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RESEARCH ARTICLE

Elective re-irradiation and hyperthermia following resection of persistent locoregional recurrent breast cancer: A retrospective study

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Abstract

Purpose: To analyse the therapeutic effect and toxicity of re-irradiation (re-RT) combined with hyperthermia (HT) following resection or clinically complete remission (CR) of persistent locoregional recurrent breast cancer in previously irradiated area.

Methods and materials: Between 1988 and 2001, 78 patients with high risk recurrent breast cancer underwent elective re-RT and HT. All patients received extensive previous treatments, including surgery and high-dose irradiation (≥50Gy). Most had received one or more lines of systemic therapy; 44% had been treated for ≥ one previous locoregional recurrences. At start of re-RT + HT there was no macroscopically detectable tumour following surgery (96%) or chemotherapy (CT). Re-RT typically consisted of eight fractions of 4Gy, given twice weekly. Hyperthermia was added once a week.

Results: After a median follow up of 64.2 months, three-year survival was 66%. Three- and five-year local control rates were 78% and 65%. Acute grade 3 toxicity occurred in 32% of patients. The risk of late ≥ grade 3 toxicity was 40% after three years. Time interval to the current recurrence was found to be most predictive for local control in univariate and multivariate analysis. The extensiveness of current surgery was the most relevant treatment related factor associated with toxicity.

Conclusions: For patients experiencing local recurrence in a previously radiated area, re-irradiation plus hyperthermia following minimisation of tumour burden leads to a high rate of local control, albeit with significant toxicity. The latter might be reduced by a more fractionated re-RT schedule.

Keywords: *hyperthermia, re-irradiation, recurrent breast cancer, local control, toxicity*

Introduction

Locoregional recurrence of breast cancer has a poor prognosis. Surgery and/or radiation often fail to provide local control [1–6]. Recurrences in previously irradiated areas present an additional challenge as the re-irradiation dose that can be given without a high risk of unacceptable toxicity is lower than considered adequate [2, 7, 8]. Furthermore, the poorly functioning microvasculature caused by previous radiation may render the tumour less sensitive to the effects of radiation and chemotherapy [9]. For these patients the addition of local hyperthermia to re-irradiation has proven to be effective and well tolerated with minor toxicity [9, 10]. In 1996 the International Collaborative Hyperthermia Group (ICHG) published the results of a combination of

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five phase III trials, demonstrating the efficacy of hyperthermia as an adjunct to radiotherapy for the treatment of recurrent breast cancer. These results were confirmed by more recent studies [11–13].

Although a reasonable amount of data exists on the combination of re-irradiation and hyperthermia for patients with macroscopically recurrent breast cancer, limited information is available about elective thermoradiation after minimisation of tumour burden to only subclinical disease for patients with locoregional recurrences in previously irradiated area. The aim of this study is to present a series of such patients who were considered to be at high risk for additional locoregional recurrence.

Methods and materials

Patients

A total of 439 patients with locoregional recurrent breast cancer in previously irradiated areas were treated at the Academic Medical Center, Amsterdam, with re-irradiation and hyperthermia in the period between January 1988 and December 2001. Seventy-eight patients with either macroscopically complete resection of their recurrence (75 patients) or clinically complete remission after chemotherapy (three patients) were the subjects of this study. Patient characteristics are summarised in Tables I and II. Seventy-seven patients were women. There was one patient with male breast cancer. The median age at study entry was 52. If patients were treated with more than one course of re-irradiation plus hyperthermia, only the first course was included in this analysis. Available data concerning patient, primary tumour, recurrence, previous and current treatment characteristics were collected from the radiotherapy and hyperthermia patient charts.

All patients had previously received surgery and radiation to a median dose of 65 Gy. A brachytherapy (21%) or external beam (79%) tumour boost was given in 81% of patients to a median equivalent dose of 15Gy. Most (69%) had received one or more lines of systemic therapy in the past either as primary adjuvant treatment or as salvage treatment for a previous recurrence, or both. Additionally, 44% of the patients had been treated for one or more previous locoregional recurrences with surgery, radiation, systemic therapy, or a combination of treatment modalities before start of re-irradiation plus HT.

