Improving radiotherapy treatment for left-sided breast cancer

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Chapter 6

DETERMINING OPTIMAL TWO-BEAM AXIAL ORIENTATIONS FOR HEART SPARING IN LEFT-SIDED BREAST CANCER PATIENTS

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6.1 ABSTRACT

Background and Purpose: The optimal intensity fluence profile of a beam depends on the profiles of other beams but most optimizations assume fixed beam orientations, *a priori*. Breast cancer radiotherapy attempts to cover the target and to spare critical structures such as the heart and lungs. The study aims are (1) to determine and document the optimal two-beam orientation that best spares the heart for left-sided breast cancer patients and (2) to investigate the influence of the treatment technique (i.e. conformal vs. intensity modulation) on the optimal objective cost function.

Materials and Methods: Ten left-sided breast cancer patients were planned using a conformal (3DCRT) and a simplified intensity modulated (sIMRT) technique using predefined segments and different two-beam orientations. Optimal segment weights were determined exhaustively for all axial two-beam combinations, in 5° increments, by minimizing a quadratic objective cost function. The resulting objective cost function was analyzed with respect to target geometry and treatment technique.

Results: The sIMRT plans are generally less sensitive to beam orientation compared to 3DCRT plans. Optimal two-beam orientations for 3DCRT and sIMRT plans exist and they correspond to a hinge angle of approximately 188° and 160° or 210° (the latter is bimodal), respectively.

Conclusions: The optimization software is a useful tool that can test many different beam combinations and estimate their associated objective cost values. Afterwards, the most promising beam orientations could be re-optimized under the TPS to fine-tune and verify the dose distributions. Optimal uniform two-beam orientations for the breast consist of opposing tangential medial and lateral beams. Optimal non-uniform two-beam orientations for left-sided breast cancers are bimodal, containing hinge angles around 160° and 210°. Non-uniform beam techniques are less sensitive to beam orientation compared to uniform beam techniques and result in significantly improved heart sparing but at a cost of slightly compromised planning target volume coverage.

6.2 INTRODUCTION

Uniform beams are employed to ensure a minimum homogeneous dose to the planning target volume (PTV). If the goals of treatment are to cover the PTV with a homogeneous dose and to spare the organs at risk (ORs) as much as possible, then conformal uniform beams are always at least as good as rectangular uniform beams since conformed blocks allow improved sparing of adjacent ORs without significantly compromising the PTV coverage.

Because beam orientations are usually decided *a priori*, the best possible PTV coverage and ORs sparing must also be constrained *a priori* since the projected geometry of the relevant volumes of interest (VOIs) are fixed for each particular beam direction. Assuming the two uniform beams are free to swing about a set isocenter and ignoring organ movement and other geometric uncertainties, different beam directions are associated with different beam’s-eye-views (BEVs) and, therefore, different projective geometries. The two-beam combinations that tend to minimize the overlap [1,2], as seen from BEV, between the PTV and ORs, will be preferred over others.
The usefulness of optimal beam orientations depends, amongst others, on the number of beams \( (n) \), the VOI geometry and the treatment technique. With a sufficient number of beams (i.e. \( n > 5 \)), optimal beam orientation becomes less important [3,4]. The marginal benefit [4,5] of each additional beam diminishes (which is why adding the tenth beam improves the dose distribution less than adding the second beam). Therefore, oligo-beam plans (i.e. \( n \leq 5 \)) with the fewest beams will tend to benefit the most from optimally directed beams. Furthermore, fewer beams means less contralateral scatter dose and, in general, simpler treatment delivery. Therefore, for the purposes of the study, the number of beams and the potential beam directions are limited to two coplanar axial BEVs.

If the PTV and ORs are far apart then more suitable beam directions become available so beam direction, in this sense, becomes less critical. The corollary to this is that beam direction is more important for VOI geometry where the PTV and ORs are, in fact, overlapping. The most difficult general case is when the OR lies within the PTV’s concavity because all the BEVs will contain some degree of overlap between the PTV and OR (e.g. a horse-shoe PTV embracing the OR). Consequently, it is impossible to ensure, simultaneously, target coverage and organ at risk sparing for overlapping VOIs due to the penetrating nature of megavoltage photons. Therefore, one must accept some clinical compromise between the PTV and the OR.

Optimal beam orientations depend on treatment technique. For uniform beams, by definition, only one segment covers the PTV. Because of its limited degrees of freedom in modulating the intensity of the beam fluence profile (compared to non-uniform beams), the beam orientation that maximizes OR sparing tends toward the beam orientation that minimizes the overlap between the PTV and OR. Technically, it is more correct to consider the intersecting volumes [6] rather than the areas of overlap, as seen from BEV, but both are highly correlated and, in practice, identical.

The above-described situation is exactly analogous to the clinical geometry found in left-sided breast cancer patients with a significant volume of heart within the irradiated field. The standard uniform two-beam orientation used in breast cancer radiotherapy (RT) is opposing tangential medial and lateral beams. This tangential two-beam arrangement must be (close to) optimal since tangentially directed beams best minimize the overlap of heart, lungs and other irradiated normal tissue. The two-beam orientation can be further optimized by correcting for beam divergence which is why treatment planners select a hinge angle usually around 185°-190°.

