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A Comparative Study of Daily 3-Gy Hypofractionated and 1.8-Gy Conventional Breast Irradiation in Early-Stage Breast Cancer

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Abstract: We retrospectively compared accelerated hypofractionation (AHF) with conventional fractionation (CF) in the radiation therapy (RT) for early-stage breast cancer patients.

Three hundred seventy-nine early-stage (pT1–2 and pN0–1a) breast cancer patients who received RT with AHF after breast-conserving surgery (BCS) were included. These patients were matched with 379 corresponding patients who received BCS and RT with CF at a different center with respect to the year BCS was performed, patient age (±3 years), and cancer stage. The AHF regimen consisted of 39 Gy in 13 fractions to the whole breast and a consecutive boost of 9 to 12 Gy in 3 to 4 fractions to the tumor bed. CF comprised whole-breast irradiation up to 50.4 Gy in 28 fractions and a boost of 9 to 14 Gy in 5 to 7 fractions to the tumor bed.

The median follow-up period was 75 months (range, 3.8–110.8 months). There was no statistically significant difference between the AHF and CF groups in terms of age distribution, T and N stage, resection margin, and histologic grade. There were 5 ipsilateral breast tumor relapse (IBTR) cases in the AHF group compared with 7 cases in the CF group. Seven and eight locoregional relapse (LRR) cases were observed in the AHF and CF groups, respectively. The 7-year rates of IBTR-free survival, LRR-free survival, and disease-free survival were 98.9%, 98.4%, and 97.1% in the AHF group and 98.1%, 97.9%, and 96.0% in the CF group, respectively ($P > 0.05$). The incident rates of grade 3 edema, hyperpigmentation, or wet desquamation at the end of RT were higher in the CF group than in the AHF group (16.4% vs 0.2%, respectively; $P < 0.01$).

AHF RT of 39 Gy to the whole breast plus a 9-Gy boost in 16 fractions showed excellent tumor control and tolerable skin toxicity, a finding that is comparable to CF RT in patients with early-stage breast cancer.

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Abbreviations: AHF = accelerated hypofractionation, BCS = breast-conserving surgery, CF = conventional fractionation, CI = confidence interval, CT = computed tomography, DCIS = ductal carcinoma in situ, DM = distant metastasis, ECG = electrocardiogram, EQD2 = equivalent dose in 2-Gy fractions, ER = estrogen receptor, HR = hazard ratio, IBTR = ipsilateral breast tumor relapse, LRR = loco-regional relapse, OS = overall survival, PR = progesterone receptor, RMH/SGOC = Royal Marsden Hospital/Sutton and Gloucestershire Oncology Centre, RT = radiation therapy, START = Standardisation of Breast Radiotherapy, UK = United Kingdom.

INTRODUCTION

With the development of the Ellis isoeffect formula in the late 1960 s,[1] the concept that the radiation tolerance of all normal tissues, except for that of the brain and bone, was determined by the skin tolerance alone was readily accepted in the field of radiotherapy. It was based on the prospect that the late effects of radiation were dependent on the tolerance of fibroblasts and capillary epithelium comprising various normal tissues. One of the prompt applications of the Ellis formula in clinical practice was the early hypofractionation of breast radiation therapy (RT), given over shorter period of time by reducing fraction number. However, this procedure led to higher-than-expected rates of late effects such as telangiectasia or subcutaneous fibrosis,[2] and the conventional fractionation (CF) of 50 Gy to the whole breast in 1.8- to 2-Gy fractions for 5 weeks has become the standard RT regimen for breast cancer ever since.[3] With better understanding of breast radiobiology with the introduction of linear-quadratic models, which describe radiation effect as the sum of lethal lesions made by single radiation track (''linear'') and 2 radiation tracks (''quadratic'') causing double-strand DNA (deoxyribonucleic acid) breaks,[4] hypofractionated RT regimens with total doses less than those of the earlier trials have emerged. These regimens were evaluated in randomized clinical studies in the United Kingdom (UK) and Canada.[5,6]

Among the various regimens of hypofractionation, that of 39 Gy in 13 fractions used in the Royal Marsden Hospital/Sutton and Gloucestershire Oncology Centre (RMH/SGOC) trial and the UK Standardization of Breast Radiotherapy (START) A trial achieved comparable tumor outcome with minimal skin toxicity at the interim analysis of 5 years.[7,8] Because both of these trials delivered 13 fractions over 5 weeks to equalize the treatment period with that of CF, we decided to deliver the same regimen using accelerated hypofractionation (AHF) that was shown to be tolerable in the START B and

