

External beam accelerated partial breast irradiation: dosimetric assessment of conformal and three different intensity modulated techniques

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Background. The aim of the study was to evaluate and compare four different external beam radiotherapy techniques of accelerated partial breast irradiation (APBI) considering target coverage, dose to organs at risk and overall plan quality. The investigated techniques were three dimensional conformal radiotherapy (3D-CRT), "step and shoot" (SS) and "sliding window" (SW) intensity-modulated radiotherapy (IMRT), intensity-modulated arc therapy (RA).

Patients and methods. CT scans of 40 APBI patients were selected for the study. The planning objectives were set up according to the international recommendations. Homogeneity, conformity and plan quality indices were calculated from volumetric and dosimetric parameters of target volumes and organs at risk. The total monitor units and feasibility were also investigated.

Results. There were no significant differences in the coverage of the target volume between the techniques. The homogeneity indices of 3D-CRT, SS, SW and RA plans were 0.068, 0.074, 0.058 and 0.081, respectively. The conformation numbers were 0.60, 0.80, 0.82 and 0.89, respectively. The $V_{50\%}$ values of the ipsilateral breast for 3D-CRT, SS, SW and RA were 47.5%, 40.2%, 39.9% and 31.6%, respectively. The average $V_{10\%}$ and $V_{40\%}$ values of ipsilateral lung were 13.1%, 28.1%, 28%, 36% and 2.6%, 1.9%, 1.9%, 3%, respectively. The 3D-CRT technique provided the best heart protection, especially in the low dose region. All contralateral organs received low doses. The SW technique achieved the best plan quality index (PQI).

Conclusions. Good target volume coverage and tolerable dose to the organs at risk are achievable with all four techniques. Taking into account all aspects, we recommend the SW IMRT technique for APBI.

Key words: accelerated partial breast irradiation; dosimetric evaluation; IMRT; RapidArc

Introduction

Several previous prospective randomized trials and their meta-analysis proved that in the treatment of breast tumours, radiation therapy is an important part of breast conserving therapy. Breast conserving surgery and the subsequent irradiation of the remaining breast tissue ensure the same survival rate as radical breast surgery.^{1,2} Nowadays,

accelerated partial breast irradiation (APBI) is becoming more and more an accepted treatment for early-stage invasive breast tumours.³⁻⁸ Two main advantages are short overall treatment time (5 days) and smaller irradiated volume, which helps for the organs at risk (OAR) to be spared.

In the first external beam APBI trials the patients were treated with 3 dimensional conformal (3D-CRT) technique.⁹ Studies with long follow up

times can be also found with brachytherapy.^{10,11} These trials have the largest number of patients treated and the longest follow-up time. In our previous paper the dosimetrical differences of the external beam and interstitial brachytherapy for APBI were evaluated.¹² It was found that the target volume can be appropriately irradiated by both techniques, but brachytherapy generally spares normal tissues and organs at risk better than IMRT. In 2006 a phase II sequential trial was launched at our institution.¹³ In the first part of the trial between 2006 and 2011 forty-four patients were treated with 3D-CRT technique, while in the second part between 2011 and 2014 sixty patients were treated with image-guided “step & shoot” intensity-modulated (IMRT) technique, using 5 coplanar fields. Currently at our institution APBI treatments are carried out with “sliding window” IMRT technique according to our preliminary study.¹⁴

In current study, we conducted a dosimetric comparison of the traditional 3D-CRT, the intensity-modulated “step & shoot” (SS), “sliding window” (SW) and “RapidArc” (RA) techniques for APBI.

Patients and methods

Patients

For this study 40 patients were selected, who were previously treated with early-stage invasive breast cancer at our institution between 2006 and 2014 in a phase II APBI trial.^{13,15} The study protocol was evaluated and accepted by the institutional and national ethics committees, and all patients provided written informed consent before enrolment. The trial was registered at ClinicalTrials.gov with identifier number NCT02003560. During breast-conserving surgery titanium surgical clips were placed in each patient to mark the boundaries of the excision cavity, which increased the accuracy of defining the resection cavity and consequently the planning target volume (PTV).

