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### Improving superficial hyperthermia treatment

*Temperature matters*

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#### Publication date

2021

[Link to publication](#)

#### Citation for published version (APA):

Bakker, A. (2021). *Improving superficial hyperthermia treatment: Temperature matters*. [Thesis, fully internal, Universiteit van Amsterdam].

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# CHAPTER 1

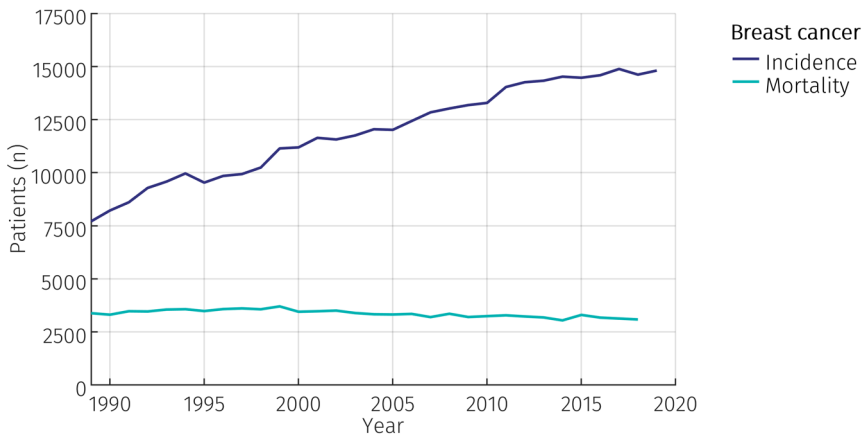
## GENERAL INTRODUCTION



## GENERAL INTRODUCTION

### Breast cancer

Breast cancer is the most common type of cancer in women around the world [1]. In the Netherlands, annually approximately 15.000 women are diagnosed with invasive breast cancer (Figure 1). For a woman in the Netherlands, the probability to develop breast cancer during life is 14 %. [2] In the past years, breast cancer mortality is slightly decreasing while the incidence is increasing [1, 2]. The increase in breast cancer incidence can partly be explained by an increased life expectancy [2], longer exposure to risk factors and life style changes [3]. The prognosis has improved due to earlier detection and advances in treatment options.



**Figure 1.** Incidence and mortality of patients with invasive breast cancer in the Netherlands [2].

### Locoregional recurrence

Locoregional recurrence of breast cancer is rare. The overall ten-year incidence after surgery is 4.3 % for a local recurrence and 2.6 % for a regional recurrence in patients with breast cancer [4]. Because of the high incidence of breast cancer, in absolute numbers many patients do develop a locoregional recurrence of breast cancer. A locoregional recurrence is defined as recurrence of the disease in the breast, chest wall, axilla, or in the infraclavicular, supraclavicular or internal mammary lymph node areas after curative treatment [5]. Factors such as tumor stage, adjuvant therapy, family history and age have all been found to be associated with the risk of locoregional recurrence [6]. Locoregional recurrences of breast cancer may cause impaired quality of life when uncontrolled, without being life-threatening at short term. In addition to the psychological distress of watching a tumor grow, symptoms such as pain, ulceration, bleeding, arm edema and brachial plexus paralysis have been seen in up to 62 % of the patients with locoregional recurrent breast cancer referred for radiotherapy [7].

A locoregional recurrence implicates a worse prognosis, both after mastectomy and breast conserving surgery [6, 8], as locoregional recurrence is an independent prognostic indicator of subsequent distant metastasis [8]. Approximately two-thirds of the recurrences after both mastectomy and breast conserving surgery are isolated, thus without distant metastasis. The treatment of patients with an isolated locoregional recurrence should be curative in intent as the five-year survival of patients with an isolated locoregional recurrence is 40 - 65 % [9, 10].

