Lake City, Utah, USA) (Turner *et al*., 1989) using the 12-channel Dodek solid-state amplifier connected to the Sigma-60 or the Sigma-Eye applicator. Hyperthermia was carried out by the institutional protocol of the Erasmus MC

Daniel den Hoed Cancer Center, in Rotterdam as follows. The frequencies used were in the range of 70-120 MHz. The initial RF-power was 400 W. The RF-power output to the applicator was increased until the patient's tolerance threshold was reached. Hereafter, SAR (specific absorption rate)- steering was applied by changing phase and amplitude settings with the aim to reduce power-limiting hot-spots (*i.e.* normal tissue temperature > 43 °C or pain complaints of the patient) and to maintain or increase the temperature in the target volume. The hyperthermia treatment consisted of a heating phase of 30 min followed by 60 min therapeutic time. The temperature of the applicator's water bolus was maintained at 20 °C. The increase in systemic temperature was limited by cooling measures, *i.e.* undressing, air- conditioning, wet towels, ice packs, and cooling bolus placed in the neck.

3.2.4 Thermometry

For thermometry, closed-tip catheters (William Cook Europe, P5.0-CE-50-SFT-NS-0, Denmark) were placed in the urinary bladder lumen, rectum, vagina, and at the perineal skin. These locations reflect tumor-contact temperature, tumor-indicative temperature, or normal tissue temperature. Tumor-contact is defined as close contact of the closed-tip thermometry catheter with the tumor; tumor-indicative is defined as the position of the closed-tip thermometry catheter in the same transverse plane as the tumor, but not in contact (Wielheesen *et al*., 2005). The hyperthermia physician decides on the assignment of the tissue type, which is deduced from the patient's CT-scan obtained in radiotherapy position. Insertion depth of the thermometry catheter was measured manually using a standard caliper by the hyperthermia technician.

Temperatures were measured using the Bowman probes (Bowman, 1976) of the BSD-2000 system. Temperature mapping was performed along the length of the catheter in 1 cm increments with a maximum mapping length of 14 cm. Thermal mapping started just prior to the start of the hyperthermia treatment and repeated hereafter with 5-min intervals. Accuracy of the temperature measurement was ±0.2 °C with a precision of ±0.1 °C. Systemic (oral) temperature was measured with regular intervals, *i.e.* just before the start of the treatment, at 15, 30, 60 min, and at the end of the treatment session.

3.2.5 Data processing

In order to perform thermal data analysis, using the BSD-2000 computer console and empty MSDOS formatted 1.44 MB (2HD) disks; the BSD data of patients was transferred from PDOS to MSDOS format. Then, the MSDOS data was imported in RHyThM in MATLAB environment. Using RHyThM, tissue type was defined for each single treatment according to the tissue map trajectory per thermometry catheter as provided by the hyperthermia physician and for the insertion length as measured by the hyperthermia technician. A step drop of the temperature profile of the first thermal map was used to verify the location of the transition between in- and outside the body, as reported by the hyperthermia technician. If necessary the location of the transition was adapted to match better with the steep temperature gradient or to correct for a small movement of thermometry catheter during the whole treatment session. For a complete description of the RHyThM program, this study refers to a previous publication by Fatehi *et al*. (2006a). The data analysis is based on the temperature readout as provided by RHyThM. The following thermal dose parameters were calculated: T_{max}, which is determined between start and end of the treatment, average of temperature (T_{mean}), T_{20}, T_{50}, and T_{90}*, which are calculated between 30 min after treatment start time and end of the treatment. The temperature readout was also restricted to the deepest 5 cm of vagina lumen and repeated the data analysis. The purpose of this limitation was to exclude a potential effect of the cold water-cooling of the perineum tissue.

3.3 Results

3.3.1 Experiences from data analysis by RHyThM

Data transfer from PDOS to MSDOS was successful for 21 patients. For one patient the data of all four treatments was lost due to a reading failure of the diskette under PDOS. Additionally, it was not possible to transfer a single treatment for three other patients. Thus, of the 104 treatments performed 97 treatment datasets were available for analysis. Hereafter, the MSDOS data was imported in RHyThM to perform the data analysis. Overall, RHyThM performed satisfactory, was able to check integrity and validate the temperature data and performed the tissue type assignment and thermal analysis for all remaining 97 treatments; however, it was necessary to adapt the insertion length

* T_X means the temperature which is exceeded by X% of all temperature readings.

for 53 out of 291 thermal map trajectories (18%) or in 39 out of the 97 treatments (40%).

3.3.2 Results of temperature analysis

An overview of the analyzed temperature data is presented in table 3.1. Overall, the vagina temperatures were slightly lower than those for bladder and rectum. Median temperature (T_{50}) in vagina tumor-contact was 39.7±0.8 °C and vagina all lumen T_{50} was 40.0±0.8 °C. When the temperature analysis was restricted to the deepest 5 cm of the vagina lumen, the T_{50} was 39.8±0.9 °C (table 3.2). The bladder tumor-indicative T_{50} was 40.8±0.7 °C *vs.* 40.6±0.7 °C for bladder all lumen T_{50}. The rectum tumor-indicative T_{50} and rectum all lumen T_{50} were 40.5±0.7 °C and 40.5±0.6 °C, respectively. If one considers all intraluminal, *i.e.* all bladder, vagina, and rectum temperature measurements, the T_{50} was 40.4± 0.6 °C. More temperature indices, *i.e.* T_{20} and T_{90} are shown in table 3.2. A strong correlation exists between T_{50} and T_{20}, as well as T_{50} and T_{90} in vagina all lumen (and also for vagina tumor-contact) (figure 3.1). The same results and similar figures (not shown) were obtained for bladder and rectum temperature.

In general, a typical temperature profile along the thermal mapping catheter inserted in the vagina starts with low temperatures at the transition between inside and outside the body, after which the temperature increases to a maximum within the first few centimeters and subsequently decreases again when reaching the deepest part of the vagina (figure 3.2). The average insertion depth in the vagina was 9.0 ± 2.1 cm. No correlation was found between treatment number and T_{50} (or T_{20} or T_{90}) either for tumor-contact or for all lumen.

Figure 3.3 shows the vagina all lumen T_{50} as obtained during the first and last treatments as a function of patient number. Additionally, the grey area shows the range of T_{50} obtained during all treatments and it demonstrates that vagina T_{50} varies substantial from one treatment to another. In six out of 21 cases T_{50} was maximal in the first treatment, in seven cases T_{50} was maximal in the last treatment, in three cases T_{50} was maximal in the first and last treatments and, finally, for five cases T_{50} was maximal in the intermediate treatments. However, in one case maximal T_{50} was in treatments 1, 3, 4, and 5.

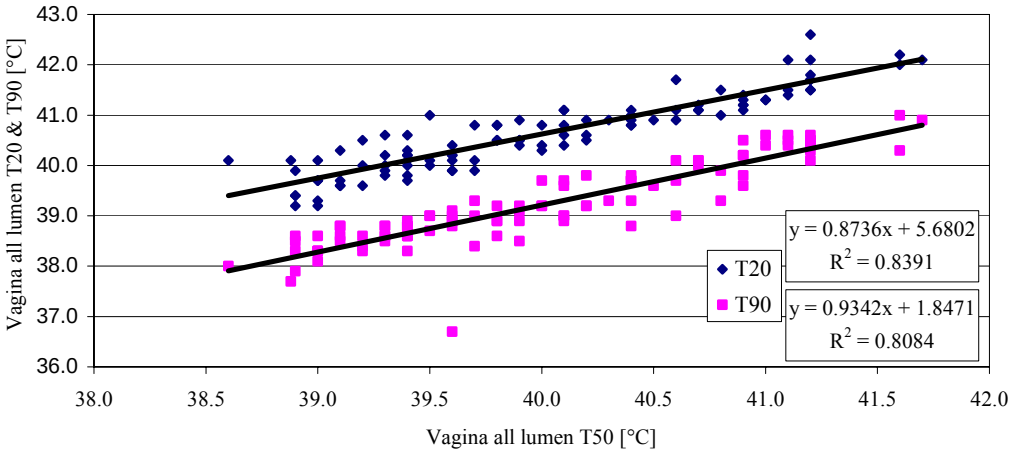

Figure 3.1: Vagina all lumen T_{20} and T_{90} *vs.* vagina all lumen T_{50}.

Table 3.1: Average temperature (°C) in bladder, vagina, and rectum as obtained during loco-regional deep hyperthermia treatment in 22 patients with locally advanced cervical carcinoma. Numbers in parentheses show 1 SD.

Index	Bladder		Vagina		Rectum	
	Tumor-indicative	All lumen	Tumor-contact	All lumen	Tumor-indicative	All lumen
T_{mean}*	40.8(0.7)	40.6(0.7)	39.8(0.8)	40.0(0.7)	40.5(0.6)	40.5(0.6)
T_{max}	41.6(0.8)	41.8(0.7)	40.7(1.0)	41.3(0.8)	41.7(0.8)	41.9(0.7)
T_{20}	41.2(0.7)	41.1(0.7)	40.2(0.8)	40.6(0.7)	40.9(0.7)	40.9(0.6)
T_{50}	40.8(0.7)	40.6(0.7)	39.7(0.8)	40.0(0.8)	40.5(0.7)	40.5(0.6)
T_{90}	40.2(0.8)	39.8(0.8)	39.2(0.7)	39.2(0.8)	39.9(0.7)	39.7(0.7)

*T_{mean}, T_{20}, T_{50}, and T_{90} are calculated between 30 min after treatment start time and end of the treatment. T_{max} is calculated between start of treatment and end of the treatment.

Table 3.2: Average T_{20}, T_{50}, and T_{90} in different locations of temperature measurement during loco-regional deep hyperthermia treatment of patients with locally advanced cervical carcinoma treated with radiotherapy, hyperthermia, and chemotherapy. Numbers in parentheses show 1 SD.

lumen	thermometry method	location of the temperature measurement	T_{20} (°C)	T_{50} (°C)	T_{90} (°C)
vagina	intra-vaginal	the deepest 5 cm of vagina lumen	40.1(0.9)	39.8(0.9)	39.2(0.8)
vagina	intra-vaginal	all vagina lumen	40.6(0.7)	40.0(0.8)	39.2(0.8)
bladder, vagina, and rectum	intraluminal	bladder, vagina, and rectum lumen	40.9(0.7)	40.4(0.6)	39.6(0.8)

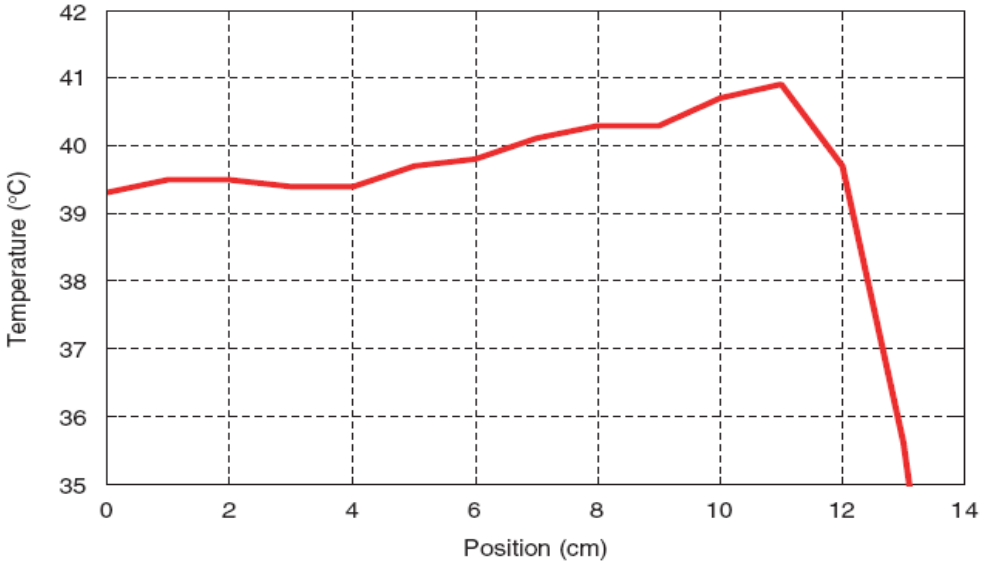

Figure 3.2: A typical temperature profile along the thermal mapping catheter inserted in the vagina lumen. Position 0 cm represents the deepest point in the lumen, whereas the transition between inside and outside the lumen is at 11-12 cm.

Another parameter investigated was the correlation between average net RF-power (W) [or average net integrated RF-power (kJ)] and T_{50} for vagina, bladder, and rectum all lumen. For both parameters no correlation was found with T_{50}. In an exploratory analysis on individual patient level, *i.e.* when applied RF-power per treatment is normalized to the average RF-power over the whole series of treatments for a patient, a positive correlation coefficient or trend was seen in 14 patients. The average net RF-power and net integrated RF-power per patient's weight was 9.7±2.0 Wkg^{-1} and 46.4±10.4 $kJkg^{-1}$, respectively. No correlation was found between the number of RF-power off-switches and T_{50} for all lumen.

3.4 Discussion

In our department hyperthermia treatment of patients with a deep-seated tumor, *e.g.* uterine cervix is applied with the BSD-2000 system using the Sigma-60 or the Sigma- Eye applicator. Our treatment strategy is to heat the target volume as homogenous and high as possible, which is achieved by SAR-steering, *i.e.* changing phase and amplitude settings. From this exploratory analysis of the 22 patients treated with radiotherapy plus hyperthermia and chemotherapy it is found that the T_{50} temperatures for bladder (40.6±0.7 °C), vagina (40.0±0.8 °C), and rectum (40.5±0.6 °C) differ 0.6 °C (table 3.1), indicating that a large volume is heated relatively homogeneously.

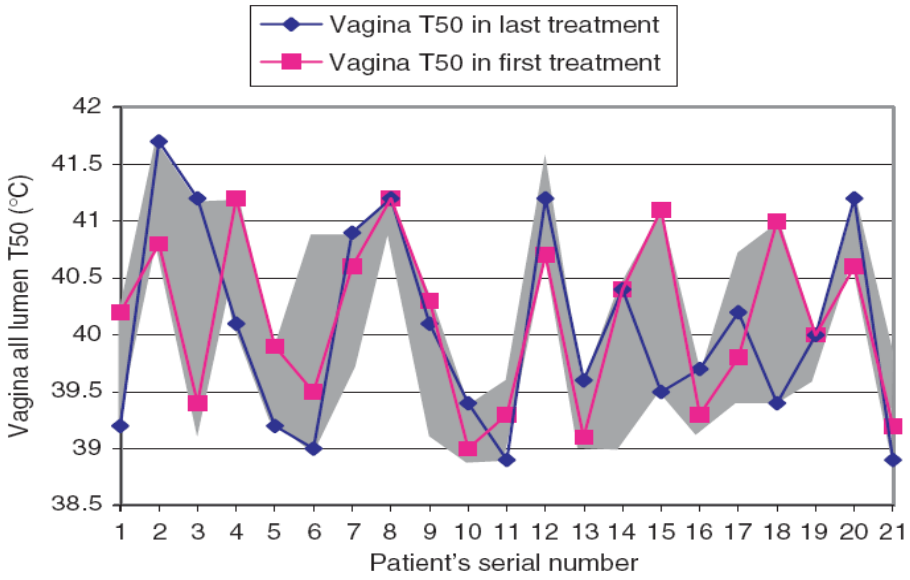

Figure 3.3: Vagina all lumen T_{50} in the first and last treatment plus range of maximum and minimum vagina T_{50} (grey area) during all of the treatments.

The substantial and rather unpredictable large standard deviation (0.8 °C) found in the vagina T_{50} among the different treatments for a patient indicates that, for this group of patients, the vagina T_{50} of the first treatment is not a good measure to discriminate between patients with a high average T_{50} and patients with a low average T_{50} or patients with '*heatable*' and '*non-heatable*' tumors (figure 3.3).

In the present study the average of all intraluminal median temperature measurements, *i.e.* all bladder, vagina, and rectum lumen T_{50} was 40.4±0.6 °C (table 3.2). The T_{50} value as reported in several publications dealing with similar patients, *i.e.* locally advanced cervical carcinoma treated with the same treatment modality, *i.e.* radiotherapy plus hyperthermia and chemotherapy, are different from these results. For example, as reported in the compilation paper by Westermann *et al.* (2005), the T_{50} value was 41.0 °C for the Dutch patients, 39.2 °C for the American patients and 41.1 °C for the Norwegian patients. In a separate publication, Jones *et al.* (2003) reported a T_{50} of 39.4±0.7 °C for a similar group of patients and treatments. The question is whether these differences are real differences in achieved temperature distribution or merely a consequence of differences in thermometry procedures of the various departments. As reported by Westermann *et al.* (2005), the T_{50} value for the Dutch patients is an average of all intraluminal and/or intratumoral temperatures measured, whereas the T_{50} reported for the American patients reflected only the temperature in the most distal 5 cm of the cervical os and the data of Norway

included intra-vaginal and tumor measurements (Jones *et al*. 2003; Westermann *et al*., 2005).

In an attempt to quantify the effect of the different manners of temperature analysis, this study has analyzed the data using the same three manners. First, including all intraluminal temperatures the T_{50} value was 40.4±0.6 °C. Secondly, if the data analysis was restricted to all intra-vaginal temperature measurements the T_{50} was 40.0±0.8 °C. Thirdly, when the analysis was limited to the deepest 5 cm of the vagina lumen the T_{50} was 39.8±0.9 °C. The typical temperature profile along the thermometry catheter in the vagina as plotted in figure 3.2 is a relatively well-known phenomenon and may reflect the variation in permittivity and blood flow at this location. As a consequence of this typical profile, the vagina T_{50} is lower when the thermal analysis is restricted to the deepest 5 cm of the thermometry catheter in the vagina. At this moment it is difficult to conclude whether this difference has relevance for the clinical outcome, however, it does matter when the T_{50} is used for comparing the quality among patient's treatments.

In addition to the uncertainty introduced by variations in the exact location of the temperature measurements comes a still unknown uncertainty associated with differences in the used probes, *e.g.* Bowman probes (the BSD users) or thermocouples (Amsterdam Hyperthermia Group) and differences in mapping intervals, *e.g.* 0.5 or 1 cm. There are a multitude of reasons why the T_{50} data for the various institutions are different. Without detailed knowledge of SAR-patterns, probe positions, patient's characteristics, use of analgesics, *etc.* it would be impossible to determine whether such differences are real, particularly when there was no '*a priori'* temperature goal set for these studies (Dewhirst, 2006).

The reported differences illustrate the need to reach consensus on new guidelines to allow a valid assessment and reliable comparison of the quality of the hyperthermia treatments performed in different clinical studies and among the various institutes. Introduction of reference points similar to radiotherapy may constitute a good solution to enable a more rigid comparison of the quality of the hyperthermia treatments delivered in different institutes. From a quality assurance point of view one of the issues of thermal data analysis is to compare the '*quality*' of the hyperthermia treatments administered by different hyperthermia groups. Given the fact that at present a standardized thermal dosimetry system is still lacking (Dewhirst *et al*., 1993; Dewhirst and Sneed,

2003), we consider flexibility as an essential requirement to easily enable a specific and reliable comparison of the quality of the hyperthermia treatment applied by different hyperthermia groups based on an identical thermal dose parameter definition.

In the clinical study reported here we had to correct the insertion depth of the thermal catheters for 53 (of 291) thermal map trajectories. Hence, in 82% the tissue assignment used in the data analysis is valid for the entire treatment duration and for the remaining 18% the tissue assignment used resembles only the tissue distribution valid at the end of the treatment. As we question whether this approach to correct for changes of the insertion depth is appropriate, we are currently investigating the need for dynamic tissue assignment based on a varying insertion depth of the thermometry catheter.

Another factor associated with assigning the correct insertion depth is the cooling effect of the coldwater bolus against the skin, especially at the perineum. Due to thermal conduction, the temperatures measured at points near the transition of the perineum tissue to the water bolus (13 °C) are substantially below normal tissue temperature (<37 °C) and thus appears to be outside the vaginal or rectal lumen. For longer preparation/installation times the cold front will be moving further into the tissue, making it more difficult to identify the correct insertion depth. The solution to this problem is difficult as the manual measurement of the insertion depth has a poor accuracy.

The availability of the full details of the RF-power applied to the patient provides the opportunity for new interesting analyses between RF-power, temperatures achieved, and pain complaints. The correlation observed in the exploratory analysis between normalized net integrated RF-power and vagina T_{50} is an experimental support for the optimization of the SAR- distribution as is being advocated for long by several theoretical studies (Paulsen *et al.*, 1999; Wust *et al.*, 1995b). This finding is a stimulus for rigid investigation (including the statistical power) of this potential relation in a dataset of a larger patient population. Our hyperthermia treatment protocol prescribes maximization of the applied RF-power during a deep hyperthermia treatment through continuous increase of the RF-power until the patient complains about discomfort. Then, phase- and amplitude steering is applied to reduce the discomfort and, if successful, RF-power is increased again until the next complaint of the patient.

3.5 Conclusion

The exploratory analysis performed for 22 patients with advanced cervical carcinoma, treated with radiotherapy plus hyperthermia and chemotherapy, demonstrated that RHyThM operates satisfactorily. The analysis also indicates some areas for further improvement. In the present thermal data analysis the intra-vaginal temperature indices were found to be slightly lower than those for bladder and rectum temperatures. Average all lumen T_{50} for bladder, vagina, and rectum differ 0.6 °C, indicating that a large volume was heated relatively homogeneously. In this group of patients the vagina T_{50} of the first treatment is not a good measure to predict '*heatablity*' and '*non-heatablity*' of the tumors. When we compare our thermometry results with the data reported from other studies we are confronted with the question whether the differences among the reported temperatures are real or merely reflect differences in the equipment and the protocols used. Hence, these differences demonstrate the necessity to reach consensus on new and tight guidelines allowing a valid comparison of the quality of the hyperthermia treatments performed in different institutes. Such guidelines are also mandatory for the quantitative evaluation of major improvements in hyperthermia technology.

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Chapter 4

Comparison of intratumor and intraluminal temperatures during loco-regional deep hyperthermia of pelvic tumors

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Abstract

Purpose: Investigate whether intraluminal thermometry provides sufficient information to apply high quality deep-hyperthermia in pelvic tumors. ***Patients and methods:*** The intratumor and intraluminal temperatures of 48 patients were analyzed per cancer type: rectum (21 male, 14 female), cervix (8), and bladder (5). Temperature dose parameters were calculated, temperature curves within each treatment session were compared, and correlation between intratumor and intraluminal temperatures was analyzed. ***Results:*** Intratumor and intraluminal temperatures at the same time points during individual treatments were highly correlated (mean correlation coefficient 0.93). However, the quantitative-level differs from 0.1 to 1.1 °C and the differences of the time-temperature graphs vary per tumor-group. Average intratumor and intraluminal temperatures were not different in the four groups. Intratumor thermometry was found not superior over intraluminal thermometry to improve tumor temperature level and homogeneity by SAR-steering. ***Conclusion:*** Intraluminal thermometry provides sufficient information to apply deep-hyperthermia to individual patient with centrally located rectum, cervix, or bladder cancer.

4.1 Introduction

In the recent decades, multimodality treatment approaches for deep-seated pelvic malignancies including surgery, radiotherapy, chemotherapy, and hyperthermia have become increasingly sophisticated (Dunst *et al*., 2005; Kim *et al*., 2005; Tilly *et al*., 2005; Windschall *et al*., 2005). When patients with deep-seated tumors are under treatment, hyperthermia groups apply intratumor and/or intraluminal thermometry for temperature data acquisition. Strong variation exists in the opinions whether intratumor thermometry provides superior information over intraluminal thermometry. Sneed *et al*. (1998b) state that intratumor thermometry is critically important; while van der Zee *et al*. (1998) and Wust *et al.* (1998a) suggest if intraluminal thermometry is available, intratumor thermometry is neither an important requirement for prevention of toxicity, nor necessary for SAR (specific absorption rate)-steering.

Van der Zee *et al*. (1998) focused on the complications and clinical limitations of intratumor thermometry during deep hyperthermia of pelvic tumors and presented a very limited thermal analysis. Wust *et al.* (1998a)

demonstrated that intraluminal measurements, specifically for cervical and rectal cancers, are suitable for estimating feasibility and effectiveness, and that there is no need for intratumor thermometry.

The present study is an extension of that by van der Zee *et al*. (1998). It provides a rigorous analysis of temperature data, acquired both intratumorally and intraluminally, of patients with a pelvic tumor, making it an independent replicate of the study by Wust *et al*. (1998a). Questions were: 1) Is there a positive correlation between intratumor and intraluminal temperatures? 2) What are the quantitative/qualitative differences between intratumor and intraluminal temperatures? 3) Can intratumor temperature distribution be improved by SAR-steering?

4.2 Patients and methods

4.2.1 Patients

Data used in this retrospective study were selected from our patients' database. Selection criteria were: 1) intratumor ***and*** intraluminal temperature measurements, 2) tumor location: pelvis, 3) tumor type: rectum, cervix, or bladder. Based on the selection criteria 58 patients (143 treatments) were selected.

Accessibility of temperature data, as registered by the BSD-2000 system, requires specific tools and it is subjected to failures as explained by Fatehi *et al*. (2006a). For the present study, it was not possible to transfer the PDOS formatted data of nine patients (16 treatments) to MSDOS. Additionally, during the data processing by means of RHyThM (Rotterdam Hyperthermia Thermal Modulator), it was not possible to access thermal data of one patient (2 treatments) and 25 single treatments.

With these limitations, 48 patients (100 treatments) were available for analysis. Patients were grouped in four categories: male rectal cancer (21 patients, 39 treatments), female rectal cancer (14 patients, 27 treatments), cervical cancer (8 patients, 21 treatments), and bladder cancer (5 patients, 13 treatments). For a detailed description of patient characteristics and tumor stage, see van der Zee *et al.* (1998).

4.2.2 Hyperthermia

Hyperthermia was performed using the BSD-2000 with the Sigma-60 applicator (BSD Corporation, Salt Lake City, Utah, USA) (Turner *et al*., 1989).

One to five (mean 4) loco-regional hyperthermia treatments were delivered to the pelvis once weekly during the period of radiotherapy or chemotherapy. Hyperthermia was started at 400 W RF-power. The treatment setting for frequency, amplitude distribution, and phase shifting at the start of the first treatment were selected according to the local protocol.

Patients were carefully instructed to mention any unpleasant sensation that might be the result of a hot-spot (van der Zee *et al*., 1998). Power output was increased to the patient's tolerance without pain. To improve the temperature distribution or to relieve pain complaints treatment settings were adapted, *i.e.* phase, power per channel, frequency, or by placing additional water boluses. Treatment duration was 60 min after any of the intratumor measured temperatures had reached 42 °C, or to a maximum of 90 min. Water bolus temperature was maintained at 20 °C. Systemic temperature was controlled by cooling measures, *i.e.* undressing, air-conditioning, wet towels, ice packs, and cooling bolus placed in the neck. The bladder was kept empty with a Foley catheter (Fatehi *et al*., 2006b).

4.2.3 Thermometry

Intratumor catheter placement was planned at least one day prior to the first hyperthermia treatment. 5-Fr polyethylene closed-tip thermometry catheter(s) (William Cook Europe ApS, Bjaeverskov, Denmark) were introduced in the tumor transgluteally under CT control. For details, see van der Zee *et al.* (1998). Intraluminal catheters were inserted in bladder, rectum, and vagina lumen (as relevant) before each treatment. After catheter placement, the intratumor and intraluminal depths were documented. Insertion length of the intraluminal catheters was measured manually using a standard caliper. Bowman probes (Bowman, 1976) were used to assess real time temperature reading (accuracy: ±0.2 °C with a precision of ±0.1 °C). Temperature mapping was performed in 1 cm increments to a maximum length of 14 cm. Thermal mapping started just before the treatment and was repeated at 5-min intervals.

4.2.4 Data processing and definitions

The method of data processing has been described extensively by Fatehi *et al*. (2006a, 2006b). In this study, the intratumor temperature is defined as temperature data acquired from within the tumor. The intraluminal temperatures are reported as normal tissue, tumor-contact, tumor-indicative, or

overall measurements. Tumor-contact means that the catheter at the site of measurement lies in contact with tumor. When the site of measurement is in the same transverse plane as tumor, but not in contact with the tumor, the temperature is called tumor-indicative (Wielheesen *et al*., 2005). The remaining measurements represent normal tissue. The overall intraluminal temperature includes all measurements within one catheter; all lumina temperature includes all measurements within all intraluminal catheters; and the related lumen temperature refers to rectum lumen temperature for rectal cancer, to vagina lumen temperature for cervix cancer, and to bladder lumen temperature for bladder cancer patients.

4.2.5 Statistical analysis

The statistical analysis was based on the temperature-dose parameters, as provided in the ASCII files by RHyThM. Temperature measurements were available per patient, per treatment session, per probe, per mapping position, and per time point. All temperature measurements below 37 ºC were excluded. The time points were scaled with respect to the starting time of the treatment. While computing averages, all observations were weighted equally.

The thermal dose parameters calculated per patient per treatment session were: average temperature (T_{mean}), T_{10}, and T_{90}. T_X means the temperature which is exceeded by X percent of all temperature readings. The averages and standard deviations were computed for all thermal dose parameters of different lumina (bladder, vagina, and rectum) and different tissue types (normal tissue, tumor, tumor-contact, and tumor-indicative). Averages of intratumor and intraluminal temperatures were compared with T-tests. The p-values are two-sided at a significance level of α=0.05. STATA program (version 9.2) was used for the statistical analysis.

4.3 Results

4.3.1 Intratumor vs. intraluminal temperatures

Temperature indices were calculated per patient, per treatment session, and per time point from start until end of the treatment. Per patient per treatment, correlation coefficients were computed between intratumor and intraluminal tumor-contact/indicative temperatures and between intratumor and intraluminal normal/all tissues temperatures. Table 4.1 shows the averages of correlation coefficients between intratumor and intraluminal temperatures and their relatio-

Table 4.1: Slopes and correlation coefficients between averages of intratumor and intraluminal temperatures in the four patients groups as obtained in the study. Numbers in parentheses show 1 SD.

	Intratumor *vs.* intraluminal tumor-contact*/indicative temperatures		Intratumor *vs.* intraluminal normal tissue temperatures		Intratumor *vs.* intraluminal overall temperatures in the related lumen @	
	Slope ©	Correlation coefficient	Slope	Correlation coefficient	Slope	Correlation coefficient
Rectal cancer ♂ (17 pts., 27 trts.)	0.80(0.23)	0.95(0.03)	0.61(0.25)	0.81(0.25)	0.70(0.27)	0.80(0.32)
Rectal cancer ♀ (13 pts., 25 trts.)	0.84(0.37)	0.95(0.05)	0.77(0.41)	0.85(0.25)	0.74(0.37)	0.88(0.20)
Cervical cancer (6 pts., 18 trts.)	0.90(0.67)	0.96(0.03)	0.78(0.27)	0.90(0.16)	0.86(0.44)	0.96(0.04)
Bladder cancer (5 pts., 12 trts.)	0.84(0.26)	0.91(0.07)	0.66(0.31)	0.74(0.35)	0.76(0.34)	0.79(0.31)

*Tumor-contact is used for the cervical cancer patients and tumor-indicative for the rectal cancer patients. In the bladder cancer patients, the numbers are average for tumor-contact and tumor-indicative.
@: Related lumen temperature refers to rectum lumen temperature for rectal cancer patients, to vagina lumen temperature for cervix cancer patients, and to bladder lumen temperature for bladder cancer patients.
©: The analysis was based on Y=aX where "a" represents the slope. The slope <1 means that intratumor temperature increases slower than intraluminal temperature and vise versa for the slope >1.

ns are summarized per treatment graphically in figure 4.1. Strong correlation was found between intratumor and intraluminal tumor-contact/indicative temperatures in the four groups (mean correlation coefficients 0.91 to 0.96). In addition, good to strong correlation existed between intratumor and intraluminal normal/all tissues temperatures in the four patients groups (average correlation coefficients varies from 0.74 to 0.96).

4.3.2 Quantitative/qualitative temperature analysis

For this part of the study, temperatures indices were calculated per relevant tissue or relevant lumen and per time intervals of 5 min. An overview of average temperature indices in the four patient groups is summarized in table 4.2. For each group of patients, a graph has been made which shows the relation between time and average temperature per relevant tissue or relevant lumen (figure 4.2).

