Article

Lung-Heart Toxicity in a Randomized Clinical Trial of Hypofractionated Image Guided Radiation Therapy for Breast Cancer

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Simple Summary: Adjuvant radiation therapy for breast cancer incurs a risk of lung and heart toxicity. In 2007, the TomoBreast randomized trial hypothesized that any-grade combined toxicities could be reduced using advanced radiation technique available at the time. The five-year results of this randomized clinical trial, with a study size of 123 patients, showed that image-guided therapy significantly improved the overall balance of lung-heart outcomes over conventional radiation therapy, with the added advantage of providing a more convenient short fractionation schedule.

Abstract: TomoBreast hypothesized that hypofractionated 15 fractions/3 weeks image-guided radiation therapy (H-IGRT) can reduce lung-heart toxicity, as compared with normofractionated 25-33 fractions/5-7 weeks conventional radiation therapy (CRT). 123 women with stage I-II operated breast cancer were randomized to receive CRT (N=64) or H-IGRT (N=59). The primary endpoint used a four-items measure of the time to 10% alteration in any of patient self-reported measure, physician clinical evaluation, echocardiography or lung function tests, analyzed by intention-to-treat without exclusion. Results found comparable survivals, but H-IGRT significantly reduced the toxicity measured by lung diffusion capacity and alveolar volume as compared with CRT, G1 in 53% (31/59) versus 72% (44/61) patients, P=0.006; G2, 29% versus 48%, P=0.020. H-IGRT significantly reduced the risk of composite cardio-pulmonary alteration at 5 years, 10.2% versus 26.7%, P=0.024. In conclusion, TomoBreast is a proof-of-concept that image-guided radiation-therapy can improve the overall balance of lung-heart outcomes in breast cancer adjuvant therapy. Furthermore, the significance of the findings supports the efficacy of a small trial size design, which can be critical when clinical research resources are limited.

Keywords: Breast; Targeted Radiotherapy; Lung injury; Heart injuries; Health-Related Quality Of Life; Irradiation toxicity.

1. Introduction

Considerable evidence has accumulated that post-operative radiation therapy for breast cancer is the foremost adjuvant treatment to reduce the risk of local recurrence and

 doi:10.20944/preprints202212.0214.v1

the risk of breast cancer mortality. However, the improvement in overall survival has been small. In a meta-analysis of 36 breast cancer trials, Van de Steene et al. observed in 2000 that adjuvant radiotherapy (using current techniques at that time, standard or "safe" fractionation) improved overall survival [1]. They retained a chronological year breakpoint of 1970. The breakpoint coincided with trials using megavoltage equipment, simulation and computerized tomography planning prior to radiotherapy, resulting in differences in target volume coverage and reduced normal tissue toxicities, and subsequent odds reduction of mortality. In addition, the authors brought forward the idea that local-regional control and overall survival are two different end points in early breast cancer treatment, linked by local-regional relapse but separated by normal tissue toxicity and prognosis for patients. They stressed the importance of reducing cardiovascular and other types of late toxicity.

At the time of three meta-analyses on the subject [1-3], breast cancer radiotherapy was conducted mostly using static opposed tangential radiotherapy fields. Low priority was given to heart and lung doses. Target coverage generously included a quarter or more of the thoracic wall, from a beam's entry point mid-sternal to the opposed tangential point at mid-axillary thickness. Constraint guidance was limited to a few geometrically specified measures. Portal images were acquired once at the first treatment session, and thereafter infrequently. Meanwhile, tomotherapy became available at the Universitair Ziekenhuis Brussel (UZ Brussel) in summer 2006 [4]. Tomotherapy is an integrated intensity-modulated radiotherapy (IMRT) helical system that combines a rotational linear accelerator delivering beamlets and a translational couch technique with integrated megavolt computed tomography allowing volumetric image guidance radiotherapy (IGRT), with the facility of online daily 3-dimensional image matching and repositioning. The system was found to be workload intensive [5]. As long as the benefit of breast radiotherapy was only in reducing the risk of recurrence, there was no reason to switch to a time-intensive technique which necessarily would reduce availability to other tumors. However, as evidence emerged that there was also a survival advantage linked to the technique (probably to a reduction in toxicity), the determination of how to improve this advantage became a compelling question. It was clear that the routine techniques had to be reconsidered. In early evaluations, tomotherapy for breast cancer appeared promising [6]. TomoBreast was designed to test the hypothesis that hypofractionated image-guided radiation therapy (H-IGRT) using tomotherapy can substantially reduce lung and heart toxicities, as compared with normofractionated conventional radiation therapy (CRT). We report herein the 5-year final results of the trial.

2. Materials and Methods

2.1. Objectives and patient selection.

The primary endpoint was combined pulmonary and cardiac toxicities, as determined by medical imaging (abandoned for lack of funding) and functional assessments. The secondary endpoint was local-regional recurrences. The study population consisted of women presenting with histologically proven stage I or II (T1-3N0 or T1-2N1 M0) invasive breast carcinoma [7]. Inclusion criteria were informed consent, age ≥ 18 years, complete surgical resection, and pre-operative imaging with computed tomography, magnetic resonance imaging, and/or positron emission tomography scan. Exclusion criteria were prior breast or thoracic radiotherapy, pregnancy, lactation, fertile patients without effective contraception, and psychiatric or addictive disorders.

The trial was approved by the UZ-Brussel ethics committee and registered on ClinicalTrials.gov, NCT00459628. All participants gave written informed consent. They were randomized to either the CRT (control arm), or the H-IGRT (experimental arm).

2.2. Radiotherapy technique.

CRT treatment planning used the Pinnacle3 planning system (ADAC-laboratories, Milpitas, CA, USA). The prescribed dose was 50 Gy in 25 fractions over 5 weeks to the

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breast/chest wall by tangential opposed beams and in cases of nodal involvement to axillary/supraclavicular areas by an anterior field. A sequential electron boost delivered 16 Gy in 8 fractions over 2 weeks to the tumor bed in lumpectomy patients ≤70 years of age [8]. The boost dose was calculated to a depth of 2-3 cm without individualized treatment plan. CRT dose constraints were not prespecified. Lung-in-field was accepted up to 3 cm central distance, and heart-in-field up to 2 cm.

For H-IGRT treatment planning, inverse-IMRT using the Tomotherapy Planning System (Accuray, Sunnyvale, CA, USA) was applied, for a prescription of 42 Gy in 15 x 2.8 Gy fractions over 3 weeks to the breast/chest wall and to nodal areas in case of positive lymph nodes, and a simultaneous integrated boost of 9 Gy in case of lumpectomy. H-IGRT dose-constraints were prespecified with the highest priority to the heart (Supplemental Material). Constraints expressed as dose-volume points were converted to mean organ dose constraints [9]. The left anterior descending coronary artery (LAD) was introduced later; the analyses applied a recommended mean dose constraint of 10 Gy [10].

