

A treatment planning comparison of contemporary photon-based radiation techniques for breast cancer

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ABSTRACT

Background and purpose: Adjuvant radiation therapy (RT) of the whole breast (WB) is still the standard treatment for early breast cancer. A variety of radiation techniques is currently available according to different delivery strategies. This study aims to provide a comparison of six treatment planning strategies commonly adopted for breast-conserving adjuvant RT and to use the Pareto concept in an attempt to assess the degree of plan optimization.

Materials and methods: Two groups of six left- and five right-sided cases with different dose prescriptions were involved (22 patients in total). Field-in-Field (FiF), two and four Fields static-IMRT (sIMRT-2f and sIMRT-4f), Volumetric-Modulated-Arc-Therapy (VMAT), Helical Tomotherapy (HT) and Static-Angles Tomotherapy (TomoDirect™ – TD) were planned. Dose volume constraints were taken from the RTOG protocol 1005. Pareto fronts were built for a selected case to evaluate the reliability of the plan optimization process.

Results: The best target dose coverage was observed for TD able to improve significantly ($p < 0.01$) the V95% in a range varying from 1.2% to 7.5% compared to other techniques. The V105% was significantly reduced up to 2% for HT ($p < 0.05$) although FiF and VMAT produced similar values. For the ipsilateral lung, V5Gy, V10Gy and Dmean were significantly lower than all other techniques ($p < 0.02$) for TD while the lowest value of V20Gy was observed for HT. The maximum dose to contralateral breast was significantly lowest for TD ($p < 0.02$) and for FiF ($p < 0.05$). Minor differences were observed for the heart in left-sided patients. Plans for all tested techniques were found to lie on their respective Pareto fronts.

Conclusions: Overall, TD provided significantly better results in terms of target coverage and dose sparing of ipsilateral lung with respect to all other evaluated techniques. It also significantly minimized dose to contralateral breast together with FiF. Pareto front analysis confirmed the reliability of the optimization for a selected case.

1. Introduction

Post-operative whole breast (WB) irradiation is the standard treatment for early-stage breast cancer and it reduces the 10-year risk of recurrence by one third and the 15-year risk of breast cancer death of almost one fifth [1], yet the use of radiation is still potentially associated to an increased risk of pneumonitis [2], fatal cardiac effects [3], acute and late skin reactions [4], as well as of a second breast cancer [5].

The treatment of WB using a photon tangential wedged field technique is still widely used within radiotherapy departments [6]. Although this approach gives excellent local control [7], in general it does not provide good results in terms of planning target volume (PTV) homogeneity and this issue becomes significant when hypofractionated

schemes are adopted [8]. Intensity Modulated Radiation Therapy (IMRT) demonstrated its potential to improve PTV dose homogeneity [9,10,11] together with the dose reduction to organs at risk (OAR) [12] and, more recently, this was further improved by means of modern IMRT solutions such as Volumetric Modulated Arc-Therapy (VMAT) [13–17], Helical Tomotherapy (HT) [17–20] and Static-Angles Tomotherapy, TomoDirect™ (TD) [17,21–23].

When comparing irradiation techniques, the clinical implications of the resulting dosimetry are rarely conclusive since different factors play an important role, from the ability of the planner to the accuracy of the calculation algorithm. In principle, dose comparison studies should be designed to compare plans calculated with the same dose algorithm and optimized according to the Pareto concept [24]. Even if huge

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improvements have been made in treatment planning systems (TPS) to provide optimization with the Pareto concept, suboptimal results have been documented [25]. Therefore, manual Pareto optimization remains the best method to obtain accurate optimized plans albeit this is too time-consuming to use on all cases in clinical practice. However, it can be used for a limited number of cases as a quality control of the plan optimization process.

The aim of this study was to compare the treatment plans designed for WB irradiation with six radiotherapy techniques commonly implemented in clinical practice: Field-in-Field (FiF), static-IMRT using two and four fields (s-IMRT-2f and s-IMRT-4f, respectively), VMAT, HT and TD. Comparison was focused on PTV coverage and homogeneity as well as on OARs sparing according to pre-defined dose-volume objectives. In order to improve the robustness of the comparison, the degree of optimization of s-IMRT-4f, VMAT, HT and TD plans for one selected case was assessed according to their respective bi-dimensional Pareto fronts built for the tradeoff between PTV coverage and ipsilateral lung mean dose. Although several planning comparisons concerning breast treatment have already been published, they included only some of the techniques presented in this paper. To our knowledge, this is the first time they are compared all together.

