Hypofractionated Radiotherapy for Breast Cancer Including Risk-adapted Boost: Update on Tolerance and Efficacy of an Accelerated START A Regime

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Abstract. *Aim: To present an update of a prospective study evaluating an accelerated hypofractionated whole breast irradiation (WBI) schedule of the START A trial plus hypofractionated boost in breast cancer patients. Patients and Methods: One hundred and forty consecutive patients ≥55 years were included in this study. Patients received postoperative WBI with 13×3.2 Gy to 41.6 Gy plus a boost of 3.0 Gy/fraction to 9-12 Gy applied in <3.5 weeks, depending on the resection margin. Prospectively planned follow-up (FU) visits, including objective and subjective assessment of treatment tolerance, were performed at 0 and 8 weeks, as well as one, two, four or more years following radiotherapy (RT). Results: The 3-year rates of local control, nodal control, disease-free and overall survival were 99%, 100%, 96% and 91%, respectively. Cosmetic outcome was very good with 99% (n=110/111), 98% (n=99/101) and 100% (n=59/59) of the patients being satisfied or very satisfied one, two and four years after RT, respectively. Conclusion: Acceleration of the START A regime with 41.6 Gy WBI plus additional boost of 9-12 Gy remained effective and well-tolerated.*

Compared to conventional fractionation with 50 Gy in 25 fractions or 50.4 Gy in 28 fractions, hypofractionation is gaining importance after long-term results of four large randomized trials that included more than 7,000 patients were published. Equal findings for conventionally fractionated *vs*. hypofractionated whole breast irradiation (WBI) in terms of both treatment outcome and toxicity were found (1-5). Despite these results, the clinical implication of hypofractionated WBI is still limited (6). While patients in the Canadian trial and START B trial were treated five times a week with 15-16 fractions of 2.66/2.67 Gy up to total doses of 40.05 Gy and 42.5 Gy, patients in the START A trial received total doses of 39 Gy or 41.6 Gy in 13 fractions on three days per week (doses per fraction=3.0 or 3.2 Gy) given over 5 weeks, in order to keep the overall treatment time comparable to the standard arm of 50 Gy in 5 weeks. A boost to the tumor bed was administered in 61%/43% of the patients using conventional fractionation with 10-14 Gy (5 fractions of 2.0 Gy per week) in START A/B. Thus, in the START A trial, the cumulative overall treatment time was longer than 5 weeks, *i.e.* not considerably shorter than with conventional WBI.

In order to provide a significantly shorter overall treatment time with expectedly equal outcome and tolerance, we introduced an accelerated postoperative hypofractionation radiation regimen of 41.6 Gy in 13 fractions plus 3-4×3 Gy boosts in our clinical routine of which first results have previously been reported (7). The recent analysis includes a larger cohort with a longer follow-up (FU) period, in order to allow a more valid estimation of the efficacy and tolerance of this hypofractionation approach.

In addition, the use of hypofractionation schedules for the boost and for ductal carcinoma *in situ* (DCIS) is discussed.

Patients and Methods

From 03/2009-12/2013, 140 patients >55 years with invasive breast cancer (n=134) or DCIS (n=6) were postoperatively treated in our Institution. The lower age limit of 55 years was decided due to the uncertainty regarding the biological iso-efficacy of the hypofractionation WBI with a total dose with 50 Gy in 2.0 Gy per fraction for younger patients. As the total dose to the tumor bed is even more important in younger patients (8), patients aged <55 were excluded to avoid potential under-dosage in younger women. Patient-related parameters are summarized in Table I.

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Table I. *Treatment and patients'-related parameters.*

Parameters	N
RT prescription dose	13×3.2=41.6 Gy: n=140
Mean age (years)	69 (range=45-92)
RT boost doses (n)	
no boost	2
1×3=3 Gy	1
3×3=9 Gy	95
4×3=12 Gy	34
5×2=10 Gy	2
8×2=16 Gy	2
10×2=20 Gy	4
RT of peri-clavicular lymphatics	3
N-status	
N0	110
N1	28
N2	1
N3	1
T-status	
DCIS	6
T1	79
T2	55
T3	0
T4	0
Grading	
G1	21
G2	70
G3	45
Not known	4
Resection margin	
R0	125
R1	15
Hormone receptor	
Positive	124
Negative	15
Not known	1
Her2 status	
Positive	16
Negative	122
Not known	2
Chemotherapy	30

The boost schedule was individually based on the resection margins as follows:

R0 resection: 41.6 Gy in 13 fractions given 4 times a week and 9 Gy boost in 3 fractions (on day 5 each week); cumulative dose: 50.6 Gy in 3.2 weeks.