Several authors [7-10] have shown a relationship between cardiac irradiation and cardiovascular mortality. The maximum heart distance (MHD) is defined as the maximum distance of the heart contour to the medial field edge, measured parallel to the caudal field edge, as seen through BEV of the rectangular medio-lateral tangential field.
Hurkmans et al [11] correlated MHD with late excess cardiac mortality. In an in-house patient review of left-sided breast cancer patients treated with only tangents, the average MHD was 1.6±0.6 cm (maximum value: 3.2 cm). Approximately 27% of patients have a MHD greater than 2.0 cm. Using Hurkmans’ best fit regression data, 2.0 cm corresponds to about 2.5% late excess cardiac mortality. The goal of heart sparing is particularly important in the light of the good prognosis and long recurrence-free survival of early breast cancer patients.

Although the standard tangential uniform two-beam orientation employed in breast RT is nearly optimal, this is not necessarily true for non-uniform beam plans (e.g. intensity modulated radiotherapy). If one considers a parallel-opposed beam arrangement, then, all else being equal, this beam orientation provides the least benefit with respect to intensity modulation since the advantage of the second beam is almost completely negated due to the penetrating nature of photons. Applying similar arguments, the tangentially oriented beams used in adjuvant breast RT, although optimal for uniform beam treatment techniques, must be sub-optimal when employing non-uniform beam treatment techniques.

Orthogonal beam orientations, in principle, will maximize the benefit of intensity modulation found in non-uniform beams. This tendency, however, is constrained by other factors, particularly the VOI geometry. In the case of the breast, an anterior oblique beam direction, although orthogonal to the tangential beam direction, is avoided since it tends to irradiate more normal tissue such as heart.

Several other authors have investigated the problem of optimal beam orientations with respect to non-uniform treatment techniques [12-15]. Stein et al [4] suggest that all valid optimizations, stochastic or exhaustive, should converge to the same optimal solution. Determining the optimal beam orientation is difficult to solve due to its non-linear nature and presence of multiple local minima [3]. Most of the optimization techniques used by these authors rely on search methods that cannot guarantee the global minimum is found. Although their solutions are probably nearly optimal, they cannot be said to be truly optimal unless an exhaustive search is first carried out to verify the claim. By exhaustive search, we mean that for all potential two-beam combinations, the respective segment weights are optimized to minimize the objective cost function. To the best of our knowledge, no such attempt has been made in the case of breast cancer.

Much of previous intensity modulated RT (IMRT) work [16-20] done in breast cancer concentrated on improving target dose homogeneity to reduce breast fibrosis. However, in the light of the growing evidence of late fatal cardiac complications, there is growing interest [11,21-23] in applying non-uniform IMRT to spare OR rather than only improving target dose homogeneity. Although a homogeneous target dose is important, our main study focus is on heart sparing.
6.3 Purpose

The study aims are: (1) to determine and document the optimal two-beam orientation that best spares the heart for left-sided breast cancer patients and (2) to investigate the influence of the treatment technique (i.e. conformal vs. intensity modulation) on the optimal objective cost function.

6.4 Materials and Methods

6.4.1 Patient Selection

Treatment planning was performed retrospectively on ten left-sided breast cancer patients previously treated at the Netherlands Cancer Institute with a MHD of at least 1.5 cm, thus having considerable overlap between the breast and heart [11]. All patients underwent CT-scanning following their breast conserving surgery. 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.

6.4.2 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 breast PTV was defined as the CTV plus a 7 mm isotropic margin (except in the superficial direction where the margin was set to 0 mm) to account for setup uncertainties, patient movement and to exclude the superficial build-up region. 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.

Patients are planned on a three-dimensional (3D) treatment planning system, TPS, (ADAC PINNACLE version 6.3b, Philips Medical Systems, Milpitas, CA). An experienced radiation oncologist delineated all volumes of interest (VOIs) except for the external surface and lungs. They were generated automatically by the TPS’ autocontouring module. The calculated photon beam dose used a convolution dose calculation [24] algorithm for segment weight optimization.
6.4.3 Treatment Techniques

Each patient undergoes two separate beam orientation optimizations for uniform and non-uniform treatment techniques. For a given beam direction, the BEV of the overlapping areas of the VOIs are used to define the beam segments. All plans are based on predefined segments to outline the individual beam aperture shapes (Figure 6-1). Customized blocks are used to shape the beam aperture. Isocentre is set to the PTV's centre of mass and only coplanar axial beam orientations (i.e. couch angle always set to zero) are considered. Easier visualization of the objective cost function is possible when reducing the search space to the two gantry parameters. Two different plans are defined as follows.

6.4.3.1 3DCRT: Conformal Breast Technique

For any given beam direction, all conformal (3DCRT) breast plans have beam apertures conformed around the breast PTV plus a 6 mm isotropic margin to account for the beam penumbra. No wedges are employed.

6.4.3.2 sIMRT: Simplified Intensity Modulated Breast Technique

The simplified IMRT (sIMRT) plans are an extension of the 3DCRT plans but with additional beam segments within each beam to allow intensity modulation. Several beam segment shapes are created for each beam direction. The rules defining the beam segments use the margin outlines, as seen through BEV, of the breast PTV+6 mm margin, the heart OR+0 mm margin and the left lung OR+0 mm margin. The areas of overlap between the different VOIs define each segment.

6.4.4 Optimization

An exhaustive "brute-force" search of every $n$-beam combination under the clinical TPS is not practical due to the inordinate amount of time required. Beam directions are quantized into 5° increments, ranging from 0° to 355°. Thus, when $n=2$, a total of 5184
(72×72 beam combinations) separate optimizations must be performed for every plan for every patient. The $n$-beam orientation optimization is decomposed into two main parts: (1) dose calculation and (2) segment weight optimization. The optimization steps are outlined in Figure 6-2.

