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Original Article

Post-operative re-irradiation with hyperthermia in locoregional breast cancer recurrence: Temperature matters

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ABSTRACT

Purpose: To investigate the impact of hyperthermia thermal dose (TD) on locoregional control (LRC), overall survival (OS) and toxicity in locoregional recurrent breast cancer patients treated with postoperative re-irradiation and hyperthermia.

Methods: In this retrospective study, 112 women with resected locoregional recurrent breast cancer treated in 2010–2017 with postoperative re-irradiation 8frx4Gy (n = 34) or 23frx2Gy (n = 78), combined with 4–5 weekly hyperthermia sessions guided by invasive thermometry, were subdivided into 'low' (n = 56) and 'high' TD (n = 56) groups by the best session with highest median cumulative equivalent minutes at 43 °C (Best CEM43T50) < 7.2 min and ≥7.2 min, respectively. Actuarial LRC, OS and late toxicity incidence were analyzed. Backward multivariable Cox regression and inverse probability weighting (IPW) analysis were performed.

Results: TD subgroups showed no significant differences in patient/treatment characteristics. Median follow-up was 43 months (range 1–107 months). High vs. low TD was associated with LRC (p = 0.0013), but not with OS (p = 0.29) or late toxicity (p = 0.58). Three-year LRC was 74.0% vs. 92.3% in the low and high TD group, respectively (p = 0.008). After three years, 25.0% and 0.9% of the patients had late toxicity grade 3 and 4, respectively. Multivariable analysis showed that distant metastasis (HR 17.6; 95%CI 5.2–60.2), lymph node involvement (HR 2.9; 95%CI 1.2–7.2), recurrence site (chest wall vs. breast; HR 4.6; 95%CI 1.8–11.6) and TD (low vs. high; HR 4.1; 95%CI 1.4–11.5) were associated with LRC. TD was associated with LRC in IPW analysis (p = 0.0018).

Conclusions: High thermal dose (best CEM43T50 ≥ 7.2 min) was associated with significantly higher LRC for patients with locoregional recurrent breast cancer treated with postoperative re-irradiation and hyperthermia, without augmenting toxicity.

Advances in diagnostic imaging and treatment have improved locoregional control (LRC) and survival of breast cancer patients [1,2]. The growing number of long term breast cancer survivors leads to an increased cumulative incidence of locoregional recurrence or second ipsilateral primary breast cancer [3]. The risk of locoregional breast cancer after treatment of early-stage breast cancer is approximately 0.5% per year [1]. Optimal management of locoregional recurrent breast cancer depends on prognostic factors and previous treatments, and requires multidisciplinary assessment and treatment to achieve durable LRC and prolong disease-free survival [1,3]. Few prospective clinical trials investigated the optimal treatment for patients with locoregional recurrent or second primary breast cancer after prior radiation therapy (RT) [1,3]. Studies showed five-year LRC and overall survival (OS) rates for ipsilateral locoregional recurrent breast cancer of 60–70% and 40–65%, respectively [4–6]. Re-irradiation combined with hyperthermia (HT) can be considered for patients with

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an (isolated) locoregional recurrence or second ipsilateral primary breast cancer [1,3]. HT involves elevation of tumor temperatures to 40–43 °C for one hour and is a clinically proven radiosensitizer, significantly enhancing efficacy of radiation treatment, also for treatment-resistant recurrent tumors [7–10]. A meta-analysis of phase II/III studies showed better complete response rates for breast cancer patients treated with (re)RT-HT (n = 1792) than for patients receiving RT alone (n = 318); 62% versus 38%, respectively [7]. However, evidence for patients with resected locoregional recurrence treated with postoperative re-irradiation with HT for plausible microscopic breast disease is limited. Single-arm observational studies (n = 445) suggest good three-year LRC for postoperative re-irradiation with HT (68–83%) [11–15].

Establishing a thermal dose–effect relationship of HT may help to assess the effectiveness of re-irradiation with HT in patients with locoregional recurrent breast cancer treated with postoperative re-irradiation with HT. Higher intratarget temperatures have been shown to be associated with improved complete response rate and LRC in patients treated with RT-HT for primary locally advanced cervical cancer [16–18], malignant melanoma [19], head and neck tumors [20], rectal cancer [21] and unresectable locoregional recurrent breast cancer [22–26]. Unfortunately, the delivered HT dose is poorly documented in many breast cancer studies [7,13–15,22]. Also, HT is generally performed using microwave antennas combined with a temperature-controlled water bolus on the skin [27,28]. Consequently skin surface temperature data are less representative of tumor temperature and less associated with clinical outcome than invasively measured temperatures [22]. Our institutional treatment guidelines therefore impose implantation of thermometry catheters for intratarget thermometry when possible [29].

In this retrospective cohort study, we analyzed the impact of achieved intratarget temperatures on LRC, OS and toxicity in patients with resected locoregional recurrent or second ipsilateral primary breast cancer treated with postoperative re-irradiation with HT.

