Radiotherapy and Oncology 131 (2019) 186–191

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Minimum breast distance largely explains individual variability in doses to contralateral breast from breast-cancer radiotherapy

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ARTICLE INFO

Article history:
Received 23 February 2018
Received in revised form 27 August 2018
Accepted 27 August 2018
Available online 18 September 2018

Keywords:
Breast-cancer radiotherapy
Contralateral breast
Individual variability
Anatomic parameters

ABSTRACT

Purpose: To provide personalized estimates of doses to contralateral breast (CB) from breast-cancer radiotherapy.
Methods: Whole-breast irradiations using 3D conformal, intensity-modulated and hybrid techniques with 50.4 Gy prescribed dose were planned for 128 breast-cancer patients. From their CT images, 17 anatomic measures were assessed and tested by model fitting as predictors for CB dose–volume characteristics.
Results: Multi-field intensity-modulated radiotherapy (IMRT) yielded mean CB doses of 0.8–7.1 Gy, with no correlation to the studied anatomic parameters. Tangential whole-breast irradiation led to much lower mean CB doses, 0.2–1.6 Gy. About 60% of this inter-patient variability was explained by individual variations in a single anatomic measure, the minimum breast distance (MBD), defined as the CB distance from the tangent to the treated breast. Per 1 cm increase in MBD, the mean CB dose decreased by 10–15%. As an alternative to MBD, dose estimates could be based on the breast-to-breast distance, which is highly correlated with MBD.
Conclusion: The results enable personalized assessment of CB doses from tangential whole-breast irradiation, based only on parameters assessable from CT data. This may help support clinical decision-making processes as well as analyse retrospective studies on CB risks.
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Adjuvant whole-breast radiotherapy is a recommended part of breast-cancer therapy after breast-conserving surgery. It reduces the recurrence rates of breast cancer, specific mortality from breast cancer as well as the overall mortality [1]. However, breast-cancer radiotherapy also increases the incidence of second cancers, mainly in the contralateral breast and in the lungs. Especially for left-sided tumours it also increases the mortality through heart disease [1,2].

Due to anatomic diversity, there is large inter-patient variability in doses to the heart, lung and contralateral breast, even for the same treatment protocol. Together with non-dosimetric factors such as the age, lifestyle and genetic background [3,4], these doses govern the patient's long-term health risks from breast-cancer radiotherapy. Maximum heart distance and central lung distance, measures of the extent by which the respective organ would be covered by a tangential breast irradiation field, represent useful predictors of individual heart and lung doses [5,6]. For contralateral breast doses, however, no dedicated anatomic measure closely linked to their variability has been proposed. Only negative results or rather weak correlations have been reported so far [7–10]. To address this issue, we present a simple method of estimating radiation doses to contralateral breast (CB) from various whole-breast

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https://doi.org/10.1016/j.radonc.2018.08.022
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irradiation techniques, based on a single anatomic parameter easily assessable from planning CT data.

Methods

Treatment planning dataset

Seventy-eight and fifty early-stage female breast-cancer patients (TNM-classification pT1-2, tumour size <3 cm, pN0, G1-3, R0) from the Departments of Radiation Oncology at University Hospitals Leipzig and Rostock, Germany (hereafter termed centres 1 and 2) were considered. The tumour, treated and contralateral breasts were contoured manually by radiation oncologists on the planning CT slices. There were minor differences in the delineation protocol between the centres, see the Supplementary Material, Section 1. The planning target volume (PTV) included the whole treated breast. The prescribed PTV dose was 50.4 Gy in 28 fractions.