In the male rectal cancer group (figure 4.2a) the average intratumor T_{mean} (40.3±0.7 °C) was slightly lower than the averages of intraluminal rectum tumor-indicative T_{mean} (ΔT=0.2 °C), rectum overall T_{mean} (ΔT=0.2 °C), and all lumina T_{mean} (ΔT=0.1 °C).

Table 4.2: Average of various temperature values (in °C) for the four patients groups. Numbers in parentheses show 1 SD.

		rectum cancer ♂ (21 pts., 39 trts.)			rectum cancer ♀ (14 pts., 27 trts.)			cervix cancer (8 pts., 21 trts.)			bladder cancer (5 pts., 13 trts.)		
		T_{90}*	T_{mean}	T_{10}	T_{90}	T_{mean}	T_{10}	T_{90}	T_{mean}	T_{10}	T_{90}	T_{mean}	T_{10}
tumor	intratumor temperature	39.4 (0.7)	40.3 (0.7)	41.2 (1.1)	39.5 (0.8)	40.4 (0.8)	41.3 (1.1)	38.3 (1.0)	39.4 (0.9)	40.0 (1.0)	39.9 (1.0)	40.9 (1.1)	41.8 (1.2)
bladder lumen	normal tissue	39.3 (1.5)	40.2 (1.2)	41.0 (1.1)	39.7 (0.6)	40.3 (0.5)	41.0 (0.6)	39.4 (0.9)	40.3 (0.7)	41.1 (0.7)	39.1 (1.1)	39.8 (1.2)	40.5 (1.3)
	tumor-contact	–	–	–	–	–	–	–	–	–	39.3 (1.0)	40.4 (1.0)	41.4 (0.9)
	tumor-indicative	39.6 (0.7)	40.2 (0.5)	40.9 (0.6)	39.8 (1.1)	40.4 (0.9)	41.0 (1.0)	39.3 (0.8)	40.1 (0.6)	40.8 (0.8)	39.5 (1.5)	40.7 (1.3)	41.7 (1.2)
	overall	39.5 (1.1)	40.2 (0.9)	41.0 (0.9)	39.8 (0.9)	40.4 (0.7)	41.0 (0.8)	39.4 (0.9)	40.2 (0.7)	41.0 (0.8)	39.3 (1.2)	40.3 (1.2)	41.2 (1.1)
vagina lumen	normal tissue	–	–	–	39.6 (1.2)	40.3 (1.0)	41.1 (0.8)	39.4 (1.1)	40.1 (1.0)	40.9 (0.9)	40.0 (1.3)	40.7 (1.1)	41.3 (0.8)
	tumor-contact	–	–	–	39.7 (1.5)	40.4 (1.1)	41.0 (1.0)	38.9 (0.9)	39.6 (0.9)	40.3 (1.0)	39.7 (1.1)	40.5 (0.9)	41.4 (0.7)
	overall	–	–	–	39.7 (1.4)	40.4 (1.1)	41.1 (0.9)	39.2 (1.0)	39.9 (1.0)	40.6 (0.1)	39.9 (1.2)	40.6 (1.0)	41.4 (0.8)
rectum lumen	normal tissue	39.8 (1.0)	40.5 (1.0)	41.1 (1.0)	39.6 (1.3)	40.5 (1.4)	41.4 (1.6)	39.2 (0.8)	40.0 (0.7)	40.9 (0.7)	39.8 (1.0)	40.4 (0.9)	41.0 (0.9)
	tumor-indicative	39.7 (1.0)	40.5 (0.8)	41.3 (0.7)	40.8 (1.1)	41.5 (1.4)	42.2 (1.6)	39.2 (0.8)	39.9 (0.8)	40.4 (1.0)	39.9 (0.4)	40.5 (0.4)	41.1 (0.4)
	overall	39.8 (1.0)	40.5 (0.9)	41.2 (0.9)	40.2 (1.2)	41.0 (1.4)	41.8 (1.6)	39.2 (0.8)	40.0 (0.8)	40.7 (0.9)	39.9 (0.7)	40.5 (0.7)	41.1 (0.7)
all lumina	intraluminal temperature	39.6 (1.1)	40.4 (0.9)	41.1 (0.9)	39.9 (1.1)	40.6 (1.1)	41.3 (1.1)	39.2 (0.9)	40.0 (0.8)	40.7 (0.9)	39.7 (1.0)	40.5 (0.9)	41.2 (0.8)

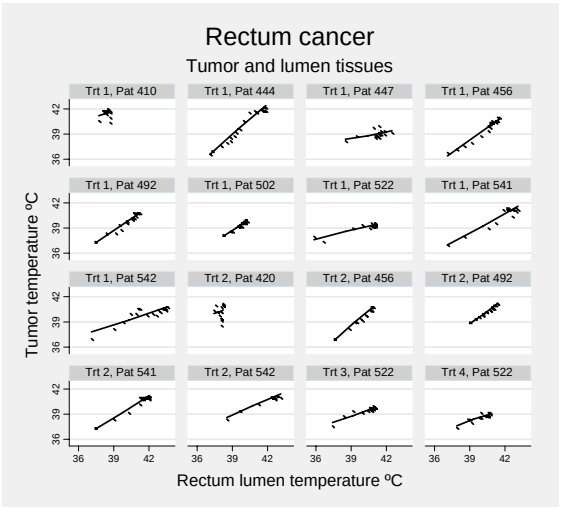
*: T_X means the temperature which is exceeded by X percent of all temperature readings.

In the female rectal cancer patients (figure 4.2b) the average intratumor T_{mean} (40.4±0.8 °C) was lower than the averages of intraluminal rectum tumor-indicative T_{mean} (ΔT=1.1 °C), rectum overall T_{mean} (ΔT=0.6 °C), and all lumina T_{mean} (ΔT=0.2 °C).

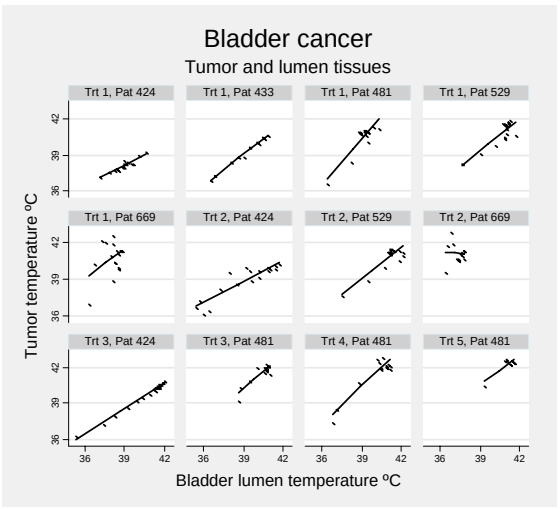
In the cervix cancer group (figure 4.2c) the average intratumor T_{mean} (39.4±0.9 °C) was slightly lower than the averages of intraluminal vagina tumor-contact T_{mean} (ΔT=0.2 °C), vagina overall T_{mean} (ΔT=0.5 °C), and all lumina T_{mean} (ΔT=0.6 °C).

In the bladder cancer patients (figure 4.2d) the average intratumor T_{mean} (40.9±1.1 °C) was slightly higher than the averages of intraluminal bladder tumor-indicative T_{mean} (ΔT=0.2 °C), bladder overall T_{mean} (ΔT=0.6 °C), and all lumina T_{mean} (ΔT=0.4 °C).

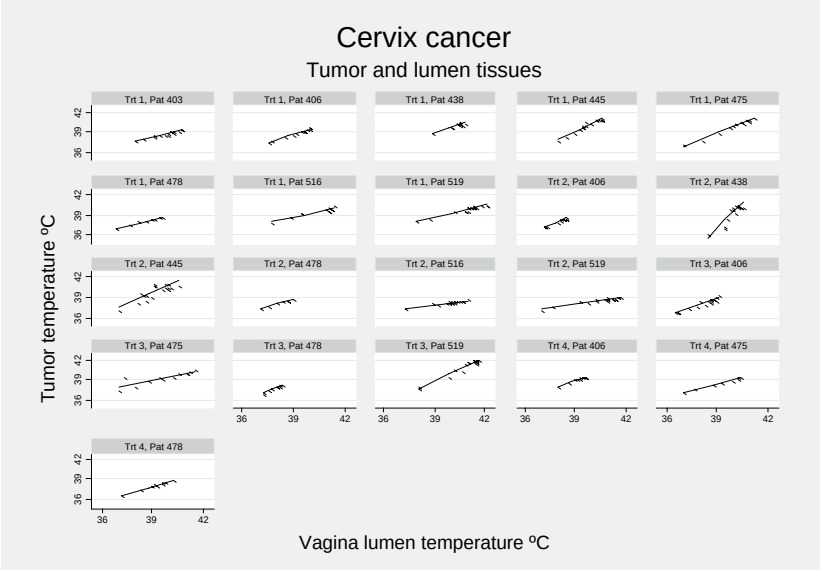
No difference was found between the intratumor and intraluminal temperatures in the four patients groups. Overall, the temperature measurement values were lowest in the cervical cancer patients group.



(a)



(b)



(c)

Figure 4.1: Intratumor temperatures *vs*. intraluminal (a) rectum overall temperatures in rectum cancers, (b) bladder overall temperatures in bladder cancers, and (c) vagina overall temperatures in cervix cancers.

4.3.3 Intratumor temperature distributions

Temperature-time profiles per mapping position were computed for intratumor temperatures in each single treatment (figure 4.3). We hypothesized that if SAR-steering is effective to improve tumor temperature homogeneity, then the temperature-time curves of a single treatment should show a homogeneous and preferable high temperature distribution. However, a clear improvement of temperature distribution was not seen in 26/27 (96%) treatments of male rectal cancers, in 25/25 (100%) treatments of female rectal cancers. This was also the case for 94% (17/18 treatments) of cervical cancers, and 92% (11/12 treatments) of bladder cancers. The 18 remaining treatments had no more than one intratumor temperature point available for analysis.

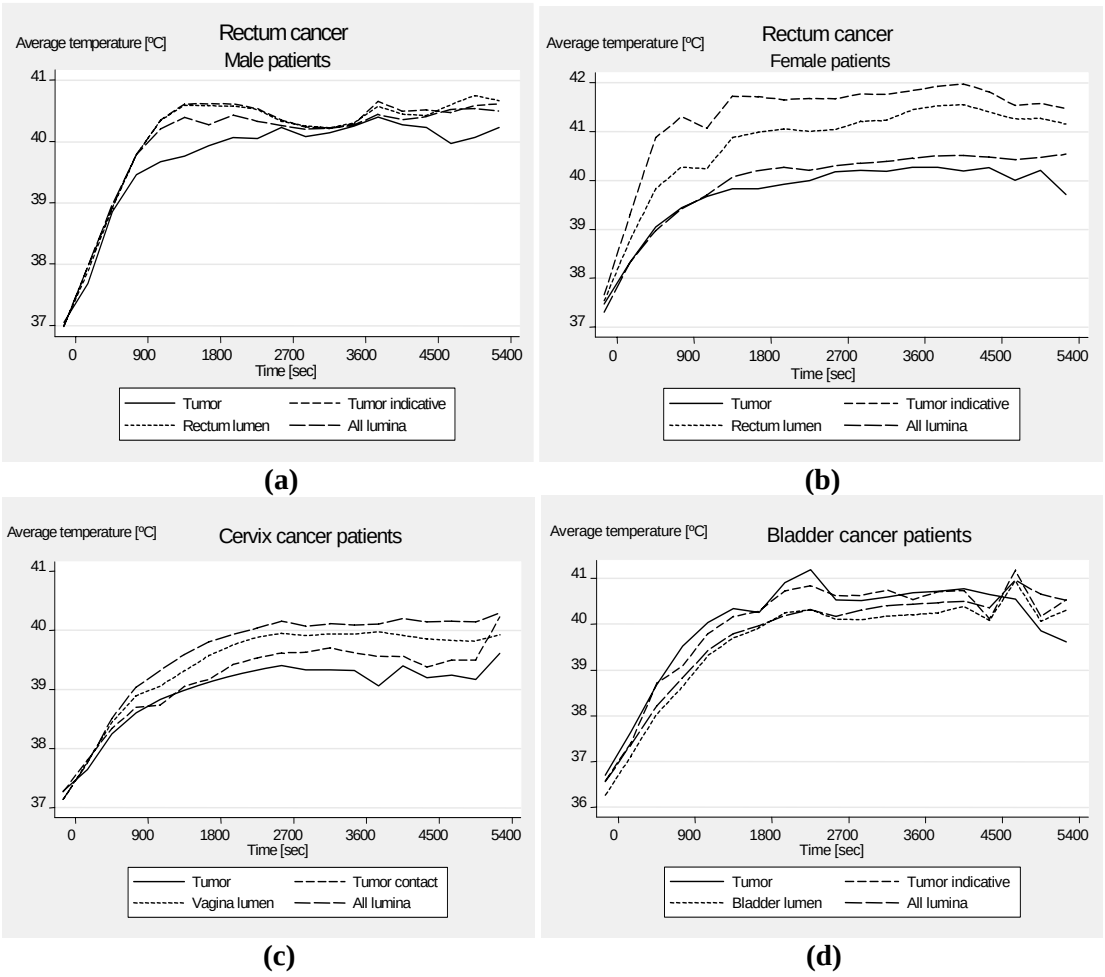


Figure 4.2: Temperature-time profiles in (a) male rectal cancer patients, (b) female rectal cancer patients, (c) cervical cancer patients, and (d) bladder cancer patients.

4.4 Discussion

Interstitial thermometry during loco-regional hyperthermia is done for two main reasons. First, to apply the best possible treatment to the individual patient, by monitoring the achieved temperature level in a large tumor volume. Second, for answering questions of more scientific nature, such as which equipment performs better in certain conditions, or which temperature increase pattern or thermal dose gives the highest probability of a good treatment result. In this study, we have focused on the question whether intraluminal temperature measurements provide sufficient information to apply hyperthermia at the maximum achievable level. This study shows:

1. The temperatures achieved with the BSD-2000 in intrapelvic tumors are generally between 39.5 and 42 °C.
2. There is a high correlation between temperatures measured intratumorally and intraluminally.

3. The intratumor and intraluminal temperature-time profiles follow similar patterns. The later two findings mean that intraluminal temperatures can be used to monitor the change of intratumor temperatures.
4. In 96% of treatments, the intratumor temperature distribution pattern remains the same during 90 min of heating, in spite of SAR-steering adjustments meant to improve the temperature distribution. This means the temperature distribution is insensitive for current SAR-steering procedures. This is not a surprising result, since the used frequency of 70 MHz does not allow small scale SAR-steering.

There were five treatments where we found a poor correlation (<0.7) between intratumor and intraluminal temperatures (figure 4.1). For four treatments, we found a clear explanation for the discrepancy. In patients 410 (treatment 1), 420 (treatment 2) [figure 4.1a], and 669 (treatments 1 and 2) [figure 4.1b] the tumor was located eccentric near the iliac crest, so that the intraluminal temperatures were measured far from the tumor. These findings show that for treatment of tumors outside the region where intraluminal thermometry is possible, intratumoral thermometry is the only way to get information on treatment quality. Patient 447 (treatment 1) [figure 4.1a] had the rectal ampulla filled with faeces during the first treatment, which may explain the much higher rectal temperatures compared to intratumor temperatures.

These results confirm the clinical impression that intratumor thermometry does not add to the quality of treatment when the BSD-2000 system is used for treatment of intrapelvic centrally located tumors, and that intraluminal temperature measurements are sufficient to apply the best possible treatment to the individual patient (van der Zee *et al.*, 1998). Wust *et al.* (1998a) came to the same conclusion, based on an analysis of relations between intraluminal and intratumoral SAR-measurements in patients with cervical and rectal cancer. Elsewhere, Hoffmann *et al*. (2002) reported rectal temperatures with MRI (magnetic resonance imaging) like those found in the present study. Likewise, Wust *et al*. (2006) and Sreenivasa *et al*. (2006) recently found that intraluminal temperatures are related to the response probability. There are no reasons to assume that this result will be different for other equipment using radiative electromagnetic heating at frequencies between 70 and 120 MHz and SAR-control by phase and amplitude steering.

Whether it is justified to use only intraluminal thermometry during treatment of intrapelvic tumors appears a matter of institute's priorities. We

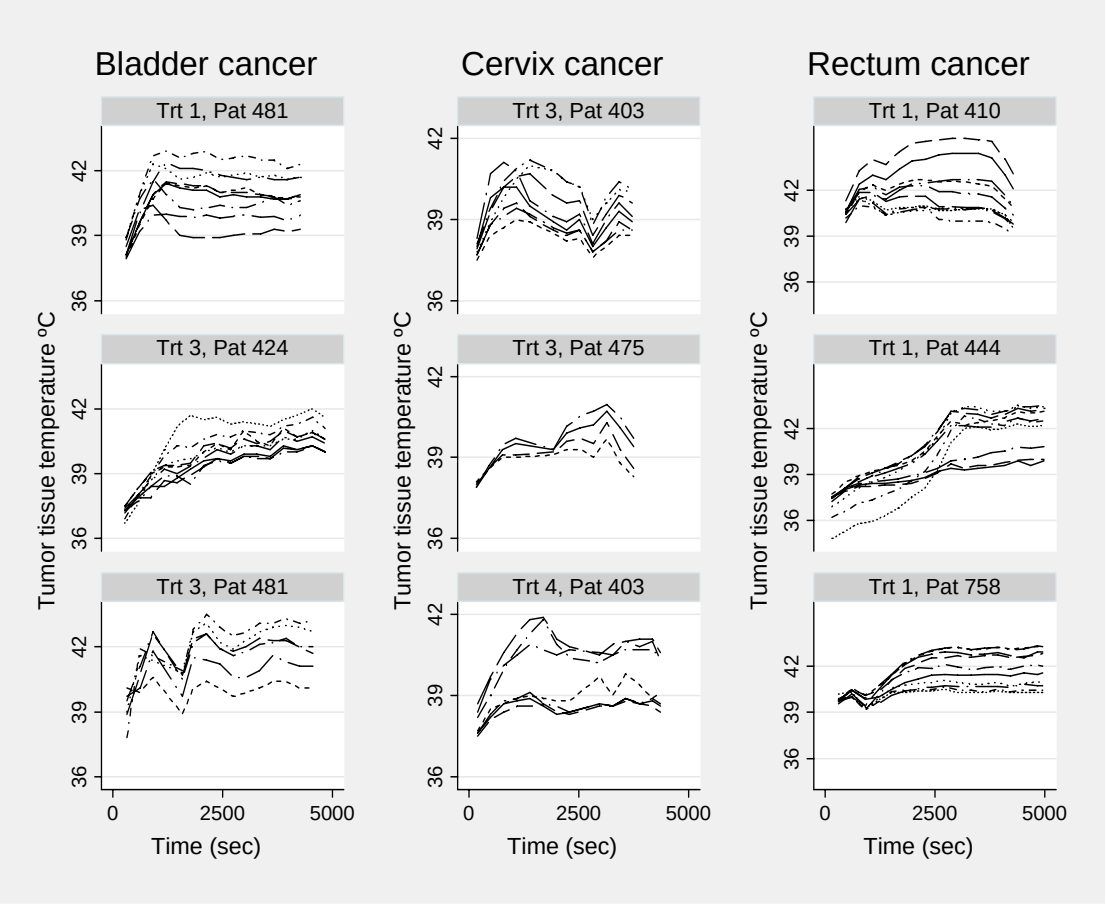


Figure 4.3: Examples of the intratumor temperature-time profiles per mapping position in different cancer-groups.

agree with Sneed *et al*. who state that the only way to calculate tumor thermal dose is to measure the tumor temperature directly (Sneed *et al*., 1998b). Intraluminal thermometry reflects, but is not equal to intratumor thermometry. However, whether this is important depends on the aim of the measurements, especially taking in account the disadvantages of intratumor thermometry, *e.g.* time-consuming, stressful, and painful for the patient, and sever side effects such as bleeding, infection, tumor seeding, *etc*. We find thermometry important for the application of hyperthermia at the maximum achievable temperature levels. For this aim, intraluminal thermometry is sufficient. In our experience, intratumor thermometry was the major cause of treatment related toxicity (van der Zee *et al*., 1998). Introduction of thermometry catheters before each separate treatment session may decrease the complication rate, but it remains an unpleasant, time-consuming, and costly procedure. The results of the detailed temperature analysis presented here and the recent publication of Wust *et al*. (2006) and Sreenivasa *et al*. (2006) support our earlier decision to abandon intratumor thermometry. Of course, this discussion becomes

redundant when non-invasive MR thermometry is widely available (van Rhoon and Wust, 2005).

4.5 Conclusion

The high correlations between intratumor and intraluminal temperatures and the current lack of possibilities to improve intratumor temperature distribution by SAR-steering justify to guide loco-regional deep hyperthermia application to centrally located tumors in the lesser pelvis with intraluminal thermometry only.

Acknowledgement

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Chapter 5

Intraluminal thermometry: Is tissue type assignment a necessity for thermal analysis?

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Abstract

Introduction: Tissue type assignment, *i.e.* differentiation tumor from normal tissue, is a normal procedure for interstitial thermometry. In our department, thermometry in patients with a tumor in the lesser pelvis is usually restricted to the intraluminal tracks. It is unknown whether discrimination between normal and tumor tissue is relevant for deep regional hyperthermia thermal dosimetry using only intraluminal tumor-contact and tumor-indicative thermometry. This study has analyzed the acquired temperature data in order to answer this question. ***Patients and methods:*** Seventy-five patients with locally advanced cervical carcinoma were selected randomly. Patients were treated with a two or three modality combination, *i.e.* radiotherapy + hyperthermia or radiotherapy + hyperthermia + chemotherapy, from October 1997 to September 2003. The first 100 hyperthermia treatments fulfilling the only selection criterion: no displacement of the thermometry catheter along the insertion length during the treatment, were included in the study, resulting in 43 patients with one-to-five treatments per patient (median 2). Using RHyThM (Rotterdam Hyperthermia Thermal Modulator), for each single treatment, tissue type was defined on the basis of information given by a CT scan in radiotherapy position. A step change in the slope of the profile of the first temperature map was identified to verify the insertion length of the catheter. ***Results:*** The average T_{50} (median temperature) in bladder tumor-indicative, vagina tumor-contact, and rectum tumor-indicative was 40.9±0.9 °C, 39.7±0.9 °C, and 40.6±0.8 °C, respectively. The average normal tissue T_{50} in bladder, vagina, and rectum was 40.8±0.9 °C, 40.1±0.9 °C, and 40.7±0.8 °C, respectively. The differences between bladder tumor-indicative T_{50} and bladder normal tissue T_{50}, and also between vagina tumor-contact T_{50} and vagina normal tissue T_{50} were significant (p=0.0001). No difference was found between rectum tumor-indicative T_{50} and rectum normal tissue T_{50}. ***Conclusion:*** At present the cause of the temperature difference is not known. However, as the difference between tumor-contact/indicative and normal tissue is very small and considering also the inaccuracy in the tissue type assignment, it can be stated that this study does not provide sufficient evidence to conclude that the statistical difference has clinical relevance. Therefore, it was concluded that at this time there is no need to differentiate between normal and tumor tissue in intraluminal thermometry.

5.1 Introduction

To facilitate analysis of hyperthermia treatment data produced by the previous generations of the BSD-2000/3D system, which operate on a PDOS machine, a program called RHyThM (Rotterdam Hyperthermia Thermal Modulator) has been created. The details of RHyThM have been described extensively elsewhere (Fatehi *et al.*, 2006a). One of the features of RHyThM is that it

connects the tissue type assignment with the thermal data. Tissue type assignment, *i.e.* discriminating tumor from normal tissue, is a normal procedure for interstitial thermometry. In our department, thermometry in patients with a tumor in the lesser pelvis is mostly limited to intraluminal sites, as indicated by the ESHO guidelines (Lagendijk *et al.*, 1998).

Commonly, the measured temperatures during deep hyperthermia are distinguished into tumor and normal tissue data, without asking the critical question whether differentiation between normal and tumor tissue for intraluminal thermometry during loco-regional deep hyperthermia is necessary. The results of our previous thermal data analysis (Fatehi *et al.*, 2006b) on 104 hyperthermia treatments (of 22 patients), do not support the need to differentiate between a thermal dose parameter assigned as normal tissue, tumor-contact, tumor-indicative, or all lumen. Thus, the hypothesis was that tissue type assignment does not provide more relevant information on intraluminal temperature distribution. To answer the mentioned question we studied the results of thermal data analysis of 100 treatments of patients with advanced cervical cancer, selected specifically to have constant thermal mapping temperature data, *i.e.* no displacement of thermometry catheters along the intraluminal track during the hyperthermia treatment session.

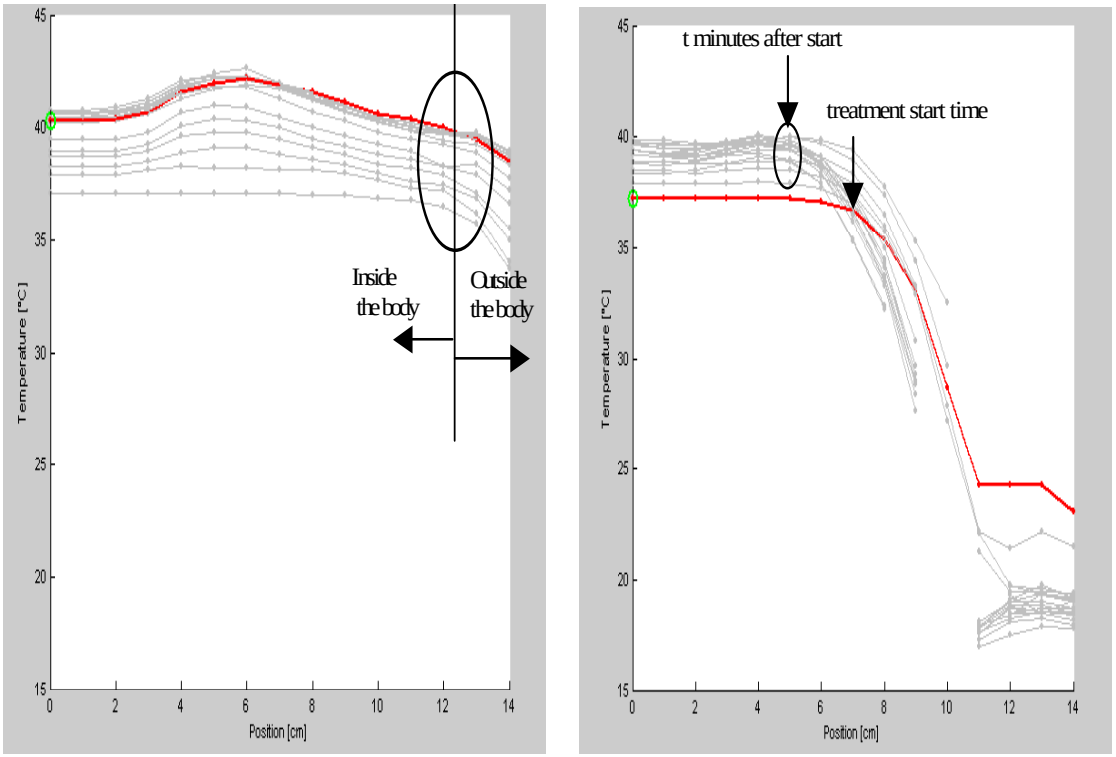
5.2 Patients and methods

5.2.1 Patients

This study planned to use a dataset including 100 hyperthermia treatments. The database consists of hyperthermia treatment data of all 320 patients with uterine cervical cancer, who have been treated from October 1997 to September 2003. Patients were treated by hyperthermia in addition to radiotherapy or radiotherapy plus chemotherapy. Seventy-five patients were selected by random number drawing and the obtained temperature mapping data assessed on stability of thermal probe position (see below). Treatment selection was completed after 43 patients, when the required dataset of 100 treatments was available.

5.2.2 Data processing

Firstly, treatments with duration of 90 min were selected. Secondly, PDOS formatted hyperthermia treatment data, generated by the BSD-2000/3D, was transferred to MSDOS. Thirdly, the MSDOS hyperthermia treatment data was



(a) **(b)**

Figure 5.1: Two typical thermal maps provided by RHyThM: (a) A thermal map, as accepted for the study, with no shift in transition between in- and outside the body during whole of the treatment session. (b) A thermal map with shift in transition between in- and outside the body, not accepted. The graph shows that the start position of the steep temperature decay moves over time towards the left.

imported in the RHyThM program and the first 100 eligible treatments were included. The only selection criterion was: no displacement of thermometry catheter along the insertion length during 90 min of the treatment (see figure 5.1). In the next step we identified a step change in the profile of the first temperature map to verify the insertion length of the thermometry catheter and location of the transition between the in- and outside of the body, as reported by the hyperthermia technician. If necessary the insertion length was adapted to match with the steep temperature gradient. The measurement points that were affected by the cooling water bolus were considered outside the body. Finally, for each treatment the tissue type was defined based on information from a CT scan in radiotherapy position.

5.2.3 Tissue type assignment

The tissue type assignment discriminates between normal tissue and tumor-contact or tumor-indicative. Tumor-contact is defined as close contact of the closed-tip thermometry catheter with the tumor; tumor-indicative is defined as

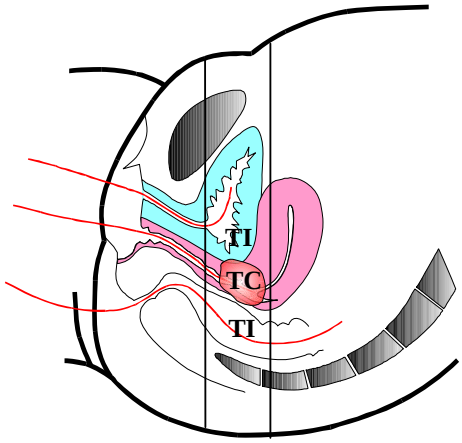


Figure 5.2: Intraluminal temperature measurement. TC (tumor-contact) is defined as close contact of the thermometry catheter with tumor; TI (tumor-indicative) is defined as the position of the thermometry catheter ventral or dorsal of the tumor in the same transverse plane as the tumor but not in contact. Figure copied from Wielheesen *et al*. (2005), with permission.

the position of the closed-tip thermometry catheter in the same transverse plane as the tumor, but not in contact (see figure 5.2) (Wielheesen *et al.*, 2005). The procedure of tissue type assignment is as follows: 1) Determination of the tumor location in cranio-caudal direction in relation to bladder neck, vaginal introitus, or anus by means of CT scan by the hyperthermia physician. 2) Measurement of catheter insertion length performed by the hyperthermia technician. 3) Verification of the insertion length by the site of step decrease in temperature, indicating the site when the catheter leaves the body.

5.2.4 Radiotherapy, chemotherapy, and hyperthermia

The patients received external beam radiotherapy to the whole pelvis (46-50.4 Gy, five fractions of 1.8-2 Gy per week) and additional brachytherapy (17 Gy, two fractions of 8.5 Gy per week). For those patients who received chemotherapy, it consisted of four-to-five courses of weekly cisplatin (40 mgm^{-2} i.v.) with standard hydration and anti-emetic pre-medication. Regional whole pelvis hyperthermia was delivered once weekly, up to five sessions, in the period of radiotherapy. Hyperthermia was started 1 to maximally 6 hrs after the radiotherapy. Hyperthermia was performed using different configurations of the BSD-2000 annular phased array system with the Quad amplifier connected to the Sigma-60 applicator and the BSD-2000-3D system using the 12-channel Dodek solid-state amplifier connected to the Sigma-60 or the Sigma-Eye

applicator (BSD Medical Corporation, Salt Lake City, Utah, USA) (Turner *et al.*, 1989). Hyperthermia was carried out by the institutional protocol of the Daniel den Hoed Cancer Center-Erasmus MC, in Rotterdam as follows.

The initial RF-power was 400 W. RF-power output to the applicator was increased until the patient's tolerance threshold was reached. SAR (specific absorption rate)- steering was applied by changing phase and amplitude settings with the aim to achieve a more homogenous temperature distribution, to reduce power-limiting hot-spots (*i.e.* normal tissue temperature >43 °C or pain complaints of the patient) and to maintain or increase the temperature in the target volume. The temperature of the applicator's water bolus was maintained at 20 °C. The increase in systemic temperature was limited by cooling measures, *i.e.* undressing, fan and air-conditioning, wet towels, ice packs, and cooling bolus placed in the neck.