Methods

One-hundred-and-twelve patients with surgically removed locoregional recurrent or second ipsilateral primary breast cancer were studied retrospectively. Surgery was performed in different hospitals. Included patients were treated according to national breast cancer guidelines [30,31] with postoperative re-irradiation combined with superficial HT, all guided with invasive thermometry, at the Amsterdam UMC, location AMC between 2010 and 2017. We conducted the study in accordance with the Declaration of Helsinki. Based on the large cohort and the anonymous inclusion of patients, individual informed consent was not deemed necessary by the local Ethics Committee, waivered on Nov 9, 2019; W19_425#19.492.

Exclusion criteria were other tumor types, absence of invasive thermometry, unresectable locoregional recurrent breast cancer, re-irradiation schedules other than 23frx2Gy or 8frx4Gy, concurrent chemotherapy, <4 HT treatment sessions, patients treated with both deep and superficial HT or unavailability of follow-up data (Fig. 1).

Data collection

Data were collected from RT and HT patient charts by one investigator (PTV). Follow-up during re-irradiation with HT consisted of weekly consultation by the treating radiation oncologist or physician assistant. After re-irradiation with HT, follow-up consisted of a telephone consultation one to two weeks after the last re-irradiation fraction, followed by a physical consultation after four to eight weeks. Thereafter, patients had regular follow-up appointments at our institute or their referring hospital. A request for missing data was sent to referring specialists and general practitioners in case of incomplete follow-up data in the patient charts.

Treatment

Radiation therapy

RT consisted of a re-irradiation schedule of 32 Gy in 8 fractions (twice a week) until 2014 [14], or 46 Gy in 23 fractions (5 times a week) from January 2015, combined with HT. Five patients received 32 Gy in 8 fractions after 2014 due to frailty or long travel distance. In January 2015 we changed to 46 Gy in 23 fractions after a consensus meeting with the three radiation oncology departments offering hyperthermia in the Netherlands. Two institutes used 32 Gy in 8 fractions with 4 HT sessions, while one institute used 36 Gy in 12 fractions with 6 HT sessions. We aimed for one schedule for better comparison and joint collection of data since HT is a small field. We chose the 2 Gy fraction schedule with the expectation that this could result in less late side-effects and for better connection with (inter)national institutes using 2 Gy fractionated schedules.

Re-irradiation was delivered using three consecutive different RT planning techniques. Up to mid-2014 the chest wall and/or regional lymph nodes areas were irradiated using two opposing anterior-posterior photon fields (AP-PA) and the anterior chest wall with electrons. This technique was developed in the 1980s and allowed for irradiation of a more extensive area of particularly the lateral chest wall as often needed in the setting of extensive macroscopic disease, while sparing the lungs. However, modern techniques became available with better sparing of organs at risk. From June 2014 our planning technique was therefore converted to an intensity-modulated radiation therapy (IMRT) technique using 5–7 beam angles. Early 2016, IMRT was replaced by volumetric-modulated arc therapy (VMAT) using two (counter)clockwise partial arcs.

For postoperative re-irradiation after salvage mastectomy or local excision (in case of a chest wall recurrence), CTV was defined as the chest wall (original location of the breast) outside the ribcage, including scar of the last resection if this extended beyond the chest wall. The CTV included an area of 3 cm around the original location of the tumor recurrence before treatment in case of a cT4 before treatment. This implies that the CTV was often larger than the postmastectomy chest wall CTV in primary breast cancer, either in the medial, the caudal or the lateral direction depending on the size and location of the initial recurrence. The CTV was extended to 1 cm in all other directions. If the thickness of the chest wall was 1 cm or less, tissue equivalent material of 0.5–1 cm was used to ensure adequate coverage of the CTV and PTV and tissue equivalent material was always applied if the skin was part of the CTV (in case of a cT4 before treatment).

Locoregional irradiation in this setting was performed if the regional lymph nodes were tumor positive initially, and/or after neo-adjuvant systemic treatment and/or surgery. From 2015, CTV's were defined as axilla level 1–4 according to the ESTRO Atlas 2015, 2016 [32]. The internal mammary chain is irradiated only in case of initial macroscopic (for instance FDG PET positive) tumor recurrence. The lungs, heart, spinal cord, thyroid, esophagus, liver, kidneys, and spleen, and the contralateral breast (if applicable) were delineated as organs at risk. We aimed at homogeneous irradiation of the PTV. Previous toxicity of prior radiotherapy was never restricting for treatment planning.