2. Materials and methods

2.1. Patient selection

Twenty-two patients were randomly selected from our database to populate two groups (G1 and G2) of eleven patients each, according to different fractionation: 50 Gy in 25 fractions (G1) and 42.4 Gy in 16 fractions (G2). These schemes are currently adopted in our clinical practice, in particular the hypofractionated treatment is preferred for patients of age > 60 years old. Each group was populated by six left- and five right-sided cases. No ethics committee approval was needed for the study where patients' planning CT scans were retrospectively involved. An expert radiation oncologist delineated all contours in the axial CT slices using Velocity software (Varian, PaloAlto, USA). The Clinical Target Volume (CTV) of the WB was considered to be all glandular breast tissue and the tissue encompassed in a wire placed clinically at the time of CT acquisition taken in free breathing conditions. PTV was defined by adding a 5-mm isotropic margin to the CTV. The mean PTV volumes and SD were $1240 \pm 644 \text{ cm}^3$ and $1060 \pm 249 \text{ cm}^3$ for G1 and G2, respectively, thus covering a full range of breast volumes [26]. A further "PTVeval" structure was introduced by retracting the PTV 5 mm from the body surface to be used for PTV dose comparison purposes in order to avoid any surface dose calculation differences between algorithms. The OARs were the ipsilateral lung (IL), contralateral lung (CL), contralateral breast (CB) and heart (H). Mean lung volumes (MLV) and SD were $2368 \pm 509 \text{ cm}^3$ and $2877 \pm 621 \text{ cm}^3$ for G1 and G2, respectively. DVH constraints were taken from the RTOG 1005 protocol [27] and were adapted according to the fractionation schemes as summarized in Table 1. The original values were modified to be stricter, because no additional dose was planned for the lumpectomy cavity.

2.2. Treatment planning techniques

Six treatment plans were generated on each CT study resulting in 132 plans overall. A medical physicist with a strong experience in treatment planning and knowledge of the TPS designed all plans involved in the study. To avoid any possible bias, no plan template nor class solutions were applied, that is each plan was optimized by choosing the most appropriate dose volume constraints and gantry angle. The radiation oncologist finally approved each treatment plan.

FiF, s-IMRT-2f, s-IMRT-4f and VMAT plans were created for Elekta Synergy Linac (Elekta AB, Stockholm, Sweden) with a 10-mm leaf width MLC.

Table 1

Dose volume objectives defined for PTVeval and OARs in terms of ideal (first column) and acceptable (second column) values to be achieved. Dmax is defined in one calculation voxel. VxGy < y% stands for "the volume receiving x Gy should be less than y% of its total".

Structure	Ideal value	Acceptable value
PTV eval	V95% > 95% D2% < 105%	V90% > 90% D2% < 110%
Contralateral Breast	Dmax < 310 cGy V186cGy < 5%	Dmax < 496 cGy V310cGy < 5%
Ipsilateral Lung	V20Gy < 20% V10Gy < 25% V5Gy < 40%	V20Gy < 25% V10Gy < 30% V5Gy < 50%
Contralateral Lung	V5Gy < 5%	V5Gy < 10%
Heart (left sided)	V20Gy < 5% V10Gy < 15% Dmean < 4 Gy	V25Gy < 5% V10Gy < 20% Dmean < 5 Gy

FiF plans were generated with six to eight 6MV photon tangential beams using XiO TPS (version 5.00.01, Elekta AB, Stockholm, Sweden). The planning technique used two classic tangential fields at a first instance, with the sequential addition of further opposing tangential beam couples sharing the same isocenter and gantry position in order to reduce PTV overdosage. Additional tangential beams were reduced in size keeping a minimum equivalent field size $> 3 \times 3 \text{ cm}^2$. Dose was calculated using the superposition algorithm with a dose grid size of $3 \times 3 \times 3 \text{ mm}^3$.

sIMRT-2f and sIMRT-4f plans were generated with Monaco TPS (version 5.00.04, Elekta AB, Stockholm, Sweden) employing Monte Carlo algorithm with a dose-grid size of $3 \times 3 \times 3 \text{ mm}^3$ and a statistical uncertainty of 0.5%. Two and four 6MV photon tangential fields were used, respectively. For sIMRT-4f, beams were spaced 10° apart from one another at each breast side. The step-and-shoot segmentation option with a minimum segment area of 2 cm^2 and a minimum number of MU per segment of 4 was used.

VMAT plans were also generated with Monaco TPS using two to four 6MV photon arcs with a span of 210° with 120 control points per arc and a minimum segment width of 2 cm.

HT and TD plans were created for the TomoHDA system (Accuray, Sunnyvale, USA) with TomoEdge™ option [28]. For both techniques, plans were generated using the convolution/superposition algorithm (Version 5.1.0.4, Accuray, Sunnyvale, USA) with a dose-grid size of $2.2 \times 2.2 \times 3 \text{ mm}^3$.

HT plans were designed with a field width of 2.5 cm, a pitch of 0.287, and a modulation factor between 2 and 3. No blocking structure was employed to avoid angular beam irradiation.

TD plans were designed using four tangential beams, two at each breast side with 10° angular spacing with a field width of 2.5 cm, a pitch of 0.25, and a modulation factor between 2 and 3.

For all techniques except HT, gantry angles were chosen to minimize the direct irradiation of the CB.

All plans were designed by the same planner who is typically involved in clinical planning using the aforementioned techniques. For inverse planning techniques, the optimization workflow was divided in three sequential steps: optimization of the PTV until an ideal DVH in terms of coverage and homogeneity is obtained, optimization of all OARs in order to fulfill the dose-volume objectives reported in Table 1, and further optimization of the PTV if compromised without violating the OARs dose-volume objectives.

