

ORIGINAL ARTICLE



The potential benefits from respiratory gating for breast cancer patients regarding target coverage and dose to organs at risk when applying strict dose limits to the heart: results from the DBCG HYPO trial

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ABSTRACT

Purpose: The potential benefits from respiratory gating (RG) compared to free-breathing (FB) regarding target coverage and dose to organs at risk for breast cancer patients receiving post-operative radiotherapy (RT) in the DBCG HYPO multicentre trial are reported.

Material and methods: Patients included in the DBCG HYPO trial were randomized between 50 Gy in 25 fractions (normofractionated) versus 40 Gy in 15 fractions (hypofractionated). A tangential forward field-in-field dose planning technique was used to cover the clinical target volume (CTV) with the intent to limit dose to the left anterior descending coronary artery (LADCA) to 20 Gy and 17 Gy in the normo- and hypofractionated arms, respectively. Treatment plan data for 1327 patients from four Danish centres was retrospectively analyzed. FB right-sided patients served as control group for the left-sided patients regarding CTV $V_{95\%}$ (relative volume receiving at least 95% of the prescribed dose), mean heart dose (MHD) and mean lung dose (MLD).

Results: Median CTV $V_{95\%}$ was for FB right-sided, FB left-sided and RG left-sided patients 94.6, 92.6 and 94.7% for normofractionated therapy, respectively, and 94.6, 91.8 and 94.4% for hypofractionated therapy and did not differ significantly for RG left-sided plans compared to FB right-sided in either study arm. CTV $V_{95\%}$ was significantly lower for FB versus RG for left-sided plans in both arms. Median MHD was 0.7, 1.8 and 1.5 Gy (normofractionated therapy) versus 0.6, 1.5 and 1.2 Gy (hypofractionated therapy), respectively. The corresponding median MLD was 9.0, 8.3 and 7.3 Gy versus 7.3, 6.4 and 5.8 Gy, respectively.

Conclusions: RG for left-sided breast cancer patients ensured similar CTV $V_{95\%}$ as for FB right-sided patients. MLD was lower for RG due to the increased lung volume. MHD was generally low due to strict protocol-defined maximum dose to LADCA, but for left-sided patients RG led to significantly lower MHD.

ARTICLE HISTORY

Received 18 September 2017
Accepted 8 November 2017

Introduction

Adjuvant radiotherapy (RT) reduces loco-regional recurrence, distant failure and improves overall survival of early breast cancer patients [1–3]. On the other hand, adjuvant RT also increases the risk of heart- and lung-related toxicity compared to women not receiving RT [4,5]. A recent study also showed a further increase in risk among women who received anthracycline-containing chemoradiotherapy [6]. Inclusion of the internal mammary node (IMN) in the RT target in women with advanced disease increases mean heart dose (MHD) compared to patients having residual breast RT only [7–9]. However, the inclusion of the IMN is justified for high-risk patients according to recent studies showing reduced risk of breast cancer recurrence and improved survival after IMN RT [10–12]. Hence, careful decisions must be made on an individual patient level regarding target coverage versus dose to organs at risk (OAR). There has been quite some interest on reducing the dose to the left anterior

descending coronary artery (LADCA) since reports have indicated an association between LADCA irradiation and the risk of ischemic heart disease [13–15]. In order to optimize target coverage while maintaining a low dose to OAR, techniques for RT with respiratory gating (RG), like enhanced inspiration gating and deep-inspiration breath hold (DIBH), have successfully been implemented in RT centres during the last decade [16–19]. These techniques exploit that during a deep inspiration the heart shifts in caudal and dorsal direction compared to the breast, moving the heart away from the high dose region of typical tangential fields. Simultaneously the lung is more inflated compared to normal breathing, reducing the relative volume of lung tissue in the high dose region. During the last decade RG radiotherapy for breast cancer patients has become standard in all Danish RT centres [20].

