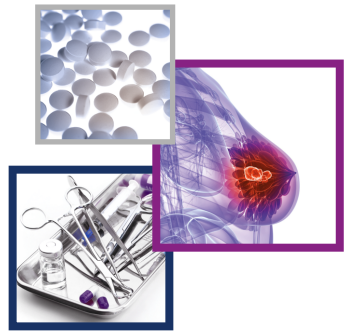
Review

Breast Cancer Management



Hyperthermia and radiotherapy combination for locoregional recurrences of breast cancer: a review

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Practice points

- Locoregional breast recurrences still occur in more or less 5–20% of patients despite receiving adjuvant radiotherapy.
- Resection alone provides limited local control with approximately 33% at 5-years compared to 42% with resection plus other oncologic treatments necessitating curative intent multidisciplinary approach.
- Hyperthermia (HT) is the use of elevated temperature to the degrees of 40–44°C for 30–60 min. The addition of HT to ionizing radiation results in a synergistic effect called radiosensitization.
- Toxicity related to HT includes generally second- and third-degree skin and subcutaneous burns, which are usually self-limited making this combination a favorable easy to use modality.
- Data addressing the use of HT in locoregional breast recurrences (LRBR) is well-validated and includes randomized trials and meta-analysis.
- Thermoradiotherapy enhances local control rates in LRBR with minimal acute, late morbidity and is even more effective in previously irradiated group.
- Two trials conducted by European Society for Hyperthermic Oncology will further clarify the multimodal treatment with chemotherapy in R1/R2 resection and neoadjuvant use of thermoradiotherapy.

Breast cancer is a second common form of malignancy and is one of the leading causes of mortality among cancer patients across the world. Locoregional recurrence occurs in 5–20% of patients despite upfront treatment. Local therapy (surgery plus minus re-irradiation) with or without systemic therapy is generally recommended for management. Local control rates vary; months to years, but a significant percentage lives 5 years. Therefore, treatment strategies to increase response rates are significant. Hyperthermia is one of the most potent radiosensitizers and data from meta-analysis and randomized trials support its use with radiotherapy. This study reviews the biologic rationale and clinical evidence about concomitant use of hyperthermia and radiotherapy in locally-recurrent breast cancer patients.

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Chest wall or whole breast irradiation with or without regional nodal sites is indicated after modified radical mastectomy and breast conserving surgery (BCS), respectively. Although adjuvant radiotherapy (RT) effectively reduces locoregional recurrences, data from randomized trials have demonstrated that this type of recurrences still occur in more or less 5–20% of patients despite receiving adjuvant RT after surgery (mastectomy or BCS) [1–6].

Although locally-recurrent breast cancer (LRBC) is usually accompanied by concurrent or subsequent distant metastases [3,7,8], a significant percentage, more than 50% live 5 years [9]. In a retrospective study of 145 patients with isolated locoregional recurrence of breast cancer following modified radical mastectomy without evidence of distant metastases, 5-year survival rates were 42% overall but it was 100% for a highly favorable subgroup [10].

Therefore, curative intent multidisciplinary approach is mandatory in the management of BC recurrence for optimal outcomes. Moreover, treatment is also important for palliative purposes because, pain, ulceration, bleeding and the image of growing tumoral lesion functionally and psychologically decreases the quality of life.

Management of locoregional recurrence

Patients with local recurrence are mainly divided into two groups: isolated locoregional recurrence and; distant recurrence with locoregional metastatic site. They had been treated initially by mastectomy plus/minus RT or breast conserving therapy (BCS + RT). Local therapy (surgery plus/minus re-irradiation [re-RT]) with or without systemic therapy is generally recommended for management of chest wall recurrences [11,12]. In breast recurrences after BCT are usually managed with mastectomy if it is feasible [13,14]. Some series also explored the role of breast conservation re-surgery and found a recurrence rate of 7–50% [15,16].

Resection alone provides a limited local control (LC) with approximately 33% at 5 years compared with 42% with resection plus other oncologic treatments [17]. In a study of Halverson *et al.*, 224 patients with isolated locoregional recurrences without prior RT, an estimated 5-year LC rate of 57% was achieved for the entire cohort (for isolated chest wall recurrence [63%], nodal recurrence [45%] and both [27%]). This study also showed that tumor control was adequate at all doses ranging from 45 to 70 Gy for completely excised, for example, subclinical disease but a minimum of 60 Gy was required if existing gross disease was less than 3 cm [9]. Tumors at previously irradiated sites have increased hypoxic cell fraction and are less sensitive to RT, so that they can need higher radiation doses to overcome this relative radioresistancy [18]. With cumulative RT doses, serious late complications such as fibrosis, osteonecrosis, rib fracture and brachial plexopathy can occur more frequently [9,19]. Novel RT approaches such as intensity modulated radiation therapy and image-guided RT can minimize radiation exposure to uninvolved critical structures and enables less toxicity profile while increasing the applied dose [20]. Combination therapies with chemotherapeutics and targeted agents as radiosensitizers are another form of increasing therapeutic gain and proved benefit in many cancer sites as the standard treatment modality [21–23].