The median time interval between treatment for the primary tumour and development of the current recurrence – the one considered in this study – was 60 months. The median time interval between the first and the second radiation course was 58.4 months. Recurrences to be analysed were categorised as consisting of one nodule, multiple nodules or being diffuse. For the recurrence evaluated in this study six patients were treated with chemotherapy, 25 with hormonal therapy and eight with a combination of both, either before, during, or after re-irradiation and hyperthermia.

Prior to re-RT plus HT three patients achieved complete remission after chemotherapy treatment; two of which had an intact breast. The other 75 patients had a macroscopically complete surgery, consisting of chest wall resection, salvage mastectomy or local resection. Thirty nine percent of patients had a R0 resection and 61% a R1 resection.

All patients were felt to be at high risk of developing a subsequent local recurrence based on (1) surgery results (microscopic residual tumour or close resection margin), (2) recurrence histology (tumour size, multi-centricity, diffuse tumour growth, angioinvasion or poor differentiation grade), (3) medical history and disease status (e.g. age at primary treatment or multiple previous recurrences at the same location). For these reasons, adjuvant re-irradiation plus hyperthermia was considered of additional value.

Treatment

Radiotherapy. Following macroscopically complete resection or complete remission of the tumour after chemotherapy, patients were scheduled to receive re-irradiation to a total dose of 32 Gy. Eight fractions of 4 Gy were given twice a week [9, 14], using high energy photons and electrons through one or multiple ports. Treatment fields were individualised for each patient. In general, the chest wall or mastectomy area up to the dorsal axillary fold was considered target area. The lateral chest wall and/or regional area were irradiated with anterior-posterior opposing photon fields (AP-PA) opposing photon fields and the anterior chest wall with electrons. The two patients with intact breast were treated with tangential fields. The upper border of the radiation fields was at the level of the coracoid process, or included the periclavicular area in case of regional recurrence. In some instances (21%) a local technique was applied, using a field limited to the recurrence area with a 3–5 cm margin.

Hyperthermia. Hyperthermia was given once a week within 1 hour after radiotherapy. Heat was induced electromagnetically, using externally applied contact flexible microstrip applicators (CFMA), operating at 434 MHz [15–17]. Treatment fields covered at least the area of surgery or of the recurrent tumour. For areas too large to be treated in one session, two weekly hyperthermia sessions were scheduled with an overlap between the treatment fields. Median field

Table I. Baseline characteristics.

Time-related factors	
Median age at current treatment	52 (29–80) years
Median time interval primary tumour – current recurrence	60.3 (14.9–297.4) months
Median time interval first RT course – reRT	58.4 (10.4–241) months
Primary tumour	
Initial tumour stage[a,b]	
T1-2	66 (93%)
T3-4	5 (7%)
Positive lymph nodes[c]	28 (41%)
Previous treatments	
Primary surgery[d]	
Breast conservation	49 (64%)
Mastectomy	24 (32%)
Other	3 (4%)
Median total RT dose (incl. boost)	65 (30–75) Gy
Surgery previous locoregional recurrences	33 (42%)
Salvage mastectomy previous locoregional recurrences	19 (24%)
Systemic therapy	
Chemotherapy	18 (23%)
Hormone therapy	21 (27%)
Both	15 (19%)

[a]According to the TNM classification of malignant tumours (30). [b]Data missing for 7 patients. [c]Data missing for 10 patients. [d]Data missing for 2 patients.

Table II. Characteristics current episode.

Current recurrence				
Site		Type[a] Single nodule	Multiple nodules	Diffuse
Breast	34 (44%)	8 (10%)	2 (3%)	22 (28%)
Chest wall	37 (47%)	22 (28%)	11 (14%)	3 (4%)
Regional lymph nodes	7 (9%)			
Positive oestrogen/progesterone receptor status[b]		39 (71%)		
Angioinvasion		28 (36%)		
Distant metastases		6 (8%)		
Current treatment				
Chemotherapy[c]		14 (18%)		
Hormone therapy[d]		33 (43%)		
Surgery				
Salvage mastectomy		31 (40%)		
Chest wall resection		6 (8%)		
Local resection		34 (44%)		
Extensive resection		4 (5%)		
None		3 (4%)		
Surgery status[e]				
R0		29 (39%)		
R1		45 (61%)		

