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CLINICAL INVESTIGATION

The Probability of Locoregional Control in Patients With Locoregional Recurrent Breast Cancer Treated With Postoperative Reirradiation and Hyperthermia (RADHY): A Continuous Thermal Dose-effect Relationship

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Purpose: Mild hyperthermia (HT) (39-43 °C) combined with reirradiation is considered for patients with locoregional recurrent (LRR) breast cancer. Studies analyzing dichotomized HT thermal dose (TD) parameters suggest that higher TD correlates with better response rates, but evidence quantifying optimal TD levels needed to achieve locoregional control (LRC) is limited. We investigated the continuous TD-effect relationship of LRC in patients with LRR breast cancer treated with postoperative reirradiation and HT.

Methods and Materials: In this historical cohort study, 112 patients with LRR breast cancer were treated in 2010-2017 with postoperative reirradiation 8 × 4 Gy (n = 34) or 23 × 2 Gy (n = 78) and 4 to 5 weekly HT sessions, TD was measured using invasive thermometry in the target region. Primary endpoint was the estimated probability of LRC at 5-years. The logarithm of highest ("Best") CEM43T50 (median cumulative equivalent minutes at 43 °C) of all HT sessions was analyzed as TD parameter based on Weibull univariate and stepwise multivariate regression analyses. Additionally, the best fitted Bayesian LRC survival model was analyzed assuming 3 informative priors: age, tumor location (breast/chest wall), and lymph node involvement.

Results: Twenty-four patients developed an infield recurrence; median time to recurrence was 3.4 years (interquartile range, 2.7-4.6 years). Increasing median Best session CEM43T50 TD range from 0.08 to 101.9 minutes was associated with increasing probability of LRC from ∼44% to 94% at 5-years, and over this range a 2-fold TD increase resulted in ∼5% to 10% increasing

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LRC. The hazard ratio for a subsequent recurrence decreased 48% (95% confidence interval, 18%-84%) with a 2-fold increase in TD over the TD range, $P = .001$. This effect was confirmed in Weibull multivariate regression analysis and in Bayesian LRC survival regression analysis.

Conclusions: Increasing TD was strongly associated with an improved LRC, showing that adequate TD must be ensured and confirming that HT is essential for strongly sensitizing efficacy of postoperative reirradiation for patients with LRR breast cancer.

Introduction

The incidence of breast cancer is widespread and also associated with a significant incidence of recurrent disease.[1,2] Previous radiation treatments limit the tolerable reirradiation dose, presenting challenges to achieve acceptable locoregional control (LRC) and disease-free survival rates. Therefore reirradiation combined with hyperthermia (HT), heating the target tumor location to temperatures of 40 to 43 °C for 1 hour,[3,4] is considered for patients with locoregional recurrent (LRR) breast cancer.[5,6]

HT provides significant tumor selective radiosensitization when combined with reirradiation for macroscopic and postoperative high-risk LRR breast cancer.[7,8] HT is typically administered using microwave antennas for superficial locations infiltrating up to 4 cm deep. Skin and invasive (ie, interstitial) temperatures are monitored during HT, from which HT temperature and thermal dose (TD) parameters can be calculated to evaluate treatment quality.[4,9] Cumulative equivalent minutes at 43 °C (CEM43) is a widely accepted HT TD parameter that incorporates both the achieved temperature and treatment duration.[10] CEM43 assumes an Arrhenius relationship, reflecting exponential enhancement of molecular reaction rates at increasing temperatures to quantify the time and temperature-dependent thermal molecular damage responsible for increased cancer cell killing and to account for protein denaturation effects that lead to thermal radiosensitization.[11]

HT quality assurance guidelines prescribe achieving a median tumor temperature exceeding 41 °C and a tumor temperature exceeding 40 °C in 90% of the tumor volume.[9] This guideline is based on studies indicating that higher invasive HT temperatures and TD are associated with better clinical outcomes for patients with breast cancer undergoing combined radiation therapy and HT.[9] However, exact CEM43 TD values of these thresholds are uncertain because studies used different HT parameters and sparse invasive thermometry.[12-15] Establishing reliable CEM43 threshold values associated with a specific significant TD-effect of HT on oncological outcomes is needed for the reliable definition of clinical TD dose prescriptions.

