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Improving superficial hyperthermia treatment

Temperature matters

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CHAPTER 9

SUMMARY

IMPROVING SUPERFICIAL HYPERTHERMIA TREATMENT TEMPERATURE MATTERS

The work presented in this thesis was aimed to improve hyperthermia treatment of patients with locoregional recurrent breast cancer. In the studies presented in this thesis, the effect of hyperthermia dose on clinical outcome was investigated, the rationale for thermal monitoring during hyperthermia was explored and we assessed the spatial resolution requirements for skin surface monitoring during superficial hyperthermia treatment. Additionally, we studied two potential thermal monitoring sheets to improve the spatial resolution of thermal monitoring of the skin surface. Finally, one thermal monitoring sheet was applied in a phase I clinical study.

A recent systematic review of double-arm and single-arm studies showed the sensitizing effect of hyperthermia to radiotherapy for patients with inoperable locoregional recurrent breast cancer. Complete response rate increased from 38.1 % to 60.2 % for patients treated with radiotherapy vs. radiotherapy combined with hyperthermia, respectively. However, the published complete response rate after radiotherapy and hyperthermia varied widely throughout the included studies; from 33 % to 95 %. The systematic review in **chapter 2** showed that the achieved hyperthermia dose was an important factor contributing to this wide variation. Twenty-two articles were included in the systematic review, reporting on 2330 patients with locoregional recurrent breast cancer treated with either neo-adjuvant or adjuvant re-irradiation and hyperthermia. Patients who received high dose hyperthermia had on average 34 % (range 27 - 53 %) more complete responses than patients who received low dose hyperthermia. High dose hyperthermia significantly improved clinical outcome - complete response, local control, and overall survival - and increased thermal toxicity for patients with locoregional recurrent breast cancer treated with re-irradiation and hyperthermia.

Due to recent advances in neo-adjuvant systemic treatment, most patients with locoregional recurrent breast cancer can receive surgery, therefore re-irradiation and hyperthermia is often given in the adjuvant setting to patients that are at risk for re-recurrence. Post-operative re-irradiation with hyperthermia appears to improve local control compared to surgery alone, but evidence from randomized trials is lacking. In **chapter 3** we investigated whether there was a hyperthermia dose-effect relationship in 112 patients with resected locoregional recurrent breast cancer treated with re-irradiation and hyperthermia from 2010 through 2017. The median follow-up period was 43 months (range 1 - 107 months). Three year local control rate was 83 % and three year overall survival was 85 %. Patients that were re-irradiated combined with high dose hyperthermia had significantly improved local control without additional toxicity compared to patients

receiving low dose hyperthermia, three year local control was 92 % vs. 74 %, respectively. Hyperthermia dose had no impact on overall survival or late toxicity. The results of this study show that high dose hyperthermia significantly improves locoregional control, this indirectly suggests the efficacy of post-operative re-irradiation with hyperthermia after resection of locoregional recurrent breast cancer.

In **chapter 4** the relationship between thermal toxicity, i.e. second degree blisters, and hyperthermia dose was retrospectively studied in 262 patients with locoregional breast cancer treated with re-irradiation (8 x 4 Gy) and hyperthermia from 2010 through 2014. Sixty-eight patients developed one or multiple sites of thermal toxicity, in total 79 sites. Thermal toxicity occurred most often on scars from previous surgical procedures (70 %). Scar tissue reached higher temperatures than other skin tissue, likely due to poorer perfusion. Thermal toxicity sites had much higher maximum temperatures than other sites (2.8 °C). Generalized linear mixed models showed that the occurrence of thermal toxicity was related to tissue type (scar vs. no scar), maximum temperature, and hyperthermia dose; i.e. the cumulative equivalent minutes at 43 °C (CEM43).

Despite using a high number of temperature sensors (median 42, range 29 - 82) on the skin surface, temperature measurements were not available for 56 % of the thermal toxicity sites in **chapter 4**. In **chapter 5** we investigated the minimum number of sensors that was required for adequate skin surface monitoring of superficial hyperthermia treatments. Hyperthermia treatments monitored with more than 60 temperature sensors were selected from a database of patients with locoregional recurrent breast cancer treated with re-irradiation (23 x 2 Gy) and hyperthermia from 2015 through 2017. Eighty patients with a total of 400 hyperthermia sessions were included. First, thermal mapping, i.e. cyclically pulling temperature sensors across the target area, was simulated for all 400 treatments. Second, 5000 times a patient and treatment were randomly selected. From this selected patient and treatment, six reduced subsets of temperature sensors with varying size were randomly selected and one complete subset. When small subsets of temperature sensors were used the maximum temperature was underestimated and the minimum temperature overestimated. We found that adequate coverage of the skin temperature distribution during superficial hyperthermia treatment (≤ 0.5 °C deviation) required the use of more than 50 temperature sensors per 400 cm² applicator. However, to adequately measure temperature hotspots on the skin, over 100 sensors per 400 cm² applicator were needed.

Presently, commercial superficial hyperthermia systems offer only eight single sensors. As a result, temperature in most of the skin surface remains unmonitored. Hence, **chapter 6** investigated two high-resolution thermal monitoring sheets that were developed for superficial hyperthermia. The first thermal monitoring sheet was a matrix of thermocouples,

consisting of multisensor thermocouple probes laced through a silicone sheet. The second thermal monitoring sheet had rows of thermistors connected by meandering copper leads, that allow stretching, mounted on stretchable printed circuit board. For both thermal monitoring sheets the accuracy, temperature resolution, stability and thermal conduction errors were considered adequate for clinical use. Both sheets could follow body contours, where the ratio air/water bolus surface was $< 5\%$. When aligned perpendicularly to either 434 or 915 MHz electromagnetic fields the meandering copper tracks used on the stretchable printed circuit board did induce self-heating, while the thermocouple probes did not. The thermocouple matrix was the most promising for clinical application meeting six out of seven of the major requirements for skin surface temperature monitoring when positioned perpendicular to the EM field.

Chapter 7 continued the investigation into the high-resolution thermal monitoring sheet (TMS) consisting of a matrix of 56 thermocouple sensors. The influence of the TMS on the applicator performance was investigated and clinical feasibility was evaluated. Phantom experiments were performed to determine the influence of the TMS on power deposition patterns, applicator efficiency, and heat transfer of the water bolus for 434 MHz and 915 MHz applicators. The clinical feasibility was evaluated in ten women with locoregional recurrent breast cancer. The skin surface temperature during consecutive treatments was monitored alternately with either standard of care thermometry or the TMS. The TMS did not significantly affect the power deposition patterns and applicator efficiency (1 - 2 %), though it reduced the heat transfer of the water boluses (51 - 56 %). This could be compensated by adjusting the water bolus flow. Skin surface temperatures were monitored reliably and no alteration of thermal toxicity was observed. Clinical application of the TMS was feasible.

This thesis is concluded in **chapter 8** with a general discussion on the current status of thermal monitoring during superficial hyperthermia and the challenges in its measurement methods, as well as clinical implications, the position of hyperthermia in oncology, future directions of research, followed by the conclusions.