Hyperthermia for the treatment of locally advanced cervix cancer

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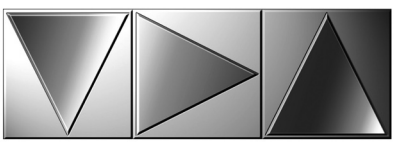

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Hyperthermia for the Treatment of Locally Advanced Cervix Cancer

Hyperthermie voor de behandeling van locaal uitgebreide baarmoederhalskanker

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Contents

Chapter 1

Introduction and outline of this thesis

Introduction

Worldwide interest in hyperthermia is on the rise, which is what one would expect in view of the considerable therapeutic benefit that has been shown in clinical studies. Even more important: hyperthermia does so without increasing acute or late side effects.

This thesis explores current clinical rationale and outcome of hyperthermia for the treatment of locally advanced cervix cancer. Further, possible ways to improve treatment quality and clinical outcome are investigated.

I. Biological rationale of hyperthermia

There is a strong biological rationale for the application of hyperthermia as an oncological treatment modality. At temperatures of ≥ 40 ^{0}C direct cytotoxicity occurs as a result of protein denaturation.[1] This hyperthermia-induced cell death specially affects cells that are in hypoxic, acidotic and nutrient-deprived areas of the tumor, which happen to be the areas in which chemotherapy and radiotherapy are least effective. This effect is also tumor-selective, as tumors generally contain more hypoxic, acidotic and nutrient-deprived areas compared to normal tissue, because their chaotic vasculature causes low perfusion in parts of the tumor. [1-3]

§ 1. The combination with radiotherapy

Several randomized trials have shown a significant improvement in clinical outcome when hyperthermia is added to radiotherapy for pelvic tumors, melanomas, breast cancer, soft tissue sarcomas, lung cancer, esophageal cancer, lymph node metastasis of head and neck tumors and glioblastoma multiforme (table 1).[4-19] When combining radiotherapy with hyperthermia, treatment efficacy is increased due to interference with DNA repair mechanisms. Also, hyperthermia decreases hypoxia, acidosis and nutrient deprivation in the tumor area, making tumor cells more susceptible to radiotherapy-induced cell death. To quantify the radiosensitizing effect of hyperthermia, the thermal enhancement ratio, or TER, is often used. The TER of normal cells as well as tumor cells is dependant on both temperature and heating time. In vivo studies have shown TER values of 1.2 – 5 with higher TER values found under hypoxic conditions, at higher temperatures and with longer exposition to heat (figure 1).[20-22] Generally, the maximum TER can be achieved by applying radiotherapy and hyperthermia simultaneously. The major drawback of simultaneous application is that hyperthermia will then enhance the radiotherapy effect in the tumor

Table 1 : Randomized trials showing significantly better outcome following a combination of radiation (RT) or chemotherapy (CT) with hyperthermia (HT), compared to the same treatment without hyperthermia

First author [ref]	Tumortype	Treatment	Patients (lesions)	Endpoint	With HT	Without HT
Valdagni[4,5]	LN of head and neck tumors	RT	41(44)	CR-rate	83 %	41 %
				5 yr LC	69 %	24 %
				5 yr OS	53 %	0 %
Overgaard[6]	Melanoma	RT	70 (138)	CR-rate	62 %	35 %
				2 yr LC	46 %	28 %
Vernon[7]	Breast	RT	306	CR-rate	59 %	41 %
Sneed[8]	Glioblastoma multiforme	S, RT	68	Med surv	85 wks	76 wks
				2 yr OS	31 %	15 %
Van der Zee[9]	Bladder, rectum, cervix	RT	298	CR-rate	55 %	39 %
				3 yr OS	30 %	24 %
Berdov[10]	Rectum	RT, S	115	5 yr OS	36 %	7 %
Colombo[11]	Bladder	CT	52	pCR	66 %	22 %
Datta[12]	Cervix	RT	64	CR-rate	55 %	31 %
Harima[13]	Cervix	RT	40	CR-rate	85 %	50 %
Kakehi[14]	Rectum	RT	14	Response	100 %	20 %
Kitamura[15]	Esophagus	RT, CT	66	CR-rate	25 %	6 %
Sugimachi[16]	Esophagus	RT, CT, S	53	Palliation	70 %	8 %
You[17]	Rectum	RT, S	122	pCR	23 %	5 %
Colombo[18]	Bladder	CT	83	Recurrence rate	58 %	17 %
Issels[19]	STS	CT	341	Response	29 %	13 %
				LRFS	45.3 mnths	23.7 mnths
				DFS	31.7 mnths	16.2 mnths

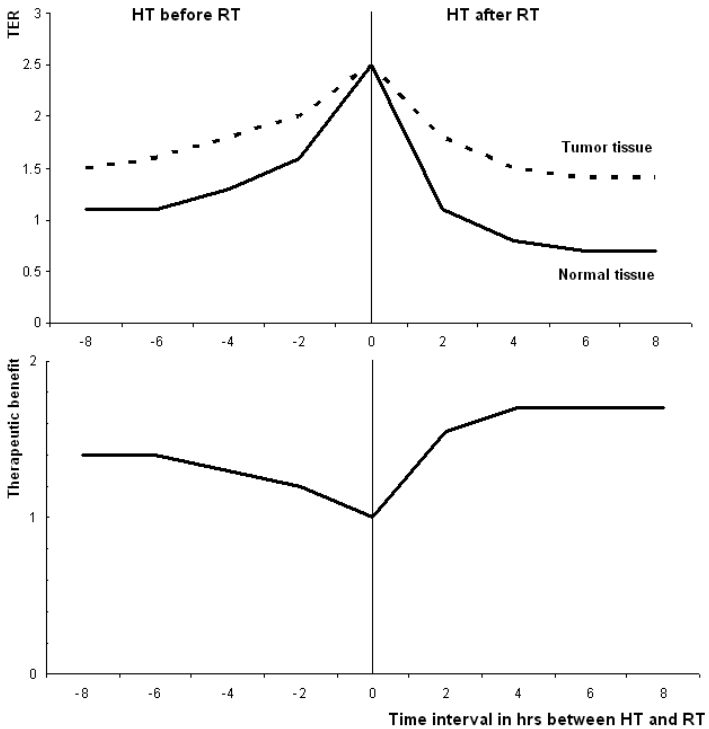
Legend: LN = lymph node metastases, S = surgery, CR-rate = complete response rate, 2 yr LC = local control 2 years after treatment, 5 yr LC = local control 5 years after treatment, 2 yr OS = overall survival 2 years after treatment, 3 yr OS = overall survival 3 years after treatment, 5 yr OS = overall survival 5 years after treatment, med surv = median survival, 3 yr OS = overall survival 3 years after treatment, pCR = pathological complete response, LRFS = local recurrence free survival, DFS = disease free survival, LC 18 mnths = local control 18 months after treatment, mnths = months, wks = weeks

and the normal tissue equally. When radiotherapy and hyperthermia are applied consecutively, the radiotherapy effect will still be enhanced in the tumor but will be much less so in the normal tissue. So when a time delay between radiotherapy and hyperthermia is introduced, there will be preferential thermal enhancement of the anti-tumor effect with minimum enhancement of the normal tissue effect.[3]

§ 2. The combination with chemotherapy

Besides the tumor-selective cytotoxicity described in the previous paragraph, there is also a synergistic effect due to spatial cooperation when combining chemotherapy with hyperthermia as the concentration of the drug is low in areas with low perfusion. The addition of hyperthermia stimulates blood flow and thereby drug delivery to the tumor. Also,

Figure 1: Thermal enhancement ratio (TER) for normal tissue and for tumor tissue as a function of the time interval between radiation and hyperthermia (figure adapted from reference 22)



Legend: HT = hyperthermia, RT = radiotherapy

hyperthermia can cause potentiation of the drug and may counteract drug resistance. Possibly, pharmacodynamics is altered by the application of hyperthermia in close sequence to chemotherapy resulting in an increased efficacy of chemotherapy and decreased excretion of the drug. The CER (Chemotherapy Enhancement Ratio) is also dependant on temperature and exposure time and ranges between 1.0 and 3.9.[1, 23-24]

II. Cervix cancer

§ 1. Background

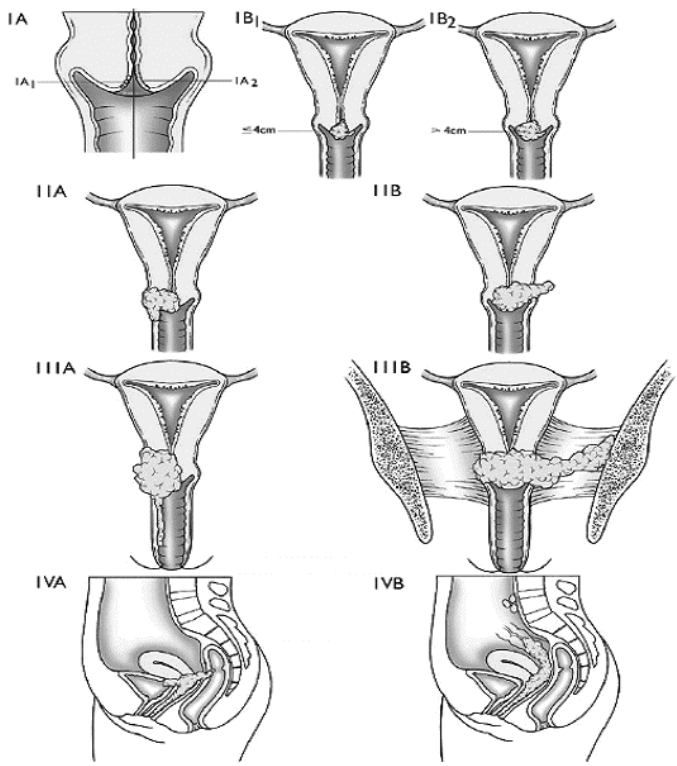
In the Netherlands, approximately 700 women are diagnosed with invasive cervix cancer each year. The disease mainly affects women between the ages of 35 and 55 and the 5-year survival rate ranges from 10 % to 98 %, depending on tumor stage.[25]

HPV infection is a central causal factor in cervix cancer. The risk of HPV infection, and thus cervix cancer, increases with the number of sexual partners, the number of live-born children, longer duration of oral contraceptive use, smoking and the use of immunosuppressive medication.[26-27]

§ 2. Current treatment of cervix cancer

The type of treatment depends on the stage of the tumor at diagnosis. For cervix cancer staging, the International Federation of Gynecology and Obstetrics (FIGO) system is commonly used (figure 2).[28-29] In the Netherlands the preferred treatment for early primary cervix cancer stage is surgery, while for higher stages radiotherapy is used.

Figure 2: FIGO (International Federation of Gynaecology and Obstetrics) staging system for cervix cancer[28,29]



§ 2.a Radiotherapy alone

For decades, radiotherapy has been the mainstay of treatment of inoperable cervix cancer (FIGO stage Ib2 to IVa). After radiotherapy alone, the locoregional failure rate still ranges

between 41 and 72 % for patients with a more advanced-stage tumor.[30-31] Researchers therefore kept on searching for ways to improve treatment outcome for these patients e.g. by combining radiotherapy with chemotherapy and/or with hyperthermia.

§ 2.b Radiotherapy and chemotherapy

In 1999 and 2000, five randomized trials were published showing a positive effect on treatment outcome when adding chemotherapy to radiotherapy for various stages of cervix cancer and in various treatment regimens.[32-36] But besides a positive effect on treatment outcome, all of these trials also showed an increase in acute treatment-related toxicity. An increase in late toxicity was not found, but follow-up was not sufficiently long, except for one of these trials.[35] So no definite conclusions can be drawn concerning the late toxicity of chemoradiation.[37]

In spite of these uncertainties, the results of these trials prompted the National Cancer Institute to issue an alert stating that 'concomitant (cisplatin-based) chemoradiation should be considered instead of radiotherapy alone in women with cervix cancer'.

Two meta-analyses confirmed the improved survival with the addition of chemotherapy to radiotherapy, but caution was advised when extrapolating the results to the general population of cervix cancer patients. Caution was indicated because of differences in trial design, methods used for patient selection, the quality of the radiotherapy applied and because only patients fit enough to receive chemotherapy were included in the trials.[38-40]

§ 2.c Radiotherapy and hyperthermia

In 1996 a randomized trial, the Dutch Deep Hyperthermia Trial (DDHT) showed a significant improvement in local control and survival when hyperthermia was added to standard radiotherapy for locally advanced pelvic malignancies.[9] The improvement was most apparent for patients with locally advanced cancer of the cervix and was not accompanied by an increase in acute toxicity like the combination with chemotherapy. The results of Dutch Deep Hyperthermia trial were supported by the results reported earlier by several smaller Asian trials that showed similar benefits of adding hyperthermia to radiotherapy (table 2).[12-13, 41-43]

Since 1996, combined radiotherapy and hyperthermia (RHT) has become a standard treatment approach for patients with locally advanced cancer of the uterine cervix in the Netherlands.[25] At present, two standard treatment approaches exist in the Netherlands for patients with locally advanced cervix cancer: chemoradiation and the combination of radiotherapy and hyperthermia.

Table 2: Randomized studies comparing radiation (RT) to radiation combined with hyperthermia (RT+HT)

First author [ref]	FIGO	n	CR-rate		Pelvic control		Overall survival	
			RT	RT+HT	RT	RT+HT	RT	RT+HT
Datta[12]	IIIB	64	58	74	46	67 ‡	73	81‡
Sharma[43]	II, III	50			50	70•		
Chen[42]	IIB, IIIB	120	48	72*				
Harima[13]	IIIB	40	50	80*	49	80 Δ*	48	58 Δ
Vasanthan[61]	IIB to IV	110			~ 80	~70 Δ	73	73 Δ

Legend: FIGO = International Federation of Gynecology and Obstetrics tumor stage, n = number of patients included in the study, CR-rate = complete response rate, RT = radiation alone, RT+HT = radiation combined with hyperthermia, * significant difference, •at 1.5 years, ‡ at 2 years, Δ at 3 years

§ 2.d Chemotherapy and hyperthermia

Historically, with 22 % local failures for locally advanced cervix cancer after radiotherapy or chemoradiation alone, around 100 patients in the Netherlands will develop a recurrent cervix cancer after previous irradiation.[25, 44] Currently the treatment options for these patients are limited. When the recurrence is resectable, no distant metastasis are found and the patient is in good clinical condition, extended pelvic surgery can be considered. At present, cisplatin is the single most effective drug in the treatment of cervix cancer with response rates of 20 to 30 %. After previous irradiation, this response rate drops to 10 %.[25]

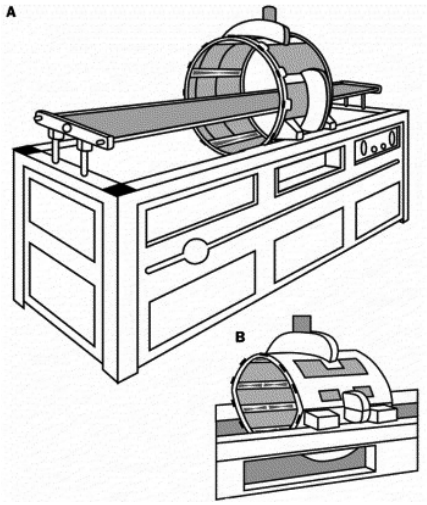
In this respect the biological effects of hyperthermia described in § 1 could of course also be of great benefit for this category of cervix cancer patients. Particularly because the poor response rate after previous irradiation is probably due to even lower perfusion post-radiotherapy.[45]

III. Application of hyperthermia for pelvic malignancies: clinical practice

§ 1. The Applicator

The BSD-2000 system (BSD Medical Corporation, Salt Lake City, Utah, USA) is being used successfully for heating tumors in the pelvic area in Rotterdam since 1990. This most commonly used deep hyperthermia system consists of a radiofrequency energy generator, twelve amplifiers and an array of eight antennas in a cylinder. The location of the microwave energy maximum can be steered by adjustments in phase and amplitude per antenna (figure 3).[46-49]

Figure 3: The BSD-2000 system with Sigma-60 (a) and Sigma-Eye (b) applicator (BSD Medical Systems, Salt Lake City, Utah, USA)[49]



§ 2. Current treatment schedules for deep hyperthermia

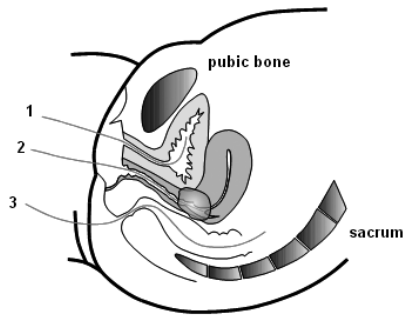
Hyperthermia is prescribed for 90 minutes. The first 30 minutes are used for heating up the patient to temperatures above 40 ^{0}C and then treatment continues for 60 minutes of actual treatment time at maximum tolerated temperatures. A minimum time window of 72 hours is observed between two consecutive hyperthermia treatments to avoid thermotolerance. Thermotolerance is the clinically observed phenomenon that, if a subsequent heat treatment is applied to soon after the previous, cells will be resistant to the effects of hyperthermia.[50]

During a hyperthermia treatment of the pelvis, temperatures are measured intraluminally in the bladder, rectum and vagina in accordance with the ESHO guidelines (figure 4).[51] These intraluminal temperatures show good correlation with the intratumorally measured temperatures and the procedure is better tolerated than interstitial measurement. [52-54]

When hyperthermia is added to radiotherapy in the treatment of cervix cancer, it is administered for a maximum of 5 sessions during the period of radiotherapy. To avoid thermotolerance hyperthermia is applied 1 to 4 hours after radiotherapy.

For hyperthermia combined with chemotherapy for recurrent cervix cancer, hyperthermia is administered simultaneously with cisplatin once weekly for a maximum of 6 sessions.

Figure 4: Thermometry in deep hyperthermia for female patients, sagittal view of the female pelvis (courtesy of D.H.M. Wielheesen)



Legend: 1 = thermometer in the bladder, 2 = thermometer in the vagina, 3 = thermometer in the rectum

§ 3. Deep hyperthermia treatment strategy

The decades of clinical experience in Rotterdam have sublimated in an application protocol for deep hyperthermia which optimally exploits the features of the BSD-2000 system. This protocol prescribes how to start a treatment and how to adjust treatment settings such as power, frequency, phase and amplitude during treatment to obtain maximum achievable temperatures in the target region. The adjustments in treatment settings are implemented based on 2 sources of information: the temperatures measured during treatment and verbal and non-verbal signs of discomfort from the patient.

The precise adjustment of the treatment settings, i.e. amount of frequency-, amplitude-, and phase-change has been decided on the knowledge available 10 to 15 years ago. At that time modelling was rather limited and for 2D or simple layered cylindrical 3D models only. Additional information on the potential of energy steering with deep hyperthermia systems was assessed experimentally using qualitative measuring devices with limited resolution in space and signal. Despite these limitations, these experience-based guidelines have proven their merits in various trials. However, these guidelines are non-patient specific and are based exclusively on limited modelling and on years of local experience.

§ 4. New developments in hyperthermia treatment strategy

Inevitably, experience-based application of hyperthermia is a major cause of differences in hyperthermia treatment quality between centers and for different applicators. A more objective approach would be preferable as it would allow a more reproducible strategy and would enable transfer of knowledge between centers and staff members. Further,

it would allow good analyses and evaluation of the treatment quality achieved in each centre and hence an important stimulant for enhancement of the treatment quality and technological improvement.

In search of such a more objective approach, a full 3D hyperthermia treatment planning system (HTPS) has been developed for the BSD-2000. This HTPS, Sigma HyperPlan (Dr. Sennewald Medizintechnik GmbH, Munich, Germany), has shown to have predictive value retrospectively.[55-57] At present, this software has no options for online optimization during a hyperthermia treatment. If it were possible to combine hyperthermia treatment planning with optimization during treatment, this may well improve the temperatures achieved during treatment.

A problem with the assessment of new technological developments in hyperthermia is the lack of an objective quality parameter. For superficial hyperthermia, a correlation between the thermal dose delivered and clinical outcome has been found.[58-60]

IV. This thesis

In this thesis, the status of hyperthermia in the treatment of locally advanced and recurrent cervix cancer in the Netherlands today is presented and factors predicting treatment outcome are identified. Further, one possible way of improving the current hyperthermia treatment quality, i.e. by using hyperthermia treatment planning is explored.

First, a brief introduction on the rationale behind hyperthermia and this thesis is presented (chapter 1). In chapter 2 the status of hyperthermia for the treatment of recurrent cervix cancer after previous irradiation is discussed. In chapter 3 the long-term results of a randomized trial of radiotherapy with or without hyperthermia for primary cervix cancer are presented. In chapter 4 the patients treated after the randomized trial closed are studied. Treatment outcome is reported and compared to the results of the randomized trial to investigate if the results of the randomized trial can be repeated in a larger and unselected group of patients and prognostic factors are identified. In chapter 5 the results of a large thermal dose analysis are presented in search of an objective treatment quality parameter.

The second part of this thesis focuses on the current status and future perspectives of the clinical use of hyperthermia treatment planning. In chapter 6 Sigma HyperPlan is employed to investigate the effect of our current hyperthermia treatment strategy on global power distribution. In chapter 7 we describe the development and first test results of a complaint-adaptive optimization routine as an additive to Sigma HyperPlan to enable online optimisation during a hyperthermia treatment. With this complaint-adaptive

optimization routine it would be possible to use Sigma HyperPlan during a hyperthermia treatment. In chapter 8 the results of a randomized trial comparing the use of Sigma HyperPlan to our current hyperthermia treatment strategy are reported. The objective of this study was to demonstrate that better or similar temperatures and thermal doses can be obtained when applying deep hyperthermia using on-line treatment planning in comparison to the current experience-based hyperthermia delivering strategy.

Finally, in chapter 9, the relevance of the findings of this research is discussed in more detail.

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PART I

Exploration of
the rationale and
clinical outcome

Chapter 2

Weekly systemic cisplatin plus locoregional hyperthermia: an effective treatment for patients with recurrent cervical carcinoma in a previously irradiated area

Franckena M, de Wit R, Ansink AC, Notenboom A, Canters RAM, Fatehi D, van Rhoon GC, van der Zee J. Weekly systemic cisplatin plus locoregional hyperthermia: an effective treatment for patients with recurrent cervical carcinoma in a previously irradiated area. Int J Hyperthermia 2007; 23: 443-450

Abstract

Purpose: Patients with recurrent cervical carcinoma within a previously irradiated area respond poorly to chemotherapy. We have treated these patients with simultaneous cisplatin and hyperthermia (CDDP+HT) and investigated response, toxicity, palliative effect and survival.

Materials and Methods: Between 1992 and 2005 47 patients received CDDP+HT. Response was evaluated by gynecologic examination and CT-scan. The Common Toxicity Criteria (CTC) scale was used for evaluation of toxicity and palliative effect. The Kaplan-Meier method was used to estimate survival, and Cox regression analysis to evaluate the influence of prognostic factors.

Results: The objective response rate was 55 %; palliation was achieved in 74 % and operability in 19 % of patients. Two patients are currently disease free at 9 years and 18+ months following treatment and 2 remained disease free until death by other causes. The median survival was 8 months and was influenced by duration of disease free interval and tumor diameter.

Grade 3-4 hematological toxicity was observed in 36 % of patients and renal toxicity was maximum grade 2.

Conclusion: CDDP+HT results in a high response rate and acceptable toxicity in patients with recurrent cervical cancer.

Introduction

Patients with cervical cancer stage IB2 or higher are usually treated with radiotherapy, which can be combined with chemotherapy or hyperthermia. The probability to achieve permanent local tumor control decreases with higher stages. Overall, 22% of patients have persistent or recurrent disease after radiotherapy.[1] In these situations therapeutic options are limited. The role of chemotherapy in metastatic or locally recurrent cervical cancer is modest. The currently most active and widely used agent is cisplatin, resulting in response rates range around 23% with a median survival of 6-8 months.[2-3]

If the disease recurs within a previously irradiated pelvic area, prognosis is particularly poor. A probable explanation for this is the decreased blood flow to the pelvis caused by vascular changes following radiotherapy. Published results in this subgroup of patients are scarce, but generally response rates are lower than in not previously irradiated tumors.

For years now, attempts have been made to improve the effect of chemotherapy and overall survival by combining cisplatin with other agents in various phase II and III trials. Thus far these new strategies were not very successful in previously irradiated patients.[4-7] Recently a phase III randomized trial comparing cisplatin alone to cisplatin and topotecan showed a modest but significant advantage in survival of the combination treatment. In this study 56-58 % of patients had received prior radiotherapy, but no attempt has been made to collect response and recurrence data relative to prior radiotherapy.[3]

Preclinical studies have shown that the addition of hyperthermia to cisplatin can greatly enhance its effectiveness. Hyperthermia has a cell killing effect preferentially in tumor tissue. There is no intrinsic difference in thermotolerance between normal cells and tumor cells, but there is a difference in physiology. Tumor tissue has chaotic vasculature resulting in hypoxic and low pH areas.[8] Hypoxia and low pH are usually not found in normal tissue and these conditions make tumor cells more sensitive to hyperthermia.[9] In addition, hyperthermia is known to enhance the effect of several chemotherapeutic agents. Hyperthermia enhances the effect of platinum analogues by increasing the cellular uptake and thereby increasing platinum-DNA adduct formation. The effect of cisplatin is enhanced with a factor 4 to 8, depending on temperature level and duration of treatment.[10-11]

We tested the feasibility and effectiveness of the combination of cisplatin and hyperthermia in patients with recurrent cervical cancer after previous irradiation in a phase I/II study. In this study, 6 weekly treatments of cisplatin and hyperthermia (CDDP + HT) applied simultaneously appeared feasible and resulted in 53% response.[12] Similar results were found in another phase I/II study on cisplatin and hyperthermia, using a similar treat-

ment scheme.[13] Following the completion of the phase I/II study, patients with unresectable local tumor recurrences in a previously irradiated area have been considered for this combined treatment as a standard treatment approach in our hospital.

Herewith we report long-term follow-up on the initial studygroup plus 28 additional patients that have been treated between 2000 and 2005. [12] We analyzed treatment, toxicity and follow-up data of all patients with recurrent cervical carcinoma treated in our hospital with CDDP+HT. Further, we evaluated the palliative effect of this treatment.

Materials and methods

All patients with recurrent cervical carcinomas treated from 1992 to 2005 with CDDP+HT were included in this analysis. Before the start of treatment all patients were informed about the rationale, procedure and side-effects of combined treatment and they were eligible for CDDP+HT after informed consent. They were required to have cytologically or histologically proven locoregional recurrent or residual cervical carcinoma and radiotherapy in the past. At diagnosis, patients underwent a gynecologic examination under anesthesia and a CT-scan was made of thorax and abdomen. The results were discussed in a multidisciplinary team of a radiologist, pathologist, gynecologic, medical and radiation oncologists. If patients were not amendable to surgery or radiotherapy, CDDP+HT was considered the treatment of choice. Exclusion criteria for CDDP were inadequate bone marrow or renal function, for HT a pacemaker or a metal implant in the pelvic region larger than 10 cm.

Chemotherapy: In the phase I/II study patients received 50 - 80 mg/m^2 cisplatin weekly with a maximum of 6 courses. After completion of the study, 70 mg/m^2 was the recommended dose, because it was well tolerated without dose-limiting toxicity.

The administration of chemotherapy started with 4 hours of prehydration with 1 liter of normal saline. Before starting infusion of cisplatin, anti-emetics were administered both orally, one hour in advance, and i.v., 30 minutes before starting cisplatin. Cisplatin was infused in 250 ml saline over 3 hours. Cisplatin infusion and heating were started simultaneously.

After cisplatin infusion all patients received 3 liters of normal saline in 12 hours as posthydration. Each patient was given oral anti-emetics at discharge.

Deep locoregional hyperthermia: Patients were mildly sedated using either 1 mg lorazepam or 0,5 mg xanax. For all treatments, the BSD-2000 3D system (BSD Medical Corpo-

ration, Utah, United States) was used. For thermometry, Bowman probes were placed intraluminally in bladder, vagina and rectum within closed tip catheters. Thermal mapping along the catheters was performed every 5 min with a step size of 1 cm with a maximum map length of 14 cm. Pulse rate and blood pressure were automatically measured before and every 5 minutes during treatment and oral temperature was measured at 0, 15, 30, 60 and 90 minutes.

Heating was started with a power output of 400 W at 77 MHz. Patients were carefully instructed to report any discomfort due to too high temperatures in normal tissue during treatment. Treatment settings for power, phase and frequency were adjusted accordingly if complaints occurred. If no complaints occurred, 100 W was added to the power output every 5 minutes. Treatment objective was to achieve intraluminal temperatures of 40-43 ^{0}C as homogeneously as possible. For all patients 90 minutes were scheduled for each hyperthermia treatment; 30 minutes of heating up and 60 minutes actual treatment time.
Response evaluation and toxicity: CT-scan and gynecologic examination were done 2-4 weeks after the last course of therapy, or earlier during the course of treatment if the patient's condition warranted such. Toxicity and pain were evaluated during treatment using the CTC (Common Toxicity Criteria) scale, version 2.0.

The response noted in this study is the maximum response achieved during follow-up for the duration of at least one month. A response was defined as a partial or complete response. A complete response was defined as the disappearance of all visible and palpable lesions, a partial response as a decrease of at least 50 % of all visible and palpable lesions. Palliative effect was defined as a decrease in pain after the last course of therapy of at least one point on the CTC scale lasting for at least one month. The duration of response was calculated from the date of maximum response to the date of local progression. The duration of palliation was calculated from the date of maximum tumor response to the date progression of pain was diagnosed. After treatment, progression of pain was assessed retrospectively from the patient's medical files. The date of progression was defined as the date the patient mentioned an increase in pain of at least one point on the CTC scale, or sought medical attention because of pain.

The influence of age, performance status, lymph node status, presence or absence of pain and distant metastasis, previous platinum-containing chemotherapy or hyperthermia, time between primary treatment and recurrence and maximum tumor diameter on overall and progression free survival was evaluated using Cox regression analysis. For survival analysis, the Kaplan-Meier method was used. P-values less than 0.05 were considered significant.

Results

Patient characteristics: From 1992 to 2005 47 patients with progressive recurrent or residual intrapelvic tumors were treated with CDDP+HT. Nineteen were treated within the framework of the phase I/II study. Median time of follow-up was 7.8 months (range: 1 - 106). All patients had received full dose radiotherapy to the pelvis (mean dose of 50.2 Gy) combined with brachytherapy (n = 43), a central boost with external radiotherapy (n = 4) or a boost to the iliac nodes (n =1).

Patient characteristics are summarized in table 1. There were no differences in patient characteristics when patients treated within the phase I/II trial are compared to those treated after the study closed. One patient received two series of CDDP+HT for 2 consecutive recurrences. She was included once in response and toxicity evaluation and survival analysis. All patients were in good general condition, WHO performance status (WHO-PS) 0-1, except for one patient who was confined to bed due to severe pain caused by the tumor recurrence (WHO-PS 3).

Table I: Patient characteristics

Patient characteristics	
Age	Mean 46 years (range: 26-72)
WHO class	
0	24
1	22
3	1
Histology	
SCC	36
AC	11
Previous chemotherapy	8
Previous hyperthermia	12
Distant metastasis	
Absent	38
Present	8
FIGO stage primary tumor	
IB	20
IIA	5
IIB	9
IIIB	8
IVA	2
IVB	3
Time to recurrence	Mean 18 months (range: 0-58)

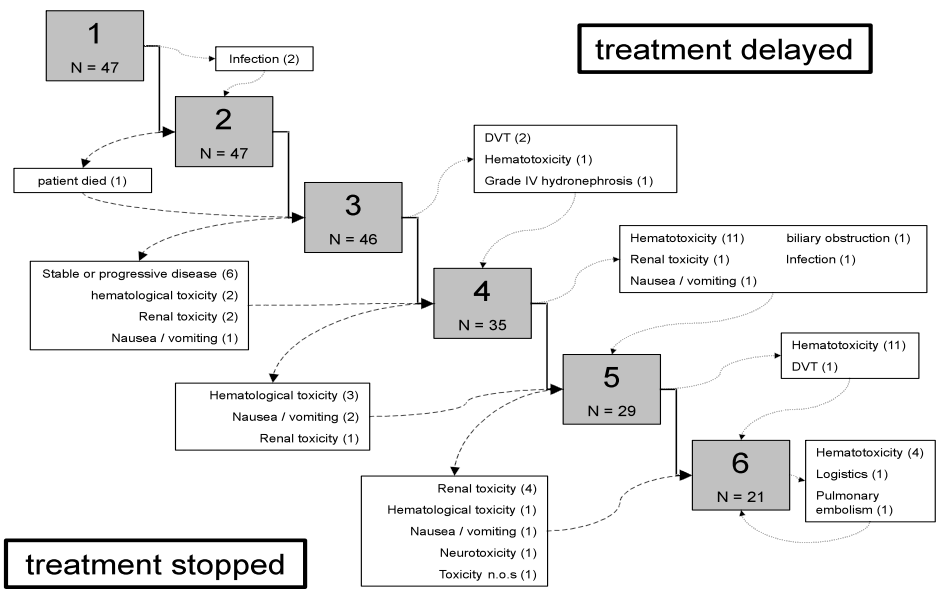
Legend: WHO class = World Health Organisation class, a measure of general condition, SCC = squamous cell carcinoma, AC = adenocarcinoma, FIGO = International Federation of Gynecology and Obstetrics tumor stage

Of 47 residual or recurrent tumors, 37 were first recurrences or residual tumors, 9 were 2nd recurrences and 1 was a 3rd recurrence. Eight patients had been treated with cisplatin-containing chemotherapy prior to CDDP+HT. Three patients had received 5 weekly courses of 40 mg/m^2 cisplatin concurrently with radiotherapy. One patient who presented with distant metastasis at primary diagnosis received 6 three-weekly courses of cisplatin (75 mg/m^2) and taxol, and 2 received cisplatin (75 mg/m^2) and taxol as neoadjuvant treatment in 3 three-weekly courses. A seventh patient received 7 courses of cisplatin 70 mg/m^2 concurrent with 4 applications of brachytherapy perioperatively. The last patient received 6 three-weekly courses of BEMP chemotherapy (Bleomycin, Vindesine, Cisplatin 50 mg/m^2 and Mitomycine C) as induction therapy because of lymfogenic metastasis. None of these 8 patients received 80 mg/m^2 cisplatin during CDDP+HT.

Treatment characteristics: Six combined weekly treatments were scheduled for every patient. A total of 226 (80%) courses of chemotherapy were administered to 47 patients, of these 216 were combined with hyperthermia.

Reasons for administering cisplatin without hyperthermia were patient refusal (5 courses, same patient), technical problems (2 courses), logistical problems (2 courses) and a deep venous thrombosis (1 course) established the day of scheduled hyperthermia. The treatment had to be postponed 39 times in 21 patients. Reasons to stop or delay chemotherapy are given in figure 1. Most common cause of delay in our patient group

Figure 1: Reasons to stop or delay treatment



was hematological toxicity (27 times), occurring after the 4th or 5th course of cisplatin. Vascular events (deep venous thrombosis, pulmonary embolism) were the reason to delay 4 treatments.

The dose of cisplatin was 70 mg/m^2 in 33 patients, given once weekly. Ten patients participating in the phase I/II study received 60 mg/m^2 (n = 5) or 80 mg/m^2 (n = 5). A lower dose was given in 4 patients. In 2 patients this was because of a poor renal function. Another patient received 40 mg/m^2 CDDP the first 3 treatments and then continued with 70 mg/m^2. The last patient was treated with CDDP+HT after she did not respond on radiotherapy which was first combined with hyperthermia (4 treatments), thereafter with CDDP (40 mg/m^2, 3 courses) and she then continued with CDDP+HT at 50 mg/m^2 (3 courses). CDDP was started at 40 mg/m^2 for fear of excess toxicity and when no complaints or deterioration of renal function occurred, she continued at 50 mg/m^2.

The mean temperatures achieved during hyperthermia were 40.6 ± 0.6 ^{0}C in the lumen of the bladder, 40.4 ± 0.7 ^{0}C in the vagina and 40.6 ± 0.7 ^{0}C in the rectum. The mean increase in systemic temperature was 1.0 ± 0.5 ^{0}C.

Toxicity: For toxicity evaluation, all patients were eligible. Forty-five percent of patients completed all 6 scheduled courses of chemotherapy. Most severe toxicity observed in each treatment series is listed in table 2. CTC grade 3-4 leucopenia occurred in 36 % of treatment series, grade 3-4 neutropenia in 35 % and grade 3-4 trombopenia in 15 %. The incidence of other grade 3-4 adverse events did not exceed 10 %. Neutropenic fever was not observed. No difference in clinically relevant toxicity was observed when the patients treated in the phase I/II study were compared to the patients treated after the study closed.

Table 2: Most severe toxicity observed per treatment series (%)

CTC grade	1	2	3	4
anaemia	38	47	9	0
trombopenia	28	19	15	0
leucopenia	9	19	21	15
neutropenia	9	14	14	21
nephropathy	51	15	0	0
constipation	13	15	3	0
diarrhea	13	4	0	2
neuropathy	21	2	0	0
hearing	7	23	0	0
fatigue	36	24	3	0
nausea	36	34	2	4

Legend: CTC = Common Toxicity Criteria, version 2.0

Hyperthermia-related toxicity occurred in 5 of 47 (11%) treatment series. All incidents were subcutaneous burns that healed without any further medical attention. These incidents did not cause any treatment delay. Neurotoxicity was not observed as a direct effect of hyperthermia.

Response rate and survival: Overall pelvic response rate (complete or partial responses) is 58 % (26 of 45, 95 % confidence interval 42 - 72) including 3 complete responses. Fifty-three percent of patients responded in the phase I/II study. The response rate of patients treated since completion of the study is 57 % (16 of 28).

Of 8 patients with distant metastasis, the response of lesions outside the hyperthermia target area is listed in table 3.

Table 3: Responses inside and outside the heated area

patient	Location of distant metastasis	Infield response	Outside response
1	para-aortal lymph nodes*	PR	SD
2	para-aortal lymph nodes*	PR	Unknown
3	bone, liver spleen	SD	PD
4	lung	PR	PR
5	liver	PR	SD
6	mediastinal lymph nodes	PD	PD
7	mediastinal lymph nodes	PR	SD
8	lung	SD	PD

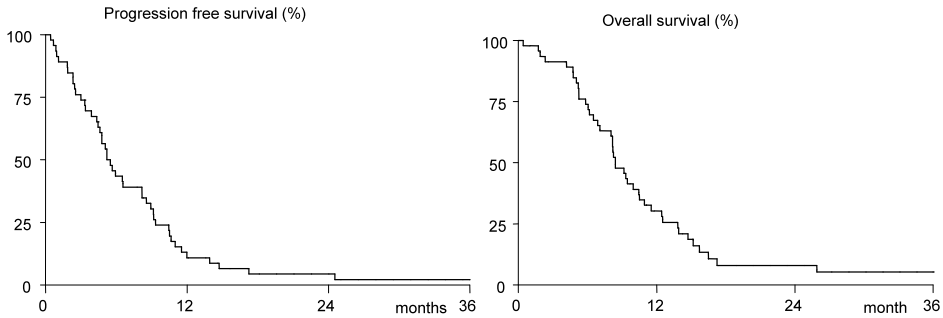
Legend: PR = partial response, SD = stable disease, PD = progressive disease, * para-aortal lymph nodes are usually located at the rim of the hyperthermia applicator

Response evaluation could not be performed in 2 patients. One patient refused response evaluation because of lack of consequence and another died suddenly after 3 combined treatments, probably due to myocardial infarction. They were both considered not evaluable for response.

All patients were evaluable for survival. Median duration of survival is 8 months with a trend towards better survival for responders (median of 10 months for responders vs. 6 for non-responders, p = 0.05). Overall and progression free survival is depicted in figure 2; 2 years after treatment, 16 % of responders are still alive, compared to none of the non-responders. Forty-six patients were evaluable for progression free survival. This was 4 months; 1.6 months for non-responders and 5.6 months for responders.

Additionally, Cox regression analysis showed that overall survival was slightly but significantly influenced by time interval between primary treatment for cervical carcinoma and date of first CDDP+HT (hazard ratio 0.97, p = 0.03) and the maximum diameter of the recurrence (hazard ratio = 1.10, p = 0.04). The mean intraluminal temperatures achieved

Figure 2: Progression free and overall survival



in the responders were not statistically different from those achieved in non-responders, assessed by an independent samples t-test.

Of 8 patients who had received platinum-containing chemotherapy in the past, 4 responded, 3 had stable disease and for one patient response could not be evaluated.

The median survival of patients with distant metastasis (7 months) was not significantly different from patients without distant metastasis (8 months, $p = 0.8$).

Salvage surgery: Of 26 responders, 9 obtained a response that enabled salvage surgery. Three patients underwent a total pelvic exenteration, another 3 an anterior exenteration and one patient had a vaginal tip resection. A suboptimal debulking was performed twice because during surgery the iliac vessels proved to be invaded by the tumor in one patient and the sacral plexus in the other patient. Two of the total pelvic exenterations and two of the anterior exenterations were microscopically radical, the others microscopically irradical. The vaginal tip resection was a radical procedure. Overall survival in this subgroup was 12 months (range: 5 – 97) (excluding one patient who underwent a total pelvic exenteration in the presence of pulmonary metastasis). There are 2 long-term disease free survivors in this subgroup. One patient died of lung cancer, 8 years after CDDP+HT followed by a microscopically radical total pelvic exenteration. A second patient is now disease free 18 months after combined treatment followed by a vaginal tip resection.

Palliation: Thirty-eight patients had tumor-related pain at the start of treatment. CDDP+HT resulted in a significant reduction of pain in 28 cases (74 %). The median duration of palliation is 5 months (range: 2 – 18). Two complete responders with pain had significant palliation. Of 18 partial responders with pain, only one did not experience a significant palliation. Of 7 patients with pain and progressive disease after treatment, 3 (43 %) had significant palliation and of 11 patients with pain and stable disease following treatment, 6 (55 %) experienced significant palliation. Information on the duration of palliation is

unknown for 7 patients, due to return of the patient to the referring clinic (n = 4), patient refusing medical interference (n = 1) or surgery before progression of pain (n = 1). One patient died after the third treatment.

Discussion

A locoregional recurrent cervical carcinoma in a previously irradiated area is a major clinical problem. In the majority cases this recurrence is unresectable due to invasion of adjacent organs or bony structures such as the pelvic sidewall. The effectiveness of chemotherapy, including cisplatin- based regimens, in previously irradiated areas is poor. These recurrences frequently cause pain, fistulae, hydronephrosis and lymphedema. Hence, the development of effective treatment strategies is warranted.