A common strategy for analyzing clinical dose-effect relationships involves dichotomizing the variable of interest in 2 patient groups, representing low and high dose.[16-18] A recent study analyzing the association between TD and LRC in patients with LRR breast cancer treated with postoperative reirradiation and HT, using a dichotomized HT TD parameter, showed a strong dose-effect relationship.[8] However, a major limitation of dichotomization is that the expected clinical effect cannot be quantitatively estimated for specific TD levels, only for the 2 large TD groups that each evidently represents a wide range of TDs. Results may also vary when cut-off points are arbitrarily chosen without a clinical reasoning or a planned statistical rationale, and using a dichotomized parameter can lead to a possible inflation of false positive conclusions that could lead to erroneously concluding a treatment is effective.[16-18]

We hypothesized that establishing a TD-effect relationship using a continuous TD parameter may better preserve information and statistical power, provide more precise estimates of the TD-effect, and may aid clinical interpretation.[16] Reporting univariate and multivariate regression analyses based on a continuous parameter has major advantages, including the ability to predict the expected clinical effect for specific dose parameter levels, allowing a more direct comparison of results from different studies.[16]

In this study, we investigated the continuous TD-effect relationship for accurately estimating the probability of LRC at 5-years in patients with LRR breast cancer treated with postoperative reirradiation and HT, using an existing cohort of LRR breast cancer patients with extensive temperature measurements ideally suitable for continuous TD analysis.[8]

Methods and Materials

Study design and population

This historical cohort study (RADHY) was approved by the ethics committee of the Amsterdam University Medical Centers on November 7, 2019 (W19_425#19.492). The study was performed in accordance with the Declaration of Helsinki and reported following the Strengthening the Reporting of Observational Studies in Epidemiology guideline for cohort studies.

Eligible patients with LRR breast cancer or second ipsilateral primary breast cancer diagnosis, who gave informed consent, were treated between 2010 and 2017 with postoperative reirradiation and superficial HT, guided by invasive thermometry. Further eligibility requirements were a pathologically confirmed adenocarcinoma at diagnosis and completion of ≥4 HT treatment sessions (Fig. 1). Patients were excluded if they had unresectable LRR breast cancer, or tumor types other than LRR breast cancer, received

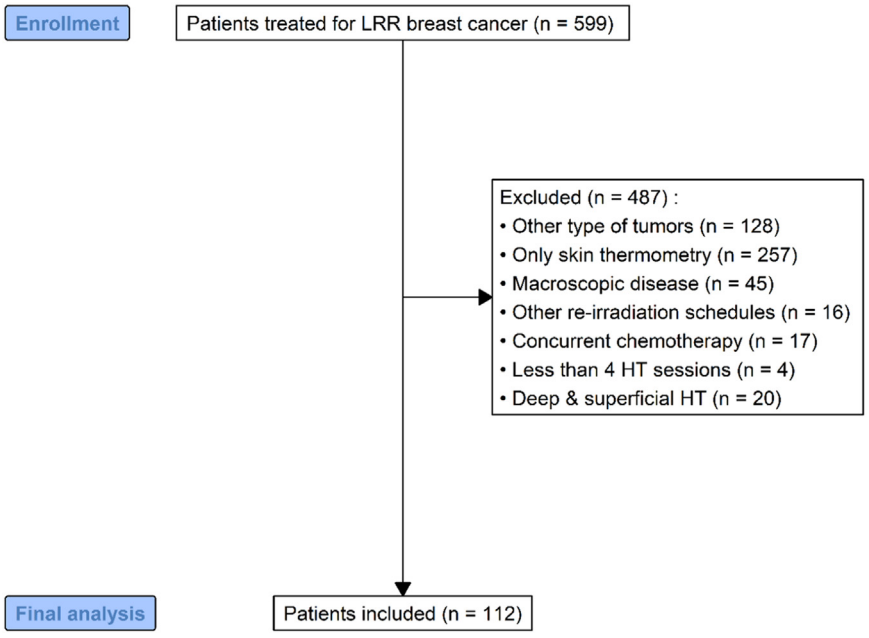

Fig. 1. RADHY flowchart. *Abbreviations:* HT = hyperthermia; LRR = locoregional recurrence; RADHY = Radiation and hyperthermia.

concurrent chemotherapy, or when tumors exceeded 4 cm tumor depth, and were treated with other HT device combinations.