5.2.5 Thermometry

Thermometry was performed using thermistors with high impedance leads (radio-frequency-inert Bowman probes) (Bowman 1976) to assess real time temperature reading. Prior to the treatment session, closed-tip thermometry catheters (William Cook Europe, P5.0-CE- 50-SFT-NS-0, Denmark) were placed in the urinary bladder, rectum, vagina lumen, and at the perineal skin. After catheter placement, the insertion length of the thermometry catheter was measured manually using a standard caliper by the hyperthermia technician and the intraluminal depth was documented. Temperature mapping was performed at 5-min intervals along the length of the thermometry catheter in 1 cm increments with a maximum mapping length of 14 cm. Accuracy of the temperature measurement was ± 0.2 °C with a precision of ± 0.1 °C. Systemic (oral) temperature was measured with regular intervals, *i.e.* just before start of treatment, at 15, 30, 60 min, and just before the end of the treatment session.

5.2.6 Statistical analysis

The statistical analysis is based on the temperature readouts, as provided in the ASCII files by RHyThM. The analysis compared the temperature of the tumor-indicative, in the bladder and rectum, or tumor-contact in the vagina lumen with normal tissue temperature of respective lumen. Descriptive and inferential statistical techniques were used in the comparison. The descriptive analysis was comprised of visualization of the data and calculation of summary statistics

(mean, minimum, median, *etc*., see below) of the temperature distribution, *i.e.* normal tissue, tumor-contact and/or tumor-indicative, overall, and separately by lumen.

The following thermal dose parameters were calculated: T_{max}, which is determined between start and end of the treatment, average of temperature (T_{mean}), T_{20}, T_{50}, and T_{90}*, which are calculated between 30 min after treatment start time and end of the treatment (*: T_X means the temperature which is exceeded by X% of all temperature readings). The Mann-Whitney test was used for inferences on the difference in only the median temperature (T_{50}) between the tumor-contact or tumor-indicative and normal tissue. Potential errors of tissue type assignment, which was performed manually, might affect the results. In order to investigate the sensitivity of 'misassignment' the tumor area was reassigned, *i.e.* the tumor-contact/indicative area was artificially increased or decreased by one-to-two mapping positions. For reasons of non-representativeness all aforementioned descriptive and inferential analyses were repeated without the outer one and two mapping positions of each thermometry probe. STATA program (version 8.2) was used for the statistical analysis.

5.3 Results

For the 100 selected treatments (one-to-five treatments per patient, median 2) extracted from 43 patients' treatment data, thermal mapping data was available for bladder lumen (97 treatments, 40 patients), vagina lumen (98 treatments, 41 patients), and for rectum lumen (99 treatments, 42 patients).

In the vagina lumen tumor-contact was indicated between positions 0-6 cm in 89% of the cases with a range of 0-11 cm. Position 0 cm represents the deepest point in the lumen. The average tumor-contact position in the vagina lumen was from position 0-4.1, SD 2 cm, with a minimum of position 0-1 cm and a maximum 0-11 cm. The number of temperature measurements in the vagina varied from 1-11. The average catheter insertion length in the vagina lumen was 8.8±1.6 cm, with a range of 6-14 cm. The average vagina lumen T_{50} for all treatments was 39.9±0.9 °C. Figure 5.3 shows a profile of the average vagina lumen T_{50} for all treatments along the thermometry catheter probe in this lumen.

Table 5.1 shows an overview of average temperature indices, *i.e.* T_{mean}, T_{20}, T_{50}, T_{90}, and maximum of T_{max} ($T_{max\ max}$) in overall, in the different tissue types, and in different lumina. Table 5.2 shows the average of the same

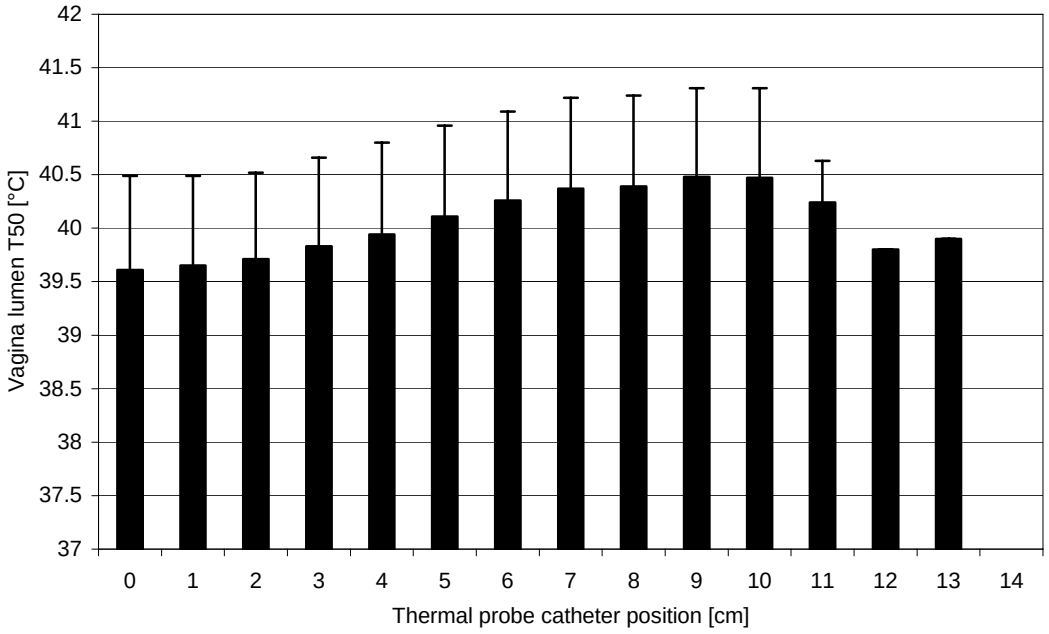


Figure 5.3: Average vagina lumen T_{50} value for all treatments *vs*. thermal probe catheter position. Position 0 cm represents the deepest point in the lumen.

temperature indices for normal tissue and tumor-contact or tumor-indicative in each lumen, *i.e.* bladder, vagina, and rectum. The average temperature parameters of tumor-contact/indicative and normal tissue show small differences. The vagina temperature indices are slightly lower than those of bladder and rectum. The differences between tables 5.1 and 5.2, for the same temperature indices per tissue type, are due to a different analysis. Each result per tissue type in table 5.1 is the average of temperature indices for that tissue,

Table 5.1: Average temperature values for T_{mean}, T_{20}, T_{50}, T_{90}, and $T_{max\ max}$ (maximum of T_{max}) as obtained in the study. Numbers in parentheses (in °C) show 1 SD.

Temperature index		$T_{max\ max}$	T_{mean}	T_{20}	T_{50}	T_{90}
Overall		43.5(1.2)	40.4(0.9)	41.2(0.9)	40.5(0.9)	39.3(0.9)
Per tissue type	Normal tissue	43.3(1.2)	40.4(0.9)	41.2(0.9)	40.5(0.9)	39.3(0.9)
	Tumor-indicative	43.2(1.2)	40.7(0.8)	41.5(0.8)	40.8(0.8)	39.6(0.8)
	Tumor-contact	42.6(1.1)	39.8(0.9)	40.7(0.9)	39.7(0.9)	38.5(0.9)
Per lumen	Bladder (n=97)*	43.5(1.2)	40.8(0.9)	41.6(0.9)	40.9(0.9)	39.6(0.9)
	Vagina (n=98)*	43.2(1.1)	40.0(0.9)	40.8(0.9)	39.9(0.9)	38.7(0.9)
	Rectum (n=99)*	43.2(1.2)	40.6(0.8)	41.3(0.8)	40.7(0.8)	39.5(0.8)

(n)*: Number of lumens with available intraluminal mapping data.

Table 5.2: Average temperature values for T_{mean}, T_{20}, T_{50}, T_{90}, and $T_{max\ max}$ (maximum of T_{max}) in different lumina. Numbers in parentheses (in °C) show 1 SD.

Temperature index		$T_{max\ max}$	T_{mean}	T_{20}	T_{50}	T_{90}
Bladder	Normal tissue	43.5(1.2)	40.7(0.9)	41.5(0.9)	40.8(0.9)*	39.6(0.9)
	Tumor-indicative	43.1(1.3)	40.8(0.9)	41.6(0.9)	40.9(0.9)*	39.6(0.9)
Vagina	Normal tissue	43.2(1.1)	40.1(0.9)	40.9(0.9)	40.1(0.9)*	38.9(0.9)
	Tumor-contact	42.6(1.1)	39.8(0.9)	40.7(0.9)	39.7(0.9)*	38.5(0.9)
Rectum	Normal tissue	43.2(1.2)	40.5(0.8)	41.3(0.8)	40.7(0.8)	39.4(0.8)
	Tumor-indicative	43.2(1.2)	40.6(0.8)	41.3(0.8)	40.6(0.8)	39.5(0.8)

*: Statistically significant difference. Other temperature indices were not tested.

i.e. normal tissue of three lumina, tumor-indicative of two lumina, and tumor-contact of one lumen. Similarly, each result per lumen in table 5.1 is the average of two temperature indices for that lumen, *i.e.* normal tissue and tumor-contact or tumor-indicative. Meanwhile, the temperature index in table 5.2 always corresponds to a single lumen. Only the difference in tumor-contact T_{50} or tumor-indicative T_{50} *vs.* normal tissue T_{50} was tested statistically on a lumen-specific base, *i.e.* for bladder, vagina, and rectum, separately. Significant differences ($p=0.0001$) were found between bladder tumor-indicative T_{50} and bladder normal tissue T_{50}, and also between vagina tumor-contact T_{50} and vagina normal tissue T_{50}. Sensitivity of the differences was evaluated by varying the outer one and two assigned mapping positions of each thermometry probe location. This did not affect the statistical significance of the differences. No difference was found between rectum tumor-indicative T_{50} and rectum normal tissue T_{50}.

The relationship between normal tissue T_{50} and tumor-contact T_{50} or tumor-indicative T_{50} was assessed in the bladder, vagina, and rectum. The results for vagina and bladder are shown in figure 5.4. As can be seen in figure 5.4a, fair-to-good correlation exists between vagina tumor-contact T_{50} and vagina normal tissue T_{50}. Likewise, fair-to-good correlation exists between bladder tumor-indicative T_{50} and bladder normal tissue T_{50} (figure 5.4b). Similar results (not shown) are obtained for rectum temperatures. Furthermore, the relationship between T_{50} and T_{20}, as well as T_{50} and T_{90} was assessed for tumor-contact or tumor-indicative in bladder, vagina, and rectum. The result for vagina and bladder are demonstrated in figure 5.5. As figure 5.5a demonstrates, strong correlation exists between vagina tumor-contact T_{50} and vagina tumor-

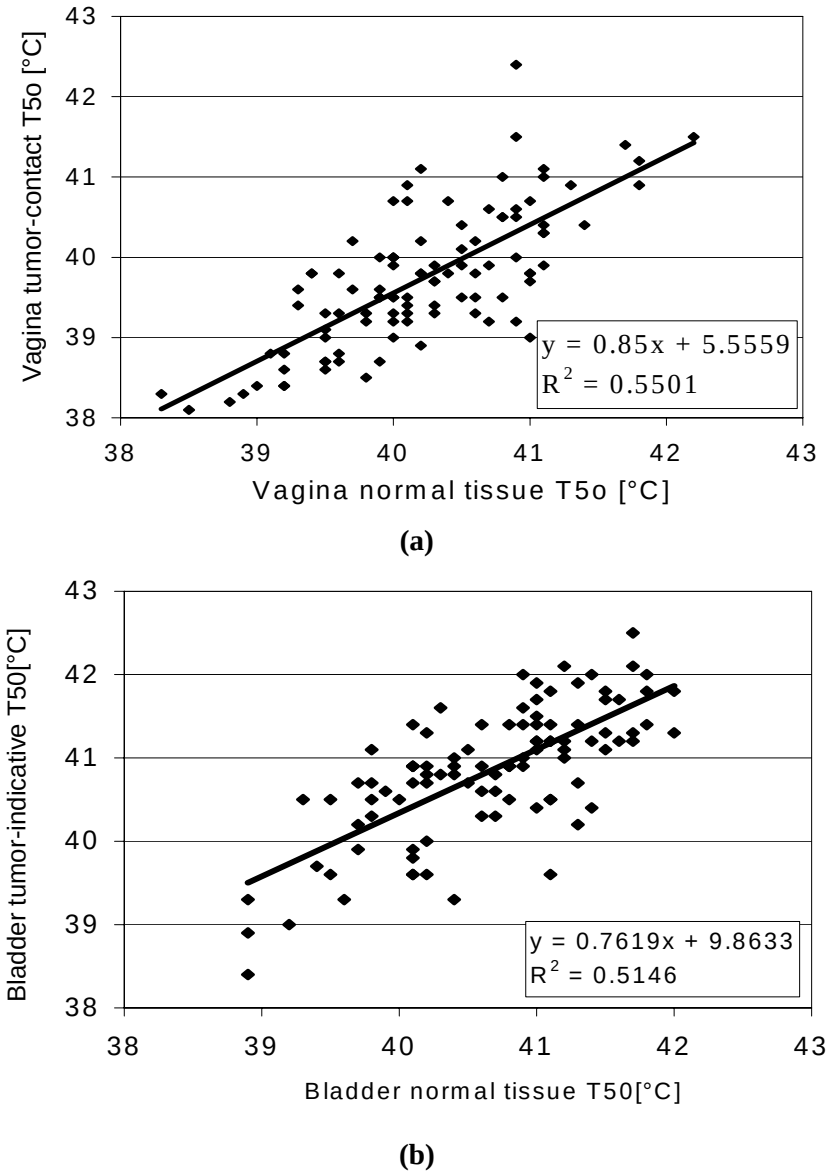
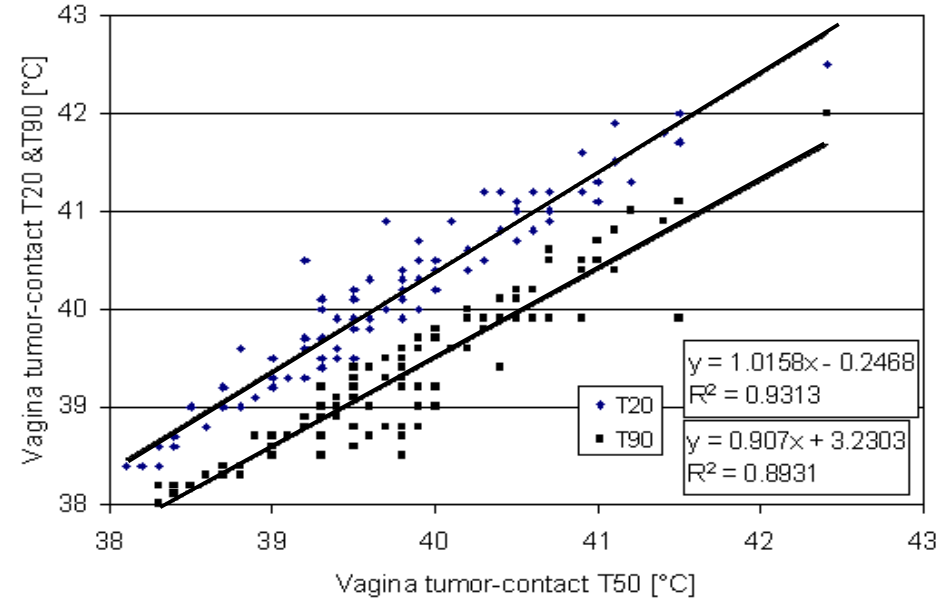


Figure 5.4: (a) Vagina normal tissue T_{50} *vs*. vagina tumor-contact T_{50}, (b) bladder normal tissue T_{50} *vs*. bladder tumor-indicative T_{50}.

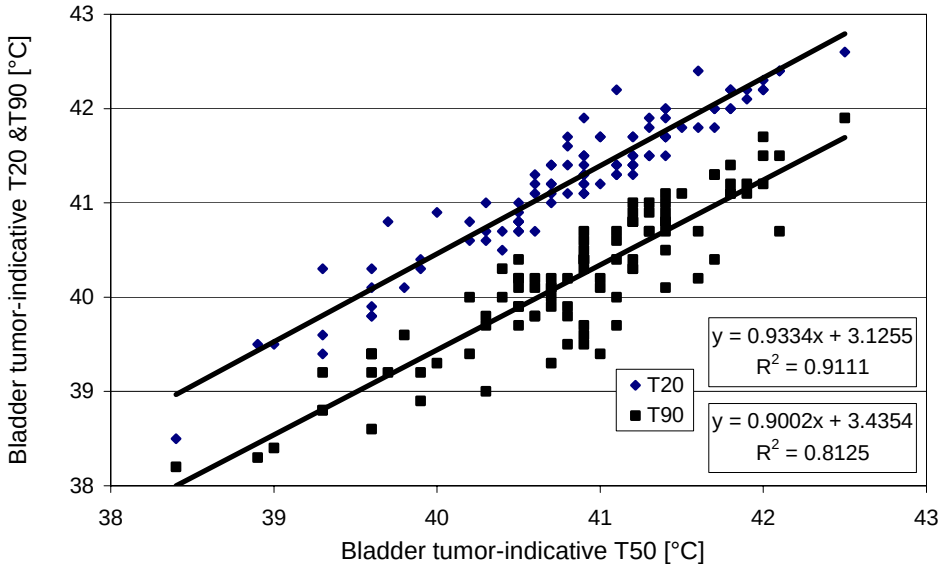
contact T_{20} or T_{90}. Analogous, strong correlation exists between bladder tumor-indicative T_{50} and bladder tumor-indicative T_{20} and/or T_{90} (figure 5.5b). Similar results (not shown) are obtained for rectum temperatures.

5.4 Discussion

During deep hyperthermia treatment, measurement of the actual temperature distribution in the tumor or adjacent tissue is important for the clinical evaluation of the treatment quality (Feldman *et al.*, 1993). Several clinical studies have shown a correlation between thermal dose (expressed as CEM43°CT_{90}, T_{max}, *etc.*) and treatment outcome (Shimm *et al.*, 1990; Sneed *et*



(a)



(b)

Figure 5.5: (a) Vagina tumor-contact T_{50} *vs.* vagina tumor-contact T_{20} and T_{90}, (b) bladder tumor-indicative T_{50} *vs.* bladder tumor-indicative T_{20} and T_{90}.

al., 1992; Oleson *et al.*, 1993; Kaap and Cox, 1995; Sherar *et al.*, 1997; Lee *et al.*, 1998; Wust *et al.*, 1998b). In these usually retrospective studies, however, thermal dosimetry is in general characterized by a low number of temperature probes (Sneed *et al.*, 1998b; Dewhirst and Sneed, 2003; van der Zee *et al.*, 2005). In interstitial thermometry, discrimination between tumor and normal tissue is without discussion. When a patient has a tumor located in the lesser pelvis, in our department, thermometry is usually restricted to the intraluminal tracks, which according to ESHO guidelines (Lagendijk *et al.*, 1998) is an

accepted procedure during hyperthermia treatment of cervical carcinoma. The question is whether differentiation between normal and tumor tissue for intraluminal thermometry during deep regional hyperthermia is needed? The present study has investigated this question. The study shows (table 5.2) that there is no statistical difference between rectum normal tissue T_{50} and rectum tumor-indicative T_{50}. A statistical difference ($p=0.0001$) exists between T_{50} of vagina normal tissue, average 40.1±0.9 °C, and T_{50} of vagina tumor-contact, average 39.7±0.9 °C, and also between T_{50} of bladder normal tissue, average 40.8±0.9 °C, and T_{50} of bladder tumor-indicative, average 40.9±0.9 °C. The differences between these temperature indices are not, however, quantitatively similar (*i.e.* 0.4 *vs.* 0.1 °C, respectively). On the other hand, the difference (statistically significant) between bladder normal tissue T_{50}, average 40.8±0.9 °C, and bladder tumor-indicative T_{50}, average 40.9±0.9 °C, (*i.e.* 0.1 °C), is quantitatively equal with the difference between rectum normal tissue T_{50}, average 40.7±0.8 °C, and rectum tumor-indicative T_{50}, average 40.6±0.8 °C, where the statistical analysis does not show a significant difference.

To explain these observations, it is pointed out that in a thermal data analysis with a very large amount of data such as the huge ASCII file data-source of the present study, a very small difference can be easily detected in a statistical analysis. During the last 60 min of each hyperthermia treatment the number of registered temperature points in each lumen is in the range of 50-140 points (9-12 thermal maps and 6-12 points per thermal map). Thus, as estimation, the dataset of 100 treatments roughly includes 7000-14000 temperature points per lumen. Therefore, the small difference between average normal tissue T_{50} and average tumor-indicative T_{50} in bladder, *i.e.* 0.1 °C, is statistically significant ($p=0.0001$).

We must consider, however, even if the difference is statistically significant, it may not be relevant. At best conditions in deep hyperthermia treatment the temperature is increased from 37 to 43 °C, *i.e.* a temperature difference of 6 °C. Although a lower temperature increase, such as the 3 °C in this study, is more realistic. Assuming that a 10% dose difference can be considered relevant, this would indicate that only a temperature difference of more than 0.3 °C between temperature indices is relevant for our hyperthermia treatment quality analysis. Hence, in authors' opinion, the 0.1 °C difference between T_{50} of bladder normal tissue and bladder tumor-indicative is not a

relevant difference, whereas the difference between vagina normal tissue T_{50} and vagina tumor-contact T_{50} (0.4 °C) is 'borderline' relevant.

Additionally, one should consider errors in the tissue type assignment. Sources of errors in thermometry probe localization are as follows. 1) In this group of patients the CT scan was made in radiotherapy position, which differs from hyperthermia position. 2) The inaccuracy in the exact position of the reference points (bladder neck, vagina introitus, and anus) as defined by CT and observed in the patient. 3) Measurement of catheter length inside the body. The errors due to manual measurement of thermal probe catheter length were investigated and a total inaccuracy of ±1 cm was found, where the systematic error was 0.35 cm and the random error was 0.65 cm (data not published). 4) The exact placement of the catheter within the bladder (pulled back until the balloon was on the bladder base), then pushed 'a little bit' inside, *e.g.* 2 mm to 1.5 cm. 5) Patient movement causing thermal catheter displacement. 6) Slipping of the thermal mapping system, *e.g.* curling, sticking and slip of the catheter, or disconnection of the catheter to the thermal mapper tube decreases the accuracy of tissue type assignment. Obviously, the cumulative effect of these errors may be large.

When one questions whether correction in changes of the insertion length is a necessity, the first issue is to decide about tissue type assignment at the border and at the exit of the catheter from the lumen. Moreover, the validity of the temperature points in regard to normal or enhanced cooling at the perineum should be considered. This problem was solved by correcting the tissue definition if very low temperatures were shown at the first thermal map. Furthermore, if necessary the location of the transition was adapted to match better with the steep temperature gradient or to correct for small movement of thermometry catheter during the whole treatment session. The statistical analysis in this study does not show any influence of varying the outer 1 or 2 cm of mapping position on the results.

Since the current method for tissue type assignment is based on the tissue map trajectories, which were deduced from the pre-treatment radiotherapy position CT scan information, it is questionable whether one can rely on this kind of information for tissue type assignment. The Rotterdam Hyperthermia Group is currently (2006) performing a new study in which the hyperthermia record data is collected from the patients who have CT scan information in hyperthermia position as well as radiotherapy position. Further,

one will continue the analysis of thermometry data and investigate the profile of the vaginal temperature in patients who have only tumor or normal tissue in the vagina lumen. The results of these studies will support the arriving at standards for thermal dosimetry and facilitate comparison of the results of the clinical studies.

5.5 Conclusion

In this thermal data analysis study no statistical difference was found between the T_{50} measured in normal tissue and tumor-indicative in the rectum. Although the differences that were found between T_{50} of normal tissue and tumor-contact in the vagina, and also between T_{50} of normal tissue and tumor-indicative in the bladder are statistically significant; it must be considered that in a statistical analysis of thermal data with a large amount of data a very small difference (*e.g.* 0.1 °C) can be detected (statistically). At this moment one doesn't know whether the temperature differences that were found in this study are real differences or are due to the error associated with the method of tissue type assignment. As the differences are non-relevant or 'borderline' relevant and also since the exact location of each temperature point is not sure, it can be concluded that there is not enough evidence to state that these statistical differences are clinically relevant. Consequently, the conclusion is that at present discrimination between normal and tumor-contact/indicative tissue in intraluminal thermometry does not provide more accurate and relevant clinical information, so there is no need to do it.

Acknowledgement

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Chapter 6

RF-power and temperature data analysis of 444 patients with primary cervical cancer: Deep hyperthermia using the Sigma-60 applicator is reproducible

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Abstract

***Background and purpose*:** Treatment reproducibility is important to guarantee reproducible treatment-outcome, a low complication rate and efficient treatment procedures. This study evaluated performance of loco-regional deep hyperthermia with four BSD-2000 configurations during 1990-2005 using the direct available parameters, *i.e.* power and temperature. ***Patients and methods*:** Primary cervical cancer patients (n=444) were all treated within the Sigma-60. Patients were grouped in three weight-groups: w<61 kg, 61≤ w≤ 70 kg, and w>70 kg. Different power and temperature indices were extensively analyzed per BSD configuration, per weight-group, and over the time-period. ***Results*:** No substantial variations were found for power/temperature indices over the four BSD configurations or for the temperature doses in similar weight-groups. The *'bare'* power indices were increased with weight; however, the derivative power-related (W/kg, W/cm^2) and temperature indices decreased with weight. Large variations were found in the power-related parameters during 1991-1996 (1st time-period), whereas they were much smaller during 1997-2005 (2nd time-period). The most relevant change noted was the adaptation of the treatment strategy with respect to power modulation. The average frequency of switched-off was 3.4 and 8.9 for the 1st and 2nd time-period, respectively, while the average duration of each switched-off time was 78.2 *vs.* 38.3 s. The yearly average of vagina T_{50} was in the range of 39.3-40.2 °C (1st time-period) and 40.0-40.5 °C (2nd time-period). In 40% of the patients, positive correlation found between normalized net integrated power per pelvic area and vagina T_{50}. ***Conclusion*:** Good reproducible heating is achieved with the BSD-2000 Sigma-60 irrespective of the regular technological upgrades of the system and variation of trained staff-members.

6.1 Introduction:

Hyperthermia is considered a valuable anti-cancer treatment modality in several Western countries. A review by Wust *et al*. (2002) on state of the art hyperthermia identifies up to March 2001 eighteen comparative, prospective phase III trials on different hyperthermia modalities. Twelve of these eighteen trials demonstrated a significant positive effect on treatment outcome of which seven showed benefit in survival. Since then, three more positive phase III trials (Colombo *et al*., 2003; Verwaal *et al*., 2003; Joens *et al*., 2005) demonstrating the efficacy of adding hyperthermia to conventional treatment have been published. For advanced cervical cancer adding hyperthermia to radiotherapy doubles the 3 years survival rate (27 *vs*. 51%) (van der Zee *et al*., 2000; van der Zee and van Rhoon, 2006). For recurrent breast cancer in earlier irradiated areas the local control rate for radiotherapy + hyperthermia is doubled or tripled compared to radiotherapy alone (24 *vs*. 68% and 39 *vs*. 79%) (Vernon *et al*., 1996; Joens *et al*., 2005). The doubling of local control or

survival rate following the addition of hyperthermia to conventional therapies without increased toxicity is, in historical perspective, an extraordinary and unsurpassed finding.

Generally, hyperthermia is applied by electromagnetic radiation and requires the use of complex high technological equipment (Stauffer, 2005). Given the continuous technological evolution of the available hyperthermia devices and growing personal experience, extended data analyses over a long period provide an excellent opportunity to study our ability to induce a reproducible temperature increase in the target region. Of course, reproducible heating is a major factor for the general acceptance of hyperthermia as a common treatment modality. Additionally, knowledge about the level of reproducibility is important for the design of treatment protocols, quality assurance procedures, and to make valid assumptions on prognostic factors. No doubt reproducibility will be reflected in ease of application, time efficiency, safety for patient, *etc.* Finally, the knowledge obtained by such studies can be fruitfully used to design education and training programs for hyperthermia staff-members.

In the last three decades several studies were performed on hyperthermia device evaluation. For instance, Egawa *et al*. (1988) have evaluated a radiofrequency (RF) and a capacitive heating apparatus in the clinical trials of combined radiotherapy and hyperthermia. Van Rhoon *et al*. (1992) also have performed an investigation of RF capacitive heating device in which they have focused mainly on thermometry. These two independent studies covered only a low number of patients (n=45 and 11, respectively). Sapozink *et al*. (1984) have analyzed the efficacy of the BSD-2000 with the annular array applicator in a two-year time-period for 46 patients with abdominal and pelvic tumor. Furthermore, in two separate studies, Sapozink *et al*. (1988a; 1988b) have also evaluated different heating devices for a longer time-period (7 years) and larger patient population (n=137 and 573, respectively). In these studies they have investigated the effect of different hyperthermia equipment on the quality of treatment, however, they analyzed the data from different tumor sites.

Since 1990 the Hyperthermia Unit of Erasmus Medical Center, uses the BSD-2000 system for deep hyperthermia treatment (Turner and Schaefermeyer, 1989; Turner *et al*., 1989). Over the period of 1990 to present (2007) the BSD Medical Corporation (Salt Lake City, Utah, USA) has upgraded three times the Rotterdam BSD-2000 hyperthermia system to follow the latest improvements.

In practice this implies that in this time-period we have used the BSD-2000 system with four different power drive systems to apply deep hyperthermia to tumors in the pelvic region. For years, the hyperthermia treatment data recorded by the PDOS-based computers of the BSD-2000 system were hard to access. Subsequently, research concerning power and temperature was postponed. The development of RHyThM (Rotterdam Hyperthermia Thermal Modulator) (Fatehi *et al*., 2006a) offered us the unique ability to perform extensive analysis of the power and temperature behavior of the various BSD-2000 hyperthermia systems. To our knowledge the present study is the first attempt, in which one used power and temperature data in patients with primary cervical cancer to analyze the long duration (15 years) performance of regional deep heating with the BSD-2000 system. The goal of this study was to evaluate the global behavior of the performance of deep hyperthermia using the BSD-2000 with the Sigma-60 applicator driven with one of four different power drive systems over the years from 1990 to 2005. As temperature is a primary indicator of treatment quality, immediately available at the end of the treatment session for quality analysis, our intention in this study was to find a power-related parameter that correlates with average temperature in the clinical situation. Our investigations regarding a relationship between thermal dose parameters and treatment outcome, a long-term variable, will be reported in a separate paper.

6.2 Patients and methods

6.2.1 Patients

All patients with primary cervical carcinoma who have been treated with hyperthermia, in addition to radiotherapy or radiotherapy plus chemotherapy, at the Hyperthermia Unit of Erasmus MC-Daniel den Hoed Cancer Center from January 1990 to December 2005 were eligible for this retrospective study. Of this group, 444 patients who have been treated with the BSD-2000 deep hyperthermia system and the Sigma-60 applicator and with accessible treatment's data were selected.

6.2.2 Radiotherapy and chemotherapy

Radiotherapy was performed at different institutes in the Netherlands. The patients received radiotherapy to the whole pelvis, conformal to the standard in the Netherlands, mostly 23-28 daily fractions of 1.8-2 Gy in 5 weeks in

combination with a brachytherapy boost, if feasible, to a total dose of 17 Gy high-dose rate or 20-30 Gy low-dose-rate. For patients with three modality treatments, in whom chemotherapy was applied in combination with radiotherapy and hyperthermia, chemotherapy consisted of at least four and maximum five courses of weekly cisplatin with standard hydration and anti-emetic pre-medication. For more details of the treatments see van der Zee *et al*. (2000), and Westermann *et al*. (2005).

6.2.3 Hyperthermia

Hyperthermia was performed using one of the four configurations of the BSD-2000 system, *i.e.* the BSD-2000 with Quad amplifier, the BSD-2000-3D with Quad amplifier, the BSD-2000-3D using a Quad amplifier with 3D drawer which divides the four channels into 12 channels, and the BSD-2000-3D with Dodek solid state amplifier. All configurations were connected to one of the two versions of the Sigma-60 applicator. The 2nd version, with the same design, was used from 1998 onward.