2.3. Dose to structures.

Doses were converted to 2Gy equivalent-doses (EQD2), according to the equation: $EQD2 = D \cdot (\alpha/\beta + D/n)/(\alpha/\beta + 2)$, where D is the total dose (in Gy) delivered, n is the number of fractions, and $\alpha/\beta = 3$ [11].

Structures available for analysis (and their constraints) were: the heart (mean dose ≤1.52 Gye), the contralateral lung (≤1.06 Gye), the ipsilateral lung (≤3.55 Gye), the contralateral breast (≤2.97 Gye), the LAD (≤6.82 Gye), and the breast/chest wall clinical target volume (CTV1; ipsilateral breast/chest wall, standard deviation ≤0.61 Gye). The dose to the CTV1, per protocol, had to be in the range of 95%–105%, or 40–44 Gy. The range was converted to a standard deviation from the rule of thumb approximating the standard deviation as one quarter of the range [12]; hence, 1 Gy, or an EQD2 of 0.61 Gye, was used as the homogeneity constraint on the dose delivered to CTV1 [13]. The standard deviation of the dose in an individual structure was abbreviated as SDi to avoid confusion with the standard deviation of measures in a population.

2.4. Trial size and data.

The trial required ≥118 patients on the hypothesis that any-grade lung-heart toxicity would be reduced from 25% with CRT [14,15], to 5% with H-IGRT, by two-sided testing with a power of 0.80 at a significance level of 0.05. Randomization was balanced by nodal status, type of surgery, and chemotherapy sequence using Efron's biased coin method [16].

Lung and heart were assessed prior to therapy, 1-3 months after therapy, and then once yearly. Data were abstracted from the patients' medical charts, including: (i) pulmonary function tests: forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), diffusing capacity of the lungs for carbon monoxide (DLCO), alveolar volume at total lung capacity (VA), residual volume (RV), and total lung capacity (TLC) [17]; (ii) echocardiography left ventricular ejection fraction (LVEF) [18]; (iii) clinical toxicity grading using the Radiation Therapy Oncology Group (RTOG) late radiation morbidity grades for lung and heart [19]; and (iv) patient's self-reported symptoms of fatigue and dyspnea abstracted from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire QLQ-C30 [20]. For the pulmonary function tests and LVEF, raw measurements were used, with predicted values discarded to avoid spurious effects caused by changes of reference [21]. Data on cosmesis, shoulder-arm morbidity, and items other than fatigue and dyspnea were collected but are not considered in the present report.

2.5. Statistical analyses.

Time measurements used the date of randomization as the origin. Toxicities over time were evaluated on an ordinal scale and on a continuous scale.

 doi:10.20944/preprints202212.0214.v1

On the ordinal scale, the lung function tests and the heart's LVEF were categorized using cutoffs adapted from the Common Terminology Criteria for Adverse Events (CTCAE v.3) [22], the RTOG grades were used as-is, and the QLQ-C30 fatigue and dyspnea scales used raw scores. The patient's largest grade change at any time during follow-up was noted. Comparison of the rates used the Chi-square test for proportions.

On a continuous scale, the "time to 10% alteration" (TTA) was defined as the time for a lung or a heart indicator to reach 10% deterioration. Generalizing on [23] to any measurement, the TTA was computed for each patient using the least square regression fit to each of the patient's sets of time measurements. If the regression showed no significant decline in any of the measurements, or if the computed TTA exceeded the patient's time to follow-up, the patient was censored for toxicity at the patient's actual follow-up time. A composite toxicity event was defined as the first occurrence of any of the following: lung TTA, heart TTA, RTOG grade increase or fatigue-dyspnea increase. The Kaplan-Meier method and the log-rank test were used to analyze the TTA composite event.

Non-protocol subgroup analyses considered age, weight, tumor laterality, type of surgery, radiation to regional lymph node areas, chemotherapy, trastuzumab therapy, and histological grade interaction with the randomization arm in a Cox proportional hazard model of the TTA. The effects of lung-heart dose constraint violations were also examined in Cox TTA models.

All analyses were by intent-to-treat without any exclusion, in contrast to our earlier reports, which used post-hoc selection [17,24-26]. Computations used R version 3.4.3 [27]. Specific R packages used were "tableone" for the layout of results tables, with the default Student's t-test for the comparison of means and Chi-square test with continuity correction for the comparison of proportions, "survival" for the implementation of the Kaplan-Meier time-to-event analysis with the log-rank test and Cox models [28], "Amelia" for multiple imputation of time series data [29], and "forestplot" for the layout of subgroup results. The survival plot layout was borrowed from Tatsuki Koyama's function 'kmplot" (Vanderbilt Biostatistics Wiki). Computation of TTA used an in-house script.

3. Results

3.1. Patients.

The trial started in May 2007 and patient recruitment closed in July 2011. A total of 123 women consented to participate. Of these, 64 were randomized to CRT and 59 to hypofractionated image guided radiation therapy (H-IGRT). Of the 64 patients allocated to CRT, 2 received H-IGRT by request. Of the 59 patients allocated to H-IGRT, three received CRT; one because of an appointment scheduling error, two because tomotherapy was unsuitable due to the patient's body size exceeding the system's limits (**Figure 1**). As of July 16th, 2021, the median follow-up of the 103 surviving was 12.0 years (range 10.0 to 14.0) from randomization. Data for the present report were curated to a 5-years cutoff period.

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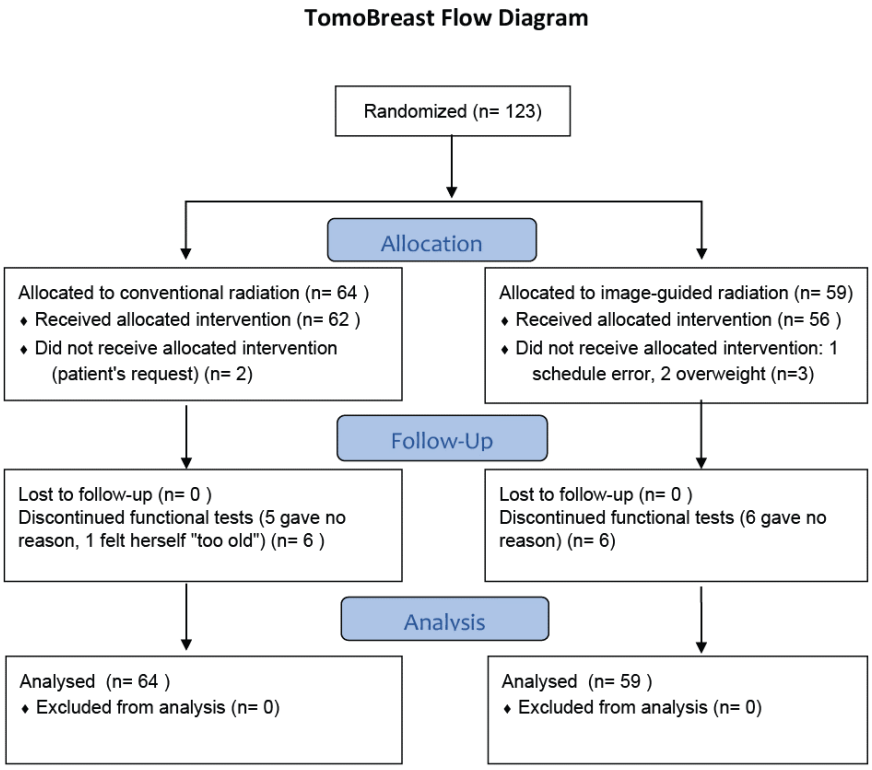

Figure 1. TomoBreast flow diagram.