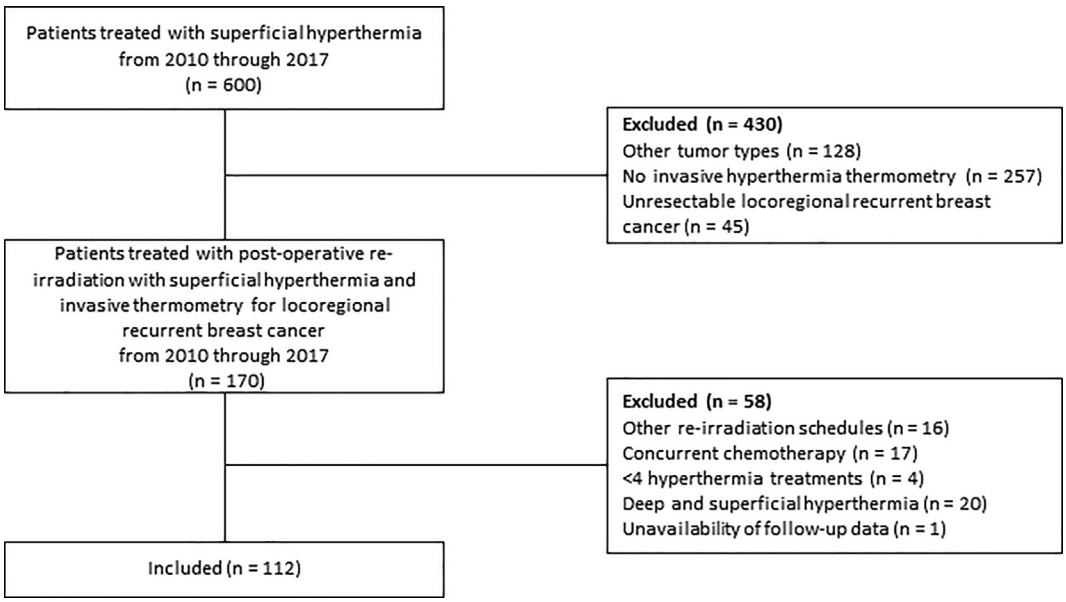

Fig. 1. Study flowchart. *Abbreviations:* HT = hyperthermia.

One-hundred-and-ten patients finished treatment according to protocol. Due to personal reasons two patients received 22 of the 23 scheduled re-irradiation fractions.

Hyperthermia

Re-irradiation was combined with a weekly HT session of the re-irradiation target volume one hour after re-irradiation (61.6 ± 14.3 min). Conformal contact (flexible) microstrip microwave applicators (Istok, Fryazino, Russia; Medlogix, Rome, Italy) operating at 434 MHz were used with a four cm heating depth from the skin (see Supplementary Fig. 1) [33]. A water bag containing temperature-controlled circulating deionized water (39–42 °C) was positioned between applicator and skin [27,33–35]. Depending on the depth of the target area, the water bag temperature and applicator output power were adjusted according to protocol to achieve the desired penetration depth with therapeutic intratarget and skin surface temperatures [28,36]. Extensive temperature monitoring was performed during treatment, exceeding present HT quality assurance guidelines [28]. Seven-sensor copper-constantan thermocouple probes (Volenec RD Inc., Hradec Králové, Czech Republic) were placed invasively (8 ± 5 sensors) for intratarget monitoring of the thermal dose (TD), and probes were placed on the skin surface (80 ± 30 sensors) to prevent temperature hotspots that might result in thermal toxicity [29]. Catheters for intratarget temperature monitoring were routinely placed when the subcutaneous target area had a thickness $\geq$ 1 cm. Temperatures were measured every 30 s [29].

HT treatment aimed at elevating the median intratarget temperature (T50) to a minimum of 41 °C for one hour, while maintaining maximum normal tissue (skin) temperatures below 43.5 °C. This goal T50 $\geq$ 41 °C could not be achieved in approximately 50% of patients, due to incidence of treatment-limiting hotspots in the target area. These generally occurred near scar tissue and often re-occurred in every consecutive HT session. All patients had scar tissue in the chest wall resulting from previous surgery. For each patient, we extracted intratarget and skin surface temperature and TD variables (see supplementary materials for details). HT dose is commonly quantified in cumulative equivalent minutes at 43 °C (CEM43T50), which incorporates both treatment duration and median temperature [37,38].

In 29 patients intratarget temperatures were not monitored during all HT treatment sessions, reasons included late catheter placement, premature catheter removal or error in temperature registration. However, this was well-balanced over both TD groups (Table 2) and analysis showed similar results for patients in whom intratarget temperature monitoring was missing in some HT sessions compared to results of patients who had intratarget monitoring in all sessions.

When considering CEM43T50 as a continuous variable, the optimal outcome-related cut-off was 1.28 min ($p < 0.0001$) where the low/high TD group sizes were $n = 12$ and $n = 100$ (Supplementary Fig. 2), this was in agreement with the 1 min cut-off point found by Ohguri et al. [17]. Because the subgroups were not reasonably balanced, we decided to consider CEM43T50 as a categorical variable and chose a cut-off TD dividing the population into equal-sized 'low' and 'high' TD groups by the best HT session with the highest CEM43T50. This is justified, since T50 was fairly reproducible over all HT sessions for an individual patient and intratarget registrations were not available for all sessions. Best CEM43T50 was <7.2 min and $\geq$7.2 min for the low and high TD group, respectively.

Table 1 summarizes the patient characteristics and Table 2 the treatment characteristics stratified by low and high TD.

Study endpoints

Actuarial LRC was calculated from the date of the first re-irradiation fraction until the first infield local and/or regional recurrence. Patients without infield locoregional recurrence at death or last follow-up were censored. Actuarial OS was calculated from the date of the first re-irradiation fraction until death. Death of any cause was an event. Patients alive at last follow-up were censored.