R1 resection: 41.6 Gy in 13 fractions given 4 times a week and 12 Gy boost in 4 fractions (on day 5 each week, afterwards daily); cumulative dose: 53.6 Gy in 3.4 weeks.

Details on treatment planning have been previously described (7).

FU: Acute toxicity was assessed weekly during radiotherapy (RT), at the end of RT and at 8 weeks following RT. Prospectively planned FU visits, including both objective and subjective assessments of treatment tolerance and satisfaction with the cosmetic result (questionnaires for physicians/patients), were performed at one (n=111), at two (n=101) and at four years (n=59) following RT. Acute toxicity and late toxicity were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

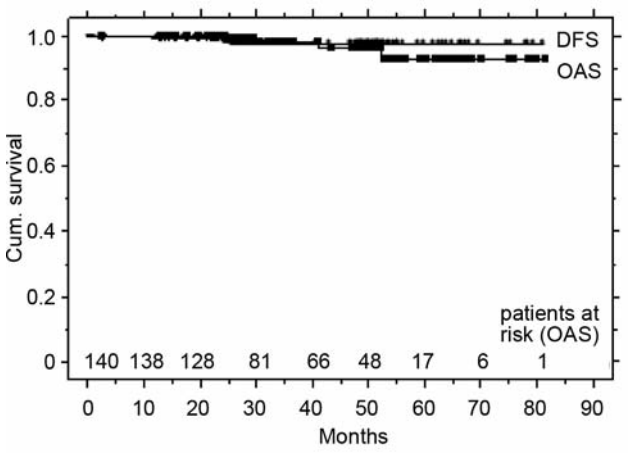

Figure 1. *Diesease-free survival (DFS) and overall survival (OAS).*

Informed consent. Informed consent was obtained from all patients for prospective data collection, including electronic photo documentation and retrospective data evaluation.

Statistical analysis. Survival analyses were performed using SPSS version 21 (http://www.ibm.com). Ordinal and binary logistic regression analyses were carried out using commercially available Minitab software version 16.2.4.3 (http://www.advanced uninstaller.com). *p*-Values of less than 0.05 were considered statistically significant.

Results

Disease control. The mean/median FU time was 40/36 months (range=2-81). No isolated local or locoregional recurrence was observed. The 3-year local control, nodal control and disease-free survival (DFS) rates were 99%, 100% and 96%, respectively. The overall survival (OAS) rate at 3 years was 91% (Figure 1: DFS and OAS). At the time of analysis, 5 patients had died after a FU of 15, 25, 30, 42 and 52, months, respectively: three patients died due to distant metastases (meningeosis, n=1; disseminated metastases, n=1; liver metastases, n=1) and two patients died from non-breast cancer-related causes (pulmonary embolism, n=1; second primary in the lung with distant metastases, n=1). Seven patients were lost in FU after 8 weeks (n=4) and 2 years (n=3) after RT completion.

Acute and sub-acute side effects. Grade 1 acute skin toxicity was observed in 82% directly after RT and in 30% at 8 weeks following RT, grade 2 acute skin toxicity occurred in 5% and 0% of patients, respectively. No grade 3 acute dermatitis was observed (Figure 2). Pain within the treated

