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Clinical Investigation

Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis

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Summary

A systematic review and meta-analysis was carried out to evaluate the treatment outcomes of locally recurrent breast cancers (LRBCs) with radiation therapy and hyperthermia. Results from 34 studies, totaling to 2110 patients, shows that radiation therapy and hyperthermia could provide a complete response in more than 60% of these patients. In those who were reirradiated, 66.6% achieved a complete response without any additional significant treatment morbidity. Thermoradiation therapy thus provides a safe and effective therapeutic option in LRBCs.

Purpose: To conduct a systematic review and meta-analysis to evaluate the outcome of hyperthermia (HT) and radiation therapy (RT) in locally recurrent breast cancers (LRBCs).

Methods and Materials: A total of 708 abstracts were screened from 8 databases according to the PRISMA guidelines. Single-arm and 2-arm studies, treating LRBCs with HT and RT but without surgery (for local recurrence) or concurrent chemotherapy were considered. The evaluated endpoint was complete response (CR).

Results: Thirty-one full text articles, pertaining to 34 studies, were shortlisted for the meta-analysis. Eight were 2-arm (randomized, n = 5; nonrandomized, n = 3), whereas 26 were single-arm studies. In all, 627 patients were enrolled in 2-arm and 1483 in single-arm studies. Patients were treated with a median of 7 HT sessions, and an average temperature of 42.5°C was attained. Mean RT dose was 38.2 Gy (range, 26-60 Gy). Hyperthermia was most frequently applied after RT. In the 2-arm studies, a CR of 60.2% was achieved with RT + HT versus 38.1% with RT alone (odds ratio 2.64, 95% confidence interval [CI] 1.66-4.18, $P<.0001$). Risk ratio and risk difference were 1.57 (95% CI 1.25-1.96, $P<.0001$) and 0.22 (95% CI 0.11-0.33, $P<.0001$), respectively. In 26 single-arm studies, RT + HT attained a CR of 63.4% (event rate 0.62, 95% CI 0.57-0.66). Moreover, 779 patients had been previously irradiated (696 from single-arm and 83 from 2-arm studies). A CR of 66.6% (event rate 0.64, 95% CI 0.58-0.70) was achieved with HT and reirradiation (mean ± SD dose: 36.7 ± 7.7 Gy). Mean acute and late grade 3/4 toxicities with RT + HT were 14.4% and 5.2%, respectively.

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Conclusions: Thermoradiation therapy enhances the likelihood of CR rates in LRBCs over RT alone by 22% with minimal acute and late morbidities. For even those previously irradiated, reirradiation with HT provides locoregional control in two-thirds of the patients. Thermoradiation therapy could therefore be considered as an effective and safe palliative treatment option for LRBCs.

Introduction

Locoregional recurrence in breast cancers (LRBCs) can occur in up to one-third of previously treated patients, and almost 80% of these usually present within the first 5 years of their primary treatment (1, 2). Even after adjuvant radiation therapy (RT), 5% to 15% of the patients could still develop locoregional recurrences (3-6). Management of these lesions is a therapeutic challenge and involves surgery, RT either alone or in combination with chemotherapy (CT), or hormonal interventions (1, 7). After mastectomy, often considered the gold standard, 2% to 31% of patients still present with a second local recurrence (8). Reirradiation (ReRT) could pose the risk of exceeding the radiation tolerance limits, thereby increasing the likelihood of both acute and late toxicities. Chemotherapy for LRBCs has also been explored, but a systematic review of randomized trials failed to provide conclusive evidence of therapeutic benefit (7).

Hyperthermia (HT), a potent radiosensitizer, has been used along with RT for the treatment of LRBCs (9-41). In 1996 Vernon et al (20) published consolidated results of RT and thermoradiation therapy (HTRT) in LRBCs from 5 randomized trials. Approximately 10% of the patients had locally advanced, inoperable breast cancers. An odds ratio (OR) of 2.3 favoring HTRT over RT alone was reported. In addition, some authors have reported using HTRT after excision of the recurrent lesions (42-45), whereas others have treated with CT either alone or with HTRT (46-50). The primary objectives of all these studies have been to provide effective palliation of recurrent lesions in patients who could be harboring coexisting metastatic disease. It is therefore highly desirable to explore a safe and effective long-term palliative therapy to improve their quality of life.

This prompted us to undertake a systematic review and meta-analysis to evaluate the efficacy of primary HTRT in patients presenting exclusively with LRBCs. A subset analysis was also carried out for those previously irradiated and considered for ReRT and HT for locoregional recurrences.

Methods and Materials

Search strategy

The systematic review and meta-analysis was conducted as per the PRISMA guidelines (51). Eight databases, including PubMed, EMBASE, SCOPUS, and Cochrane library were searched, and the last search was performed on May 27, 2015 (Fig. 1). The Medical Subject Headings terms used were "Breast neoplasms" AND "Radiotherapy" AND "Hyperthermia, Induced." The search was not limited to any date or language. Additional articles were retrieved through a hand search.

Inclusion criteria

Both single-arm and 2-arm studies (randomized and nonrandomized) fulfilling the following criteria were included: (*1*) LRBCs treated with local HT and external RT (those using surgery, concurrent CT, and/or interstitial brachytherapy for LRBCs were excluded), (*2*) treatment outcome in terms of defined complete responses (CRs) were reported, and (*3*) full-text articles in English were available.

Study selection

After exclusion of duplicates, articles were screened according to their titles and abstracts. Topics unrelated to breast cancers, management of LRBCs, *in vitro* thermoradiobiological studies, technical articles on HT instrumentation, thermal dose, HT in locally advanced breast cancers, reviews, case reports, use of interstitial brachytherapy/thermobrachytherapy, nanotechnology, and non-English articles were excluded (Fig. 1). Articles updated in a later publication by the same author/s and those with mixed patient groups for which the outcomes for LRBCs were not documented separately were excluded. Thus, of the 55 full-text articles considered for detailed study, 24 were further omitted (42-50, 52-66). Reasons for their omission are listed in Supplementary Table 1 (available online at www.redjournal.org).

Data extraction and quality assessment

The primary endpoint of interest was CR at the end of treatment, and all studies that reported CR after HTRT were considered. Patients with microscopic disease or excision of LRBCs were excluded because an objective assessment of the extent of response would not be possible. Details of the pretreatment patient characteristics and RT and HT parameters were noted (Table 1). Although most studies reported the CR in terms of number of patients (23 of 34), 11 studies expressed with respect to number of lesions (Table 1).