In this study, CDDP+HT resulted in a 55 % response rate. These results confirm those of the previous phase I/II studies in which response rates of approximately 50 % were achieved, with acceptable toxicity.[12-13] The toxicity profile in the current study is similar to that found in our phase I/II study, without clinically relevant toxicity. None of our patients has developed neutropenic fever and neurotoxicity did not exceed CTC grade 2 in any of the patients.

The additive effects of hyperthermia when combined with chemotherapy can be explained by spatial cooperation. Drug concentration will be less in insufficiently perfused tumor regions, where cells are specifically sensitive to hyperthermia. In addition, heat potentiates many drugs. Generally, interaction is only seen when the two treatments are given in close sequence. The most important mechanisms for an interactive effect are an increased intracellular drug uptake, enhanced DNA damage and higher intratumor drug concentrations, resulting from an increase in blood flow. An interactive effect was observed for virtually all cell lines treated at temperatures above 40°C for platinum analogues, with enhancement ratios of between 4 and 8, depending on temperature and exposure time. Increased renal toxicity has only been observed with core temperatures of 41°C and higher.[10-11]

Four randomized trials have compared chemotherapy alone to chemotherapy and hyperthermia. In 2 intravesical Mitomycine C was combined with local hyperthermia to the bladder and the combined approach lead to a significantly higher response rate and less recurrences in patients with superficial bladder cancer.[14-15] In another trial, patients with metastatic liver cancer were treated with intra-arterial chemotherapy or the same

chemotherapy plus hyperthermia.[16] In this trial, response rate in the chemotherapy alone group was 7 % and in the combination therapy group 40 %. In the fourth, patients with advanced carcinoma of the esophagus also responded better to the combined approach.[17]

It is difficult to compare the results of our study to those published by others on chemotherapy without hyperthermia in recurrent cervical cancer. First, a schedule of 70 mg/m^2 cisplatin once weekly for 6 courses is not commonly prescribed. Second, the results achieved in this particular group of patients with a tumor in a previously irradiated volume are usually not reported separately. Studies reporting results of chemotherapy in patients with recurrent cervical cancer in previously irradiated areas are summarized in table 4. Only those studies that specify results in this particular subgroup are mentioned.[18-28]

Following cisplatin alone, response rates have ranged from 0 to 50 %. Taking all available data together, the overall response rate is 21 %. When cisplatin is combined with various other chemotherapeutic agents, the response rate in previously irradiated areas has remained relatively low: 4 to 24 %, for an overall response rate of 15 %. When the results of our current study and the study by Rietbroek et al. are combined, the response rate is 54 %, which appears to be superior to that obtained by chemotherapy alone.[13]

We found one other study reporting the palliative effect of treatment in patients with recurrent cervical carcinoma. Chambers et al. achieved pain relief in 66 % of the patients treated with a combination of Bleomycin, Vincristin, Mitomycine C and cisplatin.[29] The 74

Table 4 : Reports in literature on response rate for irradiated recurrent cervical carcinomas (reponses / no. evaluable) (only studies with ≥ 10 patients with previously irradiated recurrent cervical cancer were included)

Author [ref]	Cisplatin	Platinum-based regimen	Cisplatin and hyperthermia
Thigpen et al. [18]	7 / 20		
Potter et al. [19]	7 / 32		
Daly et al. [20]	7 / 14		
De Murua et al. [21]		2 / 13	
Lele et al. [22]		1 / 24	
Ramm et al. [23]		3 / 20	
Brader et al. [24]		3 / 57	
Papadimitriou et al. [4]		3 / 11	
Piver et al. [5]		3 / 10	
Rose et al. [25]		5 / 21	
Burnett et al. [26]		3 / 10	
Fiorica et al. [27]		4 / 14	
Gebbia et al. [28]		3 / 11	
Matulonis et al.[7]		1 / 12	
Rietbroek et al. [13]			12 / 23
Current study			26 / 47
Overall:	14 / 66 (31 %)	31 / 203 (15 %)	38 / 70 (54 %)

% palliative effect in this study is similar to that. No quality of life analysis was performed in either study, but is seems reasonable to assume that relief of pain has a positive effect on the quality of life.

Seven percent of patients obtained long-term disease free survival with this treatment. One patient is currently free of disease, 9 years after her second series of CDDP+HT, another died of non-related cause 8 years after CDDP+HT followed by a pelvic exenteration and yet another died of late complications of radiotherapy becoming disease free after CDDP+HT followed by a pelvic exenteration. A fourth patient is currently disease free 18 months after CDDP+HT and additional surgical treatment. It would be interesting to know what factors are responsible for these remarkable responses. However, we have not been able to identify any distinguishing parameters in this patient group, which could be due to the heterogeneity of the group.

As a phase III trial comparing cisplatin alone to CDDP + HT for recurrent, previously irradiated cervical carcinoma was not feasible due to the limited number of patients, and in view of the good results that we have seen, we consider this combined treatment a standard treatment approach for patients with locally recurrent or residual cervical carcinoma within a previously irradiated area. The high response rate and acceptable toxicity found in these patients further cleared the way for combining radiotherapy with cisplatin and hyperthermia for primary cervical carcinoma, a combination that proved to be quite promising.[30]

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Chapter 3

Long-term improvement in treatment outcome after radiotherapy and hyperthermia in locoregionally advanced cervix cancer: An update of the Dutch Deep Hyperthermia Trial

Franckena M, Stalpers LJA, Koper PCM, Wiggenraad RGJ, Hoogenraad WJ, van Dijk JDP, Wárlám – Rodenhuis CC, Jobsen JJ, van Rhoon GC and van der Zee J. Long-term improvement in treatment outcome after radiotherapy and hyperthermia in locoregionally advanced cervix cancer: An update of the Dutch Deep Hyperthermia Trial. Int J Radiat Oncol Biol Phys 2008; 70: 1176-1180

Abstract

Purpose: The local failure rate in patients with locoregionally advanced cervical cancer is 41-72 % following radiotherapy alone (RT), while local control is a prerequisite for cure. The Dutch Deep Hyperthermia Trial (DDHT) showed that combining radiotherapy with hyperthermia (RT+HT) improves three-year local control from 41 to 61% as we reported earlier. In this study we evaluate long-term results of the DDHT after 12 years of follow-up.
Methods and materials: Between 1990 and 1996, 114 women with locoregionally advanced cervical carcinoma were randomized to RT or RT+HT. RT was applied to a median total dose of 68 Gy. HT was given once weekly. The primary endpoint was local control; secondary endpoints were overall survival and late toxicity.
Results: At 12 years follow-up local control remained better in the RT+HT group (37% vs. 56%, p = 0.01). Survival was persistently better after 12 years; 20% (RT) and 37% (RT+HT) (p = 0.03). WHO performance status was a significant prognostic factor for local control. WHO performance status, FIGO stage and tumor diameter were significant for survival. The benefit of HT remained significant after correction for these factors. EORTC grade ≥ 3 radiation-induced late toxicity was comparable in both groups.
Conclusions: For locoregionally advanced cervical cancer, the addition of hyperthermia to radiotherapy results in long-term major improvement of local control and survival, without increasing late toxicity. This combined treatment should be considered for patients who are unfit to receive chemotherapy. For other patients, the optimal treatment strategy is subject of ongoing research.

Introduction

Radiotherapy is mainstay in the management of locoregionally advanced cervix carcinoma. After radiotherapy alone, locoregional failure rates for the more advanced stages range between 41-72 %.[1-2] Local control is a prerequisite for cure, and locoregional failure generally indicates a fatal course of the disease. If locoregional tumor control can be achieved definitively, the potential gain in survival is estimated to be 50-60%.[3-4]

Several large trials have shown an advantage of combining radiotherapy with chemotherapy both in terms of improved local tumor control and better overall survival. Similar advantages have been found in trials that combined radiotherapy with hyperthermia.[5]

Hyperthermia, the artificial elevation of tissue temperature to 40 - 44 ^{0}C, is an effective cytotoxic agent especially in cells that are in a hypoxic, nutrient-deprived and low pH environment. These conditions are commonly found in malignant tumors and make cells relatively resistant to radiotherapy.[6] Besides directly killing cells at temperatures of 40-44 ^{0}C, hyperthermia also increases the cytotoxic effect of radiotherapy. Experimental studies have shown that it interferes with the cellular repair of radiation-induced DNA damage, thereby enhancing the cytotoxic effect of radiotherapy.[7] Hyperthermia also increases blood flow, which may improve tissue oxygenation and make cells more sensitive to radiotherapy.[8] Several randomized studies have shown an increase in response rate and tumor control in various tumor sites when radiotherapy is combined with hyperthermia.[9-12]

In 1990, the Dutch Deep Hyperthermia Trial (DDHT) started investigating the effect of the addition of hyperthermia to standard radiotherapy in patients with locally advanced rectal, bladder and cervical cancer and the first results were published in 2000.[13,14] A significant improvement in response rate and local control was found with the addition of hyperthermia. Overall survival was also significantly improved after adjustment for prognostic factors. For patients with primary or recurrent rectal cancer, no improvement in local control or survival could be demonstrated and for patients with bladder cancer, the initial gain in local control disappeared during follow-up. Although there were no significant interactions between treatment group and tumor site for complete response, local control and overall survival, the subgroup of patients with locally advanced cervical cancer appeared to benefit most from the addition of hyperthermia. However, with a median of 43 months, the follow-up time was relatively short. In this study we report on long-term pelvic control, overall survival and toxic effects in patients with locally advanced cervical cancer who had been treated in the Dutch Deep Hyperthermia Trial.

Material and methods

Patients

Patients were eligible for the trial if they required primary standard radiotherapy for cervical cancer FIGO (International Federation of Gynecology and Obstetrics) stage IIB (with extension to the lateral parametrium), IIIB (fixation to the pelvic wall or ureter obstruction causing hydronephrosis) or IVA (invasion of the bladder or rectum). In all patients, diagnosis was confirmed by histopathological examination. Patients needed to be in reasonable general condition defined as WHO performance status less than 2 and an expected survival exceeding 6 months. Patients with a pacemaker or a metal implant in the pelvic region larger than 10 cm were excluded, as these are absolute contraindications for hyperthermia.

The study was approved by the local Medical Ethics Committees of all participating hospitals.

Following informed consent, patients were randomized to receive standard radiotherapy (RT) or standard radiotherapy plus hyperthermia (RT+HT).

Radiotherapy

External beam radiotherapy was given in 23-28 fractions of 2.0 - 1.8 Gy to a total dose of 46.0 to 50.4 Gy (mean external beam dose 48.3 Gy, SD 5.9 Gy) using a 4-field box technique with 6-10 MV photons. In the Daniel den Hoed Cancer Center the para-aortal lymph nodes were routinely included in the external radiotherapy field; in the other institutes the para-aortic region was included only if there were metastases in the common iliac or para-aortic lymph nodes. Fifty-two women (46 %) received para-aortic irradiation, 27 (48 %) in the RT-group and 25 (43 %) in the RT+HT-group. In patients with inguinal lymph node metastases, the inguinal regions were included.

In the Rotterdam area, high-dose rate brachytherapy was given to 50 women (70 %) either to a total dose of 17 Gy, applied in two fractions of 8.5 Gy or to 18 Gy in three fractions of 6.0 Gy to point A. In the Amsterdam area, 36 women (84 %) received a single brachytherapy application of 20-30 Gy at 1 Gy/hr medium dose rate to achieve a total dose of 70 Gy to point A. At randomization, stratification was by radiation institute, so the brachytherapy schedules were equally distributed over both arms of the study.

An additional external beam sidewall boost was given to 34 patients with residual tumor in the parametrium at the time of the first brachytherapy application. These patients received 3 to 7 boost fractions of 1.8 to 2 Gy, up to a total pelvic side wall dose of 60 Gy

using two small opposed 6 to 10 MV photon fields. Of these, 14 patients were randomized in the RT-group and 20 in the RT+HT group. The patients with involved lymph nodes were similarly boosted to a total dose of 60 Gy.

Dose specifications and target volume definition were according to the International Commission on Radiation Units and Measurements (ICRU) report 50. The median overall treatment time was 48 days in the RT+HT-group (range: 35 –116) and 50 days in the RT-group (range: 35-121).

Hyperthermia

Deep locoregional hyperthermia was prescribed once weekly to a total of 5 times during the 5 weeks of external beam radiotherapy.

Of 90 minutes treatment time, maximum 30 minutes were used for warming up to intratumor temperatures above 42 ^{0}C. The next 60 minutes intrapelvic temperatures were kept as high and homogeneous as patient tolerance permitted. Patients were carefully instructed to mention any uncomfortable feelings that could be suggestive of hotspots during treatment. If complaints occurred, treatment settings such as phase, amplitude, frequency and power were adjusted accordingly.

For thermometry in Rotterdam, Bowman probes were placed in bladder, rectum and vagina. Thermal mapping was performed every 5 minutes with a step size of 1 cm and a maximum map length of 14 cm. Pulse rate and blood pressure were measured automatically before and every 5 minutes during treatment; oral temperature was measured at 0, 15, 30, 60 and 90 minutes. In the two other centers multi-sensor thermocouple probes have been read out during power off pulse of the heating system.

Patients were recruited by 11 radiotherapy institutes in The Netherlands. Radiotherapy was given in the recruiting institute and for their weekly hyperthermia treatment patients were referred to one of 3 institutes with hyperthermia facilities. In the Daniel den Hoed Cancer Center, the BSD-2000 system was used (BSD Medical Corporation, Salt Lake City, Utah, USA). In the other centers, custom built systems were used: a 4-waveguide applicator system was used in the AMC, Amsterdam and a Coaxial TEM applicator in UMC-Utrecht. For the three systems the energy distribution in a human pelvic-size phantom is the same.[15]

Study design

Primary endpoints of the trial were complete response and pelvic tumor control. Follow-up visits were scheduled 1 month after treatment, once every three months during the

first two years and every 4-6 months thereafter. After the first two years, follow-up visits were planned in accordance with the Association of Cancer Centers Guidelines. Generally patients visited a gynecologic oncologist and a radiation oncologist alternately.

A complete response was defined as disappearance of all tumor in the irradiated volume; this was established 3 months after treatment. Response was assessed by anamnestic information and physical examination, and if indicated supplemental examinations. Patients who did not show a complete response were considered local failures at day 0.

Duration of pelvic tumor control was defined either as the time between the date of randomization and the date of local progression within the irradiated volume or as death due to toxicity.

Secondary endpoints were overall survival and toxic effects from radiotherapy or hyperthermia. Overall survival was defined as the time between randomization and death or last follow-up. Late toxicity (effects occurring 3 months or longer after the last radiotherapy) was scored using the radiation morbidity scoring criteria of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC).[16]

Data acquisition

Follow-up visits were usually planned in the institutes where radiotherapy was administered. Information on pelvic tumor control, overall survival and late toxicity was collected from correspondence and medical charts from radiation oncologists, gynecologic oncologists and patients' general practitioners. If no further medical information could be gathered, the population registry was consulted. The information was gathered by the first author and reviewed by one other author (JZ). Only grade ≥ 3 late toxicity is reported here, so as to prevent bias caused by under reporting of grade 1 and 2 toxicity in the medical charts.

Statistical analysis

The analysis was done by intention to treat. Overall survival and pelvic tumor control were described by Kaplan-Meier curves. Cox's regression analysis was used to analyze differences in pelvic tumor control, overall survival and late toxicity between the treatment groups. Differences with a p-value below 0.05 were considered significant. The prognostic factors that were significant in univariate analysis were entered in the multivariate analysis. In univariate analysis, FIGO stage, WHO performance status, age, Hb level, maximum tumor diameter, histology and grade of the tumor were entered. As the lymph node status was unknown for nearly 60 % of patients, this factor was not entered. For the analysis, the Statistical Package for Social Sciences was used, version 9.0 (SPSS Inc. Chicago, Illinois, USA). This analysis represents an updated subgroup analysis of cervical cancer patients.[14]

Results

Response rate, acute toxicity and 3-year pelvic tumor control and overall survival rates have been reported previously.[13-14] The most important information will be summarized here and extended with new data.

From 1990 to 1996,114 patients with locally advanced cervical cancer were randomized. Characteristics of the patients and the tumors are summarized in table 1. Nodal status was assessed in 50 of 114 patients with a CT-scan done for radiation therapy purposes. Eighty

Table 1: Patient characteristics and prognostic factors

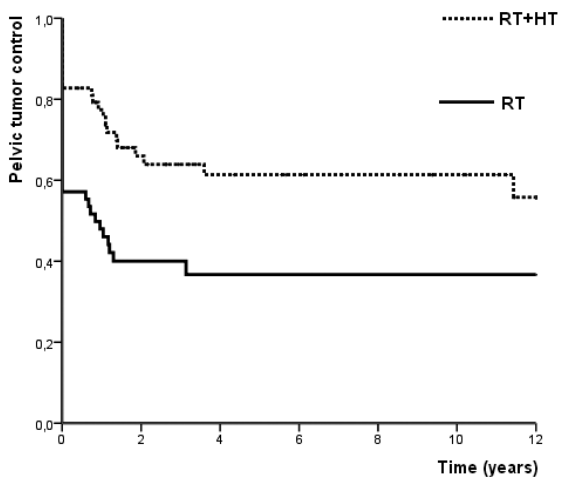
		RT + HT	RT
Number of patients		58	56
Median Age	(range)	51 (26-75)	50 (30-82)
WHO performance			
	0	45	39
	1	13	17
Hemoglobin			
	< 7 mmol.l-1	16	14
	> 7 mmol.l-1	37	38
	Unknown	5	4
FIGO stage			
	IIB lateral	11	11
	IIIA		1
	IIIB	40	40
	IVA	7	4
Nodal status on CT-scan			
	N0	9	6
	N1	16	19
	Nx	33	31
Histology			
	Squamous cell	51	46
	Adenocarcinoma	4	7
	Other	3	3
Differentiation			
	Well	4	4
	Moderate	21	29
	Poor	23	15
	Undifferentiated	1	0
	Unknown	9	8
Maximum tumor diameter			
	< 60 mm	13	12
	60-80 mm	26	27
	> 80 mm	19	13
	unknown	0	4

Legend: FIGO = International Federation of Gynecology and Obstetrics tumor stage, N0 = no positive lymph nodes detected, N 1 = positive lymph nodes detected, Nx = no lymph node detection performed

percent of patients had a FIGO stage IIIB or IVA tumor, 70 % had positive pelvic lymph nodes on CT-scan, and in 77 % the tumor diameter was 6 cm or larger. The distribution of prognostic factors was balanced equally over the two treatment groups. Median follow up time for survivors was 11 years.

Pelvic tumor control: Eighty-three percent of patients in the RT+HT group (48 / 58) achieved a complete response and 57 % (32 / 56) in the RT group (p = 0.03). At follow-up, the difference in pelvic tumor control was sustained with 5-year pelvic tumor control rates of 61 % in the RT+HT group and 37 % in the RT group. At 12 years the pelvic tumor control rate was 56 % in the RT+HT-group and remained 37 % in the RT-group. This difference was significant (p = 0.01, figure 1).

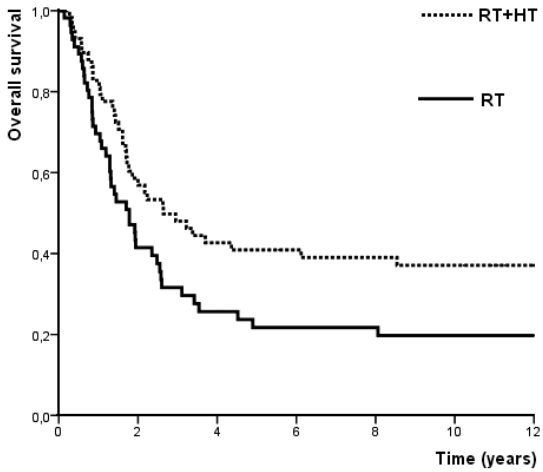
Figure 1 : Pelvic control



In the univariate analysis, pelvic tumor control was associated with WHO performance status (p = 0.04). In a multivariate analysis, the treatment arm remained an independent prognostic variable with significant better pelvic tumor control in the RT+HT-arm (p = 0.02, HR 0.53, 95 % confidence interval 0.31 – 0.92).

Overall survival: The overall survival at 12 years follow-up was 37 % in the RT+HT -group and 20 % in the RT-group (p = 0.03, figure 2). The median overall survival was 2.64 years in the RT+HT-group and 1.78 years in the RT-group. In a univariate analysis, survival was associated with WHO performance status (p = 0.006), FIGO stage (p = 0.04) and maximum tumor diameter (p = 0.004). In a multivariate analysis, the treatment arm remained an independent prognostic factor with a significant advantage in overall survival after RT+HT (p = 0.03, HR 0.60, 95 % confidence interval 0.38 – 0.95).

Figure 2: Overall survival



Sites of failure: Following a complete response, 25% of patients in the RT+HT-group (12 of 48) and 31 % of patients in the RT-group (10 of 32) developed a pelvic recurrence during follow-up. Of patients with continuing pelvic tumor control, 31 % (11 of 36) in the RT+HT-group developed distant metastasis compared to 32% in the RT-group (7 of 22). This difference is not significant (p = 0.92).

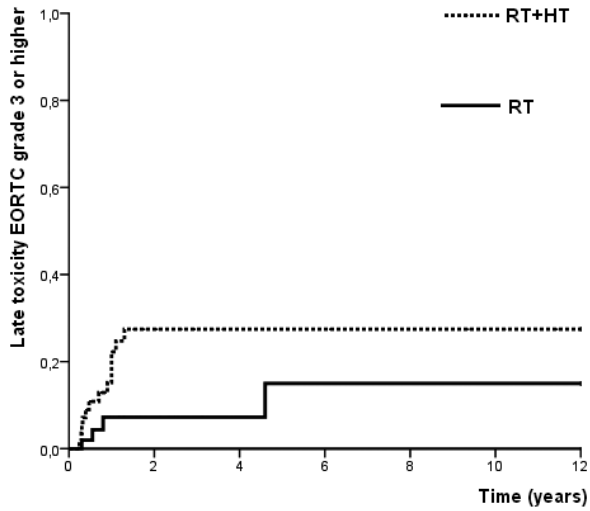
Late toxicity: Figure 3 shows the cumulative incidence of EORTC grade 3-5 radiation-induced toxicity in both groups of patients. The difference in incidence is not statistically significant (p = 0.281). Two patients (one in each group) died of late toxic effects. One patient died because of a perforation of the small intestine. She developed an untreated ileus due to stenosis of the rectosigmoid. The other died post-operatively after resection of an ischemic part of the small intestine.

Discussion

Long-term follow-up in the Dutch Deep Hyperthermia Trial (DDHT) shows a sustained improvement in local control and overall survival after 12 years by combining radiotherapy and hyperthermia (RT+HT). Hyperthermia did not significantly add to radiation-induced toxicity compared to radiotherapy alone.

The Dutch Deep Hyperthermia Trial was the first randomized trial that showed a survival advantage of radiotherapy with hyperthermia in women with locoregionally

Figure 3: Late toxicity



advanced cervical carcinoma. This advantage was comparable to studies that combined radiotherapy with chemotherapy.[5] The Dutch Deep Hyperthermia Trial was criticized for the poor overall outcome compared to literature, the relatively low median dose of 68 Gy that was administered and the large variation in radiation dose. The poor outcome in the RT-alone arm can be explained by the poor prognostic factors of the patients included in this study. Their median age was relatively low (50 years), their tumors were large (in 77% the maximum tumor diameter was at least 6 cm), a large proportion of patients in whom a CT-scan was performed, showed pathologically enlarged lymph nodes; and patients with a FIGO stage IIB tumor all had tumor extension close to the pelvic sidewall. Younger age, larger tumors, positive lymph nodes and extension to the pelvic sidewall have all been associated with poorer outcome in several studies.[2, 17] The impact of tumor size has been shown e.g. by Kapp et al., who reported 40 % pelvic tumor control at three years of follow-up in a subgroup of patients with tumors larger than 6 cm, which is comparable to the pelvic-control rate in the control arm of this study.[18]

The planned radiotherapy comprised 46 – 50.4 Gy of external beam irradiation combined with brachytherapy either in 2 high dose-rate applications of 17 Gy or one low dose-rate application of 30 Gy, which is considered adequate. The variation in radiation dose is partly explained by the fact that different brachytherapy techniques were used, depending on availability in the referring institute. For reasons explained in the original report, a relatively large number of patients (23 %) did not complete radiotherapy as planned.[12] The analysis was done by intention to treat; a subgroup analysis of patients

who did complete radiotherapy showed a beneficial effect comparable to that found in the primary analysis.[14]

Since the study was closed in 1996, RT+HT became the standard treatment for locoregionally advanced cervical cancer in a number of Dutch radiotherapy institutes, and is in other centers recommended for all patients with a medical contraindication for chemoradiotherapy. In 1999 and 2000, 5 randomized studies were published that all showed a clear benefit of adding chemotherapy to radiotherapy (RT+CT), with a 12 % absolute benefit in survival.[19-24] In 1999, the National Cancer Institute (NCI) issued an alert based on these 5 studies, stating that 'strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer'.[25] Many centers followed this call, and the results of this and other hyperthermia studies received little attention.

Although RT+CT is widely accepted, there are still many uncertainties concerning which patients benefit. First, there were great variations in the designs of the trials and in the doses and schedules of cisplatin (table 2).[20-24, 26] Only one trial exclusively compared standard radiotherapy with the same radiotherapy and cisplatin. This trial demonstrated no significant difference in overall and progression free survival, and it was published after the NCI-alert.[26] Second, the patients who were included in most RT+CT trials were a select subgroup of cervical cancer patients. Patients with more advanced stages of cervical cancer were included in the trials only if the para-aortal lymph nodes were clinically unaffected. In two of the protocols, patients even underwent a para-aortal lymph node dissection to exclude para-aortal lymph node metastasis.[22-23] Third, in several trials the overall treatment time exceeded 9 weeks; local control is a prerequisite for cure in cervical cancer and an increase in overall treatment time is accompanied by decreasing chances of local control.[27] The effect of adding cisplatin to optimal radiotherapy thus remains unclear, in particular for the more advanced stages. Fourth, only patients who were fit to receive chemotherapy entered these trials.

In all RT+CT trials an increase in acute toxicity was found, compared to radiotherapy alone.[28] Further, both animal and human studies have provided evidence for a relationship between acute and late gastro-intestinal toxicity.[29-30] To date, no increase in late toxicity was found in the clinical trials, but the duration of follow-up was sufficient in only one trial.[23] Therefore no definite conclusions can be drawn with respect to late complications of the RT+CT combination.[28]

Other authors have also investigated the effect of adding HT to RT for patients with locally advanced cervical cancer in randomized trials (table 3).[31-35] The majority of patients

Table 2: Cisplatin and radiotherapy studies

Author [ref]	n	FIGO > II	PAO+	Control arm	Experimental arm	CDDP schedule	Median OTT (days)	FU (mths)
Keys [20]	369	0 %	no	RT+ S	RT+CDDP+ S	40 mg/m^2 once a week	50	36
Morris [21]	368	30 %	no	RT*	RT*+CDDP+5FU	75 mg/m^2 once per 3 weeks	58	43
Rose [22]	353	47 %	no	RT+HU	RT+CDDP RT+CDDP+HU	40 mg/m^2 once a week	~ 63	35
Whitney [23]	368	36 %	no	RT+HU	RT+CDDP+5FU	50 mg/m^2 twice during RT	64	104
Pearcey [26]	253	32 %	no	RT	RT+CDDP	40 mg/m^2 once a week	49 and 51	82
Peters [24]	243	0 %	no	RT	RT+CDDP+5FU	70 mg/m^2 once per 3 weeks	41 and 43	42

Legend: n = number of patients included, FIGO = percentage of included patients with a International Federation of Gynecology and Obstetrics stage higher than II, PAO+ = where patients allowed to have lymph node metastases to the para-aortic lymph nodes or not, RT = radiation, S = surgery, HU = Hydroxyurea, CDDP = cisplatin, 5 FU = 5- fluoro-uracil, OTT = overall treatment time, mnths = months

* patients in the control arm received radiotherapy to the pelvic and para-aortic region, patients in the experimental arm received radiotherapy only to the pelvic region

treated in these studies had FIGO tumor stage IIIB or higher. Three studies report significantly better results following RT+HT and one showed a tendency towards better pelvic tumor control at 2 years. [31-34] In the most recent study, no significant improvement was found when radiotherapy was combined with hyperthermia.[35] A probable explanation for this is that an adequate hyperthermia dose has been applied to only part of the tumor.[36-37]

This current update of the DDHT is the first systematic long-term follow-up available for RT+HT. After 12 years of follow-up, a considerable improvement in pelvic tumor control and overall survival is found without increased late toxicity.

The magnitude of the beneficial effect of hyperthermia is similar to that of chemotherapy; the odds ratios for pelvic tumor control in the RT+CT trials were between 0.48 and 0.79, and 0.48 in the DDHT. The relative hazard ratios for death were between 0.39 – 0.74

Table 3: Randomized studies comparing radiation (RT) to radiation combined with hyperthermia (RT+HT)

First author [ref]	FIGO	n	CR-rate		Pelvic control		Overall survival	
			RT	RT+HT	RT	RT+HT	RT	RT+HT
Datta[31]	IIIB	64	58	74	46	67 ‡	73	81‡
Sharma[32]	II, III	50			50	70•		
Chen[33]	IIB, IIIB	120	48	72*				
Harima[34]	IIIB	40	50	80•	49	80 Δ*	48	58 Δ
Vasanthan[35]	IIB to IV	110			~ 80	~70 Δ	73	73 Δ

Legend: FIGO = International Federation of Gynecology and Obstetrics tumor stage, n = number of patients included in the study, CR-rate = complete response rate, RT = radiation alone, RT+HT = radiation combined with hyperthermia, * significant difference, •at 1.5 years, ‡ at 2 years, Δ at 3 years

in the RT+CT trials, and 0.53 in the DDHT.[5] In a Cochrane meta-analysis, RT+CT was less beneficial in trials with a high number of advanced-stage patients or bulky tumors, while in the DDHT 80 % of the patients had an advanced-stage cancer and 77 % of patients had a tumor larger than 6 cm.[19] We therefore feel that RT+HT should seriously be considered for patients suffering from locally advanced cervical cancer and even more so if they are not suited to receive chemotherapy. However, in many countries, the option of hyperthermia is not considered or even not available, as an equivalent alternative for chemotherapy.

Despite the improved prognosis of women with locoregionally advanced cervical cancer after either RT+HT or RT+CT, still many will die from the disease, either from local recurrence or distant metastases. The combination of radiotherapy with both hyperthermia and cisplatin, the most active chemotherapeutic agent in cervical cancer, could possibly further improve the outcome of treatment. The first results of an international multicenter phase I/II trial recently showed that this trimodality treatment is feasible.[38] In our view, the most interesting next step would have been a randomized three-arm study comparing both RT+HT and RT+CDDP with the trimodality treatment. Such a trial could provide an answer to the questions remaining on the addition of cisplatin to RT+HT and the addition of HT to RT+CDDP in terms of effectiveness and toxicity. It could also tell us if certain subgroups of patients respond better to the addition of HT or of CDDP. However, such a study appeared to be unfeasible, because many centers did not accept a control arm without CDDP. Currently there are 2 complementary trials in progress: an international multicenter phase III trial comparing RT+CDDP to the trimodality treatment, and a Dutch multicenter phase III trial comparing RT+CDDP to RT+HT (RADCHOC, RADiotherapy Combined with Hyperthermia Or Cisplatin).

In conclusion, the combination of radiotherapy with hyperthermia in locoregionally advanced cervical cancer results in long-term major improvement of local control and survival without an increase in toxicity, compared to radiotherapy alone. The benefit of adding hyperthermia to radiotherapy is of the same magnitude as that of adding chemotherapy to radiotherapy. Patients who are unfit for chemotherapy should be offered radiotherapy with hyperthermia as an equivalent alternative. For all other patients with locoregionally advanced cervical carcinoma, the best treatment approach has yet to be determined in ongoing trials.

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Chapter 4

Radiotherapy and hyperthermia for treatment of primary locally advanced cervix cancer: results in 378 patients

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Abstract

Purpose: To report response rate, pelvic tumor control, survival and late toxicity following treatment with radiotherapy and hyperthermia (RHT) for patients with locally advanced cervical carcinoma (LACC) and compare the results to other published series.

Materials and methods: From 1996 to 2005 378 patients with LACC (FIGO stage IB2 – IVA) were treated with RHT. External beam radiotherapy was applied to 46 – 50.4 Gy and combined with brachytherapy. Hyperthermia was prescribed once weekly. Primary endpoints were complete response and local control. Secondary endpoints were overall survival, disease specific survival and late toxicity. Patient, tumor and treatment characteristics predictive for the endpoints were identified in univariate and multivariate analyses.

Results: Overall, a complete response was achieved in 77% of patients. At 5 years, local control, disease specific survival and incidence of late toxicity CTCAE grade ≥ 3 were 53%, 47% and 12% respectively. In multivariate analysis, the number of hyperthermia treatments emerged as a predictor of outcome, in addition to commonly identified prognostic factors.

Conclusions: Complete response rate, local control and survival rates are similar to previously observed results of RHT in the randomized Dutch Deep Hyperthermia Trial. Reported treatment results for currently applied combined treatment modalities (i.e. radiotherapy with chemotherapy and/or hyperthermia) do not permit definite conclusions on which combination is superior. The present results confirm previously demonstrated beneficial effects from adding hyperthermia to radiotherapy and justify the application of RHT as first line treatment in patients with LACC as an alternative to chemoradiation.

Introduction

In the Dutch Deep Hyperthermia Trial (DDHT) radiotherapy alone (RT) was compared to radiotherapy plus hyperthermia (RHT). Complete response rate and pelvic tumor control were significantly improved with the addition of hyperthermia, as was overall survival after adjustment for prognostic factors.[1-4] At 12 years follow-up these results were sustained.[3] The therapeutic benefit observed with the addition of hyperthermia was at the cost of limited hyperthermia-induced toxicity whereas radiation-induced toxicity was unaffected.

After the DDHT closed in 1996, RHT became the standard treatment approach for patients with locally advanced cervical cancer (LACC) in the majority of Dutch radiotherapy departments. Radiotherapy is administered at one of 14 referring radiotherapy institutes that adopted RHT as a standard approach. Hyperthermia is applied once weekly at the Erasmus MC Daniel den Hoed Cancer Center.

Although the addition of cisplatin-based chemotherapy to radiotherapy gained widespread acceptance, RHT remained the treatment of choice for patients with FIGO stage ≥ IIB lateral and/ or large tumor volume in several Dutch radiotherapy institutes whereas others reserve RHT for those who are unfit to receive concurrent chemotherapy.

From 1996 until 2005 we have treated 378 patients with LACC with RHT at our department. In the present study we report response rates, pelvic tumor control, overall survival and radiation-induced toxicity of these patients and compare the results to those of the DDHT and other treatment approaches.

Methods

Patients

Patients were eligible for RHT if they required primary radiotherapy for bulky (central tumor diameter ≥ 4 cm) and /or locally advanced cervical cancer. Most radiotherapy institutes refer patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIB lateral - IV, in concordance with the inclusion criteria of the DDHT. At MAASTRO clinic, patients with cervical cancer FIGO stage IB2 –IV are routinely treated with RHT. All radiotherapy institutes refer patients who are unfit to receive chemotherapy because of poor general condition, insufficient renal function or because the para-aortic lymph nodes are included in the radiation field.

In order to facilitate comparison with the DDHT we used the 4th edition of the UICC TNM Classification instead of the newer 6th version, which classifies all patients with positive para-aortic lymph nodes as FIGO IVB.[4] In all patients, diagnosis was confirmed by histopathological examination. All patients received a standard diagnostic work-up including a gynecologic examination under anesthesia with a cystoscopy, a CT-scan of the abdomen and a chest X-ray. An acceptable cardiac condition defined as ASA (American Society of Anesthesiologists) classification of 2 or less was required and patients' expected survival had to exceed 6 months. Patients with a pacemaker or a metal implant in the pelvic region larger than 10 cm were excluded, as these are absolute contraindications for hyperthermia.

Radiotherapy

External beam radiotherapy was delivered with megavoltage equipment using an equally weighted 4-field box technique with 6-10 MV photons to treat the primary tumor, the (proximal) vaginal wall, the parametria, and the draining pelvic lymph nodes. The same technique was applied when the para-aortic region was included up to the level of L2-3 in case of positive lymph nodes along the common iliac artery. In case of para-aortic lymph node metastasis two parallel opposed anterior-posterior fields were used to include the draining lymph nodes up to the level of Th10-11. Customized blocks were designed to spare the small bowel, the rectum and caput femoris. In 23-28 daily fractions of 2.0-1.8 Gy, 5 times a week, a total dose of 46.0-50.4 Gy was delivered to the pelvic structures. The dose to the para-aortic lymph nodes was restricted to 43.2– 46 Gy. Patients with residual parametrial tumor at the time of first brachytherapy usually received an additional pelvic sidewall boost, thus increasing the total dose delivered to the pelvic sidewall up to 60 Gy, taking into account the dose contributed by brachytherapy.

Brachytherapy (BCT) was delivered using Iridium-192 (HDR) to a total dose of 17 Gy applied in two fractions, or 18 - 21 Gy in three fractions; using Cesium-137 (MDR) in a single fraction of 20-24 Gy in 20-24 hours or 30 Gy in 60 hours (LDR). The BCT technique used depended on availability in the institute where radiotherapy was administered, and might have changed during the study period (i.e. some institutes switched from LDR to PDR and / or HDR). Dose specifications and homogeneity requirements were according to the ICRU 50 report. Typically, the maximal total dose accepted in critical normal tissue structures considered in treatment planning was 50 Gy for the small bowel, 70 Gy for the rectum and 80 Gy for the bladder.

Hyperthermia

Deep locoregional hyperthermia was prescribed once weekly to a total of 5 times during external beam radiotherapy. For all hyperthermia treatments the BSD-2000 (3D) system was used (BSD Medical Corporation, Salt Lake City, Utah, USA) with the Sigma-60 or Sigma-eye applicator depending on the patients' size.

Patients were mildly sedated with 1 mg lorazepam or 0.5 mg alprazolam, taken 30 minutes before treatment. For thermometry Bowman probes were placed in bladder, rectum and vagina. Thermal mapping was performed every 5 minutes with a step size of 1 cm and a maximum map length of 14 cm. The standard prescribed duration of a treatment was 90 minutes, during which temperatures were increased to as high and homogeneous as patient tolerance and normal tissue temperatures permitted: normal tissue temperatures should not exceed 43 ^{0}C during the first 60 minutes of a treatment, and not 44 ^{0}C during the last 30 minutes. Besides the measured temperatures, information on too high temperatures (hotspots) came from the patient. Patients were carefully instructed to mention any uncomfortable feelings that could be suggestive of hotspots during treatment.

Pulse rate and blood pressure were measured automatically before and every 5 minutes during treatment; oral temperature was measured at 0, 15, 30, 60 and 90 minutes. During treatment, the patients' well being, vital signs and temperatures were carefully monitored by a physician. If there were signs of distress, we took the appropriate measures designated in our protocol, i.e. power was turned off to alleviate distress and in case of hotspots, treatment settings such as phase, amplitude, frequency and power were adjusted by a technician to relieve the symptoms.

Study endpoints

Primary endpoints were complete response rate and pelvic tumor control. Follow-up visits were planned in accordance with the Dutch Association of Cancer Centers guidelines. Patients alternatively visited a gynecologic oncologist and a radiation oncologist.

A complete response was defined as the clinical disappearance of all tumors in the irradiated volume. Response was assessed by anamnestic information and physical examination, and if indicated supplemental examinations. The maximum tumor response achieved is recorded in this study. Patients who did not achieve a complete response were considered pelvic failures at day 0.

Duration of pelvic tumor control was defined either as the time elapsed since the date of the last radiotherapy fraction and the date of local recurrence within the irradiated volume, or death of any cause.

Secondary endpoints were overall survival, disease specific survival and late radiation-induced toxicity. Overall survival was defined as the time between date of the last fraction of radiotherapy and death or last follow-up. Late toxicity (effects occurring 3 months or longer after the last radiotherapy) was scored using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.

Data acquisition

Follow-up visits were usually planned at the referring institutes. Information on pelvic tumor control, survival and late toxicity was collected from correspondence and hospital charts from radiation oncologists, gynecologic oncologists and patients' general practitioners. If no further medical information could be gathered, the population registry was consulted for an update of the survival status. The information was gathered by the first author and reviewed by one other author (JZ). Only grade ≥ 3 late toxicity is reported here, to prevent bias caused by under reporting of grade 1 and 2 toxicity in the medical charts.

Statistical analysis

The Kaplan-Meier method was used to estimate pelvic tumor control, overall survival, disease specific survival and the incidence of late toxicity. For univariate and multivariate analyses on response rate, logistic regression was used. Cox regression analysis was used for univariate and multivariate analyses on overall and disease specific survival and late toxicity. Two-sided p-values below 0.05 were considered significant. The following prognostic factors were entered in univariate analysis: FIGO stage of the tumor, World Health Organization performance status (WHO-PS), lymph node status, histology, tumor grade, patient age, tumor diameter, overall treatment time, dose of external beam radiotherapy, having had brachytherapy or not (BCT+/-) and the number of hyperthermia treatments given (#HT). Because information on hemoglobin level before and during treatment was missing for 111 patients (27%), this parameter was not included in further analyses. The overall treatment time and maximum tumor diameter were entered both as continuous and categorical variables. The number of hyperthermia treatments was entered as a categorical variable. All prognostic factors that were significant in univariate analysis were entered in multivariate analysis. For toxicity evaluation, patients were censored when a local recurrence was diagnosed. If a patient developed more than one toxic event, the event with the highest grade was scored. For comparison with results of the DDHT, the influence of lymph node status was not assessed, because 56 % of patients included in

the trial, were Nx. For the analyses, the Statistical Package for Social Sciences was used, version 14.0 (SPSS Inc. Chicago, Illinois, USA).

Results

Patient- and tumor characteristics

Between September 1996 and June of 2005 424 patients with LACC were treated with RHT at our department. Of these 424 patients, 23 were treated in the framework of a phase II trial testing the feasibility of combined radiotherapy, chemotherapy and hyperthermia.