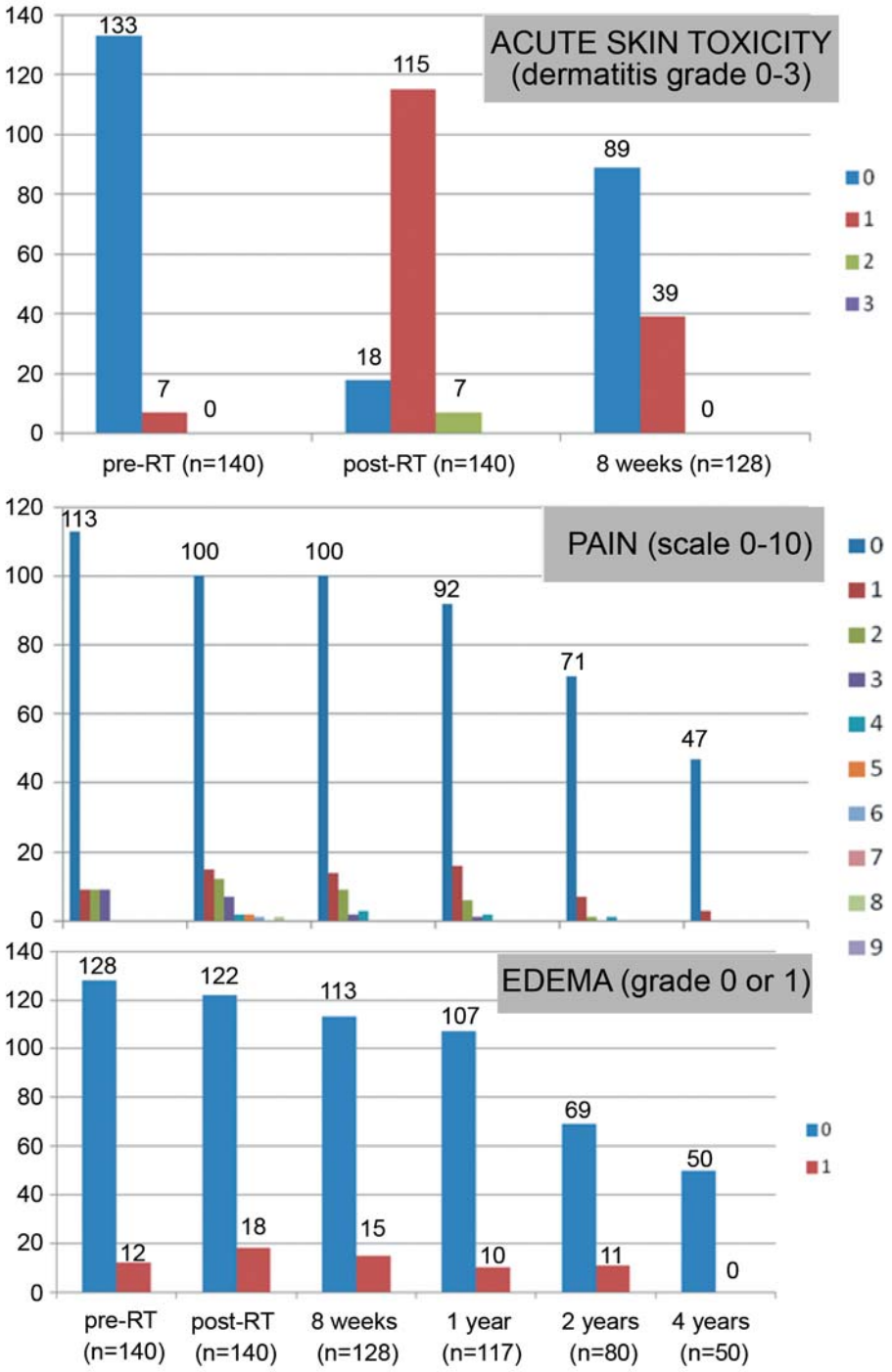

Figure 2. *Acute skin toxicity (grade 0-3), pain (scale 0-10) and edema (grade 0-1) pre-radiotherapy, directly post-radiotherapy, and 8 weeks after completion of RT. Assessment of pain and edema additionally 1 year, 2 years and 4 years late.*

breast was reported in 19% of patients prior to RT (grade 1 of 10: 7%, grade ≥2: 12%) and in 29% (grade 1: 11%, ≥grade 2: 18%) and 20% of patients (grade 1: 11%, ≥grade 2: 9%) directly and 8 weeks following RT. Early edema of the breast was seen in 9% of patients prior to postoperative RT and in 13% and 12% of patients directly and 8 weeks following RT, respectively. In 6/12 (50%) pre-RT edema patients, edema was resolved at treatment completion.