Patient immobilization and CT acquisition

During planning CT scan, patients were positioned supine in a wingboard fixation device (Civco, USA). Around both breasts and on the surgical scar metal wires were placed to increase the precision of contouring. CT scans started from the mandible and included the complete volume of the lungs

and the volumes of both breasts. The most crucial part of partial breast irradiation is the exact localization of the excision cavity. Using titanium clips and the 3 mm thickness of the planning CT slices, the borders of surgical cavity could be defined in acceptable precision.

Contouring

The contouring and 3D-CRT plans were made with Pinnacle 8.0m (Philips, The Netherlands) treatment planning system, while for the plans of SS, SW and RA the Eclipse 11 (Varian, USA) planning software was used. In the first step of target volume definition, the tumour bed was contoured by the radiation oncologist based on the seroma and the surrounding clips. In the second step, on the basis of the intact surgical margins and pathological results, it was expanded in 6 directions with margins of different size to define CTV. The minimal and maximal value of the extension between the tumour bed and the CTV was 5 and 18 mm, respectively.¹⁶ The CTV was limited by the border of ipsilateral breast tissue. The safety margin between the CTV and PTV was 5 mm. As the skin is an organ at risk during partial breast irradiation, a 5 mm thick volume of the skin was cropped from PTV to create PTV_{eval}. Heart, ipsilateral and contralateral breasts and lungs, non-target breast were contoured as organs at risk. Non-target breast was created with the extraction of PTV from ipsilateral breast.

Planning purposes

36.9 Gy in 9 fractions was delivered on 5 consecutive days, twice a day with at least 6 hours interval between fractions. 100% of the PTV_{eval} had to be covered with at least 95% of the prescribed dose. The allowed maximum dose was 110%. To make the techniques comparable, the same target coverage was achieved for all plans. Based on our protocol, the dose limits of the organs at risk were as follows: $V_{100\%} < 35\%$ and $V_{50\%} < 60\%$ for the ipsilateral breast, $V_{30\%} < 20\%$ for the ipsilateral lung, $V_{15\%} < 10\%$ for the heart in case of right sided tumours, while in case of left sided tumours, the value of heart $V_{5\%}$ had to be smaller than for conventional whole breast irradiation. $V_{xx\%}$ is the percentage of a region of interest (ROI) receiving at least the XX percent of the prescribed dose. These requirements were fulfilled in all of the plans. For contouring and for planning aims the NSABP B-39/RTOG 0413¹⁷ guideline was used.

Planning

The 3D-CRT plans were created with 4 or 5 wedged conformal non-coplanar fields from tangential directions (Figure 1). The IMRT plans were created with 5 or 6 coplanar fields covering 190°, four of these fields positioned in the medial “first” and lateral “last” 30°. The RA plans consisted of two coplanar arcs created between the most medial field of the IMRT plans and gantry angle of 180° (Figure 1). Avoidance sectors were not applied, only strict constraints were given for ipsilateral lung, heart and spine. All plans were created for linear accelerator equipped with 5 mm wide MLC and 6 MV photon energy was used. CCC algorithm in Pinnacle and AAA algorithm in Eclipse were used for dose calculations.

Evaluation

For all techniques and all contoured organs volumes, minimum -, maximum and mean doses were recorded. Also $V_{xx\%}$ and $D_{xx\%}$ parameters were evaluated for all ROIs.

For the PTVEval homogeneity index and conformation number were calculated. Homogeneity index was calculated according to the ICRU83:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}}$$

And the conformation number is:

$$CN = \frac{PTV_{ref}}{V_{PTV}} \times \frac{PTV_{ref}}{V_{ref}}$$

where PTV_{ref} is the volume of PTVEval which is covered by the reference isodose, V_{PTV} is the volume of PTVEval and V_{ref} is the tissue volume encompassed by the reference isodose curve.¹⁸ The plan quality index (PQI), defined by Leung *et al.*¹⁹, was calculated for all plans to include all the previous parameters in one quantity. The sum of monitor units (MU) was also recorded.

