BIOLOGICAL OPTIMIZATION
OF ANGLE OF INCIDENCE AND INTENSITY MODULATION
IN BREAST AND CERVIX CANCER RADIATION THERAPY

Brigida da Costa Ferreira

Division of Medical Radiation Physics
Karolinska Institutet and Stockholm University
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ABSTRACT

Biological treatment optimization aim at improving radiation therapy by accounting for the radiobiological tumour and normal tissues response properties when optimizing the dose delivery. Generally traditional methods, using only dosimetric measures, disregard the non-linear radiation response of different tumours and normal tissues. The accumulated knowledge on tissue response to radiation, in the form of more accurate dose response relations, cell survival models and their associated biological parameters, alongside with the tools for biological treatment plan optimization, has allowed the present investigation on the potential merits of biologically based treatment optimization in radiation therapy.

With a more widespread implementation of intensity modulated radiation therapy in the clinic, there is an increasing demand for faster and safer treatment delivery techniques. In this thesis biological treatment plan optimization, using the probability to achieve complication free tumour control as the quantifier for treatment outcome, was applied to radiation therapy of early breast cancer and advanced cervix cancer. It is shown that very conformal dose distributions can generally be produced with 3 or 4 optimally orientated coplanar intensity modulated beams, without having clinically significant losses in treatment outcome from the optimal dose distribution.

By using exhaustive search methods, the optimal coplanar beam directions for intensity modulated photon beams for early breast cancer and the optimal non-coplanar directions for an advanced cervix cancer were investigated. Although time consuming, exhaustive search methods have the advantage of revealing most features involving interactions between a small number of beams and how this may influence the treatment outcome. Thus phase spaces may serve as a general database for selecting an almost optimal treatment configuration for similar patients. Previous knowledge acquired with physically optimized uniform beam radiation therapy may not apply when intensity modulated biological optimization is used. Thus unconventional treatment directions were sometimes found.
LIST OF PAPERS

This thesis is based on the following papers, which will be referenced in the text by their Roman numeral.


IV. Panayiotis Mavroidis, Brigida Costa Ferreira, Roger Svensson, Bengt K. Lind, Kyriaki Theodorou and Anders Brahme. Quantification of differences between planned and delivered IMRT dose distributions in terms of complication-free tumor cure. (Submitted to Strahlentherapie und Onkologie).
1 - INTRODUCTION

To provide the best possible radiation treatment the optimal dose delivery has to be found. This should cure the patient from tumour growth without causing normal tissue damage. Several variables determine the quality of the delivered dose distribution and some of the most important degrees of freedom are: the fractionation schedule, number of beam portals, direction of incidence, field shapes, multileaf collimator settings, beam modality, energy spectrum and most importantly the intensity and radiation quality modulation of the beams. The simultaneous optimization of all of these degrees of freedom will generally create the best possible dose distribution.

In forward planning with uniform beam treatment techniques routinely used for radiation therapy, a large number of these variables are fixed. Most commonly beam modulation, beam modality, beam energy and dose fractionation are fixed and standardized. Depending on experience of the treatment planner a good dose distribution can be achieved by trial and error successively adjusting beam directions, beam cross section and beam weights. With high resolution, intensity modulated radiation therapy (IMRT), the number of available degrees of freedom increases enormously (15) and the plan optimization has to be made by powerful computer algorithms. Even so, due to the mathematical complexity of the problem some of the available treatment variables, like beam modality or dose fractionation, are still kept constant. During the present thesis the variables investigated were mainly beam direction and intensity modulation. Thus when the term optimal dose distribution is mentioned, it refers to the optimal feasible dose distribution under a number of fixed conditions and therefore optimal is restricted to direction and intensity.

Objective functions have the purpose to express or score the quality of treatment plans and replace the subjective decision of the planner. Because different normal tissues and tumours respond differently and non-linearly to radiation, the most suitable objective function is a biological objective function that takes the radiobiological properties of the tissues into account. The ultimate objective is to produce the best possible dose distribution which will provide the highest quality of life to the patient, through an optimal balance between the probability of tumour control and causing normal tissue injuries.

The use of biological objective functions to optimize intensity modulated treatment plans is relatively recent (3,15,42). The uncertainty of the biological parameters and models used to quantify the response of a tissue to radiation and the lack of knowledge about the individual patient radiosensitivity has probably delayed its introduction into the clinical practice. However, the increasing interest in biological optimization in recent years, combined with the development of 3D treatment planning tools and more advanced imaging
techniques, has triggered the development of more accurate models for cell survival (48) and the collection of biological parameters (2,27,71). Additionally, the development of accurate predictive assays will provide additional information about the radiosensitivity of an individual patient (5,13,81,86).

The shape of the dose distributions produced by biological objective functions may deviate from the common preferences accumulated over the years with uniform treatment techniques or using physical objective functions. Small dose heterogeneities inside the target volume, such as a dose reduction in the neighbourhood of an organ at risk in biologically optimized plans are commonly found (95). Thus, concepts previously gathered with uniform beam dose delivery or with physical optimization methods must be studied and re-analysed. The conventional wisdom about the optimal number of beam portals, beam directions or beam energies might not necessarily apply when biologically optimized IMRT is being used.

Nowadays IMRT has already been implemented in several clinics around the world and the first follow-up results start to be reported (65,106,113). Not only photon beams, but also protons (41) and carbon ions (67,90) are being utilized. For the more difficult cancers, for which IMRT brings the largest benefits, a reduction in the probability of injury allows a dose escalation, increasing the probability of tumour control. With increasing experience, the clinical personnel are becoming more confident and significant reductions in treatment time and quality assurance are being seen (113). Therefore, it will eventually become possible to apply IMRT to most curative patients. A further reduction in the dose delivered to the organs at risk represents a higher quality of life for the patient due to reduced morbidity and a decline in the hospital costs spent in the treatment of early and late radiation injuries. This is of considerable importance for young patients with a significant life expectancy (40). Also the reduction of the dose delivered in the organs at risk might allow for further radiation therapy in case of recurrent tumours.

To make this possible a simple and fast treatment technique, with a low number of beams, must be implemented. As the number of degrees of freedom is reduced with the decrease in the number of beam portals, beam direction becomes increasingly important (10,95,98). However, the problem of optimizing beam direction is not simple and several attempts have been made to solve these problem (10,51,83,85). Therefore today most intensity modulated beam treatments are delivered with a large number of beams, generally 5 or more (54,64,113). Due to target motion and setup errors a large number of beams may smear out the high dose regions. Nevertheless this involves long treatment times, reducing the comfort and immobilization of the patient and the number of patients that can be treated. To reduce the planning and treatment time a simpler treatment technique with a lower number of beams can be implemented. In this case the treatment is less sensitive to setup errors, an increased accuracy and
safety of the dose delivery and verification procedures are possible. However, the simpler technique shouldn’t compromise the treatment outcome and almost equally good plan with a lower number of beams optimally positioned can often be produced (95, Paper I and III).

In the present thesis different beam directions for IMRT for early breast cancer (paper I) and an advanced cervical cancer (paper III) were investigated using an exhaustive search method for a small number of beam portals. The main purpose with this approach is to investigate how the beams interact with each other during IMRT optimization and thus to identify clinically advantageous beam directions of incidence for a test patient. Phase space diagrams are very useful for a small number of beams, to find suitable beam directions for angular optimization. As the number of beams increases, this methodology becomes increasingly time consuming due to the large number of possible combinations of beam portals that need to be studied. For example, a plan with 2 coplanar beams of a given radiation modality implies the calculation of some 300 plans, when 15° increments are used, while for 4 coplanar beams this number increases to almost 13000. However, with more beams the need for an exhaustive search is considerably reduced since the large number of beam directions decreases the need to displace them significantly to find the optimal directions (51).

Although a quite good treatment outcome can often be obtained with a treatment configuration using only 2 beams (paper I, 98), there is room for improvement when one or two beams more are used. In this thesis, for simplicity 1 to 3 beams were locked at close to optimal beam directions (paper I and III), disregarding that those beams directions may not remain optimal as further beams were added to the plan. The associated phase space will thus provide information about the quasi optimal beam orientations of the new beam portals.

The calculation time for a full phase space is prohibitive in clinical practice. But the main shape of the phase space is rather robust with only small variations with patient geometry or biology and beam energy (Paper I, 7). Thus the conclusions from this study can be transferred to similar tumour sites. Since “all” beam direction combinations are tested, the positions of local and global extrema are generally found. Therefore, with this information even the gradient method can be used for angular optimization, without getting trapped in local minimum if the domain of search is restricted to regions covering the global maxima.

In paper I the optimal or close to optimal beam directions for an early breast cancer with involved lymph nodes were investigated. The role of radiation therapy is to treat the microscopic disease left by the surgical procedure. It was found that 3 to 4 biologically optimized intensity modulated beams may be enough to achieve an almost optimal dose distribution. The best dose distribution for the 3 beam plan was found when close to tangential directions, with a 210°
beam separation, were complemented by a beam around 15°. The large number of degrees of freedom available with a 4 coplanar intensity modulated beam plan reduces the need for angular optimization.

However the conclusions drawn in paper I are valid for patients of average radiosensitivity. Syndromes like ataxia telangiectasia or hypoxic tumour cells are well known to cause large deviations in the radiation response of the tissue. For those cases, a larger number of beams is recommended and a slight variation in optimal directions may be expected.

In paper III the target is located in a patient with an advanced cervix cancer that cannot undergo brachytherapy and therefore the prescribed dose can most effectively be delivered with IMRT. Two non-coplanar beam configurations, using one and two non-coplanar beams, were exhaustively investigated and compared with the optimal 4 coplanar beam plan. It was shown that with biologically optimized IMRT an equally good treatment plan can be obtained with a simpler optimal coplanar treatment geometry as the more complex non-coplanar beam configuration. This simplifies the treatment delivery and reduces the chances of setup errors due to rotation of the couch.

While papers I-III covered optimal dose distributions, the accuracy in the delivery was the aim of the investigation in paper IV. The transformation of the optimal dose distribution into a deliverable and delivered plan may introduce errors, due to limitations in the actual treatment planning systems and treatment units. A uniform pelvic phantom was irradiated and the delivered and planned dose distributions were compared. This study clearly suggested that not only physical but preferably biological measures should be used in the evaluation of the delivered dose distribution, since these reflect better the expected outcome of the radiation therapy.
2 - TREATMENT PLANNING AND OPTIMIZATION

ORBIT (Optimization of Radiotherapy Beams using Iterative Techniques) research version (51) was the treatment planning system used in paper III. This algorithm was later integrated in the treatment planning system Pinnacle, which was used in the calculations of paper I and II.

ORBIT is composed by several independent modules that describe the treatment unit, the treatment technique, the dose engine, the patient, the biological models and the optimization algorithm. The user interface available divides these modules into 3 main components: the patient geometry and biology, the treatment and the optimization.

In the patient section all information about the patient anatomy, including organs at risk and target volume, discretized in voxels elements, are defined. The biology of each organ at risk is specified by setting the biological parameters of the relative seriality model, like $D_{50}$, $\gamma$, $\alpha/\beta$ and the relative density of the organ at risk in each voxel. The dose prescription and fractionation schedule is also defined here.

In the treatment section all the characteristics about the beam configuration are defined. Once the number of beams used in the plan is decided, for each beam the radiation modality, the beam energy, the gantry and couch angles, the source to isocenter distance and the multileaf collimator characteristics need to be set. Also for each beam the variables to optimize have to be specified. The available variables were: beam weight, bixels weights, gantry angle and position of the leaves of the multileaf collimator.

In the optimization section the objective function was selected. Using the steepest descent algorithm, variables were iteratively optimized in order to maximize the biological objective function: the probability of complication free cure, $P$.