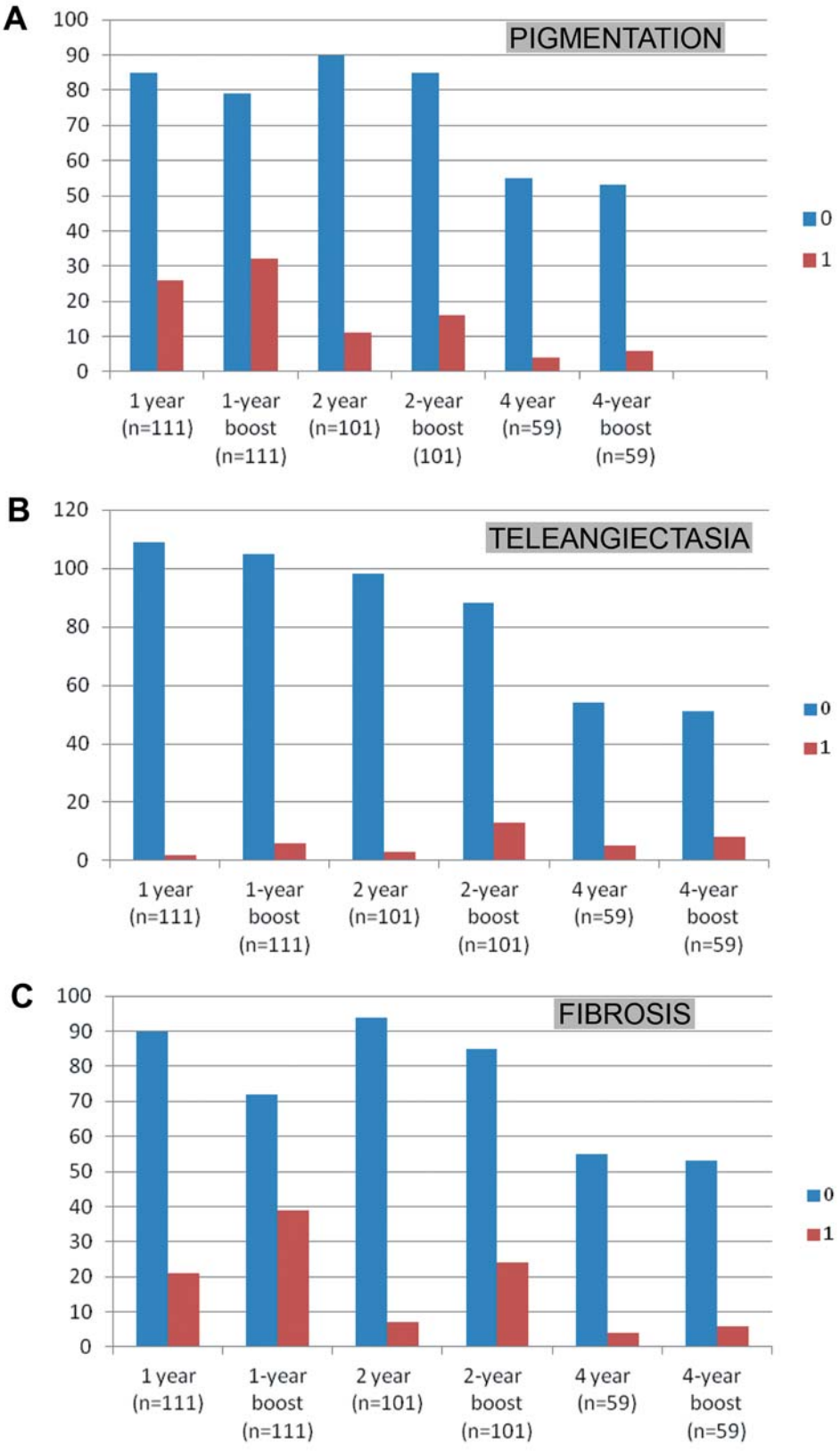

Figure 3. *A-C: Late toxicity: A=pigmentation (grade 0-1), teleangiectasia (grade 0-1), fibrosis (grade 0-2) 1 year, 2 years and 4 years after completion of radiotherapy. Additional evaluation of the boost regions seperately within the same time periods.*