Canadian trials.[5,9] Thus, we conducted a phase II trial of accelerated, hypofractionated whole-breast irradiation of 39 Gy in 13 fractions followed by a tumor bed boost sequentially delivering 9 Gy in 3 fractions administered daily over 3.2 weeks for early-stage breast cancer from 2007.[10] After a median follow-up of 57 months, we reported a 5-year locoregional recurrence of 1.4% and a disease-free survival of 97.4% with tolerable skin toxicity.[10] Because the results of AHF were excellent at 5 years, we decided to compare the 7-year results with the outcomes of the conventional regimen. Therefore, analogous patients who were treated with CF of 50.4 Gy to the whole breast followed by a tumor bed boost of 9 Gy in 1.8-Gy fractions were also analyzed. The AHF and CF as well as other fractionation schedules of the key trials mentioned above are summarized in Table 1. This is a retrospective, comparative study of AHF and CF in radiotherapy of early-stage breast cancer patients after breast-conserving surgery (BCS).

MATERIALS AND METHODS

Patients

The patients diagnosed with pT1–2 and pN0–1a breast cancer who received RT with AHF after BCS from January 2007 to December 2010 at the National Cancer Center (Goyang-si, Gyeonggi-do, Korea) were included. The patients with ductal carcinoma in situ (DCIS) without an invasive component were excluded. Reexcision to achieve a clear margin was allowed. All of the patients underwent surgical axillary staging through either sentinel lymph node biopsy or axillary lymph node dissection. Adjuvant chemotherapy was completed before RT, and hormone therapy was started with radiation. The molecular subtypes of the tumors were classified into 4 categories: luminal A, luminal B, human epidermal growth factor receptor-2 (HER-2), and triple negative.[11] The patients with pT2 or pN1 tumor disease and a positive HER-2 status were given trastuzumab. There was no restriction of breast size for both the AHF and CF groups. Of the 394 eligible patients, 15 were excluded because of second malignancies other than DCIS, cervical carcinoma in situ, or thyroid cancer: 4 with non-small cell lung cancer, 1 with stage III cervical cancer, 1 with hepatocellular carcinoma, 1 with multiple myeloma, 1 with chronic eosinophilic leukemia, 1 with low-grade chondrosarcoma, 1 with metachronous ipsilateral, and 5 with metachronous contralateral breast cancer. Thus, 379 patients were included in the AHF group. These patients were matched with 379 corresponding patients who received BCS and RT with CF at Seoul National University Hospital (Seoul, Korea) with respect to the year BCS was performed, age (±3 years), and cancer stage. The entire process of this study was approved by the institutional review boards of both centers.

Radiotherapy

All of the patients underwent computed tomography (CT)-based simulation in the supine position using the breast board. The planning target volume for whole-breast irradiation in the AHF group was defined as the whole breast with 1-cm margin. We used a surgical clip-based protocol for the boost in AHF patients as previously reported.[10] The AHF patients were treated with the field-in-field technique. We used heart block for the left-sided breast cancer patients with tumors located in the upper part of the breast, age >50 years, and luminal subtype from 2009 in the AHF group. The CF patients underwent conventional CT planning without heart blocks. The RT field in the CF group was bordered by the sternoclavicular junction superiorly and the line 2 cm below the inframammary fold inferiorly. The medial border was the midline of the anterior chest and the lateral border was the midaxillary line. Surgical clips were not routinely used for the CF patients and the boost for the CF patients was given on the lumpectomy cavity, determined by comprehensive reference to the pre- and post-operative images, wound, and surgical pathology, plus a 2-cm margin. No regional nodal irradiation was delivered in either group. Most of the patients were treated with 6-MV tangential fields for whole-breast irradiation. In some cases with a long distance between the medial and lateral borders, 15 MV with wedges was utilized. The boosts were given using electron beams with an adequate energy ranging from 6 to 12 MeV, determined by the depth of the surgical cavity. Both centers used the CT-based planning.

The AFH regimen was delivered as 39 Gy in 13 fractions to the whole breast and 9 Gy in 3 consecutive fractions for the boost to the lumpectomy cavity. The boosts for the patients with

TABLE 1. Comparison of CF and AHF With Different Hypofractionation Schedules of Key Randomized Clinical Trials

	CF		AHF	RMH/SGOC		START A		START B	Canadian
Whole breast irradiation									
Whole breast dose (Gy)	50.4	5	39	39	42.9	39	41.6	40	42.5
Fraction size, Gy	1.8	2	3	3	3.3	3	3.2	2.67	2.66
Fraction number	28	25	13	13		13		15	16
Treatment period, wk	5.5	5	2.6	5		5		3	3.2
Boost to tumor bed									
% of patients receiving boost	100	—	100%	75%		61%		39%	0%
Boost dose, Gy	9	10	9	14		10		10	—
Fraction size, Gy	1.8	2	3	2		2		2	—
Treatment period, wk	1		0.6	1.4		1		1	—
Whole breast + boost									
Total dose, Gy	59.4	60	48	53	56.9	49	51.6	50	42.5
Total treatment period, wk	6.5	6	3.2	6.4		6		4	3.2