[a]Data missing for 3 patients. [b]Data missing for 23 patients. [c]Data missing for 1 patient. [d]Data missing for 2 patients. [e]Data missing for 1 patient.

size was 336 cm^2 (64–440 cm^2). For all patients temperatures were measured on the skin. In 15 patients additional invasive temperature measurements were performed using a flexible subcutaneous catheter. Target temperature was 41–43°C for one hour. Applied power and temperature of the water bolus were adjusted to the desired temperature distribution without exceeding the

Table III. Treatment parameters.

Treatment variable		Number
RT technique	Local	16 (21%)
	Locoregional	62 (79%)
Target location	Chest wall	69 (88%)
	Breast	2 (3%)
	Regional (axilla, parasternal, periclavicular)	5 (6%)

Thermal dose indicators

Average in °C	Min	Mean	Max	*N* patients[a]
T_{90} skin	37.7	41.1	42.4	73
T_{90} invasive	38.7	40.2	41.2	15
T_{50} skin	39.0	42.2	43.4	73
T_{50} invasive	40.0	41.2	42.2	15
T_{10} skin	41.1	43.2	44.5	73
T_{10} invasive	41.0	42.5	44.5	15
Average in minutes	**Min**	**Mean**	**Max**	***N* patients[a]**
CEM 43°C T_{90} skin	1.5	22.3	107.7	58
CEM 43°C T_{90} invasive	0.5	7.4	18.0	15
CEM 43°C T_{50} skin	9.4	104.1	269.0	58
CEM 43°C T_{50} invasive	3.3	37.3	96.0	15

[a]Data were not available for all patients, or not applicable.

maximum normal tissue temperatures (45°C) or patient tolerance (e.g. pain, general discomfort). Thermal dose indicators accounting for both temperature distribution and duration of treatment were calculated over steady-state periods of the number of given hyperthermia sessions per patient and averaged over the total number of patients. These indicators included the minimal temperature, T_{90}, the median temperature, T_{50}, and the maximum temperature, T_{10}. Additionally the CEM 43°C T_{90} values were determined, which account for the cumulative equivalent minutes (CEM) at 43°C exceeded by 90% of the measured temperatures in the target volume [12, 18–22]. All patients were scheduled to receive at least four hyperthermia sessions. Details concerning treatment parameters are given in Table III.

Endpoints and data analysis

Local control and survival. Both local control (LC) and survival rate were calculated from the date of salvage surgery or, if not available, date of first re-irradiation fraction. Duration of LC and survival were analysed by the actuarial method of Kaplan and Meier [23]. Local failure was defined as in-field relapse. Patients dying with LC, or with continuing LC at last follow-up, were censored at the date of death or last follow-up, respectively. For overall survival patients known to be alive at last-follow-up were censored at that date.

Toxicity. Grade 3-4 acute and late toxicity were assessed according to The National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 [24]. Toxicity was considered acute when occurring within 3 months after the first re-RT treatment and late when occurring >3 months after the first re-RT treatment. The specific toxicities reviewed were telangiectasia, moist desquamation, ulceration, upper extremity oedema, frozen shoulder, brachial plexopathy, fibrosis, soft tissue necrosis, osteonecrosis, fracture, osteoneuropathy, pneumonitis and cardiomyopathy. Late toxicity incidence was calculated by the actuarial method of Kaplan and Meier [23], starting from date of first re-irradiation fraction to date of worst late toxicity notification. Patients without late toxicity were censored at date of last follow-up.

Prognostic factors. Statistical analysis was carried out using the statistical program R version 2.6 and SPSS version 16 (SPSS, Chicago, IL). Associations of primary tumour, current recurrence, previous treatment and current treatment variables with clinical outcome and the development of late toxicity were calculated using the Cox regression test. Associations with acute toxicity were analysed by binary logistic regression. The 2-tailed Pearson correlation test was used to determine correlation coefficients between covariates. The level of statistical significance was considered <0.05 for all calculations.

