Study of Dose Escalation Protocols in Prostate Cancer Radiation Therapy with Patient Realignment by Using Internal Fiducial Markers

by

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Abstract

Use of internal fiducial markers and electronic portal imaging (EPID) to realign patients has been shown to significantly reduce positioning uncertainties in prostate radiation treatment. This creates the possibility of improving the treatment by decreasing the planning target volume (PTV) margin added on the clinical target volume (CTV), which in turn may allow dose escalation. As a first step we do test on 3 patients. Conformal treatment plans for 3 prostate cancer patients were evaluated by using different PTV margins with dose prescription of 70Gy/35fr initially. Two beam arrangements, 4-Field-Box (4FB) and 4-Field-Oblique (4FO), were used. Then, two dose escalation schemes, 74Gy and 78Gy, with tighter prescribed PTV margins chosen from the first simulation were tested. A Monte Carlo model was developed to simulate the daily organ motion and calculate the dose to organs. After the whole treatment, dose-volume histograms were produced and tumour control probability (TCP), equivalent uniform dose (EUD) and the effective dose to critical organs ($D_{eff}$) were calculated. By comparing the biological factors, optimized dose escalation schemes were found. The results show that using internal fiducial markers and EPID, the prescription dose can be escalated to 78Gy/37fr with a 4mm PTV margin. Based on the available dose-response data for intermediate risk prostate patients this is estimated to result in a 20% increase of TCP and significantly reduced rectal complications. From these results, another test on 20 patients was performed to test the general validity of the dose escalation, which counts the second step of this project. We compared the outcome of two plans: one is 70Gy/35fr, 10mm PTV margin and without patient realignment (Reference Plan) and another is 78Gy/39fr, 5mm PTV margin with patient realignment (Escalated Plan). Four-field-oblique (gantry angles 35°, 90°, 270°, 325°) beam arrangement was used. Using the same method described before. Results show that for intermediate risk prostate patients by using dose escalation to 78Gy/39fr with a 5mm PTV margin will provide a 20% increase of local control and significantly reduced rectal complications.
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CHAPTER 2

Internal fiducial markers can assist dose escalation in treatment of prostate cancer:
Result of organ motion simulations
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This project is an interdisciplinary work performed by the cooperation of graduate student (Miao Zhang), medical physicists (Vitali Moiseenko, PhD and Dr. Tim Craig, PhD), and radiation oncologist (Mitchell Liu, MD). Chapter 2 of this thesis is coauthored with Vitali Moiseenko, Tim Craig, and Mitchell Liu. Chapter 3 of this thesis is coauthored with Vitali Moiseenko and Mitchell Liu.

Miao Zhang, the first author of each paper, is the primary researcher in this work. He did the treatment planning, Matlab simulation, data collection, data analysis, paper writing, and public presentation.

Dr. Vitali Moiseenko, medical physicist in BCCA-Fraser Valley Centre, is the research supervisor of Miao Zhang. He proved the general idea of this work. During the research, he was closely involved, giving instructions and guiding the direction of this work.

Dr. Tim Craig, medical physicist in Princess Margaret Hospital, proved prototype of the Matlab simulation code, and gave suggestions on this work.

Dr. Mitchell Liu, radiation oncologist in BCCA-Fraser Valley Centre, proved the patient data and gave suggestions from an oncologist’s point of view.
CHAPTER 1

Introduction and literature review

From Canadian Cancer Society's annual statistics\(^1\), an estimated 149,000 new cases of cancer and 69,500 cancer related deaths would occur in Canada in 2005. Cancer is the leading cause of premature death in Canada: 954,000 potential years of life were lost in 2000 as a result of cancer. This represents 31% of the potential years of life lost resulting from all causes of death. Cancer is primarily a disease of old: in Canada 44% of new cancer cases and 60% of cancer deaths will occur among those who are at least 70 years old. There may be complex interactions between social problems that are a direct result of the cancer and those social problems that are an underlying reflection of lifestyle, social status or economic status of the individual cancer patients.

