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Simplified intensity-modulated radiotherapy using pre-defined segments to reduce cardiac complications in left-sided breast cancer

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Abstract

Background and purpose: Left-sided breast cancer patients pose a difficult clinical challenge when significant heart and contralateral breast irradiation are present, particularly with tangential uniform beams. The aims of the study are: (1) to design and evaluate a simplified intensity-modulated radiotherapy (IMRT) (SI) solution using pre-defined segments, (2) to compare the SI technique with a conformal (CN) and a full fluence IMRT (FI) approach using two sets of beam orientations, clinical (-C) and optimal (-O), and (3) to quantify the benefits of treatment technique and beam orientation.

Patients and methods: Nine left-sided breast cancer patients with a maximum heart distance of at least 2.0 cm were planned using three different techniques and two different beam orientations. All three techniques were planned using clinical orientations (i.e. CN-C, FI-C and SI-C). Two techniques were planned using more optimal orientations (i.e. FI-O and SI-O). Dose-volume histograms and radiobiologic modelling are used for plan evaluation.

Results: The average mean planning target volume (PTV) doses are 91.6 ± 4.5 , 98.4 ± 6.3 , 102.0 ± 8.7 , 100.0 ± 5.9 and $103.9 \pm 8.3\%$ for the CN-C, FI-C, SI-C, FI-O and SI-O plans, respectively. The average normal tissue complication probabilities for late excess cardiac mortality are 2.1 ± 0.6 , 0.2 ± 0.1 , 0.2 ± 0.1 , 0.1 ± 0.0 and $0.1 \pm 0.0\%$, respectively. For a given beam orientation, FI plans are the best and CN plans are the worst. The dose distributions for the SI-C and FI-C plans are almost identical with significant heart sparing but at a cost of some target underdosage. The dose distributions are better conformed around the PTV with more optimal beam orientations, resulting in better sparing of adjacent organs at risk. FI-C plans are inferior to SI-O plans.

Conclusions: For clinical uniform two-beam orientations, significant heart sparing is possible with the addition of intensity modulation but at the expense of worsening target coverage. Simplified IMRT can, for all intents, be substituted for full IMRT with clinical beam orientations. Applying more optimal non-uniform beam orientations improves PTV coverage while maintaining significant heart sparing but increases the PTV dose heterogeneity.

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Keywords: Intensity-modulated radiotherapy; Breast cancer; Simplified intensity-modulated radiotherapy; Predefined segments

1. Introduction

The rationale behind adjuvant post-operative radiotherapy (RT) following breast-conserving surgery (BCS) is the sterilization of the tumour bed of any residual subclinical disease that may be present after surgical excision. Adjuvant RT has been shown to be effective in reducing the risk of local recurrence in early stage disease [7,13,14] and some studies also demonstrate improved survival in high-risk pre-menopausal women [30,31]. The widespread adoption of BCS and adjuvant post-op RT,

especially in good prognosis young women with early stage breast disease, increases the importance of late complications due to the long expected disease-free interval.

As the clinical importance of late excess cardiac mortality becomes better recognized and, given that a substantial subset of patients are over-treated, the cardiac effects of RT has assumed a greater role in treatment plan evaluation [5,20,29]. There is strong empirical evidence showing a correlation between cardiac irradiation and late excess cardiac mortality [17,18,32]. The maximum heart distance (MHD) is an estimate of the amount of irradiated heart and is defined as the maximum distance of the heart contour to the medial field edge, measured parallel to

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the caudal field edge, as seen on a beam's eye view (BEV) of the medio-lateral tangential field. A study, by Hurkmans et al. [20], correlated an MHD of 2.0 cm with approximately 2.5% risk of late excess cardiac mortality.

Although adjuvant post-operative breast irradiation is clearly associated with significantly improved local control, whether it improves overall survival is still a controversial issue [2,3,15,26,33]. Several published meta-analyses confirm an improved cause-specific survival but suggest this benefit is offset by an increase in non-breast cancer-specific mortality, particularly ischemic cardiac mortality [1,8,38]. The simplest and obvious interpretation of the evidence is that adjuvant breast RT, although effective in improving local control and breast cancer-specific survival, is associated with detrimental cardiovascular complications.

The corollary is that if the associated cardiovascular complications could be reduced or eliminated, then an overall survival advantage would be discernable. The inclusion of right-sided and small MHD breast cancer patients may be contributing confounders to the apparent lack of improvement in overall survival. Therefore, improved RT treatment in breast cancer would be of particular concern and interest for left-sided patients with large irradiated heart volumes who are at greatest risk for cardiac complications and further efforts should be directed at reducing the risk of cardiac complications as low as reasonably possible without compromising the coverage of the breast target volume.

Tangential two-beam orientations are selected a priori so the projective geometry of the volumes of interest (VOI) is fixed. Patients with substantial MHDs are particularly challenging to treat due to the overlapping volumes of the breast and heart, as seen through BEV. For uniform tangential conformal beams, one must decide whether to maintain a homogenous target dose distribution and thereby potentially overdose the heart or to spare the heart adequately but at the cost of compromised target coverage.

Even intensity-modulated radiotherapy (IMRT), with its greater degrees of modulation freedom, cannot simultaneously satisfy both the constraints of target homogeneity and organ at risk sparing. The feasibility and advantage of more optimal two-beam orientations for heart sparing in left-sided breast cancer patients was investigated in another in-house study. It was found that the optimal uniform two-beam orientations were identical to those used clinically, with a hinge angle (i.e. the arc angle subtended between the central axes) near 185–190° to minimize the dorsal edge divergence. Optimal non-uniform two-beam orientations in patients with an MHD >2 cm were bimodal with hinge angles approximately 160 and 210°. For the purposes of the study, the latter hinge angle of 210° was selected for the class solution due to the risk of contralateral breast irradiation with the former.