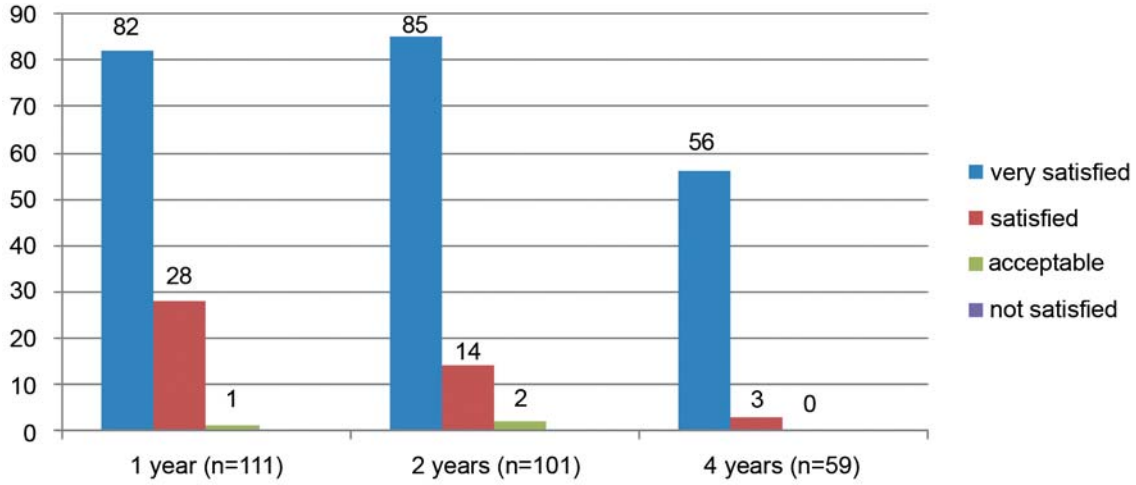

Figure 4. *Cosmetic satisfaction 1 year, 2- and 4 years after completing radiotherapy (four grades of satisfaction: very satisfied to not satisfied).*

Late side-effects (whole breast). Grade 1 edema of the breast was observed in 9% (10/111), 0% (0/80) and 0% (0/50) of patients after one, two and four years, respectively. Hyperpigmentation of the whole breast was observed in 23%, 14% and 6% of patients after one, two and four years, respectively. After one, two and four years, telangiectasia of the irradiated breast was present in 2%, 4% and 10% of patients, respectively (Figure 3), and fibrosis was found in 19%, 4% and 2% of patients, respectively (Figure 3).

Late side-effects (boost region). Hyperpigmentation of the boost region was observed in 29%, 20% and 12% of patients after one, two and four years, respectively. Telangiectasia of the boost region was present in 5%, 16% and 16% of patients (Figure 3), fibrosis in 35%, 20% and 12% of patients after one, two and four years, respectively (Figure 3).

Late side-effects (patient satisfaction, pain). The proportions of the patients who were satisfied or very satisfied were 99%, 98% and 100% after one, two and four years, respectively (Figure 4).

One year after completion of RT, 23% of patients (25/111) complained about pain (grade 1 of 10: 14%, ≥grade 2: 9%; Figure 3). After two and four years, pain was still present in 11% (9/80) (grade 1: 9%, ≥grade 2: 2%) and 6% (3/50) of patients, respectively. No pain grade 2 or higher was described after four years.

Predictive value of early symptoms on later tolerance. Nine out of 28 patients complaining about pain before RT start complained about persistent pain during further treatment (no analgesic medication required). Pain status before, after RT and 8 weeks later did not correlate with the presence of pain in further FU period. Also, edema of the breast immediately after RT did not correlate with its persistence during FU.

Volumetric considerations. The mean pre-RT volume of the breast planning target volume (PTV) was 689 cm^3 (range=256-1,612). The mean volume of the boost PTV region was 98 cm^3 (range=20-328). Additionally, we assessed the volume of 105%, 110% and 115% isodoses outside the boost PTV. The mean volume of 43.7 Gy (105%), 45.8 Gy (110%) and 47.8 Gy (115%) isodose was 158 cm3 (range=0-1349), 81 cm3 (range=0-815) and 48 cm3 (range=0-512), respectively.

No continuous correlation in logistic regression analyses was found in acute and late toxicity and dose-volume parameters like breast- and boost-volume, boost dose or different isodose levels.

Discussion

An accelerated regimen of the hypofractionated arm of the START A regimen with a hypofractionated boost has been clinically implemented and evaluated.

Early results were previously evaluated (7). Herein, we present an update of the prospectively assessed data of our single-institution accelerated hypofractionated WBR schedule with 3.2 Gy per fraction with a sequential resection margin-adapted hypofractionated boost. We found that the vast majority of patients were satisfied or very satisfied with cosmetic outcomes. The used regimen was well-tolerated and resulted in high locoregional control rates (Tables II and III).

Late tolerance and patients' cosmetic results. Late tissue tolerance is a major concern in the context of

Table II. *Literature review: randomized studies with different hypofractionation schedules in breast cancer patients, LR, local recurrence; CTx, chemotherapy; RT ln, radiotherapy periclavicular of lymph nodes; ccb, concomitant boost dose escalation; PB, partial breast.*