1. Introduction to cancer radiation therapy

1.1. Cancer

Cancer develops when cells begin to grow out of control. Because cancer cells continue to grow and divide, they are different from normal cells, which divide only to replace worn-out or dying cells and to repair injuries in the adulthood. Instead of dying, cancer cells outlive normal cells and continue to form new abnormal cells. Cancer cells also have an ability to invade surrounding tissues and spread through blood or lymphatic system to form distant metastasis. Most cancers lead to formation of a solid tumor, an abnormal mass of tissue. In contrast, leukemia, a cancer that affects blood-forming tissues, does not lead to solid tumor.

1.2. Radiation Therapy

Radiation has been used for cancer therapy shortly following the discovery of x-rays by William Roentgen and radioactivity by Marie and Pierre Curie, about 100 years ago. Advances in technology and a better understanding of radiation effects on the body have made radiation therapy an important part of cancer treatment. In fact, about half of all people with cancer will receive radiation during their cancer treatment.

1.2.1. Treatment
Radiation therapy for the cancer treatment can be given in two different ways. In external beam irradiation, the most common method, treatment is delivered to a specific area of the body using radiation produced by linear accelerators (Linac) or radioactive sources housed in so called teletherapy machines. The prescribed treatment dose and fractionation depend on the type and stage of cancer, and the treatment objective (cure or palliation). The other method of delivering radiation treatment is called brachytherapy. In this method, radiation sources are inserted either directly into or placed close to the tumor to produce dose distribution that conforms to the target volume (tumor plus margin).

The planning of radiation therapy is as important as the actual treatment. The first part is called simulation. The patient is placed on a couch in a position mimicking that on the treatment unit to ensure that the delivery of radiation delivery is performed in the same setup as in the planning procedure. While the patient lies in the treatment position, x-rays or a CT scan is obtained of the area to be treated. Several small skin marks are put to assist consistent setup. Treatment planning is an inter-disciplinary task. The radiation oncologist delineates the area to be treated on the x-rays films or CT scan obtained during the simulation; designs the treatment field and special shielding blocks, which are used to shape the radiation beam to the treatment field and help shielding the normal tissue from the radiation beam. Afterwards, dosimetrist or physicists develop computer plans that achieve the objectives stated by a radiation oncologist. A variety of accessories, wedges, compensators etc. are introduced at this point.

In the actual treatment, the patient is placed in the treatment position. The laser lights are used to make sure the patient is level and straight on the table. Several x-ray films or electron portal images (EPID) may be taken prior to the first few fractions of the treatment to ensure that beam shape “as delivered” coincides within tolerance with “as planned”.

1.2.2. Limitations
In external beam radiation therapy, radiation is directed at the tumor and the immediate surrounding area to account for microscopic spread and uncertainties associated with setup and organ motion. This margin assigned to the tumor to account for geometric uncertainty
inevitably includes normal tissue. Because radiation affects both normal and cancerous cells, radiation fields have to be carefully shaped and angled to include the entire target volume and exclude uninvolved critical organs and tissues. Therefore, all the time, we try to balance dose sufficient to eradicate the tumor while keeping radiation-induced normal tissue complications at acceptable level. Modern technology allows us to conform radiation field to a target volume. The term “conformal avoidance” designates treatment delivery designed to most effectively spare organs at risk that may be in the vicinity of the target volume.

1.3. Thesis outline
This work focuses on prostate radiation therapy with new geometric control methods using internal fiducial markers and electronic portal imager (refer to Geometric uncertainty in radiation therapy). Its objective is (a) to determine the minimum but adequate margin to be added to the tumor volume and (b) to derive the gain in dose escalation resultant from better normal tissue sparing.

The basic concept of geometric uncertainty and uncertainty control and the biological modeling used for plan evaluation is discussed in the literature review part of this chapter. In Chapter 2, the first detailed test of margin shrinkage and dose escalation on 3 patients is presented. In Chapter 3, the specific reduced margin and dose escalation schemes derived from the three patients study are applied and tested on 20 patients to establish its validity. Finally, in Chapter 4, the main conclusions of the thesis and possible future work are summarized.

2. Geometric uncertainty in radiation therapy
The goal of radiation therapy is to deliver a high dose to the tumor while minimizing the dose to the surrounding healthy tissue, or, at least, maintaining it within the tolerance limits. This requires a complex series of tasks that include delineation of target volume to be irradiated, calculation of an optimized 3D dose distribution, accurate and reproducible patient positioning during treatment and accurate delivery of radiation.