The patients' characteristics were well balanced between the two arms, with the exception of a higher frequency of axillary lymph node dissection (P = 0.043) and HER2 overexpression (P = 0.055) in the H-IGRT patients (**Table 1**).

Table 1. Patients' characteristics. RT, radiotherapy; sd, standard deviation.

Characteristic	Unit or Level	CRT (N=64)	H-IGRT (N=59)	p
Age at randomization: mean (sd)	Years	57.8 (11.6)	55.1 (11.5)	0.198
median (range)	Years	54.8 (35.7, 81.0)	52.7 (31.7, 80.0)	
Karnofsky Performance Status: mean (sd)	%	94.1 (8.4)	94.7 (7.2)	0.678
	N Missing	1	4	
Weight: mean (sd)	*kg*	67.0 (12.3)	69.5 (15.4)	0.335
Height: mean (sd)	*cm*	161.5 (6.7)	163.4 (6.5)	0.118
Body Mass Index: mean (sd)	*kg/m2*	25.7 (4.2)	26.0 (5.4)	0.720
Smoker status: N (%)	No	46 (71.9%)	38 (64.4%)	0.493
	Yes	8 (12.5%)	12 (20.3%)	
	Former	10 (15.6%)	9 (15.3%)	
Smoking quantity: mean (sd)	Packyear	6.8 (14.3)	7.1 (14.2)	0.925
	N missing	2	1	
Mastectomy: N (%)	Yes	19 (29.7%)	26 (44.1%)	0.142
Axillary Dissection: N (%)	Yes	19 (29.7%)	29 (49.2%)	0.043
Chemotherapy: N (%)	No	38 (59.4%)	29 (49.2%)	0.499
	Before RT	7 (10.9%)	7 (11.9%)	
	Concomitant RT	19 (29.7%)	23 (39.0%)	

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Hormone therapy: N (%)	No	9 (14.1%)	8 (13.6%)	0.155
	Tamoxifen	26 (40.6%)	16 (27.1%)	
	Aromatase inhibitor	26 (40.6%)	26 (44.1%)	
	LHRH agonist	3 (4.7%)	9 (15.3%)	
Trastuzumab therapy: N (%)	Yes	3 (4.7%)	10 (16.9%)	0.055
Nodal irradiation: N (%)	Yes	16 (25.0%)	20 (33.9%)	0.376
Node-positive: N (%)		16 (25.0%)	21 (35.6%)	0.279
Laterality: N (%)	Right	31 (48.4%)	24 (40.7%)	0.402
	Left	32 (50.0%)	35 (59.3%)	
	Bilateral	1 (1.6%)	0 (0.0%)	
Histological Grade: N (%)	1	18 (30.0%)	16 (28.1%)	0.549
	2	25 (41.7%)	29 (50.9%)	
	3	17 (28.3%)	12 (21.1%)	
	N Missing	4	2	
Stage: N (%)	I	28 (43.8%)	25 (42.4%)	0.577
	IIA	31 (48.4%)	26 (44.1%)	
	IIB	5 (7.8%)	8 (13.6%)	
Tumor Size Pooled: mean (sd)	*mm*	19.8 (11.0)	20.3 (11.6)	0.820
Estrogen receptor positive: N (%)	Yes	56 (87.5%)	48 (81.4%)	0.489
Progesterone receptor positive: N (%)	Yes	46 (71.9%)	46 (78.0%)	0.569

Baseline measurements were also comparable between the two arms, with the exception of a better LVEF as a continuous measure (not as an ordinal one), and a better FEV1 in the H-IGRT arm, which was cancelled when entered into the ratio FEV1/FVC, P = 0.321 (**Table 2**). H-IGRT patients were 2 years younger than CRT patients, but the difference did not reach significance.

Table 2. Baseline measurements. FEV1, forced expiratory volume in 1 s. FVC, forced vital capacity. DLCO, diffusing or transfer capacity of the lungs for carbon monoxide. VA, alveolar volume at total lung capacity. RV, residual volume. TLC, total lung capacity. LVEF, left ventricular ejection fraction.

Measurement	**CRT (n=64)**	**H-IGRT (n=59)**	**p**
FEV1 Liters, mean (SD)	2.44 (0.56)	2.65 (0.59)	0.041
FVC Liters, mean (SD)	3.26 (0.67)	3.47 (0.67)	0.084
FEV1/FVC ratio, mean (SD)	0.75 (0.07)	0.76 (0.07)	0.321
DLCO mL/mmHg/min, mean (SD)	18.74 (3.98)	18.97 (3.42)	0.611
VA Liters, mean (SD)	4.46 (0.68)	4.62 (0.68)	0.177
DLCO/VA ratio, mean (SD)	4.20 (0.67)	4.12 (0.57)	0.553
RV Liters, mean (SD)	1.90 (0.51)	1.85 (0.51)	0.637
TLC Liters, mean (SD)	5.20 (0.70)	5.36 (0.78)	0.258
LVEF % ordinal			0.270
50-60% (%)	15 (26.8)	9 (16.4)	
>60% (%)	41 (73.2)	46 (83.6)	
LVEF % continuous, mean (SD)	62.62 (4.54)	64.82 (5.92)	0.047
Fatigue raw score, mean (SD)	1.90 (0.62)	2.06 (0.75)	0.207

 doi:10.20944/preprints202212.0214.v1

Dyspnea raw score, mean (SD)	1.33 (0.67)	1.46 (0.79)	0.352

Appendix A details the patterns of missing data. Appendix B outlines the imputation of missing LVEF.

3.2. Radiation doses.

With circumspection that CRT doses did not include the boost, H-IGRT was associated with a significantly higher dose to CTV1 and to the contralateral lung, although the differences were small (**Table 3**). H-IGRT was associated with a reduced average dose to the LAD, 4.8 Gy_e vs. 7.6 Gy_e, P=0.095. CRT was significantly associated with more dose heterogeneity (higher SDi) to the ipsilateral lung, P>0.001, to the heart, P=0.054, and to the LAD, P<0.001. H-IGRT was associated with significantly more heterogeneity to the contralateral breast, P<0.001.

Table 3. Summary of achieved treatment planning. CRT, conventional arm. H-IGRT, tomotherapy arm. CTV1, breast/chest wall clinical target volume. SD, standard deviation. SDi, standard deviation of the individuals' dose distribution in the structure. EQD2, equivalent 2 Gy dose with α/β of 3. (*) SDi missing, 20 in CRT, 2 in H-IGRT. Boost doses were omitted from planning in the conventional arm.

