



UvA-DARE (Digital Academic Repository)

Improving superficial hyperthermia treatment

Temperature matters

Bakker, A.

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].

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

CHAPTER 4

THERMAL SKIN DAMAGE DURING RE-IRRADIATION AND HYPERTHERMIA IS TIME-TEMPERATURE DEPENDENT

Akke Bakker
M. Willemijn Kolff
Rebecca Holman
Caspar M. van Leeuwen
Linda Korshuize-van Straten
Rianne de Kroon-Oldenhof
Coen R.N. Rasch
Geertjan van Tienhoven
Hans Crezee

Published in Int J Radiation Oncol Biol Phys 2017; 98(2) 392-399, doi: 10.1016/j.ijrobp.2017.02.009

ABSTRACT

Background: During re-irradiation plus hyperthermia for recurrent breast cancer, thermal skin damage (TSD) occurs in a median of 21.4 % of patients. TSD presents as a 2nd degree burn and may result in long-term ulceration. Current clinically used temperature threshold values are based on healthy human skin data. Patients with recurrent breast cancer have had previous surgery and/or irradiation. Scar tissue, particularly when irradiated, is less perfused than healthy skin and might be more at risk of developing TSD.

Methods: In this observational study, temperature characteristics of HT sessions were analyzed in 262 patients with recurrent breast cancer treated in the AMC from 2010 through 2014 with re-irradiation and weekly hyperthermia for one hour. Skin temperature was measured using a median of 42 (range 29 - 82) measurement points per hyperthermia session.

Results: Sixty-eight patients (26 %) developed 79 sites of TSD; after the first ($n = 26$), second ($n = 17$), third ($n = 27$) and fourth ($n = 9$) hyperthermia session. 70 % of TSD occurred on or near scar tissue. Scar tissue reached higher temperatures than other skin tissue ($0.4\text{ }^{\circ}\text{C}$, $p < 0.001$). One-hundred-and-two measurement points corresponded to actual TSD sites in 35/79 sessions where TSD developed. TSD sites had much higher maximum temperatures than non-TSD sites ($2.8\text{ }^{\circ}\text{C}$, $p < 0.001$). Generalized linear mixed models showed that the probability of TSD is related to temperature and thermal dose values ($p < 0.001$) and that scar tissue is more at risk (odds ratio 0.4, $p < 0.001$). Limiting the maximum temperature of a measurement point to $43.7\text{ }^{\circ}\text{C}$ would mean that the probability of observing TSD was at most 5 %.

Conclusion: Thermal skin damage during re-irradiation plus hyperthermia for recurrent breast cancer was related to higher local temperatures and time-temperature isoeffect levels. Scar tissue reached higher temperatures than other skin tissue, and TSD occurred at lower temperatures and thermal dose values in scar tissue compared with other skin tissue. Indeed, TSD developed often on and around scar tissue from previous surgical procedures.

INTRODUCTION

Based on clinical evidence [1] re-irradiation with hyperthermia (reRT-HT) is standard therapy for patients with locoregional recurrent breast cancer in previously irradiated area in the Netherlands [2] and other countries [3, 4]. Hyperthermia involves elevation of the temperature of the re-irradiated area to 40 - 44 °C for one hour and is given once or twice weekly during the re-irradiation series. In poorly perfused areas, such as scar tissue or fibrosis, hotspots with temperatures exceeding 43 °C may occur. Scar tissue and fibrosis are present in most recurrent breast cancer patients since they have had previous surgery and/or irradiation. Pain sensation may be compromised in these areas, hotspots are therefore not always noticed by the patient. These hotspots may lead to acute thermal skin damage (TSD), presenting as 2nd degree burns, potentially becoming ulcers. Typically, these ulcers take a long time to heal and may require additional therapy. Thus, there is a need for clear guidelines on temperature limits to prevent the occurrence of TSD.

In 1947 Moritz and Henriques [5] investigated time-temperature thresholds for thermal injury of human skin in 8 subjects in the temperature range 44 - 60 °C. They found a clear exponential time-temperature relationship for complete necrosis of the skin. Heating human skin to 44 °C for 5 h resulted in mild hyperemia in two subjects, while heating at 44 °C for 6 h resulted in complete epidermal necrosis. Stoll and Greene [6] found that the pain threshold occurs at about 45 °C in three human subjects, much lower than the skin damage threshold. The onset of skin damage depended strongly on both temperature and time, for example the threshold of a blister was found at 53 °C for 30 seconds. Partially based on these studies [5, 6], Sapareto and Dewey [7] proposed to convert time-temperature data achieved during hyperthermia to cumulative equivalent minutes at 43 °C (CEM43). More recently, Greenhalgh et al. [8] investigated the TSD threshold in 18 patients undergoing removal of redundant skin in the temperature range of 42.5 - 44 °C. Heating well-perfused skin for 8 h at 43 °C did not result in TSD. Using numerical simulations, Viglianti et al. [9] found the threshold for a significant decrease in cell viability at the basal cell layer to be at 100 CEM43.

However, patients with recurrent breast cancer treated with reRT-HT have had previous irradiation, and usually previous surgery and/or chemotherapy. The resulting scar tissue as well as fibrotic tissue is less perfused than normal skin [10, 11]. In our institute, the presently allowed maximum temperatures during superficial hyperthermia treatment for heavily pre-treated skin are based on the data of Moritz and Henriques [5] and Stoll and Greene [6] of healthy human skin and may therefore underestimate the risk on thermal injury for this patient group.

The complication rate from HT in breast cancer patients has been shown to increase with a higher thermal dose [12–17]. Complications can be avoided by implementing a lower normal tissue temperature limit, but unfortunately this conflicts with the therapeutic effect as treatment outcome is also positively related to thermal dose, i.e. the higher the tumor temperature the better the tumor response [17–28]. It is thus important to know the time-temperature relationship of TSD in recurrent breast cancer to minimize toxicity and maximize treatment response.

Aim of our study was to investigate the relationship of TSD to time-temperature isoeffect levels for patients with breast cancer recurrence treated with reRT-HT at the AMC. To this end, temperatures at the actual site of TSD immediately prior to the development of TSD were compared to temperatures measured during other hyperthermia sessions, a distinction was made between scar and other skin. Furthermore, we investigated whether the treatment history of previous treatments (scar tissue) is a risk factor for TSD.

