



Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Original Article

Volume matters: Breast induration is associated with irradiated breast volume in the Danish Breast Cancer Group phase III randomized Partial Breast Irradiation trial

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ARTICLE INFO

Article history:

Received 28 July 2022

Received in revised form 22 September 2022

Accepted 29 September 2022

Available online xxx

Keywords:

Partial breast irradiation
Dose volume relationship
Randomised trial
Quality
Assurance

ABSTRACT

Purpose: The relation between breast induration grade 2–3 at 3 years after radiation therapy and irradiated breast volume was investigated for patients in the Danish Breast Cancer Group (DBCG) Partial Breast Irradiation (PBI) trial. **METHODS** Treatment plan data was obtained from the Danish radiotherapy plan database. Dosimetric parameters for breast and organs at risk were determined. Breast induration data was obtained from the DBCG database. The volume of the whole breast (CTVp_breast) treated to various dose levels was determined for treatment plans in both arms. Logistic regression was used to assess the frequency of induration on breast volume irradiated to ≥ 40 Gy. **RESULTS** PBI and WBI was given to 433 and 432 patients, respectively. Median and interquartile ranges (IQR) for CTVp_breast were 710 mL (467–963 mL; PBI) and 666 mL (443–1012 mL; WBI) ($p = 0.98$). Median and IQR for CTVp_breast treated to ≥ 40 Gy was 24.9% (18.6–32.6%; PBI) and 59.8% (53.6–68.5%; WBI). Grade 2–3 induration was observed in 5% (PBI) and 10% (WBI) of the patients. A dose–response relationship was established between irradiated breast volume and frequency of breast induration. From the model, 5% and 10% risks of breast induration were observed for ≥ 40 Gy delivered to CTVp_breast volumes of 177 mL (95%CI, 94–260 mL) and 426 mL (95%CI, 286–567 mL), respectively. **CONCLUSION** The frequency of breast induration increased significantly with increasing irradiated breast volume, strongly favouring small volumes and PBI. Thus, treated breast volume – not the breast size itself – is the risk factor for induration. This is the first report directly linking the 40 Gy irradiated breast volume to breast induration.

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Radiation therapy (RT) of the whole breast used to be the standard care after breast-conserving surgery and was shown to significantly lower the risk of local, regional and distant failure and improve overall survival [1]. However, for patients with a relatively low-risk breast cancer partial breast irradiation (PBI) has gained more interest to reduce adverse events by irradiating smaller volumes [2] without a higher risk of local recurrence.

In 2009 the Danish Breast Cancer Group (DBCG) initiated two randomized controlled trials with moderately hypofractionated external-beam RT of 40 Gy in 15 fractions (fr) to patients operated

with breast-conservation for node-negative breast cancer with an indication for whole breast irradiation (WBI): the DBCG HYPO trial [3] and the DBCG PBI trial [4]. The PBI trial was similar to two of the arms in the IMPORT LOW trial, i.e., WBI versus PBI with 40 Gy in 15 fr [5]. The primary endpoint in the DBCG PBI trial was 3-year grade 2–3 breast induration and the rate of induration at 3 years was 9.7% (95% CI 7.0 to 12.9) for WBI and 5.1% (95% CI 3.2 to 7.6) for PBI [4]. Breast size was significantly associated with induration with a 3-year incidence of 13% (WBI) and 6% (PBI) for large size versus 6% (WBI) and 5% (PBI) for small size, whereas only few loco-regional recurrences were detected and unrelated to PBI, showing less late effects for patients treated with PBI without compromising the local control rate [4]. Other studies have also reported more breast induration in large-breasted patients, thus

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indicating an association between breast size and induration [6,7]. However, depending on the location of the tumour in the breast, PBI of large-breasted patients may result in a small irradiated volume not reflected in breast size. Therefore, it may be more accurate to report the risk of induration in relation to irradiated breast volume. This study investigated the frequency of breast induration grade 2–3 in the DBCG PBI trial at 3 years after RT versus the breast volume irradiated to ≥ 40 Gy.