Statistical analysis was performed for all parameters with repeated measures ANOVA and Tukey post hoc test or Friedman test and Dunn post hoc test in GraphPad Instat (GraphPad Software, USA).

Results

Volumes

The mean volume of the tumour bed, CTV and PTV were 15.4 cm³, 80.8 cm³ and 155.5 cm³, respectively. The ratios of CTV and PTV to the ipsilat-

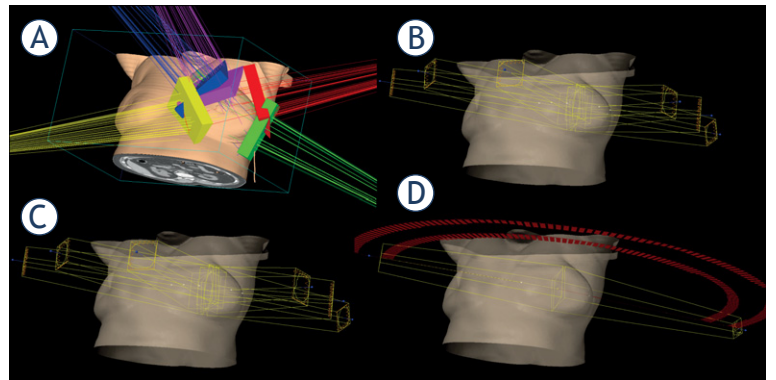


FIGURE 1: Typical beam arrangements in 3D-CRT (A), SS (B), SW (C) and RA (D) treatment plans.

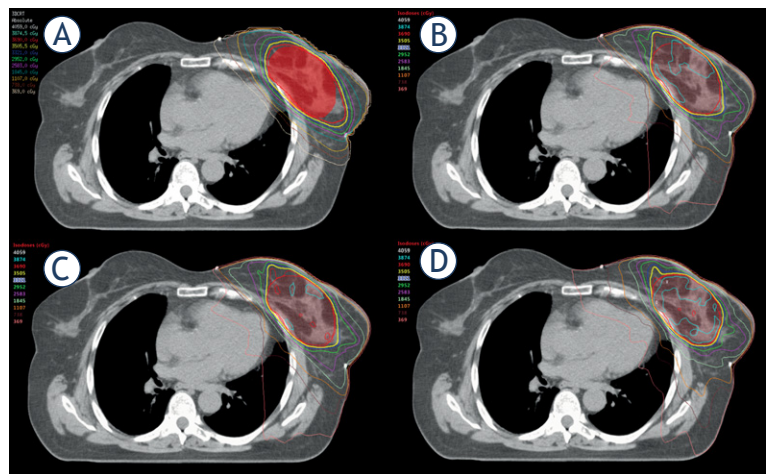


FIGURE 2: Representative dose distributions for a left sided case with 3D-CRT (A), SS (B), SW (C) and RA (D).

eral breast volume was 8.6% (range: 4–19.1%) and 16.8% (range: 8.3–40.1%), respectively.

Target volume coverage

For each technique the $V_{95\%}$ value of PTVEval was at least 99.5%, except for 5 cases with 3D-CRT technique. There were no significant differences between the techniques in the values of $V_{95\%}$ and $V_{90\%}$ (Table 1), neither for PTVEval nor for CTV. Figure 2 shows dose distributions for the four irradiation techniques in a representative case. The homogeneity index was significantly better with SW technique than with 3D-CRT, SS or RA techniques. The difference between 3D-CRT and RA technique was also significant. The average conformation numbers of 3D-CRT, SS, SW and RA were

