Improving radiotherapy treatment for left-sided breast cancer

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Chapter 8

DISCUSSION AND FUTURE DIRECTIONS
8.1 OVERVIEW

For breast conserving therapy, the typical treatment plan for adjuvant radiotherapy employs two tangentially oriented wedged uniform beams. Generally, the field borders are determined clinically at the time of simulation and the central slice is used to optimize the target dose homogeneity. Regions of high dose are found in the breast, tangential to the beam, particularly the infra-mammary and areolar regions. Wedges are often used as missing tissue compensators to improve dose homogeneity along the axis of the dose gradient but, because they only wedge along a single axis, they cannot completely compensate the breast in orthogonal directions. The standard wedged tangential uniform 2-beam treatment technique has several disadvantages and this chapter discusses the ramifications of the study results on the problems identified.

8.2 DOSIMETRIC CONCERNS

Treatment planning based on the central slice, as done with the standard treatment technique, introduces several potential dosimetric errors. Because the central contour is not representative of the entire breast, the standard technique ignores missing tissue effects and tends to underestimate regions of high dose often found in the infra-mammary fold of the breast. Furthermore, the inherent setup uncertainty associated with treatment planning (due to sampling error from the CT scan) and treatment execution (due to stochastic repositioning of the patient) tends to “blur” the target dose distribution and adds to the dose calculation errors.

The influence of setup uncertainty is made more complicated by the variant effects of contour changes and tissue inhomogeneities. Many studies assume the dose distribution, as a function of setup uncertainty, is modeled analytically with rigid body translations and rotations [1-4]. For some disease sites, such as prostate, the influence of these variant effects on the dose distribution is limited. Although not necessarily true for all cases, it greatly simplifies the modeling because dose convolution is fast compared to dose recalculation.

For the breast, however, both effects are in play so assuming invariant dosimetric effects is inaccurate. The variant effect of contour changes can be demonstrated by example. Consider a uniform beam exactly conforming around a spherical target with a 5 cm radius suspended in air. Suppose there is a 1 cm setup error along, say, the positive lateral axis. If we assume the dose distribution to be invariant, like a rigid body, and translate the dose distribution 1 cm along the positive lateral axis then we ignore the contour outline of the target and (incorrectly) assume dose in air.

The variant effect of tissue inhomogeneities is more difficult to quantify. Ginestet et al determined the dosimetric influence of pelvic tissue inhomogeneities, such as bowel gas and bone, and found up to 3.1% underdosage at the ICRU point when correcting
for tissue inhomogeneities [5]. This effect is small relative to other sites, such as lung [6], where contour changes and tissue inhomogeneities can significantly influence the dose distribution, violating the assumption of an invariant dose distribution. A correct model should accurately incorporate variant effects (i.e. contour changes and tissue inhomogeneities) by recalculating the dose distribution for each setup error before convoluting it with the probability density function. The magnitude and significance of these variant effects are difficult to quantify since incorporating these variant effects into the dose calculation are computationally expensive.

Based on the study in Chapter 2, we conclude that variant effects can be ignored in most clinical cases if the setup uncertainty is symmetrical. This is particularly useful finding suggests that all previous work involving convolution of a rigid invariant dose distribution, although theoretically incorrect, is still dosimetrically valid as long as the convolution function is clinically reasonable and symmetric. (Symmetrical convolution functions have a mean of zero).

A fast, efficient method using a splinic interpolation algorithm is described in Chapter 2 and applied to correct for variant effects. Interpolation can efficiently calculate the variant effects on the dose distribution as a function of setup uncertainty.

Often the setup uncertainty is divided into random and systematic errors [3,7]. In general, systematic errors are more significant than random errors, in part, because random errors tend to be symmetrical and, thus, self-compensating. Organ motion can behave like a random or a systematic error, depending on the properties of movement. Organ motions that are cyclical, have a cycle frequency much shorter than the treatment time and associated with small displacements, tend to behave more like random errors and are, therefore, less dosimetrically important. The dosimetric effect of this type of organ movement can be ignored, such as breathing and cardiac motion. This has been confirmed by a study by Engelsman et al [8] who concluded that respiratory movement was less significant than systematic errors. Other organ movements, such as bladder or rectal filling, behave like systematic errors due to the long filling time cycle relative to the treatment time.