### *Treatment*

Treatment options are limited in patients with locoregional recurrence of breast cancer in previously irradiated area [11, 12]. The best treatment results are achieved by early detection of the locoregional recurrence, systemic therapy, adequate surgical removal and high dose radiotherapy [13]. Recurrences in previously irradiated areas present an additional challenge. Hypoxia induced by previous radiotherapy renders the tumor less sensitive to radiation, thereby reducing the chance of achieving local control by radiotherapy treatment alone [7, 14–16]. There are only few prospective clinical trials regarding the optimal treatment for patients with locoregional recurrence or second primary breast cancer after prior radiotherapy. Re-irradiation combined with hyperthermia can be considered for patients with an (isolated) locoregional recurrence of breast cancer [11]. Hyperthermia, a potent radiosensitizer, has been used along with radiotherapy in the treatment of locoregional recurrent breast cancer since 1978 to achieve tumor-selective radiosensitization [17–19]. Presently, re-irradiation with hyperthermia is applied both to patients with inoperable locoregional recurrent breast cancer [17, 20, 21] and to patients as adjuvant treatment after surgical removal of the locoregional breast cancer recurrence [22–25]. Radiotherapy and hyperthermia will be described in more detail in the next paragraphs.

Combined results of five randomized trials showed significant benefit of the addition of hyperthermia to irradiation in the treatment of patients with inoperable locoregional recurrent breast cancer. The overall complete response rate with radiotherapy alone was 41 %, whereas with radiotherapy and hyperthermia it reached 59 %, resulting in an odds ratio of 2.3. The combined therapy was well tolerated with minor toxicity. It should be pointed out that in four out of the five combined randomized trials a proportion of the patients (33 %) received high dose radiotherapy (25 x 2 Gy + 5 x 3 Gy boost) for primary or recurrent breast cancer, this category benefitted less from the combined treatment than patients treated for recurrent disease in previously irradiated area. The randomized trial of the European Society of Hyperthermic Oncology (ESHO) included solely patients with inoperable locoregional recurrent breast cancer in previously irradiated area (n = 56). Hyperthermia was given within 30 - 60 min after re-irradiation (8 x 4 Gy). In this trial

an overall complete response rate of 38 % for re-irradiation alone compared to 78 % for re-irradiation with hyperthermia was found, resulting in an odds ratio of 5.7 in favor of the combined treatment with hyperthermia. The Medical Research Council trial for recurrent breast cancer included 149 patients, where approximately 80 % of the patients had a recurrence in previously irradiated area. Hyperthermia was given  $\geq 90$  minutes after radiation therapy (25 x 2 Gy or 8 x 3.6 Gy) to ensure tumor-selective radiosensitization. In this trial an overall complete response rate of 29 % for (re-)irradiation alone compared to 57 % for (re-)irradiation with hyperthermia was found. The odds ratio of 3.2 was again in favor of the addition of hyperthermia. [17]

Re-irradiation with hyperthermia is also effective as an adjuvant treatment, e.g. in patients who have a high-risk of developing a re-recurrence after surgical removal of their local recurrence or in patients who achieved a complete response after neo-adjuvant chemotherapy [22–25]. Patients are deemed as high-risk for re-recurrence when the surgery results show microscopically involved or close resection margins, lymph angio-invasion, multicentricity, size of the recurrence  $\geq 4$  cm, or when a patient had multiple previous recurrences at the same location [22, 24–26]. For surgery alone, data are scarce. In the few series available, local control is achieved in 63 - 96 % of patients for salvage mastectomy [27] to 24 - 55 % for local resection of chest wall recurrences [7, 28]. Adding re-irradiation and hyperthermia after macroscopic complete resection, results in a local control rate of 75 - 83 % in various series [22–25]. Comparison of the local control rates for locoregional recurrent breast cancer of salvage surgery alone and salvage surgery combined with re-irradiation and hyperthermia is difficult. Series describing surgery alone tend to describe mainly patients with low risk for re-recurrence, i.e. patients with smaller tumors, which were removed with large margins. On the other hand, series describing additional re-irradiation (with or without hyperthermia) after surgery have a tendency to consist of patients who are deemed high risk for re-recurrence. Considering this potential selection bias, addition of re-irradiation plus hyperthermia appears to improve subsequent local control, but evidence from randomized controlled trials is lacking.

### **Radiotherapy**

Radiotherapy is a cancer treatment generating DNA damage by ionizing radiation [29]. Radiotherapy may be prescribed by radiation oncologists as curative or palliative treatment. Palliative radiation focuses on local disease control and or symptomatic relief in patients for whom cure is not expected, whereas curative radiation has the intent to cure the patients. The treatment intent depends on the tumor type, location, and stage, as well as the general condition of the patient. The treatment intent determines the radiotherapy dose and fractionation schedule.