METHODS

Patients with locoregional recurrent breast cancer treated with reRT-HT at the AMC from 2010 through 2014 were included. Patients were treated with 8 x 4 Gy twice a week in four weeks with weekly hyperthermia sessions per tumor area. Hyperthermia treatment objectives were to elevate intratumoral temperatures to a minimum of 41 °C for 1 h while maintaining maximum normal tissue temperatures below 44 °C. Hyperthermia started within 30 - 60 minutes following radiation therapy. Conformal Contact Flexible Microstrip Applicators (CFMA, Istok, Fryazino, Russia) operating at 434 MHz were used (1 - 2 applicators, effective field size 64 - 702 cm²). A flat water bag containing temperature controlled circulating deionized water was positioned between antenna and skin [29–31], with a heat transfer coefficient varying between 350 - 850 W m⁻² °C⁻¹ depending on antenna type. Water temperature was adjusted to maintain a therapeutic temperature level of 42 °C as recorded on the skin surface.

Tumor and normal tissue temperature monitoring was performed during treatment with multisensory copper-constantan thermocouple probes (ELLA-CS, Hradec Králové, Czech Republic) placed on the skin, perpendicular to the dominant direction of the electromagnetic field to avoid selfheating of the thermocouple probes [32]. Power of the microwave device was on for 25 seconds and then off for 5 seconds to enable undisturbed temperature measurements. At least seven 7-point thermocouple probes were placed in or at the target area. Typically one 7-point thermocouple probe was positioned invasively, 2 - 3 probes were placed on areas with low-perfusion, such as scar tissue, and the remaining probes were spread out over the target area. This resulted in at least 42 measurement points located on the skin. Temperature measurements were performed every 30 seconds.

Data analysis

In patients who developed TSD, temperature characteristics of sessions during which TSD developed were compared to sessions before and after TSD occurrence. Patients who developed TSD were thus their own control group to compare session temperature characteristics: the maximum temperature (T_{max}), T10, T50, and T90 (the temperature exceeded by 10, 50 and 90 % of all measurement points during the pre-heating and steady state of the session, respectively).

Furthermore, the temperature data were analyzed per measurement point and the tissue type of each point was characterized as either invasive-, scar tissue-, or other target skin tissue. Measurement points positioned on a TSD site were identified. Temperature characteristics of individual measurement points on a TSD site were compared to measurement points on unaffected skin during sessions before and after the occurrence of TSD. Per measurement

point the maximum temperature ($T_{t_{max}}$), T_{t10} , T_{t50} , T_{t90} (the temperature exceeded by 10, 50 and 90 % of all temperature measurements per measurement point during the pre-heating and steady state of the session, respectively) and the cumulative equivalent minutes at 43 °C (CEM43) were calculated,

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

where Δt = time interval (min), T = average temperature during time interval Δt (°C) and R represents the sensitivity to temperature change. R is commonly set to 0.25 for $T < 43$ °C and 0.5 for $T \geq 43$ °C [7, 33, 34]. When there was temporal variation in the temperature of a measurement point, the time at each temperature was determined and the CEM43 summed. The resultant CEM43 value represents the cumulative equivalent thermal isoeffect dose during the entire history of exposure [33, 34].

The time-temperature distribution of measurement points on TSD and on unaffected skin were compared per tissue type. The probability of TSD was calculated for intervals (bins) of $T_{t_{max}}$ and CEM43.

Statistical analysis

Patient treatment history was presented using descriptive statistics. Logistic regression was used to examine associations between the occurrence of TSD and previous chemotherapy, previous surgery, number of surgical procedures and type of disease at referral for reRT-HT; microscopic or macroscopic. Firstly, we used univariate logistic regression. Then we performed a stepwise backwards selection to obtain a multivariable model. Subgroup analyses were done, no corrections for multiple testing were performed.

A generalized linear mixed model (GLMM) was developed to examine associations between treatment characteristics and TSD. Treatment characteristics may vary between patients and between treatment weeks, therefore we used random intercepts for patients and for weeks (for details, see supplementary material). Parameter estimates and 95 % Wald confidence intervals (CI) were reported for fixed effects [35].

Linear mixed models (LMM) with a random intercept for patient were developed to investigate if temperature characteristics of sessions and measurement points were influenced by the presence of TSD, the location of measurement points (TSD site;

scar or other skin) and by timing (session before, during or after TSD). Parameter estimates and 95 % Wald CI were reported for fixed effects. Post-hoc analysis was done to determine differences between sessions before and after TSD.

We used SPSS version 20 to estimate logistic regression parameters and R version 3.3.1 to estimate the parameters in the mixed effects models. A $p \leq 0.05$ was used to determine statistical significance.

RESULTS

In all, 262 women were treated for locoregional recurrent breast cancer with reRT-HT in the AMC from 2010 through 2014. In 38 patients the intact breast was treated and in 211 patients the chest wall, of whom 167 had a primarily closed mastectomy scar, 36 a latissimus dorsi reconstruction and 8 a split skin graft, 13 patients were treated at other sites, such as supraclavicular. Patients were treated with 57.4 ± 13.8 W (mean \pm SD) and a water bolus temperature of 40.5 ± 1.9 °C. Sixty-eight patients (26.0 %) developed one or multiple sites of TSD. Previous chemotherapy was the only variable in the final step of the logistic regression model (Table 1). The model described the relationship between treatment history and TSD well ($\chi^2(6) = 6.151, p = 0.406$). In a subgroup of 211 patients, in whom the chest wall was treated, a history of two or more surgical procedures was associated with the development of TSD ($p = 0.019$).

The location of TSD was mostly (55 cases; 70 %) on or within one cm of scar tissue from previous surgical procedures (Figure 1). Another frequent location was at prominent body parts, such as the breast, axilla or most caudal rib.

