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Clinical Investigation

Robotic Stereotactic Boost in Early Breast Cancer, a Phase 2 Trial



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Summary

This phase 2 trial of single-dose stereotactic boost after conventional breast irradiation in early breast cancer showed excellent local control, toxicity profile, and quality of life on general and breast-specific items with a median follow-up of 38 months.

Purpose: To evaluate the feasibility and toxicity of a single-fraction 8-Gy stereotactic boost after whole-breast irradiation in early breast cancer. The primary aim of this phase 2 study was to evaluate cutaneous breast toxicity using National Cancer Institute Common Terminology Criteria for Adverse Events (version 4) 3 months after the boost. Secondary objectives were local control, survival, and patient-reported quality of life using the European Organisation for Research and Treatment of Cancer QLQ-C30 and breast-specific European Organisation for Research and Treatment of Cancer QLQ-BR 23 questionnaires.

Methods and Materials: Patients with invasive ductal or lobular pT1-2 breast cancer treated with lumpectomy with clear margins and pN0 were included. Patients requiring chemotherapy were excluded.

Results: Twenty-eight eligible patients received the planned boost, and 26 had hormonal therapy. The procedure was technically successful without procedural complications. A median of 3 fiducials were tracked, and 115 beams were used. There were 22 acute grade 1 breast skin toxicities, including fibrosis, pain, erythema, or pigmentation. There were 2 acute grade 2 erythemas. Median skin boost dose was inversely correlated with acute skin toxicity ($P = .028$). QLQ-C30 scores revealed acute dyspnea and arm symptoms without correlation to the boost dose. Breast symptom

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QLQ-BR23 scores did not deteriorate, although upset with hair loss and systemic side effects of hormonal therapy were observed. After a median follow-up of 38 months, 1 patient had in-boost-field relapse, and there were 5 late grade 1 and 1 grade 2 skin toxicities.

Conclusions: Single-fraction stereotactic boost after conventional whole-breast irradiation in early breast cancer is feasible with minor toxicities. Quality of life and specific breast items showed excellent patient acceptance. © 2018 Elsevier Inc. All rights reserved.

Introduction

Based on breast cancer radiobiology and boost versus no-boost trials,¹⁻⁶ accelerated partial breast irradiation can now be recommended in selected patients with low-risk early breast cancer.⁷⁻⁹ According to the guidelines, a hypofractionated boost can be recommended for deep-seated tumors or positive margins. Stereotactic irradiation yields steep dose gradients using multiple minibeam targeting the tumor bed. It has been used as accelerated partial breast irradiation for early breast tumors¹⁰⁻¹³ and in the neoadjuvant setting.¹⁴ We evaluated the efficacy of a stereotactic boost on early toxicity and local control as well as toxicities at 3 years after adjuvant whole-breast irradiation (WBI) in early breast cancer.

Methods and Materials

An institutional review board—approved phase 2 clinical trial of adjuvant single-fraction robotic stereotactic boost after conventional WBI was launched to evaluate 3-month breast cutaneous tolerance using National Cancer Institute Common Terminology Criteria for Adverse Events (version 4). Secondary objectives were 3-year local control, survival, and patient-reported quality of life using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and breast-specific EORTC QLQ-BR 23 questionnaires. Patients with breast cancer (invasive ductal, or lobular pT1-2 unifocal noninflammatory, pN0) who were aged ≥ 18 years, had a performance status of 0 to 2, and had been treated with lumpectomy with clear margins were eligible. Patients with residual microcalcifications requiring chemotherapy or who had been previously irradiated were excluded. Patients provided informed consent before being included in the study.

Three to 5 surgical clips were placed perioperatively around the tumor bed. Interventional radiologists implanted 3 to 4 additional gold fiducials (4 mm \times 0.8 mm) within 40 mm of the tumor bed under ultrasound guidance and with use of local anesthesia during week 2 of WBI. Fiducials were noncoplanar ≥ 20 mm from one another and $\geq 15^\circ$ between each other 2 to track translational and rotational target movements using the CyberKnife Synchrony Respiratory Tracking System (Accuray Incorporated, Sunnyvale, CA). WBI was delivered as 50 Gy in 25

2-Gy fractions over 5 weeks with the free-breathing “field-in-field” technique.

Another 1-mm-thick computed tomography (CT) scan was performed on fraction 16 of WBI 1 week after fiducial placement with patients in the supine position in a body vacuum mattress, with arms placed along the body. The clinical target volume was 5 mm around the surgical clips, excluding a 5-mm-thick skin RT structure. The planning target volume (PTV) was 5 mm to account for respiratory motion and setup uncertainties.¹⁴ The ribs ipsilateral to the tumor were delineated 2 cm below and above the PTV. The heart, lungs, and whole breasts were also delineated.