Table 1: Patient- and tumorcharacteristics for patients in the current analysis and those enrolled in the Dutch Deep Hyperthermia Trial (DDHT, 1990-1996)

		Patients treated with RHT after 1996 (n = 378)		Patients treated with RHT in DDHT (n = 58)	
FIGO stage	IB2	13	(3 %)	-	
	IIA	28	(7 %)	-	
	IIB	132	(35 %)	11	(19 %)
	IIIA	21	(6 %)	-	
	IIIB	142	(38 %)	40	(69 %)
	IVA	42	(11 %)	7	(12 %)
Age	median	58 years	(22 – 89)	51	(26 – 75)
WHO-PS	0	234	(62 %)	45	(77 %)
	1	111	(29 %)	13	(23 %)
	2	30	(8 %)	-	
	3	3	(1 %)	-	
Histology	SCC	322	(85 %)	51	(88 %)
	AC	32	(9 %)	4	(7 %)
	Other	24	(6 %)	3	(5 %)
Grade	I	16	(4 %)	4	(7 %)
	II	141	(37 %)	21	(36 %)
	III	125	(33 %)	24	(41 %)
	unknown	96	(25 %)	9	(16 %)
N-status	not assessed	40	(11 %)	33	(57 %)
	N0	223	(59 %)	n.c.	
	N1	115	(30 %)		
Tumor size	median	9.0 cm	(3.9 – 16.5)	7.6 cm	(5.2-9.9)
Brachytherapy	yes	330	(87 %)	48	(83 %)
	no	51	(13 %)	10	(17 %)
#HT	4 or more	339	(90 %)	40	(69 %)
OTT	median	39 days	(7 - 83)	48 days	(35-116)

Legend: FIGO = International Federation of Gynecology and Obstetrics, WHO-PS = World Health Organisation performance status, SCC = squamous cell carcinoma, AC = adenocarcinoma, N-status = affected lymph nodes; because of the large percentage Nx in the DDHT, numbers are not comparable (n.c.), #HT = number of hyperthermia treatments, OTT = overall treatment time (days)

These patients were excluded from this analysis and have been reported on elsewhere.[5] Another 23 received induction chemotherapy prior to RHT, they were also excluded from this analysis. Patient- and tumor characteristics of 378 patients that were exclusively treated with radiotherapy and hyperthermia are summarized in table 1.

Almost half (49%) of the patients were staged FIGO IIIB/IVA, 30% had evidence of positive lymph nodes on CT-scan and 93% had a tumor larger than 6 cm, measured on CT-scan. Three patients with a WHO-PS of 3 were bedridden due to tumor-related complaints such as cachexia or pain. Mean follow-up time for survivors was 44 months.

Treatment characteristics

Radiotherapy: Radiotherapy was administered in 14 different institutes in the Netherlands. The most common institutes of referral were the Daniel den Hoed Cancer Center and the MAASTRO clinic. Together they supplied 66% of the patients.

Radiotherapy was not completed as planned in 13% (n=48) of the patients. The reasons for not completing radiotherapy as planned were insufficient regression of the tumor to perform BCT (n=29), poor general condition (n=7), distant metastasis diagnosed during treatment (n=4), patients' refusal (n=2), death during treatment (n=3, see further), unknown (n=2) and acute radiation toxicity necessitating adjustment of the total dose (n=1). The overall treatment time for radiotherapy including BCT was more than 50 days in 13% of the patients.

Hyperthermia: Hyperthermia was administered 0.5 to 4 hours after radiotherapy and was generally well tolerated; 74% of patients received 5 hyperthermia treatments as planned. Fifteen percent of patients received 4 hyperthermia treatments and 10% received 3 or less. The reason for not completing all hyperthermia treatments was patient- or tumor-related in 79% and for logistical reasons in 18%. In 3% the reason is unknown or due to a combination of factors. During treatments, a mean intraluminal temperature of 40.6 ^{0}C was achieved.

Response

The tumor response to RHT is listed in table 2.

Complete response rate: Overall, 77% of patients achieved a complete response (95% confidence interval: 73-81%). For 7 patients (2%), information about response was not available due to death during treatment (n=3, see further), distant metastasis during treatment (n=2), return to the country of origin after treatment (n=1) or treatment stopped at patient's request (n=1). These patients were considered immediate pelvic failures.

Table 2 : Complete response rate, pelvic tumor control, disease specific survival and overall survival at 5 years (95 % confidence interval)

a. For the various FIGO stages

FIGO	CR-rate	PTC[1]	DSS[1]	OS[1]
IB2	100 %	69 % (44-94)	68 % (41-94)	68 % (41-94)
IIA	82 % (67-97)	58 % (36-80)	34 % (1-67)	35 % (1-68)
IIB	89 % (84-95)	68 % (59-77)	64 % (54-74)	57 % (46-67)
IIIA	86 % (69-100)	55 % (29-81)	45 % (13-78)	31 % (6-57)
IIIB	63 % (55-71)	40 % (31-49)	33 % (24-42)	27 % (18-35)
IVA	71 % (57-86)	42 % (24-60)	35 % (25-44)	25 % (10-40)
Overall	77 % (73-81)	53 % (48-59)	47 % (41-53)	40 % (34-46)

b. Per tumor diameter

Diameter	CR-rate	PTC [1]	DSS [1]	OS[1]
< 6 cm	85 % (70-99)	65 % (44-86)	85 % (64-100)	77 % (55-99)
6 - 8 cm	86 % (79-93)	60 % (48-71)	51 % (39-63)	44 % (32-56)
> 8 cm	73 % (68-79)	50 % (43-77)	43 % (36-50)	36 % (28-42)

c. For patients who did and did not receive brachytherapy

	CR-rate	PTC[1]	DSS[1]	OS[1]
no	35 % (21-49)	24 % (11-37)	26 % (12-39)	17 % (6-28)
yes	84 % (80-88)	58 % (51-64)	50 % (44-57)	44 % (37-50)

d. For patients who received 1-3 hyperthermia treatments, or 4-5

	CR-rate	PTC[1]	DSS[1]	OS[1]
1 - 3	46 % (30-63)	28 % (12-44)	34 % (16-53)	25 % (8-42)
4 - 5	81 % (77-85)	56 % (50-62)	49 % (43-55)	42 % (35-48)

Legend: CR-rate = complete response rate, PTC = pelvic tumor control, DSS = disease specific survival, OS = overall survival, [1] Kaplan-Meier estimate at 5 years (95 % confidence interval)

Table 3: Univariate analysis (n = 378)

	CR-rate	PTC	OS	DSS
FIGO	0.000	0.001	0.000	0.000
WHO -PS	0.001	0.000	0.000	0.000
Tumor diameter	0.000	0.010	0.000	0.000
Age	ns	0.044	ns	ns
N-status	ns	ns	ns	ns
Histology	ns	ns	ns	ns
Hospital	ns	ns	ns	ns
ERT dose	ns	ns	ns	ns
Treatment time	ns	ns	ns	ns
#HT	0.000	0.003	0.003	0.005
BCT+/-	0.000	0.000	0.000	0.000
Tumor diameter (c)[1]	0.031	ns	0.008	0.008
Treatment time (c)[2]	ns	ns	ns	ns

Legend: FIGO = International Federation of Gynecology and Obstetrics, WHO-PS = World Health Organisation performance status, N-status = affected lymph nodes, ERT dose = dose of external beam radiotherapy, #HT = number of hyperthermia treatments, BCT+/- = patient did or did not receive brachytherapy, (c)[1] three categories; smaller than 6 cm, between 6 and 8 cm and larger than 8 cm, (c)[2] three categories; 42 days or less, between 43 and 50 days and more than 50 days, ns = not significant, i.e. p-value ≥ 0.05

Table 4: Multivariate analysis (n = 378)

	CR-rate	PTC	OS	DSS
FIGO	0.011	0.011	0.000	0.002
WHO-PS	0.612	0.169	0.004	0.095
Tumor diameter	0.033	0.272	0.027	0.001
Age	--	0.005	--	--
#HT	0.058	0.172	0.132	0.019
BCT+/-	0.000	0.002	0.001	0.001

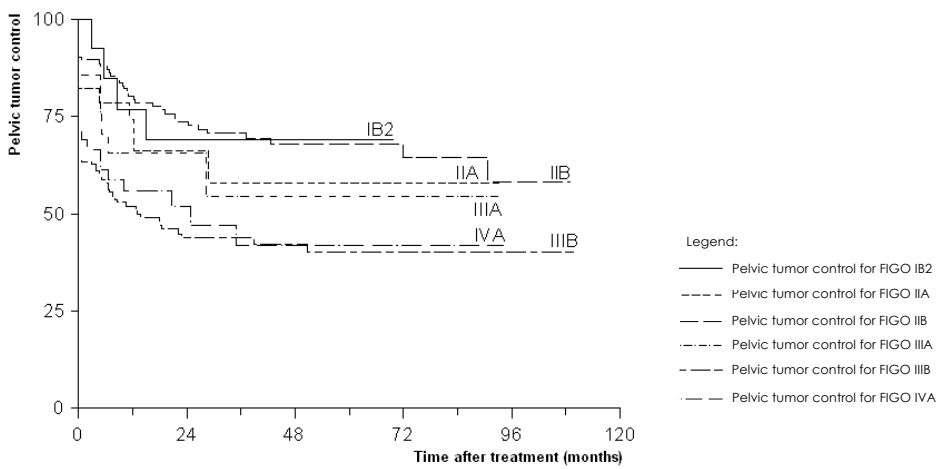
Legend: CR-rate = complete response rate, PTC = pelvic tumor control, OS = overall survival, DSS = disease specific survival, FIGO = International Federation of Gynecology and Obstetrics, WHO-PS = World Health Organisation performance status, N-status = affected lymph nodes, ERT dose = dose of external beam radiotherapy, #HT = number of hyperthermia treatments, BCT+/- = patient did or did not receive brachytherapy. -- = not entered in the multivariate model

In univariate analysis FIGO stage, WHO-PS, tumor diameter, BCT+/- and #HT were significant factors predictive of response (table 3). In the multivariate model, FIGO stage, tumor diameter and BCT+/- kept their significant influence (table 4).

Pelvic tumor control: In figure 1 pelvic tumor control (PTC) is shown per FIGO stage. Five-year PTC was 53% for all patients (95 %CI: 48–59%). In univariate analysis FIGO stage, WHO-PS, tumor diameter, age, BCT+/- and #HT were significant factors predictive of PTC (table 3). In multivariate analysis, FIGO stage, age and BCT+/- remain of significant influence (table 4).

Distant metastasis: During follow-up, 279 patients (74%) developed distant metastasis, including para-aortic lymph node metastasis. One hundred of these patients (36%) developed metastases without signs of a pelvic recurrence.

Figure 1: Pelvic tumor control by FIGO stage

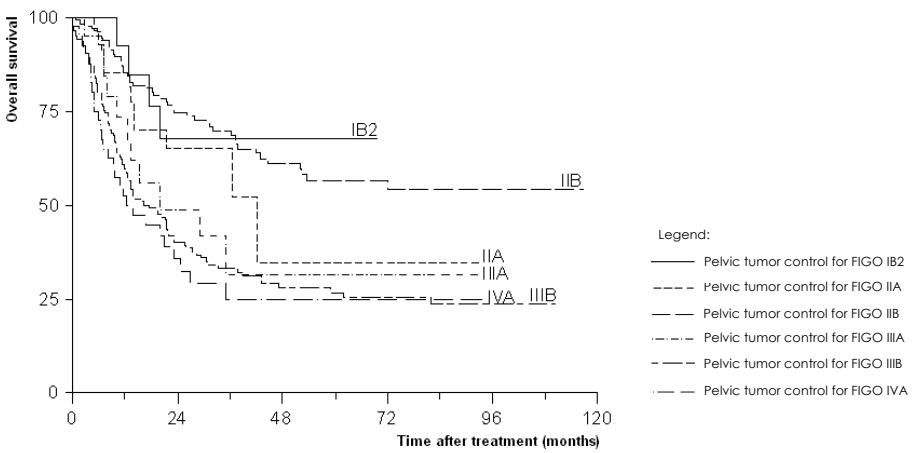


Disease specific survival: Eighteen percent of patients (n=68) died of noncancer-related causes and therefore disease specific survival (DSS) is also reported here. At 5 years, DSS is 47% (95% CI 41-53 %). Four patients (1%) died during the course of treatment. The cause of death was not tumor- or treatment-related in 3 of them. They died of acute coronary problems, sepsis, and a massive pulmonary embolus respectively. One patient, 78 years old, died during the course of treatment because of poor general condition and acute gastro-intestinal radiation toxicity.

In univariate analysis FIGO stage, WHO-PS, tumor diameter, lymph node status, BCT+/- and #HT were significantly associated with DSS (table 3). In the multivariate model including all factors that were significant in univariate analysis, #HT remained of significant influence on DSS (table 4).

Overall survival: Figure 2 shows the overall survival (OS) per FIGO stage. The overall survival rate was 40% at 5 years (95 % CI: 34 - 46%). In univariate analysis FIGO stage, WHO-PS, tumor diameter, BT+/- and #HT were significantly associated with OS (table 3). In the multivariate model, except for #HT, all factors remained significant (table 4).

Figure 2: Overall survival by FIGO stage



Late radiation-induced toxicity: In the first year after radiotherapy, 6% of patients developed grade ≥ 3 late toxicity (95% CI 3–9%). Five years after treatment, the incidence was 12% (95%CI 7–18%). All events are summarized in table 5. None of the factors tested had a significant influence on the incidence of late toxicity in this analysis. Four patients (1%) died of radiation-induced complications. The first patient presented with urinary incontinence and malnutrition due to an elaborately fistulating process in the pelvic area. In spite of

Table 5: Late toxicity CTC grade ≥ 3

patnr	delay	grade	event
781	3	4	Bowel perforation
1504	3	3	Vesicovaginal fistula
1149	4	3	Radiation-induced enteritis
1133	5	3	Radiation-induced enteritis
1071	6	3	Vesicovaginal fistula
1208	6	5	Bowel perforation
1220	6	3	Osteonecrosis
811	7	4	Bowel perforation
996	7	3	Fibrosis causing hydronephrosis
1237	7	3	Pelvic fibrosis causing ileus
1584	7	3	Gastrointestinal obstruction due to fibrosis
1229	8	5	Rectovaginal fistula
1190	9	3	Rectovaginal fistula
1471	9	3	Rectovaginal fistula
798	11	3	Vesicovaginal fistula
1054	11	3	Massive fibrosis pelvic area causing hydronephrosis
1543	11	3	Radiation-induced enteritis
1234	15	5	Bowel perforation
1413	15	3	Rectovaginal fistula
1189	19	3	Rectovaginal fistula
946	22	3	Vaginal fibrosis causing great sexual problems
1255	24	3	Radiation-induced enteritis
959	30	5	Necrotic process in pelvic area
1315	32	3	Osteonecrosis
1135	46	3	Radiation-induced enteritis
916	95	3	Radiation-induced enteritis

Legend: patnr = patient identification number, in chronological order, delay = time between last fraction of radiotherapy and diagnosis in months, grade = grade of the event on the CTCAE v3 - scale

various necrotectomies involving the gluteal muscles and the sacrum, necrosis remained progressive with unmanageable pain and metabolic dysregulation due to malabsorption. Her request for euthanasia was granted 31 months after RHT was completed. The second patient had had a urinary deviation and colostomy prior to radiotherapy because of a vesicovaginal fistula. She presented with strangulation of the small intestine 6 months after completion of RHT. The strangulation was treated conservatively, but the next day she developed a perforation and died. The third patient developed an ileus 8 months after treatment, which was treated with a partial resection of the small intestine. An entero-vaginal fistula and disturbances of liver function complicated her postoperative recovery. She ultimately died 3 months after the first surgery due to sepsis – the source was her i.v. system - resulting multiple organ failure. The last patient developed a bowel perforation 4 months after the completion of treatment and died. In all cases an autopsy was performed and no signs of recurrent tumor were found.

Comparison to the results of the DDHT

All FIGO stages: Fifty-eight patients were treated with RHT in the DDHT. Overall, 83% of those patients achieved a complete response. This CR-rate is comparable to the 77% we found in the present study (p = 0.348). In addition, PTC, DSS and OS were also comparable (p = 0.203, 0.917 and 0.735).

FIGO stage IIB (n=11): The baseline characteristics of these patients (table 1) were comparable to those of the patients treated since the study closed (n=132). In the study 82% of patients responded completely compared to 89% of patients treated since then (p = 0.450).

PTC and DSS were comparable for patients treated in the DDHT and thereafter, with a 5-year PTC rate of 68% for patients treated after the study closed and 72% for DDHT-IIB patients (p = 0.631) and DSS at 5 years of 64 and 61% respectively (p = 0.968).

FIGO stage IIIB (n = 40): Unlike the FIGO IIB-patients, the 2 groups of FIGO IIIB-patients differed significantly in baseline characteristics. On average, patients treated since the study closed were more often in a poor general condition (49% had a WHO-PS > 0 after the study, compared to 17.5% of DDHT-IIIB patients, p = 0.003), patients treated after the study closed, had larger tumors on average (9.4 vs. 7.8 cm, p = 0.000) and were older on average (59.8 vs. 51.8 years, p 0.003). To account for these differences, we performed multivariate analyses on CR-rate, PTC and DSS for this subgroup.

CR-rate of patients treated in the DDHT is 88% compared to 63% for patients treated after the DDHT closed (p = 0.006). After adjustment for WHO-PS, age and tumor diameter, the difference in CR-rate remained significant (p = 0.038).

PTC one year after treatment was 71% for patients treated in the study (95%CI 57-86) and 51% for those treated thereafter (95%CI 43-60 %). At 5 years, PTC was 60% for DDHT-IIB patients (95%CI 42–75%) and 40% for patients treated afterwards (95%CI 31–49%, p = 0.03). After adjustment for WHO-PS, age and tumor diameter, the difference in PTC was no longer significant (p = 0.093).

DSS at one year after treatment was 77% for patients treated in the study and 64% for patients treated afterwards. At 5 years, this was 43% for DDHT-patients (95% CI 27-58%) and 33% for patients treated afterwards (95%CI 24-42%, p = 0.149). After adjustment for WHO-PS, age and tumor diameter, the difference remained insignificant (p = 0.680).

FIGO stage IV: The CR-rate for patients staged FIGO IVA was 71% for patients treated after the DDHT closed (95% CI 57–86%). As only 11 FIGO stage IVA-patients were included in the DDHT, of who 7 received HT with their radiotherapy, a meaningful statistical comparison for outcome measures is not possible.

Of our 378 patients, 20 had para-aortic lymph node metastasis (FIGO stage IVB). Of these, 60% achieved a complete response and one year PTC and DSS were 44% (95%CI 22–66%) and 60% (95%CI 37–83 %) respectively.

Discussion

The current study represents the first large-scale observational study on the results of RHT since the Dutch Deep Hyperthermia Trial closed in 1996. Overall, 77 % of our patients achieved a complete response, pelvic tumor control at 5 years was 53 %, disease specific survival 47 % and overall survival 40 %. The incidence of late grade ≥ 3 toxicity was 12% at 5 years, which is not different from what is reported for radiotherapy alone.[6-12] Our 1% grade 5 complications was also previously found for radiotherapy alone.[8]

Multiple randomized trials have demonstrated the benefit of adding hyperthermia to radiotherapy in a variety of tumors. To date, 6 randomized trials have been published on the additive effect in LACC.[2, 13-17] In 4 of these trials, a significant benefit was observed for the experimental arm using the CR-rate, PTC, DFS and/or OS as endpoint.[2, 14-16] In one trial, hyperthermia added to chemoradiation yielded superior CR-rates compared to standard radiotherapy only or combined with either hyperthermia or chemotherapy.[13]

In only one of these trials no beneficial effect of adding hyperthermia to standard radiotherapy was demonstrated.[17] Experts have criticized this trial for several reasons, the most important points of criticism being the hyperthermia technique used and the fact that the thermometry data obtained fell considerably short according to published guidelines.[18-19] In fact, an inadequate heating technique has been the most plausible explanation for not finding an effect of adding hyperthermia to standard treatment with radiotherapy in several published trials.[20-22] In view of results of the randomized trials published so far and the cost effectiveness of hyperthermia, RHT became a standard treatment approach in the Netherlands.[23]

We considered the DDHT population the most appropriate group for comparison to our current group, as this trial was also conducted in our hospital and patient populations are expected to be identical. However, we realize that comparing our current results to those of the DDHT results in small subgroup analyses and the results should be interpreted with care, especially since there is evidence that the prognostic characteristics of our patient group have worsened since the trial closed.

A remarkable finding in the present series is the predictive value of the number of hyperthermia treatments (#HT). As #HT is probably influenced by patient and tumor-related characteristics, we expected its predictive value to disappear in multivariate analysis, but this was not the case for survival. If #HT is the only treatment-related predictor variable that is entered in the multivariate models, i.e. if BCT is left out, #HT remains its significant influence on all outcome measures. A probable explanation for the strong influence of #HT is that an increasing number of hyperthermia treatments corresponds with an increasing thermal dose administered to the patient which has been shown to correlate with better treatment outcome.[24-27]

As compared to our previous results obtained in the DDHT trial, pelvic tumor control and survival rates in the present series were relatively low, which can partly be explained by worse patient- and tumor-characteristics (table 1). This is most obviously reflected by the baseline characteristics of FIGO IIIB-patients. Those who were treated after 1996 were significantly older, in worse general condition and had larger tumors than their DDHT-counterparts. All of these factors are known to have a negative influence on treatment outcome.[6, 28-32] In addition, an extra set of factors negatively influencing treatment outcome of our current group of patients can be designated as a referral bias. A substantial number of patients referred for treatment since 1996 were unfit to receive chemotherapy, because of poor general condition or renal function, or because of intended radiotherapy to the para-aortic region. Since chemoradiation was not widely used during the DDHT period, the referral bias was less evident during that period.

One way to further improve the relatively low local control and survival rates, is to increase the radiation dose administered to the gross tumor volume. Recently, Pötter et al. reported an expected absolute gain in survival of 10-20% in patients with LACC by using image-guided (interstitial) brachytherapy, applying strict rules for normal tissue constraints.[33] Intensity-modulated radiation therapy (IMRT) is another technique currently explored for this purpose.[34-35] Another, widely used option to improve clinical outcome, is to combine radiotherapy with chemotherapy (chemoradiation).

Since the National Cancer Institute's clinical alert in 1999, the combination of radiotherapy and platinum-based chemotherapy (RCT) has gained wide acceptance, although many important questions remain to be answered.[36] Most RCT trials excluded patients with proven or suspected para-aortic lymph node metastasis, whereas relatively few patients with advanced-stage tumors (FIGO > II) were included. Two recent meta-analyses suggested that the impact of adding chemotherapy to radiotherapy is less obvious in advanced-stage tumors.[37-39] In contrast, in 4 of 6 randomized trials demonstrating a benefi-

cial effect of adding hyperthermia to radiotherapy the fraction of patients with FIGO stage IIIB was 70 - 100%. [14, 16] The odds radio (OR) for pelvic control and relative hazard ratio (RHR) for death from the DDHT are comparable to those of the RCT trials.[40] From this we might speculate that patients with higher stage or more bulky tumors may benefit more from the addition of hyperthermia to radiotherapy than the addition of chemotherapy. As the lower-stage tumors (FIGO stage IB2, IIA and IIBmedial) were not included in the DDHT, the effect of RHT in this patient group has never been evaluated until now.

Also, the RCT-combination increases acute treatment-induced toxicity, compared to radiotherapy alone, whereas for RHT such an increase cannot be demonstrated.[1-3,41-42] Although limited information is available, RCT does not seem to add to late radiation-induced toxicity and neither does RHT. [3,37, 39,41] The situation in the Netherlands, where the 2 treatment approaches coexist for LACC, gives us the unique opportunity to compare the 2 approaches in a randomized multicenter phase III trial that was recently launched.

A third approach to improve treatment outcome in patients with LACC is to combine radiotherapy with both chemotherapy and hyperthermia as hyperthermia can be expected to enhance the cytotoxicity of both radiotherapy and hyperthermia.[43] The first results of an international multicenter phase I/II trial recently showed that this trimodality treatment is feasible and currently an international randomized multicenter phase III trial comparing RT+CDDP to the trimodality treatment is ongoing.[5]

Conclusion

Overall, treatment results in this large group of patients treated with RHT are comparable to historical controls in DDHT. The subgroup of patients with FIGO stage IIIB did worse since the trial closed. A plausible explanation can be found in a referral bias, with consequentially worse patient characteristics, since RCT became another standard treatment approach for LACC in the mid nineties.

From the available literature data no definite conclusion can be drawn regarding the preferred combined treatment in LACC. Based on our extended experience in this patient population, combined RT and HT should be considered as standard treatment in those not fit for combined radiotherapy and chemotherapy. For other patients, the optimal treatment strategy is subject of ongoing research.

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Chapter 5

Hyperthermia dose-effect relationship in 420 patients with cervical cancer treated with combined radiotherapy and hyperthermia

Franckena M, Fatehi D, de Bruijne M, Canters RAM, van Norden Y, Mens JW, van Rhoon GC and van der Zee J. Hyperthermia dose-effect relationship in 420 patients with cervical cancer treated with combined radiotherapy and hyperthermia. Eur J Cancer 2009; 45: 1969-1978.

Abstract

Adding hyperthermia to standard radiotherapy (RT+HT) improves treatment outcome for patients with locally advanced cervical cancer (LACC). We investigated the effect of hyperthermia dose on treatment outcome for patients with LACC treated with RT+HT.

We collected treatment and outcome data of 420 patients with LACC treated with hyperthermia at our institute from 1990 to 2005. Univariate and multivariate analyses were performed on response rate, local control, disease specific survival and toxicity for these patients to search for a thermal dose response relationship.

Besides commonly identified prognostic factors in LACC like tumor stage, performance status, radiotherapy dose and tumor size, thermal parameters involving both temperature and duration of heating emerged as significant predictors of the various endpoints. The more commonly used CEM43T90 (cumulative equivalent minutes of T90 above 43^0C) was less influential than TRISE (based on the average T50 increase and the duration of heating, normalized to the scheduled duration of treatment).

CEM43T90 and TRISE measured intraluminally correlate significantly and independently with tumor control and survival. These findings stimulate further technological development and improvement of deep hyperthermia, as they strongly suggest that it might be worthwhile to increase the thermal dose for LACC, either by treatment optimization or by prolonging the treatment time. These results also confirm the beneficial effects from hyperthermia as demonstrated in our earlier randomized trial, and justify applying radiotherapy and hyperthermia as treatment of choice for patients with advanced cervical cancer.

Introduction

At our department patients with locally advanced cervical cancer (LACC) have been treated with combined radiotherapy and hyperthermia (RT+HT) since 1990. From 1990 to 1996 a randomized trial was conducted, in which radiotherapy alone was compared to RT+HT for the treatment of locally advanced pelvic tumors.[1] It showed a significant improvement in local control and overall survival with the addition of hyperthermia. The improvement was most apparent for patients with LACC, and a recent update showed that the improvement is persistent after 12 years follow-up.[2-3] After the randomized trial was completed, RT+HT became a standard treatment approach for patients with LACC in the Netherlands.[4] From the clinical studies thus far performed, it is clear that RT+HT improves treatment outcome compared to radiotherapy alone. However, as the pelvic tumor control rate is still only 53 % at 5 years, there is still a strong need to search for ways to improve our treatment strategy.[4] As has previously been shown for radiotherapy dose escalation and the addition of chemotherapy to RT+HT, we anticipate that optimizing the thermal dose delivered may further improve treatment results in this patient group.[5-8] For a variety of other tumor types that are treated with radiotherapy and superficial hyperthermia, various thermal dose parameters have been shown to relate to treatment outcome significantly.[9-17] For deep hyperthermia, much less is known about the relationship between temperatures measured during treatment and treatment outcome.[18-21]

In this report we present the results of the retrospective evaluation on which thermal dose parameters are of prognostic value for treatment outcome when patients with LACC are treated with RT+HT. We investigated the relation between various thermal dose parameters and complete response rate, pelvic tumor control, disease specific survival and acute and late toxicity.

Patients and methods

From May 1990 to July of 2005 458 patients with LACC were treated with RT+HT at the Erasmus Medical Center Rotterdam. Of 420 patients, temperature and power data are available. For 38 patients, temperature and power data was inaccessible.[22]

Patients

Patients were eligible for RT+HT if they required primary standard radiotherapy for cervix cancer FIGO (International Federation of Gynecology and Obstetrics) stage IB2–IV. For staging, we used the 4th edition of the UICC TNM Classification of malignant tumors. In all patients, diagnosis was confirmed by histopathological examination. All patients received a standard diagnostic work-up including a gynecologic examination under anesthesia with a cystoscopy, a CT-scan of the abdomen and a chest X-ray. An acceptable cardiac condition defined as ASA (American Society of Anesthesiologists) classification of 2 or less was required and patients' expected survival had to exceed 6 months. Patients with a pacemaker or a metal implant in the pelvic region larger than 10 cm were excluded, since these are absolute contraindications for hyperthermia.

Radiotherapy

Radiotherapy was prescribed in accordance with the Dutch Society for Radiotherapy and Oncology guidelines. External beam radiotherapy was given in 23-28 daily fractions of 2.0-1.8 Gy, 5 times a week, to a total dose of 46.0 to 50.4 Gy using a 4-field box technique with 6-23 MV photons. The para-aortic region was included in case of positive lymph nodes along the common iliac artery or aorta. An additional pelvic sidewall boost was given to patients with residual tumor in the parametrium at the time of first brachytherapy. Twenty-two patients received chemotherapy prior to radiotherapy because of positive lymph nodes or bulky tumor load.

Brachytherapy was scheduled for all patients and was delivered using Iridium-192 (HDR) to a total dose of 17 Gy, applied in two fractions, or 18 - 21 Gy in three fractions, or 30 Gy in 60 hours (LDR). Dose specifications and target volume definition were according to the International Commission on Radiation Units and Measurements (ICRU) report 50. Further details have previously been published.[4]

Hyperthermia

Deep hyperthermia was prescribed once weekly to a total of 5 times during the 5 weeks of external beam radiotherapy. For all hyperthermia treatments the BSD-2000 system was used (BSD Medical Corporation, Salt Lake City, Utah, USA), with the Sigma-60 or Sigma-eye applicator depending on the patients' size.[23]

For thermometry Bowman probes were placed in bladder, rectum and vagina. Thermal mapping was performed every 5 minutes with a step size of 1 cm and a maximum map length of 14 cm. The standard prescribed duration of a treatment was 90 minutes, during

which temperatures were increased to as high and homogeneous as patient tolerance and normal tissue temperatures permitted: normal tissue temperatures should not exceed 43 ^{0}C during the first 60 minutes of a treatment, and not exceed 44 ^{0}C during the last 30 minutes. Besides the measured temperatures, information on too high temperatures (hotspots) came from the patient. Patients were carefully instructed to mention any uncomfortable feelings that could be suggestive of hotspots during treatment. If such complaints occurred, treatment settings such as phase, amplitude, frequency and power were adjusted to alleviate the complaints.

Temperature and power measures

Based on the temperatures measured intraluminally, several treatment parameters were calculated using RHyThM (Rotterdam Hyperthermia Thermal Modulator), which has been described elsewhere in detail.[24] The hyperthermia-related parameters are described in table 1. Cumulative Equivalent Minutes of T90 at 43^{0}C (CEM43T90) is a mathematical description of the exponential relationship found in vivo and in vitro, between temperature and exposure time; it is calculated as follows:[22]

$$CEM43T90 = \sum_{n=1}^{n=5} \int_{0}^{90} \Delta t \, R^{(43-T90)}$$

n = number of treatment
Δt = time interval of treatment (min)
T90 = average all lumen T90 during Δt
R = a constant;
when T > 43 ^{0}C R = 0.5
when T < 43 ^{0}C R = 0.25

In our treatment schedule only T90 is a real independent variable for each patient. The overall heating time can not be considered as such because the number of treatments and the duration of a treatment is prescribed a priori, i.e. 5 times 90 minutes. Hence, we anticipated that a thermal dose parameter expressing the temperature as dose but with the actual treatment time normalized to the overall treatment time of 450 min may be worthwhile parameter to investigate.

$$TRISE = \frac{\sum_{n=1}^{n=max} (ALT50 - 37\ ^0C) \times dt}{450}$$

n = number of treatment
dt = duration of treatment
ALT50 = all lumen T50, table 1

Table 1: Description of thermal parameters

Abbrev.	Parameter description
ALT20	Temperature exceeded by 20 % of monitored sites in bladder, vaginal and rectal lumen together and averaged over all treatments per patient (All Lumen T20)
ALT50	Temperature exceeded by 50 % of monitored sites in bladder, vaginal and rectal lumen together and averaged over all treatments per (All Lumen T50)
ALT90	Temperature exceeded by 90 % of monitored sites in bladder, vaginal and rectal lumen together and averaged over all treatments per patient (All Lumen T90)
VT50	Temperature exceeded by 50 % of monitored sites in the whole vaginal lumen and averaged over all treatments per patient (Vagina T50)
BT50	Temperature exceeded by 50 % of monitored sites in the whole bladder lumen and averaged over all treatments per patient (Bladder T50)
RT50	Temperature exceeded by 50 % of monitored sites in the whole rectal lumen and averaged over all treatments per patient (Rectum T50)
NIP	Mean Net Integrated Power, averaged over all treatments*
CEM43T90	Cumulative equivalent minutes at a T90 of 43 ^{0}C as described by Fatehi et al.[22]
TRISE	Custom made thermal dose parameter based on ALT50 and duration of heating

Legend :

NIP (mean Net Integrated Power) : $\sum_{t=0}^{t=max} \int$ (Pforward- Preflected) x Δt

t = 0 is start of treatment
t = max is end of treatment,
$P_{forward}$ = power forwarded during Δt
$P_{reflected}$ = power reflected during Δt and
Δt is the timeperiod during which was measured

TRISE incorporates temperature and duration of heating, but instead of transposing the measured temperatures to equivalent minutes at a reference temperature, we simply multiplied the T50 increase above 37 ^{0}C during treatment with the duration of treatment for all treatments, and normalized it to 450 minutes; the scheduled total treatment time for all patients.

Treatment outcome

Follow-up visits were planned in accordance with the Dutch Association of Cancer Centers Guidelines. Information on complete response, local control, survival and late toxicity were gathered retrospectively.

Complete response rate was defined as the complete disappearance of tumor within the irradiated volume and was assessed by anamnestic information, gynecological examination and supplemental investigations if indicated. Patients who did not achieve a complete response were considered pelvic failures at day 0.

Duration of pelvic tumor control was defined either as the time elapsed since the date of the last radiotherapy fraction and the date of local recurrence within the irradiated volume, or death of any cause.

Disease specific survival was defined as the time between date of the last fraction of radiotherapy and death due to cancer-related cause, treatment-induced toxicity or last follow-up.

For acute hyperthermia-related toxicity analysis, the worst grade toxicity a patient developed was included in this analysis. The grading system used for acute hyperthermia-related toxicity is described in table 2. Acute hyperthermia-related toxicity was defined as symptoms developing within 24 hours after a hyperthermia treatment.

Late radiation-induced toxicity was defined as toxicity due to treatment that occurred at least 3 months after the last fraction of radiotherapy and was classified according to the CTC (Common Toxicity Criteria) scale, version 3. Patients who developed a local recurrence were censored at the time of recurrence.

Table 2: Grading system used for classification of acute hyperthermia-related toxicity

Grade	Definition
1	Symptoms caused by hyperthermia treatment that lasted less than 3 days
2	Symptoms caused by hyperthermia treatment that lasted 3 to 14 days
3	Symptoms caused by hyperthermia treatment lasting 14 days or longer, or causing a delay or interruption of treatment
4	Symptoms caused by hyperthermia treatment that required surgery

Statistical analysis

The primary endpoints were complete response rate, pelvic tumor control and disease specific survival. Secondary endpoints were acute hyperthermia-related and late radiation-induced toxicity.

For the thermal dose analyses, only patients were included for whom temperature measurements were available of at least 50 % of the treatments they received, to ensure the temperature measures depict a patients' treatment accurately. For patients with treatments without thermometry, the total thermal dose was obtained through adding the average temperature dose of all treatments with thermometry. This concerned 221 treatments in 128 patients. In the temperature analyses, all patients were included, because variation between treatments is relatively small. In contrast to TRISE, CEM43T90 was not normally distributed, so its natural logarithm (lnCEM43T90) was entered in the analyses.

The following baseline characteristics were entered in univariate analysis (table 3): FIGO stage of the tumor, World Health Organization performance status (WHO-PS), lymph node

Table 3: Patient, tumor and treatment characteristics

Characteristic		n	%
FIGO stage	IB2	14	(3 %)
	IIA	27	(6 %)
	IIB	146	(35 %)
	IIIA	21	(5 %)
	IIIB	158	(38 %)
	IVA	54	(13 %)
N -status	Nx	47	(11 %)
	N0	239	(57 %)
	N1	134	(32 %)
Histology	SCC	358	(85 %)
	AC	38	(9 %)
	Other	20	(5 %)
	Unknown	4	(1 %)
WHO-PS	0	262	(62 %)
	1	123	(29 %)
	2	33	(8 %)
	3	2	(1 %)
Chemotherapy	yes	22	(5 %)
	no	398	(95 %)
RTc	yes	360	(86 %)
	no	60	(14 %)
Number of HT	1	15	(3 %)
	2	16	(4 %)
	3	17	(4 %)
	4	73	(16 %)
	5	299	(73 %)
Age	mean	57 years	(range: 22 – 89)
Overall treatment time	mean	40.5 days	(range: 7 – 115)
Tumor size	mean	8.9 cm	(range: 3.9 – 16.5 cm)

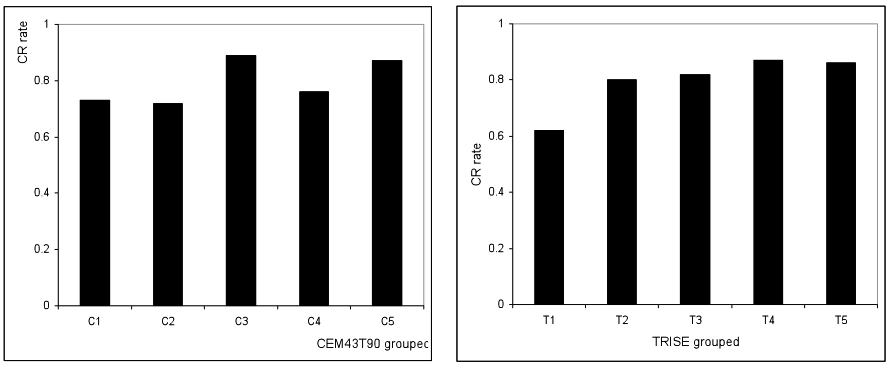
Legend: FIGO = International Federation of Gynecology and Obstetrics stage, N-status = lymph node status, SCC = squamous cell carcinoma, AC = adenocarcinoma, WHO-PS = World Health Organisation Performance Status, RTc = radiotherapy completed as planned (yes) or not (no), HT = hyperthermia treatments

status (N-status), histology, patient age, having received induction chemotherapy and tumor size. For radiotherapy dose, we entered a bivariate parameter indicating whether radiotherapy was given and completed as prescribed, i.e. 23-28 daily fractions of 2.0-1.8 Gy external beam radiotherapy combined with LDR, PDR or HDR brachytherapy at their appropriate schedules, or not (RTc). To ensure fair-sized subgroups, FIGO stage and WHO-PS were regrouped for the multivariate analyses; FIGO stage IIA and B were taken together (equivalent to T2 of the TNM classification) as were FIGO stage IIIA and IIIB (T3 of the TNM classification). WHO-PS was regrouped as WHO 0 or larger than 0.

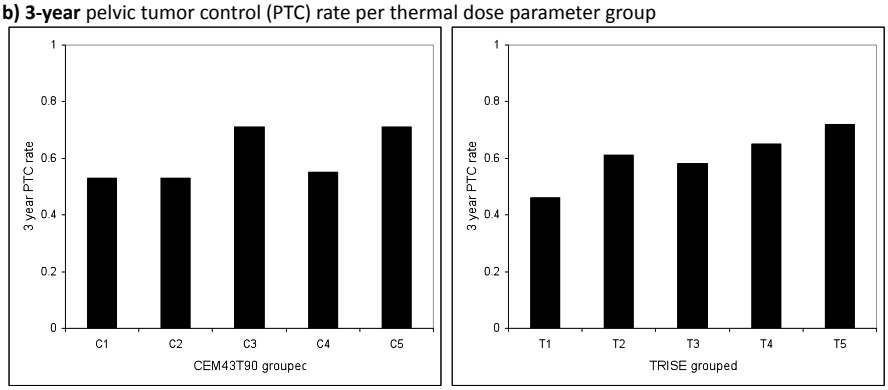
For the toxicity analyses, the subcutaneous fat thickness, patients' anterior-posterior and lateral diameter were also entered. These measures were determined on the CT-scan

Figure 1: Clinical outcome by thermal dose parameter group

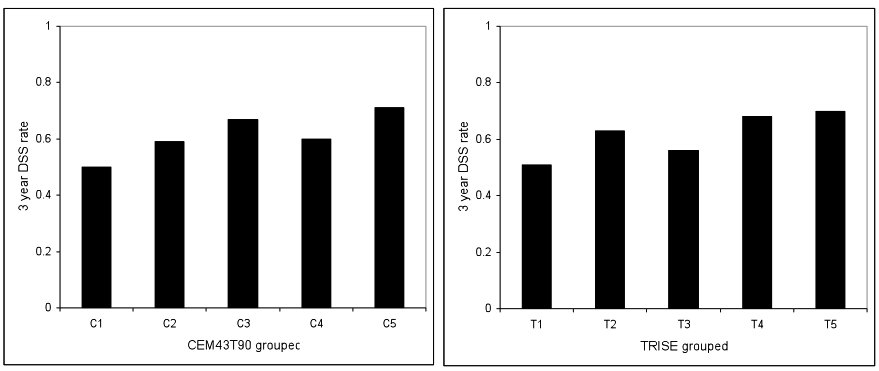
a) Complete response rate (CR-rate) per thermal dose parameter group



b) 3-year pelvic tumor control (PTC) rate per thermal dose parameter group



c) 3-year disease specific survival (DSS) rate per thermal dose parameter group



Grouping CEM43T90:
Group C1: minimum to 1.78
Group C2 : 1.79 to 3.17
Group C3 : 3.18 to 4.97
Group C4 :4.98 to 7.58
Group C5 :7.59 to maximum

Grouping TRISE:
Group T1 : minimum to 2.38
Group T2 : 2.39 to 2.81
Group T3 : 2.82 to 3.25
Group T4 : 3.26 to 3.75
Group T5 : 3.76 to maximum

made for treatment planning. For each significant thermal parameter, multivariate models were constructed incorporating all significant baseline characteristics on any endpoint.

For analyses on response rate and acute hyperthermia-related toxicity, logistic regression was used. Cox regression was used for analyses on pelvic tumor control, disease specific survival and late toxicity. P-values below 0.05 were considered significant.

For depicting the relationship between thermal dose and treatment outcome (figure 1), we grouped the thermal dose parameters at their 20th percentiles.

Results

Baseline characteristics of the 420 patients with LACC are summarized in table 3.

Thermal parameters: Hyperthermia treatment parameters are summarized in table 4.

Overall, the temperatures measured are comparable to what we and others found previously with an ALT50 of 40.6 ^{0}C.[19, 22] The CEM43T90 was relatively low and showed wide variation, with a mean of 5.05. Our new parameter TRISE was 2.96 on average. Correlation between various thermal parameters is shown in table 5.