The rationale behind the use of hyperthermia (HT) combined with other treatment modalities was reviewed by so many authors [24–27]. Clinical outcome improved in various tumor sites, for example, bladder cancer and cervical cancer [28,29]. Data addressing the use of HT in LRBC is also well validated with randomized evidence. Numerous factors such as disease status whether it is primary/recurrent, stage, number of metastatic sites, additional systemic therapies, total RT dose and schedule, the way of HT application and number of HT sessions may affect outcome. Despite positive results with HT, its use is limited to a few centers because it necessitates special equipments and experienced team. HT is also recommended by National Comprehensive Cancer Network (NCCN) for localized recurrences and metastasis [30].

In this current study, we aimed to review the biologic rationale and clinical evidence about concomitant use of HT and RT in LRBC patients.

Hyperthermia

HT is the use of elevated temperature to the degrees of 40–44°C for 30–60 min for its antitumoral effect. Hallmarks of HT were nicely summarized by Issels *et al.* [31]. Direct cell killing effect that is mainly based on the denaturation and aggregation of cellular proteins which is cell-type independent predominates with temperature ≥41°C but normal tissue toxicity impedes its role above 44–45°C in clinical setting. Cells struggle with various types of stress by upregulation of specific proteins, which are heat shock proteins in the case of HT and are responsible for transient thermotolerance which is an unwanted side effect that could be overcome by prolonged heating [32,33].

The addition of HT to ionizing radiation results in a synergistic effect called radiosensitization. Heat-induced enhancement of ionizing radiation effect is generally due to direct and indirect mechanisms. Possible mechanism responsible for direct effect is that heat primarily interferes with the ability of cells to deal with radiation-induced DNA damage. Production of DNA double-strand breaks is thought to be the main mechanism of damage after RT and cells are more susceptible to this effect in the G2 & M phase of cell cycle. On the other hand, cells yield sensitivity to heat in the M & S phase. The difference in cell cycle sensitivity refers to the diversity of molecular mechanisms of cell death induction after HT. Heat inhibits the repolymerization step in the repair of base damages which lead to the formation of secondary DNA double-strand breaks. Moreover, mild HT can also interfere with the homologs recombination process thus, block double-strand break DNA repair process [26,34,35].

As mentioned above, there is also an additional indirect effect of heat that causes killing of the radioresistant hypoxic cells. Malignant cells have different physiology with specialized microenvironment and chaotic vasculature

that makes them hypoxic and acidic. Unlike RT, this architecture makes tumoral cells more prone to HT. Additionally, compromised blood flow further deteriorates microenvironmental conditions leading to increased thermal enhancement. The vascular supply to a tumor can also play a role. This can be illustrated by the fact that larger tumors are generally less well perfused than smaller tumors and as a result contain a higher heat sensitive proportion. Another vascular-mediated thermoradiosensitization is related to the effect of heat on the tumor vasculature, in other words, at high thermal doses blood flow decreases and it increases at low doses. This can directly be translated to tumor oxygenation status; so that high temperature yields decreased tumor oxygenation and mild HT yields increased tumor oxygenation. HT-mediated direct cytotoxicity predominates when cells are hypoxic and RT effect predominates regarding oxygenated cells [26,35,36].

HT and RT combination (thermo-RT) can also affect the immune system. Cell death by necrosis can lead to inflammation due to loss of cellular membrane integrity and the release of danger signals. Combined therapy with HT and RT fosters the release of danger signals such as HMGB1 and HSP. Local HT increases the infiltration and function of dendritic cells which have the main role in immune activation of innate and adaptive immune response finally leading to specific antitumor immunity [32]. Immunotherapy has made notable progress in cancer therapy in the recent years, combination with HT can also be a promising approach for cure [37].

The main target for the most conventional systemic chemotherapeutics is DNA but with a different mechanism of action, for example, platins inhibit DNA synthesis and anthracyclines inhibit topoisomerase-2 thus blocks DNA replication. Possible mechanisms for the thermal chemosensitization include an increased rate of alkylation, an increase in drug uptake and the inhibition of drug-induced sublethal or lethal damage repair [33,38]. Chemotherapy and heat interaction depends on the agent used in some extent. Platins and alkylating drugs show linear enhanced cytotoxicity with heat whereas antimetabolites like 5-fluorouracil do not interact. Another possible mechanism for chemosensitization is the increased blood flow and vascular permeability within the tumoral tissue by heat, which causes enhanced drug uptake. It has been shown, for example, for cisplatin that heat could revert acquired drug resistance also [39]. However, studies on the combination of HT and chemotherapy in the management of BC are beyond the scope of this article so this topic is not explained in detail.

Recently, Dewhirst *et al.* reviewed the new features of HT biology, for example, altered metabolism, evasion of immune destruction, tumor-promoting inflammation and cellular microenvironment in an attempt to present emerging fields of study on this subject [40].