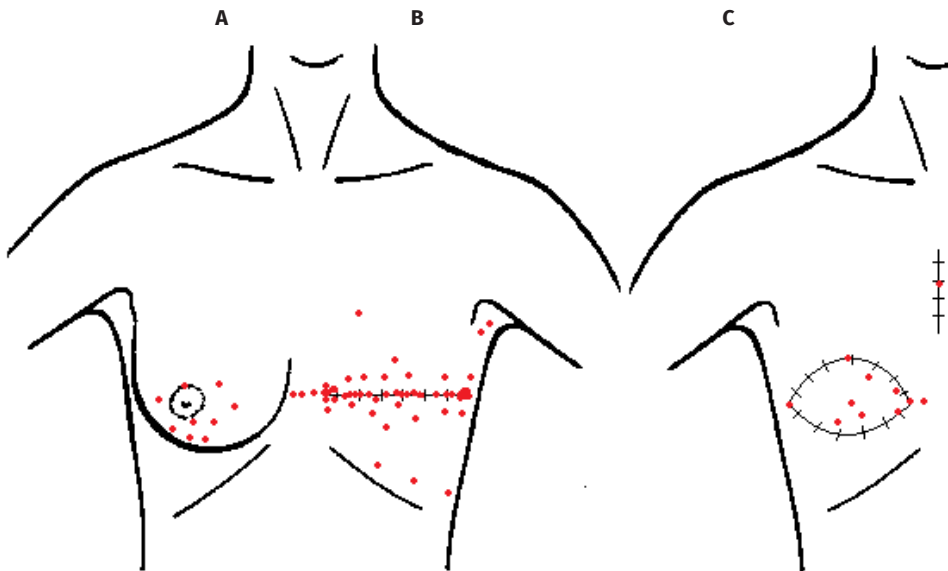


Figure 1. Schematic drawing of the location of thermal skin damage (TSD; red dot). A) depicts an intact breast ($n = 38$), B) a standard mastectomy scar ($n = 167$), C) a latissimus dorsi reconstruction scar ($n = 36$). One patient developed TSD on a cardiac surgery scar.

Table 1. Treatment history of patients with locoregional recurrent breast cancer with and without thermal skin damage (TSD).

Treatment history	Patients (%)		Total (n = 262)	Univariate analysis		Multivariable analysis	
	TSD (n = 68)	No TSD (n = 194)		OR	95 % CI	OR	95 % CI
Type of disease							
Microscopic	31 (46 %)	85 (44 %)	116	1.3	0.7 to 2.5		
Macroscopic	37 (54 %)	109 (56 %)	146				
Previous radiotherapy (yes)	68	194	262				
Previous chemotherapy							
Yes	32 (47 %)	131 (69 %)	163	2.2	1.3 to 4.0	2.4	1.3 to 4.1
No	36 (53 %)	63 (31 %)	99				
Previous surgery							
Yes	67 (99 %)	183 (94 %)	250	0.4	0.0 to 3.5		
No	1 (1 %)	11 (6 %)	12				
Number of surgical procedures							
0 or 1	12 (18 %)	57 (29 %)	69	1.8	0.8 to 3.9		
2 or more	56 (82 %)	137 (71 %)	193				

Abbreviations: CI = confidence interval; OR = odds ratio.

Odds ratios and corresponding 95 % CIs are reported for univariate analysis and for the final step of multivariable analysis, which included previous chemotherapy.

The 68 patients who developed TSD underwent a total of 335 hyperthermia sessions (median of 4 sessions per patient); in 51 of the 335 sessions a different target region than the region where TSD occurred was treated. These sessions were not included in the analysis. There were 79 incidences of TSD and they occurred at the first (26), second (17), third (27) and fourth (9) hyperthermia session, respectively. LMMs indicated that T_{\max} and T10 were not the same for sessions before TSD, sessions that resulted in TSD and sessions after TSD ($p < 0.001$, Figure 2). The sessions of patients without TSD had a significantly lower T_{\max} and T10 than the sessions where TSD occurred ($p < 0.001$).

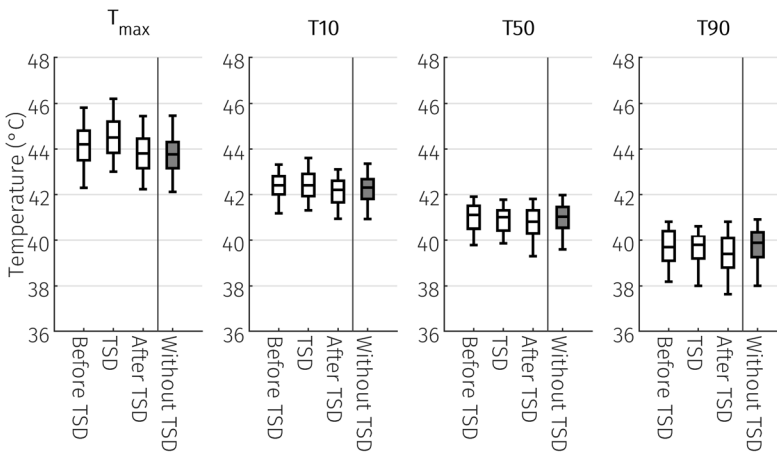


Figure 2. Tukey boxplots of hyperthermia session temperature characteristics (median, 25th, 75th percentile, minimum and maximum) of sessions before (85), during (79) and after (120) thermal skin damage (TSD) occurred. Grey boxplots indicate sessions of patients without TSD (851).

During a hyperthermia session the temperature was measured using on average 42 (range 29 - 82) measurement points on the skin, of which 26 % (2779) were located on scar tissue. Scar tissue reached higher temperatures than other skin tissue (0.4 °C, 95 % CI 0.4 to 0.5 °C, $p < 0.001$), see Figure 3. Figure 1 in the supplementary materials shows a similar plot solely for measurement points on TSD sites. In 35 out of 79 sessions, at least one measurement point (102 in total) was present at the site where TSD developed. The LMM indicated that TSD sites had higher temperatures and thermal dose values than measurement points before (4423) and after (6164) TSD (2.8 °C, 95% CI 2.6 to 3.0 °C; 94.4 CEM43, 95 % CI 90.4 to 98.5 CEM43, $p < 0.001$). Post-hoc analysis showed that temperatures and thermal dose values were significantly lower in sessions after TSD than in sessions before TSD (-0.3 °C, 95 % CI -0.3 to -0.2 °C, $p < 0.001$). TSD occurred, relative to the size of the scar and the number of measurement points, more often on scar tissue ($p < 0.001$).

