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Original article

Reirradiation and hyperthermia for irresectable locoregional recurrent breast cancer in previously irradiated area: Size matters

Sabine Oldenborg [a,*], Vanessa Griesdoorn [a], Rob van Os [a], Yoka H. Kusumanto [a], Bing S. Oei [b], Jack L. Venselaar [b], Paul J. Zum Vörde Sive Vörding [a], Martijn W. Heymans [c], Merel Willemijn Kolff [a], Coen R.N. Rasch [a], Hans Crezee [a], Geertjan van Tienhoven [a]

[a] Department of Radiation Oncology, Academic Medical Center, University of Amsterdam (AMC); [b] Department of Radiation Oncology, Institute Verbeeten (BVI), Tilburg; and [c] Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

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ABSTRACT

Background/purpose: Treatment options for irresectable locoregional recurrent breast cancer in previously irradiated area are limited. Hyperthermia, elevating tumor temperature to 40–45 °C, sensitizes radio-and-chemotherapy. Four hundred and fourteen patients treated with reirradiation + hyperthermia (reRT + HT) in the $AMC_{(n=301)}$ and the $BVI_{(n=113)}$, from 1982 to 2005 were retrospectively analyzed for treatment response, locoregional control (LC) and prognostic factors for LC and toxicity.

Patients/methods: All patients received previous irradiation (median 50 Gy). reRT consisted of 8 × 4 Gy-2/week (AMC) or 12 × 3 Gy-4/week (BVI). Hyperthermia was added once (AMC)/twice (BVI) a week.

Results: Overall clinical response rate was 86%. The 3-year LC rate was 25%.

The number of recurrence episodes, distant metastases (DM), tumor site, tumor size, time to recurrence and treatment year were significant for LC.

Acute ⩾grade 3 toxicity occurred in 24% of patients. Actuarial late ⩾grade 3 toxicity was 23% at 3-years. In multivariable analysis reRT fraction dose was significantly related to late ⩾grade 3 toxicity.

Conclusion: reRT + HT is an effective curative and palliative treatment option for patients with irresectable locoregional recurrent breast cancer in previously irradiated area. Early referral, treatment of chest wall recurrences ⩽5 cm in the absence of distant metastases, provided the highest local control rates. The cumulative effects of past and present treatments should be accounted for by adjusting treatment protocol to minimize toxicity.

For patients with irresectable local recurrent breast cancer in previously irradiated area reirradiation is the only local treatment option, but the dose that can be given without a high risk of unacceptable toxicity is lower than considered adequate [1–3]. Furthermore, the dysfunctional microvasculature caused by previous radiation and/or surgery may render the tumor less sensitive to the effects of both radiotherapy and chemotherapy [4,5].

Hyperthermia, the elevation of tumor temperature to 40–45 °C, is a well-established radio- and chemotherapy sensitizer. It is known to inhibit DNA repair processes, affect tumor blood flow and oxygenation and cause direct cytotoxicity to cells that are acidotic and nutrient deprived [6–11]. In 1996 the International Collaborative Hyperthermia Group (ICHG) published the results of a combination of 5 small phase III trials, investigating the efficacy of hyperthermia as an adjunct to radiotherapy for the treatment of irresectable recurrent breast cancer. Analyses were complicated by differences in eligibility criteria, HT delivery and RT regimens between the trials. Not all trials demonstrated an advantage for the combined treatment. The greatest effect was observed in 120 patients (2/5 trials) with recurrent lesions in previously irradiated areas, with a 26% increase in complete response rates and a 20% improvement in the 3 year LC rate. Toxicity was not increased [5]. Two other independent prospective trials investigated the effect of adding HT to (re)RT on response rates of different superficially located tumor entities. One study confirmed the incremental gain of the addition HT in previously irradiated areas, but only 37 patients with recurrent breast cancer were included [12]. The other also included a limited number of breast cancer patients (35), but found no effect of adding HT [13]. In addition, part of these patients received primary high dose RT.

* Corresponding author at: Department of Radiation Oncology, Z1-215, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, P.O. Box 22660, Amsterdam, The Netherlands.