### 8.3 Treatment Technique

The past experience in adjuvant breast RT dealt almost exclusively with uniform tangentially oriented beams (with or without wedges). Some studies [9,10] suggest that to impact overall survival, the target should also include the internal mammary chain (IMC) lymph nodes. Because the IMC lies, anatomically, near the upper medial aspect of the breast, inclusion of these lymph nodes in the planning target volume (PTV) greatly complicates treatment by effectively increasing the volume of heart within the tangential irradiating fields, increasing the overlap between the PTV (i.e. breast and IMC) and the heart.
In Chapter 3, three different planning techniques were compared:

**Wide split tangent technique.** These are essentially a uniform conformal technique with a partial heart block. In order to maintain adequate PTV coverage, the optimization accepts relatively more dose to the heart.

**Oblique electron technique.** An abutting oblique parasternal electron field is added to irradiate the IMC superficially and to spare the deeper structures such as the lungs and heart. Junctioning between electrons and photons are always problematic and can add significantly to the target dose heterogeneity. Some treatment planning systems cannot optimize electron and photon field weights simultaneously so these must be done by hand. There is a tendency for the electron field to underdose the IMC compared to the breast.

**Intensity Modulated Radiotherapy technique.** This is almost identical to the wide split tangent technique, with respect to beam setup, but with non-uniform rather than uniform beams. As noted earlier, it is a superset of the wide split tangent technique and, thus, must be at least as good.

For a given treatment setup and treatment technique, there is a theoretical limit to the best achievable dose distribution. This is, in part, related to the area of overlap between the PTV and organ at risk (OR), as seen by beam's eye view (BEV), especially if the OR is superficial to the PTV. In this situation, because of greater beam attenuation with depth, the OR receives a higher dose than the PTV from a single ray (or beamlet). Non-uniform beams can adjust the beamlet weights to minimize its associated cost. Uniform beams, due to their limited degrees of freedom, cannot modify the intensity of individual beamlets and are, therefore, unable to spare the OR adequately without significantly underdosing the remaining PTV. Mixed modality beam techniques, in effect, divide the medial beam into two "segments": the parasternal electron field and the medial photon field. In this sense, these plans have an intermediate degree of freedom, in between the uniform and non-uniform plans. The IMRT plans are visibly inferior to the 3DCRT wide split tangent plans with respect to target coverage but this is compensated by the relative advantage attributable to the superior heart sparing.

Optimal non-uniform beams have more degrees of freedom so they are, in principle, always at least as good as optimal uniform beams. However, the marginal benefit of non-uniform beams diminishes with less overlap between the PTV and the OR. Therefore, for right sided patients and patients with small maximum heart distances (MHDs), the standard conformal uniform beam techniques are, for the most part, adequate. Non-uniform beams are better suited to treat high-risk patient subsets with large MHDs or very concave target geometry (e.g. when the internal mammary lymph node chain included).
We conclude that the IMRT plans result in improved cardiac sparing but at the expense of some target underdosage (corresponding to the overlap between the PTV and heart). The heart sparing found in the oblique electron plans was similar to the IMRT plans but the IMC coverage was suboptimal. Non-uniform beams are best suited for high-risk patients with large MHDs. The wide split tangent plans tend to overdose the heart compared to the other plans. Despite the optimization and presence of a partial heart block, the limited degrees of freedom of the uniform beam handicaps the best achievable dose distribution. As long as significant projective overlap between the PTV and OR exists, a clinical trade-off must be made. Beam fluence optimization, by itself, cannot adequately resolve this clinical trade-off because tangential beam orientations limit the benefit of intensity modulation. Intensity modulation is least advantageous when beam orientations are parallel. The projective overlap between the PTV and OR can be reduced if other more optimal beam orientations are considered.

8.4 Treatment Complications

Early stage breast cancer patients have long disease-free survivals and excellent overall prognoses. Immature follow-up and under-recognized treatment complications will tend to overestimate the therapeutic index and the lead-time bias may unfairly favor one treatment plan over another. In the past, most IMRT studies concentrated on treatment outcomes, specifically target dose homogeneity, with less emphasis on treatment complications [11-14]. Late cardiovascular complications are associated with cardiac dose [15-22] but its true incidence is difficult to estimate due to: long latency interval, population baseline prevalence and lack of reliable dosimetric and volumetric data correlated with treatment outcome. Therefore, the standard adjuvant breast RT technique used on patients with large MHDs will overestimate the therapeutic index if these associated treatment complications are ignored.