### *Biology*

Ionizing radiation carries enough energy to ionize, or eject electrons, from molecules within cells. Radiation damage to DNA can occur directly or indirectly when ionizing radiation passes through the nucleus of a cell. For direct damage to occur the radiation must hit the DNA. Since the volume of the DNA is small compared to the entire cell, the probability of that happening is remote. If the radiation interacts in close proximity to the DNA, the interaction with other molecules may create free oxygen radicals that can indirectly damage the DNA. [30, 31] Damage to the DNA can consist of single strand breaks and double strand breaks. Double strand breaks are more difficult to repair and are potentially lethal to cells if left unrepaired. They are repaired by homologous recombination, non-homologous end-joining or backup non-homologous end-joining. Non-homologous end-joining and backup non-homologous end-joining are error-prone, but they can operate during any phase of the cell cycle. By contrast, homologous recombination is much more reliable but restricted to the proliferating phases of the cell; the S and G<sub>2</sub> phases. [29]

One of the major limitations of radiotherapy is that often significant parts of solid tumors are less well-oxygenated than normal tissue [32]. Solid tumors can outgrow their blood supply, locally causing a low-oxygen state known as hypoxia. Presence of less oxygen means creation of less oxygen radicals during radiotherapy, thus hypoxic tumor cells may be three times more resistant to radiation damage than tumor cells in a normal oxygen environment [33]. Furthermore, tumors recurring in previously irradiated area have an even higher fraction of treatment-resistant hypoxic cells [16]. Combining radiotherapy with hyperthermia is an option to resolve this problem, as hyperthermia is capable of inducing re-oxygenation of the tumor [34, 35], as well as inducing direct cytotoxicity of hypoxic tumor cells [36, 37].

### *Dose*

The radiation dose used in radiotherapy is measured in gray (Gy), and varies depending on the type and stage of cancer being treated. For primary breast cancer, the typical dose ranges from 26 Gy in five fractions to 40 Gy in 15 fractions [38, 39], while locoregional recurrent disease in previously irradiated area is treated with 32 Gy in 8 fractions or 46 Gy in 23 fractions [13, 21, 24]. The total dose is fractionated (spread out over time) for several reasons. Fractionation allows normal cells time to recover, while tumor cells are generally less efficient in repairing all DNA damage between fractions. Fractionation also allows hitting tumor cells in various phases of the cell cycle. Similarly, tumor cells that were chronically or acutely hypoxic (and therefore more radioresistant) may re-oxygenate between fractions, improving the chance of achieving complete tumor cell kill.

## Hyperthermia

Hyperthermia, i.e. treatment with heat, is historically applied to a wide range of diseases, including cancer. Its use as a treatment for breast cancer is mentioned in the Egyptian Edwin Smith Surgical Papyrus, which dates back to about 3000 B.C.. At present, the most common application of hyperthermia is in the treatment of cancer. Hyperthermia is applied as either mild hyperthermia, heating the tumor for approximately one hour at 40 - 44 °C, or as thermal ablation, a technique where the tumor is heated to  $\geq 50$  °C or frozen to  $\leq -75$  °C (hypothermia). Ablation is a minimally invasive alternative for surgery for tumors less than 4 cm in diameter, such as small bone, liver, brain and pancreatic tumors. Different ablation techniques are available such as laser ablation, radiofrequency ablation (RFA), microwave ablation (MWA), high intensity focused ultrasound (HIFU) treatments and cryoablation. Unlike thermal ablation, mild hyperthermia is only marginally effective against cancer as a single modality, but it is a potent sensitizer for radiotherapy and chemotherapy. Throughout this thesis the term hyperthermia refers to mild hyperthermia.

