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LETTER TO THE EDITOR

Two-year toxicity of hypofractionated breast cancer radiotherapy in five fractions

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Introduction

After breast conserving surgery (BCS) for breast cancer, radiotherapy (RT) reduces the risk of locoregional recurrences and improves overall survival [1,2]. Despite the benefits, late toxicity may occur months to years after RT [3–6] and can have a negative impact on breast cosmesis and on quality of life of patients [7,8].

In fractionated RT, the total duration of treatment also influences the quality of life negatively [9]. Conventional RT schedules for whole breast irradiation (WBI) consist of 25–28 fractions over a period of at least 5 weeks. The duration of treatment can be extended to 6 or 7 weeks if an additional 'boost' to the tumor bed is applied. Reducing the number of fractions can reduce the burden of treatment. A simultaneous integrated boost (SIB), i.e., integrating the boost dose in WBI treatment, is a way to reduce the total treatment time by 1–2 weeks [10–12]. Hypofractionation, i.e., using less treatment fractions with a higher dose per fraction, is another option. Compared to 25 fractions, similar or even less toxicity was seen with 15 or 16 fractions in the UK START trials and the Canadian hypofractionation trial [13–15].

Retrospective studies have investigated the feasibility of further acceleration to 5 fractions over 5 weeks [16–18]. These preliminary results show acceptable early and late toxicity and good local control and survival. The UK FAST trial randomized between a 5-fractions schedule, 1 fraction a week and the traditional 25-fractions schedule. With a median follow-up of 3 years, moderate/marked toxicity was similar after 28.5 Gy/5 fractions and 50 Gy/25 fractions, but higher after 30 Gy/5 fractions [3]. Ten-year results of the FAST trial confirmed these findings [19]. These studies delivered the five fractions once-weekly, with an overall treatment time of still 5 weeks. From a radiobiological point of view, it might be more optimal to shorten the overall treatment time [20].

In this analysis, the 2-year toxicity of hypofractionation in 5 fractions (HF5) given over 10–12 d is investigated in patients receiving RT after BCS. A matched-case analysis was done with patients treated with hypofractionation in 15 fractions to the whole breast (HF15). Differences with the above-mentioned studies are the shorter treatment duration and the inclusion of patients receiving lymph node irradiation (LNI) and SIB. Acute toxicity of the study population was reported in an earlier matched-case analysis: less acute toxicity was seen in the HF5 group [21].

Methodology

In this retrospective analysis, patients receiving HF5 to the whole breast with or without LNI after BCS were included. They participated in prospective clinical trials investigating the feasibility of accelerated radiation schedule between January 2015 and April 2018 (NCT04098926 and NCT03121248 on www.clinicaltrials.gov). The patients received 5 fractions of 5.7 Gy to the whole breast with, if indicated, a SIB of five times 6.2–6.5 Gy and/or LNI (five times 5.4 Gy). If indicated, patients received adjuvant chemotherapy (4 times Epirubicin-Cyclophosphamide and 12 times Paclitaxel) and hormone therapy (either tamoxifen or an aromatase inhibitor). Chemotherapy was always preceding RT and a minimal interval of 3 weeks between chemotherapy and RT was respected. Hormone therapy was given concomitantly with RT.

The control group consisted of patients from the European REQUITE study (www.requite.eu), treated in the same center with a HF15-scheme. In this cohort, the UK START schedule of 15 fractions of 2.67 Gy was used for WBI and LNI. Boost, if applied, was administered either sequentially (four fractions of 2.5 Gy or 6 fractions of 2.48 Gy) or simultaneously (SIB of 3.12 Gy per fraction). Control patients were recruited from June 2014 until September 2016. The same treatment protocols regarding delineation, dose prescription and the same planning techniques were used as in the experimental group.

Each HF5 patient was matched with one control, selected by means of a propensity scoring method. An exact method for LNI [22,23], boost [24] and postmenopausal status, and a nearest neighbor method for breast volume [25,26] and age [27] were used.

Toxicity was scored at 24 months after the end of RT (range 1–2 months), in the HF5 group using the LENT-SOMA scale, in the HF15-group using criteria specific to the REQUITE study. For both, scoring was done by a physician. Endpoints

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Table 1. Patient and treatment characteristics and 2-year toxicity.