Although the gradient method is a fast optimization algorithm compared to stochastic methods, it has the significant disadvantage of getting easily trapped in local maxima unless a good initial guess is provided. For instance in paper III this method was used for angular optimization of the coplanar beams. Since frequently the algorithm converged in local maxima, the optimization had to be systematically restarted with different initial guesses of the optimal coplanar directions to assure that the global maximum had been found. This made the procedure extremely time consuming and impractical to be used in clinical practice.

Thus prior information about the orientation of the global maximum, even that only approximate, is very valuable since it can driven the algorithm directly into the global maximum. Since in a phase space “all” beam combinations are simulated, the positions of the local and global maxima are shown. Additionally, the robustness of these diagrams with patient geometry and beam energy (paper I,
makes them the ideal tool to identify initial beam directions to be used in angular optimization.

Finally, for biologically optimized intensity modulated radiation therapy, for which no previous knowledge exists regarding the optimal orientations, phase spaces instruct us to select directions of incidence by understanding how the beams interact with each other. Sometimes those diagrams may even indicate good and useful treatment configurations somewhat contrary to conventional wisdom and that could hardly have been found by any other means (paper I and III). For example, 2 different beam configurations with the same expected treatment outcome give the freedom to the patient or the medical doctor to select the probability of tumour control at a cost of which injury they find more tolerable.

2.1 - FINITE-PENCIL BEAM MODEL

The dose in ORBIT-Research is computed using a pencil beam algorithm developed by Gustafsson et al (34). To speed up the algorithm some approximations were made: the patient is considered homogeneous and both the energy spectrum and the angular distribution of the photon beam are invariant. Thus, the dose distribution in a deposition point, \( \vec{r}_o \), in a patient resulting from a photon beam with an incident energy fluence, \( \Psi'(\vec{r}_o) \), incident on the patient surface in \( \vec{r}_o \), is given by,

\[
D(\vec{r}_o) = \int \int p(\vec{r}_o, \vec{r}_s) \Psi'(\vec{r}_o) dS
\]

Eq. 2.1

where \( p(\vec{r}_o, \vec{r}_s) \) is the polyenergetic pencil beam for the photon beam, representing the dose delivered by a finite photon beam, with the size of the fluence pixel, and generally calculated with Monte Carlo techniques (26).

The same formalism was used in Pinnacle in the calculations of Paper I and II. However, corrections for heterogeneities were made in the primary direction of the beam, while secondary scatter is treated as homogeneous. Thus, lung injury was generally underestimated, while the response in other tissues remained almost the same (89).

2.2 - COLAPSED CONE-CONVOLUTION-SUPERPOSITION

ADAC Pinnacle is a true 3D treatment planning system since both primary and secondary radiation are tracked in the 3D patient volume and corrected to account for heterogeneities. The dose delivered by an external photon beam is computed from the convolution-superposition of the kernels with the total energy released in the medium per unit mass (TERMA). The dose resulting from electron contamination, modelled by an exponential falloff, is posteriorly added to the total photon dose (4,8,55,74).
The primary energy spectrum and the shape of the incident beam coming out from the accelerator is determined from the comparison between measured depth dose curves and cross-beam profiles and the corresponding computed curves in a water phantom. The beam is modeled by adjusting the model parameters to fit the measured data. Thus, a 2D array simulating the initial beam fluence is modeled to account for all components inside the treatment head, i.e., the flattening filter, the accelerator head materials and beam modifiers, like wedges, blocks and compensators (103).

This initial energy fluence is then projected into the patient using a ray tracing technique to determine the distribution of Total Energy Released per Unit Mass (TERMA), defined as,

$$T(\vec{r}) = \frac{\mu}{\rho} \Psi(\vec{r})$$

Eq. 2.2

where $\mu/\rho$ is the mass attenuation coefficient and $\Psi(\vec{r})$ is the primary energy fluence distribution in the interaction point, $\vec{r}$. To account for the beam attenuation in a heterogeneous patient, irradiated with a polyenergetic beam, this is determined as,

$$T(\vec{r}) = \frac{\mu}{\rho} (\vec{r}) \bar{E}(\vec{r}) \bar{F}(\vec{r}) \Phi_o$$

Eq. 2.3

where $\frac{\mu}{\rho}$ is the average mass attenuation coefficient over the energy fluence distribution in the interaction point; $\bar{E}$ is the average energy over the fluence distribution in the interaction site and $\bar{F}$ is the average attenuation in the patient over the incident fluence differential in energy at the surface, $\Phi_{o,E}$, given by

$$\bar{F}(\vec{r}) = \frac{\int e^{-\rho d'} \Phi_{o,E} dE}{\int \Phi_{o,E} dE}$$

Eq. 2.4

where $d'$ is the patient depth at the interaction point along the vector $\vec{r}$.

The dose is obtained by the convolution-superposition of the TERMA distribution with the energy deposition kernel. For a monoenergetic parallel photon beam of energy $E$, incident on a homogeneous phantom, the dose in the deposition point, $\vec{r}_d$, is defined by the convolution equation as,

$$D(\vec{r}_d, E) = \int T(\vec{r}) K(\vec{r}_d - \vec{r}, E) d^3\vec{r}$$

Eq. 2.5

where $K(\vec{r}_d - \vec{r}, E)$ is the kernel representing the energy spread away from the point of the primary photon interaction per unit TERMA. These kernels are
generally obtained from Monte Carlo for monoenergetic beams. In the more realistic clinical situation, the incident beam is composed by an energy spectrum and an average polyenergetic kernel over the energy spectrum at the surface, \( K(\vec{r}, \vec{r}_d - \vec{r}_i) \), has to be used and is determined from,

\[
\bar{K}(\vec{r}, \vec{r}_d - \vec{r}_i) = \frac{\int \frac{\mu(E)}{\rho} \Psi_E(\vec{r}_o, E) K(\vec{r}_d - \vec{r}_i, E) dE \int \frac{\mu(E)}{\rho} \Psi_E(\vec{r}_o, E) dE}{\int \frac{\mu(E)}{\rho} \Psi_E(\vec{r}_o, E) dE}
\]

Eq. 2.6

where \( \Psi_E(\vec{r}_o, E) \) is the energy fluence differential in energy at the patient surface. This kernel is inverted so that the dose calculation is done from the dose deposition point of view and thus it can be computed in only a region of the patient, reducing computation time. Correction factors for hardening of the energy spectrum with depth and off-axis softening are also introduced.

The dose spread kernels are distorted to account for variations in patient density. Thus, the average density between the interaction voxel and the dose deposition voxel, \( \bar{\rho} \), is determined and dose is computed from,

\[
D(\vec{r}_d) = \int T(\vec{r}) \left( \frac{r_o}{r_d} \right)^2 \frac{\rho(\vec{r})}{\bar{\rho}} \bar{K}(\bar{\rho} \cdot l(\vec{r}_d - \vec{r}_i), \vec{r}_d - \vec{r}_i) d^3 \vec{r}_i
\]

Eq. 2.7

where the dose spread kernel is distorted using a density-scaling according to the radiological distance between the interaction and deposition sites, \( \bar{\rho} \cdot l(\vec{r}_d - \vec{r}_i) \). \( \rho(\vec{r}) \) is the density in the interaction point and \( \left( \frac{r_o}{r_d} \right)^2 \) is a inverse square correction factor performed at the dose deposition site, introduced to correct for the kernel tilting effect due to beam divergence, with \( r_o \) as the source-surface distance.

A direct summation over the above integral involves a large number of operations and a reduction in computation time is possible when using the collapse cone approximation (4). In this case the kernel is discretized into conical elements and the energy released in each cone is transported, deposited and attenuated on the cone axis, i.e. collapsed on the cone. A lattice of rays, using the cone axis, is this way constructed so that each cartesian voxel is crossed by at least one ray or cone axis. Thus, instead of using all dose grid points, only the energy from voxels crossed by a ray is used to calculate the dose in the deposition point.
3 - OBJECTIVE FUNCTIONS

3.1 - PHYSICAL OBJECTIVES

Objective functions were developed from the need to score more accurately and objectively the quality of regular treatment plans (66,109). With the introduction of inverse treatment planning, these became a requirement due to the enormous number of variables that had to be optimized (15). The natural sequence of events was to analytically implement the knowledge acquired with experience into the form of physical objectives, like a quasi uniform dose in the target volume limited by the tolerance dose of the surrounding organs at risk. Therefore it became common to specify objectives or constraints such as uniformity, minimum dose, maximum dose or points in the dose volume histogram (DVH), each associated with an empirical and subjective importance weight. The physical objective function will then try to reach the dose selected based on the experience acquired with uniform treatment techniques, quantifying the accuracy of the optimized dose distribution from the pre-defined prescribed dose levels.

Such objectives must be specified in the beginning of the optimization when the optimal dose distribution which result in the highest treatment outcome, is not known. Furthermore, such simple objectives do not reproduce the nonlinear response of tissues to radiation and cannot be related to the expected outcome. For example, a cold spot in the target volume will not significantly affect the score of the physical objective function, unless a minimum dose constraint is specified, but may result in tumour recurrence. On the other hand, if the maximum dose delivered in an organ at risk is lower than the tolerance dose, no penalty is imposed on the score function, but complications may be expected. Dose volume effects and normal tissue architecture are not considered. Still acceptable dose distributions can be produced when the tumour is surrounded by organs with a serial organization of its functional components, since the dose maximum is a good biological descriptor and simple definable constraint. However, for parallel organs the mean dose is a more suitable dose volume objective, but difficult to specify in the form of DVH (108). Multiple dose volume constraints can be defined to simulate the radiobiological properties of a tissue and avoid the above limitations, but without accurately reproducing the response of tissues to radiation. Satisfactory dose distributions can be obtained, but by successively adjusting or adding new objectives (111). Yet when the optimization criteria are met, the optimization stops and doesn’t try to find for a better solution (101).
3.2 - PHYSICAL-BIOLOGICAL OBJECTIVES

The mean dose in the target volume and the relative standard deviation of the dose distribution are important quantifiers of the treatment outcome. Therefore, these and the maximum and minimum dose are routinely used for dose prescription, evaluation, delivery and reporting (1). However, these concepts do not consider the exact response of a tissue to radiation, even though they may allow heterogeneous dose distributions required in the treatment of certain tumours (14). With increasing information regarding the radiobiological properties of tumour and normal tissues an evolution in treatment planning optimization is possible by taking these properties into account to improve dose delivery.

3.2.1 - D_{eff}

The effective uniform dose, defined by Brahme (11) is the dose that produces the same treatment outcome as the uniform dose distribution and is approximately given for tumours and normal tissues by

\[
D_{\text{t,eff}} = D \left(1 - \frac{\gamma}{2P(D)} \left(\frac{\sigma_p}{D}\right)^2\right) \quad \text{and} \quad D_{\text{n,eff}} = D \left(1 + \frac{\gamma}{2(1-P(D))} \left(\frac{\sigma_p}{D}\right)^2\right)
\]

Eq. 3.1

where \(\bar{D}\) is the mean dose delivered, \(\gamma\) is the maximum normalized value of the dose-response gradient, \(P(D)\) is the probability of tumour control or the probability of injury in the normal tissues, respectively, and \(\sigma_p/D\) is the relative standard deviation. Thus, for small dose variations, the mean dose and the relative standard deviation reflect the treatment outcome, but as the dose heterogeneities in the target volume are increased \(D_{\text{eff}}\) is reduced below \(\bar{D}\) (1).