The delineation of target volume consists of identifying and outlining (contouring) the
diseased areas on a series of transverse computed tomography (CT) images to define a **clinical target volume** (CTV) that comprises both the gross tumor and areas of potential microscopic disease. Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET) may be used in conjunction with CT imaging to define the CTV. The definition of CTV given by ICRU\(^2\) is: “The CTV is a tissue volume that contains a gross tumor volume (GTV) which is the gross palpable or visible/demonstrable extent and location of the malignant growth, and/or subclinical microscopic malignant disease, which has to be eliminated. This volume has to be treated adequately in order to reach the aim of therapy: cure or palliation.” The CTV is not fixed in space, since patient’s repositioning uncertainties and internal organ motion may result in its displacement with respect to the treatment beam. The random variation in the position of the CTV can be accounted for by defining a **planning target volume** (PTV) by adding a 3D safety margin to the CTV. “PTV is a geometrical concept, and it is defined to select appropriate beam sizes and beam arrangements, taking into consideration the net effect of all the possible geometrical variations and inaccuracies in order to ensure that the prescribed dose is actually absorbed in the CTV.”\(^2\)

In radiation therapy of prostate, the focus of present work, the PTV includes the nearby critical organs at risk (OAR), namely the bladder and the rectum. The larger the margin added to the CTV, the larger the volume of critical tissues included in the PTV and, therefore, the higher the dose to the bladder and the rectum. Minimizing the dose to the critical organs, therefore, requires minimizing the margin (or the PTV) which, in turn, requires minimizing the geometrical errors.

### 2.1. Geometric uncertainty and margin assessment

The geometric uncertainty in radiation therapy has two components: (a) **systematic errors** due to patient positioning on the imaging device, organ motion during scanning and target delineation; and (b) **random errors** during treatment delivery due to organ motion and patient positioning.

For prostate radiation therapy, the direction and magnitude of the prostate motion depends on the relative filling of the rectum and bladder. This has been well documented\(^3-7\) by either
repeating CT scans or tracking the movement of internal fiducial markers with ultrasound. Assuming that the geometric uncertainties obey Gaussian distribution, the mean and the standard deviation of the measured uncertainties have been reported as systematic and random errors, respectively. As an example, Table 1-1 shows the reported magnitude of such errors in the superior-inferior (SI), anterior-posterior (AP) and lateral (LAT) directions.

<table>
<thead>
<tr>
<th></th>
<th>Systematic (mm)</th>
<th>Random (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SI</td>
<td>AP</td>
</tr>
<tr>
<td>Geometric uncertainty</td>
<td>3.6</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Table 1-1 The standard deviation of geometric uncertainty used in the simulations. (Full uncertainty)

After quantifying the geometric error, the adequate PTV margin can be found mathematically. Physicists simulate organ motion fraction by fraction (stochastic way) or by considering organ location probability (deterministic way) of the whole treatment; the two different ways of analysis will be introduced in the subsequent paragraphs. The underlying assumption for all the inter-fractional organ motion simulation introduced here are: (a) organ deformation is disregarded; and (b) organs move in a correlated manner. The rigid motion assumption will be addressed in detail in the following paragraph. With this assumption, the variation in dose to organs can be calculated accurately by using the static dose distribution from the treatment planning system.

2.1.1. Organ motion simulation: Rigid motion assumption

**Single Organ Motion:** Organ movement in prostate radiation therapy has been intensively studied from several different aspects by different groups of scientists. Most of the researchers focus on a single organ, the target (prostate), which is considered as a solid organ and therefore subjected to minimal volume change and deformation. As a first approximation, therefore, organ deformation can be neglected. Then the motion of that simplified solid organ can be studied statistically assuming that the distribution of motion obeys the Gaussian distribution. A more sophisticated way of solving the single organ motion without the rigid motion assumption uses the finite-element-analysis (FEA), which
generates possible organ shapes from the biomechanical properties of tissue. The FEA method is well established but very tedious mathematically.