Because the treatment planning, delivery and verification of IMRT is more complex than conventional RT, class solutions are a highly attractive answer for the routine

implementation of IMRT. The main criteria a class solution (compared to standard conventional techniques) must fulfill are: (1) that it does not require significantly more time, effort and/or resources to plan and deliver, (2) that the resulting dose distributions are as good (or better) and (3) that it can be applied or easily tailored to a wide variety of cases within the class (e.g. left-sided breast cancer patients). Class solutions have been used for other disease sites such as prostate [9] and our study attempts to apply similar methods to the breast.

A simplified IMRT (SI) method using pre-defined beams segments based on the projective VOI geometry is proposed as a general two-beam class solution. This SI technique is applied to two different beam orientations, clinical and optimal. The clinical beam orientations are the standard tangential beams typically used for breast RT. Clinical beam orientations tend to minimize the overlap between the breast and the heart as well as limit the contralateral breast irradiation. For clarity, all plan names using clinical beam orientations have the suffix '-C' appended to their name (e.g. SI-C) while optimal beam orientations use the suffix, '-O'.

The purpose of the study is: (1) to design and evaluate an SI solution using pre-defined segments, (2) to compare the SI technique with a conformal (CN) and a full fluence IMRT (FI) approach using two sets of beam orientations, clinical (-C) and optimal (-O), and (3) to quantify the benefits of treatment technique and beam orientation.

2. Methods and materials

2.1. Treatment planning

2.1.1. Patient selection

Treatment planning was performed retrospectively on nine left-sided breast cancer patients previously treated at the Netherlands Cancer Institute. All patients underwent CT-scanning following their breast conserving surgery. The images were obtained with the patients lying supine with the ipsilateral arm abducted above their heads. The scans included the entire lung in 5 or 10 mm thick CT slices and extended approximately from the mid-clavicle to the upper abdomen. All patients had an MHD of at least 2 cm.

2.1.2. Volumes of interest

The breast clinical target volume (CTV) included all visible breast parenchyma as seen on the CT slices, excluding 5 mm from the superficial skin surface. The planning target volume (PTV) was defined as the CTV plus a 7 mm isotropic margin (except in the superficial direction which was set to 0 mm) to account for set-up uncertainties and patient movement. The heart was defined as all the visible myocardium, excluding the pericardium, from the apex to the right auricle, atrium and infundibulum of the ventricle. The pulmonary trunk, root of the ascending aorta and the superior vena cava were excluded. An experienced

radiation oncologist delineated all VOIs except for the external surface and lungs which were generated automatically by the autocontouring tool of the treatment planning system (TPS) described below.

2.1.3. Treatment techniques

2.1.3.1. 3D conformal solution. Although the standard technique generally consists of tangential rectangular fields, tangential conformal fields will yield comparable target coverage with reduced cardiac irradiation [20,25] for similar beam parameters (such as direction and weight). Since one of the main clinical end-points evaluated in this study is risk of cardiac complication, conformal, not rectangular, fields as defined in the CN plans were used as our standard plan for comparison.

In the CN plan, we used (near) parallel, opposed medial and lateral tangential beams as selected by an experienced treatment planner. The gantry angles are optimized manually to minimize the beam divergence along the dorsal beam edge to reduce irradiation of the heart and lungs with a typical hinge angle of 185–190°. The isocentre is localized automatically to the PTV's centre of mass.

An isotropic margin of 6 mm around the PTV is used to define the field size and field shape (as seen from BEV) to account for the beam penumbra. For each beam direction, an open field and a 55° wedged field are defined for a total of four beams. In our treatment unit, the collimator orientation determines the wedge orientation. The collimator rotation is set at 180° to ensure the thick end of the wedge faces anteriorly. Multileaf collimators (MLCs) automatically shape the beam aperture. Beam weights (and thus, wedge angles) are optimized using the TPS with an objective cost function described in Section 2.1.4. The voxel size for dose calculation is $4 \times 4 \times 4 \text{ mm}^3$ and the dose grid is defined to cover the entire external surface contour plus a 5 mm margin. All plans of this type are called CN-C (i.e. three-dimensional (3D) conformal with clinical beam orientations).

2.1.3.2. Full intensity-modulated solution. The beam parameters (such as beam direction and isocentre) are identical to the CN plan and no wedged fields are present. The TPS generates the beam intensity profile with a bixel (or beam element) size of $5 \times 5 \text{ mm}^2$ and the same objective cost function used for the CN and SI plans (see Section 2.1.4). Therefore, each FI plan consists of two beams. The resulting full fluence profile does not undergo any sequencing and represents the best possible theoretical intensity profile, given the beam directions and the stated objective cost function optimized under the TPS (Fig. 1).

Identical clinical beam orientations found in the CN-C plans are used and these are called FI-C plans (i.e. full IMRT with clinical beam orientations). Likewise, another plan was created but with more optimal beam orientations. The optimal beam orientation is based on the results of