At the same time, the Danish Breast Cancer Group (DBCG) initiated the DBCG HYPO trial 'Hypofractionated

Versus Standard Fractionated Whole Breast Irradiation to Node-negative Breast Cancer Patients' (clinicaltrials.gov NR NCT00909818). Women eligible for adjuvant whole breast RT after breast conserving surgery of early breast cancer were randomized between normofractionated RT (50 Gy in 25 fractions) versus moderately hypofractionated RT (40 Gy in 15 fractions).

The aim of the current work was to report the potential benefits regarding target coverage and dose to OAR for patients treated with RG compared to the free-breathing (FB) technique in the DBCG HYPO trial irrespective of fractionation scheme.

Material and methods

Patients

Patients receiving adjuvant RT after lumpectomy for early breast cancer were included in the clinically controlled randomized DBCG HYPO trial between May 2009 and March 2014 at four centres in Denmark. A total of 1883 patients were randomized, of these radiation treatment plans from 1522 patients were submitted to the Danish Treatment Plan Bank and used in the present study [21]. Detailed information on target coverage and dose to OAR was extracted on an individual patient basis. In order to avoid summation issues of dose from primary and boost treatment, only primary treatment plans were included in the current study. Whether a patient was treated using RG or not was retrieved from the DBCG trial database.

Clinical target volumes, OAR and dose planning

Patients were CT scanned on a breast board in an elevated position with either both arms or the ipsilateral arm above their head and with a CT slice thickness of 2–3 mm depending on institutional guidelines. The clinical target volume (CTVp_{breast}) defined as the residual breast tissue and OARs (heart, lung and LADCA) were delineated according to the national guidelines at time of start of inclusion in the trial [22,23]. The planning target volume (PTV) was created by expanding the CTVp_{breast} by typically 5 mm. Both CTVp_{breast} and PTV were cropped to 5 mm below the skin.

Treatment plans consisted of tangential medial and lateral field-in-field beams with energies between 6 MV and 18 MV and field edges around 5 mm from the PTV. A skin flash of minimum 2 cm was used in all centres. Centre 1 used a collapsed cone algorithm as implemented in Pinnacle (Philips Radiation Oncology Systems, Fitchburg, WI), Centre 2 the enhanced collapsed cone algorithm as implemented in Oncentra External Beam (Elekta AB, Stockholm, Sweden), Centre 3 an analytical anisotropic algorithm in Eclipse (AAA, Varian Medical Systems, Palo Alto, CA, USA), and Centre 4 initially used a pencil beam algorithm in Eclipse which was changed to the AAA in Eclipse in 2012.

Target coverage and dose to OARs were prioritized in the following order: tumor bed defined by surgical clips > LADCA > heart > lung > CTVp_{breast} > PTVp_{breast} > contralateral breast. The PTV should be covered by 95–107%

and 95–105% of the prescribed dose in the normo- and hypofractionated arms, respectively. In the hypofractionated arm the CTVp_{breast} volume receiving between 105 and 107% of the prescribed dose should be kept below 2% of the CTVp_{breast} volume. For both treatment arms, the volume receiving 107–110% dose should be <2 cm³. In the normofractionated arm, the dose constraints for the OAR were: maximum LADCA dose ≤20 Gy, heart V_{20Gy}≤10% and V_{40Gy}≤5%, ipsilateral lung V_{20Gy}≤25% and mean lung dose (MLD) ≤18 Gy. Correspondingly in the hypofractionated arm: maximum LADCA dose ≤17 Gy, heart V_{17Gy}≤10% and V_{35Gy}≤5%, ipsilateral lung V_{17Gy}≤25% and MLD ≤16 Gy.

Gating techniques

Centre 1 and 2 used the Active Breathing Coordinator™ (ABC) system (Elekta AB, Stockholm, Sweden) and Centre 3 and 4 the Real-Time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA, USA) for gating. In all centres the patients were trained in using the equipment before the planning CT. When using RPM the treatment was given when the ventral chest wall was in a predefined window measured by an external marker block. When using the ABC system a valve in the mouth-piece made further inhalation impossible when the predefined amount of inhaled air was reached. In Centre 1–3 using DIBH, the patients were asked to take a 'comfortable deep inspiration' to ensure reproducible fixation. In Centre 4, using enhanced inspiration gating (EIG), the patients were encouraged to breathe as deeply as comfortable to achieve a higher inspiration level compared to FB. Exclusion criteria from gating in all four centres were: Not being able to maintain breath hold for at least 20 s (DIBH), or in case of EIG not being able to obtain reproducibly high amplitude. Furthermore, patients should be able to understand the necessary commands including audio guidance for RG. Patients unable to achieve an airtight seal around the mouth piece of the ABC system were also excluded from gating.