In centre 1, 45 left- and 33 right-sided breast-cancer patients were planned for 3D conformal radiotherapy without and with the use of compensatory wedges (3DCRT – w and 3DCRT + w, respectively). In addition to these forward-planned treatments, hybrid techniques were considered that used the same main tangential fields to deliver 70–80% of the prescribed PTV dose plus additional inversely planned saturating fields. These hybrid techniques were planned both with the use of flattened (FF) and flattening filter-free (FFF) beams; wedges were not applied. 3DCRT + w and hybrid FF techniques were planned for 6 MV photons delivered by Siemens Primus (Siemens AG, Healthcare, Erlangen, Germany), 3DCRT – w for a combination of 6 MV and 10 MV photon beams from the same machine, while hybrid FFF was planned for 7 MV photons from Siemens Artiste.

In centre 2, 27 left- and 23 right-sided patients were planned for multi-field intensity-modulated radiotherapy (IMRT) aimed at sparing the heart, ipsilateral lung and CB. To enable comparisons with data from centre 1, 3DCRT – w plans were also calculated for each patient. The plans were generated for photon beams provided by a Siemens Oncor Impression Plus machine.

Treatment planning was performed by a single planner in centre 1 and by another single planner in centre 2, using the same treatment planning system (TPS) Oncentra Masterplan (version 4.3, software 4.3.0.410, Nucletron – Elekta Company). Dose calculation was based on the collapsed cone algorithm, with centre- and linac-specific beam model tuning as used in clinical routine.

Tumour-bed boosts were considered too. The respective results can be found in the Supplementary Material, Section 2.

Anatomic parameters

The present work is a part of PASSOS, a German national project on long-term health risks following medical application of ionizing radiation [11]. To assess how patient-specific doses to critical organs relate to individual anatomy, in both centres for each patient the following parameters were determined: tumour laterality and its location in (or between) breast quadrants, volumes of the treated breast and the considered critical organs, and 17 parameters assessed from CT images to reflect details of the patient's anatomy in the thorax region. These parameters included two CB-dedicated measures (Fig. 1): Minimum breast distance (MBD) was defined as the CB distance from the tangent to the treated breast within the midplane axial CT slice. Breast-to-breast distance (BBD) was measured directly as the minimum separation of the contoured breasts in the midplane CT slice. The thickness, width and height of the treated breast were also determined. Section 3 of the Supplementary Material includes detailed definitions

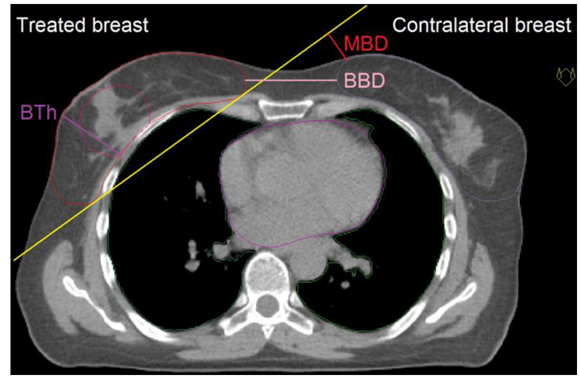

Fig. 1. Minimum breast distance (MBD), breast-to-breast distance (BBD) and breast thickness (BTh).

of these parameters and of 12 further ones that were introduced primarily to capture doses to the heart and lungs.

Analysis of treatment planning data

Not only mean doses but also other dose–volume characteristics are considered in this work, motivated by their relevance for risk assessment [12,13]: Estimates of risk per unit dose at low CB doses in atomic bomb survivors are higher than those at intermediate to high doses in radiotherapy patients [14]. Hence, mean organ doses may be insufficient to estimate the risk. Therefore, we analysed patient-specific mean doses and additional dose–volume characteristics, e.g. doses to the highest exposed 10% of the organ ($D_{10\%}$) or volume fraction exposed to at least 0.5 Gy dose ($V_{0.5\ Gy}$), as calculated by the TPS. CB dose–volume measures from both centres and for both tumour lateralities were analysed together, since separate analyses did not provide significantly varying results. A single patient with a tangential field extending into the contralateral breast (MBD < 0) was excluded from the analysis.