3.2.2 - EUD

The concept of Equivalent Uniform Dose (EUD) was defined for tumours by Niemierko (68) and later extended to normal tissues (69), as the biologically equivalent dose that if given uniformly will lead to the same cell kill in the tumour volume or organ at risk as the real non uniform dose distribution and can be expressed as

\[
EUD = \left(\sum_{i=1}^{N} v_i D_i^a\right)^{1/a}
\]

Eq. 3.2

where \(N\) is the number of voxels in the organ, \(D_i\) is the dose in voxel \(i\), \(v_i\) is fractional volume of the region of interest irradiated with the dose \(D_i\) and \(a\) is the parameter that describes the dose-volume effect of a tissue. For tumours \(a\)
should take negative values, so that EUD approaches the minimum dose. Thus, while a hot spot in the tumour will have no effect on EUD, a very small tumour region with a lower dose will significantly reduce EUD. Nevertheless, even when this dose is zero EUD is not zero (60). Therefore, when used as an optimization objective, high dose heterogeneities in the tumour can be produced with no significant effect on the plan score, whereas cold spots will severely affect the quality of the plan. For organs at risk with a serial behaviour \( a \) should be large positive, so that EUD is close to the maximum dose, while for organs with a large volume effect the dose response closely follows the mean dose and therefore \( a \) should be small and close to 1 (69). This behaviour reproduces more accurately the response of tumours and normal tissues to radiation than physical dose volume objectives.

The higher degeneracy of EUD provides a larger search space to find a better dose distribution than with physical objective functions. During this transition period, when there is a growing interest in physical-biological objectives, EUD is perhaps the most commonly used (22,101,111). This is because it is simpler than biological objective functions and it is roughly insensitive to uncertainties in the biological parameters and models used, which are still not accurately known. Also, the parameters: \( a \) and EUD, specific for each organ and endpoint and derived from clinical data, are the only parameters required in the optimization. Furthermore, for tumours EUD can easily be related with conventional dose prescriptions delivered with uniform treatments, for which clinicians are very experienced. However, despite the relation between EUD and the probability of tumour control or the probability of injuries in the organs at risk, EUD doesn’t provide an estimate of the expected treatment outcome. Additionally, it is not possible to know the clinical significance of different EUD, unless the dose response curve is known (68).

3.2.3 - \( \bar{D} \)

The biologically effective uniform dose, \( \bar{D} \), was defined by Mavroidis et al 2001 (60) as the dose that causes the same probability of tumour control or normal tissue complications as the real dose distribution, \( D(\bar{r}) \), on a complex patient, i.e,

\[
P(\bar{D}) = P(D(\bar{r}))
\]

Eq. 3.3

The \( \bar{D} \) notation is used to show that an average over dose and biological information of the complex patient was done. For example, \( \bar{D} \) can be obtained from,

\[
P_{it} = P_{it}(\bar{D}) \cdot P_{ln}(\bar{D}) = P_{it}(D(\bar{r})) \cdot P_{ln}(D(\bar{r}))
\]

Eq. 3.4
where the target volume is composed by 2 different regions: PT the primary tumour region and LN the surrounding lymph nodes involved with the disease. Therefore, it can be used for multiple targets with different radiobiological responses, independently of the models, dose region, endpoints or tumour type (60).

Although $D_{ef}$ and $EUD$ are a good approximation for single targets of uniform radiosensitivity, they are not suitable for more complex targets requiring heterogeneous dose distributions, since these are limited to only one region of interest and the success of the treatment depends on the control of all targets involved.

![Figure 3.1](image_url)  

Figure 3.1 – Two different treatment plans (Rot and Seg) are compared using as a scaling unit the biological effective uniform dose of the normal tissue injury (right). Therefore, $P_+^*$ for both plans coincides. On the left $\overline{D}_{ITV}$ is used as a scaling unit and now the probability of benefit for the 2 plans coincide. In this case the selection of the best plan is made according to the dose distribution that has the lowest probability of injury (60).

However, the main purpose of $\overline{D}$ is to compare different treatment plans, rather than to be used as an objective. Since $\overline{D}$ depends only on the radiobiological characteristics of the targets involved and not the shape of the dose distribution, the dose response curves remain in the same position independently of the dose distribution used. This facilitates the dose prescription and the comparison between different plans. Thus, when used as the scaling unit, the dose response curves for the probability of benefit of different plans (or injury) coincide and the prescription dose can be selected according to the lowest probability of injury (or largest tumour control), see Figure 3.1. If the best treatment plan is ambitioned then the maximum $P_+^*$ selects the prescription dose.
3.3 - BIOLOGICAL OBJECTIVES

Although, the above concepts contain some radiobiological information, these are specified in terms of dose. Ultimately, it is the radiobiological effect that is of interest. Dose-response curves estimate the probability of tumour control and normal tissue injury for a certain delivered dose and when incorporated into treatment planning systems can be used as optimization objectives. Thus, maximize tumour control subjected to a fixed probability of injury or tolerance dose in the normal tissue, or opposite, can sometimes be used.

In this thesis, the linear-quadratic-Poisson model was used to describe the dose response of tumours and normal tissues to radiation. This accounts for the fractionation schedule and is expressed as:

\[ P(D) = \exp\left(-\exp(e^{\gamma} - \alpha d - \beta n d^2)\right) \]  

where \( P(D) \) is the probability of response in an tissue when it is uniformly irradiated with the total dose \( D \). \( d=D/n \) is the dose per fraction, assumed here constant, and \( n \) is the number of fractions. \( \gamma \) is the maximum normalized value of the dose-response gradient, and \( \alpha \) and \( \beta \) are the fractionation parameters of the linear quadratic model, accounting for the early and late tissue effects. Because the ratio \( \alpha/\beta \) is approximately known for several normal tissues and tumours, \( \alpha \) and \( \beta \) can be determined using,

\[ \alpha = \frac{e^{\gamma} - \ln 2}{D_{50} \left(1 + \frac{d}{\alpha/\beta}\right)} \]  

\[ \beta = \frac{e^{\gamma} - \ln 2}{D_{50} \left(\alpha/\beta + d\right)} \]  

where \( D_{50} \) is the dose that causes a 50% probability of response. The parameters \( D_{50} \) and \( \gamma \) are organ and endpoint specific and are derived from clinical data. The number of variables from which these depend is so large that it is today impossible to obtain parameters that will accurately predict the response of tumours or normal organs to new irradiation techniques. The long follow-ups, required to observe late complications, test old treatment techniques irradiating different tissue regions with different total doses and fractionation schedules. Furthermore, old dose prescriptions were based in 2D treatment planning systems for which organs delineation, made in one slice and disregarding organ motion, was somewhat uncertain. It may therefore be expected that the same organs at risk may, to some extent, respond differently when irradiated with new radiation techniques.

Also the clinical derived biological parameters reflect an average radiosensitivity of the population used in the trial. However, several factors may cause the individual patient to deviate from this average radiosensitivity. Patients with atypia telangiectasia or hypoxic tumour cells are most well known to cause
increased radiosensitivity and radioresistance, respectively. Less striking factors, like the administration of systemic therapy, sometimes even used as radiosensitizers, can also increase radiosensitivity (9,16,93). Furthermore, the averaging of the biological response of many individuals produces a shallower $\gamma$ value than expected for the individual patient (11). Finally, for biologically optimized treatment planning, ideally biological parameters should be based on individual patient radiosensitivity. The association of tissue radiation response with genetic factors (5) has triggered the investigation of predictive assays, but it may take some time until these are introduced into the clinical practice (81,86). Thus, to make the biologically optimized plan more robust to uncertainties to the biological parameters, a patient with more radiosensitive normal tissues and more radioresistant tumour cells may be simulated (44).

The normal tissues are generally irradiated with a heterogeneous dose distributions, thus the probability of injury of organ $j$ was determined using the relative seriality model by Källman et al (42), using,

$$P_i^j = \left[ 1 - \prod_{i=1}^{M} \left( 1 - P(D_i) \right)^{\Delta V_i} \right]^{s_{ij}}$$

Eq. 3.7

where $P(D_i)$ is the probability of injury of the organ $j$ in the voxel $i$ described by Eq. 3.5, $\Delta V_i = \Delta V_i/V_{ref}$ is the relative volume that is irradiated with the dose $D_i$, $M$ is the total number of voxels for that organ and $s$ is the relative seriality parameter that describes the tissue architecture of the organ. Organs with serial tissue architecture have relative seriality values close to 1, while organs parallel like will have values of $s$ close to 0. The probability of tumour control for the target volume $j$ is determined using,

$$P_{\text{tv}}^j = \prod_{i=1}^{M} P(D_i)^{w_i}$$

Eq. 3.8

To account for all organs at risk or target volumes, the total probability of injury and tumour control, respectively, are given by,

$$P_i = 1 - \prod_{j=1}^{N_{org}} (1 - P_i^j)$$ and $$P_{\text{tv}} = \prod_{j=1}^{N_{tv}} P_{\text{tv}}^j$$

Eq. 3.9

where $N_{org}$ is the number of organs at risk in the patient and $N_{tv}$ is the number of different target volumes considered.

When investigating new treatment techniques a comparison with uniform beam techniques in terms of the probability of tumour control or probability of injury might be useful. Thus, for tumour types with large reported tumour
control for conventional therapies, it may be of interest to investigate the reduction in the probability of injury for the same tumour control probability. By contrary for tumours with low tumour control, a certain level complications is accepted if a further increase tumour control probability may be achieved with more advanced treatment techniques. However, with IMRT the therapeutic window is increased both due to a reduction in normal tissue complications probability but also an increase in the probability of tumour control. Thus by constraining tumour control probability or injury probability it is not possible to obtain the best possible radiation treatment. Furthermore it is not possible to know which constraint, in $P_b$ or $P_i$, will result in the largest gain for the patient, unless both cases are tested.

3.4 - BIOLOGICAL OBJECTIVE FUNCTION: $P_i$

Dose volume histograms reduce the information contained in the 3D dose distribution, in the same way as objectives like EUD, $P_b$, $P_i$ or $P_r$ reduce the dose distribution into a single scalar. This not only simplifies the comparison between different treatment plans, but also gives a greater freedom to the optimization algorithm to try to find a solution that satisfies all the treatment objectives. A further advantage with biological objective functions, like $P_i$, is that they achieve the optimal dose distribution in a single step and without manual intervention.

A biological objective function should reflect the expected outcome and preferably the quality of life of the patient after the treatment, not only in terms of tumour control but also the resulting side-effects from the radiation therapy. However the quantification of such injuries is a difficult task. The acceptable spectrum of complications may depend on the judgement of the medical team or the patient preferences and age. Nevertheless due to the large impact on the quality of life or even patient survival, severe injuries can be equally weighted against tumour control. The selection of the normal tissue injury endpoints should therefore be done so that an ideal balance between tumour control and severe injuries is obtained. This is the basis for the biological objective function used throughout this thesis the probability of complication free tumour control $P_i$ given by,

$$P_i = P_b - P_{b\cap}$$

Eq. 3.10

where $P_b$ is the probability of tumour control and $P_{b\cap}$ is the probability of simultaneously having tumour control and severe injuries. This can be approximated by,

$$P_i = P_b - P_i + \delta P_i (1 - P_b)$$

Eq. 3.11
where $P_I$ is the probability of causing severe injury to the normal tissue and $\delta$ specifies the fraction of patient with tumour control and injury in the organs at risk as statistically independent endpoints. Thus the first terms of Eq. 3.10 refers to correlated responses between $P_B$ and $P_I$, while the second term represents the increase due to an uncorrelated response. Since most patients have correlated responses (approximately 80%) (3), for simplicity $\delta$ is often approximated by 0, reducing $P_+$ to

$$P_+ = P_B - P_I$$  \hspace{1cm} \text{Eq. 3.12}$$

This form of objective function is ideal for treatment planning comparison in high risk patients, with low chances of tumour control and high probability of severe complications, since it eliminates subjective importance weights quantifying the severity of each injury endpoint. However, with IMRT or even for some standard uniform radiation treatments, the role of treatment optimization may become more about reducing the incidence of non-severe side-effects. Moreover, the impact of prevalent non-severe injuries may be stronger for patients experiencing a long survival (40). In that case, some terms should be introduced in this biological objective function to consider this type of complications, weighted according to their influence on the patient quality of life.
4 - TUMOUR LOCATIONS

4.1 - EARLY BREAST CANCER

Breast cancer is the most common type of cancer for women and in the year 2000 nearly 6400 new cases were diagnosed in Sweden, representing 30% of all female cancers. Increased exposure to risk factors may be the cause for the raise in the incidence of this malignancy in the last 20 years. However, the relative survival rates have slowly increased probably due to earlier diagnosis and more effective treatments (62).