E-mail address: s.oldenborg@amc.uva.nl (S. Oldenborg).

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Table 1
Previous treatments.

Previous treatments	
Primary Surgery[a]	374 (91%)
Breast conservation	134 (32%)
Mastectomy	234 (57%)
Other	6 (2%)
Median RT fraction dose[b]	2 (1.8–8) Gy
Median total RT dose[c]	50 (17.2–66) Gy
Median RT boost[d]	16 (2.5–30) Gy
Surgery previous locoregional recurrences (1–8 episodes)[e]	195 (47%)
Salvage mastectomy previous locoregional recurrences	94 (23%)
Systemic therapy	330 (80%)
Chemotherapy (1–5 episodes)	89 (22%)
Hormone therapy (1–5 episodes)	108 (26%)
Both	133 (32%)

[a] Data missing for 1 patient.
[b] Data missing for 19 patients.
[c] Data missing for 16 patients.
[d] Data missing for 16 patients.
[e] Data missing for 1 patient.

So, although some randomized evidence exists that HT enhances reRT for locally recurrent breast cancer, these studies are too small to derive state of the art information about the general outcomes of this treatment in terms of subsequent local control and (late) morbidity.

Our study includes the largest series of locoregional recurrent breast cancer patients treated with reRT + HT, reported in the literature to date. We aim to describe long-term LC and morbidity of reRT + HT for irresectable recurrent breast cancer in previously irradiated area. We also performed multivariable analyses of patient-, tumor- and treatment related factors, influencing LC and toxicity.

Patients and methods

Patients

According to the Dutch National Guideline for Breast Cancer patients with irresectable locoregional recurrent breast cancer in previously irradiated area are treated with reRT + HT. Currently, the AMC and the BVI treat approximately 70 new patients each year.

For the current study patients with irresectable disease were included from 1982, the year clinical hyperthermia was started in the Netherlands, up to 2006 to enable long-term follow-up

Table 2
Characteristics current episode.

Current recurrence				
Median age at current treatment		57 (18–90) years		
Median TI primary tumor – current recurrence		54 (3–469) months		
Previous LR (1–13 episodes per patient)		308 (74%)		
Presence/history of DM		148 (36%)		
Presence/history of regional disease		188 (45%)		
Presence/history of contralateral disease		92 (22%)		
Size tumor area[a]				
<3 cm		51 (12%)		
3–5 cm		36 (9%)		
5–10 cm		126 (31%)		
>10 cm		196 (48%)		
Lymphangitis		63 (15%)		
Tumor site		Type		
		Single nodule	Multiple nodules	Diffuse
Breast	36 (9%)	13 (3%)	8 (2%)	15 (4%)
Chest wall	325 (78%)	69 (17%)	202 (48%)	54 (13%)
Chest wall + breast	16 (4%)	2 (1%)	10 (2%)	4 (1%)
Regional lymph nodes	37 (9%)			
Current treatment				
R2 surgery[b]		27 (7%)		
Salvage mastectomy (R2)		5 (2%)		
Incomplete local resection		20 (5%)		
Median reRT field size[c]		3.0 dm^2 (0.30–15.60)		
ReRT dose[d]				
6 × 4 Gy		32 (8%)		
8 × 4 Gy		202 (49%)		
10 × 4 Gy		39 (9%)		
12 × 3 Gy		94 (23%)		
Other (3–35 × 2–5 Gy)		44 (11%)		
ReRT technique[e]				
Electrons		158 (40%)		
Photons		72 (18%)		
Photons + electrons		162 (41%)		
Systemic treatment[f]		167 (40%)		
Chemotherapy		63 (15%)		
Hormone therapy		122 (30%)		
Number of tumor locations >1		71 (17%)		
Tumor present outside reRT field		29 (7%)		

Abbreviations: TI = time interval; LR = locoregional recurrent disease; DM = distant metases.
[a] Estimated size; data missing for 5 patients.
[b] Prior to reRT plus HT; data missing for 2 patients.
[c] Data missing for 15 patients.
[d] Data missing for 3 patients.
[e] Data missing for 22 patient.
[f] Data missing for 1 patient.

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