**Figure 6-2.** Schematic flow-chart for beam orientation optimization program. The two main parts are: dose calculation and segment weight optimization.
6.4.4.1 Dose Calculation

All simplified dose calculations were done under QUIRT [25], a software library of useful tools developed in-house. A simplified dose calculation algorithm, based on an exponential linear attenuation model, was implemented to speed up the optimization process. The attenuation coefficient was manually fitted to the depth dose profile of the matching 6 MV beam as calculated by the clinical TPS (i.e. linear attenuation coefficient, $\mu = 0.03 \text{ cm}^{-1}$).

A beam direction is selected and the delineated VOIs, as seen from BEV, define the beam segments. The penumbral and build-up dose region is simulated by a Gaussian convolution, similar to other methods determining geometric uncertainties analytically [26,27]. The convolution function for the lateral penumbral and the superficial build-up region uses a standard deviation (SD) of 0.44 cm and 0.5 cm, respectively.

From the CT volumetric data, a ray-tracing routine is employed to estimate the radiological path length. All relevant VOIs are seeded with 2000 random points. A percentage depth dose look-up table, based on an exponential linear attenuation model, is used to calculate point dose values at depth. Beam divergence is accounted for by an inverse square correction factor. All segment doses are calculated. A new beam direction is selected and the dose calculation is repeated until all segments for all directions are exhausted. The advantage of separating the beam orientation optimization into their component parts is that the dose calculation needs only be done once and can be reused for different segment weight optimizations.

6.4.4.2 Segment Weight Optimization

After obtaining the dose distribution for each beam segment for each beam direction, a subset of beam directions to be optimized is selected (i.e. $n = 2$). The program then optimizes the segment weights, $i_s$, within this subset by minimizing the objective cost function. The beam orientations, segment weights and objective cost value are stored. The next beam direction/combination subset is tested until all combinations are exhausted.

The actual optimization is performed under MATLAB v.6.0.0.88 Release 12 with the Optimization toolbox (MathWorks Inc., Natick, MA) on a 350 MHz Pentium III personal computer with 512 MBytes of RAM. Included in the toolbox is the $fmincon$ optimization function that finds a minimum of a constrained nonlinear multivariable function. A sequential quadratic programming (QP) method is used where the QP subproblem is solved at each iteration. A full description of the mathematical details of the constrained optimization is beyond the scope of the paper and interested readers are referred to relevant references [28,29].
6.4.4.3 Objective Cost Function

A quadratic objective cost function with different penalty weights for over- and/or underdosage is defined. The “costlets” applied in the optimization are described in Table 6-1.

\[ F_{\text{min}} = \frac{1}{N_{\text{ROI}}} \sum_{j=1}^{N_{\text{ROI}}} \sum_{i=1}^{w_j} s_j \cdot (d_{i,j} - d_p)^2 \]  \hspace{1cm} (1)

\[ s_j = \begin{cases} 1, & \text{if } d_p \leq d_{i,j} \text{ and max constr} \\ 1, & \text{if } d_p \geq d_{i,j} \text{ and min constr} \\ 0, & \text{otherwise} \end{cases} \]  \hspace{1cm} (2)

\[ d_{i,j} = \sum_{i=1}^{N_{\text{ROI}}} i_k \sum_{k=1}^{N_{\text{seg}}} d_{k,j} \]  \hspace{1cm} (3)

where \( F_{\text{min}} \) is the minimized objective cost value, \( N_{\text{ROI}} \) is the total number of points within the VOI, \( N_{\text{ROI}} \) is the total number of VOIs, \( w_j \) is the importance weighting factor associated with the \( j \)th VOI, \( s_j \) is a step function associated with the \( j \)th VOI, \( d_p \) is the prescribed point dose, \( d_{i,j} \) is the calculated point dose, \( N_{\text{beam}} \) is the total number of beams (same as \( n \)), \( N_{\text{seg}} \) is the total number of beam segments associated with the \( l \)th beam, \( i_k \) is the intensity weighting factor associated with the \( k \)th segment of the \( l \)th beam and \( d_{k,l} \) is the point dose for the \( k \)th segment of the \( l \)th beam. The segment intensity weights, \( i_k \), undergo optimization to minimize \( F \).

Table 6-1. Objective cost function parameters used in treatment planning and optimization. Dose-volume point constraints are quadratic penalties. The constraints are listed with their associated end-point of interest. (EOI=end-point of interest, max=overdosing costlet, min=underdosing costlet, NA=not applicable, VOI=volume of interest).

<table>
<thead>
<tr>
<th>VOI</th>
<th>TYPE</th>
<th>DOSE (Gy)</th>
<th>VOLUME (%)</th>
<th>WEIGHT</th>
<th>EOI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BREAST</td>
<td>min</td>
<td>47.5</td>
<td>100</td>
<td>20</td>
<td>local control</td>
</tr>
<tr>
<td>BREAST</td>
<td>max</td>
<td>60</td>
<td>0</td>
<td>10</td>
<td>fibrosis</td>
</tr>
<tr>
<td>HEART</td>
<td>max</td>
<td>24</td>
<td>0</td>
<td>5</td>
<td>late excess cardiac mortality</td>
</tr>
<tr>
<td>LUNGS</td>
<td>max</td>
<td>15</td>
<td>0</td>
<td>2.5</td>
<td>radiation pneumonitis</td>
</tr>
<tr>
<td>EXTERNAL</td>
<td>max</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
</tbody>
</table>

Similar costlets yielded clinically acceptable plans in previous studies [11,21]. The minimum dose costlet for the PTV is based on the ICRU recommendations [30]. The costlet for the heart is based on the estimated tolerance of the heart [31]. An additional costlet based on the external VOI (called EXT) is defined to ensure the optimization tends to minimize the integral dose within the patient. The EXT VOI contains all the internal VOIs.
6.4.5 Evaluation and Analysis

The objective cost function and its associated surface are evaluated and analyzed. The dosimetric accuracy and optimization reliability was verified by comparing the optimized segment weights selected by the clinical TPS using PINNACLE's Inverse Planning IMRT Module with matching objective cost functions and our $n$-beam orientation optimization program. PINNACLE's optimization is performed by means of a steepest gradient search algorithm as implemented in the TPS. The maximum number of iterations was 25.