A paired, two-sided Wilcoxon signed rank test was used to test whether two irradiation techniques provided significantly different mean CB doses. To address the inter-patient variability and its link to the patient anatomy, diverse dose–volume characteristics were fitted by generalized linear models (GLM) [15] with logit link function, subsequently testing all the recorded parameters and their combinations as predictors in univariate or multivariate models. Logit GLM models were chosen since they account for data with both lower (0 Gy dose, 0% volume fraction) and upper constraints (given by the prescribed dose or 100% volume fraction). The models were generated with Matlab version R2016a (The MathWorks Inc., Natick, MA, USA), using the sum-of-squared-error fitting criterion, which is directly related to the fraction of variability explained (coefficient of determination). Since doses to even the most-exposed CB parts are much lower than the prescribed PTV dose, their logit models can be approximated by logarithmic ones. Further details are reported in the Supplementary Material, Section 4.

Results

TPS-calculated mean CB doses from different techniques of whole-breast radiotherapy are characterized in Table 1 by their mean values and standard deviations within the patient groups. While 3DCRT – w and FF were not significantly different ($p = 0.34$), all other technique pairs differed at $p < 0.001$. The individual patients' mean CB doses from alternative techniques are plotted in Fig. 2. Among the patients in centre 1 (Fig. 2A), mean

Table 1
Mean values and standard deviations of the patients' mean contralateral breast doses from different irradiation techniques.

Centre	Technique	Mean (Gy)	Standard deviation (Gy)
Centre 1	3DCRT – w	0.58	0.13
	3DCRT + w	0.87	0.16
	Hybrid FFF	0.44	0.10
	Hybrid FF	0.58	0.14
Centre 2	3DCRT – w	0.95	0.23
	IMRT	2.56	1.50
Centres 1 + 2	3DCRT – w	0.72	0.25

CB doses from 3DCRT – w (filled squares and line; used as a reference for comparing alternative techniques) ranged from 0.2 to 0.9 Gy. For every single patient in the study, mean CB dose from hybrid FFF (filled circles) was lower than that from 3DCRT – w, typically by 0.1–0.2 Gy, while dose from 3DCRT + w (filled triangles) was considerably higher than that from 3DCRT – w, typically by 0.2–0.4 Gy. Doses from the hybrid FF technique (empty circles) were very similar to those from 3DCRT – w. Mean CB doses from 3DCRT – w among the patients in centre 2 (Fig. 2B) amounted to 0.5–1.6 Gy. Multi-field IMRT (hexagrams) frequently resulted in considerably higher doses than 3DCRT – w, and for some patients exceeded 5 Gy.

Large fractions of the inter-individual variability in CB doses from alternative whole-breast irradiation techniques could be explained by the minimum breast distance (MBD). This anatomic parameter served as the best predictor of patient-specific mean CB doses from alternative techniques. Models for mean CB dose and further CB dose–volume metrics for 3DCRT – w are presented in Fig. 3 and Table 2. For instance, 56% of the inter-patient variability in mean CB dose from 3DCRT – w was covered by

$$D_{\mathrm{mean}} = D_0 \exp(-0.0154\,\mathrm{mm}^{-1} \times \mathrm{MBD}) \qquad (1)$$

Here the reference dose D_0 is centre-specific, 0.86 Gy for centre 1 and 1.31 Gy for centre 2, i.e. 1.7% and 2.6% of the prescribed PTV dose. It is a fit value that extrapolates to MBD = 0 the patient data with MBD ranging from about 5 to 80 mm. Care has to be taken in interpreting D_0 as the expected mean CB dose for a patient with MBD = 0. The doses exponentially decrease with increasing MBD, by about 1.5% per 1 mm. For instance, at MBD = 25.4 mm, the mean value for the analysed patients, mean CB doses are 0.58 Gy and 0.89 Gy (1.2% and 1.8% of the prescribed PTV dose) in centre 1 and 2, respectively.