Table 4: Hyperthermia treatment parameters

Parameter	Average	Standard deviation
ALT20	41.1 ^{0}C	0.31
ALT50	40.6 ^{0}C	0.55
ALT90	39.8 ^{0}C	0.55
VT50	40.3 ^{0}C	0.74
BT50	40.8 ^{0}C	0.61
RT50	40.6 ^{0}C	0.51
NIP	630 kJ	126
CEM43T90	5.05 min	4.18
TRISE	2.96 ^{0}C	2.96

Complete response rate (CR-rate): Three hundred and twenty-nine patients (78%) achieved a complete response following RT+HT, 65 (16%) patients had a partial response, 13 (3%) stable disease and 5 (1%) patients had progressive disease during treatment. For 8 patients, no information on tumor response could be gathered (2 %). FIGO stage, tumor size, N- status, WHO-PS and RTc emerged as significant baseline characteristics from the univariate analyses (table 6a). The mean intraluminal temperature measured (ALT50) for complete responders (CRs) was similar to that of the non-complete responders (NCRs) (40.5 ^{0}C and 40.6 ^{0}C respectively). There was a slight difference in CEM43T90 between the

Table 5: Pearson's correlation coefficients of thermal parameters

	CEM43T90	TRISE	NIP
ALT20	0.36	0.31	0.07
ALT50	0.76	0.54	-0.04
ALT90	0.77	0.53	-0.02
VT50	0.72	0.43	-0.09
RT50	0.65	0.43	0.11
BT50	0.65	0.54	0.04
NIP	-0.05	0.19	xx
TRISE	0.65	xx	0.19

CRs and the NCRs; 5.23 versus 4.35. Of the thermal parameters, TRISE and lnCEM43T90 were significant. In multivariate analysis, the influence of lnCEM43T90 became lost its significance (p=0.195), but TRISE remained significant (p = 0.013). The CR-rate per thermal parameter-group is depicted in figure 1a.

Pelvic tumor control (PTC): PTC was 65% (95% confidence interval (CI) 60–70%) one year after treatment, and 53% (95%CI 47–58%) at 5 years. From univariate analysis, FIGO stage, tumor size, N-status, age, WHO-PS and RTc emerged as significant baseline characteristics (table 6a).

Table 6a: Univariate analysis for patient and tumor characteristics and thermal parameters on complete response rate (CR-rate), pelvic tumor control (PTC) and disease specific survival (DSS) (p-values)

	CR-rate	PTC	DSS
FIGO stage	0.000	0.000	0.000
N-status	0.027	0.034	0.047
Tumor size	0.000	0.022	0.002
Histology	0.050	0.374	0.209
WHO-PS	0.000	0.000	0.001
Age	0.319	0.037	0.166
CTx	0.092	0.103	0.240
RTc	0.000	0.000	0.000
OTT	0.246	0.185	0.671
ln CEM43T90	0.025	0.002	0.002
TRISE	0.000	0.000	0.000
NIP	0.070	0.015	0.007
ALT20	0.683	0.051	0.036
ALT50	0.878	0.108	0.038
ALT90	0.990	0.091	0.048
VT50	0.259	0.424	0.125
BT50	0.795	0.043	0.062
RT50	0.479	0.098	0.027

Legend: FIGO = International Federation of Gynecology and Obstetrics stage, N-status = lymph node status, WHO-PS = World Health Organisation Performance Status, CTx = chemotherapy received or not, RTc = radiotherapy completed as planned or not, ln CEM43T90 = natural logarithm of CEM43T90

Table 6b: Multivariate analysis after adjustment for other significant factors (p-values)

	CR-rate	PTC	DSS
ln CEM43T90	0.195	0.019	0.001
TRISE	0.027	0.021	0.002
NIP	0.757	0.129	0.060
ALT20	0.891	0.320	0.212
ALT50	0.331	0.702	0.318
ALT90	0.323	0.685	0.370
VT50	0.194	0.942	0.354
RT50	0.810	0.510	0.166
BT50	0.347	0.565	0.645

The mean intraluminal temperature measured (ALT50) for patients who developed a pelvic failure was similar to that of patients who did not (40.5 ^{0}C and 40.6 ^{0}C respectively). There was a slight difference in CEM43T90 between the two groups; 4.40 versus 5.50. After adjustment for other significant factors, lnCEM43T90 and TRISE remained of significant influence (p = 0.019 and 0.021, table 6b). The 3-year PTC rate per thermal parameter-group is depicted in figure 1b.

Disease specific survival (DSS): DSS was 75% one year after treatment (95%CI: 71–79%) and 47% at 5 years (95%CI: 41–53%). Significant baseline characteristics in univariate analysis were again FIGO stage, tumor size, N-status, WHO-PS and RTc (table 6a). CEM43T90 for patients who ultimately died of cervical cancer was 4.45 on average and 5.47 for patients who did not die of cervical cancer. The ALT50 was again comparable in both groups, 40.5 ^{0}C versus 40.6 ^{0}C. After adjustment for significant baseline characteristics in multivariate analysis, lnCEM43T90 and TRISE remained of significant influence on DSS (p=0.001 and 0.002, table 6b). The 3-year DSS rate per thermal parameter-group is depicted in figure 1c.

Acute hyperthermia-related toxicity: One hundred and fifty three patients developed acute hyperthermia-related toxicity to the subcutaneous tissues. Fifty-one percent (80/153) were grade 1, 39% grade 2 (60/153), 9% were grade 3 (16/153) and only one patient required a surgical intervention due to her subcutaneous burn (0.6% grade 4). In univariate analysis, the mean power applied (NIP) was significant as well as TRISE (table 7). Patients who developed acute hyperthermia-related toxicity received 46 kJ more than those who did not and their TRISE was 1.7 ^{o}C higher. Because of the expected mechanism behind the development of subcutaneous burns, extra anatomy-related factors were entered in univariate analysis, such as the thickness of the subcutaneous fat and the patients' size. In patients who developed toxicity the dorsal subcutaneous fat was thicker (0.7 cm) and they were larger in anterior-posterior (0.9 cm) and lateral (1.5 cm) direction.

Table 7: Univariate analysis for acute hyperthermia-related skin/subcutaneous toxicity

	p-value
FIGO stage	0.362
N-status	0.118
Tumor size	0.942
Histology	0.484
WHO-PS	0.046
Age	0.953
CTx	0.363
OTT (days)	0.219
RTc	0.025
Thickness subcutaneous fat dorsal	0.004
ventral	0.072
lateral	0.360
Patient size anterior to posterior	0.008
Patient size lateral to lateral	0.001
ln CEM43T90	0.234
TRISE	0.002
NIP	0.000
ALT20	0.911
ALT50	0.377
ALT90	0.728
VT50	0.061
RT50	0.909
BT50	0.061

Legend: FIGO = International Federation of Gynecology and Obstetrics stage, N-status = lymph node status, WHO-PS = World Health Organisation Performance Status, OTT = overall treatment time, CTx = chemotherapy received yes or no, RTc = radiotherapy completed as planned or not

After adjustment for these factors, NIP lost its significant influence, but TRISE did not (p = 0.010).

Fourteen patients developed complaints related to the peripheral nervous system during and/or after a hyperthermia treatment. For 12 patients, complaints were restricted to CTC grade 2, and 5 developed grade 3 neurotoxicity. A detailed description and evaluation of significant factors influencing neurotoxicity after deep hyperthermia was previously published.[25]

Late radiation-related toxicity: Late toxicity CTC grade 3 or higher was diagnosed in 6% of patients in the first year after treatment, and in 12% of patients at 5 years after treatment (95%CI: 7–17%). Of all factors studied, only patient size was of significant influence on long-term radiotherapy-induced toxicity, both the AP-direction and the lateral direction (p=0.01 and p=0.02).

Discussion

To our knowledge, this study is the largest study investigating the relation between various simple and complex thermal dose parameters and complete response rate, pelvic tumor control, disease specific survival and acute and late toxicity in patients with LACC treated with RT+HT. We found a significant relationship between those thermal parameters that include both height of temperature and duration of heating (CEM43T90 and TRISE) and all disease control endpoints. After adjustment for other correlating factors in multivariate analysis, TRISE remains significantly correlated with response and survival and CEM43T90 with survival.

Overall, treatment outcome is relatively meager in comparison to other published series, both since and before 1996. It was a major point of criticism of the Dutch Deep Hyperthermia Trial (DDHT) and can be explained by the bad prognostic characteristics of the patients that were included in the trial.[3] The same applies to the patient population presented here. Even more: since we have shown the large benefit of the addition of hyperthermia to radiotherapy, we tend to accept patients who are older, have larger tumors and are in worse general condition compared to the period of the DDHT.[4] Large tumor, older age and worse general condition have a negative influence on treatment outcome for patients with cervical carcinoma, as was previously shown by others.[7, 26-30]

For the patient group presented here, there is no real control group to which we can compare the results. What we have done is an evaluation of the results compared to those in the RT+HT arm in de DDHT. We found that, after adjustment for differences in prognostic factors, the results are similar and indirectly confirm the beneficial effects from hyperthermia that we have shown in our earlier randomized trial.[4]

Other researchers have previously shown a similar beneficial effect of adding hyperthermia to standard radiotherapy for LACC (table 8).[31-35] Only one of 6 randomized trials

Table 8: Randomized studies comparing radiation (RT) to radiation combined with hyperthermia (RT+HT)

First author [ref]	FIGO	n	CR-rate		Pelvic control		Overall survival	
			RT	RT+HT	RT	RT+HT	RT	RT+HT
Datta[31]	IIIB	64	58	74	46	67 ‡	73	81‡
Sharma[32]	II, III	50			50	70•		
Chen[33]	IIB, IIIB	120	48	72*				
Harima[34]	IIIB	40	50	80•	49	80 Δ*	48	58 Δ
Vasanthan[35]	IIB to IV	110			~ 80	~70 Δ	73	73 Δ

Legend: FIGO = International Federation of Gynecology and Obstetrics tumor stage, n = number of patients included in the study, CR-rate = complete response rate, RT = radiation alone, RT+HT = radiation combined with hyperthermia, * significant difference, •at 1.5 years, ‡ at 2 years, Δ at 3 years

showed no beneficial effect of adding hyperthermia and this trial was criticized because of flaws in study design and inadequate heating techniques.[35-37]

The combination of chemotherapy and radiation is currently the standard of treatment in most countries, but recently a meta-analysis based on individual patient data further strengthens earlier suggestions that the addition of chemotherapy to radiotherapy is less beneficial in the higher stages, while hyperthermia has shown its additional value specially in the higher stages.[38-39]

Many of the parameters that we found to be of prognostic importance in our patient group, are known prognostic factors for patients with cervical carcinoma. FIGO stage, tumor size measured on CT-scan, lymph node status, general condition, patient age and radiation dose are known prognostic factors for patients with cervical carcinoma. The prognostic importance of hyperthermia dose, even after adjustment for all other prognostic factors, is a new finding in this study. Previous research in this area was limited to populations too small to allow for a multivariate analysis.[18-21]

The finding of a thermal dose effect relationship for dose parameters derived from intraluminal measurements is further important for deep hyperthermia treatment guidelines. Apparently, interstitial measurements are not required to monitor the quality of treatment for cervical cancer.

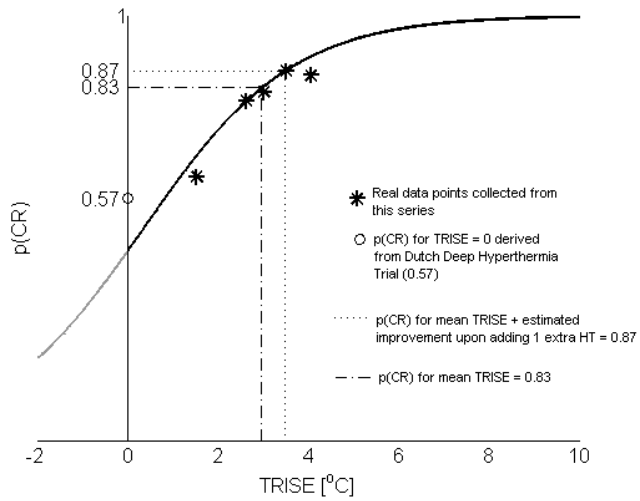
Our finding of a thermal dose effect relationship suggests that the clinical outcome of RT+HT for LACC can be improved by an increase in thermal dose (figure 2). The dose-effect curve in figure 2 was constructed using the coefficients, ß0 and ß1, found in univariate analysis. From this figure, we can hypothesize that adding one treatment to the current schedule, results in a 4 % increase in the probability of a complete response for patients who receive the average TRISE dose or less.

Naturally, a higher dose can be achieved in 2 ways; higher temperatures, or longer duration of heating. We do not expect to achieve higher temperatures with our currently used strategy as it already aims at heating to maximum patient tolerance. To further increase temperature, hyperthermia treatment planning may be a useful tool.[40] Wust et al. conducted a simulation study and concluded that an increase in T90 of 1.9 ^{0}C can be achieved with temperature optimization using hyperthermia treatment planning. However, data on the clinical effectiveness of hyperthermia treatment planning is limited to date. In view of our current and previous results, longer duration of heating seems a worthwhile option to explore, especially for patients in the lower thermal dose groups.

In conclusion, the results in this large group of patients treated with RT+HT, confirm the results of RT+HT that we have seen in the DDHT and form an external validation of

Figure 2: Complete response probability or p(CR) as a function of TRISE

p(CR) = 1 / (1 + EXP(- ß1 * X1+ ß0)) = 1 / (1 + EXP (-0.607 * TRISE - 0.369) ß0 and ß1 are the coefficient and constant derived from univariate analysis



* data points derived from the actual data (figure 1)

° indicates complete response rate for patients with locally advanced cervical cancer treated with radiotherapy alone, i.e. thermal dose = 0, derived from Van der Zee et al.[3]

that trial. Currently, combined radiotherapy and cisplatin is considered standard treatment for patients with cervical carcinoma worldwide. However, we also find it justified to combine radiotherapy with hyperthermia instead of cisplatin, since the beneficial effects of both modalities are of the same magnitude.[41] In any case, we strongly recommend RT+HT for patients with a contraindication for cisplatin, due to e.g. poor general condition, insufficient renal function, or extended field radiotherapy and many Dutch radiotherapy institutes have adopted this view since 1996.

The situation in the Netherlands, where in fact two standard treatment approaches coexist for locally advanced cervical cancer, gives us the unique opportunity to compare the two approaches. In an ongoing Dutch multicenter phase III trial, the two combined treatments are compared questioning which patients benefit most from which additional treatment. Another interesting question is of course whether the effect of radiotherapy plus cisplatin can be further improved by addition of hyperthermia to the treatment schedule. This question is addressed in an international multicenter phase III trial.

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PART II

Towards improvement
of treatment quality and
clinical outcome

Chapter 6

Steering in locoregional deep hyperthermia: Evaluation of common practice with 3D-planning

Van der Wal E, Franckena M, Wielheesen DHM, van der Zee J and van Rhoon GC. Steering in locoregional deep hyperthermia: Evaluation of common practice with 3D Planning. Int J Hyperthermia 2008; 24:682-693

Abstract

Purpose: In Rotterdam, 15 years of clinical experience with deep hyperthermia has sublimated in empirical treatment guidelines. In this paper, a treatment planning system (HTPS) is employed to investigate the effect of these guidelines on global power distribution, their effectiveness and the rationale behind each guideline.

Materials and methods: Four guidelines were investigated. The first 2 prescribe steering actions for balancing intraluminal temperatures and alleviating complaints of deep-seated pain or pressure. The third guideline handles superficial complaints of pain or heat sensation. The last guideline states that frequency should be increased from 77 MHz upwards in case of multiple, opposite, painful regions uncontrollable by the previous steering actions.

For all steering actions, it is assumed that input power is increased until complaints occur. Sigma HyperPlan was used to calculate SAR (Specific Absorption Rate) distributions for 5 patient models with locally advanced cervical cancer. Absorbed power ratios of different regions of interest were evaluated to illustrate steering efficacy and complaint reduction.

Results and conclusions: Phase steering is effective in shifting the central power distribution to the periphery, and is an appropriate method to balance temperatures or to handle deep-seated complaints. Reduction of amplitude is the proper action to alleviate superficial complaints of heat or pressure. Compression of the SAR distribution, mainly in the lateral direction, is predicted with increasing frequency. Hence, for complaints in the lower back or on the sides, a frequency increase should be considered.

We conclude that the results of the HTPS are in close agreement with the empirical steering guidelines.

Introduction

In the Netherlands, adjuvant locoregional deep hyperthermia (DHT) in combination with radiotherapy is standard treatment for locally advanced cervical cancer. In Rotterdam, over 15 years of experience in the application of DHT treatments with the BSD 2000-3D system (BSD Medical Corporation, Salt Lake City, Utah, United States) has provided vast experience and benefited many hundreds of patients.[1-3]

To gain more insight in the heating process, detailed knowledge of the absorbed power and temperature distribution by radiofrequency (RF) radiation is required. In situ monitoring however is complicated. Conventional temperature or E-field probes can be used only at a limited amount of sites. Recently, much effort is invested in non-invasive, spatially resolved, temperature measurement techniques.[4-5]

Alternatively, the introduction of planning systems (HTPS) in hyperthermia has improved both the development of new applicators as well as the understanding of patient-specific modelling factors on the distribution of power and temperature. Due to the considerable effort required to build patient models, systematic use of treatment planning systems to prescribe or support an optimized treatment strategy has not yet been realized.

Parallel to the development of hyperthermia treatment planning, the experience obtained in Rotterdam over the last 2 decades has sublimated into empirical steering guidelines resulting in an effective application of DHT. [1-3] These steering guidelines not only provide the initial antenna settings to start a treatment, but also give a power on/off policy and indicate how to adjust settings in case of patient complaints concerning hotspots or too high or unevenly distributed measured temperatures.

In this paper we compare these 2 approaches. For the first time, a HTPS is used to evaluate a selection of rules from the Rotterdam empirical steering guidelines (RESG). That is, we investigate the effect of some of these guidelines on the global power distribution, and check their effectiveness under the conditions they are imposed. Further, we check whether the rationale behind each guideline is correct.

Absolute and detailed verification of planning systems for patient-specific modelling is cumbersome and subject to ongoing research.[6-7] Therefore, in this study we are only looking for general similarities and differences between the guidelines and the planning results. We will not address power absorption in specific hotspots.

Four guidelines are evaluated. Firstly, a guideline is introduced prescribing how to correct for an unbalanced temperature distribution. Second, a guideline on how to treat deep-seated pain/pressure is evaluated. Thirdly, a guideline prescribing how to alleviate

superficial heat complaints is introduced and finally the fourth 'if-everything-fails' frequency steering guideline is outlined. A detailed description of these guidelines can be found in the following section.

Materials and methods

In this section, we first describe the selected steering guidelines that will be evaluated in this paper. Then, the treatment planning system and patient model construction are outlined, and finally, the methods for comparison and analysis of the calculations are discussed.

Steering guidelines

Specific Absorption Rate (SAR) steering is the term to address all changes in antenna settings that affect the distribution of dissipated power. This can be done by introducing a phase-shift between the various antennas of an applicator, by varying the relative amplitudes of the antennas or by changing the frequency of the signal.

In general, the RESG state that: In case of complaints from the patient, the preferred order of steering actions is: phase steering, amplitude steering, and finally, frequency steering. In this study, we evaluated the actions in the same order. For efficiency evaluation, we divided the patient models in separate regions (figure 1). The division is based on the complaints related by patients during deep hyperthermia.

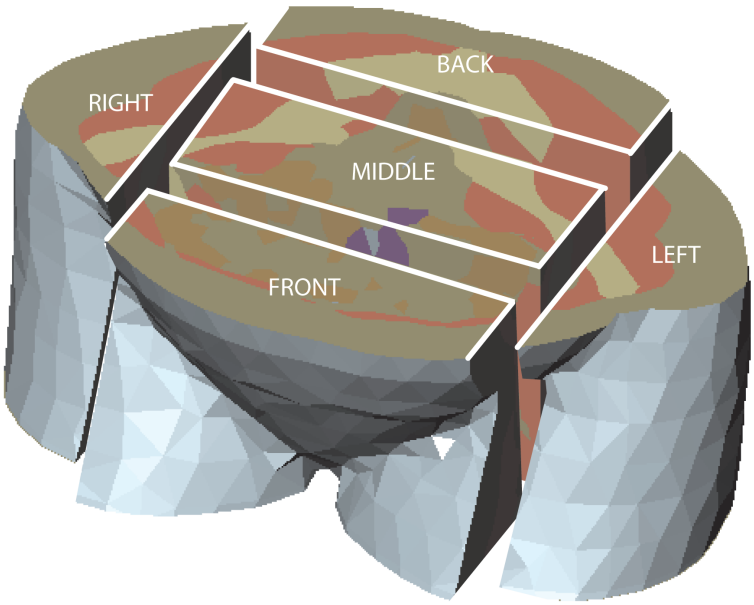
Steering is necessary in case of overheating of healthy or tumor tissue or complaints of the patient due to hotspots. Also other non-verbal signs, like abnormal changes in pulse or blood pressure, may indicate discomfort.

In absence of complaints, steering is used to optimize the temperature distribution; otherwise steering is used to reduce pain complaints. In the absence of complaints or healthy tissue temperatures above 43°C, and without contraindications, power is increased by 100 W every 5 minutes. Increase of power is ceased when the patient indicates discomfort, and is resumed only after a complaint-free period of 5 minutes.

Guideline 1. How to correct for unbalanced temperature distribution

Thermometry during treatment is limited. Based on the available thermometry the physician decides on the most preferable temperature distribution depending on tumor size, location, and distance to the temperature probes.

Figure 1: Partitioning of the transversal slice located at the target region into front, middle, back, left and right part. The central region is constrained by the smallest box containing the vagina, tumor and uterus.



Every 5 minutes, the temperature distribution is evaluated by thermal mapping and, if necessary, antenna phase settings are adjusted to obtain a more suitable distribution.

For a centrally located target, e.g. most cervical tumors, often an evenly distributed temperature profile is desired based on the bladder, vaginal and rectal temperature. If in a thermal mapping, the bladder temperature is on average higher than the rectal temperature phase settings are adjusted to shift the focus to the rear and if the rectal temperature is higher on average than the bladder temperature, the focus is shifted in the opposite direction.

Guideline 2. How to manage deep-seated pain or pressure

Only superficial heat is perceived as heat since thermosensation is restricted to the skin.[8] Other tissues are nociceptive for temperatures above 43°C.[9] Therefore, patients indicate deep-seated hotspots as pressure or dull pain.

In practice, deep-seated hotspots are often indicated as a sensation of pressure inside, diffuse pain, pain in the back, nausea, urinary urgency, or mistakenly identified as pressure by the water bolus.

After verifying that the deep-seated complaints are power-related, by switching off the power and observe whether the pain reduces, phase steering in the opposite direction of the painful area is used to reduce the pain or pressure.

Guideline 3. How to alleviate superficial heat complaints

High superficial temperatures are mostly indicated by the patient as heat. Again, after verifying that the complaints are power-related, the relative amplitude is reduced at the painful side, thus increasing the amplitudes on the other sides. The total power output of all antenna pairs combined remains equal.

Guideline 4. Frequency steering

When deep-seated complaints persist with all steering strategies, or if complaints are indicated at opposite sides at the same time, the frequency of the RF signal is changed. It is hypothesized that the SAR distribution is more localized at higher frequencies.[10] Drawback of a more localized distribution might be the occurrence of cold spots (i.e. areas below therapeutic temperatures) in the target area. The standard operating frequency at the start of a treatment is 77 MHz for the Sigma-60.

Treatment planning

Patient modelling and finite element (FE) electro-magnetic (EM) calculations are performed using Sigma HyperPlan (Dr. Sennewald Medizintechnik GmbH, Munich, Germany).[▽] [11] The workflow for modelling using a FE method in Sigma HyperPlan has been outlined before. [7, 12]

In short, CT data are resampled to a slice distance of 1 cm. Automatic segmentation of tissue boundaries is performed for bone, air, muscle, and fat, based on Hounsfield units. Subsequently, all slices are manually segmented by a physician to include bladder, kidney, uterus, myelum, heart, liver, spleen, vagina, intestine, lung and stomach in addition to the automatically segmented tissues. Frequency depended dielectric parameters for these tissues are obtained from Gabriel et al. (table 1). [13] Note that the tabulated dielectric values in literature scatter for as much as 50%. [14] Small and irregular structures are left out or smoothed to improve the quality of the patient model.

After segmentation the boundary surfaces are tiled by triangulation and simplified. Usually, some manual adjustments have to be made to improve the quality of the recon-

[▽] Formerly AMIRA Hyperplan, Konrad-Zuse-Zentrum fur Informationstechnik, ZIB, Berlin

Table 1 : Tissue types that are distinguished in the segmentation of the CT data. Dielectric properties are calculated from Gabriel et al.[13] are used.

Tissue Types		
Exterior	Air/Bubbles	Bone
Fat	Muscle	Target (m)
Bladder	Heart	Intestine
Kidney	Liver	Lung
Myelum	Spleen	Stomach
Uterus (m)	Vagina	

m: values for muscle are used.

structed surface. From this triangulated surface a tetrahedral grid model is generated (the patient model).

In this study the Sigma-60 applicator (BSD Medical Corporation, Salt Lake City, Utah, USA) is used, a model of which is included in Sigma HyperPlan.[10] Again, a tetrahedral grid is constructed from the applicator, the water bolus and the surrounding air volume.

The applicator grid and the patient grid are combined to give a so-called extended grid. This extended model is used for the EM calculations.

A FE method is used to solve the EM-fields, followed by a full network analysis to account for coupling between the antenna pairs and the feeding networks. The calculations result in the complex EM fields per antenna-pair, which can be superposed with different antenna feeding vectors. SAR and EM-field magnitude distributions can be calculated and visualized in Sigma HyperPlan. According to the RESG, power has to be increased until the patient indicates pain or discomfort. For this reason, all SAR distributions for all patients were normalized to 400 W input power into the patient model.

Note however that not all power distributions acquired by superposition of the individual antenna pairs translate into possible treatment settings for the BSD. For extreme antenna settings (e.g. amplitude ratios between antenna pairs below 0.5), the network analysis may not adequately describe the cross-talk between antenna pairs.[15] Further, the efficiency may be very low for extreme antenna settings, thus limiting the total power input into the patient.

Patient models

CT data of 5 patients with advanced cervical cancer have been processed. One of the patients had a tumor classified as International Federation of Gynecology and Obstetrics (FIGO) stage IIA, two as IIB, one as stage IIIA, and one as IVA. All 5 tumors showed invasion of the parametria. One of them showed invasion of the lower 1/3 of the vagina, 4 others

showed invasion into the upper 1/3 of the vagina. Further, one patient had hydronephrosis of the left kidney. No selection was applied to include patients.

CT data was acquired at a resolution of 512×512 pixels, 161 slices in total, corresponding to a 1×1×5 mm^3 voxel cube. Patients were scanned in DHT treatment position, i.e. in the same sling that is used in the DHT treatment setup. The scan region ranged from 40 cm cranial to 40 cm caudal with respect to the cranial margin of the pubic bone. Patient model generation and extended model generation was successful for all 5 patients. The average edge length for all patient models was 2.0 cm.

After patient model generation, the Sigma-60 applicator was placed around the patient model. Positioning in the lat-lat (LL) direction was done with respect to the center of the patient bounding-box. Positioning in the cranial-caudal direction was done at 2 cm cranial with respect to the tumor center, in agreement with the empirical guidelines for patient positioning. Positioning of the patient in the anterior-posterior (AP) direction is less clearly described in the guidelines and has been under discussion for quite a while within our clinic. Roughly, for craniocaudal positioning in our patient models, we centered the applicator at the center of the mass (figure 1). In our view, this approach resembles the clinical practice quite well. To check this, 5 of our medical assistants, who are routinely involved in patient positioning, were offered a side view of the five patient models inside the Sigma-60 applicator. They were asked to center the patients inside the applicator in the AP direction according to their clinical experience. On average the patient models were positioned 2.1 cm below the position determined by the approach described above (with a mean standard deviation of 1.5 cm per patient).

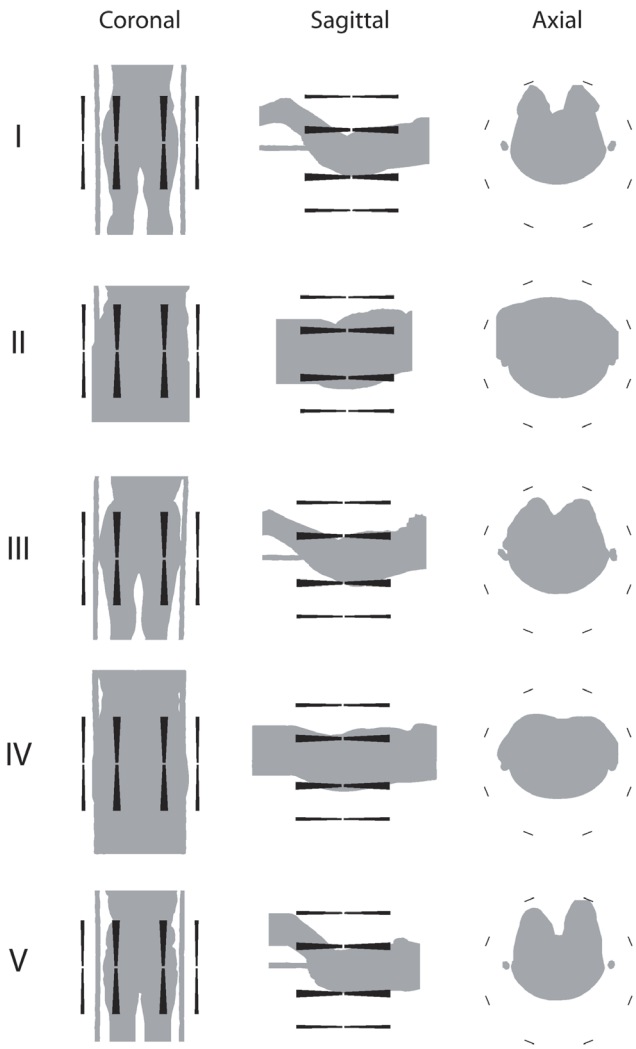
In figure 2 projections of the patient models are shown inside the Sigma-60 applicator. The first column gives the coronal projections, the second the sagittal projections, and the last column the axial projections. The rows show the different patients that were used in this study. Note that the patient models for patient II, IV and V are extended at the legs.

Patient centering in the LL direction is symmetrical for all patients. Note that it is difficult to determine visually whether the patient models are centered in the AP direction.

Analysis

We used SAR instead of temperature for the analyses because of the many uncertainties that surround thermal modelling for the pelvic area to date. We felt there is insufficient knowledge about which vasculature model can be used best and which perfusion coefficients should be entered in these models. Further, to accurately model perfusion, dynamic

Figure 2: Coronal, sagittal and axial projections of the 5 patient models inside the Sigma-60 applicator



models are needed as perfusion changes with both temperature and time. By using SAR modelling we excluded these uncertainties from our analyses.

To investigate the effect of the steering actions as described in the materials and methods section, the patient models were divided into separate regions as shown in figure 1. A transversal slice through the pelvic area is defined by the region contained between the top of uterus and the lowest part of the vagina. Within this slice a central region (middle) is assigned to the smallest box containing the uterus, tumor and vagina. In the LL direction

this region was extended up to the middle of the crista iliaca and the sacro iliac joint. We refer to this region as the target region. The remaining of the transversal slice is divided in a front, back, left, and right part. The purpose of the assignment of these regions is to present a global view of what happens to the SAR distribution when different steering strategies are applied.

Sigma HyperPlan is not able to calculate cumulative SAR values per region of interest directly. However, dose-volume histograms (DVH) can be given per region of interest and per tissue type. A simple trapezoidal integration scheme was used to integrate the cumulative DVH. The result was multiplied with the volume of a bin to give the integrated power absorption (PA) in the specified region. This procedure was repeated for all defined regions.

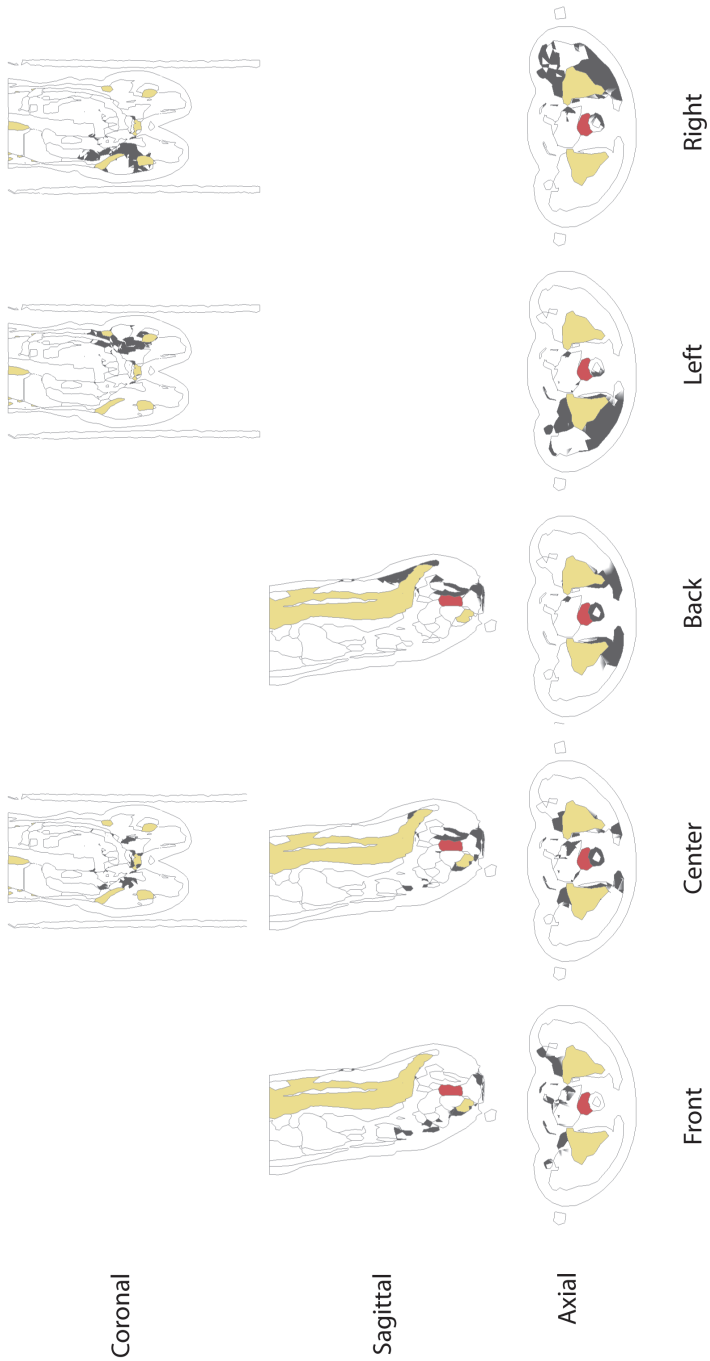
Results

To evaluate the impact of the steering strategies as described by the RESG, we first address the influence of phase, amplitude and frequency steering separately. In the discussion section of this paper we will combine these results to assess the rationale of the guidelines in comparison with the model outcomes.

Phase and amplitude steering

To get an impression of the effect of amplitude and phase steering on the SAR distribution, the effect of AP and LL phase steering is shown in figure 3 for patient I. Since the effect of amplitude steering is qualitatively quite similar to phase steering; only the latter is shown. For all cross sections, the tetrahedra are filled (dark grey) that have an average SAR equal or larger than the 90% SAR percentile for synchronous phase settings and equal amplitudes. Note that the hotspots, which are present on the legs and chest, can not be observed in these pictures. Often these superficial hotspots are not power-limiting since they can be cooled quite effectively. Further, bone is indicated by the yellow areas and the tumor by the magenta area. In the top row, coronal cuts are plotted at the position of the supporting rods (front view). In the middle row sagittal cuts are shown at the center of the patient model, and in the bottom row, axial cuts are shown through the center of the tumor (top view). In the columns the effect of 120 degrees phase difference (which corresponds to roughly a 8 cm focus shift on the BSD console, the maximum allowed according to the RESG) is shown in the specified direction (Front: a positive phase dif-

Figure 3: Cross sections of the threshold SAR distributions for different phase settings for patient I. Regions with SAR levels above the 90 % SAR percentile for synchronous settings are colored dark grey. Bone and target are indicated in yellow and magenta respectively. For all steering directions, a positive phase difference of 120 degrees is applied in the direction indicated at the bottom.



ference of 120 degrees of the anterior antennas with respect to the posterior antennas, Center: synchronous settings, Back: -120 degrees phase difference, Left: a positive phase difference of 120 degrees of the left antennas with respect to the right antennas, right: -120 degrees phase difference).

For synchronous settings, the SAR distribution looks rather scattered within the pelvis, but the center of mass of the distribution is located quite central. Some areas of high SAR are located in the vicinity of the target area. Further, (SAR) hotspots can be identified in the lower back associated with the lower vertebrae, at the vulva, at the pelvic bones, and anterior in the intestine right below the fat layer and at the pubic bone. When steering to the front, the focus of the SAR distribution is clearly shifted towards the front. The ventral hotspots are emphasized while removing the dorsal hotspots. Steering to the back does the opposite. The same is observed for steering in the LL direction, shifting of the average SAR focus and expression of the anatomical hotspots. As expected, phase steering in the LL direction is symmetrical. These observations also hold for amplitude steering. Stepwise phase steering calculations showed that steering in the LL directions results in a much more gradually shifting SAR distribution when compared to steering in the AP direction.

Steering efficacy

To see how efficient phase and amplitude steering are in moving power from one side to the other, the patient models were divided in separate regions, depicted in figure 1. Starting from synchronous phase settings and equal amplitudes, phase and amplitude steering can be used to transfer power from the center region towards one of the outer region. In figure 4, for all 5 patients the effect of AP phase and amplitude steering is shown on the ratio of power deposited in the center region and power deposited in the region at the front and back. Lowering of this ratio indicates that power was transferred from the center towards the front or the back. All plots were normalized on synchronous phase settings and equal amplitudes.

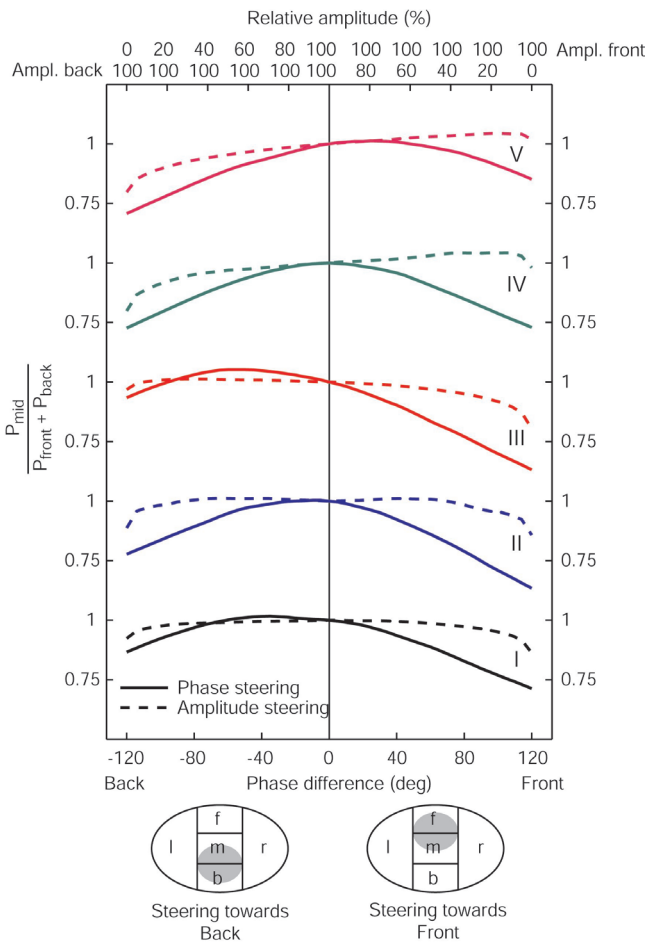
The phase difference is expressed as phase delay of the posterior antennas with respect to the anterior antennas. Again, a maximum phase difference of 120 degrees is applied, corresponding to a focus shift of 8 cm according to the BSD console. Relative amplitudes for the anterior and posterior antennas are indicated at the top axis. Full lines show the effect of phase steering, dashed lines the effect of amplitude steering.

Firstly, we see that the change in this AP power transfer ratio is rather symmetrical with respect to central focus settings. Steering to the front or to the back has roughly the same impact on the transferal of power from the central to the outer parts. For patients I and III,

we see that the power transfer ratio can be slightly increased by phase steering to the back (i.e. more power is deposited in the target region compared to the outer parts). This can be explained by the fact that for all patients the target region is located a few centimeters posterior with respect to the applicator center.

Further, compared to amplitude steering, we see that phase steering is much more effective in transferring power from the center region to the outer parts. Only for extreme amplitude settings, e.g. in case of switching off all amplifier channels on the front or back-

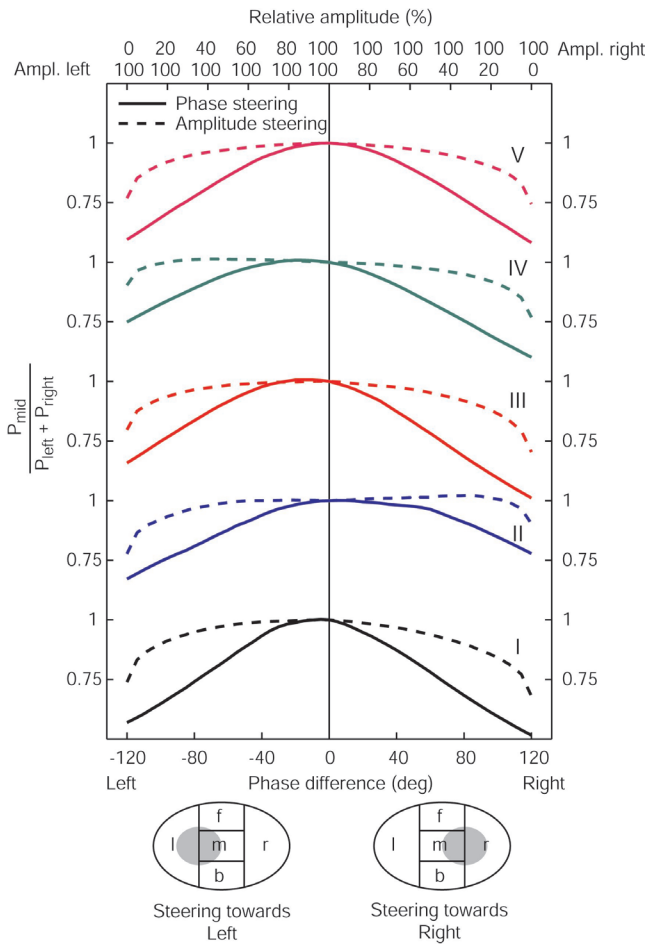
Figure 4: The effect of AP phase (full lines) and amplitude steering (dashed lines) on the AP power transfer ratio for all 5 patient models. The AP phase difference is varied from -120 up to 120 degrees with respect to the top antennas of the Sigma-60, corresponding to a focus shift of roughly 8 cm, the maximum according to the RESG. For steering posterior, the amplitude of the bottom antennas of the Sigma-60 is varied from 0 to 100%, for steering anterior, the amplitude of the top antennas are varied from 0 to 100%. All other amplitudes are kept at 100%.



side, there is a noticeable effect on the AP power transfer ratio. It is clear that, if the aim is to shift the power distribution away from the central focus in the AP direction, phase steering is the appropriate steering action.