Results

Treatment compliance

Most patients finished the treatment according to protocol. Two patients could neither complete radiotherapy nor hyperthermia treatment: one received only 5/8 RT fractions and 1 HT session because of severe skin toxicity and one refused treatment after 5 RT fractions and 3 HT sessions. Additionally, two patients could not complete hyperthermia treatment. The last hyperthermia session was cancelled for one patient because of skin toxicity and for the other due to deterioration of physical condition and fever.

Clinical outcome

Median follow-up time was 64.2 months (range, 8–151) for patients still alive at last follow-up. The three- and five-year overall survival rates were 66% and 49%, with a median survival of 59.2 months (Figure 1). The overall three- and five-year local control rates were 78% and 65%, respectively (Figure 2). The absolute infield failure rate was 27%.

Twenty three (29%) patients had out of field progression without infield relapse. Of the three patients who were treated following complete remission after chemotherapy, two had local failures after 12.3 and 40.1 months, respectively. The other patient died after 16.7 months, without evidence of subsequent local recurrence.

Toxicity

During hyperthermia treatment 41% of patients experienced mild complaints, varying from pain to discomfort. Pain was frequently related to the delicacy of the treatment area caused by previous surgery and was often solvable during treatment. In only three patients complaints caused the hyperthermia session to be terminated prematurely, i.e. before the treatment duration of 60 minutes was completed.

In 32% of patients acute grade 3 toxicity occurred, mostly moist desquamation (Table IV). From two patients data on acute toxicity could not be retrieved. No grade 4 acute toxicities were noted.

Hyperthermia-induced acute side effects consisted of blisters (<grade 3) in 23% of patients and fat necrosis (<grade 3) in 4% of patients. It should be noted that aggravation of pre-existing toxicities from previous treatments as well as toxicities of uncertain cause were regarded as new toxicities related to current treatment. Late toxicity-free interval is shown in Figure 3. The absolute grade 3–4 late toxicity rate was 43%.The actuarial risk on grade 3–4 late toxicity after one year was 24% and after three years 40%. Toxicity data were missing for three patients because they were lost to follow-up. The number of late grade 3 and 4 toxicities is reported in Table V and consisted most frequently of ulceration. Eventually, all grade 4 ulcerations and fistula were resolved. No treatment-related deaths were observed.

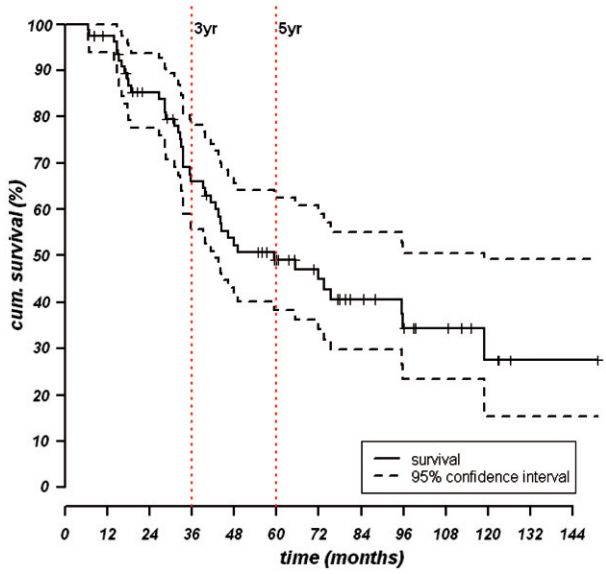

Figure 1. Overall survival.

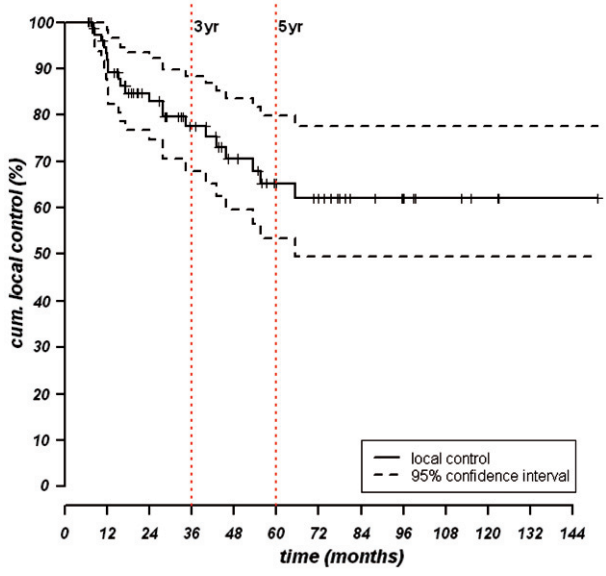

Figure 2. Infield local control.

