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ORIGINAL ARTICLE

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A comparison of conventional and dynamic radiotherapy planning techniques for early-stage breast cancer utilizing deep inspiration breath-hold

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ABSTRACT

Background: For breast cancer patients, radiotherapy increases the risk of cardiac disease. Conventional three-dimensional conformal radiotherapy (3D-CRT) in deep inspiration breath-hold (DIBH) has demonstrated substantial reduction in cardiac doses as compared to treatment in free breathing. The purpose of this treatment planning study is to investigate if dynamic techniques in combination with DIBH could improve the quality of the treatment plans and further reduce the doses to the heart and other organs at risk for early-stage breast cancer patients.

Material and methods: CT series in DIBH of 16 patients from a previous study were used. For each patient, treatment plans were generated with the following three techniques: 3D-CRT, tangential intensity-modulated radiotherapy (tIMRT) and volumetric modulated arc therapy with partial arcs (pVMAT). The treatment planning was performed focusing on planning target volume (PTV) coverage, $V_{95\%} >95\%$. Dose-volume histograms were calculated and compared. Doses to the heart, left anterior descending (LAD) coronary artery, ipsilateral and contralateral lung as well as the contralateral breast (CB) were assessed.

Results: All plans fulfilled the criterion on PTV coverage. Compared to 3D-CRT, the dynamic plans obtained better dose homogeneity and conformity. The mean heart dose was similar for 3D-CRT and tIMRT, 1.3 and 1.1 Gy, respectively, but significantly higher for pVMAT, 1.6 Gy. The median $V_{25\ Gy}$ to the heart was 0% for all techniques. The LAD doses were generally lower with the dynamic techniques. The mean doses to the ipsi- and contralateral lung and CB were similar with tIMRT and 3D-CRT but significantly higher with pVMAT. $V_{20\ Gy}$ to the ipsilateral lung was significantly lower with tIMRT compared to 3D-CRT.

Conclusion: tIMRT and 3D-CRT with DIBH are better techniques for sparing heart tissue and other organs at risk without compromising target coverage in early-stage breast cancer irradiation compared to VMAT.

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Background

Tangential radiotherapy after breast conserving surgery has been a part of the standard treatment for early-stage breast cancer for decades, with equal results as mastectomy [1]. Gradually, the knowledge of the risks associated with irradiation of the heart has increased [2,3] and new techniques for sparing heart tissue have emerged. Respiratory gating utilizes the increased distance between the breast and heart during inspiration and has demonstrated considerable reduction of heart dose [4–6].

In recent years, intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) have been proposed as ways of reducing heart doses and improve target dose homogeneity for breast cancer [7,8]. The question is whether the new dynamic techniques can replace conventional three-dimensional conformal radiotherapy (3D-CRT) in combination with deep inspiration breath-hold (DIBH). Previous studies have shown that tangential IMRT (tIMRT) for early-stage breast cancer [9] and VMAT for locoregional breast irradiation [10] can reduce the heart doses compared to 3D-CRT, when breath-hold is used for all techniques. There are also breath-hold studies which compare tIMRT with VMAT [11,12] and with TomoTherapy [13]. We are however not aware of any study comparing 3D-CRT, IMRT and VMAT treatment planning of early-stage breast radiotherapy during DIBH. In our opinion, it is important to compare 3D-CRT with the dynamic techniques. If the results are similar, there is no need to increase the complexity of the treatment and the number of MU. The purpose of this treatment planning study is to investigate if tIMRT or VMAT in combination with the DIBH technique can improve the quality of the treatment plans and further reduce the doses to the heart and other organs at risk (OAR) for early-stage breast cancer.

Material and methods

In this treatment planning study, CT series of 16 patients from a previous study were used [6]. Information on patients,

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Supplemental data for this article can be accessed here.