In early stages of the disease, *Stage I and II*, the primary tumour is less than 5cm and the loco-regional lymph nodes are involved in stage II. The most common pattern of spread of the disease is through the axillary lymph nodes, internal mammary chain and finally supraclavicular fossa from the axillary lymph nodes (46), see Figure 4.1. For more advanced stages, *Stage III and IV*, the tumour is larger than 5cm and might have extended to the chest wall or skin, with involvement of regional lymph nodes. In the final stage, metastasis will be found in the bone, lung, liver and brain (77).

![Figure 4.1 – Schematic representation of the lymph nodes irradiated in radiation therapy of breast cancer stage II.](image)

The treatment of *early stages* has evolved from radical mastectomy (where the entire breast and axillary lymph nodes are removed) to breast conserving therapy. In this case the breast is preserved and only the tumour and a safety margin are removed with a more conservative dissection of the axillary lymph nodes. Radiation therapy is posteriorly administered to eradicate the microscopic disease left by the surgery (23,30). This combined therapy provides better cosmesis and is less aggressive for the patient. For the earlier stages, with no lymphatic spread, radiation therapy irradiates the remaining breast parenchyma and no chemotherapy is administered. The 10 year survival and local relapse rates for these cases are around 80% and 10%, respectively (87,88). And a low incidence of complications is generally reported (82). For patients *stage II*, loco-regional radiation therapy and in 70% of the patients systemic therapy (chemotherapy or hormonal therapy) is administered (50). The survival for these...
patients is around 70% at 10 years, with a local recurrence rate of 10% (30,87). For more advanced stages, chemotherapy followed by mastectomy, or recently lumpectomy if downstaging of the disease is seen, and loco-regional radiation therapy are becoming common practice. If radical mastectomy is no longer viable due to the large extension of the disease, chemotherapy is used followed by high dose radiation therapy. The 10-year overall survival rates vary between 35-60%, with local recurrence rates between 10-19% (17,35).

4.1.1 - Uniform beam radiation therapy

The radiation therapy of breast tumours stage I is usually done with just 2 nearly parallel opposed tangential photon beams with their posterior edge coplanar. The inclusion of the loco-regional lymph nodes enlarges the target volume and its concavity, considerably increasing the volume of ipsilateral lung, heart and contralateral breast inside the treatment fields. Therefore, more complex techniques for planning, delivery and verification were developed to raise the treatment outcome, either to improve target volume coverage but mainly to reduce the dose in the organs at risk (38,46,58,91,92,110). Most commonly a pair of almost parallel opposed tangential photon beams are used to irradiate the breast parenchyma. If not included in the tangential beams, the internal mammary lymph node chain may be treated with a set of abutted anterior electron and photon beams. The axillary and supraclavicular lymph nodes are then irradiated by 2 anterior photon beams of different energies or anterior-posterior photon beams. However, the use of different sets of beams, especially if having different modalities, creates difficulties in matching the penumbra both in the planning and delivery process. Blocks, asymmetrical fields or couch rotations are methods to minimize hot and cold spots resulting from this beam matching (38,91,92). Wedges or compensators are some of the tools available to improve dose homogeneity in the target volume.

The most important complications associated with such uniform beam techniques occur in the lung and heart: radiation pneumonitis (with an incidence of around 14%), pulmonary fibrosis (7.7%), coronary artery disease, myocardial infarction, transient pericarditis and most important cardiac mortality (2-8%). Other reported complications are neuropathy, decreased arm and shoulder movement (5%), lymphedema (14%), fat necrosis, breast thickening or fibrosis (29%), rib fracture (4%) and secondary tumour induction (28,32,40,49,61,75,82,94).

4.1.2 - IMRT

Eighty percent of breast cancer patients undergo radiation therapy, corresponding to more than 30% of the workload in the clinics (50). Thus even small improvements obtained with modern delivery techniques might benefit a large
number of patients. Despite the success obtained with modern fractionation and uniform beam techniques, with high survival rates and low incidence of complications, the long expected survival for breast cancer patients requires a maximal reduction of the dose delivered to the organs at risk to avoid the late complications recently reported (40). Additionally, there is a subgroup of breast cancer patients with less chances of obtaining a good treatment outcome with uniform beam radiation therapy. The concave shape of the target volume, when the lymph nodes have to be irradiated, increase the volume of heart and ipsilateral lung inside the treatment fields (36,75,33). Also, it is difficult to produce a good dose distribution for large breasted women (39,107). Finally an increase in radiotoxicity was reported for patients undergoing chemotherapy or hormonal therapy (9,49,72,73,82). Therefore, more efficient treatment techniques have to be investigated.

The large impact in the treatment outcome of dose heterogeneities seen in large breasted women, more specifically on cosmesis (39,107), has motivated the development and clinical implementation of a simplified intensity modulation treatment technique using a small number of segments (19,21,29,45,104). For example, van Asselen et al (104) and Evans et al (29) generated the segments by dividing the beams eye view projection of the target volume, obtained from the CT data or the portal images, into segments of similar equivalent path length. Cho et al (19) uses 3 segments corresponding to the projection of the target volume, the ipsilateral lung and the heart. On the other hand, Kestin et al (45) first determines the dose distribution produced by open tangential beams and uses the beams eye view projection of the isodoses to conform the segments to each isodose in 5% increments. The weight of each segment is posteriorly optimized to produce a homogeneous dose distribution in the target volume. Using this technique Vicini et al (106) reported an incidence of grade 2 acute skin toxicity of 43% and grade 3 of 1%

The fairly smooth beam profiles obtained for a full resolution intensity modulated treatment technique of early breast cancer, suggest that a simplified intensity modulated beam plan, using a small number of segments, might indeed produce an acceptable dose distribution even that not optimal. This has significant advantages for treatment verification and delivery. Furthermore, this method might introduce fewer errors due to breathing motion compared to full-IMRT. However, further improvements can be obtained with IMRT (19).

The low exit dose delivered by charged particle beams is one of the major advantages of this type of beam modality, thus eliminating the larger volume of low doses usually delivered to the surrounding normal tissues with photon IMRT. Li et al (47) using physical optimization showed that, even that target coverage is the same for the techniques investigated, the same reduction in the volume of high doses can be obtained either by a plan using 9 photon intensity modulated beams or by the combination of 4 photon intensity modulated beams plus a 20°
oblique uniform electron beam. Furthermore, for the multimodality technique, the same volume of low doses as for a standard uniform beam plan was obtained. Although the increase in the skin dose was not discussed, as argued by Ma et al (53), that modulated electron beams in intensity and energy, the increase in the skin dose could be beneficial for the cases where the primary tumour is close from the surface. Otherwise, photon beams combined with electron beams were recommended. Most importantly, since no margins to correct for internal motion are needed when anterior electron beams are used, the maximum dose delivered to the organs at risk decreased compared to a photon intensity modulated beam plan (53).

4.2 - ADVANCED CERVIX CANCER
Effective screening programs, like cervical and vaginal Pap smears, have reduced the incidence of cervical cancer by half over the past 40 years. Thus in Sweden nearly 450 women in the year 2000 were diagnosed with this disease, representing 2% of female cancers and 17% of all gynaecological malignancies (62).

In the early stages of the disease, stage 0-IIA, the tumour is confined to the cervix and the upper region of the vagina. Although some specific patients, like pre-menopausal women or tumours less than 4cm can be treated with surgery, these tumour stages are mainly treated with radiation therapy and chemotherapy. Overall survival rates at 10 years between 70-90% and local control rates between 100-60% were obtained (20,24,25,79). In advanced stages, stage IIB-IVA, the tumour has spread beyond the cervix, reaching the lower third of the vagina and obstructing the ureters. The bladder and the rectum are the first distant organs to be infiltrated with the disease. The lymphatic system is invaded through the paracervical and parametrial lymph nodes, spreading into the obturator, the hypogastric and external iliac lymph nodes. The pelvic lymphatics drain into the common iliac and periaortic lymph nodes, see Figure 4.2. Lymphatic vessels from the posterior part of the cervix also drain into the pre-sacral lymph nodes. Despite the significant improvements obtained in survival and local control with radio-chemotherapy compared to radiation therapy alone (24,102), the value of this combined therapy is still much debated for such advanced stages (25). Overall survival of 50-70%, with local control at 10 years of around 50-80% are generally reported (25,63,79,20). For patients with a tumour stage IVB, distant metastases, more common among women with lymphatic invasion, spread mostly to the lower vagina, vulva, lungs, liver and brain. Chemotherapy is then the primary treatment modality to reduce the spread beyond the pelvis.
4.2.1 - Uniform beam radiation therapy

Radiation therapy is administered to 83% of the cervix-uteri cancer patients, of which 56% received external radiation therapy alone, 13% brachytherapy alone and 31% received combination (50). In this case, the conventional radiation treatment for patients with advanced cervix cancer consists of external radiation therapy to the primary tumour and locoregional lymph nodes, delivered with a four-field box beam configuration plus a pair of an anterior and posterior beams with a midline shield to protect the rectum and bladder. Thus, the uterus, the cervix, the vagina and the lymphatic nodes are irradiated. When indicated, the para-aortic lymph nodes are also included in the target volume. Generally a total dose of 40-60Gy is delivered. Brachytherapy, low or high dose rate, is then used to boost the gross tumour in the cervix to a total dose in point A of at least 85Gy (25,62).

![Diagram of lymph nodes irradiated in radiation therapy of a locally advanced cervix cancer](image)

Figure 4.2 – Schematic representation of some of the lymph nodes irradiated in radiation therapy of a locally advanced cervix cancer (reproduced from 46).

Patients with large tumour volumes, an unfavourable anatomy, due to obesity or uterus abnormalities and severe medical conditions, due to bleeding or pain, cannot undergo brachytherapy. This is an invasive and uncomfortable procedure for the patient and provides inadequate target volume coverage (18). A dose of 65Gy is then delivered through external radiation therapy (62). However, for these patients a lower tumour control was reported compared with the combined therapy, due to the limited delivered doses aiming to minimize organs at risk complications (78).

With the above treatment techniques high doses are generally delivered to large volumes of small bowel, rectum and bladder, resulting in gastrointestinal and genitourinary side-effects, where 10% of the patients are hospitalized, 2% develop severe early morbidity and 5-10% late severe toxicity. Moderate to severe gastrointestinal complications are seen in 9% of the patients. The most common complications in the small bowel are malabsorption and obstruction (2% to 3%) and in the large bowel: haemorrhage, rectal ulceration, proctitis and fistula.
Severe rectal complications, like severe bleeding, rectal stricture and rectovaginal fistula have an incidence of around 3%. Moderate to severe urological complications have a 7 to 9% incidence and the most serious are rectovaginal or vesicovaginal fistulas (1% to 2%). Sexual dysfunction after treatment was experienced by 50% of the women, with severe bleeding (12%) and vaginal stenosis (54%). There is also a 20% incidence of secondary cancer radiation induction, where the bone marrow is the most sensitive site (24,56,76,80).

4.2.2 - IMRT

The survival and tumour control rates, with the pelvis as the major site of failure, and the incidence of severe late toxicity obtained with conventional therapies demand for more efficient treatment techniques (20,76,79).

Söderström (95) investigated the optimal directions for 1 to 3 beams for a locally advanced cervix tumour using the 3 dimensional phase space of $P$. It was found that $90^\circ$ and $180^\circ$ are the optimal directions for a 2 intensity modulated beam plan biologically optimized. A small increase in treatment outcome was obtained for a 3 beam plan with the optimal directions $105^\circ$, $180^\circ$ and $240^\circ$, mainly due to a reduction in small bowel injury and increase in tumour control of the surrounding lymph nodes. No further significant increase in treatment outcome was obtained for a larger number of beams. Interestingly for the 2 and 3 intensity modulated beam plans, despite the location of the rectum or bladder, a posterior beam orientation has shown to be the most advantageous direction of incidence, since the dose distributions were shaped to avoid rectum and bladder irradiation. When comparing a uniform beam box configuration, with and without boost, with this optimal 3 intensity modulated beam plan, an increase of 55% and 23% in $P$ was obtained, respectively (96).