TABLE 1. Quality indices and total number of monitor units of the four irradiation techniques

		Mean values (%)				ANOVA p value	Post hoc tests results					
		3D-CRT	SS	SW	RA		3D-CRT vs. SS	3D-CRT vs. SW	3D-CRT vs. RA	SS vs. SW	SS vs. RA	SW vs. RA
PTV eval	V _{95%}	99.5	99.8	99.8	99.8	0.96	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	V _{90%}	100	100	100	100	0.875	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
CTV	V _{95%}	99.9	100	100	100	0.001	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	V _{90%}	100	100	100	100	0.123	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	HI	0.068	0.074	0.058	0.081	<0.001	n.s.	p<0.05	p<0.05	p<0.05	n.s.	p<0.05
	CN	0.6	0.8	0.82	0.89	<0.001	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05
	PQI	0.5	0.36	0.34	0.43	<0.001	p<0.05	p<0.05	p<0.05	n.s.	p<0.05	p<0.05
	MU	677	814	1077	1136	<0.001	n.s.	p<0.05	p<0.05	p<0.05	p<0.05	n.s.

3D-CRT = three dimensional conformal radiotherapy; n.s. = not significant; RA = intensity-modulated arc therapy; SS and SW = „step and shoot“ and „sliding window“ intensity-modulated radiotherapy

TABLE 2. Dose to the organs at risk

		Mean values (%)				ANOVA p value	Post hoc tests results					
		3D-CRT	SS	SW	RA		3D-CRT vs. SS	3D-CRT vs. SW	3D-CRT vs. RA	SS vs. SW	SS vs. RA	SW vs. RA
Ipsilateral breast	V _{100%}	14.3	13.9	12.1	12.7	<0.001	n.s.	p<0.05	p<0.05	p<0.05	p<0.05	n.s.
	V _{75%}	31.5	26.1	25.8	21	<0.001	p<0.05	p<0.05	p<0.05	n.s.	p<0.05	p<0.05
	V _{50%}	47.5	40.2	39.9	31.6	<0.001	p<0.05	p<0.05	p<0.05	n.s.	p<0.05	p<0.05
	D _{max}	105.3	108.2	106.3	110.3	<0.001	p<0.05	n.s.	p<0.05	p<0.05	p<0.05	p<0.05
Ipsilateral lung	V _{10%}	13.1	28.1	28	36	<0.001	p<0.05	p<0.05	p<0.05	n.s.	p<0.05	p<0.05
	V _{30%}	3.9	3.6	3.6	6	<0.001	n.s.	n.s.	p<0.05	n.s.	p<0.05	p<0.05
	V _{40%}	2.6	1.9	1.9	3	<0.001	p<0.05	p<0.05	n.s.	n.s.	p<0.05	p<0.05
	MLD	5.6	7.4	7.4	9.9	<0.001	p<0.05	p<0.05	p<0.05	n.s.	p<0.05	p<0.05
Heart (left sided tumour)	MHD	2.4	2.9	2.8	5.4	<0.001	n.s.	n.s.	p<0.05	n.s.	p<0.05	n.s.
	V _{5%}	8.7	19.3	17.5	38.9	<0.001	n.s.	n.s.	p<0.05	n.s.	n.s.	p<0.05
	V _{15%}	3	1.5	1.2	7.8	0.043	n.s.	n.s.	n.s.	n.s.	n.s.	p<0.05
Heart (right sided tumour)	MHD	0.8	1.6	1.6	3	<0.001	n.s.	n.s.	p<0.05	n.s.	p<0.05	p<0.05
	V _{5%}	1.3	8.1	7.8	22.2	<0.001	p<0.05	n.s.	p<0.05	n.s.	n.s.	p<0.05
	V _{15%}	0.6	0.1	0.2	0.5	0.711	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Contralateral lung	V _{5%}	0	3.4	3.2	9.6	<0.001	p<0.05	p<0.05	p<0.05	n.s.	p<0.05	p<0.05
	V _{10%}	0	0.1	0.1	0.1	0.001	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	D _{5%}	0.5	4	4	5.4	<0.001	p<0.05	p<0.05	p<0.05	n.s.	p<0.05	p<0.05
	D _{10%}	0.4	3.2	3.1	4.7	<0.001	p<0.05	p<0.05	p<0.05	n.s.	p<0.05	p<0.05
Contralateral breast	V _{5%}	0.7	3.1	3.1	1.9	<0.001	p<0.05	p<0.05	p<0.05	n.s.	n.s.	n.s.
	V _{10%}	0.3	0.2	0.2	0.0	0.013	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	D _{5%}	1.2	3.8	3.7	3.8	<0.001	p<0.05	p<0.05	p<0.05	n.s.	n.s.	n.s.
	D _{max}	5.6	8.5	8.5	7.8	<0.001	p<0.05	p<0.05	p<0.05	n.s.	n.s.	n.s.