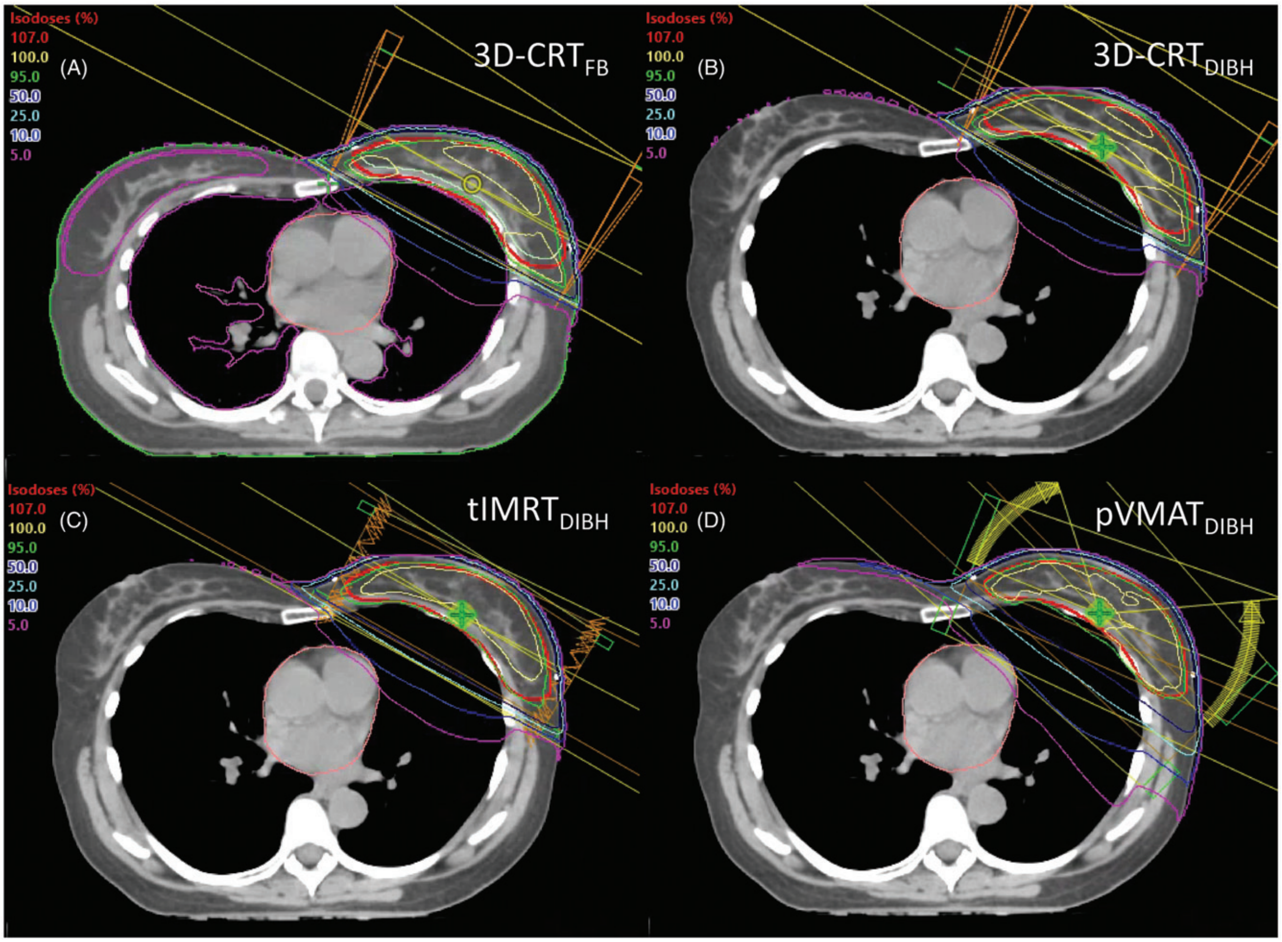

Figure 1. Dose distribution for a typical patient. A 3D-CRT plan in FB (A) and three plans with DIBH: 3D-CRT (B), tIMRT (C) and pVMAT (D). DIBH: deep inspiration breath-hold; FB: free breathing; 3D-CRT: conventional three-dimensional conformal radiotherapy; tIMRT: tangential IMRT; pVMAT: VMAT with partial arcs.

respiratory gating, CT scanning and delineation has been described previously. In brief, the patients were referred for adjuvant radiotherapy after breast conserving surgery and the median age was 60 (range: 29–70) years. The following two CT series were acquired for each patient: the first during free breathing (FB) and the second during DIBH with slice thickness 3 mm. The Varian RPM^{TM} system (Varian Medical Systems, Palo Alto, CA, USA) was used to monitor the respiratory pattern. A video camera registered the respiration dependent anteroposterior motion of an infrared reflecting marker and placed on the patient, normally over the xiphoid process. Audio-visual guidance was used with a gating window of 2 mm.