**Multiple Organ Motion:** A more realistic approach is to consider the inter-organ motion of both the target and the critical organs within the PTV. The rigid organ motion assumption is still a good first approximation. However, more advanced ways of simulation have been proposed by two groups. At Memorial Sloan-Kettering Cancer Centre, ten patients were imaged to acquire a set of three repeat CT scans on each (for a total of 30 scans) to provide a data base for organ motion. The organ motion for any other patient was then obtained by sampling this data base and applying it, appropriately scaled, to the organs of the patient under study. This method is based on real patient data, but the drawback of their study is that the data base is too small, and can not represent all possible organ motions. A second method of considering inter-organ motion simulation has been proposed by Fontenla et al, in which the organ shape is represented by a multi-dimension vector. The inter-organ motion was simplified to find the conditional probability of the vector distribution. The details of this method are beyond the scope of present work.

In summary, the rigid organ motion model is not be the best way to describe the nature of organ motion, but still a good approximation and widely accepted by researchers.

2.1.2. Organ motion simulation: Stochastic way

With the knowledge of standard deviations of geometric errors, Monte Carlo simulation can be performed by sampling the error distributions. In such a simulation, one history represents a complete treatment of one virtual patient, having the same anatomy as the planning patient. From the definition of geometric errors, the systematic error is taken to be constant for all fractions. The random error, however, is re-sampled for every fraction. The total movement of organ for every fraction will then be the sum of the two sampling results. The dose contribution from each fraction is summed voxel by voxel for a particular organ. The flow chart for this simulation is shown in Fig. 1-1.
2.1.3. Organ motion simulation: Deterministic way

For a specific patient, the geometric errors influence the radiation dose to organs by blurring the static dose distribution generated by the treatment planning system (random errors), and displacing the static dose distribution with respect to the CTV (systematic errors). The random errors blur the static dose distribution by a linear addition of the dose distribution for each fraction (Eq. 1.1). For every single patient, it is obtained by convolving the static dose distribution with all random variations to estimate the cumulative dose distribution.

\[
D_{\text{blurred}}(\vec{r}) = D_{\text{static}}(\vec{r}) \otimes \text{Error}_{\text{rand}}(\vec{r})
\]  

1.1

Then, the cumulative dose distribution in the CTV is determined by shifting the blurred dose distribution by a given systematic error. Thus,

\[
D_{\text{cum}}(\vec{r}) = D_{\text{blurred}}(\vec{r} - \vec{r}_{\text{sys}})
\]  

1.2

However, in order to get population based information, the probability distribution of systematic errors is used to compute what fraction of the patient population receives a certain dose distribution. This is done by adding all the possible cumulative doses for a single patient together. In other words, the sum of all normalized possible doses equals the dose distribution probability, as if it is the same patient experiencing the same treatment repeatedly. Therefore, this population based result can be obtained by further convolving the blurred dose.
distribution with systematic errors.

\[ D_{\text{population}}(r) = D_{\text{blurred/sin gle}}(r) \otimes \text{Error}_{\text{sys.}}(r) \]

If we put the procedures together, it shows:

\[ D_{\text{population}}(r) = D_{\text{static}}(r) \otimes \text{Error}_{\text{sys.}}(r) \otimes \text{Error}_{\text{rand.}}(r) \]

By knowing the dose distribution to the organ that has been generated to include organ motion, the proper margin to be added onto the CTV can be assessed by using a number of different criteria. This is usually done by generating a dose-population histogram (DPH), which shows what portion in whole population will receive dose higher than a certain value. A typical DPH for PTV in prostate radiation therapy is illustrated in Fig. 1-2.

![Fig. 1-2 Typical DPH for PTV in prostate radiation therapy.](image)

The derived margin from the blurred dose distribution is then evaluated by inspecting the resultant dose-population histogram to assess whether it meets a defined criterion. An example of such a criterion selected by the research group in the Netherlands is: “for 90% of the patient population, the minimum dose to the CTV must be 95% of the nominal dose (i.e., the prescription dose at a specification point) or higher.” As for the dose used in calculation,
either real dose or biologically weighted dose, i.e. Equivalent Uniform Dose (EUD), Tumor Control Probability (TCP), Effective Dose ($D_{eff}$), or Normal Tissue Complication Probability (NTCP), can be used from different aspects of view. The smallest acceptable margin around the CTV that meets the criterion is assumed to minimize the damage to the organ at risk (OAR).