Materials and methods

Patients ≥ 60 years operated with breast-conservation for early unilateral, unifocal, estrogen receptor (ER) positive $\geq 1\%$, human epidermal growth factor receptor 2 (HER-2) negative, grade 1–2, non-lobular breast cancer < 21 mm (International Union Against Cancer stage pT1 pN0 M0) with a surgical margin of minimum 2 mm, requiring RT to the residual breast were eligible for inclusion in the DBCG PBI trial. Stratification factors were use of endocrine therapy (yes/no) and institution. The patients were randomized to WBI versus PBI with 40 Gy/15fr/3weeks. A written informed consent according to Good Clinical Practice guidelines and local and national rules of participating institutions was obtained. The trial was approved by the Ethics Committees of all participating centres ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT00892814).

Treatment preparation was according to DBCG RT guidelines and details were reported in Offersen et al. [4]. In short, surgical clips localized the tumour bed. For the RT planning, the patient was positioned supine in the institutional standard fixation allowing a daily reproducibility of approximately 5 mm. The institutional guideline for respiratory gating was followed. The clinical target volume for the whole breast (CTVp_{breast}) was delineated following the guidelines of DBCG and ESTRO [8,9]. The partial breast volume (CTVp_{PB}) was based on delineation of the tumour bed (guided by clips, seroma and pre-operative imaging). From the tumour bed volume, the CTVp_{PB} was generated by adding a 15 mm margin (cropped inside the whole breast volume). The planning target volume margin depended on institutional guidelines (in most cases 5 mm), and was cropped 5 mm inside the skin surface. The RT was based on a 3D conformal technique with two tangential fields and forward planned field-in-field segments for a homogeneous dose distribution. The CTV was to be covered with doses in the range 95–105%, however an absolute volume of up to 2 mL of the CTV could receive a dose in the range 105–110% of the prescription dose ($V_{42\text{Gy}_{\text{breast}}} \leq 2$ mL). In PBI treatment plans it was the aim that less than 50% of the CTVp_{breast} was irradiated to ≥ 40 Gy ($V_{40\text{Gy}_{\text{breast}}} < 50\%$). Dose constraints for lung, heart and left anterior descending coronary artery (LADCA) were $V_{17\text{Gy}_{\text{lung}}} \leq 25\%$, $V_{35\text{Gy}_{\text{heart}}} \leq 5\%$, $V_{17\text{Gy}_{\text{heart}}} \leq 10\%$, $D_{\text{max}_{\text{LADCA}}} \leq 17$ Gy. Regional node RT was not allowed. During the accrual

period, RT plans for the patients were stored in the Danish national RT data bank (DcmCollab) [10].

All patients were invited for morbidity evaluation and breast photos at baseline and at follow up visits yearly 1–5, and at 10 years after RT. The primary endpoint was grade 2–3 breast induration reported as cumulative incidence at 3 years and crude incidence rates at 3 and 5 years after RT. For this study, the reported endpoint crude incidence of grade 2–3 breast induration at 3 years after RT was used. However, sensitivity analyses were performed using cumulative incidence at 3 years and crude incidence rate at 5 years as endpoints [4].

Information about treatment arm and breast induration was obtained from the DBCG database. Volumes of the delineated structures and dose-volume histograms were collected from DcmCollab, allowing determination of the volume of structures irradiated to various dose levels in each treatment plan.

Patient and treatment characteristics were compared using Chi-squared test (categorical data) and Wilcoxon rank-sum test or Students *t*-test (continuous data). The model was developed on individual patient data using logistic regression with log-transformed volumes:

$$p(\text{induration}) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 \ln(\text{volume}))}}$$

β_0 and β_1 are reported with 95% CI. For visualization, patients were binned in quintiles for each treatment arm and actual incidence rates for each group were plotted with the model. C-statistics was used to compare models based on different volume parameters. Wald test was used to compare coefficients from two models in sensitivity analysis on different endpoints. All analyses were performed using Stata 17.0 (StataCorp LLC, Texas, USA).