2.3. Plan analysis

To avoid possible differences caused by various DVH computing algorithms, dose distributions were exported to Velocity where the DVHs of the treatment plans were recomputed.

Mean values of parameters reported in Table 1 were used to

compare the different planning techniques and for statistical analysis. In addition, for the PTV_{eval}, the conformity index (CI) and the homogeneity index (HI) were also computed (see [Supplementary material](#) for definitions).

2.4. Statistical analysis

The Wilcoxon matched-paired signed-rank test was used to compare the dose-volume results calculated from the planning techniques with a significance level $p \leq 0.05$.

2.5. Plan quality analysis

To summarize the differences between techniques a Plan Quality Score (PQS) was arbitrarily chosen and assigned to each plan. A score of ± 1 (+ best, – worst result) was assigned to calculated parameters that had a difference that was statistically significant with respect to all others and a score of ± 0.5 (+ best, – worst result) to calculated parameters statistically significant compared to at least four others. Otherwise, 0 was assigned. Techniques that performed better returned higher scores.

2.6. Pareto front evaluation

Pareto fronts were built for four techniques (s-IMRT 4f, VMAT, HT and TD) for one selected case of G1. They were not built for FiF (forward planning technique) and s-IMRT 2f (smaller number of available beamlets). Bidimensional Pareto fronts represented the trade-off between V95% of PTV_{eval} and the mean dose of the IL. The dose to all other OARs was held constant according to the original plan so that a dose deviation of a maximum of 0.5 Gy on average and maximum doses was accepted. The plans were obtained by gradually increasing the penalty values for the IL objective [29,30].

If the original plan lied on the front, its optimization was considered mathematically optimal at least concerning the dose tradeoff evaluated.

3. Results

Overall, all the techniques were able to meet the acceptable dose volume objectives with the exception of CB maximum dose which was found slightly higher than the acceptable value for some of the techniques, as it will be summarized in the following.

[Fig. 1](#) shows the dose distributions of a single left-sided patient. The lowest number of Monitor Units (MUs) was observed for FiF technique in G1 and G2 groups ($360/422 \pm 43/55$ MU, respectively, $p < 0.05$), VMAT required $875/1010 \pm 95/99$ MU, respectively, to deliver the treatments while the two IMRT techniques lied in between. In terms of treatment time, HT techniques required $660/710 \text{ s} \pm 58/63 \text{ s}$ as the longest beam-on-time (BOT) ($p < 0.01$), followed by TD with $390/411 \text{ s} \pm 90/110 \text{ s}$. FiF resulted as the fastest technique in terms of BOT with $96/111 \text{ s} \pm 15/18 \text{ s}$ ($p < 0.01$).

3.1. PTV_{eval}

No significant difference ($p = 0.42$) was observed between the mean PTV_{eval} volumes.

All techniques fulfilled the dose objectives of D2% and V90% in both groups ([Tables 2 and 3](#)). In contrast, the objective V95% > 95% was not achieved by FiF in G1 and by s-IMRT 2f in both groups.

The lowest significant mean PTV_{eval} dose value was observed for HT in both groups ($p < 0.05$). The best significant PTV_{eval} dose coverage was achieved for TD in both groups ($p < 0.01$). s-IMRT 2f produced the lowest significant values of D98% and V95% in both groups ($p < 0.01$). HT significantly produced the lowest values of D2% in both groups ($p < 0.05$). The highest value of CI was obtained for VMAT and it was significant in G1 ($p < 0.05$). TD achieved the best HI

value while s-IMRT 2f achieved the worst one in both groups.

3.2. Contra-lateral breast (CB)

In both groups, the D5% objective was achieved in FiF, s-IMRT 4f, s-IMRT 2f and TD while it was slightly higher than the acceptable value for VMAT and HT. The lowest D5% values were found in FiF (significant in G2, $p < 0.05$) and TD. For D_{max}, TD was found to be well within the ideal value in both groups as well as FiF in G2. The other techniques did not meet the acceptable value and, in particular, the two rotational techniques resulted in the lowest dose-sparing of the CB.

3.3. Ipsilateral lung (IL)

All techniques satisfied the objective for V5Gy, V10Gy and V20Gy in both groups. The lowest V5Gy and V10Gy were found in TD in both groups (significant in G1, $p < 0.02$). The higher V5Gy values were found in VMAT and HT. The highest significant value of V20Gy was found for FiF ($p < 0.02$) and the lowest value for HT in both groups. Lowest D_{mean} was achieved in TD in both groups while the highest value was observed in FiF in G1 and VMAT in G2.

3.4. Contra-lateral lung (CL)

FiF, s-IMRT 4f, s-IMRT2f and TD largely satisfied the dose objective of V5Gy < 5% being equal or very close to zero in both groups. VMAT and HT gave significantly higher values for V5Gy as well as D_{mean} and D_{max} ($p < 0.001$).