The average time-temperature distribution of measurement points on all sites during sessions before and after TSD and measurement points on TSD sites is shown in Figure 4. A distinction is made between scar and other skin tissue. Figure 2 in the supplementary materials shows a similar plot solely for measurement points on TSD sites.

In the GLMM, the measurement point characteristics Tt_{max} and tissue type had an OR (95 % CI) of 2.2 (1.9 to 2.5) and -1.1 (-1.8 to -0.5), respectively. The GLMM for CEM43 and tissue type had an OR of 7.1 (5.9 to 8.3) and -1.0 (-1.6 to -0.3), respectively. The fitted logit function for scar and other skin tissue on the probability of Tt_{max} and CEM43 is displayed in Figure 5. According to these models, limiting the maximum temperature of scar tissue at any given measurement point to 43.7 °C and the CEM43 to 66 min would mean that the probability of observing TSD at that measurement point was at most 5 %.

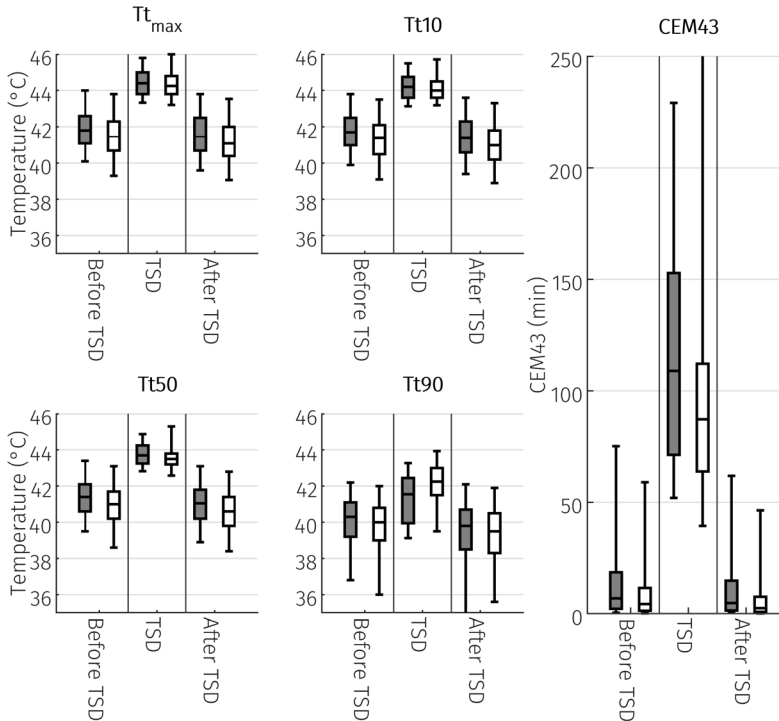


Figure 3. Tukey boxplots of temperature and thermal dose values (median, 25th, 75th percentile, minimum and maximum) of patients with thermal skin damage (TSD) calculated from individual skin measurement points at TSD sites (102) during the development of TSD and at all sites during sessions before (4423) and after (6164) TSD. Scar tissue is displayed with grey boxplots, other skin tissue is displayed with white boxplots.

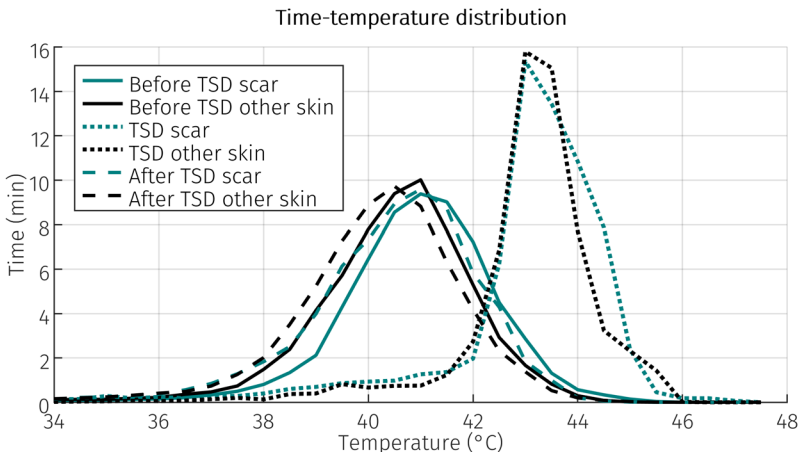


Figure 4. The average time-temperature distribution of all measurement points of patients with TSD during sessions before TSD ($n = 958$, $n = 3465$ for scar and other skin, respectively), sessions after TSD ($n = 1203$, $n = 4961$ for scar and other skin, respectively) and at TSD sites during the session where TSD developed (TSD; $n = 44$, $n = 58$ for scar and other skin, respectively).

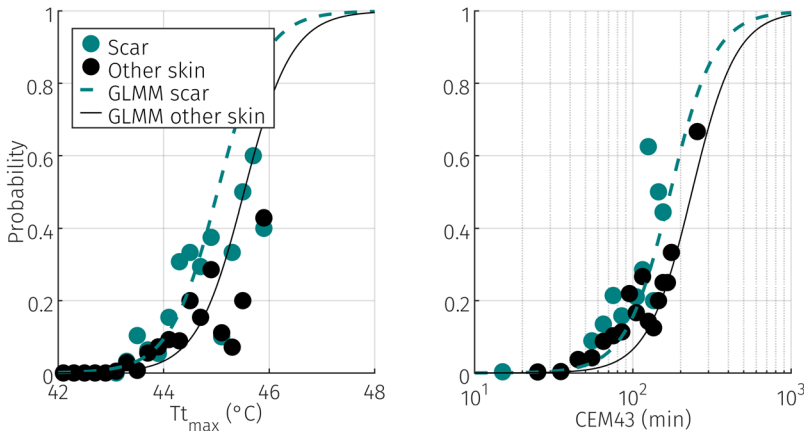


Figure 5. The probability of thermal skin damage (TSD) at a measurement point on the skin related to its maximum temperature (left), and cumulative equivalent minutes at 43 °C (CEM43; right) during the hyperthermia session. The actual data (TSD sites ($n = 102$) vs. measurement points before (4423) and after (6164) TSD in 30 bins) are presented with circles, the lines indicate the generalized linear mixed model (GLMM), scar tissue is displayed in green, other skin tissue in black.