AHF = accelerated hypofractionation, CF = conventional fractionation, RMH/SGOC = Royal Marsden Hospital/Sutton and Gloucestershire Oncology Center, START A = Standardisation of Breast Radiotherapy (START) A trial, START B = Standardisation of Breast Radiotherapy (START) B trial.

a close margin were given as 12 Gy in 4 fractions. CF was composed of whole-breast irradiation up to 50.4 Gy in 28 fractions, followed by a boost of 9 Gy in 5 fractions. The boost dose was augmented to 14 Gy in 7 fractions for a close-margin status. At both centers, radiation was delivered once every day from Monday to Friday.

Follow-Up

The patients were followed up at 2 or 3 months and again at 6 months after RT and yearly thereafter. The medical history was recorded, and a physical examination was performed at each follow-up. For evaluation of RT complications, medical photographs were taken before RT, immediately after RT completion, 6 months after RT, and at yearly visits thereafter. The RT-related skin toxicities such as edema, erythema/hyperpigmentation, and wet desquamation were selected to compare the pure effect of 2 different RT regimens on the breast cosmesis. These toxicities were graded qualitatively using a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) at baseline before RT, immediately after RT completion, and at each follow-up visit. Any change in breast appearance including breast edema, erythema/hyperpigmentation, wet desquamation, and fibrosis was recorded at each follow-up. Low-dose steroid-containing cream or ointments in patients who needed symptomatic treatment was used in both groups. Antibiotic ointments were added if necessary. The toxicities for the AHF group were graded by one radiation oncologist (KHS), and the toxicities for the CF group were graded by a different physician (SWL). In patients who received chemotherapy, we performed regular electrocardiogram (ECG) and any patients with abnormal finding in the ECG underwent echocardiography.

Endpoints and Statistics

All of the endpoints were calculated from the date of surgery. Ipsilateral breast tumor relapse (IBTR) was defined as recurrence in the treated breast. The occurrence of either local or regional relapse was defined as locoregional relapse (LRR). The relapse detected anywhere else was considered distant metastasis (DM). The overall survival (OS) was calculated based on the date of death, for the deceased patients, or the date of the last follow-up visit, for the surviving patients. The survival rates, survival plots, and cumulative incidences were obtained by Kaplan-Meier survival analysis. The 5-year event rates and their 95% confidence intervals (CIs) were derived from the survival curves. The hazard ratios (HRs) of IBTR for the AHF versus CF groups were estimated using univariate Cox proportional hazards regression models. The comparisons of patient characteristics, treatment-related factors, and toxicities between the AHF and the CF groups were performed using t test, χ^2, and Fisher's exact tests. Statistical significance was defined at the α level of .05. The statistical analyses were performed using the SPSS (Version 17, SPSS Inc, Chicago, IL).

RESULTS

Patient, Tumor and Treatment-Related Characteristics

The median follow-up period was 75 months (range, 3.8–110.8 months). The patient and tumor characteristics, as well as treatment-related factors, are summarized in Table 2. There was no statistically significant difference in age distribution between the AHF and CF groups (median age 49 years [range, 26–81 years] vs 50 years [range 27–80 years]). The AHF group comprised 259 patients with T1 stage and 120 patients with T2 stage cancer, whereas the CF group comprised 265 patients with T1 stage and 114 patients with T2 stage cancer ($P = 0.82$). Likewise, there were 319 patients with N0 stage and 60 patients with N1 stage in the AHF group, and 325 patients with N0 stage and 54 patients with N1 stage in the CF group ($P = 0.54$). Thus, the pathologic T and N stages were distributed evenly between the 2 groups.

The pathology was mainly ductal carcinoma, with an even distribution of the histologic grade and resection margin status between the 2 groups. There was no statistically significant difference in the distribution of the molecular subtype between the 2 groups. The proportion of patients who were given trastuzumab therapy did not differ between the 2 groups (12 in the AHF group vs 21 in the CF group; $P = 0.11$). However, there were more patients with estrogen receptor (ER) or progesterone receptor (PR) positivity in the AHF than the CF group (301 [79.4%] vs 267 [70.4%], respectively; $P < 0.01$). Consequently, more patients received hormonal therapy in the AHF group than the CF group (298 [78.6%] vs 271 [71.5%], respectively; $P = 0.02$). More patients received chemotherapy in the AHF group than the CF group (275 [72.6%] vs 219 [57.8%], respectively; $P = 0.02$).