Furthermore, the optimal photon beam spectrum should contain both a low and a high energy component. While the sharper penumbra of photons of low energy is more suitable to irradiate the tumour edges, the photons with larger energies and thus a larger build-up depth, is more adequate to irradiate the central tumour region (97). Åsell et al (7) investigated the optimal beam directions for a 2 intensity modulated beam plan when combining electron and photon beams of different energies. The same $P$ value was obtained when using either a photon beam treatment plan or using a combination of an electron and a photon beam, in this case placed at $230^\circ$ and $270^\circ$, respectively. Furthermore, although the $P$ value did not increase significantly when using increasing beam energies, the selection of beam direction became less critical for higher electron or photon beam energies.

In the University of Chicago the team of Mundt-Roeske (64,65) reported the first follow-up results of IMRT in the treatment of gynaecological disease. A treatment technique using 7 or 9 equidistant intensity modulated photon beam technique was used and compared with the results obtained with a conventional
box technique. Subsequently brachytherapy was administered to the gross disease. Although the clinical significance of these numbers is still unknown due to the limited number of non-randomized patients and short follow-up, chronic gastrointestinal toxicity decreased from 50% with conventional treatment to 11% with IMRT. The incidence of genitourinary complications grade 2 was reduced from 20% to 10%, respectively. And the percentage of women requiring antidiarrheal medication decreased from 75% to 34% with IMRT (64,65). Most interestingly due to the higher conformity of the dose distribution, a reduction in hematologic toxicity was also reported, especially among the patients that were also receiving chemotherapy. Although bone marrow sparing was not initially specified as an objective in the treatment optimization, it was introduced. A significant reduction in the volume of high doses in the bone marrow was then seen, without compromising tumour coverage or the sparing of the rectum or bladder, at a cost of clinically insignificant increase in the volume of small bowel irradiated. Thus, with a reduction in the radiation dose delivered with IMRT, a dose escalation in the chemotherapy dose was suggested, so far used only as a radiosensitizer and also reducing the risks of distant metastasis (16,52).

Kavanagh et al (43) applied concomitant integrated IMRT boost prior to brachytherapy and concurrent chemotherapy. Although the small number of patients, only grade 2 or lower complications were seen with a complete clinical response within the IMRT fields after 3 months of the treatment. Such approach was already tested with uniform techniques with some success in terms of tumour control but with unacceptable complications rates in the organs at risk. By reducing the dose in the healthy tissues with IMRT, dose escalation in the primary tumour enhanced by the chemo-radiosensitizers will thus be possible.
5 - TREATMENT TECHNIQUES AND RESULTS

5.1 - EARLY BREAST CANCER UNIFORM BEAM RADIATION THERAPY

Some of the techniques used in the treatment of early breast cancer with lymphatic spread were selected (38,91,92,110) and biologically optimized using the biological objective function complication free tumour control probability, $P^+$. Four post-operative patients were used in this comparison, with the same positioning, patient delineation and tissue biology as in paper I. In brief, the clinical target volume (CTV) is formed by the remaining breast tissue left by the surgery and the surrounding lymph nodes, i.e. axillary, internal mammary chain, infra and supraclavicular lymph nodes. A margin of about 5mm was added to the CTV to form the internal target volume (ITV), except at the skin surface. The organs at risk are the heart, the left and right lung, considered as separate structures, the contralateral breast, the spinal chord and the remaining surrounding normal tissue.

The different techniques are denoted depending on beam direction, where the subscript indicates the region of the target volume mainly covered by that beam. For example, $2\text{TG}+\text{APPAscvax}$ shows that the target volume at the level of the breast was irradiated by 2 tangential beams (TG). When the entire internal target volume was covered by tangential beams the subscript ‘itv’ is then added. The target volume from the supraclavicular lymph nodes (scv) to the remaining axillary lymph nodes (ax), not covered by the tangential beams, were irradiated by anterior-posterior (AP) and posterior-anterior (PA) photon beams.

Technique 1. $2\text{TGitv}$. In this technique, and the following unless stated otherwise, one isocenter located in the patient chest wall was used. A simple plan with just 2 nearly parallel opposed tangential conformal photon beams of 6MV, with their posterior beam edges parallel, irradiated the internal target volume (Figure 5.1). This sharpens the penumbra of the dose distribution and a slightly smaller field size can thus be used, reducing the volume of normal tissue irradiated with high doses.

Technique 2. $2\text{TGW}+\text{APPAscvax}$. Two nearly parallel opposed tangential wedged photon beams of 6MV, with the posterior edge matching and conformal to the target volume, were used to irradiate the breast parenchyma and surrounding lymph nodes (internal mammary chain and axillary lymph nodes). Because only 2 nearly parallel opposed tangential beams were used to treat this area, no blocks can be used to protect the heart or lung without compromising target volume coverage. Depending on the patient, an anterior and/or posterior photon beams of 6 or 18MV were used to cover the supraclavicular and axillary lymph nodes. The matching of the different set of beams was made by slightly rotating the couch for the tangential beams to align the edges with the anterior-posterior beams (Figure 5.1).
Figure 5.1 – Schematic representation of the uniform beam techniques investigated. TG stands for tangential beams, AP for anterior-posterior and PA for a posterior-anterior beam. W indicates that a 15° wedge was used. scv stands for supraclavicular lymph nodes, ax for axillary lymph nodes and itv for internal target volume. e/ph shows that an abutted electron and photon beams were used.

**Technique 3.** 2TG+APAscvakx. The same treatment geometry as the previous technique was now used but without wedges in the tangential beams.

**Technique 4.** 2TG+APe/ph+APAscvakx. The same isocenter as before was used for the photon beams, while a second isocenter, placed on the skin surface at a source-surface distance of 100cm, was used to position the electron beam. Two tangential photon beams, with the posterior edge parallel, were used to irradiate the breast parenchyma and the surrounding axillary lymph nodes. The internal mammary chain was covered by a slightly oblique electron beam, with energies selected to adequately cover the parasternal lymph nodes. To reduce hot and cold spots, resulting from the matching of the electron and tangential photon beams, the beam edges where matched on the skin surface (92) and the electron beam was rotated by 5° to 10° away from the posterior edges of the tangential photon beams, see Figure 5.1 (91,110). The supraclavicular and axillary lymph nodes are
again irradiated with anterior-posterior photon beams, matched with the tangential beams as described above for technique 2 and 3.

**Technique 5. 2TGitv+APPA.** In this mono-isocenter technique 3 or 4 photon beams were used: two almost parallel opposed tangential beams, with a beam separation of around 200° and with blocks to protect the organs at risk, irradiate the entire internal target volume. Thus, more posterior lateral tangential directions from 145° to 160° were used. Wedges were not utilized due to the large target volume and the deficient linear compensation provided by this device in such cases. Depending on the patient, an anterior and/or posterior beam or 2 anterior photon beams of different energies were used to improve the irradiation of the surrounding lymph nodes not adequately covered by the tangential beams. Generally this beam, or beams, irradiated the parasternal lymph nodes not irradiated by the lateral tangential beam (Figure 5.1, paper I).

**Technique 6. 4TG+AP.** This technique almost reproduces the standard uniform beam treatment adopted for this type of tumour at Karolinska University-Hospital, since target volume delineation is somehow different than used in this thesis. This technique uses 5 photon beams, with one isocenter placed at the level of the 5th intercostals space. Two half blocked tangential photon beams, depending on the patient with the posterior edges matching, covered the lower half of the target volume, consisting of the breast parenchyma. The superior half, including the remaining breast tissue and loco-regional lymph nodes, were irradiated with a second pair of half blocked tangential beams plus one anterior photon beam. This beam division allowed the use of different gantry angles and beam weights by the two pairs of tangential beams, avoiding heart irradiation when the internal mammary chain is integrated in the target volume. Because the match of this set of beams is made in the beam axes, hot or cold spots in the penumbra regions are avoided. Protective blocks were used to spare heart and lung irradiation, as long as the target volume coverage was not compromised.

5.1.1 - Results
The average response probabilities for the different techniques studied are shown in Table 5.1 and in Figure 5.2, also showing some of the most important dosimetric data for the target volume, left lung and heart, respectively. The dose distributions for 2 representative patients with the respective response probabilities are shown in Figure 5.3.

**Technique 1. 2TGitv.** With the standard technique used in the treatment of breast cancer stage I, the average $P_+$ value of 69.1% was obtained. Despite the high tumour control probability of 88.6% (Table 5.1), the inclusion of the surrounding lymph nodes in the target volume significantly increased the concavity of the target and thus the volume of normal tissue irradiated with the prescription dose. Therefore, the high injury in the ipsilateral lung and heart, limit the usefulness of this simple but inadequate radiation treatment technique.
Technique 2. 2TGW+APPAscvax. This is one of the most common techniques in radiation therapy of early breast cancer with lymphatic invasion. The small improvement in tumour control was offset by the increase in the injury in the organs at risk, resulting in the same average $P_+ \text{ value as the above technique (Table 5.1). In fact, for two patients this technique has shown to be inferior to the technique 2TGivt, due to the larger left lung injury obtained when wedges were used (Figure 5.3, left side).}

The need to rotate the couch to obtain a good match between the tangential and the anterior or posterior beams becomes an important drawback when using this treatment technique. However, for small-breasted woman this can be avoided, by matching the beams in the axes using instead half blocked beams (37,92).

Table 5.1 – Average response probabilities obtained for the different uniform treatment techniques investigated. $\bar{P}_{\text{LLL}}, \bar{P}_{\text{LH}}$ and $\bar{P}_{\text{LSN}}$ are the average probability of injury in the left lung, heart and surrounding normal tissue, respectively. $\bar{D}_{\text{cb}}$ is the average of the mean dose in the contralateral breast for the 4 patients used in the study. One standard deviation is shown for each of the response probabilities. Details on the abbreviations used to denote the treatment techniques were explained in the caption of Figure 5.1.