DISCUSSION

Earlier reported percentages of TSD in patients with recurrent breast cancer are median 21.4 % (range 2.3 - 67 %) [14, 16, 17, 24, 26, 28, 36–47], compared to 26 % in our series. Patients in our series with a recurrence on the chest wall (n = 211) who previously had two or more surgical procedures in the heated area had a higher risk of TSD ($p = 0.019$), as was found by Linthorst et al. [16]. We showed that TSD occurred significantly more often in scar tissue than in other skin tissue. In contrast to the findings of Linthorst et al. [15] we found a significant association between previous chemotherapy and less TSD. We have no explanation for this association.

In this study, scar tissue reached higher temperatures than other skin tissue (0.4 °C, $p < 0.001$, Figure 3 - 5), which can be attributed to poorer perfusion of scar tissue resulting in lower heat removal. An additional explanation for the occurrence of TSD on and around scars may be impaired skin sensitivity around the scar due to loss of small sensory nerves, this results in less pain complaints and therefore no reduction of power during treatment. Furthermore, a difference in threshold was shown for the development of TSD between scar and other skin tissue (Figure 5).

To our knowledge no analysis linking temperatures to exact locations of TSD has been published before. In the literature, solely overall maximum temperatures of hyperthermia sessions have been related to thermal toxicity in recurrent breast cancer patients [12–17]. The temperature thresholds found by Linthorst et al. [16] suggest that TSD occurs at lower temperatures than our data indicate; they found TSD in 15 % of the patients who had a T_{\max} lower than 43 °C. However, they may have systematically underestimated the actual temperature at the TSD site prior to the development of TSD as they used only 24 measurement locations. This may also be the case in papers that reported no correlation between thermal toxicity and thermal parameters [28, 36, 44].

Our data showed that the probability of TSD increases with higher temperature and dose values (Figure 5). However, CEM43 is calculated from skin temperatures, which is in our study an underestimation of CEM43 at the basal cell layer. To gain a deeper heat penetration in tissue, our water bolus was cooler (40.5 °C) than the skin temperature during treatment. This results in a temperature peak not at the skin but subcutaneously [25, 48]. In scar tissue, this difference may be even stronger. The maximum CEM43 will be at the surface when using a higher water bolus temperature, however, this treatment strategy results in less penetration depth. When this higher water bolus temperature strategy is used the apparent threshold will be higher than the thresholds found in this study. This also explains why higher CEM43 damage threshold values were reported in literature: values for skin vary

from 21 - 40 CEM43 for minor damage to skin function [5, 6, 33], whereas Greenhalgh et al. [8] found that 240 CEM43 caused no damage and heat between 480 - 960 CEM43 caused immediate burns, to 288 - 15000 CEM43 for complete necrosis [5, 6, 33].

Figure 5 can be used to limit the occurrence of TSD, by determining a maximum acceptable temperature in the target area. The models in Figure 5 are based on temperature measurements at the exact location of TSD. Despite using a high number (42) of measurement points, temperature measurements were only available for 44 % of the TSD sites. In hyperthermia centers where less thermometry is used it is even less likely to measure at the exact location of TSD, in which case the threshold values should be taken more conservatively. TSD mostly occurs on and around scar tissue, therefore we recommend to monitor those areas in particular when less thermometry is available. An important disadvantage is that when the maximum allowed temperature is restricted too much, the risk of underdosage of the target area is increased. This is reflected in the lower temperatures measured in the sessions after the development of TSD. Apparently, the hyperthermia technicians became more cautious after TSD, resulting in lower temperatures. Modification of the surface temperature can be used to reduce the risk for TSD while maintaining the thermal dose and taking the depth of tumor involvement into account [25, 48]. As mentioned previously, a higher thermal dose yields a higher tumor response [17, 18, 27, 28, 19–26]. Future investigations should focus on determining the optimal thermal dose to achieve the best tumor response and the least side effects.

Limitations

Temperature measurements during hyperthermia are influenced by the type of temperature measurement, the hyperthermia equipment and the settings of the equipment. In this study we measured surface temperatures which do not give an accurate estimate of the potentially higher temperature at the level of the basal layer of the epithelium [33, 49]. Settings of the hyperthermia equipment, such as the flow rate and temperature of the water bolus [50], influence (sub-) cutaneous temperatures. Therefore, thresholds found in this study may need to be modified when different hyperthermia equipment, protocols or temperature measurement techniques are used.

CONCLUSION

Thermal skin damage during re-irradiation plus hyperthermia for recurrent breast cancer was related to higher local temperatures and time-temperature isoeffect levels. Scar tissue reached higher temperatures than other skin tissue. Furthermore, thermal skin damage occurred at lower temperatures and thermal dose values in scar tissue compared to other skin tissue. Indeed, thermal skin damage developed often on and around scar tissue from previous surgical procedures.