One to 5 (mean 4.5) loco-regional deep hyperthermia treatments were delivered to the whole pelvis volume once weekly during the period of radiotherapy. Hyperthermia was carried out by the institutional protocol of the department as follows. The frequencies used were in the range of 70-120 MHz. The initial RF-power was 400 W. Every 5 min the RF-power output to the applicator was increased, in steps of 100W, (up to 1600 W); until the patient's tolerance threshold was reached. Hereafter, we applied SAR (specific absorption rate)- steering by changing phase and amplitude settings with the aim to reduce power-limiting hot-spots (*i.e.* normal tissue temperature >43 °C or pain complaints of the patient) and to achieve intraluminal temperatures of 40-43 °C as homogeneous as possible. This protocol has changed over the years, *i.e.* in the early years we reduced power after the patient complained of a hot-spot, nowadays we react with a short power-off period followed by phase/amplitude steering.

Patients were carefully instructed to mention any unpleasant sensation that might be the result of a hot-spot, such as a burning sensation, a feeling of pressure, any pain, and bowel or bladder spasm. If the patient reported pain, which disappeared within one minute following power-decrease, it was considered to indicate a too high temperature, and then the treatment settings were adjusted to decrease power input at the specific location. Adjustments of

treatment settings could be as follows: adaptation of phase settings, amplitude, and frequency, or by placing additional water boluses. For deep pain complaints phase steering was preferred while for superficial pains amplitude steering was applied.

Deep hyperthermia treatment consisted of a heating phase of 30 min followed by 60 min therapeutic time. The temperature of the applicator's water bolus was maintained at 20 °C. Increase in systemic temperature was limited by cooling measures, *i.e.* undressing, air-conditioning, wet towels, ice packs, and cooling bolus placed in the neck. The bladder was kept empty with a Foley catheter.

6.2.4 Thermometry

For thermometry closed-tip catheters (William Cook Europe, P5.0-CE-50-SFT-NS-0, Denmark) were inserted intraluminally in the urinary bladder, rectum, and vagina lumen at the beginning of each treatment session. Thermistors with high impedance leads, *i.e.* the Bowman probes, as standard delivered by the BSD-2000 system were used to assess real time temperature reading (Bowman, 1976).

After catheter placement, the intraluminal depths were documented, *i.e.* using a standard caliper the hyperthermia technician measured the insertion length of the thermometry catheters manually. Temperature mapping was performed along the length of the thermometry catheter in 1 cm increments to a maximum mapping length of 14 cm. Thermal mapping started just before the hyperthermia treatment and was repeated hereafter at 5-min intervals. The accuracy of the temperature measurement was ± 0.2 °C with a precision of ± 0.1 °C.

The temperature data were measured intraluminally, in total conformity with the ESHO guidelines for deep hyperthermia (Lagendijk *et al*., 1998). The intraluminal temperatures were recorded as normal tissue, tumor-contact, tumor-indicative, and overall measurements. Tumor-contact means that the catheter at the site of measurement lies in contact with tumor. When the site of measurement is in the same transverse plane as tumor, but not in contact with the tumor, the temperature is called tumor-indicative (Wielheesen *et al*., 2005). The remaining measurements represent normal tissue. The overall intraluminal temperature includes all measurements within one catheter.

6.2.5 Data processing

The RHyThM software was used to access and analyze the hyperthermia data. An extensive description of this program and the methods of data analysis are included in two previous publications by Fatehi *et al*. (2006a; 2006b). The patients were grouped in three weight-groups, *i.e.* weight-group 1 ($w<61$ kg), weight-group 2 ($61\leq w\leq 70$ kg), and weight-group 3 ($w>70$ kg), such that each subgroup holds approximately one third of the treatments. Then the relationship between different power and temperature indices was computed irrespective and respective to the BSD-2000 configurations, weight-groups, and over the time-period.

6.2.6 Variables

The following variables were used for the analysis:

- patient's age (years),
- patient's weight (kg),
- pelvic area (cm^2), see equation 6.3,
- mean forward power (W),
- maximum forward power (W),
- mean net power (W), which is defined as mean forward power minus mean reflected power,
- mean net power per pelvic area (Wcm^{-2}),
- mean net power per weight (Wkg^{-1}),
- mean net integrated power or more specifically '*delivered energy'* (kJ), see equation 6.2,
- mean net integrated power per pelvic area ($kJcm^{-2}$),
- mean net integrated power per weight ($kJkg^{-1}$),
- frequency of RF-power switched-off,
- total switched-off time (s),
- average duration of each switched-off time (s),
- vagina T_{50}, which is T_{50} of overall intraluminal measurements within vagina lumen. T_X means the temperature that is exceeded by X percent of all temperature readings.
- all lumina T_{50}, which is defined as overall bladder, vagina, and rectum lumen T_{50},

- vagina T_{90}, which is T_{90} of overall intraluminal measurements within vagina lumen. The T_{90} is representative for minimum temperature.
- all lumina T_{90}, which is defined as overall bladder, vagina, and rectum lumen T_{90},
- CEM43°CT_{90} (cumulative equivalent minutes at 43°C based on T_{90} temperatures), which the formulation takes the following form:

$$\mathrm{CEM43^{\circ}C} = \mathrm{tR}^{(43 - \mathrm{T})} \tag{6.1}$$

where t is time of treatment (min), T is average temperature (°C) during desired interval of heating, and R is a constant. When the temperature is higher than 43 °C, R=0.5. When the temperature is lower than 43 °C, R=0.25.

6.2.7 Calculations and normalization of power and temperature

The following calculations were performed in order to find a positive correlation between normalized net integrated power and temperature. In the first step net integrated power (NIP) was calculated by:

$$\mathrm{NIP} = \sum_{i=0}^{n} (P_{fwd} - P_{rfl}) \cdot \Delta t \tag{6.2}$$

where P_{fwd} and P_{rfl} are forwarded and reflected power (W), respectively, n is number of measurements and Δt is time interval between two measurements (s). In the next step, the pelvic area (A) was computed by:

$$A = 0.25\pi.\mathrm{AP} \cdot \mathrm{Lat} \tag{6.3}$$

where AP is the anterior posterior and Lat is the transverse dimension of the pelvis (cm), measured at the CT scan slice at the centre of the tumor in cranio-caudal direction. The net integrated power per pelvic area for individual treatments (x) follows then through NIP/A_x ($\mathrm{kJcm^{-2}}$). In the next step, we computed the mean of net integrated power per pelvic area for all treatments per individual patient. Then, percentage of normalized (nrm) net integrated power per pelvic area [$_{\mathrm{nrm}}$(NIP/A)] for the individual treatment was calculated by:

$$_{\mathrm{nrm}}(\mathrm{NIP/A})_x = \frac{(\frac{\mathrm{NIP}}{A})_x}{\frac{\sum_{x=1}^{n} \frac{\mathrm{NIP}}{A}}{n}} \times 100 \tag{6.4}$$

where the net integrated power per treatment is normalized to the average net integrated power over the whole series of treatments (n) for a patient.

Furthermore, percentage of normalized vagina T_{50} for each individual treatment ($_{nrm}VagT_{50\,x}$) was calculated using the following formula:

$$_{nrm}VagT_{50\,x} = \frac{VagT_{50\,x}}{\frac{\sum_{x=1}^{n} VagT_{50}}{n}} \times 100 \qquad (6.5)$$

where the vagina T_{50} per treatment is normalized to the average vagina T_{50} over the whole series of treatments (n) for a patient.

Finally, the relationship between the percentages of normalized net integrated power per pelvic area and normalized vagina T_{50} was evaluated for individual patients, and the results were summarized per patient graphically. The curves, the trend lines, the slopes of the trend lines, and the correlation coefficients were computed. The curves with a slope of trend line ≥ 0.01 and the correlation coefficient ≥ 0.5 were considered positive correlation. Patients with less than 3 treatments were excluded from this part of analysis. Variations ≤ 2% in the power data were considered as noise.

6.2.8 Statistical analysis

The statistical analysis was based on the temperature-dose parameters, as provided in the ASCII files by RHyThM. Temperature measurements were available per patient, per treatment session, per probe, per mapping position, and per time point. A temperature below 37 ºC was considered indicative for the measuring point to be outside the lumen or to be the effect of local tissue cooling by one of the cold-water boli resulting in non-representative low temperatures. Therefore, all these points were excluded from the analyses. The time points were scaled with respect to the starting time of the treatment. While computing averages, all observations were weighted equally. The T_{50} and T_{90} were calculated per patient, per treatment, and per lumen. The CEM43°CT_{90} was calculated per patient and per treatment. The averages and standard deviations were computed for the thermal dose parameters of different lumina (bladder, vagina, rectum, and all lumina) and different tissue types (normal tissue, tumor-contact, tumor-indicative, and overall). One-way ANOVA was used to compare the average power or temperature in different BSD configurations or weight-groups. In case of a significant difference, we used Bonferroni as a Post Hoc test to address the individual difference. A linear reg-

Table 6.1: The number of primary cervical cancer patients/treatments as analyzed in this study, per weight-group and time-period, in which the Sigma-60 applicator and four configurations of the BSD-2000 system used by the Rotterdam Hyperthermia Group from 1991 to 2005.

BSD-2000 Configuration connected to the Sigma-60	time-period	weight-group *	nr. of patients	nr. of treatments
BSD-2000 with Quad amplifier	March 1991 - May 1998	W<61 kg	45	180
		61≤ W≤ 70 kg	25	105
		W>70 kg	35	146
			sum: 105	sum: 431
BSD-2000-3D with Quad amplifier	June 1998 - May 1999	W<61 kg	23	63
		61≤ W≤ 70 kg	6	14
		W>70 kg	10	28
			sum: 39	sum: 105
BSD-2000-3D with Quad amplifier and 3D drawer, which divides the four channels into 12 channels	June 1999 - July 2000	W<61 kg	20	78
		61≤ W≤ 70 kg	14	64
		W>70 kg	14	61
			sum: 48	sum: 203
BSD-2000-3D with Dodek solid-state amplifier	August 2000 - December 2005	W<61 kg	83	248
		61≤ W≤ 70 kg	84	351
		W>70 kg	85	334
			sum: 252	sum: 933
			total: 444	total: 1672

* Weight-groups are based on the 33 and 66 percentile of weight of all patients.

ression model was used to assess the effect of age, adjusted for weight, on the power and temperature indices. The p-values are two-sided at a significance level of α=0.05. SPSS program (version 12) was used for the statistical analysis.

6.3 Results

There were two types of limitations for the patient/treatment selection: a) It was not possible to transfer the hyperthermia PDOS data of 11 patients to MSDOS, and b) RHyThM failed to access the MSDOS data of 205 treatments. With these limitations and based on the selection criteria, in total 1672 hyperthermia treatments' data of 444 primary cervical cancer patients, treated from March 1991 to December 2005, were available for the analysis. The 1672 deep hyperthermia treatment sessions were delivered using four distinct power amplifiers of the BSD-2000 configurations all provided similar drive of the Sigma-60 applicator, *i.e.* 431 treatments by the first configuration, 105 treatments by the second, 203 treatments by the third, and 933 treatments by the fourth configuration (table 6.1).

The evaluations were done per BSD per weight-group, per BSD configuration, per weight-group, and over the time-period. Additionally, the evaluation on relations between normalized power and temperature is presented in the last section of the results. In the following text the *'bare'* power-indices refer to the mean forward power, maximum forward power, mean net power, and mean net integrated power. All reported numbers are per treatment session, unless otherwise mentioned.

6.3.1 Analysis per BSD per weight-group

In this part of the study we evaluated the RF-power and temperature data obtained by each configuration of the BSD-2000 for the three weight-groups. The average values of the patient's characteristics, power and temperature data are presented in table 6.2a-d.

- ***First BSD configuration***

The average of mean and maximum forward power increased from weight-group 1 to 3. The highest values for the derivative power related indices belonged to weight-group 2, with the lowest values for weight-group 3. Exception was the mean net integrated power for which the lowest value belonged to weight-group 1 (table 6.2a). A significant difference (p=0.000) was seen for the *'bare'* power indices in weight-group 1 *vs.* 2 and 3. Furthermore, a significant difference (p=0.000-0.003) was found for the mean net power per weight (or per pelvic area) in weight-group 3 *vs.* 1 and 2. The mean net integrated power per weight (or per pelvic area) in weight-group 2 was significantly different (p=0.000-0.005) from weight-groups 1 and 3.

The average frequency of switched-off was roughly equal for weight-groups 1 and 3, both higher than weight-group 2. The average of total switched-off time for weight-group 2 was lower than those for weight-groups 1 and 3, with the highest value for weight-group 1 (table 6.2a). The average of each switched-off duration time was decreased slightly from 86, 75, to 67 s for weight-group 1 to 3, respectively. However, none of the differences between the switched-off variables was statistically significant.

The averages of vagina lumen T_{50}, all lumina T_{50}, and CEM43°CT_{90} decreased slightly from weight-group 1 to 3. The averages of vagina T_{90} and all lumina T_{90} were equal for weight-groups 1 and 2, both slightly higher than weight weight-group 3 (table 6.2a). All temperature indices for weight-group 3

Table 6.2: Average values of patients' characteristics, RF-power, and temperature data per treatment. The results are summarized per weight-group for configurations 1 to 4 of the BSD-2000 hyperthermia system in table (a) to (d), respectively. Numbers in parentheses show 1 SD.
@WG: Weight-group; I: W<61 kg, II: 61≤ W≤ 70 kg, III: W>70 kg. * Statistical significant different from the other values in the same column.

BSD	WG @	nr. of pts.	nr. of trts.	age (yrs.)	weight (kg)	pelvic area (cm^2)	mean forward power (W)	max forward power (W)	mean net power (W)	mean net integrated power (kJ)	mean net power per weight (Wkg^{-1})	mean net power per pelvic area (Wcm^{-2})	mean net integrated power per weight ($kJkg^{-1}$)	mean net integrated power per pelvic area ($kJcm^{-2}$)	nr. of switched -off	total switched -off time (s)	temperature indices				CEM 43°C T_{90} (min)
																	T_{90} (°C)		T_{50} (°C)		
																	vagina lumen	all lumina	vagina lumen	all lumina	
I	I	45	180	55.8 (13.0)	52.8 (5.6)	532 (124)	549* (132)	676* (184)	510* (117)	2546* (805)	9.7 (2.1)	0.99 (0.3)	48.2* (14.5)	5.0 (1.8)	2.9 (3.0)	248 (263)	39.6 (0.9)	39.9 (0.7)	40.4 (0.9)	40.7 (0.7)	1.4 (1.4)
	II	25	105	54.2 (14.9)	66.9 (2.9)	640 (113)	722 (136)	903 (193)	648 (125)	3480 (746)	9.7 (1.8)	1.04 (0.3)	52.1* (11.1)	5.6* (1.5)	2.4 (2.3)	180 (190)	39.6 (0.9)	39.9 (0.7)	40.3 (0.9)	40.6 (0.6)	1.4 (1.4)
	III	35	146	56.8 (13.8)	79.5 (8.0)	733 (120)	734 (139)	912 (192)	647 (115)	3420 (687)	8.2* (1.5)	0.90* (0.2)	43.2 (8.7)	4.8 (1.1)	3.0 (2.6)	199 (229)	39.3* (0.8)	39.7* (0.6)	40.0* (0.9)	40.4* (0.7)	0.9* (1.0)
(a)																					
II	I	23	63	58.5 (12.1)	55.2 (4.9)	528 (57)	614* (108)	767* (118)	511* (105)	2675* (591)	9.3 (2.1)	0.98 (0.2)	48.8 (12.1)	5.1 (1.4)	5.1 (3.0)	290 (278)	39.5 (0.9)	39.8 (0.7)	40.1 (0.8)	40.5 (0.7)	1.2 (1.4)
	II	6	14	51.8 (8.6)	67.9 (2.6)	631 (43)	781 (191)	962 (249)	659 (172)	3541 (1192)	9.7 (2.3)	1.04 (0.3)	51.6 (16.6)	5.6 (1.8)	3.6 (2.7)	152 (196)	39.5 (0.7)	40.0 (0.7)	40.0 (0.8)	40.5 (0.8)	1.1 (1.0)
	III	10	28	62.2 (12.2)	79.9 (13.3)	749 (155)	840 (131)	1048 (166)	691 (126)	3464 (937)	8.7 (1.4)	0.95 (0.2)	43.7 (10.9)	4.7 (1.4)	4.9 (2.8)	233 (247)	39.3 (0.7)	39.6 (0.6)	40.0 (0.8)	40.3 (0.7)	0.8 (0.7)
(b)																					
III	I	20	78	52.1 (15.7)	55.0 (3.8)	529 (82)	682 (101)	844 (151)	595 (93)	3047 (613)	10.8* (1.8)	1.15* (0.3)	55.7* (11.5)	5.9 (1.5)	7.4 (5.0)	273 (214)	39.3 (0.6)	39.9 (0.5)	40.2 (0.7)	40.6 (0.6)	1.1 (0.9)
	II	14	64	56.7 (14.4)	66.6 (2.8)	590 (91)	680 (169)	828 (206)	583 (148)	2993 (812)	8.8 (2.3)	1.03* (0.4)	45.2 (12.5)	5.3 (1.9)	7.8 (5.2)	290 (230)	39.4 (0.8)	39.8 (0.7)	40.1 (0.8)	40.5 (0.7)	1.1 (1.0)
	III	14	61	63.7 (13.3)	80.2 (9.1)	783 (137)	783* (108)	970* (155)	657* (100)	3363* (794)	8.3 (1.5)	0.86* (0.2)	42.3 (10.8)	4.4* (1.3)	7.3 (5.4)	254 (231)	39.3 (0.8)	39.7 (0.6)	39.9 (0.7)	40.2* (0.7)	0.8 (0.8)
(c)																					
IV	I	83	248	58.4 (15.2)	55.7 (5.0)	538 (95)	628* (130)	812 (192)	547* (117)	2689* (743)	9.9* (2.1)	1.03* (0.3)	48.6* (13.4)	5.1* (1.6)	10.2* (5.5)	399 (293)	39.6* (0.9)	39.9* (0.7)	40.4* (0.9)	40.7* (0.7)	1.4* (1.1)
	II	84	351	55.9 (16.0)	66.0 (2.7)	610 (105)	670* (111)	836 (151)	579* (103)	2859* (624)	8.8* (1.6)	0.97* (0.2)	43.4* (9.5)	4.8* (1.3)	12.4 (5.9)	432 (260)	39.4 (0.8)	39.7 (0.6)	40.2 (0.8)	40.5* (0.6)	1.1* (1.0)
	III	85	334	57.7 (13.4)	82.8 (9.4)	763 (138)	745* (142)	927* (185)	627* (119)	3091* (737)	7.6* (1.4)	0.84* (0.2)	37.6* (8.9)	4.1* (1.1)	11.7 (5.4)	396 (212)	39.4 (0.8)	39.6 (0.7)	40.0 (0.8)	40.3* (0.7)	0.9* (0.8)
(d)																					

were significantly different (p=0.000-0.01) from the other two groups.

- ***Second BSD configuration***

The results are shown in table 6.2b. The average of *'bare'* power indices increased from weight-group 1 to 3. Again, the highest values for the derivative power related indices belonged to weight-group 2, with the lowest values for weight-group 3. A significant difference (p=0.000-0.001) was found for the *'bare'* power indices in weight-group 1 *vs.* 2 and 3.

Similar to the 1st BSD, the average frequency of switched-off was roughly equal for weight-groups 1 and 3, where both were higher than weight-group 2. The average of total switched-off time for weight-group 2 was lower than those for groups 1 and 3, with the highest value for weight-group 1 (table 6.2b). The average of each switched-off duration time was 57, 42, and 48 s for the weight-groups 1 to 3, respectively. The averages of all temperature indices were roughly equal for weight-groups 1 and 2, while both were slightly higher than weight-group 3 (table 6.2b).

- ***Third BSD configuration***

The results are presented in table 6.2c. The average of forward power and net power increased from weight-group 1 to 3. The lowest and highest values of maximum forward power and mean net integrated power found for weight-groups 2 and 3, respectively. The derivative power related indices decreased slightly from weight-group 1 to 3. Significant differences (p=0.000-0.03) were found between *'bare'* power indices for weight-group 3 *vs.* 1 and 2. Furthermore, a significant difference (p=0.0000-0.03) was found for the derivative power related indices between weight-group 1 *vs.* 2 and 3.

The average frequency of switched-off was roughly equal for weight-groups 1 and 3; both were slightly lower than weight-group 2. The average of total switched-off time for weight-group 2 was higher than those for groups 1 and 3, with the lowest value for weight-group 3 (table 6.2c). The average of each switched-off duration time was 37, 37, and 35 s for the weight-groups 1 to 3, respectively, all shorter than those for the 2nd BSD configuration.

The averages of vagina T_{50}, all lumina T_{50}, and CEM43°CT_{90} decreased slightly from weight-group 1 to 3. The averages of vagina T_{90} and all lumina T_{90} were equal for the three weight-groups (table 6.2c). No difference was found for the all temperature indices in the three weight-groups, except for all

lumina T_{50} of weight-group 1, which was significantly different (p=0.008) from weight-group 3.

- ***Fourth BSD configuration***

See table 6.2d. The average of the *'bare'* power indices increased from weight-group 1 to 3. In contrast, the average for the derivative power related indices decreased from weight-group 1 to 3. All, except one, power indices of weight-group 1 were significantly different (p=0.000-0.03) from weight-group 2 and 3 as well as for weight-group 2 *vs*. 3. The exception was the maximum forward power for which a significant difference (p=0.0000) was seen between weight-group 3 *vs.* 1 and 2.

The average frequency of switched-off was roughly equal for weight-groups 2 and 3, which both were slightly higher than group 1. The average of total switched-off time for weight-group 2 was slightly higher than those for weight-groups 1 and 3. The average of each switched-off duration time was decreased slightly from 39, 35, to 34 s for weight-group 1 to 3, respectively. A significant difference (p=0.000-0.005) was found for the frequency of switched-off in weight-group 1 *vs.* 2 and 3. No difference was seen for the total switched-off and each switched-off duration time in the three weight-groups.

The averages of all temperature indices were decreased slightly from weight-group 1 to 3 (table 6.2d). All temperature indices for weight-group 1 were significantly different (p=0.000-0.02) from the other two groups. Additionally, the all lumina T_{50} and CEM43°CT_{90} were significantly different (p=0.000-0.05) for weight-group 2 *vs*. 3.

- ***Comparing the four BSD configurations used to treat similar weight-groups***

In this part of the study we compared the variables from similar weight-groups treated with different BSD configurations. The statistical analysis presented here is limited to the following variables: mean net integrated power, mean net integrated power per weight, total switched-off time, (assuming that they are representative for all other power indices), and all five temperature indices.

Comparing the mean net integrated power for weight-groups 1, a significant difference (p=0.001-0.03) was found for the 3rd BSD *vs*. the other three configurations. When we compared weight-groups 2, a significant difference (p=0.000-0.003) was found for configuration 1 *vs*. 3 and 4, also for configuration 2 *vs*. 4. In comparison for weight-group 3, a significant

difference (p=0.000) was found only for the 1st BSD configuration *vs*. the 4th. Figure 6.1a shows an overview of the net integrated power for the three weight-groups as function of the BSD configuration.

Comparing the mean net integrated power per weight for weight-groups 1, a significant difference (p=0.001-0.02) was found for the 3rd BSD configuration *vs.* the other three. Comparison of weight-groups 2 shows a significant difference (p=0.000-0.03) for configuration 1 *vs*. 3 and 4, as well as for configuration 2 *vs*. 4.

In comparison for weight-groups 3, a significant difference (p=0.000-0.01) was found for the 4th BSD *vs*. other three configurations. Figure 6.1b shows an overview for the net integrated power per weight for the three weight-groups treated by the four BSD.

Comparing the total switched-off time in weight-groups 1 shows a significant difference (p=0.000-0.03) for configuration 4 *vs*. the other three. Similarly, when we compared weight-groups 2, a significant difference (p=0.000-0.03) was found among configuration 4 *vs*. the other three, as well as for configuration 1 *vs*. 3. For weight-groups 3, again a significant difference (p=0.000-0.001) was found for the 4th BSD *vs*. the other three configurations.

With one exception no difference was found for the achieved temperatures among similar weight-groups treated by different BSD configurations (see figure 6.1c). Only a significant difference (p=0.02) was found for the all lumina T_{90} in weight-groups 2 treated by the 1st and 4th BSD (tables 6.2a and 6.2d).

6.3.2 Analysis per BSD configuration

In this part of the study the analysis was performed for the four BSD configurations regardless of the weight-group. The average values of the power and temperature data are shown in table 6.3. The power indices showed small variation (±10%) over the four BSD configurations. The lowest values of mean and maximum forward power belonged to the 1st BSD (647±163 W and 803±221 W, respectively); the highest values of these variables to the 3rd BSD (711±135 W and 876±181 W, respectively). Significant different (p=0.000-0.01) was seen for the mean and maximum forward power of the 1st BSD *vs*. the other three configurations. The averages of mean net integrated power were almost equal for the configurations 1-3 (2981-3125 kJ), but for the 4th configuration they seem to be lowest (2889±723 kJ).

Table 6.3: Average values of patients' characteristics, RF-power, and temperature data per treatment for the four configurations of the BSD-2000. Numbers in parentheses show 1 SD.

BSD	nr. of pts.	nr. of trts.	age (yrs.)	weight (kg)	pelvic area (cm^2)	mean forward power (W)	max. forward power (W)	mean net power (W)	mean net integrated power (kJ)	mean net power per weight (Wkg^{-1})	mean net power per pelvic area (Wcm^{-2})	mean net integrated power per weight ($kJkg^{-1}$)	mean net integrated power per pelvic area ($kJcm^{-2}$)	nr. of switched -off	total switched -off time (s)	temperature indices				
																T_{90} (°C)		T_{50} (°C)		CEM 43 °C T_{90} (min)
																vagina lumen	all lumina	vagina lumen	all lumina	
I	105	431	55.7 (13.7)	65 (13)	623 (148)	647* (163)	803* (221)	585 (138)	3042 (877)	9.2 (2.0)	0.97 (0.3)	47.6 (12.5)	5.0 (1.6)	2.8* (2.8)	214* (236)	39.5 (0.9)	39.8 (0.7)	40.3 (0.9)	40.6 (0.7)	1.3 (1.3)
II	39	105	58.6 (12)	63.5 (13.3)	601 (133)	696 (163)	868 (198)	578 (146)	2981 (871)	9.2 (2.0)	0.98 (0.2)	47.9 (12.7)	5.1 (1.5)	4.9* (2.9)	256* (263)	39.4 (0.8)	39.8 (0.7)	40.0 (0.8)	40.4 (0.7)	1.1 (1.2)
III	48	203	57.1 (15.3)	66.2 (11.8)	624 (149)	711 (135)	876 (181)	610 (118)	3125 (744)	9.4 (2.2)	1.03 (0.3)	48.6 (13.0)	5.3 (1.7)	7.5* (5.2)	273* (224)	39.5 (0.8)	39.8 (0.6)	40.1 (0.8)	40.4 (0.6)	(1.0) (0.9)
IV	252	933	57.3 (14.9)	69.1 (12.6)	645 (148)	684 (136)	861 (182)	587 (117)	2889* (723)	8.7* (1.9)	0.94* (0.2)	42.8* (11.4)	4.6* (1.4)	11.5* (5.7)	410* (254)	39.5 (0.8)	39.7 (0.7)	40.2 (0.8)	40.5 (0.7)	1.1 (1.0)

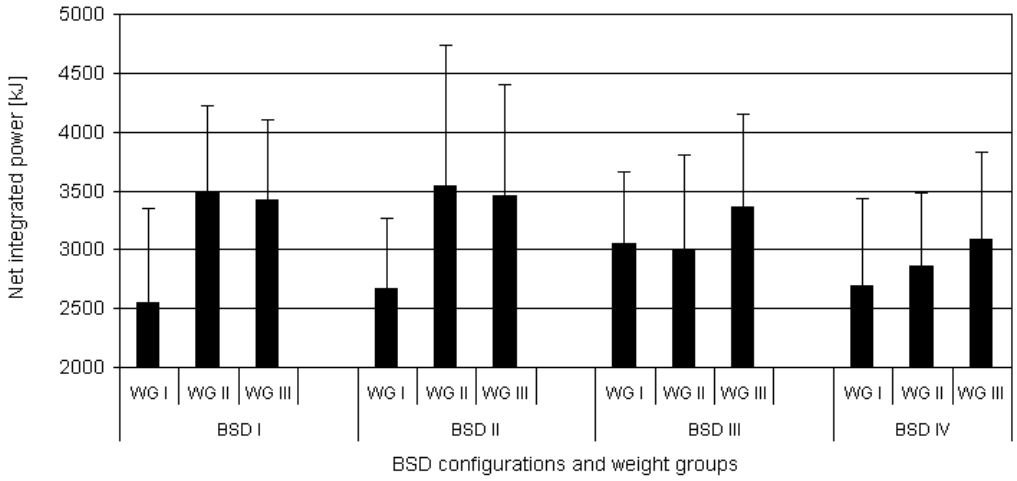
* Statistical significant different from the other values in the same column.

Table 6.4: Average values of patients' characteristics, RF-power, and temperature data per treatment for the three weight-groups. Numbers in parentheses show 1 SD.

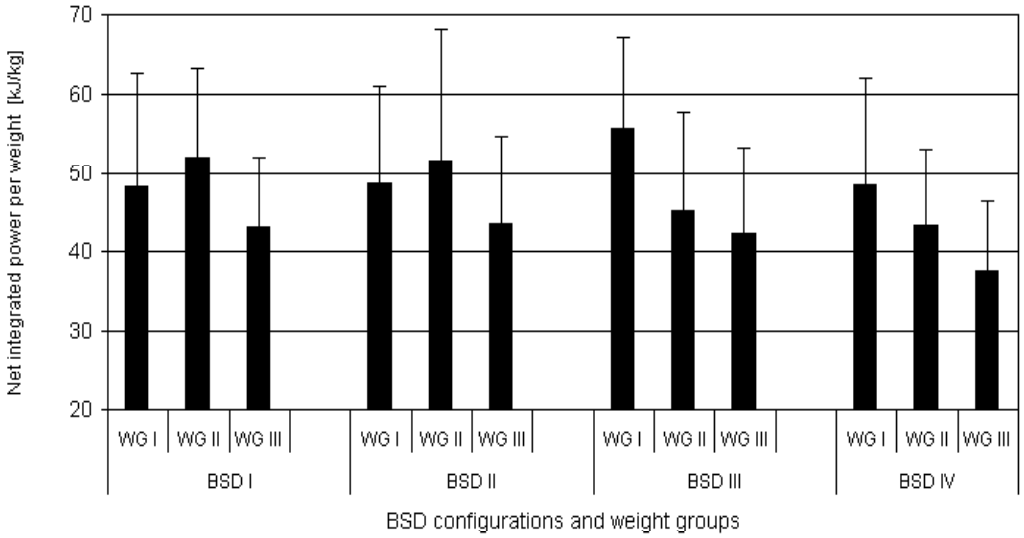
WG @	nr. of pts.	nr. of trts.	age (yrs.)	weight (kg)	pelvic area (cm^2)	mean forward power (W)	max. forward power (W)	mean net power (W)	mean net integrated power (kJ)	mean net power per weight (Wkg^{-1})	mean net power per pelvic area (Wcm^{-2})	mean net integrated power per weight ($kJkg^{-1}$)	mean net integrated power per pelvic area ($kJcm^{-2}$)	nr. of switched -off	total switched -off time (s)	temperature indices				
																T_{90} (°C)		T_{50} (°C)		CEM 43°C T_{90} (min)
																vagina lumen	all lumina	vagina lumen	all lumina	
I	171	569	56.8 (14.4)	54.6 (5.2)	533 (100)	609* (132)	768* (189)	538* (116)	2686* (747)	9.9* (2.1)	1.03 (0.3)	49.4* (13.6)	5.2 (1.6)	7.0* (5.6)	322 (280)	39.6 (0.9)	39.9* (0.7)	40.3* (0.9)	40.6* (0.7)	1.3* (1.2)
II	129	534	55.6 (15.4)	66.3 (2.8)	614 (105)	684* (129)	852* (173)	596* (119)	3013* (733)	9.0* (1.8)	0.99 (0.2)	45.5* (11.0)	5.0 (1.4)	9.7* (6.6)	358 (265)	39.5 (0.8)	39.8* (0.7)	40.2* (0.8)	40.5* (0.6)	1.1* (1.1)
III	144	569	58.4 (13.6)	81.5 (9.4)	757 (135)	751* (139)	934* (185)	638* (117)	3216* (755)	7.9* (1.5)	0.86* (0.2)	39.8* (9.5)	4.3* (1.1)	8.8* (6.1)	324 (237)	39.3* (0.8)	39.7* (0.7)	40.0* (0.8)	40.3* (0.7)	0.9* (0.9)

@ WG: Weight-group; I: W<61 kg, II: 61≤ W≤ 70 kg, III: W>70 kg.