3.5. Heart (H)

For left-sided patients, the objective V20Gy < 5% was achieved for all techniques in both groups apart from FiF in G1. Its lowest value, was found in VMAT and HT in both groups (statistically significant for HT in G1, $p < 0.001$). No significant differences were observed for V10Gy nor for D_{mean} in both groups.

For right-sided patients, major differences were found for D_{mean}: FiF and TD were able to reduce up to 2.5 Gy the mean dose in both groups with respect to VMAT and HT (statistically significant for FiF in both groups, $p < 0.05$).

3.6. Plan quality analysis

The results of the plan quality analysis ([Tables 1 and 2 of Supplementary material](#)) showed that in G1, TD resulted in the highest PQS (4) while s-IMRT 2f resulted in the lowest one (–1.5). The other techniques were equivalent. Similarly, in G2, TD resulted in the highest PQS (2.5) while HT showed the lowest results (–3). VMAT and s-IMRT 2f scored –1. FiF and s-IMRT 4f were found to be nearly equivalent (–0.5 and 0, respectively).

3.7. Pareto front evaluation

[Fig. 2](#) presents the Pareto fronts obtained for the four techniques together with the corresponding DVH point value of the planned case. The planned cases lied on their Pareto fronts for all techniques except for VMAT where the D_{mean} of the IL was found to be 0.3 Gy greater than the Pareto front value. The best Pareto front was found for TD while the worst for HT.

4. Discussion

Treatment planning studies should require improved standards for designing the studies and reporting the results [31], Pareto fronts were built for four techniques in order to evaluate the degree of plan optimization. Our analysis suggests that our plans are all Pareto optimal for

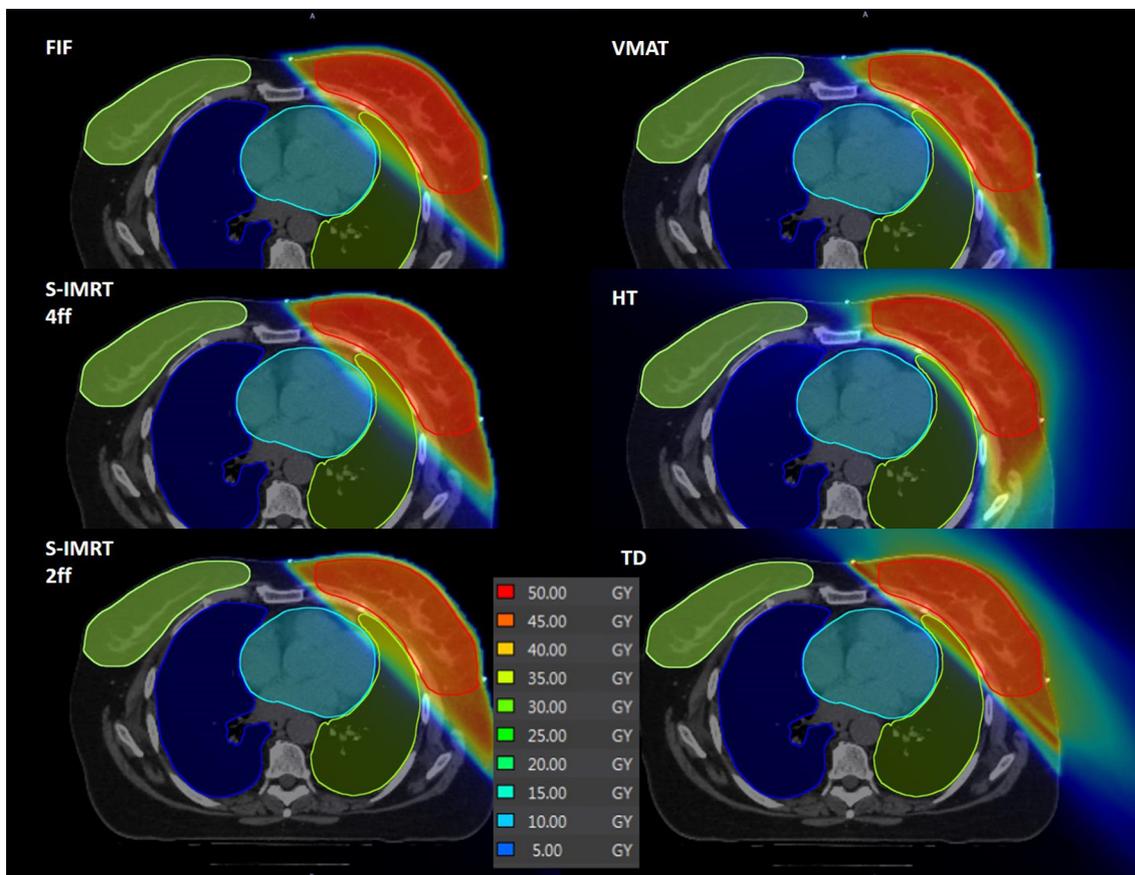


Fig. 1. Dose distributions of the six different techniques for a patient of G1.

the specific dose trade-off evaluated increasing the reliability of our conclusions. To our knowledge, this is the first time an attempt to evaluate the quality of the optimization is conducted in a planning comparison study.