Considering an alpha/beta of 3 for breast cancer, we used a single 8-Gy dose as an equivalent to 16-Gy total dose in 8 2-Gy fractions,¹⁵ with 95% of the PTV covered by the 80% isodose and 99% of the PTV receiving a minimum of 90% of the prescription dose. The boost was delivered immediately after WBI with no planned gap. Three light-emitting diodes were placed on a synchrony tracking vest or on patients' clothes. Target location was determined using orthogonal x-rays to visualize fiducials at various phases of the respiration cycle while the breathing pattern was synchronously monitored using light-emitting diodes to model target positions using the tracking system. Patients with large breasts underwent 2 CT scans with and without a synchrony tracking vest, with either of these scans chosen based on treatment room acquisitions during the respiratory modeling phase.

Patients underwent weekly follow-up visits during radiation therapy, every 3 months during the first year, and every 6 months thereafter, with mammographs and ultrasound 6 months after radiation therapy and once yearly thereafter. Hormonal therapy was started after radiation therapy after paraclinical examinations as per standard practice.

Statistical comparisons were performed using the χ^2 or Fisher's exact tests for categorical data and the Student' *t* test or Mann-Whitney test for continuous variables. Overall survival was defined as the time between dates of consent and death. Local, regional, and distant relapse-free survival was the time between dates of consent and local, regional, and distant relapse, respectively. Survival curves were computed with the Kaplan-Meier method. Patients were censored at the time of death or at last follow-up. Differences in QLQ-BR23 and QLQ-C30 scores were obtained between inclusion and 3 months, then between baseline and

36 months, after robotic stereotactic irradiation. Dimensional consistency was calculated using Cronbach's alpha with its 95% confidence interval (bootstrapping method). Data entry and management were performed on the capture system (Ennov Clinical). Statistical analyses were performed with 5% alpha risk using R.3.2.2 software.

Results

Patient, tumor, and treatment characteristics are shown in Table 1. Twenty-eight patients received the 8-Gy stereotactic boost (Fig. 1). One patient was excluded as a result of acute constrictive pericarditis during WBI. There were no procedural complications of fiducial placement, but it was difficult in 1 patient who had undergone oncoplasty. After 12 patients had been treated, analyses revealed that rotations could not be used. Subsequently, 4 of 16 patients were treated using a vest because more fiducials in treatment position were tracked using their planning CT scan with a vest than without a vest. One patient had all 4 fiducials

tracked; the other 3 patients had 2 fiducials tracked because of the proximity between fiducials. CTV and PTV were not correlated with rotation tracking capability ($P = .755$ and $P = .649$, respectively) (Table 2). More fiducials were tracked in smaller breasts (A + B) versus large breasts ($\geq C$) (3-4 vs 1-2, respectively). CTV and PTV were not associated with treatment time ($P = .7$, $P = .8$). Large breasts had longer treatment times (mean, 102.1 minutes [standard deviation (SD), 38.4] vs 68.1 minutes [SD, 14.6]; $P = .029$).

All patients were alive at last follow-up. Median follow-up was 38 months (minimum, 21.3; maximum, 69.1). Two patients with triple-negative breast cancer had a nodal relapse or a local in-boost-field relapse at 20 and 38 months, respectively. They subsequently underwent salvage treatment and were alive at last follow-up.

There was no correlation between boost dose and local relapse. Median boost dose to the skin correlated with cutaneous grade 1 to 2 toxicity ($P = .028$) with 4.1 Gy (mean, 4.8 [SD 2.6]) in patients with toxicities ($N = 8$) and 7.9 Gy (mean, 7.0 [SD, 3.4]) without