Clinical target volume (CTV) including the whole left breast was delineated in both series by the same oncologist for all patients according to Norwegian national guidelines [14]. A margin of 5 mm from CTV to the planning target volume (PTV) was applied. CTV and PTV were cropped 5 mm beneath the skin surface. The contralateral breast (CB) was also delineated by the same oncologist. Heart, left anterior descending coronary artery (LAD) and lungs were delineated by a radiation technologist and reviewed by the oncologist.

Treatment planning

The 3D-CRT plans in FB and DIBH from the previous study were recalculated in Eclipse (Varian Medical Systems) using the Analytical Anisotropic Algorithm (AAA) version 10.0.28. The prescribed dose was 50 Gy in 2 Gy fractions. Two opposing tangential fields were used and complemented with low weighted sub fields (Figure 1(A,B)). The beam quality of the main fields was 6 MV, but for the sub fields 15 MV was occasionally used.

The tIMRT planning in DIBH was performed with the same geometry as the 3D-CRT plans (Figure 1(C)). The level of complexity between 3D-CRT and tIMRT gradually increased and the effect of the optimizing algorithm could be investigated without introducing other geometrical changes.

VMAT plans in DIBH were also generated, utilizing partial arcs (pVMAT) to minimize the heart dose (Figure 1(D)). The mean width of the partial arcs was 51°, and the mean start and stop angles were 292° (range 288–297°) to 342° (range 337–348°) for the medial arcs and 86° (range 80–105°) to 136° (range 135–145°) for the lateral arcs. To increase the possibility of finding the optimal solution, the partial arcs were multiplied eight times, giving the algorithm around 400° for optimizing the fluence on each side. Collimator angles were for most patients 10 and 30° for the medial arcs and 330 and 350° for the lateral arcs.

Planning criteria in order of priority are given in Supplementary 1. The OAR doses had lower priority than the PTV dose, ie, the criterion of PTV coverage should be fulfilled, even if the limit for an OAR dose was exceeded.

Table 1. Summary of treatment planning data for target volumes and organs at risk, for the 16 breast cancer patients included in this study, with deep inspiration breath-hold (DIBH), tangential IMRT (tIMRT) and VMAT with partial arcs (pVMAT).