Mathematically, the PTV margin is given by:

$$m_{ptv} = \alpha \Sigma + \gamma \sigma'$$

The systematic error $\Sigma$ and the random errors $\sigma'$ are the standard deviations of their respective Gaussian distributions. Using the values of the parameters $\alpha$ and $\gamma$ derived from deterministic analysis that ensures that 90% of the population got 95% isodose line cover the CTV:

$$m_{ptv} = 2.5\Sigma + 0.7\sigma'$$

By using the values of $\Sigma$ and $\sigma'$ from Table 1-1, the 3D margin can be calculated as:

- 10.75 mm superior-inferiorly
- 12.49 mm anterior-posteriorly
- 9.54 mm laterally

Based on evaluation factors derived from Equivalent Uniform Dose (EUD) and Tumor Control Probability (TCP) rather dose, Van Herk et al. and Liu et al. suggest a small correction to Eq. 1.6, as follows:

$$m_{ptv} = 2.5\Sigma + 0.7\sigma' - 3\text{mm}$$

with the resultant 3D margin calculated as:

- 7.75 mm superior-inferiorly
- 9.49 mm anterior-posteriorly
- 9.54 mm laterally

This margin ensures that 90% of patients receive at least 98% EUD.

In general, different centers, based on their clinical experience and treatment technique, may use different margins for prostate radiation treatment. At British Columbia Cancer Agency, oncologists typically use a 10mm 3D uniform PTV margin in a 4-field Bedford technique ($35^\circ$, $90^\circ$, $270^\circ$, $325^\circ$) and a prescription of 70 Gy in 35 fractions. At Netherlands Cancer
Institute/Antoni van Leeuwenhoek Hospital, a simultaneous boost is applied in which two PTVs are irradiated. The PTV of the primary treatment, PTV1, is obtained by adding a 10mm uniform margin to the CTV. The boost PTV, PTV2, consists of the same CTV with 0mm margin towards the rectum and 5mm margin elsewhere. The dose to PTV1 is 68Gy and to PTV2 is 78Gy. At Memorial Sloan-Kettering Cancer Center, the nominal 10mm margin is reduced to 6mm in the overlap region with the rectal wall. The prescription dose is from 70.2Gy to 75.6Gy with a 6-field arrangement (45°, 90°, 135°, 225°, 270°, 315°). At M. D. Anderson Cancer Center using a six-field beam arrangement, the field apertures are defined by block edge around the CTV that is 1.25-1.5 cm in the anterior and inferior directions and 0.75-1.0 cm in the posterior and superior directions to account for both the geometric error and beam penumbra. The rationale behind such protocols is that use of non-uniform margins ensures delivery of adequate dose to CTV while minimizing the irradiated volume of rectum and thereby reduces rectal toxicity.

2.3. Geometric uncertainty control: fiducial markers

In 1995, Balter et al. first introduced the use of fiducial markers to visualize the location of prostate during treatment. In the last decade, this has evolved into a very useful tool to monitor tumor location information in other organs like lung and liver. The fiducial markers are implanted under ultrasound guidance into the organs. Using fluoroscopy and/or EPID to track the markers (and, therefore, the organ), both the inter-fraction variations in the location of the organs due to set-up errors and organ motion, and the intra-fraction motion introduced by respiration may be determined.

The reliability of using fiducial marker has been studied by several groups. Based on a study of 31 prostate patients Shirato et al. concluded that the use of 3 fiducial markers (one each at the base, posterior midportion and apex) is adequate for precise setup of prostate patients in spite of the transient swelling of prostate after marker insertion. From a study of 10 prostate patients, Dehnad et al. reported that during the course of the treatment the markers appear to move closer to each other, although whether this was a result of marker migration or prostate shrinkage was not clear. The same effect was observed in Kitamura et al.'s study of 14 prostate patients. However Kitamura et al. concluded that there was no increase in the
incidence or degree of migration with time, and the degree of possible migration of the markers was within limits of accuracy of the CT measurement. Further, the intra-prostatic marker migration has not been noted at Princess Margaret Hospital\textsuperscript{27} in their six years experience with fiducial markers. In summary, the use of three fiducial markers is adequate to track and correct for the geometric uncertainties of the prostate location in radiation therapy.