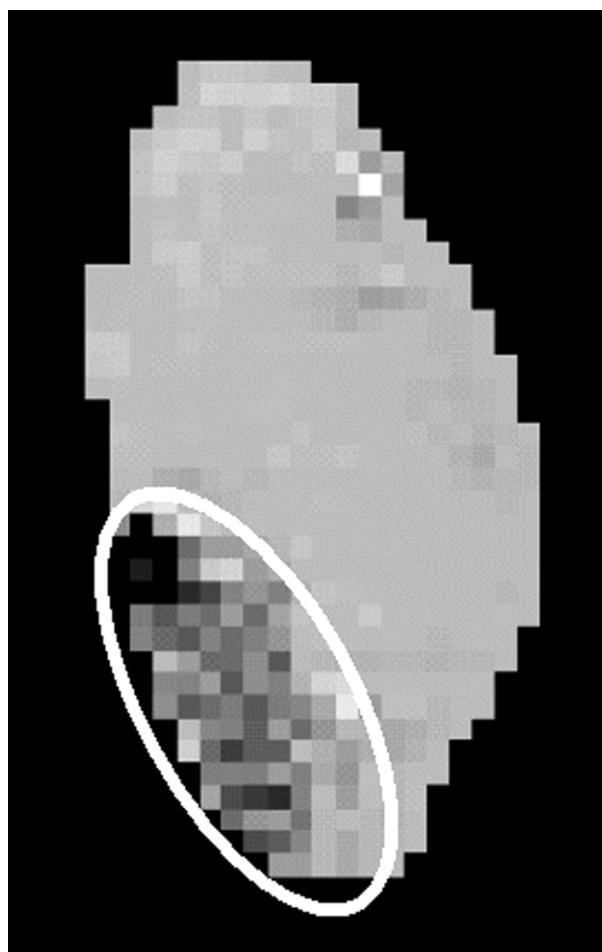


Fig. 1. A typical full fluence intensity profile seen from a tangential beam's-eye-view used in the full IMRT plans. Note the outlined region of low intensity overlying the heart that corresponds to the heart outline depicted in Fig. 2.

a beam orientation optimization program developed in-house. All plans of this type are called FI-O (i.e. full IMRT with optimal beam orientations).

2.1.3.3. Simplified intensity-modulated solution. The SI plan is an extension of the CN plan but with additional segments. For the purposes of the paper, when more than one field shape is present for a given beam direction, they are defined as segments. The rules defining the beam segments use the PTV + 6 mm margin, the heart + 0 mm margin and the left lung + 0 mm margin outlines, as seen from BEV (Fig. 2). A 6-mm margin is added to the PTV for the penumbra width. The PTV with a 6-mm margin (identical to the CN plan) defines segment A. Segment B is defined as segment A minus the heart outline. Segment C is defined as segment B minus the left lung outline, giving $3 \times 2 = 6$ segments in total. Segment weights are optimized using the TPS with the same objective cost function applied to the CN plans (discussed later). Identical beam orientations found in the FI plans are used. They are called SI-C (i.e. simplified IMRT

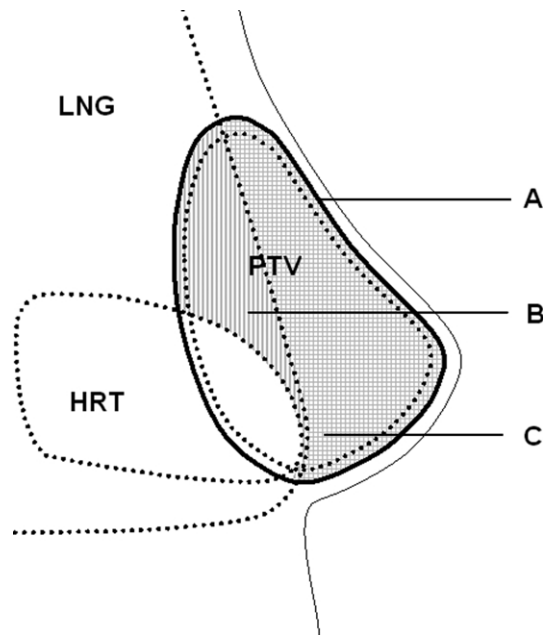


Fig. 2. Representative diagram showing a tangential beam's-eye-view with pre-defined segments (A–C) used in the simplified IMRT plans. The dotted lines represent the outlines for the planning target volume (PTV), the heart (HRT) and the left lung (LNG). The solid line around the PTV represents segment A, defined as the PTV with a 6 mm margin. Segment B is defined as segment A minus the heart outline shown single hatched. Segment C is defined as segment B minus the left lung outline shown cross-hatched. For clarity, margins are not drawn to scale.

with clinical beam orientations) and SI-O (i.e. simplified IMRT with optimal beam orientations) plans, respectively. No wedges are used.

2.1.4. Optimization

All the patients are planned using a 3D TPS (ADAC PINNACLE³ version 7.1a, Philips Radiation Oncology Systems, Milpitas, CA, USA). The photon beam dose is calculated using an adaptive convolution dose algorithm for the CN and SI plans. The FI plan uses a combination of a generalized Batho correction method and a collapsed cone dose calculation [28] algorithm. To ensure agreement between the different dose calculation algorithms, the CN and SI plans for a single patient were recalculated using the collapsed cone dose calculation algorithm and the resulting DVHs compared. The curves essentially overlapped, suggesting differences, if present, were minor.

All beam (and segment) weights and full fluence intensity profiles are optimized using PINNACLE's Inverse Planning IMRT Module. Optimization is performed by means of a steepest gradient search algorithm. The maximum number of iterations was set to 25.

We defined a quadratic objective cost function with different penalty weights for over- and/or underdosage. The terms or 'costlets' applied in the optimization are described in Table 1. The overall objective cost function consists of four costlets, two for the PTV, one for the heart and one for

Table 1

The objective cost function and the dose-volume costlets used for the optimization in Pinnacle's Inverse Planning module

VOI	Constraint	Dose (Gy)	Volume (%)	Weight	EOI
PTV	Minimum	47.5	100	20	Local control
PTV	Maximum	55	0	10	Fibrosis
HRT	Maximum	24	0	5	Late excess cardiac mortality
EXT	Maximum	1	0	0.0001	None

The volumes of interest (VOI) used are the planning target volume (PTV), the heart (HRT) and the external contour (EXT). The latter is used as a general constraint to minimize the integral dose. Also shown are the end-points of interest (EOI).

the external contour. These costlets yielded clinically acceptable plans in previous studies [5,20]. The minimum target dose costlet for the PTV is based on ICRU recommendations [21]. The costlet for the heart is based on the estimated tolerance of the heart [11]. No lung costlets are defined. The external contour costlet ensures the integral dose is minimized.

2.1.5. Dose prescription

All plans use 6 MV photons and the 100% isodose surface is prescribed to receive a total dose of 50 Gy in 25 daily equal fractions over 5 weeks (2 Gy/day). It is important to point out that the PTV mean dose is, in effect, a free parameter of the cost function and subject to optimization.