6.5 RESULTS

6.5.1 Objective Cost Function

Typical examples of the objective cost surface and dose-volume histograms (DVHs) are shown in Figure 6-3 and Figure 6-5. In general, the non-uniform beam plans have significantly lower cost values than the uniform beam plans. Table 6-2 summarizes the objective cost values for the different plans. For uniform and non-uniform beam plans, the mean optimal hinge angles are 188° and 195°, respectively. The distribution of the latter, after closer inspection, turns out to be bimodal with peaks near 160° and 210°.

Plotting the objective cost surface visualizes the influence and interaction between the objective cost and beam orientation. We make the following observations. First, all plans have a single large peak near a gantry angle of 255° that corresponds to the worst possible beam direction, opposite the breast, irradiating the long way around to reach the target. The maximum objective cost value is identical for both the corresponding one-beam and two-beam plans since the latter can be viewed as a superset of the former (which is why the maximum cost values are identical). Similarly, non-uniform beams can also be viewed as a superset of uniform beams. Thus, all the objective cost values for the uniform beam plan must be equal to or greater than the corresponding beam directions for the non-uniform beam plan.
Figure 6-3. Typical objective cost function surface and contour plots corresponding to plans 3CDRT (A and B) and sIMRT (C and D). The ordinate axis is the optimized objective cost value while the abscissas represent the gantry angles for the corresponding beams. The 'X's mark the global minimum at (300°, 130°) and (130°, 300°) for uniform beams and (305°, 105°) and (105°, 305°) for non-uniform beams. Beam transposition does not affect the cost so two global minima exist. Figure 6-3D shows the bimodal solutions near (305°, 105°) and (300°, 155°) with a local maximum at (300°, 130°).
Figure 6-4. Typical axial dose distributions comparing 3CDRT (A) and sIMRT (B) plans. Notice the redistribution of dose within the breast, shifting dose away from the heart and the medial aspect of the breast.
Figure 6-5. Renormalized (A) and un-normalized (B) dose-volume histograms (DVHs) comparing optimized segment weights for a typical patient. The lines represent the optimal 3DCRT and sIMRT beam orientations using maximum breast dose thresholds of 55 Gy (sIMRT55) and 60 Gy (i.e. sIMRT60). The volumes of interest are the breast and the heart. The 3DCRT DVH has excellent target coverage but limited cardiac sparing. The sIMRT60 DVH has excellent target coverage with dramatic heart sparing but increased target dose heterogeneity. The sIMRT55 DVH has similar heart sparing, improved target dose homogeneity but slightly inferior target coverage (as measured by the volume enclosed by the 95% isosurface) compared to sIMRT60.
Table 6.2: Summary of the mean, maximum and minimum objective cost values (in arbitrary units) following segment weight optimization for the different treatment techniques (3DCRT vs. sIMRT). Also listed are the beams’ gantry directions, hinge angles and time required for the optimization. The first number is the average over all patients and the second number (following the ‘±’ symbol) represents 1 standard deviation. The maximum and minimum objective cost values correspond to the worst and best beam orientations.

<table>
<thead>
<tr>
<th>OBJECTIVE COST</th>
<th>3CDRT</th>
<th>sIMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean (×10³)</td>
<td>2.22±0.18</td>
<td>1.47±0.12</td>
</tr>
<tr>
<td>max (×10³)</td>
<td>13.09±1.11</td>
<td>13.03±1.16</td>
</tr>
<tr>
<td>gantry1 (°)</td>
<td>245±4</td>
<td>245±4</td>
</tr>
<tr>
<td>gantry2 (°)</td>
<td>245±4</td>
<td>245±4</td>
</tr>
<tr>
<td>angle (°)</td>
<td>0±0</td>
<td>0±0</td>
</tr>
<tr>
<td>min (×10³)</td>
<td>0.62±0.13</td>
<td>0.40±0.07</td>
</tr>
<tr>
<td>gantry1 (°)</td>
<td>132±6</td>
<td>138±21</td>
</tr>
<tr>
<td>gantry2 (°)</td>
<td>304±10</td>
<td>303±12</td>
</tr>
<tr>
<td>angle (°)</td>
<td>188±8</td>
<td>195±25</td>
</tr>
<tr>
<td>time (s×10³)</td>
<td>2.4±0.2</td>
<td>31.1±6.4</td>
</tr>
</tbody>
</table>

Second, a consistent, systematic reduction in the objective cost value is always found when going from uniform to non-uniform beams for identical PTVs and identical BEVs. Therefore, with respect to the objective cost and all else being equal, non-uniform beam plans always provide a dose distribution at least as good as the uniform beam plans.

Third, there is an axis of symmetry along the ascending diagonal of the objective cost surface since beam order does not change the associated objective cost value. Transposing beam directions is a trivial operation. Applying similar arguments, if all beams have the same orientation (and thus, the same beam segment shapes), then the objective cost is identical to that of a single beam with the same orientation. Thus, the diagonal line of symmetry corresponds to the optimal objective cost plot for the corresponding single beam (i.e. \( \pi = 1 \)). This has been confirmed when segment weights for a single beam were re-optimized.