	HF5 ($n=71$)	HF15 ($N=71$)	Significance p Value
Characteristics			
Boost			<.001*
SIB	64 (90%)	14 (20%)	–
SEB	0 (0%)	50 (70%)	–
Lymph node irradiation	20 (28%)	20 (28%)	1.0
Postmenopausal	71 (100%)	71 (100%)	1.0
Age (mean)	73 years	65 years	<.001*
Breast volume (mean)	871cc	870cc	1.0
Smoking	2 (3%)	6 (8%)	.1
Postoperative infection	2 (3%)	1 (1%)	.6
Chemotherapy	24 (34%)	24 (34%)	1.0
Hormone therapy			.9
Tamoxifen	41 (58%)	43 (61%)	–
Aromatase inhibitor	12 (17%)	10 (14%)	–
Mean tumor volume	20 mm	17 mm	.5
Treatment position			.9
Supine	23 (32%)	24 (34%)	–
Prone	48 (68%)	47 (66%)	–
CTV boost volume (mean)	52 cc	81 cc	<.001*
Toxicity			
Breast retraction	14 (20%)	27 (38%)	.01*
Breast edema	11 (15%)	21 (30%)	.07
Telangiectasia	3 (4%)	12 (17%)	.01*
Fibrosis out of tumor bed	14 (20%)	5 (7%)	.05
Fibrosis in tumor bed	13 (18%)	15 (21%)	.6
Pigmentation changes	16 (23%)	20 (28%)	.4
Pain	4 (6%)	12 (17%)	.03*

HF5: hypofractionation in 5 fractions; HF15: hypofractionation in 15 fractions; SIB: simultaneous integrated boost; SEB: sequential boost; CTV: clinical target volume.
*$p < .05$.

were identical and to allow comparison of the data based on different scoring systems, only presence and deterioration of toxicity were taken into account. Baseline toxicity was defined as toxicity that was present before the start of RT. Radiation-related toxicity was defined as baseline toxicity that deteriorated during or after RT and toxicity that arose during or after RT and was not present at baseline. For the presence of pain, it was not possible to define radiation-related toxicity since many patients reported pain at baseline which disappeared with time. Therefore, presence of pain at 2 years was compared as such between both groups. Statistical differences were evaluated with a double-sided paired Mc Nemar test.

Results

A total of 71 patients receiving HF5 were included in the test group. Of these, 20 patients received LNI and 64 of them received a boost. A total of 203 controls were available for matching. For each patient in the test group, an exact match based on target volume, boost and post-menopausal status was found. The mean difference in age was reduced to 8 years and for breast volume to 1 cc by using the nearest neighbor method. A significant difference between both groups was seen for age, boost volume ($p < .001$) and type of boost ($p < .001$). Patient and treatment characteristics are shown in Table 1.

In Figure 1, toxicity is displayed in three categories: baseline toxicity that did not deteriorate during or after RT, baseline toxicity that deteriorated during or after RT and toxicity that arose during or after RT and was not present at baseline. In the latter two categories, RT might have had an influence on toxicity and, therefore, they are defined as radiation-related toxicity. Retraction and fibrosis in the tumor bed are common at baseline, but only in a few patients, baseline toxicity deteriorates during or after RT. Although retraction was three times more common in the HF5 group than in the HF15 group at baseline, radiation-related retraction was significantly less seen in the HF5-group at 2 years (p=.01). Telangiectasia was uncommon in HF5 patients, while almost one out of six patients of the HF15 group presented with telangiectasia at 2 years (p=.01). The incidences of radiation-related fibrosis in the tumor bed and pigmentation changes were comparable in both groups (p= .6 and .4, respectively), but the presence of fibrosis outside of the tumor bed was higher in the HF5 compared to the HF15 group (p= .05). The incidence of radiation-related breast edema was halved in HF5 patients compared to HF15 patients (p=.07).

Pain is reported significantly less frequent in the HF5 group than in the HF15 group (p=.03) 2 years after RT. In none of the patients, brachial plexopathy was observed.