Results

Between May 2009 and March 2016, 880 patients from five Danish centres were recruited and of those 865 were eligible [4]. The clinical study on WBI versus PBI was analysed as ‘intention-to-treat’ with 434 patients assigned to WBI (4 treated with PBI) and 431 patients assigned to PBI (2 treated with WBI) [4]. The present analysis was performed ‘by-protocol’ and thus includes 432 patients receiving WBI and 433 receiving PBI and treatment plans were available for analysis from all patients but one (Table 1). The patient, tumor and outcome characteristics were balanced between the PBI and WBI cohorts except for the incidence of grade 2–3 induration (Table 1 and Supplementary Fig. 1). A more than fivefold increase in median volume from tumour bed to CTVp_{PB} and also from CTVp_{PB} to CTVp_{breast} was observed for both treatment arms. As expected, $V_{40\text{Gy}_{\text{breast}}}$ was larger for WBI than PBI (Fig. 1). For PBI, a much smaller volume of the breast was treated, thus median 24.9% (IQR: 18.6–32.6%) of the breast volume was

Table 1

Patient characteristics and grade 2–3 breast induration 3 years after radiation therapy. The values are given as median values with interquartile ranges or numbers with percentage of total numbers.

	Partial breast irradiation (PBI) n = 433	Whole breast irradiation (WBI) n = 432	p-value
Age [years], n = 865	66 (63–69)	66 (64–69)	0.34
Laterality, n = 865			
Left	230 (53%)	210 (49%)	0.18
Right	203 (47%)	222 (51%)	
Breast volume (CTVp _{breast}) [mL], n = 865	710 (467–963)	666 (443–1012)	0.98
Partial breast volume (CTVp _{PB}) [mL], n = 842	122 (84–180)	121 (86–175)	0.76
Tumour bed volume [mL], n = 808	22 (14–39)	22 (13–40)	0.79
Breast induration at 3 years follow up [n], n = 743			
Grade 0/1	350 (95%)	336 (90%)	0.005
Grade 2/3	18 (5%)	39 (10%)	

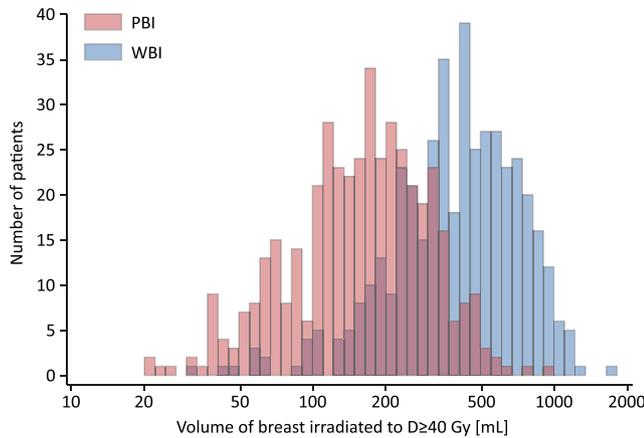


Fig. 1. Distribution of volume of breast irradiated to $D \geq 40$ Gy.

covered with ≥ 40 Gy (Table 2 and Supplementary Fig. 2). Table 2 and Supplementary Fig. 2 also show the percentages of breast volumes treated to 38 Gy ($V_{95\%_breast}$), the absolute breast volume irradiated to ≥ 42 Gy, the number of treatment plans with $V_{42Gy_breast} > 2$ mL, and the hot spot dose reported as the dose to the 1% of the CTV_{p_breast} covered with highest doses ($D_{1\%}$). For most patients $D_{1\%}$ were less than 42 Gy and no treatment plan had an absolute maximum dose (D_{max}) above 44 Gy (110%); the maximum D_{max} was 43.3 Gy and 43.9 Gy in the PBI and WBI arms, respectively (Supplementary Fig. 2). Data on lung, heart and LADCA doses are given in Table 2 and Supplementary Fig. 2.