REFERENCES

- [1] Datta NR, Gómez Ordóñez S, Gaipal US, et al. Local hyperthermia combined with radiotherapy and/or chemotherapy: Recent advances and promises for the future. *Cancer Treat Rev* 2015; 41: 742–753.
- [2] Breast cancer guideline version 2.0, http://richtlijndatabase.nl/en/richtlijn/breast_cancer/breast_cancer.html (2012, accessed 21 March 2020).
- [3] Harms W, Budach W, Dunst J, et al. DEGRO practical guidelines for radiotherapy of breast cancer VI: Therapy of locoregional breast cancer recurrences. *Strahlentherapie und Onkol* 2016; 192: 1–10.
- [4] Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Ann Oncol* 2014; 25: 1871–1888.
- [5] Moritz AR, Henriques FC. Studies of thermal injury II. The relative importance of time and surface temperature in the causation of thermal burns. *Am J Pathol* 1947; 23: 695–720.
- [6] Stoll AM, Greene LC. Relationship between pain and tissue damage due to thermal radiation. *J Appl Physiol* 1959; 14: 373–382.
- [7] Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. *Int J Radiat Oncol Biol Phys* 1984; 10: 787–800.
- [8] Greenhalgh DG, Lawless MB, Chew BB, et al. Temperature threshold for burn injury: An oximeter safety study. *J Burn Care Rehabil* 2004; 25: 411–415.
- [9] Viglianti BL, Dewhirst MW, Abraham JP, et al. Rationalization of thermal injury quantification methods: Application to skin burns. *Burns* 2014; 40: 896–902.
- [10] Gurtner GC, Werner S, Barrandon Y, et al. Wound repair and regeneration. *Nature* 2008; 453: 314–321.
- [11] O’Sullivan B, Levin W. Late radiation-related fibrosis: Pathogenesis, manifestations, and current management. *Semin Radiat Oncol* 2003; 13: 274–289.
- [12] Ben-Yosef R, Kapp DS. Persistent and/or late complications of combined radiation therapy and hyperthermia. *Int J Hypertherm* 1992; 8: 733–745.
- [13] Kapp DS, Cox RS, Fessenden P, et al. Parameters predictive for complications of treatment with combined hyperthermia and radiation therapy. *Int J Radiat Oncol Biol Phys* 1992; 22: 999–1008.
- [14] Lindholm C-E, Kjellen E, Nilsson P, et al. Prognostic factors for tumour response and skin damage to combined radiotherapy and hyperthermia in superficial recurrent breast carcinomas. *Int J Hypertherm* 1995; 11: 337–355.
- [15] Linthorst M, van Geel AN, Baaijens M, et al. Re-irradiation and hyperthermia after surgery for recurrent breast cancer. *Radiother Oncol* 2013; 109: 188–193.
- [16] Linthorst M, Baaijens M, Wiggenraad R, et al. Local control rate after the combination of re-irradiation and hyperthermia for irresectable recurrent breast cancer: Results in 248 patients. *Radiother Oncol* 2015; 117: 217–222.
- [17] Seegenschmiedt MH, Karlsson UL, Sauer R, et al. Superficial chest wall recurrences of breast cancer: Prognostic treatment factors for combined radiation therapy and hyperthermia. *Radiology* 1989; 173: 551–558.
- [18] Cox RS, Kapp DS. Correlation of thermal parameters with outcome in combined radiation therapy-hyperthermia trials. *Int J Hypertherm* 1992; 8: 719–732.
- [19] Refaat T, Sachdev S, Sathiaselan V, et al. Hyperthermia and radiation therapy for locally advanced or recurrent breast cancer. *Breast* 2015; 24: 418–425.

- [20] Sherar M, Liu FF, Pintilie M, et al. Relationship between thermal dose and outcome in thermoradiotherapy treatments for superficial recurrences of breast cancer: Data from a phase III trial. *Int J Radiat Oncol Biol Phys* 1997; 39: 371–380.
- [21] Gabriele P, Ferrara T, Baiotto B, et al. Radio hyperthermia for re-treatment of superficial tumours. *Int J Hyperth* 2009; 25: 189–198.
- [22] Gonzalez Gonzalez D, van Dijk JD, Blank LE. Chestwall recurrences of breast cancer: Results of combined treatment with radiation and hyperthermia. *Radiother Oncol* 1988; 12: 95–103.
- [23] Hand JW, Machin D, Vernon CC, et al. Analysis of thermal parameters obtained during phase III trials of hyperthermia as an adjunct to radiotherapy in the treatment of breast carcinoma. *Int J Hyperth* 1997; 13: 343–364.
- [24] Hiraoka M, Nishimura Y, Nagata Y, et al. Site-specific phase I, II trials of hyperthermia at Kyoto University. *Int J Hyperth* 1994; 10: 403–410.
- [25] Lee HK, Antell AG, Perez CA, et al. Superficial hyperthermia and irradiation for recurrent breast carcinoma of the chest wall: Prognostic factors in 196 tumors. *Int J Radiat Oncol Biol Phys* 1998; 40: 365–375.
- [26] Phromratanapongse P, Steeves RA, Severson SB, et al. Hyperthermia and irradiation for locally recurrent previously irradiated breast cancer. *Strahlentherapie und Onkol* 1991; 167: 93–97.
- [27] van der Zee J, van Putten WLJ, van den Berg AP, et al. Retrospective analysis of the response of tumours in patients treated with a combination of radiotherapy and hyperthermia. *Int J Hyperth* 1986; 2: 337–349.
- [28] van der Zee J, van der Holt B, Rietveld PJM, et al. Reirradiation combined with hyperthermia in recurrent breast cancer results in a worthwhile local palliation. *Br J Cancer* 1999; 79: 483–490.
- [29] Gelvich EA, Mazokhin VN. Contact flexible microstrip applicators (CFMA) in a range from microwaves up to short waves. *IEEE Trans Biomed Eng* 2002; 49: 1015–1023.
- [30] Correia D, Kok HP, De Greef M, et al. Body conformal antennas for superficial hyperthermia: The impact of bending contact flexible microstrip applicators on their electromagnetic behavior. *IEEE Trans Biomed Eng* 2009; 56: 2917–2926.
- [31] Kok HP, De Greef M, Correia D, et al. FDTD simulations to assess the performance of CFMA-434 applicators for superficial hyperthermia. *Int J Hyperth* 2009; 25: 462–476.
- [32] de Leeuw AAC, Crezee J, Lagendijk JJW. Temperature and SAR measurements in deep-body hyperthermia with thermocouple thermometry. *Int J Hyperth* 1993; 9: 685–697.
- [33] Dewhirst MW, Viglianti BL, Lora-Michiels M, et al. Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. *Int J Hyperth* 2003; 19: 267–294.
- [34] Yarmolenko PS, Moon EJ, Landon C, et al. Thresholds for thermal damage to normal tissues: An update. *Int J Hyperth* 2011; 27: 320–343.
- [35] Burnham KP, Anderson DR. Formal Inference From More Than One Model: Multimodel Inference (MMI). In: *Model selection and multimodel inference: a practical information-theoretic approach*. Springer-Verlag New York, 2002, pp. 149–205.
- [36] Linthorst M, van Rhooen GC, van Geel AN, et al. The tolerance of reirradiation and hyperthermia in breast cancer patients with reconstructions. *Int J Hyperth* 2012; 28: 267–277.
- [37] Oldenburg S, van Os RM, van Rij CM, et al. Elective re-irradiation and hyperthermia following resection of persistent locoregional recurrent breast cancer: A retrospective study. *Int J Hyperth* 2010; 26: 136–144.
- [38] Oldenburg S, Griesdoorn V, Van Os R, et al. Reirradiation and hyperthermia for irresectable locoregional recurrent breast cancer in previously irradiated area: Size matters. *Radiother Oncol* 2015; 117: 223–228.