2.2. Evaluation and analysis

We evaluate the dose-volume histograms (DVHs) and the dose distribution for the relevant VOIs. The normal tissue complication probabilities (NTCPs) for late excess cardiac mortality [16] and radiation pneumonitis [24] are based on published data. The tumour control probability (TCP) model assumes an α -value of 0.3 Gy^{-1} , a normally distributed population of α -values with a standard deviation (SD) of 0.13 Gy^{-1} , an α/β -ratio of 10 Gy and a clonogen density of $10^{2.1} \text{ cm}^{-3}$. These parameter values were derived from cell line data published by Brenner [4] and fitted by Fenwick [12], representing the best fit to the available clinical data, and are phenomenological rather than realistic values. The TCP model is fully described by Webb et al. [37] and incorporates fractionation effects and heterogeneous clonogen populations (with heterogeneous radiosensitivities).

3. Results

3.1. Clinical example

Axial views with overlaid dose wash for all plans are shown in Fig. 3 along with their corresponding DVHs in

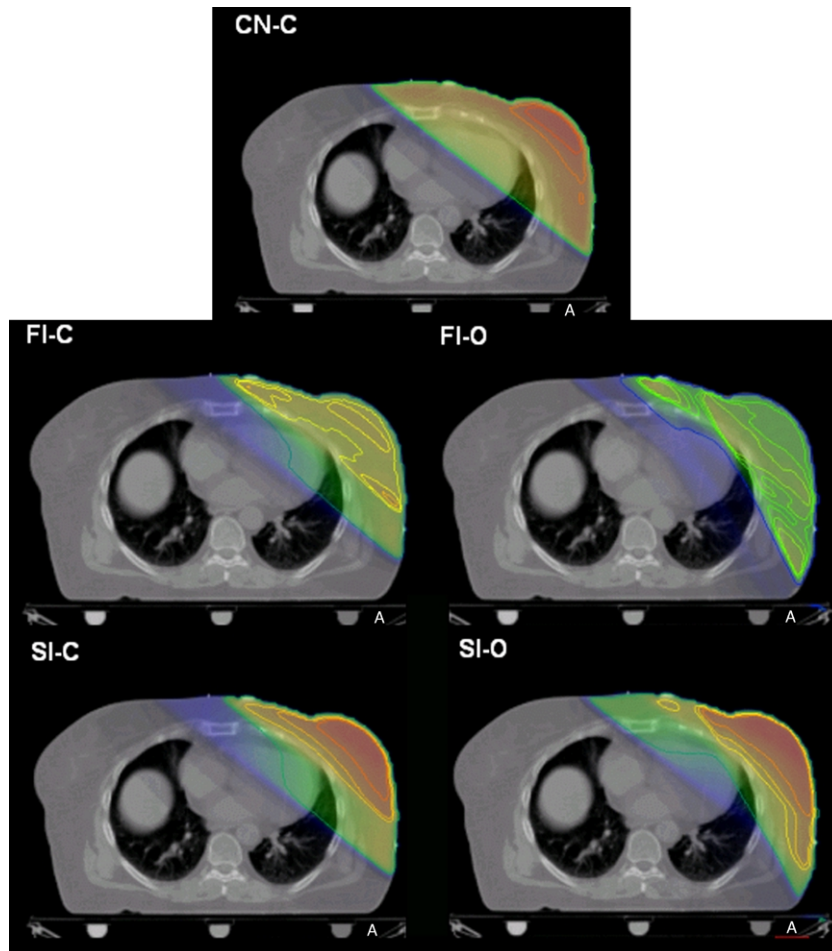


Fig. 3. The axial view with a dose wash for a patient for all the plans: 3D conformal with clinical beam orientations (CN-C), full intensity modulation with clinical beam orientations (FI-C), simplified intensity modulation with clinical beam orientations (SI-C), full intensity modulation with optimal beam orientations (FI-O) and simplified intensity modulation with optimal beam orientations (SI-O). The dose washes are normalized to the maximum dose and the curves outlined correspond to the 25, 47.5, 50 and 55 Gy isodose lines. The uniform beams of the CN-C plan do not allow modulation of dose to the heart while the non-uniform beams of the FI-C and SI-C plans do. The optimal beam orientations clearly allow better conformality of dose to the target.

Figs. 4 and 5 for a particularly difficult patient. In the CN-C plan, the breast and heart are covered with a homogenous dose wash while the FI-C and SI-C plans down-modulate the intensity of the segment overlying the heart. By doing so, the peripheral medial and lateral ends of the target are underdosed. The dose distributions of the FI-C and SI-C plans are, for the most part, very similar.

Concave targets are better covered with non-parallel beams. By introducing more optimal beam orientations, the FI-O and SI-O plans are able to conform more tightly around the breast and spare the heart. In Fig. 3, the competing goals of minimizing target underdosage and organ at risk overdosage can be seen. Increasing the effective segment intensity overlying the heart will tend to reduce target underdosage but will also tend to increase organ at risk overdosage. Both the SI plans (i.e. SI-C and SI-O) have greater target dose inhomogeneity compared to the FI plans. Plans using clinical beam orientations have poorer target coverage compared to optimal beam orientations.

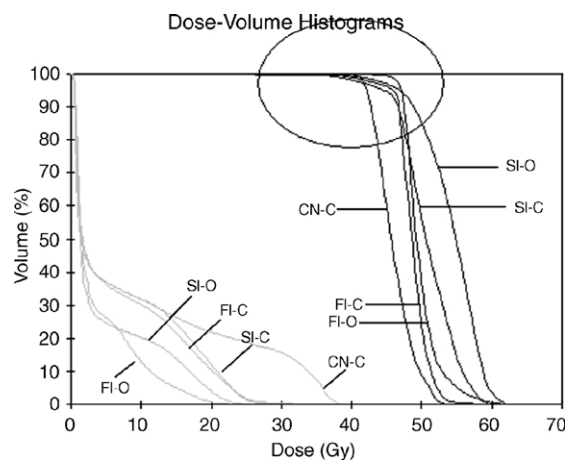


Fig. 4. Typical dose-volume histograms corresponding to the plans in Fig. 3 for the planning target volume (PTV) and the heart (HRT). The lines on the right represent the PTV and the lines on the left represent the HRT. There is significant sparing of the heart when going from uniform (e.g. CN-C plans) to non-uniform (e.g. all other plans) beams. The encircled portion is magnified and corresponds to the region of underdosage where the PTV and HRT overlap.