### *Biology*

From a biological view, hyperthermia is a complex treatment since there are many mechanisms through which hyperthermia acts. Hyperthermia alone may cause direct cytotoxicity to tumor cells [36]. In combination with radiotherapy or chemotherapy, hyperthermia acts as a sensitizer. On a macroscopic level, heating the tumor causes local vasodilatation, which improves the blood flow, and thereby increases tumor oxygenation resulting in higher effectiveness of radiotherapy [40–43]. Furthermore, due to increased blood flow and vessel permeability, chemotherapeutic agents can better penetrate the tumor [34, 42, 44]. At a molecular level, hyperthermia can stimulate the immune system locally and systemically [45, 46]. Finally, hyperthermia can inhibit the repair of DNA damage caused by radiotherapy and chemotherapy by temporarily inhibiting the homologous recombination repair pathway [47] and other pathways [48]. Blocking DNA damage repair leads to an accumulation of unrepaired DNA damage and therefore survival of fewer cancer cells.

The contribution of each of these mechanisms to the tumor response depends among others on the oxygen and nutrient status of the tumor cells. In general, hypoxic tumors are easier to heat and in prolonged hypoxic and nutrient deprived tumors the contribution of direct cytotoxicity of hyperthermia is increased.

Both the direct effect and the sensitizing effect of hyperthermia also depend on the achieved temperature and duration of heating. In vitro studies show that there is an increase in direct cell death [49–51] and DNA damage repair inhibition [52] when tumor cells are heated longer or to a higher temperature. There is a temperature threshold

around 42 °C for direct cell death and the rate of cell killing is dependent on temperature and duration of heating. [53] The optimal inhibition of DNA damage repair by homologous recombination is achieved by subjecting cells to hyperthermia at temperatures of 42 °C or higher for 60 min, where the minimum thermal dose to achieve defects in the DNA damage repair pathway is one hour at 41 °C [52]. The optimal temperature and duration of heating differ for different cell lines for both the direct effect and DNA damage repair inhibition [52, 54]. In vivo studies showed that improvement of tumor re-oxygenation after hyperthermia occurs at lower thermal doses (39 - 43 °C), and lasts for as long as 24 - 48 hours after heating. While higher thermal doses (> 44 °C) cause vascular damage and lead to decreases in tumor oxygenation. [40, 42, 43] Activation of the immune system occurs at 40 - 41 °C [45, 55, 56]. Several clinical studies underline the importance of duration of heating and achieved temperature during hyperthermia treatment [57, 58].

The effect of hyperthermia increases with a longer heating time, but during and after exposure to heat the onset of thermotolerance is induced, temporarily reducing sensitization during prolonged heating [53]. Exposure to heat induces the production of heat shock proteins. The presence of these heat shock proteins results in a temporarily reduced sensitivity to heating typically starting ~6 hours after the onset of hyperthermia. [59, 60] This reduced effectiveness of hyperthermia is transient and persists for several days [60]. Therefore, clinical hyperthermia treatments are limited to 1 - 1.5 hour sessions, and given only once or twice weekly.

Furthermore, the amount of radiosensitization by hyperthermia is strongly dependent on the sequence and time-interval between radiotherapy and hyperthermia. In vitro, in vivo and clinical studies show that the effect is largest when hyperthermia and radiotherapy are given simultaneously. [37, 61, 62] The enhancement of radiotherapy by hyperthermia rapidly decreases when the time interval between radiotherapy and hyperthermia is more than 1 hour [61].

### *Dose*

As a result of the observed relationship between duration of heating and the achieved temperature [49-51, 57, 58], hyperthermia treatments are usually quantified by calculating a thermal isoeffective dose, which captures the impact of both temperature and duration. The most commonly used thermal isoeffective dose is the cumulative equivalent minutes at 43 °C (CEM43) [53, 63], which is based on the direct cell killing effect of hyperthermia alone, where the rate of cell killing increases exponentially with temperature and linearly with the duration of heating. This generally used definition of CEM43 takes into account temperature variation during heating between time  $t = 0$  and  $t = \text{total}$ :