Survival Outcomes

The 5-year event rates for both groups are summarized in Table 3. There were 5 incidents of IBTR in the AHF group, yielding a 5-year event rate of 0.8% (95% CI, 0.2–2.4). There were 7 cases of IBTR in the CF group at the time of analysis, with a 5-year event rate of 1.6% (95% CI, 0.7–3.5). The HR for the occurrence of IBTR was 0.8 (95% CI, 0.2–3.0) for the AHF group compared with the CF group (Figure 1A). The 7-year IBTR-free survival rates of the AHF and CF groups were 98.9% and 98.1%, respectively ($P = 0.56$). These differences were not statistically significant.

Two patients (5-year event rate: 0.5% [95% CI, 0.4–2.6]) in the AHF group and 1 patient (0.3% [95% CI, 0.1–1.9]) in the CF group developed axillary or other regional nodal relapse ($P = 0.35$). In the AHF group, one patient had a nodal relapse in the internal mammary region at 13 months after surgery, and the other patient had an axillary recurrence at 42 months after surgery. One patient treated with the CF regimen was diagnosed with axillary failure at 12 months after surgery. Seven LRR events occurred in the AHF group, with a 5-year event rate of 1.3% (95% CI, 0.5–3.1). Eight women in the CF group developed LRR (5-year event rate: 1.6% [95% CI, 0.7–3.5]). The 7-year LRR-free survival rate was estimated to be 98.4% in the AHF group and 97.9% in the CF group ($P = 0.79$).

There were total 6 (5-year event rate: 1.6% [95% CI, 0.8–3.5]) cases of DM to the bone, lung, and liver in the AHF group. The CF group included 10 (2.4% [95% CI, 1.3–4.5]) women with documented DM to the contralateral axillary lymph node, bone, brain, and lung. The 7-year DM-free survival rate was estimated to be 97.1% in the AHF group and 96.0% in the CF group ($P = 0.55$).

The number of total deaths did not differ between the 2 groups at 5 years ($P = 0.48$). Three (5-year event rate: 0.8% [95% CI, 0.2–2.4]) patients in the AHF group died at the time of analysis, but one of these deaths was from a cause other than breast cancer. Four (1.1% [95% CI, 0.4–2.8]) patients expired in the CF group, all of whom had a relapse of their disease. The 7-year OS rates for the AHF and the CF groups were 99.2% and 98.9%, respectively ($P = 0.70$). At the time of analysis, 367

TABLE 2. Patient, Tumor, and Treatment-Related Characteristics

	Hypofractionation (N = 379) *N* (%)	Conventional Fractionation (N = 379) N (%)	*P*
Age, y	Median 49 (range 26–81)	Median 50 (range 27–80)	0.69
≤39	50 (13.2)	46 (12.1)	
40–49	150 (39.6)	134 (35.4)	
≥50	179 (47.2)	199 (52.5)	
Tumor location			0.05
Right	204 (53.8)	187 (49.3)	
Left	175 (46.2)	192 (50.7)	
Tumor pathology			0.84
Ductal	340 (89.7)	334 (88.1)	
Others	39 (10.3)	45 (11.9)	
Pathologic T stage			0.82
T1	259 (68.3)	265 (69.9)	
T2	120 (31.7)	114 (30.1)	
Pathologic N stage			0.54
N0	319 (84.2)	325 (85.8)	
N1	60 (15.8)	54 (14.2)	
Resection margin			0.11
>1 mm	367 (96.8)	358 (94.4)	
≤1 mm	12 (3.2)	21 (5.5)	
Histologic grade			0.08
1	36 (9.5)	44 (11.6)	
2	218 (57.5)	168 (44.3)	
3	121 (31.9)	160 (42.2)	
Unknown	4 (1.1)	7 (1.8)	
Molecular subtype			0.053
Luminal A	210 (55.4)	193 (50.9)	
Luminal B	91 (24.0)	73 (19.3)	
HER-2	29 (7.7)	43 (11.3)	
Triple negative	49 (12.9)	69 (18.2)	
Chemotherapy			0.02
Yes	275 (72.6)	219 (57.8)	
No	104 (27.4)	160 (42.2)	
Hormone therapy			0.02
Yes	298 (78.6)	271 (71.5)	
No	81 (21.4)	108 (28.5)	

(96.8%) patients in the AHF group and 364 (96%) patients in the CF group were alive without LRR or DM. The 7-year disease-free survival was estimated to be 97.1% in the AHF group and 96% in the CF group ($P = 0.55$; Figure 1B).