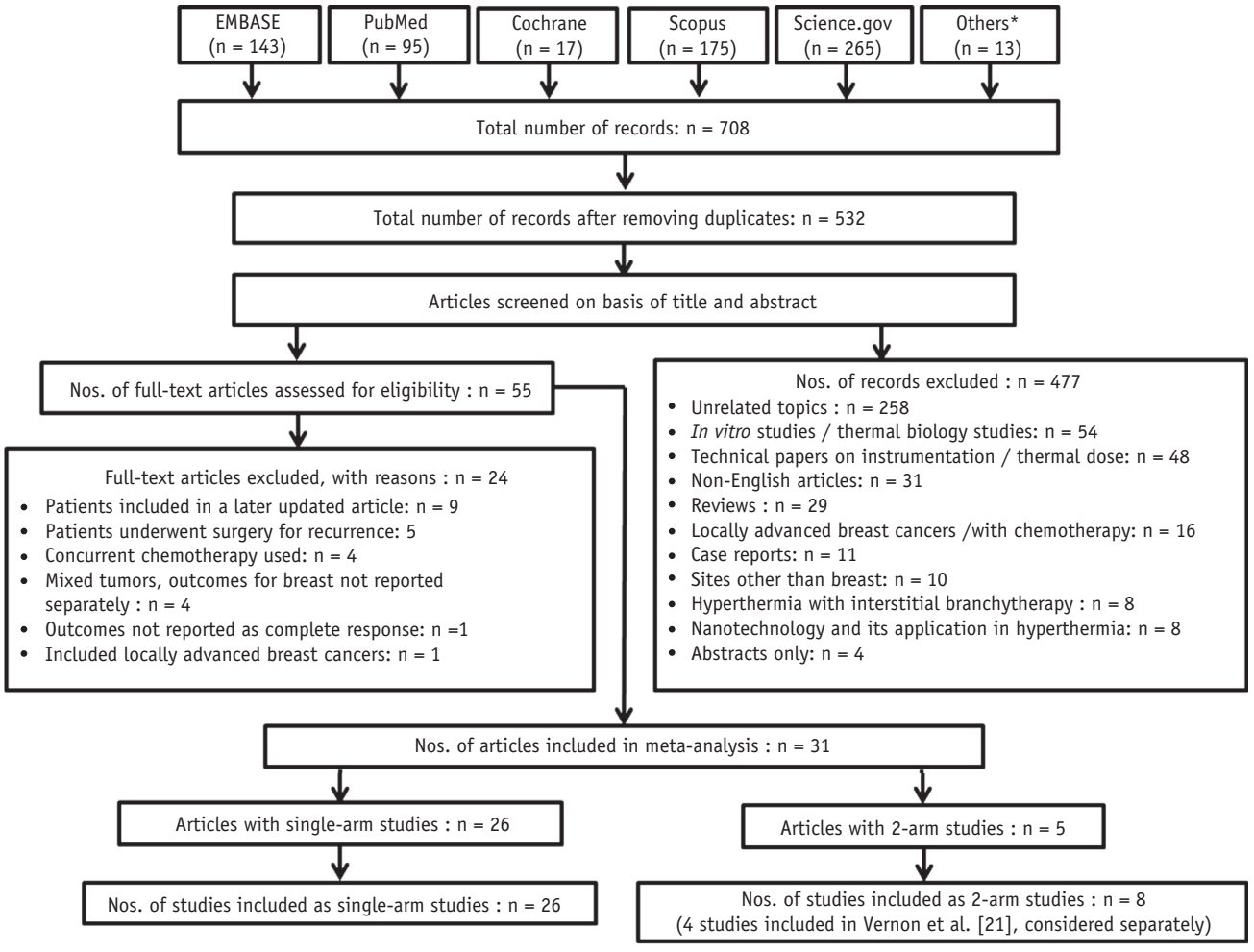


Fig. 1. Flowchart indicating the study selection procedure.

Acute and late toxicities were checked in each of the 31 articles. Because these studies were reported over 34 years (1981-2015), uniform toxicity scoring criteria could not be expected. The toxicity and scoring criteria when available are listed in Table 1.

The articles were extracted independently by 2 authors (N.R.D. and S.G.O.), and in case of discrepancy a consensus was reached between the authors. The shortlisted articles were reviewed by co-authors (N.R.D., E.P., S.G.O., and S.B.) to ascertain the correctness of all entries.

Critical appraisal

On the basis of the predefined study criteria, study quality was assessed according to the PRISMA guidelines (51). Factors related to patient characteristics and treatment parameters that could have an impact on the outcome were assessed. Quality assessment was independently performed by 2 co-authors (N.R.D. and E.P.). Only those studies that reported a CR for the patients treated with RT and HT, or for which a CR could be calculated from the data presented in the articles, were considered.

Statistical methods

The Comprehensive Meta-analysis Software package (version 3.0) was used to execute the meta-analysis (67). Other descriptive statistical analysis was carried out using IBM SPSS version 21.0 (68). Complete response after HTRT was considered as an event. For single-arm studies, the event rate was computed (from n = 26) and also for the subset that had undergone ReRT and HT (from n = 16). The odds ratio (OR), risk ratio, and risk difference were calculated from the 2-arm studies and the values expressed using a 95% confidence interval (CI). Heterogeneity was assessed by the I^2 statistic, which represents the proportion of observed variance that is due to variation in true effects. A random-effects model was used for all analyses. The potential publication bias was evaluated by funnel plots and rank correlation tests with Kendall's τ (69). Subgroup analysis and meta-regression were performed to look for

Table 1 Salient features of the 31 articles, pertaining to 34 individual studies that have been included in the meta-analysis

Author, y (reference)	Study type (single-/2-arm)	RT + HT (n)	RT alone (n)	Primary RT dose in Gy (range)*	Interval between primary RT and ReRT (mo)*	RT dose (Gy) (range)*	HT (MW/RF/US)	HT-RT sequence (before or after RT)
Datta et al, 2015 (10)	Single-arm	24	—	Mean: 53.7 (30-70)	Mean: 7.6 (24-264)	Mean: 36.8 (20-50)	MW	HT before RT
Linthrost et al, 2015 (12)	Single-arm	248	—	Mean: 49 (18-70)	Mean: 90 (5-485)	32	MW	HT after RT
Gabriele et al, 2009 (13)	Single-arm	44† (23 pts)	—	45-63	NA	Mean: 31.8 (20-60)	MW	HT after RT
Wahl et al, 2008 (14)	2-arm, NR	36	18	Median: 60 (19.6-82)	Median: 38 (1-1215)	Median: 48 (7-48)	NA	NA
Ben-Yosef et al, 2004 (15)	Single-arm	15	—	NA	NA	30-60	MW	HT after RT
Li et al, 2004 (16)	Single-arm	75† (73 pts)	—	Mean: 58 (0-100)	NA	Mean: 50.5 (12-74.4)	MW, RF, US	HT after RT
Hehr et al, 2001 (17)	Single-arm	30	—	Median: 50 Gy (40-115)	58 (12-271)	Median: 60 (30-68)	RF	HT before RT
van der Zee, et al, 1999 (18)	Single-arm	119	—	Median: 45 (15-66)	Median: 41 (4-204)	Median: 32 (12-36)	MW	HT after RT
Lee et al, 1998 (19)	Single-arm	178† (151 pts)	—	Median: 40 (32.5-70)	NA	Median:40 (30-70)	MW	HT after RT
DHG trial, Vernon et al, 1996 (20)	2-arm, R	19	19	NA	NA	32-50	MW	HT after RT
UK MRC BrR trial, Vernon et al, 1996 (20)	2-arm, R	90	59	NA	NA	28.8-50	MW	HT after RT
ESHO trial, Vernon et al 1996 (20)	2-arm, R	27	21	NA	NA	32	RF, MW	HT after RT
PMH trial, Vernon et al, 1996 (20)	2-arm, R	17	16	NA	NA	32-50	MW	HT after RT
Pattaranutaporn et al, 1996 (21)	Single-arm	7	—	0-70	NA	50-60	MW	HT before or after
Nishimura et al, 1995 (22)	Single-arm	18	—	-	-	Mean: 53.4 (20-70)	MW	HT after RT
Lindholm et al, 1995 (23)	Single	69	—	Median: 48 (14-75)	Median: 54 (11-377)	Median: 34.5 (23.6-36.8)	MW	HT after RT
Engin et al, 1994 (40)	Single	20	—	0-75	5-133	Mean: 40 (30-50)	MW	NA
Engin et al, 1993 (41)	Single	30	—	NA	NA	Mean: 45 (13-80)	MW	HT after RT
Kapp et al, 1991 (24)	Single	89	—	Mean: 54.2 (10-104)	Mean: 52.8 (4.8-367.2)	Mean: 39.8 (12.6-75.6)	MW	HT after RT
Perez et al, 1991 (25)	2-arm, R	39	42	50-60 Gy	NA	32	MW	HT after RT
Phromratanapongse et al, 1991 (26)	Single-arm	44	—	Mean: 59.7 (35-66.2)	NA	Mean: 29.4 (16-56 Gy)	MW	HT after RT
Amichetti et al, 1991 (27)	Single-arm	30† (26 pts)	—	Mean: 43 (30-68)	NA	Mean: 37.4 (19.8-60)	MW	HT after RT
DuBios et al, 1990 (28)	Single-arm	34	—	50-60	Median: 36 (3-372)	Median: 30 (8.5-41)	MW	HT after RT
Tsukiyama et al, 1990 (29)	Single-arm	21† (Pt nos. NA)	—	NA	NA	40-60	MW and RF	HT after RT