	Free breathing		Deep inspiration breath hold	
	3D-CRT$_{FB}$	3D-CRT$_{DIBH}$	tIMRT	pVMAT
Homogeneity index, HI	0.11 ± 0.01 (0.01–0.12)	0.11 ± 0.01 (0.09–0.13)	0.10 ± 0.01 (0.09–0.12)*	**0.10** ± 0.01 (0.07–0.11)*
Conformity index, CI	0.69 ± 0.04 (0.61–0.78)*	0.72 ± 0.05 (0.64–0.82)	0.80 ± 0.05 (0.72–0.86)*	**0.90** ± 0.03 (0.82–0.95)*
MU[a]	197 ± 6 (184–211)	**198** ± 8 (187–211)	310 ± 63 (223–478)*	342 ± 41 (280–442)*
CTV, $V_{95\%}$ (%)	97.6 ± 0.7 (96.3–98.6)	97.3 ± 0.8 (95.8–98.4)	**99.5** ± 0.4 (98.7–99.9)*	97.9 ± 0.8 (96.1–99.3)*
PTV, $V_{95\%}$ (%)	96.8 ± 0.6 (95.9–98.0)	96.3 ± 0.7 (95.1–97.7)	95.9 ± 0.6 (95.0–97.4)*	**96.5** ± 0.9 (95.2–98.6)
Heart				
Mean (Gy)	6.2 ± 4.4 (2.4–16.4)*	1.3 ± 1.1 (0.8–5.1)	**1.1** ± 0.6 (0.7–3.4)	1.6 ± 1.0 (0.9–4.9)*
Median $V_{25\ Gy}$ (%)	2.2 ± 4.3 (0.2–13.7)*	0.0 ± 1.9 (0.0–7.5)	0.0 ± 1.0 (0.0–4.0)	**0.0** ± 0.5 (0.0–2.2)*
Number of patients with $V_{25\ Gy}$ >5%	3 (18.8%)	1 (6.3%)	**0** (0%)	**0** (0%)
$D_{2\%}$ (Gy)	25.3 ± 16.3 (4.6–48.6)*	7.5 ± 11.1 (2.6–46.9)	**6.1**±8.2 (2.3–36.3)	6.5 ± 5.5 (3.3–26.3)
LAD coronary artery				
Mean (Gy)	17.9 ± 12.4 (1.9–43.8)*	6.7 ± 8.0 (1.6–32.0)	**4.6**±4.7 (1.6–21.1)*	5.3 ± 4.0 (1.9–19.2)
$D_{2\%}$ (Gy)	37.9 ± 15.3 (3.7–49.5)*	16.3 ± 16.1 (2.5–48.1)	10.7 ± 10.1 (2.3–41.8)*	**10.1** ± 7.1 (2.7–32.7)
Ipsilateral lung				
Mean (Gy)	6.8 ± 1.2 (5.1–8.7)	6.3 ± 1.1 (4.1–8.6)	**5.7**±1.0 (4.5–7.9)	7.0 ± 1.1 (4.9–9.3)*
$V_{20\ Gy}$ (%)	11.3 ± 2.5 (7.9–14.8)	10.1 ± 2.0 (6.2–14.4)	**9.1**±2.1 (6.1–13.3)*	10.2 ± 2.0 (5.7–14.6)
Contralateral breast, mean (Gy)	0.4 ± 0.3 (0.1–1.0)	0.4 ± 0.3 (0.1–1.2)	**0.3**±0.4 (0.1–1.9)	2.5 ± 1.3 (0.8–6.3)*

The prescription dose was 50 Gy in 2 Gy fractions. Data are shown as mean values with one standard deviation and range in brackets. Most favourable value in deep inspiration breath hold is marked in bold.
*Significant difference ($p < .05$) relative to 3D-CRT$_{DIBH}$.
[a]No skin flash was used. With skin flash, the number of MU for tIMRT and pVMAT would have been higher. The reference conditions where 100 MU equals 1.0 Gy were 10 × 10 cm^2 field size and 10 cm depth in water at SSD 90 cm.

The overall maximum point dose should preferably be below 107%, but smaller areas with higher doses were accepted.

Only 6 MV was used for the tIMRT and pVMAT planning. The Eclipse optimizing algorithms were DVO for tIMRT and PRO for pVMAT, both with version 10.0.28. In this treatment planning study, no limit on maximum MU was set and no extra planning bolus to account for movement of the breast (skin flash) was added, which in clinical practice would be recommended.

The present study does not include plans with FB tIMRT or FB VMAT, since the benefit of deep inspiration breath-hold compared to free breathing has been demonstrated several times [4–6]. The aim of this study was to investigate if any of the dynamic techniques could improve the results even further compared to conventional 3D-CRT with DIBH. However, data for FB 3D-CRT are included in the figures and tables for comparison.

Evaluation of the treatment plans

Dose-volume histograms (DVHs) were compared for all plans. Mean doses to CTV, PTV and OAR were obtained from the DVH statistics. The relative volume V_x, irradiated to a minimum dose x (in Gy or %), eg, $V_{25\ Gy}$ for the heart, $V_{20\ Gy}$ for the ipsilateral lung and $V_{95\%}$ for PTV, was registered from the DVH graph as well as the near maximum dose $D_{2\%}$. The DVH endpoints were chosen according to national guidelines [14] and for comparison with previous studies.

Plan quality parameters, homogeneity index (HI) [15] and conformity index (CI) [16], were also calculated (definitions in Supplementary material).