Treatment procedures

Reirradiation

Approximately 6 weeks after undergoing salvage mastectomy or local resection of all macroscopic recurrence in the chest wall and/or lymph node areas, patients underwent a planning computed tomography scan (planning CT) from the chest wall or mastectomy area up to the lower ears with 2.5 mm slice thickness. If there was lymph node involvement in most cases a planning fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) was made or the planning CT was matched with the most recent PET-CT if the PET-CT was made within 2 months before start of the radiation therapy. Patients were irradiated during 4 to 5 weeks in supine position. Clinical target volume (CTV) was delineated by the treating radiation oncologist. CTV was defined as the chest wall outside the thoracic cage, always including the former entire breast area and including at least a 3 cm margin around the original tumor location in the chest wall directions. In case of lymph node involvement the affected regional lymph node areas were delineated as CTV, that is, axilla or internal mammary lymph node region. From 2015, CTVs were defined according to the ESTRO Atlas 2015, 2016.[19] Planning target volume was defined by adding 10 mm margin in any direction. When the chest wall had a thickness of ≤1 cm, an equivalent tissue material of 0.5 to 1 cm was used for adequate planning target volume coverage. Regional lymph nodes were irradiated in case of lymph node involvement. Treatment was delivered either by anterior-posterior/posterior-anterior fields to the anterior chest wall with 6 to 10 MV energy with connecting anterior-posterior electron field at the chest wall part covering the lung (energy ranging from 6 to 15 MeV), or intensity modulated radiation therapy or volumetric modulated arc therapy with 6 to 10 MV photons. Until 2014 patients received a total dose of 32 Gy delivered in twice-weekly fractions of 4 Gy, thereafter generally 46 Gy in daily fractions of 2 Gy.[8] Patients with positive lymph nodes received a total dose of 32 Gy in 8 fractions of 4 Gy or 46 Gy in 23 fractions on the previously irradiated lymph node areas. In case of lymph node recurrence in previously nonirradiated area a sequential boost of 8 Gy in 2 fractions of 4 Gy was given. Since the introduction of the 23 × 2 Gy schedule all previously not irradiated lymph node regions have been treated with: a sequential boost of 4 Gy in 2 fractions of 2 Gy, or a simultaneous integrated boost (SIB) of 4.6 Gy in 23 fractions of 0.2 Gy. When prior pathologic lymph nodes were still visible on our planning CT/planning PET-CT with no FDG activity, a SIB of 9.2 Gy in 23 fractions of 0.4 Gy was given; if the lymph nodes were FDG PET positive a SIB of 15.2 Gy in 23 fractions of 0.66 Gy was used. Also, if possible a match was made with the previous radiation therapy (data were always collected from the referring institutes) to correctly establish the nonirradiated area(s).

Hyperthermia treatment

Once a week, HT was administered within 1 hour after reirradiation. Following our standard clinical protocol and according to the quality assurance guidelines, the aim was to elevate invasive and skin temperatures to a minimum of

41 °C and a maximum of 43 °C.[9] Each HT session consisted of a warming-up time of maximally 15 minutes, after which the steady state period of 1 hour was started.

The target volume was heated using 434 MHz contact flexible microstrip applicators (CFMA: SRPC Istok, Fryazino, Moscow region, Russia; ALBA4000: Medlogix SRL, Rome, Italy) with an effective heating depth of 4 cm. Applicators use an integrated temperature-controlled water bag between antenna and skin to couple the electromagnetic energy into the target volume. Every 30 seconds invasive temperatures were monitored with 1 or 2 seven-sensor copper-constantan thermocouple probes (Volenec RD Inc). Several multisensor thermometry probes were also placed on the skin to monitor skin temperatures and to minimize the occurrence of hotspots, keeping skin temperatures below 43 °C. The HT applicator power and water bag temperature were carefully adjusted to achieve both the desired invasive and skin surface therapeutic temperatures.[9] Skin surface temperature data were not included in the analysis as these temperatures are influenced by the water temperature, and thus less representative of tumor temperature.[20]

TD calculation

Based on the Arrhenius relationship, the cumulative equivalent minutes at 43 °C, or CEM43, was calculated[10] using:

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

where t is time of treatment, T is the average invasive temperature during time interval Δt (in minutes), R is a constant (when a temperature ≥43 °C is reached, R is set to 0.5; at a temperature <43 °C R is set to 0.25).