$$\text{CEM43} = \sum_{t=0}^{t=\text{total}} R^{(43-T)} \Delta t$$

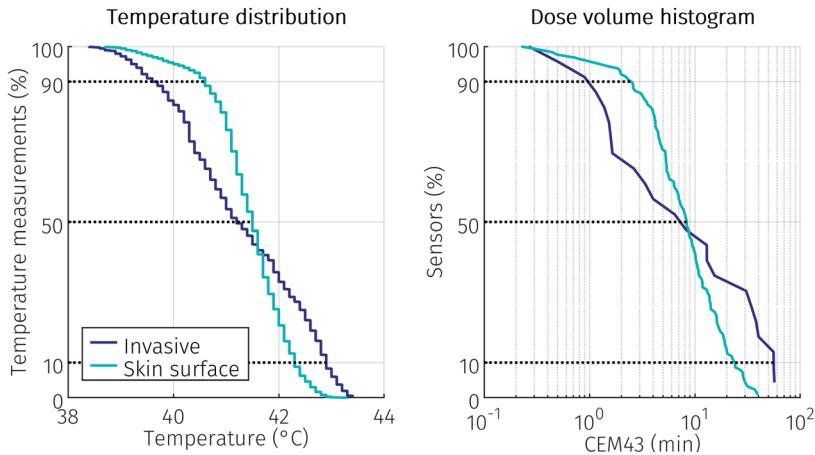
where  $\Delta t$  (min) is the time between two temperature measurements,  $T$  ( $^{\circ}\text{C}$ ) the average temperature during  $\Delta t$ ,  $R$  is the number of minutes needed to compensate for  $1^{\circ}\text{C}$  temperature change either above or below the breakpoint at  $43^{\circ}\text{C}$ .  $R$  is commonly set at 0.25 for  $T < 43^{\circ}\text{C}$  and 0.5 for  $T \geq 43^{\circ}\text{C}$ . [53] The CEM43 correlates well with thermal damage in a variety of tissues and is typically used to describe thermal thresholds for tissue damage [64]. At this moment there is not yet a single treatment related parameter that includes both the direct effect of hyperthermia and its sensitizing effect to radiotherapy or chemotherapy.

The distribution of the achieved temperature and the dose-volume histogram of the CEM43 are used to describe hyperthermia treatments (Figure 2). Parameters representing the quality of treatment can be derived from the temperature distribution and the dose-volume histogram. Often the maximum and minimum temperature are presented, as well as the T10, T50 and T90. Where the T10, T50 and T90 are the temperatures exceeded by 10 %, 50 % and 90 % of the temperature measurements during the hyperthermia treatment without the pre-heating period. The quality assurance guidelines for superficial hyperthermia from the ESHO technical committee set a minimum goal of reaching a T90 of  $40^{\circ}\text{C}$  and T50 exceeding  $41^{\circ}\text{C}$  for 60 minutes throughout the target volume [65]. To illustrate this concept, during the treatment presented in Figure 2, the invasive and skin surface T90 was  $39.7^{\circ}\text{C}$  vs.  $40.6^{\circ}\text{C}$  and the T50 was  $41.2^{\circ}\text{C}$  vs.  $41.5^{\circ}\text{C}$ , respectively.

For thermal dose, the maximum CEM43 (CEM43 T0) and minimum CEM43 (CEM43 T100) are often presented, as well as the CEM43 T10, CEM43 T50 and CEM43 T90, representing the thermal dose exceeded by 10 %, 50 % and 90 % of the temperature sensors during the hyperthermia treatment without the pre-heating period [65]. During the treatment presented in Figure 2, the invasive and skin surface CEM43 T50 was 7.2 min vs. 8.4 min and the CEM43 T90 was 1.0 min vs. 2.5 min, respectively. Other parameters, such as the TRISE, e.g. the T50 temperature increase above  $37^{\circ}\text{C}$  normalized for treatment duration [66, 67], the time above a certain temperature or the percentage of temperature measurements above a certain temperature, are less frequently used to characterize thermal dose during hyperthermia treatment.

In contrast to radiotherapy and chemotherapy, where a prescribed dose can be given, during hyperthermia it is not easy to deliver the prescribed dose across the target tissue and surrounding normal tissues. Several factors influence the achieved thermal dose, such as limitations of the hyperthermia equipment, the heterogeneity of the tissue properties, blood flow in the target area and treatment limiting hotspots. Because of these factors, the target area is likely to receive a heterogeneous hyperthermia dose. Hotspots in the target

area limit the amount of applicator power that can be applied during treatment, resulting in less penetration depth and lower invasive temperatures. These hotspots can result in thermal toxicity, which can have long lasting consequences and may require hyperbaric oxygen therapy or surgery. Less sensitization and direct cell kill by hyperthermia occurs in areas with lower temperatures. Thus, the heterogeneity of the hyperthermia dose in the target area has direct implications for clinical outcome and possible side effects.