For the statistical analysis 3D-CRT with DIBH was selected as the reference technique with which the other techniques were compared. Paired Wilcoxon test was used for statistical analysis of the differences with IBM SPSS software version 23. A nonparametrical test was chosen due to the relatively small number of patients and because the results were not normally distributed. Data were considered statistically significant for $p < .05$.

Results

All plans fulfilled the planning criterion on PTV coverage, $V_{95\%}$ ≥95% (Table 1). There was a small but statistically significant difference in $V_{95\%}$ between tIMRT and 3D-CRT, 95.9 and 96.3%, respectively ($p = .04$). CTV coverage was significantly better in the dynamic plans compared to 3D-CRT, 99.5% ($p < .01$) and 97.9% ($p = .05$) for tIMRT and pVMAT, respectively, versus 97.3% for 3D-CRT. The mean DVH for the PTV is shown in Figure 2(A) and for the CTV in Supplementary 2a.

The homogeneity and conformity of the dynamic plans were significantly better than the 3D-CRT plans (Table 1). HI and CI for 3D-CRT were 0.11 and 0.72, respectively. HI was 0.10 for both tIMRT and pVMAT ($p < .01$), and the CI was 0.80 and 0.90, respectively (both $p < .01$). However, the maximum point dose in the contoured body volume was significantly lower with 3D-CRT (Supplementary 3).

The mean heart dose of the different techniques was 1.3 Gy (range 0.8–5.1 Gy) for 3D-CRT, 1.1 Gy (range 0.7–3.4 Gy) for tIMRT and 1.6 Gy (range 0.9–4.9 Gy) for pVMAT (Table 1). There was no significant difference in mean heart dose between tIMRT and 3D-CRT, but with pVMAT, it was significantly higher ($p = .02$). For 3D-CRT and tIMRT, 7 of the 16 patients (44%) had a mean heart dose below 2 Gy, while for pVMAT, the proportion was 3/16 (19%) (see Supplementary 3). The median $V_{25\ Gy}$ to the heart was 0% for all techniques in DIBH (Table 1). However, $V_{25\ Gy}$ was significantly lower with pVMAT than 3D-CRT ($p = .04$). For 3D-CRT, there was one patient with $V_{25\ Gy}$ above 5%, while both dynamic techniques