Breast induration scores at 3 years after RT were available for 743 (86%) of the patients [4] and were significantly different between treatment arms; 18/368 (5%) patients in the PBI arm had grade 2–3 breast induration versus 39/375 (10%) in the WBI arm, $p = 0.005$ (Table 1).

The frequency of induration versus V_{40Gy_breast} is shown in Fig. 2 demonstrating an increasing frequency of induration with increasing irradiating breast volume. The model parameters are: $\beta_0 = -7.359$ (95% CI, -9.753 to -4.965) and $\beta_1 = 0.853$ (95% CI, 0.449 – 1.256). According to the model, it is estimated that the risk of breast induration is 5% and 10% when the 40 Gy treated volume is 177 mL (95% CI, 94–260) and 426 mL (95% CI, 286–567), respectively. The model presented in Fig. 2 is based on crude incidence rates of grade 2–3 breast induration at 3 years after RT. In a sensitivity analysis (Supplementary Fig. 3), the model is compared with models based on crude incidence rates at 5 years after RT and on cumulative incidence at 3 years after RT [4]. These models are not statistically different from the model presented in Fig. 2.

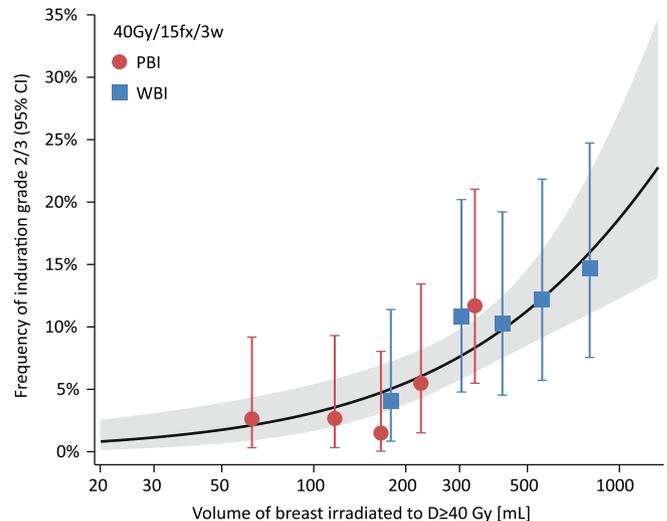


Fig. 2. Frequency of grade 2–3 induration at 3 years after RT versus volume of breast irradiated to $D \geq 40$ Gy. Model is based on individual data and presented with 95% CI (grey area). For each treatment arm, patients are binned in quintiles and actual incidence rates in each group are presented for comparison.

For the same volume of breast irradiated above a given dose, the frequency of grade 2–3 breast induration increased for increasing irradiation dose. However, a close similarity of the relation was found for irradiation doses in the range 2 Gy to 40 Gy reflecting the tangential field technique used in the study (Fig. 3A and 3B).

The irradiated breast volume is correlated with the total breast volume, and with the strongest correlation for WBI (Supplementary Fig. 4A). When risk of induration is modelled using total breast volume, either with WBI, PBI, or combined, the models are weak (Supplementary Fig. 4A). The models are stronger and comparable when risk of induration is modelled using irradiated volume and stratified in WBI versus PBI even though the ranges of volumes are only partly overlapping (Supplementary Fig. 4B). Thus, the strongest model is obtained with irradiated volume in the combined cohort.

For comparison with a previous study [11], models with irradiated volumes are compared with models based on the $V_{95}/\text{whole-breast volume ratio}$ (V_{38Gy_breast} [%]) in patients treated with PBI vs WBI (Supplementary Fig. 5).

