Superficial Hyperthermia for the Treatment of Breast Cancer Recurrence

MARIANNE LINTHORST

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Op de voorpagina en de titelpagina's staat het portret Carmen, gemaakt door Tony van de Vorst in 2002;
www.tonyvandevorst.eu
Carmen is gemaakt als een gepassioneerde onafhankelijke vrouw en daarin volledig vrij (vanuit zichzelf). De mannen hadden daar meer problemen mee en uiteindelijk moest ze sterven.

Superficial Hyperthermia for the Treatment of Breast Cancer Recurrence

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CONTENTS

Chapter 1

General introduction and outline of this thesis

INTRODUCTION

In 1978, a clinical research program on the use of adjuvant local hyperthermia in recurrent breast cancer was started in the Erasmus MC Cancer Institute. At that time, no effective treatment for locoregional failures in previously irradiated regions existed. In general, effectiveness of reirradiation at low dose was anticipated to be very poor and tolerance limits for reirradiation were not known [1,2,3].

Over time, multiple trials reporting strongly improved clinical results have generated a growing interest in and enthusiasm for applying hyperthermia in combination with other cancer treatment modalities [4]. Importantly, toxicity of adjuvant hyperthermia is acceptable.

Three and a half decades later, extensive progress has been made and hyperthermia is considered regular treatment for recurrent breast cancer in previously irradiated areas in the Netherlands.

This thesis summarizes the Rotterdam clinical research on superficial hyperthermia and shows the results of reirradiation and hyperthermia in patients with microscopic and macroscopic breast cancer recurrences, the tolerance of reirradiation and hyperthermia in breast cancer patients with reconstructions and the results of patients with radiation-induced angiosarcoma treated with reirradiation and hyperthermia. Further, it describes the innovations and adaptations in hyperthermia application procedure, technology, registration and treatment schedule that have been realized and it indicates future ways to improve treatment quality and clinical outcome.

HYPERTHERMIA

Hyperthermia is the use of elevated temperature for the treatment of cancer, i.e. tissue temperatures between 40 to 45°C. In general, treatment duration is 30-60 minutes and treatments are applied 2-6 times once or twice weekly. Hyperthermia results in cell death, by direct cytotoxicity. The direct cytotoxic effects are augmented in a nutritionally deprived chronically hypoxic and acidic environment in tumor tissue [5]. Hence heat alone applied at a temperature of 43°C can selectively destroy tumor cells without damaging normal tissue cells.

The quality of the hyperthermia treatment, i.e. the temporal behavior of the temperature in the tumor is usually expressed as the cumulative equivalent time at 43°C (CEM43) [6], using the formula:

$$CEM43 = \int_0^t R^{(43-T)} dt \text{ [min]}$$

In this formula T represents the actual applied temperature of the target tissue and R the factor to compensate for a 1°C temperature change. R is experimental determined and has been set at a value of 0.5 for T>43°C, i.e. the equivalent time doubles per degree temperature increase, and 0.25 for T£43°C, i.e. the equivalent time decreases by a factor of four per degree temperature decrease. In clinical practice the temperature distribution is heterogeneous. The quality of a hyperthermia treatment can be summarized by $CEM43T_{90}$ or $CEM43T_{50}$. T_{90} or T_{50} indicates the level where 90% or 50% of the temperature readings is above.

HYPERTHERMIA IN COMBINATION WITH RADIOTHERAPY

Hyperthermia has both complementary and sensitizing effects to radiotherapy.

Hyperthermia is especially effective in the hypoxic areas of the tumor, where radiotherapy is less effective. The sensitization effects of hyperthermia take place through multiple biological principles such as improving tumor blood flow and oxygenation, and inhibition of DNA repair [7-11]. Radiation induces DNA double strand breaks (DSBs) and elevated temperature interacts with various DNA repair processes [12]. For example, Krawczyk et al. [11] demonstrated that raising temperature results in degradation of BRCA2 and subsequently inhibits homologous repair of DNA damage. Further hyperthermia may cause an increase in tumor blood flow and an improvement in tumor oxygenation, which then results in a temporarily increased radiosensitivity [13-16].

The thermal enhancement ratio (*TER)* of normal cells as well as tumor cells depends on the height of the temperature and the duration of treatment at elevated temperature [4]. The maximum TER is realized when radiotherapy and hyperthermia are combined simultaneously, but then there is no difference between TER for tumor and normal tissue. In this case, a therapeutic gain is obtained only when the tumor is heated to a higher temperature than the normal tissue. On the other hand, when radiotherapy and hyperthermia are applied consecutively, the radiotherapy effect will remain enhanced in tumor much longer than in normal tissue. So, in order to obtain a satisfactory TER in tumor tissue with minimum or no enhancement in normal tissue, it is common practice to apply hyperthermia with a time interval between radiotherapy and hyperthermia.

Several studies have examined the effect of sequence and interval between radiotherapy and hyperthermia on mouse tumors and normal skin [17,18]. For the sequence of radiotherapy followed by hyperthermia, they showed that the TER of radiotherapy damage in skin returns to 1 within 2 hours after the radiotherapy treatment; whereas even after 8 hours the TER for tumor cells is still at 1.5. Therefore, therapeutic gain is achieved, when radiation and hyperthermia are combined with a time interval. With a 2-4 hours interval the TER in normal tissue may have completely disappeared (Figure

1). Only when selective tumor heating can be achieved, simultaneous heating can be considered, resulting in maximum therapeutic gain.

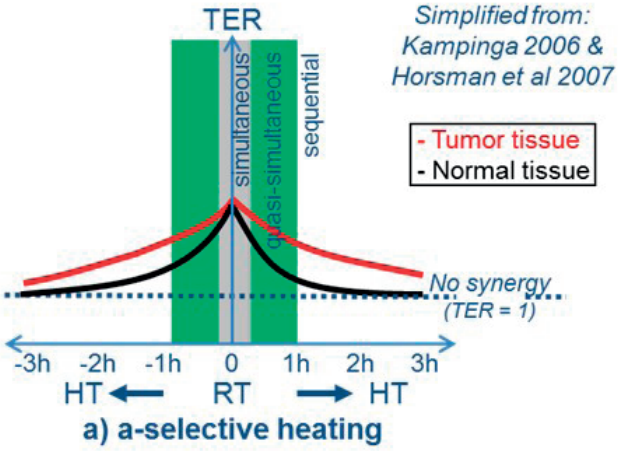

Figure 1. A-selective heating: Top panel; Thermal enhancement ratio (ratio of the radiation doses for radiation alone and radiation plus heat to produce the same tumor effect) as a function of the time interval and sequence between heating and irradiation. First part, heat before irradiation and second part, heat after irradiation. Lower panel; Clinical impact of TER (= 1.5) for simultaneous or sequential heat and radiation treatments in tumors assuming equal temperature of normal and tumor tissue (courtesy of M.M. Paulides).

The effectiveness of hyperthermia added to radiotherapy for multiple cancer types has been shown in several randomized trials [4,19-37].

Superficially hyperthermia combined with radiotherapy is mainly applied in the treatment of locally advanced breast cancer, malignant melanoma, and advanced neck nodes. Improved treatment outcome was found in all these tumor types with a TER of approximately 1.5.

Ten randomized trials investigated the value of superficial hyperthermia in combination with radiotherapy. Five of these trials on breast cancer were combined into one study and are published by Vernon et al. [19]. The study of Jones et al. compared addition of low vs. high dose hyperthermia to radiotherapy [20]. Six trials show significant improvement of complete response and/or local control. All studies are summarized in Table 1.

Table 1. Results of randomized clinical trials in superficial hyperthermia

Study	N	Tumor type	RT+HT (%)	RT (%)	Significant difference
Perez et al. [38,39]	236 patients	Superficial tumors (primarily chest wall and neck nodes)	32	30	No
DHG [19]	38 patients	Chest wall and some intact breast	74	74	No
MRC-BrI [19]	30 patients	Intact breast	56	67	No
MRC-BrR [19]	149 patients	Chest wall and some intact breast	57	29	Yes
ESHO [19]	56 patients	Chest wall and some intact breast	78	38	Yes
PMH [19]	33 patients	Chest wall	29	31	No
Overgaard et al. [29]	128 lesions	Melanoma	62	35	Yes
Egawa et al. [37]	92 patients	Various	82	63	Yes
Valdagni et al. [22,27]	41 lesions	Lymphnodes of head and neck tumors	83	41	Yes
Jones et al. [20]	122 patients	Superficial tumors (primarily chest wall and neck nodes; melanoma)	66 (no prior RT)	42	Yes

Legend to Table 1:
RT = Radiotherapy; HT = Hyperthermia

The greatest benefit of adding hyperthermia to radiotherapy has been seen in patients previously irradiated. In the study by Jones et al. [20] previously irradiated patients had a complete response rate of 24% after radiotherapy plus low dose hyperthermia and 68% after radiotherapy plus high dose hyperthermia. In the ESHO trial (published in [19]) the complete response rates were 38% after reirradiation alone, and 78% after combined treatment. The Jones et al. trial [20] confirmed the results of the ESHO and the MRC-BrR trials. In four trials there was no apparent difference between the treatments. The lack of therapeutic gain can be explained by the small number of patients and/or poor quality of the hyperthermia treatment [38]. All trials show comparable acute and late toxicity in both treatment arms: radiotherapy alone versus radiotherapy and hyperthermia, except for a higher incidence of thermal blisters in the hyperthermia group.

HYPERTHERMIA IN COMBINATION WITH CHEMOTHERAPY

In combination with chemotherapy hyperthermia has similar complementary and sensitizing effects. The concentration and the effect of chemotherapy will be less in the insufficiently perfused regions [40]. The most important mechanisms for interactive effect of hyperthermia and chemotherapy are an increased intracellular drug uptake, enhanced DNA damage and higher intratumor drug concentrations, resulting from thermally induced increased blood flow. The elevated temperature initiated inhibition

of DNA damage repair interferes with multiple pathways, through unclear mechanisms [7-13]. Several clinical studies on the addition of hyperthermia to chemotherapy has shown improved treatment outcome. The latest study of Issels et al. [35,36] showed in a large randomized trial that hyperthermia added to chemotherapy improves the overall 5 years survival in patients with soft tissue sarcoma by 12%.

BREAST CANCER RECURRENCE

Background

A locoregional breast cancer recurrence can occur at the chest wall region or in the axillary, infraclavicular, parasternal or supraclavicular lymph nodes after primary treatment [41]. In a comprehensive literature review of Clemons et al. [42] the overall 10-year incidence of relapse is 13% after mastectomy and 12% after breast conserving therapy (BCT). The chance of developing a local recurrence is mainly depending on the tumor stage and age. In ductal carcinoma in situ the 10-year local recurrence chance is 10-15% after BCT and 0-4% after mastectomy. Half of these recurrences is invasive [43,44].

In trials that randomized between mastectomy and BCT the local recurrence rate after mastectomy is usually lower than after BCT without affecting survival, including in the long term [45,46]. Young age is specifically for BCT an unfavorable prognostic factor for the probability of local recurrence [45-47].

Treatment of breast cancer recurrence

For patients with a recurrent breast cancer the treatment of choice is surgery. If surgery results in an irradical resection additional treatment is required. For radiotherapy naïve patients, full dose radiotherapy provides a good probability of local control.

The treatment of locoregional failures (microscopic or macroscopic) in previously irradiated regions presents a difficult problem as the radiation dose that can be given without a high risk of unacceptable toxicity is lower than considered adequate [1-3,35,36]. For these patients the recommended treatment is reirradiation combined with hyperthermia.

In the Netherlands patients are selected for reirradiation and hyperthermia on the following criteria: recurrent tumor, inoperable or after microscopically incomplete excision; and systemic therapy is either inadequate to control regional tumor, or is deemed inappropriate, in the absence of (symptomatic) systemic disease [48].

Many patients [49] who experience a recurrence have disease that has metastasized or spread throughout the body. These patients require systemic treatment; this includes chemotherapy, hormonal therapy, and targeted therapies, such as Herceptin (chemical name: trastuzumab) [50,51].

APPLICATION OF RADIOTHERAPY PLUS HYPERTHERMIA FOR BREAST CANCER RECURRENCE: CLINICAL PRACTICE

Current treatment schedules for superficial hyperthermia treatment

When we started combining reirradiation with hyperthermia, the tolerance limits for reirradiation were not known. Initially the radiation dose was low, with total doses of 12–25 Gy, in fraction sizes of 2 to 4 Gy. After a period of cautiously increasing the dose we arrived at the current reirradiation schedule of 8 times 4 Gy, twice weekly [48,52]. This appeared to be a safe, effective and well tolerated schedule and was therefore selected as the standard. In this schedule hyperthermia was given twice weekly after radiotherapy with at least 3-day intervals to avoid thermotolerance [53].

In 1996 we had a capacity problem for superficial hyperthermia. In view of the results of several published randomized studies comparing a low with a high number of hyperthermia treatments, usually one versus two treatments per week, which showed no difference in results [54], we decreased the number of hyperthermia sessions to four.

Technique/ procedure

Hyperthermia is prescribed for 60 minutes, including a heating-up period of 10 minutes, and is applied after radiotherapy. Before the first treatment catheters for thermometry are inserted subcutaneously in the treatment volume, with preferably at least one interstitial temperature measuring point below each antenna.

Multisensory probes are always placed in the catheters and multi- or single-sensor probes are placed superficially, prior to each hyperthermia treatment [55]. The temperature of the tissue surface is controlled by a temperature controlled, perfused water bolus. The temperature of the circulating water in the bolus is selected in accordance to the desired heating depth as published in a previous paper [56].

Superficial hyperthermia strategy

Superficial hyperthermia has been used for more than 3 decades in the Netherlands. The Erasmus MC protocol "superficial hyperthermia" prescribes how to start a treatment and how to adjust treatment settings such as power and water bolus temperature during treatment to obtain maximum achievable temperatures in the target volume.

The adjustments in treatment settings are based on 2 sources of information: interpretation of the measured temperatures during treatment and feedback of the patient. The aim is to have all interstitial temperatures above 40°C throughout the target volume. The allowed interstitial normal tissue temperature is maximum 43°C during the first 30 minutes, thereafter maximum 44°C. In tumor tissue at a distance of more than 10 mm from normal tissue higher temperatures are allowed. A power-related unpleasant feel-

ing reported by the patient is considered as a too high temperature and reason to adjust treatment settings [45,57].

The Rotterdam superficial hyperthermia system

In most centers applying hyperthermia, microwaves are used for tissue heating. The custom-built Rotterdam superficial hyperthermia system consist of six solid-state amplifiers, operating at 433 MHz and each capable of delivering an RF-output of 200W for the Lucite Cone applicators (LCAs) [58].

The LCA has a square aperture of 10 x 10 cm^2; the effective field size is up to 80% of the aperture. With six applicators combined an area of 20 x 30 cm^2 can be effectively heated to a depth of up to 4 cm [45,55]. In comparison to the effective field size of a conventional waveguide the heating area of the LCA is ± 2.5 times larger [58]. The applicator array is chosen such that the radiation field is widely covered with an overlap of the applicator aperture by 10 mm all around [54].

For thermometry, a 24-channel fiber-optic system (in this study: FT1210 and FT1310, Takaoka, Japan) is used with five multisensor probes (with up to four sensors per probe) and four single-sensor probes for continuous measurements during treatment [54].

The system provides automatic data registration. The software provides remote continuously control of the RF-output (0-200W) per LCA and visualization of forward and reflected power (Figure 2). Temperatures are measured interstitially, within catheters, and on the surface. The monitor shows time-temperature plots of each measurement point under its corresponding LCA footprint and the actual temperature distribution is shown onto a representation of the patient anatomy for ease of interpretation (see Figure 3).

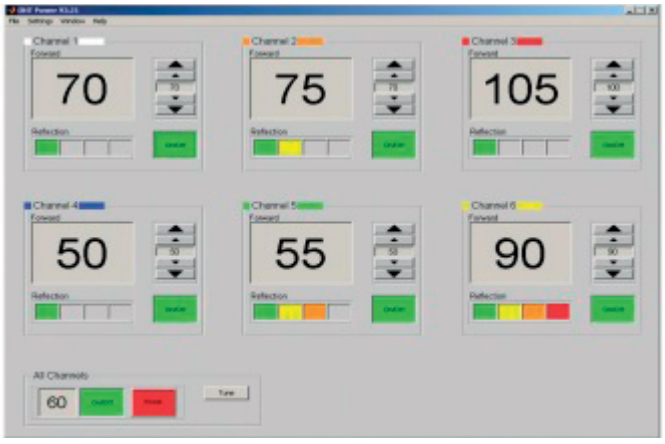

Figure 2. Monitor for superficial hyperthermia treatments for power steering. In large font the measured forward power is indicated and in small font the power setpoint. The reflected powers are represented graphically in a color code (green <5%, yellow 5-10%, orange 10-15%, red >15% reflected power). (Figure adapted from van der Zee [54]).

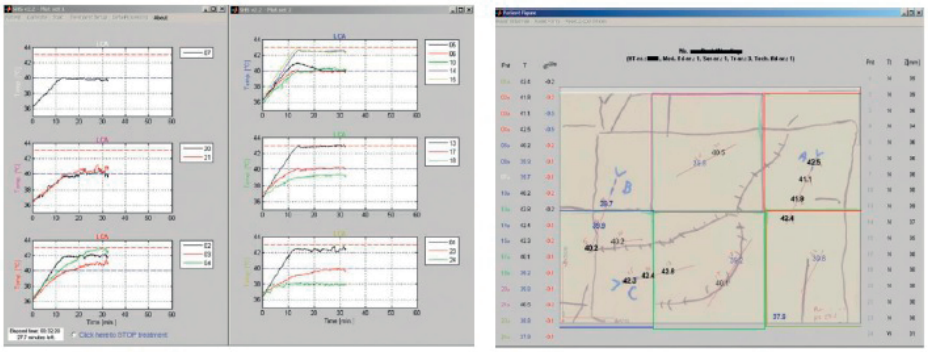

Figure 3. Screenshot of the temperature monitoring. On screen (a), temperature-time graphs for the sensors below each applicator are shown. On screen (b), the measured temperatures are mapped onto a sketch that includes anatomical features, the location of the tumor and scar tissue, apertures of the applicators, catheter tracks and margins of the radiation field. For each measurement point the tissue type, depth, temperature and temperature difference over 20 seconds is also shown. (Figures adapted from van der Zee [54]).

During treatment, the hyperthermia technician uses the presented interstitial and skin temperatures and the feedback of the patient to optimize treatment.

For each treatment the Tmax, Tave, T90 and CEM43 is calculated from measurements taken after the 10 minutes heating-up phase and stored in the treatment report together with the complaints of the patient.

HYPERTHERMIA TREATMENT QUALITY

From experimental studies it is clear that the effect of hyperthermia depends of temperature elevation and duration of treatment. Defining the thermal dose for a clinical treatment, however, is difficult due to the temporal and spatial inhomogeneity of temperature distribution. Currently there is no objective indicator for hyperthermia treatment quality. Several thermal dose parameters derived from measured temperatures, and SAR coverage of the target volume have been suggested and investigated as quality indicators.

Thermal dose-effect studies

For thermal dosimetry analysis the minimum, mean, maximum or other values representing the temperature distribution over time or CEM43 have been studied. For all kind of thermal dose parameters, a dose-effect relationship has been demonstrated in one or several retrospective studies but not consistently. [19,39,60]. A major point of concern

for those studies is that the parameter found retrospectively, might well be just a surrogate for another important prognostic parameter.

For instance, de Bruijne et al. [59] demonstrated that the $CEM43T_{90}$ dose effect relationship with complete response disappeared after correction for the relation between $CEM43T_{90}$ and tumor volume.

The clinical study of Jones et al. [20] and the animal study of Thrall et al. [64] have prospectively shown the existence of a thermal dose effect. Thrall et al. [64] treated canine sarcomas with radiotherapy and hyperthermia. They randomized the dogs for hyperthermia treatments with a low (2-5 $CEM43T_{90}$) or high (20-50 $CEM43T_{90}$) thermal dose. Jones et al. [20] treated superficial tumors with thermoradiotherapy. All patients received hyperthermia for 60 minutes for a test treatment and, when deemed heatable, these patients were randomized between further treatment with or without hyperthermia. The patients in the hyperthermia group were given up to a maximum of 10 hyperthermia treatments in order to apply a $CEM43T_{90}$ of at least 10 minutes. A critical remark should, however, be made for both studies. The high dose was obtained by increasing the duration and number of the hyperthermia sessions. Control of the temperature distribution was not easy even though Thrall et al. used extensive thermometry and the animals were anesthetized during treatment [64]. In Jones et al. [20] thermometry was limited to one catheter, so that it can be questioned how reliable the derived T90 represented the actual temperature distribution.

Following the study of Jones et al. [20] we evaluated the prognostic value of $CEM43T_{90}$ for complete response rates in our patients. Similar complete response rates were found for patients who were deemed heatable or unheatable according to the Jones et al. [20] criterion and for patients who received less or more than 10 $CEM43T_{90}$ during the whole treatment series. We also did not find a dose-effect relationship for $CEM43T_{90}$ in multivariate analysis.

SAR dose-effect studies

In other studies, the prognostic value of energy distribution was investigated. Myerson et al. [65] and Lee et al. [66] demonstrated that coverage of the tumor by the applicator's 25% iso-SAR (2D) contour correlated positively with both complete response rate and local tumor control. A retrospective study by our group demonstrated the impact of heating technology: large tumors (diameter > 3 cm) heated with 433 MHz (penetration depth (PD) 3.5 cm) responded much better than those heated with 2450 MHz (PD 1.7 cm), i.e. a complete response rate of 65% versus 31%, respectively [45]. In the same publication we reported that it is important to heat the whole volume at risk, in practice the whole radiotherapy field.

Potential of hyperthermia treatment planning

An objective approach to define treatment quality would be to use the 3-dimensional (3D) energy distribution predicted by hyperthermia treatment modeling. In recent years, hyperthermia treatment planning has been developed to a useful tool. With hyperthermia treatment planning, a complete 3D SAR and temperature distribution in the treatment volume can be calculated. Different dose parameters derived from the energy distribution can be used to study relationships with clinical outcome retrospectively, using the actual applicator set-up. If such a SAR dose-effect relation can be demonstrated, SAR steering can be used to optimize hyperthermia treatments in a prospective manner and interstitial thermometry can be abandoned.

Kumuradas and Sherar [67] were the first to demonstrate the ability of hyperthermia treatment planning to predict the 3D SAR and temperature distribution obtained during heating of a patient with a superficial chest wall tumor. The superficial hyperthermia treatment planning system available at the Erasmus MC, SEMCAD X (= Qimulation platform for ElectroMagnetism Compatible, Antenna Design and Bosimetry), has been shown to predict energy distribution reliably [68]. The performance of the 433 MHz applicators in phantoms is predicted well by the system [69]. The use of SEMCAD X in five patients with various unusual problems was very helpful in either acceptance of these patients for hyperthermia treatment, or for selection of an effective treatment technique [70].

THIS THESIS

In this thesis, the development in the use of hyperthermia in patients with breast cancer recurrence in the Erasmus MC Cancer Institute is presented and the research in this patient group is presented.

In **chapter 1** a brief introduction to the rationale behind hyperthermia and my research is presented. **Part 1** of this thesis includes studies on clinical results in subgroups of these patients. **Chapter 2** describes the development of superficial hyperthermia for breast cancer recurrences at the Erasmus MC, presenting the treatment procedure and clinical results over the years and the lessons learned. This chapter further contains a summary of published clinical results with complete response rates varying widely from 20% to 95%, whereas the Erasmus MC group achieves complete response rates of 65% to 87%. In **chapter 3** the effect of a combined treatment of surgery, reirradiation and hyperthermia therapy in radio-induced angiosarcoma of the chest wall is presented. **Chapter 4** presents toxicity and local control following reirradiation and hyperthermia in breast cancer patients with reconstructions. In **chapter 5** the results in 248 patients with macroscopic disease treated with 4 hyperthermia treatments and the impact of

prognostic factors are described. Treatment outcome is compared to the results of randomized trials to investigate whether the high complete response rate achieved in randomized trials is maintained in a large unselected group of patients. **Chapter 6** presents the results of reirradiation and hyperthermia after surgery for recurrent breast cancer showing that treatment with reirradiation plus hyperthermia results in long lasting local control.

Part 2 of this thesis focus on the current role and future perspectives of the clinical use of hyperthermia treatment planning. In **chapter 7** the procedure for creating a 3D model for superficial hyperthermia treatment planning is described. The objective of this work was to apply treatment modeling for superficial hyperthermia in a well-defined group of patients to investigate the potential of predicted 3D energy as source for a dose parameter that is prognostic for treatment outcome. In **chapter 8**, the development and first results of a 3D model for superficial hyperthermia in breast cancer patients to enable optimization before the start of the hyperthermia treatment is described.

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Part 1

Motivation and clinical studies

Chapter 2

Reirradiation combined with hyperthermia in breast cancer recurrences: Overview of experience in Erasmus MC

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ABSTRACT

For superficial hyperthermia a custom-built multi-applicator multi-amplifier superficial hyperthermia system operating at 433 MHz is utilised. Up to 6 Lucite Cone applicators (LCA) can be used simultaneously to treat an area of 600 cm.

Temperatures are measured continuously with fibre optic multi-sensor probes. For patients with non-standard clinical problems, hyperthermia treatment planning is used to support decision making with regard to treatment strategy.

In 74% of our patients with recurrent breast cancer treated with a reirradiation scheme of 8 fractions of 4 Gy in 4 weeks, combined with 4 or 8 hyperthermia treatments, a complete response (CR) is achieved, approximately twice as high as the CR rate following the same reirradiation alone. The CR rate in tumours smaller than 30 mm is 80–90%, for larger tumours it is 65%. Hyperthermia appears beneficial for patients with microscopic residual tumour as well.

To achieve high CR rates, it is important to heat the whole radiotherapy field, and to use an adequate heating technique.

INTRODUCTION

Reirradiation combined with hyperthermia is an effective treatment for recurrent breast cancer. Results from five randomised trials have shown that the complete response (CR) rate in breast cancer recurrences increases from 41% to 59% when hyperthermia is added to radiotherapy [1]. For the subgroup of patients treated within the ESHO 5-88 trial with a reirradiation schedule of 8 fractions of 4 Gy, applied twice weekly, the CR rate even increased from 38% after radiation alone to 78% after combined treatment.

In Rotterdam, the first patient with recurrent breast cancer was treated with hyperthermia in 1978. Over the years, many alterations were made in hyperthermia and thermometry equipment, in treatment procedure, registration and treatment scheme. In this review we take you through some of the history of hyperthermia in our department, and present the resulting treatment procedure and a summary of our clinical results.

HISTORY OF EQUIPMENT USED

Heating equipment

In 1978 we started our clinical research on hyperthermia with the Pomp-Siemens whole body hyperthermia cabin which included several applicators for local hyperthermia [2]. These were condenser plates operating at 27 MHz and dipole antennas operating at 433 MHz or 2450 MHz. With these applicators, originally designed for physiotherapy, we treated patients who were reirradiated for palliative reasons, among whom patients with recurrent breast cancer.

The first applicators developed in our department were air-filled waveguides operating at 2450 MHz with aperture sizes of 8×4 cm^2 and 8×6 cm^2. The rectangular shapes allowed us to use combinations of up to eight applicators at the same time. The number of amplifiers was still limited so that up to four applicators were coupled to one power supply, without the possibility to control power supply to the individual applicators. Surface cooling, when necessary, was performed by directing air currents under the applicators.

In 1985 we started using custom built water-filled waveguides operating at 433 MHz with a radiating opening of 10×10 cm^2. Until 1987 we could use maximally two applicators simultaneously, thereafter five and some time later six. Each applicator was supplied with independent power control [3]. These standard waveguides were replaced in 1996 by Lucite cone applicators (LCA), with a larger effective field size (EFS). The EFS of the LCA is approximately 100 cm^2, which is considerably larger than the 33 cm^2 of the standard waveguide [4]. The performance of both waveguide types was tested in the clinical setting by treating patients alternately by standard waveguides and LCA arrays. The

average invasive temperature was 0.28°C higher with the LCA's than with the standard waveguides, which was primarily the result of higher temperatures in the periphery of the treatment field. A perfused waterbolus was used with the 433 MHz waveguide applicators to control surface temperatures.

Waterbolus dimensions and selection of waterbolus temperature

The waterbolus placed between water-filled waveguides and skin (Figure 1) has two functions: improvement of coupling between the applicators and tissue and control of superficial temperature.

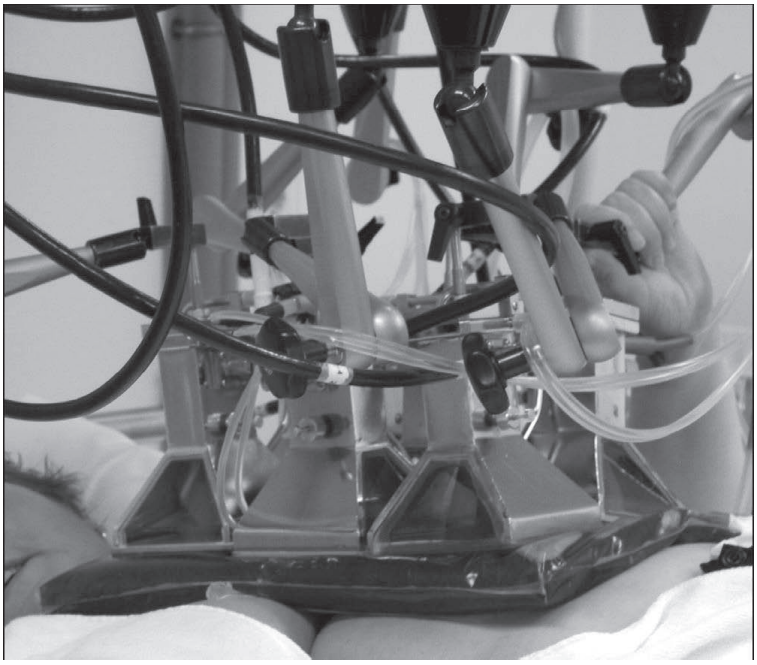

Figure 1. Close-up of the applicators placed above the thoracic wall, on top of the perfused waterbolus.

We investigated the effects of waterbolus configuration on the EFS of the LCA [5]. Placement of the LCA near the waterbolus edge reduced the EFS considerably. With waterbolus heights of more than 2 cm the EFS became more sensitive to distance to the waterbolus edge.

Based on the results, the guideline now is that the height of the waterbolus should not exceed 2 cm and the waterbolus should extend the LCA aperture at least 2.5 cm, especially at the Lucite windows. The two main parameters used for optimizing the temperature distribution are the electromagnetic power and the waterbolus temperature. A 3D model was set up to simulate an abstraction of the treatment. In the model a convec-

tion coefficient for the waterbolus to skin surface was employed, which was measured for waterboluses of different sizes. The effect of perfusion and fat layer thickness were investigated in a layered model.

The performance of the general model was verified against clinical data. The model was found to predict the temperature distribution well on a global view, and was used to set up guidelines, specific for our equipment, for the waterbolus temperature selection for various target depths and applicator arrays [6].

Thermometry

We started with thermocouples, either single sensor probes within a needle, or multi-sensor probes within a catheter. These probes had to be placed perpendicular to the direction of the electric field (E-field) and temperatures were measured every 5 minutes with the power shut off. Since 1987 temperatures are measured continuously during treatments by a 24-channel fiber-optic system, with which five multi-sensor probes (up to four sensors) and four single sensor probes are available (Takaoka FT1210).

Closed-tip catheters are placed interstitially immediately before the first treatment and left in place till after the last treatment. The aim is to have both interstitial and superficial thermometry under each applicator. Usually, these catheters cause no clinical problems [7].

Use of hyperthermia treatment planning

Hyperthermia treatment planning tools have a significant potential to further improve the quality of hyperthermia treatments, by providing insight into the 3D absorbed power distributions. In some patients with non-standard clinical problems, SEMCAD X [8] hyperthermia treatment planning was successfully used to support decision making with regard to the treatment strategy [9]. Two cases are shortly described here.

A patient with recurrent breast cancer had undergone open heart surgery in the past, and sternal cerclage wires were within the target volume for hyperthermia. Treatment planning showed that the distortion of the electromagnetic field by the cerclage wires was neglectable with the E-field direction perpendicular to the cerclage wires. This patient was treated without problems with the applicator configuration advised by the planning. The tumour of a patient with a recurrent breast cancer in the infraclavicular region was located at a depth of 37 to 54 mm below the skin, which is beyond the superficial system's standard maximum target depth of 40 mm. However, the subcutaneous fat layer in this patient was above average: 29 mm. Because the effective conductivity of fatty tissue is relatively low, it could be anticipated that power absorption in the fat layer would be limited, and that the remaining power at depth would be sufficient within the tumour.

This was confirmed by hyperthermia treatment planning, and during hyperthermia treatment the intratumor temperature reached therapeutic levels.