Toxicity was defined according to the Common Terminology Criteria of Adverse Events (CTC-AE) version 5.0 [39]. Toxicity was considered acute when occurring within three months, and late when occurring more than three months after the first re-irradiation fraction. Actuarial late toxicity was calculated from the date of the first re-irradiation fraction until the first grade 3–5 late toxicity. Patients without grade 3–5 late toxicity at death or last follow-up were censored.

Table 1
Tumor and patient characteristics, stratified by low and high thermal dose (TD).

		Low TD (n = 56)	High TD (n = 56)	p
Best CEM43T50 (minutes)		3.4 (0.1–7.1)	15.9 (7.4–101.9)	<0.001
Age (years)		63.2 ± 12.8	64.1 ± 8.8	n.s.
Initial breast cancer				
Pathological tumor stage [a]	(y)pT0-T2	52 (94.6%)	55 (98.2%)	n.s.
	(y)pT3-T4	3 (5.4%)	1 (1.8%)	
Pathological lymph nodes stage [a]	(y)pN0	33 (59.8%)	37 (66.1%)	n.s.
	(y)pN+	22 (40.2%)	19 (33.9%)	
Present recurrent breast cancer				
Time interval initial diagnosis - present recurrence (years)		10.1 (0.1–27.5)	9.8 (2.1–28.8)	n.s.
Time interval previous breast cancer - present recurrence (years) [b]		8.3 (0.1–27.0)	7.4 (1.4–28.8)	n.s.
Pathological tumor stage	(y)pT0	0 (0%)	0 (0%)	n.s.
	(y)pT1-T2	42 (75.0%)	44 (78.5%)	
	(y)pT3-T4	14 (25.0%)	12 (21.5%)	
Pathological lymph nodes stage	(y)pN0	37 (66.1%)	47 (83.9%)	n.s.
	(y)pN+	19 (33.9%)	9 (16.1%)	
Lymphovascular invasion		31 (55.4%)	22 (39.3%)	n.s.
Contralateral lymph nodes		13 (23.3%)	7 (12.5%)	n.s.
Distant metastasis [c]		5 (8.9%)	2 (3.6%)	n.s.
Histological type	Invasive carcinoma NST	46 (82.1%)	39 (69.6%)	n.s.
	ILC	8 (14.3%)	15 (26.8%)	
	DCIS	1 (1.8%)	2 (3.6%)	
	Other	1 (1.8%)	0 (0%)	
BR differentiation grade [d]	Well-differentiated (G1)	2 (3.8%)	4 (7.3%)	n.s.
	Moderately differentiated (G2)	26 (49.1%)	30 (54.5%)	
	Poorly differentiated (G3)	25 (47.2%)	21 (38.2%)	
Estrogen receptor +		37 (66.1%)	41 (73.2%)	n.s.
Her2neu + [a]		8 (14.5%)	7 (12.5%)	n.s.
Triple negative		15 (26.8%)	13 (23.2%)	n.s.

Values indicate mean ± standard deviation, median (range) or the number of patients (%).
a. Data missing for 1 patient in low thermal dose group; b. previous breast cancer = initial diagnosis or locoregional recurrence or second ipsilateral primary breast cancer; c. contralateral lymph nodes are not counted as distant metastasis; d. data missing for 3 patients in the low thermal dose group and 1 patient in the high thermal dose group.
Abbreviations: TD = thermal dose; Best CEM43T50 = the median intratarget thermal dose of the best session; NST = No Special Type; ILC = Invasive Lobular Cancer; DCIS = Ductal Carcinoma In Situ; BR = Bloom Richardson; G = grade; n.s. = not significant.

Statistical analysis

Differences between characteristics of the two TD groups were investigated using Fisher's exact test, the independent samples t-test and the Mann-Whitney U-test depending on the type of data.

Duration of LRC, OS and late toxicity were analyzed by the actuarial method of Kaplan and Meier [40]. Groups were compared by the log-rank test. The impact of re-irradiation schedule/technique was also evaluated by separately analyzing the 8frx4Gy and 23frx2Gy subgroups.

Multivariable analysis of LRC, OS and late toxicity was performed by (backwards) stepwise Cox regression. Associations between LRC, OS or late toxicity and independent variables were investigated. Inverse probability weighting using propensity score was performed to obtain an unbiased estimate of the causal effect of TD [41,42], see supplementary materials for more details.

All analyses were performed using R (version 3.6.3) with packages survival (version 3.2-7) and survminer (version 0.4.8), the tests were two-sided and $p < 0.05$ was considered significant. Accuracy of statistical estimates is reported using 95% Wald confidence intervals.

Results

Besides the achieved TD, there were no significant differences in patient and treatment characteristics between the low and high TD groups (Tables 1, 2). The median follow-up period was 43 months (range 1–107 months).