Statistical analysis

Data are presented in box-whisker plots showing first and third quartile, whiskers indicate range excluding outliers. Outliers are plotted as individual points and are defined as data further away from the quartiles than 1.5 times the interquartile range. The interpercentile range (0.16–0.84) corresponding to 68% of data is given. Group distributions are compared using Mann–Whitney *U*-test. *p* values below .05 are considered significant.

Results

Data from a total of 1522 Danish patients was available. At the time of data extraction, missing data on laterality and gating status and omission of summed primary and boost plans led to exclusion of 192 treatment plans from the present study. Three right sided patients were gated and hence these were omitted from the analysis as well. The remaining 1327 treatment plans were distributed among Centres 1–4 as

212 (57 FB left-sided and 52 with RG), 244 (22 FB left-sided and 102 with RG), 710 (203 FB left-sided and 161 with RG) and 161 (11 FB left-sided and 76 with RG), respectively. The treatment plans were divided into three groups: FB right-sided, FB left-sided and RG left-sided treatment plans and further separated by fractionation arm. Patient characteristics are given in Table 1. Target coverage for the CTVp_breast was available but not for the PTVp_breast. The present study is a dose planning study comparing potential benefits from RG irrespective of fractionation scheme and hence the physical doses were not transformed into biologically equivalent doses.

Median values, interpercentile range (0.16–0.84) and ranges for target coverage and dose to OARs are summarized in Table 2. The V_{20Gy} and V_{17Gy} constraints for the lung were violated for 5 and 1 treatment plans in the normo- and hypofractionated arms, respectively.

The FB right-sided treatment plans were considered a reference group for what could be achieved in terms of target coverage when heart dose was not limiting target coverage as for left-sided treatment plans. FB left-sided treatment plans showed lower CTVp_breast $V_{95\%}$ compared to the reference group, however, the use of RG improved CTVp_breast $V_{95\%}$ to the level of the reference group. For left-sided

Table 1. Patient characteristics in the normo- and hypofractionated arm.

Characteristic	Normofractionated			Hypofractionated		
	Right-sided FB	Left-sided		Right-sided FB	Left-sided	
		FB	RG		FB	RG
No. of patients	354	176	199	345	176	192
Age (years)	58	60	60	59	59	59
	50–67	53–68	51–58	50–68	51–68	51–67
	42–83	42–80	42–83	41–77	41–82	42–75
CTVp_breast volume (mL)	617	697	602	619	661	613
	328–1072	340–1105	339–997	313–1138	336–1163	305–1011
	86–3041	69–2501	74–2467	97–2454	98–2164	90–2624
Heart volume (mL)	625	582	594	628	610	601
	521–720	481–699	508–710	513–751	491–733	512–714
	333–980	376–1027	346–1132	341–932	396–1137	334–931
Ipsilateral lung volume (mL)	1542	1219	2170	1544	1226	2233
	1257–1906	961–1572	1756–2598	1255–1922	994–1559	1843–2564
	757–2790	703–2613	1026–3642	917–2890	626–2682	833–3316

Values presented are median, interpercentile range (0.16–0.84) and range.

Table 2. Median values, interpercentile range (0.16–0.84) and range for dose optimization parameters in the normo- and hypofractionated arm.