Treatment scheme

When we started combining reirradiation with hyperthermia, the tolerance limits for reirradiation were not known. We started cautiously, with total doses of 12-25 Gy, in fraction sizes of 2 to 4 Gy. To avoid thermotolerance, we chose a treatment scheme of hyperthermia twice weekly with at least 3-day intervals. In order to sensitize every radiation fraction, radiation was also given twice weekly, in fractions of 4 Gy. Hyperthermia was given after radiotherapy on the basis of experimental studies showing that maximum therapeutic benefit can be obtained with that sequence [10-14].

When we did the first evaluation of the results of reirradiation and hyperthermia in 97 patients with recurrent breast cancer, we found a large influence of the applied reirradiation dose on CR rate. With a total dose of less than 29 Gy the CR rate was 24%, while it was 58% after a dose of 30 to 32 Gy. Time till progression was median 4 months after a partial response (PR) and 26 months for CR [15]. The reirradiation schedule of eight fractions of 4 Gy appeared safe, effective and well tolerated and was therefore selected as the standard scheme.

In 1996 we had a capacity problem for superficial hyperthermia. Taking in mind the results of several published randomised studies comparing a low with a high number of hyperthermia treatments, usually one versus two treatments per week, which showed no difference in results [16-21], we decreased the number of hyperthermia sessions to four.

The number of patients was insufficient to do a randomised trial ourselves and we planned to evaluate the results after treating a sufficient number of patients with the new schedule. We did a first analysis of results in patients treated with four hyperthermia sessions in 2004 [22] and compared these to those in patients who received eight hyperthermia sessions: 40 patients received four and 132 patients eight hyperthermia treatments. For patients with a maximum tumour diameter ≤ 30 mm CR rate was 86% after eight treatments and 82% after four treatments (not significant).

For patients with larger tumours, CR rate was 59% after eight treatments and 65% after four treatments (not significant). The preliminary conclusion is that a decrease in number of hyperthermia treatments does not lead to inferior results. On the other hand, the hoped-for decrease in hyperthermia toxicity was not observed as well.

A problem with this comparison is that, at around the same time that we changed the number of hyperthermia treatments, we also replaced the standard waveguide with the LCA, with which we achieved average 0.28°C higher temperatures. Although it is unlikely that a 0.28°C higher temperature compensates for 240 minutes treatment duration, we

will perform a detailed analysis of prognostic factors including thermal dose parameters in these patients.

Footnote;

A retrospective evaluation was performed to compare the outcome in patients with breast cancer recurrence treated with reirradiation and either 8 or 4 hyperthermia treatments. One hundred forty-four patients were treated with 8 hyperthermia treatments and from 1996 to 2010, 394 patients were treated with 4.

Hyperthermia was given in addition to reirradiation with 8 fractions of 4 Gy in 4 weeks. The median follow-up for all patients was 52 months. Overall, CR was achieved in 73% of all patients, 79% with 8 hyperthermia treatments and 70% with 4 hyperthermia treatments ($p = 0.083$). One, 3 and 5 years LC rates with 8 hyperthermia treatments were 79%, 57%, and 57%, and with 4 hyperthermia treatments 73%, 58%, and 58%, respectively, not significantly different ($p = 0.679$).

Thermal parameters were similar. The cumulative incidence of late toxicity was 2.6%, 5.0% and 6.2% at 1, 3 and 5 years, respectively. Late grade 3 and 4 toxicity was seen in 25 patients, four in the 8 hyperthermia group and 21 in the 4 hyperthermia group ($p = 0.172$). A detailed analysis of prognostic factors including thermal dose parameters in these patients is currently studied and will be published in the near future.

A problem with this comparison is that; Around the same time, we also replaced the standard waveguide with the LCA, with which we achieved average 0.28°C higher temperature compensates for 240 min treatment duration, the population changed from only macroscopic tumors to a group with more microscopic and less macroscopic tumors, the quality of the treatment of patients with breast cancer recurrences has undergone evolutionary changes over the last 30 years. The use of chemotherapy and hormonal therapy has been changed over the time.

LESSONS LEARNED

No electromagnetically induced hyperthermia in anesthetized patient

We started our clinical hyperthermia research with the idea to apply local hyperthermia during whole body hyperthermia, in order to achieve a more homogeneous temperature distribution.

In the first patient in whom we tried whole body hyperthermia, it appeared that a core temperature > 40°C was not tolerated by the conscious patient. We therefore gave subsequent treatments under general anesthesia. During the third treatment, core temperature was increased to a temperature of 41.6°C and the recurrent tumour at the chest wall was simultaneously heated with 433 MHz. One of the thermometry probes suddenly showed a steep temperature increase to maximum 47°C.

After the treatment, the patient developed a severe third degree burn of the thoracic wall with a diameter of 100 mm and including ribs [23].

We have seen similar toxicity in two other patients who were treated under general anesthesia. During normothermic regional isolation perfusion of the leg for multiple skin metastases of malignant melanoma, local hyperthermia was given to one of the metastases.

Hyperthermia was given with a 2450 MHz dipole antenna with a diameter of 80 mm and interstitial temperatures were average between 39.2°C and 40.9°C.

In two of three patients treated this way, in whom the measured maximum temperature had been 41.4°C and 40.3°C, a third-degree burn developed.

Unnoticed hot spots resulting in toxicity can occur in conscious patients as well, at sites of decreased sensitivity due to previous surgery, but usually some sensation of pain limits the extent of the damage.

No stray irradiation near linear accelerator

For a short period of time, we treated our patients in an orthovoltage room which was located next to a linear accelerator. The microwave equipment at that time consisted of a circular field dipole antenna connected to a generator operating at 433 MHz. In the Netherlands, 433 MHz can be used without shielding. The linear accelerator was a CGR-MeV Sagittaire. We found that the stray microwave radiation, at intensities of about 0.4 mW/cm^2 in the control room of the accelerator interfered with the beam energy settings. The microwave interference caused an increase in beam energy. At maximum power output this was a change from 25.5 to 29.1 MeV [24]. The most practical solution to this problem was to transfer the hyperthermia treatment to another room.

Heating technique is important for treatment outcome

In the first evaluation of treatment results in the group of patients treated with eight fractions of 4 Gy and hyperthermia, we found a CR rate of 58% [15]. When we evaluated later a larger group of patients, the CR rate was 71%.

A multivariate analysis showed that two factors were independent and significantly associated with local control probability: tumour size (maximum diameter < 3 cm or > 3 cm) and used equipment (2450 MHz or 433 MHz equipment) [25]. The better overall results were the effect of a large improvement in CR rate in the larger tumours: 31% with 2450 MHz heating and 65% with 433 MHz heating.

In tumours < 3 cm the results of 2450 and 433 MHz heating were not different; approximately 90% CR. The CR rate achieved with 2450 MHz in the larger tumours was similar to the results of reirradiation with 8×4 Gy without hyperthermia: 28% in the RTOG study [26] and 38% in the ICHG study [1]. Apparently, 2450 MHz heating was inadequate

for the larger tumours. A disadvantage of using 2450 MHz compared to 433 MHz is the smaller penetration depth and thereby a smaller heated volume.

From this experience we learned that patients should not be accepted for hyperthermia treatment if we expect that we cannot adequately heat the whole target volume.

Whole reirradiation volume is target for hyperthermia

Until July 1987, the aim of treatment was to heat the macroscopic tumour. With that approach, we observed in a few patients tumour regrowth within the radiation field, outside the margin of the hyperthermia field. At the same time, there was no regrowth within the combined treated field. Since then we choose the applicator set-up such that the radiation field is widely covered.

Further experiences suggest that hyperthermia is an effective additional treatment for microscopic tumour. The patient population in which we found better outcomes after 433 MHz heating compared to 2450 MHz heating included total 15 patients with microscopic disease. Three patients treated with 2450 MHz equipment all developed in-field tumour regrowth 10-12 months after start treatment.

In 12 patients treated with 433 MHz equipment only two in-field re-recurrences occurred, 10 and 13 months after start treatment. Three patients died with a locally controlled tumour after median 10 months and seven patients were still alive with a locally controlled tumour 16-70 months after treatment. This is a significant difference, suggesting that good-quality hyperthermia is effective here as well [25].

A tumour near the eye can be treated successfully

A patient was referred with a metastatic lesion of breast cancer in the lower eyelid, recurring after two radiation treatments with partially overlapping fields. The tumour was progressive under second-line hormonal therapy and she was unfit for chemotherapy. The first local treatment of this tumour had been irradical resection (positive surgical margins) and radiotherapy, 10×3 Gy plus boost of 10×2 Gy. The tumour recurred 9 months later at the margin of the radiotherapy field, was treated again with irradical surgery and 15×2 Gy. Four months later the tumour recurred again. With the patient two treatment options were discussed: surgery, including enucleation of the eye, or reirradiation with hyperthermia, with unknown risk of toxicity like eyelid fibrosis, retina damage, cataract and glaucoma. The patient preferred radiotherapy and hyperthermia. During radiotherapy the eyeball was shielded with a leaden contact lens.

We applied eight fractions of 4 Gy and four hyperthermia treatments of 60 minutes. The tumour regressed fast with a complete regression established one week after the last treatment. During follow-up, local tumour control was maintained.

The only side effect was a dry eye for which the patient used eyedrops. Vision was unchanged. The patient died 22 months after the last treatment owing to a cerebrovascular accident, unrelated to breast cancer [27].

No excessive toxicity in patients with tissue transfers

Between 1992 and 2009, 36 patients were treated on total 37 tissue transfers, including split skin grafts (15), transverse rectus abdominis myocutaneous (1), latissimus dorsi (14) or rhomboid (1) flaps or a combination of grafts and flaps.

The guidelines for treating these patients were not different from those for other patients. Hyperthermia toxicity (according to CTCAE version 3) grade 2 (minimal medical intervention required, no interference with ADL (activities of daily life) occurred in four patients and grade 3 (surgical intervention required and/or interference with ADL) in three. The incidence of toxicity appears not much different from that observed in patients without tissue transfer and is acceptable [28].

CURRENT TREATMENT PROCEDURE

Patient selection

In the Netherlands, national guidelines prescribe reirradiation and hyperthermia for recurrent breast cancer after previous irradiation in the same area, when the expected survival is 6 months or more. This concerns inoperable tumours, irradically resected tumours (tumour positive surgical margins), or radically resected tumours with a high risk of re-recurrence (multifocal recurrences or second recurrences).

The aim of the treatment is a CR, which means that it must be possible to heat the whole target volume. The target volume should be within 40 mm from the skin surface, but on occasion subcutaneous fat can be subtracted from this distance. It must be feasible to place the applicators parallel to the surface of the treatment area.

When the area is larger than 20×30 cm^2, two (or more) hyperthermia applications are scheduled for one treatment. We consider a pacemaker a contraindication for hyperthermic treatment. Metallic implants larger than surgical clips may give problems, e.g. a portacath has to be removed. In case of doubt we will model a treatment with SEMCAD X.

The patients receive a detailed explanation of the treatment procedure and information on their own role in monitoring the temperature distribution, specifically instructions concerning the mentioning of complaints induced by hot spots.

Preparation before first treatment

The treatment team of physician or nurse practitioner, physicist and technician examine the treatment area and decide which applicator set-up will be used. The aim is to cover the whole radiotherapy field with the footprint of the applicator array with an overlap of 1 cm all around.

Thereafter the closed tip catheters are placed under local anaesthesia, with the aim to have interstitial thermometry under each of the applicators. The catheters are fixed to the skin with Histoacryl® tissue adhesive (B. Braun, Melsungen AG, Germany) and Tegaderm® transparent dressing (3M, USA). The interstitial length and depth of each catheter are measured.

A life-size drawing of the treatment area is made on a transparent sheet including some anatomical landmarks (prominent bones, scars, and birth marks), the radiotherapy field margins, the location of macroscopic tumour, the location of the applicators, and the location of interstitial and superficial thermometry probes [29]. All necessary information is loaded into the computer program for treatment monitoring, steering and registration.

The patient is positioned on the treatment bed in a position as comfortable as possible, and up to 23 thermometry probes are placed within the catheters and on the skin. Multi-sensor probes with four measuring points at 20 mm spacing are placed in the catheters, some of the superficial probes are placed on scars.

The applicator position is indicated on a gauze which is placed on the surface of the treatment area and then wetted. The waterbolus is placed such that it extends the planned position of the applicators with at least 25 mm. The waterbolus temperature is selected depending on the size of the waterbolus and the depth of the target volume.

Usually the applicators are placed “clockwise”: adjacent applicators have their E-field direction perpendicular to each other [4].

Treatment

The treatment is administered by the technician. All necessary information is visible on PC screens during treatment: the position of all applicators and thermometry probes in relation to the patient’s anatomy, the power output and reflected power per applicator, the course of temperature under each applicator and the current temperature at each measuring site (Figures 2 and 3). The first treatment starts with a power of 30 W per applicator. The increase of power per applicator depends on the steepness of temperature increase under the specific applicator.

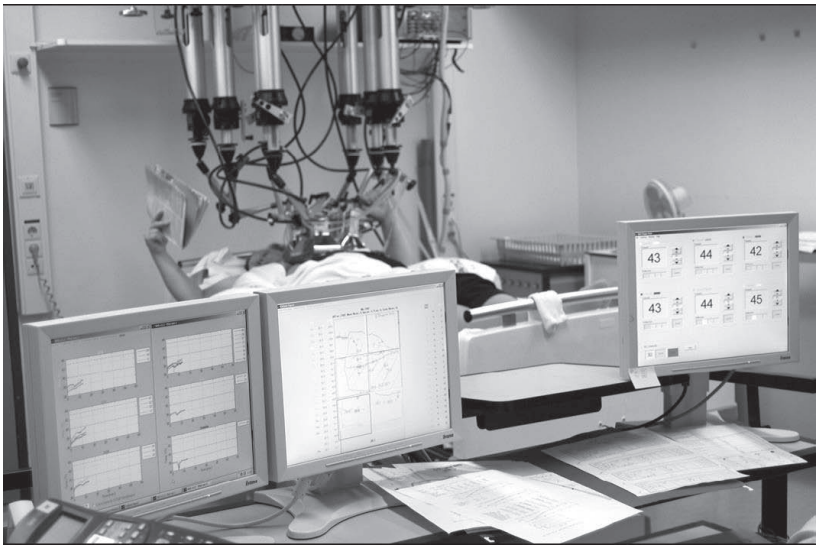

Figure 2. The superficial hyperthermia treatment set-up. The technician observes both the patient and the temperature and power information. The PC screens show, from left to right (left) the course of temperatures over time, per applicator; (middle) the drawing of the treated area with location of applicators and actual temperature per measuring site (details are shown in Figure 3), and (right) the power output per applicator.

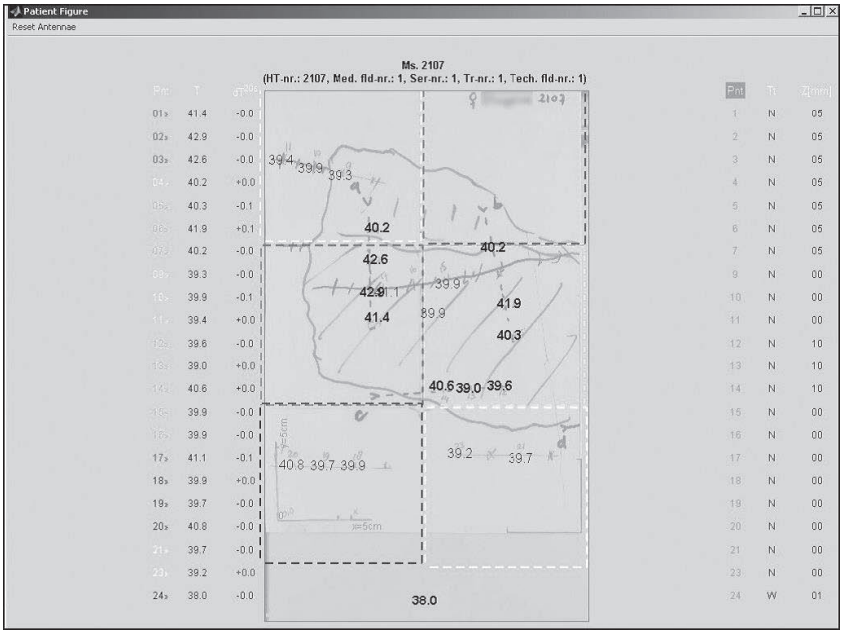

Figure 3. An example of the middle PC screen during treatment with the drawing of the ventral treatment area. The drawing shows the tumour tissue, the mastectomy scar, four interstitially placed catheters, the footprints of the applicators, and actual interstitial (in bold) and superficial temperatures.

The aim is to have all interstitial temperatures above 40°C. An interstitial temperature of maximum 43°C is allowed during the first 30 minutes, thereafter maximum 44°C.

In tumour tissue at a distance of more than 10 mm from normal tissue higher temperatures are allowed. The treatment duration is 60 minutes with power on.

Evaluation between treatments, the course of the previous treatment is discussed with the whole team and adjustments for the application of the next treatment determined.

Special attention is paid to cold spots (average temperature below 40°C), treatment limiting hot spots, and the temperature distribution in depth. If a cold or a hot spot can be explained by the expected SAR distribution, the position of the applicators or their E-field direction is changed.

If superficial temperatures were power-limiting during treatment, the waterbolus temperature is decreased. If the treatment quality is limited by tumour related pain, general stress or anxiety, appropriate medication will be given during subsequent treatments. A detailed description of this evaluation can be found in [30].

RESULTS

Effect on tumour

Since we use 433 MHz for the application of hyperthermia, the results are rather stable. In 1999 we published a CR rate of 74% for the total group of patients treated with eight fractions of 4 Gy and eight hyperthermia treatments, 87% for patients with tumours smaller than 30 mm and 65% for patients with larger tumours [25]. With the same reirradiation schedule combined with four hyperthermia treatments, the overall CR rate is 73%; 82% for small tumours and 65% for larger tumours [22].

The median duration of local tumour control is 32 months. In patients treated for a microscopic tumour residual, the local tumour control rate till death or date of last follow-up was 83% for the patients who received eight hyperthermia treatments and 84% for those receiving four hyperthermia treatments.

Toxicity

Acute radiation toxicity usually is no problem with this schedule with an incidence of epidermolysis in 11% of the patients [25]. In the randomised trial, no increase in radiation toxicity was found [1]. One case report even suggests a decrease in late toxicity (telangiectasis) with the addition of hyperthermia [31]. Hyperthermia toxicity is rather frequent in these patients. In 1999 we reported second-degree burns in 19% of the patients and third-degree burns in 7% and subcutaneous burns in 3% after eight 433 MHz treatments. In 71 patients who received four treatments we observed second-degree burns in 31%, third-degree burns in 10% and subcutaneous burns in 7%. These side-effects usually are grade 2

or less according to the Common Terminology Criteria for Adverse Events version 3.0 scoring system. The hyperthermia-induced burns generally cause no pain because they occur at sites of decreased sensitivity. Late radiation toxicity was evaluated in 121 patients treated with reirradiation (8 × 4 Gy) and hyperthermia (eight treatments) between 1992 and 2000. The overall incidence of late radiation toxicity was 12%: a skin ulcer in six patients, bone necrosis or fracture in seven patients, and both an ulcer and bone fracture in one patient.

The incidence of late radiation toxicity however increased with longer follow-up durations. In 38 patients with a follow-up duration >3 years it was 18%, and in eight patients followed longer than 5 years it was 38%. The median follow-up of all patients was between 1 and 2 years [van der Zee, unpublished results].

DISCUSSION

In approximately three-quarter of our patients, reirradiation with eight fractions of 4 Gy combined with hyperthermia results in a CR, which lasts for a median duration of 32 months.

In over 80% of the patients treated for microscopic disease, local tumour control lasts till death or date of last follow-up. We do not expect that a locally controlled chest wall recurrence will influence overall survival. Nevertheless, the absence of symptomatic local tumour can result in an improvement in quality of life [32]. In our view, the achievement of a partial response is less worthwhile, since regrowth is observed after median 4 months and we find it unlikely that hyperthermia influences time to progression. That is the reason that we do not accept patients for hyperthermia treatment when we can heat only part of the target volume.

We have not included a test heating session in the patient selection procedure. Patients are selected on the basis of tumour location and extension in depth. We assume that a target volume can be adequately heated when the depth is limited to 4 cm from the skin surface and the applicators can be placed parallel to the surface over the whole target area. The results of the randomised trial of Jones et al., for which patients were eligible after a test treatment had shown "heatability" (the achievement of a hyperthermia dose of 0.5 CEM43°CT90) [33], has triggered us to evaluate retrospectively this thermal dose parameter in our patients.

CR rates were the same for patients who were heatable and unheatable, and for patients who received less or more than 10 CEM43°CT90 during the whole treatment series [34].

Many clinical studies on hyperthermia in addition to radiotherapy included patients with recurrent breast cancer after previous irradiation. The results in this specific subgroup, however, are not always reported separately. Table 1 summarizes CR rates in this subgroup which are available from published experience [1,21,26,35-52]. This table includes three studies in which not all but the majority of patients were reirradiated,

and one study reporting CR combined with partial response with >80% regression. Four studies included a control group treated with the same radiation alone: 3 randomised studies and one study in which patients with multiple lesions received radiation alone to 1 lesion and combined treatment to another. CR rates following reirradiation and hyperthermia vary widely, from 20% to 95%.

Table 1. Results of reirradiation and hyperthermia in recurrent breast cancer.

Reference	RT dose and scheme	HT technique and scheme	CR after RT (total n), %	CR after RT+HT (total n), %
35	F 2-2.5, T 20-30, 3/wk	A 2450, R-H, D 35-40, N 6-8		(15) 53%
36 *M, *reRT 72%	F 3, T 30, 5/wk	A 2450, 915, R-H, D +45, N 4	(17) 35%	(28) 64%
37	F 4, T 24, 2/wk	A 433, R-H, D 60, N 6		(26) 77%
38 *R	F 2, T 35-75, 5/wk	MW or RF, D 40, N 4-8	(10) 40%	(9) 67%
39	F 4, T 32, 2/wk	A 200-700, R-H, D 60, N8		(30) 57%
40	F 2-2.5, T 20-80, mean 47	A 915, 2450, R-H, D 40, N mean 12		(20) 80%
41	F 3.5-4.5, T 30-41, 2-3/wk (7 pts T < 30)	A 2450, R-H, D +45, N 3-10		(34) 65%
42	9 pts F 1.8-2, T 20-58 4 pts F 4, T 28-44	A 430,2450, 8 or 13.5, R-H, D 30-60, N 2-10, mean 6		CR+PR >80% (13) 92%
26 91 *R	F 4, T 32, 2/wk	A 915, R-H, D 60, N 8	<3 cm (10) 40% >3 cm(29) 28%	(13) 62% (29) 21%
43	F2-5, T 16-56, mean 29.4, 2-5/wk	A 300-1000, R-H, D 60, N 2-9, mean 5		(44) 41%
21	F 3, T 30, or F 2.3, T 34.5, 5/wk	A2450, 915, R-H, D +45, N 4, 3 or 6		(69) 71%, no difference between 3 schemes
44	F 1.8-5.2, T 8-68, 2-5/wk ETD mean 42	A 915 patchwork, D 60, N 1-5, mean 1.3		(20) 95%
1 (ESHO) *R	F 4, T 32, 2/wk	A 433, R-H, D 60, N 4-8	(29) 38%	(27) 78%
1 (MRC-BrR) *R, reRT 81%	F 3.6, T 28.8, 4wk 28 pts T > 33 Gy	A 433, 2450, R-H, D 10+60, N 3	(59) 29%	(90) 57%
1 (PMH) *R, *reRT 61%	F 1.8, T 32.4, 5/wk 13 pts T 51-60	A 915, R-H, D15+30, N 2	(16) 31%	(17) 29%
45 *reRT 51%	F1.8-2, T2-70, median 46.5, 5/wk, or F 4, T20-66, median 32, 2/wk	915 (few 60-130 or US), R-H, D +45, N 1-11 median 8		(178) 63%
25	F 4, T 32, 2/wk	A 2450, R-H, D 60, N 8 A 433, R-H, D 60, N 8		(24) 58% (95) 74%
46	F 2-4, T 30, 3/wk	A 915 or US, R+H simultaneously, D 60, N 1-6 mean 3.3		(15) 79%
47	F 1.2-2, T 36-60, mean 45, 5-9/wk, *C	A 915, R-H, D 60, N 1-5 mean 3.9, HT simultaneously with chemotherapy		(18) 22%
48	F 1.8, T 30.5, 5/wk, *C	A 433, R-H, D 60, N 6, HT simultaneously with chemotherapy		(15) 20%
49	F 1.8-2, T 30-40, 5/wk	A 915, R-H, D 45, N 2-6		(24) 42%
50	F 1.8-2, T 12-74, median 43, 5/wk	A 8, 13.5, 430, 2450 or US, R-H, D 30-60, N 2-9 mean 4.5		(41) 56%
51	F ~2, T14-72, median 48, 5/wk	Multi-institutional review; no details on HT treatment reported		(36) 67%
52	F1.8-2, T20-60 mean 31.8	A 433, R-H, D +30, N median 6		(44) 66%
Summation			*(170) 32%*	*(974) 61%*

Legend to Table 1:

Reference: *M: matched lesions; *R: randomized study; *reRT: % of patients that was reirradiated; RT = radiotherapy.

RT dose and scheme: F = fraction size; T = total dose in Gy; n/wk = number of fractions per week; *C: treatment schedule included chemotherapy as well; ETD = equivalent total radiation dose based on linear quadratic model; HT = hyperthermia.

HT technique and scheme: A = application technique: microwave frequency, US = ultrasound, MW = microwave equipment and RF = radiofrequency equipment, not otherwise specified; R-H = HT after RT; D = duration per treatment in minutes (+: extra heating-up time); N = number of treatments.

CR after RT+HT: [a] = no difference between 3 schemes

This is not surprising, since the used radiotherapy schedule varies between studies and also within studies, and the prognostic variables of included patients will differ between studies as well. A summation of the data results in 61% CR after combined treatment and 32% after radiotherapy alone. In the majority of studies, hyperthermia is combined with radiotherapy only and applied after radiation. Unusual approaches are simultaneous combination of radiation and hyperthermia and the addition of chemotherapy.

Myerson et al. [46] tested the simultaneous combination of radiotherapy and hyperthermia in 15 patients and achieved a CR in 79%. Feyerabend et al. [47] applied once weekly epirubicin and ifosfamide, simultaneously with hyperthermia, in the period of radiotherapy. Kouloulias et al. [48] applied once monthly liposomal doxorubicin 3 to 40 hours before hyperthermia, once during the perod of radiotherapy and 5 times thereafter. The CR rates in the last two studies were lower than in all other studies: 22% and 20% respectively.

We find the schedule of 2 fractions of 4 Gy per week attractive in view of the palliative aim of the treatment. The overall duration of a treatment series is 3.5 weeks, during which period patients have to come to the hospital only twice weekly for around 2 hours, so the inconvenience is limited. On the other hand, the incidence of late toxicity can be expected to be lower with a radiation schedule with smaller fraction sizes [53,54].

Oldenborg et al. recently reported a 40% incidence of ≥ grade 3 toxicity at three years in 78 patients treated with 8 x 4 Gy and hyperthermia for microscopic disease [55]. In our patients it was 38% at five years follow-up. For the majority of patients late toxicity will not be a problem in view of the limited overall survival, but for the patients with a longer expected overall survival smaller fraction sizes may be considered.

We are now investigating the potential use of predicted 3D SAR (Specific Absorption Rate) coverage as a prognostic indicator for treatment outcome. Patient-specific treatment planning is done with SEMCAD X [8].

Predicted SAR-volume histograms, total absorbed energy per tissue type and calculated temperatures will be compared with measured temperatures, and we will analyse whether the predicted treatment quality correlates with treatment outcome.

A correlation of predicted treatment quality with measured temperatures, and/or with clinical outcome, would allow to abandon interstitial thermometry, to prescribe treatments of a certain quality, and to apply reproducible treatments.

CONCLUSIONS

It is feasible to achieve CR rates of 65 to 90% in breast cancer recurrences when reirradiation is combined with hyperthermia. The burden to the patient can be limited to four 2-hour visits to the clinic. To achieve high CR rates, it is important to heat the whole

radiotherapy field, and to choose an adequate heating technique. In special cases, hyperthermia treatment planning can be applied to support clinical decisions.

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Chapter 3

Effect of a combined surgery, reirradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall

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ABSTRACT

Purpose: Radiation-induced angiosarcoma (RAS) of the chest wall/breast has a poor prognosis due to the high percentage of local failures. The efficacy and side effects of reirradiation plus hyperthermia (reRT + HT) treatment alone or in combination with surgery were assessed in RAS patients.

Patients and methods: RAS was diagnosed in 23 breast cancer patients and 1 patient with melanoma. These patients had previously undergone breast conserving therapy (BCT, n=18), mastectomy with irradiation (n=5) or axillary lymph node dissection with irradiation (n=1). Treatment consisted of surgery followed by reRT + HT (n=8), reRT + HT followed by surgery (n=3) or reRT + HT alone (n=13). Patients received a mean radiation dose of 35 Gy (32–54 Gy) and 3–6 hyperthermia treatments (mean 4). Hyperthermia was given once or twice a week following radiotherapy (RT).

Results: The median latency interval between previous radiation and diagnosis of RAS was 106 months (range 45–212 months). Following reRT + HT, the complete response (CR) rate was 56%. In the subgroup of patients receiving surgery, the 3-month, 1- and 3-year actuarial local control (LC) rates were 91, 46 and 46%, respectively. In the subgroup of patients without surgery, the rates were 54, 32 and 22%, respectively. Late grade 4 RT toxicity was seen in 2 patients.

Conclusion: The present study shows that reRT + HT treatment-either alone or combined with surgery-improves LC rates in patients with RAS.

INTRODUCTION

Radiation induced angiosarcoma (RAS) of the chest wall/breast is one of the most aggressive types of tumor that can develop in an irradiated area after breast conserving therapy (BCT) [19,25,31,39,40]. It constitutes less than 1% of all breast cancers [39]. RAS is thus a relatively rare complication of BCT, but its incidence is likely to increase as more women undergo this treatment [12,24,32]. In three published series, the median times between BCT and RAS diagnosis were 59, 91 and 74 months [6,7,8]. Most cutaneous angiosarcomas are not amenable to surgical resection and a number of patients show metastases at diagnosis or develop them shortly after [1]. The prognosis of RAS patients is poor and the reported 5-year overall survival (OS) rate varies from 10 to 38% [9, 13, 39]. The most common cause of death is local progression along the chest wall [9]. Establishment of local control (LC) is thus important for preventing distressing symptoms [27].

The occurrence of RAS in a previously irradiated field limits the therapeutic options. In many cases, surgery is unfeasible and even after obtaining negative margins by simple mastectomy, additional local tumors recur in approximately 70% of patients (29–100%) [3,7,13,16,20,23,28,29]. Full-dose reirradiation is usually not possible and reirradiation alone does not improve survival rate [21]. Reirradiation plus hyperthermia (reRT + HT) is an effective treatment for recurrent breast cancer with acceptable toxicity. Results from five randomized trials have shown that the complete response (CR) rate for breast cancer recurrences increases from 41 to 59% when hyperthermia is combined with radiotherapy [36]. Multimodal therapies comprising surgery and reRT + HT may improve local tumor control in the treatment of angiosarcoma [26].

In an attempt to improve LC rates, we have treated RAS patients with a combination of surgery wherever this was feasible, and reRT + HT. Results of a retrospective analysis are reported here.

MATERIALS AND METHODS

Patient characteristics

Between 2000 and 2011, 24 patients with pathologically confirmed RAS of the chest wall underwent surgery where feasible, and reRT + HT. Hyperthermia treatments were applied in the Erasmus MC-Daniel den Hoed Cancer Center (DHCC, n=21) and the Bernard Verbeeten Institute (BVI, n=3). Of the 24 patients, 23 had been treated for primary breast cancer by modified radical mastectomy followed by either radiotherapy (n=4) or BCT (n=19). One patient had been treated for axillary melanoma.

RAS presentation varied and included purple cutaneous discoloration, eczematous rash, swelling of the breast and regional lymphadenopathy [22]. In all cases, the RAS

diagnosis had been confirmed pathologically. Patient and tumor characteristics are summarized in Table 1.