Structure	Units	Constraint	CRT (N=64)	H-IGRT (N=59)	P
CTV1	N missing		1	2	
Volume, Mean (SD)	mL		375 (238)	402 (334)	0.596
Average dose, Mean (SD)	EQD2		49.7 (2.1)	50.7 (2.6)	0.023
SDi, Mean (SD)	EQD2	0.61	1.3 (0.9)	1.1 (0.7)	0.173
Contralateral breast	N missing		2	0	
Volume, Mean (SD)	mL		512 (286)	630 (385)	0.056
Average dose, Mean (SD)	EQD2	2.97	1.0 (5.3)	1.6 (1.7)	0.355
SDi, Mean (SD)	EQD2		0.4 (0.8)	1.5 (1.3)	< 0.001
Ipsilateral lung	N missing		1	0	
Volume, Mean (SD)	mL		1473 (320)	1383 (317)	0.119
Average dose, Mean (SD)	EQD2	3.55	4.2 (2.4)	4.0 (1.8)	0.588
SDi, Mean (SD)	EQD2		8.4 (2.2)	6.3 (2.0)	< 0.001
Contralateral lung	N missing		1	0	
Volume, Mean (SD)	mL		1444 (358)	1462 (310)	0.767
Average dose, Mean (SD)	EQD2	1.06	0.1 (0.4)	0.3 (0.2)	0.010
SDi, Mean (SD)	EQD2		0.3 (0.9)	0.2 (0.3)	0.437
Heart	N missing		1	0	
Volume, Mean (SD)	mL		445 (117)	454 (106)	0.667
Average dose, Mean (SD)	EQD2	1.52	0.8 (1.5)	1.0 (0.8)	0.325
SDi, Mean (SD)	EQD2		2.1 (2.5)	1.3 (1.5)	0.054
Left anterior descending artery	N missing		1	2	
Volume, Mean (SD)	mL		1.3 (0.6)	1.4 (0.9)	0.247
Average dose, Mean (SD)	EQD2	6.82	7.6 (10.9)	4.8 (7.1)	0.095
SDi, Mean (SD) (*)	EQD2		8.7 (14.5)	2.0 (2.5)	< 0.001

Non-compliance in any of the constraints occurred in 90.1% of the patients (109 of 121 patients) overall, but, significantly more often with CRT [96.8% (61/63)], than with H-IGRT [82.8% (48/58)], P=0.022. By structure, constraint violations affected the CTV1 in

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88.9% of CRT vs. 59.6% of H-IGRT cases, P<0.001 (**Table 4**). Constraint violations affected the contralateral breast in 3.2% of CRT vs. 16.9% of H-IGRT cases, P=0.026. The lungs, heart, and LAD constraint violations did not differ significantly.

Table 4. Constraint violations. CTV1 (SDi), breast/chest wall clinical target volume standard deviation of the dose distribution in the structure; CRT, conventional arm; H-IGRT, tomotherapy arm; EQD2, equivalent 2Gy dose with α/β of 3; NA, not assigned.

Structure	Priority	Constraint (EQD2)	CRT (N=64) N violations (%)	H-IGRT (N=59) N violations (%)	Total (N=123) N violations (%)	P
CTV1 (SDi)	12	0.61	56 (88.9%)	34 (59.6%)	90 (75.0%)	< 0.001
N missing			1	2	3	
Contralateral breast	9	2.97	2 (3.2%)	10 (16.9%)	12 (9.9%)	0.026
N missing			2	0	2	
Ipsilateral lung	3	3.55	32 (50.8%)	30 (50.8%)	62 (50.8%)	1.000
N missing			1	0	1	
Contralateral lung	2	1.06	1 (1.6%)	1 (1.7%)	2 (1.6%)	1.000
N missing			1	0	1	
Heart	1	1.52	7 (10.9%)	10 (16.9%)	17 (13.8%)	0.482
N missing			0	0	0	
Left anterior descending artery	NA	6.82	22 (34.9%)	12 (21.1%)	34 (28.3%)	0.139
N missing			1	2	3	

3.3. Outcomes.

Overall and disease-free survival did not differ, P = 0.728 and P=0.907, respectively (**Figure 2**). The estimated 5-year overall survival rates were 95.3% in the CRT arm and 96.6% in the H-IGRT arm. The estimated 5-year disease-free survival rates were 87.5% in the CRT arm and 86.4% in the H-IGRT arm.

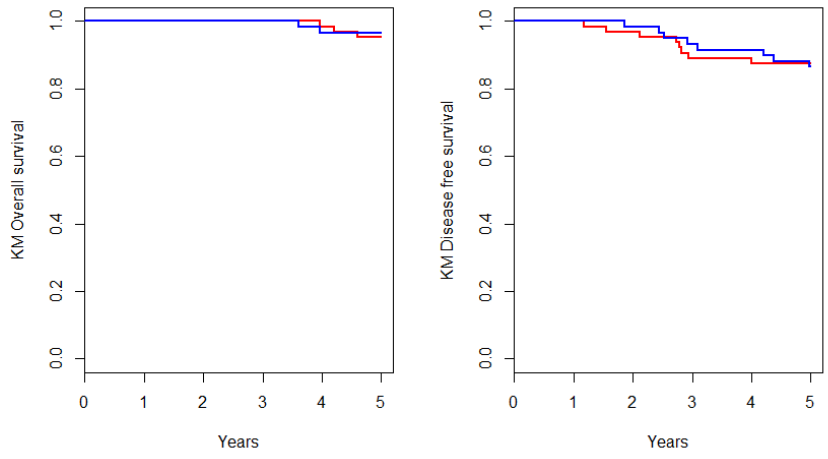

Figure 2. Overall and disease-free survival.

On an ordinal scale, there were no findings of Grade 3 or 4 toxicity except for "RVinv" in 2%–3% of the cases, attributable to the scale change from inverting the RV (**Table 5**). By

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DLCO, 72% (44/61) of the CRT patients had more Grade 1-2 deterioration, as compared with 53% (31/59) of the H-IGRT patients, P = 0.006. By VA, 48% (29/61) of the CRT patients had more Grade 1-2 deterioration, as compared with 29% (17/59) of the H-IGRT patients, P = 0.020. RTOG lung and heart toxicity scores were higher with CRT, P=0.049 and P=0.091, respectively.

Table 5. Ordinal deterioration and toxicity grades relative to baseline.