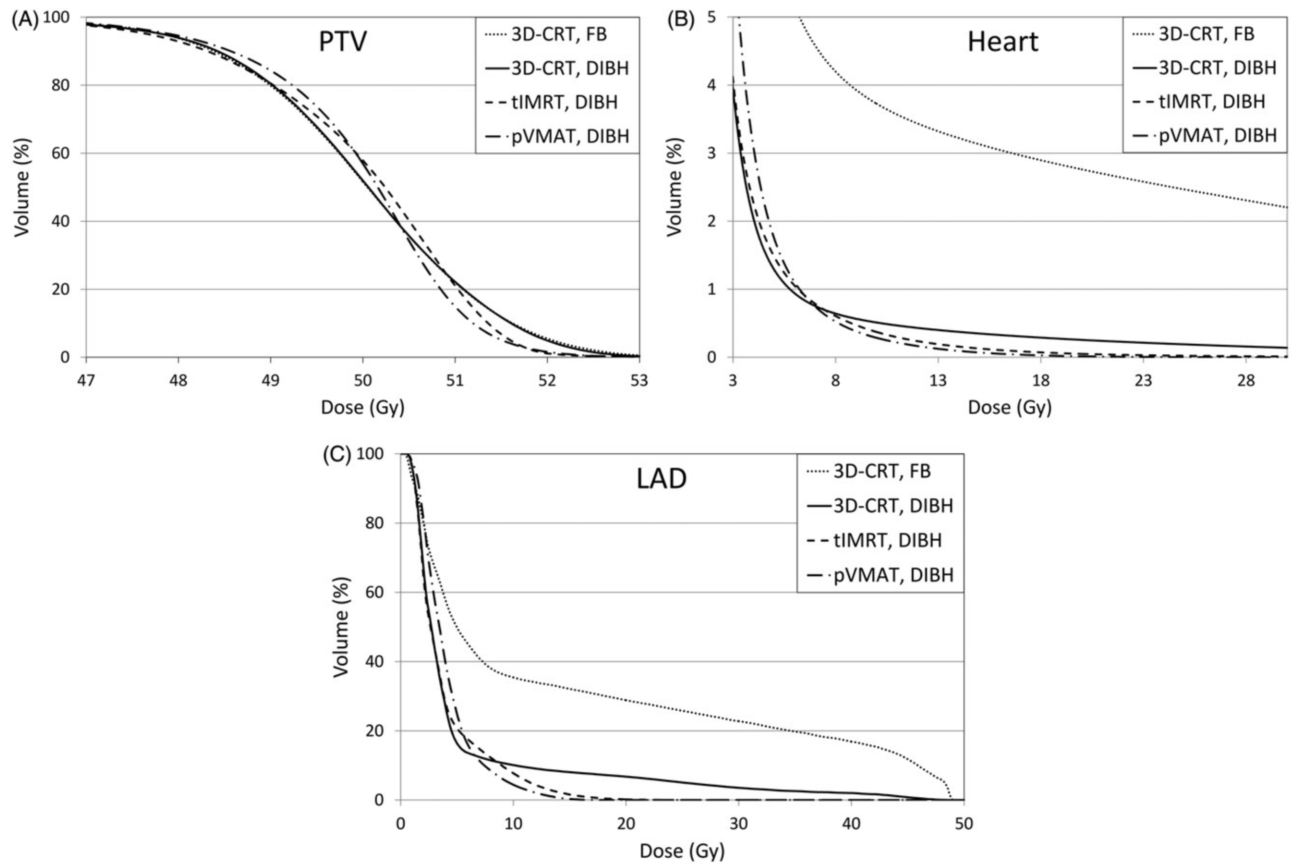

Figure 2. Mean dose-volume histograms averaged for all 16 patients for the PTV (A), the heart (B) and the LAD (C) with 3D-CRT in FB (dotted line), 3D-CRT in DIBH (solid line), tIMRT in DIBH (dashed line) and pVMAT in DIBH (mixed dashed and dotted line). DIBH, deep inspiration breath-hold; FB, free breathing; 3D-CRT, conventional three-dimensional conformal radiotherapy; tIMRT, tangential IMRT; pVMAT, VMAT with partial arcs.

were able to plan all patients with $V_{25\ Gy}$ below 5%. There were no significant differences in $D_{2\%}$ in the dynamic plans compared to 3D-CRT. Mean DVHs of the heart doses between 3 and 30 Gy are shown in Figure 2(B) and between 0 and 6 Gy in Supplementary 2b.

The LAD doses were generally lower with the dynamic techniques (Table 1 and Supplementary 3). For tIMRT, there was a significant difference for all parameters, mean dose ($p = .03$), $V_{25\ Gy}$ ($p = .03$) and $D_{2\%}$ ($p = .02$), while for pVMAT, the only significant difference was for $V_{25\ Gy}$ ($p = .03$) compared to 3D-CRT. The mean DVH for the LAD is shown in Figure 2(C).

The mean dose to the ipsilateral lung was lowest with tIMRT (Table 1), 5.7 Gy compared to 6.3 Gy for 3D-CRT ($p = .06$). The mean lung dose with pVMAT, 7.0 Gy, was significantly higher than with 3D-CRT ($p < .01$). $V_{20\ Gy}$ was significantly lower with tIMRT than with 3D-CRT, 9.1 vs 10.1% ($p = .03$). For the contralateral lung, the mean dose was significantly larger with pVMAT, 0.6 Gy compared to 0.1 for 3D-CRT ($p < .01$). There was no significant difference between tIMRT and 3D-CRT. Data for the contralateral lung and mean DVHs for both lungs are shown in Supplementary material.

The mean dose and the near maximum dose in the CB were similar with tIMRT and 3D-CRT (Table 1 and Supplementary 3). $D_{2\%}$ was significantly lower with tIMRT compared to 3D-CRT ($p = .01$). The pVMAT plans partially irradiated the CB resulting in a significantly higher mean dose (2.5 Gy) and $D_{2\%}$ (6.6 Gy) compared to 3D-CRT (0.4 and 0.8 Gy, $p < .01$). The mean DVH for the CB is shown in Supplementary 2e.