<table>
<thead>
<tr>
<th># Tech.</th>
<th>Technique</th>
<th>$\bar{P}_{\text{LLL}}$/%</th>
<th>$\bar{P}_{\text{LH}}$/%</th>
<th>$\bar{P}_{\text{LSN}}$/%</th>
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<tbody>
<tr>
<td>1</td>
<td>2TGivt</td>
<td>69.1 ± 5.1</td>
<td>88.6 ± 1.1</td>
<td>19.5 ± 4.9</td>
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<tr>
<td>2</td>
<td>2TGW+APPAscvax</td>
<td>69.1 ± 6.3</td>
<td>89.4 ± 1.7</td>
<td>20.4 ± 4.9</td>
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<tr>
<td>3</td>
<td>2TG+APPAscvax</td>
<td>70.8 ± 5.5</td>
<td>88.9 ± 1.6</td>
<td>18.1 ± 4.8</td>
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<tr>
<td>4</td>
<td>2TG+APe/ph+APPAscvax</td>
<td>78.9 ± 1.6</td>
<td>90.2 ± 1.3</td>
<td>11.3 ± 2.5</td>
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<td>5</td>
<td>2TGivt+APPA</td>
<td>77.5 ± 3.9</td>
<td>89.5 ± 2.0</td>
<td>12.0 ± 2.4</td>
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<tr>
<td>6</td>
<td>4TG+AP</td>
<td>80.0 ± 3.2</td>
<td>90.3 ± 1.4</td>
<td>10.3 ± 2.1</td>
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<table>
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<tr>
<th># Tech.</th>
<th>Technique</th>
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<th>$\bar{P}_{\text{LH}}$/%</th>
<th>$\bar{P}_{\text{LSN}}$/%</th>
<th>$\bar{D}_{\text{cb}}$/Gy</th>
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<tr>
<td>1</td>
<td>2TGivt</td>
<td>13.5 ± 7.4</td>
<td>4.1 ± 1.8</td>
<td>1.7 ± 0.3</td>
<td>3.0 ± 0.9</td>
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<td>4.0 ± 1.8</td>
<td>1.5 ± 0.4</td>
<td>2.6 ± 1.0</td>
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<tr>
<td>3</td>
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<td>12.7 ± 6.7</td>
<td>3.6 ± 1.3</td>
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<td>2.4 ± 0.9</td>
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<td>4</td>
<td>2TG+APe/phi+APPAscvax</td>
<td>6.9 ± 3.1</td>
<td>0.8 ± 0.6</td>
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</tr>
<tr>
<td>5</td>
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<td>1.5 ± 0.6</td>
<td>2.5 ± 0.7</td>
<td>4.3 ± 1.8</td>
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<tr>
<td>6</td>
<td>4TG+AP</td>
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<td>1.2 ± 0.5</td>
<td>2.4 ± 0.6</td>
<td>5.3 ± 0.9</td>
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</tbody>
</table>

Technique 3. 2TG+APPAscvax. Wedged tangential beams increased the dose homogeneity in the target volume, but this improvement resulted in a larger dose delivered in the organs at risk (Figure 5.2). To show this, the previous technique was compared with the same beam configuration but using now conformal open tangential beams. A further increase in the average treatment outcome of 1.7% was then obtained, due to a reduction of 2.3% in the probability of injury, mainly from the left lung injury (Table 5.1). The reduction in tumour control probability due to the removal of the wedges was negligible, since the
lower probability of injury allowed a slight dose escalation in the target volume (Figure 5.2).

This result may be a consequence of the high weight given to lung injury since severe radiation pneumonitis was used as an optimization endpoint (31). A reduction of the importance of such endpoint could effectively strengthen the usefulness of wedges. Nevertheless, the main rational to obtain a homogeneous dose distribution in breast cancer radiation therapy is to achieve a good cosmetic result (39). Although the significant psychological and physiological impact on the patient, it is debatable if this objective should be equally weighted against tumour control.
**Technique 4. 2TG+APe/ph+APPAscvax.** The high probability of injury obtained in the left lung and heart with the previous techniques can be substantially reduced by the use of an anterior electron beam irradiating the parasternal lymph nodes. In that case, the average $P_i$ value was increased to 78.9%, making this one of the most interesting treatment techniques for this tumour site. Although only a small increase in tumour control was obtained, the left lung injury was further reduced by 46% and the heart injury decreased by 78%. Additionally, a substantial reduction in the dose delivered in the contralateral breast was also possible (Table 5.1).

Some care is recommended regarding the average response values presented. This technique has in fact shown to be the most efficient for half of the patients used in the study (see patient on the right side of Figure 5.3).

However, this technique has some shortcomings. Since 2 isocenters had to be used, translations and couch rotations are required, increasing the probability of set-up errors and treatment time. Overdosage and underdosage in the junction of beams of different modalities are almost unavoidable (Figure 5.3), increasing the probability of matching fibrosis or tumour recurrence, respectively (105). Furthermore, the larger skin doses delivered by the electron beam cause a less satisfactory cosmetic outcome (39). To reduce this problem, generally a low weight photon beam is used to lower the skin dose, but at a cost of a larger injury in the left lung and heart. In this study since skin was not delineated as an organ at risk, the optimization sometimes removed this anterior photon beam. As a simple test, for the patient on the right of Figure 5.3 the anterior photon beam was manually set to 30% of the weight of the electron beam. A reduction in $P_i$ of 7% was then seen due to the significantly larger left lung injury and a slight increase in heart injury.

**Technique 5. 2TGtv+APPA.** A simple modification from the previous techniques was made by irradiating the entire ITV with tangential beams and by positioning the lateral tangential beam to an almost posterior direction. An anterior photon beam is now needed to cover the regions of the ITV, mainly the internal mammary lymph nodes, not covered by the lateral tangential beam due to the protection blocks used (Figure 5.1). This significantly reduced the injury in the ipsilateral lung and heart compared to technique 3, without compromising tumour control (Table 5.1). However, a larger injury in the surrounding normal tissue was obtained due to the hot spot created in the entrance of the lateral tangential beam (left side of Figure 5.3, Figure 5.2). Compared to technique 4, using an electron beam, a further reduction in the injury in the left lung was possible, though a slightly lower $P_i$ value was obtained. This was a consequence of the larger heart and surrounding normal tissue injury and contralateral breast irradiation when using only photon beams.

However, the beauty of this technique is its simplicity for planning and delivery, with no couch rotations or wedges. Also, because no electron beam is used, a larger skin protection is possible.
**Technique 6. 4TG+AP.** The larger number of degrees of freedom by this somewhat complex technique caused the further increase in the average $P_+$ to 80%. The division of the 2 tangential beams into 4, using different weights and gantry angles, provides the largest normal tissue sparing and tumour control probability (Table 5.1). Furthermore, wedges can be used to improve dose homogeneity, but with no significant advantages in terms of uncomplicated tumour control probability (result not shown). Compared to the electron technique a slightly larger heart injury was obtained, but lung injury was further reduced.

![Dose distributions for 2 representative patients for the uniform beam techniques investigated. For the patients in the figure and for technique 4 (2TG+APe/ph+APPAscvax), the anterior photon beam aiming to irradiate the internal mammary chain was removed by the optimization of $P_+$ and therefore the technique is denoted here only 2TG+APe+APPAscvax. For the patient in (b) this technique had the largest $P_+$ value.](image)

Figure 5.3 – Dose distributions for 2 representative patients for the uniform beam techniques investigated. For the patients in the figure and for technique 4 (2TG+APe/ph+APPAscvax), the anterior photon beam aiming to irradiate the internal mammary chain was removed by the optimization of $P_+$ and therefore the technique is denoted here only 2TG+APe+APPAscvax. For the patient in (b) this technique had the largest $P_+$ value.
5.1.2 - Discussion

A technique using only two almost parallel opposed uniform tangential beams is not adequate for the treatment of the complex target volume produced in a patient with breast cancer with lymphatic spread. As the technique becomes more complex and thus with a larger number of degrees of freedom, an improvement in treatment outcome was seen. Interestingly, the tumour control probability remained almost the same, while the largest benefit was from the reduction of damage to the organs at risk. A significantly lower injury in the left lung and heart was then obtained, while the injury in the surrounding normal tissue was increased and a larger average dose was delivered in the contralateral breast (Figure 5.2 and Table 5.1).

With biological optimization it was not possible to achieve the standard dosimetric recommendations (1,37) for the target volume and organs at risk (Figure 5.2). Indeed the selected group of patients represent difficult cases for uniform beam radiation therapy, due to the large breast, ITV and large target volume concavity. Furthermore, the main goal of biological optimization is not to achieve a homogeneous dose in the target volume, but to obtain the largest treatment outcome for the patient. Therefore, commonly a low dose in the internal margin was obtained, resulting in the low dose minimum in the ITV (Figure 5.2). Also a large dose maximum in the ITV was generally seen, especially for the multi-modality technique due to the hot spot in the junction of the different beams (Figure 5.3). Even that the reported values of dose maximum and dose minimum may seem quite extreme, the clinical significance of these is not known, since they involve very small volumes. Although, these may be of importance for normal tissues with a serial structural organization, it is less critical for parallel organs. Otherwise, dose constraints can be added to the optimization to reduce the maximum dose in the organs at risk and increase the dose minimum in the target volume. Finally, the suggested dose escalation should be considered with care, since the optimal prescribed dose depends on the biological parameters selected, which are not so accurately known (paper I and II).

Generally the supraclavicular and axillary lymph nodes are irradiated with a beam configuration using an anterior photon beam or a set of APPA photon beams. In the first case, an insufficient coverage of the deeper axillary lymph nodes was usually seen. Also, a high dose region in the shallower supraclavicular lymph nodes and normal tissues was seen. Although brachial plexus neuropathy or paralysis was considered as an endpoint in the optimization, for the most difficult patient a probability of neuropathy of around 14% was estimated. Furthermore, this anterior photon beam also increased considerably the injury in the ipsilateral lung. Alternatively, a pair of APPA photon beams did improve target volume coverage, but at a cost of an increase in the dose delivered to the surrounding normal tissues. If these lymph nodes are instead irradiated with tangential beams (like for the techniques 2TGitv+APPA or 4TG+AP), reduced left
lung injury and good target coverage was generally obtained. However the longer beam path through the patient caused large hot spots in the beam entrances, increasing the incidence of arm edema.

The last 3 techniques studied are the best for the treatment of an early breast cancer stage II when biologically optimized uniform beams are used (Figure 5.1 and Table 5.1). A fair comparison between these techniques is difficult, since these are a result of a trial and error procedure and a better outcome could probably be obtained if a longer search had been made. Also, different patients were better treated with different treatment techniques (Figure 5.2 and Figure 5.3). Only 4 patients were used in this study and a larger number of patients may be useful to correlate the appropriate technique to patient features. Although, a trend was seen between the maximum distance of lung inside the target volume curvature (Figure 5.2), no correlation was found with breast size, as generally reported in the literature (39,107). Finally, as mentioned above, all the techniques have advantages and disadvantages in terms of treatment planning, delivery or outcome. The simplicity of technique 5 (2TGtv+APPA), using only 3 or 4 photon beams makes it an attractive technique for planning and delivery. As for technique 6 (4TG+AP), the avoidance of couch and collimator rotations, or even wedges, and the skin sparing are positive aspects to consider. All of which are drawbacks for technique 4 (2TG+APe/ph+APPAscavax) using an electron beam. Technique 6 has the slight disadvantage of being quite complex to plan. But this might be a minor difficulty for an experienced planner. The additional increase in treatment outcome compared to the previous techniques may justify the increase in treatment planning and delivery time (Table 5.1).

Although the multi-modality beam technique resulted in large $P_+$ values (Table 5.1), a further improvement could be expected by modulating the electron beam energy (6). Generally, one energy for the electron beam was used to irradiate the parasternal lymph nodes, providing a good heart and left lung sparing. However, due to the different depths of the internal mammary chain lymph nodes, it was difficult to select a suitable electron beam energy that will adequately cover this part of the target volume. Even that a bolus could somewhat reduce this problem, it would increase skin dose and the complexity of the delivery. Also, for this beam modality a reduction in the breathing margins when an anterior electron beam is used is possible, thus further reducing the dose maximum delivered in the organs at risk (53).

5.2 - EARLY BREAST CANCER IMRT

For the best uniform treatment technique, using 5 photon beams, an average $P_+$ value of 80% was obtained. Although, this is a rather complex treatment technique with a large number of uniform beams, presently it is still simpler to deliver than intensity modulated radiation therapy, requiring a large quality
control protocol prior to the delivery. However, a significant improvement in treatment outcome, of around 12%, can be obtained by using 3 or 4 intensity modulated photon beams biologically optimized to treat this tumour site. This was due to an increase in tumour control probability and a significant reduction in the probability of injury (paper I).

For a 2 intensity modulated photon beam plan 3 different beams configurations with almost the same treatment outcome were found (Table 2 in paper I). These use a pair of almost parallel opposed tangential directions around 300° and 150° (peak T in Figure 5.4 - 2 BEAMS); one tangential medial beam coupled to an anterior beam (peak A) or a perpendicular beam configuration with an oblique beam around 45° and a lateral tangential beam (peak P). Still, standard tangential directions will probably be always preferred, even for IMRT.