Evaluation	Grade	CRT	H-IGRT	p
		N = 64	N = 59	
FEV1	0	25 (40%)	22 (37%)	0.872
	1	34 (55%)	33 (56%)	
	2	3 (5%)	4 (7%)	
FVC	0	25 (40%)	24 (41%)	0.346
	1	36 (58%)	31 (53%)	
	2	1 (2%)	4 (7%)	
DLCO	0	17 (28%)	28 (47%)	0.006
	1	42 (69%)	24 (41%)	
	2	2 (3%)	7 (12%)	
VA	0	32 (52%)	42 (71%)	0.020
	1	29 (48%)	15 (25%)	
	2	0 (0%)	2 (3%)	
RVinv	0	58 (98%)	57 (97%)	1.000
	4	1 (2%)	2 (3%)	
TLC	0	30 (50%)	37 (63%)	0.266
	1	28 (47%)	19 (32%)	
	2	2 (3%)	3 (5%)	
LVEF	0	56 (88%)	46 (78%)	0.351
	1	7 (11%)	12 (20%)	
	2	1 (2%)	1 (2%)	
RTOG Lung	0	51 (81%)	44 (76%)	0.049
	1	3 (5%)	10 (17%)	
	2	9 (14%)	4 (7%)	
RTOG Heart	0	58 (92%)	58 (100%)	0.091
	1	4 (6%)	0 (0%)	
	2	1 (2%)	0 (0%)	
Fatigue raw score	0	20 (32%)	19 (32%)	0.986
	1	35 (56%)	32 (54%)	
	2	8 (13%)	8 (14%)	
Dyspnea raw score	0	23 (37%)	25 (42%)	0.517
	1	35 (56%)	27 (46%)	
	2	5 (8%)	7 (12%)	

On a continuous scale using a composite outcome that combined lung tests (FEV1/FVC, DLCO/VA, TLC), echocardiography (LVEF), clinical RTOG grades, and patient's self-assessed fatigue-dyspnea scores over time, lung-heart toxicity was significantly reduced with H-IGRT, log-rank P=0.024. The composite toxicity rate in the CRT arm increased from 6.3% (95% confidence interval (CI): 0.3–12.2%) at 1 year to 18.8% (95% CI: 9.2–28.3%) at 3 years, and to 26.7% (95% CI: 15.8–37.6%) at 5 years. In contrast, H-IGRT increased from 1.7% (95% CI: 0.0–5.0%) at 1 year to 10.2% (95% CI: 2.5–17.9%) at 3 years, and then remain unchanged at 10.2% (95% CI: 2.5–17.9%) at 5 years (**Figure 3**). By Cox

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analysis of the time to alteration, the H-IGRT hazard ratio was 0.36 (95% CI: 0.14–0.91), P=0.030, corresponding to a statistically significant 64% proportional reduction of composite toxicity.

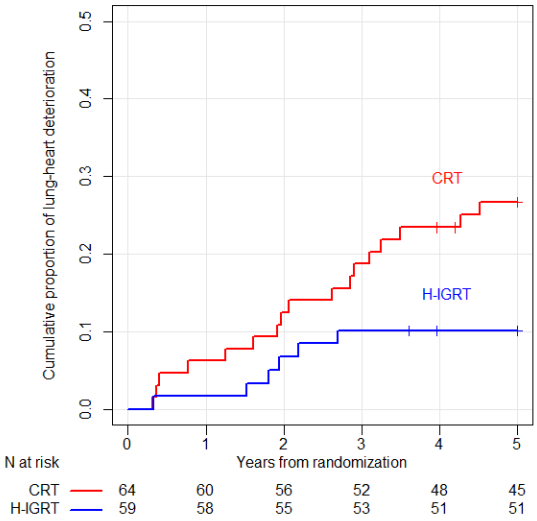

Figure 3. Cumulative composite lung-heart deterioration.

Post-hoc subgroup analysis found no significant interaction (**Figure 4**). The forest plot suggested that H-IGRT might be more advantageous in women <50 years old, in the left or bilateral breast, and after lumpectomy, but the hazard ratios were all < 1, arguing that all subgroups could derive a benefit from H-IGRT.

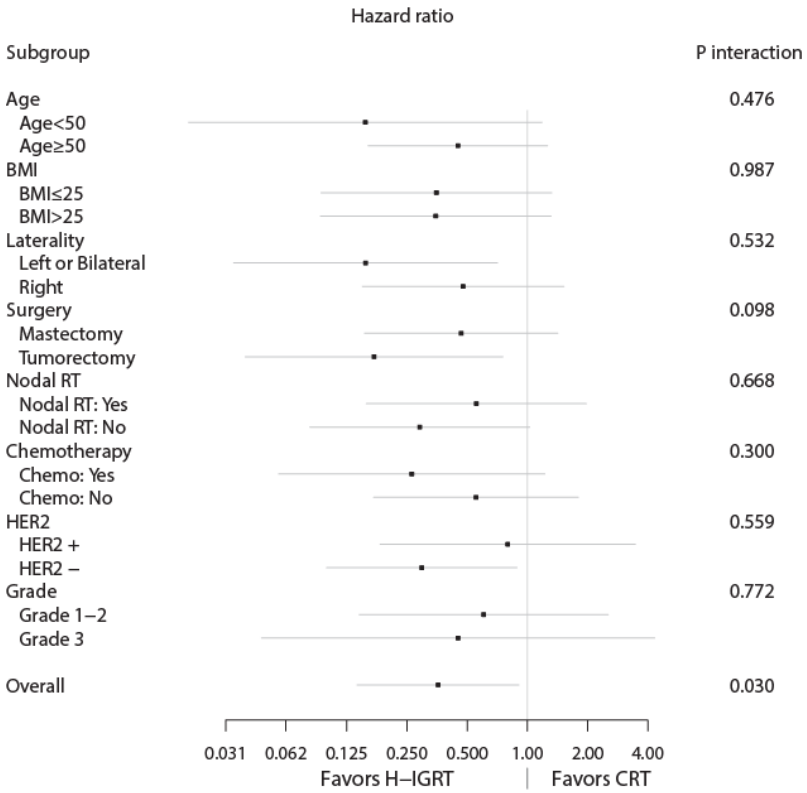

Figure 4. Forest plot of hazard ratios of lung-heart composite toxicity.

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Analyses of outcomes outside the realm of heart or lung constraints also found no significant interaction. The H-IGRT hazard ratio in subgroups defined by compliance were in the range of 0.30–0.40, suggesting a reduction of the risk of lung or heart alteration independent of compliance, possibly attributable to H-IGRT daily volumetric imaging.

4. Discussion

4.1. Positive result, with a caveat.

Numerous studies of irradiation techniques other than partial breast irradiation, including prone, deep inspiration breath hold (DIBH), intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), proton therapy, and combined techniques [30] have theoretically shown that the doses to organs at risk can be reduced [31,32]. These new techniques require a considerable investment in equipment, human resources, and expertise, however, so their availability to patients might be limited [5,33,34]. There is therefore a need to evaluate the real advantage of alternative techniques. The present study is a proof of concept that there is a measurable benefit among patients receiving H-IGRT. The benefit is detectable early and improves with longer follow-up. The reduction in composite lung-heart toxicity in the H-IGRT group compared with controls was 16.5% (10.2% vs. 26.7%) at 5 years (**Figure 3**).

The 26.7% CRT deterioration matches the expected 25% CRT deterioration for all-grade toxicities, but the H-IGRT deterioration was twice the expected 5%. Radiation oncologists and dosimetrists are trained to give precedence to CTV, as reiterated in guidelines [35,36]. In daily practice, staffs review and approve to exceed organ constraints when that ensures a better dose coverage to targets.