Calculation of the thermal dose applied in HT has been successfully integrated into the concept of a 'thermal isoeffect dose' in which heating time periods at different temperatures are converted into equivalent heating minutes at 43°C. For consecutively applied heat treatments, the thermal isoeffect dose for each single treatment can be added to give the cumulative equivalent minutes at 43°C (CEM43) [41].

There are several ways for applying HT: superficial; interstitial and intracavitary; regional; and whole body HT. Temperature increase is mostly generated with electromagnetic waves by various technologies. Electromagnetic waves are delivered via capacitor plates and radiative antennas. Capacitor plates can cause overheating of fatty tissues. Radiative heating yields more favorable temperature distributions for superficial heating [42]. Monitoring of the temperature in the tumor and the surrounding tissue is mandatory. It can be performed by temperature probes or noninvasive methods. Guidelines to improve quality assurance problems have been recently outlined by Trefna *et al.* [43].

Toxicity of combined therapies is mainly related to RT and chemo and the site of treatment. Toxicity related to HT includes generally second- and third-degree skin and subcutaneous burns, which are usually self-limited [44]. In a prospective randomized trial of superficial tumors (<3 cm depth) comparing RT versus HT combined with RT, almost half of the patients (46%) experienced HT-related thermal burns but only one of whom was grade 3 and healed with conservative measures [41]. Invasive catheters for thermometry can also be problematic. In the aforementioned study, three patients had pain which required analgesics and two had infection which required topical antibiotics.

Literature search

A broad search was conducted between November 2015 and December 2016 on Pubmed (National Library of Medicine [45]) using all field and entering *"Hyperthermia, Radiotherapy and Breast Cancer"*. Clinical studies with patient number <50 and nonhuman studies were excluded. Electronic copies of relevant studies in English were obtained via hospital library.

Clinical data

Thermo-RT studies are summarized in Table 1.

High level of evidence for BC recurrences

The first data were from the radiation therapy oncology group, with protocol number 8104 a randomized Phase III trial [48]. They included 307 patients with superficial tumors (single lesion, n = 250; multiple lesions, n = 57), 68 of which (RT, n = 33; RT + HT, n = 35) had breast or chest wall recurrences (22%; <3). RT was consisting of 4 Gy per fraction twice weekly to a total of 32 Gy concurrent with two HT sessions weekly to a total of eight. However, only half of the patients received planned treatment in the combined arm. The primary end point was the rate of complete response (CR), which was 30 versus 32% in favor of combined arm without statistical significance. Subset analysis showed improved outcome in the lesions of breast and chest wall <3 cm with a CR rate of 62–40% in favor of HT-arm without statistical significance. Survival was poor, <10% at 2 years which was attributed to patients' advanced metastatic stage. Toxicity related to HT (thermal blisters) was seen in 30% in combined arm versus 0% in the RT only arm otherwise it was well balanced between the two. Authors did not mention the severity of thermal injury and how they managed to treat it.

For unresectable BC recurrences, HT added to RT has been shown to be effective in a combined analysis of five randomized trials [47]. Due to poor patient accrual, it was decided to pool data so as to increase statistical power. A total of 306 patients (RT arm, n = 135; RT + HT, n = 171) were enrolled and approximately 50% were free of distant disease. Randomization was done according to treating center, one-to-one or two-to-three to provide more information on thermal parameters. The patients were stratified according to previous RT and area, diameter and depth of disease in different centers. There were three sets of patients: untreated primary inoperable BC; those with recurrent disease in sites not previously irradiated; and those with recurrences in sites having previously been irradiated of which 71% was at chest wall. A total of 95% received planned treatment. Applied RT doses were 60–69.3 Gy for previously untreated sites and 39.8–47.2 Gy for treated sites. Two centers showed statistically significant benefit for the addition of HT and three of them did not. This may be because of variations in heat prescriptions, number of patients involved, different clinical characteristics and RT dose. Overall, thermo-RT enhanced CR rates approximately 20% (41 vs 59%; $p < 0.001$). No significant difference was found between treatment arms according to the treatment area. The HT effect was somewhat less with deeper tumors without statistical significance. The benefit was greater in previously irradiated sites so that CR rate was 57 versus 31% in favor of combined arm. During follow-up of the patients who achieved a CR, local relapse was observed in 17 and 31% in RT + HT and only RT arm, respectively. LC was better in combined arm. (HR: 0.67; 95% CI: 0.5–0.89; p = 0.007). Median overall survival (OS) was 18 months for the entire cohort and there was no statistically significant difference in OS between HT and no HT-arm (the 2-year OS was 36 and 41 months). Overall both treatments are well tolerated; patients generally completed prescribed RT and HT schedules. Since a detailed comparative analysis of the degrees of toxicity experienced was not possible, only common acute and late adverse effects were recorded and apparently treatment related side effects were observed more commonly in RT + HT arm (n = 127, n = 226).