3D-CRT = three dimensional conformal radiotherapy; MHD = mean heart dose; MLD = mean lung dose; n.s. = non-significant; RA = intensity-modulated arc therapy; SS and SW = „step and shoot“ and „sliding window“ intensity-modulated radiotherapy

0.60, 0.80, 0.82 and 0.89, respectively, being all differences significant. The average values of homogeneity index, conformal number and PQI and the significance levels are summarized in Table 1.

The organs at risk

Table 2 contains all the dosimetric values of the critical organs and their comparisons between different techniques.

With respect to the ipsilateral breast, the best results for dose reduction were achieved with RA technique which was also confirmed by the conformation number. The $V_{50\%}$ values of non-target breast for 3D-CRT, SS, SW and RA were 39.6%, 29.9%, 29.6%, 19.8%, respectively. In the non-target ipsilateral breast the maximum doses were 105.1%, 105.8%, 103.8% and 106.4%, respectively.

With respect to the ipsilateral lung, we received significantly better results for dose-volume values for non-coplanar 3D-CRT in low dose ranges such as 10% of the prescribed dose, while RA resulted in the largest low dose bath ($V_{10\%}$). For higher dose ranges the two static IMRT techniques achieved significantly better results for $V_{40\%}$ than the other two.

The heart was better protected from low doses by the 3D-CRT technique. For the $V_{15\%}$ values RA technique still provided the worst results, while the static-filed IMRTs reached the lowest doses for the heart.

Both contralateral lung and contralateral breast received low dose with all techniques. Noticeable values and differences can only be found at 5% of the prescribed dose, and only very small volume received a higher dose than 10%. For both organs the 3D-CRT had significantly better results. With 3D-CRT technique, the average maximum doses for the contralateral lung and the contralateral

breast were 0.8 Gy and 2.1 Gy, respectively. With static-field IMRT techniques the average values were 3 Gy and 3.1 Gy and with RA 3.5 Gy and 2.5 Gy, respectively.

The PQI values of 3D-CRT, SS, SW and RA techniques were 0.50, 0.36, 0.34 and 0.43. By definition, low PQI values mean high overall plan quality. The two static-field IMRT PQI values were significantly better than the ones for the other two techniques, and RA was also significantly better compared to 3D-CRT. With respect to monitor units, 3D-CRT (677 MU) and SS (814 MU) techniques were significantly lower than with SW (1077 MU) and RA (1136 MU). The difference between SW and RA was also significant.

The results of this study in comparison with other dosimetric studies in APBI can be found in Table 3²⁰⁻²² and Table 4 for the 3D-CRT and IMRT techniques, respectively.