4.2. Cardiac damage and radiation pneumonitis.

Cardiac damage and pneumonitis resulting from clinical radiation are rare. The Canadian MA.20 trial of regional nodal irradiation [37] and the EORTC 22922/10925 trial of internal mammary and medial supraclavicular lymph node chain irradiation [38] used contemporary CRT. At a median follow-up of 9.5 years, the Canadian trial reported delayed pneumonitis or fibrosis in seven patients (0.4% of 1820) and delayed cardiac events in 12 (0.7%). At a median follow-up of 15.7 years, the EORTC reported any-grade pulmonary fibrosis in 142 of 4004 patients (3.5%) and cardiac fibrosis in 60 (1.5%).

Two randomized studies comparing techniques reported on heart toxicities [39,40]. The University of Michigan assessed pulmonary and cardiac perfusion and function in 28 patients receiving IMRT with active breath hold vs. 26 patients receiving CRT in free breathing [39]. At one year, there were no significant symptoms, no differences for lung perfusion or function or for LAD perfusion defects. However, six free-breathing CRT patients had >5% LVEF decrease, vs. one IMRT-breath hold patient, P=0.02. The Johns Hopkins study randomized 57 patients to active breathing control versus no breathing control [40]. Out of 43 cases analyzed at 6 months, both groups had significant decrease in perfusion in apical and LAD segments, and active breathing control did not prevent the perfusion defects.

Regarding pulmonary toxicity, no randomized trial other than the University of Michigan compared the effect of technique on lung function. A retrospective series comparing ten proton therapy cases with ten matched photon irradiation cases found significantly increased asymptomatic CT lung density (fibrosis) with proton therapy, P = 0.018 [41]. A 6-month observation reported Grade 1-2 lung toxicity in 2% (3/169) of patients who had received tomotherapy, versus 3% (7/234) of patients who had received CRT [42]. A tomotherapy vs. VMAT comparison reported no pulmonary toxicity among 73 patients at 3 months [43]. A prospective non-randomized study reported Grade 1 pneumonitis in 2/43 patients at 3 months and 0/35 patients at 12 months after DIBH CRT. The study did not mention free-breathing CRT; lung density score was increased at 12 months in 77.1% (27/35) of the patients receiving DIBH vs. 60% (9/15) of the free-breathing patients [44]. A retrospective comparison reported radiographic pulmonary change in 20% of 174 IMRT

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patients vs. 34% of 134 CRT patients, without any Grade 2 pulmonary symptoms [45]. A retrospective study with 14.5 months median follow-up reported Grade 2 radiation pneumonitis in 5% of 437 free-breathing CRT patients, 2.5% of 488 DIBH, 0.7% of 821 VMAT, and 0% of 101 prone patients [46].

Likewise, TomoBreast observed no Grade 3-4 RTOG lung or heart toxicity (**Table 5**). Unfortunately, the scarcity of trials with technique comparators and lung-heart monitoring allows no inference regarding this observation.

4.3. Ten percent deterioration.

Grade 1 toxicity designates mild adverse events [22], which would be questionable as a reason to change therapy. The TTA used a 10% threshold. On a 0-5 grade scale, 10% maps to "Grade 0.5", i.e., very tenuous toxicity. This begs the question, “why 10%?”, and why does it matter?

This choice was made in consideration of the need to avoid the bias pitfall of selecting an optimized cutoff from the data at hand, and the need to apply the cutoff value to various measurements of dissimilar types. From the perspective of dose-response studies on chemical-genotoxic risks to the population, an extra risk of 10% is a standard reporting level for quantal data [47]. Furthermore, 10% response level is at or near the limit of sensitivity in most cancer bioassays and in noncancer bioassays, which is the case with echocardiographic LVEF [18] and pulmonary function tests [48,49]. From the perspective of patient-reported outcomes, many studies applied a threshold change of 10 points on a scale of 0-100 [50]. The 10% threshold is in keeping with a vast body of literature and fitted well with the types of study data.

Ionizing radiation is the most studied medical environmental human-made hazard [51,52]. Unlike drug-therapy, which might depend on absorption and metabolism, the toxicity of radiotherapy is highly predictable. The biological effects of ionizing radiation on molecules and cells are almost instantaneous [53]. In each cell of an irradiated tissue, 1 Gy causes ~100,000 ionizations, damage to >1000 DNA bases, including ~1000 single-strand DNA breaks, and 20–40 double-strand breaks [54]. Up to 20 Gy, the number of DNA double-strand breaks is directly proportional to the dose [55]. Individual radiosensitivity repair and recovery affect the outcomes [56,57], but the dose is the main determinant. With increasing dose, the energy absorbed increases and the probability of repair decreases; essentially, the higher the dose delivered, the more damage will result. Time and time again, whenever an imaging or a functional study has been done, deteriorations have been evident, repeatedly showing that increased irradiation to an organ proportionally increases alterations to that organ [58-61]. The 10% alteration level set in this study is not a goal. We view it as an indicator of damage. The outcome over time will depend on the radiosensitivity of the patients, which we did not measure. However, the study was randomized, so we expect that the distribution of radiosensitivities would not differ markedly, and that the difference in TTA between H-IGRT and CRT will persist over time, possibly with higher toxicity grades seen with CRT.

4.4. Contralateral breast and lung cancers.

A high risk of secondary breast cancer following irradiation has been reported in younger women [62]. This could raise concerns about the impact of H-IGRT dose to the contralateral breast and contralateral lung. At 12 years follow-up, four patients were diagnosed with a new contralateral breast cancer: one (1.7% of 59 patients) 66.5-year-old patient who had received H-IGRT, and three (4.7% of 64 patients) who had received CRT. The patients who developed contralateral breast cancer after CRT were 35.7 years-old (micro-invasive), 54.4 years-old (in-situ carcinoma), and 67.6 years-old (invasive carcinoma). The rate of contralateral invasive breast cancer represents 0.20% per year, comparable to the 0.20% per year rate in the MA.20 trial [37], and half the 0.42% per year rate in the EORTC trial [38].

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Two of the patients, one who had received H-IGRT and one who had received CRT, were diagnosed with a new primary lung cancer, representing a rate of 0.14% per year. That is lower than the 0.34% per year rate of new lung primary cancer seen at 8.9 years median follow-up in 6612 out of 220296 women with primary breast cancer who did not receive radiotherapy [63].

The low new cancer rates in TomoBreast give reasonable assurance that our patients presented no excess breast or lung cancer, compared with the literature.

4.5. Limitations and strengths.

In abstraction, the different fractionation levels between the control and experimental arms can be a confounder. However, a randomized trial monitoring lung function found no difference between hypofractionated CRT and normofractionated CRT [64]. The different sequences of boost (simultaneously integrated in H-IGRT, sequential in CRT) could also be a confounder. Two randomized trials comparing integrated to sequential boost reported that the boost sequence made no difference at 2 and 5 years [65,66]. These trials indicate that fractionation and boost sequence are unlikely to confer a large confounding effect.