Also for doses to the most exposed 10%, 5%, 2% and 1% of the organ or in the volume fraction exposed to at least 2 Gy ($V_{2\,\mathrm{Gy}}$), more than 50% of the individual variability was explained by variations in MBD. A considerable fraction of individual variability was covered even for the low-dose region, e.g. for $D_{50\%}$ or $V_{0.5\,\mathrm{Gy}}$ (Table 2 and Table S1). For other tangential techniques of whole-breast irradiation, MBD-based models covered 55–63% of the inter-patient variability in mean CB doses (Table 2). All the listed models were highly significant ($p < 0.001$).

Alternatively, the direct breast-to-breast distance (BBD) might be used as a predictor instead of MBD, explaining only slightly lower fractions of individual variability (Supplementary Material, Section 5). Using the triplet of parameters MBD, BBD and the thickness of the treated breast, overall the results got moderately improved, with considerable improvements seen in the low-dose region (Supplementary Material, Section 5), which may be important for risk assessment.

Doses from multi-field IMRT did not show any systematic pattern that could be exploited by the models: None of the 17 anatomic parameters analysed was related to mean CB doses from IMRT at a 5% significance level. Even at a reduced significance level, only 7% (or 26%) of individual variability could be covered by univariate (or tri-variate) models (results not shown).

Discussion

Mean CB doses from tangential whole-breast irradiation ranged from 0.2 to 1.6 Gy in this study, comparable to or lower than the measured or calculated values reported for modern radiotherapy protocols [16–25,9,10]. The lowest CB doses resulted from FFF beams. Flattening filters or wedges as sources of scatter radiation increased peripheral doses, including those to the CB. For the vast majority of patients, mean CB doses from IMRT were considerably higher than those from 3DCRT. This trend has been reported by others [26,20] and is in line with results for more distant organs [27]. Studies that report the opposite trend [28,29] used tangential IMRT (called hybrid techniques in this work) or complex non-coplanar IMRT, and/or compared IMRT with wedged techniques, and hence do not contradict the present results.

Mean CB doses and other dose–volume metrics largely varied among patients, by factors of 3 – 4 in both centres. Inter-patient variability was particularly pronounced for the high-dose metrics such as $D_{1\%}$. Large parts of the variability could be explained by a single anatomic parameter, the minimum breast distance (MBD),