Table 1 Patient characteristics

Patient characteristics	n (%)
Age, median [range], y	60.5 [43-82]
ECOG performance status 0-1/2	25 (89.2%)/3 (10.7%)
Body mass index, median [range], kg/m ²	25.2 [19.7-36.8]
Menopausal status, yes/no	24/4
Chest size (85-110), mm	Very small, 0 (0%); small, 3 (10.5%); medium, 7 (25%); large, 5 (18%); very large, 5 (18%); unknown, 8 (28.5%)
Breast size (A-F)	Very small, 4 (14%); small, 4 (14%); medium, 7 (25.5%); large, 5 (18%); unknown, 8 (28.5%)
Tumor characteristics	
Histology: ductal/lobular/mixed	24 (85.7%)/3 (10.7%)/1 (3.6%)
Associated in situ carcinoma component of low, intermediate, and high grade	16 (57.1%), with 6, 5, and 3 cases, respectively
Tumor grade 1/2/3	12 (43.0%)/15 (53.5%)/1 (3.5%)
T stage 1a/1b/1c/2	3/13/11/1 (3.6%)
Tumor diameter, median [range], mm	10 [3-18]
Tumor quadrant superoexternal, central, other	12, 8, 8
Tumor site: right/left breast	13 (46.4%)/15 (53.5%)
Estrogen receptor-/progesterone receptor-positive	25 (89.2%)/19 (67.8%)
HER2-positive	1 (3.6%)
Molecular classification, luminal A B, triple negative	6 (21.4%), 19 (67.9%), 3 (10.7%)
Ki67, median [range]	10 [2-60]
Perineural invasion/vascular emboli	0 (0%)/1 (3.6%)
Treatment characteristics before stereotactic boost	
Lumpectomy/zonectomy	25 (89.2%)/3 (10.6%)
Oncoplasty	1 (3.6%)
Margins, median [range], mm	5 [0-5], 1 patient with additional margins 0 mm (pectoral aponeurosis)
Sentinel biopsy/axillary dissection	27 (96.4%)/1 (3.6%)
Time from surgery to whole breast EBRT, median [range], d	50 [36-82]
Radiodermatitis before boost grade 1/2	22 (78.6%)/6 (21.4%)
Fibrosis/edema before boost grade 1/2	4 (14.3%)/1 (3.6%)
Breast hematoma before boost	4 (14.3%)

Abbreviations: EBRT = external beam radiation therapy; ECOG = Eastern Cooperative Oncology Group.

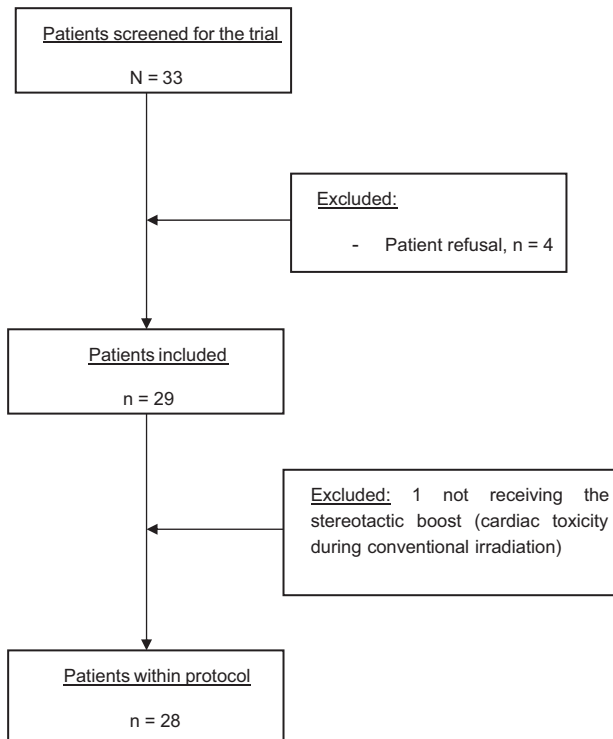


Fig. 1. Flow chart of the trial.

toxicities (N = 20). This was an unexpected finding for which we have no reasonable explanation. At 3 months, there were 22 grade 1 cutaneous toxicities, including breast fibrosis, pain, erythema, and pigmentation in 11, 4, 5, and 2 cases, respectively, and 2 grade 2 cases of erythema. All but 2 patients underwent hormonal therapy after radiation therapy. At 36 months, there were 5 skin toxicities, including fibrosis (N = 3), erythema (N = 1), and pigmentation (N = 1), and 1 case of grade 2 skin fibrosis.

Quality-of-life scores at 3 and 24 months are shown in Tables 3 and 4. EORTC QLQ-C30 dyspnea and arm symptoms had significantly deteriorated compared with baseline (P = .01). There was no correlation between boost dose to the lungs and dyspnea (P = .85) or between lung mean dose with WBI and dyspnea (P = .15). Patients receiving (N = 25) or not (N = 3) receiving hormonal therapy had dyspnea scores of 17 and 33, respectively (P = .7). EORTC QLQ-BR23 scores showed steady breast symptom scores, whereas upset with hair loss and systemic therapy side effects worsened after the end of irradiation and initiation of hormonal therapy. Scores for items specific to breast irradiation did not deteriorate. There was no correlation between cutaneous toxicities assessed by physicians and toxicity assessed by the patients (P = .88), nor was there a correlation with other toxicities.