In figure 5, we see that the same principle holds for phase and amplitude steering in the LL direction. As expected, the effect of steering in the LL direction on the LL power transfer ratio is equal for steering to the left or to the right due to the high degree of lateral symmetry. For all 5 patients, the tumor was located in the center of the applicator in the LL direction. Again we see that phase steering is much more effective in transferring power from the center towards the outer parts compared to amplitude steering.

Figure 5: The effect of LL phase (full lines) and amplitude steering (dashed lines) on the LL power transfer ratio for all 5 patient models.

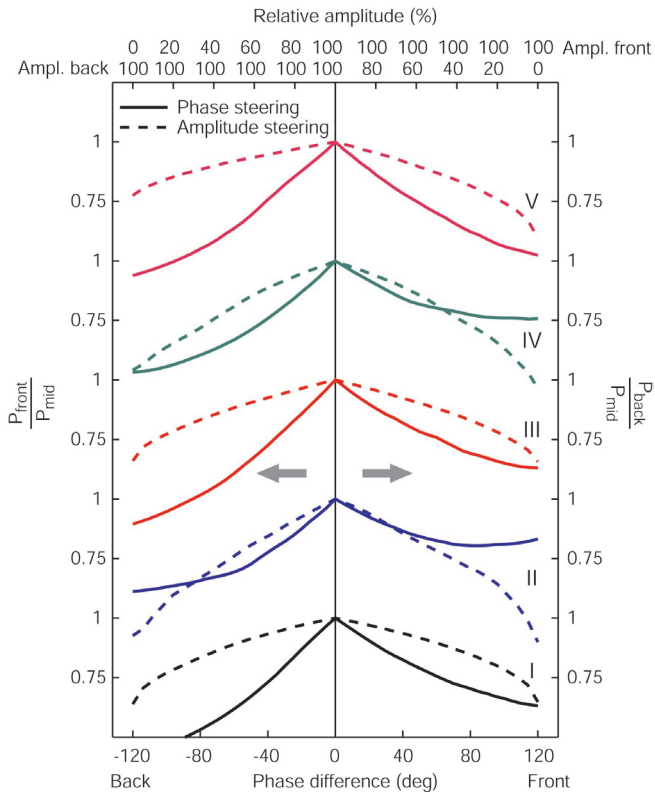


Complaint reduction

Apart from the ability to shift the focus of the SAR distribution, another important feature of steering actions is to alleviate pain complaints outside the target region. For this purpose, again we divide the patient model in 5 transversal sections as depicted in figure 1. To illustrate the effect of complaint reduction, we look at the reduction of power in a painful peripheral area compared to the power still present in the target (central) region. This ratio expresses the ability to reduce complaints and still heat the target region effectively.

In figure 6, this complaint reduction ratio is plotted for AP phase and amplitude steering. For steering posterior, i.e. in case of complaints located ventrally, this ratio is expressed by the power absorbed in the front region divided by the power absorbed in the central region. For steering anterior, i.e. in case of complaints located dorsally, the ratio is expressed by the

Figure 6: The effect of AP phase (full lines) and amplitude steering (dashed lines) on the AP complaint reduction ratio for all 5 patient models. For steering posterior, this ratio is expressed as the power remaining in the (painful) front region compared to the power still deposited in the central (target) region. For steering anterior, this ratio is the PA in the back region divided by the PA in the central region.

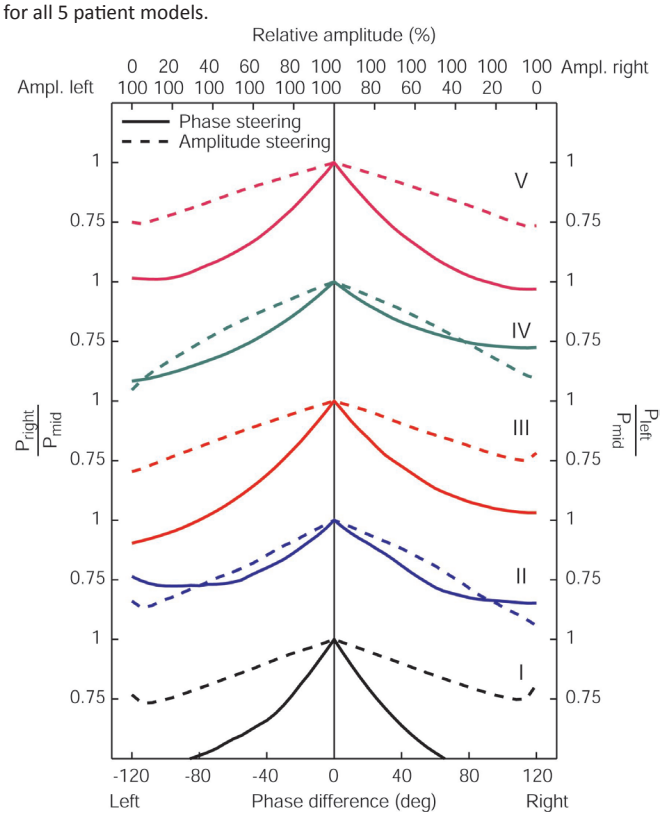


power absorbed in the back region divided by the power absorbed in the central region. Again, all plots were normalized on synchronous phase settings and equal amplitudes.

Whereas the sensitivity of the complaint reduction ratio for phase and amplitude steering is different, both steering actions can lower the ratio considerably. That is, both phase and amplitude steering are effective in lowering the PA in the outside areas and still heat the target (central) region. We observe that for all patients the relation between the complaint reduction ratio and absolute phase difference is convex and the relation between the complaint reduction ratio and the amplitude is concave.

Again these same principles hold for steering in the LL direction (figure 7). As expected, the LL complaint reduction ratio is nearly symmetrical for steering to the left or to the right. Again, this symmetry is more pronounced when compared to AP steering.

Figure 7: The effect of LL phase (full lines) and amplitude steering (dashed lines) on the LL complaint reduction ratio for all 5 patient models.

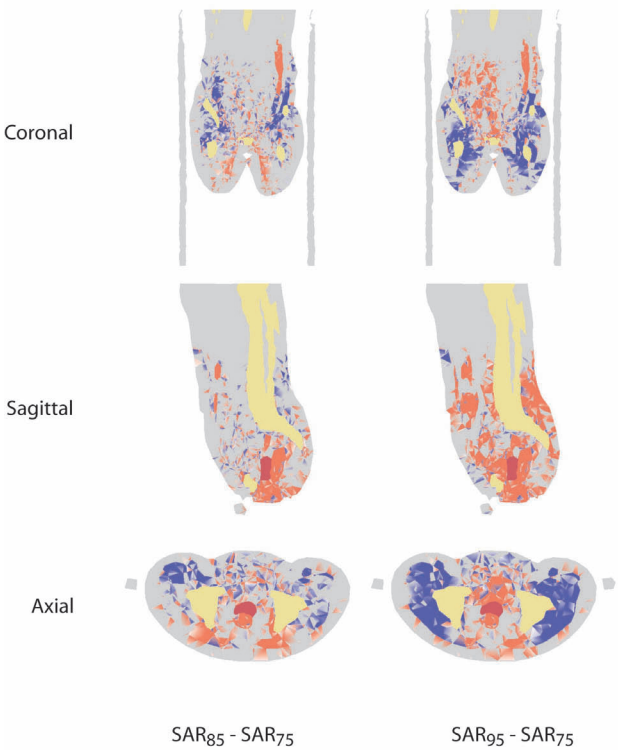


Frequency steering

In figure 8, the effect of increasing the frequency with steps of 10 MHz is shown for patient I. The effects are representative for all 5 patients. In the cross-sectional views red shows the regions where the SAR difference of the distribution at 85 or 95 MHz and the distribution at 75 MHz is larger than a threshold of $5 \cdot 10^3$ W/kg for a total input power of 400 W. In blue the regions are indicated were this difference is below $-5 \cdot 10^3$ W/kg. On the left the profiles are shown for the difference between 85 and 75 MHz, on the right for the difference between 95 and 75 MHz. Note that the total integrated power in the patient models was the same for all 3 frequencies. For these calculations synchronous phase settings and equal amplitudes were used. Another possibility would have been to optimize each SAR distribution individually.

From the coronal and axial views it is clear that power deposited at the sides is transferred to the center for increasing frequency.

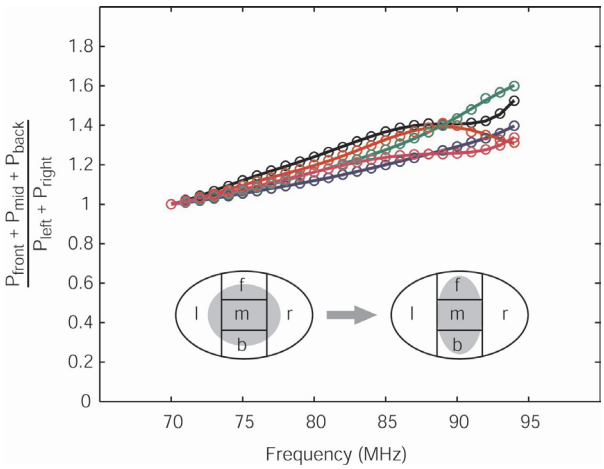
Figure 8: Cross sections of threshold difference SAR distributions for patient I. In the left column cross sections of the difference between SAR levels at 85 and 75 MHz, both for synchronous phase settings and equal amplitudes are plotted. On the right, SAR differences are plotted between 95 and 75 MHz.



Further, at 85 MHz the power is removed mainly from above the pelvis, whereas at 95 MHz this region is shifted downwards. This effect of a cranial shift of the SAR focus was observed for patients I, III, and V, for patients II and IV, the effect was unclear.

To quantify the effect of lateral confinement of the power distribution, again the 5 patient models were partitioned as depicted in figure 1. As a measure for the transfer of power, the energy in the front, middle, and back regions is summed and divided by the power absorbed in the left and right part. In figure 9 this confinement ratio is plotted versus frequency. The ratios are normalized at 70 MHz. The confinement ratios gradually increase with increasing frequency for all 5 patients. At 95 MHz there is an increase of 30-50% power transferred from the lateral parts (left, right) towards the center parts (front, middle, back).

Figure 9: LL compression of the SAR distribution in the transversal target slice as a function of frequency for all 5 patients normalized to 70 MHz. The compression is expressed as the PA in the front, middle, and back regions divided by the PA in the left and right regions. Lines are to guide the eye.



Discussion

In this paper, we have used a treatment planning system for a somewhat unconventional purpose. Instead of using it to predict patient and antenna specific power distributions, we employed the HTPS to check the non-patient-specific rationale behind the empirical guidelines that are being used in our clinical practice for over 15 years now. These guidelines, based on experience, past research and patient safety, were established in a time when hyperthermia treatment planning was not available.

We have to stress that we are looking for qualitative similarities and differences between the guidelines and the planning results. It is not our aim to prove or disprove the correctness of neither planning system nor the guidelines.

Firstly, we discuss some issues concerning patient positioning and anatomical hotspots. Then the impact of the HTPS results for each guideline separately is treated, followed by some general remarks concerning the methodology.

Patient models and positioning

The stature of the 5 patients included in this study was rather diverse. At the transversal slice as defined in figure 1, fat volume percentages for patients I to V were 13, 34, 14, 26 and, 11% respectively.

The 5 tumors have an average volume of 93 cm^3. The average location of the tumors in the LL direction is only 2 mm off from the center of the rods. The offset in the AP direction is 1.9 cm posterior with respect to the center of mass of the front, middle and back regions in the transversal slice.

The homogeneity of the target location combined with the heterogeneity of the patient population makes the results of this study generally applicable for all cervical tumors.

As we mentioned, AP positioning of the patient models inside the applicator is not trivial. In practice, measurement of the patient height inside the applicator is difficult due to absence of symmetry (like in the LL direction) or a clear reference point (like the cranial margin of the pubic bone for positioning in the caudal cranial direction). Accurate positioning is also hampered by the effect of filling the water bolus on the final position of the patient, especially in the AP direction. Seebass et al. showed that T90 temperatures are most sensitive for positioning errors in the AP direction.[16]

In our opinion, the method to center the patient models in the AP direction, as explained previously, comes close to the approach that is used in clinical practice. Further, there is a need for an unambiguous and highly reproducible method for AP centering in the clinic.

Hotspots

To our knowledge, an extensive review on the location of clinically observed hotspots and their frequency of occurrence during deep hyperthermia on the pelvis has not been published yet. However, Anscher et al. reported for 21 patients with locally advanced prostate cancer intolerance and pain in the hips, thighs, and pubis, corresponding to the quadrant of maximum power delivery.[17] Further, Wust et al. reported for 43 locally advanced tumors of different locations a topographical classification of local side effects

including their frequencies.[18] Their list overlaps the hotspot areas we qualitatively identified for our 5 patients based on the SAR distribution plots (compare figure 3). These areas include the lower ventral abdomen, the ventral adipose tissue, the suprapubic region and the dorsally located sacral region. Also hotspots at the perineum/vulva could be identified both clinically and in our model calculations. Hotspots on the inside and on top of the thighs were also observed but are not shown in figure 3. Hotspots at skin folds, rima ani and the inguinal region were not found probably due to the coarse level of modelling.

The hotspots listed above are considered to be anatomical, since they show higher SAR values than their immediate surroundings, and their location cannot be gradually shifted by steering actions.

In this paper we did not consider the effect of these anatomical hotspots on the steering strategies. We focused on the power transfer between a target and 4 rather large peripheral regions. Although we think this is an adequate description, the effect of the different steering strategies may be different when we consider the effect for specific, power-limiting hotspots.

Implications for the guidelines

Guideline 1. How to correct for unbalanced temperature distribution

For a typical patient with cervical cancer, 3 intraluminal temperature probes are used: one in the bladder, one in the vagina, and one in the rectum. These probes are all located in the mid-sagittal plane.

To change the temperature distribution, we can use either phase or amplitude steering. Phase differences and amplitude settings are compared by the maximum change allowed by the RESG.

Restrictions to the allowed phase or amplitude differences are based on clinical experience and not imposed by any technical limitations of the current BSD 2000-3D system. The maximum allowed phase difference is approximately 120 degrees, corresponding to an absolute shift of ~8 cm of the SAR focus in an abdomen equivalent phantom according to the BSD console. The maximum decrease of amplitude per channel is 50%. However, in case of high reflected power or malfunctioning of the equipment, it is allowed to proceed with the specific channel switched off (i.e. with 0% amplitude). During the last 5 years, for 5 patients the Sigma-60 applicator was operated the entire treatment with only 3 channels.

Instead of balancing the amplitude ratios, amplitude steering is accomplished by simply lowering the amplitude on one side while keeping the total power the same. This idea is closely associated with how the BSD console is operated, where also the relative amplitude is changed with respect to the three other channels.

For a centrally located tumor, especially the bladder and rectal temperatures are balanced; the vaginal temperatures are often somewhat lower (for a population of 22 patients Fatehi et al. reported all lumen T50 for bladder, vagina, and rectum of 40.6 ^{0}C, 40.0 ^{0}C and 40.5 ^{0}C respectively).[19]

From figure 4 we see that in general phase steering is more effective in transferring power from the central region towards the front or back compared to amplitude steering. That is, the position of the center of mass of the SAR distribution (the SAR focus) is much more sensitive for changes in phase difference than it is for changes in amplitude settings. From figure 5 we see that the same holds for steering in the LL direction. We conclude that phase steering is the appropriate steering action in case of temperature differences.

Guideline 2. How to treat deep-seated pain or pressure

The implications of the HTPS outcomes in the case of deep-seated pain or pressure are similar to the first guideline. To reduce deep-seated complaints, the power absorbed in the painful region has to be removed. This can be accomplished by shifting the SAR focus away from this region. As we stated above, it was observed that for a centrally located region the global power distribution can be effectively shifted with phase steering.

Guideline 3. How to alleviate superficial heat complaints

For a centrally located tumor, peripheral complaints, often perceived as heat, may still be power-limiting. Figure 6 shows that steering in the opposite direction, away from the painful region can be done effectively with either phase or amplitude steering. For both types of steering the complaint reduction ratio can be decreased. However, phase steering shifts the SAR focus away from the target region, thus lowering the efficiency (fraction of the total power input into the patient that is absorbed in the target region). Thus we conclude that amplitude steering is appropriate in case of superficial complaints. From figure 7 we see that the same holds for steering in the LL direction.

Note that the peripheral regions we defined in figure 2 extend up to the target region. From additional calculations it was found that the effect of peripheral complaint reduction is even more pronounced when focusing on peripheral regions that are located more superficially.

Guideline 4. Frequency steering

In Rotterdam, the standard operating frequency for the Sigma-60 is 77 MHz. Within the range of possible BSD 2000-3D frequencies, 75-120 MHz, this choice is rather low. Historically, higher standard operating frequencies were not considered for several reasons. The idea is that a low frequency implies a larger heating volume, thus avoiding cold spots in the target volume and possibly pre-heating blood that enters the tumor. Further, high frequencies resulted in a high reflected power and in instabilities. The guidelines now limit the frequency range to 75-90 MHz.

In figure 8 and 9 the effect of an increase in frequency on the SAR distribution is illustrated. Remarkably, the compression of the SAR distribution with increasing frequency is much more apparent in the LL direction than in the AP direction. Further, we see a clear longitudinal shift of the SAR distribution with changing frequency. No clear compression of the SAR distribution is observed in this direction.

This is in agreement with the findings of van Rhoon et al. They reported that the size of the longitudinal 50% iso-SAR area in a cylindrical phantom is independent of the operating frequency (within a range of 70-100 MHz).[10] This can be attributed to the limited distance of the antennae to the load. In this case the extension of the SAR distribution is merely dominated by the antenna lengths. Further, they found the extension of the SAR distribution in the axial direction to be dependent on the frequency. A decrease of 15.3 to 9.7 cm was reported when increasing the frequency from 70 to 100 MHz.

Seebass et al. and Paulsen et al. also treated the effect of a frequency increase for antenna configurations resembling the Sigma-60 applicator (one antenna ring with 4 antenna pairs).[16, 20] Both studies showed clearly that for an increasing number of antennas and antenna rings, higher frequencies (>100 MHz) result in higher gain factors. Surprisingly, for the specific Sigma-60 configuration and for centrally located tumors, they found decreasing gain factors. Paulsen did not report a longitudinal shift in SAR distribution with increasing frequencies from 100 to 150 or 200 MHz. However, neither of these studies focused on frequencies in the range of 70-100 MHz.

It is evident that the idea of increasing the frequency in case of multiple peripheral complaints at opposite locations has to be adjusted. Based on the model outcomes we can be more specific when an increase in frequency is appropriate. First of all, according to figure 9, increasing the frequency from 77 MHz will result in increased SAR levels within the pelvis. This would suggest that higher frequencies would always be preferable. However, SAR levels are also increased at the anterior and posterior hotspot locations.

From this work we cannot conclude whether a higher frequency than 77 MHz is in general more profitable.

However, for 3 of the patients we found that an increase of 77 to 85 MHz resulted in less power in the back. Thus for specific complaints in the back, increasing the frequency to 85 MHz would be an option. Further, for pressure or heat at the lateral hip regions, the model predicts that an increase in frequency would be beneficial.

Final remarks

A general assumption behind the steering guidelines and the partitioning depicted in figure 1, is that the steering actions affect only the SAR distribution in the transversal plane. From figure 3 it can be seen that this is valid for phase (and amplitude) steering. However, for frequency steering (figure 8), there is a considerable longitudinal effect. This effect is also visible in figure 9 at high frequencies, where power is also transferred out of and into the transversal plane. It should be stressed that these effects, that are quite patient specific, have to be taken into account when considering frequency steering, and may cause unexpected hotspots.

Further, when performing steering actions, also the efficiency of power input into the patient may be changing. This requires that power should always be increased until complaints occur, or at least one should verify that average temperatures near the target region are not decreasing. Choosing the most inefficient steering parameters is not a sensible strategy to avoid complaints.

Conclusions

In this work we evaluated the Rotterdam empirical steering guidelines with model calculations using Sigma HyperPlan as a treatment planning system (HTPS).

For all steering actions it is assumed that input power is increased until complaints occur.

Four guidelines were investigated. The first one states that phase steering is appropriate to balance intraluminal temperatures. Model calculations showed that the power distribution can be effectively shifted peripherally by increasing phase differences of opposite antenna pairs. This type of steering action is also to be used in case of deep-seated pain complaints or other discomfort, which is stated in the second guideline.

Further, it was found that to alleviate superficial complaints of heat or pressure, reducing amplitude indeed is the proper action of choice.

The last guideline states that frequency has to be increased from 77 MHz upwards in case of multiple, opposite painful regions that cannot be avoided by phase or amplitude steering. The HTPS calculations confirmed compression of the SAR distribution, mainly in the LL direction. For complaints in the lower back, a frequency increase should be considered.

The results of the HTPS are in close agreement with the empirical steering guidelines.

Acknowledgments

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Chapter 7

Complaint adaptive PD-optimization as a tool for HTP-guided steering in deep hyperthermia treatment of pelvic tumors

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Abstract

For an efficient clinical use of HTP (Hyperthermia treatment planning), optimization methods are needed. In this study, a complaint-adaptive PD (power density)-optimization as a tool for HTP-guided steering in deep hyperthermia of pelvic tumors is developed and tested.

PD distribution in patients is predicted using FE-models. Two goal functions, Opt1 and Opt2, are applied to optimize PD distributions. Optimization consists of 3 steps: initial optimization, adaptive optimization after a first complaint, and increasing the weight of a region after recurring complaints. Opt1 initially considers only target PD whereas Opt2 also takes into account hotspots. After patient complaints though, both limit PD in a region. Opt1 and Opt2 are evaluated in a phantom test, using patient models and during hyperthermia treatment.

The phantom test and a sensitivity study in 10 patient models, show that HTP-guided steering is most effective in peripheral complaint regions. Clinical evaluation in 2 groups of 5 patients shows that time between complaints is longer using Opt2 ($p=0.007$). However, this does not lead to significantly different temperatures [T50's of 40.3(Opt1) vs. 40.1^{o}C (Opt2) ($p=0.898$)].

HTP-guided steering is feasible in terms of PD-reduction in complaint regions and in time consumption. Opt2 is preferable in future use, because of better complaint reduction and control.

1. Introduction

Hyperthermia, i.e. heating of the tumor, is used as an adjuvant modality to radiotherapy or chemotherapy in the treatment of various cancer types. Since 1990, hyperthermia treatments of pelvic tumors in the Erasmus MC (Rotterdam, The Netherlands) are carried out using a BSD-2000 system (BSD Medical Corporation, Salt Lake City, Utah, USA).[1] The vast majority of pelvic tumors are treated in the Sigma-60 applicator that contains a single ring of 8 dipole antennas.[2] Antennas are coupled in pairs into 4 independent channels. Phase and amplitude of each channel can be controlled.

Intuitively, a higher power input is expected to lead to higher temperatures inside the tumor. In a recent study, Fatehi et al. confirmed this expectation.[3] For individual patients a positive correlation of average target temperature and the total power delivered into the patient was found. At the same time this study reported that increasing the power input to the patient is often limited by painful hotspots. This emphasizes the need for a better understanding of the power distribution inside the patient and its dependency on amplitude and phase settings.

Commonly, phase and amplitude of the antennas are empirically adapted to modify the absorbed energy distribution in reaction to patient complaints. In Rotterdam, the strategy for patient complaints in deeper situated tissues is to change phase settings to move the focus away from the complaint region. Amplitude is used to respond to superficial complaints. This steering strategy is further referred to as empirical steering.[4] A serious shortcoming of this empirical steering protocol however, is the inability to predict the effects of the steering actions.

Fortunately, the currently available HTP (hyperthermia treatment planning) systems provide excellent opportunities to improve the understanding of both power and temperature distribution. HTP may also be beneficial for steering during treatment, since it has the potential to predict the effects of the steering actions. Sigma HyperPlan, a HTP system, is capable of calculating PD (power density) and temperature 3D distributions.[5-6] Temperature distribution however, is very sensitive to the selected blood perfusion values, which vary between patients and over time, limiting the practical reliability of predicted temperature distributions. Although PD does not provide a direct picture of heating, it provides a time- and perfusion- independent indication of power absorption in the patient. Therefore this study focuses on PD optimization with amplitude and phase as variables.

Calculating optimized starting settings is becoming common practice in hyperthermia. However, a role of HTP controlled PD optimization to reduce PD in a complaint region is

highly desirable. This is likely to lead to a more controlled treatment quality. This second step is further referred to as HTP-guided steering. In this study, the tools necessary for HTP-guided steering, using the Sigma-60 applicator, are developed and the sensitivity of HTP-guided steering is tested pre-clinically in a phantom and in 10 patient models. Next, the feasibility of HTP-guided steering is evaluated clinically in a small group of 10 patients.

2. Nomenclature

The nomenclature used is explained in table 1.

Table 1: Nomenclature

Unit	Description
V_i [m^3]	i-th percentile of the patient volume inside inpplicator, i.e. i-th percentage with the highest PD
V_i (n)	i-th percentile of the volume of region n, i.e. i-th percentage with the highest PD
PD [W/m^3]	Power density
PD_i [W/m^3]	PD exceeded in i% of the patient volume
$PD(V_i)$ [W/m^3]	Average PD inside V_i
PD_i –coverage [-]	Part of the target that is covered by at least PD_i
PD_{target} [W/m^3]	Average PD in target volume
PD_{tot} [W/m^3]	Average PD in patient volume
PD_{target_ratio} [-]	Ratio of PD_{target} and PD_{tot}
$PD_{target\_ratio\_0}$ [-]	Optimized PD_{target_ratio}
PD_{ratio}(n) [-]	Ratio of PD in region n and PD_{tot}
$PD_{targ\_hs\_ratio}$ [-]	Ratio of $PD(V_1)$ and PD_{target}
$PD_{targ\_hs\_ratio\_0}$ [-]	Optimized $PD_{targ\_hs\_ratio}$
$PD_{targ\_hs\_ratio}$(n) [-]	Ratio of $PD(V_1(n))$ and PD_{target}
Homogeneity Coefficient [-]	Measure for the homogeneity: ratio of PD_{75} and PD_{25}
Hotspot Volume [m^3]	Volume where $PD>PD_{target}$
Hotspot Volume ratio [-]	Ratio of hotspot volume and patient volume

3. Methods

The methods section is subdivided in the subsections Sigma HyperPlan model and hyperthermia equipment (3.1), Optimization method (3.2), Phantom test setup (3.3), treatment protocol for clinical testing (3.4) and Model sensitivity study, clinical treatment and statistical methods (3.5).

3.1 The Sigma HyperPlan model and the hyperthermia equipment

3.1.1.From CT-scan to patient model

In this study, for each patient included a CT-based anatomic model is made in Sigma HyperPlan. The CT is segmented into the tissues named in table 2, where also dielectric properties of the tissues are presented at 77 MHz.[7-8] This is the standard treatment frequency used in Rotterdam. Given the relatively large confidence interval with which the dielectric parameters are currently known, the temperature dependency of εr and σ is neglected.

After segmentation a tetrahedral grid of patient and Sigma-60 applicator is created. Models on average consist of 220.000 tetrahedra, with edge length between 0.3 and 2.5 cm. The E-field is calculated as described in Gellermann et al.[6] The coordinate system used in the models is the following: X is the lateral (left-right) direction, Y the ventral-dorsal direction and Z the caudal-cranial direction.

Table 2: Used tissues and their electrical properties at 77 MHz [7,8]

Tissue	ε_r	σ [S/m]
Fat	13	0.07
Muscle	69	0.70
Bone	16	0.06
Rod	1	0
Target	69	0.70
Bladder	24	0.29
Heart	99	0.70
Intestine	108	1.62
Kidney	109	0.77
Liver	75	0.46
Lung	35	0.71
Myelum	6	0.04
Spleen	101	0.77
Stomach	82	0.89
Uterus	69	0.70
Vagina	69	0.70

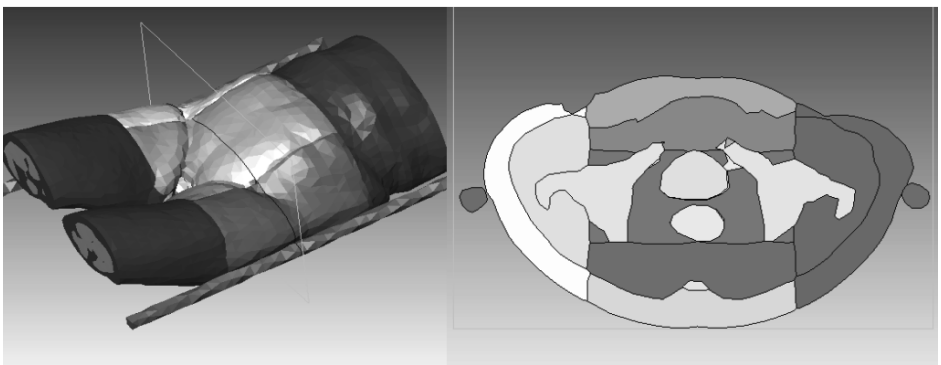
3.1.2.Definition of regions for HTP-guided steering

To respond to patient complaints during HTP-guided steering, different regions need to be defined a priori. The size of these regions reflects the precision of complaint localization by the patient and the technical ability to adapt the PD distribution. Each region can be constrained in HTP-guided steering to reduce PD in that region after complaints occur.

Existing tissue types are used as a basis for the definition of these regions. Steering of the Sigma-60 is effective in the XY-plane in the pelvic region. Most pelvic tissue types are either

restricted to a limited volume or have intrinsic low energy absorption, like for example bone. Only fat and muscle tissues occur throughout the whole XY-plane. Therefore in the pelvic region fat and muscle tissue are each divided into 5 separate regions: left, right, top middle and bottom. In figure 1 an axial slice of a patient model is shown with all defined regions

Figure 1: Regions defined in model. The slice (right) shows muscle and fat are divided into 5 regions: top, mid, bottom, left and right.



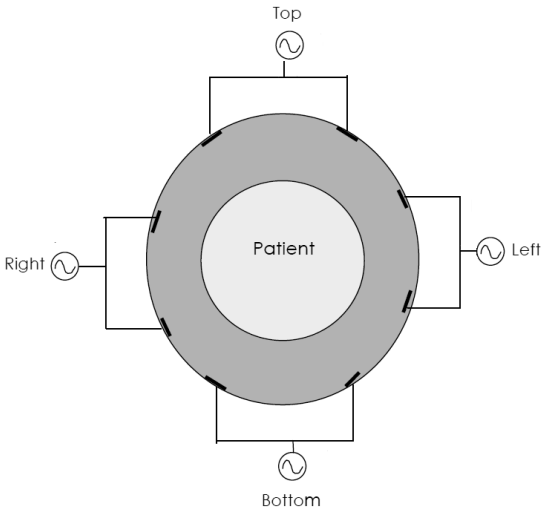
3.1.3.The hyperthermia equipment

All patients presented in this study were treated for cervical cancer in the BSD Sigma- 60.[2] This applicator has a diameter of 60 cm and a length of 50 cm. Furthermore, it consists of a ring of 8 dipole antennas that are coupled in 4 channels of two antennas each, which is schematically depicted in figure 2. Amplitudes and phases of each of these channels can be controlled independently. The optimization methods in this study use amplitudes and phases as optimization variables, i.e. amplitudes and phases of each channel is adapted to create an optimal PD-distribution.

3.2 Optimization method

HTP-guided steering has to meet the following demands to be advantageous above empirical steering. First, PD in the tumor area has to be maximized. Second, HTP-guided steering requires the possibility to impose constraints upon a priori defined complaint regions. A patient's complaint triggers a steering action. Constraining the optimization after complaints is expected to lead to a better balance in maximization of tumor PD and minimization of PD in the complaint region. Third, a weight factor proportional to the severity of the complaint is given to the imposed constraints. With this weight factor the balance in optimization is shifted between tumor and complaint region, dependent on the intensity of the complaint.

Figure 2: Axial view from the caudal direction of the Sigma-60 applicator, with the 4 channels, each connected to 2 antennas and a combined patient-applicator model



Two possible goal functions for HTP-guided steering are proposed in this study. The first goal function maximizes target PD and reduces PD in hotspots only after complaints and is commonly known from literature.[9-10] The second goal function maximizes PD, while minimizing hotspots a priori, and is derived from a previous study.[11] On complaints, hotspots in the complaint region are further reduced. The 2 goal functions are further referred to as Opt1 and Opt2. In both strategies an optimization in 3 steps is used: an initial optimization to obtain starting settings for a treatment, addition of a complaint-region related term to the goal function if a patient complaint occurs, and an increase of the weight of the complaint-related term if another complaint occurs.

Both goal functions are optimized in Matlab using the 'fmincon' function to find a global minimum of the goal function varying amplitude and phase. Amplitude has an upper bound of 1 logically, and a lower bound of 0.5, because of BSD amplifier stability reasons.[12-13] Phase has no upper or lower bounds.

3.2.1 Goal functions in optimization

Opt1: maximizing target PD

The first step in Opt1 is an initial optimization. In this first step, the goal function has the following form:

$$\max\left(\overline{PD}_{\text{targ\_ratio}}\right) = \max\left(\frac{\overline{PD}_{\text{target}}}{\overline{PD}_{\text{tot}}}\right) = \overline{PD}_{\text{targ\_ratio\_0}} \tag{1}$$

In Seebass et al for example, similar objective functions were used.[14] $\overline{PD}_{\text{targ\_ratio\_0}}$ considers only target behavior and no hotspots. $\overline{PD}_{\text{targ\_ratio\_0}}$ is the result of this optimization.
The second step is initiated after a complaint occurs during a treatment. A second term is added to (eq. 1) to minimize PD in a complaint region. This results in (eq. 2).

$$\max\left[\left(\frac{\overline{PD}_{\text{targ\_ratio}}}{\overline{PD}_{\text{targ\_ratio\_0}}}\right) - \sum_{n \in regions} 0.25 \cdot w(n) \cdot \frac{\overline{PD}_{\text{ratio}}(n)}{\overline{PD}_{\text{ratio\_0}}(n)}\right] \tag{2}$$

Hotspots are now taken into account by using the full goal function (eq. 2), with w(n) set to one for the complaint region n. The first term in (eq. 2) is equal to the goal function of step 1, normalized on the outcome of the initial optimization (eq. 1). The second, complaint-induced term of (eq. 6) consists of $\overline{PD}_{\text{ratio}}(n)$, the PD-ratio in region n, defined as:

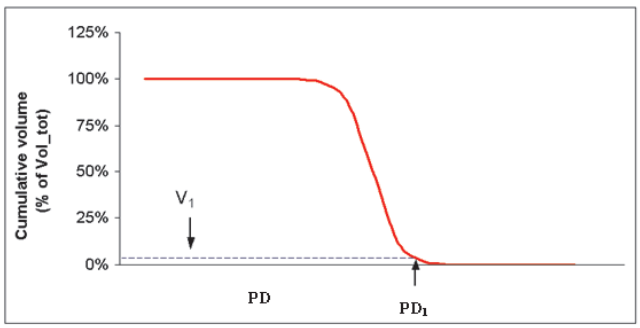
$$\overline{PD}_{\text{ratio}}(n) = \frac{\overline{PD}(n)}{\overline{PD}_{\text{tot}}} \tag{3}$$

and is also normalized on the outcome of step 1.
The third step in optimization is induced by a recurrent complaint in a region. In that case the weight of the complaint-induced term of (eq. 2) is increased by adding one to w(n) (the weight factor) for complaint region n. The maximum value for the sum of w(n) is chosen to be 4. From our experience with empirical steering we expect 4 steering steps to be sufficient during treatment. A larger number would either reduce the influence per step too much or over-increase the influence of the hotspot part of (eq. 2). To ensure that the maximum value of this hotspot part of (eq. 2) is always smaller than the target part, the weight factor has to be multiplied by 0.25. (an equivalent approach would be to range the weight factors from 0 to 1 in steps of 0.25)

Opt2: maximizing the ratio of target PD and hotspot PD

Opt2 is, like Opt1, divided in 3 steps. The first step, the initial optimization, is a minimization, chosen equivalently to a goal function in Wust et al. and has the following form: [15]

Figure 3: Definition of V_1. A cumulative SAR histogram is depicted to illustrate the V_1 definition. V_1 is defined as the 1st percentile. PD_1 is defined as the PD exceeded in 1% of the volume, thus the PD enclosing V_1.



$$\min\left(\overline{PD}_{\text{targ\_hs\_ratio}}\right)=\min\left(\frac{\overline{PD}(V_1)}{\overline{PD}_{\text{target}}}\right)=\overline{PD}_{\text{targ\_hs\_ratio\_0}} \tag{4}$$

with $\overline{PD}(V_1)$ the average PD within V_1. V_1 is the 1st volume percentile of the patient that is enclosed by the applicator (figure 3). $\overline{PD}_{\text{targ\_hs\_ratio\_0}}$ is the result of the optimization.
The second step is initiated after a complaint occurs during a treatment, adding an additional hotspot term to the goal function, changing it to (eq. 5), with w(n) set to one for region n.

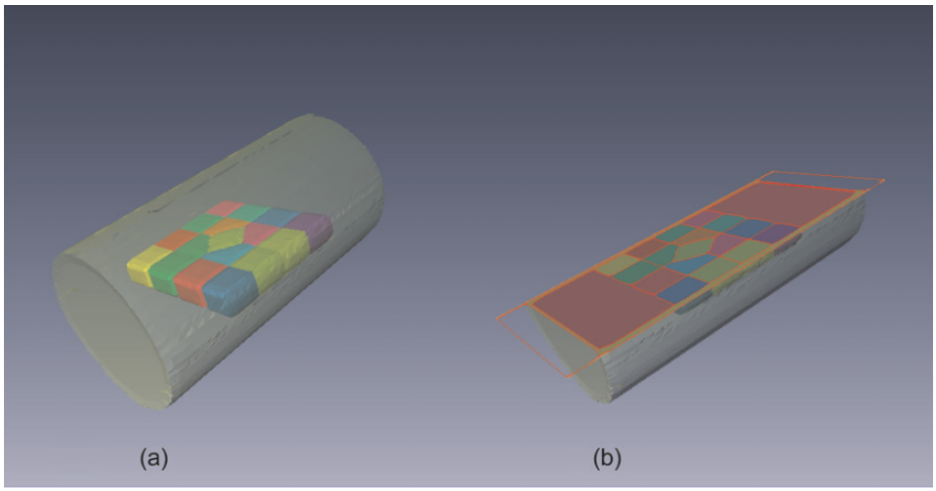
$$\min\left[\left(\frac{\overline{PD}_{\text{targ\_hs\_ratio}}}{\overline{PD}_{\text{targ\_hs\_ratio\_0}}}\right)+\sum_{n\in regions}0.25\cdot w(n)\cdot\frac{\overline{PD}_{\text{targ\_hs\_ratio}}(n)}{\overline{PD}_{\text{targ\_hs\_ratio\_0}}(n)}\right] \tag{5}$$

Equivalently to Opt1, the second part of the goal function (eq. 5) is a hotspot-related term,

$$\overline{PD}_{\text{targ\_hs\_ratio}}(n)=\frac{\overline{PD}\left(V_1(n)\right)}{\overline{PD}_{\text{target}}} \tag{6}$$

normalized on it's initial value $\overline{PD}_{\text{targ\_hs\_ratio}}(n)$. $\overline{PD}\,(V_1(n))$ is the average PD within $V_{1(n)}$. $V_{1(n)}$ is the 1st percentile of region n where PD exceeds $PD_{(n)1}$.
The third step, increasing the weight of the second term in (eq. 5) after recurrent complaints, is equivalent to Opt1.

Figure 4: Regions defined in the phantom (a) and the XZ-plane, in which the measurements take place (b)



3.3 Phantom test setup

Before the optimization routine can be used as HTP-guided steering tool during clinical treatments, it is tested in a phantom setup for its effectiveness in steering. We used a 2g/l NaCl saline water phantom as described by Van Rhoon et al.[2] Subsequently a model of the phantom is made, in which a number of possible complaint regions are defined (figure 4).

We measured the reduction of PD in the constraint region when a weight factor is applied using E-field sheets with Schottky diodes, placed in the XZ-plane.[2] Diode positions are depicted in figure 5.

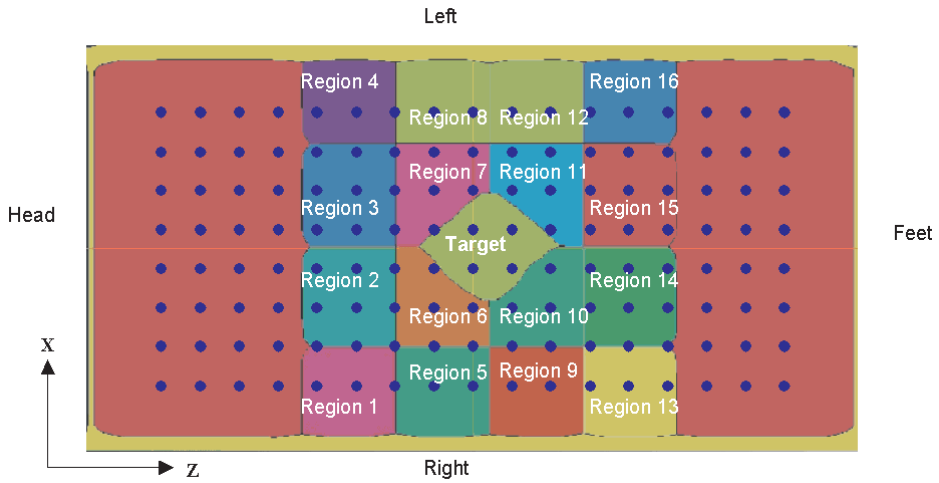
The square of the diode voltage output is proportional with PD. The average PD in a region can be calculated as follows:

$$\overline{PD}(region)_{\text{measurement}} = \frac{\sum_{n \in region} |E(n)|^2}{nr\_of\_diods(region)} \tag{7}$$

in which $E_{(n)}$ is the E-field at diode n. The E-field sheets measure only in the XZ-plane (figure 5). However, since the regions are only small in Y-direction we assume that (eq. 7) is a valid approximation for average PD in a region. PD is normalized on PD_{tot}, which is derived from $P_{forward}$-$P_{reflected}$. This is further referred to as:

$$PD_{ratio}(region)_{measurement} = \frac{\overline{PD}(region)_{\text{measurement}}}{\overline{PD}_{\text{tot\_measurement}}} = \frac{\overline{PD}(region)_{\text{measurement}}}{\left(P_{\text{forward}} - P_{\text{reflected}}\right)/V_{\text{tot}}} \tag{8}$$

Figure 5: Regions defined in the XZ-plane and diode positions in that plane



To compare measurements with the model, PD-values are extracted from the model exactly at the diode spots. $\overline{PD}\ (region)_{model}$ can then be calculated similar to $\overline{PD}\ (region)_{measurement}$. $\overline{PD}_{tot\_model}$ is defined as total absorbed power calculated by the model divided by total volume. Thus $PD_{ratio}(region)_{model}$ is defined as:

$$PD_{ratio}(region)_{model} = \frac{\overline{PD}(region)_{model}}{\overline{PD}_{tot\_model}} \tag{9}$$

For comparison of model and measurement, the PD-ratio is normalized to the maximum PD-ratio measured with zero phase and amplitude 1 on all channels. This is necessary because $PD_{measurement}$ is based on a measured E-field, which can only qualitatively be interpreted.