Table 1. Characteristics of patients and tumors (n=24)

Patient number	Previous surgery	Primary radiotherapy dose (Gy)	EQD2 (α/β=2) (Gy)	Boost (Gy)	Age[a]	Tumor maximum diameter (mm)	Depth (mm)	Metastases	Interval[b]
1	Mastectomy	46	46	0	66	0	30	No	47
2	Mastectomy	47.3	47	0	61	80	25	No	134
3	BCT	50	50	20	72	0	25	No	68
4	Mastectomy	45	51	0	46	22	30	No	118
5	BCT	52	52	0	68	85	30	Yes	69
6	Mastectomy	50	50	10	88	78	30	No	45
7	BCT	50	50	16	75	292	30	No	77
8	LND	40	60	0	79	300	30	No	113
9	BCT	50	50	16	68	0	30	No	136
10	BCT	50	50	20	50	0	40	No	68
11	BCT	50	50	16	76	90	30	No	120
12	BCT	50	50	0	72	40	30	No	106
13	BCT	50.68	48	13.72	57	340	30	No	52
14	BCT	50	50	0	76	0	30	No	154
15	BCT	50	50	16	72	0	30	No	71
16	BCT	50	50	16	79	150	30	No	95
17	BCT	50	50	16	84	60	30	No	103
18	BCT	50	50	20	73	0	30	No	98
19	BCT	50	50	16	63	9	30	Yes	58
20	BCT	50	50	16	64	13	40	Yes	66
21	BCT	50	50	16	82	80	30	No	212
22	BCT	50	50	16	68	100	30	No	202
23	BCT	50.68	48	13.72	57	190	30	No	70
24	BCT	50	50	26	74	0	30	No	53

Legend to Table 1:
EQD2 equivalent dose in 2 Gy fractions, BCT breast conserving therapy, LND lymph node dissection. [a]Age in years at diagnosis of angiosarcoma [b]Interval in months between primary radiotherapy and angiosarcoma [c]Surgery after radiotherapy and hyperthermia.

TREATMENT CHARACTERISTICS

Surgery

Surgery is the first choice of treatment for angiosarcoma and was performed wherever feasible.

The surgery was scored an "R0 resection" if no microscopic tumor was found at the margin. An "R1 resection" indicates a microscopically positive margin after an otherwise complete resection and "R2 resection" indicates gross residual disease left behind after mastectomy.

Radiotherapy

Following surgery or recurrence confirmed by biopsy, patients received elective external beam radiation weekly. Radiotherapy was administered in 2–5 Gy fractions up to a total dose of 32–54 Gy (mean: 35 Gy), depending on previous therapy and tumor dimensions,

or at the discretion of the radiation oncologist. All patients had received prior irradiation and were treated using a radiation technique comprising photons (6–15 MV linear accelerators), electrons (6–10 MeV) or a mixture of photons and electrons. Type and energy of the radiation beam, as well as the particular application method varied depending on the clinical situation.

Patients received reirradiation to the chest wall, breast, reconstructed breast and/or regional nodes. The planning target volume (PTV) for radiation therapy included the clinical target volume (CTV) plus a margin of 1 cm. PTV could be defined for 8 patients and varied from 0.52 to 6.13 dm^3 (median: 1.35 dm^3). The field size for radiation therapy included the recurrent tumor with a generous margin or the entire ipsilateral chest wall. Field size ranged from 175 to 1125 cm^2 (median: 444 cm^2) [17,30,38].

Hyperthermia

Hyperthermia treatments at DHCC were given once a week following the radiotherapy, for a total of four treatments. Hyperthermia was delivered using Lucite cone applicators and a 433 MHz technique, as previously described [2,4]. The applicator setup was chosen to heat the whole reirradiation volume [35]. At BVI, hyperthermia treatments were given twice a week for a total of six sessions. Hyperthermia was delivered using contact flexible microstrip applicators (CFMA) operating at 434 MHz [10,15].

Treatment fields covered at least the area of surgery or recurrent tumor. For treatment areas too large to be covered by one applicator setup (those exceeding 20 by 30 cm^2), the treatment was carried out in two applications.

Hyperthermia field size ranged from 200 to 1200 cm^2 (median: 600 cm^2). The hyperthermia treatment was given after the radiotherapy fraction on the same day.

The aim of the treatment is to maintain all interstitial temperatures between 40 and 43°C [5]. At DHCC, surface temperature control was performed using a perfused water bolus, with the temperature depending on various applicator arrays and target depths [34]. At BVI, the water bolus temperature was usually set at 42°C. The standard prescribed duration of treatment was 60 min. This included a heating-up period of 10 min, during which the temperatures were increased homogeneously to values as high as patients' tolerance and normal tissue temperatures permitted (max. 44°C). Temperatures were either measured interstitially and on the skin (n=18), or only on the skin (n=6).

Endpoints

The primary endpoint of this study was defined by the duration of local control (DLC).

DLC was defined as the time between the start of treatment (surgery or radiotherapy) and the first observation of progression within the reirradiation field, made on either the day of death or at the last follow-up examination. Secondary endpoints were CR and acute or late toxicity due to either reirradiation or hyperthermia. Patients with persistent

locoregional disease at the end of treatment had local failure (F) at time zero. Toxicity observed during or within 24 h after completion of a hyperthermia session was considered to be hyperthermia induced toxicity. All toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [33]. Only the maximum grade recorded was included in the analysis.

Temperature parameters

Using the interstitial temperature data, various dose parameters were calculated. These included: the maximum (*Tmax*) and the average temperature (*Tave*) that was recorded over all temperature probes during the steady state period of each heating session (beginning 10 min after the start of heating); the temperature exceeded by 90% of all temperature probes during the steady state (T_{90}) and the thermal isoeffect dose expressed in cumulative equivalent minutes at a reference temperature of 43°C, based upon the temporal development of T_{90} in the target (CEM43°CT90). For this analysis, the mean values of *Tmax*, *Tave* and T_{90} temperatures were used. The formulation for CEM43°CT90 used in this study has been previously described and used extensively [6,11,14].

Statistical analysis

Kaplan–Meier analysis was performed for DLC and OS duration. Univariate Cox regression was used to investigate which parameters were associated with LC and toxicity. For all calculations, p-values less than 0.05 were considered significant. For analysis, the Stata Statistical Software, release 11 was used (StataCorp, 2009).

RESULTS

Median age was 70 years, with a range of 46 to 88 years. The 3-month, 1- and 3-year OS rates for the entire patient group were 91, 45 and 11%, respectively. After diagnosis of RAS, the duration of the follow-up period ranged from 1 to 78 months, with a median of 12 months.

Surgery was per formed on 11 patients (46%). Of these 11 patients, 3 underwent radiotherapy preoperatively and 8 postoperatively. The remaining 13 patients received reRT + HT alone.

Tumor response and local control

All patients were eligible for response evaluation (Table 2).

Table 2. Characteristics of patients and outcome of treatment (n=24)

Patient number	Radiotherapy dose (Gy)	EQD2 (α/β=2) (Gy)	Surgical treatment	Margins	No. of hyperthermia treatments	Tmax (°C)	Tave (°C)	T90 (°C)	CEM43T90 (min)	Outcome	DLC[a] (mo)	OS[a] (mo)
1	32	48	Excision	R1	4	43.8	41.8	40.6	1.70	CR	8	9
2	50	50	–	–	5	43.5	40.8	39.4	0.40	CR	9	15
3	32	48	Mastectomy	R1	4	43.2	41.3	40.2	1.33	CR	10	10
4	54	54	–	–	4	–	–	–	–	CR	51	78
5	32	48	–	–	4	43.6	40.9	39.0	0.23	NR	0	4
6	32	48	–	–	4	–	–	–	–	CR	6	12
7	32	48	–	–	4	43.0	40.4	38.7	0.13	CR	14	23
8	32	48	–	–	4	43.7	41.2	39.4	0.49	PD	0	5
9	32	48	Mastectomy	R1	4	43.6	41.4	40.0	0.78	CR	52	52
10	50	50	Mastectomy	R0	4	43.3	40.8	39.4	0.38	CR	8	21
11	32	48	–	–	3	42.7	39.6	37.8	0.28	PR	0	4
12	32	48	–	–	4	43.2	41.7	40.6	1.88	CR	35	35
13	40	60	Mastectomy[c]	R2[b]	4	43.3	41.4	39.4	0.46	PR	0	9
14	32	48	Mastectomy	R1	4	42.6	40.6	39.4	0.40	CR	13	13
15	36	54	Mastectomy	R1	4	–	–	–	–	CR	7	15
16	32	48	–	–	4	42.3	40.2	38.8	0.18	CR	4	4
17	32	48	–	–	4	42.6	41.3	40.4	3.93	NR	0	1
18	32	48	Mastectomy	R1	4	–	–	–	–	CR	10	10[c]
19	32	48	–	–	4	43.8	40.6	38.7	0.15	CR	3	3[c]
20	32	48	–	–	4	–	–	–	–	PR	0	1[c]
21	32	48	Mastectomy[c]	R0[b]	4	44.0	40.8	39.1	0.23	CR	2	2[c]
22	36	45	–	–	6	–	–	–	–	PR	0	1
23	36	45	Mastectomy[c]	R0[b]	5	37.3	38.2	36.5	–	CR	2	2[c]
24	36	45	Mastectomy	R0	6	39.3	41.0	37.8	–	CR	8	9

Legend to Table 2:
EQD2 equivalent dose in 2 Gy fractions, *Tmax* maximum steady state temperature, *Tave* average steady state temperature, T_{90} steady state temperature exceeded by 90% of all probes, CEM43°CT90 development of T_{90} at 43°C in cumulative equivalent minutes, DLC duration of local control, OS overall survival, CR complete response, NR no response, PR partial response, mo months, min minutes [a]Patients with local control or still alive at the date of last follow-up [b]Surgery after radiotherapy and hyperthermia [c]Still alive.

At the completion of reRT + HT treatment in 16 patients with measurable tumors-excluding the 8 patients with microscopic disease-9 patients (56%) exhibited CR, 4 (25%) partial response, 2 (13%) showed no change and 1 (6%) had progressive disease. In one patient who had received surgery after reRT + HT, a pathological CR was achieved. Including the patients with microscopic disease, 3-month, 1- and 3-year LC rates were 71, 38 and 29%, respectively. Median DLC was 8 months (range: 2–52 months). In the surgery group, 3-month, 1- and 3-year LC rates were 91, 46 and 46%, respectively. Recurrence on the chest wall between 7 and 8 months was observed in 4 patients. In the no-surgery group, 3-months, 1- and 3-year LC rates were 54, 32 and 22%, respectively and 4 patients had a recurrence on the chest wall between 6 and 51 months. These results are presented in Figure 1.

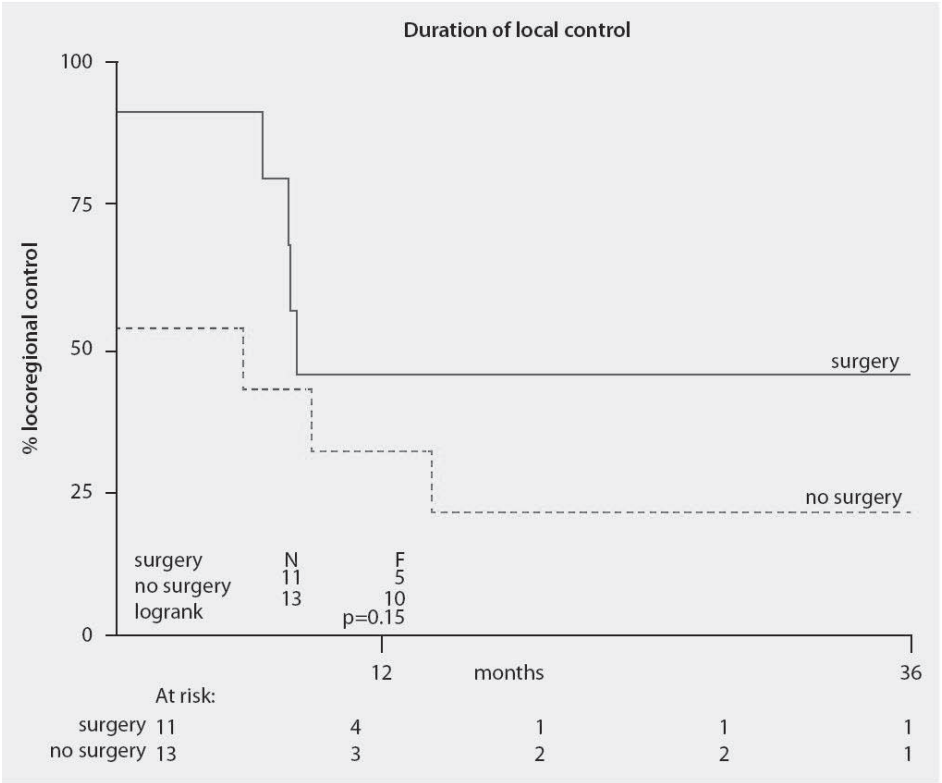

Figure 1. Duration of local control for patients undergoing surgery versus no surgery. N number, F failure

Prognostic factors

We assessed several factors for prognostic significance to DLC using univariate analysis (Table 3). None of the parameters showed a significant correlation with the DLC, presumably due to the small number of patients in this study.

Survival

The median latency interval between previous radiation and diagnosis of RAS was 106 months (range: 45–212 months). The median survival time after reRT + HT for all 24 patients was 12 months (range: 1–78 months). The median survival time following RAS diagnosis was 18 months (range: 2–79 months). Patients who had undergone surgery (median survival: 13 months, range: 1–51 months) showed a trend toward better survival rates compared to patients who received reRT + HT alone (median survival: 5 months, 1–78 months), but this was not statistically significant ($p = 0.719$, Figure 2). The 4 patients treated by complete resection and the 7 undergoing incomplete resection had median survival times of 9 and 10 months, respectively.

Table 3. Association of patient, tumor and treatment characteristics with duration of local control (DLC, n=24)

Parameter	HR	p-value
Radiotherapy dose (Gy)	0.95	0.634
Age[a] at diagnosis of angiosarcoma	1.01	0.673
Margin of operation (radical/irradical)	0.29	0.214
Interval between primary radiotherapy and angiosarcoma (mo)	0.99	0.225
Tumor diameter (mm)	1.00	0.427
Interval between primary radiotherapy and hyperthermia (mo)	0.99	0.233
Radiotherapy field size (cm^2)	1.00	0.318
T90 (°C)	0.75	0.388
Hyperthermia field size (cm^2)	1.00	0.400
Number of hyperthermia treatment sessions (3–4/5–6)	1.65	0.449
CEM43T90 (min)	1.08	0.855
Tmax (°C)	0.97	0.886
Tave (°C)	0.98	0.973

Legend to Table 3:
HR hazard ratio, mo months, min minutes, *Tmax* maximum steady state temperature, *Tave* average steady state temperature, T_{90} steady state temperature exceeded by 90% of all probes, CEM43°CT90 development of T_{90} at 43°C in cumulative equivalent minutes. [a]Age in years at diagnosis of angiosarcoma.

At the last follow-up, 5 patients were still alive 1–8 months after the start of treatment (mean: 2 months); 1 had distant metastases and 1 had both local failure and distant metastases.

The 19 deaths occurred 1–77 months (median: 8 months) after commencement of treatment. Causes of death were locoregional recurrence (n = 11), distant metastases (n = 3) and a combination of both (n = 5).

Toxicity

The duration of hospitalization for the surgical procedure in 11 patients varied between 3 and 12 days. Acute adverse effects from reirradiation included moderate to pronounced erythema, dry desquamation (21%), and moist desquamation (13%).

The effects were generally self-limiting and healed a few weeks after treatment. In one patient, acute grade 3 radiotherapy toxicity appeared after 2 months.

This patient developed an infection and required wound debridement of the chest wall. Thermal blisters occurred in 6 patients. No subcutaneous burns were observed. Grade 3 toxicity related to hyperthermia did not arise. Late grade 4 radiotherapy toxicity was seen in 2 patients, 7 and 11 months after the treatment. One of these patients developed osteoradionecrosis of the chest wall and required resection of this necrotic area. The other patient required debridement for a chronic wound.

DISCUSSION

Secondary angiosarcomas have been associated with previous surgery, irradiation or long-standing extremity edema in Stewart–Treves syndrome [19].

As BCT has become the standard treatment for patients with noninvasive and early breast cancer, the development of post-BCT angiosarcoma has become a well-documented complication, with an incidence rate ranging from 0.05 to 1.11% [8,18,39]. This low incidence hinders conduction of large randomized studies on patients with angiosarcoma of the chest wall, and most available data has been determined from retrospective analyses (Table 4).

Table 4. Surgery, reirradiation and hyperthermia

Reference	Patients (n)	Tx	Local tumor progression	Follow-up (mo)	OS (2yrs)	OS (5yrs)	LC (1yr)	LC (3yrs)	LC (5yrs)
Surgery									
Billings et al. [3]	23	WLE, M, RT, CT	14 (61%)	44 (12–91)	–	–	–	–	–
Jallali et al. [13]	13	7 complete M, WLE	6 (86%)	15 (3–72)	42%	10%	–	–	–
		6 incomplete M, WLE	6 (100%)	15 (3–72)	0%	0%	–	–	–
Lindford et al. [16]	9	M, WLE	3 (33%)	81 (4–122)	66%	66%	–	–	–
Monroe et al. [20]	75	M	55 (73%)	12 (no range)	–	–	–	–	–
Seinen et al. [29]	31	S	19 (29%)	27 (1–151)	32%	–	–	–	–
Surgery and reRT ± HT									
de Jong et al. [7]	3	S, reRT, HT	0	10 (8–68)	67%	67%	–	–	–
Currrent study	11	S, WLE, reRT, HT	4 (36%)	13 (4–51)	14%	0%	46%	46%	–
Palta et al. [23]	14	S, HART	4 (29%)	9	86%	86%	–	71% (2yrs)	64%
Scott et al. [28]	16	S, HART	1 (6%)	44(2–343)	85%	75%	–	–	92%
reRT + HT									
de Jong et al. [7]	13	reRT, HT	3 (23%)	12 (8–68)	23% (3yrs)	–	–	31%	–
Current study	13	reRT, HT	4 (31%)	11 (1–77)	19%	9%	32%	22%	–

Legend to Table 4:
reRT ± HT reirradiation plus/minus hyperthermia, reRT + HT reirradiation plus hyperthermia Tx treatment, M mastectomy, WLE wide local excision, LND lymph node dissection, CT chemotherapy, HART hyperfractionated and accelerated radiotherapy, RT radiotherapy, reRT reirradiation, HT hyperthermia, S surgery, com complete, income incomplete, OS overall survival, LC local control, mo months, yr(s) year(s).

A total of 151 patients who had received surgery alone could be identified in the literature [3,13,16]. The local tumor progression rate was 68% with a period of 12–81 months (median: 21 months) to relapse.

A total of 44 patients-including 11 from our series-received surgery plus radiotherapy (± hyperthermia) [7,20,28]. Response to treatment was observed for 46–92% of patients, with local recurrence in 20% after 8-19 months.

One patient undergoing surgery after reRT + HT had a pathological CR following the combined therapy. In 26 patients, reRT + HT was the only treatment applied for an unresectable tumor. Local tumor progression occurred in 27% of patients after a follow-up of 1–77 months (median: 12 months). The 3-year LC rate was 22% in the current study and 31% in the study of de Jong et al. [7].

Radical surgery is not always possible. Seinen et al. [29] report that in 23 out of 31 patients who underwent surgery, the primary treatment resulted in R0 resections. Nevertheless, due to the multifocal growth of angiosarcoma and residual tumor tissue, nearly two-thirds of these patients developed a local recurrence, even if the surgical margins were considered free.

Radical excision of RAS is important not only for long-term LC, but also for OS; Jalalli et al. [13] found median survival times of 42 and 15 months for patients who had complete and incomplete resection, respectively, and Lindford et al. [16] reported a median OS of 81 months for 9 patients in whom the tumor could be widely resected. Combination therapy comprising surgery and reirradiation seems to improve both LC and OS in comparison to patients treated by surgery alone. Palta et al. [23] reported an LC rate of 71%, 2 years after postoperative radiotherapy with a median dose of 60 Gy. Side effects included moist desquamation, which healed with antibacterial and antifungal agents within a few weeks. One patient developed recurrent pleural effusion 5 years after treatment.

Scott et al. [28] reported 5-year LC and OS rates of 92% and 75%, respectively, among patients receiving postoperative hyperfractionated accelerated radiotherapy (HART) with 1 Gy given three times daily to a total dose of 60 Gy. No patients developed CTCAE grade 3 or more severe complications, despite a high cumulative dose of radiation. In the current study, postoperative hypofractionated reRT + HT resulted in a 1- and 3-year LC rate of 46%, which is lower than that reported by Palta et al. [23] and Scott et al. [28]. These differences may be due to patient selection criteria.

The limitations of the current study are its retrospective nature and the relatively small sample size, which preclude firm conclusions. Furthermore, it is difficult to compare the results with those of other studies and to establish the effect of hyperthermia. The outcome in the subgroup with a radiotherapy dose of 36–54 Gy (n=8) was a LC rate of 75%, with a median of 7 months (range: 0–51 months). In the subgroup of patients with a radiotherapy dose of 32 Gy (n=16), the LC rate was 69% for a duration of 0–52 months (median: 5 months, p=0.634). Late grade 4 toxicity developed in 2 patients; one in each subgroup.

CONCLUSIONS

Although the chest wall already has been irradiated in patients with RAS, reirradiation is still possible and improves postoperative LC rates. The best published LC rates were achieved by combining surgery and HART. With the increasing incidence of angiosarcoma, a prospective study comparing different radiotherapy schemes with or without hyperthermia may be possible in the future. Initial treatment for angiosarcoma should

be wide surgical resection (wherever feasible) followed by radiotherapy, which may be more effective when combined with hyperthermia. For initially inoperable tumors, the effect of reRT + HT alone can still be beneficial.

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Chapter 4

The tolerance of reirradiation and hyperthermia in breast cancer patients with reconstructions

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ABSTRACT

Background: Breast cancer recurrences in previously irradiated areas are treated with reirradiation (reRT) and hyperthermia (HT). The aim of this retrospective study is to quantify the toxicity of HT in breast cancer patients with reconstruction.

Methods: Between 1992 and 2009, 36 patients were treated with reRT with a scheme of 8 fractions of 4 Gy in 4 weeks, and HT on a total of 37 tissue reconstructions. The types of reconstructions were: split-thickness skin graft (15), transverse rectus abdominis myocutaneous flap (1), latissimus dorsi flap (14), rhomboid flap (1) or a combination of grafts and flaps (6). Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Patient, tumour, and treatment characteristics predictive for the endpoints were identified in univariate and multivariate analyses. The primary endpoint was HT toxicity. Secondary endpoints were acute and late radiotherapy (RT) toxicity, complete response (CR), local control (LC) and overall survival (OS).

Results: The median follow-up time was 64 months. Grade 2 HT toxicity occurred in four patients and grade 3 in three. The three patients with grade 3 HT toxicity required reoperation. None of the evaluated parameters showed a significant relationship with HT toxicity. The CR rate in 15 patients with macroscopic disease was 80%. The 3 and 5 year LC rates were 74% and 69%; the median OS was 55 months.

Conclusions: Combined reRT and HT in breast cancer patients with reconstruction is safe and effective.

INTRODUCTION

The treatment of breast cancer recurrences can involve a multimodal therapy that includes surgery and radiotherapy (RT), and, in the event of reirradiation (reRT), hyperthermia (HT). RT of breast or chest wall is indicated for patients on the basis of the following criteria: (1) recurrent tumour; (2) inoperable tumour; (3) microscopically incomplete excision. The standard therapy offered to patients with locoregional recurrent breast cancer in previous irradiated area in The Netherlands is reRT combined with HT [1,2]. The therapeutic benefit of HT when combined with RT has been documented in randomized comparative studies in various tumour types, including breast cancer [3-8].

After mastectomy or local excision, surgical defects may be covered using grafts or flaps. To cope with the psychological and aesthetic consequences of mastectomy, some patients choose a form of breast reconstruction. The options for reconstruction include myocutaneous flaps or tissue expander with subsequent placement of a prosthetic expander/implant, and, if necessary, reconstructions with grafts to cover wounds as a result of the surgical resection.

When postoperative RT is required, many surgeons avoid breast reconstruction for fear of wound complications [9-13]. Published experience on the tolerance of reconstructions with grafts and flaps in previously or subsequently irradiated regions suggest that significant complications are limited, and that the cosmetic results are acceptable [14-23]. Reports in the literature on the tolerance of reconstructions with a graft or flap to HT in combination with reRT are scarce and are mostly single patient reports. We are aware of three studies that mention side effects from the combination therapy on reconstruction with a graft [24-27]. In this retrospective study we analyzed the occurrence of HT toxicity solely in patients with breast reconstruction suffering breast cancer recurrence after treatment with a combination of reRT and HT in attempt to inform the oncology committee on the benefit and toxicity risks in a larger patient group.

PATIENTS AND METHODS

Patients

We retrospectively analyzed 36 patients with 37 breast reconstructions, 7% of all the patients, who had received postoperative reRT combined with HT at the Erasmus MC/ Daniel den Hoed Cancer Centre between 1992 and 2009. Thirty-five patients had recurrent adenocarcinoma of the breast and 1 patient had angiosarcoma. Fourteen patients (39%) had undergone surgery with breast reconstruction after their first diagnosis of breast cancer, 21 (58%) had undergone breast reconstruction after their recurrence and one (3%) patient had undergone two breast reconstructions, for the left- and right-sided

chest wall after both recurrences. The median age at time of diagnosis was 59 years (range: 39–74 years).

Patient files were reviewed with regard to relevant medical history, details on breast reconstruction, use of chemotherapy and hormonal therapy, details of tumour and previously applied RT. Indication for reRT was recurrent tumour, inoperability or microscopically incomplete excision and systemic therapy was either inadequate or was deemed inappropriate, in the absence of systemic disease.

Distant metastasis was diagnosed before the start of the treatment in four patients. Table 1 summarizes patient and tumour characteristics.

Table 1. Patient and tumor characteristics in relation to time period between reconstruction and HT and reRT

	Median; range	*n*	%
Interval between HT and reRT and reconstruction (weeks)	12; 4–282		
Graft		15	41
Flap		16	43
Combined		6	16
Dose RT given previously (Gy)	50; 40–54		
Number of prior surgeries			
1		2	5
2		17	46
≥3		18	49
Number of prior chemotherapies			
0		15	41
1		12	32
2		7	19
≥3		3	8
Number of prior hormonal therapies			
0		18	49
1		15	41
≥2		4	11
Concurrent hormonal therapy		15	41
Macroscopic tumour			
Single lesion		6	16
≥3		7	19
Tumour maximum diameter (mm)	53; 5–320		
Maximum depth of target volume (mm)	30; 15–40		
Subclinical disease		22	59
Bloom-Richardson biological grading system			
Good		2	5
Moderate		5	14
Poor		22	59
Unknown		8	22

Legend to table 1: *Dose to chest wall without the boost.

Surgery

In all patients, a breast reconstruction was placed after mastectomy or local excision. Three patients had their reconstruction before the initial radiation. The surgical technique was not the same in all patients, because they had been operated on in different hospitals. The following breast reconstructions were included: split-thickness graft (15), latissimus dorsi flap (14), transverse rectus abdominis myocutaneous flap (1), rhomboid flap (1), a combination: latissimus dorsi flap and split-thickness graft (1), or a combination: omentum and split-thickness graft (5). A brief explanation will follow to show the diversity in tissue vascularity and perfusion in the treated areas which may influence the risk of toxicity.

Explanation of different surgical techniques

Split-thickness graft (described by the German surgeon Karl Thiersch in 1874) is a sheet of tissue containing epidermis and some dermis taken from a donor site. It is obtained by shaving the skin with an appropriate knife or blade. A skin graft depends for its survival on receiving adequate nutrition from the recipient bed. As it will contract to a certain extent, it will provide a far less aesthetic and durable form of coverage than a vascularised flap. Skin grafts may also be used as an adjunct for coverage of large defects (Figure 1a and Figure 2a and Figure 2b). The mesh graft is a partial or split-thickness skin graft that has had multiple slits cut into it.

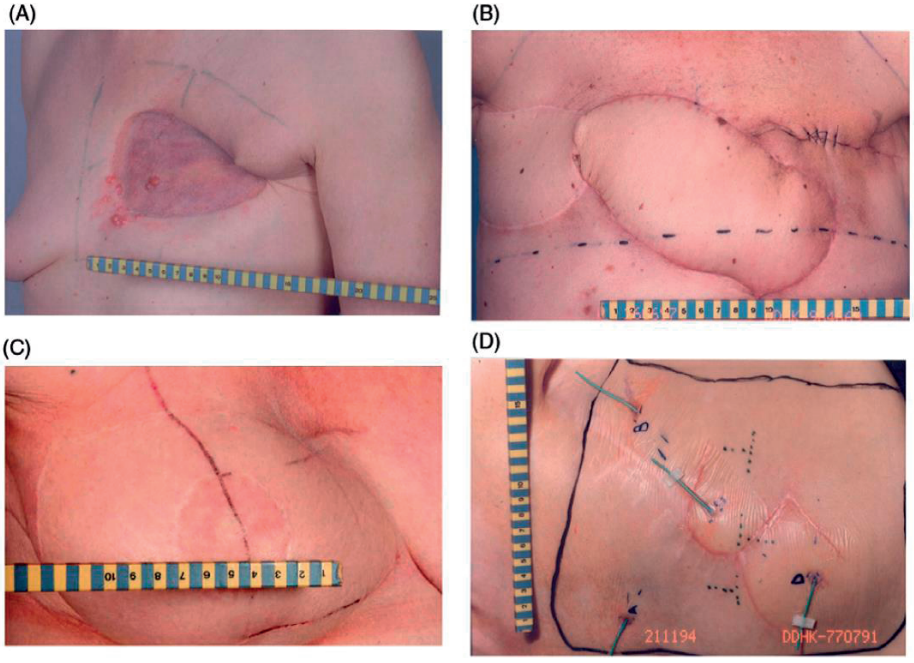

Figure 1. a. Split-thickness graft, b. Latissimus dorsi flap, c. Transverse rectus abdominis muscle, d. Rhomboid flap.

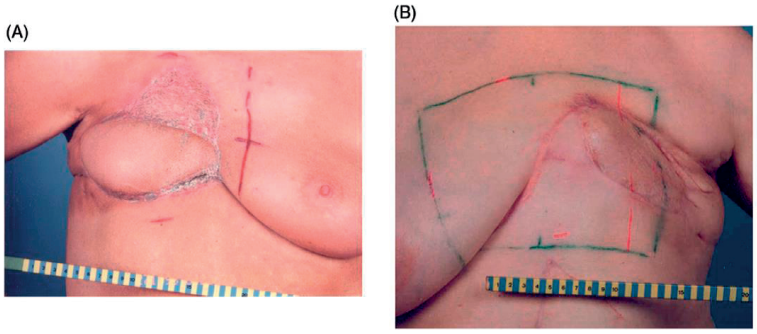

Figure 2. a. Combination split-thickness skin graft and latissimus dorsi flap, b. Combination split-thickness skin graft and omentum flap.

These allow the graft to be stretched to several times its original size, and thus to cover a larger area on the recipient. They also facilitate acceptance of the graft by permitting fluids to escape from beneath the graft.

A latissimus dorsi flap takes advantage of the thoracodorsal vessels, which enter the muscle just below its insertion into the humerus as a consequence their vascularity is generally robust. Even if these vessels have been ligated, the latissimus dorsi flap may survive on collateral blood flow between the thoracodorsal and serratus branches. The great advantages of the latissimus dorsi flap chest wall reconstruction are that it can be used as a muscle flap alone to cover a large defect, or the muscle can be used to transplant a small island of skin. It can be used as a pedicled flap for breast or chest wall reconstruction. It can also be used as a free flap. In our study only pedicled flaps were used (Figure 1b and Figure 2a).

The transverse rectus abdominis myocutaneous provides an alternative flap to the latissimus dorsi muscle. It has the advantage that it can normally transplant sufficient autologous tissue to avoid the need for an implant. The flap can also be used to reconstruct the chest-wall defects (Figure 1c).

A Rhomboid (or Limberg) flap, is as its name suggests, a flap with the shape of an equilateral parallelogram - a lozenge shape. It is designed to contain the maximal blood supply, and takes advantage of well-known principles of flap surgery. The base of the flap should be centred over a regional blood supply source, and the length of the flap should be aligned along the principal direction of the subcutaneous vessel work. Rotation and transposition flaps should also be designed to be large enough to enable adequate movement and closure without tension (Figure 1d).

The highly vascularised omentum flap is a large flap and can be used as a pedicle or a free flap to cover chest-wall and sternal wounds. It is usually folded as an apron utilizing the left gastroepiploic vessels, but occasionally, if additional length is needed, either of the gastroepiploic vessels can be used. It has been used as a pedicled flap covered with a skin graft to treat RT injury to the chest wall (Figure 2b).

TREATMENT

Radiation

The post-operative external beam irradiation therapy of eight fractions of 4 Gy, twice weekly, was given to 35 patients on 36 breast reconstructions. In one patient a higher total dose of 60 Gy, 30 fractions of 2 Gy five times weekly, was given because of an inoperable third recurrence of breast cancer. There was one patient with subclinical disease on the left and a macroscopic tumour on the right side of the chest wall for which she received combined treatment in different time periods. This patient was evaluated as two different breast reconstructions.

Radiation techniques included electrons (n = 12), photons (n = 11) or a combination (n = 14) depending on the tumour location and depth. The RT field included the full-thickness chest wall. A summary of treatment characteristics is given in Table 2.