Per patient the CEM43 was calculated from the start of the preheating time up to the end of the 1-hour steady state period. More specifically, we calculated the CEM43 per session, per sensor. The invasive temperature is measured >120 times with approximately 7 to 14 sensors per session, for each session we establish the CEM43 distribution, where the CEM43 at the sensor with highest CEM43 is defined as the CEM43T0, the CEM43 achieved at 10%, 50%, and 90% of the sensors as the CEM43T10, CEM43T50, and CEM43T90, respectively, and the CEM43 at the sensor with lowest CEM43 is defined as CEM43T100.

To summarize the quality of the HT treatment series, the following invasive TD parameters were calculated per patient: the average and sum of the CEM43T0, CEM43T10, CEM43T50, CEM43T90, and CEM43T100 over all HT sessions. Furthermore, we determined per patient the CEM43T0, CEM43T10, CEM43T50, CEM43T90, and CEM43T100 for the session with highest median CEM43 (Best CEM43T50).

Clinical TD model development

To develop a general clinical HT TD model for accurately estimating the probability of LRC at 5-years, the primary endpoint, specific analyses were performed to investigate which continuous TD parameter shows the best predictive value. First, various parametrizations of CEM43 were performed and evaluated through Weibull univariate and multivariate regression with a stepwise variable selection procedure, where except for continuous CEM43 as the exposure variable, 3 significant covariates were included in the final (linear-log) models, that is, tumor location (breast/chest wall), lymph node involvement, and age. The Weibull multivariate regressions revealed that the logarithm of TD for the "Best CEM43T50" invasive HT session was the most informative and interpretable, with the available thermometry data (Table E1). Finally, the impact of age (continuous and quadratic) on LRC was analyzed through a sensitivity analysis. The use of a quadratic term permitted to analyze the expected U-shaped effect relationships with age.[21]

Bayesian and sensitivity analyses

Robustness of estimation is important because of the relatively small population. Therefore, we further analyzed the LRC model using the Bayesian approach, a proven suitable method to validate robustness.[22]

The same covariates as the Weibull multivariate analysis: age, tumor location (breast/chest wall), and lymph node involvement, were identified through literature search and clinical knowledge as relevant risk factors associated with LRC for high-risk LRR breast cancer.[5,8] Consecutively, these covariates were used as relevant informative priors to further analyze through a Bayesian framework. The hazard ratios collected from the covariates were transformed into prior distributions for the corresponding regression parameters (Table E2).

Furthermore, we performed a logistic regression analysis as a means to illustrate LRC and the Best CEM43T50 in a dose-effect relationship curve, and we analyzed separately the impact of the Best CEM43T50 TD on LRC in both 8 × 4 Gy and 23 × 2 Gy reirradiation schedules.

Statistical power and analysis

Descriptive statistics (mean-standard deviation, range-median, or count-percentage) were used to summarize patient, tumor and treatment characteristics.

An empirical power evaluation through simulation showed a power above 80% for identifying an increase of 0.5 on the log(CEM43T50) scale for a n = 112 sample size. This is lower than a 2-fold increase in the transformed scale based on a Weibull regression model, assuming a rate equal to $\lambda = 0.008$ (ie, 0.008 events occur per day), a shape parameter equal to 0.8, thus, decreasing hazards, and censoring based on a uniform proxy distribution ranging between 0 to 3283 days.[23]

All analyses were performed using R (version 4.4.0) with packages survival, survminer (version 3.7-0; 0.4.9), and rjags

(version 4-15) for the Bayesian models. All reported tests were considered statistically significant at $P < .05$.

Results

Study population

A total of 112 patients were included in this study. Baseline patient and clinical characteristics are presented in Tables 1 and 2. The tumor was located in the breast in 71 patients (63%) or in the chest wall in 41 patients (37%); most patients (n = 85, 76%) had an invasive LRR. Of the 71 patients with a recurrence in the breast, only one patient refused to undergo salvage mastectomy, for this patient a relumpectomy was performed. For the patients with a chest wall recurrence a local excision was performed. Twenty-eight patients (25%) had node-positive disease, of whom 20 patients (18%) had contralateral node-positive disease. In 11 of the 20 patients with contralateral nodal involvement an axillary dissection was performed, in 3 patients the contralateral nodal involvement was discovered during a sentinel node procedure, in 2 patients during a marking axillary lymph nodes with radioactive Iodine seeds-procedure,[24] and 4 patients did not undergo lymph node surgery after a complete response on imaging after chemotherapy.

Overall, 24 patients experienced a subsequent LRR after reirradiation combined with HT, with a median interval of 3.4 years (interquartile range, 2.7-4.6 years). The cumulative LRC at 3-years and 5-years was 83.2% and 74.4%, respectively (Fig. E1).