However, the significant increase in treatment outcome when a third beam is added to the plan, recommends that at least 3 intensity modulated beams biological optimized, placed in the optimal directions, should be used in radiation therapy of breast cancer stage II. For a 4 intensity modulated beam plan, only a slight improvement in treatment outcome was obtained and if at least 2 beams have quasi parallel opposed tangential directions, angular optimization becomes almost unnecessary. Even so, the third and fourth beams should be placed avoiding parallel opposed configurations and if possible with large beam separation.

In paper I to find the optimal directions for a 3 beam configuration, an exhaustive search was made fixing one beam in 165°. This approximation was based on the efficiency of this direction for a 2 beam plan (Figure 5.4 - 2 BEAMS) and the particular target geometry favouring tangential orientations. Due to the efficiency of a 3 intensity modulated beam plan in the treatment of this tumour site (paper I), further calculations were made to verify if a better plan could be found when using different gantry angles for the fixed beam $\Omega_3$ (Figure 5.4 – 3 BEAMS). Additionally, it is shown that the similarity between the 2 beam phase space and the 3 beam phase space when $\phi=165^\circ$ (paper I), stands for other directions of $\Omega_3$. Thus it is possible to estimate the directions of the local maxima for a 3 beam plan from the 2 beam phase space. I.e., the 3 beam phase space local maxima are placed in the same angular intervals of the 2 beam phase space local maxima, but shifted by at least 15° to escape to the influence of the fixed beam $\Omega_3$ (Figure 5.4). The phase space with $\phi=90^\circ$ was simulated to clearly illustrate this feature. Since in the 2 beam phase space no local maxima existed in the neighbourhood of 90°, when $\phi=90^\circ$ the shape of the resulting 3 beam phase space is extremely similar to the 2 beam phase space (compare the 2 beam phase space with the 3 beam phase space when $\phi=90^\circ$ in Figure 5.4). Interestingly, now the global maximum was moved to find a perpendicular beam configuration and not to escape to the fixed beam.
Figure 5.4 – The 2 beam phase space (above) and several 3 beam phase spaces with different gantry directions of beam $\Omega_3$, $\varphi_3$. The solid diagonal lines show plans with 1 and 2 beams for the 2 and 3 beam phase space, respectively, because 2 beams are coinciding. The diagonal dotted lines indicate perpendicular beam configurations and dashed lines indicate parallel opposed beams. The white solid lines show the direction of the fixed beam $\Omega_3$, while the dashed white lines specify the exit of the same beam. The circle indicates the optimal direction for a 1 beam plan. The open diamonds and stars show the maximum $P_+$ value for each phase space, while the same closed symbols show the maximum $P_+$ value for a 2 and 3 beam plan, i.e. $\hat{P}_2^+$ and $\hat{P}_3^+$, respectively.

Even that a similar treatment outcome was obtained for the local maxima of the different 3 beam phase spaces in Figure 5.4, as found in Paper I, the optimal directions for a 3 intensity modulated beam plan biologically optimized are $(15^\circ,165^\circ,315^\circ)$ with a $\hat{P}_3^+$ value of 91%. Although a 1% lower $P_+$ value was
obtained when $\Omega_3(\varphi=135^\circ)$, in the directions $(135^\circ,180^\circ,300^\circ)$, this phase space showed some interesting results, since almost the same $P_+$ values were obtained independently of the orientations of the beams $\Omega_1$ and $\Omega_2$. Thus when such lateral tangential direction is used, the selection of the beam directions of the additional portals becomes less critical.

A pencil beam dose engine was used in these calculations. This method corrects for patient heterogeneities in the primary beam direction, but no corrections are made for secondary scatter. Thus, an error is introduced (89), by mainly underestimating lung injury, while the response probability of the other tissues remains almost the same. Although this do not affect the general shape of the phase space, it is possible that the optimal directions found will slightly vary. For example, the small difference in treatment outcome seen between the optimal 3 beam plans using the lateral tangential beams in $165^\circ$ or $135^\circ$ may be reduced, since the error in $165^\circ$ is expected to be larger than for $135^\circ$ due to the longer beam path along lung tissue for the former, once the computation of the dose in the penumbra is less accurate.

Several factors may cause the optimal directions to deviate slightly from the ones found in this thesis. The patient or energy selected, the biological parameters describing tissue response to radiation, the resolution of the phase space and perhaps the dose engine used. However, the general shape of the phase spaces will still be valid, since this is mainly determined by the patient anatomy. Furthermore, the optimal directions found in this study are only a starting point for individual angular optimization, for which the precision used in this work is sufficient.

5.3 - FROM UNIFORM RT TO IMRT ON AN ELLIPTICAL PHANTOM

For the same number of beam portals the most elaborate uniform beam technique can never be as efficient as an intensity modulated beam treatment plan, due to the significantly larger number of degrees of freedom available with IMRT. To increase the number of beams is another method to increase the number of degrees of freedom. But, then the interaction between the beams increases, reducing the effective number of degrees of freedom that in reality are available and a saturation in the treatment outcome is seen. On the other hand, for a small number of beams, angular optimization searches for directions that maximize the treatment outcome by finding the most efficient degrees of freedom. Thus depending on the tumour site, the optimal number of beams is often around 3 to 5 (Paper I,51,98).

To investigate the interaction between photon beams of 50MV and how they affect the optimal directions of 4 uniform or intensity modulated beams, an elliptical phantom with a central spherical tumour was used. Three coplanar beams were fixed and equidistantly placed at 0°, 120° and 240°, while the
direction of the fourth beam was systematically changed to gantry directions from 0° to 180° and non-coplanar angles of 0°, 20° and 40° (Figure 5.5). This configuration was denoted $\Omega_{3+1}$ to indicate that 3 beams are fixed in the plane, while one beam is moving in and out of the plane (paper III).

In Figure 5.5 the variation in the probability of tumour control, the probability of complication free tumour control, and the probability of injury as a function of the gantry angle of beam $\Omega_4$, $\varphi_4$, and for different non-coplanar angles, $\theta_4$, using uniform and intensity modulated beams, are shown.

For a coplanar uniform beam plan (dotted line UNIF 0° in Figure 5.5), as expected, the maximum $P$ value was obtained for the gantry angles $\varphi_4=180°$ and almost as good at 60°, since those directions correspond to parallel opposed beam configurations. The minimum $P$ value was found when 2 beams are coinciding, i.e., for $\varphi_4=0°$, 120° or 240° and therefore the plan has effectively 3 beams. A parallel opposed configuration, though most efficient for uniform beams, becomes the less suitable for IMRT. Thus, for a 4 coplanar intensity modulated beam plan it is in $\varphi_4=60°$ and 180° that the smallest $P$ values were found (solid line IMRT 0° in Figure 5.5). A larger beam separation, either achieved by placing the beam $\Omega_4$ in a different gantry or non-coplanar angle, resulted in an increase in $P$. Thus for a coplanar intensity modulated beam plan the local maxima of $P$ occurred for directions of “maximum” beam separation, such as 30°, 90° and 150°, while for a non-coplanar plan the maximum was found when beam $\Omega_4$ was 40° out of the plane (solid line IMRT 40° in Figure 5.5). Furthermore in this case, $P$ becomes almost independent on the gantry angle of beam $\Omega_4$. This improvement in the treatment outcome is due to an increase in tumour control probability but mainly a reduction in the probability of injury.

The left side of Figure 5.6 shows the uniform beam fluence, $\Psi$, for the 4 beams used in the configuration $\Omega_{3+1}$ in function of the gantry angle of beam $\Omega_4$, for the non-coplanar angles 0° (lower panel), 20° (middle panel) and 40° (top panel). The same is illustrated for IMRT on the right side. Only gantry angles lower than 90° are illustrated due to the periodicity of the phenomenon.

For uniform beams the weight of each beam is based on their proximity. For a coplanar plan, when $\varphi_4 = 0°$, $\Omega_1$ and $\Omega_4$ are coinciding and therefore the weight of these 2 beams was equally shared. Thus it can be assumed that this plan has 3 effective beams (left side of Figure 5.6-lower panel) with approximately the same weight.

As beam $\Omega_4$ moved from 10° to 60°, it became further away from $\Omega_1$ and closer from the exit of $\Omega_3$. Therefore $\Psi_4$ and $\Psi_1$ are increased, while $\Psi_3$ is reduced. The minimum of $\Psi_4$ is thus found for a parallel opposed configuration, i.e. when $\varphi_4 = 60°$. Due to the large distance between $\Omega_4$ and $\Omega_2$, this last beam is not influenced by $\Omega_1$ and $\Psi_2$ remains almost the same. Only when $\Omega_4$ is placed in gantry angles larger than 60°, $\Omega_2$ interacts with $\Omega_4$ and both $\Psi_2$ and $\Psi_4$ are reduced, while $\Omega_3$ and $\Omega_1$ are free to successively increase their weight as the distance to $\Omega_4$ increases.
Figure 5.5 - Schematic representation of the beam configuration studied for an elliptical phantom with a central spherical tumour. $D_0$ and $\gamma$ for normal tissue was 60Gy and 2 and 80Gy and 3 for the internal target volume. Three coplanar beams are fixed in 0°, 120° and 240°, while a fourth beam systematically takes different gantry, $\phi_4$ and/or non-coplanar angles, $\theta_4$. (Upper panel) Probability of tumour control, $P_B$, (middle panel) probability of complication free tumour control, $P_+$ and (lower panel) probability of injury, $P_I$ in function of the gantry and non-coplanar angle of beam $\Omega_4$. 
Figure 5.6 – Beam fluence, in beam’s eye view, of the 4 beams used in configuration $\Omega_{3+1}$ in function of the gantry angle of beam $\Omega_4$, $\phi_4$ and for different non-coplanar angles: 0° (bottom), 20° (middle) and 40° (top), for uniform and intensity modulated radiation therapy. The fluence is normalized for the beam with the largest weight for uniform and intensity modulation radiation therapy, respectively. Therefore no relation exists between the weight of uniform and intensity modulated beams.

Because treatment outcome is a result of the fluence of all the beams in the plan, for uniform beams a parallel opposed configuration combined with directions that allowed a large weight in the beam placed in an anterior/posterior
direction, resulted in the highest $P_+$ values (compare the $P$ values also shown in Figure 5.6).

The pattern of interactions seen for uniform beams was repeated for intensity modulated beams, i.e., the same beams that were influenced by $\Omega_4$ in the uniform plans, had their degrees of freedom reduced in intensity modulated plans (compare right and left side of Figure 5.6). However, the larger number of degrees of freedom available in IMRT reduced the intensity of the perturbation. For example, for $\phi_4 = 10^\circ$, $\Omega_1$ interact with $\Omega_4$, but only the intensity of the lateral bixels from these beams was reduced to minimize the regions of beam overlap. For “maximum” beam separation, i.e., when $\phi_4 = 30^\circ$ or $90^\circ$, $\Omega_1$ is minimally perturbed by $\Omega_4$ and the local $P_+$ maxima were then obtained. The global maximum was found in $90^\circ$ since this is the direction that causes the lowest reduction in the number of degrees of freedom in $\Omega_1$. As $\Omega_4$ approaches a parallel opposed configuration, i.e. $60^\circ$, both $\Omega_4$ and $\Omega_3$ have their weight reduced.

As moving out in the plane the same basic principles apply. For uniform radiation therapy, when $\Omega_4$ takes a non-coplanar orientation, the larger separation allowed to increase beam’s weight, especially of the non-coplanar beam, and thus $P$. For a technique using a non-coplanar intensity modulated beam, the perturbation caused by $\Omega_4$ to the fixed beams can be further reduced and for the non-coplanar angle $40^\circ$ almost no interactions occurred between the 4 beams. Thus nearly all degrees of freedom available from each beam are used, resulting in the largest treatment outcome.