Table 1 Salient features of the 31 articles, pertaining to 34 individual studies that have been included in the meta-analysis *(continued)*

HT (fx/wk)	HT (Mean temp) (in °C)*	HT (time in min)	HT sessions (range)*	CR with RT + HT, n (%)	CR with RT alone, n (%)	Acute grade 3/4 toxicity with RT + HT (%)	Late grade 3/4 toxicity with RT + HT (%)	Additional remarks
1-2	Mean: 40.6 (41-43)	60	Mean: 7.3 (2-11)	16 (66.7)	—	4.1	0	All previously irradiated and unresectable patients. Those who achieved CR maintained this until their last follow-up or death.
1	41.2	60	4	174 (70)	—	9	1.2	Patients included 1996-2011, no surgery or CT, all unresectable, all preirradiated, 70 patients received concurrent hormone, CR better than no hormones ($P = .006$)
2	43.0	35	Mean: 5 (1-8)	29† (65.9)	—	0.0	0.0	Mixed study population, except group A with 23 patients of breast recurrence, all patients were preirradiated, most outcomes given as nos. of lesions, late toxicity NA
NA	NA	NA	NA	24 (63.1)	7 (38.8)	NA	NA	All patients preirradiated, data of 36 patients treated with ReRT + HT alone and 18 treated with ReRT alone have been considered, toxicity profiles for these groups not stated separately, HT techniques not detailed
2	45.0 (max)	45	2-7	5 (33.3)	—	20.0	13.3	14/15 patients preirradiated, primary RT dose not stated, HT ave. temperature NA, 6/15 received concurrent CT
1 or 2	42.3	30-60	Mean: 4.5 (2-9)	39† (52)	—	8.0	9.7	Outcomes based on no. of lesions; 41/75 lesions had received prior RT, CR for preRT patients was 56% (23/41) vs 47% (16/34) for those not preirradiated ($P = .40$)
2	43.0	60	Median: 7 (2-12)	12 (40)	—	50.0	6.6	62% patients were preirradiated, outcomes for preirradiated patients not stated separately, 30 of the 39 patients who had gross tumor or R2 resections were only considered
2	40.1	60	8	84 (71)	—	15.6	3.7	All preirradiated patients, excluded 15 patients who had an R1 resection before ReRT + HT
2	43	45	Median: 8 (1-11)	113† (63.4)	—	27.0	17.0	51% (99/151) patients had received prior RT, outcomes presented as no. of lesions; 17 microscopic lesions after surgery excluded; acute toxicity stated for II-IV
2	43	60	4-8	14 (74)	14 (74)	16.6‡	0§	31 patients had not received previous RT
1	43	60	3-6	51 (57)	17 (29)	5.1‡	0§	Br I trial not included because it offered primary treatment for T3,4 tumors; 11 patients of each group had not received previous RT
2	43	60	4-8	21 (78)	11 (38)	14.8‡	11.1§	All patients had received prior RT
Once in 14-21 days	42.5	30	2	5 (29)	5 (31)	5.8‡	0§	6 and 7 patients in RT alone and HT group, respectively, had not received prior RT
1	43	NA	5	3	—	0	0	2 of 4 preirradiated patients had achieved CR
1	42.5	40-50	1-6	14	—	—	—	Mixed group of 53 patients with superficial and subsurface tumors, 56% had received prior RT, 18 breast cancer patients treated with RT + HT considered, separate toxicity profile for breast patients not listed
1-2	42.5	45	Median: 4 (3-6)	49	49 (71)	14	19	All previously irradiated patients (14-75 Gy, median 48 Gy), 3 different hyperthermia schedules used, toxicity scored according to WHO, 1979
2	38.9 (Min)	60	Mean: 9 (multiple-field HT used over multiple sessions)	19 (95)	—	20	NA	16/17 preirradiated patients achieved CR, 5 patients received chemotherapy along with RT + HT, multiple-field HT was used on 4 d/wk
2	43	60	Mean 5.5	17 (56.6)	—	NA	NA	30/126 superficial tumors were from breast
2	42.4	45	Mean: 3.1 (1-12)	46 (52)	—	—	—	68% patients preirradiated; complication scoring criteria not stated; complications listed in terms of treatment fields; 2/75 fields required surgical intervention for complications
2	43	60	8	14 (33.3)	12 (30.7)	NA	NA	Includes all superficial tumors; 50% received prior RT to 50-60 Gy, outcomes for 81/307 breast cancers only incorporated; toxicity criteria not stated and given separately for breast; acute and late complications reported similar in 2 groups
2	43	60	Mean: 5 (2-9)	18 (41)	—	7.4	NA	All preirradiated patients, toxicity as per WHO modified scale
2-3	42.5	30	Median: 2 (1-9)	20† (66.6)	—	7.6	NA	30.7% patients had received previous RT; outcomes reported in terms of no. of lesions; toxicity reported as per WHO criteria
2	42	45	9	22 (64.7)		11.9	0	Only 34/42 patients treated by ReRT and HT have been considered; toxicity by WHO criteria given for all 42 patients
2	42	40-60	6-10	13† (61.9) (Pt nos. NA)	—	NA	NA	Mixed group of 134 patients with 161 superficial tumors, only 21 lesions in recurrent breast cancer considered, outcomes stated in terms of lesions, toxicity criteria not stated

(Continued)

Table 1 Salient features of the 31 articles, pertaining to 34 individual studies that have been included in the meta-analysis

Author, y (reference)	Study type (single-/2-arm)	RT + HT (n)	RT alone (n)	Primary RT dose in Gy (range)*	Interval between primary RT and ReRT (mo)*	RT dose (Gy) (range)*	HT (MW/RF/US)	HT-RT sequence (before or after RT)
Li et al, 1990 (30)	2-arm, NR	30† (Pt nos. NA)	22* (Pt nos. NA)	40-65	NA	Mean: 47 (20-80)	MW	HT after RT
Bicher et al, 1990 (31)	Single-arm	91† (Pt nos. NA)	—	NA	NA	NA	MW	Either before or after RT
Seegenschmiedt et al, 1989 (32)	Single-arm	95† (49 pts)	—	Mean: 56 (44-84)	NA	Mean: 36.8 (16-60)	MW	HT after RT
Sannazzari et al, 1989 (33)	Single-arm	11	—	20-50	NA	Mean: 33.4 (20-50)	MW	HT before RT
Dragovic et al, 1989 (34)	Single-arm	30	—	Median: 50 (34.7-70)	NA	32	MW	HT after RT
Gonzalez Gonzalez et al, 1988 (35)	Single-arm	45† (35 pts)	—	0-70	<3 y: 30% 3-5 y: 29% >5 y: 31%	Mean: 24 (24-40)	MW	HT after RT
Scott et al, 1988 (36)	Single-arm	54	—	0	—	60	MW	HT after RT
Perez et al, 1986 (37)	2-arm, NR	48	116	≥ 50 Gy (in 75% patients of ReRT + HT	NA	20-60 (For ReRT alone) 20-40 (for ReRT + HT)	MW	HT after RT
Bicher et al, 1986 (38)	Single-arm	53† (Pt nos. NA)	—	NA	NA	20 Gy/10 fr or 40 Gy/20 fr	MW	HT after RT
Perez et al, 1981 (39)	Single-arm	9† (7 pts)	—	NA	NA	32-40	MW	HT after RT

Abbreviations: CR = complete response; DHG = Dutch Hyperthermia Group; ESHO = European Society for Hyperthermic Oncology; fx = fractions; HT = hyperthermia; MW = microwave; NA = not available; NR = nonrandomized; PMH = Princess Margaret Hospital/Ontario Cancer Institute; Pt/pts = patient(s); R = randomized; ReRT = reirradiation; RF = radiofrequency; RT = radiation therapy; UK MRC = United Kingdom Medical Research Council; US = ultrasound; WHO = World Health Organization.