Continuous Best CEM43T50 TD relationship

The average Best CEM43T50 was 13.2 minutes, and the median Best CEM43T50 was 7.2 minutes (interquartile range, 3.4-15.9 minutes; range, 0.08-101.9). All CEM43 TD parameters used are presented in Table 3.

The continuous Best CEM43T50 TD parameter, based on Weibull regression analysis, showed that a higher TD was significantly associated with increasing LRC ($P = .001$). See Table E1 for significant associations between CEM43 TD parameters and LRC. The estimated probability of LRC as a function of continuous Best CEM43T50 is illustrated in Figure 2, showing that over a large TD range the probability of LRC at 5-years increases with circa 5% to 10% for a 2-fold increase in TD. When Best CEM43T50 increases from ~1.0 to ~102.0 minutes LRC increases from ~44% to ~94%.

Univariate and multivariate Weibull regression analysis showed that a 2-fold increase in Best CEM43T50 (equivalent to a ~0.5 °C temperature increase) was associated with a 48% decrease in hazard ratio (95% confidence interval, 18%-84%; $P = <.001$) and a 29% decrease in adjusted hazard ratio for LRR (95% confidence interval, 5%-57%; $P = .013$), respectively. The final Weibull model revealed that age was

Table 1 Baseline patient and tumor characteristics

Characteristic	n = 112
Age at entry (y)	63.6 ± 11.0
Primary breast cancer	
Pathologic tumor (T) category*	
ypT0	13 (12%)
ypT1-T2	94 (84%)
ypT3-T4	4 (4%)
Pathologic lymph nodes (N) category*	
ypN0	70 (63%)
ypN1	31 (27%)
ypN2	6 (6%)
ypN3	4 (4%)
Present recurrence	
Pathologic tumor (T) category	
ypT1-T2	87 (78%)
ypT3-T4	25 (22%)
Pathologic lymph nodes (N) category	
ypN0	84 (75%)
ypN1	22 (19%)
ypN2	3 (3%)
ypN3	3 (3%)
Presence of distant metastases	
Yes	7 (6%)
Contralateral lymph nodes	
Yes	20 (18%)
Histologic type	
Invasive carcinoma NST	85 (76%)
ILC	23 (20%)
DCIS	3 (3%)
Other	1 (1%)
BR differentiation grade†	
G1	6 (7%)
G2	56 (51%)
G3	46 (42%)
Lymphovascular invasion	
Yes	53 (47%)
Estrogen receptor status	
Positive	78 (70%)
Negative	34 (30%)
Progesterone receptor status	
Positive	55 (49%)
Negative	57 (51%)
HER2 status*	

(Continued)

Table 1 (*Continued*)

Characteristic	n = 112
Positive	15 (14%)
Negative	96 (86%)
Triple positive	5 (4%)
Triple negative	28 (27%)

Values are presented as mean (standard deviation) or number of patients (%).

Abbreviations: BR = Bloom Richardson; DCIS = ductal carcinoma in situ; G = grade; HER2 = human epidermal growth factor receptor type 2; ILC = invasive lobular cancer; NST = no special type.

* Data missing for 1 patient.

† Data missing for 4 patients.

Table 2 Baseline treatment characteristics

Characteristic	n = 112
Prior systemic therapy	
Chemotherapy*	
Yes	35 (31%)
No	77 (69%)
Hormone therapy*	
Yes	27 (24%)
No	85 (76%)
HER2-targeted-drug therapy*	
Yes	6 (5%)
No	106 (95%)
Present systemic therapy	
Chemotherapy*	
Yes	55 (49%)
No	57 (51%)
Hormone therapy†	
Yes	66 (59%)
No	46 (41%)
HER2-targeted-drug therapy†	
Yes	9 (8%)
No	103 (92%)
Reirradiation schedule	
8 × 4 Gy	34 (30%)
23 × 2 Gy‡	78 (70%)
Hyperthermia sessions	
4 sessions	38 (34%)
5 sessions	74 (66%)

Values are presented as number of patients (%).

Abbreviation: HER2 = human epidermal growth factor receptor type 2.

* Neo-adjuvant or adjuvant.

† Neo-adjuvant, concurrent, and/or adjuvant.

‡ Two patients received 22 × 2 Gy by own choice.