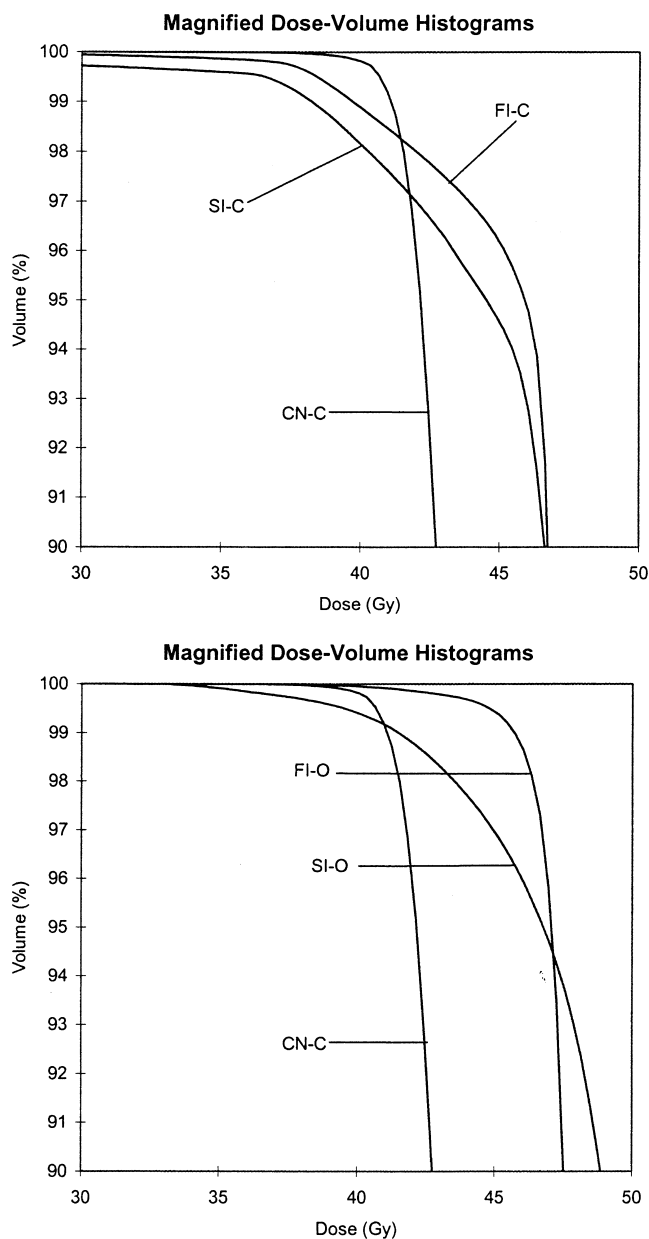


Fig. 5. Magnified views of the dose-volume histograms shown in Fig. 4. Comparing CN-C to FI-C to SI-C, target coverage becomes worse (but with significant heart sparing). Comparing CN-C to FI-O to SI-O, target coverage and heart sparing improves but with greater target dose inhomogeneity. There is less target underdosage going from clinical to optimal beam orientations and better cardiac sparing with the IMRT plans (compared to the CN-C plans).

3.2. Target dose coverage

The results are summarized in Table 2. The FI-C and FI-O plans have average mean doses closest to 100% but are also associated with the highest average maximum target dose, suggesting that the maximum dose applies to a relatively small part of the target volume (compared to the SI-C and SI-O plans). The greatest target dose inhomogeneities, as measured by the SD of the differential DVHs

(dDVHs), are found in the SI-C and SI-O plans and the least, in the CN-C plans.

3.3. Organ at risk sparing

The highest NTCPs for late excess cardiac mortality are found with the CN-C plans (e.g. 2.1%). However, adding intensity modulation dramatically reduces the NTCP to $\leq 0.2\%$. The highest NTCPs for radiation pneumonitis (e.g. 4.7%) are associated with the more optimal beam orientation since more left lung is irradiated from the lateral beam. The relevance of these numbers is discussed in Section 4.4.1.

4. Discussion

4.1. General

The most challenging RT cases are when the PTV and the OR are anatomically adjacent to each other. ICRU report 50 [21] recommends the PTV receives between 95 and 107% of the prescribed dose. The adequacy of the treatment plan's dose distribution depends on the PTV coverage (as defined by the isodose surfaces encompassing the target), the conformality of treatment and the target dose homogeneity. ICRU report 50 does not, however, make explicitly clear how to handle intersecting volumes (where a voxel is a member of both the PTV and OR) or the related problem of overlapping volumes (when the PTV overlaps the OR, as seen through BEV) with conflicting constraints. Part of the difficulty is that ICRU report 50 recommendations are based on uniform (conformal) beam experience which may not directly translate to non-uniform (intensity-modulated) beams.

It is common practice to renormalize the mean PTV dose to the prescribed dose. Renormalization is permissible for other breast cancer patient subsets, such as right-sided or small MHDs, where the irradiated heart volume is small. However, renormalization of patients with large MHDs and, therefore, large irradiated heart volumes, poses a difficult clinical dilemma.

In general, OR sparing usually involves: (1) minimizing dose (usually to a larger irradiated volume) or (2) minimizing the irradiated volume (usually associated with an increase in dose). Patients with large MHDs, by definition, have relatively large irradiated heart volumes so OR sparing is usually achieved by minimizing the heart dose. Unnormalized beam weights of the CN-C plans, compared to the renormalized plans, are decreased by approximately 10% (i.e. from 100 to 91.6%) but, due to the non-linear relationship between dose and NTCP, this modest 10% decrease in cardiac dose results in a dramatic NTCP reduction from 3.7 to 2.1%.