Owing to the low rate of late toxicities, it was not statistically relevant to investigate relationships

Table 2 Stereotactic boost treatment characteristics

Stereotactic boost treatment characteristics	Median (%) [range]
CTV, mm ³	6526 [1830-56117]
PTV, mm ³	20167 [8490-103534]
No. fiducials placed, 5/4/3	1 (4%)/21 (75%)/6 (21%)
No. fiducials tracked	3 [1-4], including 2 patients with 4 fiducials too close to one another
Patients for whom rotations were tracked	4, including 2 with increased tolerances to 5°
No. beams	115 [78-197]
Circular collimator, mm	20 [10-35]
Isodose line	80 [78-81]
Time per fraction, min	45 [38-55]
No. online images during fraction	83 [54-262]
Stereotactic boost prescription dose, cGy	800
CTV, cm ³	4.5 [1.8-17.9]
PTV, cm ³	16.1 [8.5-40.0]
Max dose to the heart, cGy	107.1 [32.7-536-3]
Mean dose to the heart, cGy	24.7 [17.9-74.4]
Max dose to the skin, cGy	471.0 [201.6-1025.6]
Max dose to the ribs, cGy	337.4 [132.3-968.3]
Max dose to ipsilateral lung, cGy	261.3 [108.3-803.0]
Mean dose to ipsilateral lung, cGy	36.0 [18.2-80.8]
Dmin to CTV, cGy	773.6 [478.5-862-7]
Dmax CTV, cGy	1000.0 [975.6-1025.6]
Dmean CTV	923.4 [792.4-976.0]
% coverage CTV	99.6 [49.8-100]
Conformity index CTV	3.23 [1.1-4.9]
Homogeneity index CTV	1.3 [1.2-1.3]
NCI	3.3 [1.4-4.9]
Dmin PTV, cGy	624.1 [148.3-784.5]
Dmax PTV, cGy	1000 [945.6-1025.6]
Dmean PTV, cGy	880.3 [724.8-908.2]
% Coverage PTV	93.7 [29.0-99.7]
CI PTV	1.2 [1.0-1.3]
nCI PTV	1.3 [1.2-3.5]
HI PTV	1.3 [1.2-1.5]

Abbreviations: CI = conformity index; CTV = clinical target volume; PTV = planning target volume.

between clinical and therapeutic effects. In contrast to scores at 3 months, quality of life deterioration with the EORTC QLQ-C30 and BR23 scores was no longer observed at 24 months, nor on previously identified items or others. At 24 months, patients had regained a quality of life equal to that reported at baseline.

Discussion

This prospective single-center study sought to evaluate the ability of a hypofractionated stereotactic boost to spare a

Table 3 QLQ-C30 between baseline, month 3, and month 24

Variable	Item	Inclusion		Follow-up at 3 mo		Follow-up at 24 mo		P value*	P value†
		Mean	SD	Mean	SD	Mean	SD		
Global health status/QoL									
Global quality of life	29,30	76.33	15.72	75	21.82	76.25	18.19	.81	.84
Functional scales									
Physical functioning	1-5	89.6	13.48	88.49	14.28	89.82	13.58	.79	.76
Role functioning	6,7	90.67	18.68	87.12	18.5	85.97	18.64	.52	.84
Emotional functioning	21-24	77.33	18.56	73.99	28.3	83.33	19.31	.64	.22
Cognitive functioning	20-25	90	15.96	88.64	15.76	80	21.36	.77	.15
Social functioning	26,27	92.67	16.72	87.3	21.02	95.83	10.64	.35	.11
Symptom scales/items									
Fatigue	10,12,18	22.67	19.9	27.78	24.67	23.33	16.87	.44	.5
Nausea and vomiting	14,15	3.33	8.33	4.55	11.71	0	0	.69	.08
Pain	9,19	20	19.84	26.52	24.48	22.5	21.81	.33	.58
Dyspnea	8	9.72	18.33	28.79	29.63	15.79	20.39	.01	.11
Insomnia	11	32	33.99	34.85	39.14	29.82	33.14	.79	.66
Appetite loss	13	2.67	13.33	4.54	11.71	5.26	12.49	.61	.85
Constipation	16	12	25.24	10.61	23.87	5	16.31	.85	.38
Diarrhea	17	1.33	6.67	3.03	9.81	8.33	18.34	.5	.26
Financial difficulties	28	10.67	23.01	10.61	26	1.67	7.45	.99	.14

Abbreviations: CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; QoL = quality of life; SD = standard deviation.