* Wherever available, the mean or median has been stated.

† Nos. of lesions.

‡ For ulceration and necrosis.

§ For bone necrosis, bone fracture, and brachial plexopathy.

covariates related to HT and RT that could influence the outcome. The cutoff limit for subgroups was based on the median values of the continuous variables. For meta-regression, all values were used as continuous variables. The Q test was used to evaluate the impact of covariates on the regression model, the goodness of fit to look for any unexplained variance, and τ^2 to estimate the variance of the true effects. All P values are 2-sided and considered statistically significant if $<.05$.

Results

A total of 708 articles were identified through the search and were screened (Fig. 1). Forty-eight articles related to HT techniques, treatment delivery, and thermal dose concepts were excluded. Thirty-four studies from 31 articles were included in the meta-analysis, of which 26 pertained to single-arm studies. Eight studies from 5 articles were 2-arm comparative trials (randomized = 5, nonrandomized = 3). A total of 1483 patients were included in the single-arm studies, whereas 627 patients were in the 2-arm studies. Of the 627 patients in the 2-arm studies, 318 received RT alone, whereas 309 were treated with HTRT. Thus, 1792 patients receiving HTRT were evaluated in this meta-analysis. Hyperthermia was delivered mostly by either microwaves or radiofrequency at 8 to 2450 Mhz. In most centers HT was applied after RT (76.5%). An average of 2 weekly HT sessions was reported in most studies, and a mean temperature of 42.5°C was attained. The mean RT dose delivered was 38.2 Gy (range, 24-60 Gy) at a dose per fraction ranging from 1.8 to 4 Gy (Table 2).

For the 26 single-arm studies, 63.4% achieved CR with HTRT, resulting in an event rate of 0.62 (95% CI 0.57-0.66)

Table 1 Salient features of the 31 articles, pertaining to 34 individual studies that have been included in the meta-analysis *(continued)*

HT (fx/wk)	HT (mean temp) (in °C)*	HT (time in min)	HT sessions (range)*	CR with RT + HT, n (%)	CR with RT alone, n (%)	Acute grade 3/4 toxicity with RT + HT (%)	Late grade 3/4 toxicity with RT + HT (%)	Additional remarks
2	41-44	40	Mean: 11.6	22† (73.3) (Pt nos. NA)	8† (36.4) (Pt nos. NA)	NA	NA	Only 30 lesions, recurrent cases considered; outcomes reported in terms of no. of lesions; 20/40 patients had received prior RT, 16/20 achieved CR with RT + HT; RT + HT used for bigger lesions, whereas RT alone for smaller lesions, toxicity not reported
2-5	42	Min.: 30		60† (65.9)	—	NA	NA	90/178 superficial tumors were from breast, no RT details given, response indicated for no. of lesions, patients treated since Sept. 1987 received hyperthermia 5 d/wk
2	41-45	45	2-10	49† (52)	—	6.3	NA	Outcomes reported based on the 95 lesions in 49 patients, 78% had previous RT,
2	42	30-45	6-10	5 (45.5)	—	10.5	5.5	Only 11 patients treated with RT + HT considered, 8 had prior RT, of which 5 had CR with RT + HT, toxicity criteria not stated
2	43	60	8	17 (57)	—	11	-	All patients had been preirradiated; toxicity scoring criteria not stated
2	43	60	6-10	27† (60)	—	22.8	6.4	45/54 lesions treated in 35 patients with RT + HT included, 39/45 lesions are preirradiated; their responses have not been stated separately.
2	43	60	9	46 (85)	—	24	16	None of the patients were previously treated with RT; all superficial tumors, only 54/133 recurrent breast cancer patients considered
2	41-43	30-60	2	35 (72.9)	47 (40.5)	25	—	Nonrandomized study, 75% of patients had previously received ≥50 Gy, outcomes not shown separately for those who had received prior RT, toxicity criteria not stated
2	42-45	60	10	38 (72)	—	NA	NA	53/135 lesions (fields) pertain to recurrent chest wall/breast. Two RT dose fractionations schedules used depending on prior RT dose and time interval, outcomes based on previously irradiated/unirradiated patients not stated; toxicity not stated separately for breast/chest wall
2	43	90	2-4	5† (71.4)	—	0	0	Prior RT details NA, outcome of 9 lesions of breast/chest wall taken from the mixed group of 29 superficial tumors,

with an I^2 of 63.1 ($P<.0001$) (Fig. 2). In the 2-arm studies, CR with RT alone was 38% versus 60.1% with HTRT. The OR was 2.64 (95% CI 1.66-4.18, $P<.0001$), corresponding to a risk ratio of 1.57 (95% CI 1.25-1.96, $P<.0001$) (Fig. 3a, b). The absolute risk difference was 0.22 (95% CI 0.11-0.33, $P<.0001$) (Fig. 3c).

ReRT and HT was reported in 16 studies (both single-arm and 2-arm) (10, 12-16, 18, 20, 21, 23, 26, 28, 30, 33, 34, 40). Of the total of 1792 patients treated with HTRT, 892 were reirradiated. The outcomes (CR) of 113 of these 892 patients were not given separately and hence could not be evaluated (32, 35). Thus, in the remaining 779 patients from 16 studies who had ReRT + HT (696 from single-arm studies, 83 from 2-arm studies), a CR of 66.6% was achieved (event rate 0.64, 95% CI 0.58-0.70, $I^2 = 55.8$, $P<.003$, Fig. 4). A mean ReRT dose of 36.7 Gy (range, 29.4-50.5 Gy) was delivered at an average dose per fraction of 2.7 Gy (range, 2-4 Gy). The toxicity profiles of these patients could not be computed because the acute and late toxicities were not always stated separately for this subset of patients. However, none of the studies reported any significant increase in toxicities with ReRT + HT.

The scoring of the acute and late toxicities was quite heterogeneous because these studies were carried out during a 34-year period. Nevertheless the toxicity criteria, wherever available, have been stated in Table 1 and the main toxicities mentioned. Acute grade 3/4 toxicity with RT and HT was reported in 24 studies, with a mean of 14.4% (SD ± 10.7%). Late grade 3/4 toxicity was mentioned in 21 studies, with a mean of 5.2% (SD ± 6.5%).

No significant publication bias was evident in the 2-arm studies (Supplementary Figs. 1-3; available online at www.redjournal.org). A series of subgroup analyses

Table 2 Consolidated summary of the key patient and treatment characteristics from the 34 individual studies (26 single-arm and 8 2-arm) considered for the meta-analysis

Parameter	No. of studies reporting	Range	Mean ± SD
HT per wk	33	1-5	1.9 ± 0.6
Average temperature (°C)	31	40.1-43	42.5 ± 0.6
Duration of HT (min)	32	30-90	53.6 ± 11.8
No. of HT fractions	32	1-12	6.3 ± 2.7
Initial RT dose (Gy)	25	0-60	48.4 ± 11.2
Median interval between initial RT and RT + HT (mo)	8	36-90	55.2 ± 11.4
RT dose along with HT (Gy)	32	24-60	38.2 ± 9.1
RT dose/fraction with HT	30	1.8-4.0	2.8 ± 0.9

Abbreviations: HT = hyperthermia; RT = radiation therapy.

and meta-regressions for patients receiving HTRT in single-arm and 2-arm studies was performed. None of the variables were significant at the 0.05 level, although the power to detect these differences was low (Tables 3 and 4; Supplementary Figs. 4 and 5; available online at www.redjournal.org).