Discussion

To avoid potential bias, a matched-case analysis approach was chosen to evaluate 2-year toxicity results of our HF5 schedule. Unfortunately, not all patient- and treatment-related factors potentially influencing toxicity, could be excluded. However, no significant difference was withheld for smoking, postoperative infection, chemotherapy, tumor volume and treatment position. The biggest weakness of this study is the difference in age between both groups with HF5 patients being on average 8 years older than HF15 patients. The boost-no boost trial showed an increase in the occurrence of severe fibrosis with age [28]. In our cohort, RT-related fibrosis outside the tumor bed was seen in one fifth of patients after 5 fractions compared to only 7% after 15 fractions (p=.05). However, the incidence of RT-related fibrosis in the tumor bed was comparable between both groups. A higher boost volume has been described as a risk factor for fibrosis [29]. However, in our data, the average boost volume was lower in de HF5 group than in the HF15 group. Possibly, the explanation can be found in the equivalent total dose in 2 Gy-fractions (EQD2), which is higher in the HF5 schedule. With an α/β value of 2.5 Gy as suggested in the UK FAST trial [3], EQD2 is 51.93 Gy for five times 5.7 Gy and 46.01 Gy for 15 times 2.67 Gy.

For breast retraction (p=.01), telangiectasia (p=.01), pain (p=.03) and breast edema (p=.07), HF5 seems to be milder than HF15. The reason for this is not clear, since α/β values for all toxicity endpoints seem to be comparable [30]. Besides age and average boost volume, the more frequent use of SIB in the HF5-group might also have affected the results, although a randomized controlled trial comparing SIB with a sequential boost did not report a difference in late toxicity [31].

Baseline cosmesis is a possible predictor of late radiation-related cosmesis [6], but according to our findings, toxicity