Parameter	Normofractionated			Hypofractionated		
	Right FB	Left		Right FB	Left	
		FB	RG		FB	RG
CTVp_breast $V_{95\%}$ (%)	94.6	92.6	94.7	94.6	91.8	94.4
	92.6–97.1	88.4–95.4	92.6–97.2	92.6–96.4	87.0–94.9	91.7–96.6
	70.6–99.1	72.0–99.3	81.4–99.7	79.4–99.4	80.0–98.7	76.8–99.0
	$p = .78$	$p < .001$	–	$p = .50$	$p < .001$	–
LADCA D_{max} (Gy)	0.6	112.9	12.6	0.4	11.8	11.0
	0.2–1.1	10.2–18.0	7.9–20.4	0.2–0.9	8.7–15.4	6.1–18.0
	0.1–26.3	0.5–48.0	2.2–29.5	0.0–19.7	0.18–39.3	2.4–32.0
	$p < .001$	$p = .56$	–	$p < .001$	$p = .22$	–
Lung MLD (Gy)	9.0	8.3	7.3	7.3	6.4	5.8
	7.0–10.9	6.2–10.3	5.7–9.0	5.6–9.0	4.9–8.3	4.6–7.2
	3.1–15.7	3.3–12.2	2.9–11.7	3.0–11.2	3.0–10.1	2.5–9.4
	$p < .001$	$p < .001$	–	$p < .001$	$p < .001$	–
Lung	16.7	15.3	13.6	16.4	14.6	12.7
V_{20Gy} (%) (normo)	12.2–21.0	10.7–19.8	9.9–17.2	12.0–21.1	10.4–19.5	9.7–16.4
V_{17Gy} (%) (hypo)	4.2–32.0	3.7–24.1	2.0–22.8	4.7–27.2	5.3–23.0	3.3–23.1
	$p < .001$	$p < .001$	–	$p < .001$	$p < .001$	–
Heart MHD (Gy)	0.7	1.8	1.5	0.6	1.5	1.2
	0.4–1.0	1.4–2.5	1.1–1.9	0.3–0.8	1.1–2.0	0.8–1.6
	0.2–2.4	0.4–9.2	0.5–3.5	0.2–2.9	0.3–4.2	0.4–4.7
	$p < .001$	$p < .001$	–	$p < .001$	$p < .001$	–
Heart	0.0	0.4	0.1	0.0	0.3	0.1
V_{20Gy} (%) (normo)	0.0–0.0	0.0–1.6	0.0–0.5	0.0–0.0	0.0–1.2	0.0–0.5
V_{17Gy} (%) (hypo)	0.0–0.8	0.0–8.4	0.0–4.1	0.0–1.1	0.0–7.0	0.0–8.9
	$p < .001$	$p < .001$	–	$p < .001$	$p < .001$	–
Heart	0.0	0.0	0.0	0.0	0.0	0.0
V_{40Gy} (%) (normo)	0–0	0.0–0.4	0.0–0.0	0.0–0.0	0.0–0.1	0.0–0.0
V_{35Gy} (%) (hypo)	0.0–0.1	0.0–4.6	0.0–1.4	0.0–0.1	0.0–2.7	0.0–4.6
	$p < .001$	$p < .001$	–	$p < .001$	$p < .001$	–

$V_x\%$ = volume (%) receiving $x\%$ of prescribed dose or higher. The p values are based on two-tailed Mann–Whitney U -tests and show whether group distributions differ from RG left-sided patient within each treatment arm.