Twenty-four patients (21.4%) developed an infield recurrence, the median time to recurrence was 41 months (range 1–107). The three-year actuarial LRC rate was 83.2%. LRC was significantly different for the low and high TD group (p = 0.0013; Fig. 2A). Three-year LRC rates for the low and high TD groups were 74.0% vs. 92.3%, respectively (p = 0.008). For patient subgroups treated with 8 fractions of 4 Gy (2010–2017, n = 34) and 23 fractions of 2 Gy (2014–2017, n = 78), three-year LRC rates for the low and high TD group were 55.6% and 81.2% (p = 0.07), and 81.6% and 97.3% (p = 0.025), respectively, see Supplementary Figs. 3 and 4A. Associations of other TD parameters with LRC are available in Supplementary Table 1.

Twenty-five patients died, and three-year OS was 85.4%. OS was not significantly different for the low and high TD group (p = 0.29; Fig. 2B). Six patients died of causes other than breast cancer and two of unknown cause.

Potential prognostic factors were evaluated for LRC and OS. In univariate analysis LRC was significantly associated with five tumor or TD related variables (Supplementary Table 2). In the backward multivariable analysis four factors remained associated with LRC (Table 3). The presence of distant metastases (HR 17.6; 95%CI 5.2–60.2), lymph node involvement (HR 2.9; 95%CI 1.2–7.2) and chest wall recurrence (as opposed to breast recurrence) (HR 4.6; 95%CI 1.8–11.6) impaired LRC. A higher TD (BestCEM43T50) improved LRC (low vs. high; HR 4.1; 95%CI 1.4–11.5). As an unbiased estimate of the causal effect of TD, inverse probability weighting analysis also confirmed that higher TD was significantly associated with better LRC (low vs. high; HR 5.1; 95%CI 4.3–5.9, p = 0.0018).

For OS, nine variables were significantly associated in univariate analysis (Supplementary Table 2). Three factors remained associated with OS in backward multivariable analysis. Patients with smaller recurrences (≤5cm; HR 0.3; 95%CI 0.1–0.8), absence of contralateral breast cancer growth (HR 3.4; 95%CI 1.3–8.6) and positive estrogen receptor (HR 0.2; 95%CI 0.1–0.5) had longer OS.

There was no significant difference in acute toxicities (≤3 months) between the TD groups (p = 0.24; Supplementary Table 3). During re-irradiation with HT treatment 14.3% of patients experi-

Table 2
Treatment characteristics of the included patients, stratified by low and high thermal dose (TD).

		Low TD (n = 56)	High TD (n = 56)	p
Previous treatment				
Previous locoregional recurrences	1	20 (35.7%)	17 (30.4%)	n.s.
	2	0 (0.0%)	2 (3.6%)	
Chemotherapy [b]		18 (32.1%)	17 (30.4%)	n.s.
Endocrine therapy [b]		16 (28.6%)	11 (19.6%)	n.s.
HER2-targeted therapy [b]		3 (5.4%)	3 (5.4%)	n.s.
Median initial total RT dose (Gy; incl. boost) [a]		64.0 (42.6–73.4)	64.0 (42.6–73.8)	n.s.
Present treatment				
Surgery	Breast conservation	0 (0.0%)	1 (1.8%)	n.s.
	Mastectomy	31 (55.4%)	39 (69.6%)	
	Local resection	25 (44.6%)	16 (28.6%)	
Chemotherapy [b]		30 (53.6%)	25 (44.7%)	n.s.
Endocrine therapy [c]		31 (55.4%)	35 (62.5%)	n.s.
HER2-targeted therapy [c]		6 (10.7%)	3 (5.4%)	n.s.
RT scheme	8frx4Gy	17 (30.4%)	17 (30.4%)	n.s.
	23frx2Gy	39 (69.6%)	39 (69.6%)	
RT boost	Sequential (2frx4Gy) [d]	1 (1.8%)	3 (5.4%)	n.s
	Sequential (2frx2Gy) [e]	9 (16.1%)	3 (5.4%)	
	Simultaneous (23frx0.66 Gy) [e]	0 (0.0%)	2 (3.4%)	
RT target	Local	33 (58.9%)	38 (67.9%)	n.s.
	Locoregional	23 (41.1%)	18 (32.1%)	
Median time interval RT-HT (min)		60.2 ± 13.2	62.9 ± 15.3	n.s.
Hyperthermia treatments	4	19 (33.9%)	19 (33.9%)	n.s.
	5	37 (66.1%)	37 (66.1%)	
Intratarget temperature	T10 (°C)	41.2 ± 0.9	42.2 ± 0.7	<0.0001
	T50 (°C)	40.0 ± 0.8	41.2 ± 0.6	<0.0001
	T90 (°C)	39.0 ± 0.9	40.1 ± 0.7	<0.0001
	Average CEM43T0 (min)	9.4 (0.1–86.6)	26.7 (3.0–144.0)	<0.0001
	Average CEM43T50 (min)	1.7 (0.0–6.6)	9.0 (2.3–49.2)	<0.0001
	Average CEM43T100 (min)	0.4 (0.0–2.8)	2.5 (0.1–24.1)	<0.0001
Missing intratarget measurement	1 session	5	5	n.s.
	2 sessions	2	3	
	3 sessions	5	5	
	4 sessions	3	1	