Another study was a randomized dose escalation trial of simultaneous thermo-RT applied to the chest wall for high-risk BC patients with minimal to no residual disease and no prior radiation therapy [49]. Patients were randomized to either as arm 1 (n = 52), receiving four HT sessions and arm 2 (n = 7) receiving eight HT sessions. All cohorts were prescribed to a dose of 46–50 Gy with a 16 Gy boost to a total of 66 Gy and 41–43°C for 60 min HT. The primary tumor site was included in HT field every time, while the adjacent area was randomized to either HT or no HT electively. Of 57 patients, 17 (30%) experienced disease recurrence, with one isolated to a total of four (7%) locoregional failures. The two chest wall recurrences were diffuse, involving both the heated and control sites. Univariate and multivariate analyses showed no statistically significant association with age, RT dose and number of HT sessions or receptor status. A total of 25 moist desquamations were observed in the chest walls; three of these were seen in heated sites and one in the control site. Late toxicity was determined beyond 3 months postradiation and eight patients had ≥grade 3. The majority of late morbidities were asymptomatic pigment changes (n = 23) with no ulceration. Although Kaplan–Meier curves for toxicity profiles were separated between heated and unheated sites suggesting that late chest wall morbidity might be greater with HT, but this difference did not reach statistical difference. The authors concluded that elective simultaneous thermo-RT for high-risk BC is feasible with acceptable toxicity and good LC. Four or may be eight HT sessions can safely be prescribed with conventionally fractioned high-dose RT.

Table 1. Thermoradiotherapy studies.

Study design	Study (year)	Patients (n)	Median dose	cHT	F-up (months)	A.tox ≥G3	L.tox ≥G3	CR	LC	Survival	Ref.
Meta-analysis	Datta *et al.* (2015)	2110	38.2 Gy (range: 26–60)	Median 7	–	14.4% in the HT+RT arm in all the studies	5.2% in all the studies	Two arms trials: 60.2% in the RT+HT, 38.1% RT; Single arm trials: 63.4% in the HT+RT	66.6% in all the studies	–	[46]
	Vernon *et al.* (1996)	306	32 Gy	Twice weekly	21 mo	14% in the RT+HT, 3% in the RT	1% in the HT+RT	59% in the RT+HT, 41% in the RT	83% in the HT+RT, 69% in the RT	Median:18 mo	[47]
Randomized	Perez *et al.* (1991)	307	32 Gy	Twice weekly	–	21% in the HT+RT, 19% in the RT	20% in the HT+RT, 15% in the RT	32% in the RT+HT, 30% in the RT	–	43% at 6 mo, 23% at 1 y for all patients	[48]
	Jones *et al.* (2005)	109	Median 41 Gy (range: 18–66) in the re-RT arm, median 60 Gy (range: 24–70) in the nonirradiated arm	Twice weekly	–	5% in the RT+HT, 2% in the RT	–	66.1% in the RT+HT, 42.3% in the RT	48% in the RT+HT, 25% in the RT	31% at the HT+RT, 15% in the RT at 2 y	[41]
	Varma *et al.* (2012)	57	46–59Gy	Simultaneously (5 days a week)	76 mo (19–120)	–	14% in all the cases	–	70% for all cases	–	[49]
Retrospective	Lee *et al.* (1997)	151	40 Gy	Once (28%) or twice (72%) weekly	11 mo	NS	17%	39%	78% at 3 y, 65% at 5 y	%8 at 5 y median: 11 mo	[50]
	Welz *et al.* (2005)	50	60 Gy (range: 44–66.4)	Twice weekly	28 mo	16%	NS	NS	80% at 3 y	89% at 3 y	[51]
	Wahl *et al.* (2008)	81	48 Gy (range: 14.4–72.5)	NS	12 mo (1–144)	5%	2%	57%	66% at 1 y	64% at 1 y	[52]
	Oldenberg *et al.* (2012)	78	32 Gy	Once weekly	64 mo (8–151)	32%	40% at 3 y	NS	78% at 3 y, 65% at 5 y	66% at 3 y median: 59.2	[53]
	Linthorst *et al.* (2013)	198	32 Gy (range: 28–36)	Once- or twice-weekly	42 mo	4%	11.9%	NS	83% at 3 y, 78% at 5 y	75% at 3 y, 60% at 5 y, 36% at 10 y median: 82 mo	[44]
	Linthorst *et al.* (2015)	248	32 Gy	Once weekly	32 mo (1–164)	Non	1%	70%	53% at 1 y, 40% at 3 y, 39 % at 5 y	66% at 1 y, 32% at 3 y, 18% at 5 y	[54]
	Oldenborg *et al.* (2015)	414	50 Gy	301 p once weekly 113 p twice weekly	17 mo (0.4–212)	24%	23% at 3 y	86%	25% at 3 y	37% at 3 y median: 17 mo	[55]
	Refeat *et al.* (2015)	127	NS	Twice weekly	13 mo (0–182)	NS	NS	52.7%	55.1%	58.3% at 1 y, 29.5% at 3 y, 22.5% at 5 y median: 16 mo	[56]

A.tox: Acute toxicity; cHT: Concurrent hyperthermia; CR: Complete response; F-up: Follow-up; LC: Local control; L.tox: Late toxicity; mo; Months; NS: Not specified; re-RT: Re-irradiation; y: years.