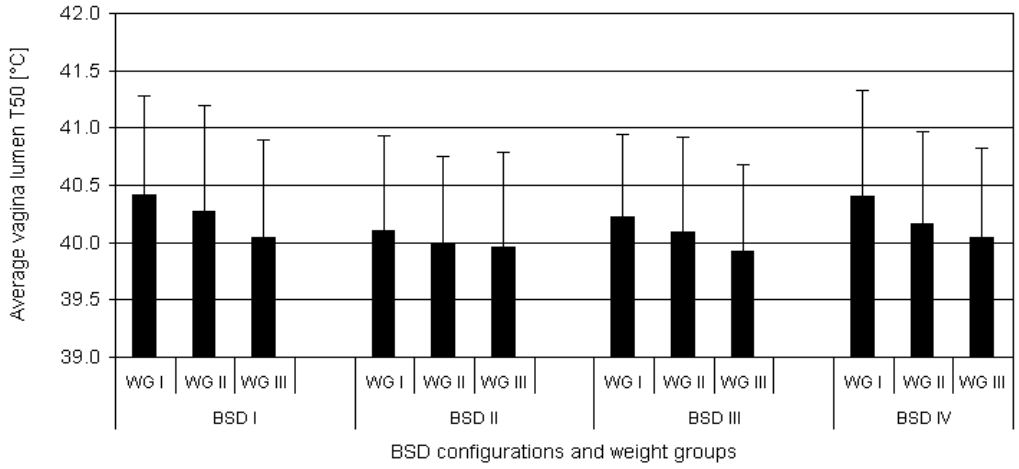
* Statistical significant different from the other values in the same column.



(a)



(b)



(c)

Figure 6.1: Average of (a) net integrated power, (b) net integrated power per weight, and (c) vagina T_{50} in the three weight-groups treated with the four configurations of the BSD-2000 and Sigma-60 applicator.

The average of mean net power per weight was 9.2-9.4 Wkg^{-1} for BSD 1-3 and 8.7±1.9 Wkg^{-1} for the 4th BSD.

The average of mean net integrated power per weight was 47.6-48.6 $kJkg^{-1}$ for BSD 1-3 and 42.8±11.4 $kJkg^{-1}$ for the 4th BSD. Similarly, the lowest values of mean net power (or mean net integrated power) per pelvic area belonged to the 4th BSD, 0.94±0.2 Wcm^{-2} (or 4.6±1.4 $kJcm^{-2}$), respectively. Significant differences (p=0.000-0.04) were found for the mean net power per weight, mean net integrated power per weight, and mean net integrated power per pelvic area for the 4th BSD *vs*. other three configurations.

Remarkably, the average frequency of power switched-off increased four-fold from 2.8 for the 1st configuration to 11.5 for the 4th BSD (table 6.3). The average of total switched-off time increased from 214 s for the 1st BSD to 410 s for the 4th. In contrast, the average of each switched-off time reduced from 76, 53, 36, to 36 s, respectively. The switched-off variables for the four BSD were significantly different (p=0.000-0.04). The range of average vagina T_{50} for the four BSD configurations was 40-40.3 °C. It was 40.4-40.6 °C for the all lumina T_{50}. The average CEM43°CT_{90} was in the range of 1.0-1.3 min (table 6.3). Additionally, the average of vagina T_{90} for the four BSD was 39.4-39.5 °C and 39.7-39.8 °C for all lumina T_{90}. No relation was found between temperature indices and BSD configuration.

6.3.3 Analysis per weight-group

This part of the analysis was performed for the three weight-groups regardless of the BSD configuration. The average values of power and temperature data are listed in table 6.4. The average of mean forward power increased from 609±132 W for weight-group 1 to 751±139 W for weight-group 3. The average of maximum forward power also increased from 768±189 W for weight-group 1 to 934±185 W for weight-group 3. This pattern of increase was also found for the averages of net power and net integrated power (figure 6.2a). However, the averages of power indices per weight (or per pelvic area) had different patterns from the *'bare'* power indices. They were roughly equal for weight-groups 1 and 2, both higher than weight-group 3 (see figure 6.2b). Significant differences (p=0.000) were seen for all *'bare'* power indices, net power per weight, net integrated power per weight, as well as net integrated power per pelvic area for the three weight-groups (table 6.4).

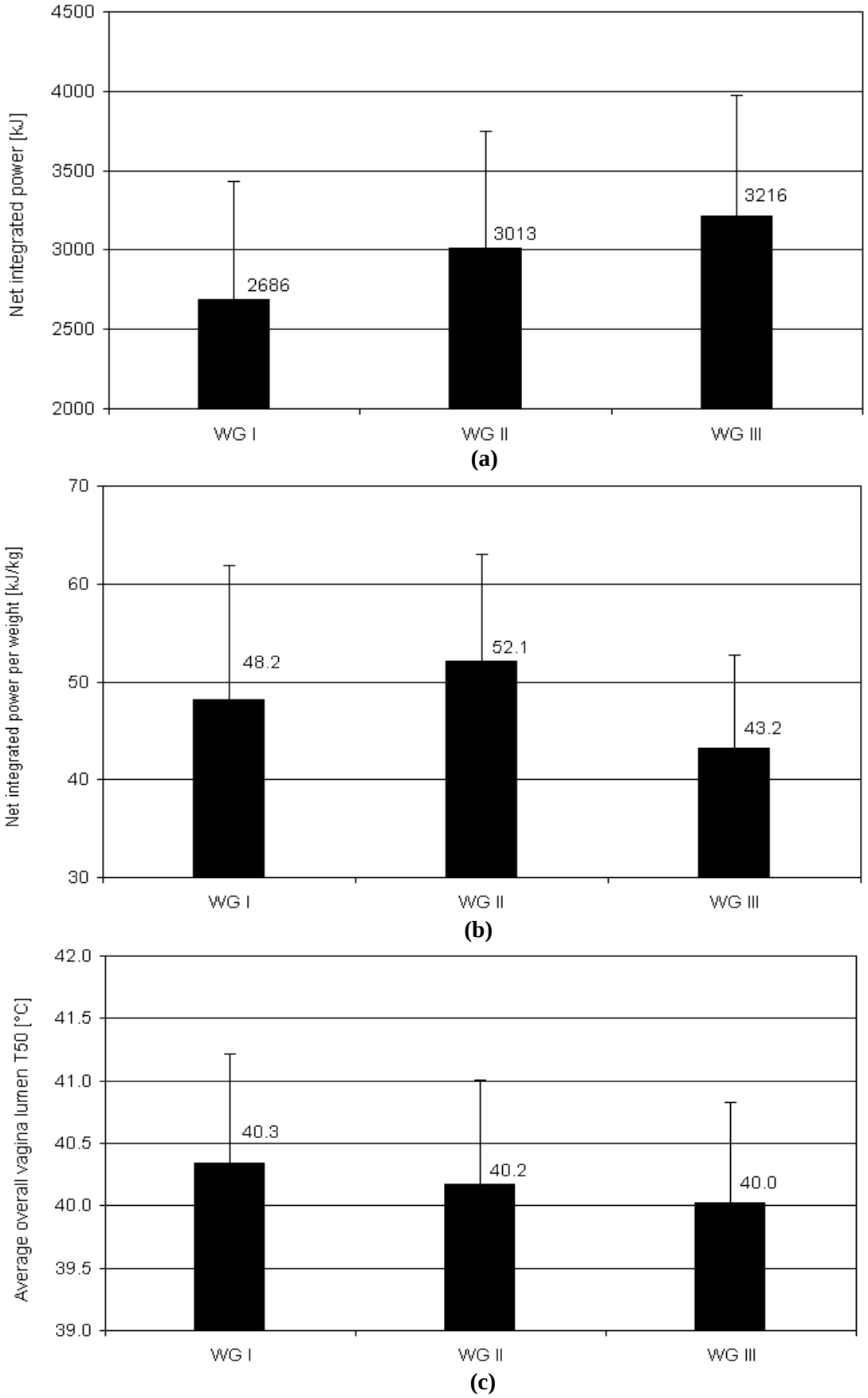


Figure 6.2: Averages of (a) net integrated power, (b) net integrated power per weight, and (c) vagina T_{50}, in primary cervical cancer patients for the three weight-groups (WG I: W<61 kg, WG II: 61≤ W≤ 70 kg, WG III: W>70 kg).

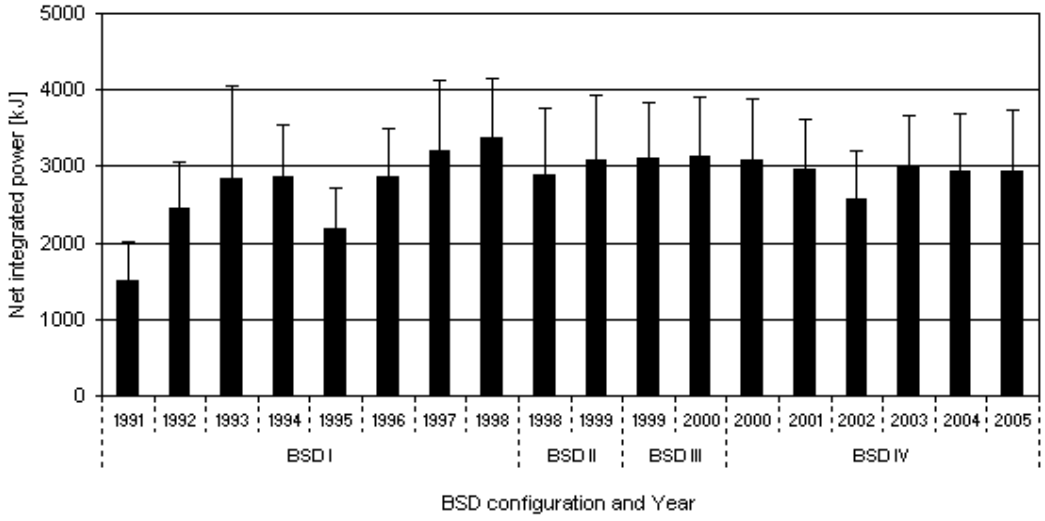
The highest average of frequency of power switched-off was 9.7±6.6 for weight-group 2, while it was 7±5.6 and 8.8±6.1 for weight-groups 1 and 3, respectively (table 6.4). The average of each switched-off time reduced from 46 s for the 1st weight-group to 37 s for weight-groups 2 and 3. The averages of total switched-off time were 322, 358, and 324 s for weight-groups 1-3, respectively. A significant difference was found for the frequency of switched-off between weight-group 1 *vs*. 2 and 3 (p=0.000) and weight-group 2 *vs*. 3 (p=0.05).

The averages of vagina T_{50} decreased slightly from 40.3 to 40.0 °C for weight-group 1 to 3 (figure 6.2c). Similarly, the all lumina T_{50}, was decreased slightly from 40.6 to 40.3 °C. The average of CEM43°CT_{90} decreased from 1.3 min for the 1st group to 0.9 min for the 3rd group. The vagina T_{90} and all lumina T_{90} also decreased slightly from weight-group1 to 3 (table 6.4). Although significant differences (p=0.000-0.04) were found for the temperature indices among the three weight-groups, their relevance is small.

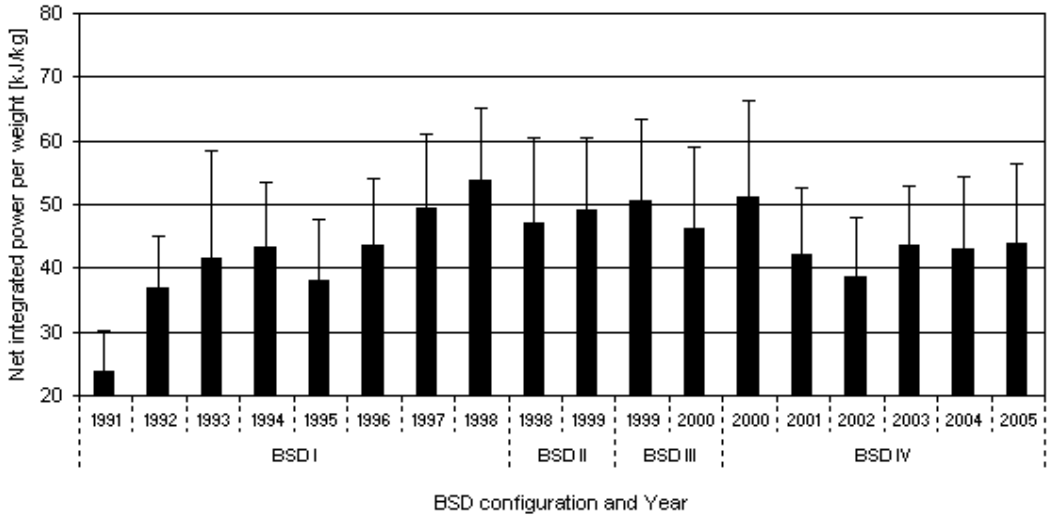
6.3.4 Analysis over the time-period

This analysis was performed regardless of the BSD configuration and the weight-group. The yearly average of the power and temperature parameters for the 15 years are shown in table 6.5 (see page 110). The lowest values for the averages of mean forward power (457±106 W), maximum forward power (567±126 W), and net power (412±98 W) were seen in the year 1995, however, the lowest mean net integrated power (1505±518 kJ) was in 1991. In the years 1991, 1995, and 2002 nearly all other power related variables were lower than those for the other years. The highest values of power indices were spread over the years 1992 to 2004.

The averages of net power and net integrated power increased during the first 3 years using the 1st BSD, however, for the other years these values were almost constant. Figures 6.3a and 6.3b respectively show the average net integrated power and net integrated power per weight over the years for the four BSD configurations. The lowest T_{50}'s were achieved in 1993 (vagina T_{50} 39.3±0.4 °C, all lumina T_{50} 39.6±0.3 °C). The minimum values for T_{90}'s were found in 1992 (vagina T_{90} 38.8±0.9 °C, all lumina T_{90} 39±0.8 °C). The lowest value for CEM43°CT_{90} (0.3±0.2 min) was seen in 1993. The highest values of average temperature indices were seen in 1997. Figure 6.3c shows the average of vagina T_{50} over the years for the four BSD configurations. The average of



(a)



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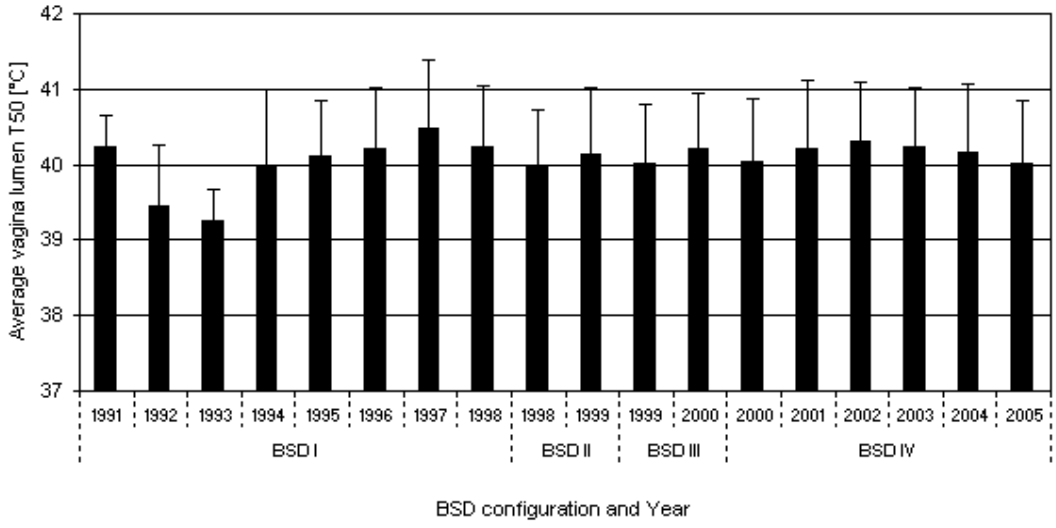


(c)

Figure 6.3: Average of (a) net integrated power (b), net integrated power per weight, and (c) vagina T_{50}, over the years in primary cervical cancer patients treated with the four configurations of the BSD-2000 and Sigma-60 applicator.

achieved T_{50} was low during the 2nd and the 3rd years of the study, however, for the other years using the four BSD configurations it was almost constant.

During the years 1991 to 1996 the number of primary cervical cancer patients referred to us were low (mean 6.8 patients per year, 25.7 treatments per year). These numbers were much higher during the years 1997 to 2005 (mean 44.8 patients per year, 168.7 treatments per year). Therefore, we discriminated between the first six years, '*study treatments time-period*', and the last nine years, '*standard treatments time-period*'.

In the first six years, there was a large variation in the yearly averages of power-related variables; however, in the last nine years it was much lower. For instance, the range of average mean net power was 412-643 W for the 1st time-period and 518-613 W for the 2nd time-period. The variations of the temperature indices were also different for the two time-periods. For example, during the 1st time-period the range of the average vagina T_{50} and T_{90} were 39.3-40.2 °C and 38.8-39.5 °C, respectively; whereas these values were 40-40.5 °C and 39.3-39.7 °C for the 2nd time-period, respectively (table 6.5).

The average values of power and temperature data for each time-period are also summarized in the table 6.5 (7th and last rows). Comparison between the average values showed that in the 2nd time-period the power-related parameters were 11-18% higher than those for the 1st time-period. The average frequency of RF-power switched-off was remarkably higher (2.6-fold) in the 2nd time-period (3.4 *vs*. 8.9).

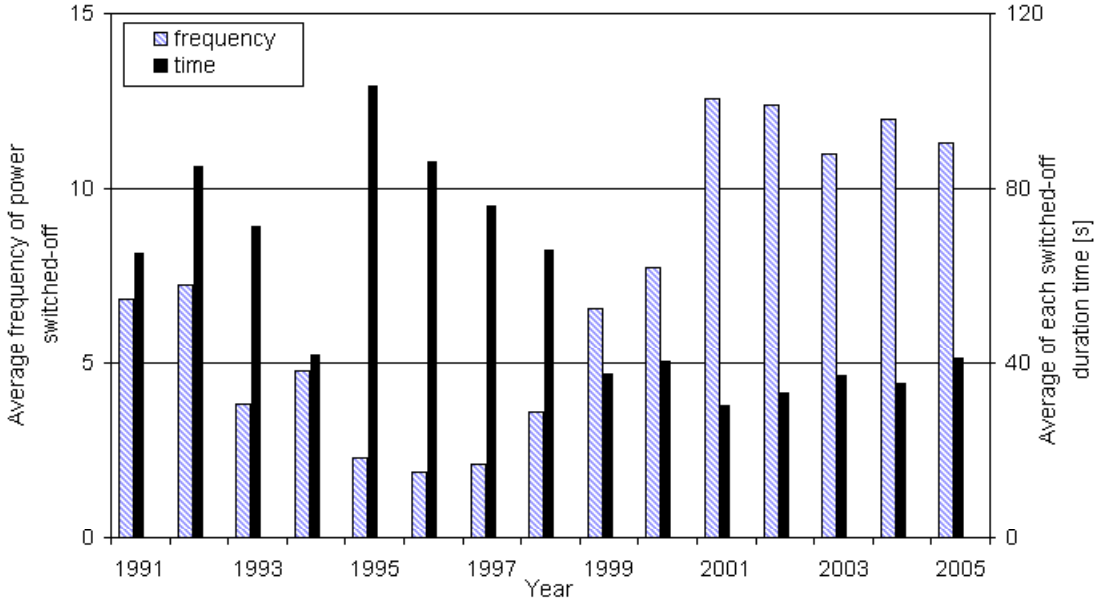


Figure 6.4: Average frequency of power switched-off and each switched-off duration time per treatment over the 15 years.

Additionally, the average of total switched-off time was also 28% higher in the 2nd time-period (266 *vs*. 341 s**).** In contrast, the average of each switched-off duration time was substantially lower in the 2nd time-period (75 *vs*. 44 s). Figure 6.4 shows the frequency of RF-power switched-off and the average of each switched-off duration time over the 15 years. Finally, the averages of the T_{50}'s in the 2nd time-period were only 0.2 °C higher than those for the 1st time-period. The difference was 0.3 °C for the averages of T_{90}'s and 0.1 min for the CEM43°CT_{90}'s.

6.3.5 Relation between power and temperature

Based on the selection criteria, 329 patients were eligible for this part of the analysis. Evaluation of relationship between the normalized net integrated power per pelvic area and vagina T_{50} showed various (poor to strong) correlations: in the 1st weight- group, positive correlation or trend was found in 40.4% (44 of 109 patients), negative correlation in 18.3% (20 patients), and no correlation in 41.3% (45 patients). In the 2nd weight-group, 40.6% (43 of 106 patients) had positive correlation or trend, 11.3% (12 patients) negative, and 48.1% (51 patients) no correlation. In the 3rd weight-group the correlation was positive in 39.5% (45 of 114 patients), negative in 8.8% (10 patients), and no correlation in 51.8% (59 patients).

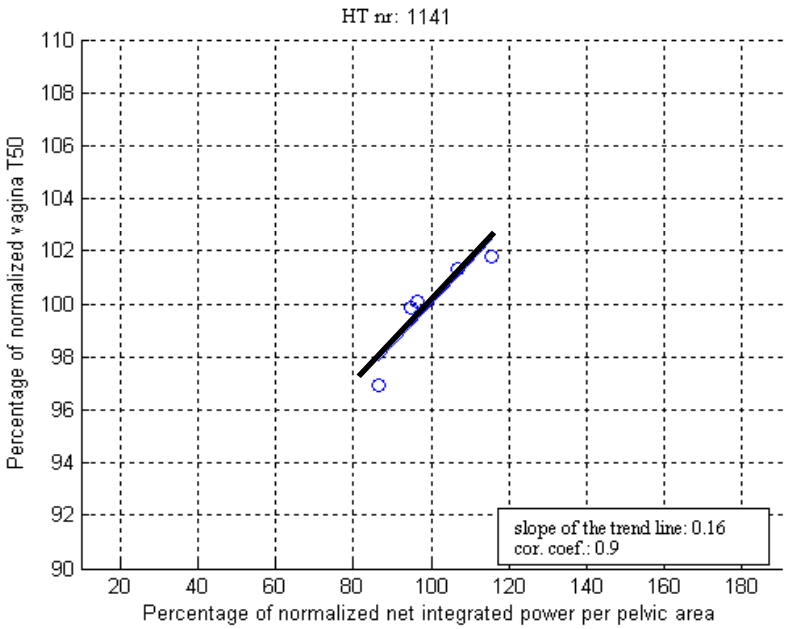


Figure 6.5: Example of correlation between percentages of normalized net integrated power per pelvic area and percentages of normalized vagina T_{50}. The slope of the trend line is 0.16 and the correlation coefficient is 0.9.

In summary, the correlation was positive in 40%, negative in 13%, and no correlation in 47% of the patients. Overall, in the three weight-groups the average value of the positive correlation coefficients was 0.7 (range 0.5-0.99) (see figure 6.5 as an example).

6.4 Discussion

Since we started applying loco-regional deep hyperthermia in 1990 with the first BSD-2000 configuration, the practice and environment in our department has undergone several substantial changes. Examples of these changes are growing clinical and technical experience, treatment protocols, introduction of newly developed equipment, *etc*. Each of these changes may have had its' own effect on the treatment. In this study a first general analysis is performed to identify whether heating quality was affected by some of these changes and patient specific characteristics. Overall, the current study shows our ability to reproducibly heat advanced cervical tumors to 40-40.5 °C with the BSD-2000 system and the Sigma-60 applicator, whereby the individual patient's characteristics (physical condition and motivation) appear to be critical for the achievable quality of the hyperthermia. The later is however a common phenomenon for every treatment modality (surgery, radiotherapy, chemotherapy, *etc*.).

6.4.1 Experience and treatment strategy

During the first six years of the study, the power indices increased slightly. For this period we noticed that power prescription changed with the growing experience of the staff-members and improvement of treatment protocols. Both aspects certainly affected the power settings. During the first 2-3 years the staffs spent large parts of their time and effort on training, learning, teaching, and developing the physical and clinical aspects of the technique for loco-regional deep heating. Especially, the understanding of when the maximum tolerance of each individual patient is reached requires a learning period. Projecting the development of the learning curve of our clinical experience we believe that a hyperthermia technician or physician needs to treat 10-20 patients before she/he has sufficient experience to work independently.

Furthermore, during 1996-1999 we gradually changed our treatment strategy. Initially, we decreased the output power with 100 W after any patient's pain complaints; perform SAR-steering and start increasing the power

again. With our growing experience we changed the strategy and refrained from decreasing the forward power at each complaint. Instead of reducing the power following a pain complaint caused by a too high temperature, we directly adjusted the treatment settings (phase or amplitude) to decrease energy deposition at the location indicated by the patient. Only when we found that phase, amplitude, and frequency steering were not able to overcome the power limiting complaints, it was decided to reduce the total forward power.

The change in treatment strategy was very well reflected by the very large variation in the frequency of RF-power switched-off over the 15 years. As is shown in figure 6.4 the number of switched-off is about six-fold higher in 2005 compared to 1996, this data is also presented in table 6.5. However, at the same time the average duration of each switched-off reduced from 86 s in 1996 to 41 s in 2005. The result of an increased frequency of power switched-off on the temperature is complex. An increase of the total switched-off time results in a drop of the total delivered energy to the patient. Whether this will result in lower measured temperatures in the target volume, depends on the ratio of heat removal for the target and hot-spot location (perfusion difference between tumor and the tissue at the hot-spot location).

6.4.2 System upgrade

In the last nine years, excluding 2002 for reasons as explained below, the average power indices showed a variation of less than 15%. For example, the yearly average of mean net integrated power was in the range of 2932-3209 kJ, which provided the vagina T_{50} in a range of 40.0-40.5 °C. When evaluating the relevance of the variation in power input it is important to consider the accuracy of the RF-power readings of the systems. For the first three BSD-2000 configurations, the RF-power to the applicator was measured with Bird Power meters. In an extensive study on quality assurance for deep hyperthermia, Hornsleth *et al*. (1997) showed that the accuracy of these meters was rather poor and depends strongly on the power output level. From this study it can be concluded that at the clinical-realistic power levels of 100 to 250 W per channel (total power 400 to 1000 W) the accuracy varies between ±10% and ±30%. For the 4^{th} configuration the power reading system was substantially improved using micro-strip bi-directional couplers integrated in the amplifier design and for the PDOS operated system the power reading accuracy is about ±20% (Kongsli *et al.*, 2006). Earlier Lee *et al.* (2003)

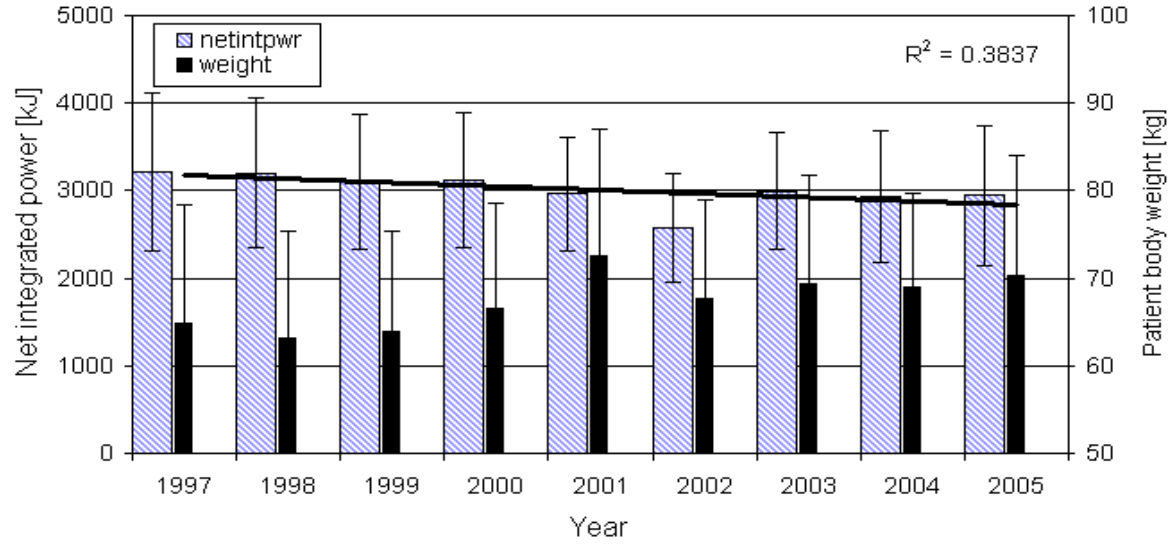
demonstrated that adding a high performance vector voltmeter system is required to obtain an accuracy of RF-power measurement below 10%. Hence, given the accuracy of the standard system we may conclude that we are able to reproducibly apply loco-regional deep hyperthermia to the primary cervical cancer patients.

As explained before, during the 15 years of patient treatment there was a gradual difference in the treatment strategy moving towards more frequent and shorter lasting power switched-off intervals. As the electronic design of the four BSD configurations differed minimally, we consider that the 3-8% lower net integrated powers that were found for the 4th BSD compared with the other three configurations could be attributed to the shift in strategy regarding frequency and duration of switched-off (see figure 6.4). The largest difference (8%, 236 kJ) for the mean net integrated power is between the configurations 3 and 4 (see table 6.3). Simple calculations show that 80 kJ, *i.e.* one third, is caused by the difference in total switched-off times (137 s) multiplied by the mean net power for these two configurations. After correction for this switched-off effect, the average net integrated power applied with the fourth system is in the same range as applied by the other three systems. At the same time it is noted that the temperature does not drop, suggesting that we indeed applied equal levels of RF-power.

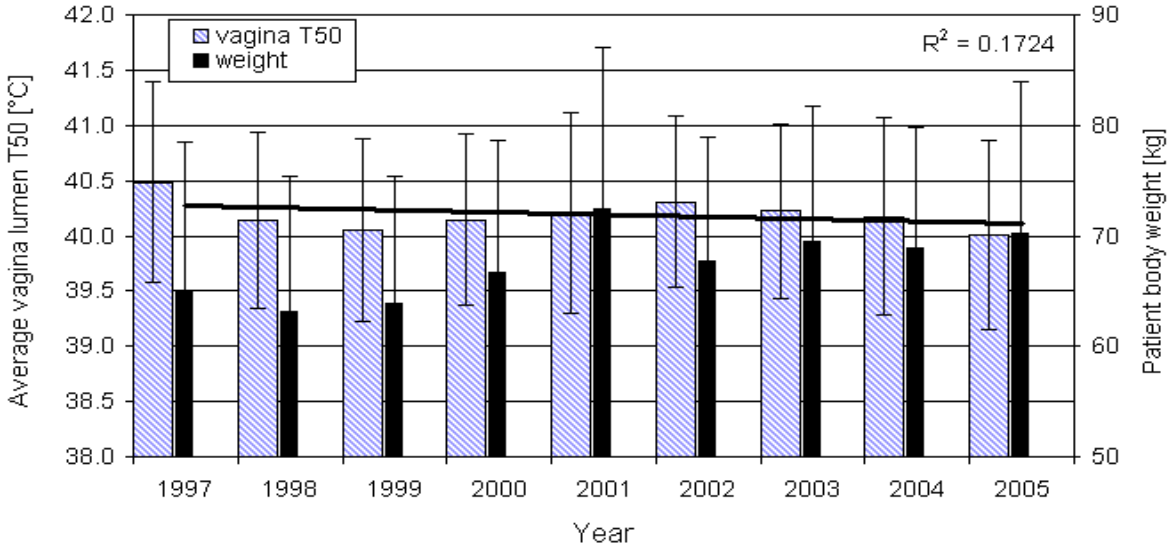
6.4.3 Weight effect

An overall view to the three weight-groups shows that the power indices per weight (or per volume) were significantly different (p=0.000) for the light-, medium-, and heavy-weight patients. As figure 6.2b shows, despite all our efforts, the power delivered per kg for weight-group 3 is considerably lower than those for the other two groups. As expected, the achieved temperature in weight-group 3 is also lower than those for the other two groups. It is interesting to note that the drop in the net integrated power per weight from weight-group 1 to 3 (figure 6.2b) is comparable to the drop in the temperature from weight-group 1 to 3 (figure 6.2c), (Δ=11.5% *vs.* 10%, respectively). This results confirms our intuitively expectation that heavy weight patients are more difficult to be heated to the goal temperature.