2.4. Geometric uncertainty control: protocols

Reducing or eliminating the uncertainties in the CTV position can reduce the size of the PTV, thus sparing healthy tissues with no reduction in tumor control. We can only control the geometric uncertainty once we localize prostate and compare its location to planning CT. By using fiducial markers and portal imaging (film or EPID), different methods of geometric uncertainty correction have been developed.

2.4.1. Off-line correction Methods

In general, there are two kinds of off-line correction protocols\textsuperscript{28}: the "shrinking-action-level" (SAL) protocol, and the "no-action-level" (NAL) protocol. They both measure setup errors from a number of delivered fractions, and evaluate the results to generate a decision to apply a correction to subsequent fractions if the error exceeds a predefined threshold value. By design, therefore, off-line correction methods aim to minimize the systematic errors; random error control is beyond their scope.

The NAL method\textsuperscript{28} makes use of EPID images acquired during a fixed number of fractions to determine the average setup error for these fractions, which is then used to realign the patient in subsequent fractions. Essentially, it samples setup errors in the first few fractions, each of which can be expressed as:

\[
\Sigma + <\sigma_i>
\]  

1.8

\(\Sigma\) is the systematic error taken to be the same for each fraction by definition, and \(\sigma'\) is the random error which may vary from fraction to fraction. Then the average of the first few fractions is used as an unbiased estimator of the systematic error as follows:

\[
<\Sigma + \sigma_i> = \Sigma + <\sigma_i> = \Sigma
\]  

1.9
The underlying assumption is that the average of the random errors for limited number of fractions is zero. A typical NAL protocol uses 3 fractions to determine the average systematic error, $\Sigma$ in Eq. 1.9. Theoretically speaking, all patients under NAL protocol need realignment. However, in practice, a threshold (e.g., 4mm) is set to maximize efficiency. In British Columbia Cancer Agency-Vancouver Island Center this protocol is used for prostate radiation therapy.

The SAL method\textsuperscript{28} has two predefined parameters: the tolerance level $\alpha$ (mm) and the maximum number of subsequent measurements without a correction, $N_{\text{max}}$. “From measurement $N=1$ onwards, the setup error was averaged over the last $N$ measurements for each measured direction, yielding a mean error $V_N$ of length $d_N$.”\textsuperscript{28} Based on this definition, $V_N$ is the average of setup errors for previous $N$ measurements, which is used as unbiased estimator of systematic errors. This length was comparing with the action level:

$$\alpha_N = \alpha / \sqrt{N}$$

1.10

The action level, the threshold $\alpha_N$, is decreasing with the fraction number $N$ increasing, with the assumption that the better estimation of the systematic error is achieved by using more averaged setup errors ($N$ times). Because the action level is shrinking with the treatment, it is possible for a patient to not experience any repositioning for the whole treatment. However, the clinical experience from same author, for any significantly reduced systematic uncertainty cases, the mean number of fractions for each patient, which need taking image to verify whether the criteria is satisfied or not, is appreciably larger than $N_{\text{max}}$.

Comparison of these two off-line correction methods was made by de Boer et al.\textsuperscript{28} by using Monte Carlo simulation for the SAL protocol and the deterministic calculation for the NAL protocol. The graph of ‘average images need to take’ vs. ‘the effective systematic dispersion after the correction protocol’ was obtained. The result shows that “the NAL protocol achieved a significantly higher accuracy than the SAL protocol for similar workloads in terms of image acquisition and analysis, as well as in setup corrections. The SAL protocol required approximately three times more images than the NAL protocol to obtain the same reduction of systematic errors.” From this, the NAL protocol is seems superior to the SAL protocol, for
its easy understandable and requires lower workload to yield the same accuracy level.