Table IV. Acute toxicity (76 patients).[a]

Toxicity	Grade 3	Grade 4
Moist desquamation	16	0
Arm oedema	4	0
Ulceration	6	0
Brachial plexopathy	1	0
None	52	76

[a]Two patients experienced more than one toxicity.

Prognostic factors

All parameters from Tables I, II and III with known or presumed prognostic value were tested in univariate analyses. Only variables available for at least 80% of the population were analysed. All prognostic factors significant in univariate analysis were entered in multivariate forward stepwise regression analysis. Covariates with strong (70–80%) or significant ($p \leq 0.05$) correlations were not included in the same multivariate model.

The results from analysis for LC and acute toxicity are presented in Table VI. The covariates tested and their treatment on entry into the models are shown in column 1.

Time interval to current recurrence was significantly related to local control in univariate analysis as were initial tumour stage and the presence of distant metastases prior to, or at start of current treatment. Treatment-related variables associated with local control were concurrent hormone treatment and re-irradiation technique. The only prognostic factor that remained significant in multivariate analysis ($n = 66$) was time interval to current recurrence. In addition, re-irradiation technique was significant ($p = 0.04$) in a two-covariate model ($n = 73$) with time interval to current recurrence ($p = 0.001$). No significant difference in local control was found between patients with in-breast failures or chest wall failures, nor was there a significant difference in prognosis when the different types of primary or current surgery were analysed. None of the thermal dose parameters was found to correlate with local control.

In univariate analysis variables related to the type of surgery for the current recurrence and anatomical site of the current recurrence were significant for acute toxicity, with chest wall resection associated with the highest risk ($p = 0.080$, OR = 4.857). Multivariate models proved inappropriate because of the small number of significant prognostic factors and strong correlation between these factors.

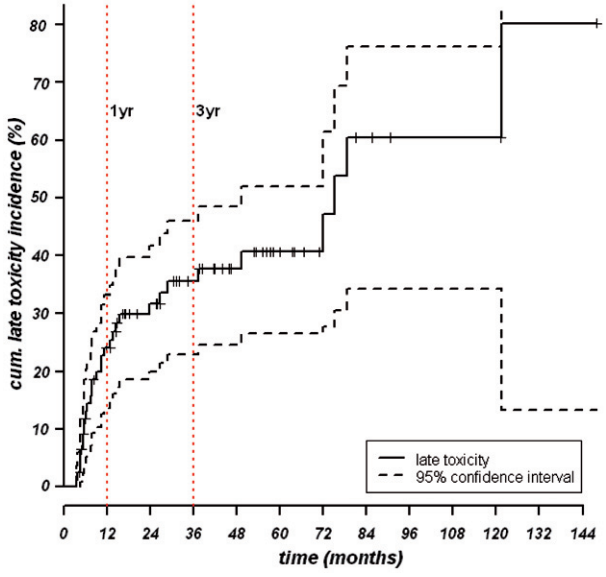

Figure 3. Late toxicity incidence.

Table V. Late toxicity (75 patients).[a]

Toxicity	Grade 3	Grade 4
Arm oedema	5	1
Ulceration	7	6
Telangiectasia	8	0
Fibrosis	7	0
Osteonecrosis	6	1
Rib fracture	0	1
Frozen shoulder	7	0
Cardiomyopathy	1	0
Osteoneuropathy	1	0
Brachial plexopathy	1	0
None	43	65

[a]Sixteen patients had more than one toxicity, in 13 patients both acute and late toxicity occurred and three patients experienced ulceration combined with fistula.

Table VIA. Univariate and multivariate Cox regression for local control.