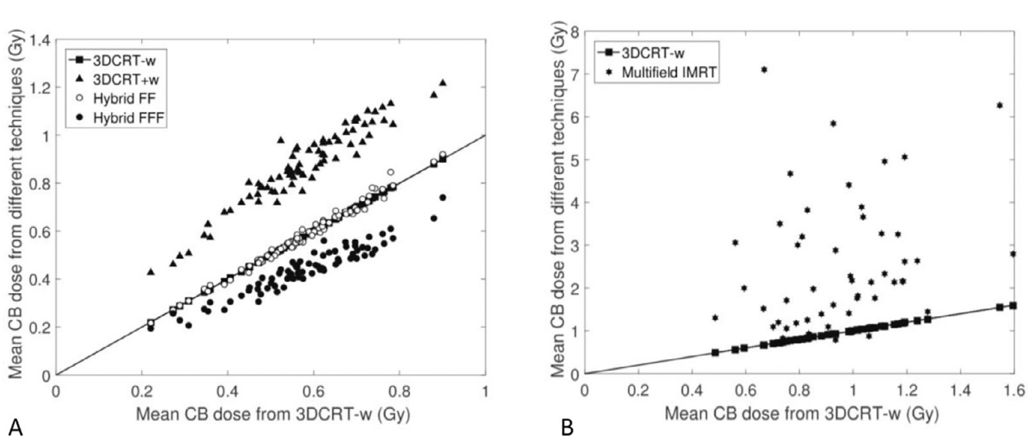

Fig. 2. TPS-calculated mean contralateral breast (CB) doses from different techniques of whole-breast irradiation, with prescribed whole-breast dose of 50.4 Gy. To facilitate the comparison of alternative techniques, all doses are plotted against those resulting from 3D conformal radiotherapy without physical wedges (3DCRT – w). Panel A: Data for 72 patients in centre 1 planned for 3DCRT – w, 3DCRT with wedges (3DCRT + w), and tangential-field IMRT with or without the use of flattening filters (hybrid FF, hybrid FFF). Panel B: 49 patients in centre 2 planned for 3DCRT – w or multi-field IMRT.

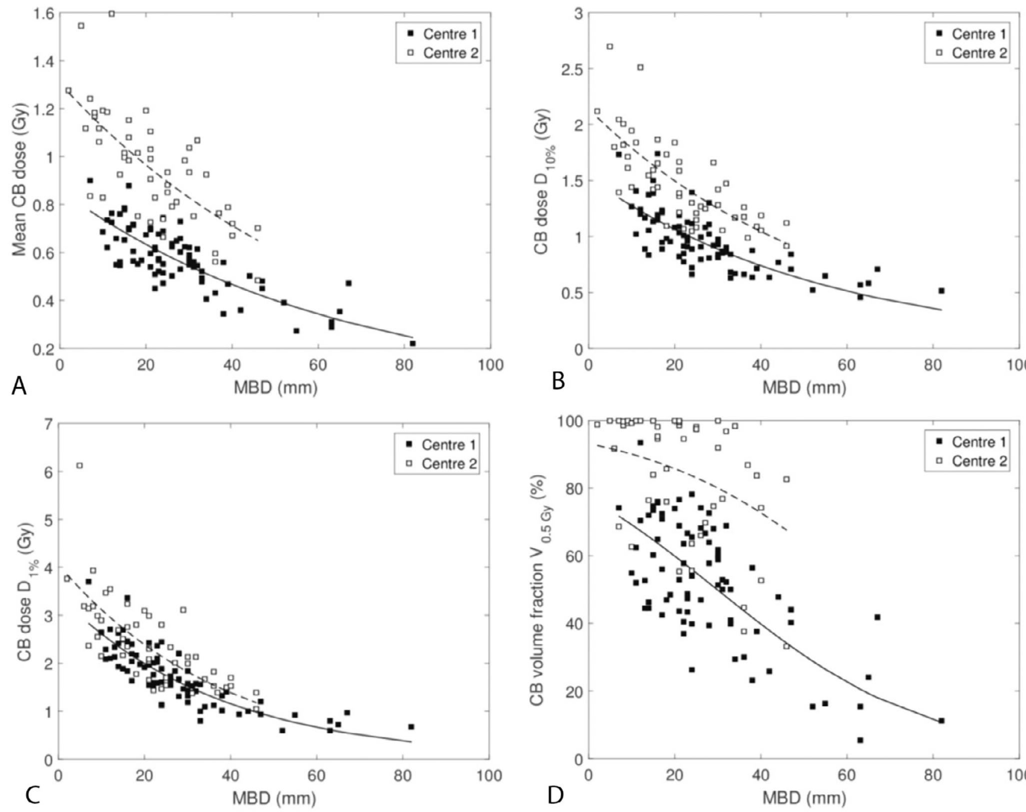

Fig. 3. Minimum breast distance (MBD) largely covers the inter-patient variability in mean contralateral breast (CB) doses (panel A) as well as in doses to 10% or 1% of the organ (panels B-C) or the fraction of the CB volume receiving at least 0.5 Gy (panel D). Data for the 3DCRT – w technique from both centres (symbols) have been analysed simultaneously as described in the text; solid and dashed lines show the fit for centres 1 and 2, respectively.