There were 5 patients with IBTR in the AHF group at the time of analysis. The characteristics associated with IBTR in the AHF group are shown in Table 4. Compared with the total IBTR 5-year event rate of 0.8% (95% CI, 0.2–2.4) in all AHF patients, grade 3 histology (2.3% [95% CI, 0.4–6.4]), luminal B subtype (2.2% [95% CI, 0.6–8.5]), and triple negative subtype (2% [95% CI, 0.3–13.6]) were related to 5-year event rates ≥2%. However, these differences were not statistically significant.

TABLE 3. Events Identified During Follow-up According to Treatment Group

	Hypofractionation (*N* = 379)		Conventional (*N* = 379)		
	Number	5-Year Event Rate (95% CI)	Number	5-Year Event Rate (95% CI)	Log-rank *P*
Ipsilateral breast tumor relapse	5	0.8% (0.2–2.4)	7	1.6% (0.7–3.5)	0.56
Regional nodal relapse	2	0.5% (0.4–2.6)	1	0.3% (0.1–1.9)	0.35
Locoregional relapse	7	1.3% (0.5–3.1)	8	1.6% (0.7–3.5)	0.79
Distant metastasis	6	1.6% (0.8–3.5)	10	2.4% (1.3–4.5)	0.31
Total deaths	3	0.8% (0.2–2.4)	4	1.1% (0.4–2.8)	0.48
Breast cancer	2	0.5% (0.1–2.1)	4	1.1% (0.4–2.8)	0.41
Other cause	1	0.3% (0.1–1.9)	0	–	0.32

CI = Confidence interval.

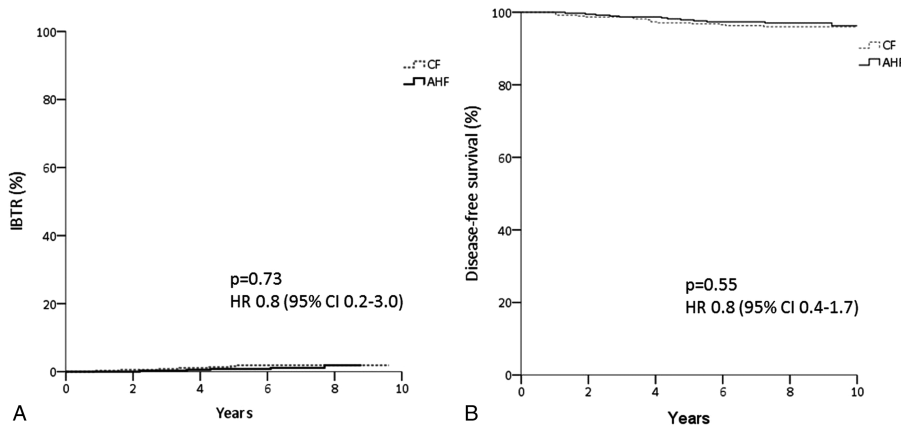

FIGURE 1. Cumulative incidence of IBTR (A) and disease-free survival (B) for patients after AHF or CF radiation therapy. AHF = accelerated hypofractionation, CF = conventional fractionation, CI = confidence interval, HR = hazard ratio, IBTR = ipsilateral breast tumor relapse.

Seven patients in the CF group developed IBTR by the time of analysis, with a 5-year IBTR rate of 1.6% (95% CI, 0.7–3.5). Similarly, grade 3 histology (2.5% [95% CI, 1.0–6.6]), luminal B subtype (2.7% [95% CI, 0.7–10.5]), HER-2 positivity (2.3% [95% CI, 0.3–15.4]), triple-negative disease (2.5% [95% CI, 0.3–10.8]), and age <50 years (2.2% [95% CI, 0.8–5.8]) were related to 5-year event rates ≥2%, without statistical significance. Thus, the factors associated with IBTR generally did not differ between the AHF and CF regimens.

Treatment-Related Skin Toxicities

The treatment-related skin toxicities in patients treated with AHF and CF are shown in Table 5. At the end of RT, skin toxicity records were available for all 379 (100%) patients in the CF group compared with only 273 (72%) patients in the AHF. The number of patients with skin toxicity data decreased in both groups to 278 (73%) in the CF group and 258 (68%) in the AHF group at 3 years. Any change in breast appearance was consistently observed higher in the CF group. There was a higher occurrence of breast edema in the CF group immediately after RT, but grade 1 breast edema was observed more in the AHF group at 6 months (AHF 56.5% [152/269] vs CF 9.5% [35/368], $P < 0.01$) and at 1 year (AHF 20.6% [60/291] vs CF 4.9% [17/346], $P < 0.01$). The incidence of erythema/hyperpigmentation remained lower in the AHF group consistently up to 3 years. At the end of RT, the CF group had a significantly higher number of patients with wet desquamation than that of the AHF group (CF 36.9% [140/379] vs AHF 0.4% [1/273], respectively; $P < 0.01$). The breast size did not affect the cosmetic outcome and hormonal therapy had no effect in breast cosmesis of the AHF group. None of the patients who were reoperated for IBTR developed impaired wound healing in both the AHF and CF groups.