A clinical compromise between PTV coverage and OR sparing must be made. In effect, the objective cost function arbitrates this clinical compromise. The costlets'

Table 2
Summary of the parameters comparing all plans

Parameter \pm SD (%)	VOI	Plan				
		CN-C	FI-C	SI-C	FI-O	SI-O
NTCP	HEART	2.1 ± 0.6	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.0	0.1 ± 0.0
NTCP	L LUNG	1.3 ± 1.1	1.3 ± 1.2	1.6 ± 1.6	4.0 ± 5.0	4.7 ± 4.4
TCP	PTV	70.4 ± 2.2	65.7 ± 6.0	62.4 ± 6.0	73.7 ± 4.6	73.3 ± 2.0
$V_{D95\%}$	PTV	26.1 ± 10.9	88.2 ± 6.0	88.4 ± 4.5	89.1 ± 2.8	88.6 ± 3.0
$V_{D95-107\%}$	PTV	26.1 ± 11.7	82.5 ± 4.8	59.7 ± 12.4	75.5 ± 6.8	46.3 ± 8.5
$V_{D95-110\%}$	PTV	26.1 ± 11.7	87.0 ± 5.6	75.7 ± 11.1	82.2 ± 5.9	64.6 ± 8.9
Mean dose	PTV	91.6 ± 1.4	98.4 ± 1.4	102.0 ± 1.6	100.0 ± 0.7	103.9 ± 1.8
SD dDVH	PTV	4.5 ± 1.1	6.3 ± 0.9	8.7 ± 1.0	5.9 ± 0.9	8.3 ± 0.6

CN-C, conformal plan with clinical beam orientations; dDVH, differential dose volume histogram; FI-C, full intensity-modulated plan with clinical beam orientations; FI-O, full intensity-modulated plan with optimal beam orientations; HRT, heart; L LUNG, left lungs; NTCP, normal tissue complication probability; PTV, planning target volume; SD, standard deviation; SI-C, simplified intensity-modulated plan with clinical beam orientations; SI-O, simplified intensity-modulated plan with optimal beam orientations; TCP, tumour control probability; $V_{Dx\%}$, relative volume enclosed by the $x\%$ isodose surface; $V_{Dx-y\%}$, relative volume enclosed between the x and $y\%$ isodose surfaces; VOI, volume of interest.

importance factors were selected such that the heart NTCP tends not to exceed 2%. In cases where the heart NTCP did exceed 2%, the optimization chose to sacrifice PTV coverage. The limited degrees of modulation freedom found in the CN-C plans mean the entire PTV dose is down-weighted in an effort to spare more heart, resulting in relatively low $V_{D95\%}$ compared to the other plans. The SI and FI plans have a greater degree of modulation freedom so they are able to down-weight only the relevant segments and bixels overlying the heart and, thereby, are able to maintain adequate PTV coverage to the remaining breast.

4.2. Dose inhomogeneity

The conventional technique used for adjuvant post-operative RT in breast cancer consists of rectangular tangential fields. Two-dimensional (2D) treatment planning relies upon only one central slice and assumes it is representative of the whole breast. Clearly this assumption is untrue since the breast is not shaped like a hemicylinder but rather like a hemisphere. As a consequence, the conventional plans tend to underestimate the true dose inhomogeneity due to the changing surface contour (particularly the inframammary and areolar regions) and due to the assumed scatter from missing tissue outside the central slice.

The dose within the PTV can vary by as much as +27% in some patients [10]. The problem of breast target volume dose inhomogeneity has been a subject of much study. SI techniques have been reported by other groups [6,10,19,23,27,29,39] but most of these studies focus on improving target dose homogeneity and cardiac sparing is generally a secondary concern. However, for the patient subset with large MHD and a two-beam tangential set-up, improving the PTV dose homogeneity will also increase the irradiated heart dose. The goal of a homogeneous target dose distribution should, in this patient subset, be balanced with the associated risk of complications.

Tangential two-beam orientations offer limited benefit with respect to heart sparing due to its fixed projective geometry (Fig. 6). Applying more optimal two-beam orientations allow better heart sparing (as seen in Table 2) but at a cost of increased target dose heterogeneity.

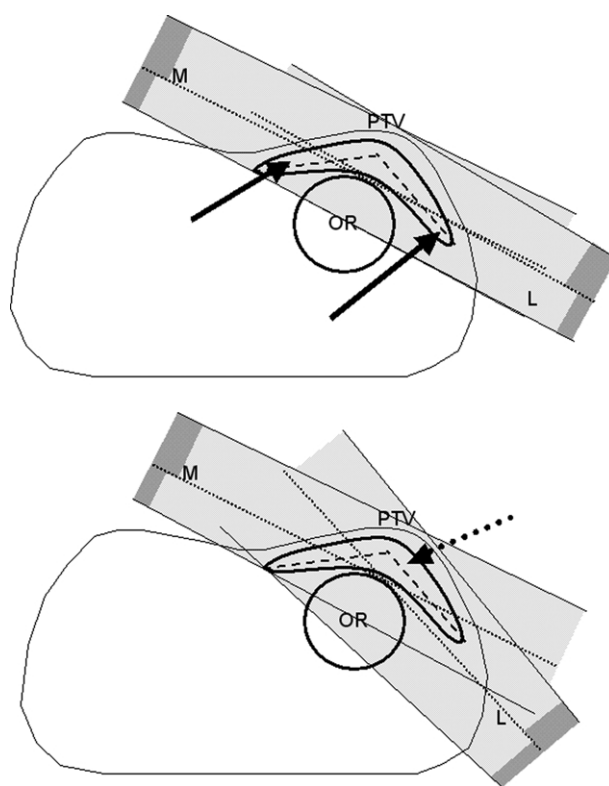


Fig. 6. A schematic diagram demonstrating the geometry of beam orientation, planning target volume (PTV) and organ at risk (OR). Parallel beams, used clinically, cannot adequately spare the OR and cover the PTV. Regions of relative underdosage are indicated by the solid arrows. More optimal beams with a hinge angle of 210° better spare the OR and cover the PTV but at the cost of increased target dose inhomogeneity. Regions of relative overdosage are indicated by the dotted arrow.