A more detailed analysis was performed on power and temperature data of 2001-2005. During these five years the averages of achieved temperature, *e.g.* vagina T_{50}, are almost similar, *i.e.* 40.2, 40.3, 40.2, 40.2, and 40.0 °C,



(a)



(b)

Figure 6.6: Averages of (a) net integrated power and patients' weight, and (b) vagina lumen T_{50} and patients' weight over the last nine years of the study.

respectively, but the mean net integrated powers are not similar, *i.e.* 2963, 2577, 2998, 2932, and 2946 kJ, respectively (figure 6.6a). We checked the patients' weight to find out an overall effect of weight on the power and temperature. As figure 6.6b shows, in these years the averages of weight are different, *i.e.* 72.5, 67.7, 69.4, 68.9, and 70.2 kg, respectively, with 2002 being the lowest. For the last five years of the study we also evaluated the overall effect of patients' age on the mean net integrated power per weight. We found a tendency for applying lower power to older patients in the three weight-groups, although the correlation coefficient was low. On the other hand, a tendency for higher vagina T_{50} was found for older patients. It will be interesting to investigate in more details to see whether the lower weight of the elderly

patient or whether anatomical and physiological differences might explain these findings.

6.4.4 Evaluation over the time-period

From 1996 onwards the combination of radiotherapy plus hyperthermia became more and more accepted as a standard treatment modality for cervical carcinoma in the Netherlands and subsequently the number of patients and treatments per year in the last nine years was about six-fold higher than in the years prior to 1996. We therefore divided the evaluation of the relationship between power and temperature in two time-periods: 1991-1996 and 1997-2005.

The larger variation in the yearly average of the achieved T_{50}'s in the first six years compared to the last nine years, 0.9 *vs*. 0.5 °C, is explained completely by the low number of patients (mean 7 patients per year) in the 1st time-period. The achieved T_{50}'s by the four BSD configurations showed the four systems have provided relatively low temperature in the treatment area. Clearly, the achieved temperature increase depends on many (uncontrollable) physiological parameters such as perfusion, regulation of perfusion, systemic temperature, thermal regulation of the whole organism, *etc*. (Wust *et al.*, 1995b). The range of yearly average temperature in the primary cervical cancer patients in this study was 39.3-40.8 °C. The recent discussion on which temperatures are optimum for the achievement of maximum treatment results discriminates between so-called 'mild' hyperthermia, the temperature range which has no negative effect on perfusion and oxygenation, and higher thermal doses which may compromise perfusion (Song *et al.*, 2005). Since the T_{50}'s that we achieved during treatment are far below the level from which one might expect a negative influence on oxygenation, our basic assumption is that, within this range, higher temperatures will result in a better treatment quality.

It is of relevance to mention here that the relatively moderate temperatures result in a considerable enhanced clinical outcome for the combined treatment of radiotherapy + hyperthermia in comparison to radiotherapy alone as has been demonstrated by the results of the Dutch deep hyperthermia phase III trial, 51% *vs*. 27% three years overall survival, respectively. We remind that the objective of the current study is to investigate the quality of the hyperthermia treatment based upon the temperatures achieved in the target region. Our group is currently also investigating the potential

relationship between treatment outcome and target temperature. The scope of that study, including the wide range of prognostic factors other than temperature, is such that the results will be reported in a separate publication. As the measured temperatures in treatment field are the only directly assessable indicators of the achieved quality of the hyperthermia treatment we consider a separate analysis of the power and temperature parameters highly warranted and of great importance for further improvement of the deep hyperthermia procedures.

6.4.5 Relation between power and temperature

Earlier, Wust *et al.* (1995b) and Paulsen *et al.* (1999) have shown in theoretical studies the importance to optimize the SAR-distribution in pelvic tumors as the maximum increase of pelvic temperature was strongly related to maximum increase of power. In these studies Wust *et al.* (1995b) and Paulsen *et al.* (1999) concluded that higher power results in higher temperatures. In a recent publication Fatehi *et al.* (2006b) observed a positive correlation between normalized net integrated RF-power and vagina T_{50}. The later can be seen as a first provisional experimental indication of a possible relation between input power and temperature, as mentioned by Wust *et al.* (1995b) *a*nd Paulsen *et al.* (1999). This result stimulated us to do more in-depth investigation of this potential relation for the larger patient population of the present study. Hereto, we looked at the correlation between net power (or net integrated power) and temperature, *e.g.* vagina T_{50}, but no correlation was found between these basic parameters. When we evaluated this relation between power indices per pelvic area *vs.* temperature, again no correlation was seen. In an attempt to look at the patient individual level, we normalized the power and temperature indices over the whole treatment series for each patient and computed the relationship between them, as we experienced it in the earlier study (Fatehi *et al.*, 2006b). The positive correlation found in 40% of the patients indicates that higher power creates higher temperature, which is in line with the earlier results from modeling studies. However, as the correlation is found in a relatively small proportion of the patients, it also indicates that other individual patient's characteristics are still very important for the power prescription.

6.4.6 Limitations

When we looked at the average power-related data over the 15 years, we recognized that the lowest mean net power or net integrated power was applied in the years 1991, 1995, and 2002. Taking into account that 1991 is the second year of the application of deep hyperthermia by our department, the low power for this year finds some justification by the fact that the experience of the hyperthermia staff-members was still growing. Additionally, as in this year only two patients (six treatments), with accessible data, were treated; the low power can also be explained by patient specific characteristic such as weight. To find the causes for the low power in the years 1995 and 2002, we checked the documentation. For 1995 the most plausible explanation for the low power values is low patients' weight of 58.4 kg on average, being the lowest over the 15 years (the average of all patients' weight was 67.4 kg). For the year 2002 the situation was more complicated. In this year there were several instances in which the amplifier or the software stopped working during the treatments, requiring a reboot of the whole system. As RF-interference to the computer was more likely to occur at high power, thus, losing the treatment data for these patients means that in 2002 the treatments with low power are relatively over represented. Another noticeable reason is that in this year the Sigma-Eye applicator went out of service for a 4-5 month period. Hence, in this period even patients, who were eligible for a Sigma-Eye treatment, *i.e.* in general smaller and of lower weight, were treated with the Sigma-60.

This study is the first attempt to find relationships between power and temperature respecting the weight and/or age. The results encourage us to further investigate these aspects within a smaller group of patients but more focused on the individual patient level and the 4th configuration of the BSD-2000.

6.5 Conclusions

- In this study we showed that the BSD-2000 Sigma-60 is able to reproducibly generate moderate loco-regional deep heating of 40-40.5 °C, as measured intraluminally, in all 444 patients. Hence, the good clinical results as reported by van der Zee *et al.* (2000) have been obtained at relatively moderate temperatures.

- The four distinct power amplifiers of the BSD-2000 configurations all provided similar drive of the Sigma-60 applicator. Throughout all upgrades over the 15 years, the heating pattern did not change significantly.
- Over the 15 years the achieved temperatures were relatively stable, even though we changed our strategy (switched-off modulations) to apply the RF-power to the patient and the increased personnel experiences.
- For heavy weight patients, higher power levels can be applied but the resulting power per weight unit (W/kg) is lower than that of low or medium weight patients. As a conclusion, lower target temperatures are achieved in heavy weight patients and thus, in general, heavy weight patients are less easy to heat adequately.
- Power prescription still depends to individual patient's characteristics.

Acknowledgements

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Table 6.5: Average values of patients' characteristics, RF-power, and temperature data per treatment over the 15 years application of loco-regional deep hyperthermia by the Rotterdam Hyperthermia Group. Numbers in parentheses show 1 SD.

time-period	year	nr. of pts.	nr. of trts.	age (yrs.)	weight (kg)	pelvic area (cm^2)	mean forward power (W)	max. forward power (W)	mean net power (W)	mean net integrated power (kJ)	mean net power per weight (Wkg^{-1})	mean net power per pelvic area (Wcm^{-2})	mean net integrated power per weight ($kJkg^{-1}$)	mean net integrated power per pelvic area ($kJcm^{-2}$)	nr. of switched -off	total switched -off time (s)	temperature indices				
																	T_{90} (°C)		T_{50} (°C)		CEM 43°C T_{90} (min)
																	vagina lumen	all lumina	vagina lumen	all lumina	
study time-period	1991	2	6	56.0 (7.7)	62.3 (8.3)	641 (73)	553 (62)	664 (91)	514 (61)	1505 (518)	8.4 (1.7)	0.8 (0.2)	23.9 (6.2)	2.3 (0.6)	6.8 (4.8)	447 (252)	39.3 (0.7)	39.6 (0.6)	40.2 (0.4)	40.4 (0.1)	0.4 (0.3)
	1992	6	23	57.5 (7.3)	68.0 (18)	670 (134)	630 (142)	861 (210)	578 (115)	2448 (609)	8.8 (1.9)	0.9 (0.2)	36.8 (8.3)	3.7 (0.7)	7.3 (4.2)	619 (440)	38.8 (1.0)	39.0 (0.8)	39.4 (0.8)	39.7 (0.6)	0.4 (0.4)
	1993	3	11	44.5 (10.1)	65.7 (8.1)	561 (79)	692 (131)	856 (185)	643 (124)	2851 (1210)	9.9 (1.6)	1.2 (0.1)	41.6 (17.0)	4.9 (1.9)	3.8 (2.7)	273 (287)	38.9 (0.5)	39.3 (0.5)	39.3 (0.4)	39.6 (0.3)	0.3 (0.2)
	1994	5	17	56.2 (9.0)	66.3 (5.2)	628 (84)	604 (152)	753 (211)	523 (137)	2853 (697)	7.9 (2.0)	0.8 (0.2)	43.2 (10.3)	4.5 (0.9)	4.8 (4.2)	199 (159)	39.4 (0.9)	39.8 (0.7)	40.0 (1.0)	40.4 (0.7)	1.0 (0.9)
	1995	8	26	51.7 (14.7)	58.4 (8.8)	546 (126)	457 (106)	567 (126)	412 (98)	2193 (520)	7.1 (1.7)	0.8 (0.2)	37.9 (9.8)	4.2 (1.3)	2.3 (2.1)	238 (232)	39.5 (0.7)	39.6 (0.6)	40.1 (0.7)	40.3 (0.7)	1.0 (0.8)
	1996	17	71	58.6 (12.6)	67.2 (13.8)	626 (139)	595 (108)	724 (175)	529 (92)	2861 (627)	8.1 (1.9)	0.9 (0.3)	43.5 (10.6)	4.8 (1.5)	1.9 (1.8)	163 (172)	39.5 (0.8)	39.8 (0.6)	40.2 (0.8)	40.5 (0.7)	1.3 (1.6)
average (1991-1996)		6.8	25.7	56 (12.2)	65.9 (13)	615 (130)	583 (137)	728 (197)	523 (118)	2630 (732)	8.2 (2.0)	0.9 (0.2)	40.8 (11.2)	4.4 (1.4)	3.4 (3.4)	266 (293)	39.2 (0.8)	39.5 (0.6)	40.0 (0.8)	40.3 (0.7)	1.0 (1.3)
standard time- period	1997	42	182	57.6 (13.8)	64.9 (13.5)	635 (164)	671 (164)	817 (217)	611 (139)	3209 (906)	9.5 (1.7)	1.0 (0.2)	49.5 (11.6)	5.2 (1.5)	2.1 (2.0)	162 (173)	39.7 (0.9)	40.0 (0.7)	40.5 (0.9)	40.8 (0.6)	1.5 (1.4)
	1998	43	150	54.4 (15.1)	63.1 (12.3)	607 (139)	698 (167)	882 (220)	606 (141)	3200 (855)	9.7 (2.0)	1.0 (0.2)	51.4 (12.6)	5.4 (1.4)	3.6 (2.6)	237 (242)	39.4 (0.8)	39.8 (0.6)	40.1 (0.8)	40.5 (0.6)	1.1 (1.0)
	1999	46	161	55.8 (15.3)	63.8 (11.5)	592 (124)	704 (142)	867 (171)	602 (126)	3103 (769)	9.6 (2.0)	1.0 (0.3)	50.1 (12.4)	5.5 (1.7)	6.6 (4.3)	246 (221)	39.5 (0.8)	39.8 (0.7)	40.1 (0.8)	40.4 (0.7)	1.0 (1.0)
	2000	36	156	59.1 (14.5)	66.6 (12.0)	620 (152)	716 (141)	880 (192)	613 (121)	3119 (770)	9.4 (2.3)	1.0 (0.3)	48.3 (14.0)	5.3 (1.6)	7.8 (5.4)	313 (243)	39.5 (0.8)	39.8 (0.7)	40.1 (0.8)	40.5 (0.7)	1.1 (1.0)
	2001	49	154	54.3 (15.1)	72.5 (14.6)	662 (151)	723 (136)	903 (183)	603 (102)	2963 (653)	8.5 (1.7)	1.0 (0.2)	42.1 (10.4)	4.7 (1.4)	12.5 (6.2)	379 (210)	39.5 (0.8)	39.8 (0.6)	40.2 (0.9)	40.5 (0.7)	1.1 (1.0)
	2002	50	196	59.6 (13.6)	67.7 (11.2)	636 (120)	620 (131)	769 (173)	518 (112)	2577 (621)	7.8 (1.7)	0.8 (0.2)	38.6 (9.4)	4.1 (1.1)	12.4 (6.2)	408 (260)	39.6 (0.8)	39.8 (0.6)	40.3 (0.8)	40.5 (0.6)	1.2 (0.9)
	2003	49	187	57.0 (13.5)	69.4 (12.3)	654 (127)	694 (123)	868 (172)	604 (106)	2998 (666)	8.8 (1.5)	0.9 (0.2)	43.7 (9.2)	4.7 (1.0)	11.0 (4.9)	409 (239)	39.5 (0.8)	39.9 (0.6)	40.2 (0.8)	40.6 (0.6)	1.2 (1.0)
	2004	43	148	54.8 (15.0)	68.9 (10.8)	658 (202)	706 (126)	902 (163)	610 (113)	2932 (754)	9.0 (1.7)	1.0 (0.3)	43.0 (11.5)	4.8 (1.5)	12.0 (5.5)	422 (227)	39.4 (0.9)	39.6 (0.8)	40.2 (0.9)	40.4 (0.7)	1.1 (1.2)
	2005	45	184	59.5 (15.7)	70.2 (13.8)	654 (144)	687 (141)	883 (184)	603 (121)	2946 (799)	8.9 (2.1)	0.9 (0.2)	43.8 (12.6)	4.6 (1.3)	11.3 (5.3)	463 (302)	39.3 (0.8)	39.5 (0.7)	40.0 (0.9)	40.3 (0.7)	0.9 (0.9)
average (1997-2005)		44.8	168.7	57 (14.7)	67.5 (12.8)	636 (149)	688 (144)	860 (191)	595 (124)	2993 (779)	9.0 (2.0)	1.0 (0.2)	45.3 (12.2)	4.9 (1.5)	8.9 (6.2)	341 (258)	39.5 (0.8)	39.8 (0.7)	40.2 (0.8)	40.5 (0.7)	1.1 (1.1)

Chapter 7

SAR-characteristics of the Sigma-60-Ellipse applicator

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Abstract

Purpose: To characterize the basic performance of the Sigma-60-Ellipse applicator. ***Materials and methods:*** The E-field distributions were measured using Schottky diode sheets in a cylindrical phantom (diameter 26 cm, length 50 cm), filled with saline-water (2 g NaCl/L). The phantom was positioned symmetrically in the Sigma-60-Ellipse applicator. The stability of the SAR-distribution was assessed as function of power and frequency. Furthermore, the accuracy of target steering was evaluated at various frequencies. Finally, the SAR-characteristics were compared with those of the Sigma-60 and the Sigma-Eye applicators. ***Results:*** The average 50% iso-SAR area increased from 241 to 296 cm^2 when the RF-power increased from 100 to 1600 W. The SAR maximum was located in the centre of the applicator for the frequencies of 75-80 MHz and it moves towards the feet for higher frequencies (up to 3.5 cm at 120 MHz). The average 50% iso-SAR area decreased from 268 to 161 cm^2 with increasing frequency from 75 to 120 MHz. The 50% iso-SAR longitudinal length was almost stable (mean 21.3 cm) at 75-120 MHz for both power outputs of 400 and 800 W. As expected the 50% iso-SAR radial length decreased with frequency from 14.9 cm at 75 MHz to 8.4 cm at 120 MHz. There was a fair agreement between requested and measured target settings. At the lower frequencies of 75-90 MHz and at 100 MHz the SAR-characteristics were almost identical to those of the Sigma-60 and Sigma-Eye applicators, respectively. ***Conclusion:*** At the frequency range of 75-90 MHz the Sigma-60 and at 100 MHz the Sigma-Eye can safely replace the Sigma-60-Ellipse applicator.

7.1 Introduction

The BSD-2000-3D system and the Sigma phased array applicators provide a new generation of equipment for planning, delivery, and control of loco-regional deep hyperthermia. The logical step in development of the Sigma applicators' family is having a group of applicators able to perform loco-regional deep hyperthermia in all patients' size, *i.e.* from small to large, with tumors in the pelvic region. One of the frequently used applicators connected to the BSD-2000-3D is the Sigma-60 (∑-60). A consequence of the 60 cm diameter of the ∑-60 applicator is that it has a large water bolus. In Rotterdam the average AP-PA dimension of the patient is 22 cm, hence, the thickness of the water column resting on the stomach of the patient is in average 19 cm. For a substantial number of patients this amount of water results in the

development of an uncomfortable pressure during the 90 min hyperthermia treatment. In reaction, the BSD Corporation has designed an upgraded and improved version of the ∑-60 applicator called the Sigma-60-Ellipse (∑-60-E), which is elliptical of shape (figure 7.1a). Due to the shorter height of the applicator the thickness of the water column above the stomach is reduced by 11.5 cm. The later is expected to reduce discomfort while still offering the possibility to treat a satisfactory large variety of different sized patients. Overall, the intention is that the ∑-60-E combines the reliability and sophisticated capability of the ∑-60 with improved provisions for patient comfort.

The ∑-60 applicator has an extensive track record with regard to quality assurance and its value has been proven in phase III trial investigations in which the benefit of adding hyperthermia to radiotherapy or chemotherapy has been demonstrated (Turner *et al.*, 1988; Leybovich *et al.*, 1991; Feldmann *et al.*, 1993; Jia *et al.*, 1994; Wust *et al.*, 1995a, 1999a, 1999b; van der Zee *et al.*, 2000; van der Zee and González, 2002). The FDA (Food and Drug Administration) accepted the ∑-60-E as a developmental packaging change in the ∑-60 applicator (BSD Medical Corporation, 2004a). Replacement of the ∑-60 applicator by the ∑-60-E is hence only acceptable after an extensive comparison on the basic characteristic of the both applicators.

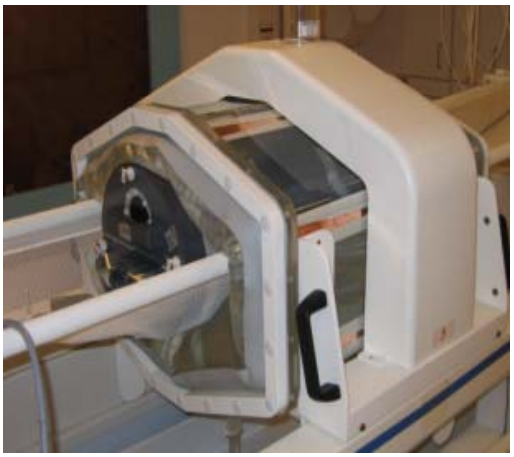
Earlier, van Rhoon *et al.* (2003b) have found that the SAR (specific absorption rate)- characteristics of the ∑-60 applicator are in a good agreement with theoretically expected values. In the current study we evaluated the SAR-distributions of the ∑-60-E as a function of frequency and power and the accuracy of target steering was assessed with the objective to characterize the basic performance of the applicator.

7.2 Materials and methods

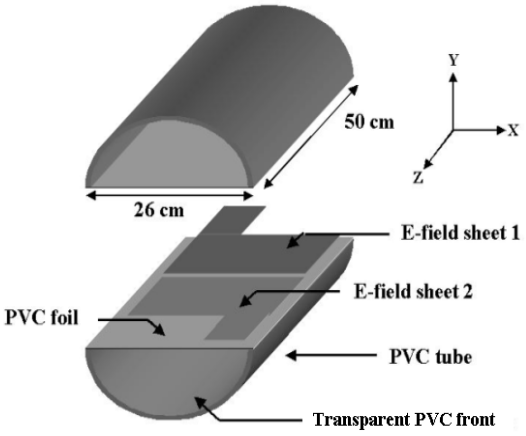
7.2.1 Equipment

- ***Applicator***

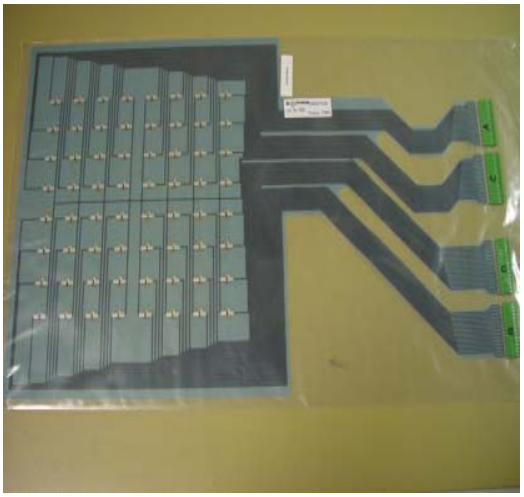
The applicator used was the ∑-60-E phased array (BSD Corporation, Salt Lake City, Utah, USA) (figure 7.1a) (BSD Medical Corporation, 2004b). The ∑-60-E is an array of 8 dipoles surrounding an octagonal-elliptical Lucite tube. Each dipole is oriented so that the radiated electric field is dominantly aligned with the central axis of the body positioned in the centre of the array. Each of these dipoles is individually dielectrically loaded by the water bolus.



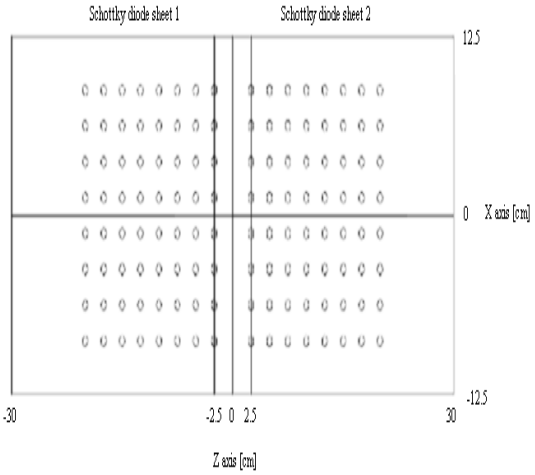
(a)



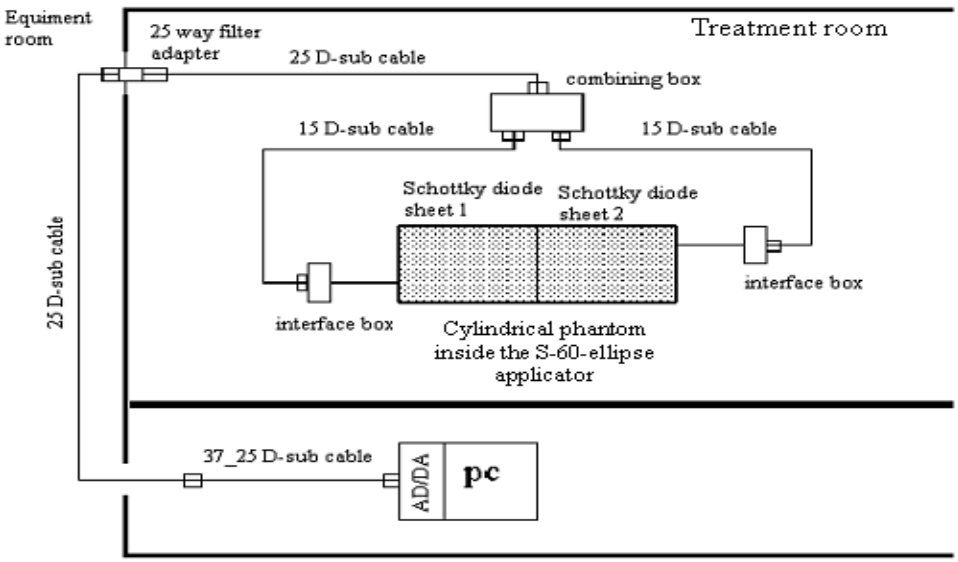
(b)



(c)



(d)



(e)

Figure 7.1: (a) The Sigma-60-Ellipse phased array applicator and the cylindrical PVC phantom as placed in the measurement setup, (b) schematic representation of the phantom and place of the E-field sheets on the half-lower split of the phantom, (c) a photo of the Schottky diode E-field sheet, (d) the top view of two Schottky diode sheets with position of the diodes, and (e) schematic representation of the measurement setup.

Internal power splitters allow power to be driven into four separate coaxial feed ports. Each of these input ports activate two adjacent dipole ports which are located at top, bottom, left, and right forming a dipole ring. The ∑-60-E basic frame is a cylinder made of Lucite glass with a nearly elliptical cross section and a central opening of 37 cm (h) × 53 cm (w).

Attached to its internal side is an integrated elastomer water bolus, with a closed silicone membrane containing deionized water for electro magnetic fields coupling and surface cooling which enables quick and easy patient setup. It fills the whole space between the patient and the outer cylinder, and serves both as a cooling device for the patient's outer surface and to direct the RF-waves into the body by impedance matching. The four channels of the Dodek amplifier drive the eight-paired antennae of the applicator (BSD Medical Corporation, 2004b).

- ***Phantom***

A simple phantom configuration was used: a cylindrical PVC tube of 26 cm diameter, length 50 cm, closed at both ends and it splits along the sagital plane into two equal parts (figure 7.1b). Each part was made watertight by gluing a PVC-foil over the surface. It was filled with saline water (2 g NaCl/L) to simulate average intra-pelvic tissue (σ = 0.4 S/m at 20 °C) (Stogryn, 1971). The details of the phantom characteristics are described extensively elsewhere (van Rhoon *et al.*, 2003b). For a homogenous phantom, the SAR-distribution is proportional to the square of the E-field distribution.

- ***Diode sheets***

The flexible Schottky diode sheet (SDS) is used to measure the E-field distributions. The SDS consists of eight arrays of eight diodes mounted on a flexible 125 mm thick polyester foil, which is capable to measure the E-field distribution with a resolution of 2.5×2.5 cm^2 (figure 7.1c). The diodes are connected through high resistive wires to the electronic readout system. A detailed description of the SDS and read-out system is given elsewhere (Kaatee and van Rhoon, 1999; van Rhoon *et al.*, 2003a).

7.2.2 Measurement setup

In order to measure the SAR-distribution of the ∑-60-E applicator in the axial (Z-X) plane the following process was performed. Firstly, two SDSs were

placed at the central cross-section of the half-lower split of the phantom; whereby no overlap of the SDSs occurred (figure 7.1b). The half-upper split phantom was placed on top of the SDSs. It was made certain that good contact was applied between the SDSs and the phantom by having a small over filling of the phantom. Then, using a level-meter the phantom was positioned symmetrically in the centre of applicator. The thickness of the water columns above and below the phantom was equal. Likewise, the water width in the left and right side of the phantom was equal (figure 7.1a). In this way, the SAR-distribution was measured by an array of 17 (columns, 16 real and 1 virtual) × 8 (rows)-diode sensors covering an area of 40×17.5 cm^2. The 9^{th} column was considered as virtual (figure 7.1d).

In the next step, the SDSs were connected to the interface boxes and the interface boxes were connected to the multiplexer (combining) box. The combining box was, through the access panel, connected to a computer and the signals were transferred by an AD/DA-converter card of the computer (figure 7.1e). The water-bolus was filled and water circulation was applied during the measurement. RF-power switch-ON was only enabled for measuring the E-field distribution; whereby the "ON"-time was as short as possible to prevent significant heating of the phantom.

A self-made MATLAB program acquired all characteristic parameters related to the SAR-distribution for the different measurements: the 50% iso-SAR area, the longitudinal length of the 50% iso-SAR area in the Z direction (LL50), and the radial length of the 50% iso-SAR area in the X direction (RL50).

7.2.3 Experiments

The following experiments were performed 3-4 times and the results are average of the measurements.

- ***Stability of SAR-distribution as function of power***

The RF-power outputs used were 100, 400, 800, and 1600 W. The reason for this experiment is that the phase path of a high power amplifier is sensitive to power output. Further, the power combiners may add additional instability. The frequency applied was 77 MHz with a synchronous exposure. The synchronous exposure means an equal phase and amplitude settings, *i.e.* target position of (0, 0) cm and 100% amplitude at top, bottom, left, and right antennae. The

frequency of 77 MHz was chosen, as it is our preference to use a low frequency for the clinical application of loco-regional deep heating.

- ***SAR-distribution as function of frequency***

The sensitivity of the SAR-distribution, expressed as 50% iso-SAR area, LL50 and RL50, was assessed for the frequencies of 75, 77, 80, 90, 100, 110, and 120 MHz, at a total RF-power output of 400 and 800 W using a synchronous exposure of the phantom.

- ***Accuracy of target steering***

This experiment was performed to evaluate the ability of the BSD-2000-3D system to perform controlled left-right SAR-steering. The target steering was performed in (Z-X) plane along the X-axis, *i.e.* left-right direction, of the phantom (see figure 6.1b). The target positions applied were from (0, -8) to (0, 8) cm by a step of 2 cm at the frequencies of 77, 100, and 120 MHz at 800 W total RF-power output in the equal amplitude (100, 100, 100, 100%) settings. The difference between requested and measured target is an indication for the accuracy of target steering.

7.3 Results

7.3.1 Stability of SAR-distribution as function of power

SAR-distributions were evaluated at the frequency of 77 MHz, (0, 0) cm target position, and 100% amplitude at the four positions (top, bottom, left, and right antennae) for different RF-power outputs. Figure 7.2 shows the 50% iso-SAR area as function of power outputs of 100, 400, 800, and 1600 W. The average of 50% iso-SAR area increased from 241±44 cm^2 at 100 W (25 W per channel) to 296±21 cm^2 at 1600 W (400 W per channel). The average LL50 (along the rows 4 and 5 of the SDSs) increased from 20.2±1.7 cm at 100 W to 21.6±1.2 cm at 1600 W. Furthermore, the average RL50 (along the columns 8 and 10 of the SDSs) increased slightly from 14.1±0.4 cm at 100 W to 15.3±0.3 cm at 1600 W. Figure 7.3 shows two examples of the profile of the SAR along row 5 and column 10 of the SDSs in target position (0, 0), at a power of 800 W, and 100% amplitude, and a frequency of 77 MHz.