Discussion

Based on the treatment plans from the eligible patients in the DBCG PBI trial and patient morbidity scores, a dose response model

Table 2

Dosimetric results listed as median values with interquartile ranges, mean values with 95% CIs, or numbers with percentage of total numbers.

	Partial breast irradiation (PBI) n = 433	Whole breast irradiation (WBI) n = 432	p-value
V_{38Gy_breast} [%, median w. IQR], n = 864	48.6 (39.5–57.9)	96.6 (95.1–98.0)	<0.0001
V_{40Gy_breast} [%, median w. IQR], n = 864	24.9 (18.6–32.6)	59.8 (53.6–68.5)	<0.0001
V_{42Gy_breast} [mL, median w. IQR], n = 864	0.00 (0.00–0.09)	0.02 (0.00–1.31)	<0.0001
Number of pts with $V_{42Gy_breast} > 2$ mL [n], n = 864	41 (9%)	85 (20%)	<0.0001
$D_{1\%}$ [Gy, mean w. 95% CI], n = 864	41.4 (41.3–41.4)	41.6 (41.6–41.7)	<0.0001
V_{17Gy_lung} [%, median w. IQR], n = 864	2.2 (1.2–3.4)	14.7 (11.4–18.1)	<0.0001
V_{17Gy_heart} (left-breast) [%, median w. IQR], n = 437	0.00 (0.00–0.00)	0.10 (0.00–0.54)	<0.0001
Number of pts with $V_{17Gy_heart} > 0\%$ [n], n = 437	39 (9%)	151 (37%)	<0.0001
V_{35Gy_heart} (left-breast) [%, median w. IQR], n = 437	0.00 (0.00–0.00)	0.00 (0.00–0.00)	<0.0001
Number of pts with $V_{35Gy_heart} > 0\%$ [n], n = 437	8 (2%)	41 (10%)	<0.0001
D_{max_LADCA} (left-breast) [Gy, median w. IQR], n = 434	2.3 (1.3–4.7)	11.0 (8.0–15.3)	<0.0001
Number of pts with $D_{max_LADCA} > 17$ Gy [n], n = 434	7 (3.1%)	38 (16.8%)	<0.0001
Mean heart dose, MHD [Gy, median w. IQR], n = 437	0.4 (0.3–0.6)	1.2 (1.0–1.6)	<0.0001