Values indicate mean ± standard deviation, median (range) or the number of patients (%).
a. data missing for 4 patients in each group; b; as neo-adjuvant or adjuvant therapy; c. as neo-adjuvant, concurrent and/or adjuvant therapy; d. patients were treated with 8frx4Gy with a sequential boost of 2frx4Gy on a lymph node metastasis in not-previously irradiated areas; e. patients were treated with 23frx2Gy with either a sequential (2frx2Gy) or in case of a lymph node metastasis in not-previously irradiated area a simultaneous (23frx0.66 Gy) boost.
Abbreviations: TD = thermal dose; RT = radiotherapy; T10, T50, T90 = The temperature exceeded by 10%, 50% or 90% of the measurements, respectively; average CEM43T0, average CEM43T50, average CEM43T100 = the average of the maximum, median and minimum thermal dose of all sessions, respectively; n.s. = not significant.

enced mild symptoms, varying from pain to discomfort (grade 1). Transient skin desquamation occurred in eight patients as a consequence of radiation dermatitis. Twenty patients (17.9%) developed burns due to HT treatment (grade 1–2).

Late toxicity grade 2, 3 and 4 after re-irradiation with HT was observed in 56.3% (n = 63), 25.0% (n = 28) and 0.9% (n = 1) of the patients, respectively; no grade 5 toxicity was reported. Six months after treatment, one grade 4 RT induced skin ulceration occurred in the high TD group (Table 4). The most frequently reported grade 3 late toxicity was fibrosis. One patient developed a grade 3 burn related to a 44.3 °C hotspot on the mastectomy scar during the first HT treatment. We found no significant associations between late toxicity and treatment-related variables including TD (p = 0.58) (Fig. 2C and Supplementary Fig. 5). Late toxicity was not significantly different between the two re-irradiation schedules, but patients treated with 23frx2Gy tended to have more 3-year late toxicity (31.3%) than patients treated with 8frx4Gy (15.2%) (p = 0.064; Supplementary Fig. 4B). The actuarial risk of grade 1–2 and grade 3–4 late toxicity after one- and three-years was 51.4% and 73.7%, and 17.0% and 25.9%, respectively.

Discussion

This study is the first to demonstrate that higher TD improved LRC rates in patients treated with postoperative re-irradiation and hyperthermia for locoregional recurrent breast cancer. TD did not have a significant effect on OS or grade late toxicity; the latter might imply that hyperthermic radiosensitization was tumor-selective, confirming the tumor-selectiveness reported in randomized RT-HT trials [7,24,25].

The three-year LRC rates reported in this study were 74.0% vs. 92.3%, for the low and high TD group respectively. Similar thermal dose–effect relationships were found for different advanced cancers [16–20] and unresectable locoregional recurrent breast cancer [22–26]. The three-year LRC rate of 83.2% for all patients and for the low TD group (74.0%) were in accordance with three-year LRC rates reported after re-irradiation with HT in patients with surgically removed locoregional recurrent breast cancer, i.e. 68–83% [11–15]. These earlier studies had insufficient intratarget TD data to analyze the prognostic value of TD.

Adequate TD was our goal in all patients. The intratarget T90 of 40.0 ± 0.7 °C and T50 of 41.2 ± 0.6 °C achieved in the high TD group matched the advised T90 ≥ 40 °C and T50 ≥ 41 °C in international superficial HT quality assurance guidelines [28] based on clinical dose–effect relationships [16–20,22–26]. The T90 and T50 in the low TD group were ~1 °C lower.

HT complements and synergizes with RT by inducing direct (hypoxic) cell death [43–46], inhibition of DNA damage repair [8,47–49], tumor re-oxygenation [50–54] and stimulation of immune response [55,56]. Achieving T50 ≥ 41 °C is important [8,46], particularly for inducing radiosensitization by inhibition of DNA-damage repair which requires T50 ≥ 41 °C [47–49] and short (<1–2 h) re-irradiation with HT time intervals [10,18,57]. Direct cell kill of hypoxic tumor cells is also likely more effective for higher T50