Patients and clinicians were not blinded to treatment allocation, and crossovers occurred. Nevertheless, results were not affected when analyses were done by actual treatment. The trial was not designed to test for subgroup effects: the present report cannot recommend which subgroup of breast cancer patients should be given priority. The study population is heterogeneous with imbalances in patients' characteristics. The trial included patients with different surgeries and/or chemotherapy treatment protocols, with or without nodal irradiation. Dose constraint compliance was not strict.

Medical imaging monitoring was not implemented. Echocardiographic strain, left ventricular mass, left diastolic function and right ventricular function can be indicators of cardiotoxicity [67,68]. However, circulating biomarkers might be more sensitive predictors of toxicity [18]. These were not assessed.

Analyses proceeded under the assumption that missing data were random. We found no evidence of non-randomness, but the possibility cannot be excluded. Fewer echocardiographies were done from the middle of year 3 and thereafter, due to the unavailability of a cardiologist; this was unrelated to patients' status (**Figure A1**).

IGRT was implemented with the tomotherapy system. Arguably comparable or even better dose distribution might be obtained with other techniques. However, comparative clinical trials reporting on lung-heart toxicity are too scarce to establish the superiority of any technique. Future studies are needed to identify the most cost-effective way to reduce lung-heart doses, and to evaluate alternative treatment paradigms such as partial breast irradiation or intraoperative radiation therapy [69,70].

Counterbalancing limitations, TomoBreast shows, in a randomized setting that toxicity can be detected early and can be significantly reduced. The same short course fractionation schedule appears feasible, with or without chemotherapy, boost, or nodal irradiation. Other strong points include the management of the patients by the same team, the integration within a normal workflow, the non-restrictive selection criteria indicating a good likelihood of translating the trial's experience to daily practice, and the large number of lung and heart function assessments over time, providing a large body of quantitative data that will contribute to knowledge in the management of breast cancer. The trial's compact design allowed it to be conducted with a minimal number of patients.

5. Conclusions

Image-guided radiation therapy improved the combined lung-heart outcomes, preserving cardiac-pulmonary function, reducing clinical toxicity and maintaining patient's quality of life, with the added advantage of a more convenient short fractionation schedule. The TomoBreast trial is a proof-of-concept that advanced radiation techniques might be considered in the adjuvant therapy of breast cancer.

 doi:10.20944/preprints202212.0214.v1

Supplementary Materials: The TomoBreast trial protocol and procedure book can be downloaded at: www.mdpi.com/xxx/s1.

Author Contributions: Conceptualization, G.S. and V.V.H.; methodology, E.C.J. and V.V.H.; software, O.G., V.V.H.; validation, E.C.J., H.V.P., N.P.N. and M.D.R.; formal analysis, V.V.H.; investigation, H.V.P.; resources, G.S. and M.D.R.; data curation, H.V.P., N.A., B.H., M.D.R. and V.V.H.; writing—original draft preparation, H.V.P., C.V., N.P.N. and V.V.H.; writing—review and editing, all authors; visualization, O.G. and V.V.H.; supervision, G.S. and M.D.R.; project administration, N.A., G.S. and M.D.R.; funding acquisition, V.V.H., G.S. and M.D.R. All authors have read and agreed to the published version of the manuscript.

Funding: The TomoBreast trial received funding from the Foundation against Cancer / Stichting tegen Kanker, grant number SCIE2006-30. Funding did not cover data analyses and reporting.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of UNIVERSITAIR ZIEKENHUIS BRUSSEL (protocol dd. 27/06/2006 – B.U.N. B14320071552, date of approval 29 March 2007).

Informed Consent Statement: Written informed consent was obtained from all patients involved in the study.

Data Availability Statement: Data will be made available on Zenodo.org.

Acknowledgments: The study owes acknowledgment and gratitude to many. Dirk Kerkhove contributed to the acquisition of the echocardiographic left ventricular ejection fraction data. The pulmonary function test data were provided by the pneumology department of the Universitair Ziekenhuis Brussel and other hospitals of the Brussels area. Harijati Versmessen handled the first 3 years follow-up data management. Truus Reynders did the treatment planning. Claudia S. Copeland provided valuable feedback and editorial advice regarding scientific English for communication of the results. Most importantly, however, the study is indebted to all the patients who participated, to whom we are deeply grateful. Starting the clinical trial was made possible thanks to the partial grant SCIE2006-30 from the Foundation against Cancer / Stichting tegen Kanker.

Conflicts of Interest: G.S. and M.D.R. declare: The Radiation Oncology department of the Universitair Ziekenhuis Brussel under the direction of Guy Storme and Mark De Ridder had a research agreement with Tomotherapy Inc., Madison, WI, USA, unrelated to the present study. H.V.P., E.C.J., O.G., N.A., B.H., C.V., N.P.N. and V.V.H. declare no conflict of interest.

Appendix A. Patterns of available or missing data.

Lung function baseline data was missing in 2 (1.6%) patients, echocardiography in 12 (9.8%) patients, and fatigue-dyspnea assessment in 1 (0.8%) patient (**Table A1**). RTOG scores were not recorded at baseline. We assumed that patients having not yet received any radiation should not have any RTOG sign of lung or heart toxicity.

Table A1. Baseline data availability.

	Baseline available	CRT	H-IGRT	p
		n (%)	n (%)	
Lung function	Yes	62 (97%)	59 (100%)	0.512
	No	2 (3%)	0 (0%)	
Echocardiography	Yes	56 (88%)	55 (93%)	0.445
	No	8 (12%)	4 (7%)	
Fatigue-dyspnea	Yes	63 (98%)	59 (100%)	1.000
	No	1 (2%)	0 (0%)	

We define waves as the nominal periods of the trial's planned assessment: baseline, 1-3 months post-therapy, then once yearly. There were less than 4 waves of lung function assessment in 8 (6.5%), echocardiography in 16 (13.0%), RTOG scoring in 8 (6.5%), and

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QLQ-C30 in 7 (5.7%) patients (**Table A2**). **Figure A1** plots the times at which the measurements were done.

Table A2. Available number of follow-up waves. RTOG, Radiation Therapy Oncology Group.