To gauge its clinical impact, the optimal two-beam orientations found by the optimization program were transferred to the TPS and the segment weights re-optimized for a test patient. The resulting DVHs are shown in Figure 6-5, comparing different treatment techniques for the same patient. Due to the concern with overly heterogeneous target dose distributions, the maximum breast dose constraint was reduced to 55 Gy (from 60 Gy) for a test patient and then re-optimized. This will force the optimization to find a more homogeneous PTV dose distribution. We found the optimal non-uniform two-beam orientation to be very robust (i.e. ±5°) even with the new constraints and that, paradoxically, a more homogeneous target dose reduces the target coverage (estimated by the volume receiving less than 95% of the prescribed dose) and increases heart irradiation (Figure 6-5A).
6.5.2 Validation

The validity and accuracy of the optimization was performed by comparing the segment weights as selected by the optimization program and by the TPS with matched objective cost functions, beam setup parameters and beam segments for six different beam combinations, corresponding to 60 individual segments, in a randomly selected patient. There is no difference between the segment weights of the optimization program and the TPS (paired \(t\)-test, \(p=1.00\)). Their relative order, with respect to objective cost values, is identical.

The optimization program and PINNACLE's Inverse Planning Module both tend to converge to similar segment weights, implying that the objective cost function, the search algorithm, the global minimum, and segment dose distributions are all comparable. Similar segment weights are only possible if all three factors (i.e. objective cost function, search algorithm, and segment dose distributions) are similar.

The dose distribution is, by definition, a composite of all the segment dose distributions whose intensity is proportional to its optimized segment weight. Because segment dose distributions are not degenerate and due to the convergence to a single global minimum, there is only one unique optimal combination of segment weights. Therefore, similar optimized segment weights must imply similar (but not necessarily identical) segment dose distributions. This was verified during the initial testing and verification of the simplified dose calculation algorithm by examining and comparing the segment DVHs from the optimization program and from the TPS which found very similar but not identical DVHs.

6.6 Discussion

6.6.1 Objective Cost Surface

The surface appearance of the uniform beam plans is distinctly different from the non-uniform beam plans. Figure 6-3B is a contour plot of a typical patient. The surface plot of the uniform beam plans display several running “notches” that represent a particularly favored beam direction. These “notches”, in fact, correspond to the beam direction that minimizes the overlap between the PTV and OR, in BEV, and are found in pairs, \(180^\circ\) from each other. The global minimum is found at \((300^\circ, 130^\circ)\) which corresponds to the intersection of these “notches”, suggesting that the optimal uniform two-beam orientation is identical to the minimized overlap between the PTV and OR for each beam.

In comparison, the non-uniform beam plans do not tend to produce convex peaks. The surface is generally more concave, flatter and clearly lower, implying greater degree of degeneracy in the solutions [32]. The “notches” found in the non-uniform plans are much less prominent, suggesting non-uniform beams are better at compensating for
sub-optimal beam orientations than uniform plans. In Figure 6-3D, the global non-uniform and uniform minima are marked at (305°, 105°) and (300°, 130°), respectively. Non-uniform beams can explore beam orientations that do not necessarily minimize the overlap between the PTV and OR since the OR segment can be (partially) blocked or down-weighted. Unlike uniform beams, non-uniform beams’ greater degrees of freedom allow segment modulation within the beam, resulting in more optimal dose distributions and, thus, lower objective cost values.

The optimal two-beam orientations found for uniform and non-uniform treatment techniques are different. Our results suggest that (nearly) parallel beams, as used in the uniform beam plans, will limit the potential benefit of intensity modulation [33]. This can be shown graphically in Figure 6-3D where local minima near (305°, 105°) and (300°, 155°) with hinge angles around 160° and 215° surround a local maximum with a hinge angle of 190° near (300°, 130°). Because of the degenerate (i.e. flat) nature of the surface, beam orientations near either of these local minima (i.e. 160° and 215°) are almost equally good and this dimpling pattern near the global minimum is characteristic of all the non-uniform plan surfaces. Therefore, the optimal tangential uniform two-beam orientation is sub-optimal when non-uniform treatment techniques are employed.

6.6.2 Objective Cost Function

ICRU Report 50 [30] 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.

Assuming a dose-effect relationship, a maximum PTV dose constraint only makes radiobiologic sense if normal tissue is admixed within the PTV. Therefore, the maximum PTV dose constraint behaves like an OR dose constraint and, therefore, should be based on normal tissue tolerance (e.g. fibrosis and telangiectasia) of the PTV and not necessarily on limiting the target dose heterogeneity (e.g. 107% of prescribed dose).

The ICRU Report 50 recommendations are not well suited to deal with intersecting volumes found in the breast. The PTV always contains some normal tissue so, in effect, the breast is both a PTV and an OR. We are not suggesting the PTV upper dose remain unbounded but, instead, that maximum normal tissue dose constraints cannot be ignored. Several studies have found a dose-effect relationship between breast fibrosis and doses greater than 50 Gy [34]. No accepted clinical threshold dose for breast fibrosis exists so 60 Gy (or 120% of prescribed dose) was selected as the maximum OR dose threshold. Although somewhat arbitrary, the maximum dose threshold value is not
discussion

overly critical since optimal two-beam orientation is relatively stable, whether one uses the 60 Gy or 55 Gy dose constraints.