We considered it useful to report dose-volume data for a well-established hypofractionated radiation schedule [32] due to the lack of such data in the literature. Further in this discussion, differences between techniques will be discussed regardless of the group unless specified.

TD produced the best PTV_{eval} coverage with a significant difference compared to all techniques except for VMAT. Both TD and VMAT coverage values were similar to those previously reported for a standard fractionation schedule [14–16,21,23]. On the other hand, s-IMRT 2f significantly resulted in the worst value. In G1, where the mean breast volume was larger, the PTV_{eval} coverage did not fulfill the ideal objective. This is due to the small number of degrees of freedom available during the optimization that caused a reduction of coverage to prevent hot spots. Although such a low value corresponds well with other findings [33], two other papers [14,16] have reported better results in terms of PTV coverage. In both studies, the mean breast volume was smaller (537 cc and 360 cc, respectively) than those herein reported. However, FiF showed better coverage, suggesting that the segmentation process implemented in Monaco TPS could be improved at least when only two fields are employed. The difference between optimal and segmented dose when only two fields were employed was observed to be quite large if compared to the same difference observed when four fields were used. The lowest significant value of D2% observed for HT in both groups confirmed results of other studies [10,34] demonstrating the increase of target homogeneity according to the increased number of beamlets.

The highest CI value returned by VMAT (significant in G1) and, in turn, by s-IMRT 4f demonstrated how the method implemented in Monaco TPS to improve the dose conformity was more effective than

the ring-based optimization usually employed in the Accuray TPS. Although the lowest CI values were observed for TD and FiF they were slightly superior to those published earlier [10,14]. The highest HI returned for TD was a consequence of the best PTV_{eval} coverage obtained for such technique.

IMRT techniques may increase CB doses, exposing patients to an increased risk of developing a secondary malignancy [35]. Our results show that both D5% and Dmax were significantly higher for the two rotational techniques. TD was the only IMRT technique that was able to almost reach the best results obtained with FiF. Although the CB dose reported in the literature is quite different, no significant differences were observed compared to previously published data [10,15]. CB dose-sparing increases when irradiating small breast volumes or when cutting the PTV at its edges [14,36]. The overexposure of the CB for HT may have been reduced by the use of blocking geometric structures. However, this may improve the OARs dose-sparing at the expense of the CI and the beam-on time [18] because of the small number of beamlets and the reduced irradiation angle. In this study, plans were designed to fulfill the clinical goals of our department that privilege the conformity of the high dose to the target volume.

The occurrence of radiation pneumonitis after breast irradiation has been associated with the age of the patient, the use of concomitant chemotherapy, and the dose delivered to the IL (V20Gy and mean dose) [37–39]. Another study also demonstrated that the V5Gy might lead significantly to the development of pneumonitis if greater than 42% [40]. Therefore, reducing IL V20Gy, V5Gy, and mean dose remains important endpoints. All plans in our study were able to maintain these three parameters well below the RTOG dose limits. HT and VMAT plans resulted in higher V5Gy, although their mean dose values were similar or even smaller than the other techniques. Overall, TD was significantly superior to all other techniques in terms of IL sparing. Compared to previous studies, IL mean values obtained from our study in G1 were

Table 2
Detailed comparison of dose distributions in G1 and statistically significant differences ($p < 0.05$) for each technique versus alternatives: a Test vs FIF; b Test vs s-IMRT 4f; c Test vs s-IMRT 2f; d Test vs VMAT; e Test vs HT; f Test vs TD. Best results are reported in bold while worst results are reported in italic. Values are underlined if they were statistically significant versus at least four out of five alternative techniques.