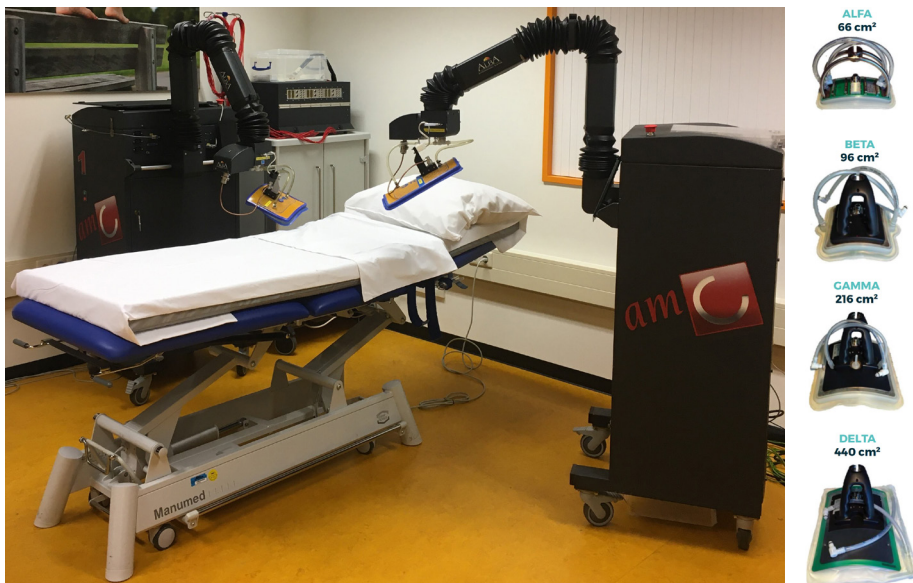
**Figure 2.** The temperature distribution (left) and the dose-volume histogram of the cumulative equivalent minutes at 43 °C (CEM43; right) of the first hyperthermia treatment of a patient with locoregional recurrent breast cancer with four invasive catheters in situ (28 sensors), and 18 thermocouple probes on the skin surface (126 temperature sensors).

### *Clinical practice*

Several hyperthermia techniques can be used to heat locoregional recurrences of breast cancer. The choice of technique depends on the target depth and lateral extent. Several techniques for superficial hyperthermia are available: electromagnetic radiative heating systems, electromagnetic capacitive systems, ultrasound heating and infrared heating. [65] The two most common superficial hyperthermia systems are the ALBA ON 4000 (Medlogix, Rome, Italy) and the BSD-500 (Pyrexar, Salt Lake City, UT, USA). These systems apply non-ionizing electromagnetic radiation with a frequency of 434 MHz and 915 MHz, respectively. With 434 MHz systems, superficial recurrences up to a depth of four cm can be treated, while 915 MHz systems can be used for recurrences up to a depth of two to three cm. When electromagnetic radiation at frequencies above 400 MHz enters the body it causes molecules with an electric dipole, such as water, to start oscillating to align with the time varying electrical field of the microwaves. Friction between adjacent oscillating molecules creates heat. [65] Another more recent superficial hyperthermia technique that is used for widespread superficial locoregional

recurrences of breast cancer, i.e. cancer en cuirasse, is the water-filtered infrared-A (wIRA) hyperthermia system. It consists of two lamps that emit water-filtered infrared-A light that can penetrate up to a depth of 15 mm. During wIRA treatment the skin surface temperature is monitored with two infrared cameras. [68, 69]

Hyperthermia is applied once or twice per week during the radiotherapy and/ or chemotherapy course. Usually, radiotherapy is given first and within one hour the tumor is heated, while chemotherapeutic agents and hyperthermia are administered simultaneously. Hyperthermia treatment objectives are to elevate intratumoral temperatures to a minimum of 41 °C for one hour, while maintaining maximum normal tissue temperatures below 44 °C. At the Amsterdam UMC, conformal Contact Flexible Microstrip Applicators (CFMA; Istok, Fryazino, Russia; Medlogix, Rome, Italy) operating at 434 MHz [70] connected to the ALBA ON 4000 system (Medlogix, Rome, Italy) are used to heat the target region (Figure 3). A flat water bag containing temperature controlled circulating deionized water is positioned between the applicator and the skin [70–72]. The water temperature is adjusted to maintain a therapeutic temperature level of 42 °C as recorded on the skin surface. A fifteen minute heating up period is required to achieve clinically relevant temperatures invasively, which are then maintained for a steady state period of one hour.