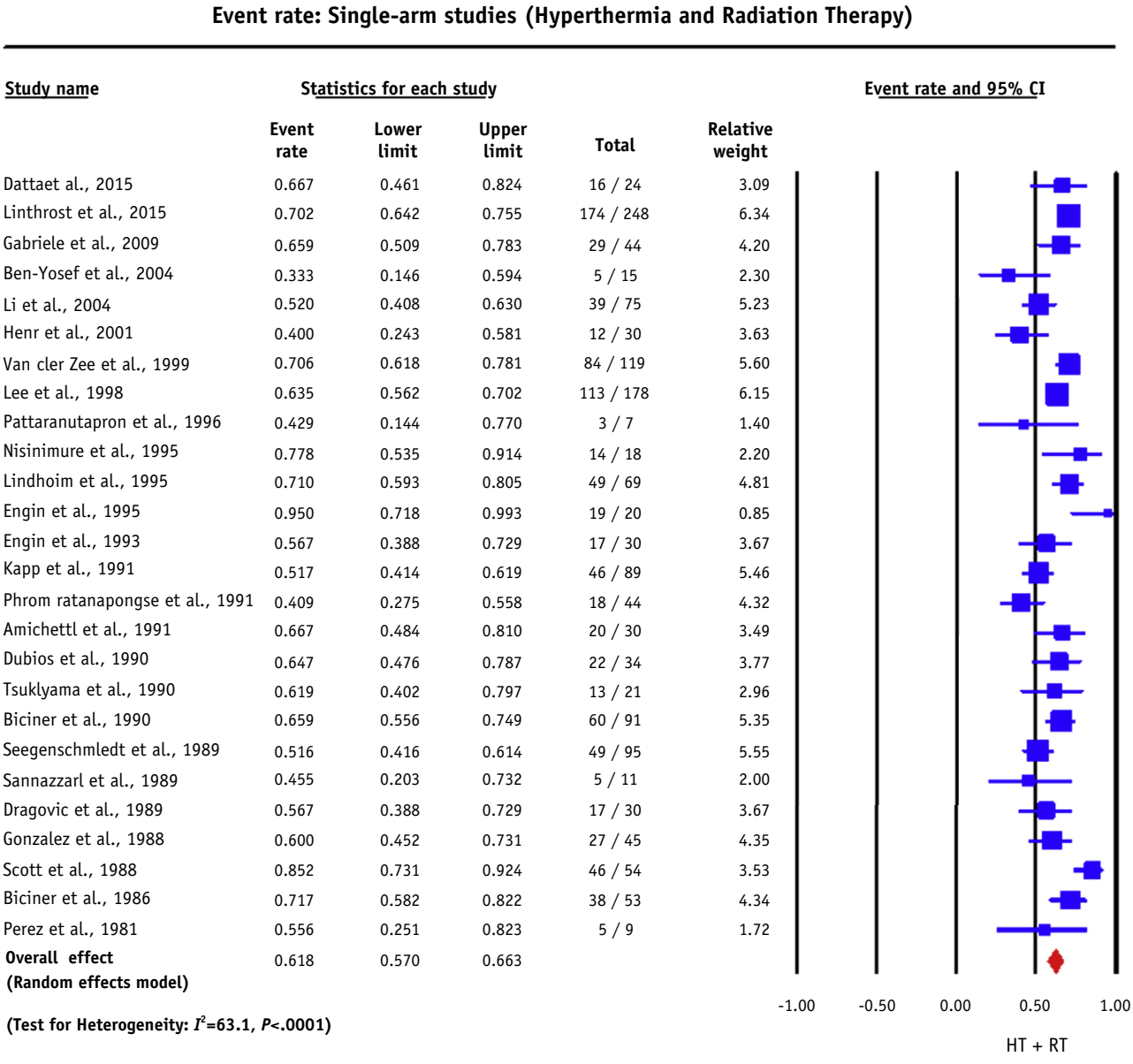
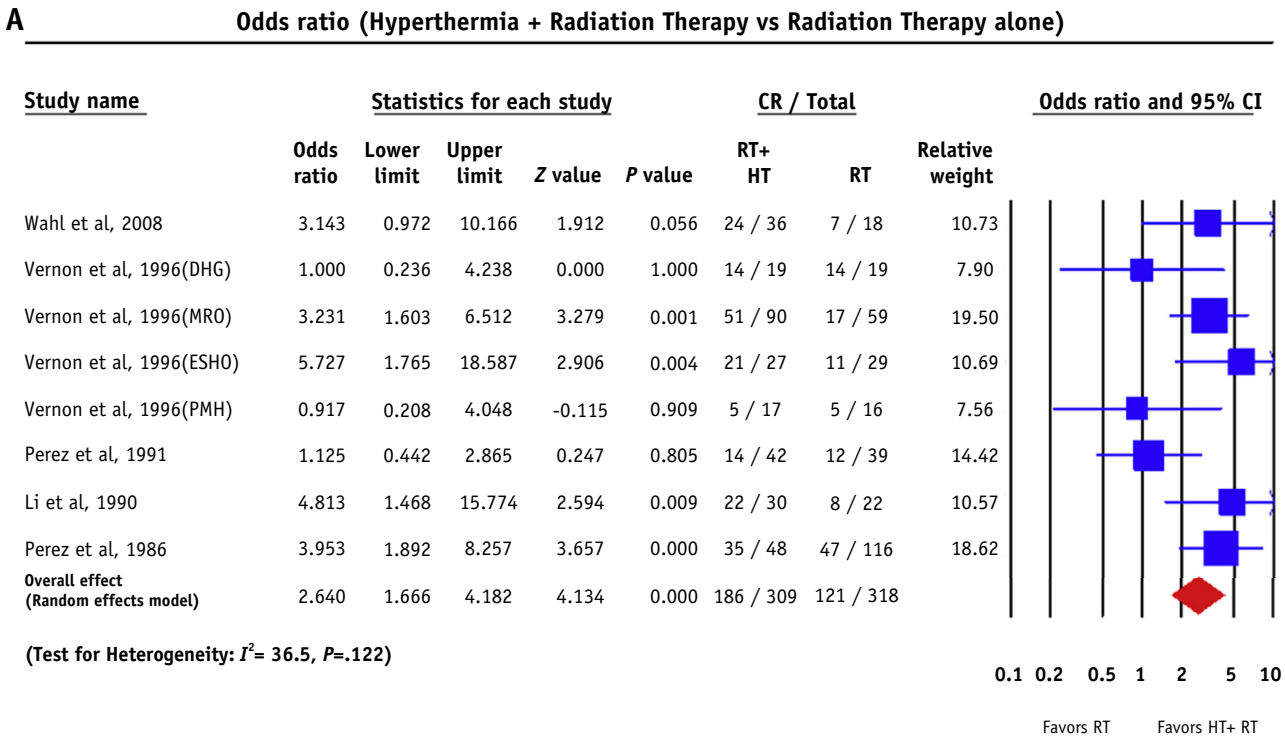


Fig. 2. Forest plots for the event rates from the 26 individual single-arm studies. *Abbreviations:* CI = confidence interval; HT = hyperthermia; RT = radiation therapy.