	Number of waves	CRT	H-IGRT	p
		N = 64	N = 59	
		N (%)	N (%)	
Lung function	<4	5 (8%)	3 (5%)	0.767
	4	6 (9%)	7 (12%)	
	>4	53 (83%)	49 (83%)	
Echocardiography	<4	9 (14%)	7 (12%)	0.530
	4	25 (39%)	29 (49%)	
	>4	30 (47%)	23 (39%)	
RTOG scoring	<4	4 (6%)	4 (7%)	0.765
	4	13 (20%)	9 (15%)	
	>4	47 (73%)	46 (78%)	
Fatigue-dyspnea	<4	4 (6%)	3 (5%)	0.228
	4	3 (5%)	0 (0%)	
	>4	57 (89%)	56 (95%)	

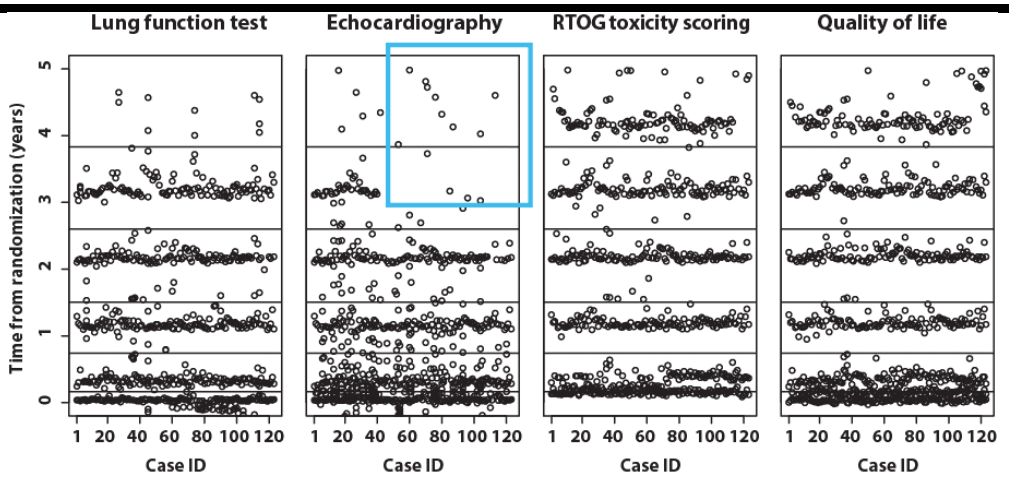

Figure A1. Distribution of measurement waves. RTOG, Radiation Therapy Oncology Group. X-axis, case ID, study number assigned to patients. Y-axis, timing of the assessments. One dot represents one measurement in a patient at the time projected on the y-axis. The blue square highlights discontinued echocardiography assessments.

Overall, there was a total of 2,192 distinct appointments/time-points of data collection for the 123 patients. The number of lung function time-points in the two arms was 659, echocardiography 712, RTOG 685, and fatigue-dyspnea 811 (**Table A3**).

Table A3. Available individual patient's time-point data. FEV1, forced expiratory volume in 1 s. FVC, forced vital capacity. FEFV, ratio FEV1/FVC. DLCO: diffusing or transfer capacity of the lungs for carbon monoxide. VA, alveolar volume at total lung capacity. KCO, ratio DLCO/VA. RV, residual volume. TLC, total lung capacity. LVEF, left ventricular ejection fraction. RTOG, Radiation Therapy Oncology Group. FA, fatigue score. DY, dyspnea score.

Available individual time point data	CRT	H-IGRT	p
Total time points	1131	1061	

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Lung function				
	FEV1, FVC, FEFV	338	321	0.887
	DLCO, VA, KCO	314	301	0.789
	RV	310	302	0.615
	TLC	312	302	0.682
Echocardiography				
	LVEF continuous	292	283	0.685
	LVEF ordinal	357	355	0.368
Clinical evaluation				
	RTOG grades	354	331	0.995
Fatigue-dyspnea				
	FA, DY	420	391	0.926

The missing/available data were quantitatively well balanced between the two randomization arms (**Tables A1-A3**).

The **Figure A1** shows that the measurement timings matched the trial's per protocol scheduling of exams, although with substantial variability. The waves were concordant across the items, except for echocardiography in which the data points were more sparsely distributed from the middle of year 3 and thereafter.

Appendix B. Imputations.

The missing lung function tests, RTOG, and QLQ-C30 scores were not imputed, on consideration that the percentage of missing data was small, and the number of data points was large.

The missing echocardiography LVEF were imputed on consideration of the 9.8% missing baseline and the truncated follow-up by mid-3 years (**Figure A1**). The imputations were done in 3 steps using expectation-maximization with bootstrapping [29].

Step 1.

Temporarily impute all lung function tests in a multivariate model that include treatment allocation, smoking status and pack years, surgery, chemotherapy type and schedule, trastuzumab, breast laterality, tumor size, lymph node ratio, boost indicator, nodal irradiation indicator, and radiation treatment planning indicators of lung, heart, target doses and volumes.

Step 2.

There were 244 echocardiography data points with ancillary echocardiographic measurements of aortic diameter, atrio-ventricular cusp, systolic and diastolic ventricular wall thickness, ventricular sizes and mass, Teichholz measures, A2, A4, BP echo mode measurements, mitral valve, pulmonary valve and tricuspid velocity. These variables were used together with patients' weight, height, age, and fatigue-dyspnea scores to model the missing LVEF among these 244 echo data points.

Step 3.

The imputed data from step 1 and step 2 were assembled to compute the remaining partially missing LVEF (ordinal LVEF available but not the quantitative measurements) and the fully missing LVEF. Imputation of the ordinal LVEF that were reported as "50-60%" were imputed by assigning a 95% confidence that the imputed value would be in the 50.05– 59.95 range. Ordinal LVEF that were reported as ">60%" were imputed with 95% confidence that the imputed value would be in the 60.05–74.00 range. The latter 74.00 as upper imputation boundary for the ">60%" ordinal was based on the consideration that LVEF population distribution characteristics from the literature [71,72 Chambers JC,

Kooner JS, Senior R. Population-based reference values for 3D echocardiographic ,73 et al. Cardiac morphology and function reference values derived from a large subset of healthy young Caucasian] match closely the TomoBreast patients LVEF normal distribution (**Figure A2**). Since 95% of normal values would be expected to be within mean ± 2 SD, applying the observed TomoBreast LVEF mean = 63.15, SD = 5.45 gave 63.15 + 2*5.45, rounded to 74.00 as the upper bound.

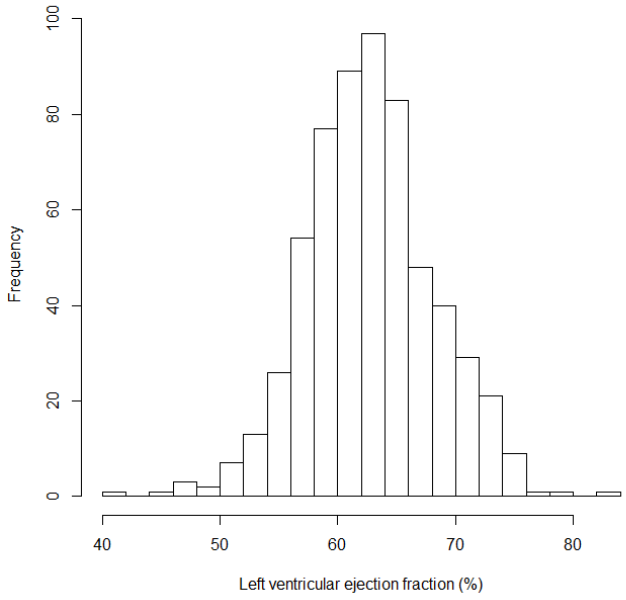

Figure A2. Histogram distribution of the baseline left ventricular ejection fraction of the TomoBreast patients.

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