Determining the best treatment technique to spare heart for left-sided breast cancer requires a fair evaluation and comparison of different treatment techniques. Similar dose distributions are assumed to result in similar outcomes. Therefore, by normalizing the target coverage of the different treatment techniques and comparing the normal tissue complication probabilities (NTCP), it is possible to rank which treatment technique is best.

For the heart, a relative seriousness model for late excess cardiac mortality with parameters derived from Gagliardi et al [20] was employed. For the lungs, the NTCP model for radiation pneumonitis from a study by Kwa et al [23] was used. Recall that the area of overlap between the PTV and OR, as seen from BEV, correlates with the difficulty in achieving an adequate dose distribution; the less the overlap, the easier it is to cover the PTV and spare the OR (and vice versa). The greater the overlap (or MHD), the worse the dose distribution and the higher the risk of late excess cardiac mortality (assuming
the same dose to the PTV). The validity of various dose-volume histogram reduction schemes and NTCP models is a source of much debate [24-30]. The models used in the study, despite their obvious shortcomings, still represent the best fit to the available clinical data.

We conclude that although the absolute model values should be viewed with caution, the relative values are helpful for inter-plan comparisons. As better, more accurate data become available, the models should continue to improve as well. For similar target coverage, modifying the treatment from a uniform 3DCRT to a non-uniform IMRT plan, reduces cardiac complication rates by almost 70%, on average. The extra degrees of freedom provided by non-uniform beams allow better conformality of dose around the breast and, therefore, better sparing of the adjacent organs at risk.

8.5 Optimal Beam Orientations

Non-uniform tangential beam techniques can achieve even better dose distributions if more optimal beam orientations are used. Hinge angles are defined as the subtended arc angle between the central beam axes. Recall that tangentially oriented beams with hinge angles near 185° are (nearly) optimal for uniform beams. However, the optimal beam orientation for non-uniform beams contain hinge angles of 160° or 210°. We expect the hinge angles to be different for uniform and non-uniform beams since parallel beam orientations limit the benefit of IMRT.

Quantifying the benefits of optimal beam orientations is not straightforward since the optimal beam orientation must be found first. Determining the optimal non-uniform beam orientation, it turns out, is extremely difficult to solve mathematically because it is a non-deterministic polynomial time (NP) hard problem if no assumptions are made about the dose corresponding to the segment [31]. The optimal solution cannot be known, a priori, without resorting to an exhaustive “brute-force” search. This is mathematically related to the presence of multiple minima within the search space and the non-linear nature of the problem. The beam orientation search space is potentially infinite and expands exponentially with every additional beam. The problem rapidly becomes impractical, even for a moderate number of beams (e.g. n>2).

The topic of optimization is a rich area of mathematical research, primarily because of its practical applicability in many diverse areas. The two main types are stochastic and deterministic. In theory, both should eventually converge to the same optimal solution (assuming the same objective cost function), unlimited time and infinite computational resources. For any given optimization algorithm, there is a compromise between speed (efficiency) and rigor (exactness).

Stochastic optimizations, such as simulated annealing algorithms, use statistical methods to select and evaluate possible solutions. These algorithms are very robust but usually
less rigorous since they do not necessarily converge to the global minimum (within a
finite time). Some deterministic optimizations, such as steep gradient search algorithms,
are extremely efficient because they exploit useful properties of the search space, such
as partial derivatives (e.g. Hessian matrices). However, this type of optimization is only
suitable for a limited class of problems with one minimum inside the feasible search
space [32]. Recall that the optimal beam orientation problem, without other assump-
tions, is NP hard. This implies that the beam orientation search space contains multiple
minima with at least one global minimum.

Due to the complexity of the problem, we initially studied the simpler case involving
uniform beams in Chapter 5 to gain insight into some of the more subtle aspects of
the problem. The clinical test case selected was a pituitary adenoma due to its difficult
anatomic location, the many nearby critical structures and closed vertex (which allows
more beam directions to be evaluated). The main study assumptions were that: 1) there
is only one conformal beam, 2) beam attenuation in media is negligible and 3) favoured
beam orientations are those that tend to avoid critical structures.