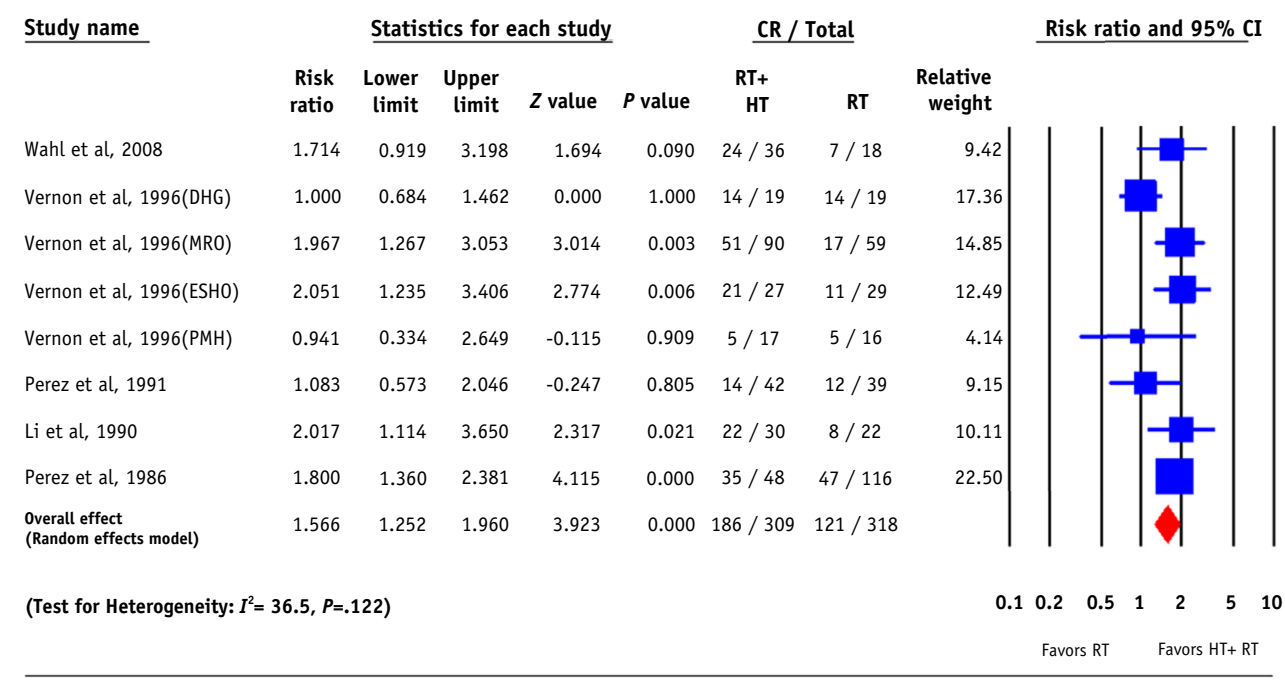


Fig. 3. Forest plots from the 8 individual 2-arm studies. The 4 trials published in Vernon et al (20) have been considered as individual trials. (a) Odds ratio; (b) risk ratio; (c) risk difference. *Abbreviations:* CI = confidence interval; CR = complete response; HT = hyperthermia; RT = radiation therapy.

Discussion

Locoregional recurrences in breast cancer pose a therapeutic challenge. They alone may not always herald a fatal outcome. Willner et al, in a study of 145 patients, reported that almost one-third of these patients were alive and free of disease at 10 years (70). Thus, presence of LRBCs should not always be a predicament for instituting a palliative

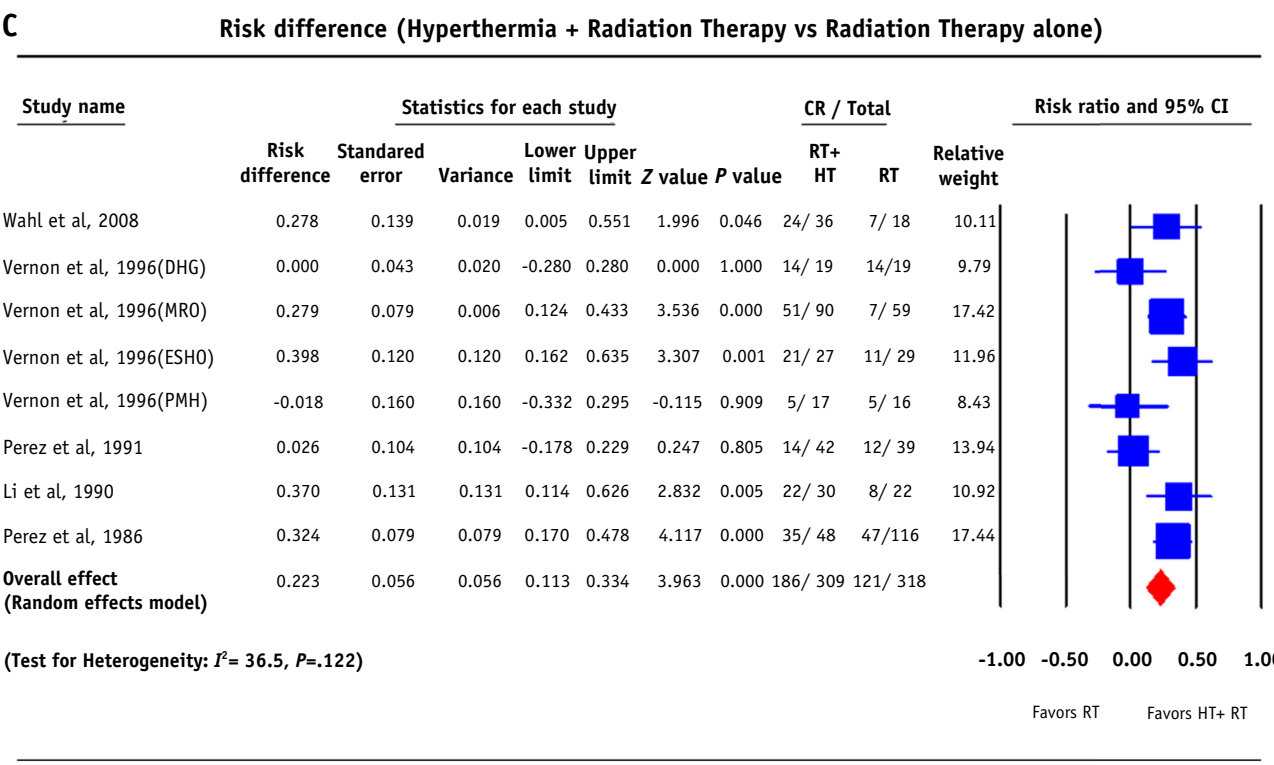


Fig. 3. (*continued*)

treatment. On the contrary, the treatment strategies for LRBCs should be effective, tolerable with minimal morbidity, and produce long-lasting local disease control to improve the quality of life.

Surgery alone may help in achieving local control in one-third of the patients, but this can only be offered to the limited number of patients with operable lesions (71, 72). The treatment offered would depend on type of prior surgery (mastectomy or breast-conserving therapy) with or without adjuvant RT (73). Although local radical surgery is usually recommended, this may not be feasible in a sizeable number of patients. Petrella et al (74) recently reported that local radical resection was feasible in 65% of their patients, and they achieved a 5-year disease free survival of 45.5%. Chemotherapy was not found to be very effective in LRBCs, but newer agents along with hormonal interventions and biological therapies are currently being evaluated in several clinical trials (7, 73).

Because most of the patients with LRBCs had received prior RT, ReRT with full RT doses could increase both acute and late morbidities. Hyperthermia along with moderate doses of ReRT is therefore one of the options that has been explored by several centers globally in LRBCs through either 2-arm randomized or nonrandomized clinical trials or as single-arm studies reporting their institutional experiences.