TRIAL (ref)	N	FU (years)	Prescription dose WBI	Local recurrence	Induration	Teleangiectasia	Breast edema	Excellent or good cosmetic outcome	Chemo-therapy	Nodal RT	Boost
Whelan "Ontario Trial" (2010) (2)	1234	10	control: 25×2Gy=50Gy 16×2.66Gy= 42,5Gy (3w)	6.7% 6.2%	10.4% 11.9%	-	-	71.3% 69.8%	11%	0%	0%
Yarnold (2005) Owen (2006) "START Pilot study" (4)	1410	10	control: 25×2Gy=50Gy 13×3.3Gy= 42,9Gy (5 w) 13×3.0Gy=39Gy (5 w)	12.1% 9.6% 14.8%	28.6% 40.8% 20.4%	13.8% 14.3% 8.6%	12.6% 20.3% 10.8%	-	14%	21%	75% (7×2Gy =14Gy)
START A (2013) (3, 5)	2236	10	control: 25×2=50 13×3.2Gy= 41.6Gy (5 w) 13×3.0Gy= 39Gy (5 w)	6.7% 5.6% 8.1%	27.1% 28.2% 21.6%	7.2% 7.1% 3.0%	13.5% 11.8% 7.3%	-	35%	14%	61% (5×2Gy= 10Gy)
START B (2013) (1, 3)	2215	10	control: 25×2Gy= 50Gy 15×2.67Gy= 40Gy (3w)	5.2% 3.8%	17.4% 14.3%	5.8% 4.2%	9.0% 5.1%	-	22%	7%	43% (5×2Gy= 10Gy)
FAST Trial (2011) (31)	915	3	control: 25×2Gy=50Gy 5×6Gy=30Gy (5w) 5×5.7Gy= 28.5Gy (5 w)	1% 0% 0.5%	9.5% 17.3% 11.1%	no results yet	no results yet	73.1% no change on photos	0%	0%	0%
IMPORT low (running) (32)	2018	-	control: 15×2.66Gy=40Gy Test arm1: 15×2.4Gy Test arm2: no WBI	no results yet	no results yet	no results yet	no results yet	no results yet	no results yet	no results yet	control: none Test arm1: 15×2.66Gy SIB Test arm2: 15×2.66Gy PB
IMPORT high (running) (33)	2568	-	control: 15×2.66Gy=40Gy Test arm1: 15×2.4Gy=48Gy Test arm2: 15×2.4Gy=53Gy	no results yet	no results yet	no results yet	no results yet	no results yet	no results yet	no results yet	control: 8×2Gy= 1 6Gy Test arm1: 15×3.2/ 2.66Gy ccb Test arm2: 15×2.6/ 3.53Gyccb

hypofractionated radiation therapy. In terms of intermediate to late tolerance, our results were comparable to the results of the four randomized trials and to other studies that used hypofractionated boost schedules or a simultaneous integrated boost (SIB) (Tables II and III).

In the present study, most patients considered the cosmetic results very satisfying or satisfying, agreeing well with the results of Scorsetti *et al*. and Kyrgias *et al*. (9,10) and compare favorably with most other studies reporting on cosmesis after hypofractionated WBI (2, 11-14).

Early side-effects. In the present study, no grade 3 acute toxicity was observed. Grade 2 skin reactions of 5% did compare well with Chadha *et al*. and Franco *et al*. (13, 15) and with most other hypofractionation studies supporting those results (14, 16-18). The above mentioned randomized trials mainly focused on late tissue effects (1-4).

Ciammella *et al*. found a statistically not-significant trend towards development of more late skin toxicity in patients with increased acute toxicity (14). In the own cohort, early treatment tolerance was high (no grade 3).

In line with Hannan *et al*. showing hypofractionated treatment of large-sized breast (PTV >1,500 cm^3) feasible in terms of outcome and toxicity, we did not find a correlation between the breast size and outcome either (19).

Local control. In the four large prospective hypofractionation trials with 10-year FU, local recurrence rates ranged from 3.8%-14.8% (1-4). In the studies with different boost regimes, shown in Table IIB with significantly shorter FU, the local recurrence rates ranged from 0-4%. Our local recurrence rate of a more aged cohort (mean=67 years, range=55-92) was 1% at 3 years. This is comparable with the corresponding age adjusted collective in the EORTC study after the same FU period (8).

Hypofractionation in patients with DCIS. In our study, six patients with DCIS were included who did receive accelerated hypofractionation following breast conserving surgery. A recently published study with a mean FU of 9.2 years showed similar outcomes for hypofractionation in patients with DCIS after breast conserving therapy with local recurrence-free survival rates of 86% for conventional fractionation and 89% for hypofractionation (20). In the hypofractionation group (n=638), 54% patients received an additional boost. Cante *et al*. showed boost application in a hypofractionated regime in patients with DCIS to be safe delivering a daily boost of 0.25 Gy in each patient summing up to a total dose of 50 Gy (45 Gy WBI) (21). In a recent review article, Nilsson *et al*. stated hypofractionated RT to be a safe option in patients with DCIS after breast-conserving surgery, while the addition of a boost to the tumor bed reduced the risk of a local recurrence in case of positive resection margins (22).