	Objective	FIF (a)		s-IMRT 4f (b)		s-IMRT 2f (c)		VMAT (d)		HT (e)		TD (f)	
		Ideal	Acceptable										
PTVeval	D2% (Gy)	52.5	55	52.0 ± 0.2 ^{b,e}	52.3 ± 0.5 ^{a,e}	52.4 ± 0.5 ^c	52.1 ± 0.5 ^e	51.1 ± 0.4 ^{b,b,c,d,f}	52.0 ± 0.5 ^c	51.1 ± 0.4 ^{b,b,c,d,f}	52.0 ± 0.5 ^c	52.0 ± 0.5 ^c	52.0 ± 0.5 ^c
	V90% (%)	–	90	99.1 ± 1.6	99.5 ± 0.4	99.7 ± 1.6	99.4 ± 0.7	99 ± 0.6	99.4 ± 0.7	99 ± 0.6	99.6 ± 0.5	99.6 ± 0.5	99.6 ± 0.5
	V95% (%)	95	–	94.5 ± 4.2 ^{c,f}	95.0 ± 2.2 ^{c,f}	91.3 ± 5.9 ^{b,d,e,f}	96.7 ± 3.2 ^c	96.5 ± 2.1 ^{c,f}	96.7 ± 3.2 ^c	96.5 ± 2.1 ^{c,f}	98.8 ± 1.5 ^{a,b,c,e}	98.8 ± 1.5 ^{a,b,c,e}	98.8 ± 1.5 ^{a,b,c,e}
Contralateral Breast	D5% (cGy)	< 186	< 310	70.5 ± 31.7 ^{b,c,d,e}	174.9 ± 73.1 ^{a,d,e,f}	179.0 ± 65.2 ^{a,d,e,f}	337.8 ± 81.0 ^{b,b,c,f}	324.8 ± 62.6 ^{b,b,c,f}	337.8 ± 81.0 ^{b,b,c,f}	324.8 ± 62.6 ^{b,b,c,f}	77.0 ± 21.6 ^{b,c,d,e}	77.0 ± 21.6 ^{b,c,d,e}	77.0 ± 21.6 ^{b,c,d,e}
	Dmax (cGy)	< 310	< 496	691.3 ± 200.5	510.4 ± 264.5 ^f	464.4 ± 187.6 ^{e,f}	617.0 ± 209.8 ^f	636.7 ± 195.2 ^f	617.0 ± 209.8 ^f	636.7 ± 195.2 ^f	290.9 ± 103.2 ^{c,d,e}	290.9 ± 103.2 ^{c,d,e}	290.9 ± 103.2 ^{c,d,e}
	V5Gy (%)	< 40	< 50	24.1 ± 5.7 ^{d,e,f}	26.6 ± 6.0 ^{d,e,f}	24.3 ± 6.9 ^{d,e,f}	32.5 ± 7.4 ^f	37.1 ± 8.0 ^f	32.5 ± 7.4 ^f	37.1 ± 8.0 ^f	20.1 ± 3.9 ^{b,b,c,d,e}	20.1 ± 3.9 ^{b,b,c,d,e}	20.1 ± 3.9 ^{b,b,c,d,e}
Ipsilateral Lung	V10Gy (%)	< 25	< 30	19.3 ± 4.9 ^f	18.3 ± 6.3 ^f	16.9 ± 5.6 ^{d,f}	19.8 ± 5.8 ^{c,f}	18.1 ± 6.0 ^f	19.8 ± 5.8 ^{c,f}	18.1 ± 6.0 ^f	14.2 ± 5.0 ^{b,b,c,d,e}	14.2 ± 5.0 ^{b,b,c,d,e}	14.2 ± 5.0 ^{b,b,c,d,e}
	V20Gy (%)	< 20	< 25	15.1 ± 4.2 ^{b,c,d,e,f}	12.1 ± 5.0 ^a	11.7 ± 5.1 ^{a,f}	10.9 ± 4.3 ^a	9.1 ± 3.4 ^a	10.9 ± 4.3 ^a	9.1 ± 3.4 ^a	9.6 ± 3.6 ^{a,e}	9.6 ± 3.6 ^{a,e}	9.6 ± 3.6 ^{a,e}
	V5Gy (%)	< 5	< 10	0.0 ± 0.0 ^{a,e}	0.0 ± 0.0 ^{d,e}	0.0 ± 0.0 ^{a,e}	8.5 ± 10.4 ^{a,b,c,f}	6.8 ± 2.5 ^{a,b,c,f}	8.5 ± 10.4 ^{a,b,c,f}	6.8 ± 2.5 ^{a,b,c,f}	0.2 ± 0.5 ^{d,e}	0.2 ± 0.5 ^{d,e}	0.2 ± 0.5 ^{d,e}
Heart (left-sided)	V20Gy (%)	< 5%	–	7.0 ± 4.5 ^{d,e,f}	4.3 ± 2.3 ^c	3.4 ± 1.9 ^e	2.4 ± 2.1 ^a	1.3 ± 1.8 ^{a,b,c,f}	2.4 ± 2.1 ^a	1.3 ± 1.8 ^{a,b,c,f}	3.2 ± 3.6 ^{a,e}	3.2 ± 3.6 ^{a,e}	3.2 ± 3.6 ^{a,e}

Table 3
Detailed comparison of dose distributions in G2 and statistically significant differences ($p < 0.05$) for each technique versus alternatives: a Test vs FIF; b Test vs s-IMRT 4f; c Test vs s-IMRT 2f; d Test vs VMAT; e Test vs HT; f Test vs TD. Best results are reported in bold while worst results are reported in italic. Values are underlined if they were statistically significant versus at least four out of five alternative techniques.