Table 2
Minimum breast distance (MBD)-based models of mean dose and further dose–volume metrics in the contralateral breast from alternative techniques of whole-breast irradiation (prescribed PTV dose of 50.4 Gy). Listed are contralateral breast doses extrapolated to MBD = 0 separately for each centre, their relative decrease with MBD (coefficients β_{MBD} ± standard errors), and the fractions of individual variability explained by the models.

Technique	Dose metric	D_0 (Gy)		β_{MBD} (mm^{-1})	Explained variability (%)
		Centre 1	Centre 2		
3DCRT – w	D_{mean}	0.86	1.31	−0.0154 ± 0.0013	56
	$D_{50\%}$	0.68	1.10	−0.0113 ± 0.0013	41
	$D_{10\%}$	1.52	2.14	−0.0184 ± 0.0015	57
	$D_{5\%}$	2.13	2.74	−0.0224 ± 0.0017	63
	$D_{2\%}$	2.85	3.46	−0.0253 ± 0.0018	65
	$D_{1\%}$	3.41	4.06	−0.0281 ± 0.0022	62
3DCRT + w	D_{mean}	1.16		−0.0106 ± 0.0012	55
Hybrid FFF	D_{mean}	0.62		−0.0131 ± 0.0016	53
Hybrid FF	D_{mean}	0.86		−0.0151 ± 0.0015	63

measured as CB distance from the tangent to the treated breast. This result reflects the physics of radiation transport: Whether the scattered radiation originates in the linac head (especially for wedged fields) or within the treated breast, the amount of scatter radiation to the CB increases with its decreasing distance from the treated breast. Only slightly lower fractions of variability were explained by the direct breast-to-breast distance (BBD), an anatomic feature that may be assessed even more easily and thus is more robust against potential measurement errors. The fraction of variability explained by the models increased further, especially at low doses potentially relevant for risk estimates, when both these measures were combined and supplemented by the thickness of the treated breast. Including further parameters or allowing for quadratic terms improved the results only marginally. No models could be formulated for multi-field IMRT, likely due to the high degree of freedom inherent to this technique.

In addition to whole-breast irradiation, boost irradiation to the tumour bed is often applied to further reduce the risk of local recurrence [30]. The present results (Supplementary Material, Section 2) highlight that brachytherapy boost is highly confined to the tumour bed. It contributed to mean CB dose on average by 0.03 Gy only. Boost with 3DCRT contributed to mean CB dose on average by 0.2 Gy but for some patients by 0.5–1 Gy, which is comparable to doses from whole-breast irradiation. The analysed anatomic features including tumour location in breast quadrants were not sufficient to explain more than about 1/3 of the individual variability (Supplementary Material, Section 6). Presumably, the CB distance from the tumour bed would have to be included to improve these results.

The present work is based on logit GLM models. Existing studies have mostly linked the variability in organ doses to anatomic features via linear models, sometimes including a quadratic dependence on the predictors [5,6]. MBD and BBD would be the best candidates for predictors also in linear models, since they closely correlated with mean CB doses (Supplementary Material, Section 5). The volumes of the treated and contralateral breasts suggested in the literature [7,8,10] did not correlate with mean CB doses at $p < 0.05$. Compared with the reported GLM models, linear MBD- or BBD-based models covered individual variability in CB doses to slightly lower extent (not shown). More importantly, linear models may predict negative CB doses or volume fractions exceeding unity at extreme predictor values. Logarithmic models, used e.g. for estimating heart doses [31], avoid negative values only. Logit GLM models such as those applied to the heart [32] or the present ones solve both these issues.

Concerning the limitations of the present study, first of all the present results rely on CB doses calculated by treatment planning systems (TPS). TPS may not accurately predict doses in regions far from the target volumes: Deviations from measured or Monte Carlo simulated doses in the order of 30–50% have been reported at relevant distances from the field edge [33]. Yet the predicted doses from CT-based planning represent the best available way of assessing individual variability, since e.g. performing Monte Carlo calculations or CB surface dosimetry [34] routinely for many patients is not realistic.