Different critical structures are given different qualitative scores, depending on their
relative importance. For a given BEV, all the ORs are identified, the type (or lack) of
overlap (e.g. proximal hit vs. distal hit vs. miss) is determined and the qualitative score is
evaluated. The BEVs are exhaustively searched and the results plotted as a Mercator
projection called a target-eye-view (TEV) map. The best beam directions tend to avoid
the most critical structures such as the lens and optic apparatus. However, the study is
limited to uniform beams and extrapolating the results to non-uniform beams may not
necessarily apply.

The next clinical site, presented in Chapter 6, is left-sided breast cancer. The study aims
are: 1) to determine and document the optimal 2-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 uniform beams vs. intensity modulated non-
uniform beams) on the optimal objective cost function. The non-uniform beam tech-
nique used is called simplified intensity modulated radiotherapy (sIMRT) that uses pre-
defined segments based on projective VOI geometry.

The axial beam directions were discretized into 5° increments so each beam had 72
possible beam directions. For 2 beams, 5184 (72x72) beam combinations need to be
evaluated and the search space increases exponentially as the number of beams, n, in-
creases (e.g. 72'). The complete search space was evaluated and the best solution se-
lected. This guarantees finding the global minimum but becomes extremely inefficient
for large search spaces.

IMRT techniques promised better PTV coverage with a homogeneous dose (between
95-107% of the prescribed dose) and better OR sparing. However, for a certain patient
subset, this cannot be achieved. More than a quarter of left-sided breast patients (i.e. 27%) present with 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.

Optimal beam orientations, in contrast to optimal beam fluence profiles, are relatively robust with respect to the objective cost function. Changing the weighting factors, even up to 4 orders of magnitude, or redefining the dose constraints 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 2-beam orientation, despite the clinically inadequate dose distributions (e.g. breast mean dose 5.5 Gy). Modifying these function parameters will modify the absolute objective cost values but the relative ranking of the different beam orientations remain essentially unchanged (e.g. ±5°).

The optimal beam orientation depends on the VOI geometry, the VOI constraints and the treatment technique (uniform vs. non-uniform). Optimal non-uniform IMRT beam orientations are, in general, different from optimal uniform 3DCRT beam orientations. For a given beam orientation, non-uniform beams are always at least as good as uniform beams, all else being equal. This is intuitively obvious since non-uniform beams are a superset of uniform beams. If we examine the non-uniform beam solution space, the region surrounding the global minimum is relatively flat but contains a local maximum near a hinge angle of 180° (see Figure 6-3D). This local maximum separates the local minima at a hinge angle of 160° and 210°. The adjacent local minimum is almost as good as the global minimum. This implies near-optimal beam orientations (±5°) and near-optimal local minima (near hinge angles of 160° and 210°) are almost as good as the global minimum of optimal beam orientations. This is consistent with the results of other studies [33-37] and justifies “fixing” the hinge angle used in the class solution to 210° [38].

The expected benefit of using optimal beam orientations compared to the tangential beam orientation is shown in Figure 7-5. This represents the average patient and it clearly demonstrates better target coverage and better organ at risk sparing with optimal beam orientations. So, although the relative benefit may appear to be small, it is, nonetheless, clinically relevant. However, the true benefit of optimal beam orientation depends on its deviation from theoretical ideal. Because the problem is NP hard, one can never be certain the stochastic optimization has converged to the true global minimum (i.e. theoretical ideal). Non-uniform optimally oriented plans have more degrees of
freedom than uniform tangentially oriented plans so they, in principle, are better since the magnitude of benefit generally tends to increase with the plan's degree of freedom.

Fewer beams, in general, means less scatter dose and simpler treatment delivery. 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. For these reasons, the number of beams was limited to two.

We conclude that the optimal hinge angles for uniform and non-uniform beams are 186° and approximately 160° or 210°, respectively. The optimal hinge angle for uniform beams minimizes overlapping VOIs by matching the beam divergence along the dorsal field edge. Moreover, the selected hinge angle exactly matches the typical clinical hinge angle, adding confidence that the exhaustive search selected the correct (i.e. best) beam orientation. The optimal hinge angle for non-uniform beams is related to the VOI geometry and maximizes the conformality of the dose distribution around the PTV.

8.6 CLINICAL IMPLEMENTATION

The specific purpose is to devise a class solution for left-sided breast cancer patients to spare heart using simplified IMRT with predefined segments. The intent is to merge all the technical improvements discussed in the previous studies under one treatment technique.