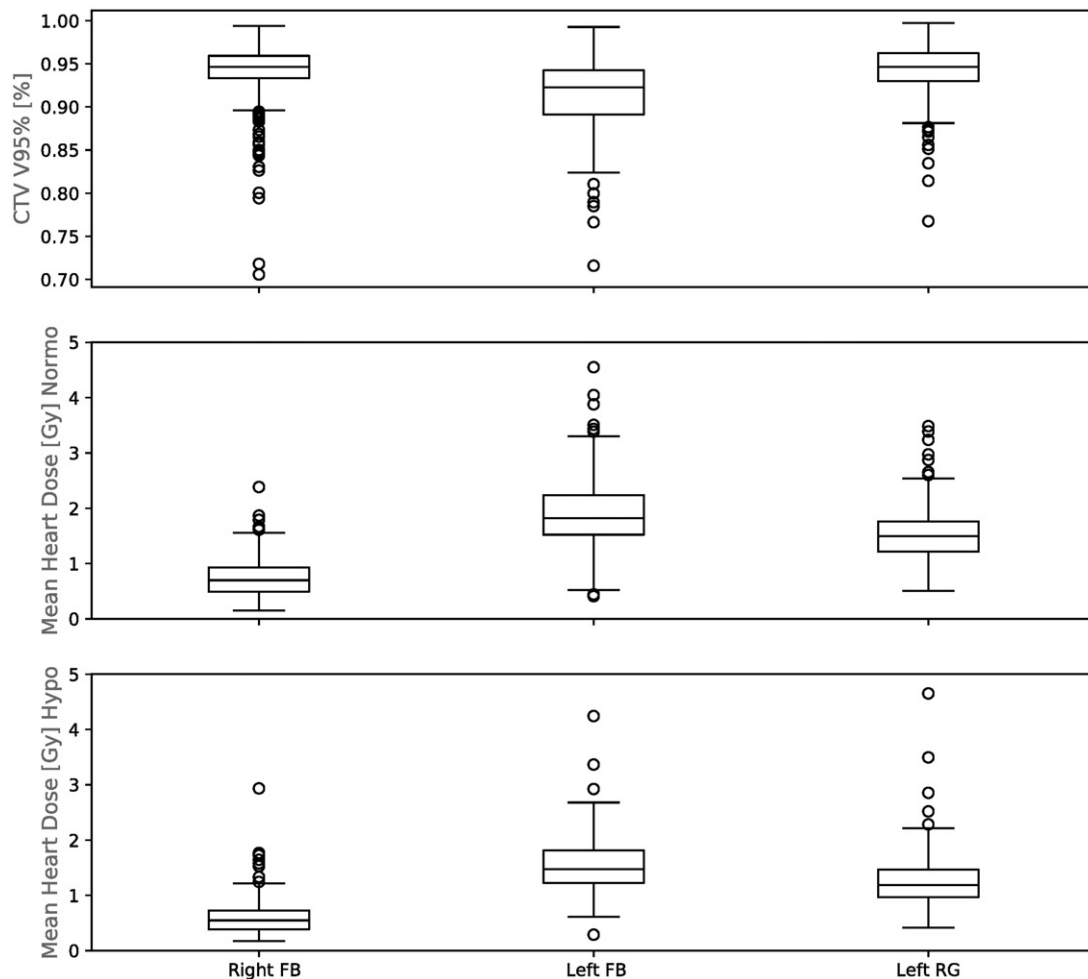


Figure 1. Box-whisker plots for (top) $V_{95\%}$ for the CTV for both normo- and hypofractionated arm, (middle) MHD for normofractionated arm, and (bottom) MHD for hypofractionated arm. $V_{x\%}$ =volume (%) receiving $x\%$ of prescribed dose or higher.

treatment plans RG resulted in lower MLD and MHD compared to left-sided treatment plans treated with FB. Figure 1 shows the corresponding box-whisker plots for CTVp-breast $V_{95\%}$ and MHD for the normo- and hypofractionated arms. CTVp-breast $V_{95\%}$ is plotted against MHD in Figure 2 for left-sided treatment plans for the two arms. The solid line indicates the shift of group mean between FB and RG left-sided treatment plans.

A comparison between FB and RG for each of the four centres regarding $V_{95\%}$ for both arms and MHD for each arm is shown in Figure 3.

Discussion

The findings in the DBCG HYPO trial confirmed the expected advantages regarding target coverage of RG over FB for left-sided breast cancer patients receiving adjuvant RT in a clinical setting where low dose to the heart had high priority: RG ensured a target coverage similar to FB right-sided patients whereas FB left-sided patients had less optimal target coverage as can be seen in Figures (1,2). From Table 2, it is seen that compared to RG left-sided treatment only target coverage for FB right-sided treatment and maximum dose to LADCA for FB left-sided treatment were not statistically different irrespective of randomization arm. The findings between

FB right-sided and FB left-sided versus RG left-sided treatments were identical in the two arms as expected. For right-sided treatment plans Essers et al. reported no gain from RG for breast only RT considering dose to OAR [24]. This supports the usefulness of considering FB right-sided treatment plans as the control group.