Discussion

The ratio of the target volume and the ipsilateral breast is a strict selection criteria in APBI, because good cosmetic outcomes are only achievable with the limitation of the irradiated volume. In our randomly selected 40 patients the median of tumour bed volume was 13.5 cm³ (3–40 cm³). Different values can be found in the literature with respect to tumour bed sizes. Vicini *et al.*²³ reported similar values to ours for the average tumour bed volume (median: 14 cm³ range: 3–70 cm³), while Oliver *et al.*²⁴ prepared plans with bigger surgical cavities (median: 63.5 cm³ range: 12–134 cm³). Compared to our average value of 0.17 for target volume to ipsilateral breast ratio Bergom *et al.*²⁵ and Moon *et al.*²⁶ reported equal or smaller ratios, while Livi *et al.*²⁷ and Rusthoven *et al.*²⁸ reported higher ratios.

TABLE 3. Comparison between our and other 3D-CRT data published in APBI studies

	Target			Ipsilateral breast (%)		Non-target breast (%)	Heart (left-sided lesions)		Ipsilateral lung	
	V_{PTV} (ccm)	V_{PTV} / V_{IB}	$V_{95\%}$ (%)	$V_{100\%}$	$V_{50\%}$	$V_{50\%}$	MHD (cGy)	$V_{5\%}$ (%)	MLD (cGy)	$V_{30\%}$ (%)
Patel <i>et al.</i> ²⁰	n.a.	n.a.	n.a.	26	52	n.a.	n.a.	n.a.	370	n.a.
Moon <i>et al.</i> ²⁶	n.a.	0.17	99.9	32.8	57.6	40.9	n.a.	n.a.	n.a.	n.a.
Qiu <i>et al.</i> ²¹	236.2	n.a.	n.a.	20.3	46.8	n.a.	76.1	6.4	193.2	4.4
Essers <i>et al.</i> ²²	176.4	n.a.	96.4	n.a.	n.a.	23.2	200	15.9	370	n.a.
Rusthoven <i>et al.</i> ²⁸	187.5	0.243	96	19.9	47	34.5	n.a.	n.a.	n.a.	n.a.
Current work	155.5	0.168	99.5	14.3	47.5	39.6	90.3	8.7	205.3	3.9

MHD = mean heart dose; MLD = mean lung dose; V_{IB} = volume of ipsilateral breast

TABLE 4. Comparison between our and other IMRT data published in APBI studies

	Target			Ipsilateral breast (%)		Non-target breast (%)	Heart (left-sided lesions)		Ipsilateral Lung	
	V _{PTV} (ccm)	V _{PTV} / V _{IB}	V _{95%} (%)	V _{100%}	V _{50%}	V _{50%}	MHD (cGy)	V _{5%} (%)	MLD (cGy)	V _{30%} (%)
Moon et al. ²⁴	n.a.	0.17	99.4	27.2	50.3	33.3	n.a.	n.a.	n.a.	n.a.
Qiu et al. ²¹	236.2	n.a.	n.a.	17.3	45.3	n.a.	35.9	0.4	123.6	1.4
Livi et al. ²⁷	123	0.21	96	n.a.	n.a.	37.5	n.a.	n.a.	n.a.	9.7
Bergom et al. ²⁵	243	0.14	99.1	16.2	39.9	n.a.	n.a.	14.6	n.a.	4.6
Rusthoven et al. ²⁸	187.5	0.243	88.8	9.4	42.1	28.1	n.a.	n.a.	n.a.	n.a.
Current work	155.5	0.168	99.8	12.1	39.9	29.6	103.6	17.5	272.1	3.6
Qiu et al. ²¹	236.2	n.a.	n.a.	18.2	44.9	n.a.	54.4	1	148	2
Essers et al. ²²	176.4	n.a.	98.9	n.a.	n.a.	19.7	100	4.3	190	n.a.
Current work	155.5	0.168	99.8	12.7	31.6	19.8	198.1	38.9	364.7	6

MHD = mean heart dose; MLD = mean lung dose; V_{IB} = volume of ipsilateral breast

In order to achieve a good cosmetic result, the dose to the ipsilateral breast must be kept under a limit. According to the NSABP B-39/RTOG 0413 protocol, the V_{50%} value of the ipsilateral breast has to be less than 60%.¹⁷ However, in a retrospective study Jagsi *et al.*²⁹ found, that the threshold value for this parameter is around 40% and above this limit worse cosmetic results can occur. In our study this threshold value was exceeded by the average values of 3D-CRT plans, while the average values of the intensity modulated techniques were at or below this threshold. However, compared to other studies with the intensity modulated techniques we reached the best results, and our 3D-CRT plans were also very close to the best values with respect to ipsilateral breast protection (Table 3 and 4).