**Figure 3.** The 434 MHz ALBA ON 4000 double superficial hyperthermia system (Medlogix, Rome, Italy) at the Amsterdam UMC connected to a 4H and 3H applicator (Istok, Fryazino, Russia). The system can also be connected to the accompanying alfa, beta, gamma and delta applicators (Medlogix, Rome, Italy) or the 1H, 2H and 5H applicators (Istok, Fryazino, Russia).

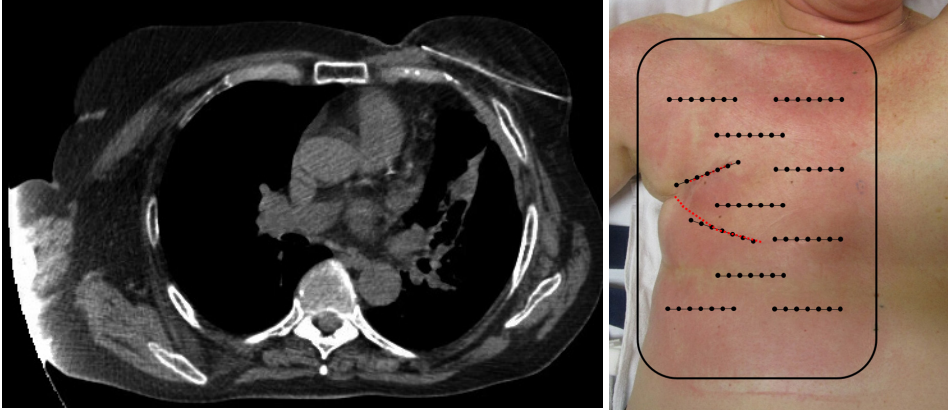
### *Thermal monitoring*

Typically, one to three invasive catheters are inserted in the target area to monitor hyperthermia treatment. Placing more catheters is not clinically practical [73]. During hyperthermia treatment, temperature probes are placed inside the invasive catheters to monitor the temperature continuously, to provide more data additional temperature sensors are positioned on the skin surface (Figure 4) [73].

Temperature measurement during superficial hyperthermia can be done with different types of sensors. Most used during hyperthermia treatment are thermistors with high resistance leads (single sensor Bowman probes), one to four sensor fiber-optic probes and one to fourteen sensor thermocouple probes (Table 1). At the Amsterdam UMC, seven or fourteen sensor copper-constantan thermocouple probes (Volenec RD Int., Hradec Králové, Czech Republic) connected to a 196 channel thermometry system (UMCU, Utrecht, the Netherlands) are used for temperature measurement. Each thermometry method has its advantages and disadvantages and the used method influences the temperature distribution. First, the number of available sensors to measure the temperature severely affects the measured temperature distribution. With thermocouple thermometry systems relatively large numbers of sensors can be positioned (up to 196 sensors) [74], whereas the thermometry systems for single sensor Bowman probes are limited to 8 - 16 sensors [75] and fiber-optic thermometry systems to 8 - 32 sensors [76], the last two consequently providing more sparse temperature measurement, particularly for large sized applicators (~600 cm<sup>2</sup>). Second, Bowman probes and fiber-optic probes are insensitive for electromagnetic radiation. Thus, they can be positioned in every direction and can measure the temperature continuously during hyperthermia treatment. Whereas thermocouple probes should be placed perpendicular to the electromagnetic field direction and can only measure the temperature undisturbed when the power is briefly turned off. In general, the latter is done every 30 seconds, so the temporal resolution of thermocouple thermometry is slightly reduced. Finally, thermocouple probes measure the temperature approximately three to five seconds after the power is turned off, thus the actual achieved temperature at the location of the thermocouple sensor is higher than the measured temperature.