- [39] Perez CA, Kuske RR, Emami B, et al. Irradiation alone or combined with hyperthermia in the treatment of recurrent carcinoma of the breast in the chest wall: A nonrandomized comparison. *Int J Hyperth* 1986; 2: 179–187.
- [40] van der Zee J, Treurniet-Donker AD, The SK, et al. Low dose reirradiation in combination with hyperthermia: A palliative treatment for patients with breast cancer recurring in previously irradiated areas. *Int J Radiat Oncol Biol Phys* 1988; 15: 1407–1413.
- [41] Vernon CC, Hand JW, Field SB, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: Results from five randomized controlled trials. International Collaborative Hyperthermia Group. *Int J Radiat Oncol Biol Phys* 1996; 35: 731–744.
- [42] Wahl AO, Rademaker A, Kiel KD, et al. Multi-institutional review of repeat irradiation of chest wall and breast for recurrent breast cancer. *Int J Radiat Oncol Biol Phys* 2008; 70: 477–484.
- [43] Welz S, Hehr T, Lamprecht U, et al. Thermoradiotherapy of the chest wall in locally advanced or recurrent breast cancer with marginal resection. *Int J Hyperth* 2005; 21: 159–167.
- [44] Engin K, Leeper DB, Tupchong L, et al. Thermoradiation therapy for superficial malignant tumors. *Cancer* 1993; 72: 287–296.
- [45] Hehr T, Lamprecht U, Glocker S, et al. Thermoradiotherapy for locally recurrent breast cancer with skin involvement. *Int J Hyperth* 2001; 17: 291–301.
- [46] Jones EL, Oleson JR, Prosnitz LR, et al. Randomized trial of hyperthermia and radiation for superficial tumors. *J Clin Oncol* 2005; 23: 3079–3085.
- [47] Li G, Mitsumori M, Ogura M, et al. Local hyperthermia combined with external irradiation for regional recurrent breast carcinoma. *Int J Clin Oncol* 2004; 9: 179–183.
- [48] van der Gaag ML, de Bruijne M, Samaras T, et al. Development of a guideline for the water bolus temperature in superficial hyperthermia. *Int J Hyperth* 2006; 22: 637–656.
- [49] Buettner K. Effects of extreme heat and cold on human skin. II. Surface temperature, pain and heat conductivity in experiments with radiant heat. *J Appl Physiol* 1951; 3: 703–713.
- [50] Lee ER, Kapp DS, Lohrbach A, et al. Influence of water bolus temperature on measured skin surface and intradermal temperatures. *Int J Hyperth* 1994; 10: 59–72.

SUPPLEMENTARY MATERIALS

Methods generalized linear mixed model

A generalized linear mixed model (GLMM) was developed with the lme4 package (version 1.1-12) in R (version 3.3.1) to identify an association between treatment characteristics and thermal skin damage (TSD) in patients with recurrent breast cancer treated with re-irradiation plus hyperthermia. Not all patients may be equally prone to developing TSD. Similarly the accumulation of radiation dose and/or thermal stresses is not equal throughout the treatment weeks. Hence, patient and treatment week were used as intercept random effects in the GLMM. Fixed effects were temperature characteristics of the sessions (T_{\max} , T10, T50 and T90).

A second GLMM was developed to identify an association between temperature characteristics of measurement points and TSD. Again, patient and week were used as intercept random effects. As fixed effects, tissue type (scar or other skin tissue) was iteratively combined with one of the temperature characteristics of measurement points (Tt_{\max} , Tt10, Tt50, Tt90, CEM43). Because CEM43 is derived from an exponential function it has a distribution with a right skew. Thus a logarithmic transformation (10 base) of CEM43 was done before performing the GLMM, resulting in a linear-log model for CEM43.

Because of the high degree of multicollinearity of temperature characteristics, combinations of multiple temperature characteristics were not tested. Resulting GLMM models were compared, and the best model was selected based on Akaike information criterion (AIC). The fit for both GLMM models was done using maximum likelihood with the Laplace approximation. Since the response variable was binomial (TSD or no TSD), a logit link-function was used. In our analysis, we considered $\Delta AIC > 6$ as sufficient evidence that the quality of a model is lower than the quality of the model with the lowest AIC (similar to a likelihood ratio < 0.05), as suggested by Burnham and Anderson [35]. Odds ratios (OR) of parameter estimates and their 95 % Wald confidence intervals (CI) were reported. Models were compared using analysis of variance (ANOVA).

Results generalized linear mixed model

The first GLMM was based on temperature characteristics of 284 hyperthermia sessions. AIC scores for the models are displayed in Supplementary Table 1. The final model included the temperature characteristic T_{\max} . The OR for T_{\max} was 1.6 (95 % CI 1.2 to 2.2). This means that the odds of TSD was multiplied by 1.6 for each 1 °C increase in T_{\max} .

Supplementary Table 1. AIC results of the generalized linear mixed models (GLMM) based on 284 hyperthermia sessions. Patient and treatment week were set as intercept random effect.

GLMM	AIC	Δ AIC
Random effect	337	
Random effect + T_{max}	329	-8
Random effect + T10	334	-3
Random effect + T50	338	+1
Random effect + T90	338	+1

Abbreviations: AIC= Akaike information criterion; T_{max} = maximum temperature; T10, T50, T90= the temperature exceeded by 10 %, 50 % and 90 % of the temperature measurements, respectively.