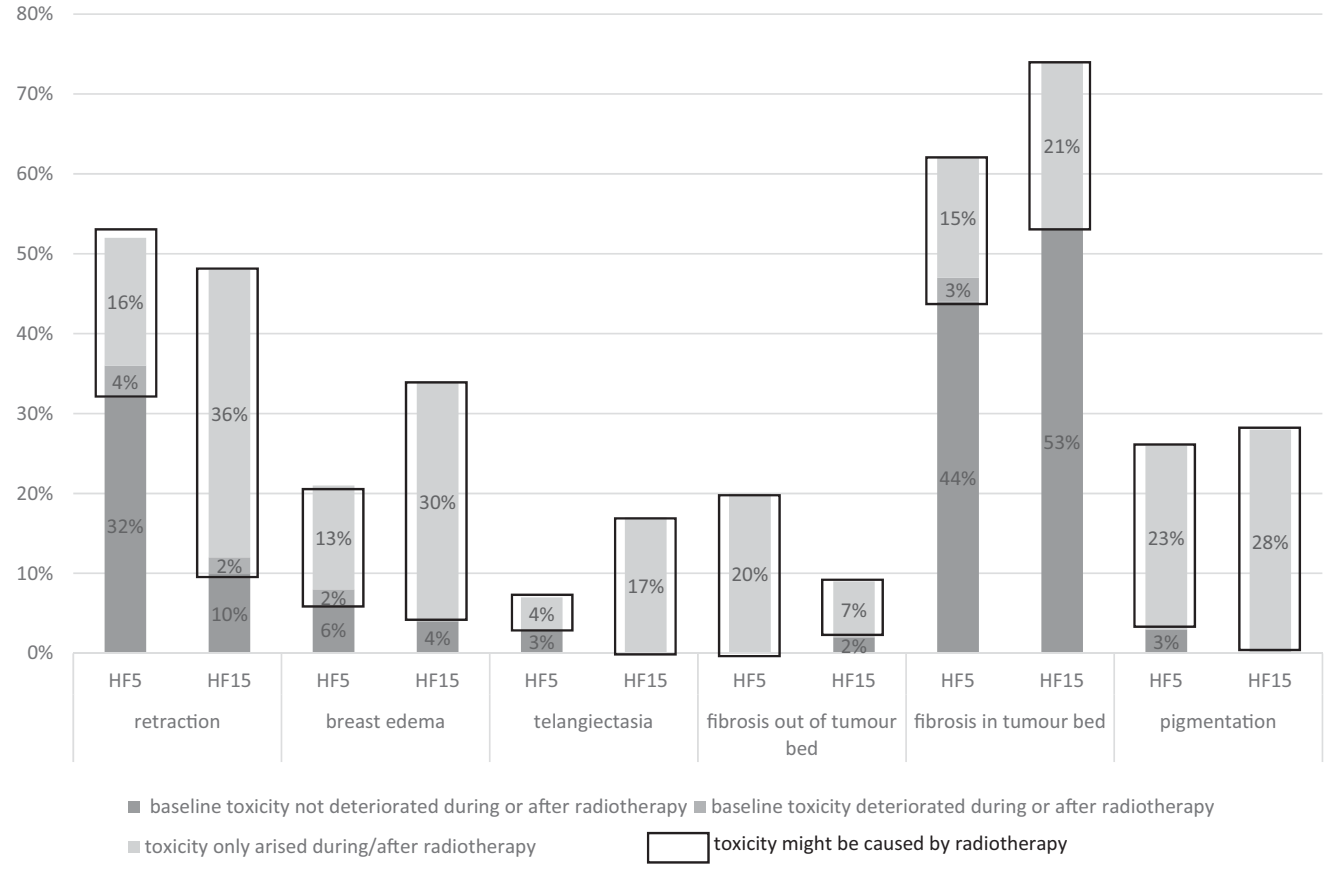

Figure 1. Two-year toxicity.

present before irradiation is seldom deteriorated by RT. For instance, significantly less radiation-related retraction was observed in the HF5 group compared to the HF15 group, while retraction was three times more frequent in the HF5 group at baseline. Thus, what we defined as radiation-related toxicity is mainly toxicity appearing during or after RT. However, we cannot be sure that RT is the sole cause of this toxicity. Interfering factors may be late effects of surgery or chemotherapy and toxicity caused by hormone therapy. The reason for the higher incidence of breast retraction at baseline in the HF5 group is unknown. However, while HF5 patients were on average older, it is possible that surgical margins were larger in the elderly to avoid re-excision. None of the patients underwent re-excision. Mean tumor volume did not differ significantly between the HF5 and HF15 group (p=.5).

It was not possible to define radiation-related pain since pain seems to be an early effect of surgery and RT disappearing after time. In the HF5-group, 60% reported pain one month after RT [21], while after 2 years only 6% of HF5-patients and 12% of HF15-patients reported pain, so pain. Pain can be caused by edema. Breast edema occurred in 21% of patients in the HF5-group *vs.* 34% in the HF15 group. One month after RT, edema was reported in over 60% of HF5 patients [21], demonstrating the temporary nature of edema.

Telangiectasia seems to be a rare side effect after HF5 [3,18]. Only 4% of the HF5-patients developed telangiectasia, as compared to 12% in the HF15-group (p= .01). We observed no significant differences in pigmentation changes between both groups.

About one-third of patients received LNI. None of the patients reported symptoms of brachial plexopathy, but longer follow-up is needed to rule out the possibility of plexopathy. In contrast to our data, the UK FAST trial observed no differences in 3-year rates of toxicity between 28.5 and 50 Gy [3]. The FAST trial only reported on moderate to marked toxicity, while we report on presence of any toxicity, including mild toxicity. This explains the higher rates of breast retraction and fibrosis in our cohort. An approach comparable to the FAST trial was not possible with our dataset due to different toxicity scoring systems. Other differences between the FAST trial and this study are the number of patients receiving a boost and patient age. In the FAST trial no boost was administered, while 90% of our patients received a boost. The mean age of the FAST group was 63 years compared to 73 years in our HF5 group. However, it was only 65 years in the HF15 group.

In conclusion, according to this matched-case control analysis, hypofractionation in 5 fractions over 10–12 d leads to significantly less retraction, telangiectasia and pain 2 years after irradiation. In contrast, fibrosis outside the tumor bed is seen more often in the HF5 group than in the control group treated with 15 fractions. For late toxicity, results of 5 years follow-up are needed. Randomized trials in larger patient cohorts and longer follow-up are needed to confirm the efficacy and safety of this accelerated treatment schedule.

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