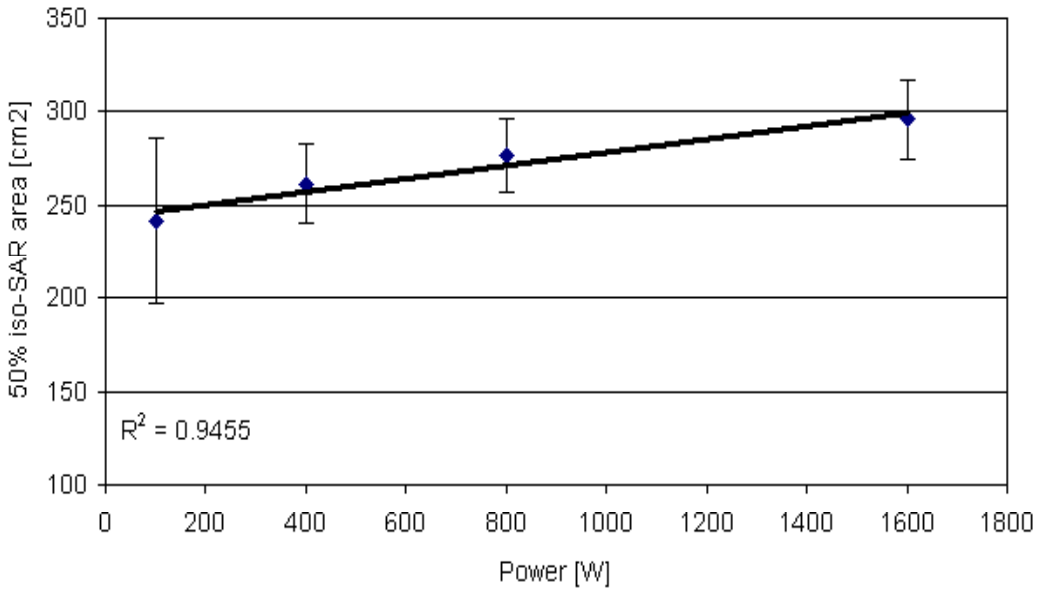
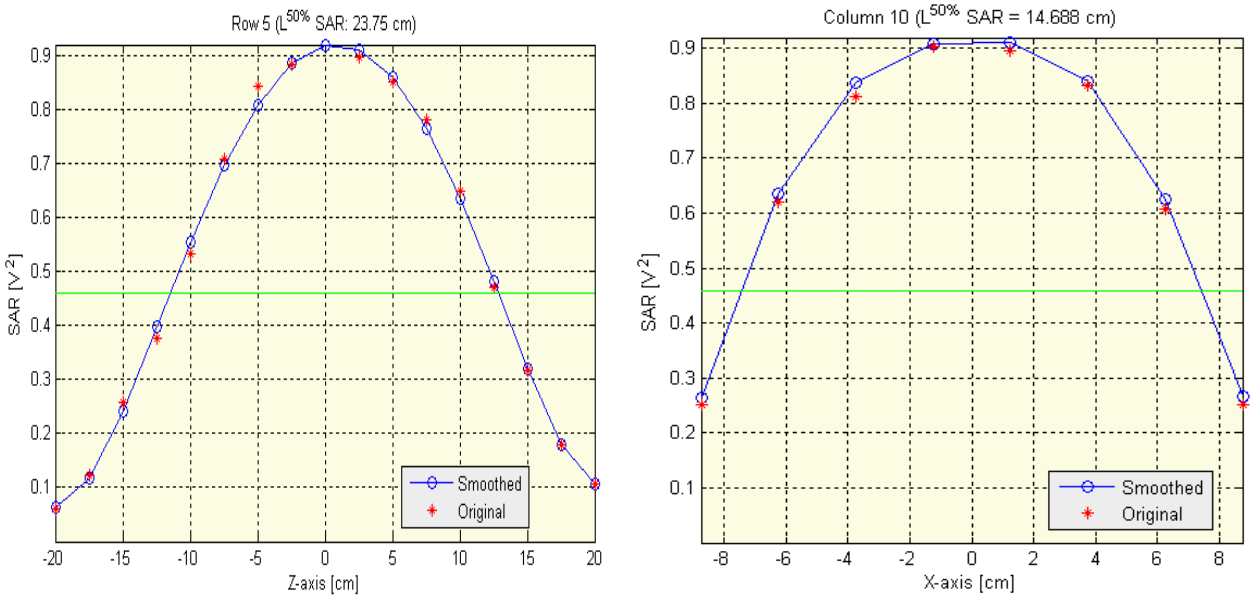


Figure 7.2: The average 50% iso-SAR area of the Sigma-60-Ellipse applicator as function of RF-power at 77 MHz, (0, 0) cm target position, and 100% amplitude.



(a) **(b)**

Figure 7.3: The profile of the SAR-distribution along (a) the 5th row and (b) the 10th column of the Schottky diode sheets in target position (0, 0) cm, 800 W total power, 100% amplitude, and a frequency of 77 MHz as obtained for the Sigma-6o-Ellipse applicator. The 50% iso-SAR longitudinal length in the Z direction (LL50) and the 50% iso-SAR radial length in the X direction (RL50) are 23.75 and 14.7 cm, respectively.

7.3.2 SAR-distribution as function of frequency

SAR-distributions were evaluated in the frequency range of 75-120 MHz, (0, 0) cm target position, 100% amplitude at the four positions (top, bottom, left, and right antennae), separately at 400 and 800 W total RF-power outputs to the four

channels. Figure 7.4 shows some examples of the contour plot of the SAR-distributions as function of frequency at a power of 800 W. The SAR maximum was located in the centre of the applicator for the lower frequencies of 75, 77, and 80 MHz. At higher frequencies, the SAR maximum was slightly moved, *e.g.* 1 cm at 90 MHz, toward the feet, with a maximum of ~3.5 cm at 120 MHz. This was similar for both 400 and 800 W applied powers.

Figure 7.5a shows the average of 50% iso-SAR area as function of frequency. As expected at both RF-power outputs of 400 and 800 W, the average 50% iso-SAR area decreased when frequency increased. For the power of 400 W, the average 50% iso-SAR area was 268±7 cm^2 at 75 MHz and decreased to 161±10 cm^2 at 120 MHz. For the power of 800 W, the average 50% iso-SAR area was 282±10 cm^2 at 75 MHz and decreased to 163±7 cm^2 at 120 MHz.

Figure 7.5b shows the average LL50 (along the rows 4 and 5 of the SDSs) as function of frequency at 400 and 800 W. At 400 W, the LL50 was stable (~21 cm) for the lower frequencies of 75-90 MHz and increased slightly

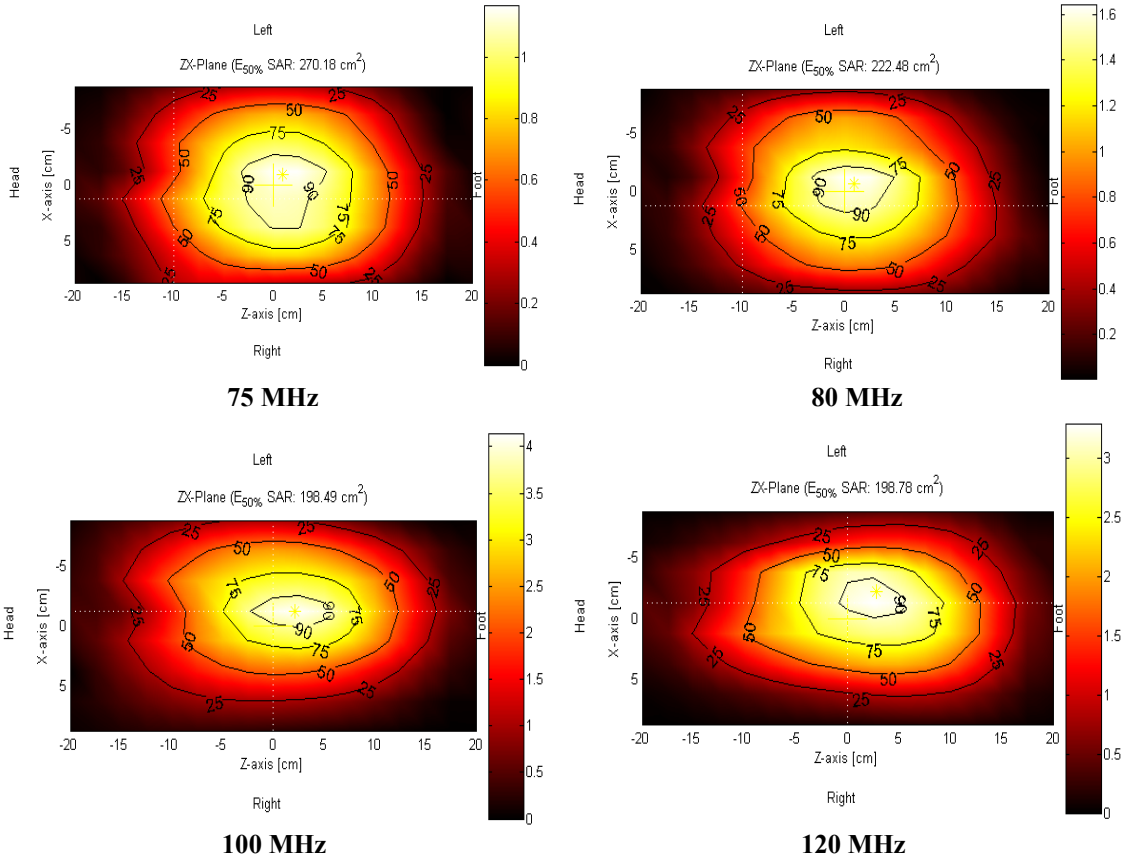


Figure 7.4: Examples of the contour plot of SAR-distributions for the Sigma-60-Ellipse applicator at different frequencies, 800 W total power, (0, 0) cm target position, and 100% amplitude.

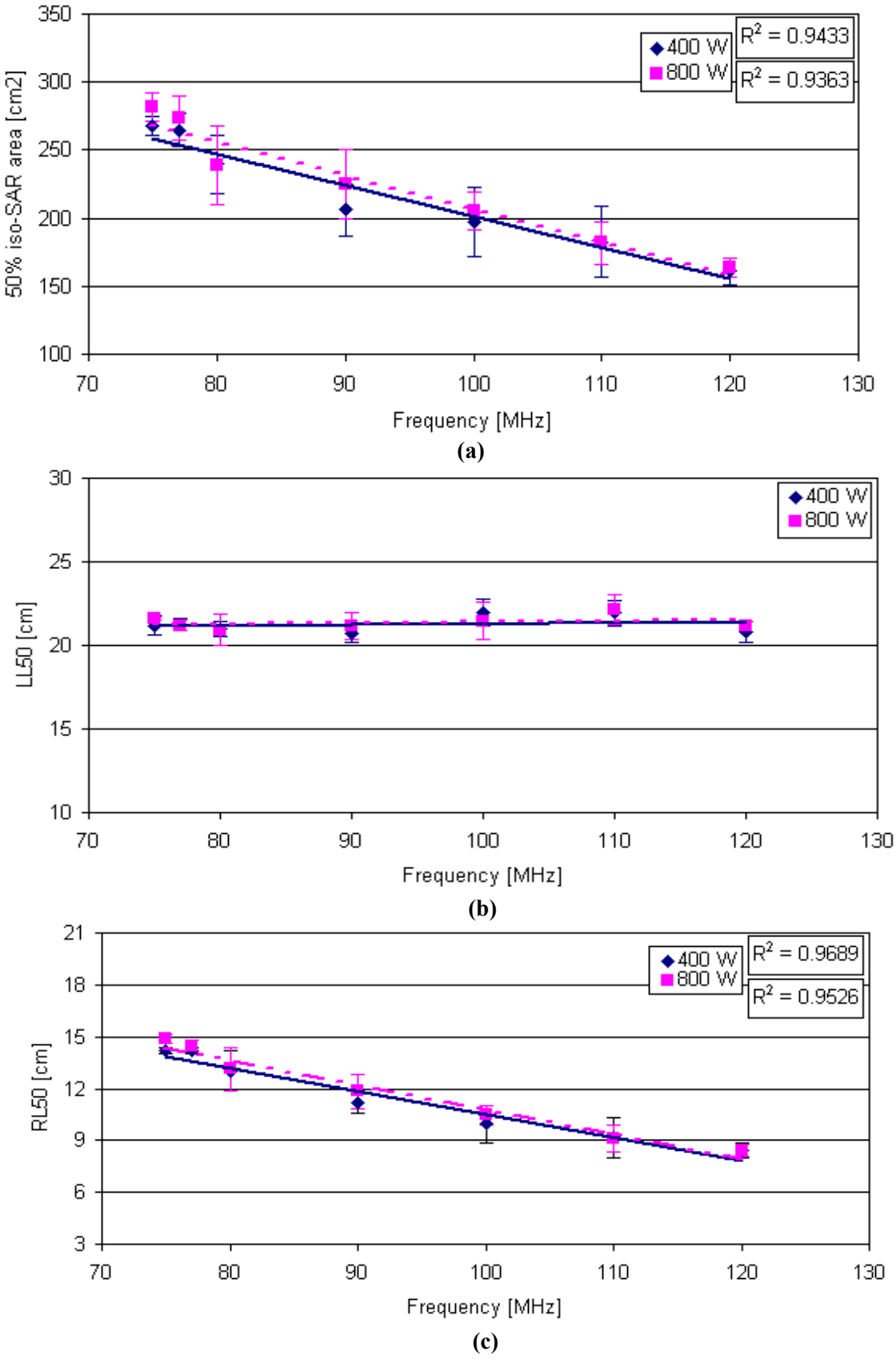


Figure 7.5: Average measurements of the Sigma-60-Ellipse applicator as function of frequency at 400 and 800 W total power, (0, 0) cm target position, and 100% amplitude: (a) 50% iso-SAR area, (b) 50% iso-SAR longitudinal length (LL50) along the rows 4 and 5, and (c) 50% iso-SAR radial length (RL50) along the columns 8 and 10 of the Schottky diode sheets.

to a maximum of 21.9±0.7 cm at 110 MHz. Overall, the mean measured LL50 was 21.3±0.5 cm. At 800 W, the minimum and maximum values for LL50 were 20.9±0.9 cm (found at 80 MHz) and 22.2±0.9 cm (found at 110 MHz), respectively (mean 21.4±0.4 cm).

Figure 7.5c shows the average RL50 (along the columns 8 and 10 of the SDSs) as function of frequency. At 400 W, the RL50 decreased from 14.2±0.2 cm at 75 MHz to 8.4±0.5 cm at 120 MHz. Similarly, for 800 W the RL50 decreased from 14.9±0.3 cm at 75 MHz to 8.5±0.3 cm at 120 MHz.

7.3.3 Accuracy of target steering

SAR-distributions were evaluated at the frequencies of 77, 100, and 120 MHz, 800 W total power, and 100% amplitude at the four positions (top, bottom, left, and right antennae), for different target settings of (0, -8) to (0, 8) cm in steps of 2 cm. Figure 7.6 shows some examples of the contour plot of the SAR-distributions in the selected target positions for frequency of 77 MHz. As figure 7.6 shows, movement of the target position along the left-right direction of the phantom was in a reasonable agreement with the requested target positions. Table 7.1 reports comparison between requested and measured target position at different frequencies.

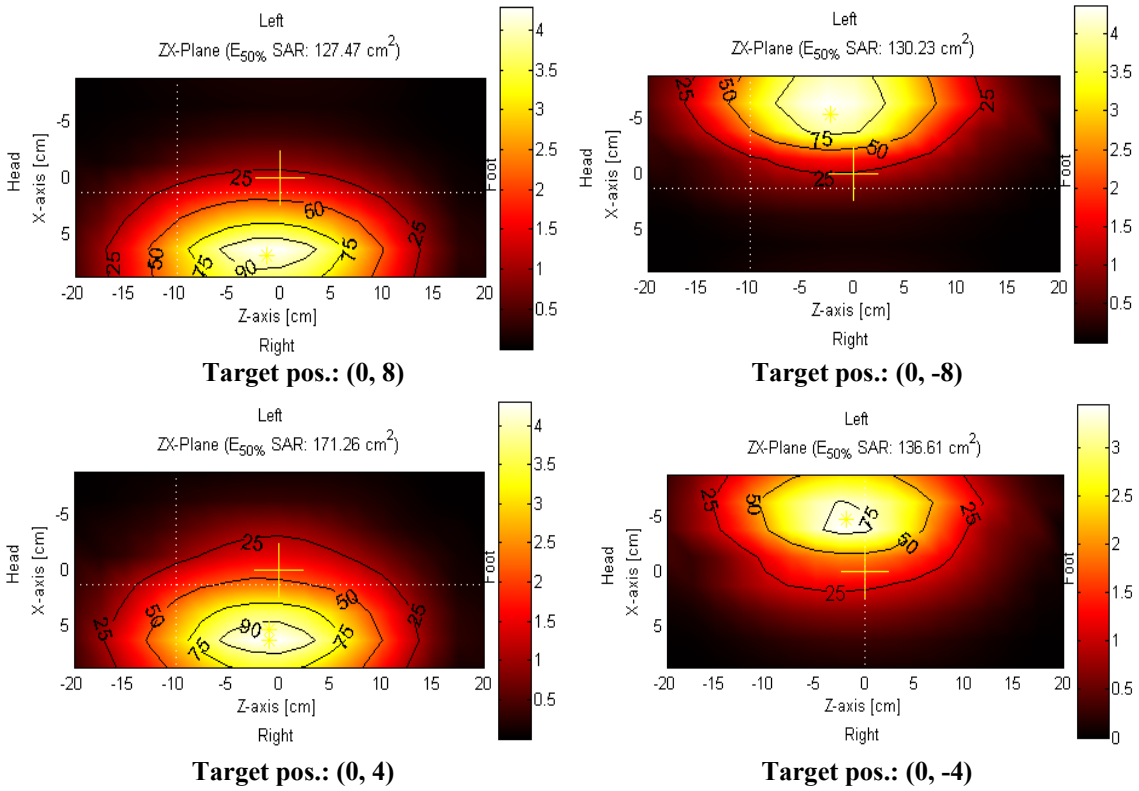


Figure 7.6: Examples of the contour plot for SAR-distributions of the Sigma-60-Ellipse applicator for the measured target positions at 77 MHz, 800 W total power, and 100% amplitude. Citations show the requested target positions.

Table 7.1: Comparison between requested and measured target position for the Sigma-60-Ellipse applicator at different frequencies, total power of 800 W, and 100% amplitude.

Requested (Z, X) cm	Average measured (Z, X) cm at frequency of		
	77 MHz	100 MHz	120 MHz
0, -8.0	-1.1, -6.6	0.5, -7.7	0.9, -8.8
0, -6.0	-1.0, -6.2	0.9, -5.9	-2.2, -5.8
0, -4.0	-0.9, -5.3	1.3, -4.0	-3.0, -3.8
0, -2.0	-0.7, -1.9	1.3, -2.2	-0.9, -1.6
0, 0.0	-0.3, -0.4	-2.0, -0.4	-0.8, -0.3
0, 2.0	-0.6, 4.3	2.4, 2.3	-2.2, 2.1
0, 4.0	-0.4, 5.2	1.4, 4.1	-2.4, 4.7
0, 6.0	-0.5, 6.3	0.9, 5.3	-1.0, 6.1
0, 8.0	-1.4, 6.6	0.3, 6.9	-0.9, 7.8

7.4 Discussion

The results of the measurements performed with the ∑-60-E applicator demonstrate that the SAR-distribution induced at the central cross-section of a homogeneous abdomen equivalent phantom possesses predominantly a Gaussian shape for the complete operational frequency range. The results also show that the SAR-characteristics increased, up to 23%, when power output increased from 100 to 1600 W. The SAR maximum was located in the centre of the applicator for the lower frequencies of 75-80 MHz and it slightly moved toward the feet up to 3.5 cm at highest frequency of 120 MHz. Earlier van Rhoon *et al.* (2003b) have found roughly similar results for the ∑-60 applicator. The reason for the unexpected shift is probably related to the specific electrical performance at higher frequencies of the unbalanced dipoles.

The largest 50% iso-SAR area was seen at the lowest frequency, *i.e.* 75 MHz, and it decreased by increasing frequency, having the smallest at highest frequency, *i.e.* 120 MHz. The reduction of the 50% iso-SAR area and the RL50 was expected given the shorter wavelength for the higher frequencies. However, the LL50 was roughly constant over the frequency range of the 75-120 MHz. For the LL50 of the SAR-distribution the length of the water bolus is decisive and therefore it is not surprising that the LL50 is roughly constant over the frequency range of the 75-120 MHz.

The SAR-distributions also show that the E-fields are quite symmetrical with respect to the right and left sides of the phantom. The target steering performance of the BSD-2000 phased array system was verified and the

experiments showed that the target could be correctly moved from the to the right side of the phantom.

Comparing our results with the reported data for the ∑-60 applicator by van Rhoon *et al.* (2003b), we considered that at different frequencies the 50% iso-SAR areas were almost equivalent for the two applicators (table 7.2). For the lower frequencies of 75-90 MHz the differences between calculated 50% iso-SAR areas of the ∑-60-E *vs*. ∑-60 were -7 to +0.3%, which is within the accuracy range of the measurement system. However, for the higher frequencies of 100-120 MHz the differences were +15 to +18%. The larger 50% iso-SAR area at the higher frequencies for the ∑-60-E is caused by the longer LL50 of the ∑-60-E compared to the ∑-60 (Δ= +10 to +16%). This difference expected as the bolus-patient contact length for the ∑-60-E is much longer than that of the ∑-60 (see table 7.3).

At the lower frequencies of 75-90 MHz the LL50s for the ∑-60-E are roughly equal to those for the ∑-60 applicator (Δ=-2 to +3%). Furthermore, the RL50 was roughly equal for the two applicators over the whole frequency range of 75-120 MHz (table 7.2).

These results show that in the frequency range of 75-90 MHz the SAR-characteristics of the ∑-60-E are almost identical for the ∑-60 applicator. Tacking in account that in Rotterdam our preference is to apply the lower frequencies (< 90 MHz) for loco-regional deep hyperthermia, then if one replaces the ∑-60 with the new ∑-60-E applicator there will be no difference in the SAR-distributions. Hence, provided that other relevant treatment parameters will not change, the quality of heating is potentially equal for ∑-60 and ∑-60-E.

Table 7.3 shows the physical characteristics of the ∑-60, the ∑-Eye, and the ∑-60-E applicators as provided by the BSD Medical Corporation (2004b). With respect to our comparison between the ∑-60 and ∑-60-E applicator, there are two important design aspects in the ∑-60-E that may affect the SAR-distribution. Firstly, the bolus-patient contact length of the ∑-60-E is ~50 cm, which is significantly larger than the ~36 cm of the ∑-60 (table 7.3, row 4). Secondly, the positioning of the dipole antennae in the elliptical shell of the ∑-60-E is such that the loading of the dipole is not symmetrical. Due to the sharp angles of the Lucite shell one side of the dipole sees more air than the other. This might result in a different behavior of the ∑-60-E with frequency compared to the fully symmetrical loaded dipole antennae of the ∑-60.

Table 7.2: Characteristic values of the Sigma-60, the Sigma-Eye, and the Sigma-60-Ellipse applicators describing the SAR-distribution as a function of frequency at 800 W total power, (0, 0) cm target position, and 100% amplitude. The results for the Sigma-60-Ellipse are average of 3-4 measurements. Numbers in parentheses show 1SD.

Frequency (MHz)	LL50[@] (cm)			RL50[@] (cm)			Calculated 50% iso-SAR area (cm^2) as an ellipse from LL50 and RL50		
	Applicator			Applicator			Applicator		
	S-60[©]	S-Eye[©]	S-60-Ellipse	S-60	S-Eye	S-60-Ellipse	S-60	S-Eye	S-60-Ellipse
75	20.9		21.6(0.1)	15.3		14.9(0.3)	251		252
80	21.4		20.9(0.9)	13.8		13.2(1.2)	232		216
90	21.7		21.2(0.8)	12.4		11.9(1.0)	211		198
100	19.6	22.5	21.5(1.1)	9.7	10.5	10.5(0.5)	149	186	176
110	19.1		22.2(0.9)	9.2		9.1(0.8)	138		159
120	18.6		21.1(0.3)	8.2		8.5(0.3)	120		140

@The LL50 and RL50 are defined as 50% iso-SAR longitudinal and radial length, respectively. ©The data presented for the Sigma-60 and the Sigma-Eye applicators are from van Rhoon *et al.* (2001; 2002; 2003b).

Table 7.3: Physical comparison of the Sigma-60, the Sigma-Eye, and the Sigma-60-Ellipse applicators as provided by the BSD Medical Corporation (2004b).

	Sigma-60	Sigma-Eye	Sigma-60-Ellipse
Frequency range (MHz)	60-120	100	80-110
Antenna length (cm)	45	14	45
Array/Diameter Max. (cm)	58	38×53	37×53
Bolus-patient contact length (cm)	~36	~50	~50
Drive ports	4	12	4
Radiators	8	24	8
E-field alignment	Long Axis	Long Axis	Long Axis
Convergent mode	2D TEM*	3D TEM	2D TEM

*TEM: transverse electro magnetic.

The ∑-60-E recommended frequency range is 80-110 MHz. The reason for this is an expected lower matching, *i.e.* increased reflected power for frequencies below 80 MHz and a lower power output at frequencies higher than 110 MHz (Turner, 2007). In our experiments the∑-60-E applicator performed equally well at 75 and 120 MHz that are outside the specific recommended frequency range.

We also compared the SAR-characteristic values of the ∑-Eye applicator reported by van Rhoon *et al*. (2001; 2002) with those for the other two applicators. The results are presented in table 7.2, row 4. The calculated 50% iso-SAR areas of the ∑-Eye and the ∑-60-E were almost equal (186 *vs*.

176 cm^2, respectively, Δ=+6%), both higher than the ∑-60 (149 cm^2). However, the LL50 of the ∑-Eye was slightly higher than the LL50 of the ∑-60-E (22.5 *vs*. 19.6 cm, respectively, Δ=+15%) and the ∑-60 (21.5 cm, Δ=+5%). The RL50 of the ∑-Eye was similar to the RL50 of the ∑-60-E (10.5 cm) but slightly higher than the ∑-60 (9.7 cm, Δ=+8%). These results show that the SAR-characteristics of the ∑-60-E (at 100 MHz) are also almost identical for the ∑-Eye. An important advantage of the ∑-60-E over the ∑-Eye applicator is that the ∑-60-E provides more space of the lateral sides of the applicator while having the same water pressure, and thus the ∑-60-E accommodates larger patients than the ∑-Eye. Finally, we consider that the characterization of the performance of hyperthermia applicators by phantom experiments has been demonstrated to be a useful tool to understand the specific behavior of an applicator and to design an applicator specific quality assurance program (Baroni *et al.*, 2001; van Rhoon *et al.*, 2003b).

7.5 Conclusion

Since at the lower frequencies of 75-90 MHz the SAR-characteristics, *i.e.* the 50% iso-SAR areas, the 50% iso-SAR longitudinal and radial lengths of the SAR-distributions of the ∑-60-E were roughly identical for the ∑-60 applicator, our conclusion is that the ∑-60 can safely replace the ∑-60-E applicator for loco-regional deep heating at this frequency range. Furthermore, for the same reason at 100 MHz the ∑-Eye also can safely replace the ∑-60-E applicator.

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7.6 Supplementary

7.6.1 SAR calculation

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* [1] where the average power (P) deposition to the material is given by:

$$P = \frac{1}{2}\sigma \cdot |E|^2 \tag{7.1}$$

where σ is electric conductivity (Sm^{-1}) and E is the complex electric field vector.
For hyperthermia the energy absorption in a material is often normalized to its mass density and is then called specific absorption rate (SAR):

$$SAR = \frac{1}{2\rho}\sigma \cdot |E|^2 \tag{7.2}$$

where ρ is mass density (kgm^{-3}). The equation 7.2 shows that the energy absorption is directly proportional to the electric conductivity and to the square of the E (complex electric field vector). The SAR_{Total} is defined as:

$$SAR_{Total} = \frac{1}{2\rho}\sigma \cdot \left(|E_X|^2 + |E_Y|^2 + |E_Z|^2\right) \tag{7.3}$$

where E_C is the electric field at "*C*" component. How well the E-field measurement with the Schottky diode sheet (SDS) represents the actual E-field, depends on the size of the X- and Y- components of the field; because the SDS measures the E-field distribution only in the main longitudinal direction (Z-component), called SAR_Z, which the formulation takes from:

$$SAR_z = \frac{1}{2\rho}\sigma \cdot |E_z|^2 \tag{7.4}$$

The SAR_Z ratio, defined as:

$$SAR_Z ratio = \frac{SAR_Z}{SAR_{Total}} = \frac{|E_Z|^2}{|E_X|^2 + |E_Y|^2 + |E_Z|^2} \tag{7.5}$$

can be used as measure of the effectiveness of the E-field measurement. Calculations from the Finite Element Method show that on average the SAR_Z ratio over the measurements is 94% (median 99%). Therefore, in the present study we used the term SAR-distribution, which with a very good approximation is representative for the E-field distribution.

[1] Van Rhoon GC. Radiofrequency Hyperthermia Systems: Experimental and clinical assessment of the feasibility of radiofrequency hyperthermia systems for loco-regional deep heating. PhD-thesis 1994;11-12.

Chapter 8

General discussion and future perspectives

8.1 General discussion

Despite technological progress, which supports non-invasive temperature monitoring and simultaneous imaging of deep-seated tumors, the majority of patients with loco-regional deep hyperthermia are still controlled by conventional thermometry, *i.e.* invasive (intratumor) and/or minimally invasive (intraluminal) placed thermometry sensors. In practice, it is critical to monitor the whole thermal range, including the minimum and maximum temperatures, in the treatment area, *i.e.* tumor, tumor-contact/indicative, and normal tissues.

Intratumor and/or intraluminal thermometry provide the important clinical data necessary to control SAR (specific absorption rate)- steering during the clinical treatment, and to perform thermal dose-response studies. Thermal monitoring also constitutes a reliable and obligatory method of treatment quality verification and to evaluate and compare the performance of heating systems. Therefore, the present thesis is intended to be an explorative study to find input parameters such as RF-power, patient weight, *etc*. that can be correlated with temperature parameters which are regarded to express the technological quality of deep hyperthermia treatment. A selection of topics have been addressed in this research: 1) How can we guarantee the integrity of the hyperthermia treatment data? 2) Do we need a reference temperature point in order to compare the results obtained by different hyperthermia groups? 3) Intratumor or intraluminal thermometry? Which one is sufficient for thermal data acquisition in hyperthermia treatment of centrally located pelvic tumors?

4) Does the assignment of a tissue type to each temperature measuring point along the thermometry catheter provide relevant additional information on the intraluminal temperature distribution? 5) What is the reproducibility of loco-regional deep heating in Rotterdam over the 15 years using four distinct configurations of the BSD-2000 hyperthermia system and the Sigma-60 applicator? 6) Can we safely replace the Sigma-60 or the Sigma-Eye applicator of the BSD-2000 with the Sigma-60-Ellipse without the risk of decreasing heating quality?

In the present thesis the data-source was the PDOS formatted hyperthermia data produced by the BSD-2000 system. Inaccessibility of the PDOS data postponed research concerning power and temperatures. Therefore, RHyThM (Rotterdam Hyperthermia Thermal Modulator) was first developed as a tool towards improvement of the accessibility of the data (chapter 2). The most important reason to develop this tool was the need to check the integrity of the data available from more than 900 patients, who have received more than 3800 treatments from the Rotterdam Hyperthermia Group with the PDOS-based configurations of the BSD-2000/3D system from 1990 until 2006.

There were some previous studies that attempted to address the issue of thermal data processing. In order to perform investigations regarding thermal dose effect relationship, some of the hyperthermia groups had developed different procedures to make the thermal data ‘accessible’. These early approaches were designed and built according to the computer facilities and data structures available in the late 1980s. Sapareto and Corry (1989) proposed a standardized database file format for hyperthermia treatments. This approach concerned mainly the recording of the data and of all events in a specific format during the treatment and it did not address the topic of the integrity validation of the data type, as it is provided by RHyThM.

RHyThM is a valuable tool enabling easy access to the data, it performs the integrity and validation check of the data, it connects the tissue assignment with the thermal data, and it offers adequate procedures to correct unrealistic temperature values. RHyThM also provides a minimum of data analysis required to make a fast assessment of the quality of the hyperthermia treatment. The newest version of RHyThM is adapted to be more intuitively operated and works also with the PC-version of the BSD-2000 operating system, which runs under Microsoft Windows.

The growing interest and participation in multi-institutional trials involving deep hyperthermia treatment is an important step towards the further consolidation of hyperthermia as an oncological treatment modality. From a quality assurance point of view, it is important to point out that difference exists in definition of the reported temperature dose by various institutions, which work on the same group of patients, using the same or nearly the same equipment. There are a multitude of reasons why the reported data varies. Without detailed knowledge of SAR-patterns, probe positions, patient's characteristics, use of analgesics, *etc.* it would be impossible to determine why such differences exist, particularly when there is no '*a priori'* temperature goal set for these kinds of studies (Dewhirst, 2006). Furthermore, the differences in the clinical procedures of hyperthermia application also raise questions as how to compare the reported temperature data obtained by the different institutes. As an example, in chapter 3, where we compared our thermometry results with the data reported in other studies, we were confronted with the question whether the differences among the reported temperatures were real or merely reflected differences in the equipment and the protocols used.