Regions of high dose within the target are not, in itself, undesirable. There is ample evidence that a dose-effect relationship exists in breast cancer. Keynes [35] reported successful primary treatment of breast cancer (with radium) as early as 1932. Bartelink et al [36] demonstrated the efficacy of RT in the adjuvant setting and significant improvement in local control following a 16 Gy boost to the tumor bed compared to the standard 50 Gy whole breast post-operative RT but at a cost of worsened cosmesis.

Clearly, the 60 Gy dose constraint for breast fibrosis will increase target dose heterogeneity. It is hoped that IMRT techniques will allow PTV coverage with a homogeneous dose (between 95%-107% of the prescribed dose) and adequate OR sparing. However, for a certain patient subset, this cannot be achieved. Recall that more than a quarter of presenting left-sided breast patients have a MHD greater than 2.0 cm. For these patients, employing overly stringent constraints on target dose homogeneity may unfairly handicap the algorithm's ability to optimize the dose. Our results suggest that optimizing beam orientations redistributes the dose within concave target volumes. The dose redistribution is most prominent with fewer beams. In practice, the dose shifts away from the heart (enclosed within the convex hull of the target) to the remaining breast volume, adding to target dose heterogeneity.

The optimal beam orientation, as a function of the objective cost function, is remarkably robust. A potential source of criticism is the lack of optimal wedges in the uniform 3DCRT plan which may unfairly bias the comparisons between the uniform and non-uniform plans. We chose not to use wedges for two reasons. First, on practical grounds, determining optimal wedges greatly complicates the optimization process. To implement optimal wedges, one needs to optimize the wedge angle and the wedge orientation. For a tangential beam direction, the thick end of the wedge usually points outward and acts like a missing tissue compensator. However, for non-tangential beam directions, it is not obvious which wedge orientation is best (e.g. for the anterior oblique beam direction).

Second, on theoretical grounds, the addition of wedges will have little (if any) effect on optimal uniform two-beam orientations themselves since the VOI geometry, not the wedges, is the dominant effect. To illustrate, suppose all uniform two-beam orientations were optimal wedged. Although the absolute objective cost values (including the global minimum) will tend to decrease for all beam orientations, the renormalized relative objective cost values are very stable and the beam combination corresponding to the global minimum will remain unchanged. Wedges only have a limited ability to modulate dose along one axis so they usually have much fewer degrees of freedom compared to non-uniform treatment techniques. Because of the limited effect of wedges and the
dominant impact of the VOI geometry, minimizing the objective cost for uniform optimally wedged two-beam plans becomes identical to minimizing the overlap between the PTV and OR.

The robustness of the optimal two-beam orientation, as a function of the objective cost function, was tested by modifying the objective cost function parameters. Changing the weighting factors, $w_i$, even up to four orders of magnitude, or redefining the dose constraints, $d_i$, to a tenth of the original values (i.e. minimum breast dose 4.75 Gy, maximum breast dose 6 Gy, maximum heart dose 2.4 Gy, etc.) has little impact on the optimal two-beam orientation when performed on a test patient. Optimal beam orientations are optimal relative to the other beam orientations so they, unlike the optimal beam fluence profile and optimal dose distributions, are relatively robust with respect to the objective cost function. Like adding wedges discussed earlier, modifying these function parameters will modify the absolute objective cost values but the relative ranking of the different beam orientations remains essentially unchanged.

Although both the optimal beam orientation and optimal beam fluence depend on the objective cost function, the former is less sensitive to the costlet parameters. Therefore, the objective cost function used to determine optimal beam orientations does not necessarily yield optimal beam fluence profiles. We recommend that this new maximum dose constraint be used in the future since reducing the maximum breast dose threshold to 55 Gy (from 60 Gy) has little influence on the optimal two-beam orientation but improves target dose homogeneity (as seen in Figure 6-5).

### 6.6.3 Optimal Beam Orientations

The optimal beam orientation depends on: the VOI geometry, the dose-volume threshold defined in the VOI costlet, the number of beams (and possible beam directions) and the treatment technique used (i.e. uniform vs. non-uniform beams). The similar appearance of the plans' objective cost surface implies an optimal beam orientation class solution exists. However, 3DCRT plans (compared to IMRT plans) are more sensitive to beam orientation.

The DVHs in Figure 6-5 graphically demonstrate the benefit of optimal beam orientations. Conformal uniform beam plans greatly limit the degrees of freedom possible under the optimization, particularly heart sparing. By geometry, for 3DCRT plans, if the PTV overlaps with the OR then one must decide whether to overdose the OR or underdose the PTV. Because the target underdosage costlet is weighted higher than the cardiac overdosage costlet, it will have a higher priority. The 3DCRT plans have a more homogeneous target dose. However, as the DVHs clearly show, this is at the price of a higher cardiac dose.
The best 3DCRT beam orientation minimizes beam divergence. The optimization found the mean optimal 3DCRT hinge angle was 188°. This is almost identical to the clinical hinge angle selected by the treatment planner and confirms that the method can determine optimal beam orientations reliably. In Table 6-2, the least optimal non-uniform two-beam orientation arises when beams are parallel (e.g. hinge angle=0°). This result is not unexpected since parallel beams limit the benefit of intensity modulation [33] because they are (almost) functionally equivalent to a single beam. In all patients studied, optimal non-uniform two-beam orientations appears to be bi-modally distributed. This suggests that a non-uniform two-beam orientation class solution is feasible. Furthermore, because these bimodal solutions are nearly degenerate, one can chose either solution without significantly increasing the objective cost value. However, these bimodal solutions are indirectly dependent on the MHD. As the MHD approaches zero, the local maximum between the bimodal minima tends to flatten out which, in effect, merges these 2 minima together.