The simplified IMRT (sIMRT) technique is designed to maintain conformal dose distributions almost as good as full fluence IMRT (fIMRT) while keeping the treatment planning and treatment delivery complexity to a minimum. sIMRT is compared to fIMRT and 3DCRT plans for 2 sets of optimal beam orientations, uniform (i.e. ~185°) and non-uniform (i.e. 210°). Optimal beam orientations are derived from the previous study.

Some authors [42,43] compared multibeam IMRT techniques (i.e. n>2) to standard conformal techniques and found the former to be better. While these papers are important to document and to establish the efficacy of IMRT, the conclusions themselves are obvious. According to set theory, additional optimized beams, all else being equal, will never degrade the plan. Clearly, an optimal 3 (or more)-beam plan is superior to an optimal 2-beam plan. We observe, however, these studies are comparing suboptimal 2-beam plans to suboptimal 3 (or more)-beam plans, with respect to beam orientation, so their conclusions are not necessarily valid when comparing an optimal 2-beam plan, like the one described in this study, with their (suboptimal) 3 (or more)-beam plan. Similarly, many studies [14,44-50] have compared tangential IMRT plans with tangential conformal plans and concluded the former are better. This conclusion is completely expected
and consistent since tangential IMRT plans are a superset of tangential conformal plans.

For optimal non-uniform beam orientations, the dose distributions are better conformed around the PTV, resulting in better sparing of adjacent ORs. fIMRT plans with optimal uniform beam orientations are inferior to the sIMRT plans with optimal non-uniform beam orientations. This is significant for two reasons. First, tangential fIMRT plans represents the best achievable dose distribution (for a given objective cost function). This implies that the plan is at least as good as all other IMRT techniques with the same beam orientation and beam modality. Because the sIMRT plan with optimal non-uniform beam orientations is better than the fIMRT plan with optimal uniform beam orientations, the sIMRT with optimal non-uniform beam orientations must be better than all other IMRT techniques with optimal uniform beam orientation and the same beam modality. Second and related to the first, all tangential IMRT technique can be improved by modifying the hinge angle from $\sim 185^\circ$ to $210^\circ$.

We conclude that for any given beam orientation, fIMRT plans are the best and 3DCRT plans are the worst. For optimal uniform beam orientations, the dose distributions for the sIMRT and fIMRT plans are almost identical. There is significant reduction in late excess cardiac NTCP, compared to 3DCRT plans, but at a cost of some target underdosage. The underdosed target volume is generally found at the medial aspect of the breast, near the heart segments. Although it tends to be small, the magnitude of underdosage varies so medially located tumors are regarded as relative contraindications, depending on the target dose distribution.

The results suggest that, for optimal uniform beam orientations (i.e. $\sim 185^\circ$), sIMRT plans can substitute for fIMRT plans without significant degradation in the dose distribution. However, this does not always hold for optimal non-uniform beam orientations. The optimal beam fluence profile depends on the beam orientation. In effect, the sIMRT plan attempts to approximate the fluence of the fIMRT plans using simple predefined segments. The rules defining segmentation assume the fluence profile is convex but, for some beam directions, this is not true so the resulting segments may be too coarse in size. Quantizing the fluence profile to more than 3 intensity levels or using wedges, at least for the optimized beam orientations, would improve the dose distribution.

However, the differences between the plans are mainly attributable to greater target dose inhomogeneity (i.e. SD dDVH) rather than target coverage (i.e. $V_{D95\%}$). The fIMRT plans can be viewed as a superset of the sIMRT plans but with “perfect” wedging. The results in Table 7-2 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. $V_{D95\text{-}110\%}$). The magnitude of heart sparing (i.e. $V_{D95\text{-}110\%}$)
heart NTCP: 0.1% vs. 0.1%) and target coverage (i.e. $V_{D99\%}$: 88.6% vs. 89.1%) are roughly comparable between both techniques. Despite the use of only 3 intensity levels, the lack of wedges and greater target dose heterogeneity, the TCPs of the sIMRT plans are comparable to those of the fIMRT plans (i.e. TCP: 73.3% vs. 73.7%).

Scripting functionality provides potentially huge saving in terms of time and efficiency. Because the segments are defined using simple rules, a generic script can be written once and applies to multiple patients.