2.4.2. On-line correction
As discussed in the previous section, the off-line correction method is good at quantifying and correcting systematic errors in fractionated radiation therapy. However, since the effect of the random errors is averaged in the method, they cannot be accounted for. One, therefore, has to resort to the so-called on-line correction method to deal with and correct for random errors. Technically, the implantation of (three) fiducial markers into the prostatic tissue and the availability of EPI to acquire portal images to provide instant geometric information of patient positioning on treatment couch, are the prerequisites for on-line correction.

On-line correction uses the patient’s digitally reconstructed radiograph (DRR), generated following CT simulation, as a reference image. For each fraction, using typically 3-5 monitor units, a pre-treatment EPI localization image is obtained, and compared to the reference DRR. The two images are shifted with respect to each other to maximize the overlap between the two sets of fiducial markers and the resulting couch shifts are derived. If the required shift is above the preset threshold, the patient is realigned, and a second EPI is acquired for quality assurance of the realignment procedure. This procedure reduces geometric error but, even with a perfect realignment, may not eliminate it. This is because the organ is a 3D object, and a full realignment requires at least 2 images in usually orthogonal planes. For the prostate, the lateral geometric error is assumed, and has been shown, to be the smallest among the three directions. As a compromise, as at Princess Margaret Hospital\textsuperscript{27}, only lateral EPID images were taken to account for the uncertainties in anterior-posterior and superior-inferior directions. The controlled geometric data is shown in Table 1-2.

<table>
<thead>
<tr>
<th></th>
<th>Systematic (mm)</th>
<th>Random (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SI</td>
<td>AP</td>
</tr>
<tr>
<td>Geometric uncertainty\textsuperscript{27}</td>
<td>0.6</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 1-2 The standard deviation of geometric uncertainty used in the simulations. (Reduced uncertainty)
3. Biological modeling

Radiation treatment planning is designed to achieve specific requirements. These requirements typically include PTV coverage and dose-volume constraints for organs at risk. Conventional forward treatment planning starts with an initial judicious choice of beam energy, field size and field placement, and proceeds by adjusting field weights, field apertures (blocking) and use of beam modifiers such as wedges to calculate an optimum dose distribution that meets the plan requirements. The plan acceptance is based on an evaluation of how well the resultant dose distribution satisfies the requirements. This is generally referred to as the dose-based planning and acceptance.

Dose-based planning and plan acceptance implicitly affects the treatment outcome. When the radiation oncologist prescribes a certain dose, the prescription is based on previously proven cure rate achievable with this dose while leading to manageable radiation-induced toxicity. Thus, the evaluation process attempts to connect the dose distribution to the expected treatment outcome. A typical example of PTV coverage requirement is that it should receive a uniform dose that is at least 95% of prescribed dose. The implicit outcome related assumption in this requirement is that this level of coverage leads to a certain cure rate. This dose based planning and evaluation is based on clinical experience.

As more complex technologies of dose delivery, IMRT, 3D CRT are implemented, radiation therapy practitioners enter *terra incognita* – conformal, non-uniform dose distributions. To take full advantage of new technologies we need to accordingly upgrade tools used in planning and plan acceptance. Obviously, the experience based on old technology can not tell us specifically what the treatment outcome is. In other words, what the biological consequences of the tissue receiving that particular dose distribution are? The questions following that are: what is the survival fraction of tumor cells for this dose? Will the tumor recur? What is the risk and possible severity of radiation-induced complications in the surrounding normal tissue?

It seems that radiation physics alone, which tries to derive everything from a few basic principles, is not adequate to understand and establish a connection between dose and its
biological consequences. This has led to the introduction of biological modeling alongside the 3D dose distributions.

An example of the power of biological modeling is its application in inverse planning process in intensity modulated radiation therapy (IMRT). IMRT can deliver dose in a way that allows extra degrees of freedom compared to conventional forward planning. Simple dose-based planning generally associated with forward planning cannot take full advantage of inverse optimization that offers extra degrees of freedom.