TPS out-of-field calculations were therefore thoroughly benchmarked against measurements, as discussed in detail in the Supplementary Material, Section 7. With increasing distance from field edge, the measured dose profile fell off approximately exponentially, which is in agreement with the GLM parameterization and the approximation in Eq. (1). In-field TPS calculations were highly accurate. However, the actual out-of-field doses were systematically underestimated by TPS calculations in centre 1 and overestimated in centre 2, although the same TPS was used in both centres. This difference likely follows from the differences in its commissioning and/or beam model tuning, which are centre-specific. The deviations of TPS from measurements increased with increasing distance from field edge (i.e. with decreasing doses), up to about 30% for doses below 0.4 Gy (0.8% of the PTV dose) or distances from the field edge above 50 mm. For even larger distances (even lower doses), the deviations did not further increase substantially. These deviations translate into a systematic uncertainty of the reported GLM models and their coefficients. Nevertheless, as discussed in the Supplementary Material, Section 7, the resulting systematic uncertainty is rather small. For mean CB doses from 3DCRT – w, for instance, this uncertainty corresponds to only about 10% of the MBD coefficient reported in Table 2.

In addition to the differences in TPS calculations between the centres, there may be additional differences related to different ways of contouring the treated and contralateral breasts, to the choice of margins, and/or to technical differences that affect the amount of beam scatter from the treatment head. Variations in CB doses may also result from differences in optimization regarding heart or lung doses or requirements on PTV coverage, which are not subject of this paper. Since CB dose is a particular criterion only, lower CB doses shall not be misinterpreted as a marker of overall plan superiority. In spite of the differences in absolute CB doses, data from both centres (and also left- and right-sided tumour data analysed separately) show the same dependence on the anatomic factors, highlighting the robustness of the findings reported in this work.

Having based the presented models on data from two independent centres indicates that they may be applicable to other centres too. The models provide the dependence on anatomic features, but need to be calibrated in order to provide centre-specific absolute estimates. It has to be noted that the results were derived for MBD ranging from about 5 to 80 mm only, and should not be extrapolated or applied to patients with unusual anatomy. For instance, for the single patient in the present study whose CB would be partially included within the tangential field (MBD = −7 mm) and who was therefore excluded from the analysis, the mean CB dose from 3DCRT – w was 3 Gy, about two times higher than the model extrapolation.

Finally, the present study analysed a limited number of whole-breast irradiation techniques. No predictive model was found for IMRT, even though the number of degrees of freedom inherent to this technique, e.g. varying the number of fields, was not fully exhausted. Compared to tangential whole-breast irradiations, only smaller fractions of individual variability in CB doses were captured by models for boost irradiations. Future studies shall address the individual variability in CB doses depending on anatomic features for irradiation techniques not studied in this work, such as volumetric arc therapy, and for irradiations using deep-inspiration breath hold [35].

Conclusion

Personalized estimates of contralateral breast doses from tangential techniques of breast-cancer radiotherapy have been presented, using only anatomic features determined from the planning CT images. The reported personalized estimates could be used to help improve retrospective analyses of data on long-term health risks from radiation therapy, provided that CT data, films or other records are available from which the anatomic parameters can be assessed. Moreover, individual estimates of contralateral breast doses may be helpful in centres where its contouring or dosimetry is not routinely performed. Most importantly, the personalized estimates may be used for patient stratification and for efficient application of techniques that spare the contralateral breast. Contralateral breast doses and subsequently the risks of radiation-induced cancer in this organ are highest in patients with short minimum breast distance (or alternatively breast-to-breast distance). Per 1 cm increase in this distance, the mean dose to contralateral breast decreases by about 10–15%.

Financial support

This work was supported by the German Federal Ministry of Education and Research (BMBF) under contract number 02NUK026 (PASSOS).

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2018.08.022.

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