DISCUSSION

The current standard for RT after BCS in early-stage breast cancer is 50 to 50.4 Gy to the whole breast and a boost of 9 to 16 Gy in 1.8- to 2-Gy fractions to the tumor bed. With the development of modern biological models for the radiation effect in the breast, the administration of AHF commenced in UK and Canada because of its marked reduction in the treatment period and the consequential reduction of cost problems and inconveniences of CF.[5–9,12,13] The long-term results of randomized trials have provided clinical and biological grounds for AHF in early breast cancer patients with a low risk of local recurrence.[6,14,15]

The RMH/SGOC trial reported 10-year IBTR rates of 12.1%, 14.8%, and 9.6% in the 50-Gy (25 fractions), 39-Gy (13 fractions), and 42.9-Gy (13 fractions) groups, respectively.[6] Although there was no statistically significant difference in tumor outcome between the 50-Gy and the 39-Gy arms, the cosmetic outcome was significantly in favor of the 39-Gy arm. Any change in breast appearance occurred in 35.4%, 27.4%, and 42.3% of the patients allocated to the 50-Gy, 39-Gy, and 42.9-Gy groups, respectively ($P < 0.001$), at the time of analysis. The UK START A trial reported 10-year local recurrence rates of 6.7%, 8.1%, and 5.6% for the 50-Gy, 39-Gy, and 41.6-Gy groups, respectively ($P = 0.39$ for the 50-Gy and 39-Gy arms).[15] The 10-year rates of moderate/marked breast edema ($P = 0.001$), telangiectasia ($P = 0.003$), and breast induration ($P = 0.03$) were significantly lower in the 39-Gy arm compared with the 50-Gy arms.[16]

Although the evidence supporting AHF has accumulated over the past few decades, this regimen has not been widely adopted internationally, including the United States, because some unanswered questions persist.[17] First, the optimal method for delivering a boost has not yet been clarified in AHF. None of the patients in the Canadian trial were given boosts.[14] Seventy-five percent of the patients in the RMH/SGOC trial received a boost of 14 Gy in 7 fractions.[7] In the START A trial, 61% were given a boost of 10 Gy in 5 fractions.[8] Both of these trials delivered boosts in 2-Gy fractions. We used a 3-Gy fraction for the AHF regimen based on its proven efficacy and lower toxicity from the results of the RMH/SGOC and START A trials.[6,8,15] Instead of reducing the fractional dose for the boost to 2 Gy as in the previous studies, we developed a regimen of 3 sequential boost fractions of 9 Gy to minimize the biological compromise of the radiation effect on the tumor. The α/β ratios, which designates the radiosensitivity characteristic of each cell type, for tumor cells and normal breast tissue were estimated to be 4.6 and 3.4, respectively, by the dose–response curves of local recurrences in the RMH/SGOC and START A trials.[18] All of the patients in this study received the boost (Table 6). The whole-breast dose of 39 Gy and the tumor bed boost dose of 9 Gy up to a total of 48 Gy achieves an equivalent dose in 2-Gy

TABLE 4. Factors Associated With IBTR Among Patients Who Received Accelerated Hypofractionation

	Patients (n/N)	IBTR 5-Year Event Rate (95% CI)*	Log-rank *P*
Total	5/379	0.8% (0.2–2.4)	
Age, y			0.56
≤39	0/50	0	
40–49	3/150	1.3% (0.3–5.2)	
≥50	2/179	0.6% (0.1–3.9)	
Histology			0.44
Ductal	5/340	0.9% (0.3–2.7)	
Others	0/39	0	
Pathologic T stage			0.18
T1	2/259	0.4% (0.1–2.7)	
T2	3/120	1.7% (0.4–6.5)	
Pathologic N stage			0.13
N0	3/319	0.6% (0.2–2.5)	
N1	2/60	1.7% (0.2–11.1)	
Resection margin			0.70
>1 mm	5/367	0.8% (0.3–2.5)	
≤1 mm	0/12	0	
Histologic grade			0.36
1	0/36	0	
2	2/218	0.5% (0.1–3.2)	
3	3/121	2.3% (0.4–6.4)	
Unknown	0/4	0	
Hormone receptor			0.25
ER or PR positive	3/301	0.7% (0.2–2.6)	
ER and PR negative	2/78	1.3% (0.2–8.8)	
Molecular subtype			0.20
Luminal A	1/210	0	
Luminal B	2/91	2.2% (0.6–8.5)	
HER-2	0/29	0	
Triple negative	2/49	2% (0.3–13.6)	
Chemotherapy			0.78
Yes	4/275	0.7% (0.2–2.9)	
No	1/104	1% (0.1–6.6)	
Hormone therapy			0.28
Yes	3/298	0.7% (0.2–2.7)	
No	2/81	1.2% (0.2–8.4)	
Trastuzumab therapy			0.71
Yes	0/12	0	
No	5/367	0.8% (0.3–2.5)	