An effort to test the clinical value of HT, based on dosimetric principles was made by Jones *et al.* [41]. Superficial tumors ≤3 cm were randomized to HT versus no HT if determined as heatable with an initial thermal dose of 0.5 CEM 43°C T_{90} in 1 h. HT arm was subject to a minimum 10 CEM 43°C T_{90}. RT was applied to the gross disease with a 2–3 cm margin and to a total dose of 30–66 Gy for previously irradiated patients and 60–70 Gy for unirradiated ones. A total of 108 patients (n = 70; 65% breast/chest wall) were randomized. Metastasis at enrollment (n = 17 vs n = 16) and additional systemic therapies (n = 34 vs n = 33) were well balanced between groups. The CR rate was 66 versus 42% in HT versus no HT arm (odds ratio [OR]: 2.7; 95% CI; p = 0.02). The improvement in LC was most obvious in previously irradiated group (CR: 68 vs 24%). At the time of analysis, a total of 38 patients were locally controlled, 26/38 were in HT arm. High dose HT was generally well tolerated, only one patient experienced third degree burn. Catheter-related complications were seen in six patients, required analgesia for pain, antibiotics for infection and first aid for hemorrhage. Overall, 17/108 patients had treatment break because of RT-related toxicity.

Apart from this randomized evidence, a systematic review and meta-analysis were carried out by Datta *et al.*, in locally recurrent BCs [46]. They included 34 studies (two-arm, n = 8; single-arm, n = 26) with a total of 2110 patients, 779 of which were previously irradiated. Patients were treated with a median of seven HT sessions and an average temperature of 42.5°C was attained. Mean RT dose was 38.2 Gy (range: 26–60 Gy). In the two-arm studies, a CR of 60.2% was achieved with RT + HT versus 38.1% with RT alone (OR: 2.64; 95% CI: 1.66–4.18; p < 0.0001). In single-arm studies, RT + HT attained a CR of 63.4% (event rate = 0.62; 95% CI: 0.57–0.66). Patients who had been previously irradiated a CR of 66.7% (event rate = 0.64; 95% CI: 0.58–0.70) was achieved. Mean acute and late grade III/IV toxicities with RT + HT were 14.4 and 5.2%, respectively. But it has to be kept in mind that these studies were reported between 1981 and 2015 so toxicity criteria are nonuniform. Based on these results, authors concluded that thermo-radiation enhances the CR rates in LRBC over RT alone by 22% with minimal acute and late morbidity and is highly effective even in previously irradiated group.

HT for irresectable BC recurrences

Recently, two retrospective studies with relatively large patient numbers came out. Oldenborg *et al.* [55] evaluated 414 patients with unresectable BC recurrences (32% isolated locoregional) who received a median 50 Gy RT previously. Radiation was given at 4 or 3 Gy per fraction, two- or four-times per week, to a total dose of 32 or 36 Gy respectively. HT was applied once or twice a week for 60 min after RT. This study had the largest cohort until today and 74% were treated for one or more previous recurrences with surgery, radiation, systemic therapy or a combination before current re-RT and HT. Treatment was well tolerated with a 95% completion rate. CR of 58% was achieved. Median follow-up was 17 months (range: 0.4–212) with a 3-year LC rate of 25%. Grade ≥3 acute and late toxicity regarding re-RT were observed in 24 and 18% respectively with five treatment related deaths. HT induced adverse effect was seen in 53 (18%) of patients, only six had grade 3 blisters. LC was negatively influenced by number of previous recurrences, presence of systemic disease, site and size of recurrence and short interval between them, which emphasizes the importance of early referral.

Linthorst and colleagues also published their experience about re-RT and HT for unresectable BC recurrences [54]. A total of 248 patients (64% isolated locoregional recurrence) were treated with twice-weekly RT to a total dose of 32 Gy in 4 Gy fractions followed by weekly HT. Median follow-up was 32 months (range: 1–164) and CR rate was 70%. LC rate at 1.3 and 5 years was 53, 40 and 39%, respectively. Acute radiation toxicity which was generally self-limited was seen in 29% of patients. Skin necrosis in three patients was assessed as grade 3 late toxicity and was treated with either surgery or hyperbaric oxygen. Grade <3 thermal burns occurred in 23% of cohort and recovered without further intervention. Authors reported a 5 and 2% LC at 5 and 10 years respectively with a 10% survival at 10 years; a relatively good outcome after locoregional recurrence indicating that optimal management is mandatory.