Table 2. Treatment characteristics.

	Median; range	*n*	%
Total reRT dose (Gy)			
60		1	3
32		36	97
Reirradiated breast reconstruction		3	8
Size of RT field (cm^2)	414; 0–1260		
Size of HT field (cm^2)	600; 324–1375		
Indent of HT sessions			
4		29	78
5		1	3
8		7	19
Number of hyperthermia applications			
1		29	78
2		7	19
4		1	3
Total duration of HT sessions (min)			
240		28	76
300		1	3
480		8	22
Number of interstitial thermometry points	10; 0–19		
Tmax temperature (°C)	43.3; 41.2–45.4		
Tave temperature (°C)	41.0; 39.2–42.8		
T90 temperature (°C)	39.5; 37.1–41.6		
CEM*43*T90* (min)	4.9; 0.0–18.3		
Water bolus temperature (°C)	39.0; 36.0–42.0		

Legend to table 2: *CEM, cumulative equivalent minutes.

Hyperthermia

HT for breast cancer recurrences is given four times once weekly after a RT fraction.

During the early part of this study HT was administered twice a week with a total of eight treatments, but since 1996 it was administered once a week with a total of four treatments. This is now the standard scheme [28].

HT was delivered using Lucite Cone applicators (LCA) with a 433 MHz technique as previously described [29,30]. The applicator set-up was chosen to heat the whole reRT volume [2]. The maximum area that can be treated in one session, using six LCAs, is 20 x 30 cm^2 (n = 27). Three fields were treated one after the other by standard waveguide applicators and LCAs to test the performance of both waveguide types in the clinical setting.

In 1996 LCAs replaced the standard waveguides primarily because of better temperatures in the periphery of the treatment field [31]. To cover larger than 600 cm^2 fields, the treatment was carried out with two (n = 7) or four (n = 1) applicator set-ups. The HT treatment was started as soon after the RT treatment as possible (usually within 30-60 minutes). Surface temperature control was performed by using a perfused water bolus. The temperature of the circulating water in the bolus is selected in accordance to the desired heating depth over the whole treatment volume as published in a previous paper [32]. The standard prescribed duration of a treatment was 60 minutes, including a heating-up period of 10 minutes, during which temperatures were increased to as high and homogeneous as patient tolerance and normal tissue temperatures permitted using the independent power control for each LCA.

In addition to measured temperatures, patients were carefully instructed and repeatedly questioned during the treatments to mention any pain or unpleasant sensation suggestive of a hot-spot. In cases of too high temperature, the power output of the concerning applicator and/or the applicator position was adjusted [33].

Thermometry

For thermometry, a 24-channel scanning fibre-optic system (FT1210 and FT1310, Takaoka Japan) was used. Five multisensory probes (up to four sensors) and four single-sensor probes were available to measure skin and interstitial temperatures continuously during treatment. Under local anaesthesia, up to four thermometry catheters were inserted subcutaneously in the treatment volume, with at least one interstitial temperature measuring point aimed below each antenna. The catheters were fixed in place with Histoacryl (B. Braun, Melsungen AG, Germany) and Tegaderm adhesive (3M, USA). They were left in place for the duration of the full reRT and HT treatment course, provided there were no signs of infection or pain. The multisensory probes were placed in the closed-end interstitial thermometry catheters and the single-sensor probes were placed superficially, prior to each HT treatment [34].

Endpoints

The primary endpoint of this study was acute HT toxicity. Acute side effects of HT occur during or within 24 hours after completion of a treatment. Acute toxicity was registered according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3 2006) [35,36] (Table 3) and the WHO scoring system (Table 4). For acute HT-related toxicity analysis, the highest CTCAE grade toxicity a patient developed was included.

Table 3. CTCAE v3 scoring of hyperthermia toxicity.

Degree	
0	None
1	Minimal symptoms; intervention not indicated
2	Medical intervention; minimal debridement indicated
3	Moderate to major debridement or reconstruction indicated
4	Life-threatening consequences
5	Death

Table 4. World Health Organization scoring of thermal burns.

Degree	
0	None
01	Erythema
2	Partial thickness injury; erythema and blister, possibly white spots, very painful
3	Full thickness injury; complete dermis thickness damaged, chalk white or charred wound that is dry and anaesthetic, no capillary refill possibly including subcutaneous fat injury
4	Burn including underling muscle tissue
5	Resulting in death

Secondary study endpoints were acute and late RT toxicity (CTCAE v3), complete response (CR), duration of local control (LC) and overall survival (OS). Acute RT-induced toxicity was defined as toxicity developing during treatment or in the three months thereafter (Table 5). Late RT-induced toxicity was defined as toxicity occurring at least three months after the last fraction of RT.

Table 5. CTCAE v3 scoring of acute radiotherapy toxicity.

Degree	
0	None
1	Faint erythema or dry desquamation
2	Moderate to brisk erythema; patch moist desquamation, mostly confined t skin folds and creases; moderate oedema
3	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion
4	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site
5	Death

CR was defined according to WHO criteria: clinical disappearance of all tumours in the irradiated volume for at least two measurements separated by visits of at least four weeks. LC duration in patients treated for subclinical disease and in patients in whom CR was achieved, was defined from the start of treatment until the first in-field tumour progression. Patients who did not show a CR were considered local failures. OS was defined as the time from the start of treatment to death from any cause or was censored at the time of the last follow-up visit in patients who survived. Assessment was based on the registered information in the files, telephone interviews and letters from medical professionals.

Temperature parameters

From the measured temperatures, *Tmax*, *Tave*, and T_{90} were derived. *Tmax* and *Tave* are the maximum and the average temperature of all invasive temperature probes and T_{90} represents the temperature exceeded by 90% of all invasive temperature points during steady state (from 10 minutes after start of heating). For this analysis, the means of the maximum, average and T_{90} temperatures for each HT session were selected.

The thermal dose parameter used in this study, CEM43°CT90, has been used extensively and has been previously described [6,33,37-41]. In a mathematical description all time-temperature data are converted to an equivalent number of minutes at 43°C, where CEM43°C is cumulative equivalent minutes at 43°C. The sum of CEM43°C ($CEM43°CT90_{tot}$) acquired per treatment ($CEM43°CT90_i$) was calculated from the number of treatments actually given, and normalised using the number for which time-temperature data was available [33].

The analysis of thermal dose was limited to interstitially measured temperatures because the temperatures measured from the thermometry probes placed on the skin were influenced by the water bolus and therefore uncertain (Table 6a).

Table 6a. Thermal parameters in relation to hyperthermia toxicity.

		p value
Tave (°C); mean ± SD* (range)	41.4 ± 0.9 (39.2–42.8)	0.108
T90 ± (°C); mean ± SD* (range)	39.7 ± 1.1 (37.1–41.6)	0.115
Tmax ± (°C); mean ± SD* (range)	43.5 ± 1.1 (41.2–45.6)	0.408
CEM43°C$T90_{tot}$ (min); mean ± SD* (range)	4.9 ± 6.9 (0–18.3)	0.587

Legend to table 6a: *SD, standard deviation.

Other treatment and patient related parameters

In addition to temperature parameters, a number of other treatment and patient related parameters were evaluated for prognostic value regarding toxicity (Table 6b).

Table 6b. Patient and treatment characteristics included in the evaluation of prognostic factors for toxicity.

		p value
Prior hormonal therapy	Yes or no	0.105
Size hyperthermia field	$<600\,cm^2$ and $\geq 600\,cm^2$	0.141
Prior chemotherapy	Yes or no	0.177
Type of tissue transfer	Graft, flap or combined	0.207
Concurrent hormonal therapy	Yes or no	0.245
Interval between RT + HT and reconstruction	Early ≥20 weeks and late >20 weeks	0.324
Number of interstitial thermometry probes	≤10 or >10	0.457
Prior surgery	1–2, or ≥3 surgical treatments	0.775
Number of hyperthermia treatment sessions	4–5 versus 8	0.814
Depth	1–4 cm	0.818
Size radiotherapy field	$\leq 400\,cm^2$ and $>00\,cm^2$	0.971

Legend to table 6b: RT, radiotherapy, HT, hyperthermia.

Statistical methods

Toxicity and response rates were evaluated for each treatment field. The association between toxicity and thermal parameters was evaluated for each HT session.

Pearson's chi-squared test was used to determine which parameters associated with acute toxicity were caused by the combined treatment. The association between toxicity and thermal dose parameters *Tmax*, *Tave*, T_{90} and CEM43°CT90, was tested using the nonparametric Kruskal-Wallis test. All data were tabulated in Excel spreadsheets and were further processed using Statistica® for Windows. Actuarial probability of LC and OS was plotted from the time of initiation of treatment using the Kaplan-Meier product-limit method. A relationship was defined to be statistically significant when the *p*-value was < 0.05. The statistical analysis was performed using Stata statistical software release 11 (StataCorp 2009) [042].

RESULTS

Toxicity

All patients were eligible for toxicity evaluation. For patients still alive at last follow-up (*n* = 13) the median follow-up time was 64 months (range 4-188 months).

HT toxicity occurred in 17 patients (46%; split-skin (Thiersch) graft 19%, latissimus dorsi flap 16%, combination of split-thickness graft and omentum 8% or transverse rectus abdominis myocutaneous flap 3%). The burns were located inside the breast reconstruction (*n* = 6), outside the breast reconstruction (*n* = 8), or on the margin (*n* = 2), and one patient had two burns, one inside and one outside the breast reconstruction. The maximum skin toxicities are shown in Table 7.

Table 7. Maximum acute HT toxicity per patient and reconstruction.

	Graft	Flap	Combined	All
Breast reconstruction CTCAE toxicity	15	16	6	
0	8 (22%)	9 (24%)	3 (8%)	20 (54%)
1	3 (8%)	4 (11%)	3 (8%)	10 (27%)
2	4 (11%)			4 (11%)
3	0	3* (8%)		3 (8%)
Burn, WHO score				
0	8 (22%)	9 (2%)	3 (8%)	30 (54%)
1	0			
2	5 (14%)	3 (8%)	3 (8%)	11 (30%)
3	2 (5%)	3* (8%)		5* (13%)
Subcutaneous	0	1 (3%)		1 (3%)

Legend to table 7: *Three ulcerations which required necrotomy.

HT CTCAE grade 3 toxicity was observed in three patients (8%). Two grade 3 HT toxicities developed in a latissimus dorsi flap and one in a transverse rectus abdominis myocutaneous flap. Removal of the latissimus dorsi flap was required in both patients.

In one patient the skin defect was repaired by primary closure and the wound healed without event. The other patient required composite reconstruction of the chest wall.

Four months afterwards she required removal of the composite reconstruction because of an infection and the wound was closed primarily. The last patient developed fever and appeared to have fat necrosis which was removed.

She required transposition of transverse rectus abdominis myocutaneous tissue with a latissimus dorsi flap.

Acute grade 3 RT toxicity appeared after 2.7 months in one patient (3%). She required wound debridement of the chest wall without removal of her split skin graft and healed with conservative treatment. Late RT toxicity was observed in two patients (5%) other than those with maximum HT toxicity. One patient had a large (14.5 cm) ulcerating

tumour mass before the start of the combined treatment. As a result of capsular contracture, her prosthesis and latissimus dorsi flap had to be removed after 12 months and the wound was closed primarily. The second patient developed skin necrosis and required hyperbaric oxygen therapy after 5.5 years. The breast reconstruction, a combination of a flap and a graft remained in situ. All patients subsequently recovered well and required no further intervention.

PATIENT AND TREATMENT CHARACTERISTICS IN RELATION TO HYPERTHERMIA TOXICITY

Table 6a shows patient- and treatment-related parameters according to maximum toxicity. All parameters are summarized in order of their *p*-value. We did not find a relationship with toxicity for any of the parameters.

The relation between acute HT toxicity and thermal dose parameters was evaluated for 46 HT applicator set-ups; for one treatment field temperature data were not available. HT-induced toxicity was not correlated with any of the thermal dose parameters, (*p*-values varying between 0.108 and 0.408) (Table 6b).

The mean thermal dose parameters for patients who had less than grade 2 toxicity were T_{90} = 39.8°C, *Tmax* = 43.5°C, *Tave* = 41.1°C, and CEM43°C$T90_{tot}$ = 5.19 min; for grade 2 toxicity T_{90} = 40.3°C, *Tmax* = 43.5°C, *Tave* = 41.6°C, and CEM43°C$T90_{tot}$ = 8.25 min; for grade 3 toxicity T_{90} = 39.7°C, *Tmax* = 43.5°C, *Tave* = 41.3°C, and CEM43°C$T90_{tot}$ = 3.65 min.

TUMOUR RESPONSE, DURATION OF LOCAL CONTROL AND OVERALL SURVIVAL

The patient with angiosarcoma of the breast was excluded from the response analysis. A CR was observed in 12 out of 15 (80%) patients with a macroscopic tumour (6 patients with a graft, 5 with a flap and 1 with a combination of a flap and a graft).

All 3 patients with less than complete response had a reconstruction with a split-thickness skin graft. Including the 21 patients with subclinical disease, the LC rate was 92%.

Local tumour control rate was 83% after 1 year, 74% after 3 years and 69% after 5 years with seven local recurrences were included to date (Figure 3). One local recurrence occurred in a field with a latissimus dorsi flap after 3 months, one in a field with a transverse rectus abdominis myocutaneous flap after 17 months, and five in a field with a split-thickness skin graft after 3, 5, 24, 25 and 46 months. Depth of target volume had no effect on duration of local control (p = 0.367).

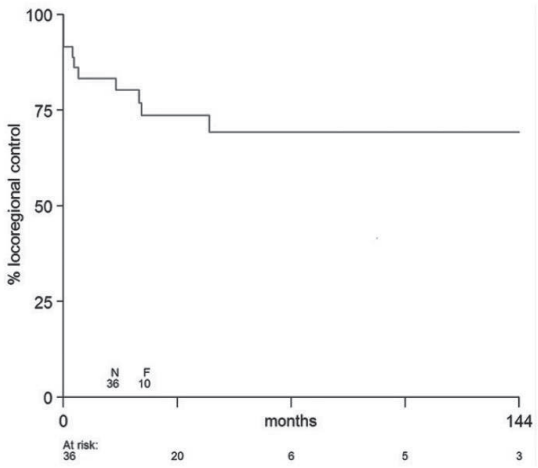

Figure 3. Duration of local tumor control for 36 tissue transfers in 35 patients from the time of initiation of treatment treatment (N = number of tissue transfer, F = number of failures).

Fourteen patients died with local tumour control, after a median survival of 50 months, whereas twelve patients were free of local disease after a follow-up period of 22-188 months (median 65 months). The OS rate was 83% after 1 year, 63% after 3 years and 46% after 5 years with a median survival of 55 months (Figure 4).

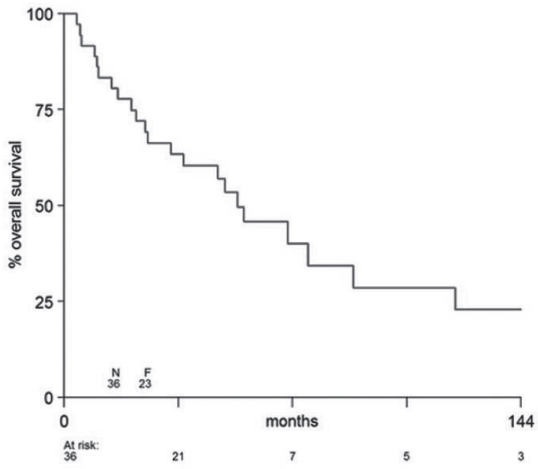

Figure 4. Overall survival for 36 tissue transfers in 35 patients from the time of initiation of treatment (N = number of tissue transfer, F = number of failures).

DISCUSSION

In our study we retrospectively evaluated the results of reRT and HT in a group of 36 patients with 37 breast reconstructions, treated between October 1992 and March 2009. We found no HT toxicity in 20 patients (54%). CTCAE Grade 1 toxicity was seen in 10 patients (27%), grade 2 in four (11%) and grade 3 in three (8%). In 12 of the 15 patients (80%) with macroscopic disease a CR was achieved and the 5-year LC rate in all patients was 69%.

Breast reconstructions are sometimes considered to be a contraindication for treatment with RT and/or HT. A problem in patients with reconstruction can be that sensitivity is disturbed, and that therefore they can not report too high temperatures. From published results and clinical experiences with reRT and HT, however, it is unclear how high the incidence of severe toxicity in breast reconstructions really is.

Kim et al. [25,26] reports on 54 patients treated postoperatively with combined RT and HT, among whom only one patient had received a skin graft. This patient was treated with two series of RT and HT to a grafted area for a locally recurrent malignant melanoma. The patient developed an acute moist reaction in the grafted area which healed within four weeks. Nishimura et al. [27] reports as late toxicity two patients who developed ulcers in grafted skin. Hehr et al. [043] treated six patients with flap reconstructions among total 39 patients, but does not report specifically on severe toxicity in this subgroup. Zagar et al. [44] reports on one patient with a third-degree burn in a transverse rectus abdominis myocutaneous flap reconstruction that healed with conservative measures. In our institute, patients with breast reconstruction are not excluded from HT treatment.

Compared to results of a previous study in patients with recurrent breast cancer [01], acute hyperthermia toxicity was similar: WHO second-degree 31% compared to 27% and WHO third-degree 14% compared to 10%.

We further found that the sensitivity impairment in patients with breast reconstruction did not stop our patients from complaining during hyperthermia treatments. The number of complaints for which power was adjusted was 0-13 (mean 5) in patients with reconstruction (0-13, mean 5, in patients with CTCAE grade 0 or 1 toxicity and 3-8, mean 5, in patients with CTCAE grade 2 or 3 toxicity) while it was 0-10 (mean 4.2) in patients without reconstruction. The side effects were usually grade 2 or less according to the CTCAE scoring system. The HT-induced burns generally caused no pain because these preferentially developed at sites of decreased sensitivity. We considered only CTCAE grade 3 as severe toxicity. HT caused in three (8%) patients a CTCAE grade 3 burn of the thoracic wall. Removal of the latissimus dorsi flap was required in two patients and the transverse rectus abdominis myocutaneous flap stayed in situ. CTCAE grade 3 late radiation toxicity developed in two patients which is not significantly different from what we found in our previous study in which the majority of patients had no graft [01]. One of

these grade 3 toxicities resulted from tumour ulceration before treatment and the other was due to skin necrosis. Data on the tolerance of breast reconstructions to adjuvant RT are limited.

The side effects in the tissue grafts and flaps after RT have resulted in acceptable rates of complications and reconstruction failures; the need for major corrective surgery was 0 - 11% [14-23]. The grafts and flaps in these published studies were placed on a skin that had not been previously irradiated. In an experimental study on the effects of reRT on vascularised breast reconstruction in 100 rats, none of the transferred flap or reirradiated receiver musculature developed radiation necrosis after 72 Gy in 8 fractions in 10 days [045].

Combined treatment with 32 Gy and HT resulted in our patients in an 80% CR in the 15 patients with macroscopic tumours and a 92% LC rate in the whole group of patients. After five years the LC rate was 69%. In patients with breast cancer recurrences, reRT combined with HT is an effective treatment.

The ESHO 5-88 study [4] which compared reRT alone (with reRT schedule of 8 x 4 Gy) with reRT plus HT has shown a large improvement by additional HT. The CR rate after combined treatment was 78% and 38% after reRT without HT. The tripling of the CR rate in various superficial tumours for reRT and high-dose HT vs. RT and low-dose HT as demonstrated in a randomized study by Jones et al. [6] made the National Comprehensive Cancer Network (NCCN) to include RT plus HT in its 2007 Breast Cancer Guidelines for recurrent breast cancer and other localized cancer recurrences. Although patients with recurrent breast cancer often are beyond cure, the achievement of local tumour control is important for the quality of life.

Bedwinek et al. [46] reported that in 62% of the patients, who experienced local recurrence, uncontrolled symptomatic local tumour can result in serious deterioration in quality of life. Liu et al. [47] also reported that achievement of LC results in an improvement of quality of life. There has been no randomized trial investigating whether HT is beneficial in the subgroup of breast cancer patients with subclinical disease. Nevertheless, we have reasons to believe that HT is effective in this situation as well.

In the first place, a larger RT dose is required to achieve high LC rates. Bedwinek et al. [46] advised to applying at least 50 Gy in 2 Gy fractions in the elective situation, and 60 Gy after microscopic irradical tumour excision.

The scheme of 8 fractions of 4 Gy in 4 weeks is biologically less effective than 50 Gy in 2 Gy daily fractions (biologically effective dose (BED) = 44.8 Gy with $\alpha/\beta = 10$ for an acutely responding tumour).

In our experience, two types of observations suggest that 8 fractions of 4 Gy indeed are insufficient to control subclinical disease [01].

Secondly, at the time that we were still developing our HT system and had only a few applicators, the aim was to apply HT to the macroscopic tumour only, or, after resection,

to the site of surgery. Five patients that had HT applied to part of the reRT field showed tumour progression within the RT field but outside the HT field, while the combined treated region remained controlled.

Another finding was the difference in tumour control between patients treated for subclinical disease with 2450 MHz or 433 MHz equipment. An important difference between the 2450 and 433 MHz technique is that the homogeneity of heating is much better with the latter technique; with 2450 MHz a large part of the treatment volume receives an insufficient heat dose. The three patients treated with 2450 MHz all had in-field tumour regrowth after 10-12 months. Only two of 12 patients treated with 433 MHz had a recurrence at 10 and 13 months after treatment, while 10 of 12 patients remained locally controlled after average 32 months. Although these numbers are small, this difference was significant.

All patient, tumour and treatment characteristics, including thermal dose parameters, have been analysed concerning their impact on the toxicity of breast reconstructions and no statistically differences were found. Of course, the retrospective nature and relatively small sample size of this study do not allow firm conclusions, but this lack of correlation makes it difficult to prevent HT toxicity by thermometry. In the near future, HT treatment planning may become a tool to prevent the occurrence of burns. Prediction of the energy distribution in the tissues will allow better power control procedures and minimize the risk of toxicity. A thorough analysis of predicted 3D SAR (specific absorption rate) coverage as a prognostic indicator for treatment outcome and hot-spots during treatment is the subject of an ongoing study in our department.

CONCLUSIONS

Based upon our results, breast reconstructions in previous irradiated areas are not a contraindication for treatment with reRT and HT, in view of the incidence of severe acute (8%) and late (5%) normal tissue reactions and the high LC rate (92%).

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Chapter 5

Local control rate after the combination of reirradiation and hyperthermia for irresectable recurrent breast cancer: Results in 248 patients

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ABSTRACT

Background and Purpose: Randomized studies have shown that adding hyperthermia (HT) to reirradiation (re-RT) improves treatment outcome for patients with breast cancer recurrences. We evaluated the efficacy and side effects in patients treated with re-RT and HT for irresectable locoregional breast cancer recurrences.

Material and methods: From September 1996 to December 2011, 248 patients with a macroscopic breast cancer recurrence were treated with re-RT and HT. Radiotherapy (RT) was applied to a dose of 32 Gy in 4 Gy fractions, twice weekly. HT was prescribed once weekly after RT. Primary endpoints for this analysis were complete response (CR) and local control (LC). Secondary endpoints were overall survival (OS), and toxicity. Patient-, tumor-, and treatment-related characteristics predictive for the endpoints were identified in univariate and multivariate analyses.

Results: The median follow-up period was 32 months. The CR rate was 70%. At 1, 3, and 5 years LC was 53%, 40% and 39%, and OS was 66%, 32%, and 18%, respectively. OS after 10 years was 10%. Thermal burns developed in 23% patients, healing with conservative measures. The incidence of 5 years late grade 3 toxicity was 1%. A few patients survived more than 10 years without evidence of disease.

Conclusions: The combination of re-RT and HT results in a high rate of long-term LC with acceptable late toxicity, and many patients remained locally controlled for the rest of their survival period.

INTRODUCTION

Addition of hyperthermia (HT) to reirradiation (re-RT) is an effective treatment for locoregional recurrences of breast cancer [1,2]. After completion of the randomized ESHO 5-88 trial, with pooled results of five trials showing a statistically significant improvement of local control (LC) with the addition of HT to RT [1], re-RT with 8 fractions of 4 Gy in 4 weeks and HT became the standard treatment for patients with recurrent breast cancer in the Netherlands. In the present study, we retrospectively evaluated complete response (CR) rate, local tumor control, overall survival (OS), and acute and late toxicity of 248 patients with macroscopic breast cancer recurrences treated with re-RT and HT at our department.

MATERIALS AND METHODS

Patients

From September 1996 to December 2011, we treated 248 patients with macroscopic breast cancer recurrences with re-RT and HT at our department. The inclusion criteria for this evaluation were as follows: previous RT to the breast or thoracic wall, biopsy confirmed locoregional recurrent adenocarcinoma of the breast, inoperable or irresectable tumor, and planned treatment with re-RT of 32 Gy and HT. Eleven patients with reconstructions included in the current study, were included in a previously published study [3]. HT was considered feasible when the tumor was located not deeper than 4 cm from the skin surface, and the antenna apertures could be placed parallel to the skin surface over the whole volume at risk.

Five patients had a tumor extending to a depth of 5 cm and were accepted since there was a fat layer of ≥1 cm between skin and tumor, and energy loss in fatty tissue is neglectable [4]. In patients with multiple tumors, maximum tumor diameter and tumor volume represent that of the largest lesion. Tumor volume was calculated according to the formula $1/6\pi a \times b \times c$, in which a and b are the largest diameters measured by calipers and c is the maximum extension in depth.

Radiotherapy

Radiotherapy (RT) was delivered using two tangential photon fields (6-15 MV linear accelerators), electrons (6-12 MeV) or a combination of photons and electrons. Type, technique and energy of the radiation beam varied depending on the location and depth.

Radiation was given at 4 Gy per fraction, twice a week, to a total dose of 32 Gy to the clinical target volume. The RT field size for chest wall recurrences usually included most of the ipsilateral chest wall.

Hyperthermia

HT was applied once weekly to a total of 4 treatments of 60 minutes each, after RT. For HT treatments, water filled Lucite Cone Applicators (LCA) were used operating at a frequency of 433 MHz [5]. This applicator has a square aperture of 10×10 cm^2; the effective field size is up to 80% of the aperture. With six applicators combined an area of 20×30 cm^2 can be effectively heated to a depth of up to 4 cm [6]. The applicator array was chosen such that the radiation field was widely covered [2].

Temperatures were measured interstitially, within catheters, and on the surface. For thermometry, a 24-channel fiber-optic system (FT1210 and FT1310, Takaoka Japan) was used used with five multisensor probes (up to four sensors) and four single-sensor probes for continuous measurements during treatment [2,6].

For each treatment the maximum (*Tmax*), average (*Tave*) and the value above which 90% of all interstitially measured temperatures had been (T_{90}) was calculated from measurements taken after the 10 minutes heating-up phase. For this analysis the means of these temperatures over all treatments were selected. The calculated thermal parameters of superficial measurements were used in the evaluation of acute toxicity. Additionally, the CEM43°CT90 represents the thermal isoeffect dose expressed in cumulative equivalent minutes at a reference temperature of 43°C. The formulation for CEM43°CT90 used in this study has been used extensively and has been previously described [7,8,9-11].

Endpoints and statistical analysis

Primary endpoints were CR and duration of LC. A CR was defined according to WHO criteria as the complete clinical disappearance of all measurable disease in the treatment field, observed twice with a time interval of at least 4 weeks. Patients who never obtained CR were considered as local failures at time zero. Duration of LC was defined from the date of initiation of treatment till the first observation of progression within the treatment volume, or censored at the day of death or last follow-up. Secondary endpoints were OS and toxicity.

Acute toxicity was observed as a result from either RT or HT. Radiation-induced acute toxicity included erythema (none, mild, moderate or severe) and moist desquamation. Thermal burns included second and third degree skin burns, and subcutaneous burns. The time to occurrence of late toxicity was defined from the start of re-RT to the date of worst late toxicity observation.

Late toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0) [12]. The Kaplan-Meier method was used to estimate the probability of LC, OS, and late toxicity. Cox regression was used to investigate which parameters were associated with duration of LC. A Chi-squares test was applied to determine parameters that were associated with CR rate or the development of acute toxicity. The non-parametric Kruskal-Wallis test was applied when the parameter is continuous or

ordinal variable. A value of $p<0.05$ (two-tailed) was considered statistically significant. For analysis, the Stata statistical software release 13 was used (StataCorp 2013).

RESULTS

Patient- and tumor-related characteristics

The median follow-up duration was 32 months. Data were collected till March 2014, or to a minimum follow-up of 2 months. Table 1 summarizes patient- and tumor-related characteristics at the time of first diagnosis. Patient- and tumor-related characteristics at the time of combined treatment are summarize in Table 2. The hormone receptor status (ER and/or PR) was unknown in 52 (21%) of the patients and HER2neu protein status was unknown in 67 (27%) of the patients, since before 2000 the receptors were not routinely checked. In 70 (28%) patients hormonal treatment was continued during re-RT and HT. Thirty-five of these patients had started hormonal therapy 2 months or longer before re-RT and HT.

Table 1. Initial patient- and tumor-related characteristics.

	$n = 248$	%
T stage		
T0	3	1
T1	75	30
T2	94	38
T3	23	9
T4	34	14
Unknown	19	8
Lymph nodal involvement		
N0	86	35
N1	83	34
N2	36	14
N3	27	11
Unknown	16	6
Differentiation		
Well	5	2
Moderately	50	20
Bad/Poor	124	50
Unknown	69	28
Estrogen receptor		
Positive	89	36
Negative	109	44
Unknown	50	20
Progesterone receptor		
Positive	70	28
Negative	125	50
Unknown	53	21
HER2/neu		
Amplified	61	24
Not amplified	120	48
Unknown	67	27
Triple negative	79	32

Table 2. Patient- and Tumor-related characteristics at the time of combined treatment.

	Mean + SD (range)	*n* = 248	%
Age (yrs)	61 + 12 (34–93)		
Interval between primary breast cancer surgery and first relapse (months)	61 + 75 (0–442)		
Interval between initial radiotherapy and re-irradiation (months)	90 + 90 (5–485)		
Presence of distant metastases		89	36
Anatomic site of current recurrence			
Breast		17	7
Chest wall		217	87
Regional lymph nodes (low axilla or supraclavicular)		6	2
Regional lymph nodes and chest wall		8	3
Tumor volume (cm^3)	242 + 331 (0,26–2026)		
Maximum diameter largest lesion (cm)	8.9 + 9.1 (0.2–50)		
Maximum depth (mm)	27 + 10 (5–80)		
Number of lesions	2 + 1 (1 ⩾ 9)		
1		94	38
2		25	10
3–9		129	52
Dose of radiotherapy given previously (Gy)*	49 + 7 (18–70)		
Number of previous surgical procedures at the same location			
1		125	50
2		45	19
⩾3		78	31
Number of previous lines of chemotherapy			
0		77	31
1		94	38
⩾2		77	31
Number of previous lines of hormonal therapy			
0		91	36
1		82	33
⩾2		75	31
Concurrent hormonal therapy		70	28

Legend to table 2:
SD = standard deviation, *dose to chest wall

Treatment-related characteristics

Radiotherapy

One hundred eight patients (44%) received RT in the Erasmus MC; 140 patients were treated in one of the 16 other radiation therapy institutes and received their HT at Erasmus MC. The

RT plan was adjusted to a lower dose in five patients. Three patients received a lower total dose because of general deterioration, and two refused further treatment. The lateral chest wall and/or regional lymph node area were treated with two tangential photon fields (6-15 MV; n=77) and the anterior chest wall with electrons (6-12 MeV; n=107); in 58 patients a combination of photons and electrons was used. In six patients the radiation technique was unknown. The average RT field size was 425 cm^2 (range 25-1485).

Hyperthermia

The HT treatments of 60 minutes each were administered after RT and generally well tolerated. Two hundred forty-one patients received 4 HT treatments as planned. Seven patients (3%) received fewer HT treatments; five patients who received a lower total RT dose treatment and fewer HT treatments, and two patients refused the fourth treatment.

The average HT field size was 604 cm^2 (range 84-1700). Most of the patients could be treated with one applicator set-up (n=194), for the remaining patients a second (n=51) or third (n=3) applicator set-up was required to treat the whole RT field (total treatment time per session 120 or 180 minutes). The median number of interstitial thermometry sensors was 13 (range 2-27).

The median *Tmax*, *Tave* and T_{90} and median CEM43°C$T90_{tot}$ values were 43.6°C (range 40.8-46.1), 41.2°C (range 38.9-42.4), 39.7°C (range 37.0-41.5) and 2.7 min (range 0.3-37.6).

COMPLETE RESPONSE RATE, LOCAL CONTROL AND OVERALL SURVIVAL

The median follow-up duration was 32 months (range, 1-164). A CR was achieved in 70% of all patients. After CR, local recurrence occurred in 56 patients. The median duration of LC was 15 months and at 1, 3, and 5 years LC rate was 53%, 40% and 39%, respectively (Figure 1). The median OS was 19 months with an OS rate of 66%, 32%, and 18% at 1, 3, and 5 years, respectively. OS after 10 years was 10%.