CI = confidence interval, ER = estrogen receptor, IBTR = ipsilateral breast tumor relapse, PR = progesterone receptor.

fractions (EQD2) of 55.3 Gy to the tumor ($\alpha/\beta = 4.6$ Gy) and 56.9 Gy to the normal breast ($\alpha/\beta = 3.4$ Gy).[15] This finding is not much different from the EQD2 of CF (50.4 Gy to the whole breast and 9 Gy to the tumor bed in 1.8-Gy fractions), which is 57.6 Gy to the tumor and 57.2 Gy to the normal breast. In light of this finding, not only the 7-year IBTR-free survival rate of 98.9%, but also the fact that none of the patients who received an additional fraction for a boost up to a total of 51 Gy (EQD2 = 58.7 Gy, $\alpha/\beta = 4.6$ Gy) for close or positive margins were free of disease, suggest that our boost regimen is effective. The American Society for Radiation Oncology (ASTRO) guideline remains equivocal concerning boosts in the AHF setting ascribing to data insufficiency.[19] It is true that none of the prospective trials on AHF have analyzed the effect of boost in a randomized fashion. Nonetheless, in addition to the phase II prospective trial on our regimen that we have reported earlier, the data are constantly being accumulated.[10] The interim efficacy of 41.6 Gy in 13 fractions and then sequential boost with the same regime as ours reported by Janssen et al[20] was a local control rate of 100% at 2 years.

After a median follow-up of 75 months, we achieved a 5-year IBTR rate of 0.8% (95% CI, 0.2–2.4) in the AHF group and 1.6% (95% CI, 0.7–3.5) in the CF group. This finding is highly comparable to the results of previous randomized studies (Table 6). The START A trial reported 5-year local relapse rates of 3.4% (95% CI, 2.3–5.1) in the 50-Gy arm and 4.4% (95% CI, 3.1–6.2) in the 39-Gy arm.[15] The 5-year local recurrence-free survival rates were 97.2% in the 42.5-Gy arm and 96.8% in the 50-Gy arm (absolute difference: 0.4%; 95% CI, -1.5% to 2.4%) for the Canadian trial.[5]

Regarding treatment-related skin toxicity, the incidences of mild breast edema, erythema/hyperpigmentation, and wet

TABLE 5. Treatment-Related Skin Toxicities for Patients Treated With AHF and CF

Toxicity	Incidence (% of Patients)									
	At Radiotherapy End		At 6 mo		At 1 y		At 2 y		At 3 y	
	AHF (n = 273)	CF (n = 379)	AHF (n = 269)	CF (n = 368)	AHF (n = 291)	CF (n = 346)	AHF (n = 260)	CF (n = 317)	AHF (n = 258)	CF (n = 278)
Any change in breast appearance	—		$P < 0.01$		$P < 0.01$		$P < 0.01$		$P < 0.01$	
	—	—	203 (74.9)	324 (87.8)	120 (40.8)	276 (79.1)	36 (13.8)	202 (63.3)	19 (7.3)	132 (46.8)
	$P < 0.01$		$P < 0.01$		$P < 0.01$		$P = 0.22$		$P = 0.20$	
Breast edema										
G0	168 (61.5)	178 (47.0)	115 (42.8)	331 (89.9)	230 (79.0)	327 (94.5)	249 (97.3)	314 (99.1)	232 (100.0)	275 (98.9)
G1	104 (38.1)	179 (47.2)	152 (56.5)	35 (9.5)	60 (20.6)	17 (4.9)	7 (2.7)	2 (0.6)	—	3 (1.1)
G2	1 (0.4)	21 (5.5)	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.6)	—	1 (0.3)	—	—
G3	—	1 (0.3)	—	1 (0.3)	—	—	—		—	—
	$P < 0.01$		$P < 0.01$		$P < 0.01$		$P < 0.01$		$P < 0.01$	
Erythema										
G0	1 (0.4)	—	114 (42.5)	51 (13.9)	203 (70.2)	92 (26.6)	179 (86.9)	185 (58.2)	110 (97.3)	223 (80.2)
G1	115 (42.3)	193 (50.9)	153 (57.1)	308 (83.9)	84 (29.1)	253 (73.1)	27 (13.1)	132 (41.5)	3 (2.7)	55 (19.8)
G2	155 (57.0)	152 (34)	1 (0.4)	8 (2.2)	2 (0.7)	1 (0.3)	—	1 (0.3)	—	—
G3	1 (0.4)	57 (15)	—	—	—		—	—	—	—
	$P < 0.01$		—		—		—		—	
Wet desquamation										
G0	271 (99.6)	239 (63.1)	—	—	—	—	—	—	—	—
G1	1 (0.4)	98 (25.9)	—	—	—	—	—	—	—	—
G2	—	38 (10.0)	—	—	—	—	—	—	—	—
G3	—	4 (1.1)	—	—	—	—	—	—	—	—