	Objective	FIF (a)		s-IMRT 4f (b)		s-IMRT 2f (c)		VMAT (d)		HT (e)		TD (f)	
		Ideal	Acceptable										
PTVeval	D2% (Gy)	44.2	46.3	44.2 ± 0.2 ^{b,e}	44.3 ± 0.2 ^{b,e}	44.4 ± 0.4 ^c	44.1 ± 0.4 ^c	43.1 ± 0.3 ^{b,b,c,d,f}	44.1 ± 0.4 ^c	43.1 ± 0.3 ^{b,b,c,d,f}	43.6 ± 0.3 ^c	43.6 ± 0.3 ^c	43.6 ± 0.3 ^c
	V90% (%)	–	90	99.8 ± 0.2	99.7 ± 0.3	99.6 ± 0.5	99.9 ± 0.1	99.3 ± 0.5	99.9 ± 0.1	99.3 ± 0.5	99.8 ± 0.2	99.8 ± 0.2	99.8 ± 0.2
	V95% (%)	95	–	95.5 ± 1.4 ^{b,f}	97.7 ± 0.8 ^{c,f}	94.2 ± 3.1 ^{b,b,d,e,f}	98.0 ± 0.8 ^c	96.9 ± 0.1 ^{c,f}	98.0 ± 0.8 ^c	96.9 ± 0.1 ^{c,f}	99.2 ± 0.4 ^{a,b,c,e}	99.2 ± 0.4 ^{a,b,c,e}	99.2 ± 0.4 ^{a,b,c,e}
Contralateral Breast	D5% (cGy)	< 186	< 310	37.4 ± 18.8 ^{b,c,d,e,f}	165.2 ± 50.1 ^{a,c,d,e}	124.8 ± 27.8 ^{a,b,d,e}	355.5 ± 97.9 ^{b,b,c,f}	297.8 ± 37.3 ^{a,b,c,f}	355.5 ± 97.9 ^{b,b,c,f}	297.8 ± 37.3 ^{a,b,c,f}	87.4 ± 72.3 ^{a,d,e}	87.4 ± 72.3 ^{a,d,e}	87.4 ± 72.3 ^{a,d,e}
	Dmax (cGy)	< 310	< 496	252.6 ± 215.1 ^{b,d,e}	539.7 ± 155.6 ^{b,f}	427.0 ± 255.0 ^d	620.9 ± 206.7 ^{b,c,f}	551.5 ± 179.2 ^{b,f}	620.9 ± 206.7 ^{b,c,f}	551.5 ± 179.2 ^{b,f}	290.8 ± 103.8 ^{b,d,e}	290.8 ± 103.8 ^{b,d,e}	290.8 ± 103.8 ^{b,d,e}
	V5Gy (%)	< 40	< 50	25.4 ± 5.5 ^{a,e}	29.2 ± 7.3 ^{d,f}	24.7 ± 6.8 ^d	36.7 ± 4.6 ^{a,b,c,f}	30.3 ± 8.9 ^{d,f}	36.7 ± 4.6 ^{a,b,c,f}	30.3 ± 8.9 ^{d,f}	19.1 ± 3.6 ^{b,d,e}	19.1 ± 3.6 ^{b,d,e}	19.1 ± 3.6 ^{b,d,e}
Ipsilateral Lung	V10Gy (%)	< 25	< 30	20.2 ± 5.1 ^{e,f}	20.1 ± 4.7 ^f	17.1 ± 5.9	21.5 ± 5.7 ^f	14.9 ± 5.5 ^{a,d,f}	21.5 ± 5.7 ^f	14.9 ± 5.5 ^{a,d,f}	13.0 ± 4.4 ^{a,b,d}	13.0 ± 4.4 ^{a,b,d}	13.0 ± 4.4 ^{a,b,d}
	V20Gy (%)	< 20	< 25	15.0 ± 3.7 ^{b,c,d,e,f}	12.4 ± 3.6 ^{a,e,f}	11.8 ± 4.5 ^{b,f}	11.3 ± 5.1 ^{b,e,f}	8.0 ± 3.2 ^{a,b,d}	11.3 ± 5.1 ^{b,e,f}	7.9 ± 3.8 ^{a,b,c,d}	7.9 ± 3.8 ^{a,b,c,d}	7.9 ± 3.8 ^{a,b,c,d}	7.9 ± 3.8 ^{a,b,c,d}
	V5Gy (%)	< 5	< 10	0.0 ± 0.0 ^e	0.0 ± 0.0 ^e	0.0 ± 0.0 ^e	3.4 ± 6.8 ^c	0.5 ± 0.2 ^a	3.4 ± 6.8 ^c	0.5 ± 0.2 ^a	0.2 ± 0.5 ^{d,e}	0.2 ± 0.5 ^{d,e}	0.2 ± 0.5 ^{d,e}
Heart (left-sided)	V20Gy (%)	< 5%	–	2.7 ± 2.3 ^{b,c,d,e,f}	1.4 ± 2.1 ^a	1.0 ± 1.2 ^{a,f}	0.1 ± 0.2 ^{a,f}	0.5 ± 0.2 ^a	0.1 ± 0.2 ^{a,f}	0.5 ± 0.2 ^a	1.3 ± 1.0 ^{b,c,d}	1.3 ± 1.0 ^{b,c,d}	1.3 ± 1.0 ^{b,c,d}