The coverage of the target volume was excellent with each technique. Based on our protocol, the V_{95%} value of the PTV_{eval} had to be higher than 99.5%, while the maximum dose should be less than 40.6 Gy. With 3D-CRT in case of 5 patients the coverage criterion was not fulfilled. We note that only Moon *et al.*²⁶ were able to get higher coverage with 3D-CRT technique than our results. With respect to intensity modulated techniques our study has the highest V_{95%} coverage compared to values published in other papers.

Considering homogeneity, the best results could be achieved with the SW technique, and the difference is significant compared to the other three. With regards to the conformation number, the average value of the RA was the highest and was significantly better than for the other techniques, while in this respect the 3D-CRT was significantly the worst.

Regarding the mean dose of the ipsilateral lung in our study the 3D-CRT plans were significantly better compared to other techniques and at least as good as reported by others. As to volumes irradiated by higher doses, such as V_{30%}, the RA resulted in the largest volumes, however these values were still in the range of the volumes published by others.

The best heart protection was achievable with 3D-CRT technique, especially in the low dose region, and our results are very similar to the data available in the literature. In this dose region (2 Gy or less) our results with intensity modulated techniques are slightly worse compared to data published by others, but well below the clinical limits. The outcome of static-field IMRT plans were better compared to RA. Other published data about dose to heart for left sided patients are also summarized in Table 3 and 4.

As for the contralateral lung and breast, each plan resulted in low doses. The 3D-CRT was significantly better as there are no fields intersecting with these organs. When applying intensity modulated techniques, only small portion of dose reaches the contralateral volumes, the average of maximum point doses varied between 2.5 and 3.5 Gy.

As for the PQI index, which takes into account the homogeneity, conformity and the dose to the organs at risk simultaneously, the two static-field IMRT techniques (SS and SW) achieved the best results; they were significantly better than the 3D-CRT and RA, but RA was significantly better compared to 3D-CRT. However, this index only takes into consideration plan quality and ignores factors, such as the overall number of MUs, treat-

ment time or the couch rotation during deliveries of the beams.

With regard to the number of monitor units, the 3D-CRT and SS technique proved to be significantly better than the SW and RA (Table 1). The table rotation applied with the 3D-CRT technique on one hand makes the treatment time longer and on the other hand can cause unintended movement of the patient, increasing the chances of intrafractional patient positioning errors, accordingly. Moreover, during planning it is difficult to take into consideration which gantry and couch angle combinations may result in collision. The RA technique provided the shortest overall treatment time, SW technique came very close to that and SS plans still could be delivered much faster than 3D-CRT plans.

Conclusions

The advantage of the 3D-CRT technique with respect to dose to majority of OAR arises from its non-coplanar tangential beams arrangement which in the same time causes its biggest disadvantage, the long treatment time with higher uncertainty of patient positioning. Owing to its high conformality, the RA technique minimizes the potential side-effects for the ipsilateral breast, provides the shortest treatment time, however, higher volumes of organs at risk are irradiated with low doses. The two static-field IMRT techniques have a relatively short treatment time, excellent homogeneity, good conformity and the doses to the organs at risk are well below the protocol constraints. The technique with the best outcome for a specific case can be anatomy, tumour bed shape, -size and -location dependent, but taking all aspects into consideration, the SW IMRT is our recommended technique for accelerated partial breast irradiations.

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