The class solution is not meant for all left-sided breast cancer patients and it is expected to be useful in only a small minority of patients who present with a large amount of heart within the tangential irradiated field. However, it is precisely this patient subset that presents the greatest radiotherapeutic challenge for radiation oncologists. Even though this subset may be small, they are important for several reasons. First, there is, at present, no simple clinical technique available. Second, despite their small relative incidence, breast cancer patients represent up to a third of new cases so the absolute number is, in fact, quite substantial. Third, treatment outcomes for early stage breast cancer are excellent so the relative importance of late complications is greater. Late cardiac complications can present more than a decade after the initial RT so (relatively) short follow-ups, even up to 5 years, must be assumed to be conservative estimates of outcome.

Criteria for an acceptable IMRT plan are a matter of clinical judgement. The following are not meant to be absolute concrete recommendations and are subject to change as our treatment evolves. At our institution, an adequate dose distribution is defined as: 1) the NTCP for late excess cardiac mortality is ≤1%, 2) ≥90% of the relative target volume receives a dose between 47.5 Gy 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 simplified IMRT plan with clinical beam orientations and re-evaluate the dose distribution. If acceptable then keep the plan.

3. If unacceptable, generate a simplified IMRT 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 fluence IMRT 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 2-beam megavoltage photons) is not feasible in practice.

8.7 FUTURE WORK

8.7.1 Biophysical Models

In the Introduction, the two related radiotherapy domains, physical and biological, are described. Technical improvements, particularly in treatment planning and radiation physics, have changed the field of radiotherapy. For the most part, the physical interactions at the microscopic level are well understood and, therefore, predictable. Accurate Monte Carlo simulations \([51-54]\) rely on the correct modeling of these atomic events. However, clinical outcomes fall within the biological domain and our understanding of tumour and normal tissue radiobiology is still incomplete.

The ultimate aim is to optimize clinical outcomes directly rather than using the dose distribution indirectly to estimate clinical outcomes. The radiation oncologist implicitly maps physical dose to clinical outcome and, thereby, arbitrates between different dose distributions. In order to optimize clinical outcome, the dose-effect relationship must be made explicitly clear. In this respect, biophysical models are expected to play an increasingly important role since they map physical dose to clinical outcome.

8.7.1.1 Target Dose Recommendations

Recently, there is growing interest in applying IMRT or similar techniques to improve the target dose homogeneity. Interestingly, employing oligo-beam IMRT to spare organs at risk increases the target dose heterogeneity. ICRU Report 50 \([55]\) recommends the PTV receive 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 exists, more dose to more volume of the target will always result in improved local control. However, the upper dose is always bounded by complications/ORS since the delineated breast PTV also contains other normal tissue (such as glandular tissue). These VOI constraints must also be considered. Therefore, maximum dose constraints should be linked to the dose-limiting PTV normal tissue tolerance (e.g. fibrosis and telangiectasia) rather than the somewhat arbitrary 107% of the dose in the PTV (as recommended in ICRU Report 50).
This also highlights another shortcoming of relative dose thresholds for ORs. By definition, the dose thresholds used for ORs are in absolute dose since relative dose thresholds are dependent on the prescribed dose to the target. For example, if a relative dose threshold of 54% of the prescribed dose is used for the heart, then it must be modified if the prescribed dose is escalated.

### 8.7.1.2 Dose Fractionation

Implicit in the definition of therapeutic index is that the index is maximal at some treatment dose. The standard target dose prescriptions are empirically derived from older conformal uniform beam techniques and do not necessarily apply to the newer non-uniform beam techniques. The dose-limiting organs at risk constrains the target dose. With IMRT, relatively more organ at risk can be spared for the same target dose. For example, with uniform beams, the dose to the organs at risk may be 60% of the prescribed target dose while it may be only 30% for non-uniform beams for similar target coverage. The greater relative dosimetric sparing of organs at risk has two related implications. First, the therapeutic index can be improved by either increasing target dose without increasing organ at risk dose and/or decreasing organ at risk dose without decreasing the target dose. Second, the therapeutic index can be improved by accelerating the fractionation without necessarily increasing the organ at risk fraction size and, therefore, improve tumour control, reduce overall treatment time and maintain similar normal tissue complications compared to uniform beam techniques. The latter point has obvious practical implications in terms of treating patients, particularly if dose escalation becomes more and more accepted and overall treatment times become longer and longer.