AHF = accelerated hypofractionation, CF = conventional fractionation.

TABLE 6. The Comparison of Ipsilateral Breast Tumor Recurrence and Late Toxicity CF, AHF, and Other Hypofractionation Regimens Adopted in Key Randomized Trials With 39-Gy Arms

	This Study		RMH/SGOC			START A		
	CF	AHF	50-Gy	39-Gy	42.9-Gy	50-Gy	39-Gy	41.6-Gy
Whole breast dose, Gy	50.4	39	50	39	42.9	50	39	41.6
Total dose, Gy	59.4	48	64	53	56.9	60	49	51.6
EQD2 for tumor, Gy	57.6	55.3	64	58.9	65.4	60	54.9	59.2
EQD2 for normal breast, Gy	57.2	56.9	64	60.2	67.2	60	56.2	60.8
Boost (%, patients)	100			75			61	
5-yr IBTR rate (%)	1.6	0.8		–		3.4	4.4	3.1
Statistical significance	No						No	
10-yr IBTR rate (%)			12.1	14.8	9.6	6.7	8.7	5.6
Statistical significance	-			No (50-Gy vs 39-Gy)			No	
Late toxicity	Any change in breast appearance (3 y)			Any change in breast appearance (10 y)			Moderate/marked change in breast appearance (5 y)	
Rate (%)	46.8	7.3	35.4	27.4	42.3	41.0	34.1	41.9
Statistical significance	Yes			Yes			No	

AHF = accelerated hypofractionation, CF = conventional fractionation, EQD2 = Equivalent dose in 2-Gy fractions (α/β ratio of tumor = 4.6 Gy; α/β ratio of normal breast = 3.4 Gy), RMH/SGOC = Royal Marsden Hospital/Sutton and Gloucestershire Oncology Center, START A = Standardization of Breast Radiotherapy A trial.

desquamation were higher in the CF group at the end of RT. Although the difference was statistically significant, it cannot be interpreted purely as actual radiation effects of the two fractionation schemes because the toxicities in each group were assessed by different physicians. The breast size did not affect the cosmetic outcome in the AHF group and it may be because of the complex interplay between size and ptosis of the breast as well as tumor bed location and volume of breast tissue removed during surgery.[18,21] CF has been the standard of care for several decades because of the concept that a larger fraction size may lead to a greater risk of normal tissue damage.[22] According to our data, grade 1 breast edema persisted for a longer period of time in the AHF group with statistical significance. However, considering the higher incidence of grade 3 toxicity observed in the CF group, it can be hypothesized that shortening the treatment time may play a role in reducing the severity of skin toxicity by completing RT before radiation dermatitis worsens further. It is difficult to directly compare our cosmetic results with those of previous randomized trials comparing hypofractionation versus CF due to the different methodologies used to analyze cosmesis and skin toxicity. Nonetheless, it is legitimate to understand our results in accordance with the current evidence, considering the superior cosmetic outcome of the 39-Gy arm compared with the 50-Gy arm in the RMH/SGOC and START A trials.[6,15,16] Concern remains regarding the late effects, even after a decade up to 2 decades, for the cardiac events.[23,24] Therefore, the comparison of AHF with CF in this study requires further maturity of the data before final conclusions can be made.

To the best of our knowledge, we are the first group to use the AHF regimen with a boost of 9 Gy in 3-Gy fractions in addition to 39 Gy on the whole breast. The present data show that, while reducing the fraction number, AHF of 39 Gy to the whole breast plus a 9-Gy boost in 16 fractions is comparable to CF, with excellent tumor control and tolerable skin toxicity in patients with early-stage breast cancer.

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