Evidence in adjuvant setting after surgery for recurrent disease

Management of subclinical disease was investigated in aforementioned randomized trial in a setting of no prior RT [49] and apart from this, Linthorst *et al.*, retrospectively reviewed 198 patients with recurrent BC treated with re-RT and HT [44]. The indication for combined therapy was microscopic residual disease following resection or systemic therapy for 91 (46%) patients and was elective purposes in areas at high risk for 107 (54%) patients. Patients were given a total of 32 Gy RT in 4 Gy fractions twice weekly. HT was administered 60 min at 72-h intervals once- or twice-weekly, to a total of four (89%) or eight (9%) sessions. A total of 9% of the patients had

distant metastases. Median follow-up was 42 months (range: 1–194) and 1-, 3- and 5-year LC rates were 93, 83 and 78% respectively. The 3 and 5 years OS rates are 75 and 60% with a median survival of 82 months. 35 patients (18%) recurred locoregionally after 1–74 months. High number of previous chemotherapies and surgeries were significantly associated with duration of LC rates in multivariate analysis which was attributed to the importance of early referral. Acute RT and HT toxicity ≥grade 3 were seen in six (3%) patients; four of which were corrected with surgical intervention and all healed uneventfully. Grade 3 and 4 late toxicity was seen in 10% after a median follow-up of 14 months (4–97). High number of thermometry sensors and depth of target volume were associated with more HT toxicity in multivariate analysis ($p = 0.021$; $p = 0.034$). The high superficial temperature was correlated with grade 2 and 3 thermal burns ($p = 0.006$). Elective treatment with thermo-RT results in longer LC with acceptable toxicity. The authors suggested this type of combined modality to high-risk patients.

The role of HT in reconstructed breast

Patients with recurrent breasts can be treated with mastectomy and local excision which needs some degree of reconstruction for wound covers or aesthetic purposes. Reliability of grafts and flaps in irradiated regions were known as safe but outcome in case of re-RT and HT is less clear. A total of 36 patients with 37 breast reconstructions treated with re-RT and HT were reviewed [57]. All patients except one received 4 Gy/frx of total 32 Gy RT twice weekly and a median four (range: 4–8) HT sessions after RT within 30–60 min to a duration of 60 min. Median follow-up was 64 months (range: 4–188 months). CR was 80% in 15 patients with macroscopic tumor and a 92% LC was achieved in 21 patients with subclinical disease. The OS was 83% after 1 year and 46% after 5 years with a LC rate of 83 and 69% at corresponding years. Acute HT toxicity was observed in 17 and three of them were grade 3 requiring surgical intervention. No correlation was found between HT-related toxicity and thermal dose parameters. Acute grade 3 RT toxicity was seen in one and recovered with conservative treatment. Two patients experienced late RT toxicity but healed well. Authors concluded that re-RT combined with HT is safe and effective.

Conclusion

HT can be administered safely without any substantial toxicity. It significantly improves CR rates and locoregional control in BC recurrences without survival benefit. Thermotherapy should be considered, particularly in patients who have undergone prior RT so that total dose of re-RT is restricted. Different outcomes between study groups may emphasize early referral of patients so that benefit with thermo-RT may be translated into the OS benefit. Moreover, advances in understanding tumor biology, for example, tumor oxygenation and risk factors of recurrence can lead to differentiation of BC subgroups that will benefit more with HT.

Future perspective

European Society for Hyperthermic Oncology (ESHO) conducted two clinical trials about local HT as a treatment modality for breast carcinoma. The first one is the prospective Phase I/II study of local HT, taxol-chemotherapy and RT in nonresectable or incomplete resected (R1/R2) breast carcinoma recurrence and the second one is the prospective Phase I/II study of noninvasive MRI-guided high temperature HT by focused ultrasound before surgery of bioptically proofed breast carcinoma. These trials can also contribute to the use of HT in different settings [58]. Immunotherapy and HT combination may also be a promising antitumor therapy [59].

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References

1. Darby S, McGale P, Correa C *et al.* The Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breastconserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomized trials. *Lancet* 378(9804), 1707–1716 (2011).
2. Fisher B, Jeong JH, Anderson S *et al.* Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N. Engl. J. Med.* 347(8), 567–575 (2002).
3. Fisher B, Anderson S, Bryant J *et al.* Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N. Engl. J. Med.* 347(16), 1233–1241 (2002).