Breast induration vs irradiated breast volume

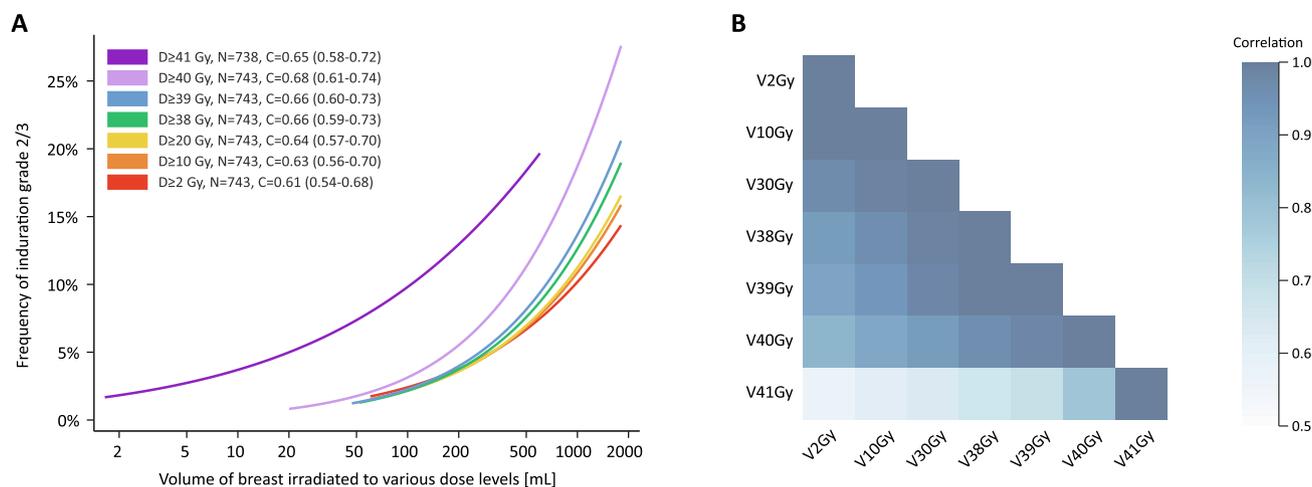


Fig. 3. Frequency of grade 2–3 induration at 3 years after RT versus volume of breast irradiated to various dose levels with C-statistics to evaluate goodness-of-fit (A). Correlations between the various dose level models (B).

for the relation between breast volume irradiated to ≥ 40 Gy and frequency of breast induration was presented. To our knowledge, this is the first report directly linking a ≥ 40 Gy irradiated breast volume to breast induration.

It was found that the frequency of breast induration increased with the volume of breast tissue irradiated to ≥ 40 Gy, thereby favouring the use of PBI especially for patients with large breasts. The frequency of induration was also modelled for various other breast doses showing a closer correlation for the models for breast volumes in the range 2 Gy to 40 Gy compared to the model for $V_{41\text{Gy}}$ due to the nature of the tangential field technique used in the trial. The field technique was based on two tangential fields with forward planned field-in-field segments to obtain a homogeneous dose in the treated volume. In agreement with earlier studies [7,15], it was possible with this rather simple technique to reduce hot spots in the irradiated breast volume to very low levels with median $D_{1\%}$ values of 41.4 Gy (103.5%) and 41.6 Gy (104%) in the PBI and WBI arms, respectively, and no treatment plans had a D_{max} above 110% of the prescription dose [8,12]. The strict dose constraint of $V_{42\text{Gy, breast}} \leq 2$ mL in the study, resulted in a violation of this constraint in only 9% (PBI) and 20% (WBI) of the treatment plans, respectively (Table 2 and Supplementary Fig. 2), and therefore it was not possible to obtain a model with sufficient statistical basis for $V_{42\text{Gy}}$.

Irrespective of treated volume, the treatment plans in this trial have a homogeneity comparable with inverse planned whole breast plans (IMRT or VMAT) [13,14]. The doses to lung and heart were low and a high compliance with the protocol-specified constraints was found. However, also for the organs at risk statistically significant lower doses were observed in the PBI plans, thus favouring PBI over WBI.

The development of this model has merely been possible because of the prospective collection of all treatment plans from the trial in DcmCollab [10]. Without this national data bank, the collection of the necessary dosimetric parameters would have been very time consuming and error-prone [15,16].

The radiation dose-volume effect for the breast has been investigated in a number of studies, and large breast size has been identified as a risk factor for late adverse effects after breast RT even after the advent of 3D conformal RT and IMRT [6,17,18]. Goldsmith et al. concluded based on patients treated in the FAST trial that large-breasted women were more likely than others to suffer adverse effects after RT even when 3D dosimetry was optimised and thereby minimising dose inhomogeneities [19]. Based on the

data presented here, it may be concluded that it is not the breast size itself but rather the volume of breast tissue irradiated to a given dose, that is the risk factor for radiation-induced morbidity.