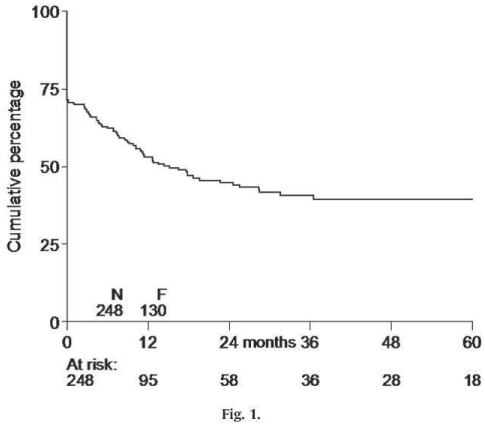

Fig. 1.

Figure 1. Duration of local control for 248 patients with irresectable breast cancer recurrences from the time of initiation reirradiation and hyperthermia. N, number of patients; F, failures.

Fourteen patients were alive with no evidence of disease 5 years after treatment, and six 10 years after treatment. The CR rate in 70 patients receiving concurrent hormonal therapy was 83%, which was significantly higher than 65% in the patients without hormonal therapy ($p = 0.006$) however the LC was not different.

The CR rate in 88 patients with distant metastasis was 63%, which was not significantly different from the CR rate in patients without distant metastasis (74%).

There was no difference in CR rate of patients irradiated in the Erasmus MC compared to patients irradiated elsewhere.

PROGNOSTIC FACTORS

A number of patient-, tumor-, and treatment-related characteristics were evaluated for an association with duration of LC (Table 3). In multivariate analysis none of the parameters remained significant.

Table 3. Results of univariate and multivariate Cox regression analyses for duration of local control.

Prognostic factor	Univariate		Multivariate	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Tumor status				
Tumor volume (per 100[b] cm^3)	1.09 (1.04–1.14)	0.000[a]	1.02 (0.93–1.12)	0.710
Maximum tumor diameter (per 100[b] cm)	1.44 (1.21–1.70)	0.000[a]	1.22 (0.90–1.64)	0.201
Estrogen + progesterone + Her2neu receptors (triple neg vs any pos)	0.57 0.38–0.86)	0.007[a]	0.66 (0.43–1.03)	0.066
Interval between primary breast cancer surgery and first relapse (months)	1.00 (0.99–1.00)	0.109		
Anatomic site of current recurrence:				
Lymph nodes vs chest wall	0.53 (0.20–1.43)	0.210		
Breast vs chest wall	1.00 (0.49–2.05)	0.994		
Initial T-stage (T2–T4 vs T0–T1)	1.37 (0.93–2.01)	0.112		
Differentiation (moderate or less vs well)	3.57 (0.50–25.65)	0.206		
Initial lymph nodal involvement (N2–N4 vs N0–N1)	1.20 (0.81–1.78)	0.371		
Patient status				
Prior chemotherapy (yes; no)	1.77 (1.18–2.65)	0.005[a]	1.46 (0.86–2.49)	0.161
Prior hormonal therapy (yes; no)	0.73 (0.51–1.03)	0.073		
Continuation of hormonal therapy during local treatment	0.71 (0.48–1.06)	0.094		
Age at hyperthermia (years)	0.99 (0.98–1.00)	0.195		
Distant metastasis	1.25 (0.87–1.79)	0.223		
Prior surgery (⩾2 vs <2)	0.86 (0.61–1.21)	0.393		
Prior radiation dose (Gy)	0.99 (0.97–1.02)	0.615		
Treatment related characteristics				
Size of hyperthermia field (per 100[b] cm^2)	1.11 (1.04–1.18)	0.002[a]	1.11 (0.94–1.31)	0.203
Size of radiation field (per 100[b] cm^2)	1.10 (1.04–1.17)	0.002[a]	0.99 (0.86–1.13)	0.834
Number of fields (2–4 vs 1)	1.67 (1.12–2.47)	0.012[a]	0.64 (0.27–1.50)	0.305
Average interstitial temperatures (°C)	0.71 (0.53–0.95)	0.021[a]	0.75 (0.30–1.83)	0.522
T90 interstitial temperatures (°C)	0.77 (0.60–0.99)	0.040[a]	1.10 (0.50–2.41)	0.805
CEM43 °CT90 (minutes)	0.95 (0.90–1.00)	0.058		
Radiation technique:				
Combination vs electrons	1.23 (0.80–1.89)	0.337		
Fotons vs electrons	0.97 (0.64–1.47)	0.874		

Legend to table 3:
CEM, cumulative equivalent minutes; HR, hazard ratio; CI, confidence interval.
[a] Statistically significant.
[b] The variables were re-scaled in the analysis by dividing by 100.

TREATMENT TOXICITY

Acute radiation toxicity included moderate to marked erythema in 49 patients (20%), and moist desquamation in 23 (9%). The effects were generally self-limiting and healed a few weeks after the treatment. Late toxicity was seen in three patients after a follow-up of 8, 10 and 124 months: radiation-induced skin necrosis, which was treated with either surgery or hyperbaric oxygen. Thermal burns occurred in 57 patients. Three patients had subcutaneously burns. All healed without further intervention (CTCAE grade 1 or 2).

All factors (Table 3) were also investigated for prognostic significance on acute HT toxicity.

Univariate analysis showed that various parameters associated with the size of the treatment field (HT and RT field size, number of thermal probes, number of HT applicator set-ups, RT technique) influenced thermal toxicity (*p*-values 0.001-0.006), with more toxicity in larger fields. None of the interstitial thermal dose parameters influenced HT-induced toxicity (*p*-values 0.319-0.970). The maximum temperature measured on the skin (n=244) did influence HT toxicity. The incidence of WHO grade 2 and 3 skin burns clearly increases with a higher superficial *Tmax*: 28% (37/130) when > 43°C, 29% (20/70) when > 43.5°C, and 40% (8/20) when > 44°C, while it was 13% (15/114) when *Tmax* < 43°C (Fisher exact *Tmax* > 43°C versus *Tmax* < 43°C, $p = 0.003$).

DISCUSSION

In this report we present a large-scale observational study of the results of planned treatment with 32 Gy re-RT combined with 4 HT treatments in patients with irresectable breast cancer recurrences. Overall, a CR was achieved in 70% of all patients, and LC rates at 1, 3, and 5 years were 53%, 40%, and 39%, respectively.

OS after 1, 3 and 5 years was 66%, 32%, and 18% respectively, and after 10 years still 10%. A few patients may have been cured.

Our results are comparable with those of combined treatment in the ESHO 88-5 phase III trial [1], in which the same re-RT scheme was used. In this study CR was 38% after re-RT alone and 78% after re-RT and HT. The achievement of a local tumor control is important for quality of life [13], and can prolong OS [14].

Of the 110 patients with less than 2 year interval between primary treatment for breast cancer and first recurrence, five survived more than 5 years after re-RT and HT, two of them without evidence of disease.

Of the whole group, 14 patients were alive without evidence of disease more than 5 years after treatment, and six more than 10 years. Patients irradiated elsewhere showed no worse results in spite of the longer time interval between re-RT and HT. Skin burns, WHO grade 2 or 3, occurred in 54 patients, and a subcutaneous burn in three patients. A higher risk of HT toxicity was seen in larger treatment fields.

No correlation was found between interstitial thermal parameters and acute toxicity, but with superficially measured temperatures above 43°C, the risk of burns was higher. Limitation of skin temperatures to a maximum of 43°C may result in a decrease of acute side effects of HT and this can be used for treatment guidelines.

The cumulative incidence of late grade 3 toxicity was 1% after 5 years follow-up. The three patients with grade 3 toxicity could be treated well with either surgery or hyperbaric oxygen.

Locoregional recurrences of breast cancer may be the cause of severe suffering when uncontrolled, with symptoms such as pain, ulceration, and bleeding.

Systemic treatment usually is less effective in a region previously irradiated [15,16]. In patients with local recurrences of breast cancer after previous RT, the treatment of choice is surgery. In extensive disease, chest wall resection may be required.

Fanyete et al. [17] report on chest wall resection in 44 patients. A re-recurrence was observed in 14% of the patients. OS after 5 years was 45%. In the thirty patients who underwent chest wall resection with curative intent, 5 years OS was 58%. Postoperative complications occurred in 41% of the patients and median duration of hospitalization was 21 days, which makes it a relatively cumbersome treatment.

Van der Pol et al.[18] treated 77 patients with curative intent. A R0 resection was possible in 64% of the patients. Complications occurred in 29 patients (38%) which were severe in 16 (21%). LC rate after 5 years was 51% and DFS 12%. Five years OS was 25%. Publications on 5 years OS after curative chest wall resection, reviewed in their article, show that this varies from 18% to 71%.

Despite that our patients were less favourable with irresectable tumors, our results are comparable. In view of the LC rates achieved, local surgery, when feasible, remains the treatment of choice, and can be followed by re-RT and HT in case of an incomplete resection. However, in view of the favourable outcome with less toxicity, re-RT and HT is preferred to extensive chest wall resection. In previous studies we have shown that re-RT plus HT for subclinical disease results in 78% 5 years LC and 60% 5 years OS [15,19], and further that it is safe and effective in patients with tissue transplants [3].

We are using the re-RT scheme of 8 fractions of 4 Gy, given twice weekly. The question is whether this is the optimal schedule, or that better results would be achieved with e.g. a higher total dose, lower fraction sizes and/or concurrent systemic therapy. A higher total radiation dose may result in better LC rates, but also in more toxicity. Published results of higher total RT doses do not show better CR rate than we found in the present study. Hehr et al. [20] treated 39 patients with an average total RT dose of 56 Gy in fractions of 1.2-2 Gy and HT. A CR was achieved in 40% of the 30 patients with an irresectable tumor; 2 years LC in all patients was 46%. Ulceration of the skin was observed in 1 patient.

Wahl et al. [15] reviewed results in 81 patients treated with re-RT, which was combined with HT in 44. Re-RT total dose was median 48 Gy and fraction size approximately 2 Gy.

In patients with macroscopic tumors combined re-RT and HT resulted in 67% CR and 58% LC after 1 year. After a median follow up of 1 year, 4 patients of the whole group had developed grade 3-4 toxicity. Li et al. [16] report 56% CR in 41 patients treated with

a mean re-RT dose of 43 Gy combined with HT, a dose biologically equivalent to our convenient schedule of 32 Gy in 4 Gy fractions. In the present study the incidence of toxicity is only 1% after a median follow up of 30 months, which is acceptable. In view of the achieved LC and limited toxicity, we prefer to continue with the hypofractionated schedule.

Another question is whether clinical outcome can be improved with concurrent systemic therapy. Published results on radiation combined with both HT and chemotherapy sofar have not shown better results. Bornstein et al. [21] report a CR rate of 53% for 34 fields in 29 patients treated with various drugs in addition to radiation and HT. Feyerabend et al. [22] report a CR rate of 44% in patients treated with epirubicin and ifosfamide in addition to radiotherapy, mean total dose 49 Gy, and HT. Kouloulias et al. [23] achieved 20% CR in 15 patients treated with 31 Gy, liposomal doxorubicin and HT. Patients did not receive chemotherapy during local treatment, but concurrent hormonal treatment was given to 71 patients. In these patients there was a trend to a higher LC.

However, the risk of selection bias in this comparison is obvious: 50% of the patients continuing hormonal therapy had started this >2 months previously, indicating that the therapy had beneficial effects. Therefore, these patients may represent a subgroup with a better prognosis.

CONCLUSIONS

The treatment of irresectable recurrent breast cancer with re-RT and HT results in 70% CR and 39% 5 years LC with acceptable toxicity, and may be curative in a small subgroup of patients. In operable cases, surgical resection is the treatment of choice and can be followed by re-RT and HT. In irresectable disease, re-RT and HT is the treatment of choice. In the Netherlands this therapy is the recommended treatment for patients with breast cancer recurrence and reimbursed by the Health Insurance.

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Chapter 6

Reirradiation and hyperthermia after surgery for recurrent breast cancer

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ABSTRACT

Purpose: Evaluation of efficacy and side effects of combined reirradiation and hyperthermia electively or for subclinical disease in the management of locoregional recurrent breast cancer.

Methods and Materials: Records of 198 patients with recurrent breast cancer treated with reirradiation and hyperthermia from 1993-2010 were reviewed. Prior treatments included surgery (100%), radiotherapy (100%), chemotherapy (42%), and hormonal therapy (57%). Ninety-one patients were treated for microscopic residual disease following resection or systemic therapy and 107 patients were treated electively for areas at high risk for local recurrences. All patients were re-irradiated to 28-36 Gy (median 32) and treated with 3-8 hyperthermia treatments (mean 4.36). Forty percent of the patients received concurrent hormonal therapy. Patient and tumor characteristics predictive for actuarial local control (LC) and toxicity were studied in univariate and multivariate analysis.

Results: The median follow-up was 42 months. Three and 5 years LC-rates were 83% and 78%. Mean of T_{90} (tenth percentile of temperature distribution), maximum and average temperatures were 39.8°C, 43.6°C, and 41.2°C, respectively. Mean of the cumulative equivalent minutes (CEM43°C) at T_{90} was 4.58 minutes. Number of previous chemotherapy and surgical procedures were most predictive for LC. Cumulative incidence of grade 3 and 4 late toxicity at 5 years was 11.9%. The number of thermometry sensors and depth of treatment volume were associated with acute hyperthermia toxicity.

Conclusions: The combination of reirradiation and hyperthermia results in a high LC-rate with acceptable toxicity.

INTRODUCTION

The treatment of locoregional failures in previously irradiated regions presents a difficult problem. When resectable, irradiation may be indicated thereafter. However, elective reirradiation is either not done at all or leads to unsatisfactory results [1].

Over the past three decades, hyperthermia as an adjunct to radiotherapy has demonstrated to be effective in the treatment of locoregional recurrences in previous irradiated breast cancer [2]. Therefore, we elected to combine radiation with hyperthermia. There are only four published studies in this regard, all including less than 90 patients [1,3,4,5].

We retrospectively analyzed the clinical outcome of all 198 patients treated by us from 1993 to 2010, which makes this the largest study sofar. The endpoints of the study were local control (LC), and treatment complications. Further we analyzed which patient and tumor characteristics as well as treatment characteristics correlated with LC and toxicity.

METHODS AND MATERIALS

Patients

The inclusion criteria for this evaluation were as follows: recurrent adenocarcinoma of the breast in previously irradiated area after resection with high risk of re-recurrence (subclinical disease: after R1 resection; elective treatment for close margins, multiple previous recurrences, and/or multicentricity), and treatment with radiotherapy plus hyperthermia. In-breast recurrences were treated by mastectomy (R0:23, R1:19), two of these patients had a reconstruction of the breast. Chest wall recurrences were removed by local excision (R0:79, R1:58). In three patients the wound was closed with a reconstruction. Recurrences caudal in the axilla or supraclavicular region were treated with a resection (R0:7, R1:7). The whole reirradiation field had to be coverable with hyperthermia applicators and the maximum accepted depth was 4 cm.

Radiotherapy

Patients received elective external beam radiation to a prescribed dose of 32 Gy at 4 Gy per fraction, twice a week, following surgery (n = 193) or when in clinical complete remission after systemic therapy (n = 5). In the majority of patients, the radiotherapy field included the whole mastectomy scar.

Hyperthermia

The hyperthermia treatments of 60 minutes each were given at intervals of at least 72h, once or twice (11 patients) a week, after radiotherapy [6,7]. Hyperthermia was delivered using Lucite Cone applicators (LCA) operating at 433 MHz as previously described [3,6,8].

This applicator has a square aperture of 10x10 cm^2; the effective field size is up to 80% of the aperture. With six applicators combined an area of 20x30 cm^2 can be effectively heated to a depth of up to 4 cm. The applicator set-up was chosen to heat the whole reirradiation volume [7]. When the radiotherapy field could not be covered with one applicator set-up, the remaining part was treated subsequently with a second applicator set-up (total treatment time 120 minutes).

Temperatures were measured interstitially, within catheters, and on the surface.

For thermometry, a fiber-optic system (FTP-5 Medical Array Sensor, Takaoka Electric Mfg, Tokyo, Japan) was used with five multisensory probes (up to four sensors) and four single-sensor probes [6,7]. From the interstitially measured temperature data various parameters were calculated: *Tmax*, *Tave*, T_{90} (tenth percentile of temperature) and CEM43ºCT90 (5).

CEM43ºCT90 represents the thermal isoeffect dose expressed in cumulative equivalent minutes (CEM) at a reference temperature of 43°C, based on the low end of the temperature distribution (T_{90}) [9,10]. For this analysis the mean of these thermal dose parameters was used. The superficially measured thermal parameters were used for evaluation of acute toxicity.

ENDPOINTS AND STATISTICAL METHODS

Only the first treated field in each patient was included in this analysis. Kaplan-Meier estimates were performed for actuarial probability of LC and late toxicity. Duration of LC was defined as the time between initiation of treatment until the first observation of progression within the treated volume, or censored at the day of death or last follow-up.

The actuarial incidence of late toxicity was calculated using the Kaplan Meyer method from the start of reirradiation to the date of last follow-up. Toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0) [11].

Cox regression, univariate as well as multivariate, was used to investigate which pretreatment and treatment parameters were associated with LC and the incidence of late toxicity. Logistic regression was used to investigate which parameters were associated with the development of acute toxicity. For analysis, the Stata statistical software release 11 was used (StataCorp 2009).

RESULTS

Patient and tumor characteristics

Table 1 summarizes the tumor characteristics at the time of first diagnosis. Table 2 summarizes the patient's characteristics at the time of reirradiation and hyperthermia.

Table 1. Initial patient and breast cancer characteristics at the time of first diagnosis.

		Median ± SD (range)	No. of patients	%
Primary diagnosis	<1990		74	37
	1990–1994		45	23
	1995–1999		43	22
	⩾2000		36	18
Age (years)		48 ± 16 (27–80)		
T-stage				
	T0		4	2
	T1		90	45
	T2		67	34
	T3		13	7
	T4		7	4
	Unknown		17	9
Lymph nodal involvement				
	N0		114	58
	N1		52	26
	N2		11	6
	N3		6	3
	Unknown		15	8
Differentiation				
	Well		11	6
	Moderately		46	23
	Poorly		95	5
	Unknown		46	23
Estrogen receptor				
	Positive		90	45
	Negative		45	23
	Unknown		63	32
Progesteron receptor				
	Positive		68	34
	Negative		67	34
	Unknown		63	32
Her2neu				
	Amplified		36	18
	Not amplified		87	44
	Unknown		75	38

Legend to table 1: SD = standard deviation

Table 2. Patient and tumor characteristics at the time of hyperthermia.

	Median ± SD (range)	No. of patients	%
Age (years)	60 ± 12 (30–85)		
Interval from initial breast cancer to first relapse (months)	89 ± 87 (2–523)		
Interval from initial radiotherapy to reirradiation (months)	112 ± 87 (13–524)		
Presence of distant metastases		18	9
Anatomic site at the time of recurrence			
Breast		46	23
Chest wall		138	70
Regional lymph nodes		7	3.5
Regional lymph nodes and chest wall		7	3.5
Tumor extent			
Microscopic residual		91	46
Elective treatment		107	54
Initial dose without boost (Gy)	48 ± 4 (20–60)		
Cumulative dose (initial dose ± re-irradiation dose) (Gy)	80 + 9 (52–98)		
Number of previous lines of chemotherapy			
0		114	58
1		62	31
⩾2		22	11
Number of previous lines of hormonal therapy			
0		87	44
1		70	35
⩾2		41	21
Number of previous surgical procedures at the same location			
1		3	2
2		94	47
⩾3		101	51
Maximum depth (mm)	26 ± 16 (10–50)		

Legend to table 2:
SD = standard deviation

TREATMENT CHARACTERISTICS

Radiotherapy

Ninety-five patients (48%) received current radiotherapy in our institute. For the others, the radiation was applied by their referring radiation oncologist in one of the other 13 radiotherapy centers.

The radiotherapy plan was adjusted in three patients. One patient received 28 Gy, as her treatment was discontinued because of general deterioration due to rapid progression of systemic disease. Two patients received 36 Gy. In one patient, the treatment was interrupted because of abscess formation due to an infection around a thermometry

catheter, and a ninth fraction was given to compensate for the delay. In another patient, a ninth fraction was given for an unknown reason.

Hyperthermia

All patients received hyperthermia in our institute. Eighty-nine percent of patients received 4 hyperthermia sessions and 9% 8, as planned. Four patients (2%) received less than the planned number of treatments. Two patients received 7 instead of 8 treatments for logistic reasons, and two patients 3 instead of 4 treatments, because of cardiac asthma and general deterioration, respectively. The mean number of hyperthermia treatments was 4.36. The average hyperthermia field size was 562 cm^2 (range 84-1700 cm^2). The mean number of interstitial thermometry sensors was 11 (range 1-25). The averages of *Tmax*, *Tave*, and T_{90} were 43.6°C, 41.2°C and 39.8°C, respectively. The average of CEM43°C$T90_{tot}$ was 4.58 minutes.

LOCAL CONTROL AND OVERALL SURVIVAL

One hundred and nine patients (55%) are still alive with a median follow-up of 42 months (range, 1-194). Thirty-five patients had a locoregional recurrence (18%) after 1-74 months (median 16). Actuarial LC-rates after 1, 3, 5 and 10 years are 93%, 83%, 78%, and 75% respectively (Fig. 1). The 3, 5 and 10 years overall survival (OS) rates are 75%, 60% and 36%, respectively, with a median survival of 82 months. Five years LC for patients from Erasmus MC is 72%, and for patients from other institutes, this is 82% ($p = 0.065$).

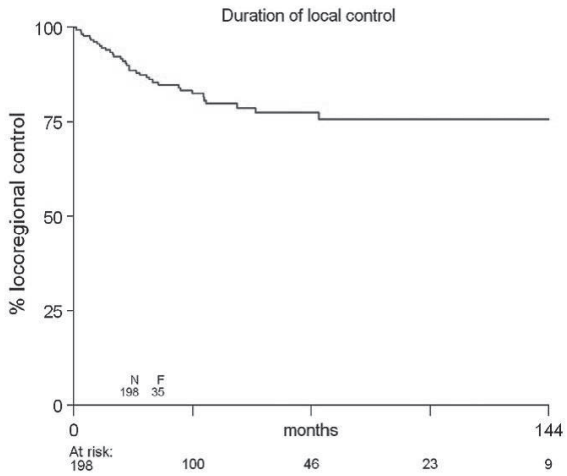

Figure 1. Actuarial local control for all 198 patients from the time of initiation of treatment. N, number of patients; F, failures.

PROGNOSTIC FACTORS

Only a high number of previous chemotherapies and surgical procedures remained significantly associated with probability of LC in multivariate analysis (Table 3).

Table 3. Results of univariate and multivariate Cox regression analysis for local control.

Prognostic factor	HR[c]	*p*-Value[c]	HR (95% CI)[d]	*p*-Value[d]
Tumor status				
Interval from initial radiotherapy to reirradiation (months)	0.992	0.005[a]	0.995 (0.980–1.010)	0.503
Interval from initial breast cancer to first relapse (months)	0.992	0.006[a]	0.999 (0.985–1.014)	0.935
Estrogen and progesteron receptor (double neg vs. any pos)	2.759	0.033[a]	2.553 (0.908–7.177)	0.075
Estrogen receptor (pos vs. neg)	0.374	0.038[a]	0.400 (0.136–1.179)	0.097
Histological grade (I, II vs. III)	1.803	0.083		
Her2neu (pos vs. neg)	2.007	0.142		
Progesteron receptor (pos vs. neg)	0.490	0.154		
Initial N-stage (0–1 vs. 2–3)	0.281	0.212		
Anatomical site of current recurrence (chest wall vs. breast)	0.606	0.304		
Estrogen + progesteron receptor + Her2neu (triple neg vs. any pos)	1.277	0.642		
Extent of surgery (R0 vs. R1)	1.111	0.757		
Initial T-stage (0–1 vs. 2–4)	0.904	0.771		
Anatomical site of current recurrence (chest wall vs. lymph nodes)	1.089	0.889		
Patient status				
Age at hyperthermia (years)	0.954	0.002[a]	0.975 (0.919–1.033)	0.393
Prior chemotherapy ⩾2	4.046	0.003[a]	6.469 (1.471–28.452)	0.013[a]
Prior surgery (⩽2 vs. >2)	2.525	0.013[a]	3.994 (1.303–12.240)	0.015[a]
Prior chemotherapy <2	2.100	0.050[a]	1.813 (0.398–8.251)	0.442
Distant metastases	1.283	0.083		
Prior radiation dose (Gy)	9.567	0.135		
Continuation of hormonal therapy during local treatment	0.655	0.245		
Prior hormonal therapy ⩾2	0.868	0.783		
Prior hormonal therapy <2	1.037	0.921		
Treatment characteristics				
Number of hyperthermia treatments (1–4 vs. 5–8)	0.426	0.044[a]	_[b]	_[b]
Institution (Erasmus MC vs. others)	1.880	0.065		
T90 interstitial temperatures (°C)	0.665	0.148		
Average interstitial temperatures (°C)	0.597	0.174		
Size of radiation field (cm^2)	1.000	0.268		
Number of thermometry sensors	1.047	0.295		
CEM43°CT90 interstitial (min)	0.828	0.324		
Concurrent radiation dose (Gy)	0.680	0.499		
Size of hyperthermia field (cm^2)	1.000	0.664		
Maximum interstitial temperatures (°C)	1.013	0.968		

Legend to table 3:
HR, hazard ratio; CI, confidence interval; CEM, cumulative equivalent minutes; pos, positive; neg, negative
[a] Statistically significant
[b] Sample size too small
[c] Univariate
[d] Multivariate

Complications of treatment

In one patient acute grade 4 radiotherapy toxicity appeared after 1 month. Radionecrosis of the chest wall occurred due to radiotherapy requiring wound debridement and reconstruction.

Grade 3 hyperthermia toxicity occurred in five patients, of which three in a flap, which all required surgical repair (12). In two patients, an abscess developed during the treatment course at the site of an interstitial thermometry catheter. One patient required surgical intervention during the treatment and completed the treatment with an extra radiation fraction. The second patient required abscess drainage after the treatment. In both patients the wound healed uneventful.

Late grade 3 and 4 toxicity was seen in 20 patients after a median follow-up of 14 months (range, 4-97 months). The cumulative incidence of late toxicity was 4.8%, 9.5%

and 11.9% at 1, 3 and 5 years, respectively. Fifteen patients developed ulceration and five osteoradionecrosis, for which they were treated with necrotomy, reconstruction and/or hyperbaric oxygen. In multivariate analysis, only the institute where patients received radiotherapy was significantly associated with late toxicity (p = 0.031) (Table 4). Late grade 3 and 4 toxicity occurred in 15% of patients from Erasmus MC and in 7% of patients from other institutes.

Influencing hyperthermia damage

Univariate analysis showed that a high number of thermometry sensors and a less deep target volume (<2.5 cm) were associated with more hyperthermia toxicity (p = 0.021, p = 0.034); in multivariate analysis these factors remained significant (p = 0.014, p = 0.032). Interstitial thermal parameters had no influence on hyperthermia induced toxicity (p-values varying between 0.148 and 0.968). Thermal parameters derived from measurements on the skin were higher in patients with WHO grade 2 and 3 burns than in patients with no and grade 1 burns (Table 5), although there was a large overlap between the ranges of temperatures. The incidence of grade 2 and 3 burns clearly increases with higher superficial Tmax: 32% (31/98) when > 43°C, 34% (18/53) when > 43.5°C, 41% (9/22) when > 44°C, while it was 15% (14/92) with Tmax < 43°C (Fisher exact Tmax > 43°C versus Tmax < 43°C, p = 0.006).

Table 4. Univariate and multivariate analysis for tumor, patient and treatment characteristics on late toxicity.

Prognostic factor	HR[b]	*p*-Value[b]	HR (95% CI)[c]	*p*-Value[c]
Tumor status				
Anatomical site of current recurrence (chest wall vs. breast)	2.52	0.046[a]	0.43 (0.16–1.20)	0.109
Interval from initial radiotherapy to reirradiation (months)	1.00	0.958		
Anatomical site of current recurrence (chest wall vs. lymph nodes)	0.00	1.000		
Patient status				
Number of previous surgical procedures	0.38	0.045[a]	0.44 (0.16–1.23)	0.118
Continuation of hormonal therapy during local treatment (yes vs. no)	0.49	0.167		
Age at hyperthermia (⩽60 vs. >60 years)	1.03	0.190		
Prior hormonal therapy (yes vs. no)	0.60	0.245		
Prior chemotherapy (yes vs. no)	0.92	0.825		
Treatment characteristics				
Institution (Erasmus MC vs. others)	2.66	0.045[a]	2.92 (1.10–7.73)	0.031[a]
Field type (combination of photons and electrons vs. electrons)	2.62	0.100		
Field type (photons vs. electrons)	2.14	0.182		
Size of radiation field (⩽400 vs. >400 cm^2)	1.00	0.183		
Maximum interstitial temperatures (°C)	0.60	0.215		
CEM43T90 surface (min)	0.94	0.270		
Average interstitial temperatures (°C)	0.60	0.311		
Total radiation dose (past plus current radiation doses)	0.98	0.362		
CEM43T90 interstitial (min)	0.84	0.424		
T90 surface temperatures (°C)	0.86	0.434		
Maximum surface temperatures (°C)	1.22	0.437		
T90 interstitial temperatures (°C)	0.78	0.508		
Average surface temperatures (°C)	0.98	0.936		

Legend to table 4:

CI, confidence interval; CEM, cumulative equivalent minutes

[a] Statistically significant.

[b] Univariate.

[c] Multivariate.

Table 5. Superficial measured thermal parameters and acute toxicity.

Skin burns WHO score	0 + 1	2 + 3	*p*-Value
Tmax	42.7 °C (range, 39.8–45.8)	43.2 °C (range, 41.0–45.8)	0.003
Tave	40.6 °C (range, 36.9–42.9)	41.0 °C (range, 38.2–42.7)	0.011
T90	39.5 °C (range, 35.4–42.1)	39.7 °C (range, 35.8–41.8)	0.067
CEM43°CT90	4.80 min (range, 0.0–36.5)	6.17 min (range, 1.0–56.7)	0.023

Legend to table 5:
CEM, cumulative equivalent minutes

DISCUSSION

This paper presents results of reirradiation and hyperthermia in patients with recurrent breast cancer treated electively or for subclinical disease following excision or systemic therapy. The 3 and 5 years actuarial LC-rates are 83% and 78%. Late grade 3 and 4 toxicity occurred in: 9.5% and 11.9% of the patients after 3 and 5 years, respectively.

The results are comparable with the results reported by others. Kapp et al. [3] have shown that reirradiation and hyperthermia for presumed or known microscopic residual tumors resulted in a 3-year LC of 68%. Welz et al. [4] treated 50 patients for microscopically involved or close margins after surgery for locoregional recurrence achieved a 3-year LC-rate of 81%.

Oldenborg et al. [5] showed a 3-year LC-rate of 78% in 78 patients all treated for microscopic residual disease.

Müller et al. [1] achieved a prolonged LC in 86% of patients with microscopically positive margins treated with reirradiation and hyperthermia. For macroscopic breast cancer recurrences, the beneficial effect of hyperthermia added to radiotherapy has been demonstrated [2]. The tripling of complete response by adding high-dose hyperthermia (compared to low-dose hyperthermia) to reirradiation in breast cancer recurrences [9], made the National Comprehensive Cancer Network (NCCN) to include radiation plus hyperthermia in its 2007 Breast Cancer Guidelines for recurrent breast cancer when failures occur after surgery and radiation.

For microscopic breast cancer recurrences, the effect of adding hyperthermia to reirradiation is less clear. We found a few small studies on the effect of reirradiation alone, in patients with a recurrence after breast conserving therapy (BCT). Racadot et al. [13]

reported on 20 patients treated with surgery and reirradiation with a median dose of 45 Gy (range, 33-65) and achieved a LC-rate of 75% after mean follow-up of 48 months.

Late complications were rib fractures in four patients (20%). Deutsch et al. [14] treated 39 women with an in-breast tumor recurrence with excision and whole breast irradiation with 50 Gy. The LC-rate after median 52 months was 76.9% without severe toxicity (< CTCAE grade 2). Harkenrider et al. [15] reviewed eight patients with nine locoregional breast cancer recurrences, treated with reirradiation (46.7 Gy). The median follow-up time was 30 months.

LC was achieved in nine fields (100%). CTCAE grade 3 late toxicity developed in two patients. In the above listed three studies, overall 87% of the patients were treated after R0 resection. Overall, reirradiation alone to a dose of 45-50 Gy results in a LC of 75 to 100% after 2-4 years of follow-up, which is similar to our 3 to 5 years LC in patients of whom 54% had a R0 resection. Müller et al. [1] report how, in R1 resected patients, hyperthermia added to reirradiation (median 60 Gy) improved LC from 50 to 86%.