The time required to calculate all beam combinations depends on the number of beam directions, the number of segments and the objective cost function. For two-beam orientation optimization, 3DCRT and sIMRT plans take, on average, at least 40 and 500 min, respectively, but the SD is large.

6.6.4 Validity

Although the segment weights between the optimization program and the TPS are not statistically different, does that necessarily imply they are not clinically different? Recall that Figure 6-3 displays “notches” on the 3DCRT surface due to the penetrating nature of megavoltage photons. The observation that these “notches” are 180° apart suggests that beam attenuation, in this patient subset, is not a dominant effect. In other words, if the simplified dose calculation algorithm used assumed no beam attenuation in media, then, after reoptimization, the same optimal beam orientations would result. If optimal beam directions are not significantly influenced by primary beam attenuation then the scattered dose would exert even less influence and can be considered a second-order effect. Therefore, optimal beam orientations are relatively insensitive to these second-order dose effects. This is consistent with the observation that optimal beam orientations are relatively robust with respect to the objective cost function.

The mean and SD of the difference in relative segment weights between the optimized relative segment weights of the optimization software and the TPS is 0.00±3.5% (paired t-test, p=1.00). Applying these arguments, the probable difference is sufficiently small so as to not significantly alter the optimal beam orientation.
6.6.5 Other Considerations

There is growing interest in applying a boost to the tumor bed following breast conserving surgery. Bartelink et al. found a significant dose effect on local tumor control, particularly in high-risk women less than 40 years of age [36]. The optimal beam orientations found in this study cannot be used and it is unlikely a simple two-beam orientation class solution exists for all boost patients (though one may exist for a patient subset). Recall that optimal beam orientation depends on the VOI geometry and the VOI costlet itself. Because different patients may have different boost volumes in different locations, this effectively changes the VOI geometry. The optimal beam orientation depends on the higher dose prescription to the boost volume assumes the residual subclinical clonogen density is higher within the surgical site. With the sIMRT plans, the target volume that is underdosed is generally found at the medial aspect of the breast, near the heart segments. Although the underdosed volume tends to be small, the magnitude of underdosage varies so medially located tumors are regarded as relative contraindications, depending on the target dose distribution.

Setup uncertainties and random movements were not included in the analysis. One could argue that by ignoring these effects, the true optimal beam orientations may, in fact, be different. However, random (as opposed to systematic) errors, over the course of curative radiotherapy, are unlikely to influence optimal beam orientations since its dosimetric effects are relatively limited for small errors [37]. A study by George et al. found no significant differences between the planned and expected dose distribution when including the intrafractional respiratory motion in breast IMRT [38]. Furthermore, if random errors are the same for all beam orientations, then its effect on the objective cost function is applied equally. One can imagine the random errors, in effect, increase the penumbral width. Dose around the periphery of the PTV is "blurred" out, resulting in less dose just inside the PTV and more dose to the adjacent ORs. Incorporating random errors will increase the optimal objective cost value but like changing the costlet's weighting factors, the overall surface appearance remains essentially unchanged.

Although the risk of second primaries in the contralateral breast following post-RT appears small [39-41], it is statistically significant. Thus, effort should be directed at removing any unnecessary radiation exposure to the contralateral breast. Full fluence IMRT plans often contain many small, off-axis segments which tend to increase the scatter dose to the contralateral breast compared to the sIMRT plans.

6.7 CONCLUSIONS

The optimization software is a useful tool that can test many different beam combinations and estimate their associated objective cost values. Afterwards, the most promis-
ing beam orientations could be re-optimized under the TPS to fine-tune and verify the
dose distributions.

Optimal uniform two-beam orientations for the breast consist of opposing tangential
medial and lateral beams. Optimal non-uniform two-beam orientations for left-sided
breast cancers are bimodal, containing hinge angles around 160° and 210°. Non-
uniform beam techniques are less sensitive to beam orientation compared to uniform
beam techniques and result in significantly improved heart sparing but at a cost of
slightly compromised PTV coverage.

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Appendix B

6.10 OBJECTIVE COST FUNCTION

6.10.1 Background

Whether the objective cost function is an accurate measure of the merit of a plan is an important question. If the objective cost value decreases by half, does that mean the plan is twice as good? By definition and by design, the objective cost function is meant to mimic the clinical decision making process of the radiation oncologist and to quantify the merits of a given dose distribution. If the more "optimal" plan with a lower cost results in clinically poorer plans, then the costlets themselves are poorly defined since they are not properly imitating the oncologist's clinical judgment. However, distilling all the relevant clinical factors of a plan into a succinct single scalar quantity is not straightforward (if possible at all).

In essence, the function, like the clinician, has to convert dose distributions from the physical dose-volume phase space to clinical outcomes in the biological phase space. The answer to whether lower objective cost values always result in better outcomes is very much dependent on understanding the relationship between the dose-volume phase space and the biologic phase space. Radiobiologic models, such as equivalent uniform dose and complication free tumour control probability, are functions that explicitly define the relationship between the physical and biological phase space. These models are an active area of research [32-37]. These models and understanding the model principles will continue to improve as longer and better prospective dosimetric and outcome data become available.

6.10.2 Well-defined Objective Cost Functions

It is possible that different function parameters could result in different optimal beam orientations and thereby invalidate the study conclusions. But even different objective cost functions, if well defined, will probably result in similar optimal beam orientations. Well defined objective cost functions are functions that: 1) contain at least 2 opposing costlets where one penalizes for overdosing (i.e. adding dose) and another penalizes for underdosing (i.e. removing dose) and 2) both types of costlets are consistent with a dose effect.