Regarding dose to lung, use of RG reduced the MLD significantly, since the irradiated volume of lung was relatively smaller in the inflated lung. The lung constraints were only violated in 6 treatment plans. However this may indicate that target coverage was compromised in other patients. Maximum dose to LADCA was exceeded in some cases but heart constraints were never violated. The MHD was lowest for FB right-sided treatment plans followed by RG left-sided treatment plans. For the whole-population MHD was significantly lower with RG compared to FB for left-sided treatment plans although not as low as for right-sided treatment plans. In general, the dose constraint for LADCA lead to low MHD as the heart was effectively shielded. The benefit from RG was also seen in better target coverage.

Taylor et al. [4] reported average MHD of about 4 Gy for left-sided breast only treatments in a review of published data for radiotherapy given between 2003 and 2013, and Lorenzen et al. reported MHD of 2.8 and 0.7 Gy for left-sided and right-sided treatment plans, respectively, treated in

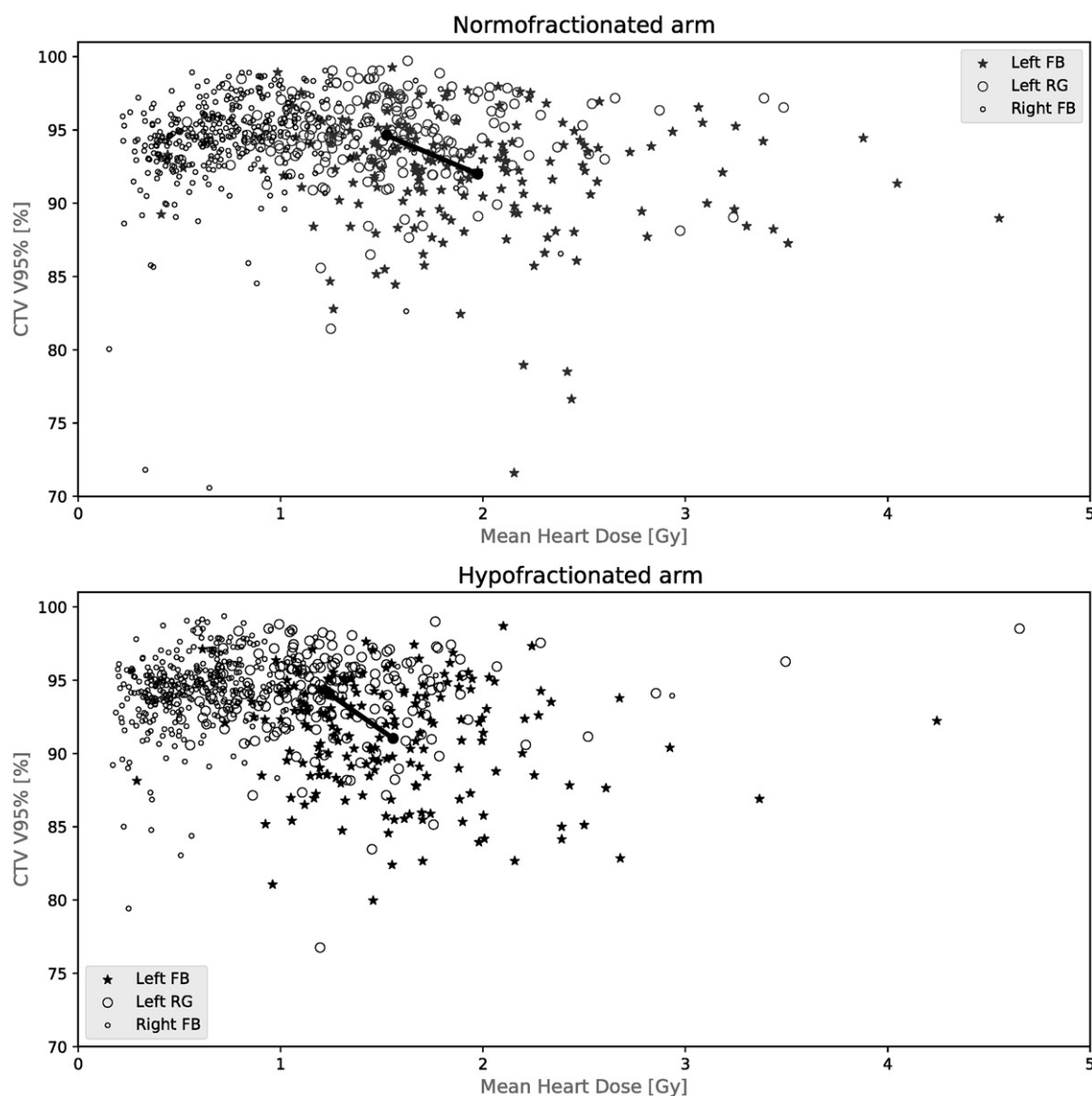


Figure 2. Target coverage of CTV against MHD for FB and RG left-sided patients for (top) normofractionated and (bottom) hypofractionated arm. The solid line indicates the shift of group mean. $V_{x\%}$ =volume (%) receiving $x\%$ of prescribed dose or higher.

Denmark with 2D tangential radiotherapy (i.e., before ~2005) [4,25]. These findings, both the international and historical national doses, are above what is reported in the current study. This is a direct consequence of the prioritization of LADCA effectively shielding the heart from irradiation.