We have more reasons to believe that elective or adjuvant radiotherapy in combination with hyperthermia is effective in locoregional recurrent breast cancer. In a previous study in our institute [3], hyperthermia was applied to only part of the reirradiation field, the site of the visible tumor, in five patients. During follow-up tumor progression was observed outside the hyperthermia field, where earlier no tumor was apparent, while the combined treated region remained controlled. Reirradiation can only be given one more time and therefore should be given to maximal effect.

Concurrent chemotherapy does not seem to improve the results of radiotherapy in recurrent breast cancer [16,17]. Surgery is another possible treatment. Chest wall resection with curative intent may result in 80% LC [18] but in this study complications requiring surgery occurred in 30% of the patients and 5-year disease-free survival was 35%.

Only two parameters were associated with duration of LC i.e. number of previous chemotherapy courses and surgical procedures. Although these parameters probably reflect a more aggressive tumor type, it could also mean that patients would have a better prognosis when referred in an earlier stage.

The cumulative incidence of late toxicity was relatively high, but such toxicity was only observed in patients with continuing LC and could be treated well with either surgery or hyperbaric oxygen, and therefore acceptable in view of the high LC rate.

The incidence of late grade 3 and 4 toxicity was significantly lower in patients from other institutes compared to patients irradiated at Erasmus MC. This may be explained by a longer time interval between radiotherapy and hyperthermia in patients irradiated elsewhere.

The general idea is that hyperthermia should be given within a short time before or after radiotherapy to get maximum enhancement. The longer time interval for patients irradiated elsewhere did not lead to a lower LC rate.

Two parameters were significant in multivariate analysis for the development of hyperthermia toxicity. An explanation for the finding between a high number of thermometry sensors and toxicity would be that more probes are inserted in a larger target area. Larger radiation fields entail an increased risk of late toxicity. Indeed, we found in this patient material a highly significant correlation between number of sensors and size of radiotherapy and hyperthermia field ($p = 0.000$, $p = 0.000$). The second parameter was depth which can be explained by the use of higher water bolus temperature for less deep target volume. No correlation was observed between interstitial thermal parameters and acute toxicity, but the superficial temperature was of prognostic significance for grade 2 and 3 toxicity (Table 5). The increase of incidence of burns at higher temperatures can be used for treatment guidelines.

Some clinically relevant questions still exist. In the first place, what is the optimal radiotherapy scheme? Lower fraction sizes might result in a lower incidence of late grade 3 and 4 toxicity. On the other hand, it also may result in lower LC-rates.

In the ESHO trial [2], using eight fractions of 4 Gy, CR-rates were 38% for radiotherapy alone and 78% for combined treatment. In the MRC BrR study with eight fractions of 3.6 Gy, these were 29% and 56%, and in the PMH trial with 18 fractions of 1.8 Gy, these were 31% and 29%, respectively [2]. Oldenborg et al. [5] report a 3-year LC-rate of 78% with the same schedule.

A few studies have reported CR and LC after smaller radiotherapy fractions to a higher total dose. Two to 4 years LC-rates varied between 75% and 100% [1,14,15], which is comparable to what we found, while there were more patients with R1 resection in our study. Reported late toxicity CTCAE grade 3 or higher varies from 0% to 25% after reirradiation with total doses of 45-60 Gy with fraction sizes of 1.8 to 2.0 Gy, after median follow-up times of 2 to 4 years. The late toxicity found by us (11.9% after 5 years) falls within this range. We have no explanation why Oldenborg et al. [5], treating 78 patients with microscopic disease with eight fractions of 4 Gy and hyperthermia, found a much higher (43%) incidence of > CTCAE grade 3 toxicity after 3 years.

Another question is how important the continuation of or change in systemic therapy is. In our study, continuation of chemotherapy during combined treatment was not allowed, but the LC-rate in 78 patients who continued hormonal therapy during treatment was not significantly higher than in the remaining patients: 86% compared to 80% ($p = 0.245$).

Waeber et al. [19] randomized patients with chest wall recurrences that were ER positive and had other good prognostic factors, to tamoxifen or placebo after complete local excision and radiation. The 5-year disease-free survival was improved in postmenopausal women with the use of tamoxifen, 33% to 61%. The 5-year OS was not different for both groups. In premenopausal women, there was no improvement in disease-free

survival by tamoxifen medication, while a decrease in OS was observed in patients taking tamoxifen (90% vs. 67%).

Results of Willner et al. [16] suggest no benefit of hormonal or chemotherapy added to postoperative radiotherapy on overall survival.

Thirdly, what the optimal number of hyperthermia sessions is. In multivariate analysis, we found no influence of number of treatments on LC. A comparison of results after four or eight hyperthermia treatments combined with reirradiation in patients with macroscopic breast cancer is the subject of an ongoing evaluation.

CONCLUSIONS

Reirradiation and hyperthermia applied to patients with breast cancer recurrence electively or for subclinical disease results in a high rate of durable LC and is well tolerated with acceptable toxicity. This combined treatment should therefore be offered to all patients with a high risk of local recurrence after surgical resection of a recurrence.

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Part 2

Towards finding a prospective quality indicator

Chapter 7

Procedure for creating a three-dimensional (3D) model for superficial hyperthermia treatment planning

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ABSTRACT

In the current clinical practice, prior to superficial hyperthermia treatments (HT), temperature probes are placed in tissue to document a thermal dose. To investigate whether the painful procedure of catheter placement can be replaced by superficial HT planning, we study if the specific absorption rate (SAR) coverage is predictive for treatment outcome. An absolute requirement for such a study is the accurate reconstruction of the applicator setup. The purpose of this study was to investigate the feasibility of the applicator setup reconstruction from multiple-view images. The accuracy of the multiple-view reconstruction method has been assessed for two experimental setups using six Lucite Cone applicators (LCAs) representing the largest array applied at our clinic and also the most difficult scenario for the reconstruction. For the two experimental setups and 112 distances, the mean difference between photogrametry reconstructed and manually measured distances was 0.25 ± 0.79 mm (mean±1 standard deviation). By a parameter study of translation T (mm) and rotation R (°) of LCAs, we showed that these inaccuracies are clinically acceptable, i.e. they are either from ±1.02 mm error in translation or ±0.48° in rotation, or combinations expressed by $4.35R(2) + 0.97T(2) = 1$. We anticipate that such small errors will not have a relevant influence on the SAR distribution in the treated region. The clinical applicability of the procedure is shown on a patient with a breast cancer recurrence treated with reirradiation plus superficial hyperthermia using the six-LCA array. The total reconstruction procedure of six LCAs from a set of ten photos currently takes around 1.5 h. We conclude that the reconstruction of superficial HT setup from multiple-view images is feasible and only minor errors are found that will have a negligible influence on treatment planning quality.

INTRODUCTION

At least 19 randomized studies have shown that adding hyperthermia (HT) to radiotherapy (RT) and/or chemotherapy leads to improved survival and tumor control in oncological patients without a significant increase in observed side effects [40]. In all these studies, the differences were remarkably large. In a multicenter randomized trial on malignant melanoma by Overgaard et al. [20], the addition of HT to RT improved the complete response (CR) from 35% to 62%, and 2-year local control (LC) from 28% to 46%. Addition of HT to RT in recurrent or advanced breast cancer improved the CR from 41% to 59% [42]. The difference in LC was maintained over the 3-year follow-up. The tripling of the CR rate in various superficial tumors for reirradiation and high-dose HT vs RT and low-dose HT as demonstrated in a randomized study by Jones et al. [13] resulted in the inclusion of radiation plus HT in the 2007 Breast Cancer Guidelines for recurrent breast cancer and other localized cancer recurrences by the National Comprehensive Cancer Network (NCCN). HT is both the ideal complementary treatment to, and a strong sensitizer of, RT and in general well tolerated by patients [14]. The HT treatment effect depends on the temperature rise and the treatment duration at the elevated temperature. In several clinical trials, a correlation between treatment outcome and thermal dose parameters was demonstrated [3,9,26,31,39,43]. However, translation of these experimental dose–effect relationships to the clinical situation is complicated. Simple approaches to describe a clinically delivered thermal dose include the use of maximum, average, or minimum temperature for the duration of the treatment or the use of measurements for temperature distribution, such as T10 or T90 (the temperature level above which 10% or 90%, respectively, of the measurements was). The temperature distribution during clinical treatment is spatially inhomogeneous due to variable tissue properties and blood flow, and changes over time due to changes in blood flow [7]. A disadvantage of thermal dose parameters is that these have been shown to depend on the number of measurement sites and on tumor characteristics such as blood flow and tumor size [4].

Major limitations for further improvement of treatment quality lay in the difficulty to improve dosimetry and in the inability to prescribe a specified thermal dose [6]. We do not consider it clinically feasible to increase the density of interstitially placed temperature probes. Furthermore, noninvasive thermometry (NIT) by magnetic resonance imaging is not realistic for superficial hyperthermia treatment (SHT), and NIT by microwave radiometry or ultrasound has not been shown to provide the required spatial resolution and temperature sensitivity.

Clinical data support that the Specific Absorption Rate (SAR) distribution is a valuable parameter to predict the CR [40]. Lee et al. [16] studied the relationship between SAR and clinical outcome in 151 patients with 196 lesions of recurrent breast carcinoma of

the chest wall. They found that both CR rate and local tumor control were statistically higher when the tumor was covered by the 25% iso-SAR contour. The clinical outcome was better predicted by SAR coverage than by thermal dose parameters. In a different way, van der Zee et al. [38] also found that the HT technique, i.e. the SAR distribution, is important for clinical outcome. In patients with recurrent breast cancer, they observed a much higher LC rate after the introduction of a better heating technique, especially in the patients with larger tumors.

In a follow-up to these findings, we started a clinical study to investigate whether the predicted three-dimensional (3D) SAR distribution from SHT modeling is prognostic for treatment outcome in patients with breast cancer recurrences in a previously irradiated area [23,24,25]. In order to adequately conductance of this study, the modeling should accurately reflect the applied HT quality.

The first step in this approach is the correct input of the tissue and applicator configuration, i.e., the 3D model.

This technical note describes our experience with making a multislice CT scan and segmenting CT images for creating a 3D patient model. The study of the relationship between the calculated 3D SAR distribution and the clinical outcome is still ongoing and will be reported later. We believe that this paper contains important information for other researchers with an interest in similar studies or designing procedures for implementation of HTP as a routine.

METHODS

Patients and Treatment

Patients with recurrent breast adenocarcinoma referred for reirradiation (8×4 Gy, twice weekly) and HT (four times, once weekly, 60 min, after RT), and with the possibility to place interstitial thermometry catheters in the treatment area were eligible for the study on predicted SAR distribution as a prognostic parameter for temperature distribution and clinical outcome. This study was approved by the Medical Ethics Committee (METC). Written informed consent was obtained from all patients.

Closed-tip catheters were placed immediately before the first HT treatment. HT was induced with 433 MHz, utilizing up to six Lucite Cone Applicators (LCA), with a perfused water bolus between the skin and applicators [33,36,37,41]. Each applicator has an independent power control. Multipoint fiber-optic thermometry probes (FTP-5 Medical Array Sensor, Takaoka Electric Mfg, Tokyo, Japan) are placed in the catheters and on the skin.

Specification of a CT Scan

The CT scans were performed with a Siemens Somatom Sensation Open with a large bore of 85 cm. The resolution of the CT scans was 512 × 512 pixels, 3.0 mm slice thickness, a slice distance of 2.5 mm, and together this corresponds to a 1 × 1 × 5 mm3 voxel cube. Between 120 and 140 slices with margins of 5 cm superiorly (including the supraclavicular region) and margins of 5 cm inferiorly (including the thoracic diaphragm) of the treatment volume were required. The CT scan was made without intravenous contrast agents.

PROCEDURE

Making the CT Scan

Thus far, a treatment-specific CT scan has been made for 26 patients (Table 1). In the first few patients, the CT scan was performed before the start of the first HT treatment, using moulds representing the LCA footprints, without stubs.

Patient No.	Ma/Mi	Target depth (mm)	Tumor size (mm)	No. of lesions (mm)	Catheters	RT field (mm)	LCA	RT field marked	CT scan	Bolus at CT scan
1	Ma	30	20 × 18	20 (1)	1	100 × 100	1	N	B	N
2	Ma	40	120 × 111	120 (1)	4	175 × 235	5	N	B	N
3	Ma	30	114 × 40	45 (4)	4	200 × 220	6	N	B	N
4	Ma	30	51 × 67	36 (3)	4	160 × 220	6	N	B	N
5	Mi	50	–	–	3	116 × 122	4	Y	B	N
6	Ma	30	150 × 90	27 (> 9)	3	190 × 210	6	Y	A	N
7	Mi	20	–	–	3	158 × 270	6	Y	A	N
8	Ma	40	150 × 114	157 (> 9)	4	190 × 169	6	Y	A	Y water
9	Ma	40	75 × 130	75 (3)	4	116 × 178	4	Y	A 2e HT	Y water
10	Ma	40	39 × 36	50 (1)	3	160 × 180	1	Y	B	Y water
11	Ma	40	150 × 145	Lymfangitis carcinomatosa	3	184 × 195	6	Y	A	Y foam
12	Mi	30	–	–	3	183 × 193	6	Y	A	Y foam
13	Ma	30	70 × 55	70 (1)	1	260 × 180	4	Y	B	Y foam
14	Mi	20	–	–	4	184 × 139	6	Y	A	Y foam
15	Mi	30	–	–	3	240 × 170	6	Y	A	Y foam
16	Ma	30	135 × 45	135 (> 9)	3	207 × 120	6	Y	A	Y foam
17	Mi	30	–	–	3	110 × 210	6	Y	A	Y foam
18	Mi	30	–	–	4	138 × 200	6	Y	A	Y foam
19	Ma	30	70 × 70	70 (1)	4	167 × 200	6	Y	A	Y foam
20	Ma	40	46 × 23	10 (> 9)	4	215 × 95	6	Y	A	Y foam
21	Mi	40	–	–	3	206 × 134	6	Y	B	Y foam
22	Mi	40	–	–	4	250 × 150	6	Y	B	Y foam
23	Ma + marker	30	32 × 28	32 (1)	3	150 × 250	4	Y	A	Y foam
24	Ma	30	24 × 15	24 (1)	4	156 × 215	6	Y	A	Y foam
25	Mi	40	–	–	2	95 × 170	6	Y	A 2e HT	Y foam
26	Mi	30	–	–	3	250 × 165	6	Y	A 2e HT	Y foam

Table 1. Patient characteristics and details of CT scanning. Ma: macroscopic, Mi: microscopic, RT: radiotherapy, HT: hyperthermia, chemo: chemotherapy, horm: hormonal therapy, B/A: before/after first HT treatment.

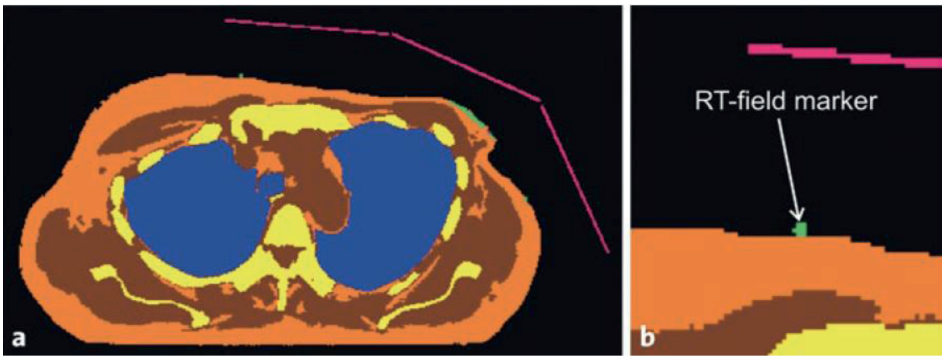
This appeared insufficient to create a patient- and treatment-specific model for SHTP: information about the margins of the RT field, the HT treatment position of the patient,

the distance of the applicators from the skin, and the location of the tumor was lacking. Therefore, the following adjustments to the procedure were made.

Marking the RT Field

In combination with reirradiation, the whole RT volume is the target for HT treatment [35].

The HT applicators are placed such that the RT field is widely covered; the RT target volume can, therefore, not be deduced from the position of the HT applicators. Thus, starting with the fifth patient, the margins of the RT field were made visible with a metal thread (Figure 1).



Figures 1a and 1b. a Axial CT image of breast tissue demonstrating a marked RT field (*green*), fat (*orange*), muscle (*brown*), bone (*yellow*), air (*blue*) and moulds (*pink*). b Location of the RT field is enlarged in this image (*green*).

CT Scan Timing and Patient Positioning

In the first 8 patients, the CT scan was made after the catheters were inserted, prior to the first HT treatment. The patients were not always lying in the same position in the CT scanner as during the HT treatment. In the next 18 patients, the CT scan was planned after the first treatment, or the treatment position was simulated before the CT scan was made.

Water Bolus

The position of the LCAs had been marked on the skin. Moulds representing the LCA footprints were used to show the position of the LCA on the thoracic wall. At first (in 7 patients), the moulds were placed 2 cm from the skin by stubs, simulating the thickness of the water bolus (Figures 2 and 3). In later patients, a water bolus was placed between the skin and the moulds. A water-filled bolus appeared inaccurate because there were no applicators to maintain its correct position (Figure 4). In Figure 5, a dummy air-filled

bolus is used which is not visible on the CT scan, but adequately shows the distance between applicators and skin.

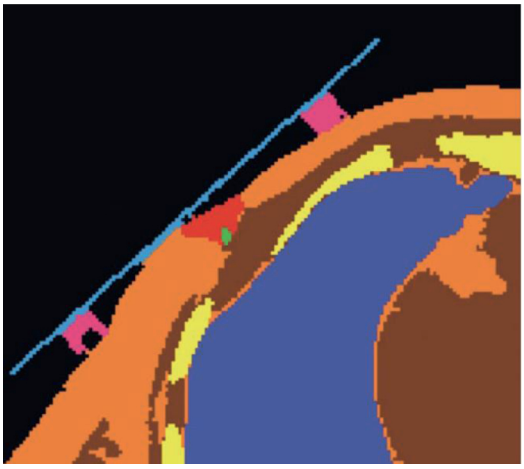


Figure 2. Axial CT image of breast tissue demonstrating tumor (*red*), catheter in tumor (*green*), fat (*orange*), muscle (*brown*), bone (*yellow*), air (blue), moulds (*light blue*) and stubs (*pink*).

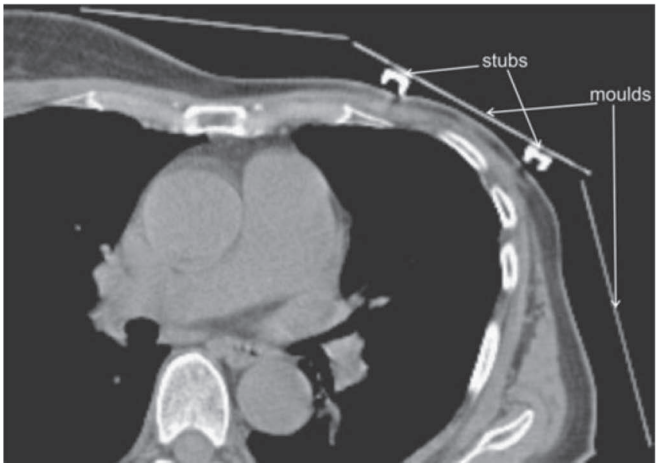


Figure 3. Axial CT image of breast tissue demonstrating moulds representing LCA footprints with stubs simulating the thickness of the water bolus.

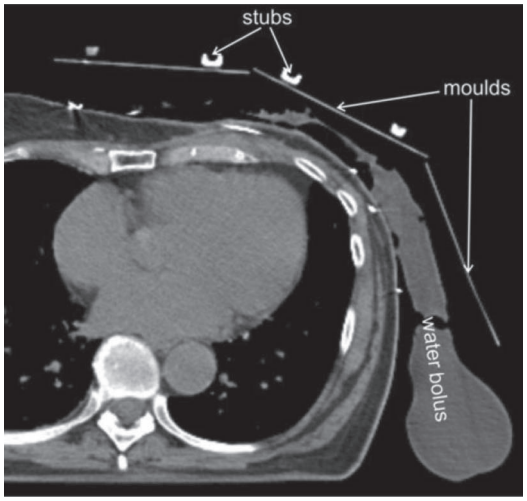


Figure 4. Moulds representing LCA footprints with stubs turned up-side down on top of the water-filled bolus.

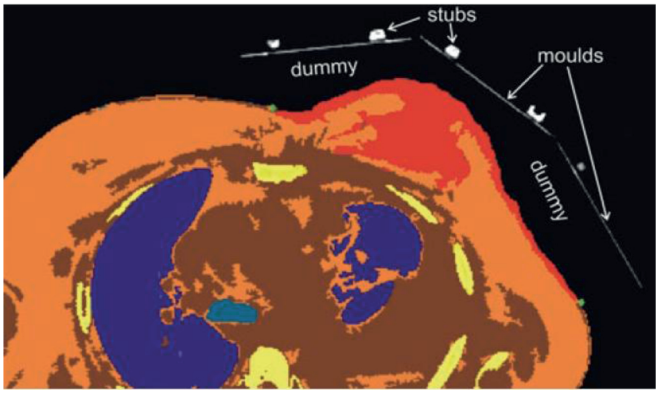


Figure 5. Moulds representing LCA footprints (not segmented) with stubs turned up-side down on top of a dummy water bolus (not visible on CT scan).

Radiolucent Catheters

During the course of the study, a change was made from radioopaque to radiolucent catheters, because the radioopaque catheters were not available anymore. Therefore, from patient 8, the radiolucent catheters were made visible with radioopaque markers (Figure 6).

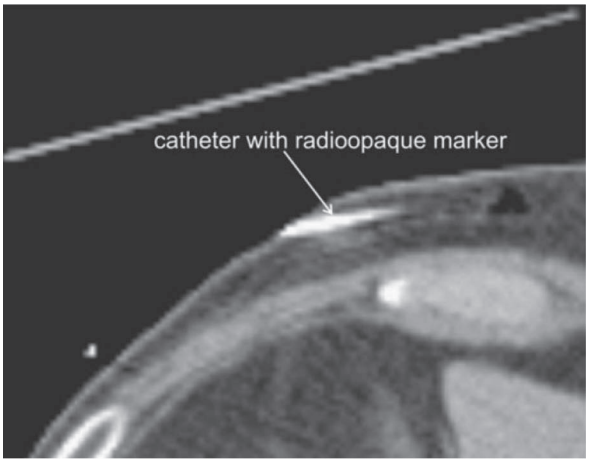


Figure 6. Enlarge image of a radiolucent catheter made visible with a radioopaque marker.

Marking the Visible and Palpable Tumor

It is not possible to predict whether a tumor will be visible on the CT scan. Therefore, the clinically apparent tumors were marked with a metal thread on the skin. This is not always possible, e.g., when there are many lesions or when the tumor is subclinical. Figure 7 shows the markers around the tumor, which by itself can be discriminated from the surrounding fat tissue.

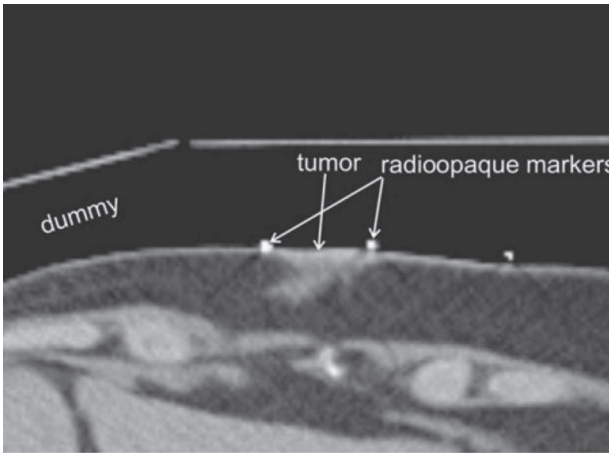


Figure 7. Axial CT image demonstrating a tumor marked with a radioopaque marker and a dummy water bolus (not visible on CT scan).

Segmentation of CT Images

The process was started by displaying a CT image in the workstation screen. The multislice CT images were transferred in DICOM (Digital Imaging and Communications in Medicine) format to the workstation for 3D visualization and model generation. For the planning system, a patient-specific model by assigning each tissue type was carried out by a HT physician (ML) using the dedicated segmentation program (i.e. iSeg). Next the model was imported into SEMCAD X, a 3D electromagnetic field simulator [28]. Previously, de Bruijne et al. [5] demonstrated that the SEMCAD model provides reliable quantitative agreement between predicted and measured SAR distributions in a homogenous model. With an obtained dose difference (DD) < 2% and distance to agreement (DTA) < 2 mm, these results are comparable to that achieved in radiotherapy treatment planning (RTP).

Marking the Visible and Palpable Tumor

The HT physician first defined the anatomical structures in the CT images.

Automatic and manual segmentation of the structures were performed by the same HT physician in order to promote uniformity. The dielectric properties assigned to the tissues are described in Table 2 [10]. Even though they may consist of significantly different tissues concerning dielectric and thermoregulatory properties (e.g., previous surgery and/or RT) [2], the tissue of any structure was considered to be homogeneous. Muscle, fat, bone, and air were segmented automatically, even though manual review and corrections of these structures were still mandatory. This manual review was performed on each image using an electronic pen on a tablet.

The automatic segmentation took 1 h. The RT field, catheters, and LCA moulds were segmented manually. The segmented structures were all visible on the CT slice. Defining the target volume could be difficult. Color photographs and a life size drawing of the HT treatment area made on a transparent sheet were available.

The tumor was segmented to evaluate the position of a hot spot during treatment, to predict the total absorbed energy in the tumor, and to compare this with the measured temperatures. Without segmentation of the tumor, the manual segmentation took 2 h; with segmentation of the tumor, it could take up to 3 h.

DISCUSSION

In this article, we present the procedure of making a CT scan and segmenting the CT images to create a patient- and treatment-specific model for SHTP that represents the real patient treatment set-up. For this aim, it is important that the CT scan is made with

the patient in the treatment position and that all relevant information is visible. Several adaptations to the original procedure were introduced during the study period.

Dummies representing the LCAs were used from the beginning. Since the irradiated volume is the target for HT and the area covered by the applicators is larger than the RT field, markers were introduced for the RT field margins. The dummy water bolus was introduced to make the distance from the applicator to the skin more realistic than with the stubs on the corners of the dummies placed on the skin. A change from radioopaque to radiolucent catheters made it necessary to place markers in the catheters.

Tumors were not always visible on the CT scan. Therefore, it was necessary to introduce marking of the visible/palpable tumor.

In order to have the same patient positioning during the actual treatments as on the CT, the same HT physician and technicians should prepare all treatments, and photographs should be taken of the patient during treatment. It is unclear how others ensured having a representative CT scan for HTP. In the study of Kumaradas and Sherar [15], the CT imaging was performed before the HT treatment to determine the position of the catheters, to predict the temperature profile, and to identify possible hot spots, but they do not provide details about the procedure they used to place the patient in the CT scanner. In studies of Sreenivasa et al. [29] and Gellermann et al. [11], a patient-specific HT planning was made but the procedure of making the CT scan is not explained in further detail. We previously made CT scans for deep HTP. A CT scan of the patient lying in a BSD sling system, i.e., in the HT treatment position, was obtained [8,34].

Since HT is almost always used in combination with RT, it would be beneficial to integrate the RT CT scan in both planning techniques [1,12,17,18,19,27,32]. However, this is not possible for SHT and deep HT treatments, since the positioning for RT differs from that for HT. For head and neck treatment, this is possible, since the positioning of the patient during the HT treatment is the same as during RT treatment. In the study of Paulides et al. [21], the patient model with a head and neck tumor, treated with the HYPERcollar, was segmented from a CT scan that was made for RTP.

A much mentioned drawback of the segmentation of the CT images is the time-consuming and subjective process, especially of the manual segmentation. Automatic segmentation takes 10–20 min and manual segmentation 2-4 h.

The time for manual segmentation can be reduced by further improvements to the program, e.g., by importing information on RT field margins from the RTP, like was done for head and neck patients [22].

We are convinced that HTP will be an important tool for quality assessment and believe that the SAR distribution has the potential to be a HT dose parameter.

The first step in HTP is to procure a high quality CT scan with the patient in the treatment position. This CT scan must provide all information which is relevant to calculate the energy distribution. The manual segmentation of tissues requires the largest amount

of time in the model creation. It is important that this time to be decreased with automatic segmentation.

CONCLUSIONS

Our results show that the construction of a representative 3D model for SHTP is feasible. We expect that the use of SHTP will translate into better HT treatment control.

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Chapter 8

Reconstruction of applicator positions from multiple-view images for accurate superficial hyperthermia treatment planning

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ABSTRACT

In the current clinical practice, prior to superficial hyperthermia treatments (HT), temperature probes are placed in tissue to document a thermal dose. To investigate whether the painful procedure of catheter placement can be replaced by superficial HT planning, we study if the specific absorption rate (SAR) coverage is predictive for treatment outcome. An absolute requirement for such a study is the accurate reconstruction of the applicator setup. The purpose of this study was to investigate the feasibility of the applicator setup reconstruction from multiple-view images. The accuracy of the multiple-view reconstruction method has been assessed for two experimental setups using six lucite cone applicators (LCAs) representing the largest array applied at our clinic and also the most difficult scenario for the reconstruction.

For the two experimental setups and 112 distances, the mean difference between photogrametry reconstructed and manually measured distances was 0.25 ± 0.79 mm (mean±1 standard deviation). By a parameter study of translation T (mm) and rotation R (°) of LCAs, we showed that these inaccuracies are clinically acceptable, i.e. they are either from ±1.02 mm error in translation or ±0.48° in rotation, or combinations expressed by 4.35R(2) + 0.97T(2) = 1. We anticipate that such small errors will not have a relevant influence on the SAR distribution in the treated region. The clinical applicability of the procedure is shown on a patient with a breast cancer recurrence treated with reirradiation plus superficial hyperthermia using the six-LCA array. The total reconstruction procedure of six LCAs from a set of ten photos currently takes around 1.5 h. We conclude that the reconstruction of superficial HT setup from multiple-view images is feasible and only minor errors are found that will have a negligible influence on treatment planning quality.

INTRODUCTION

Several randomized studies have shown a benefit when adding hyperthermia to the radiotherapy treatment for superficial diseases such as melanoma and breast cancer recurrences at the chest wall [14,18,27]. Hyperthermia treatment (HT) quality is generally assessed by superficially and interstitially placed temperature measurement probes. Temperature measurements at the skin are in general affected by the water bolus temperature so temperature measurements in tissue are required for an accurate thermal dose evaluation, especially if the tumour extends to depths over 5 mm [24].

The procedure to place invasive catheters is labour intensive, causes patient discomfort and increases the risk of infection, as they stay in place up to 4 weeks. Aiming to replace invasive thermometry by predictive HT planning, we investigate the predictive value of the specific absorption rate (SAR) coverage for the treatment outcome. Superficial HT planning is not standardly applied in the clinical practice. The value of pretreatment superficial HT planning in situations where (1) the treatment area is close to critical organs or metal and (2) when the tumour extends more than 4 cm from skin, i.e. the maximal allowed depth at 434 MHz, was demonstrated by de Bruijne et al. [8].

Superficial HT planning can also be used as a tool for detailed 3D retrospective analyses of treatment quality and to evaluate the appropriateness of applicator selection, applicator positions and applied power during HT. In clinical practice, the HT setup strongly depends on patient acceptance and comfort. Hence, the applicator position applied to the patient is determined at the start of the first treatment. Consequently, superficial HT planning in clinical practice demands an accurate, automatic and fast procedure to reconstruct the treatment setup.

A number of techniques (optical, laser scanning, etc) [4] are available to reconstruct the superficial HT setup; however, they differ substantially in cost and 'user friendliness'. Reconstruction from multiple-view images is one of the methods used in radiotherapy practice for creation and documentation of the patient position during treatment [2,22]. Bert et al. [3] showed that an accuracy of 1 ± 1.2 mm for the simulated patient positioning is feasible using a commercially available 3D surface imaging system for accelerated partial-breast irradiation. In comparison to radiotherapy treatment, where cameras have clear visibility to the reconstructed patient anatomy, the superficial HT setup at our clinic is more complex. Fixation arms holding the antennas in treatment positions, power cables and inflow–outflow tubes for circulating deionized water make the reconstruction scene more irregular. This prevents using the photogrametry systems used in radiotherapy.

The objective of this study was to investigate the feasibility to accurately reconstruct the lucite cone applicator (LCA) array from multiple-view images. Threshold for acceptable reconstruction accuracy was set at 2 mm following the accuracy for predicting the

SAR profile of a single LCA, as demonstrated by de Bruijne et al. [7]. The accuracy of the reconstruction procedure was studied on setups with one and six LCAs. As a first step, we compared reconstructed and real dimensions of the LCAs. In the next step, we compared reconstructed and manually measured distances among subsequent applicators in six-LCA array configuration.