The costlet is consistent with a dose effect when more dose to the same or greater volume never reduces the penalty contribution for an overdosing costlet (and vice versa for underdosing costlets). At a surface minimum, by definition, the opposing costlets are balanced such that any small changes will increase the overall objective cost. Equivalently, the surface gradient at the minimum is zero (which is exactly what the optimization attempts to find).
The overdosing costlets deal with any ORs while underdosing costlets refer to PTVs. All well-defined objective cost functions must converge to the same solution since a hypothetical ideal dose distribution exists assuming no intersection between PTV and ORs VOIs. The ideal dose distribution is when the PTV receives an adequate dose (greater than the underdosing dose-volume threshold penalty) and no dose everywhere else. However, the ideal dose distribution can never be achieved with penetrating radiation. In reality, dose distributions are less than ideal. To reach the target, the radiation must travel through the patient and may irradiate part of an OR before and beyond the target. The optimization uses the objective cost function to arbitrate the trade-off between underdosing the PTV and overdosing the OR. Eventually the optimization will settle on a segment/beamlet weight that equally balances the costs of the PTV and OR.

Now consider the same objective cost function except that the overdosing costlet is made more important by increasing its weight and, hence, its contribution to the overall cost. In that case, the optimization will settle on a new equilibrium point with different segment/beamlet weights and different costs. However, the relative ranking of the optimal objective cost values for different beam directions changes very little since changing the new OR costlet's weighting factor is applied equally for all beam directions.

### 6.10.3 Robustness of Optimal Beam Orientations

Imagine two different optimized non-uniform beams from different directions and the OR costlet is increased by a weighting factor of 100. Because the OR costlet contribution is greater, after re-optimization of segment/beamlet weights, the segments/beamlets that irradiate the OR will be weighted lower to reduce the OR penalty at the expense of partly underdosing the PTV until a new minimum cost is reached but, overall, the new objective cost value increases. However, the segment with less overlap between PTV and OR will have, in general, a lower overall objective cost value since smaller volumes of the OR and PTV are overdosed and underdosed, respectively. Consequently, the relative ranking of the beams' optimized objective cost values remains, essentially, unchanged. Changing the costlets' weighting factors is like changing the stretch factor of the objective cost axis while retaining the same overall surface shape. If all costlet weights are increased by a factor of 100, then the resulting surface will appear identical except the objective cost axis has stretched by a factor of 100.

This result is somewhat counter-intuitive since one expects the objective cost function to exert some influence on the optimal beam orientation. However, a distinction should be made between optimal beam orientations and optimal beam intensity fluence profiles. Although the data suggests optimal beam orientations are relatively insensitive to costlet weighting factors, optimal beam fluence profiles are highly sensitive to weighting factors because clinical outcomes depend on the absolute dose distribution. Consequently, the objective cost function associated with optimal beam fluence profiles can
also be used to determine optimal beam orientations but the converse is not necessarily true. That is, the objective cost function associated with optimal beam orientations may not be appropriate for clinically optimal beam fluence profiles. Therefore, much more care is required when defining the objective cost function with respect to optimal beam fluence. A full discussion on what and how one defines the objective cost function is beyond the scope of this paper. However, for the purposes of the study and bearing the above caveat in mind, we assume the defined objective cost function is a valid measure of plan merit.

6.10.4 Factors Influencing Optimal Beam Orientations

Optimal beam orientations are influenced by the costlets’ dose-volume threshold (and not by its weight). For example, if the PTV costlets remain unchanged and the heart costlet is modified to only penalize heart voxels receiving a dose greater than 60 Gy, then the optimization will, in effect, ignore the heart and make little effort to spare it. The main determinants of optimal beam orientations are VOI geometry and the dose-volume threshold defined in VOIs’ costlet itself for a given number of beams and treatment technique.

The only exception is when the costlet’s weighting factor is made so small that the opposing costlet dominates. If its contribution to the overall objective cost is less than the optimization’s termination tolerance parameter, $\varepsilon$, then the optimization will ignore that costlet and fail to find the true optimal beam orientation (e.g. $\varepsilon < 10^{-15}$). The objective cost function behaves in an ill-defined fashion since it, in effect, violates the first condition necessary for well-defined functions.

As a rudimentary check, the costlet weighting factors were changed (up to 4 orders of magnitude) for a patient and then the optimal beam orientation for a two-beam plan was determined. For this particular patient, the optimal gantry angles varied from 130-145° and 280-285°. The local area near the surface minimum is relatively flat which implies near optimal beam orientations (e.g. ±5°) are probably sufficiently good.

Most radiobiologic models are well defined objective cost functions so their optimal beam orientations should be very similar as long as matching dose-volume thresholds are used. However, how one matches dose-volume thresholds between physical dose-volume constraints and radiobiologic constraints is not obvious and whether optimal beam orientations using radiobiologic objective cost functions are indeed similar has not yet been confirmed or established.

6.10.5 Relevant Costlets

Defining a suitable objective cost function is critically important. All relevant ORs should be modeled explicitly since the optimization depends completely on the objective cost function in determining optimal beam orientations. For example, if only breast
and heart costlets are defined, then the optimization will find a suitable beam orientation to cover the PTV and spare the OR but the dose distribution usually has regions of high dose outside the breast and heart since other VOIs were not explicitly penalized. The objective cost function used in the study has costlets corresponding to the PTV, breast fibrosis, late excess cardiac mortality, radiation pneumonitis and a general normal tissue costlet applied to the external contour (Table 6-1). The external VOI costlet pushes the optimization to minimize the dose outside the PTV and the major ORs (i.e. breast, heart and lungs). Because of their dependency on the VOI geometry, different VOIs will have different optimal beam orientations.