The risk of cardiac disease is increasing linearly with MHD with a rate of 4.1–7.4% per Gy MHD depending on endpoint [4,5]. Thus, due to the low values of MHD observed in this study the risk of cardiac disease is expected to be low.

The median $V_{95\%}$ of 94.8 and 94.7% for the CTV_{p-breast} in the normo- and hypofractionated arms for RG left-sided treatment plans is somewhat lower than what was reported by Nissen and Appelt in a similar study [16]. In addition, the MHD dose was higher in their study which can be explained by the dose limits on LADCA in the present study. Schönecker et al. [26] reported for patients using DIBH a MHD of 1.3 Gy (based on 50 Gy in 25 fractions) which was very similar to 1.2 Gy presented in the current study [26].

Inherently different target delineation practices, algorithms and set-up guidelines exist among centres of which the consequences are not clear from Figure 1. Therefore a comparison between FB and RG for left-sided treatment plans within each centre was performed for target coverage and MHD as shown in Figure 3. Although the same constraints were applied in each centre differences are seen regarding target coverage and MHD. It is seen that the outliers in target coverage seen in Figure 1 can be explained by the data from Centre 2 showing inferior target coverage compared to the others. The origin is not clear but can have several causes: Differences in the medial and dorsal/lateral border of the CTV_{p-breast} will lead to larger compromises regarding target coverage in order to fulfill the LADCA constraint. Depending on the centre-specific depth dose curves in the treatment planning system the target coverage in the superficial part of the CTV_{p-breast} can be either over- or underestimated in the four dose planning systems.