Finally, the clinical feasibility of photogrametry reconstruction was demonstrated using photos taken during superficial HT in which an array of six LCAs was applied.

METHODS

Lucite cone applicator

The LCA is the standard applicator for superficial HT at the Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam, the Netherlands [25]. It is a waveguide-based applicator working at 434 MHz with a horn aperture of 100 × 100 mm (inner dimensions) [21,26]. Clinically, up to six applicators can be combined in a non-coherent antenna array, allowing to cover an area of 200 × 300 mm^2 with the effective field size, defined in Hand et al. [11], Bakker et al. [1] and de Bruijne et al. [5].

Treatment planning procedure

To document interstitial catheters, radiotherapy margin and the LCAs, a hyperthermia specific computer tomography (CT) scan is made. During the CT scan, up to six plastic squares were placed at the patient to indicate the positions of the LCAs during the treatment. The CT scan typically consists of 120 slices with 2.5 mm distance between slices. From this CT, a 3D patient specific model is created in iSeg (version 3.1, Zurich Med Tech AG, Zurich, Switzerland) [17]. Subsequently, the patient model is imported into the finite difference time domain (FDTD) based software SEMCAD X (v.14.6, Schmid & Partner Engineering AG, Zurich, Switzerland) for electromagnetic and temperature simulations. SEMCAD X has been evaluated for clinical use in our institute for both superficial and deep HT [8,19,20]. The LCA array, reconstructed from multiple-view images, was imported into SEMCAD X and placed in treatment position on top of the patient model. The LCA array was positioned such that it matched the plastic squares from the CT. The dielectric properties of normal tissues are taken from Gabriel et al. [9] (see table 1) and the properties for tumour tissue were chosen with respect to the measurements made by Jones et al. [13].

Table 1. Dielectric tissue properties at 434 MHz.

Tissue	ϵ_r (–)	σ (S m^{-1})	ρ (kg m^{-3})
Bone	13.1	0.09	1990
Fat	5.6	0.042	888
Muscle	56.9	0.8	1050
Lung	23.66	0.38	655
Tumour	57.9	0.85	1040
Deionized water	78	0.046	1000

Reconstruction procedure

For the setup reconstruction, we apply the photogrametry method in which geometric properties of real objects are determined using multiple-view images [12]. We used the commercial photogrametry package PhotoModeler Scanner (v.6.3, Eos Systems Inc., Vancouver, Canada) for the applicator setup reconstruction. The reconstruction procedure is done through assignment of selected points on each applicator at the individual photos.

Points visible in at least two photos can be reconstructed but the highest accuracy is achieved for pairs of photos taken under a 90°spatial angle. To ensure good visibility of the points at every photo, we fixed all power cables and deionized water tubes to the arms holding the applicator in treatment position, as in figure 1.

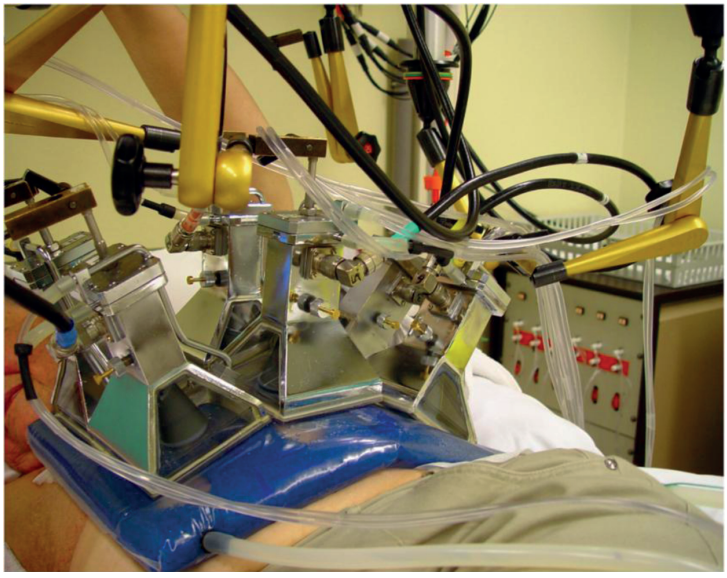

Figure 1. Example of photo from superficial HT used for photogrametry reconstruction.

The photos are taken using a standard SONY (Minato, Tokyo, Japan) DSC F707 CyberShot camera which was in manual mode to ensure that all photos have identical settings.

EXPERIMENTAL VALIDATION

Experimental validation of the reconstruction procedure was first performed using single LCA setups, where we compared reconstructed and real dimensions of the six LCAs. Afterwards, reconstructed and manually measured distances among subsequent applicators were compared for six-LCA array configuration. For clarity, we define

- dimension differences-differences between the dimensions of the reconstructed wireframe LCA (figure 2(c)) and the real LCA (figure 2(a)),
- distance differences-differences between the distances among the LCAs in array configuration of the wire-frame LCA array model and the experimental HT setup (figure 3).

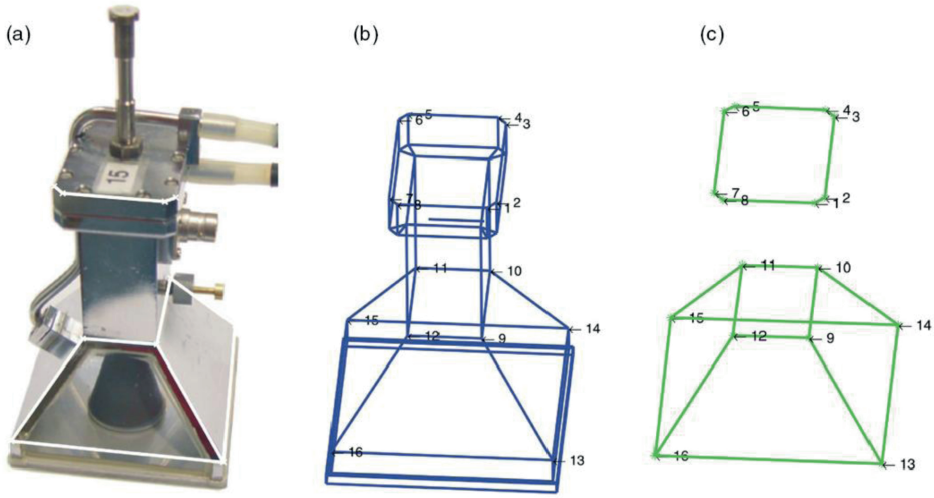

Figure 2. (a) Photo of LCA, (b) 3D LCA model created from manual measurements of real applicators, (c) reconstructed wire-frame LCA model from PhotoModeler with 16 indicated reconstructed points.

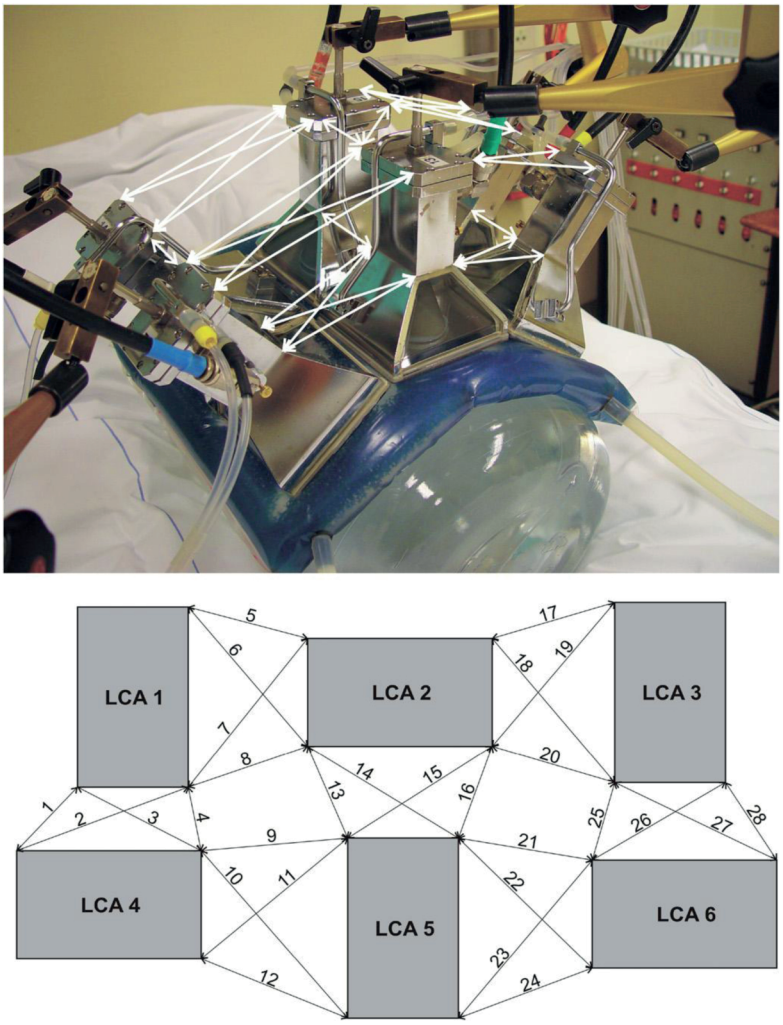

Figure 3. (a) Photo of the experimental setup for a six-LCA array with highlighted several measured distances, (b) top view of the middle part of LCAs (points 9–12 from the 3D LCA model in figure 2) with 28 measured distances.

EXPERIMENT 1: SINGLE LCA RECONSTRUCTION

Single LCA reconstruction was applied to each of the six clinically available LCAs and eight photos were taken per applicator. Sixteen dimensions of individually reconstructed LCA models were compared with the real physical dimensions of the tested applicators. Because there are no other objects present in the photos but the applicator itself, the single LCA case represents the 'easiest' reconstruction scenario.

Figure 2(b) shows a 3D LCA model created from manual measurements of clinically available LCA (see figure 2(a)). To improve accuracy of the reconstruction procedure, a specific LCA model was developed for each of six real applicators.

Sixteen points characterizing the LCA were selected to describe the physical model, i.e. eight points at the top (1–8), four in the middle part (9-12) and four at the bottom (13-16) of the LCA.

Using the PhotoModeler package, 16 corresponding points were connected creating the wire-frame LCA model (see figure 2(c)). We compared sixteen dimensions for each LCA, i.e. eight in the top part (between points 1–8, 2–7, 3–6, 4–5, 6–7, 5–8, 1–4 and 2–3), four in the middle part (points 9–12, 10–11, 9–12 and 11–12) and four in the bottom part (points 13–16, 14–15, 13–14 and 15– 16). By comparing the dimensions of the reconstructed wire-frame LCA model with the real dimensions of the LCA, an indication of the accuracy of the photogrametry reconstruction was obtained.

EXPERIMENT 2: LCA ARRAY RECONSTRUCTION

To verify the correctness also of an LCA array reconstruction from multiple-view images, we reconstructed two setups consisting of six LCAs (figure 3). A setup with six LCAs represents the most challenging scenario for the photogrametry reconstruction due to the presence of power cables and inflow–outflow tubes for each LCA. Two setups were build to mimic two sequential superficial HT sessions, where the LCAs are rotated with a 90°angle [5,25]. The LCAs were placed on top of a $420 \times 310 \times 20$ mm^3 water bolus lying on a cylindrical water tank (diameter 290 mm) simulating a curvature similar to the clinical practice [6]. Fourteen photos from different view angles were taken for the first setup and nine for the second one.

As in experiment 1, we calculated the dimension differences of the reconstructed wireframe LCAmodels with their dimensions in reality. Subsequently, the reconstructed wire-frame LCA array model was imported into a MATLAB (v.2011a, Natick, MA, USA) interface. In this interface, we minimized position differences between the 3D LCA models and the wire-frame model by optimizing translation and rotation of the 3D LCA models using a particle swarm optimization algorithm. After optimization, 112 distance differences among the applicators were calculated by comparing the reconstructed six-LCA array with experimental setup shown in figure 3. Some of the 112 measured distances among LCAs are also shown in figure 3(a). Figure 3(b) shows a top view of the middle parts of LCAs (points 9–12 from the 3D LCA model in figure 2) with 28 measured distances.

In the same way, we derived distances for the top part of LCAs and also second experimental setup, i.e. in total 2(28 + 28) = 112 distance differences were measured.

CLINICAL RELEVANCE OF THE REMAINING DISTANCE DIFFERENCES

In order to assess the clinical relevance of our method, we studied the dependence of the distance differences obtained in experiment 2 on translation *T* (mm) and rotation *R* (°) of the LCAs. Using two virtual 'reference setups' corresponding to the two-LCA array setups from experiment 2, we created 1000 virtual setups (500 for each reference model) by varying *T* and *R* of each of the six LCAs. For each of the 1000 virtual setups, we calculated the mean ± standard deviation of the 112 distance differences found between the new (virtual) and the reference setups, i.e. we obtained 1000 means and 1000 standard deviations.

The mean value of the 1000 standard deviations SD distance differences obtained in experiment 2 on translation *T* (mm) and rotation *R* (mm) was compared to the standard deviation found in experiment 2, i.e. SD_{exp2} (mm). For the situation where $SD_{exp2} = SD_{m1000}$, we assume that such translation and/or rotation of the LCAs would lead to the same distance differences measured in experiment 2.

EXPERIMENT 3: CLINICAL SETUP RECONSTRUCTION

To demonstrate the feasibility to reconstruct a clinical applicator setup, we selected a representative patient with a recurrent breast cancer treated with a six-LCA array configuration. The LCAs were positioned and the quantitative 3D SAR distribution was calculated.

RESULTS

Experiment 1: single LCA reconstruction

Figure 4(a) shows the histogram of the 96 dimension differences (six LCAs, 16 dimensions per LCA) between the reconstructed wire-frame LCA models and the real applicators. The small difference of -0.73 ± 0.53 mm (mean ± 1 standard deviation) shows the high accuracy of the photogrametry reconstruction. The negative mean value is due to the fact that measured dimensions of the LCAs were generally larger than the reconstructed ones.

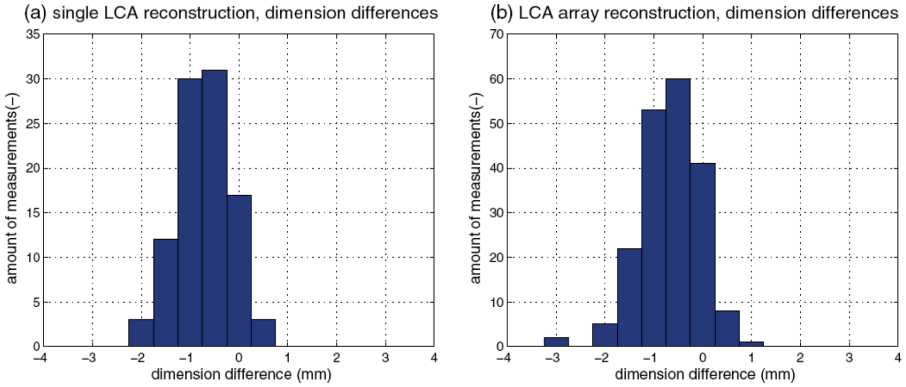

Figure 4. Histogram of the dimension differences between the dimension of the wire-frame models and their corresponding physical dimensions of the real applicators. (a) Single LCA reconstruction (n = 96, six LCAs, 16 dimensions per LCA), mean dimension difference −0.73 ± 0.53 mm; (b) LCA array reconstruction (n = 192, six LCAs, 16 dimensions per LCA, two setups), mean dimension difference −0.66 ± 0.61 mm.

Experiment 2: LCA array reconstruction

Figure 4(b) shows the dimension differences between the reconstructed wire-frame LCAs and the real applicators for the two studied array configurations. For the 192 (six LCAs, 16 dimensions per LCA, two setups) dimension comparisons, we found a mean difference of -0.66 ± 0.61 mm. These results, and those from the single LCA experiment, show that the accuracy of the photogrametry reconstruction method is comparable for the reconstruction of the single LCA and the reconstruction of a six-LCA array. Figure 5 shows a histogram of the 112 distance differences between distances obtained from the reconstructed wire-frame model and the distances measured manually on the two experimental LCA setups. The mean distance difference was found to be 0.25 ± 0.79 mm (setup is shown in figure 3).

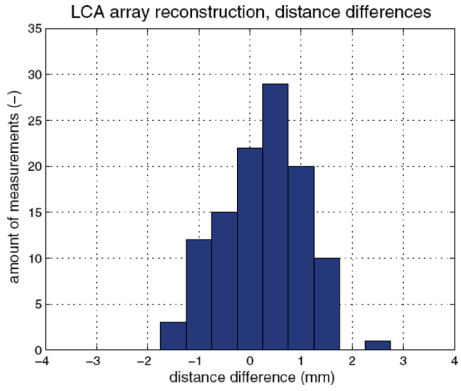

Figure 5. Histogram of the 112 distance differences between distances measured on the reconstructed wire-frame model and distances manually measured on two experimental LCA setups, mean distance difference 0.25 ± 0.79 mm.

CLINICAL RELEVANCE OF REMAINING DISTANCE DIFFERENCES

Figure 6 shows the mean value of the 1000 standard deviations (SD) calculated for all combinations of virtual and reference models. T and R of each LCA were changed from -2 to 2 mm and from -1° to 1°, respectively, allowing the comparison of SD_{m1000} with the standard deviation measured in experiment 2 (SD_{exp2} = ±0.79 mm). The iso-contour in figure 6, defined by SD_{m1000} = ±0.79 mm, represents maximum errors in translation T = ±1.02 mm (for R = 0°) and in rotation R = ±0.48° (for T = 0 mm). The maximum combined uncertainties can mathematically be described by the following approximate elliptic function: $4.35R^2 + 0.97T^2 = 1$.

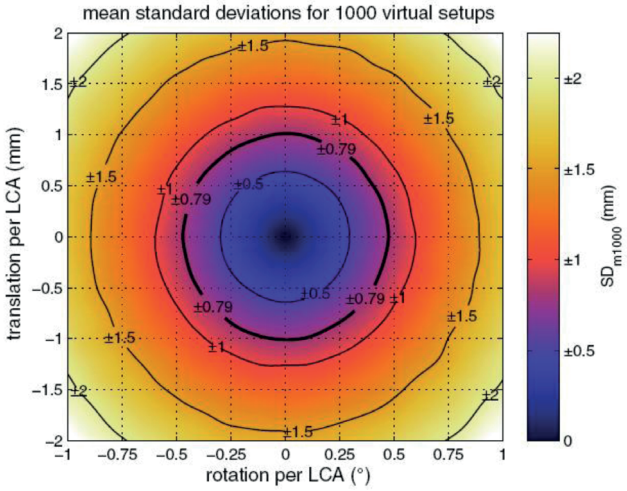

Figure 6. Mean value of the 1000 standard deviations (SD_{m1000}) calculated between the virtual and the reference models. The area defined by the SD = ±0.79 mm iso-contour represents the combinations of uncertainty in T and R that leads to the same errors in distance differences measured for the two experimental setups.

EXPERIMENT 3: CLINICAL SETUP RECONSTRUCTION

To demonstrate the clinical feasibility of the photogrametry method, we reconstructed the superficial HT setup for a recurrent breast cancer patient treated with six LCAs using ten photos. The reconstructed wire-frame LCA array model together with the camera positions in PhotoModeler is shown in figure 7(a). In total, the reconstruction of 79 points was possible and a mean dimension difference of -0.88 ± 0.85 mm was found for the 68 dimensions. Figure 7(c) shows the final superficial HT planning setup in SEMCAD X after placement of the LCA array in the treatment position. Combining the individual 3D SAR (IEEE-1529,1 g) distributions for all six LCAs, taking into account the actual HT power fed

in each LCA, the final 3D SAR (IEEE-1529,1 g) iso-surface of 30 Wkg^{-1} was calculated (see figure 7(d)). In this particular setup, the 30 Wkg^{-1} contour represents the 25% isoSAR surface coverage (i.e. 25% of the maximum SAR inside the patient model) 1 min before the end of the HT.

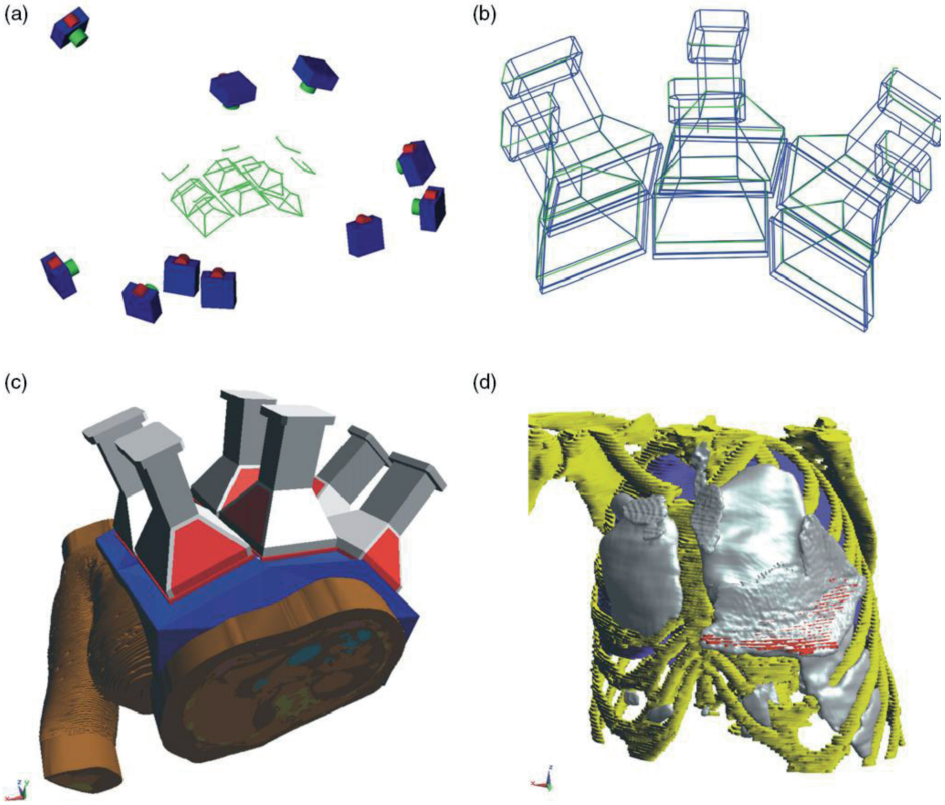

Figure 7. (a) Reconstructed wire-frame LCA array model together with ten camera positions in PhotoModeler, (b) best fit of the six applicator specific 3D LCA models with the reconstructed wire-frame LCA array model, (c) superficial HT planning setup in SEMCADX, (d) 3D SEMCAD X-1529,1 g) iso-surface of 30 Wkg^{-1} 1 min before the end of the superficial HT.

DISCUSSION

In this study, we investigated the feasibility to accurately reconstruct superficial HT applicator setups using multiple-view images.

As a first step, the accuracy and the reproducibility were studied by analysing the reconstruction accuracy of the LCAs dimensions, and a mean difference of -0.73 ± 0.53 mm for six individual LCA (experiment 1) was found.

For the situations where LCAs were reconstructed from the setups of six LCAs, we found a mean dimension difference of -0.66 ± 0.61 mm (phantom; experiment 2) and -0.88 ±0.85 mm (clinic; experiment 3). The smaller dimension of the reconstructed applicators leading to the negative mean value is caused by the difficulty in the manual procedure to correctly assign all the selected points at the photos for LCAs with blended edges required for secure clinical handling. Clear visibility experienced to be an important aspect for the reproducibility of the reconstruction process, i.e. the highest reproducibility (SD =±0.53 mm) was found for a single LCA reconstruction. However, the inaccuracies in the reconstructed dimensions for six LCA setups were acceptable, i.e. the most difficult case (clinic; experiment 3) was within 1.73 mm (mean+1SD).

The clinical feasibility of the reconstruction procedure was studied on two realistic setups consisting of six LCAs. For these two setups, the distance differences varied from -1.6 to 2.7 mm with a mean value of 0.25 ± 0.79 mm. This is affected by the inaccuracy from the manual measurements during six-LCA array phantom experiments where we had limited access to the LCAs, especially in the middle part of the array. Finally, we demonstrated that a SD of ±0.79 mm corresponds with translation errors of maximum 1.02 mm or rotation errors of maximum of 0.48° for the most challenging case, i.e. six LCAs. We anticipate that such small changes will not have a relevant influence on the SAR distributions. However, this is the topic of future studies.

At this moment, practical implementation of the reconstruction procedure from multipleview images requires a number of manual steps. It takes around 1.5 h to complete a reconstruction of six LCAs from a set of ten photos. This time is acceptable for retrospective superficial HT planning, but clinically unacceptable.

Prospective clinical application requires a fully automatic reconstruction of the superficial HT setup, so planning can be done prior to treatment. The first step in automation of the reconstruction procedure is possible by placing coded targets to specific points at each LCA, i.e. marks that PhotoModeler can automatically recognize. Every coded target has a specific number and it is every time reconstructed under this number. Using this method, the LCA positions in the array configuration can be automatically assigned. The second step of clinical application of superficial HT planning requires monitoring of the LCAs positions with respect to the patient anatomy.

During the current retrospective planning procedure, we manually placed the reconstructed LCA array on the top of the patient model in order to overlap plastic LCA footprints. Automation of this procedure is possible by placing coded targets at predefined, always visible, locations on the patient body and reconstructs them automatically together with LCA array. However, this requires assigning these points also at the CT and segmenting them along with the patient anatomy.

A potential limitation of the photogrametry reconstruction technique could be the requirement of full coded target visibility on every photo, which is affected by the pres-

ence of power cables and water tubes. Hence, the treatment system would need to be redesigned to facilitate this.

The feasibility of the superficial HT setup reconstruction procedure for six-LCA array can also be extended to other applicators. Contact flexible microstrip applicators (CFMA) are one of the most common used applicators in clinical practice [10,16,23]. They are usually placed directly on the patient body and stretched to cover the treatment area.

In combination with coded targets placed on the outer surface of the CFMA, it is feasible to use automatic reconstruction inside PhotoModeler Scanner to document e.g. the realistic curvature during the superficial HT, which has been shown to influence SAR pattern [15]. Hence, this method also holds promise for other applicator systems.

CONCLUSIONS

This study demonstrates the feasibility of accurately reconstructing the superficial hyperthermia applicator setup using multiple-view images. The accuracy of our photogrametry reconstruction technique was assessed by comparing 112 photogrametry reconstructed and manually measured distances in two configurations of the six-LCA array. For the patient treated with six LCAs in the chest wall region, we demonstrated the feasibility of superficial HT setup reconstruction for clinical conditions.

This study shows that applying photogrametry allows the reconstruction of the clinically applied LCA array setup with an accuracy of ±1 mm, which fulfils our accuracy requirement of 2 mm. This method will be developed further to enable the automatic fast reconstruction of the treatment setup to meet time requirements for prospective treatment planning for superficial HT.

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Chapter 9

General discussion and conclusions

GENERAL DISCUSSION, FUTURE CONSIDERATIONS AND CONCLUSIONS

Superficial hyperthermia in combination with reirradiation

At the time that the combination of reirradiation plus hyperthermia was introduced for treatment of recurrent breast cancer in previously irradiated areas no effective treatment was available for this patient group. Reirradiation alone was considered ineffective, while hyperthermia appeared to be an interesting sensitizer of radiotherapy as described in chapter 1. Chapter 2 describes the process of finding the optimal treatment schedule, technological developments and other lessons learned. When I started my work on the studies described in this thesis, reirradiation with 8 fractions of 4 Gy combined with 4 fractions of hyperthermia had become standard care. Long term results of the treatment and the effect in specific subgroups were missing.

The best published local control rates in patients with radiation-induced angiosarcoma were achieved with surgery combined with hyperfractionated and accelerated radiotherapy (HART) [1,2]. The data reported in chapter 3 demonstrate that for initially inoperable tumors the effect of reirradiation and hyperthermia can be worthwhile. It would be interesting to investigate whether addition of hyperthermia to HART will improve the probability for local control.

Tissue transfers are sometimes considered to be a contraindication for treatment with radiotherapy and/or hyperthermia. In our retrospective study (chapter 4) in 33 patients we found an incidence of 8% acute and 5% late grade 3 toxicity. In view of the high control rate this is acceptable, therefore there is no reason to withhold the treatment from patients with tissue transfers.

In chapters 5 and 6 results in patients with gross and subclinical disease, respectively, are reported in detail. A complete response was achieved in 70% of the patients with irresectable breast cancer, which is comparable to the complete response rate in the ESHO 88-5 phase III trial [3]. Local tumor control rate at 1, 3, and 5 years was 53%, 41% and 39%, respectively. The overall survival rate at 1, 3, 5 years, and 10 years was 67%, 32%, 18% and 10%, respectively. For subclinical disease the local tumor control rates at 1, 3, 5 and 10 years are 93%, 83%, 78%, and 75% respectively. The 3, 5 and 10 years overall survival (OS) rates are 75%, 60% and 36%, respectively, with a median survival of 82 months. Remarkable in both studies is the overall survival after 10 years, contradicting the initial assumption that the treatment is only palliative. Moreover, these effects are achieved with acceptable toxicity.

An alternative treatment for chest wall recurrences is chest wall resection. Publications on 5 years overall survival after curative chest wall resection, reviewed in van der Pol et al. [4], show that this varies from 18% to 71%.

The 5 years overall survival of 18% for irresectable recurrences as achieved in our study falls within this range, despite that our patients had worse prognostic characteristics

(i.e. irresectable tumors, appearance of metastasis). Further, morbidity after chest wall resection can be severe, even resulting in death [5].

For post-operative radiotherapy of primary recurrences 5 years survival ranging from 49 to 59% have been reported [6,7,8,9], where we found 60%.

An interesting finding in both studies is that the incidence of hyperthermia toxicity (skin burns) considerably increased when the maximum temperature measured on the skin is 43°C or higher. Another interesting finding is that both complete response and local tumor control are not worse in patients receiving radiotherapy outside the Erasmus MC in whom the time interval between radiation and hyperthermia is longer. At the same time the incidence of late grade 3 toxicity was lower in patients with subclinical disease radiated in another institute.

Today, the Dutch Association of Comprehensive Cancer Centers guidelines consider reirradiation plus hyperthermia for recurrent breast cancer in previously irradiated areas regular care in the Netherlands (www.oncoline.com).

HYPERTHERMIA DOSE EFFECT RELATIONSHIP INDICATES THE NEED FOR IMPROVED HEAT DELIVERY

From experimental studies, we know that the biological effectiveness of hyperthermia depends on the height of the temperature and the duration of treatment at elevated temperature [10], and this has been confirmed in clinical studies. Therefore, there is a clear need to monitor and optimize the quality of the hyperthermia treatment.

Due to the variation in tumor size, shape, dielectric and thermal (i.e. blood flow) properties and localization relative to other dielectric interfaces of the body, the treatment quality varies from patient to patient. Hyperthermia treatment planning tools can provide a method to calculate the 3D SAR (Specific Absorption Rate) or temperature distributions and derive predicted hyperthermia-dose parameters from these distributions. In some patients with non-standard clinical problems, the benefits of SEMCAD X (= Simulation platform for ElectroMagnetism Compatible, Antenna Design and Dosimetry) [11] treatment planning have been shown to be a useful tool for decision making in superficial hyperthermia treatment.

The main benefit is the insight in the 3D SAR coverage of the target in specific anatomies. At present, most superficial hyperthermia treatments are applied empirically, i.e. experience and dedication of the treatment team plays a major role in the achieved treatment quality. In general, the occurrence of too high temperatures, either measured or reported by the patient, limits the overall temperature increase during hyperthermia.

Commonly, the strategy is to monitor temperatures with interstitial thermometry. In general, the quality of any dose parameter derived from measured temperatures will be

subject to great variations from patient to patient (large versus small target areas) and varies from center to center based on their ability and readiness to insert a high number of interstitial thermometry catheters. Neither the patient nor the clinician appreciates increasing the density of interstitial temperature measuring points. Nevertheless, we often are able to insert four interstitially thermometry catheters per hyperthermia treatment field, whereby the aim is to have at least one temperature sensor under each applicator. It must be noted that the current number provides only a sample of the 3D temperature distribution which might provide a good representation of the mean and standard deviation, however, the number is insufficient to perform a good spatial, 3D optimization of thermal dose. At present there are no realistic options available to improve the temporal and spatial resolution of temperature monitoring. The use of non-invasive thermometry (NIT) by MRI is not realistic for superficial hyperthermia, due to respiratory motion and artifacts, and NIT by microwave radiometry or ultrasound has not been demonstrated to provide the required spatial resolution and temperature sensitivity.