Boost application in hypofractionated RT schedules. Recently, Bartelink *et al*. published the 20-year FU data of the EORTC 22881-10882 trial "boost *versus* no boost" confirming improvement of local control with the addition of a sequential boost to the tumor bed after conventionally fractionated WBI (8). Since hypofractionation gains importance, the question arises whether and how to integrate a higher dose to the tumor bed in hypofractionation schedules. The four randomized hypofractionation trials applied either no boost or a conventionally fractionated boost of 5-7×2 Gy in 43-75% of the patients (Table II). This procedure led to a prolongation of the overall treatment time of at least one week and, therefore, reduced the time sparing effect.

Both SIB and sequential boost have been shown to be feasible and effective in hypofractionation treatment of breast cancer patients (Table III). The published regimes using a SIB were heterogeneous with respect to the doses per fraction administered to the whole breast and to the tumor bed. Doses per fraction of WBI ranged between 2.2 Gy and 2.8 Gy, with doses per fraction of the boost irradiation between 2.5 Gy and 3.4 Gy. In the regimens that included a sequential boost, the doses per fraction ranged from 2.6 Gy to 3.4 Gy for the whole breast and from 2.65 Gy to 8.0 Gy in the boost region. The two approaches were compared in one retrospective study, which showed statistically significant slightly worse cosmetic results in those patients who received a SIB (23). However, since the two approaches have not yet been compared in a randomized trial, it is not yet clear whether the regimen using a SIB is inferior to the regimen including a sequential boost. Lacking high-level of evidence, the American Society for Radiation Oncology (ASTRO) stated that the boost indication is not clearly defined in hypofractionation (24). The IMPORT HIGH and LOW trials may provide us with more information regarding the efficacy and the tolerance of SIB using hypofractionated regimens (Table II).

Our regimen represents a further acceleration of the START A regimen that includes a shorter overall treatment time than most other hypofractionation schedules (Table II). Boost doses in the own cohort were defined according to the resection margin (<2 mm *vs*. ≥2 mm) (25).

Logistic regression analyses did not reveal any correlation of acute or late effects and isodose levels, PTVs of breast and/or boost or boost dose (9 Gy *vs*. 12 Gy).

In line with Kouloulias *et al*. and Ciamella *et al*., we did not find application of chemotherapy to be a risk factor for an enhanced skin reaction (14, 25).

Conclusion

According to this intermediate-time update of our prospective study, acceleration of the START A regime plus hypofractionated boost was effective, well-tolerated and associated with a high patient satisfaction regarding the cosmetic results.

Competing Interests

The Authors declare that they have no competing interests.

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Table III. *Different boost schedules in breast cancer treatment with hypofractionated RT.*