Covariate	Cases (%)	HR (95% CI)	*P*-Value[a]	*P*-Value[b] ($n = 66$)
TI primary tumour – current recurrence ≤60.3 months: >60.3 months	94	0.176 (0.063–0.492)	0.001	0.004
Hormone treatment current recurrence Yes: No	94	2.948 (1.070–8.123)	0.037	0.242
Initial tumour stage T1-4	87	2.108 (1.002–4.434)	0.049	0.217
Metastases No: Yes	96	3.384 (0.990–11.562)	0.052	0.685
Reirradiation technique Local: Locoregional	96	0.411 (0.157–1.077)	0.070	0.101

[a]Univariate. [b]Multivariate.
TI, time interval; HR, hazard ratio; CI, confidence interval

Table VIB. Univariate binary logistic regression for acute toxicity.

Covariate	OR (95% CI)	*P*-value	Cases (%)
Type of surgery for current recurrence Extensive surgery: Local resection	0.303 (0.103–0.890)	0.030	96
Anatomical site of current recurrence Chest wall: Breast	2.862 (1.017–8.055)	0.046	91

OR, odds ratio; CI, confidence interval.

For late toxicity no significant plausible prognostic variables could be found.

Discussion

Clinical outcome

Although our study population is small and heterogeneous, all patients did receive the same treatment on a similar target area, resulting in a three- year local control rate of 78%. This is superior to the 38–45% reported in historical series of re-irradiation and hyperthermia alone for recurrent breast cancer [9–13]. An explanation might be found in the absence of macroscopic tumour load at the onset of re-RT plus HT. Radiobiological and clinical experience showed in general that the excision of solid tumours prior to radiotherapy leads to better tumour control since the number of clonogenic cells is reduced [25]. Additionally, the absence of macroscopic disease has already shown to be correlated to prognosis [26].

To our knowledge there is little information on elective re-RT plus HT for patients at high risk of recurrent breast cancer, without macroscopic disease. Kapp et al. [27] and Welz et al. [28] investigated (re)irradiation and hyperthermia for subclinical residual or high-risk primary or recurrent breast cancer. Despite differences in patient and treatment characteristics, their results (three-year local control rates of 68% and 81%, respectively) are in line with ours, indicating that subsequent local control after re-irradiation with hyperthermia for a locoregional recurrence in previously irradiated area may be improved by eliminating macroscopic disease by surgery or systemic therapy.

For surgery alone reported failure rates range from 4–37% for salvage mastectomy [29] to 48–76% [2, 3] for local resection of chest wall recurrences. Our five-year failure rate of only 35% is comparable to the results of salvage mastectomy [29]. This indicates the beneficial effect of elective re-RT plus HT, particularly since our patient group had a comparatively poor prognosis.

No comparable studies exist assessing the effect of re-irradiation alone for patients at high risk for subsequent failure after removal of macroscopic disease. One study [25] reports on radiation for patients with isolated chest wall recurrences without distant metastases, following initial mastectomy with or without post-operative RT. A subgroup of 51 patients was irradiated with doses ranging from 20–79 Gy after excision of the recurrent tumour mass. The absolute infield failure rate of this subgroup was 31%, which is in the same range as our 27% infield failure rate. However, it is not clear how many of these patients received primary high-dose RT for the recurrence.

Another study [30] reports on a group of 13 patients treated with re-irradiation of 30–61.2 Gy (median 50.4 Gy) after a R0 or R1 resection for recurrent breast cancer. Four of these patients received concurrent chemotherapy. Local control was ≈90% after two years. Similar results were reported by Wahl et al. [13] for a comparable subgroup of 16 patients treated with a median re-irradiation dose of 48 Gy. However, for both studies the follow-up time was too short and the size of the patient group too small to draw conclusions.

Most associations with clinical outcome found after univariate and multivariate analysis in the present study are in agreement with results from previous reports [10, 12, 27, 31]. A clear relationship between treatment-related variables and clinical outcome could not be found in this study. However, a large re-RT field size appeared to have a positive effect on duration of local control compared to a small field size. This, in combination with our finding that 29% of outfield relapses occur without infield regrowth, suggests that RT margins should be enlarged.