4. Li S, Yu KD, Fan L, Hou YF, Shao ZM. Predicting breast cancer recurrence following breast-conserving therapy: a single-institution analysis consisting of 764 Chinese breast cancer cases. *Ann. Surg. Oncol.* 18(9), 2492–2499 (2011).
5. Min SY, Lee SJ, Shin KH *et al.* Locoregional recurrence of breast cancer in patients treated with breast conservation surgery and radiotherapy following neoadjuvant chemotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 81(5), 697–705 (2011).
6. German Breast Cancer Study Group (GBSG). Therapy of small breast cancer four year results of a prospective non-randomized study. *Breast Cancer Res. Treat.* 34(1), 1–13 (1995).
7. Aberizk JW, Silver B, Henderson IC *et al.* The use of radiotherapy for treatment of isolated locoregional recurrence of breast carcinoma after mastectomy. *Cancer* 58, 12–18 (1986).
8. Bedwinek JM, Lee J, Fineberg B *et al.* Prognostic indicators in patients with isolated local-regional recurrence of breast cancer. *Cancer* 47(9), 2232–2235 (1981).
9. Halverson KJ, Perez CA, Kuske RR *et al.* Isolated local-regional recurrence of breast cancer following mastectomy: radiotherapeutic management. *Int. J. Radiat. Oncol. Biol. Phys.* 19(4), 851–858 (1990).
10. Willner J, Kiricuta IC, Kölbl O. Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis. *Int. J. Radiat. Oncol. Biol. Phys.* 37(4), 853–863 (1997).
11. Clemons M, Hamilton T, Mansi J *et al.* Management of recurrent locoregional breast cancer: oncologist survey. *Breast* 12(5), 328–337 (2003).
12. Schwaibold F, Fowble BL, Solin LJ *et al.* The results of radiation therapy for isolated local regional recurrence after mastectomy. *Int. J. Radiat. Oncol. Biol. Phys.* 21(2), 299–310 (1991).
13. Salvarodi B, Marubini E, Micele R *et al.* Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. *Br. J. Surg.* 86(1), 84–87 (1999).
14. Alpert TE, Kuerer HM, Arthur DW *et al.* Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs salvage breast conservation surgery and prognostic factors for salvage breast preservation. *Int. J. Radiat. Oncol. Biol. Phys.* 63, 845–851 (2005).
15. Kurtz JM, Jacquemier J, Amalric R *et al.* Is breast conservation after local recurrence feasible? *Eur. J. Cancer* 27(3), 240–244 (1991).
16. Dalberg K, Mattsson A, Sandelin K, Rutqvist LE. Outcome of treatment for ipsilateral breast tumor recurrence in early-stage breast cancer. *Breast Cancer Res. Treat.* 49(1), 69–78 (1998).
17. Dahlstrøm KK, Andersson AP, Andersen M, Krag C. Wide local excision of recurrent breast cancer in the thoracic wall. *Cancer* 72(3), 774–777 (1993).
18. Okunieff P, Urano M, Kallinowski F *et al.* Tumors growing in irradiated tissue: oxygenation, metabolic state, and pH. *Int. J. Radiat. Oncol. Biol. Phys.* 21(3), 667–673 (1991).
19. Harkenrider MM, Wilson MR, Dragun AE. Re-irradiation as a component of the multidisciplinary management of locally recurrent breast cancer. *Clin. Breast Cancer* 11(3), 171–176 (2011).
20. Buwenge M, Cammelli S, Ammendolia I *et al.* Intensity modulated radiation therapy for breast cancer: current perspective. *Breast Cancer (Dove Med. Press)* 9, 121–126 (2017).
21. Eifel PJ, Winter K, Morris M *et al.* Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90–01. *J. Clin. Oncol.* 22(5), 872–880 (2004).
22. Mak RH, Hunt D, Shipley WU *et al.* Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined modality therapy: a pooled analysis of radiation therapy oncology group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J. Clin. Oncol.* 16(4), 1310–1317 (1998).
23. Al-Sarraf M, LeBlanc M, Giri PG *et al.* Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized intergroup study 0099. *J. Clin. Oncol.* 16(4), 1310–1317 (1998).
24. van der Zee J. Heating the patient: a promising approach? *Ann. Oncol.* 13(8), 1173–1184 (2002).
25. Wust P, Hildebrandt B, Sreenivasa G *et al.* Hyperthermia in combined treatment of cancer. *Lancet Oncol.* 3(8), 487–497 (2002).
26. Horsman MR, Overgaard J. Hyperthermia: a potent enhancer of radiotherapy. *Clin. Oncol. (R. Coll. Radiol.)* 19(6), 418–426 (2007).
27. Moyer HR, Delman KA. The role of hyperthermia in optimizing tumor response to regional therapy. *Int. J. Hyperthermia* 24(3), 251–261 (2008).
28. Franckena M, Stalpers LJ, Koper PC *et al.* Long-term improvement in treatment outcome after radiotherapy and hyperthermia in locoregionally advanced cervix cancer: an update of the Dutch deep hyperthermia trial. *Int. J. Radiat. Oncol. Biol. Phys.* 70(4), 1176–1182 (2008).
29. Colombo R, Da Pozzo LF, Salonia A *et al.* Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. *J. Clin. Oncol.* 21, 4270–4276 (2003).
30. NCCN Guidelines. www.nccn.org/professionals/physician_gls/pdf/breast.pdf