To the best of our knowledge, the only meta-analysis reporting outcome of HTRT in LRBCs was by Vernon et al in 1996 (20), limited to 5 randomized trials. They had shown that the overall CR with RT alone was 41%, whereas with RT and HT it reached 59%, resulting in an OR of 2.3. However, the study included both recurrent and local advanced inoperable breast cancer (Medical Research Council BrI trial). Our result, with an OR of 2.6 from 8 2-arm trials is in close agreement with that of the meta-analysis reported by Vernon et al (20). Furthermore, the event rate from the 26 single-arm trials also supports that HTRT could be an effective strategy for LRBCs. Even patients who were previously irradiated experience, a similar CR to lower doses of RT with HT with minimal acute and late morbidities.

Considerable variation in patient characteristics and in the treatments offered was observed in these studies. Hence, to have a uniform patient population, we included only those who were treated with RT and HT alone for LRBCs and excluded those subjected to surgery and/or concurrent CT. In most of the studies, patients continued hormonal therapy during HTRT and were included. Other variables that could have influenced the outcome were the type of lesion (superficial diffuse or nodular), size of the lesion, time interval between the first treatment and retreatment, presence or absence of coexisting metastatic disease, menopausal status, and other key factors. It was difficult to identify a favorable patient subset because these factors were not usually reported (Table 1).

It was also observed that of the 34 studies reporting outcomes after HTRT, 23 studies reported a CR of 63.4% in 1121 patients, whereas it was 61.8% for the 671 lesions

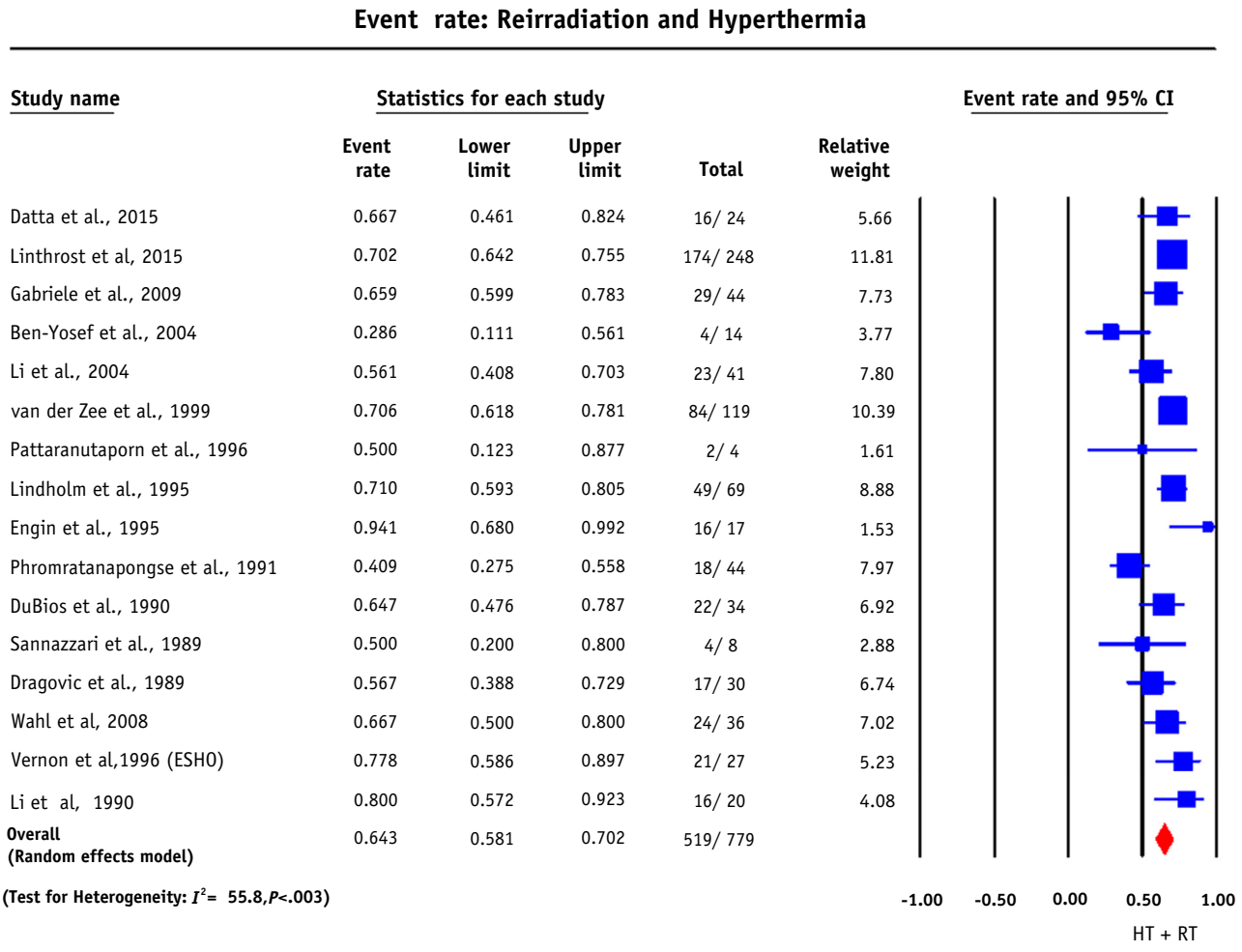


Fig. 4. Forest plots for the event rates from the 16 individual studies with reirradiation along with hyperthermia. Only those studies indicating that patients had been previously irradiated and in which complete response rates were stated separately have been included. Of the 16 studies, 13 are single-arm studies, whereas 3 are 2-arm studies. *Abbreviation:* CI = confidence interval.

reported in 11 studies. Because the primary objective of this study was to evaluate the CR after HTRT, all studies reporting CR were included. In respect to the treatment offered, there was also a variation in the RT dose and HT treatment schedules (Table 1). This might be due to a lack of consensus on the optimal schedule of RT and HT. Furthermore, the choice of RT doses could have been influenced by the patient's general condition, disease status, comorbid conditions, prior RT dose, time interval between the first RT and ReRT, institutional policies, and logistics on the sequencing of RT and HT. Certainly, these factors need to be considered to individualize the treatment, but it also calls for defining an optimum schedule of such treatment. A subgroup analysis and meta-regression failed to identify any RT or HT treatment variables that could influence the treatment outcome (Tables 3 and 4 and Supplementary Figs. 3 and 4; available online at www.redjournal.org).

There was no significant heterogeneity noted in the 2-arm studies (I^2 = 36.5, P=.122) (Fig. 3). However, significant heterogeneity was noted in the 26 single-arm studies with HTRT (I^2 = 63.1, P<.0001) (Fig. 2) and also for the 16 studies included in ReRT + HT (I^2 = 55.8, P<.003) (Fig. 4). We looked at the individual studies to ascertain the cause of heterogeneity and repeated the meta-analysis by excluding the outliers. After excluding the 5 trials that had extreme event rate values (outliers) [0.33 (15), 0.41 (26), 0.43 (21), 0.85 (36), and 0.95 (40)], the event rate in the 21 remaining studies was still maintained at 0.63 (95% CI 0.59-0.66, P<.0001), but the I^2 decreased considerably from 63.1 (P<.0001) to 37.7 (P=.04). In the case of the 16 studies for ReRT and HT, excluding the 2 outliers [0.27 (15) and 0.94 (40)], the event rate again was almost the same at 0.65 (95% CI 0.59-0.70, P<.0001), but I^2 decreased markedly from 55.8 (P<.003) to 42.4 (P=.05).