Table 3 CEM43 thermal dose parameters

Parameters	n = 112
Average (min)	
CEM43T0	20.0 (9.0-30.9)
CEM43T10*	19.8 (8.6-30.6)
CEM43T50	3.9 (1.7-8.9)
CEM43T90*	1.3 (0.6-3.9)
CEM43T100	0.9 (0.4-2.5)
Best session (min)†	
CEM43T0	25.8 (12.4-50.2)
CEM43T10	25.3 (12.0-48.9)
CEM43T50	7.2 (3.4-15.9)
CEM43T90	2.5 (1.1-7.2)
CEM43T100	1.4 (0.5-4.8)
Sum (min)	
CEM43T0‡	96.4 (41.7-147.4)
CEM43T10§	96.3 (41.1-138.9)
CEM43T50‡	17.0 (8.0-38.4)
CEM43T90§	5.5 (2.1-15.2)
CEM43T100‡	3.6 (1.6-9.6)

Values are presented as median (interquartile range) and were determined from invasive temperatures.

Abbreviations: CEM43 = the cumulative equivalent minutes at 43 °C; CEM43T0 = maximum CEM43; CEM43T10, CEM43T50, and CEM43T90 = temperature achieved in 10%, 50%, and 90% of the sensors during the steady state of hyperthermia treatment, respectively; CEM43T100 = minimum CEM43.

* Data missing for 2 patients.

† Calculated from the session with the "highest" CEM43T50.

‡ Data missing for 29 patients.

§ Data missing for 31 patients.

an effect modifier. Sensitivity analysis showed that the quadratic effect of age was related to LRC, where the hazard ratio for a subsequent LRR decreases until the age of 40 years achieving a constant plateau.

The Bayesian survival parametric alternative model led to comparable decreasing hazard ratios of a subsequent recurrence when the achieved Best CEM43T50 during HT treatment increased. See Supplementary Results (Description of (Bayesian) Accelerated Failure Time Survival models) for more detailed information.

Univariate and multivariate logistic regression analysis confirmed that LRC significantly improves as TD increases ($P = .003$ and $P = .03$, respectively). The estimated LRC by the Best CEM43T50 based on univariate logistic regression is illustrated in Figure 3. The estimated LRC based on multivariate logistic regression also showed that patients with a LRR in the breast without lymph node involvement (Fig. 3A), had better LRC compared with patients where the LRR was located in breast combined with lymph node involvement or patients with chest wall recurrence in

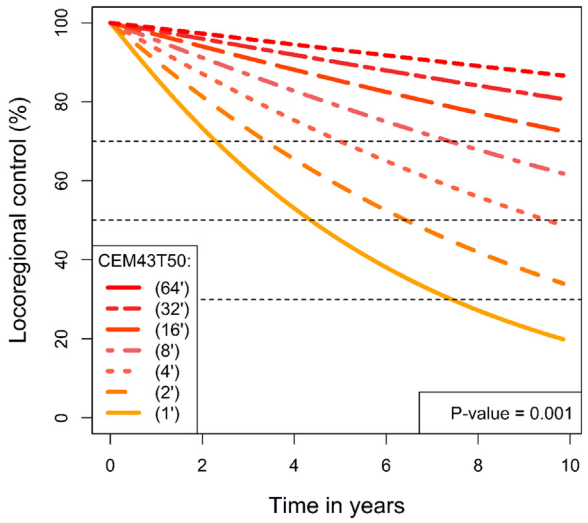

Fig. 2. Estimated probability of locoregional control based on the continuous Best CEM43T50 TD using Weibull univariate regression analysis. The figure illustrates that a 2-fold increase of the continuous Best CEM43T50 TD increases the probability of locoregional control with ~5% to 10% over most of the CEM43T50 TD range at 5-years. *Abbreviations:* CEM43 = the cumulative equivalent minutes at 43 °C; CEM43T50 = temperature achieved in 50% of the sensors during the steady state of hyperthermia treatment; TD = thermal dose.

combination with or without lymph node involvement (Fig. 3B-D).

Figure E2 shows the impact of the Best CEM43T50 on LRC for different reirradiation schedules. Overall patients treated with 8 × 4 Gy reirradiation schedule had a worse prognosis compared with patients treated with 23 × 2 Gy (Figs. E3 and E4 show LRC curves based on multivariate logistic regression analysis). However, despite this overall difference in prognosis, a sufficiently high HT TD above ~20 minutes yields a high LRC for both schedules.