Solving the problem of optimal dose prescriptions requires a better understanding of biophysical models, particularly accurate and precise tumour control probability and normal tissue complication models. Truly effective treatment cannot be developed without explicitly understanding the relationship between the physical and biological domain spaces. Better recording, analysis and follow-up of patients are necessarily to provide more accurate and precise model parameters. This is complicated by the long latency period for some late effects such as radiation induced cardiac mortality. More effort should be directed in developing and validating surrogates for late effects. Mature data of several decades is needed but if some reliable short term surrogate, such as cardiac perfusion scans, could be shown to correlate with late cardiac mortality, then it would greatly help in the understanding and prediction of late complications.

### 8.7.2 Imaging

Due to advances in technology, there has been much interest in incorporating sophisticated imaging into the radiotherapeutic chain. Imaging can be broadly divided into two main groups: anatomical and functional. These groups are not mutually exclusive since
some modalities can be used in novel ways, providing both anatomical and functional information.

### 8.7.2.1 Anatomical Imaging

Volumetric data, usually a CT scan obtained at the beginning of treatment, is necessary for full 3D treatment planning. However, this introduces a sampling error since the patient geometry used during treatment planning is not always the same as treatment delivery. As a result, wider target margins are needed to ensure adequate PTV coverage. Simulator films are taken at the time of treatment delivery to ensure correct patient positioning. However, the simulator films are of poor image quality, inconvenient and resource intensive.

Mammography is widely used for breast imaging but, unfortunately, distorts the breast anatomy due to compression. Cone beam CT imaging [56-58] provides higher quality images and full 3D volumetric data. Several studies [59,60] conclude that cone beam CT can “potentially provide significantly better low-contrast detectability of breast tumors and more accurate location of breast lesions” compared to mammography. Better localization of breast lesions should result in tighter surgical margins and, hopefully, less post-operative morbidity.

Another interesting solution is incorporating treatment delivery and imaging into one unit, combining two links of the radiotherapeutic chain into one. Prototypes combining a linear accelerator with a cone-beam CT are currently being investigated [61]. Because high quality volumetric information can be acquired at the time of treatment, the treatment fraction can be adjusted and/or repositioned on a daily basis and, thereby, minimize systematic setup errors. As treatment planning systems become faster and more sophisticated, a new daily treatment plan, incorporating previous fractions and patient geometry, can be re-planned on the fly, allowing the treatment to be tailored to each individual.

Some breast lesions are difficult to localize with conventional x-ray imaging due to: their small size, possible organ movement, lesion density similar to normal glandular tissue as well as obscuring fibro-glandular tissue. Other modalities, such as MRI, are being investigated. MRI can be used for both anatomical and functional imaging, depending on its image acquisition settings. Qualitative morphical features, such as radial gradient and margin sharpness analysis, were correlated with the likelihood of malignancy using linear discriminant analysis [62,63]. The desired image sensitivity and specificity can be adjusted by modifying the appropriate receiver operating characteristic. Computerized MRI analysis a tool to aid in diagnosis and not meant to replace the radiologist.
8.7.2.2 Functional Imaging

After obtaining a CT scan, the treatment planning system must be explicitly told which voxels belong to which VOI. This process is called delineation and accurate delineation is a well known problem [64-66]. Hurkmans et al [67] found the ratio of the common over the encompassing delineated breast volumes to be approximately 0.80 and 0.43 for intra- and inter-observers, respectively. Higher quality imaging and pathologic studies correlating disease with glandular breast tissue are expected to reduce observer variation.

Following lumpectomy, the breast, in principle, should not contain any gross tumour. However, delineation of the breast may be inaccurate or imprecise due to lack of clearly visible tissue planes and poor anatomic detail. With functional imaging, one can selectively visualize specific physiological processes, such as perfusion and metabolism. At present, occult sub-clinical residual disease cannot be easily seen on CT so the whole breast is considered at risk. However, if sub-clinical disease can be visualized with functional imaging, then regions of high clonogen density can be localized. Tumour control can be improved by adding a boost dose to these regions. Bartelink et al [68] demonstrated significantly improved local control after boosting the surgical bed (50+16 Gy) compared to no boost (50 Gy), particularly patients younger than 50 years of age. Imaging disease and modifying dose, assuming a non-uniform clonogen density, implies heterogeneous target dose distributions which are better suited to IMRT, rather than 3DCRT, techniques.

8.8 References