PREDICTED 3D SAR COVERAGE: A PROGNOSTIC INDICATOR FOR TREATMENT OUTCOME IN SUPERFICIAL HYPERTHERMIA FOR BREAST CANCER RECURRENCES AT THE CHEST WALL

The development of the patient and applicator models as described in chapters 7 and 8 was an important step to enable a clinical study to evaluate the potential of calculated 3D SAR distribution as a predictive parameter. Patients with breast cancer recurrences referred for reirradiation and hyperthermia treatment at the chest wall were eligible for the study, summarized in figure 1. After written informed consent a CT scan was made before the start of the first treatment, after placement of thermometry catheters and in hyperthermia treatment position. Figure 2 shows an example of a study patient with tumor localized in and around the ribs, who was treated with an applicator set-up of four Lucite Cone Applicators (LCAs).

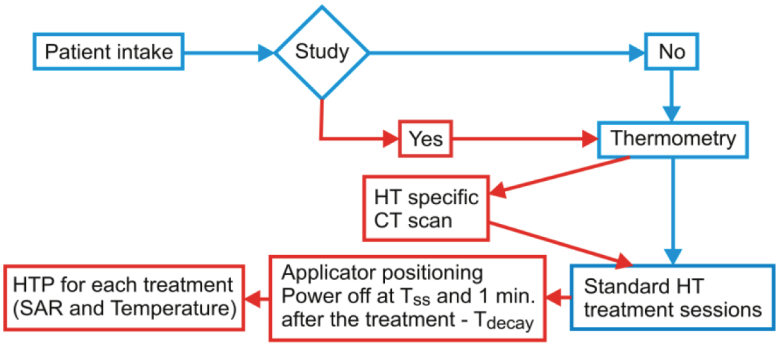

Figure 1: Study schematic diagram.

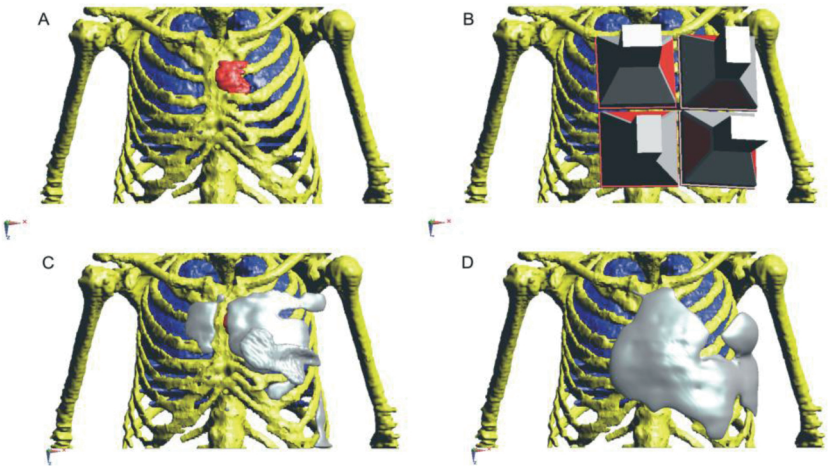

Figure 2: A - Example of patient model in SEMCAD X, B - simulation setup including four LCAs, C-iso surface of 25 % spatial peak SAR (IEEE-1529,1g), D-iso-surface for a temperature of 40 °C.

Clearly, the accuracy of hyperthermia treatment planning is strongly dependent on the accurate translation of the modelled applicator configuration to the clinically applied applicator configuration. Hence, continuous evaluation of the positioning of the patient from the start to the end of the treatment is very important for reliable assessment of the SAR distribution with the SEMCAD X platform.

Preliminary analyses in 41 patients showed a local control rate of 90% after a median follow up duration of 9 months. We found a significant positive correlation between SAR_{25}, i.e. the absolute SAR value that is applied to upper 25% of tumor volume, with the probability of local control. Longer follow-up of this data is needed to assess the full value of this finding as a great number of the patients included had microscopic tumor at the start of the treatment. Nevertheless, this finding is encouraging as it is a first time

ever indication that hyperthermia treatment planning can play a substantial role in clinical hyperthermia for patient selection and optimization of the SAR distribution.

FUTURE WORK AND PERSPECTIVES IN THE HYPERTHERMIA TREATMENT OF BREAST CANCER RECURRENCE

Application of hyperthermia in a more controllable manner, and less labor intensive while maintaining its clinical effectiveness would promote its wider acceptance. One way to achieve this is to have reliable hyperthermia treatment planning. Realization of this still requires substantial efforts in the development of hyperthermia equipment, thermal dosimetry and fast hyperthermia treatment planning.

A first step will be to confirm that in superficial hyperthermia the predicted SAR distribution is related to the measured interstitial temperature distribution. Further, it is relevant to verify that SAR coverage is related to treatment outcome in a larger patient group.

Concerning the treatment scheme of radiotherapy plus hyperthermia there are a number of remaining questions, regarding radiotherapy scheme, number of hyperthermia treatments, time interval between the two modalities, and concomitant systemic therapy.

For patients with an expected longer overall survival optimization of the radiation dose with smaller fraction sizes may be considered [12], i.e. to adjust the radiation schedule of 8 times 4 Gy twice weekly to 23 times 2 Gy daily. With smaller fraction size the incidence of late toxicity might be lower [13,14], though it should be verified that this does not affect tumor control. In our patients with irresectable tumors late grade 3 toxicity occurred in only 1%, so for this group the 8 x 4 Gy schedule is acceptable and convenient.

In the past we changed the hyperthermia schedule from 8 hyperthermia treatments to 4. Preliminary analysis showed no significant differences between 8 versus 4 hyperthermia treatments, but a definitive analysis should demonstrate that there is indeed no clinical benefit of 8 hyperthermia treatments.

Further improvement of the local control rate in breast cancer recurrences is still possible. Adding chemotherapy to radiation plus hyperthermia is one of the strategies under investigation. Sofar, the experience with concomitant chemotherapy has not clearly shown improvements of clinical outcome. Bornstein et al. [15] report a complete response rate of 53% for 34 fields in 29 patients treated with various drugs in addition to radiation and hyperthermia. Feyerabend et al. [16] report a complete response rate of 44% in patients treated with epirubicin and ifosfamide in addition to radiotherapy, mean total dose 49 Gy, and hyperthermia. Kouloulias et al. [17] achieved 20% complete

response in 15 patients treated with 31 Gy, liposomal doxorubicin and hyperthermia. At the same time there is no evidence to suggest that the addition of chemotherapy adds to the toxicity of radiotherapy.

We found that a longer time interval between radiotherapy and hyperthermia had no negative influence on local control rates, while it did decrease late toxicity in patients with subclinical disease. It would be interesting to investigate this prospectively.

GENERAL CONCLUSIONS

- Reirradiation plus hyperthermia is the treatment of choice for patients with recurrent breast cancer and should be available for each of these patients.
- The clinical results achieved in patients with a high risk of local recurrence after surgical resection of a recurrence strongly suggest that hyperthermia is beneficial for these patients as well.
- For patients with irresectable radiation-induced angiosarcoma the effect of reirradiation and hyperthermia is worthwhile.
- Breast reconstructions in previous irradiated areas are not a contraindication for treatment with reirradiation and hyperthermia as the incidence of acute and late toxicities is acceptable in view of the high local tumor control rates.
- For reliable superficial hyperthermia treatment planning, it is important that the CT-scan is made with the patient in treatment position and that all relevant information is visible.
- For superficial hyperthermia treatment planning the hyperthermia device should be validated in detail.
- Dose-effect relationship studies in hyperthermia are required for improvement of treatment strategy.

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Chapter 10

Summary

Hyperthermia is the use of elevated temperature for the treatment of cancer, increasing the tissue temperatures to between 40°C to 44°C for 1 hour or longer.

Several randomized trials have shown that hyperthermia in addition to radiotherapy and/or chemotherapy can substantially improve the clinical outcome in a variety of tumor types. The ESHO 5-88 study in recurrent breast cancer, for example, has shown that addition of hyperthermia to reirradiation increases the local control rate from 38% after reirradiation only to 78% after combined treatment. In the Netherlands, Germany, Switzerland, Czech, Italy and Greece, the combination of radiotherapy and hyperthermia is offered to patients with breast cancer recurrence at the chest wall. In the Netherlands, treatment of these patients consists of radiotherapy, 8 x 4 Gy (2fr/wk) combined with 4 hyperthermia treatments, given once weekly (www.oncoline.nl/mammacarcinoom).

For many years, we have continuously invested in the improvement of the systems for superficial hyperthermia. Over the years this resulted in an increase of the average invasive tissue temperature by 1.3°C [unpublished results]. In 1999 we showed a doubling of the complete response rate from 31% to 65% for larger tumors (diameter > 3 cm) tumors when adequate heating technology was used. Within the hyperthermia community there is general consensus that .

In this thesis, the current status of hyperthermia in the treatment of breast cancer recurrence at the chest wall in the Netherlands is presented and factors related to treatment outcome are identified. A potential way to improve the understanding of the quality of hyperthermia is to apply treatment modeling that is to calculate 3-dimensional (3D) SAR or temperature distribution and derive predicted hyperthermia dose parameters from these distributions. Next, these parameters can be used in future research for dose-effect relationships and optimization of treatment quality.

Chapter 1 describes the rationale for using hyperthermia in cancer treatment, and the current practice of treatment of patients with breast cancer recurrences. An overview of randomized trials shows that hyperthermia in addition to radiotherapy for superficial tumors can significantly improve outcome.

PART 1 MOTIVATION AND CLINICAL STUDIES

The history and details of superficial hyperthermia treatments in breast cancer recurrences at the Erasmus MC are reviewed in **chapter 2**. For hyperthermia treatments we used, the water filled Lucite Cone Applicators (LCAs), operating at a frequency of 433 MHz. With six applicators combined an area of 20 x 30 cm^2 can be heated effectively to a depth of up to 4 cm. Temperatures are measured interstitially with fiber-optic multisensor probes. In some patients with special clinical problems hyperthermia treatment planning can be applied to support decision making with regard to the treatment

strategy. In 74% of the patients with macroscopic breast cancer recurrences a complete response is achieved with a reirradiation scheme of 8 fractions of 4 Gy in 4 weeks, combined with 4 or 8 hyperthermia treatments, approximately twice as high as the complete response rate following the same reirradiation alone as demonstrated by in the randomized trial. To reach a high complete response and local control the whole volume at risk should be regarded as target and an adequate heating technique has to be used.

In **chapter 3** the effect of a combined treatment of surgery, reirradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall is presented. In the subgroup of patients treated after surgery, the 3 months, 1 and 3 years actuarial local control rates were 91%, 46% and 46%, respectively. In the subgroup of patients without surgery, the rates were 54%, 32% and 22%, respectively. Late grade 4 radiotherapy toxicity was seen in two patients, 7 and 11 months after the treatment. Wide surgical resection is the current treatment of choice for the treatment of radiation-induced angiosarcoma. The best published local control rates were achieved by combining surgery and hyperfractionated accelerated radiotherapy. For initially inoperable tumors, the effect of reirradiation and hyperthermia alone can still be beneficial.

Chapter 4 describes the toxicity of the combination of reirradiation and hyperthermia in breast cancer patients with reconstructions. When postoperative radiotherapy is required, many surgeons avoid thoracic wall resection for fear of wound complications. In our study, an incidence of severe acute (8%) and late (5%) normal tissue reactions was observed in 36 patients with 37 reconstructions. At the same time, the treatment resulted in a complete response in 12 of 15 (80%) patients with a macroscopic tumor. For all patients, local tumor control rate was 83% after 1 year, 74% after 3 years and 69% after 5 years. Based upon these results, we consider breast reconstructions in previous irradiated areas not a contraindication for treatment with reirradiation and hyperthermia.

In **chapter 5** results in 248 patients with macroscopic breast cancer recurrence treated with reirradiation and hyperthermia from 1996 to 2011 are described. Overall, the treatment resulted in a complete response rate of 70%, 3 and 5 years local tumor control rates of 40% and 39%, respectively. Ten years overall survival was 10%. The acute and long-term toxicity was acceptable. Grade 3 hyperthermia toxicity occurred in five patients and grade 4 in one patient. The 5 years incidence of late grade 3 toxicity was 1%.

Chapter 6 describes the results for 198 patients after surgery for recurrent breast cancer, who were treated electively or for subclinical disease with reirradiation and hyperthermia between 1993 and 2010. The 3 and 5 years local control rates were 83% and 78%. Late grade 3 and 4 toxicity was seen in 20 patients with a cumulative incidence of 11.9% after 5 years. At 10 years after diagnosis the overall survival was 36%.

PART 2 TOWARDS FINDING A PROSPECTIVE QUALITY INDICATOR

In **chapter 7** the development and implementation of the CT scanning procedure specific for superficial hyperthermia treatment planning, including an indication of the positions of the LCAs and the interstitial thermometry catheters, is described. Further, the procedure of segmenting the CT-images to create a patient and treatment specific 3D model, that mimics the real patient treatment set-up, is presented. Automatic segmentation takes 10–20 min and manual segmentation 2–4 h. The time for manual segmentation can be reduced by improving the program.

In **chapter 8** accurate reconstruction of the applicator setup from multiple-view images and calculation of the specific absorption rate, SAR, distribution using the actual applicator set-up is described. The total reconstruction procedure of six LCAs from a set of ten photos takes around 1.5 h. Minors errors of ±1.02 mm in translation or ±0.48° in rotation were found with negligible influence on treatment planning quality.

Chapter 11

Nederlandse samenvatting

Hyperthermie is een kankerbehandeling waarbij de temperatuur wordt verhoogd tussen 40°C en 44°C gedurende 1 uur of langer. Gerandomiseerde studies hebben aangetoond dat hyperthermie in combinatie met radio- of chemotherapie de klinische resultaten voor verschillende tumortypes aanzienlijk kan verbeteren. De ESHO 5-88 studie in recidief borstkanker, bijvoorbeeld, heeft aangetoond dat toevoeging van hyperthermie aan herbestraling de lokale controle van 38% na herbestraling alleen verhoogt tot 78%. In Nederland, Duitsland, Zwitserland, Tsjechië, Italië en Griekenland, wordt de combinatie van radiotherapie en hyperthermie aangeboden aan patiënten met recidief borstkanker. In Nederland bestaat de behandeling voor deze patiënten uit 4 weken radiotherapie met een schema van 8 fracties van 4 Gy, twee keer per week, gecombineerd met 4 hyperthermiebehandelingen, eenmaal per week (Richtlijn "Behandeling van het mammacarcinoom 2012").

Jarenlang is sterk ingezet op continue verbetering van onze systemen voor oppervlakkige hyperthermie. Een van die verbeteringen resulteerde in een stijging van complete respons van 31% naar 65% bij grote tumoren (diameter > 3 cm). De gemiddelde weefseltemperatuur steeg met 1.3°C (ongepubliceerde data). Er bestaat algemene consensus dat de klinische uitkomst sterk beïnvloed wordt door de kwaliteit van de hyperthermie behandeling.

Deze thesis beschrijft toepassing van hyperthermie als deel van de behandeling van recidief borstkanker in Rotterdam en voorspellende factoren voor de uitkomst van de behandeling. Een mogelijkheid om de huidige oppervlakkige hyperthermie te verbeteren is, om een 3-dimensional (3D) model van de behandeling te ontwikkelen, waarmee in 3D de specifieke absorptie ratio (SAR) en/of de temperatuurverdeling berekend kan worden. Vervolg onderzoek moet aantonen of deze berekende waarden voorspellend zijn voor de uitkomst van de behandeling.

Hoofdstuk 1 beschrijft de rationale voor toepassing van hyperthermie als onderdeel van de kankerbehandeling, behandelingsmogelijkheden van patiënten met recidief borstkanker. Eede klinische resultaten significant verbetert bij oppervlakkige tumoren.

DEEL 1 MOTIVATIE EN KLINISCHE STUDIES

Een overzicht van de ervaringen met oppervlakkige hyperthermie bij de behandeling van recidief borstkanker in het Erasmus MC wordt gegeven in **hoofdstuk 2**.

In Rotterdam wordt oppervlakkige behandeling uitgevoerd met Lucite Cone applicatoren (LCAs) bij een frequentie van 433 MHz. Met zes applicatoren kan een veldgrootte van maximaal 20 x 30 cm^2 met een diepte van maximaal 4 cm effectief worden verwarmd. Temperaturen worden interstitieel gemeten met glasvezel temperatuursensoren. Bij enkele patiënten met specifieke klinische problemen is een hyperthermie planningssys-

teem gebruikt ter ondersteuning van het behandelplan. Met het behandelschema van 8 fracties van 4 Gy in 4 weken gecombineerd met 4 of 8 hyperthermiebehandelingen wordt bij 74% van de patiënten een complete respons bereikt. Dit is ongeveer tweemaal zo hoog als het complete responspercentage met deze herbestraling zonder hyperthermie. Voor een hoge kans op complete respons en lokale controle is het belangrijk om het gehele risicogebied te verwarmen, en een goede verwarmingstechniek te gebruiken.

In **hoofdstuk 3** wordt het resultaat van behandeling met herbestraling en hyperthermie, al dan niet voor of na chirurgie, bij patiënten met bestralingsgeïnduceerd angiosarcoom van de borstwand gepresenteerd. In de subgroep van patiënten met chirurgie is de lokale controle na respectievelijk 3 maanden, 1 en 3 jaar, 91%, 46% en 46%. In de subgroep van patiënten zonder chirurgie is dit 54%, 32% en 22%. Late graad 4 radiotherapie toxiciteit werd gezien bij twee patiënten, 7 en 11 maanden na de behandeling. Ruime chirurgische resectie is de huidige voorkeursbehandeling van bestralingsgeïnduceerd angiosarcomen. De beste lokale controle wordt bereikt door het combineren van chirurgie samen met gehyperfractioneerde en geaccelereerde radiotherapie. Voor inoperabele tumoren kan herbestraling en hyperthermie gunstige effecten hebben.

Hoofdstuk 4 beschrijft de toxiciteit van de combinatie van herbestraling en hyperthermie in 36 borstkankerpatiënten met 37 reconstructies van de borstwand. Wanneer postoperatieve radiotherapie geïndiceerd is, vermijden veel chirurgen borstwandresecties vanwege het risico op wondcomplicaties. De incidentie van respectievelijk acute en late graad ≥3 toxiciteit na herbestraling met hyperthermie was 8% en 5%. Tegelijkertijd was de kans op complete respons in 15 patiënten met een macroscopische tumor 80%. De lokale tumor controle voor alle patiënten was 83% na 1 jaar, 74% na 3 jaar en 69% na 5 jaar. Reconstructies van de borstwand in eerder bestraalde gebieden zijn dus geen contra-indicatie voor herbestraling gecombineerd met hyperthermie.

In **hoofdstuk 5** worden de resultaten bij 248 patiënten met een irresectabel recidief borstkanker na herbestraling met hyperthermie beschreven. Een complete respons werd gezien bij 70% van de patiënten. De kans op lokale tumorcontrole na respectievelijk 3 en 5 jaar was 40% en 39%, en de 10-jaars overleving was 10%. De cumulatieve incidentie van late graad 3 toxiciteit was 1% na 5 jaar.

Hoofdstuk 6 beschrijft de resultaten bij 198 patiënten die na chirurgie voor recidief borstkanker werden behandeld met herbestraling en hyperthermie. De kans op lokale tumorcontrole na respectievelijk 3, 5 en 10 jaar was 83%, 78% en 78%. Late graad 3 en 4 toxiciteit werd gezien in 20 patiënten met een cumulatieve incidentie na respectievelijk 1, 3 en 5 jaar van 4.8%, 9.5% en 11.9%. De 10-jaars overleving na de gecombineerde behandeling was 36%.

DEEL 2 OP WEG NAAR EEN PROSPECTIEVE KWALITEITSINDICATOR

In **hoofdstuk 7** wordt de ontwikkeling van een procedure voor het maken van een CT scan specifiek voor het modelleren van patiënt en behandelopstelling ten behoeve van hyperthermie treatment planning beschreven. Op de CT scan moeten hiervoor ook de posities van de LCA's en de thermometriecatheters zichtbaar zijn. Verder wordt de procedure van het segmenteren van de CT-beelden beschreven, waarmee de werkelijke behandelsituatie driedimensionaal in het berekeningsmodel kan worden opgenomen. Voor automatische segmentatie is 10 tot 20 minuten nodig, en voor manuele segmentatie 2 tot 4 uur. De benodigde tijd voor segmentatie kan nog teruggebracht worden door verbetering van het programma.

In **hoofdstuk 8** wordt beschreven hoe de applicator setup nauwkeurig kan worden gereconstrueerd met behulp van uit meerdere hoeken gemaakte foto's, en hoe de verdeling van de specifieke energie absorptie (SAR) voor de actuele applicator setup berekend kan worden. De nodige tijd voor het reconstrueren van een combinatie van 6 LCA's vanuit een serie van 10 foto's is ongeveer 1,5 uur. De gevonden afwijkingen waren ±1.02 mm in positie, en ±0.48° in rotatie, met een verwaarloosbare invloed op de kwaliteit van de treatment planning.

Chapter 12

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dag dokter van Geel, kreeg ik als antwoord; Ik heb ook een naam en die is Bert. Vanaf dat moment was het ijs gebroken en we hebben een leuke samenwerking gehad met 2 artikelen. Een strenge dokter met een warm en gevoelig hart.

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Verder wil ik mijn vrienden en vriendinnnen bedanken voor de altijd weer nieuwe interesse in mijn komende proefschrift en komende promotiedatum En nog veel belangrijker, voor het zorgen van ontspanning, dat ik even mijn gedachten op iets anders kon zetten, zoals de tochtjes naar musea, de (kleding)winkels in Amsterdam, Maastricht, Parijs (FR) en Hasselt (B), dierentuinen, speeltuinen, pretparken en in de keuken theedrinken. Of een koffie shot halen in een café. Ik hoop dat dit niet afgelopen is als ik klaar ben met mijn promotie.

Hilko Wiersema, beste Hilko, iedere keer als je met een congres meeging, hoorde ik een nieuw verhaal. Bedankt voor je leuke en positieve inzichten en je mooie verhalen. Een leuke ontmoeting met iemand die gelooft in elfjes en de goedheid van de mensheid.

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Jacqueline Pomp, beste Jacqueline, door jou kreeg ik interesse in onderzoek en raakte ik geprikkeld door verder te kijken dan mijn neus lang is. Bedankt voor de leuke samenwerking en voor de zet van de eerste stappen in het indrukwekkende gebied van onderzoek.

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Rens Litjens, lieve Rens, ook al komen we uit dezelfde stad, toch hebben we elkaar in Rotterdam pas leren kennen. Ook onze vriendschap bestaat nog niet zo lang, maar heeft al heel wat meegemaakt. Altijd sta je voor me klaar met auto als ik weer ergens naar toe moet en door de tijd het allemaal net niet zou redden. Bedankt voor de leuke uitstapjes naar theater, musicals, films met diner, kennismaking in de juwelenwereld als ook de leuke koffiemomenten. Sjiek dat je mij paranimf wil zijn.

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Lieve Emre, mijn beste maatje, mijn lieve man. Ik weet niet wat de afgelopen jaren onze grootste opdracht was, promoveren, samen de kinderen opvoeden, samen een huis bouwen. Maar deze opdracht is ook weer af. En veel leuke en spannende opdrachten staan nog te wachten. Bedankt voor je geduld, hulp en liefde.

Curriculum vitae

Marianne Linthorst werd geboren op 12 november 1975 te Nijmegen. In 1995 behaalde zij haar VWO-diploma aan het Maartenscollege in Maastricht.

Zij begon haar geneeskunde studie in Diepenbeek, Belgie. Een jaar later werd zij ingeloot en begon ze haar studie geneeskunde in Leiden aan het Leids Universitair Medisch Centrum. Zij behaalde haar doctoraal in 2000. Na 2 jaar onderzoek is ze gestart met haar co-schappen in Maastricht, waarop ze in 2004 haar artsendiploma ontving. Na een jaar AGNIO Interne Geneeskunde in het Spaarne ziekenhuis en 1 jaar AGNIO op de afdeling radiotherapie van het Erasmus Medisch Centrum, begon ze aan dit promotieonderzoek. Zij werkte voor de ene helft als arts op de hyperthermie afdeling en voor de andere helft aan haar promotieonderzoek.

Inmiddels is Marianne gestart met haar opleiding tot jeugdarts in het Centrum voor Jeugd en Gezin in Rotterdam.

Marianne is getrouwd met Emre Almaç en heeft 3 kinderen, Geraldine (2008), Deniz (2008) en Amélie (2010).

Publications in peer-reviewed journals

Procedure for creating a three-dimensional (3D) model for superficial hyperthermia treatment planning. Linthorst M, Drizdal T, Joosten H, van Rhoon GC, van der Zee J. Strahlenther Onkol 2011;187:835-841.

The tolerance of reirradiation and hyperthermia in breast cancer patients with reconstructions. Linthorst M, van Rhoon GC, van Geel AN, Baaijens M, Ghidey W, Broekmeyer-Reurink MP, van der Zee J. Int J Hyperthermia 2012;28:267-277.

Effect of a combined surgery, reirradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall. Linthorst M, van Geel AN, Baartman EA, Oei SB, Ghidey W, van Rhoon GC, van der Zee J. Strahlenther Onkol 2013;189:387-393.

Reirradiation and hyperthermia after surgery for recurrent breast cancer. Linthorst M, van Geel AN, Baaijens M, Ameziane A, Ghidey W, van Rhoon GC, van der Zee J. Radiother Oncol 2013;109:188-193.

Local control rate after the combination of reirradiation and hyperthermia for irresectable recurrent breast cancer: Results in 248 patients. Linthorst M, BaaijensM, Biesta J, Creutzberg C, Ghidey W, van Rhoon G, van der Zee J. Radiother Oncol 2015;117:217-222.

The clinical feasibility of deep hyperthermia treatment in the head and neck: new challenges for positioning and temperature measurement. Paulides MM, Bakker JF, Linthorst M, van der Zee J, Rijnen Z, Neufeld E, Pattynama PM, Jansen PP, Levendag PC, van Rhoon GC. Phys Med Biol 2010;55:2465-2480.

Reirradiation combined with hyperthermia in breast cancer recurrences: overview of experience in Erasmus MC. van der Zee J, de Bruijne M, Mens JW, Ameziane A, Broekmeyer-Reurink MP, Drizdal T, Linthorst M, van Rhoon GC. Int J Hyperthermia 2010;26:638-648.

Reconstruction of applicator positions from multiple-view images for accurate superficial hyperthermia treatment planning. Drizdal T, Paulides MM, Linthorst M, van Rhoon GC. Phys Med Biol 2012;57:2491-2503.

The influence of pre-operative radiotherapy on the expression of p53 and adhesion molecules: correlation with treatment results in patients with squamous cell carcinoma or adenocarcinoma. Pomp J, Blom J, Linthorst M, Zwinderman AH, van Krimpen C. Oncol Rep 2002;9:621-625.

A reassessment of bone scintigraphy and commonly tested pretreatment biochemical parameters in newly diagnosed osteosarcoma. Stokkel MP, Linthorst MF, Borm JJ, Taminiau AH, Pauwels EK. J Cancer Res Clin Oncol 2002;128:393-399.

Presentations at international congresses

Linthorst M, Drizdal T, Joosten H, van Rhoon GC, van der Zee J. Procedure for creating a three-dimensional (3D) model for superficial hyperthermia treatment planning. 25th Annual Meeting of the European Society for Hyperthermic Oncology (ESHO), 2009, Verona, Italy

Linthorst M, van Rhoon GC, van Geel AN, Baaijens M, Ghidey W, Broekmeyer-Reurink MP, van der Zee J. The tolerance of reirradiation and hyperthermia in breast cancer patients with reconstructions, 26th Annual Meeting of the European Society for Hyperthermic Oncology (ESHO), 2010, Rotterdam, the Netherlands

Linthorst M, van Geel AN, Baaijens M, Ameziane A, Ghidey W, van Rhoon GC, van der Zee. Reirradiation and hyperthermia after surgery for recurrent breast cancer. 27th Annual Meeting of the European Society for Hyperthermic Oncology (ESHO), 2011, Aarhus, Denmark

Linthorst M, BaaijensM, Biesta J, Creutzberg C, Ghidey W, van Rhoon G, van der ZeeJ. Local control rate after the combination of reirradiation and hyperthermia for irresectable recurrent breast cancer: Results in 248 patients. 11th International Congress on Hyperthermic Oncology (ICHO), 2012, Kyoto, Japan

Honors

Kim Award (Medicine) of the 27th Annual Meeting of the European Society for Hyperthermic Oncology (ESHO), 2011, Aarhus, Denmark

Young Investigator Travel Award of the 11th International Congress on Hyperthermic Oncology (ICHO), 2012, Kyoto, Japan

Three times a travel award, two times to the European Society for Hyperthermic Oncology (ESHO) and one time to the International Congress on Hyperthermic Oncology (ICHO)

Portfolio

Summary of PhD training and teaching activities **ECTS**

Name: M.F.G. Linthorst
Erasmus MC Department: Radiation Oncology/ Hyperthermia
Promotor: Prof.dr. G.C. van Rhoon
Copromotor: Dr. J. van der Zee

PhD training

General academic skills

– PhD day 2008	0.2
– Biomedical English Writing and Communication 2008-2009	4
– Workshop printing thesis Rotterdam 2015	0.6

Research skills

– Classical methods for data-analysis (NIHES) 2008	5.7
– Basisdidactiek course at the EUR 2009	1.6
– Basis introduction course on SPSS 2009	1.6

In-depth courses (e.g. Research school, Medical Training)

– Introductie tot de Klinische en Fundamentele Oncologie 2008	1.8

Presentations

– Practical translation of specific CT scan for superficial hyperthermia into treatment planning tool SEMCAD X (co-author) 2009	0.2
– CT scan for superficial hyperthermia treatment planning 2009	0.6
– Predicted 3D-SAR coverage for treatment outcome in superficial hyperthermia 2009	0.6
– CT scans in superficial hyperthermia treatment 2009	0.6
– Progress in heating head and neck tumors using the hypercollar (co-author) 2010	0.2
– Integration of technology into the clinic to facilitate focused treatment of advanced head and neck tumors (co-author) 2010	0.2
– Hyperthermia treatment of advanced head and neck cancer: integration of technology into the clinic (co-author) 2010	0.2
– The tolerance of skin transfers for reirradiation and hyperthermia 2010	0.6
– High local control rate after combined surgery, re-irradiation and hyperthermia for radio-induced angiosarcoma of the chest wall (presentation and poster) 2x 2011, 2012	2.4
– Hyperthermia and reirradiation in the treatment of microscopic recurrent breast cancer 2011	0.6
– Reconstruction of the superficial hyperthermia treatment setup from multiple-view images (co-author) 2011	0.2
– Local control rate after the combination of re-irradiation and hyperthermia for recurrent breast cancer: Results in 400 patients 2012, (co-author) 2014	0.8
– Comparison of 4 to 8 hyperthermia treatments combined with re-irradiation for breast cancer (presentation and poster) 2012	0.8
– Local control rate after the combination of re-irradiation and hyperthermia for recurrent breast cancer: Results in 250 patients (presentation and poster) 2012	0.8
– Radiofrequency Electromagnetic Hyperthermia: where is Rotterdam going? (co-author) 2013	0.2
– Long-term results of reirradiation and hyperthermia in recurrent breast cancer 2013	0.6

International Conferences

– 25th Annual Meeting of the European Society of Hyperthermic Oncology, Verona, Italy 2009	2.0
– 26th Annual Meeting of the European Society for Hyperthermic Oncology (ESHO), Rotterdam, the Netherlands 2010	2.0
– 27th Annual Meeting of the European Society for Hyperthermic Oncology (ESHO), Aarhus, Denmark 2011	2.0
– 11th International Congress of Hyperthermic Oncology (ICHO), Kyoto, Japan 2012	2.0

Others

– Writing Research Protocol sent to the Medical Ethical Committee (in Dutch: Medisch Ethische Toetsingscommissie or METc), Rotterdam, the Netherlands 2007	2.0
– Writing patient information for research study, the Netherlands 2007	1.0
– Presentation at the Radiotherapy clinic, Westeinde Den Haag, the Netherlands 2009	0.6
– Presentation at the Clinical working group on hyperthermia, Rotterdam, the Netherlands 2x 2009	1.0
– Writing Research Protocol Head and Neck Hyperthermia treatment 2009	1.0
– Presentation at the Clinical working group on hyperthermia, Tilburg, the Netherlands 2010	0.6
– Presentation at the Clinical working group on hyperthermia, Amsterdam, the Netherlands 2011	0.6
– Presentation at the Department Minimally Invasive Healthcare, Philips Research and Department of Biomedical Engineering / Biomedical NMR at the University of Technology, Eindhoven, the Netherlands 2011	0.6
– Presentation at the Dutch Society of Surgery, Ede, the Netherlands 2011	0.6
– Presentation at the refer evening in Daniel den Hoed – Erasmus MC 2008, 2012	1.0
– Presentation at the Department Minimally Invasive Healthcare, Philips Research and Department of Biomedical Engineering / Biomedical NMR at the University of Technology, Eindhoven, the Netherlands 2013	0.6
– Presentation at the Maastro clinic, Maastricht, the Netherlands (co-author) 2014	0.6
Total	**43.3**