Study (ref)	N	Mean FU (mo)	Prescription dose WBI	N with T boost R	Boost dose (SIB or sequential)	OTT (weeks)	Local recurrence	Acute skin reaction	Late skin reaction	Excellent/good cosmetic outcome	Chemo-therapy
Liau *et al*., 2010 (26)	563	58	15×2.66Gy= 40Gy	338	3×3Gy=9Gy (60%) (seq)	3.6	0.9%	-	-	-	20.2%
Guenzi *et al*., 2010 (27)	65	24	13×3Gy=39Gy and 3×3Gy	65	3×3Gy=9Gy (seq)	3.8	-	-	-	-	14%
Pinnaro *et al*., 2010 (16)	39	43	10×3.4Gy=34Gy	39	1×8Gy after 1 week (seq)	3	0%	G1: 41% G2: 10%	G1: 28%	-	28%
Scorsetti *et al*., 2012 (9)	50	12	15×2.7/3.2Gy= 40.05/48Gy	50	15×0.5Gy= 7.5Gy (SIB)	3	0%	-	-	100%	0%
Chadha *et al*., 2012 (15)	50	2	15×2.7/3.0Gy= 40.05/45Gy	50	15×0.3Gy= 4.5Gy (SIB)	3	0%	G2: 4%			
Van Parijs *et al*., 2012 (17)	37	28	15×2.8/3.4Gy= 42/51Gy IMRT	37	15×0.6Gy= 9Gy (SIB)	3	-	G1: 59.5% G2: 27% G3: 8.1%	≥G1: 30%	-	54%
Hannan *et al*., 2012 (19)	129	10	16×2.66Gy= 42.6 IMRT	129	4×2.4Gy= 9.6Gy (seq)	4	0%	G1: 69% G2: 25%	G1: 57% G2: 0%	-	-
Kim *et al*., 2013 (11)	276	60	13×3Gy=39Gy	276	3×3Gy=9Gy (seq)	3.2	1.4%	G1: 53% G1: 2%	83%	74%	
Cante *et al*., 2013 (12)	375	60	20×2.5/2.75Gy= 45/50Gy	375	15×0.25Gy= 3,75Gy (SIB)	4	0%	-	"few" >G2	96%	
Zygogianni *et al*., 2013 (18)	81	24	20×2.3/2.7Gy= 46/54Gy *vs*. 16×2.65Gy=42.4+ 4×2.65Gy=53Gy	81	4×2.65Gy=10.6Gy (seq) *vs*. 20×0.4 Gy=8Gy (SIB)	4	0%	G1: 66%/24% G2: 33%/4% (SIB/seq)	G1: 22/4% (SIB/seq)	-	-
Freedman *et al*., 2013 (29)	75	69	20×2.2/2.85Gy= 45/56Gy IMRT	75	20×0.55Gy= 11Gy (SIB)	4	2.7%	-	G2: 21%	scale 1-4: mean 1.79	11%
Kyrgias *et al*., 2013 (10)	27	24	20×2.3/2.7Gy= 46/54Gy	27	20×0.4Gy= 8Gy (SIB)	4	-	G1: 67% G2: 30% G3: 4%	G1: 22% (1y)	100%	
Franco *et al*., 2014 (13)	82	12	20×2.25// 2.5Gy=45/50Gy	82	20×0.25Gy= 5Gy (SIB)	4	0%	G1: 51% G2: 6% G3: <1%	G1: 23% G2: 3%	91%	25%
Ciammella *et al*., 2014 (14)	212	34	15×2.67Gy= 40.05Gy	53	3×3=9Gy (seq) (25%)	3.6	0%	G1: 68% G2: 15% G3: 1%	G1: 18% G2: 2%	93%	21%
Kouloulias *et al*., 2014 (25)	116	24	16×2.66Gy= 43Gy	116	3-4+2.66Gy= 8-10.6Gy (seq)	4	0%	G1: 27.6% G2: 7.8% G3: 2.6%	-	-	100%
Dellas *et al*., 2014 (29)	141	-	16×2.5/3Gy= 40/48Gy 3-D or IMRT	141	16×0.5Gy= 8Gy (SIB)	3.2	-	G1-2:48%	-	-	43.6%
Lalani *et al*., 2014* (20)	638 -	110	16×2.5/ 2.75Gy=40-44Gy	489	seq (schedule not mentioned)	>3	4%	-	-		
Hathout *et al*., 2013* (30)	440	53	16×2.66Gy= 42.5Gy and 4×2.5Gy=10Gy	125	seq (4×2.5Gy= 10Gy)	4	3%	-	-	-	
Pinnaro *et al*., 2010 (34)	39	43	10×3.4Gy=34Gy	39	seq 1×8Gy electrons, after 1 week gap	3	-	G2: 10%	G1: 28%	-	33%

Table III. *continued*

Table III. *continued*

Study (ref)	N	Mean FU (mo)	Prescription dose WBI	N with T boost R	Boost dose (SIB or sequential)	OTT (weeks)	Local recurrence	Acute skin reaction	Late skin reaction	Excellent/good cosmetic outcome	Chemo-therapy
Ahlawat *et al*., 2016 (35)	83	40	11×3.33Gy= 36.6Gy over 11 days	83	seq 4×3.33Gy= 13.3Gy	3	2.4%	G2: 34%, G3: 1%	G2: 1% G3: 2%	94%	31%
Present study	140	34	13×3.2Gy= 41.6Gy	99%	3-4×3Gy= 9/12Gy (seq, day 5)	3.2	1%	G1/2 82/2.5% post RT; G1 27% 8w post RT	19% (1y) 4% (2y) 2% (4y)	99% (1y) 98% (2y) 100% (4y)	22%

SIB, Simultaneous integrated boost; seq, sequential boost; LR, local recurrence; CTx, chemotherapy; OTT, overall treatment time. *DCIS study.

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