The DBCG PBI trial was similar to two of the arms in the IMPORT LOW trial, and patients were treated with 40 Gy in 15 fr/3 weeks for both PBI and WBI [5]. In the RAPID trial, patients were randomised to accelerated PBI (APBI) with 38.5 Gy in 10 fr/1 week versus WBI with either 42.5 Gy in 16 fr/3 weeks or 50 Gy in 25 fr/5 weeks. In the WBI arm boost was permitted [20]. More late effects were found in the group of patients treated with APBI compared to WBI. An exploratory analysis showed that a $V_{95/\text{whole breast volume}} < 0.15$ was associated with a lower risk of cosmetic deterioration [11]. Due to the use of two tangential fields for PBI in the DBCG PBI trial rather than a technique with 3–5 non-coplanar fields as used in the RAPID trial, no PBI patients in the study presented here had a $V_{95/\text{whole breast volume}}$ below 0.15 (Supplementary Fig. 2A), however, the $V_{95/\text{whole breast volume}}$ on a continuous scale was correlated with the frequency of breast induration (Supplementary Fig. 5). In the APBI-IMRT-Florence Trial, the patients treated with APBI (30 Gy in 5 fr/2 weeks) had less late toxicity than the patients treated with WBI (50 Gy in 25 fr/5 weeks plus a 10 Gy boost) [21]. In the randomised trial reported by Strnad et al, all patients in the APBI arm were treated with brachytherapy whereas a total dose of 50–50.4 Gy in 25–28 fr was used in the WBI arm [22]. They found that late toxicity profiles and cosmetic results were similar in the two treatment arms [23]. In partial breast brachytherapy the irradiated volume is smaller than in external beam irradiation. However, the NSABP B39/RTOG 0413 trial, where patients were randomised to PBI administered as either external beam radiation with 38.5 Gy in 10 fr/1 week or 34 Gy with brachytherapy versus WBI with 50 Gy in 25 fr/5 weeks, did not find the same worse late effect pattern for APBI as found in the RAPID trial although only one fourth of the APBI patients were treated with brachytherapy [24]. The delivery of 38.5 Gy in 10 fr corresponds to 53 Gy in 2-Gy fractions whereas 40 Gy in 15 fr corresponds to a dose of 46 Gy 2-Gy fractions [25]. Thus, the fractionation in the APBI studies correspond more closely to 50 Gy in 25 fr than 40 Gy in 15 fr.

In parallel to the DBCG PBI trial, the DBCG also conducted the DBCG HYPO trial during 2009–2014 [3]. That trial randomized 1880 node-negative early breast cancer patients treated with WBI to 40 Gy in 15 fr versus 50 Gy in 25 fr (sequential boost optional). Treatment plans from the 1550 Danish patients in the trial are collected into the DcmCollab [10], and a validation of

our dose response model is planned to also include 50 Gy in 25 fr and sequential boost which allows for a comparison with the result from the boost-no boost trial [26].

A limitation of the model is that only patients 60 years or older were eligible for the trial and the model is thus restricted to prediction of the risk of induration for elderly patients. Therefore, any age dependence in the adverse effects of radiotherapy was not considered [27]. This may also be further investigated with the DBCG HYPO data where patients 41 years or older were eligible for the trial.

The one-week schedule tested in the FAST-forward trial is biologically more equivalent with 40 Gy in 15 fr [28]. Instead of reducing the treatment course further from 40 Gy, and considering the very low recurrence rates using PBI in selected patients, the DBCG has decided to go in another direction for this patient group by offering the patients inclusion in the DBCG Natural study ([ClinicalTrials.gov Identifier: NCT03646955](https://clinicaltrials.gov/Identifier/NCT03646955)), where patients are randomised to either 40 Gy in 15 fr PBI or no RT. The primary endpoint is 5-year local recurrence risk aiming to be max 4% in patients not irradiated.

In conclusion, no differences in tumour bed, partial and whole breast volumes were observed between the patients in the two arms of the DBCG PBI trial, but the irradiated breast volume was significantly smaller with PBI. The frequency of breast induration increased significantly with increasing irradiated breast volume, showing that it is not the breast size itself but rather the volume of breast tissue irradiated to a given dose, that is the risk factor for radiation-induced morbidity. This is the first report directly linking a 40 Gy irradiated breast volume to breast induration, and the dose response relationship will be further validated in the DBCG HYPO trial.

Acknowledgement

We thank the patients who participated in this trial and the staff at participating centres and in the DBCG office.

Disclaimer

The authors have no conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2022.09.024>.

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