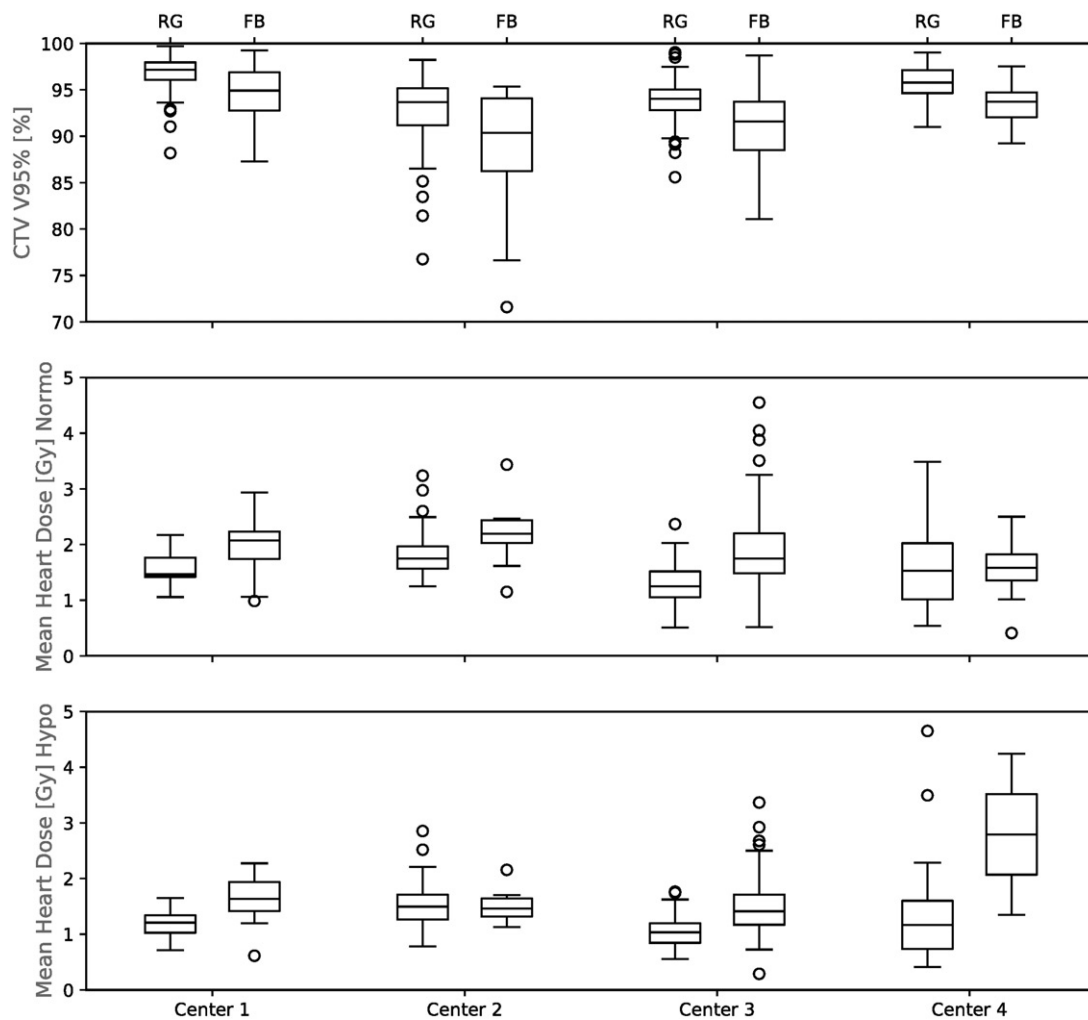


Figure 3. Box-whisker plots for each centre comparing RG versus FB for (top) target coverage for left-sided patients, (middle) MHD in the normofractionated arm, and (bottom) MHD in the hypofractionated arm. $V_{x\%}$ =volume (%) receiving $x\%$ of prescribed dose or higher.

A limitation in the present multicentre study is the variations such as prioritization of target coverage over dose to OARs on an individual patient level, more strict local constraints for hotspots and more dose from high energy photons. However, all centres showed increased $V_{95\%}$ target coverage and similar or lower MHD when using RG irrespective of the system being used compared to FB in the same centre. For Centre 4 only two patients were treated in FB in the hypofractionated arm which can explain the large MHD and spread in the hypofractionated arm.

Conclusions

In this, to our knowledge, largest multicentre study on the effects of RG for left-sided breast cancer patients we have shown that separation of heart and target is feasible to an extent where target coverage is comparable to that of FB right-sided patients. MLD is lower using RG because of an absolute increase in lung volume causing a relative decrease in irradiated volume. MHD is reduced for RG compared to FB and lower than typically reported due to strict maximum dose to LADCA. Two RG techniques were used in the study and were found to be equal in terms of target coverage and sparing of the heart. Although differences were seen in

target coverage and dose to OARs between centres improved target coverage was seen within each centre when RG is applied in all cases.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Center for Interventional Research in Radiation Oncology (CIRRO) and BVO was supported by the Danish Cancer Society.

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