Discussion

This historical cohort study is the first to investigate the TD-effect relationship as a continuous parameter for accurately estimating the probability of LRC at 5-years in patients with LRR breast cancer treated with postoperative reirradiation and HT. Complementary to our previous publication, where we used a dichotomization approach,[8] we here demonstrate that the session with the highest (Best) invasive CEM43T50 is a suitable continuous TD parameter to accurately estimate LRC in patients with LRR breast cancer treated with postoperative reirradiation and HT. The TD-effect relationship found shows that a 2-fold increase in TD led to approximately a 5% to 10% increase in LRC over a large TD range.

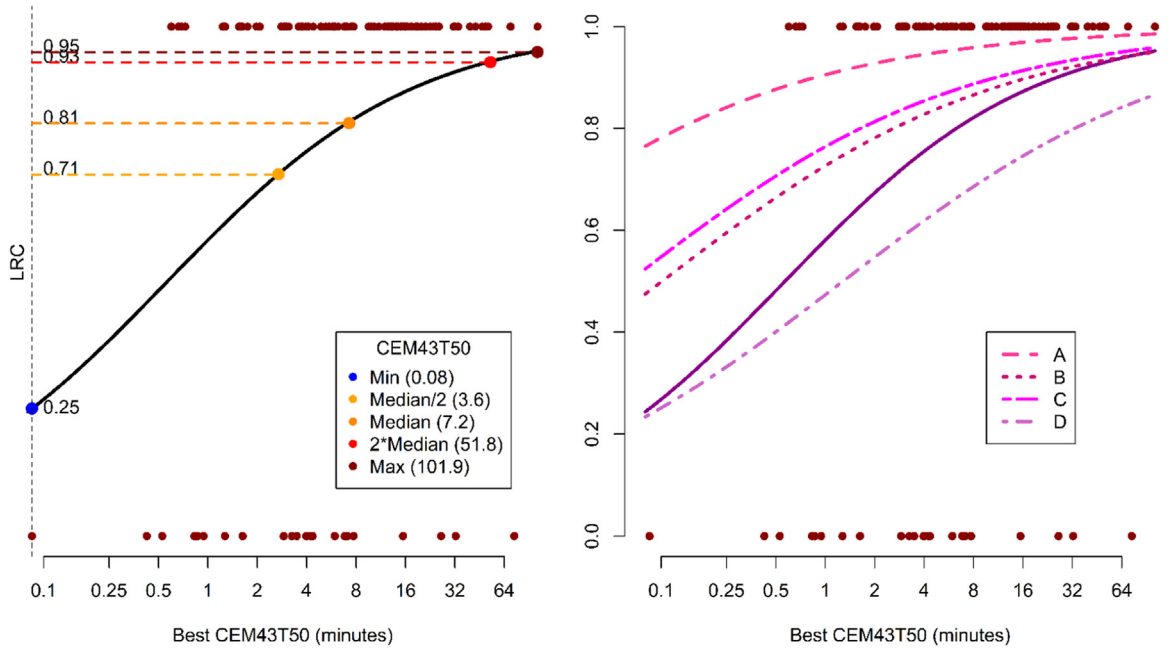

Fig. 3. Locoregional control curves based on univariate (left/black line) and multivariate (right/pink color lines) logistic regression analysis. Dots at the top represent patients without a subsequent LRR; dots at the bottom represent patients with a subsequent LRR. The solid pink line on the right accounts only for age and corresponds to the quadratic effect of age. Followed by A = patients with tumor location breast and no lymph node involvement; B = patients with tumor location chest wall and no lymph node involvement; C = patients with tumor location breast and lymph node involvement; and D = patients with tumor location chest wall and lymph node involvement. *Abbreviations:* CEM43 = the cumulative equivalent minutes at 43 °C; CEM43T50 = temperature achieved in 50% of the sensors during the steady state of hyperthermia treatment; LRC = locoregional control; LRR = locoregional recurrence; Max = maximal; Min = minimal.