Obviously, comparing results from different institutes needs analysis in a similar fashion. An important restriction is that the temperature data reported in the clinical papers are mostly intended to represent the tumor temperature achieved, and not to provide materials to compare the quality of equipment and procedures in different institutes. The differences shown in chapter 3 demonstrate that there exist a clear need to arrive at consensus on new and tight guidelines allowing a valid assessment and comparison of the quality of the hyperthermia treatments performed in the various clinical studies and among the different institutes. Such guidelines are also mandatory for the quantitative evaluation of major improvements in hyperthermia technology. Introduction of reference points similar to radiotherapy may constitute a good solution to enable a more rigid comparison of the quality of hyperthemia treatments delivered by different institutes.

Over the years several tumor thermal doses have been proposed (*e.g.* minimum temperature, median temperature, cumulative time above a reference temperature, temperature percentiles, thermal iso-effect dose, *etc.*) (Sapareto and Dewey, 1984). Most of these thermal parameters, especially those associated with the low end of the measured temperature distribution have been shown to correlate significantly with complete response, duration

of local control, and survival (Cox and Kapp, 1992; Oleson *et al.,* 1993; Kapp and Cox, 1995; Hand *et al.*, 1997; Sherar *et al.*, 1997). Given the fact that at present a standardized thermal dosimetry system is still lacking (Dewhirst *et al.*, 1993; Dewhirst and Sneed, 2003) and as far as there is not yet a universal measurement or a clearly defined minimum level of thermal dose (van der Zee *et al.,* 2006) we consider flexibility as an essential requirement to easily enable a specific and reliable comparison of the quality of the hyperthemia treatment applied by different groups based on an identical thermal dose parameter definition.

When patient with deep-seated tumors are under treatment, hyperthermia groups may apply intratumor and/or intraluminal thermometry. In some institutes the approach is to measure temperature invasively in one or two treatment sessions and use the settings for these treatments as a reference for all following treatments. No studies have been reported to validate the appropriateness of this approach. It should be noted that we showed in chapter 3 that the temperatures among treatments vary substantially, whereas averaged over all treatments the achieved temperatures are reproducible over the time.

In the Rotterdam Hyperthermia Unit, thermometry in patients with a tumor in the lesser pelvis is usually restricted to the intraluminal tracks. Strong variation exists in the opinions whether intratumor thermometry provides superior information over intraluminal thermometry. In chapter 4 the relationship between intratumorally and intraluminally measured temperatures was analyzed to assess whether intraluminal thermometry provides sufficient information on the temperatures obtained within the tumor during loco-regional deep hyperthermia in pelvic tumors. It was found that intraluminal temperatures are highly correlated with those obtained intratumorally and that intratumor thermometry is not superior to intraluminal thermometry for improvement of tumor temperature level and homogeneity. Furthermore, improvement of the intratumor temperature distribution by SAR-steering with the current BSD-2000 hyperthermia system appeared not to be feasible. Of course intratumor measurement provides directly the tumor temperature. Additionally, the quality of the information about the three dimensional (3D) temperature distribution from a very limited numbers (1-5) of intratumor measuring points should not be overestimated. As a conclusion, this part of the project verifies that intraluminal thermometry provides sufficient information

to apply loco-regional deep hyperthermia treatment to individual patient with rectum, cervix, or bladder cancer.

As far as we aware, tissue type assignment, *i.e.* differentiation tumor from normal tissue, is a usual procedure for interstitial thermometry. As mentioned before, in the Rotterdam Hyperthermia Unit, thermometry in patients with a tumor in the lesser pelvis is limited to the intraluminal tracks. It was unknown whether discrimination between normal and tumor tissue is relevant for loco-regional deep hyperthermia thermal dosimetry using only intraluminal tumor-contact and tumor-indicative thermometry. Therefore, in chapter 5 we analyzed temperature data of 100 selected hyperthermia treatments to answer this question. The hypothesis was that tissue type assignment does not provide more relevant information on intraluminal temperature distribution. Although a significant difference was found between T_{50} of vagina tumor-contact (or bladder tumor-indicative) and normal tissue, it must be realized that in a statistical analysis of thermal data with a huge amount of data, such as the dataset of this study with 10000 mean temperature readings per lumen, a very small difference (*e.g.* 0.1 °C) can be easily detected statistically. However, this does not mean that the difference is relevant. Given the error associated with our method of tissue type assignment, the exact location of each temperature point may vary by 1-2 cm. Also with regard to the large temperatures range in which hyperthermia is effective, we can state that the temperature difference should be greater than 0.3 °C in order to be considered relevant (in the range of 37-43 °C, 0.3 °C equals a 10% temperature increase). With the current equipment even a difference of 0.4°C, which found between T_{50} of vagina tumor-contact and normal tissue, is only 'borderline' relevant. Therefore, our conclusion is that at present discrimination between normal tissue and tumor-contact/indicative in intraluminal thermometry does not provide additional information of clinical relevance. Consequently, in intraluminal thermometry there appears to be no need to perform tissue type assignment.

Hyperthermia is considered a valuable anti-cancer treatment modality in several Western countries. Commonly, loco-regional deep hyperthermia is applied by electromagnetic radiation and requires the use of complex high technological equipment (Stauffer, 2005). Given the continuous technological evolution of the available hyperthermia devices and growing personal experience, extended data analyses over a long period provide an excellent

opportunity to study the ability to induce a reproducible temperature increase in the target volume. Clearly, reproducible heating is a major factor for the general acceptance of hyperthermia as a common treatment modality. Furthermore, knowledge about the level of reproducibility is important for the design of treatment protocols as well as quality assurance procedures and to make valid assumptions on prognostic factors. No doubt reproducibility will reflect in ease of application, time efficiency, safety for patient, and so forth. Finally, the knowledge obtained by such studies can be fruitfully used to design education and training programs for hyperthermia staff-members.

As long as the PDOS hyperthermia treatment data produced by the BSD-2000 system were not easily accessible, research concerning power and temperature was postponed. The development of RHyThM and its unique feature, *i.e.* full access to the details of RF-power values, enabled us to perform extensive analysis of the power and temperature behavior of the BSD-2000 hyperthermia system. In chapter 6 we presented an investigation towards the relationship between applied RF-power and achieved temperature in 444 primary cervical cancer patients treated over the 15 years application of deep hyperthermia in Rotterdam. The goal of this part of the project was to evaluate the reproducibility of the loco-regional deep hyperthermia applied with the BSD-2000 and the Sigma-60 applicator driven with one of four different power systems. As temperature is a primary indicator of treatment quality, immediately available at the end of the treatment session for quality analysis, our intention was to find a patient- or RF-power related parameter that correlates with average temperature in the clinical situation. To our opinion, these kinds of investigations contribute to provide the information needed to plan future prospective studies, *e.g.* to find power or patient related parameter(s) that correlate with temperature in the clinical situation.

The study in chapter 6 showed that the BSD-2000 Sigma-60 applicator was able to reproducibly generate moderate loco-regional deep heating with intraluminal temperatures of 40-40.5 °C in primary cervical cancer patients. We also found that despite some changes in the total applied power, switched-off modulation, personnel experience, and treatment strategy the achieved temperature did not change much over the 15 years. Clearly, the comfort of the treatment has improved as the majority of our patients now fulfill the whole treatment procedure. Unfortunately, this part of the study did not result in a set of patient- or RF-power related parameter with a clear prognostic value for

temperature. The results on one hand show the reproducibility of the application of loco-regional deep hyperthermia to primary cervical cancer patients, but on the other hand, demonstrate the difficulty to increase thermal dose and that the power prescription still depends to individual patient's characteristics.

The characterization of the performance of hyperthermia applicators by phantom experiments has been demonstrated to be a useful tool to understand the specific behavior of an applicator and to design an applicator specific quality assurance program (Baroni *et al.*, 2001; van Rhoon *et al.*, 2003b). Obviously, replacement of an old clinical effective applicator by a newly designed applicator is only acceptable after an extensive comparison between the basic characteristics of the new and old applicators. In the last part of the present project (chapter 7) the energy distribution of the Sigma-60-Ellipse applicator was evaluated to establish whether its SAR-characteristics are equivalent to those of the Sigma-60 and the Sigma-Eye. In this study the stability of the SAR-distribution was assessed as function of power and frequency; and the accuracy of target steering was evaluated at various frequencies. We found that at the lower frequencies of 75-90 MHz and at 100 MHz the SAR-characteristics, expressed as the 50% iso-SAR areas and the longitudinal and the radial lengths of the 50% iso-SAR area, were almost identical to those of the Sigma-60 and Sigma-Eye applicators, respectively. Therefore, our conclusion is that at the frequency range of 75-90 MHz the Sigma-60 and at 100 MHz the Sigma-Eye can safely replace the Sigma-60-Ellipse applicator carries the same potential of achieving an adequate heat quality.

8.2 Future perspectives

Nowadays, hyperthermia is considered as a valuable adjuvant to conventional cancer treatment modalities in several Western countries. Thermometry and temperature monitoring are two crucial issues in hyperthermia. Conventional thermometry, *i.e.* intratumor and/or intraluminal thermometry methods are still applied by the majority of the hyperthermia groups. Notes that the clinical results showing a benefit of adding hyperthermia to radiotherapy and/or chemotherapy have been obtained using these conventional techniques.

Future development in thermometry will depend to whether a clear correlation between hyperthermia treatment outcome and a thermal dose can be

identified. However, if treatment outcome will be more related to other physiological parameters such as $PO_{2,}$ blood flow, *etc.* then the need for extensive thermometry can be questioned. At this time more and more publications are available demonstrating in retrospective analysis that a correlation between treatment outcome and CEM43°CT_{90} may exist. Assuming that temperature is not a confounder of another tumor characteristics, then accurate assessment of the 3D temperature distribution will be an essential requirement for controlled application of hyperthermia.

At present the most advanced method to obtain the 3D temperature distribution is non-invasive thermometry using MRI (magnetic resonance imaging) (van Rhoon and Wust, 2005; Gellermann *et al.*, 2005a). As shown by the hyperthermia centers in Charité Virchow Klinikum in Berlin, Germany, (Gellermann *et al.*, 2005b) and Duke University in Durham, USA, (Das *et al.*, 2001) the development of a hybrid system, combining non-invasive thermometry by MRI and loco-regional deep hyperthermia by the BSD-2000, requires a strong technological effort.

Furthermore, for economical reasons, widespread use of non-invasive thermometry by MRI is expected to progress slowly in coming years and potentially only for loco-regional deep hyperthermia treatments with increased survival gain. Routine use of non-invasive thermometry by MRI for other hyperthermia treatments with a more palliative intention may appear not realistic. Other, less costly, techniques for non-invasive thermometry are still lacking or do not provide the required spatial resolution and temperature sensitivity. Alternatively, enhancing the quality of thermal dosimetry by increasing the density of intratumoral or minimal invasive temperature measuring points will clearly not be appreciated either by the patient or by the clinician. Hence, the only way left to obtain a better 3D assessment of the temperature distribution is to exploit current existing 3D hyperthermia treatment planning system (Wust *et al.*, 1996; Gellermann *et al.*, 2000; Lagendijk, 2000) to provide a 3D reconstruction of a predicted hyperthermia dose parameter, for instance SAR-coverage or ‘temperature’. Such work is currently in progress within the Rotterdam Hyperthermia Group. The promising results obtained in the hyperthermia treatment planning study, demonstrate the need to continue the work presented in this thesis and to find a hyperthermia treatment planning predictable parameter that correlates with treatment outcome.

Chapter 9

Summary

Summary

The present thesis is intended to be an explorative study to find input patient- or RF-power related parameters that can be correlated with temperature parameters which are regarded to express the technical/physical quality of deep hyperthermia treatment, whereby the quality of the treatment is related with treatment outcome.

A first global contemplation of thermal data acquired over 15 years applying loco-regional deep hyperthermia in Rotterdam confronted us with a number of questions for which a satisfactory answer was not available. Therefore, in this thesis following topics have been addressed: 1) How can we guarantee the integrity of the hyperthermia treatment data? 2) Do we need a reference temperature point in order to compare the results obtained by different hyperthermia groups? 3) Intratumor or intraluminal thermometry? Is intraluminal thermometry sufficient for thermal data acquisition for hyperthermia treatment of centrally located tumors in the lesser pelvis? 4) Does the assignment of a tissue type to each temperature measuring point along the thermometry catheter provide relevant additional information on the intraluminal temperature distribution? 5) What is the reproducibility of loco-regional deep heating in Rotterdam over the 15 years using four distinct configurations of the BSD-2000 hyperthermia system and the Sigma-60 applicator? 6) Can we safely replace the Sigma-60 or the Sigma-Eye applicator

of the BSD-2000 with the Sigma-60-Ellipse without the risk of decreasing heating quality?

Chapter 1 provides a general introduction to hyperthermia. A brief background, an overview of maturation of technology, a description of the loco-regional deep hyperthermia procedure, thermometry in loco-regional deep hyperthermia, and a summary of the most impressive clinical results are presented.

In this thesis the main data-source was the PDOS-based formatted hyperthermia treatment data generated by the BSD-2000 system (BSD Medical Corporation, Salt Lake City, Utah, USA). An important disadvantage of the older BSD-2000 systems is that the treatment data is stored on PDOS formatted disk, which cannot be accessed by PC running under Microsoft Windows. Only after the availability of a PDOS to MSDOS environment program, the data became accessible and was a special program developed to analyze the encrypted data. This program, *i.e.* RHyThM (Rotterdam Hyperthermia Thermal Modulator) is presented in *Chapter 2*. RHyThM performs an integrity check (*i.e.* it verifies whether the data falls within an '*a priori'* defined range), provides a graphical user interface, with which the tissue type for each measuring point can be easily assigned, and offers an efficient method to correct for unrealistic temperature values. Furthermore, RHyThM prepares a minimum of data analysis necessary for a quick evaluation of the treatment quality directly at the end of the treatment.

In *Chapter 3* an exploratory analysis was performed on 22 patients with advanced cervical carcinoma, who have been treated with radiotherapy plus hyperthermia and chemotherapy. When we compared our thermometry results with the data reported in other studies for the same group of patients, using the same or nearly the same equipment, we were confronted with a number of limitations in current procedures for temperature measurement and reporting results. Using the current practice of thermometry, including the way to report the results, it is impossible to decide whether the difference between the results is a real difference or just is reflecting variations in the applied equipment and protocols. This part of the study concluded that there exists a clear need to arrive at a consensus on new and tight guidelines to allow a valid evaluation and comparison of the quality of the hyperthermia treatments carried out in different institutes and among various clinical studies. Such guidelines are also

obligatory for an objective and quantitative assessment of major improvements in hyperthermia technology.

In *Chapter 4* the relation between intratumorally and intraluminally measured temperatures was analyzed to evaluate whether intraluminal thermometry provides sufficient information on the temperatures obtained from within the tumor during loco-regional deep hyperthermia of bladder, cervical, and rectal tumors. We found that intraluminal temperatures are highly correlated with those obtained intratumorally and that intratumor thermometry is not superior to intraluminal thermometry for improvement of tumor temperature level and homogeneity. Moreover, improvement of the intratumor temperature distribution by SAR (specific absorption rate)- steering with the current BSD-2000 hyperthermia system seemed not to be feasible. Consequently, this part of the study confirms that intraluminal thermometry provides sufficient information for an adequate application of loco-regional deep hyperthermia to individual patient with rectum, cervix, or bladder cancer. The outcome of this part of the study is especially relevant for patients whose tumor is located centrally in the lesser pelvis, as it spares them from the painful and cumbersome procedure of intratumor thermometry.

In *Chapter 5* temperature data of 43 patients with advanced cervical cancer were extensively analyzed to know whether tissue type assignment, *i.e.* discrimination between normal and tumor-contact/indicative tissue, is relevant using only intraluminal thermometry. The hypothesis was that the tissue type assignment does not add relevant information to the overall intraluminal temperature distribution. For this part of the project 100 hyperthermia treatments were selected specifically having constant quality of the thermal maps, *i.e.* no displacement of thermometry catheters along the intraluminal track during the 90 min treatment. No difference was found between rectum normal tissue T_{50} (40.7 °C) and rectum tumor-indicative T_{50} (40.6 °C). Significant different ($p<0.0001$) was found between vagina normal tissue T_{50} (39.7 °C) and vagina tumor-contact T_{50} (40.1 °C). Similarly, significant different ($p<0.0001$) was found between bladder normal tissue T_{50} (40.8 °C) and bladder tumor-indicative T_{50} (40.9 °C). We should notice though, that in a statistical analysis of a huge dataset, such as the temperature data of this study with 10000 mean temperature readings per lumen, a very small difference (*e.g.* 0.1 °C) can be easily detected statistically. However, this does not mean that the difference is clinically relevant. With the current equipment even a

difference of 0.4 °C is only marginally relevant. So, at present differentiation between normal and tumor-contact/indicative tissue in intraluminal thermometry does not support additional relevant clinical information. As a conclusion, in intraluminal thermometry there seems to be no need to perform tissue type assignment.

In *Chapter* 6 the global behavior of the performance of loco-regional deep heating was evaluated over the years from 1990 to 2005. The BSD-2000 system was applied together with the Sigma-60 applicator driven with one of the four different power systems. As temperature is a primary indicator of treatment quality, available at the end of the treatment session, the intention, in this part of the study, was to find a patient- or RF-power related parameter that correlates with average temperature in the clinical situation. Unfortunately, this part of the project did not result in a set of patient- or RF-power related parameter with a clear prognostic value for temperature. The study shows a dependence of temperature on the weight of the patient, for heavy weight patients the average all lumina temperature was significantly lower than those for the low weight patients ($W<61$ kg, $T_{50} = 40.6$ °C; $61 \leq W \leq 70$ kg, $T_{50} = 40.5$ °C; $W>70$ kg, $T_{50} = 40.3$ °C). Furthermore, the study shows that the four configurations of the BSD-2000 amplifiers driving the Sigma-60 provided almost similar power outputs and were able to reproducibly generate moderate heating at intraluminal temperatures of 40-40.5 °C. Temperatures and heating pattern did not change significantly over the 15 years application of hyperthermia, while the experience of hyperthermia staff-members and treatment protocols had certainly improved.

In *Chapter 7* the energy distribution of the Sigma-60-Ellipse applicator was assessed to find out whether the SAR-characteristics, expressed as the 50% iso-SAR areas and the longitudinal/radial length of the 50% iso-SAR area, of the new applicator match to those of the Sigma-60 and the Sigma-Eye. The stability of the SAR-distribution was evaluated as function of power and frequency; and the accuracy of target steering was assessed at various frequencies. At the frequency range of 75-90 MHz the SAR-characteristics were almost identical to those of the Sigma-60 and at 100 MHz for the Sigma-Eye applicator. Hence, our conclusion is that at the lower frequencies of 75-90 MHz the Sigma-60 and at 100 MHz the Sigma-Eye can safely replace the Sigma-60-Ellipse applicator.

Chapter 8 discusses the findings of the project towards assessing improvement of the technical/physical quality of loco-regional deep hyperthermia treatment. The chapter provides the final conclusions and end with future perspectives concerning the development of accurate and patient friendly thermometry for loco-regional deep hyperthermia treatment.

Chapter 10

Samenvatting
(Summary in Dutch)

Samenvatting

Dit proefschrift kan gezien worden als een exploratief onderzoek met als doel het identificeren van mogelijke prognostische inputparameters tijdens de behandeling met diepe hyperthermie, zoals rf-vermogen, patiënt gewicht, welke correleren met de gemeten temperaturen. Uitgangspunt daarbij is dat de temperatuurparameters een goede maat zijn voor de technische/fysische kwaliteit van de diepe hyperthermie behandeling, waarbij de kwaliteit van de behandeling gecorreleerd is met de effectiviteit van de behandeling.

Een eerste oppervlakkige beschouwing van de temperatuur data verzameld over een periode van meer dan 15 jaar klinische loco-regionale, diepe hyperthermie in Rotterdam confronteerde ons met een aantal vragen waarvoor een bevredigend antwoord niet beschikbaar was. In reactie hierop worden in dit proefschrift de volgende onderwerpen behandeld: 1) Hoe kunnen wij de integriteit van de gemeten data tijdens de hyperthermiebehandeling waarborgen? 2) Is een valide vergelijking van de, door de verschillende hyperthermiegroepen, gerapporteerde resultaten alleen mogelijk als de temperatuur (dus de technische kwaliteit van de behandeling) in een referentiepunt gegeven wordt? 3) Intratumor of intraluminale thermometrie? M.a.w. volstaat intraluminale thermometrie voor een representatieve temperatuur registratie tijdens een diepe hyperthermiebehandeling van tumoren centraal gelegen in het kleine bekken? 4) Geeft weefseltypering van elk

afzonderlijk temperatuur meetpunt langs de intraluminale thermometrie katheter relevante aanvullende informatie over de temperatuurdistributie? 5) Hoe reproduceerbaar was de toepassing van loco-regionale, diepe hyperthermie in Rotterdam in de afgelopen 15 jaar, waarin vier verschillende configuraties van het BSD-2000 hyperthermiesysteem met de Sigma-60 applicator zijn gebruikt? 6) Is het verantwoord dat de Sigma-60-Ellips, de Sigma-60 of de Sigma-Eye applicator vervangt zonder verlies van kwaliteit tijdens diepe hyperthermie?

Hoofdstuk 1 geeft een algemene inleiding over hyperthermie. Na een korte uitleg van de biologische rationale, worden achtereenvolgens de volgende onderwerpen toegelicht: de ontwikkeling van de technologie, de methodiek van verwarmen en het meten van de temperatuur verdeling bij loco-regionale diepe hyperthermie, en tenslotte een samenvatting van de meest aansprekende klinische resultaten.

Het onderzoek gerapporteerd in dit proefschrift is geheel gebaseerd op de retrospectieve analyse van de gegevens zoals die door het BSD-2000 diepe hyperthermie systeem (BSD Medical Corporation, Salt Lake City, Utah, USA) tijdens elke hyperthermie behandeling worden vastgelegd. Een belangrijk nadeel van de oudere BSD-2000 hyperthermie systemen is dat de gemeten gegevens in PDOS-format op een floppy disk bewaard worden. Het PDOS format is helaas niet leesbaar met een personal computer die onder Microsoft Windows werkt. Pas nadat er in PDOS een conversie programma beschikbaar kwam om de data onder MSDOS format op te slaan, kon er lokaal een speciaal computer programma ontwikkeld worden om de gecodeerde meetgegevens te analyseren. Dit programma, *d.w.z*. RHyThM (Rotterdam Hyperthermia Thermal Modulator) wordt beschreven in *Hoofdstuk 2*. RHyThM is een waardevol hulpmiddel, dat de gebruiker op eenvoudige wijze toegang geeft tot alle gemeten behandelgegevens. RHyThM voorziet in een integriteitscontrole van de gegevens (*d.w.z.* valideert of de gemeten data binnen vooraf vastgestelde grenzen ligt), een grafische gebruikersinterface (hiermee kan het weefsel type per meetpunt ingevoerd worden) en biedt een efficiënte procedure voor het corrigeren van onrealistische temperatuurwaarden. Verder voert RHyThM een basale gegevensanalyse uit, waarmee direct na afloop de kwaliteit van de diepe hyperthermie behandeling geëvalueerd kan worden.

Hoofdstuk 3, rapporteert een oriënterende analyse uitgevoerd op de gemeten behandeldata van 22 patiënten met vergevorderde

baarmoederhalskanker, welke behandeld werden met radiotherapie plus hyperthermie en chemotherapie. Toen wij onze temperatuurgegevens wilden vergelijken met de resultaten gerapporteerd door andere onderzoekers bij dezelfde groep van patiënten en behandeld met identieke of vrijwel identieke apparatuur, werden wij geconfronteerd met een aantal ernstige beperkingen in de huidige procedures van temperatuurmeting en rapportage. Klaarblijkelijk geven de afspraken voor thermometrie nog zoveel vrijheid in de exacte plaatsing van de temperatuurmeters, dat een goede vergelijking van de gerapporteerde temperatuur data niet mogelijk was. Hierdoor kon niet vastgesteld worden of het verschil tussen de gerapporteerde temperaturen een echt verschil in kwaliteit van verwarmen representeert of dat de verschillen in temperatuur enkel en alleen een weerspiegeling is van de variaties in de gebruikte apparatuur en lokale protocollen. De conclusie van dit deel van de studie is dat er binnen hyperthermie een duidelijke behoefte bestaat aan consensus over nieuwe richtlijnen met strakke regels omtrent de temperatuurmeting en rapportage. Pas nadat hieraan voldaan is, kunnen de, door verschillende instituten, gerapporteerde temperaturen op een valide manier worden vergeleken. Dergelijke richtlijnen zijn ook een absolute voorwaarde om de effectiviteit van belangrijke technische verbeteringen van de hyperthermie apparatuur op een objectieve wijze te kwantificeren.

In *Hoofdstuk 4* wordt de relatie tussen intratumor en intraluminaal gemeten temperaturen geanalyseerd om vast te kunnen stellen of intraluminale thermometrie tijdens loco-regionale, diepe hyperthermie van blaas, cervix en rectum tumoren voldoende informatie geeft over de bereikte temperaturen in het doelgebied. In deze studie tonen wij aan dat intraluminale temperaturen in hoge mate gecorreleerd zijn met de intratumor temperaturen en dat de intratumor thermometrie niet superieur is aan intraluminale thermometrie voor verbetering van niveau en homogeniteit van de tumortemperatuur. Bovendien werd duidelijk dat temperatuurdistributie gemeten in de tumor niet verbeterd kan worden door energiesturing met het huidige BSD-2000 hyperthermie systeem. Derhalve bevestigt dit deel van de studie dat intraluminale thermometrie voldoende informatie verstrekt om loco-regionale, diepe hyperthermie op adequate wijze uit te voeren bij patiënten met centraal in het kleine bekken gelegen rectum-, baarmoederhals- of blaastumoren. Dit resultaat is met name van belang voor het welbevinden van de patiënt, omdat hiermee de pijnlijke en belastende intratumor thermometrie achterwege kan blijven.

In H*oofdstuk 5* worden de temperatuurgegevens van 43 patiënten met vergevorderde baarmoederhalskanker uitgebreid geanalyseerd om vast te stellen of het, bij intraluminale thermometrie, relevant is om onderscheid te maken tussen normaal weefsel en tumor-contact/indicatief, *d.w.z.* weefseltypering. De hypothese was dat weefseltypering bij intraluminale thermometrie geen relevantere informatie geeft. Voor dit onderzoek werden 100 hyperthermie behandelingen geselecteerd, waarbij de thermometrie katheters gedurende de gehele duur van de behandeling (90 minuten) niet verschoven zijn, *d.w.z.* de kwaliteit van de temperatuurmeting langs de katheter (de 'thermal map') is constant. In deze studie werd geen verschil gevonden tussen rectum normaal weefsel T_{50} (40.7 °C) en de tumor-indicatieve T_{50} (40.6 °C). Een significante verschil ($p<0.0001$) werd wel gevonden tussen vagina normaal weefsel T_{50} (39.7 °C) en tumor-contact T_{50} (40.1 °C). Eveneens werd een significant verschil ($p<0.0001$) gevonden tussen blaas normaal weefsel T_{50} (40.8 °C) en tumor-indicatieve T_{50} (40.9 °C). Opgemerkt dient te worden dat bij een statistische analyse van een zeer grote dataset (in deze studie gemiddeld 10.000 temperatuur uitlezingen per lumen) een zeer klein verschil (*b.v.* kan 0.1 °C) gemakkelijk statistisch significant wordt. Dat wil echter niet nog niet betekenen dat het verschil ook klinisch relevant is. Met de huidige apparatuur is zelfs een verschil van 0.4 °C maar marginaal relevant. Samengevat, de gevonden verschillen tussen de normaal en tumor-contact/indicatief temperaturen geven geen extra klinische informatie tijdens intraluminale thermometrie en de weefseltypering kan dus achterwege blijven.

Hoofdstuk 6 geeft een evaluatie van de reproduceerbaarheid van de toepassing van loco-regionale, diepe hyperthermie vanaf de allereerste behandeling in 1990 tot 2005. Gedurende deze gehele periode werd verwarmd met het BSD-2000 Sigma-60 systeem, waarbij vier verschillende versies van het systeem werden gebruikt. De verschillen tussen de versies betroffen vooral het gedeelte van de RF-versterkers. Aan het einde van elke behandeling kan op basis van de gemeten temperatuurverdeling (een primaire indicator) de kwaliteit van de behandeling vastgesteld worden. Helaas, binnen deze studie werd geen duidelijke patiënt- of RF-power gerelateerde parameter gevonden, welke prognostisch is voor de gemeten temperatuurverdeling. Wel liet de studie zien dat de temperatuur bij zwaardere patiënten lager was dan bij lichtere patiënten ($W<61$ kg, T_{50} = 40.6 °C; $61\leq W\leq 70$ kg, T_{50} = 40.5 °C; $W>70$ kg, T_{50} = 40.3 °C). Daarnaast volgde uit de studie dat de kwaliteit van verwarmen

zeer reproduceerbaar is, met gemiddelde intraluminale temperaturen in de range van 40.0-40.5 °C, en onafhankelijk is van het versie nummer van het BSD-2000 Sigma-60 systeem. De temperatuurverdeling en het patroon van het temperatuurverloop is gedurende de afgelopen 15 jaar niet wezenlijk gewijzigd, hoewel zowel de ervaring van het hyperthermiepersoneel als ook de behandelprotocollen zeker zijn verbeterd.

H*oofdstuk 7* geeft onze procedure om de energiedistributie van de Sigma-60-Ellips applicator te beoordelen. Doel van deze studie is om vast te stellen of de SAR (specific absorption rate)- karakteristieken, zoals vorm en oppervlak van het 50% iso-SAR gebied en ook de longitudinale/radiale lengte van het 50% iso-SAR gebied, van de nieuwe Sigma-60-Ellips applicator overeenkomen met die van de oudere Sigma-60 en Sigma-Eye applicator. Tevens werd de stabiliteit van de SAR-distributie geëvalueerd als functie van RF-vermogen en frequentie, als ook de nauwkeurigheid van SAR-sturing gemeten als functie van de frequentie. Bij frequenties tussen 75-90 MHz zijn de SAR-karakteristieken van de Sigma-60-Ellips nagenoeg identiek aan die van de Sigma-60 en bij 100 MHz aan die van de Sigma-Eye applicator. Onze conclusie is dat de Sigma-60-Ellips een adequate vervanging kan zijn voor de Sigma-60 en de Sigma-Eye applicator mits de applicator werkt op de juiste frequentie.

Tot slot worden in *Hoofdstuk 8* de bevindingen besproken van het gehele onderzoek gericht op het meten en verbeteren van de technische/fysische kwaliteit van loco-regionale diepe hyperthermiebehandeling. Het hoofdstuk geeft tevens de finale conclusies van het onderzoek, doet een aantal suggesties voor verder onderzoek en besluit met een toekomst perspectief over de ontwikkeling van goede en patiënt vriendelijke thermometrie tijdens loco-regionale diepe hyperthermie.

Chapter 11

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Chapter 12

Appendix

Abbreviations

2D	Two Dimensional
3D	Three Dimensional
AD	Analog to Digital
AP	Anterior Posterior
ASCII	American Standard Code for Information Interchange
ASETUP	Applicator setup
CEM	Cumulative Equivalent Minutes
CT	Computer Tomography
DA	Digital to Analog
DDHK	Daniel den Hoed Klinik
EMF	Electro Magnetic Field
ESHO	European Society for Hyperthermic Oncology
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
Gy	Gray (unit of absorbed dose 1Gy=1J/kg)
hrs	Hours
Lat	Lateral
min	Minute
MRI	Magnetic Resonance Imaging
MS	Micro Soft
MSDOS	Micro Soft Disk Operating System
NaN	Not a Number
NED	No Evidence of Disease
PA	Posterior Anterior
PC	Personal Computer
PDOS	Public Domain Data Operating System
PRBLC	Probe Location
p	Probability
pts.	patients
RCA	Radiative Cone Applicator
RF	Radiofrequency
RHyThM	Rotterdam Hyperthermia Thermal Modulator
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAR	Specific Absorption Rate
SD	Standard Deviation
SDS	Schottky Diode Sheet
TEM	Transverse Electro Magnetic
ThmapX	X^{th} Thermal map
trts.	treatments
T_X	Temperature which is exceeded by X percent of all temperature readings
vs.	versus
WHO	World Health Organization
yrs.	years
Σ-60	Sigma-60 applicator
Σ-60-E	Sigma-60-Ellipse applicator

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List of publications:

A: Full papers in international journals:

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The cover shows a three-dimensional temperature curve provided by means of RHyThM (Rotterdam Hyperthermia Thermal Modulator): thermal data validation to check for probe movement and for unrealistically high temperature gradients in position and time.