Discussion

In this treatment planning study, 3D-CRT, tIMRT and pVMAT, all with DIBH, were compared for the irradiation of early-stage breast cancer. tIMRT showed the lowest heart and lung doses. tIMRT plans also had better homogeneity and conformity compared to 3D-CRT. pVMAT had the most conform and homogeneous plans and the lowest V_{25Gy} to the heart but significantly higher mean heart dose as well as most other OAR doses. 3D-CRT showed a low mean heart and lung dose (no significant difference from tIMRT) but had larger volumes of heart and lung tissue in the high dose regions and poorer homogeneity and conformity compared to the dynamic plans.

There are other studies on heart dose reduction with breath-hold and different techniques in radiotherapy of early-stage breast cancer. Mast et al. [9] compared 3D-CRT with tIMRT, both with breath-hold, and concluded that tIMRT reduces heart and LAD doses compared to 3D-CRT. The percentage reduction of the mean heart dose is similar to the results in this study. The same group has also compared tIMRT with TomoTherapy during breath-hold [13]. The latter was able to further reduce the mean heart and LAD dose for both structures compared to IMRT, but the combination of

TomoTherapy and breath-hold was not yet feasible. We could not achieve the same reduction with pVMAT in this study. The reason could be differences in the Varian and TomoTherapy systems in terms of hardware and software. Another reason could be the percentage increase of the lung volume in the two studies. With a larger distance between the heart and the breast, the tangential geometry is more favorable and the possibility for VMAT to further reduce the heart dose by optimization decreases. In a recent study, Sakka et al. [12] compared the dose-sparing effect of IMRT and VMAT for early-stage breast cancer in FB and DIBH. They conclude that IMRT reduces the mean heart dose by approximately 30% compared to VMAT. The present study confirms this result and in addition compares the dynamic techniques with 3D-CRT, the most common technique used for breast irradiation. Fogliata et al. [17] compared two different planning strategies for breast treatment with VMAT in DIBH. The plans with partial arcs (pVMAT), very similar to the ones used in this study, showed lower OAR doses compared to the plans with two half rotations and strengthens the choice of VMAT technique in this study. The pVMAT results were similar to the ones in the present study when renormalized to 50 Gy.

The relative heart dose reduction in our study is, as mentioned above, similar to what has been previously reported by others. However, the mean heart dose with DIBH was lower than in the above and other comparable breath-hold studies, both for 3D-CRT [9,18], IMRT [9,12] and VMAT [12,17], when the results are normalized to 50 Gy. This, again, is probably due to the larger increase in lung volume during DIBH in this study compared to most other studies.

With dynamic techniques, it is possible to reduce the LAD dose [9]. In spite of the low priority on LAD dose, our study confirms this, as shown in Figure 2(C). With more focus on LAD in the optimization, a more significant reduction could have been achieved also with pVMAT.tIMRT achieved the lowest ipsi- and contralateral lung doses, a low dose to the CB and a significant dose reduction in the majority of measured OAR parameters, as compared to 3D-CRT. The lung doses were comparable with other studies [9,12], but the reduction with tIMRT versus 3D-CRT was smaller in our study compared to the study by Mast et al. [9], probably due to the larger lung volumes. pVMAT showed inferior results compared to the other techniques for most of the OAR parameters.

A comparison of treatment plans with different techniques is difficult to perform in an objective and unbiased way. The results are strongly depending on choices made during planning and on the time spent on optimizing the plans. Especially dynamic plans can vary a lot, depending on the constraints used and how much they are modified during optimization. For treatment planning in some regions, eg, prostate, it is possible to standardize the field angles and constraints to fit most patients. The breast anatomy is highly variable, making it difficult to standardize the IMRT or VMAT treatment planning. In this study, a template was used, but the constraints were often changed considerably to fulfill the prioritized planning criteria for PTV and heart. The results could have been very different with less focus on the mean heart dose, especially for pVMAT.