Earlier clinical studies analyzing TD-effect relationships in patients with LRR breast cancer also found significant associations between TD parameters and LRC.[12,14,25,26] However, establishing a specific plausible continuous TD dose-effect relationship for estimating LRC from these earlier studies was challenging because of the limitations of a dichotomized approach, limited number of parameters analyzed, limited number of invasive temperature sensors, different ways of calculating TD parameters, a choice of break temperature other than the reference temperature at 43 °C that can affect TD calculation, and heterogeneous cut-off points of the TD parameters used to analyzed the outcome.[12,14,25,26]

Earlier phase 3 randomized controlled trials for patients with recurrent breast cancer with macroscopic tumor lesions treated with reirradiation and HT have not only shown a benefit for HT, but also a dose-effect relationship with a significantly better local control for patients who received a median TD of 11.1 to 14.3 minutes.[14,25] Sherar et al[14] found a continuous increase in complete response from ~20% to ~80% when the Best session minimum TD CEM43T100 increased from 0.1 to 50.0 minutes for patients with unresectable breast cancer. Our current results in patients with a different tumor stage and only microscopic disease, appear to display a similar continuous dose-effect relationship as reported by Sherar et al[14] for macroscopic lesions. Direct comparisons with these earlier studies must be regarded with care, because Jones et al[25] included various types of superficial malignancy in the study population. Also, the percentage of breast cancer patients with a primary or recurrent disease and the percentage of breast cancer patients with prior radiation therapy were unclear, and the endpoint, local control, was defined differently.[14,25]

Fundamentally, the current study shows the important role of HT and of TD to significantly improve LRC in patients with LRR breast cancer with microscopic disease treated with reirradiation, confirming that it is crucial to achieve sufficiently high temperatures in the treatment area, to achieve optimal LRC.[8] Achieving sufficient TD proved challenging in some patients because of occurrence of treatment-limiting local hotspots near scars, these can be resolved by local suppression of the power deposition at hotspot locations. HT was added to 2 different reirradiation schedules, results in Figure E2 demonstrate that high TD can compensate for the less optimal prognosis associated with the 8 × 4 Gy schedule.

The demonstrated TD-effect of CEM43T50 as a continuous parameter appears to follow an Arrhenius relationship, which can be explained by the fundamental working mechanisms of HT.[11] Hyperthermic effects sensitizing tumor cells to radiation include protein denaturation-based mechanisms such as direct kill of hypoxic tumor cells and inhibition of repair of radiation-induced DNA damage. Preclinical research showed that these hyperthermic mechanisms are associated with a strong Arrhenius-like dose-effect relationship.[27−30] Other mechanisms of action include activation of immune-response and induction of vasodilation enhancing blood perfusion, and tumor reoxygenation,[31] which are also associated with a modest dose-effect relationship.[27,30,32]

The current study has limitations. The TD-effect relationship found for LRC is only representative for high-risk LRR breast cancer treated with reirradiation and HT, and cannot be generalized to other types of cancers. The sample size (n = 112) in this study was also low. To address the latter, we performed an additional advanced analysis technique, Bayesian survival regression analysis, which confirmed the validity of the results despite the small sample size. The major effect size can explain why the relatively small sample size sufficed to demonstrate a significant dose-effect relationship.

The study strength is the continuous approach used leading to more accurate quantitative estimates of the TD-effect relationship on LRC, showing ~50% difference in LRC between the lowest and the highest TD achieved. Our previous paper with a dichotomized analysis found ~20% difference between low and high TD groups,[8] and thus significantly underestimated the benefit of adding HT to reirradiation. This underestimation is due to the effect of substantial TD variation within the 2 dichotomized TD groups.[8] Another benefit of reporting a univariate regression analysis based on a continuous parameter, including the ability to predict the expected clinical effect for specific parameter levels, is that it allows a direct comparison of results from different studies.[16] Moreover, the Bayesian method applied as a supplementary analysis validated the robustness of the study results, which very closely reflects the real TD-effect relationship. Additionally, to avoid biases, this study was carried out with well-defined and widely accepted relevant a priori tumor characteristics criteria for patients with high-risk LRR breast cancer.

Everything considered, these results show that the continuous "Best" CEM43T50 is a robust predictive TD parameter for patients with LRR breast cancer treated with postoperative reirradiation combined with HT, and a higher TD is associated with significantly improved LRC. This outcome strongly supports the clinical rationale of adding HT to a postoperative reirradiation schedule for these patients.

Conclusions

Every 2-fold increase in continuous TD during HT treatment and postoperative reirradiation in patients with LRR breast cancer significantly increased the probability of LRC over a very large continuous TD range, resulting in a major overall increase in probability of LRC. These results reconfirm the benefit of adding HT to postoperative reirradiation in LRR breast cancer, and the strong continuous dose-effect relationship of TD emphasizes the need for good temperature monitoring and control.

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