It is generally assumed that patients with locoregional failures after initial breast conserving therapy have a better prognosis than patients who received initial mastectomy. This was not the case in our study in which patients were treated with re-RT plus HT based on the presence of one or more risk factors after salvage surgery. In fact, patients with in-breast failures had a slightly worse prognosis. There is some controversy in literature on this subject. A study by van Tienhoven et al. [6] showed the risk of subsequent locoregional failure after salvage treatment for local recurrence after breast conserving therapy to be still quite high and not significantly different from the risk after primary mastectomy (five-year failure rate of 37% versus

38%). The time interval from primary tumour to locoregional recurrence was the most important predictor for local control. The very same results are found in the present study suggesting that an early locoregional recurrence is an indicator of a biologically aggressive tumour and carries a poor prognosis, irrespective of the type of primary surgery.

Though most studies on hyperthermia combined with radiation report a positive relationship between treatment outcome and higher invasive thermal doses [11, 19, 20, 22, 27, 32], no such relationship could be found in our study. However, our temperature measurements were mostly limited to the skin, which might be a poor substitute for invasive thermometry in this patient group. In a previous small-scale study at our institute we did find a correlation between achieved temperatures and complete response rates when temperatures were measured intratumourally and subcutaneously [33]. This stresses the importance of invasive measurements until reliable non-invasive techniques for monitoring delivery of HT become available.

Toxicity

The overall occurrence of grade 3–4 toxicity was considerable in the present study, with an actuarial risk of 40% after three years.

Previous randomised controlled trials have shown hyperthermia not to add significantly to relevant acute or late toxicity over irradiation alone, even in patients who had received prior radical RT [9]. To our knowledge the present analysis is the first long-term review to report detailed grade 3 and grade 4 toxicity after re-irradiation with 8×4 Gy plus hyperthermia for recurrent breast cancer. Only one other study reviewed chest wall re-irradiation plus hyperthermia, using the 8×4 Gy schedule (10). Compared to that study we observed more acute toxicity concerning moist desquamation (21% versus 11%). Our absolute late toxicity rate (43% versus 29%) was also higher, including an increase in telangiectasia (11% versus 2%) and ulceration (17% versus 10%). In addition we observed limited cases of bone necrosis, fractures and brachial plexopathy. It is difficult to compare toxicity rates, however, as our primary irradiation dose was higher (median: 65 Gy versus 45 Gy) and other toxicity scoring and patient inclusion criteria (e.g. subclinical versus 89% macroscopic disease) were used. Also, both median follow up and median survival duration were different (64.2 versus 21 months and 59.2 versus 20 months, respectively).

Several reasons might account for the high percentage of grade 3–4 toxicity observed in the present study. First, our follow-up time is relatively long with high survival rates. This obviously results in a higher cumulative percentage of late toxicity. Second, due to the retrospective character of this study it was not possible to discriminate between toxicities already induced by previous treatments and the current treatment. Therefore, our reported toxicity should be considered the cumulative effect of previous and current treatments. Third, an increase in toxicity is to be expected as our patient group received re-irradiation plus hyperthermia only shortly after extensive surgery in an area already subjected to multiple previous treatments.

Acute toxicity appeared to be most affected by the type of surgery for the current recurrence: patients with a local excision had the lowest risk on acute toxicity compared to patients undergoing mastectomy or chest wall resection, whereas the risk was highest for the latter patients.

In addition, patients with scar dehiscence or post-operative infection seemed to present a vulnerable group with respect to skin toxicity. The hypofractionated schedule (biological effective dose of 8×4 Gy is 96 Gy2 if α/β is considered as 2) is another possible reason to expect a high late toxicity rate.

A more fractionated re-RT schedule might minimise the incidence of $\geq$grade 3 toxicity in this patient population [27, 28].

Conclusion

For patients experiencing local recurrence in a previously radiated area, re-irradiation plus hyperthermia following minimisation of tumour burden leads to a high rate of local control, albeit with significant toxicity. The latter might be reduced by a more fractionated re-RT schedule.

Declaration of interest: Actual or potential conflicts of interest do not exist. Neither copyrighted information nor patient photos were used.

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