A high score for a functioning scale and for the global QoL scale represents a better level of functioning, whereas a high score for a symptom scale or a single-item scale denotes a high level of symptoms or problems.

* Comparison between baseline and month 3.

† Comparison between month 3 and month 24.

significant volume of breast tissue, thus reducing toxicity.^{12,14,16,17} Another underlying hypothesis was that hypofractionation could be as efficient as 2-Gy fractions.

There was 1 in-field local relapse (4%).¹⁸ Acute breast toxicity 3 months after the boost was low to moderate on all items. Median skin dose received using a boost inversely correlated with dermatitis. Toxicity was low

overall, and the boost did not add any grade ≥ 3 toxicities. Because fibrosis is a late effect, longer follow-up is necessary.¹⁹

Consistent with other studies,²⁰ toxicity scoring differed between physicians and patients. Also, patients did not report any deterioration of their body image and breast symptoms. They reported dyspnea and arm problems that

Table 4 QLQ BR23 between baseline, month 3, and month 24

Variable	Item	Inclusion		Follow-up at 3 mo		Follow-up at 24 mo		P value*	P value†
		Mean	SD	Mean	SD	Mean	SD		
Functional scales									
Body image	9-12	88.89	14.04	85.83	21.13	91.67	14.05	.58	.31
Sexual functioning	14,15	79.86	24.56	64.03	27.92	69.3	30.05	.06	.58
Sexual enjoyment	16	26.67	26.29	35.9	21.35	33.33	35.14	.38	.84
Future perspective	13	66.67	26.01	55	36.31	68.34	25.31	.24	.19
Symptom scales/items									
Systemic therapy side effects	1-4,6-8	8.93	7.6	19.3	22.5	13.21	14.5	.05	.3
Breast symptoms	20-23	22.92	21.17	20.42	19.21	14.17	15.32	.68	.26
Arm symptoms	17-19	6.02	11.34	19.44	18.34	13.89	19.03	.01	.35
Upset by hair loss	5	0	0	46.67	38.01	33.33	33.34	.05	.57

Abbreviations: CI = confidence interval; EORTC = European Organisation for Research and Treatment of Cancer; SD = standard deviation.

Scores range from 0 to 100. A high score for a functioning scale represents a better level of functioning, whereas a high score for a symptom scale or a single-item scale denotes a high level of symptoms or problems.

* Comparison between baseline and month 3.

† Comparison between month 3 and month 24.

were unnoticed by their physicians. Although there was no clear explanation, dyspnea was probably not attributable to the boost. Similarly, arm symptoms were more likely the result of WBI²¹ (negligible boost dose to ipsilateral humeral head). Patients reported hair and systemic symptoms that were certainly the result of hormonal therapy.²²

Finally, acute cutaneous toxicities observed by physicians appeared insignificant to patients. From both patients' and physicians' standpoints, our data corroborate the acceptance of a hypofractionated boost.^{19,23} Overall, the current study shows that a stereotactic boost offers a convenient single-fraction treatment option after WBI. After a median follow-up of 38 months, excellent tolerance and efficacy were observed.

Because final pathologic diagnosis was warranted for inclusion in the clinical trial, fiducials were placed post-operatively under ultrasound guidance with specific purposes compared with surgical clips: They must not be coplanar or too close to one another, to ensure stereotactic tracking.²⁴ Rotations were rarely tracked in this study, but we previously showed that rotational amplitudes of 2 to 3°¹⁴ are manageable with 5-mm margins from CTV to PTV. Altogether, dosimetric improvements using stereotactic boost irradiation appear to be more significant than those with intensity-modulated RT.^{25,26}

Study limitations include the small sample size and fiducial placement modality. Median follow-up was 38 months but will be prolonged. Extrapolation of results to patients under the age of 40 years or those with high local relapse risk should be done cautiously. Finally, specific radiologist training for fiducial placement is warranted, and larger setup margins may be necessary in conditions that do not allow optimal rotation tracking.^{27,28}

Conclusion

This phase 2 trial shows the feasibility of a follow-up single-dose stereotactic boost in early breast cancer. There were 22 and 2 acute grade 1 and 2 toxicities, respectively. There were few and low-grade late toxicities (5 grade 1 toxicities and 1 grade 2 skin fibrosis at 3 years). The quality of life and breast-specific items showed excellent acceptance by patients and even improved on all items between 3 and 36 months after the stereotactic boost. Larger studies investigating the efficacy and tolerance of a hypofractionated stereotactic boost would be very appropriate and should be proposed after this phase 2 study.

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