The heart is spared by redistributing the dose within the PTV concavity towards the areolar region and this effect is most pronounced for fewer beam plans (Fig. 6). For more optimally oriented two-beam plans, decreasing the heart dose is associated with an increase in dose elsewhere in the PTV.

The three constraints: sparing the heart (i.e. heart ≤ 24 Gy) and maintaining a homogenous target dose (i.e. breast ≥ 47.5 Gy and breast ≤ 53.5 Gy) are infeasible. However, satisfying two of the three constraints, such as sparing the heart and maintaining target coverage (i.e. breast ≥ 47.5 Gy), are feasible. Several studies have found a dose–effect relationship between breast fibrosis and doses > 50 Gy [22,34–36]. For these reasons, the maximum PTV dose constraint was relaxed from the ICRU report 50 recommended 107% to 110%, rather than removed entirely.

As all the post-optimized plans have optimally converged to the global minimum, with respect to segment weights, relaxing some constraints has the effect of tightening others. In this study, it was noted that more PTV dose heterogeneity, in general, allows better OR sparing and better PTV coverage. However, this is at the expense of greater risk of breast fibrosis and telangiectasia.

4.3. Treatment technique

Conceptually, these pre-defined segments can be thought of as the resulting segments following sequencing of the full fluence intensity profile quantized into three intensity levels corresponding to the segments shown in Fig. 1. The segmentation definition assumes there is some correlation between the optimal beam fluence profile and the projective VOI geometry. Pre-defined segments have several practical advantages. By defining only (relatively) large segments, small and off-axis segments are avoided (which may result from full fluence segmentation) and patient-specific quality assurance and dose verification is less onerous.

The dose distributions of the SI-C plans are almost as good as the FI-C plans, suggesting similar fluence profiles between them (Fig. 3). More importantly, it implies that the three intensity levels used in the SI-C plans are sufficient (to approximate the full fluence profiles of the FI-C plans) for clinical beam orientations.

The segment definitions used for the SI plans assume the intensity fluence profile is convex in shape. This assumption is valid for the clinical beam orientations but is not necessarily true for the more optimal two-beam orientations. The pre-defined segments used in optimal beam orientations are less able to approximate the full intensity fluence profile, resulting in less agreement between the dose distributions of the SI-O and FI-O plans. Thus, quantizing the fluence profile to more than three intensity levels or using wedges, at least for the optimized beam orientations, would improve the dose distribution.

However, the differences between the SI-O and FI-O plans are mainly attributable to greater target dose inhomogeneity (i.e. SD dDVH) rather than target coverage (i.e. $V_{D95\%}$). The FI-O plans can be viewed as a superset of the SI-O plans but with ‘perfect’ wedging. The results in Table 2 suggest that more intensity levels or optimal wedging will improve the target dose homogeneity by increasing the PTV volume enclosed between the 95 and 110% isodose surfaces (i.e. $V_{D95-110\%}$: 64.6 vs. 82.2%). The magnitude of heart sparing (i.e. heart NTCP: 0.1 vs. 0.1%) and target coverage (i.e. $V_{D95\%}$: 88.6 vs. 89.1%) are roughly comparable between both techniques. Despite the use of only three intensity levels, the lack of wedges and greater target dose heterogeneity, the TCPs of the SI-O plans are comparable to those of the FI-O plans (i.e. TCP, 73.3 vs. 73.7%).

When comparing the influence of intensity modulation and beam orientation, the reduction in heart NTCP is mainly attributable to the increased degrees of modulation freedom but at the cost of slightly inferior target coverage. The CN-C plans can be viewed as a subset of the SI-C plans which, in turn, can be viewed as a subset of the FI-C plans. So the FI-C plans are expected to be superior. However, even with full intensity modulation, the tangential beam orientations limit to what is achievable in terms of heart sparing and target coverage.

The FI-C plans represent the best achievable dose distribution (as defined by the given objective cost function). If the dose distribution adequately covers the PTV and spares the OR, then the FI-C can be replaced by the corresponding SI-C plan without any significant degradation of the dose distribution. However, if the FI-C plans are clinically unacceptable (due to excessive cardiac irradiation), then the dose distribution can only be improved by changing beam orientations or changing treatment modalities (e.g. adding electrons).

Applying more optimal beam orientations has the effect of increasing the maximum PTV dose and increasing the $V_{D95\%}$ while maintaining dramatic heart sparing (from 2.1 to 0.2%). As a result, better local control and fewer late cardiac complications are expected. However, this is at the cost of increased target dose heterogeneity and an increased risk of breast complications.

4.4. Radiobiologic models

4.4.1. Normal tissue complication probabilities

An accurate absolute NTCP model of excessive late cardiac mortality requires accurate clinical data. However, several factors limit the accuracy of these models. These include a long latency period before clinical complications arise, the relatively low incidence of radiation induced cardiac complications with newer RT techniques, the relatively high prevalence of ischemic heart disease in

the general population and the absence of good dosimetric and volumetric data in retrospective studies.

The major dose limiting structure in the breast RT of these patients is the heart. Non-uniform beam intensity techniques (e.g. SI and FI) can dramatically reduce the risk of late excess cardiac mortality (from 2.1 to 0.2%). The validity of the NTCP models must be carefully assessed. Although the absolute NTCP values should be viewed with caution, they are fitted to clinical outcome data and are useful approximations of risk. Relative NTCP values are helpful for inter-plan comparisons and a small but significant reduction in relative risk is of clinical relevance due to the severity of the complication. Moreover, lower NTCP values will likely result in a lower risk of complication compared to higher values. Even as the NTCP model parameter uncertainty improves with more accurate fitting to available data, the relative ranking of the NTCP values should not significantly change.