The phantom test

First Opt1 and Opt2 are optimized for both a centrally positioned target as well as a target positioned more peripheral (in region 5 of figure 5) to check their performance in optimization. Next, the effects of HTP-guided steering actions are evaluated in case of complaints in a specific region (experiment nr 1-4, table 3), recurring complaints in a specific region (experiment nr 5-8, table 3) and in case of complaints in multiple regions on the same or opposite side of the phantom (experiment nr 9-11, table 3).

In the tests with a single complaint region, (i.e. experiment 1 to 8), attention is focused on region 1, 2, 5 and 6, all situated in one quadrant of the phantom. This is representa-

tive for the other regions due to symmetry of the phantom. Measuring reductions for weight factors 1 and 4 tests also the effect of increasing the weight factors. To simulate the occurrence of multiple complaints, 3 additional distributed complaint regions are chosen,

Table 3: Experiments in the phantom test, varying complaint regions and value of the weight factors

Experiment number	Experiment
1	Complaint in region 1, weight factor = 1
2	Complaint in region 5 weight factor = 1
3	Complaint in region 2, weight factor = 1
4	Complaint in region 6, weight factor = 1
5	Complaint in region 1, weight factor = 4
6	Complaint in region 5, weight factor = 4
7	Complaint in region 2, weight factor = 4
8	Complaint in region 6, weight factor = 4
9	Complaint in region 1 and 5, weight factor = 1 in both regions
10	Complaint in region 1 and 8, weight factor = 1 in both regions
11	Complaint in region 1 and 16, weight factor = 1 in both regions

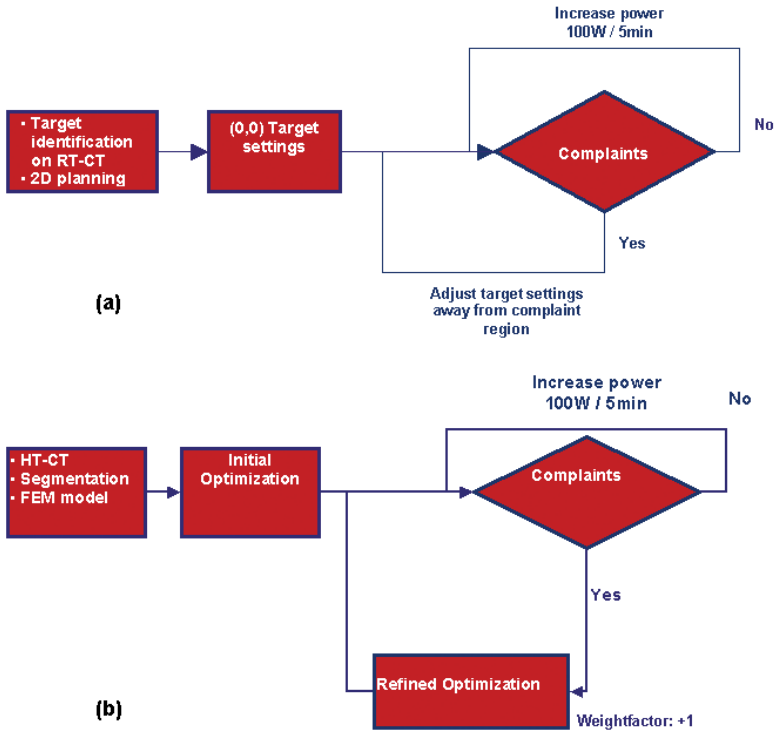
located both at the same side of the phantom as region 1 (region 5) and opposite to region 1 (regions 8 and 16).

3.4 Treatment protocol for HTP-guided steering

In figure 6, the treatment protocols for both empirical steering and HTP-guided steering are highlighted. In all treatments, both with empirical steering and HTP-guided steering, the patient is the indicator of his/her tolerance for heating. We instruct the patients before treatment to indicate if any discomfort is occurring. Of course the tolerance for heat is different per patient, but this is inherent in the hyperthermia treatment. Since thermometry is only done in the different lumina of the patient, the largest part of the pelvic area is not covered by thermometry. Therefore the patient as an indicator of temperature is absolutely necessary. If however, a patient does not complain in case of discomfort, this becomes quickly visible by increased heart rate or observed unrest of the patient. In both cases, the operator communicates with the patient to find out what is causing the discomfort, and adapts settings according to the information received from the patient. An indication of discomfort is further referred to as ‘complaint’ in this study.

In the empirical steering protocol, a treatment is started with (0,0) target settings (i.e. balanced amplitudes and phases).[4] If no complaint occurs, power is increased with 100 W per 5 minutes. If however a complaint occurs, the focus of the EM field is shifted away from the complaint region, by adjusting the phases.

Figure 6: Flowchart for empirical (a) and HTP (hyperthermia treatment planning) - guided steering (b)



A new treatment protocol for HTP-guided steering is developed to provide optimized treatment settings for the start of treatment and in case of hotspot-related complaints. Treatment is started with optimized settings for phase and amplitude, obtained from the first step in the optimization routine. As before, input power is increased by 100 W after every 5 minutes interval without complaints, indicative of hot spots.

After a complaint, a constraint is put on the matching region with weight factor 1, and the second optimization step is calculated. If the response time is long, power is temporarily lowered by 50 W for the duration of the calculation. When the new settings are available, power is increased again by 50 W and calculated settings are put into effect. To reduce response time, amplitude and phase settings are precalculated for a number of common complaints. Again, after 5 minutes without complaints, power is raised by 100 W. Besides complaints, also temperatures from intraluminal measurements in healthy tissue exceeding 43 ^{0}C, are a reason for putting a constraint on the matching region.

The moment a new complaint occurs, a weight factor of 1 is added for the new complaint region as long as the sum of all weight factors is less than 4. After a complaint occurs

while the sum of weight factors is already 4, but the sum of weight factors in the complaint region is below 4, one weight factor is added to the complaint region. At the same time for the region most distant from the complaint region a weight factor is subtracted.

If a complaint occurs in a region where the sum of weight factors is already 4, we assume that amplitude and phase steering are not sufficient. In that case, a frequency change is applied, similarly to our empirical protocol, after which the PD is re-optimized using the previous weight factors. Given the total treatment time of 90 minutes, we have chosen to apply a maximum of 2 frequency changes.

If none of the above steering actions reduce complaints (or temperatures in healthy tissue exceeding 43°C) to an acceptable level, we assume that the maximum possible heating is reached. All amplitude and phase settings are kept at the same level, after which power is reduced in steps of 50 watts until complaints (or temperatures in healthy tissue exceeding 43°C) disappear.

3.5 Sensitivity study, clinical treatment and statistical methods

A sensitivity study was performed for 10 patients. Equivalently to the phantom test initial optimization and reduction in possible complaint regions is evaluated. Besides PD_{target} various other quality indicators are evaluated:

- PD_5 coverage of the target (the part of the target exceeding PD_5)
- homogeneity coefficient (ratio of PD_{25}(targ) and PD_{75}(targ))
- $PD(V_1)$/PDtarg (see §3.2)
- hotspot volume ratio (part of the patient above 2 times PDtarg).

Table 4: Patient characteristics

Patient characteristics	Opt1 (range)	Opt2 (range)
Age (year)	59 (45-82)	65 (55-84)
WHO-PS	0	0
Height (cm)	162 (158-171)	168 (161-176)
Weight (kg)	60 (51-73)	68 (50 -80)
Diameter AP (cm)	20 (19-22)	23 (18-26)
Diameter lat-lat (cm)	37 (36-40)	40 (34-44)
Tumor size (cm^3)	116 (57-184)	96 (46-184)
FIGO stage		
Ib	1	1
IIb	2	2
IIIb	2	0
IVa	0	1
IVb	0	1

Legend: WHO-PS = World Health Organization Performance Status, AP = anterior-posterior, lat-lat = lateral to lateral, FIGO = International Federation of Gynecology and Obstetrics

For the same patients, HTP-guided steering using Opt1 and Opt2, is tested during actual treatment, each in a group of 5 patients. Opt 1 and Opt2 are compared on complaint frequency and obtained temperatures. In table 4 patient characteristics are summarized.

Results obtained from the treatments, are compared statistically between Opt1 and Opt2, using a χ^2 test in case of percentages, and a two sample t-test in case of number of complaints and time between complaints.

Patient characteristics of the 10 patients are depicted in table 4.

4. Results

4.1 Phantom measurements

Initial optimization (step1)

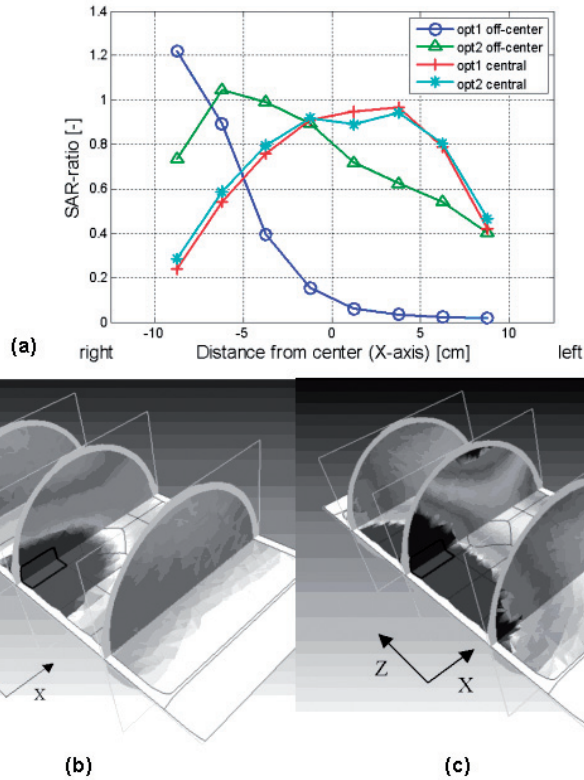
Both Opt1 and Opt2 lead to approximately similar PD distributions in a cylindrical phantom with central (0,0) target settings and optimization. Figure 7a shows the shape of measured PD-ratio for Opt1 and Opt2 in X-direction at Z=0 (center of phantom is at the center of the Sigma-60 applicator). However for both optimization routines the maximum seems to be shifted slightly to the left, probably due to positioning uncertainties. To get more insight in the performance of the 2 optimization routines, the target region is shifted from the center to the peripheral region 5, after which new treatment settings are calculated using both optimization routines. The measured PD_{target}-ratio of both optimization routines for an off-center target is presented in figure 7a. In figure 7b and 7c results predicted by Sigma HyperPlan for the off-center target situation using respectively Opt2 and Opt1 are presented to illustrate the measurements in figure 7a and to provide a 3D overview.

In the off-center target situation there is a clear difference between Opt1 and Opt2. The width of the focus in Z-direction is longer for Opt1, while the width in X-direction is smaller.

Reduction in complaint regions (step 2 and 3)

The results of the tests (mentioned in table 3) for Opt1 and Opt2 are presented in figure 8. For both optimization routines, the PD-ratio in regions more peripheral with respect to the target is easier reduced (regions 1 and 5) than in regions adjacent to the target (regions 2 and 6) (see experiment 1-4). For Opt2 this effect is stronger and with weight

Figure 7: a) Measured normalized PD-profile along the X-axis at Z=0 for both optimization methods in a central target and an off-center target, b) PD-distribution in off center target using Opt2 and c) off center target using Opt1

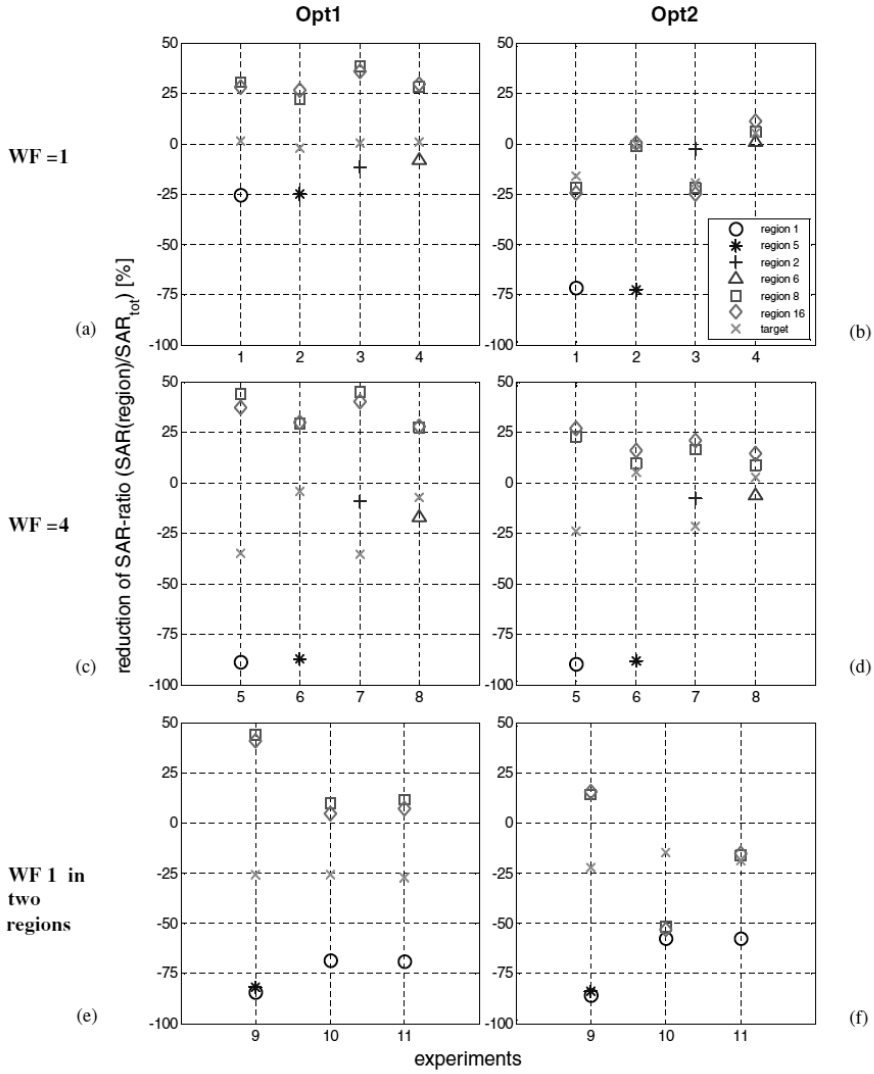


factor 1 almost no reduction takes place in the regions (regions 2 and 6) adjacent to the target. For all steering actions, reduction in PD-ratio of the complaint region is larger than the reduction in the target, which means that all experimentally tested steering actions are effective in terms of complaint reduction and PD-maximization.

Increasing the weight factor to 4 (experiment 5-8), increases the reduction of PD-ratio in peripheral regions for both Opt1 and Opt2. The regions adjacent to the target appear to be less influenced by increasing the weight factor.

Adding weight factors to 2 complaint regions (experiment 9-11) reduces the PD-ratio in both complaint regions using Opt2. Opt1 reduces the PD-ratio's in both regions when on the same side of the phantom (regions 1 and 5). However, when opposite to region 1 (regions 8 and 16), a reduction is more difficult to achieve. Still though, in the regions

Figure 8: Results of the phantom test: Measured reduction on using weight factors with Opt1 (left) and Opt2 (right). Experiment numbers refer to the following experiments:



Experiment number	Experiment
1	Complaint in region 1, weight factor = 1
2	Complaint in region 5 weight factor = 1
3	Complaint in region 2, weight factor = 1
4	Complaint in region 6, weight factor = 1
5	Complaint in region 1, weight factor = 4
6	Complaint in region 5, weight factor = 4
7	Complaint in region 2, weight factor = 4
8	Complaint in region 6, weight factor = 4
9	Complaint in region 1 and 5, weight factor = 1 in both regions
10	Complaint in region 1 and 8, weight factor = 1 in both regions
11	Complaint in region 1 and 16, weight factor = 1 in both regions

Regions[1]

4	8	12	16
3	7	11	15
2	6	10	14
1	5	9	13

T

[1] The numbered regions in the square signify different regions in the body and T stands for centrally located tumor

opposite to region 1 (region 8 and 16), PD-ratio is lower than in experiment 1 (only a weight factor on region 1).

Accuracy of amplitude and phase settings and Monte Carlo analysis

The clinical value of HTP-guided steering is highly dependent on the accuracy of the equipment, i.e. the accuracy of the BSD amplitude and phase settings. Using a vector voltmeter, during the phantom test we measured an average deviation of amplitude of -0.01 with a standard deviation of 0.02.[16] The average deviation of phase measured was -5° with a standard deviation of 5° (phases of channel 1 are set to 0 as reference). The 95% confidence interval of the amplitude and phase deviation then is approximately [-0.05, 0.03] and [-15°, 5°].

To test how this deviation influences tumor PD in a calculated optimum, a Monte Carlo analysis is conducted on both Opt1 and Opt2. One hundred thousand random phase-amplitude combinations are generated, distributed uniformly around the optimum amplitude-phase combination within the found confidence intervals. For each amplitude-phase-combination, PD_{target}-ratio is calculated.

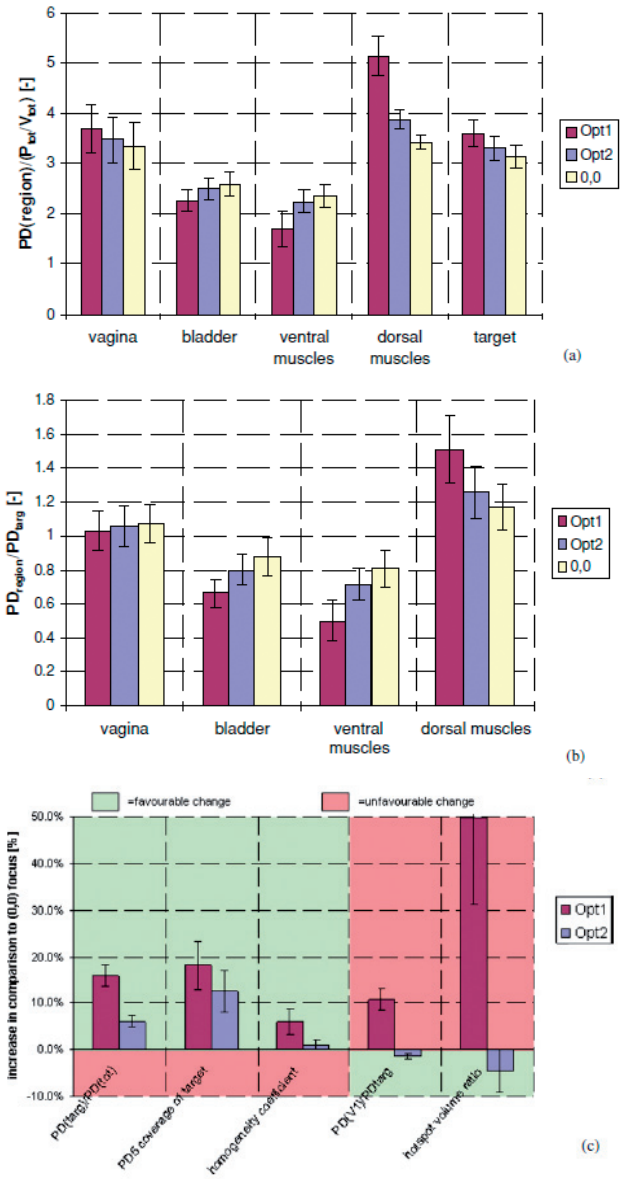
For Opt1 the calculated distribution of PD_{target}-ratio is within 2.5% of the optimum, while for Opt2 a distribution of PD_{target}-ratio within 2.9% of the optimum was found.

4.2 Results in patient models for Opt1 and Opt2

For the 10 patients treated using HTP-guided steering, the effectiveness of steering actions in different regions is theoretically evaluated using Sigma HyperPlan, and optimized settings were calculated using both Opt1 and Opt2. The results of modelling for both optimization routines are presented in figure 9, where PD-levels of Opt1, Opt2 and a central focus are compared, relative to PD_{tot} (figure 9a) and PD_{target} (figure 9b). In figure 9c various other quality indicators (see §3.5) are depicted.

Figure 9a and 9b show that PD levels are more equally distributed in Opt2 than when using Opt1, both absolute as well as relative to target PD. A central focus however, seems to lead to even more equally distributed PD-levels. Taking into account figure 9c, though, makes clear, that Opt2 is nevertheless advantageous over the central settings. PD_{target} is higher, $PD(_{V1})/PD_{target}$ (see eq. 4) is lower, a substantially larger part of the target is covered by the PD_5 contour, hotspot volume is smaller and homogeneity of the target is slightly higher. Opt1 has also some advantages over central focus, for example an increase of 16% in target PD compared to (0,0) settings. A serious drawback for this optimization routine, though, is the 50% higher hotspot volume. However, since hotspots in initial optimization of Opt1 are not taken into account, this is not surprising.

Figure 9: a) PD in regions normalised on PDtot b) PD in regions normalised to PDtarget and c) PD increase of various quality indications with respect to central target settings CCH



Using a vector voltmeter, we measure on average higher amplitudes in the top antennas and higher phase in the bottom antennas in Opt1(table 5).[16] This confirms the PD distribution from the model in figure 9 where PD is shifted more to dorsal in Opt1

Table 5: Measured difference Δ in amplitude (A) and phase(φ) between Opt1 and Opt2

A		Δ Opt1- Opt2	Standard deviation
	left	0.01	0.06
	bottom	0.14	0.06
	right	-0.12	0.04
	top	-0.32	0.08
φ			
	left	8	7
	bottom	27	5
	right	11	7
	top	3	4

Patient-specific models showed that reduction of PD-ratio in a complaint region is effective, which means that reduction in the region is larger than reduction in the target (figure 10). Similar to the phantom measurements (§ 3.1), PD in dorsal- and ventral abdominal muscles (peripheral) was relatively well reduced using weight factors, while the vagina region (adjacent to target) was less reduced. Opt1 generally reduced PD better than Opt2. However, reductions in Opt1 as well as Opt2 were in the same range when PD is normalized to PD_{target}. Moreover, Opt1 reduced PD_{target} with approximately 20%, while Opt2 hardly reduced PD_{target}. This is consistent with the findings in the phantom test in § 4.1. Finally, an increase of weight factors always led to an increased reduction in the complaint region.

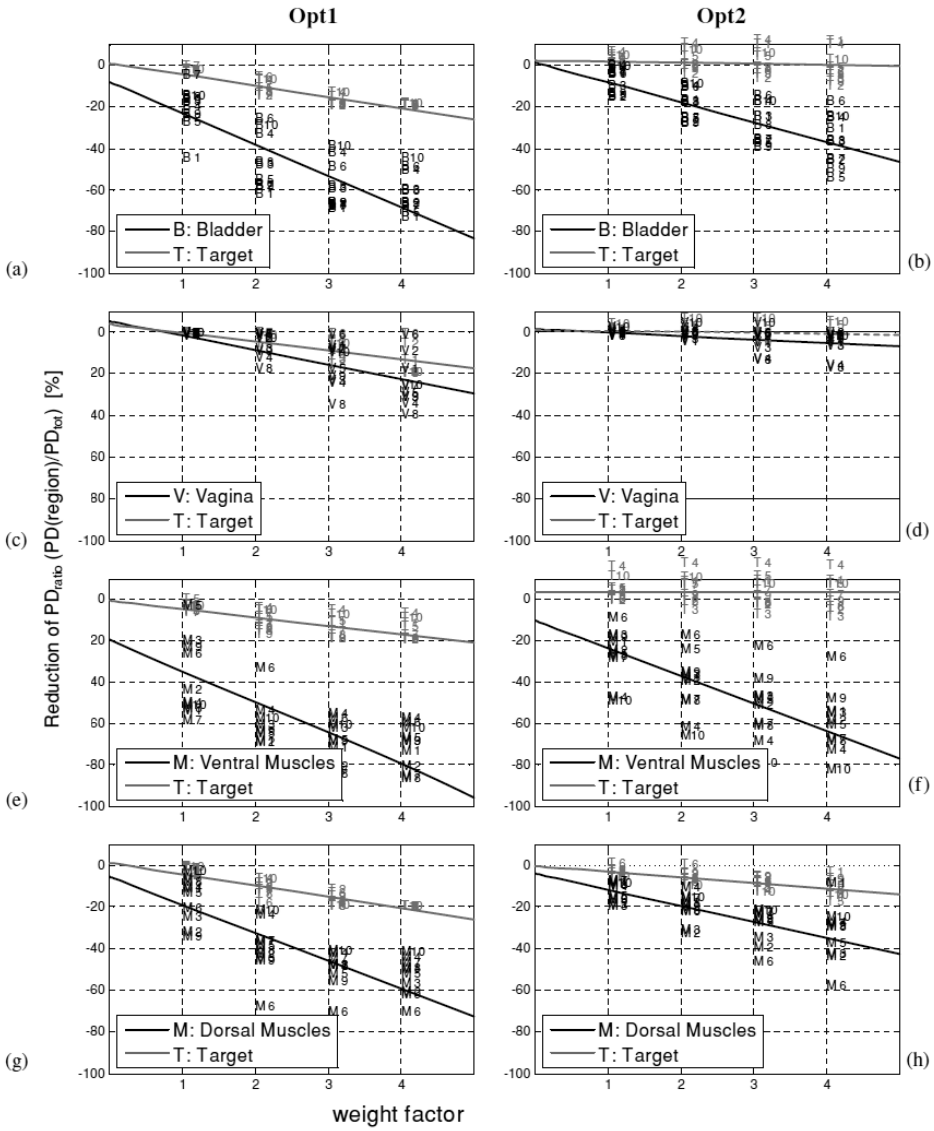
4.3 Treatment outcome and feasibility

Since the results of the phantom experiments were satisfactory, we also tested both Opt1 and Opt2 in clinical practice. Five patients were treated using Opt1 and another five using Opt2.

Using a number of precalculated settings for the most common complaints, a real-time response to complaints is possible. For rarely occurring complaints, settings are calculated during treatment, which takes approximately one minute. Treatment characteristics are represented in table 6.

For both Opt1 and Opt2, complaints mostly occur in the dorsal muscles, followed by the ventral muscles. All the rest of the regions are responsible for less than 15% of the complaints. Generally complaints disappear for a significantly longer time ($p=0.007$) using Opt2. Temperatures turn out to be generally well within the range (table 7), we normally obtain in DHT of patients with cervical carcinoma.[3] However, no significant differences between Opt1 and Opt2 are measured.

Figure 10: Results from the patient model sensitivity study. Reduction on complaints in the bladder (a and b), vagina (c and d), ventral muscles (e and f) and dorsal muscles (g and h) for Opt1 and Opt2.



An analysis of the powers during the steady state of the treatments (table 8) shows that average powers, maximal powers, the time of Pmax, and the power difference between begin and end of steady state, do not differ significantly between Opt1 and Opt2. Also the number and the total time of off-switches is not significantly different between Opt1 and Opt2. The variation in power level during the steady state however, is significantly larger for Opt1.

Table 6: Treatment characteristics of the two groups of 5 patients treated using either Opt1 or Opt2.

Evaluation criteria	Opt1 (± se)	Opt2 (± se)	p
Time between complaints (min)	4.8 ± 0.4	6.3 ± 0.4	0.007
Number of complaints during treatment	14 ± 1	11 ± 1	0.128
Complaint disappears for ≥ 10 min (%)	12 ± 3	20 ± 4	0.109
Complaint disappears for ≥ 5 min (%)	53 ± 5	67 ± 5	0.041
Location of complaints			
Dorsal muscles (%)	45 ± 5	57 ± 5	0.089
Ventral muscles (%)	36 ± 5	37 ± 5	0.799
Dorsal and ventral muscles (%)	5 ± 2	3 ± 2	0.579

se = standard error

Table 7: Temperature outcome for the two groups of 5 patients treated with respectively Opt1 and Opt2

	Opt1 (± se)	Opt2 (± se)	p
T90	39.3 ± 0.2	39.5 ± 0.2	0.167
T50	40.3 ± 0.2	40.1 ± 0.2	0.898
T20	40.9 ± 0.2	40.6 ± 0.2	0.609

Legend: T90 = temperature exceeded by 90 % of monitored sites in bladder, vaginal and rectal lumen together and averaged over all treatments per patient in ^{0}C, T50 = temperature exceeded by 50 % of monitored sites in bladder, vaginal and rectal lumen together and averaged over all treatments per patient in ^{0}C, T20 = temperature exceeded by 20 % of monitored sites in bladder, vaginal and rectal lumen together and averaged over all treatments per patient in ^{0}C. se = standard error

Table 8: Power during the steady state of the treatment for both Opt1 and Opt2

	Opt1(± se)	Opt2(± se)	p
Power (W)	801 ± 38	797 ± 49	0.94
ΔP_{SS} (W)	58 ± 7	31 ± 4	0.004
P-max (W)	885 ± 32	854 ± 51	0.61
Time P-max (min)	63 ± 5	61 ± 6	0.88
$P_{beginss}$-P_{endss} (W)	-93 ± 32	-47 ± 25	0.26
# off-switches	18 ± 2	16 ± 1	0.35
Total time off (min)	11 ± 1	9 ± 1	0.45

Legend: P = Power, ΔP_{SS} = variation in power during steady state, P-max = maximum power, Time P-max = time to maximum power, $P_{beginss}$-P_{endss} = difference between power at the beginning and end of steady state, # off-switches = number of off-switches. se = standard error

5. Discussion

In this study HTP-guided steering has shown to be applicable in clinical treatment optimization. This study is a first step in introducing HTP-guided steering during treatment. The results obtained in this study are quite specific, in terms of using one single applicator and a single frequency. However, in our opinion, the feasibility of this way of optimization can be extrapolated to all phased array applicators, used for loco-regional heating in the pelvic region. Regardless of the fact that other applicators may have different numbers of antennas and other frequency ranges, the optimization procedure presented in this

study should lead to an optimized distribution of powers. For applicators that use incoherent EM-waves (e.g. the superficial Lucite Cone applicators for superficial heating) other optimization variables might be needed with more emphasis on for example the power level of the different antennas.[17]

Although the validation of the Sigma HyperPlan model is mostly qualitative so far, it has been shown to be reliable. The research, reported in several studies showed good correlations between the Sigma HyperPlan model and measurements.[5, 18] The number of tetrahedra used in this study is in the same order as comparable studies.[19] When refining the model, we found that this number of tetrahedra was sufficient to converge to a correct solution. Furthermore, using more tetrahedra would lead to clinically unacceptable long calculation times.

The initial optimization routines were derived from the functions used in several studies by other institutes.[9-10, 15, 20-21] An advantage of this approach is the possibility of solving the optimization analytically, as an Eigen value problem. [22-23] This leads to short calculation times. However, this approach causes problem when using upper and lower bounds of amplitude. The initial optimization function (eq. 4) for Opt2 has similarities to the functions reported by other studies.[9, 15, 20] For practical reasons V_1 is chosen as a measure for hotspots, since the hotspot definition by Wust et al. makes the goal function highly nonlinear.[15] The complaint-induced part of the goal function is introduced equivalently to Opt1.

Hotspots contain a varying number of tetrahedra at different amplitudes and phases. This makes it impossible to solve the goal function of Opt2 analytically. Therefore a SQP (sequential quadratic programming) optimization method was used, that is far more time consuming than analytical solving.[24] However, when using the Sigma-60, optimization is still fast enough for use in clinical situations. Future research should investigate other optimization methods like genetic algorithms for possibilities in speed improvement. Also a deeper look into multi-objective optimization may offer benefits, using Pareto optimal sets to visualize the effect of using weight factors in advance.

For both optimization routines weight factors are used to change the goal function on complaints, instead of using fixed constraints. Fixed constraint steps of 10% in a region per weight factor was tested and appeared to over-constrain the optimization easily, especially when facing complaints in more regions. We assume that optimization of the PD-distribution and a subsequent increase of power as long as patient comfort is not endangered, provides maximum treatment results. A change of phases after adaptation of the optimization, could lead to a small change in applicator efficiency, i.e. the total absorbed power in the patient changes. However, based on patient complaints, the power

is increased or decreased to constantly remain at the maximum that the patient can tolerate. Therefore, this change of applicator efficiency during treatment should not influence the treatment quality. Including frequency in the optimization would be beneficial. However, with the current version of Sigma HyperPlan, this requires an E-field calculation for each frequency, which is at present too time-consuming in clinical practice.

In the phantom test setup, as described in § 3.3, Schottky diode sheets were used to measure the E-fields. These sheets provide only a limited spatial resolution and measure E-field only in the Z-direction. Considering the wavelength (approximately 45 cm at 77 MHz) however, the 2.5 cm interval of the diodes is sufficient to display the behavior of the E-field.

The results of the phantom test in § 4.1 clearly show that steering actions are effective in both optimization routines. Both routines reduce PD in complaint regions effectively if necessary. However, regions more peripheral to the target show a larger reduction of PD than regions adjacent to the target. In peripheral regions, Opt2 caused more PD-reduction in complaint regions than Opt1, while target PD was reduced less. In regions close to the target, Opt1 caused more PD-reduction in a complaint region than Opt2, but in most cases target PD was also reduced more in Opt1. For other regions than the complaint region or the target, Opt2 is generally more beneficial, since it prevents an increase of these regions that is larger than Opt1. This makes the net effectiveness of steering actions better for Opt2.

The phantom test also showed that deviations of amplitude and phase from the set value are similar to deviations found in Kongsli et al.[13] A Monte Carlo analysis showed that the influence of these deviations is only small.

The sensitivity study of 10 patients showed that Opt1 clearly has a disadvantage in terms of hotspot volume (figure 8c). The high value of PD in the dorsal muscles and the substantially larger hotspot volume while using Opt1, raised the question whether to use this optimization in clinic. However, in figure 8b the difference in PD in dorsal muscles between Opt1 and Opt2 is not significant, and we expect hotspot volume to be efficiently reduced after possible complaints. In terms of reduction after complaints, the findings in the sensitivity study confirm those of the phantom test, i.e. PD reduction is better in peripheral regions than in regions adjacent to the target for both Opt1 and Opt2. For Opt1 in most regions PD reduction is larger than for Opt2. The most likely cause of this difference is the fact that Opt1 shifts the focus regardless of hotspots elsewhere in the patient, thus being able of larger reductions in the complaint region. However, normalized to PD_{target} both Opt1 and Opt2 perform more or less equally. Often, it may be hard to achieve the power increase needed to compensate for reductions in PD_{target}, since steering

may induce new complaints. Opt2 has less possibilities of reduction, since new hotspots would immediately increase the goal function. This leads to more moderate reductions that are beneficial to PD_{target}. From these patient-specific models therefore Opt2 seems preferable above Opt1.

The results of the clinical treatments confirmed the result of the sensitivity study. Using Opt1, the majority of complaints appeared to occur in the dorsal muscles, closely followed by the ventral muscles, and was not easily solved with steering. Using Opt2, complaint locations again were situated mostly in the dorsal muscles, followed by the ventral muscles. Average time between complaints was significantly higher in Opt2 (6.3 vs. 4.8 minutes, p=0.007). Both Opt1 and Opt2 led to tumor temperatures within the therapeutic range with T50's of 40.3°C and 40.1°C, and both were equally feasible in terms of calculation times. An analysis of the powers used during steady state shows that only the variation in powers during steady state is larger in Opt1. The difference between Opt1 and Opt2 in the clinical settings is considered rather small, compared to the results we obtained in the phantom test. Only the complaint interval was found to be significantly different. On one side this can be caused by the small number of 5 patients in each group and a difference in the patient characteristics.[3] On the other hand, during treatment there were other variables that are yet to be controlled better, like for example patient positioning. This transition from HTP to clinic has to be controlled better, which current research is aimed at. However, considering the lower hotspot PD in the sensitivity model study and the longer complaint interval in the treatments, Opt2 is the best choice for HTP-guided steering.

In a currently running study, patients with primary cervical carcinoma are treated in the Sigma-60 applicator, using HTP-guided steering with Opt2 to test effectiveness of HTP-guided steering.

6. Conclusion

HTP-guided steering has proved to be feasible in terms of calculation times and effectiveness of PD-reduction in complaint regions. Moreover, tumor temperatures achieved in treatments using HTP-guided steering are well within the therapeutic range.

The performance of the optimization routines tested in clinical practice indicate that Opt2 is more effective than Opt1. The effectiveness of HTP-guided steering in terms of ability to improve tumor temperatures must be demonstrated in a specifically designed clinical study.

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Chapter 8

Clinical implementation of hyperthermia treatment planning guided steering: a cross over trial to assess its current contribution to treatment quality

Franckena M, Canters RAM, Termorshuizen F, van der Zee J and van Rhoon GC. Clinical implementation of hyperthermia treatment planning guided steering: a cross over trial to assess its current contribution to treatment quality. Int J Hyperthermia, 2010; 26:145-157.

Abstract

Purpose: To assess the current feasibility and its contribution of online hyperthermia treatment planning guided steering (HGS) to treatment quality in deep hyperthermia for locally advanced cervical cancer in a cross over trial.

Materials and methods: 36 patients were randomized to receive either their 2nd and 4th (arm A) or their 3rd and 5th (arm B) hyperthermia treatment of the series with the aid of HGS. The other treatments were conducted according to our empirical steering guidelines (RESG or Rotterdam Empirical Steering Guidelines).

Results: During period I (2nd and 3rd treatment of the series) similar results were found for HGS and RESG with a slight, non-significant difference found in favor of HGS. The average temperature (T50) was 40.3 ^{0}C for both ($p = 0.409$) and the dose parameter CEM43T90 was 0.64 for RESG and 0.63 for HGS ($p = 0.154$). However, during period II (4th and 5th treatment of the series) HGS performed less well, with significant lower thermal dose parameters, minimum, mean and maximum intraluminal temperatures, acute toxicity measures and net integrated power. T50 was 40.4 ^{0}C after RESG and 40.0 ^{0}C after HGS ($p = 0.001$) and CEM43T90 0.57 and 0.38 ($p = 0.01$) respectively.

Conclusion: We found that the procedure of online treatment planning guided steering is feasible. For maximal exploitation of its possibilities, however, better control and understanding of several patient, tumor and technical parameters is required. This study has been very helpful in identifying some of the challenges and flaws that warrant further investigation in the near future, such as patient positioning and the prevention of hotspot- related complaints. With the progress that has been made during this study, we hope to perfect the principle of hyperthermia treatment planning guided steering in the near future. The progress that has been made during this study in the objective-based procedure for SAR (Specific Absorption Rate) steering is already of great value to exploit the more advanced SAR steering opportunities of the Sigma-Eye applicator.

Introduction

In the Netherlands, combined radiotherapy (RT) and deep hyperthermia (DHT) has been part of regular health care for patients with locally advanced cervical cancer (LACC) since 1996. Several randomized trials showed that the addition of deep hyperthermia to radiotherapy improves local control and survival for these patients and most recently we demonstrated a 5-year local control rate of 53 %.[1-8] Not withstanding this encouraging result in a group of patients with relative poor prognosis, i.e. large primary tumors, there is still ample room for further improvement of treatment outcome and we should continue to search for better treatment strategies.[9-10]

In this perspective, the finding of a significant correlation between the thermal dose delivered during treatment and patient outcome in a group of 420 patients with LACC treated with radiotherapy and deep hyperthermia clearly opens a window for further research.[11] This thermal dose-effect implies that better results should be obtained when higher thermal dose levels can be delivered. Obviously, the most elegant possibility to increase the thermal dose delivered is to aim for more tumor-selective and patient-specific heating than is currently achieved.

At present, most deep hyperthermia treatments are applied empirically, i.e. experience and dedication of the treatment team plays a major role in the final treatment quality. In general, the occurrence of hotspots, or areas of discomfort to the patient due to uncomfortable temperatures locally, limit temperatures achieved during hyperthermia.

Commonly, the strategy to manage hotspots is to apply a short break in the power applied, followed by adjustment of phase and amplitude settings to the antennas in order to steer the energy away from the hotspot. The precise approach of this strategy and thereby its effectiveness varies from center to center. Of course, a more objective approach would be preferable as it would allow a more systematic strategy and would also enable transfer of knowledge between centers and education of new staff. If the clinical application of such a systematic strategy were useful and effective, it would mean a major step forward. For the first time in the history of hyperthermia standardization, improvement of treatment quality, a priori assessment of potential quality of treatment and better treatment quality in centers new to the field can be expressed as an objective quality index. For these reasons a hyperthermia treatment planning system is considered a great aid as hyperthermia treatment planning can help us better understand the effects of phase and amplitude adjustments on power and temperature distribution and even predict the effect of the adjustments during treatment.[12-15] Consensus exists that the combination of Hyperthermia treatment planning with optimization of treatment settings to maximize

power deposition in the tumor and minimize hotspots, will improve temperatures in deep hyperthermia.[16]

The use of a hyperthermia treatment planning is becoming common practice in hyperthermia, but for its online use during treatment an optimization routine is necessary that not only optimizes power deposition in the tumor, but also reduces deposition in a complaint-related area (hyperthermia treatment planning guided steering, or HGS).[12-20] Although not yet demonstrated in a clinical situation, the development of HGS for standardization and improvement of treatment quality is a very important step in the further development of hyperthermia. Such a strategy would promote uniformity of treatment quality and comparison of treatments among the various institutes applying deep hyperthermia. On the other hand, the preparation process is time-consuming and labor intensive and our current treatment approach (i.e. following the Rotterdam Empirical Steering Guidelines or RESG) proved its effectiveness in several clinical trials.[14] Further, the RESG are based on decades of clinical experience and it will be difficult to improve its results with a new technique that has never been used in a clinical setting before. As a first step, we designed a clinical trial to compare the two treatment approaches in terms of temperatures achieved during treatment, thermal dose delivered and acute toxicity. This study provides us with an assessment of the current status and performance of HGS in a clinical situation and show how clinical results compare to our golden standard of the RESG.