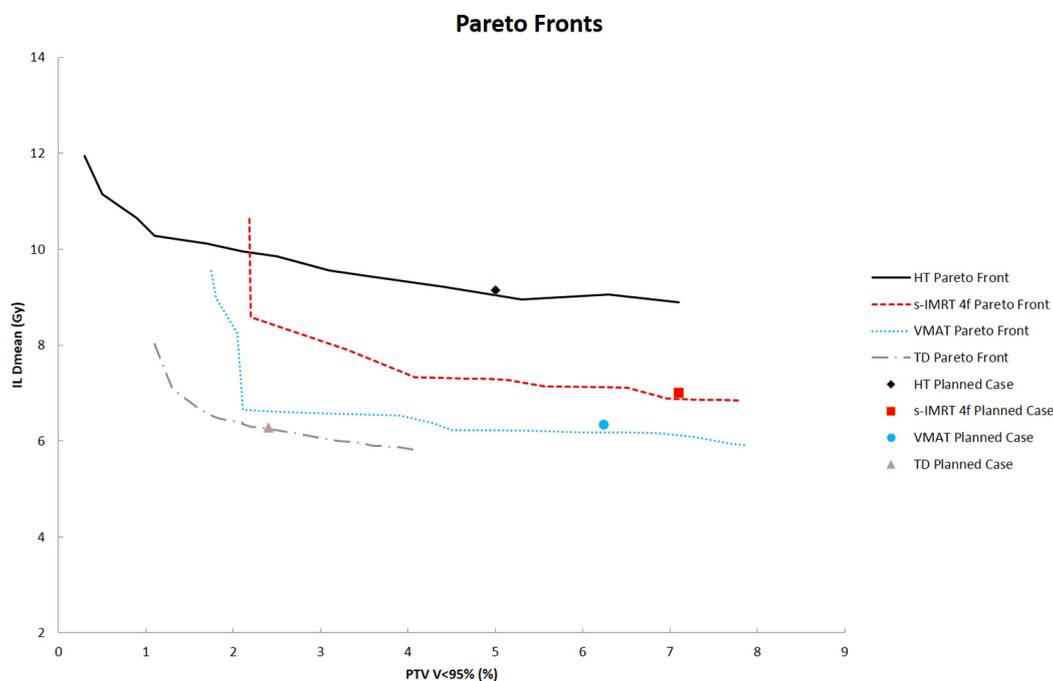


Fig. 2. Pareto fronts comparison for a selected case of G1. The plot also reports the values for the planned case.

similar for FiF [10,15,16,32], s-IMRT 2f [14–16,31], s-IMRT 4f [14,31,32], VMAT [10,14–16] and HT [10,18,32] while for TD it was lower than those previously published [23,32].

Rotational techniques significantly increased the low dose spillage to the contra-lateral lung as highlighted in particular by the V5Gy values that still remained well below the dose constraints as well as the endpoint for radio-induced pneumonitis.

For left-sided breast irradiation, cardiovascular late toxicity progresses over time and may manifest after decades [41]. Darby et al. reported that the rate of ischemic heart disease increases linearly with the mean dose to the heart by 7.4%/Gy, with no apparent threshold [42]. Furthermore, several studies observed substantial radiation-induced heart disease when the heart receives more than 40 Gy [43,44]. Although the use of IMRT has demonstrated to reduce doses delivered to the heart by 25–75% when compared with standard tangential fields [45,46], an increase in cardiovascular morbidity was still observed [47,48]. Hence, the use of technological advances, such as VMAT or TD to reduce cardiac dose, may be of increasing importance particularly when associated to deep inspiration breath-hold (DIBH) techniques [49]. In the present study, volumetric modulated irradiation techniques provided worse results in terms of mean dose, as expected, even though they were still within acceptable values and aligned with values found in literature [10,15,16,18,31]. On the other hand, it is worth noting that the higher degree of fluence modulation lowered the V20Gy. The significant increase of the mean dose observed in this study when using HT and VMAT for right-sided patients suggests to avoid such techniques for these patients since this may lead to a potential increase of the risk of ischemic disease > 20%. However, patients included in Darby's study were irradiated with old techniques supposed to deliver either very high or very low doses to heart. Therefore, the linearity between heart disease and mean dose may be mitigated or even no longer exists with the use of modern RT techniques as VMAT and HT.

TD returned the highest PQS in both groups. This was explained by its superior results in terms of target coverage and IL dose-sparing and good results also for CB, CL and heart. The poorest score was obtained by s-IMRT 2f and was somewhat expected due to the lower degree of modulation available. However, this latter mainly affected the PTVval coverage while the technique showed results similar to the others for doses to the OARs.

Homogeneous results were found between groups for all techniques except for HT. The poorest results obtained by HT for the CL returned in G2 were probably due to the smaller mean target volume compared to G1. It reduced the amount of attenuating tissue, leading to an increase of the transmitted dose to the CL.

Six different treatment planning techniques used for whole-breast irradiation were compared in terms of calculated dose to PTV and OARs. Although all techniques were able to fulfill the dose limit criteria adapted from RTOG 1005, TD was significantly superior to others in terms of target coverage and sparing of the ipsi-lateral lung. It also resulted, together with FiF, the best option to spare contra-lateral breast. HT and VMAT were observed to significantly increase the dose spillage to contra-lateral OARs. Pareto front analysis confirmed the reliability of the optimization for a selected case.

Conflict of interest statement

R. Moeckli is holding a grant from Accuray Inc. for a research project in Tomotherapy. However, the present work is not directly related to that grant.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.phro.2018.08.002>.

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