The average NTCP for radiation pneumonitis depends on beam orientation. For clinical beam orientations, independent of treatment technique, the average risk is relatively low (i.e. $\leq 1.6\%$). However, for optimized beam orientations, the risk is higher (i.e. $\leq 4.7\%$).

For several practical reasons, lung costlets were not included in the objective cost function. Following optimization, the segment weights have converged to the global minimum such that any changes to the segments weights will always increase the objective cost value. The primary goal of the study was to spare as much heart as possible while maintaining adequate target coverage. Inclusion of other OR constraints, such as lung, will always worsen target coverage and/or heart sparing.

The average mean dose for the left lung, for all plans, is relatively low (≤ 12.4 Gy) with the right lung receiving a negligible dose (≤ 0.3 Gy) which is well below the 20 Gy threshold used in other lung studies. Because only the left lung was considered, the estimated NTCP for radiation pneumonitis is an upper bound. If both lungs are considered as a single parallel organ, then the NTCP is approximately halved. Given that heart sparing and target coverage are the priorities and that the mean lung dose is within acceptable clinical limits, we made the clinical decision not to sacrifice heart or breast to spare more lung (which including the lung costlet, in effect, does).

4.4.2. Tumour control probabilities

Like the NTCP models, TCP estimates require cautious interpretation of their absolute values. Using $V_{D95\%}$ by itself is problematic and sometimes misleading since tumour control is a function of the volume and the magnitude of target underdosage. For example, the $V_{D95\%}$ for the SI-C and the SI-O plans are similar (e.g. 88.2 vs. 88.6%) but the SI-C has a lower TCP (62.4 vs. 73.3%) due to the magnitude of target underdosage. In this respect, TCPs are helpful in comparing the relative target coverage between different

plans. These values are not meant to be absolute values but, instead, are to provide some biological basis for comparison between the plans. The highest TCPs are found in the optimally oriented plans, SI-O and FI-O. The SI-C and FI-C plans have slightly inferior target coverage compared to the CN-C plans but this allows significant reduction in the cardiac dose as can be seen by the dramatic reduction in cardiac NTCPs.

4.5. Clinical considerations

The problem of ‘skin flash’ was not fully discussed. However, it can significantly affect the optimization due to the inclusion of the build-up region. A dummy VOI, based on the expansion of the PTV, is created such that its superficial boundaries extend at least 1 cm into air. The rules defining segments in the SI plans use the dummy VOI, ensuring the segments handle the skin flash appropriately while the original PTV is used for optimization.

All described plan techniques require a CT scan. Delineation of the VOIs can be time consuming and tedious but is necessary for optimization. Once the beam directions are determined and an isocentre selected, the segments can be defined using the rules described previously. These rules are intentionally simple so any BEV capable TPS can be used.

Moreover, if the TPS has a macro scripting function, a script can be devised to automate the entire treatment planning process from segment definition to segment weight optimization (such as using PINNACLE’s scripting language). In practical terms, this provides a significant saving in time and treatment planning resources. As only six segments are defined in the SI plans, the optimization is relatively quick compared to the FI plans (usually within 15 min). If the target delineation or beam shaping around the high dose volume is improperly done then part of the superficial dose build-up region will be inside the PTV, resulting in spurious regions of low dose which can hamper the optimization.

While designing the class solution, regional lymph node irradiation was excluded purposely to avoid complicating the comparisons and evaluations. However, in principle, one can easily modify the SI plan to irradiate the supraclavicular or axillary lymph nodes by adding a hanging block, by adding a table rotation or by using a mono-isocentric technique. As these additional fields are unlikely to contribute significantly to the heart or lung dose, they are not expected to alter the study’s conclusions.

Before the SI technique can be implemented clinically, quality assurance and verification must be performed. These potential problems must be addressed before the technique can be implemented clinically. Future work includes applying similar methods to the irradiation of other target volumes such as simultaneous boost treatment and inclusion of the internal mammary lymph node chain.

4.6. Clinical guidelines

The criteria for an acceptable IMRT plan are a matter of clinical judgement and, therefore, subject to change as the treatment evolves. At our institution, an adequate dose distribution is defined as: (1) the NTCP for late excess cardiac mortality is $\leq 1\%$, (2) $\geq 90\%$ of the relative target volume receives a dose between 47.5 and 55 Gy, and (3) the tumour bed receives adequate dose (so medial tumours are relatively contraindicated). Based on these study results, we follow these clinical guidelines at our centre:

1. Generate a conformal plan with clinical tangential beam orientations and evaluate the dose distribution (particularly heart overdosage and breast underdosage). If the dose distribution is acceptable then keep the plan.
2. If unacceptable (as expected for left-sided breast cancer patients with large MHD), generate a SI plan with clinical beam orientations and re-evaluate the dose distribution. If acceptable then keep the plan.
3. If unacceptable, generate an SI plan with a hinge angle of 210° and re-evaluate the dose distribution. If acceptable then keep the plan.
4. If unacceptable, generate a full FI plan with a hinge angle of 210° and re-evaluate the dose distribution. If acceptable then keep the plan.
5. If unacceptable, the treatment technique should be reconsidered (such as applying additional beams, modifying beam directions to include non-coplanar beams, changing treatment modality to include electrons or avoiding RT altogether) since a better dose distribution using this technique (i.e. non-uniform two-beam megavoltage photons) is not feasible in practice.

5. Conclusions

For clinical uniform two-beam orientations, significant heart sparing is possible with the addition of intensity modulation but at the expense of worsening target coverage. Simplified IMRT can, for all intents, be substituted for full IMRT with clinical beam orientations. Applying more optimal non-uniform beam orientations improves PTV coverage while maintaining significant heart sparing but increases the PTV dose heterogeneity.

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