A close perusal of these studies revealed that 2 studies (15, 21) had small sample sizes of 15 and 7 patients, respectively, and had used 1.8 to 2 Gy per fraction of RT. This is lesser than the mean dose per fraction of 2.8 Gy (SD ± 0.9 Gy) used in other studies (Table 2).

Table 3 Comparative subgroup analysis for various radiation therapy and hyperthermia treatment variables for the event rates from 34 studies treated with radiation therapy and hyperthermia included in the meta-analysis based on mixed-effects analysis

				95% CI		Total between		
Subgroups	No. of studies	Total patients (n)	Event rate	Upper	Lower	*Q* value	df (*Q*)	*P*
A: Single- vs 2-arm studies								
Single-arm	26	1483	0.617	0.566	0.666	0.017	1	.896
2-arm	8	309	0.610	0.513	0.699			
B: Randomized vs nonrandomized studies								
Randomized	5	195	0.539	0.416	0.657	1.798	1	.180
Nonrandomized	29	1597	0.627	0.580	0.672			
C: Year of publication (before or after 1994)								
Before 1994	17	756	0.603	0.540	0.663	0.339	1	.560
After 1994	17	1036	0.629	0.565	0.689			
D: No. of hyperthermia sessions (≤7 vs >7)								
≤7	16	925	0.562	0.497	0.626	5.326	2	.070
>7	16	740	0.665	0.601	0.725			
Not available	2	127	0.662	0.495	0.797			
E: Average temperature during hyperthermia sessions (≤42.5°C vs >42.5°C)								
≤42.5°C	16	977	0.646	0.585	0.703	2.212	2	.331
>42.5°C	15	744	0.579	0.511	0.644			
Not available	3	71	0.626	0.437	0.784			
F: Radiation therapy dose delivered with hyperthermia (≤35.6 Gy vs >35.6 Gy)								
≤35.6 Gy	16	863	0.587	0.517	0.653	1.361	2	.506
>35.6 Gy	16	817	0.641	0.573	0.703			
Not available	2	112	0.644	0.458	0.795			
G: Radiation therapy dose/fx with hyperthermia (≤2.15 Gy vs >2.15 Gy)								
≤2.15 Gy/fx	15	612	0.570	0.501	0.637	3.107	2	.211
>2.15 Gy/fx	15	1002	0.651	0.589	0.709			
Not available	4	178	0.633	0.508	0.742			
H: Sequence of hyperthermia and radiation therapy (HT before RT vs HT after RT)								
HT then RT	5	322	0.584	0.452	0.705	1.186	3	.756
RT then HT	27	1427	0.622	0.571	0.670			
Both before/after	1	7	0.429	0.117	0.809			
Not available	1	36	0.667	0.398	0.858			

Abbreviation: CI = confidence interval; fx = fraction; HT = hyperthermia; RT = radiation therapy.

The cut-off limit for each of the subgroups is based on the median values of the respective covariates (for continuous variable alone). Subgroups for the following parameters were not evaluated: A: hyperthermia sessions per week because 32 of 34 studies had used 2 sessions per week; B: hyperthermia treatment time, because only 1 study used treatment time of more than the median time of 60 minutes.

Phromratanapongse et al (26) observed a relatively low CR of 40.9% in their 44 patients. They reported that those with a mean thermal dose >50 Eq 42.5°C had a CR of 53.5% (n = 30), compared with 14.3% with <50 Eq 42.5°C (n = 14, $P = .017$). Moreover, the CR was also found to be associated with tumor size (≤6 cm^2 vs > 6 cm^2: CR 64.7% vs 25.9%, $P = .013$). These could be some of the possible reasons that could have attributed to a relatively lower CR rates in these 3 studies.

The other 2 studies that showed a relatively higher CR were also reviewed. The highest CR of 95% (40) could be due to their unique multiple-field HT technique. Although the lesions were diffuse (up to 2900 cm^2), all patients had tumors limited to 3 cm depth. Moreover, they reported using HT for up to 4 days per week to treat different areas of the same patient. Scott et al (36) reported a CR of 85% in 54 of their "breast/adenocarcinoma" patients from a total pool of 117 evaluable patients with superficial malignant tumors, yet the CR observed for all patients was 65%. They concluded that this could be consequent to the relatively high number of "good" hyperthermia sessions (those averaging at least 43°C for 45 minutes) in these patients—84.8% in contrast to 54.1% in other superficial tumors.

Linthorst et al have recently published their results of ReRT + HT in LRBCs, with and without prior salvage surgery (12, 42). Of the 198 patients who received surgery, 179 had R0/R1 resections. The 5-year local control after postexcisional ReRT + HT was 78%, with a grade 3/4 late toxicity of 11.9% (42). In their subsequent publication in 248 patients with unresectable tumors, a ReRT with 32 Gy and local HT produced a CR of 70% with a local control of 39% at 5 years (12). Late grade 3 toxicity was evident in only 1% of patients. No significant prognostic variable was reported on multivariable analysis. These 2 outcomes from the same institution, with homogenous patient treatment schedules, indicate that surgery followed by HTRT can significantly improve the local disease-free survival for patients with operable LRBCs. Thermoradiation therapy

Table 4 Meta-regressions using a random-effects model showing the logit-event rate using the covariates pertaining to radiation therapy and hyperthermia for the studies included in the meta-analysis

Covariate	Coefficient	SE	95% Confidence interval		Z value	P
			Lower	Upper		
Intercept	8.14	6.34	−4.28	20.56	1.28	.20
HT sessions per wk	0.11	0.31	−0.49	0.71	0.37	.71
Duration of HT (min)	−0.01	0.01	−0.03	0.01	−0.77	.44
Average temperature (°C)	−0.21	0.15	−0.50	0.08	−1.43	.15
Dose of RT with HT (Gy)	0.03	0.01	0.00	0.05	1.76	.08
RT dose per fraction (Gy/fx)	0.24	0.15	−0.06	0.53	1.57	.12

Abbreviations: fx = fraction; HT = hyperthermia; RT = radiation therapy; SE = standard error.
Thermoradiation therapy sequence not used as a covariate because the model could not run owing to problem of collinearity.
Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
$Q = 5.80$, df = 5, $P = .3257$
Goodness of fit: Test that unexplained variance is zero
$\tau^2 = 0.1864$, $\tau = 0.4317$, $I^2 = 65.73\%$, $Q = 61.29$, df = 21, $P = .0000$
Comparison of model with the null model
Total between-study variance (intercept only)
$\tau^2 = 0.1794$, $\tau = 0.4236$, $I^2 = 69.05\%$, $Q = 84.01$, df = 26, $P = .0000$
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.00 (computed value is −0.04)

alone also achieves high CRs with minimal toxicity and is a reasonable approach for inoperable lesions.

The limitations of the present analysis include the time span of the studies (34 years), the variability in the HT delivery, RT dose, and the heterogeneity of acute and late toxicity reporting. However, none of the treatment-related parameters were found to influence the outcomes. It is evident that HTRT is an effective and a safe modality for management of LRBCs. Moderate doses of RT with HT could be expected to enhance the CR by 22% compared with RT alone, without adding to significant morbidity. The number of patients needed to treat is 4.5. The lack of large randomized trials therefore should not hinder its routine application in clinics.

However, randomized trials are still needed to refine the patient selection criteria, the optimal RT dose and fractionation schedules, and ideal HT treatment parameters. Future trials could also stratify patients on the basis of some of the key prognostic factors, like hormone receptor and HER2 status, to identify specific prognostic groups that could benefit from HTRT over RT alone. Thus, the therapeutic efficacy and safety of HTRT warrants serious consideration in the management of LRBCs, with treatment parameters tailored to the individual patient characteristics, comorbidities, prior therapies, and expected survival.

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