Several academic groups have investigated solutions to improve the temporal and spatial resolution of thermal monitoring during superficial hyperthermia. These methods include thermal mapping, i.e. pulling a limited number of temperature sensors through a fixed trajectory several times during treatment [78], and increasing the number of temperature sensors by purchase and clinical implementation of additional multi-channel thermometry systems [74, 76, 79, 80]. The latter option may be combined with a thermal monitoring sheet [80, 81]. Unfortunately, these methods

for thermal monitoring during superficial hyperthermia are not yet readily available for all hyperthermia centers, since they are either too expensive, take too much time, are not commercially available, CE marked or FDA approved, or require too much expertise.



**Figure 4.** CT-scan of a patient with locoregional recurrent breast cancer with an invasive catheter in situ enabling invasive temperature measurements during hyperthermia treatment (left). Schematic representation of the standard thermometry method of the Amsterdam UMC, where multiple seven-sensor thermocouple probes are positioned on the skin of a patient with surgically removed locoregional recurrent breast cancer (right). The mastectomy scar is depicted in red, the dimensions of the 3H applicator (Istok, Fryazano, Russia) as a black rectangle.

At the moment, commercial microwave hyperthermia systems generally offer only eight single sensors (ALBA ON 4000, Medlogix, Italy; BSD-500, Pyrexar, Salt Lake City, UT, USA). As a result, temperature in most of the tumor and the skin surface remains unmonitored and the quality assurance of superficial hyperthermia treatment is not adequate.

**Table 1.** Characteristics of three sensor types that are typically used for temperature measurement during hyperthermia; Bowman probes (thermistors with high resistance leads), fiber-optic probes and thermocouple probes.

<b>Characteristic</b>	<b>Bowman probes</b>	<b>Fiber-optic probes</b>	<b>Thermocouple probes</b>
Sensors per probe	1 [75]	1 - 4	1 - 14
Sensors per thermometry system	8 - 16 [75]	8 - 32 [76]	8 - 196 [74, 77]
Electromagnetically compatible	Yes	Yes	Yes <sup>1</sup>
Continuous temperature measurement	Yes	Yes	No <sup>2</sup>

<sup>1</sup> Provided that the probes are positioned perpendicular to the main direction of the EM field and power is turned off for temperature measurement.

<sup>2</sup> Typically, power is turned off every 30 seconds for 3 - 5 seconds to enable undisturbed temperature measurement.

## AIM & THESIS OUTLINE

The general aim of this thesis is to improve treatment delivery of superficial hyperthermia treatment in patients with locoregional recurrent breast cancer. High-resolution thermal monitoring provides better quality assurance during treatment to realize an adequate thermal dose and reduces the occurrence of thermal toxicity. This results in improved treatment quality of patients with locoregional recurrent breast cancer treated with re-irradiation and hyperthermia. To achieve this goal a number of steps are required as outlined below:

In **chapter 2** a systematic review is performed to investigate whether there is a hyperthermia dose-effect relationship in patients with locoregional recurrent breast cancer treated with re-irradiation and hyperthermia. The observational study in **chapter 3** investigates whether there is also a hyperthermia dose-effect relationship in 112 patients with surgically removed locoregional recurrent breast cancer treated with post-operative re-irradiation and superficial hyperthermia at the Amsterdam UMC from 2010 through 2017. **Chapter 4** investigates the relationship between thermal toxicity and the achieved temperature and thermal dose in a retrospective dataset of 262 patients with locoregional recurrent breast cancer, treated with re-irradiation and superficial hyperthermia at the Amsterdam UMC from 2010 through 2014. **Chapter 5** contains a numerical analysis to determine the required number of sensors to adequately monitor the skin surface temperature distribution during superficial hyperthermia treatment. In **chapter 6** the feasibility of two high-resolution thermal monitoring sheets for improved skin surface temperature monitoring during superficial hyperthermia is assessed. **Chapter 7** describes the influence of the most feasible high-resolution thermal monitoring sheet on applicator performance, together with the first clinical application in 10 patients with locoregional recurrent breast cancer treated with re-irradiation and superficial hyperthermia. Finally, **chapter 8** contains a general discussion on the current status of thermal monitoring during superficial hyperthermia and the challenges in its measurement methods, as well as future directions of research.

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