The tangential geometry is optimal for most patients, and the 3D-CRT and tIMRT plans showed very low heart doses. Also, with pVMAT, it was possible to achieve acceptable heart doses, however not as low as with the tangential techniques. This confirms the results of previous studies [9,12], as discussed earlier. Attempts were also made with half arcs for three of the patients, but the mean heart dose increased (data not shown). The optimizing algorithm for VMAT does not yet appear to be able to find the best solution for irradiation of the breast and minimizing the mean heart dose.

On the other hand, the optimizing algorithms in the dynamic plans are able to reduce the high-dose regions in the heart compared to the 3D-CRT plans [9,10], which is shown in Figure 2(B). In this study, nearly every tIMRT and pVMAT plan had a $V_{25\ Gy}$ of 0% and no plans over 5%. $V_{25\ Gy}$, or equivalents utilizing other fractionation regimes, has been used as a criterion for many years, and it is debatable in which parameters have the strongest correlation with heart disease, the mean dose or V_{25Gy}.

No limit on maximum MU was used for the dynamic planning. There is evidence that conventional radiotherapy in early-stage breast cancer increases the risk of second primary cancers [19]. Higher MU yields more head scatter and increases the low dose outside the treatment region, which could further increase the risk of induced second cancers [20]. If, by using a dynamic technique to reduce the heart dose, a major increase in MU is obtained, the gain of reduced major heart events may be cancelled by the increased risk of second cancers. However, if the flattening filter is removed from the beam the head scatter is reduced by a large proportion [21]. Thus, if treating breast cancer patients with IMRT or VMAT, flattening filter free beams may be considered. In contrast, the lateral parts of a flattening free beam have lower dose. Compared to a plan with flattening filter, it may then be necessary to increase the number of MU, to obtain good coverage in the whole PTV and hence the benefit with lower head scatter could be decreased.

Based on the results of this study, VMAT does not appear to be the best standard technique for radiotherapy of early-stage breast cancer. However, there may be special cases where VMAT could give better results than IMRT or 3D-CRT, eg, bilateral breast cancer. Also, for patients where the CB is protruding and in conflict with the tangential fields, VMAT may be a better solution.

Practical considerations with tIMRT and pVMAT

To account for setup errors, movement and swelling of the breast throughout the treatment a PTV margin outside the skin (skin flash) should be added if dynamic techniques are used to irradiate the breast. One solution is to add a bolus during optimization and then remove it and recalculate [22]. To save time in the planning process this was not done in this study. A point to be aware of is that the use of skin flash for the dynamic plans will increase the number of MU.

The choice of eight partial arcs on each side was made to get the maximum effect of the optimization for the chosen geometry. For clinical treatment with pVMAT, the number of arcs could be reduced in order to save treatment time. However, if arranging the start and stop angles so that the gantry moves back and forth, multiple arcs are not very time consuming.

Patients are normally comfortable with holding their breath up to 30 seconds. With partial arcs, the patient can breathe between the arcs, but if longer arcs are used the arc will sometimes be interrupted if the patient has to breathe. It is however easy to resume treatment after the interruption, at least on TrueBeam (Varian Medical Systems).

For breast irradiation with VMAT the isocenter must be more dorsal than with the other techniques to avoid collision between the gantry and the couch. Caution must then be taken regarding the distance to the arms of the patient and the immobilization.

In a clinical setting, a margin should be added to LAD and possibly the whole heart to account for heart movement.

A question is whether treatment planning of dynamic techniques is more resource consuming. When implementing IMRT or VMAT for breast, the treatment planning time will increase during a transition period. Another resource consuming aspect of IMRT and VMAT might be the quality control of the dynamic plans.

Conclusion

tIMRT and 3D-CRT with DIBH are better techniques for sparing heart tissue and other OAR without compromising target coverage in early-stage breast cancer irradiation compared to pVMAT. The OAR doses are lower with tIMRT compared to 3D-CRT, but the relatively small difference must be weighed against the risk associated with higher MU for tIMRT.

Disclosure statement

No potential conflict of interest was reported by the authors.

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