Materials and methods

Clinical background

For patients with LACC, 5 hyperthermia treatments of 90 minutes each are planned for each patient during the period of external beam radiotherapy. For all hyperthermia treatments in this study, the BSD-2000 3D system (BSD Medical Corporation, Salt Lake City, Utah, USA) was used with the Sigma-60 applicator.[21-23] The standard operating frequency of the Sigma-60 is 77 MHz. The treatment is started at a power output of 400 Watts and was increased with steps of 100 Watts for every 5 minutes as long as the patient has no hotspot-related complaints or normal tissue temperatures do not exceed 43 ^{0}C. In case of hotspot-related complaints or normal tissue temperature > 43 ^{0}C, the power is briefly turned off until the discomfort subsides or temperature is below 43 ^{0}C, and phase, amplitude or frequency settings are adjusted to prevent recurrence. The further increase of power is not resumed until a complaint-free period of 5 minutes has been established.

These principles were maintained over all treatments in this study. For a detailed description of the procedure and its rationale we refer to the paper of Van der Wal et al.[14]

Study design

For this study, all patients with LACC and an indication for deep hyperthermia were eligible if thermometry could be performed in bladder, vagina and rectum. After informed consent, patients were randomized to receive either the 2nd and 4th or the 3rd and 5 th hyperthermia treatment with HGS. A cross-over design was chosen because interpatient variation was observed to be larger than the intrapatient variation as we learned from previous data.[9] Further, as the effect of a hyperthermia treatment on intraluminal temperatures is short lived, it is unlikely that the outcome of a previous treatment influences the outcome of a consecutive treatment (i.e. probably no carry over effect). To account for the influence of progression of the treatment series on patient tolerance, both treatments were repeated per individual patient.The first treatment was excluded from the study in order to allow the patient to become acquainted with the principles of the hyperthermia treatment and equipment.

Primary endpoints for this study were temperature, thermal dose and treatment-limiting hotspots. For temperature, we chose to use the T20 (the temperature exceeded by 20% of monitored sites per patient in bladder, vagina and rectum), T50 (temperature exceeded by 50% of monitored sites per patient in bladder, vagina and rectum) and T90 (temperature exceeded by 90% of monitored sites per patient in bladder, vagina and rectum). For thermal dose, we chose CEM43T90 (cumulative equivalent minutes of T90 at 43 ^{0}C as described by Fatehi et al.) and TRISE (a custom made thermal dose parameter based on T50 and the duration of heating).[24] This second parameter has been shown retrospectively to correlate very well with treatment outcome in our patient group.[11]

For treatment-limiting hotspots, we chose the number of off-switches (NOS), the total duration of off-switches (DOS) and the time from start of treatment to first complaint (TTFC) as measures. An off-switch is defined as turning off the power of the BSD-2000 system longer than 20 seconds to reduce a hotspot-related complaint. Shorter off-switches are mostly caused by hyperthermia staff entering or leaving the treatment room and do not effect the intraluminal temperature profile during treatment.

Further we chose the net integrated power as described by Fatehi et al. as a secondary outcome measure, because an increase in net integrated power is expected to be accompanied by an increase in target temperature.[16, 24]

Temperature and thermal dose data preparation

For thermometry, Bowman probes (BSD Medical Systems, Salt Lake City, Utah, USA) were placed in 5 French polyethylene closed-tip catheters (William Cook Europe ApS, Bjaeverskov, Denmark). These closed-tip catheters were placed in the patient's rectal, vaginal and bladder lumen. The rectal thermometer was inserted to a maximum insertion depth of 15 cm and the vaginal thermometer is inserted until the tip touches the cervix. The bladder thermometer is inserted alongside a urine catheter. The tips of both the urine catheter and the thermometer reach 4 cm inside the bladder; this insertion depth is fixed because a balloon is inflated after insertion to keep the urine catheter in place. The insertion depths are checked using a tape measure after they are inserted and reproduced during consecutive treatments of the same patient.

Current treatment approach using the RESG [14]

Preparation: Currently, all patients are positioned in the same way in the Sigma-60 applicator in the anterior-posterior and lateral directions. The preferred craniocaudal position is derived from the CT (Computed Tomography)-scan made for radiotherapy treatment planning. From this CT-scan the distance from the center of the tumor to a bony landmark, in this case the pubic bone is calculated. The patient is positioned so that the center of the pelvis is in the center of the Sigma-60 applicator. In the craniocaudal direction, the patient is positioned such that the tumor center is located 4 cm caudal to the center of the Sigma-60 applicator. The start-up settings for phase and amplitude are the same for every patient, namely (0,0) for phase and 100% amplitude for all BSD channels.

Optimization during treatment: The RESG state that in case the patient has a hotspot-related complaint, the preferred order of steering actions is: phase steering (in 2 cm steps), amplitude steering (in 20 % steps) and finally frequency steering (in 10 MHz steps). In addition, phase steering is thought to be more appropriate in case of pressure-like, deep-seated complaints and amplitude steering in case of burning, superficially located sensations. For example, when a patient complains of uncomfortable pressure on the abdomen, the phase is shifted 2 cm to the back and when a patient complains of a burning sensation to the buttocks, the amplitude of the dorsal BSD antenna is lowered with 20 %. The power is only lowered when phase, amplitude and frequency steering proved ineffective. Besides avoiding and diminishing hotspot-related complaints, we also aim for a homogeneous intraluminal temperature distribution during treatment by means of phase and amplitude steering.[14]

Treatment approach using hyperthermia treatment planning guided steering (HGS)

Preparation: Prior to the first hyperthermia treatment, a CT-scan was made of each patient lying in hyperthermia treatment position which is identical to the position in the Sigma-60 applicator, i.e. in a BSD sling system specially mounted on the CT-scanner for the hyperthermia treatment planning CT-scans. All CT-scans were made using a multislice CT-scanner (Siemens Somatom Sensation Open, Siemens Medical Solutions USA Inc., Malvern, Pennsylvania, United States) with a slice distance of 0.5 cm. The scanned length of the patient had to be at least 80 cm to cover the length of the Sigma-60 cm with 10 cm extra at each end (cranial and caudal). The methods employed for hyperthermia treatment planning have been described elsewhere in detail.[12-13, 20, 26] After resampling the CT-data to 256 x 256 x 80 pixels, the following tissue types were segmented: tumor, muscle, fat, bone, liver, spleen, kidney, heart, lung, uterus, intestine, stomach, bubbles of air in the bowel system and vagina. Note that we segmented the actual anatomy instead of taking a single permittivity and conductivity as an average for the whole intestine in the pelvic region. The large vessels were not segmented separately but as muscle because of the lack of specific perfusion information and the fact that SAR and not temperature optimization was performed. The permittive and conductive properties assigned to the specific tissue types were derived from Gabriel et al. and are described in table 1 .[27] Segmentations were performed by an experienced physician (MF) who did all segmentations in order to promote uniformity. After construction of a tetrahedral model, the SAR distribution inside the patient was calculated using the finite element method (FEM)-module of Sigma HyperPlan (Dr. Sennewald Medizintechnik GmbH, Munich, Germany). Then this SAR distribu-

Table 1: Dielectric parameters used for treatment planning [27,32]

Tissue	ε_r	σ (S/m)	ρ (kg/m³)
Fat	13	0.07	900
Muscle	69	0.70	1000
Bone	16	0.06	1600
BSD sling support rods	1	0	1000
Target	69	0.70	1000
Bladder	24	0.29	1000
Heart	99	0.70	1000
Intestine	108	1.62	1000
Kidney	109	0.77	1000
Liver	75	0.46	1000
Lung	35	0.71	500
Spinal cord	6	0.04	1000
Spleen	101	0.77	1000
Stomach	82	0.89	1000
Uterus	69	0.70	1000
Vagina	69	0.70	1000

tion was optimized using a custom-made complaint adaptive power density optimization tool providing us with patient-specific optimal treatment settings to start a treatment.[20]

Patient positioning: For patient positioning during HGS treatments, the preferred craniocaudal position was derived from the CT-scan made for hyperthermia treatment planning similar to the currently used method. The anterior-posterior distances of the patient's contour to the water bolus were measured in the Sigma HyperPlan model and, as accurately as possible (preferably <1 cm)[12, 17, 28] reproduced in the clinical setting using 2 ultrasound measurement probes integrated in the Sigma-60 ring. Before the first HGS-treatment, an initial SAR optimization was performed, providing us with patient-specific start-up settings for phased and amplitudes.

Optimization during treatment: During the HGS treatments hotspot-related complaints reported by the patient were dealt with similar to the RESG. That is, power was turned off until the patient was comfortable again and then power was turned back on with the adjusted treatment settings; the exact amplitude and phase settings were dictated by custom-made optimization software.[20] We needed to define specific hotspot-related regions in the model to allow for the limitation of SAR in that specific region, while still optimizing SAR in the tumor region. In case of a hotspot-related complaint in the abdomen, a constraint was assigned to the ventral abdominal muscles and new treatment settings were calculated with optimal power delivery to the tumor and minimal power to the ventral abdominal muscles. Homogeneity of measured intraluminal temperatures was not a goal during these treatments.

Statistical analysis

Prior to the start of the study, a power analysis showed that 36 patients would be needed to show a 0.3 ^{0}C difference in temperature measures with this double cross over design with a power (1-ß) of 80 % and a significance level (α) of 95 %.

First, we compared treatment parameters between the arms of the study using a T-test for two independent samples (comparison 1). This was done separately for period I (the 2nd and 3rd treatment) and II (the 4th and 5th treatment). The aim of this analysis was to assess whether a carry-over effect was present. In case no carry-over effect was present (i.e., no difference between the two randomization arms), the data were analyzed according to the cross over design of the study.[29] If a carry-over effect was present, the data should be analyzed according to a standard parallel group design, i.e. restricted to the first episode of period I cq II.

According to the cross-over design, we compared the patient's first RESG-treatment with the patient's first HGS treatment and the patient's second RESG-treatment to the patient's second HGS-treatment using a paired T-test, disregarding the arm of randomization (comparison 2).

To test whether effect estimates differ between period I and II, a regression model was designed with treatment (RESG vs. HGS), and period (I vs. II) as covariates and an additional term for interaction between treatment and period (comparison 3).

For all statistical analyses, STATA version 10.1 was used (StataCorp, Texas, United States). P-values below 0.05 were considered significant. For comparison 3, the possible correlation between measurements from the same patient in the course of her treatment was taken into account by including a random effect for the intercept in the models. This was done by using the xtmixed regression module of STATA.[30]

Results

Patient- and tumor characteristics of the 36 patients included in this study are summarized in table 2. No significant differences were observed between the 2 arms as assessed using a T-test.

One patient did not receive any HGS-treatments because of a rapid deterioration of her clinical condition during treatment due to gastro-intestinal toxicity. In table 3, the model properties for each of the 35 remaining patients are summarized.

In table 4, the various outcome measures of this study are reported by type of treatment (RESG or HGS) for periods I and II and for arm A and B separately.

Table 2: Patient and tumor characteristics

		Arm A	Arm B
FIGO stage	IB2	1 (5 %)	3 (19 %)
	IIA	0 (0 %)	1 (6%)
	IIB	6 (30 %)	3 (19 %)
	IIIA	2 (10 %)	1 (6 %)
	IIIB	6 (30 %)	1 (6 %)
	IVA	2 (10 %)	3 (19 %)
	IVB	3 (15 %)	4 (25 %)
WHO-PS	0	12 (65 %)	10 (69 %)
	1	7 (35 %)	5 (18 %)
	2	0 (0%)	2 (13 %)
Lymph node status	Nx	9 (45 %)	4 (25 %)
	N0	3 (15 %)	7 (44 %)
	N1	8 (40 %)	5 (31 %)
Age (years)	Mean (range)	60 (30 – 84)	55 (35 – 79)

Legend : Arm A = 2nd and 4th hyperthermia treatment of the series with the aid of hyperthermia treatment planning guided steering (HGS), Arm B = 3rd and 5th hyperthermia treatment of the series with the aid of HGS, FIGO = International Federation of Gynecology and Obstetrics, WHO-PS = World Health Organisation Performance Status, Nx = lymph node status unknown, N0 = no pathological lymph nodes detected, N1 = pathological lymph nodes detected

Table 3: Average model properties for all 35 patients who received HGS treatments

Patient	Number of tetrahedra	Maximum edgelength of a tetrahedron		Minimum edgelength of a tetrahedron		Tetrahedra volume	
		Mean(cm)	SD (cm)	Mean(cm)	SD (cm)	Mean(cm^3)	SD(cm^3)
1	219262	3.48	1.97	1.81	1.14	4.13	10.18
2	234484	3.63	2.15	1.92	1.25	5.01	12.00
3	212570	3.80	2.14	2.01	1.24	5.31	12.00
4	197587	3.47	1.86	1.82	1.08	3.86	9.47
5	200939	3.51	1.98	1.84	1.15	4.22	10.19
6	198775	3.56	2.00	1.87	1.16	4.37	10.50
7	201501	3.45	1.92	1.80	1.12	3.94	9.69
8	182699	3.47	1.82	1.81	1.06	3.71	8.83
9	206770	3.36	1.83	1.75	1.07	3.58	9.04
10	223556	3.33	1.88	1.75	1.08	3.65	9.36
11	207982	3.26	1.71	1.69	1.00	3.13	8.05
12	200855	3.54	2.00	1.87	1.16	4.36	10.37
13	198907	3.30	1.76	1.72	1.03	3.30	8.33
14	201024	3.44	1.87	1.80	1.10	3.85	9.57
15	207030	3.48	1.96	1.82	1.15	4.15	10.07
16	233736	3.15	1.88	1.64	1.09	3.31	8.79
17	240469	3.25	1.97	1.69	1.15	3.73	9.84
18	353697	2.52	1.65	1.29	0.93	1.98	6.74
19	283914	2.70	1.73	1.38	1.00	2.33	7.17
20	250641	2.89	1.69	1.47	0.99	2.47	7.10
21	204519	3.29	1.80	1.72	1.05	3.38	8.58
22	296232	2.65	1.78	1.37	1.02	2.35	7.43
23	278368	2.95	1.89	1.50	1.10	3.00	8.71
24	266723	2.85	1.77	1.44	1.03	2.58	7.53
25	275863	2.88	1.81	1.46	1.06	2.72	7.97
26	259504	2.98	1.83	1.52	1.08	2.94	8.29
27	268183	2.94	1.80	1.49	1.06	2.80	8.12
28	268499	2.84	1.80	1.44	1.06	2.66	7.81
29	301996	2.87	1.88	1.45	1.10	2.90	8.73
30	366561	2.58	1.75	1.35	0.99	2.30	7.67
31	273816	3.11	1.92	1.58	1.12	3.33	9.35
32	302384	2.64	1.77	1.36	1.01	2.34	7.39
33	269534	2.94	1.76	1.49	1.03	2.71	7.84
34	288728	2.88	1.72	1.46	1.01	2.55	7.66
35	366685	2.62	1.63	1.37	0.92	2.11	7.11
Average over all patients:							
	246391	3.15	1.85	1.63	1.08	3.32	8.83

Comparison 1 : Cross over effect

In table 4 p-values in the 5th and 8th column (both marked with ∞) represent the significance levels for the differences between arm A and arm B. So we can conclude that no carry over. effect is present in this study as the differences between arm A and arm B are insignificant.

Table 4: Estimate (standard deviation) for the outcome measures per arm of the study

Period I					Period II		
Variable		RESG	HGS	total	RESG	HGS	total
Duration	Arm A	88.2 (8.3)	89.5 (1.7)	88.8 (6.0)	88.4 (6.0)	90.0 (0.9)	89.0 (4.3)
(min)	Arm B	86.6 (8.9)	89.7 (1.2)	88.1(6.5) ∞ 0.6218	86.94 (7.8)	85.9 (13.0)	86.5 (10.5) ∞0.1626
	total	87.3 (8.6)	89.5 (1.6)‡ 0.1445	88.5 (6.2)	87.7 (6.9)	88.1 (8.6) ‡ 0.7508	87.9 (7.7)
CEM43T90	Arm A	0.61 (0.80)	0.73 (0.64)	0.67 (0.71)	0.55 (0.53)	0.42 (0.42)	0.48 (0.48)
(min)	Arm B	0.69 (1.10)	0.55 (0.48)	0.62 (0.85) ∞0.7853	0.64 (0.44)	0.33 (0.31)	0.49 (0.41) ∞0.9826
	total	0.64 (0.94)	0.65 (0.57)‡ 0.9110	0.65 (0.77)	0.57 (0.48)	0.38 (0.37) ‡ 0.0124	0.49 (0.45)
TRISE	Arm A	3.33 (0.92)	3.40 (0.63)	3.37 (0.78)	3.22 (0.83)	2.97 (0.80)	3.10 (0.81)
(^{0}C)	Arm B	2.98 (0.80)	3.22 (0.67)	3.10 (0.73) ∞0.1493	3.34 (0.71)	2.78 (0.73)	3.08 (0.76) ∞0.9149
	total	3.17 (0.89)	3.33 (0.64)‡ 0.1544	3.25 (0.77)	3.26 (0.77)	2.89 (0.76) ‡ 0.0044	3.09 (0.79)
T20	Arm A	40.9 (0.8)	40.9 (0.7)	40.9 (0.7)	40.9 (0.8)	40.6 (0.8)	40.7 (0.8)
(^{0}C)	Arm B	40.7 (0.9)	40.8 (0.7)	40.7 (0.8) ∞0.2741	41.0 (0.8)	40.4 (0.7)	40.7 (0.8) ∞0.9385
	total	40.8 (0.9)	40.9 (0.7) ‡ 0.6452	40.8 (0.8)	40.9 (0.8)	40.5 (0.8) ‡ 0.0006	40.7 (0.8)
T50	Arm A	40.4 (0.8)	40.4 (0.6)	40.4 (0.7)	40.3 (0.8)	40.0 (0.8)	40.1 (0.8)
(^{0}C)	Arm B	40.1 (0.9)	40.2 (0.7)	40.2 (0.8) ∞0.2499	40.5 (0.7)	39.9 (0.6)	40.2 (0.7) ∞0.6547
	total	40.3 (0.9)	40.3 (0.7) ‡ 0.4093	40.3 (0.8)	40.4 (0.8)	40.0 (0.7) ‡ 0.0009	40.2 (0.8)
T90	Arm A	39.5 (0.8)	39.7 (0.6)	39.6 (0.7)	39.4 (0.8)	39.2 (0.8)	39.3 (0.8)
(^{0}C)	Arm B	39.4 (0.8)	39.5 (0.7)	39.4 (0.8) ∞0.4203	39.7 (0.6)	39.1 (0.6)	39.4 (0.6) ∞0.5859
	total	39.4 (0.8)	39.6 (0.6) ‡ 0.1033	39.5 (0.7)	39.5 (0.7)	39.2 (0.7) ‡ 0.0051	39.4 (0.7)
NOS	Arm A	13.2 (5.2)	15.3 (6.9)	14.2 (6.1)	13.8 (4.9)	16.1 (6.1)	14.9 (5.6)
	Arm B	14.0 (5.5)	14.3 (6.4)	14.1 (5.9) ∞0.9469	14.2 (6.7)	18.6 (6.8)	16.3 (7.0) ∞0.3528
	total	13.6 (5.3)	14.9 (6.6) ‡ 0.2754	14.2 (6.0)	14.1 (5.7)	17.1 (6.4) ‡ 0.0245	15.5 (6.2)
DOS	Arm A	8.4 (3.7)	10.5 (4.9)	9.4 (4.4)	8.9 (3.1)	12.6 (6.4)	10.8 (5.3)
(min)	Arm B	8.8 (3.9)	10.8 (5.8)	9.7 (5.0) ∞0.7770	7.5 (4.1)	12.6 (4.8)	10.0 (5.1) ∞0.5328
	total	8.5 (3.8)	10.6 (5.3) ‡ 0.0300	9.6 (4.6)	8.3 (3.6)	12.6 (5.7) ‡ 0.0002	10.4 (5.2)

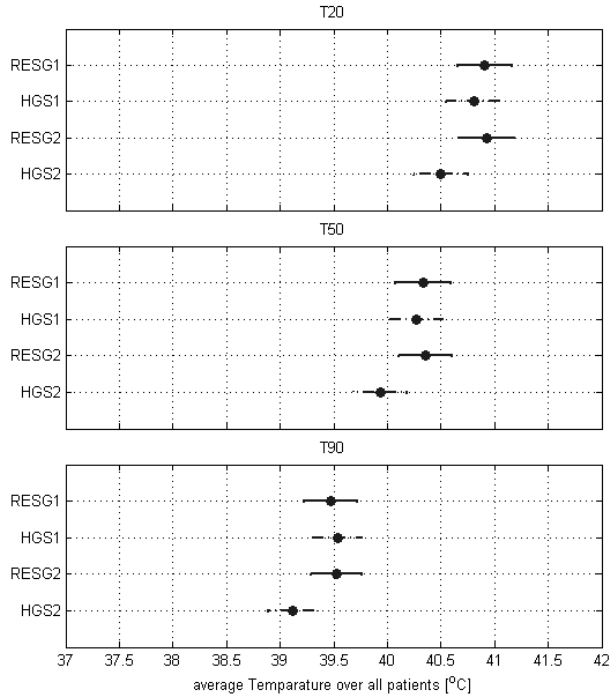
continued

Period I					Period II		
Variable		RESG	HGS	total	RESG	HGS	total
TTFC	Arm A	26.4 (11.2)	28.8 (11.1)	27.6 (11.1)	24.9 (10.3)	28.2 (14.7)	26.6 (12.6)
(min)	Arm B	25.6 (13.3)	22.6 (8.9)	24.2 (11.3) $\infty^{0.2106}$	22.5 (9.7)	20.5 (6.2)	21.5 (8.1) $\infty^{0.0591}$
	total	26.0 (12.2)	26.1 (10.5) ‡ 0.9890	26.0 (11.2)	23.8 (10.1)	24.8 (12.2) ‡ 0.6455	24.3 (11.1)
NIP	Arm A	3028 (651)	2972 (504)	3000 (575)	3051 (486)	2776 (480)	2913 (497)
(kJ)	Arm B	2890 (692)	3009 (601)	2948 (642) $\infty^{0.7166}$	2919 (548)	2602 (695)	2766 (633) $\infty^{0.2741}$
	total	2941 (655)	2988 (539) ‡ 0.6080	2977 (601)	2987 (517)	2702 (579) ‡ 0.0002	2849 (561)

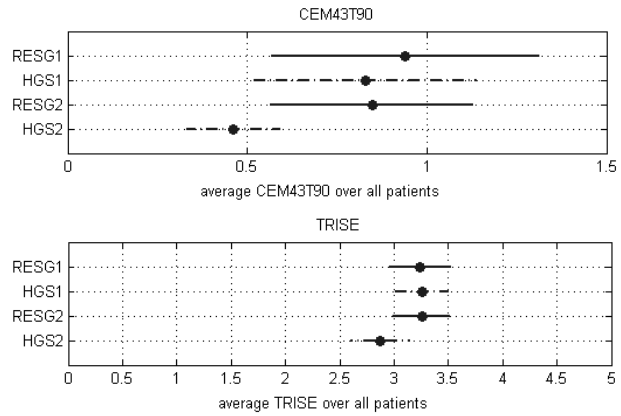
Legend: Period I = first part of hyperthermia treatment series, i.e. treatments 2 and 3, Period II = second part of hyperthermia treatment series, i.e. treatments 4 and 5, RESG = currently used treatment approach following the Rotterdam Empirical Steering Guidelines[14], HGS = treatment approach using Hyperthermia treatment planning Guided Steering, Duration = overall duration of treatment, CEM43T90 = cumulative equivalent minutes of T90 at 43 ^{0}C as described by Fatehi et al.[25] TRISE = a local custom-made thermal dose parameter based on T50 and the duration of heating[11], T20 = temperature exceeded by 20 % of the monitored sites in bladder, vagina and rectum, T50 = temperature exceeded by 50 % of the monitored sites in bladder, vagina and rectum, T90 = temperature exceeded by 90 % of the monitored sites in bladder, vagina and rectum, NOS = number of off-switches during treatment, indicating the amount of treatment-limiting hot spots, DOS = duration of off-switches during treatment, indicating the severity of treatment-limiting hot spots, TTFC = time to first complaint, or duration from start of treatment until the patient has her first hot spot related complaint, indicating the quality of optimization, NIP = Net Integrated Power as described by Fatehi et al.[25] , ‡ = p-value for comparison of RESG vs HGS, disregarding the arm of the study, ∞ = p-value for comparison of arm 1 vs arm 2, disregarding the number of the treatment

Figure 1: Outcome per period and per treatment type (with 95 % confidence intervals)

a) temperature measures



b) thermal dose parameters



Legend: Period I = first part of hyperthermia treatment series, ie treatments 2 and 3,Period II = second part of hyperthermia treament series, ie treatments 4 and 5 RESG1 = currently used treatment approach following the Rotterdam Empirical Steering Guidelines[14] during period I, HGS1 = treatment approach using Hyperthermia treatment planning Guided Steering during period II, RESG2 = currently used treatment approach following the Rotterdam Empirical Steering Guidelines[14] during period I, HGS2 = treatment approach using Hyperthermia treatment planning Guided Steering during period II, CEM43T90 = cumulative equivalent minutes of T90 at 43 ^{0}C in minutes as described by Fatehi et al.[24], TRISE = a local custom-made thermal dose parameter based on T50 and the duration of heating in ^{0}C[11], T20 = temperature exceeded by 20 % of the monitored sites in bladder, vagina and rectum, T50 = temperature exceeded by 50 % of the monitored sites in bladder, vagina and rectum, T90 = temperature exceeded by 90 % of the monitored sites in bladder, vagina and rectum

Comparison 2 : RESG versus HGS effect

In table 4, the p-values in the 4th and 7th column (both marked with ‡) represent the significance levels for the differences in treatment outcome measures between RESG and HGS, irrespective of whether the treatments were performed in arm A or arm B.

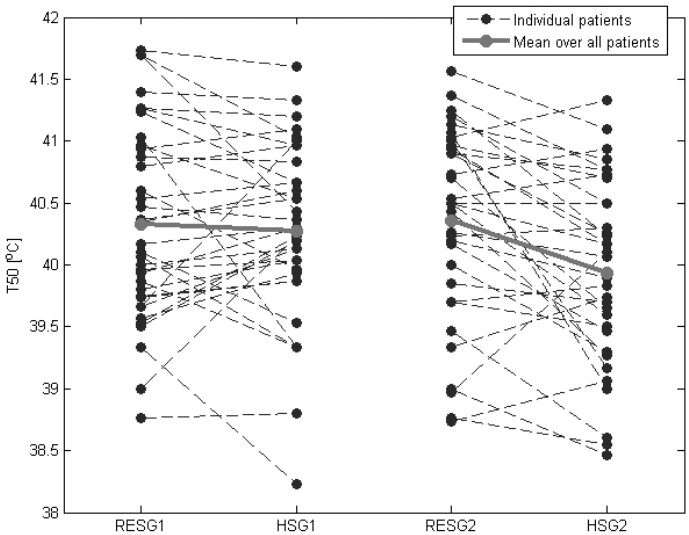
In period I only the duration of off-switches is significantly longer in the HGS-treatments with a difference of 2.1 minutes (p = 0.03), indicating less efficient coping with hotspot-related complaints during HGS-treatments. Further, there were favorable trends towards longer duration of treatment (87.3 min for RESG and 89.5 min for HGS, p = 0.14), lesser number of off-switches (13.6 for RESG and 14.9 for HGS, p = 0.28), higher net integrated power (2941 kJ for RESG and 2988 kJ for HGS, p = 0.61) and higher TRISE (3.17 ^{0}C for RESG and 3.33 ^{0}C for HGS, p = 0.15) during HGS-treatments, although these trends were not significant (table 4, figure 1).

The analysis for period II shows a different picture. The HGS-treatments in the second period show significantly lower thermal dose (figure 1, table 4). The average CEM43T90 was 0.57 min for the RESG-treatments in period II and 0.38 for the HGS-treatments in that period (p = 0.01, table 4). For the average TRISE, a similar significant difference was found; 3.26 ^{0}C for RESG-treatments and 2.89 ^{0}C for HGS-treatments in period II (p = 0.00, table 4). Further, intraluminal temperatures were significantly lower in period II (T20 with a 0.4 ^{0}C difference, T50 with 0.4 ^{0}C and T90 with 0.3 ^{0}C, figure 1). Figure 1 illustrates the differences in thermal dose and temperature measures per period and per treatment type. It becomes clear that although the differences are statistically significant, their clinical relevance may be minimal. Figure 2 illustrates the variation in T50 per period and per patient and it shows that there is considerable variation between patients; some do worse with HGS compared to RESG, and some do better. Acute toxicity seems less well handled in period II (number of off-switches was increased by 3, duration of off-switches was prolonged with 4.3 minutes, p = 0.02 and 0.00 respectively) and net integrated power decreased (279 kJ more was administered during RESG-treatments).

Comparison 3 : Differences between treatment period and type of treatment

The interaction between treatment period and type of treatment is significant for TRISE (p = 0.001), T20 (p = 0.002), T50 (p = 0.001) and T90 (p = 0.001), indicating a significant difference in the effect of HGS vs RESG between period I and period II. This is in accordance with the results of comparison 2, where the effects of HGS and RESG during period I and II are analysed separately.

Figure 2: T50 per period and per treatment type, interpatient variation



Legend: RESG1 = currently used treatment approach following the Rotterdam Empirical Steering Guidelines[14] during period I, HGS1 = treatment approach using Hyperthermia treatment planning Guided Steering during period I, RESG2 = currently used treatment approach following the Rotterdam Empirical Steering Guidelines[14] during period II, HGS2 = treatment approach using Hyperthermia treatment planning Guided Steering during period II, T50 = temperature exceeded by 50 % of the monitored sites in bladder, vagina and rectum

Learning effects encountered during study

Advanced understanding of applying treatment planning guided optimization

During the study it became clear that our primary optimization method (Opt1 from Canters et al.)[20] insufficiently dealt with hotspot-related complaints to allow for a meaningful and swift reaction to clinical situations. We therefore adjusted the optimization method to not only optimize power deposition in the tumor, but also to minimize power deposition in a specific hotspot-related area in the model while maximizing power deposition in the tumor (Opt2 from Canters et al.).[20] The main difference between the 2 methods is that Opt1 considers only SAR in the tumor region, while Opt2 also takes hotspots into account. In phantom studies, Opt2 showed better hotspot reduction and spatial control and based on this finding, we switched from Opt1 to Opt2 in this study. As a result, the first 5 patients who entered the study were treated using Opt 1 during HGS treatments. The other 30 were treated using Opt 2.

Improved patient positioning

Another problem we encountered during the course of the study was that the accuracy of currently used positioning techniques was somehow inadequate for use in conjunction with a HGS. When trying to reproduce the patient's position from the CT-based computer model to the actual patient position in the Sigma-60 applicator, we encountered problems with patients' legs touching the outer rim of the Sigma-60 when the anterior-posterior position measured in the model was copied to clinical situation. A closer look at our current patient positioning protocol in clinical practice and the protocol used for hyperthermia treatment planning CT-scans, revealed that most patients were positioned much more cranially during the CT-scan than during treatment. The reason for this was our demand for a single, continuous CT-scan for the hyperthermia treatment plan, which was only possible when the patient was positioned more cranially in the CT-scanner. This problem with patient alignment was solved when specific attention was paid to the craniocaudal positioning of the patient in the BSD sling, no more problems were encountered with patient positioning.

Outcome for patients who were correctly positioned

When repeating comparison 2 for patients who were correctly positioned, no differences in outcome measures were observed when comparing them to the results of comparison 2 for the whole group of patients. For period I only the duration of off-switches is significantly longer for HGS-treatments ($p = 0.03$), all other differences were not significant. For period II, again HGS tends to lead to more and longer off-switches, lower thermal dose and lower temperatures compared to RESG. The same outcome we observed in the whole group, namely that results are similar for HGS and RESG for period I, but during period II HGS performs less well, also holds true for this subgroup.

Discussion

In this article we present our first experience with taking hyperthermia treatment planning guided steering, or HGS, to the clinic. HGS proved to be feasible in every day clinical practice. Early on in a treatment series HGS performs as well as RESG and in view of the fact that the RESG were developed based on years of clinical experience, this is a very worthwhile result.

During the first part of a treatment series (period I, 2nd and 3rd treatment) only the duration of off-switches, a measure for treatment-limiting hotspots, was significantly longer during HGS treatments. During each hyperthermia treatment, the power is turned off

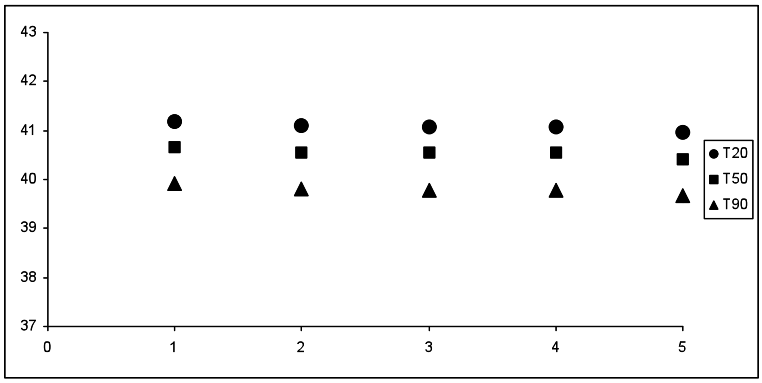
when a patient shows signs or symptoms indicating a hotspot-related complaint. During RESG treatments, the power is turned on again when the patient indicates the complaint has subsided. During HGS treatments, the power was turned on again when the complaint has subsided and new treatment settings were calculated with a custom-made add-on to Sigma HyperPlan(upto 2 min).[20] The calculation time required by Sigma HyperPlan could well explain the difference in the duration of off-switches. For thermal dose parameters, maximum temperature and time to first complaint, a slight, non-significant difference in favor of HGS could be found for period I.

The analysis for period II (4th and 5th treatment of the series) shows a more complicated picture. HGS treatments now show significantly lower power, intraluminal temperatures (with a difference of 0.4 ^{0}C for T20, 0.4 ^{0}C for T50 and 0.3 ^{0}C for T90) and thermal dose (with a difference in TRISE of 0.37 ^{0}C and in CEM43T90 of 0.19 min). Whether these differences have a clinical meaning, remains seen. Our previous thermal dose analysis showed a significant correlation between thermal dose parameters and treatment outcome, but with great dispersion of the data.[11] For intraluminal temperature measures, no significant relationship was found for various outcome measures. Further, it remains questionable whether intraluminal temperatures represent intratumoral temperatures as well in more tumor-selective heating (HGS) as in the more empirical regional heating that is obtained using the RESG. We must realize that changing heating strategy may cause historical correlations are no longer valid. For example, Fatehi et al. showed good correlation between intraluminal and intratumoral temperatures, i.e. when treatment settings are adjusted to obtain a homogeneous intraluminal temperature distribution.[30] During HGS treatments, treatment settings are not adjusted to aim for a homogeneous intraluminal temperature distribution, but to obtain maximum SAR in the tumor. If this is done sufficiently selective, this could paradoxally cause a decrease of intraluminal temperatures as a consequence of the more targeted treatment strategy.

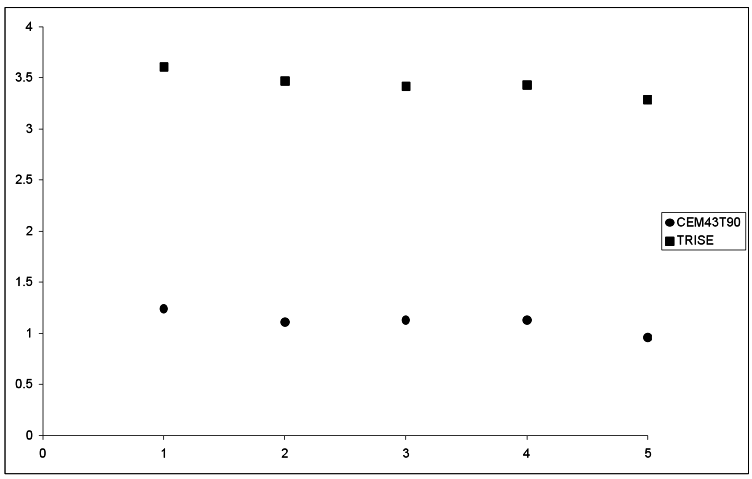
In our previous thermal dose analysis, it was already apparent that patients become harder to heat as treatment progresses (figure 3).[11] A possible explanation for this finding is that as treatment progresses patient tolerance decreases due to the cumulating fractions of radiotherapy administered; acute radiation-induced toxicity and fatigue set in. Also, the applications of brachytherapy are usually administered in the 4th and 5th week of treatment, greatly increasing the sensitivity and tenderness of a patient's pelvic area. As this previously found difficulty with heating a patient as treatment progresses, is also expected to play a role in this study, we decided to introduce the analysis per period (period I and period II) in order to account for this. The difference between RESG and HGS

Figure 3: Evolution of temperatures (a) and thermal dose (b) over treatment series based on the data of reference 11.

a) Temperatures (^{0}C)



b) Thermal Dose (CEM43T90 in min, TRISE in ^{0}C)



Legend: CEM43T90 = cumulative equivalent minutes of T90 at 43 ^{0}C as described by Fatehi et al. [24], TRISE = a local custom-made thermal dose parameter based on T50 and the duration of heating [11], T20 = temperature exceeded by 20 % of the monitored sites in bladder, vagina and rectum, T50 = temperature exceeded by 50 % of the monitored sites in bladder, vagina and rectum, T90 = temperature exceeded by 90 % of the monitored sites in bladder, vagina and rectum

becomes much more apparent in period II, which could be explained by the fact that RESG is a much simpler optimization model compared to HGS. RESG leaves more room for individual interpretation, making it more flexible and better equipped to deal with decreasing patient tolerance. Another important aspect which may affect proper assessment of the performance of HGS in period II is whether anatomical information as obtained from the pretreatment CT-scan is still valid. During the course of treatment, the tumor shrinks,

patients may loose weight and the chemical balance in the intestine may change due to diarrhea. In parallel with the anatomical changes, the biological and physiological characteristics of the tumor will also change during treatment. All of these factors may affect the energy and temperature distribution in the patient and are not taken into account in the treatment plan at the start of treatment. These factors may very well explain why HGS performs less well as the treatment progresses and the original anatomy gets distorted.

From a technological point of view, HGS performs much more like a traditional feedback system than RESG. As explained, HGS is critically dependant on the robustness of the input parameters at the start of treatment. In contrast, the clinician's observation of the patient's condition provides the clinician with an update of the subjective and difficult-to-quantify input parameters for RESG at the beginning of each successive hyperthermia treatment.

Clearly, the design of future studies should include updating of the treatment planning based on the changing anatomy and, if feasible, input of changing biological and physiological characteristics of the tumor.

Although the results of this trial show that HGS in its current status can be of merit when applying deep hyperthermia, the 0.3 ^{0}C improvement with HGS this study was designed to detect, could not be found. Since the study closed, we performed a number of theoretical studies that showed that with optimization using the Sigma-60 the maximum SAR improvement that can be reached is within the order of 5 %. Using the bioheat equation, this 5 % SAR should lead to a rise in temperature of 0.2 ^{0}C, an increase that is within the resolution of our currently used thermometry.[27, 31] In retrospect, our estimated 0.3 ^{0}C profit using HGS may have been too high a goal with the hyperthermia equipment we used.

Lessons learned from the clinical implementation of hyperthermia treatment planning guided steering

As to be expected when putting any new technique to clinical use, we encountered a number of challenges. Early on, we noticed that our first optimization routine insufficiently addressed hotspot-related complaints reported by the patients. This prompted the development of a new optimization routine that not only maximized power deposition in the tumor, but also minimized power in a specific hotspot-related area.[18]

We also encountered problems in patient positioning, which we were able to overcome with the currently available positioning techniques, although we would like to stress the importance of further improvements needed in this area. When correct patient positioning fails, high resolution optimization procedures are useless.

A much mentioned drawback of hyperthermia treatment planning in general is the time-consuming nature of the process. In this study, one of the rules was that the CT-scan made for hyperthermia treatment planning had to be made at least 3 days before the first study treatment took place. As we gained more experience with the segmentation process, we were able to improve speed. The time required was reduced from 8-9 hours per CT-scan in the beginning to 3-4 hours near the end of the study. This may be further improved in the future using atlas-based segmentation. On average, calculation time was 15 hours, a value which may change in time depending on computer speed and segmentation resolution.

Technical limitations

This study was designed to evaluate the efficacy of currently available hyperthermia treatment planning possibilities in the Sigma-60 applicator, with its inherent limitations. From the study by Canters et al. the potential of HGS to optimize the SAR distribution in the Sigma-60 appears to be limited, due to the small amount of degrees of freedom.[28] The potential appearing from this model study could easily be lost due to inaccuracies in the hyperthermia treatment planning software, the dielectric constants and in the translation from model to clinic.

Two important limitations of the system we used in this study are the lack of optimal steering possibilities and the unknown influence of transforming networks. Also, the focus that is created by the BSD-2000 system and the Sigma-60 applicator is quite large and with extreme settings its performance decreases.

Clinical implications

We have no doubt that hyperthermia treatment planning is a necessary and inevitable next step in the development of hyperthermia as an oncological treatment modality. It enables patient-specific optimization of treatment, which should eventually lead to a more standardized application of hyperthermia and better treatment quality. For now, we recommend the use of HGS for clinicians with no or limited experience in the field of hyperthermia as this study shows that with the use of HGS clinical results can be obtained that are approaching our results with 18 years of experience.

Hyperthermia treatment planning also proved to be a helpful tool in the evaluation of clinical indications; it may help clinicians decide in advance whether a tumor at a specific location can be heated to therapeutic temperatures or not. Further, it can be a great aid in education and training of new hyperthermia staff.

It can also be a helpful tool in the development of new hyperthermia systems.[33-37] When a hyperthermia treatment planning system is used to develop a new system the technical capabilities can be made better in line with the clinical demands.

Last but not least, hyperthermia treatment planning can be an important tool in more controlled treatment quality.

Future directions

We found that the procedure of online hyperthermia treatment planning guided steering is feasible. For maximal exploitation of its possibilities, however, better control and understanding of several patient, tumor and technical parameters is required.

As a whole, this trial has been very useful in terms of assessing what we currently can and can not do with treatment planning for deep hyperthermia. Some lessons were quickly learned, while more time is needed for others.

For example, it is mandatory to get more insight into relation between intraluminal temperatures with intratumorally temperature. One could argue that better focusing of energy in the target area could lead to a decline in intraluminal temperatures for some patients, and an increase in others, depending on patient anatomy and tumor vasculature and shrinkage.