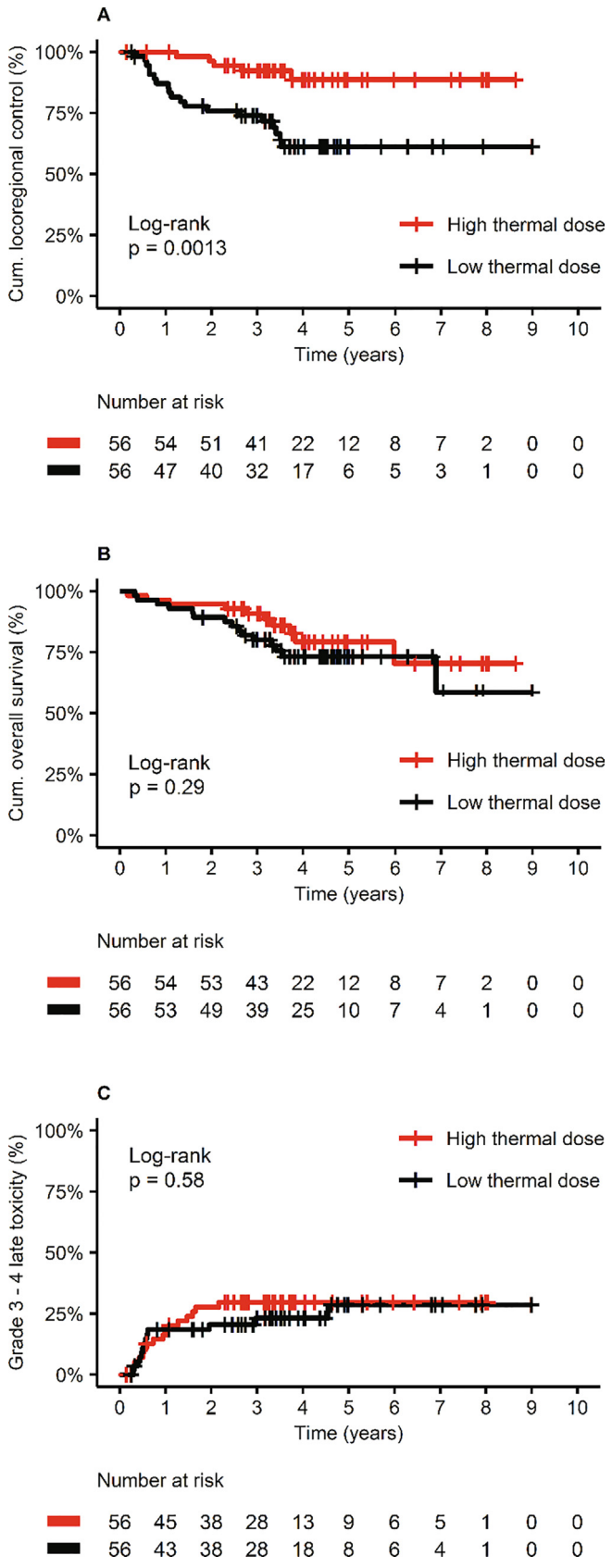

Fig. 2. Kaplan-Meier survival analysis for A) locoregional control, B) overall survival and C) grade 3–4 late toxicity for the high thermal dose group (red) and the low thermal dose group (black). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Prognostic factors for locoregional control and overall survival after backwards stepwise multivariable Cox regression.

	HR (95% CI)	*p*
Locoregional control		
Distant metastases (yes/ no) [a]	17.6 (5.2–60.2)	<0.001
Location (chest wall/ breast)	4.6 (1.8–11.6)	0.001
Best CEM43T50 (low/ high)	4.1 (1.4–11.5)	0.009
Tumor-positive lymph nodes (yes/ no)	2.9 (1.2–7.2)	0.019
Overall survival		
Estrogen receptor (+/ -)	0.2 (0.1–0.5)	<0.001
Contralateral breast cancer growth (yes/ no)	3.4 (1.3–8.6)	0.011
Tumor size (≤5 cm/ > 5 cm)	0.3 (0.1–0.8)	0.016

a. Contralateral lymph nodes are not counted as distant metastasis.
Abbreviations: HR = Hazard ratio; CI = 95% Wald confidence interval; Best CEM43T50 = the best median intratarget thermal dose of all hyperthermia sessions.

[8,58], independent of time interval [57]. Hyperthermic eradication of hypoxia is intrinsically tumor-selective, and highly relevant for overcoming radiotherapy-resistance in recurrent tumors [9]. Supplementary Fig. 6 depicts photos before and after treatment with re-irradiation and hyperthermia for two patients with either post-operative and inoperable locally advanced recurrent breast cancer.

All 112 patients in our cohort study underwent similar RT and HT treatments, minimizing bias. The difference in impact of treatment-limiting hotspot incidence in the low and high TD group might be thought to indicate patient selection. However, the occurrence and severity of hotspots is largely determined by certain anatomical features with reduced local perfusion, such as scar tissue. There were no baseline imbalances between the low and high TD groups (Tables 1,2), where type of surgery was included in the baseline. All patients had scars, only scars in the low TD group led to treatment-limiting hotspots on the skin surface, limiting the overall intratarget treatment temperature. TD was thus an independent prognostic variable in multivariable analysis, which included other prognostic factors for LRC (Table 3). Furthermore, inverse-probability weighting using propensity score was performed; a statistical method that removes confounding by creating a "pseudo-population" in which the distribution of measured baseline covariates is independent of the achieved TD. The estimated effect of TD on LRC remained statistically significant after this analysis. Thus, insufficient TD appears to be the sole explanation for worse tumor control in the low TD group.

The three-year OS rate of 85.4% in our study was higher than the OS rates reported earlier, 66–75% [12,14]. This difference likely reflects the continuous improvements in earlier breast cancer diagnosis/treatment and treatment quality, including increased use of diagnostic breast MRI and PET-CT, more effective systemic treatment and improved RT planning and techniques. Note that in our study patients treated with 23frx2Gy postoperative re-irradiation with IMRT/VMAT planning and HT achieved 89.5% LRC. Moreover, in both the 8frx4Gy and 23frx2Gy subgroups, LRC was 16–26% higher for patients treated with a high TD vs. low TD.