The second GLMM was based on 10689 measurement points during the 284 sessions. AIC scores for the models are displayed in Supplementary Table 2. The best model included the thermal dose variable CEM43 and tissue type. The OR for CEM43 was 7.1 (95 % CI 5.9 to 8.3) and for tissue type -1.0 (95% CI -1.6 to -0.3). This means that the odds of TSD was multiplied by 7.1 for each $^{10}\log(\text{CEM43})$ increase in CEM43 and by -1.0 when the measurement point was located on other skin tissue.

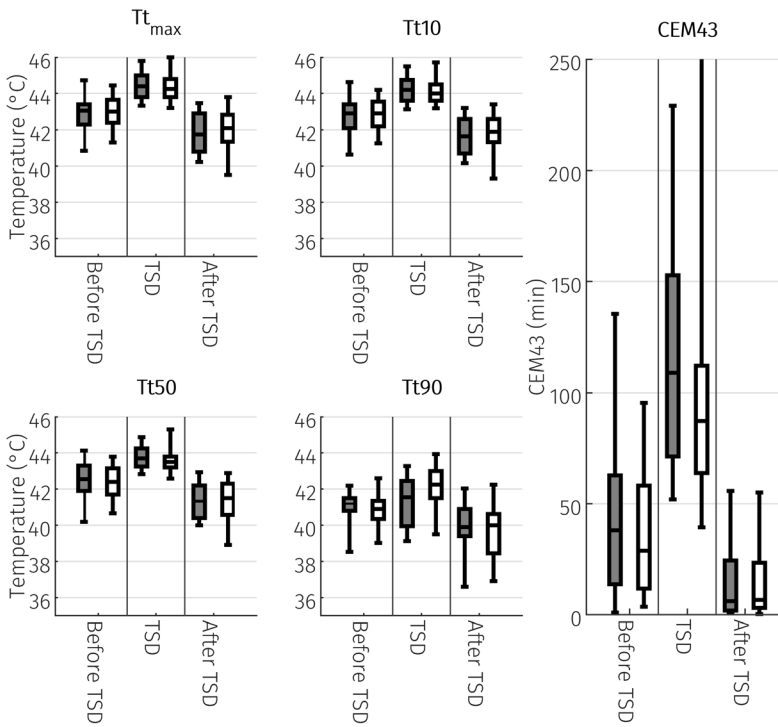
Tt_{max} and CEM43 are temperature characteristics often used in hyperthermia literature and easily reproducible, therefore the results of these models are displayed on the actual data, see Figure 5 in the manuscript. The model with Tt_{max} differed from the best model with Δ AIC = 60. The OR of Tt_{max} was 2.2 (95 % CI 1.9 to 2.5) and tissue type -1.1 (95 % CI -1.8 to -0.5). This means that the odds of TSD was multiplied by 2.2 for each 1 °C increase in Tt_{max} and by -1.1 when the measurement point was located on other skin tissue.

Because the outcome of both GLMMs are binary, under- or overdispersion could not be determined.

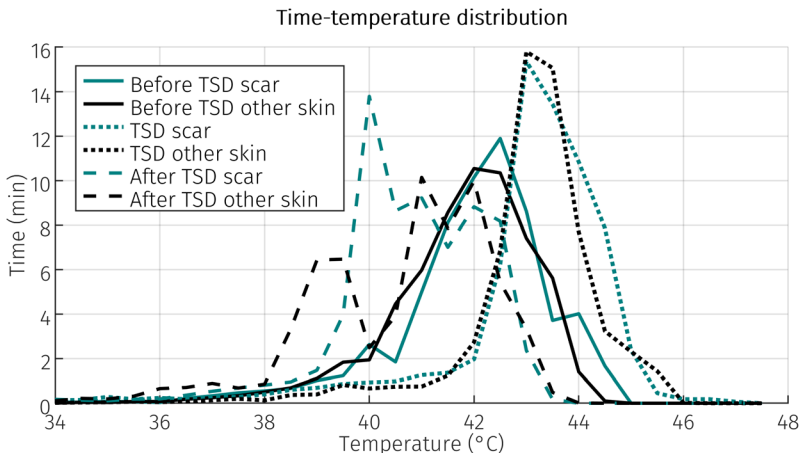
Supplementary Table 2. AIC results of the generalized linear mixed models (GLMM) based on 10689 measurement points. Patient and treatment week were set as intercept random effects.

GLMM	AIC	Δ AIC
Random effects	1033	
Random effects + Tt _{max}	577	-456
Random effects + Tt10	549	-484
Random effects + Tt50	555	-478
Random effects + Tt90	817	-216
Random effects + CEM43	524	-509
Random effects + tissue type	1015	-18
Random effects + tissue type + Tt _{max}	567	-466
Random effects + tissue type + Tt10	541	-492
Random effects + tissue type + Tt50	548	-485
Random effects + tissue type + Tt90	806	-227
Random effects + tissue type + CEM43	517	-516

Abbreviations: AIC= Akaike information criterion; Tt_{max}= The maximum temperature per measurement point; Tt10, Tt50, Tt90= the temperature exceeded by 10 %, 50 % and 90 % of all temperature measurements per measurement point during the pre-heating and steady state of the session, respectively; CEM43 = cumulative equivalent minutes at 43 °C.



Supplementary Figure 1. Tukey boxplots of temperature and thermal dose values (median, 25th, 75th percentile and the minimum and maximum) of patients with thermal skin damage (TSD) calculated from individual skin measurement points at TSD sites ($n = 44$, $n = 58$ for scar and other skin respectively) during the development of TSD and during sessions before ($n = 30$, $n = 76$ for scar and other skin respectively) and after TSD ($n = 54$, $n = 41$ for scar and other skin respectively). Scar tissue is displayed with grey boxplots, other skin tissue is displayed with white boxplots.



Supplementary Figure 2. The average time-temperature distribution of skin measurement points at the TSD sites of patients with TSD, before TSD occurred (n = 30, n = 76 for scar and other skin respectively), when TSD occurred (TSD; n = 44, n = 58 for scar and other skin, respectively) and after TSD occurred (n = 54, n = 41 for scar and other skin respectively).