31. Issels R, Kampmann E, Kanaar R *et al.* Hallmarks of hyperthermia in driving the future of clinical hyperthermia as targeted therapy: translation into clinical application. *Int. J. Hyperthermia* 32(1), 89–95 (2016).
32. Schildkopf P, Ott OJ, Frey B *et al.* Biological rationales and clinical applications of temperature controlled hyperthermia – implications for multimodal cancer treatments. *Curr. Med. Chem.* 17(27), 3045–3057 (2010).
33. Issels RD. Hyperthermia adds to chemotherapy. *Eur. J. Cancer* 44(17), 2546–2554 (2008).
34. Krawczyk PM, Eppink B, Essers J *et al.* Mild hyperthermia inhibits homologous recombination, induces BRCA2 degradation, and sensitizes cancer cells to poly (ADP-ribose) polymerase-1 inhibition. *Proc. Natl Acad. Sci. USA* 108(24), 9851–9856 (2011).
35. Vaupel P, Kallinowski F, Okunieff P. Blood flow oxygen and nutrient supply, and metabolic microenvironment of human tumors: a review. *Cancer Res.* 49(23), 6449–6465 (1989).
36. Vaupel P, Mayer A, Hockel M. Tumor hypoxia and malignant progression. *Methods Enzymol.* 381, 335–354 (2004).
37. Strauch ED, Fabian DF, Turner J. Combined hyperthermia and immunotherapy treatment of multiple pulmonary metastases in mice. *Surg. Oncol.* 3(1), 45–52 (1994).
38. Issels RD, Lindner LH, Verweij J *et al.* Neo-adjuvant chemotherapy alone or with regional hyperthermia for localized high-risk soft-tissue sarcoma: a randomized Phase 3 multicentre study. *Lancet Oncol.* 11(6), 561–570 (2010).
39. Hettinga JV, Konings AW, Kampinga HH. Reduction of cellular cisplatin resistance by hyperthermia – a review. *Int. J. Hyperthermia* 13(5), 439–457 (1997).
40. Dewhirst MW, Lee CT, Ashcraft KA. The future of biology in driving the field of hyperthermia. *Int. J. Hyperthermia* 32(1), 4–13 (2016).
41. Jones EL, Oleson JR, Prosnitz LR *et al.* Randomized trial of hyperthermia and radiation for superficial tumors. *J. Clin. Oncol.* 23, 3079–3085 (2005).
42. Kok HP, Crezee J. A comparison of the heating characteristics of capacitive and radiative superficial hyperthermia. *Int. J. Hyperthermia* 33(4), 1–9 (2017).
43. Trefna HD, Crezee J, Schmidt M *et al.* Quality assurance guidelines for superficial hyperthermia clinical trials: II. Technical requirements for heating devices. *Strahlenther. Onkol.* 193(5), 351–366 (2017).
44. Linthorst M, van Geel AN, Baaijens M *et al.* Re-irradiation and hyperthermia after surgery for recurrent breast cancer. *Radiother. Oncol.* 109(2), 188–193 (2013).
45. NLB. http://www.ncbi.nlm.nih.gov
46. Datta NR, Puric E, Klingbiel D *et al.* Hyperthermia and radiation therapy in locoregional recurrent breast cancers: a systematic review and meta-analysis. *Int. J. Radiat. Oncol. Biol. Phys.* 94(5), 1073–1087 (2015).
47. 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 cotrolled trials. International Collaborative Hyperthermia Group. *Int. J. Radiat. Oncol. Biol. Phys.* 35(4), 731–744 (1996).
48. Perez CA, Pajak T, Emami B *et al.* Randomized Phase III study comparing irradiation and hyperthermia with irradiation alone in superficial measurable tumors. *Am. J. Clin. Oncol.* 14(2), 133–141 (1991).
49. Varma S, Myerson R, Moros E *et al.* Simultaneous radiotherapy and superficial hyperthermia for high-risk breast carcinoma: A randomized comparison of treatment sequelae in heated versus non-heated sectors of the chest wall. *Int. J. Hyperthermia* 28(7), 583–590 (2012).
50. Lee HK, Antell AG, Perez CA, *et al.* Superficial hyperthermia and irradiation forrecurrent breast carcinoma of the chest wall: prognostic factors in 196 tumors. *Int. J. Radiat. Oncol. Biol. Phys*. 40(2), 365–375 (1998).
51. 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. Hyperthermia* 21(2), 159–167 (2005).
52. Wahl AO, Rademaker A, Krystina D *et al.* Multi-institional review of repeat irradiation of chest wall and breast for recurrent breast cancer. *Int. J. Radiat. Oncol. Phys.* 70(2), 477–484 (2008).
53. Oldenborg 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. Hyperthermia* 26(2), 136–144 (2010).
54. 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.* 117(2), 217–222 (2015).
55. Oldenborg S, Griesdoorn V, Os R *et al.* Re-irradiation and hyperthermia for irresectable locoregional recurrent breast cancer in previously irradiated area: size matters. *Radiother. Oncol.* 117(2), 223–228 (2015).
56. Refeat T, Sachdev S, Sathiaseelan V *et al.* Hyperthermia and radiation therapy for locally advanced or recurrent breast cancer. *Breast* 24(4), 418–425 (2015).
57. Linthorst M, Van Rhon GC, Van Geel AN *et al.* The tolerance of re-irradiation and hyperthermia in breast cancer patients with reconstructions. *Int. J. Hyperthermia* 28(3), 267–277 (2012).
58. European Society for Hyperthermic Oncology. Studies on breast cancer. www.esho.info/professionals/studies/breast.html

59. Toraya-Brown S, Fiering S. Local tumor hyperthermia as immunotherapy for metastatic cancer. *Int. J. Hyperthermia* 30(8), 531–539 (2014).