Another point that requires further investigation is the relationship between a patient's hotspot-related complaint and a hotspot in the Sigma HyperPlan model, as temperature causes hotspots and not SAR, on which we optimized. This could, in part, explain our difficulties in clearing hotspot-related complaints during the HGS-treatments. In addition, the indication of hotspot-related complaints by a patient is subjective by definition and in our experience there is great variation in how well patients are able to describe sensations in their body during hyperthermia.

Conclusion

In spite of the problems we encountered during this study and the inherent limitations due the equipment and the current state of hyperthermia treatment planning, HGS performs equally well in treatment two and three when compared to the RESG based on our two decades of clinical experience. This study has been very helpful in identifying some of the challenges and flaws that warrant further investigation in the near future, such as patient positioning and the prevention of hotspot-related complaints. With the progress that has been made during this study, we hope to perfect the principle of hyperthermia treatment planning guided steering in the near future.

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Chapter 9

General discussion and conclusions

Hyperthermia in the treatment of primary cervix cancer

Fifteen randomized trials have shown significantly improved outcome after radiotherapy combined with hyperthermia (RHT) compared to radiotherapy alone.[1-17] Moreover, this improvement is not accompanied by increased acute toxicity. Our recent update of one of these trials in locally advanced cervix cancer showed that local control and overall survival rates remain significantly higher in the plus hyperthermia arm with 19% and 17 % absolute difference respectively at 12 years follow-up in favor of the hyperthermia arm.[18] This translates into nearly a doubling of the survival rate. In addition, the results of this trial proved to be reproducible in a larger group of patients (n = 378) with worse prognostic characteristics.[19]

In the last decade, combined radiotherapy and chemotherapy (RCT) has gained large-scale acceptance in the treatment of cervix cancer. Despite the undisputed benefit for the lower stages of cervix cancer, it can seriously be questioned whether this benefit also exists for the more advanced stages of cervix cancer. In the last 10 years, 4 reviews have been published and all conclude that the beneficial effect of RCT is clearly present for cervix cancer FIGO (International Federation of Gynecology and Obstetrics) stage I and II, while the gain in 5 year overall survival may only be 3 % for patients with FIGO stage III-IVa.[20-23] At the same time there is evidence to suggest that the addition of chemotherapy adds to the toxicity of radiotherapy. Hyperthermia, however, equally enhances treatment outcome while generally no additional toxicity is observed. [7, 18, 24-25] Recently, the Cochrane Collaboration published a meta-analysis on combined radiotherapy and hyperthermia that further corroborates these conclusions. The authors stress hyperthermia has clear therapeutic benefits in terms of a doubling of the local control rate, improved survival, limited restrictions for its clinical application and low costs. Therefore, the combination of radiation and hyperthermia warrants further investigation and should absolutely be offered to patients with locally advanced cervix cancer with a contraindication for chemotherapy. [26]

The convincing studies mentioned above have led to the inclusion of hyperthermia in the Dutch Association of Comprehensive Cancer Centers guidelines. As a consequence of acceptance of hyperthermia by the medical profession, the Dutch health care authorities have decided to reimburse hyperthermia.

Despite all the clinical evidence, in most other countries, hyperthermia is not part of standard health care, and reimbursement is lacking or insufficient, which results in limited availability and applicability of hyperthermia.

For patients who are amendable for both RHT and RCT, the optimal treatment strategy remains unclear as the overall odds ratio for both combined treatments, RCT and RHT, are comparable. [27]

In order to gain more scientific evidence for selecting the optimal treatment strategy for these patients, two phase III trials are currently ongoing. The first trial randomizes between either RHT or RCT to identify which patients benefit most from one of the two combined modalities. The second study randomizes between RCT or trimodality treatment (i.e. radiotherapy combined with both chemotherapy and hyperthermia). Previously, a phase II trial showed that this trimodality approach was well tolerated and demonstrated high response rates. In the phase III trial an improvement in overall survival of 15% is expected when RCT is combined with hyperthermia.[28]

Hyperthermia in the treatment of recurrent cervix cancer

The response rate for patients with recurrent cervix cancer after previous irradiation can be improved from 10-15 % with chemotherapy alone to > 50 % when the standard chemotherapy-regimen is combined with hyperthermia.[29-31] Although the prognosis for these patients remains grim, with the addition of hyperthermia, 5-10 % of patients can achieve long-term local control and disease free survival.[31]

Besides its chemosensitizing effect, hyperthermia is especially effective in a post-radiation setting because of improved perfusion and thus better drug delivery that occurs at temperatures ≥ 39 ^{0}C. [32-33] Cisplatin has been the agent of choice for the systemic treatment of cervix cancer for decades and currently the combination of cisplatin and hyperthermia is the standard treatment approach for patients with a recurrent cervix cancer after previous radiation.

Recently, a randomized trial showed significantly improved treatment outcome when topotecan was added to cisplatin for patients with locally advanced, persistent or recurrent cervix cancer. The response rate for patients who were given only cisplatin was 13 %, compared to 27 % for patients treated with topotecan as well.[34] In this trial the response rate after previous irradiation is not specified and there are no data available on the combination of topotecan and hyperthermia. Nevertheless one could hypothesize that the combination of cisplatin, topotecan and hyperthermia may further improve treatment outcome for patients with recurrent cervix cancer after previous irradiation. After all, the main mechanism of synergy for chemotherapy and hyperthermia, namely improved

perfusion resulting in improved drug delivery and improved oxygenation, will also hold for topotecan. However, as the combination of hyperthermia and chemotherapy may also lead to increased side effects or biological inactivity of the drug, proper preclinical research is essential before taking this combination into a clinical setting.[32-33]

Another way to improve the currently poor outlook for patients with recurrent cervix cancer after previous irradiation is to combine hyperthermia (with or without cisplatin) with a targeted therapy. A targeted therapy blocks the growth of cancer cells by interfering with specific target molecules needed for tumor growth and metastasis. As these agents have a different mode of action and different toxicity profile, the combination of these targeted therapies with chemotherapy seems attractive. The combination of a targeted therapy and chemotherapy already proved successful in the treatment of metastatic colorectal and breast cancer.[35-37]

The biological effects of hyperthermia could further promote the clinical efficacy of such a combination, so currently we are conducting a phase I trial on the combination of cisplatin, hyperthermia and lapatinib, a reversible inhibitor of tyrosine kinase and the EGFR receptor.[38]

Another promising possibility for improvement is the recent development of thermosensitive liposomes: a chemotherapeutic agent is packed into a lipid bilayer which disintegrates at temperatures around 40-42 ^{0}C. After intravenous administration, these liposomes accumulate specifically in the tumor tissue. As there is enhanced leakage of the tumor vascular system under thermal stress, hyperthermia will also enhance drug delivery to the tumor area and control its release. So, a triple gain is expected as the drug concentration in the tumor and its effectiveness is increased while its side effects are decreased.[39-45]

In view of the strong biological rationale and the firm clinical results described above, the limited acceptance of RHT worldwide is remarkable. Potential reasons for this limited use are mainly found in practical and organizational issues. As indications are still few, institutes are often reluctant to invest and, as a consequence, clinical trials accrue slowly. Most of the randomized trials are relatively small, which is justified because the differences in clinical outcome are large and thereby significant. On the other hand, the lack of large clinical trials hinders further acceptance.

Although 15 of the randomized trials that incorporated hyperthermia show a positive result, [2-15] [46-48] there are also 8 trials not showing a significant difference.[49-57] Inadequacy of the heating technique used has been allocated as the main cause of failure to show a significant added effect of hyperthermia. An important problem is that currently, no

universally applicable and accepted indicator of hyperthermia treatment quality is available.[58]

Hyperthermia dose effect relationship

From experimental studies, we know that the biological effectiveness of hyperthermia is dependant on both height of temperature and duration of heating.[59] In a clinical setting, options for thermometry are limited while a large need for extensive thermometry exists as heterogeneous temperature distributions have to be characterized. Facing this dilemma, the results from the largest dose-response analysis of deep hyperthermia to date are remarkably encouraging when searching for a universally applicable indicator for the evaluation of hyperthermia treatment quality.[60]

In a large, retrospective analysis, we found that two well-defined dose-response parameters that incorporate both heating time and height of temperature show a significant correlation with treatment outcome. This finding has implications on a technological level as well as a clinical level as a well-defined, clinically relevant thermal dose parameter is crucial for comparison and monitoring of hyperthermia treatment strategy and quality.

New technological developments to improve hyperthermia treatment quality

In Rotterdam, years of successful clinical application of hyperthermia resulted in experience-based 'conventional' guidelines that proved their merits in various clinical trials, but their empirical nature makes them susceptible to variations in expertise and experience of the hyperthermia staff. An objective and reproducible treatment strategy would be preferable as this will greatly aid hyperthermia treatment quality.

With hyperthermia treatment planning we should be able to obtain more tumor-selective and patient-specific heating than with the conventional guidelines. Moreover, a more systematic approach would facilitate the transfer of knowledge from center to center and the training of new staff. It is the most logical way for a more uniform and standardized treatment quality within an institute and between institutes; a prerequisite for multi-institutional trials.

For the commercially available BSD-2000 3D system we use in Rotterdam, a hyperthermia treatment planning system has been developed, Sigma HyperPlan. This system has shown to be feasible and to have good correlation with clinically attained measurements.[61-62] With the help of Sigma HyperPlan we were able to check the rationale behind our conventional guidelines. The results of treatment planning were in close agreement with the conventional guidelines.[63]

For efficient clinical use of Sigma HyperPlan during treatment, an optimization method is mandatory. We created 2 such methods that differed from one another in that the first only considers the energy level in the tumor region and the second also takes hotspots into account. From phantom studies we concluded that hyperthermia treatment optimization performs best in the periphery of the phantom. Hotspots in the center of the pelvis, i.e. near the tumor, are more difficult to deal with due to the large heating area of the applicator. [64] As the second optimization method shows better complaint reduction and spatial control, we tested this optimization method in a randomized trial.

This randomized trial represents the first effort to bring hyperthermia treatment planning guided steering into everyday clinical practice. The results of this randomized trial show that hyperthermia treatment planning guided steering is equally effective to our conventional guidelines during the first part of a treatment series. During the second half (4th and 5th treatment) hyperthermia treatment planning guided steering performs significantly worse than our empirical guidelines on nearly all endpoints.[65] Although this difference is statistically significant, its clinical relevance remains to be seen. A significant correlation between thermal dose and treatment outcome has been observed, but with great dispersion of the data. Changes in patient and tumor anatomy and physiology are expected to contribute to the change in treatment planning effectiveness we observed in the second half of the treatment. Also, the translation from computer screen to clinical practice proved to be complex. Correct modelling of transforming networks in the treatment planning system and more accurate patient positioning will improve treatment planning effectiveness in the near future. Continuous evaluation proved to be key in the process of translation from computer screen to clinical practice and helped to reveal disturbances early.

Major issues that remain to be investigated are how the relationship between intratumor and intraluminal temperatures behaves when we are able to achieve more tumor-selective heating and the correlation between hotspots mentioned by the patient and energy levels in the treatment planning model.

Besides the development and implementation of hyperthermia treatment planning guided steering, another technological advancement will help improve hyperthermia treatment quality in the coming years.

Non-invasive thermometry using the Hybrid BSD-2000 system, i.e. a radiofrequency multiantenna hyperthermia applicator that can be operated in a commercially available MRI system will bring us numerous opportunities for further understanding the process of deep hyperthermia. Already the non-invasive temperature measurements show good correlation with directly measured temperatures in both phantom experiments and treatments for rectal cancer and sarcomas of the extremities. [66-67] There is no doubt that non-invasive thermometry will help us to gain better insight in temperature distributions during treatments and for evaluation of new technological developments such as hyperthermia treatment planning.

The future of hyperthermia in the treatment of cervix cancer

An important next clinical step is the prospective validation of the thermal dose response relationship we found retrospectively. Not only will such a prospective validation mean a great leap forward in quality assurance and evaluation of new technological developments, but it would also indicate that our current doubling of the local control rate for patients with locally advanced cervix cancer may even be further improved when the thermal dose is increased.

Increasing the thermal dose delivered can be achieved by treating patients longer or more often, but in spite of little toxicity, a deep hyperthermia treatment is a demanding treatment for the patient, so prolonging hyperthermia treatment time should not be taken lightly. Another, more desirable, way to increase the thermal dose is to aim for higher temperatures through a combination of more tumor-selective heating, better positioning techniques and the introduction of more advanced applicator designs and heating strategies.

Besides increasing the thermal dose delivered, treatment outcome for patients with cervix cancer can be improved by optimization of the radiation dose delivery. In the near future dose-painting with allocation of the target volume based on functional imaging, MRI-assisted delivery of brachytherapy and tracking motion and deformation of target volumes during radiation are expected to allow further optimization of the radiation dose distribution. With further optimization of the radiation dose delivered, hyperthermia

could be used to lower the physical radiation dose while maintaining the same biological equivalent dose.[68-72]

From the results of our randomized trial on treatment planning and its associated parameter studies, we can conclude that more selective tumor heating is very limited with the currently available Sigma-60 deep hyperthermia applicator. An inherent limitation of the Sigma-60 that was used in the reported research is that the energy focus can only be steered in 2 dimensions. Currently, we are investigating if the Sigma-Eye applicator that allows for 3 dimensional steering allows for more selective tumor heating. In theory, an increase of 1.5 ^{0}C can be expected with the use of the Sigma-Eye. How this theoretical increase can also be reproduced in vivo warrants further research. Most recently, the Dutch Cancer Society granted us a new research program (EMCR 2009-4448) with a specific focus on the development of new tools to enable 3 dimensional steering of the energy focus with the Sigma-Eye. To achieve this, further research is needed in order to make the translation from 3-dimensional energy distributions on the computer screen to the actual energy distributions as achieved in the patient's body more reliable.

Finally, an improved and reliable hyperthermia treatment planning system will certainly add to a more widespread acceptance of hyperthermia worldwide. The ultimate goal is to replace the empirical application of hyperthermia that is subject to changes in expertise and experience of the hyperthermia staff with and application that is objectively controlled under guidance of a hyperthermia treatment planning system.

Conclusion

Part I: Exploration of the rationale and clinical outcome

- Hyperthermia is a worthwhile additive to standard chemotherapy for patients with recurrent cervix cancer after previous irradiation
- For patients with locally advanced cervix cancer, radiation and hyperthermia should be considered as a first-line treatment as its therapeutic benefit is at least comparable to that of chemoradiation, while toxicity is not increased
- Besides, and after adjustment for, known prognostic factors such as tumor size and tumor stage, the number of hyperthermia treatments significantly correlates with clinical outcome.
- Thermal dose parameters that include both height of temperature and duration of heating correlate significantly to treatment outcome indicating that treatment out-

come can be improved by increasing thermal dose. This finding opens a clear window of opportunity for improvements in hyperthermia treatment quality, clinical decision-making and evaluation of new heating technologies.

Part II: Towards improvement of treatment quality and clinical outcome

- Hyperthermia treatment planning enables retrospective evaluation of hyperthermia treatments and patient-specific generation of treatment plans. The results demonstrate comparable clinical quality compared to the currently used empirical treatment guidelines. This offers the opportunity to change from subjective, experience-based application of hyperthermia to objective, treatment-planning controlled application, facilitate clinical decision-making and an a priori prescribed hyperthermia dose.
- To enable the online use of hyperthermia treatment planning, an optimization method is needed to not only optimize the energy deposition or temperature in the tumor region, but also reduce the energy or temperature in certain other regions. Such a method was developed in this research and demonstrated with favorable results.
- When using a hyperthermia treatment planning system for steering during a hyperthermia treatment, results are comparable to those of the currently used guidelines for the first part of a treatment series.
- Hyperthermia treatment planning is a necessary next step in the evolution of hyperthermia. Even though it performs less in the second part of a treatment series, it offers controllability of a hyperthermia treatment, and controllability offers much better options for improvement of quality than the current, empirical approach. Further research is needed into the translation of a predicted energy distribution from computer screen to an energy distribution in the patient's body.

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Chapter 10

English summary

There is a strong biological rationale for the use of hyperthermia as a treatment modality for cancer. Fifteen randomized trials have shown a significant improvement in clinical outcome when hyperthermia was added to radiotherapy, chemotherapy or both. At temperatures ≥ 40 ^{0}C, heat can cause direct cell death, especially affecting cells that are relatively resistant to chemotherapy and radiotherapy.

When combined with radiotherapy, hyperthermia increases the efficacy of radiotherapy by improving tumor oxygenation, thereby enhancing radiotherapy-induced cell death, and interfering with DNA repair mechanisms. In the Netherlands, the combination of radiotherapy and hyperthermia is offered to patients with cervix cancer, among others. For these patients, 5 weeks of radiotherapy are combined with 5 hyperthermia treatments, given once weekly.

In combination with chemotherapy, hyperthermia increases the drug concentration in the tumor area and it interferes with DNA repair mechanisms. In addition, hyperthermia improves oxygenation. This makes some drugs more effective and may potentiate of the drug, counteract drug resistance or alter pharmacodynamics. In the Netherlands, the combination of chemotherapy and hyperthermia is also used for treating cervix cancer. Patients with recurrent cervix cancer after previous radiotherapy can be treated with 6 weekly courses of chemotherapy combined with 6 simultaneous hyperthermia treatments. In Chapter 1 a short introduction into hyperthermia and the treatment of cervix cancer is provided.

In this thesis, the current status of hyperthermia in the treatment of locally advanced and recurrent cervix cancer in the Netherlands is presented and factors predicting treatment outcome are identified. Further, one possible way of improving the current hyperthermia treatment quality, i.e. by using hyperthermia treatment planning is explored.

Part I: Exploration of the rationale and clinical outcome

In Chapter 2, the clinical results of the combination of hyperthermia and chemotherapy for the treatment of recurrent cervix cancer after previous irradiation are described in detail. The prognosis for patients with a local recurrence after previous irradiation is grim with only 10 % of patients responding to chemotherapy. When standard chemotherapy was combined with hyperthermia in 47 patients, 55 % of patients responded. These results show that for patients with recurrent cervix cancer after previous irradiation, the

combination of chemotherapy and hyperthermia should be offered as the response rate is more than twice as high, good palliation is often achieved and toxicity is acceptable.

Several randomized trials have shown that hyperthermia significantly improves clinical outcome when it is added to standard radiotherapy for primary locally advanced cervix cancer (LACC) at standard follow-up of 3 to 5 years. Chapter 3 describes the long-term follow-up for 114 patients with LACC who were treated in a randomized trial with radiation or radiation plus hyperthermia (the Dutch Deep Hyperthermia Trial, or DDHT) between 1990 and 1996. At 12 years follow-up, the addition of hyperthermia significantly improved both local control by 17 % and overall survival by 19 %. This improvement in clinical outcome was achieved without an increase in acute or long-term toxicity.

Chemoradiation is the current treatment of choice for the treatment of LACC. Although the addition of chemotherapy to radiation also significantly improves treatment outcome, it also increases toxicity. Moreover, adding chemotherapy is especially beneficial for patients with lower stage cervix cancer (FIGO stage Ib-IIa), while adding hyperthermia proved to be beneficial in the advanced stages (FIGO IIb-IVa). Therefore, the results presented in chapter 3 justify the addition of hyperthermia to radiation as a first line treatment for patients with LACC. A recent Cochrane meta-analysis also showed that patients who are unfit to receive chemotherapy should be offered the combination of radiation and hyperthermia. For patients who are fit to receive chemotherapy, the best treatment approach has yet to be determined in ongoing trials.

In Chapter 4, patient and tumor characteristics and treatment outcome for all patients with LACC treated with radiation plus hyperthermia from 1996 to 2005 at Erasmus MC Daniel den Hoed are analyzed.

Overall, treatment outcome for these 378 patients was comparable to treatment outcome for patients treated in the DDHT with a 5-year local control rate of 53 % and 5 -year disease specific survival of 47 %. In multivariate analysis, not only tumor stage and tumor size were prognostic. The number of hyperthermia treatments also significantly influenced treatment outcome in this patient group. This implies that better results should be obtained when higher thermal dose levels are delivered.

This influence of thermal dose on treatment outcome (thermal dose effect) was further analyzed in Chapter 5. The correlation of various patient- and tumor-specific factors, radiation treatment parameters and hyperthermia treatment parameters (such as minimum, mean and maximum temperature, applied power and heating time) to treatment outcome was analyzed in detail. Treatment parameters that include both heating time and height of temperature correlate significantly with tumor control and survival in this analysis.

This suggests that treatment outcome may improve when the thermal dose is increased. Furthermore, the finding of a significant correlation between thermal dose and treatment outcome opens the door to new technological developments in hyperthermia.

Part II: Towards improvement of treatment quality and clinical outcome

Currently, hyperthermia treatments are applied empirically by applying non-specific steering actions based on general principles of physics and both the experience and dedication of the staff plays a role in the final treatment quality. A hyperthermia treatment planning system (HTPS) can help us understand the influence of adjustments in treatment settings on energy and temperature distribution. It may even predict the effect of adjustments in treatment settings on the energy and temperature distribution during treatment (hyperthermia treatment planning guided steering, or HTP-guided steering).

The use of HTP-guided steering enables more tumor-selective and patient-specific heating than with the currently applied generic treatment strategy. In Chapter 6 the current treatment strategy and HTP-guided steering were compared. The current treatment strategy is based on years of clinical experience and has proved its value in several clinical trials, but a detailed analysis of the underlying principles was not possible before the development of a HTPS. In this study, these underlying principles proved to be valid and the results of the treatment planning system were in close agreement with the current strategy.

However, for efficient use of a HTP-guided steering during treatment, an optimization method is mandatory. A HTPS should not only be able to predict the effect of adjustments of treatment settings, but also be able to react to feedback provided by the patient. If during a hyperthermia treatment, the energy level becomes uncomfortably high, a patient will experience discomfort (a hotspot) and treatment settings must be adjusted. For a hyperthermia treatment to be effective, treatment settings must be adjusted to lower the energy in the hotspot, while maximizing the energy in the tumor (optimization). In Chapter 7 two optimization methods are described and tested. The first optimization method only considered the energy level in the tumor at initial optimization, while the second optimization method also considered energy levels at hotspots at initial optimization. The second optimization method showed better spatial control and phantom tests demon-

strated that it improved the ability to take patient complaints into account compared to the first method.

Subsequently, the second optimization method was used in a randomized trial comparing our current treatment strategy to HTP-guided steering in 36 patients with LACC described in Chapter 8. During the first part of a treatment series, HTP-guided steering performed as well as our current strategy, but during the second half HTP-guided steering performed worse.

From both the preparatory work for this trial, as well as from its results, many important lessons were learned. Prior to completion of the trial, a better-performing optimization method was developed (as described in Chapter 7) and a more accurate patient positioning technique was introduced. As hyperthermia treatment planning offers a controllable an objective treatment strategy, it deserves a place in modern clinical hyperthermia. Additional research is needed to study the impact of changes in patient and tumor anatomy during the course of treatment and the correlation between hotspots mentioned by the patient and energy levels in the treatment planning model. Also, the potential of HTP-guided steering to optimize the energy distribution with the currently used equipment (Sigma-60 applicator) appears to be limited. Recently we have received a Dutch Cancer Society Grant to further study these factors.

An improved HTPS can also play an important role in gaining more widespread acceptance of hyperthermia worldwide as it will help us abandon the empirical application that is subject to changes in expertise and experience of the hyperthermia staff.

Hyperthermia is an effective addition to the pallet of treatment modalities for patients with locally advanced cervix cancer. Particularly for primary locally advanced cervix cancer, the merits of hyperthermia are evidence-based, both regarding long-term results as well as for unselected patients. Correct implementation of the many recent technological innovations will translate into to better reproducibility and improved quality of hyperthermia treatments, in turn resulting in improved clinical outcome and more widespread acceptance.

Chapter 11

Nederlandse samenvatting

Er is een sterke biologische rationale voor het gebruik van hyperthermie als oncologische behandelingsmodaliteit. Vijftien gerandomiseerde onderzoeken hebben een significante verbetering laten zien in klinische uitkomst als hyperthermie wordt toegevoegd aan radiotherapie, chemotherapie of een combinatie van die twee voor verschillende tumorsoorten. Een korte introductie over de biologische en technische achtergrond van de hyperthermie en de huidige behandeling van baarmoederhalskanker wordt gegeven in hoofdstuk 1.

Bij temperaturen ≥ 40 ^{0}C kan hyperthermie direct celdood veroorzaken, in het bijzonder in het bijzonder bij die cellen die relatief ongevoelig zijn voor het celdodende effect van chemotherapie en/of radiotherapie.

In combinatie met radiotherapie verhoogt hyperthermie de effectiviteit van de radiotherapie door de zuurstofvoorziening van de tumor te verbeteren, waardoor het celdodende effect van de radiotherapie versterkt wordt. Ook interfereert de hyperthermie met de reparatie van DNA-schade, waardoor de bestraling nog effectiever wordt. De combinatie van radiotherapie en hyperthermie wordt in Nederland onder andere aangeboden aan patiënten met baarmoederhalskanker, waarbij de patiënte tijdens de ca. 5 weken durende bestralingsserie 1 keer per week behandeld wordt met hyperthermie.

Als chemotherapie wordt gecombineerd met hyperthermie, zal hyperthermie ook interfereren met de reparatie van DNA schade en ervoor zorgen dat de concentratie van de chemotherapie in de tumor hoger wordt. Ook hier verbetert hyperthermie de zuurstofvoorziening van de tumor waardoor het effect van sommige middelen versterkt wordt. Hyperthermie kan ook zorgen voor het verhogen van de potentie van het middel, resistentie tegenwerken en de farmacodynamiek veranderen.

Ook de combinatie van chemotherapie en hyperthermie wordt in Nederland gebruikt voor de behandeling van baarmoederhalskanker. Patiënten met een recidief baarmoederhalskanker na eerdere bestraling, kunnen worden behandeld met 6 wekelijkse chemotherapie-kuren die gecombineerd worden met 6 hyperthermiebehandelingen.

In dit proefschrift wordt de huidige status van hyperthermie in de behandeling van baarmoederhalskanker in Nederland gepresenteerd. Verder worden factoren die de klinische uitkomst bepalen geïdentificeerd en wordt onderzocht of de kwaliteit van de behandeling verbeterd kan worden met behulp van een hyperthermie planningssysteem.

Deel I: Verkennen van de rationale en klinische uitkomsten

In hoofdstuk 2 worden de klinische uitkomsten beschreven van de combinatie van hyperthermie en chemotherapie voor de behandeling van recidief baarmoederhalskanker in eerder bestraald gebied. De prognose voor deze patiënten is slecht, omdat slechts 10 % reageert op de standaard behandeling met chemotherapie. Als die standaard behandeling wordt gecombineerd met hyperthermie, stijgt het responspercentage naar 55 % bij de 47 onderzochte patiënten. Deze resultaten tonen aan dat voor patiënten met een recidief baarmoederhalskanker het toevoegen van hyperthermie aan chemotherapie meer dan een verdubbeling geeft van het responspercentage en goede palliatie oplevert, terwijl de bijwerkingen alleszins acceptabel zijn.

Meerdere gerandomiseerde onderzoeken hebben aangetoond dat hyperthermie significant de klinische uitkomst verbetert, als het wordt toegevoegd aan de standaard radiotherapie voor primair locaal uitgebreide baarmoederhalskanker (LUBK) na een standaard follow-up periode van 3 tot 5 jaar. Hoofdstuk 3 beschrijft de lange-termijn resultaten van een gerandomiseerd onderzoek naar radiotherapie of radiotherapie gecombineerd met hyperthermie voor 114 patiënten met LUBK (de Dutch Deep Hyperthermia Trial of DDHT). Na 12 jaar follow-up, zijn zowel de locale controle als de overleving significant beter na toevoegen van hyperthermie met respectievelijk 17% en 19 %. Deze verbetering van de klinische uitkomst werd bereikt zonder dat deze gepaard ging met een verergering van de bekende bijwerkingen.

Chemoradiatie, de combinatie van radiotherapie en chemotherapie, is momenteel de standaard behandeling voor patiënten met LUBK, maar hoewel het toevoegen van chemotherapie aan radiotherapie ook een significante verbetering geeft van de klinische uitkomst, geeft het toevoegen van chemotherapie ook meer bijwerkingen. Ook is uit onderzoek gebleken dat het toevoegen van chemotherapie aan radiotherapie in het bijzonder voordeel oplevert voor patiënten met lagere stadia van de ziekte (FIGO stadium Ib-IIa), terwijl het toevoegen van hyperthermie met name voordeel oplevert bij gevorderde stadia (FIGO IIb-IVa). Daarom rechtvaardigen de resultaten die in hoofdstuk 2 worden getoond het aanbieden van de combinatie radiotherapie met hyperthermie als eerstelijns behandeling voor patiënten met LUBK. Dit werd onlangs bevestigd in een meta-analyse van de Cochrane Library. Patiënten met een contra-indicatie voor chemotherapie zouden radiotherapie met hyperthermie aangeboden moeten krijgen. Voor patiënten die wel met chemotherapie behandeld zouden kunnen worden, wordt de beste behandelmethode momenteel nog onderzocht in een tweetal lopende studies.

In hoofdstuk 4 worden patiënt eigenschappen, tumor- en behandelingskarakteristieken en klinische uitkomsten geanalyseerd voor alle 378 patiënten met LUBK die tussen 1996 en 2005 zijn behandeld met radiotherapie en hyperthermie in het Erasmus MC Daniel den Hoed. De klinische uitkomst voor deze patiënten is vergelijkbaar met de klinische uitkomsten in de DDHT met 53 % locale controle 5 jaar na behandeling en 47 % ziektevrije overleving 5 jaar na behandeling. In de multivariate analyse komt, naast de bekende prognostische factoren als het tumorstadium en de tumorgrootte, het aantal hyperthermie behandelingen naar boven als onafhankelijke significante factor gerelateerd aan de klinische uitkomst. Deze dosis-effect relatie impliceert dat betere behandelingsresultaten bereikt kunnen worden door de thermische dosis te verhogen en dit effect wordt nader onderzocht in hoofdstuk 5. De correlatie van verschillende patiënt- en tumor-specifieke factoren, bestralingsdosisparameters en thermische dosisparameters (bijvoorbeeld de minimaal, gemiddeld en maximaal behaalde temperatuur, totaal toegediend vermogen en verwarmingsduur) met de klinische uitkomst werd geanalyseerd. De thermische dosisparameters die zowel de verwarmingsduur als de hoogte van de temperatuur in zich dragen, correleren significant met de locale controle en overleving in deze analyse. Een verbetering van de klinische uitkomst zou dus inderdaad te verwachten zijn als de thermische dosis wordt verhoogd. Naast het nog verder verbeteren van de klinische uitkomst, opent het vinden van een significante correlatie tussen thermische dosis en klinische uitkomst de deur voor nieuwe technologische ontwikkelingen binnen de hyperthermie.

Deel II: Verbeteren van de behandelingskwaliteit en klinische uitkomst

Het verhogen van de temperatuur tot ≥ 40 ^{0}C wordt in de kliniek bewerkstelligd door het te verwarmen lichaamsdeel te omringen met antennes die radiofrequente straling uitzenden. Voor het verwarmen van het kleine bekken wordt in het Erasmus Medisch Centrum de BSD-2000 gebruikt (zie figuur 3 uit hoofdstuk 1). Door tijdens de behandeling het toegediend vermogen en de samenspraak tussen verschillende antennes te variëren, wordt de tumor maximaal verwarmd, terwijl de omringende weefsels zo minimaal mogelijk worden verwarmd. Als een omringend weefsel te warm wordt, kan dit oncomfortabel zijn voor de patiënt (hotspot), waardoor het vermogen tijdelijk moet worden uitgezet. De hotspot verdwijnt dan, maar ook de tumor koelt af.

Al jaren worden het toegediend vermogen en de samenspraak van de antennes tijdens de behandeling aangepast op basis van algemene fysische principes en de ervaring en

toewijding van het personeel speelt een rol in de uiteindelijke behandelingskwaliteit. Een hyperthermie planningssysteem kan beter inzicht bieden in het effect van veranderingen van de behandelingsinstellingen op de energieverdeling binnen de patiënt, zodat het mogelijk is om nog selectiever de tumor te verwarmen en hotspots te vermijden.

In hoofdstuk 6 wordt de huidige manier van behandelen vergeleken met het gebruik van een hyperthermie planningssysteem tijdens de behandeling. De huidige manier van behandelen is gebaseerd op algemene fysische principes en jarenlange klinische ervaring. Deze manier heeft zijn waarde bewezen in verschillende gerandomiseerde onderzoeken, maar een gedetailleerde analyse van de onderliggende fysische principes was niet mogelijk zonder hyperthermie planningssysteem. De onderliggende principes bleken correct en de resultaten van het planningssysteem waren in nauwe overeenstemming met de resultaten van de huidige behandelstrategie.

Om een hyperthermie planningssysteem ook tijdens de behandeling te kunnen gebruiken, is een optimalisatieroutine noodzakelijk. Het planningssysteem moet namelijk niet alleen het effect van aanpassingen van de behandelinstellingen kunnen voorspellen, maar ook kunnen reageren op feedback van de patiënt betreffende hotspots. Voor een zo effectief mogelijke behandeling, moeten de behandelinstellingen zo worden aangepast dat de energie in de regio van de hotspot wordt geminimaliseerd, terwijl de energie in de tumor zo maximaal mogelijk blijft (optimalisatie). In hoofdstuk 7 worden 2 optimalisatiemethodes gepresenteerd en gedemonstreerd. De eerste houdt alleen rekening met het energieniveau in de tumor bij aanvang van de behandeling, terwijl de tweede ook alvast rekening houdt met te verwachten hotspots. De tweede methode zorgt voor betere ruimtelijke controle over de energieverdeling en bij fantoomtesten bleek dat met deze methode beter rekening kon worden gehouden met de hotspot-klachten van een patiënt.

De tweede optimalisatieroutine hebben we vervolgens gebruikt in een gerandomiseerd onderzoek waarbij onze huidige behandelstrategie werd vergeleken met het gebruik van het hyperthermie planningssysteem tijdens de behandeling bij 36 patiënten met LUBK. De resultaten van dit onderzoek worden beschreven in hoofdstuk 8. Tijdens het eerste deel van de in totaal 5 behandelingen, bereikten we met het hyperthermie planningssysteem vergelijkbare resultaten als met onze huidige strategie. Maar in de 4^{e} en 5^{e} behandeling waren de resultaten slechter bij gebruik van het planningssysteem. Hoewel hyperthermie treatment planning niet meer weg te denken is uit de moderne klinische hyperthermie, is aanvullend onderzoek nodig.

Van zowel de voorbereidende handelingen die noodzakelijk waren als van de resultaten van dit onderzoek hebben we al een aantal belangrijke lessen geleerd. Zo hebben

we een beter werkende optimalisatieroutine ontwikkeld (hoofdstuk 7). Er is ook een manier gevonden om de positie van de patiënt tijdens de behandeling beter overeen te laten komen met de positie van de patiënt in het computermodel van het hyperthermie planningssysteem. Maar daarmee hebben we het verschil tussen het eerste deel van de behandeling, waarbij het planningssysteem even goed werkt als de huidige strategie, en het tweede deel waarbij dat niet het geval is, nog onvoldoende verklaard.

Verder onderzoek is vooral nodig op het gebied van de invloed van veranderingen in anatomie en fysiologie van de patiënt en de tumor tijdens de behandeling. Maar ook de correlatie tussen hotspots die de patiënt aangeeft en energieniveaus in het computermodel verdient meer aandacht. Daarnaast lijkt het potentieel van hyperthermie planning voor het optimaliseren van de energieverdeling beperkt te worden door de huidige apparatuur. Recent hebben we een nieuwe subsidie gekregen van de Nederlandse Kankerbestrijding om deze factoren nader te onderzoeken (EMC 2009-4448).

Een verbeterd hyperthermie planningssysteem kan immers en belangrijke tol spelen in het vergroten van de acceptatie van hyperthermie als oncologische behandelingsmodaliteit en het verbeteren van de kwaliteit van de behandeling.

Uit dit proefschrift blijkt dat hyperthermie een effectieve oncologische behandelingsmodaliteit is voor patiënten met lokaal uitgebreide baarmoederhalskanker, met bovendien weinig bijwerkingen. In het bijzonder voor behandeling van primaire locaal uitgebreide baarmoederhalskanker is het nut van hyperthermie evident, ook op lange termijn en in een grote groep ongeselecteerde patiënten. Recente technologische ontwikkelingen zullen uiteindelijk leiden tot betere reproduceerbaarheid en kwaliteit van de behandelingen en daarmee de acceptatie vergroten.

Chapter 12

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Student award of the 24th annual meeting of the European Society for Hyperthermic Oncology (ESHO), 2007, Prague, Czech Republic

Young Investigator Travel Award of the International Congress on Hyperthermic Oncology (ICHO) 2008, Munich, Germany

Curriculum vitae

Martine Franckena werd geboren op 10 maart 1978 te Rotterdam. In 1996 behaalde zij haar VWO diploma aan het Sint Laurenscollege in Rotterdam.
Een jaar later begon ze aan haar studie Geneeskunde aan de Erasmus Universiteit, waarop zij in 2003 haar artsendiploma ontving.

Na een jaar AGNIO-schap op de afdeling Neurologie van het Erasmus Medisch Centrum en een korte periode als AGNIO Interne Geneeskunde in het Reinier de Graaf Gasthuis, begon ze aan dit promotieonderzoek.

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Real integrity is doing the right thing, knowing that nobody's going to know whether you did it or not (Oprah Winfrey)

Perpetual optimism is a force multiplier (Colin Powell)

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Drs. D.H.M. Wielheesen en Dr. E. van der Wal: Beste Dennis en Edwin, dank voor jullie vrolijke en energieke begeleiding van mijn eerste stapjes in de wonderenwereld van de hyperthermie!

Ik denk altijd goed na voor ik iets stoms zeg (Loesje).

Dr. Ir. I.M.M. Paulides: beste Maarten, met name van je opbouwende kritiek, maar zeker ook je gevoel voor humor en je sterke relativerende vermogen heeft deze promovenda graag en veel gebruik gemaakt. Bedankt voor je geduld (omdat ik inderdaad meestal goed nadenk voordat ik iets stoms zeg)!

The road to success is dotted with many tempting parking places (anoniem)

Ir. R.A.M. Canters: Beste Richard, kom op, nog een klein stukje! Na jaren gezamenlijk worstelen met de problemen en uitdagingen rondom de invoering van hyperthermie treatmentplanning wil ik je graag bedanken voor je hulp aan en geduld met deze simpele dokter.

Drs. N.C.M.G. van der Voort van Zijp: Lieve Noelle, ook jij moet nog maar een klein stukje! En jij komt natuurlijk speciaal in dit dankwoord voor, omdat het erg fijn is om een lotgenoot te hebben die de meeste problemen als geen ander begrijpt, omdat ze met dezelfde worstelt. Ik hoop dan ook dat we elkaar nog vaak op kunnen monteren en een beetje verder helpen.

De koffie smaakt altijd net iets beter als iemand anders hem voor je zet (anoniem)

Laurens, Lia, Pia, Greta en Heleen: Met bewondering en waardering heb ik gezien hoe jullie bij iedere patiënt toch weer de juiste toon wisten te treffen.

Jurriaan, Thomas en Zef: Dank voor jullie vrolijke, soms nuttige en soms zinloze verhalen aan de koffietafel en natuurlijk ook voor het verlenen van allerlei hand- en spandiensten, met name op het computer vlak.

En Sandra en Astrid natuurlijk ook heel erg bedankt voor de praktische ondersteuning op allerlei gebied.

Vrienden zijn net als bomen; ze steunen je en geven rust als je door de bomen het bos niet meer ziet (anoniem)

Omdat dit in mijn ervaring ook voor goede (ex-)collega's geldt: Radiotherapeuten en radiotherapeuten (niet meer) in opleiding, dank voor jullie interesse en steun de afgelopen jaren!

When you come to the end of your rope, tie a knot and hang on (F.D. Roosevelt)

.. en gelukkig kan ik dan mijn vrienden en vriendinnen altijd bellen om stoom af te blazen! Ontzettend veel lol en steun heb ik van jullie gehad de afgelopen jaren, en ik hoop dat dat nog heel lang zo gaat blijven!

If you live to be a hundred, I want to live to be a hundred minus one day, so I never have to live without you (Winnie the Pooh)

Lieve Joost, Grote Liefde, steun en toeverlaat, ik hou van jou!

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: M. Franckena	PhD period: March 2005 – May 2008
Erasmus MC Department: Radiation Oncology	Promotor: Prof. dr. P.C. Levendag
Research School: Erasmus Postgraduate School Molecular Medicine	Supervisor: Dr. J. van der Zee and Dr. G.C. van Rhoon

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
- Biomedical English Writing and Communication	2006-2007	4 ECTS
Research skills		
- Classical methods for data-analysis (NIHES)	2005	5.7 ECTS
In-depth courses (e.g. Research school, Medical Training)		
- Introductie tot de Klinische en Fundamentele Oncologie	2005	1 week
Presentations		
- Randomized study on the effect of 3D SAR planning on temperature in the target volume during deep hyperthermia treatment in patients with cervical cancer	2006	
- The Dutch Deep Hyperthermia Trial: updated results in cervix cancer	2007	
- Deep hyperthermia in the treatment of locally advanced cervix cancer: current status and future perspectives	2008	
- Radiotherapie met hyperthermie voor de behandeling van locaal uitgebreid cervix carcinoom	2008	
- Hyperthermia in the treatment of locally advanced cervix cancer	2009	
- Cervix carcinoom met para-aortale lymfekliermetastasen: de rol van neoadjuvante chemotherapie	2009	
- Clinical implementation of hyperthermia treatment planning guided steering: a cross over trial to assess its current contribution to treatment quality	2010	
- Clinical procedure of deep hyperthermia	2010	
International conferences		
- 23rd annual meeting of the European Society for Hyperthermic Oncology (ESHO), Berlin, Germany	2006	
- 24th annual meeting of the European Society for Hyperthermic Oncology (ESHO), Prague, Czech Republic	2007	
- 10th International congress on Hyperthermic Oncology (ICHO), Munich, Germany	2008	
- 14e Jahrestagung der Deutschen Gesellschaft fur Radioonkologie (DEGRO), Vienna, Austria	2008	
- 25th annual meeting of the European Society for Hyperthermic Oncology (ESHO), Verona, Italy	2009	
- 2010 Society for thermal medicine meeting, Clearwater, Florida, USA	2010	
- 26th annual meeting of the European Society for Hyperthermic Oncology (ESHO), Rotterdam, the Netherlands	2010	
Seminars and workshops		
- Professional training 'Hyperthermia treatment planning with HyperPlan version 1.1'	2006	2 days
- Imaging workshop for MDs	2010	0.25 ECTS

2. Teaching activities		
	Year	**Workload (Hours/ ECTS)**
Lecturing		
- Onderwijs 'Hyperthermie' voor de oncologie-verpleegkundigen in opleiding	2010	3 hrs
- Model in 1 dag, TU Delft	2010	16 hrs
Supervising Master's theses		
- Ms. S. Heijkoop, medical student		
Other		
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