The use of a simple patient, with no local organs at risk but surrounding sensitive normal tissue, help to clearly illustrate the interactions between the beams and to correlate this with treatment outcome. Furthermore, the best directions of incidence were also identified. From this analysis, the gantry angle $0^\circ$ or $180^\circ$ were the best directions of incidence for 2 reasons: 1) the shallower tumour depth and 2) the smallest volume of normal tissue irradiated. Although treatment outcome is a result of the dose delivered by all beams, whenever the anterior/posterior directions had the largest weight or effective number of degrees of freedom, i.e., was minimally perturbed by the presence of other beams, large $P_+$ values were obtained. Thus for this configuration $\Omega_{3+1}$, $90^\circ$ becomes the best direction of incidence for $\Omega_4$ since it is the gantry angle that causes the least perturbation to the more useful beam, $\Omega_1$.

The above results suggest that the use of non-coplanar treatment techniques could increase treatment outcome compared to a coplanar configuration. In fact for this hypothetical patient, a plan using 2 anterior antisymmetrical non-coplanar intensity modulated beams resulted in an increase of $P$ to 93.7%. When this was compared to the 4 optimally placed coplanar beam plan, it represented a difference between the best coplanar and the best non-coplanar plan of less than 1%. However, for this simple patient the clinical significance of this increase is not known.
The motivation to use non-coplanar beams is that by separating the beams the smaller beam overlap reduces the volume of hot spots generally delivered in the normal tissues. Also, better directions of incidence may be found avoiding the irradiation of the organs at risk and thus providing a better coverage of the target volume. Nevertheless, this results in a longer beam path through the patient. Also treatment delivery time and set up errors due to couch rotations are increased.

When applying the configuration \(\Omega_{3+1}\) to a real patient with a locally advanced cervix tumour (paper III), the more elongated target volume and the organs at risk, rectum and bladder, increase the perturbation in the beam fluence. These anatomical features somewhat reduce the effective number of degrees of freedom for anterior-posterior directions and slightly favours lateral orientations. Even so, the main shape of the phase space for these 2 different patients was rather similar, but for the real patient the global maximum was found in the plane for the directions \((0°,120°,240°,90°)\).

However, the best 4 intensity modulated beam treatment technique found was actually for a non-coplanar configuration. This was composed by two anti-symmetrical posterior non-coplanar beams combined with 2 coplanar beams in 90° and 240° (paper III). Despite the location of the organs at risk, the beam’s arrangement anterior/posterior plus lateral is so efficient, that the largest \(P\) values in the phase space were achieved when these directions were used and combined with favourable oblique directions (Figure 3 in paper III, 98). Therefore oblique orientations should be selected with great care.

When comparing the best coplanar technique with the best non-coplanar configuration, no significant difference in treatment outcome was seen (Table 2 in paper III). Thus, when the direction of the 4 coplanar beams is optimally selected, a patient with an advanced cervix cancer can be equally well treated by such simpler coplanar plan. The proximity between the organs at risk and the target volume, make it hard to significantly reduce the volume of high doses in the normal tissues even with non-coplanar techniques. Also, for a small number of beams the regions of overlapping beams is minimized, reducing the need for more time consuming non-coplanar beam techniques.

5.4 - DELIVERY OF IMRT
During this thesis only theoretical dose distributions were investigated and these represent benchmarks of the expected outcome for a real delivery. The magnitude of the reduction in treatment outcome from the optimal dose distribution depends on the limitations of the optimization algorithm, the treatment delivery unit and to some extent of the imaging system.

Image fusion combining CT anatomical data and PET functional imaging improve target localization, but also display heterogeneous tumour regions, like hypoxic compartments, that need to be irradiated with larger therapeutic doses to achieve tumour control (70). Recently, fast 4D CT imaging systems can even scan
the patient during different phases of the breathing cycle. Nevertheless, a complete understanding of patient anatomy is necessary to accurately delineate organs at risk and tumour regions (46,84).

Intensity modulated radiation therapy is generally delivered using a step and shoot technique or dynamic multileaf collimation. Less commonly tomotherapy machines are also clinically available (54). However, a further improvement in treatment outcome and delivery time is expected by using scan beams combined with multileaf collimators. Thus, the physical characteristics of multileaf collimator and scan beams are of extreme importance, since these significantly influence the quality of the real dose delivery (100).

An advanced cervix cancer was used to quantify the reduction in treatment outcome from the optimal dose distribution to a step and shoot technique using a total of almost 90 segments and a leaf width of 1.25cm at the isocenter (112). A 4 beam coplanar and non-coplanar configurations, similar to the best plans found in paper III, were selected for this comparison. Although, no significant difference was obtained in $P$ between the theoretical coplanar and non-coplanar plans (Figure 5.7), this difference increased for the deliverable dose distributions, mainly due to the better irradiation of the target volume for the non-coplanar plan. This was a consequence of the significant loss in treatment outcome, of around 8%, between the optimal dose distribution and a step and shoot delivery technique. Smaller differences would be expected for higher resolution multileaf collimators, especially if combined with scan beams, thus approaching the conclusions taken from the theoretical dose distributions (paper III).

Table 5.2 – Biological parameters for the most important tissues used in the optimization of an advanced cervix tumour. Nevertheless, the kidneys, spinal chord and femur heads were also considered as organs at risk. SNT stands for surrounding normal tissue, representing all remaining normal tissue in the body (2).

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$D_{50}$/Gy</th>
<th>$\gamma$</th>
<th>$s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph Nodes</td>
<td>62</td>
<td>4.2</td>
<td>-</td>
</tr>
<tr>
<td>Cervix</td>
<td>64</td>
<td>4.2</td>
<td>-</td>
</tr>
<tr>
<td>Rectum</td>
<td>80</td>
<td>2.2</td>
<td>1.50</td>
</tr>
<tr>
<td>Bladder</td>
<td>80</td>
<td>3.0</td>
<td>0.18</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>54</td>
<td>2.3</td>
<td>1.50</td>
</tr>
<tr>
<td>SNT</td>
<td>65</td>
<td>2.5</td>
<td>0.86</td>
</tr>
</tbody>
</table>

The addition of internal and setup margins to the clinical target volume to correct for intra and inter-fraction organ motion and setup errors in uniform radiation therapy, are not strictly valid when delivering IMRT due to the interplay between organ motion and multileaf travel. For uniform radiation therapy, this correction method leads to an underestimation of the incidence of
Figure 5.7 – Two different slices of a coplanar plan with the beams placed at (90°, 130°, 180°, 230°) and a non-coplanar plan with the coplanar beams at (90°, 230°) and the non-coplanar beams in the gantry angle 180° and non-coplanar angles ±20°. These are compared for the optimal theoretical dose distribution and the dose distribution that can be delivered with a step and shoot technique using almost 90 segments. $P_{\text{I,R}}$, $P_{\text{I,B}}$ and $P_{\text{I,SB}}$ are the probability of injury in the rectum, bladder and small bowel, respectively.

$D/\text{Gy}$: 80, 70, 60, 50, 40, 30

$P_{\text{I,R}}$, $P_{\text{I,B}}$, $P_{\text{I,SB}}$
complications when organ motion and setup errors are disregarded and treatment planning is done in a static patient (59). In IMRT, the steep dose gradients in the boundaries of the target volume, requires for a high precision delivery technique and a reproducible patient set-up. Several methods that follow organ motion and account for anatomical distortions during the radiation therapy are becoming available. Thus image guided radiation therapy reduces motion artefacts by gating organ movement and tracking target volume position with time (57). A reduction in the conventional margins used to define the internal and planning target volume are then possible, resulting in a smaller irradiation of healthy tissue.

When high energy photon beams are used in radiation therapy the activation of tissues due to photonuclear reactions, leads to the emission of positrons with an intensity that is approximately proportional to the absorbed dose delivered. By detecting this signal through PET-CT imaging, this data can be used to adapt the plan during the course of the therapy, correcting for any type of treatment uncertainties. More interestingly by quantifying the tumour response to radiation during the first weeks of the treatment, individual tumour radiosensitivity may be estimated and included in the biological treatment plan optimization (13, paper II).

Current protocols (1,37) describing quality assurance procedures are based on dosimetrical comparisons. However, not only these are of interest, but biological measures, reflecting the expected outcome of the delivered dose distribution should also be examined. Using a pelvic phantom, the planned and delivered dose distributions were compared in Paper IV, resulting in an acceptable difference of less than 3% in the mean dose delivered in the phantom. However this corresponded to a reduction in the treatment outcome by more than 7%. Therefore it may be more clinically relevant to evaluate the delivered dose distribution in terms of loss in tumour control probability and probability of injury in the organs at risk. Furthermore, the resolution of the dose matrix and organs segmentation used in most treatment planning systems, generally around 5mm, may significantly affect the estimation of the treatment outcome. Therefore, due to the high resolution of film dosimetry, allowing almost continuous dose delivery monitoring in a real patient, the delivered dose distribution should be reported, recorded and used to derive dose response parameters.
6 - CONCLUSION

In radiation therapy suitable beam directions for a given target volume are effectively described in the phase space of complication free cure, illustrating the variation of the treatment outcome with the angle of incidence of the beam portals. Since the main shape of the phase space depends mostly on the tumour site, the robustness of these diagrams with patient anatomy, patient radiosensitivity and photon energy, make them the ideal tool to identify suitable or even optimal angular intervals for a plan with a small number of beams, i.e. between 1 and 3. Because the exact optimal directions for an individual patient depend on similar variables, the global maximum found in the phase space, simulated for a test patient, can be used as starting points for angular optimization. This considerably reduces treatment planning time and generally avoids trapping at local maxima. If the region of the global maximum is well defined, the search may be reduced to a small area of the phase space. In the present study a few local maxima of almost equal value were found and therefore the search must be extended to all these local maxima to find the optimal beam directions for an arbitrary patient.

When selecting directions of incidence for a 4 beam configuration, although beam separation is generally advised, for an advanced cervix tumour this property was not so important provided the beams were separated by more than 30°-35°. Then, treatment outcome was mainly influenced by using the most optimal beam directions, i.e., an anterior-posterior beam combined with a lateral beam and suitable oblique directions. For breast cancer patients, almost parallel opposed tangential beams are most efficient and even a separation of about 15° between the beam’s axis may result in a closely optimal treatment outcome.

For a breast cancer patient, with nodal involvement and average radiosensitivity, 3 well selected intensity modulated beams biologically optimized are generally sufficient to produce a closely optimal dose distribution. For some patients, a 3 beam plan can produce a large hot spot in the entrance of the lateral tangential beam, which could be eliminated in a 4 beam plan. No large improvements in treatment outcome were obtained when using a larger number of beams. However for a more difficult case, e.g. a patient with radiosensitive normal tissues and a very radioresistant tumour, there may be a need for more than 4 intensity modulated beams.

For an advanced cervix tumour closely surrounded by organs at risk, an optimal coplanar intensity modulated beam biologically optimized treatment technique can deliver a dose distribution with nearly the same clinical outcome as a more complex non-coplanar beam configuration. This is mainly because no significant reduction in the volume of high doses delivered in the organs at risk.
was possible with non-coplanar beams. This simplifies the treatment delivery and reduces set up errors.

Not only the dosimetric data, but also biological response measures should be evaluated and reported when comparing planned and delivered treatments. Quantification of the biological treatment outcome should be made based on the delivered dose distribution. The high resolution of conventional verification systems, most often film based, can image the continuous delivered dose better than the finite voxels used in treatment planning systems. High resolution dosimetry may thus provide a accurate source of feedback for the modelling of biological response parameters.

The clinical and practical advantages of an irradiation technique with a small number of beams are numerous. Using biologically based treatment plan optimization, close to optimal dose distributions can be produced with such a low number of beams in radiation therapy of early breast cancer and advanced cervix cancer. The uncertainties in the biological models, dose-response parameters and lack of knowledge about individual patient radiosensitivity are reasons to improve the robustness of biological optimized treatment plans by simulating the worst case scenario of a patient with radiosensitive normal tissues and a radioresistant tumour. Thus, more research should be devoted to these areas, since improved treatment outcome is expected when using biologically optimized radiation therapy.
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