Prognostic factors associated with LRC or OS found in multivariable analysis in our study are in agreement with previous reports [1,11,14,59,60]. Estrogen receptor positivity reflects a favorable treatment-sensitive tumor biology. Distant metastases, tumor positive lymph nodes, larger locoregional tumor size and contralateral breast cancer growth reflect a higher disease burden and poorer prognosis [1,11,14,59,60]. For patients with an isolated locoregional recurrence, often more aggressive strategies are used aiming for cure [1]. The poor prognosis for locoregional recurrences on the chest wall compared to local recurrences in the breast is in line with recent literature [1].

Table 4
Number and type of late toxicities (≥3 months after the first re-irradiation fraction) according to CTCAE v5.0, stratified by thermal dose group. Patients can have multiple late toxicities, 59.8% of the patients (n = 67) had more than one type of late toxicity. The differences in late toxicity between the low and high thermal dose groups were not significant. The observed grade 3–4 toxicity reflects a cumulative effect of previous and present treatments.

CTC-AE score	Low thermal dose (n = 56)		High thermal dose (n = 56)	
	Toxicity	n (%)	Toxicity	n (%)
1–2	Lymphedema	20 (35.7%)	Lymphedema	19 (33.9%)
	Chest(wall) pain	13 (23.2%)	Chest(wall) pain	17 (30.4%)
	Fibrosis	13 (23.2%)	Fibrosis	17 (30.4%)
	Telangiectasia	12 (21.4%)	Telangiectasia	15 (26.8%)
	Rib fracture	9 (16.1%)	Rib fracture	17 (30.4%)
	Hyperpigmentation	7 (12.5%)	Hyperpigmentation	8 (14.3%)
	Joint range of motion decreased	10 (17.9%)	Joint range of motion decreased	4 (7.1%)
	Pneumonitis	3 (5.4%)	Pneumonitis	2 (3.6%)
	Skin ulceration	2 (3.6%)	Skin ulceration	3 (5.4%)
	Burn	3 (5.4%)	Burn	1 (1.8%)
	Brachial plexopathy	1 (1.8%)	Brachial plexopathy	1 (1.8%)
	Arrhythmia	1 (1.8%)		
3	Fibrosis	13 (23.2%)	Fibrosis	12 (21.4%)
			Chest wall pain	3 (5.4%)
			Burn consequences	1 (1.8%)
			Rib fracture	1 (1.8%)
4	–		Skin ulceration	1 (1.8%)
5	–		–	

The overall grade 3–4 late toxicity rate in this study was 25% and 0.9% for grade 3 and 4, respectively, for the 8frx4Gy subgroup it was 11.8% and 2.9%, respectively. The latter is much lower than previously published rates for patients treated with 8frx4Gy prior to 2001 (43%) [14,61,62]. This lower incidence can likely be attributed to major improvements in re-irradiation technique and in planning [61]. A higher fraction dose was often considered to be associated with higher risk of late toxicity. Recent results for primary breast cancer treated with hypofractionated RT indicate that this might not be the case [63]. Our observed trend of higher incidence of toxicity for 23frx2Gy also suggests the total dose to be a more dominant factor than fraction dose. Importantly, the present study showed no significant differences in late toxicity between low and high TD. In addition, the observed grade 3–4 toxicity reflects a cumulative effect of previous and present treatments [64]. Baseline toxicity could be poorly assessed due to the retrospective nature of our study. Serious late toxicity influences quality of life of breast cancer survivors, postoperative re-irradiation with HT can only be acceptable if the gain in tumor control is meaningful. Re-irradiation with HT does appear meaningful in our study with 18.3% gain in LRC for high TD.

The retrospective nature of our study introduces some limitations. Firstly, the occurrence of a locoregional recurrence, survival and late toxicity might be underreported or reported at a later date. Secondly, baseline toxicity before re-irradiation with HT was not consistently evaluated, making it difficult to establish whether late toxicity was induced by the present treatment or by previous treatments. We included patients with sufficiently large target volumes to allow intratarget monitoring. Consequently, the absolute toxicity, OS and LRC rates in our study may deviate from rates for re-irradiation with HT patients with thin chest wall target volumes [64]. Intratarget monitoring was missing in some sessions, this does not result in bias between low vs. high TD groups (Table 2).

Conclusion

Both multivariable and inverse probability weighting analysis showed that thermal dose, defined as Best CEM43T50, was significantly associated with LRC for patients with locoregional recurrent breast cancer treated with re-irradiation combined with HT. Patients with high TD HT had 18.3% higher LRC compared to patients receiving low TD, without augmenting toxicity. This thermal dose–effect relationship suggests that postoperative re-irradiation with HT is effective after surgery, and that HT is of additional value to postoperative re-irradiation. Confirmation of these results in other, preferably randomized, studies is desirable. Our study underlines the necessity to achieve high TD and to measure target temperatures invasively during hyperthermia treatment.

Conflict of interests

No disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.12.036.

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