A long-standing assumption of dose-based planning and evaluation has been the requirement of uniform dose distribution over the PTV. Does this necessarily lead to a better treatment outcome? Is there a place for intentional heterogeneity? Several authors have considered the effect of partially boosting tumor dose distributions in an effort to improve tumor control probability (TCP)\textsuperscript{29-32}. Further, considering the tumor regression, spatial distribution of tumorlet, and cold spot in the margin are expected to 'hit' the tumor on fewer fractions than a similar cold spot in the middle of the tumor, leaving small cold spots on the edge of the PTV or even the CTV may be even less detrimental. That makes tumor boosts may be even more beneficial. Having dose heterogeneity pattern delivered to patient, our previous experience of doing plan evaluation, which is based on uniform dose to partial or whole organ will no longer be accurate. In such situations, dose may not be a surrogate for biological response since the goal of radiation therapy is maximize TCP and simultaneously minimize normal tissue complication probability (NTCP). Ideally, optimization algorithms should use objective functions which incorporate biological factors, such as total dose, dose per fraction, overall treatment time, time between fractions, dose rate, volume irradiated, that account for the various parameters associated with radiobiological response in radiation treatment. In a wider context, planning should also account for other factors, such as hypoxic regions and tumor proliferation rate, accompanying diseases, performance status.

Biological models were developed to describe the dose response behavior of different normal tissues and tumors\textsuperscript{33}. Based on their approach, they can be divided classified in to empirical models and mechanistic models. Empirical models use predefined mathematic expressions
based on experiment and/or some basic assumptions, such as the use of Gaussian distribution of large number of random incidents to fit the experimental data regardless of the underlying mechanism. In contrast, mechanistic models try to find basic properties of the biological subunit in the organ from radiation biophysics principle, and then derive the whole organ behavior by considering involved levels of radiation-induced effects from microscopic (cellular) to macroscopic (tissue, organ). However, because of the complicated nature of radiation biophysics, the widely used biological models are mainly empirical models. The limitation and a potential hazard of an empirical model is that although it can give accurate fit in the region where data are available; elsewhere it relies on extrapolations and/or predictions based on the model.

3.1. Radiation induced cell death and Linear-Quadratic model

Radiation-induced cell death is a result of inducing lethal lesions which, in turn, can be tracked to molecular damage produced by particle tracks traversing the cells. In radiation therapy, cell death is reproductive, which is, the damaged cells die while attempting to complete a cell division. Although a damaged cell may survive a few divisions, ultimately it dies in an un-programmed way or gives rise to descendants which also die within a few generations.

The Linear-Quadratic (LQ) model is widely used to model cell survival. The generalized equation for the surviving fraction (SF), following acute delivery of radiation dose D is:

$$SF = \exp(-\alpha D - \beta D^2)$$

\(\alpha\) and \(\beta\) are associated with intra-track and inter-track production of lethal lesions respectively. The exponent represents the mean number of lethal lesions per cell with Poisson distribution for lethal lesions among cells invoked. The lethal lesion yield is connected with molecular damage produced by particles tracks traversing the cells. The molecular damage is has been firmly associated with DNA double-strand breaks (DSB), i.e., breaks to both strands, such that the DNA is transected. The linear portion of the LQ model, the term \(-\alpha D\), may be due to a wide range of different DNA-damaging events. Contribution from the inter-track pathway of lethal lesion production, the quadratic term \(-\beta D^2\), requires interaction between DNA breaks produced by different tracks.
Equation 1.11 defines a survival curve that is convex downwards on a semi-log plot shown in Fig. 1-3. It fits well over the first two decades of survival (surviving fraction from 1.0 to 0.01), at least for most mammalian cell lines. The LQ model provides useful tools to analyze and interpret survival data. It also allows quantification of dose fractionation/protration, radiation quality and, to some extent, cell proliferation.

![Survival Fraction vs. Dose](image)

Fig. 1-3 Cell survival following Linear-Quadratic Model

3.2. Dose fractionation effect

It has been found that fractionating the radiation treatment results in a better therapeutic ratio for most tumors than delivering the treatment as a single dose. The biological explanation is that tumor cells and normal tissue cells have different shape of the survival curve. Fractionation can take advantage of this difference to minimize the damage to normal tissue and maximize the tumor cell kill.

In general, different fractionation schemes will lead to different treatment outcomes. To compare different fractionation schedules, total dose and dose per fraction have to be
converted to a normalized dose. The LQ model provides a basis for this conversion. From Eq. 1.11, the normalized total dose (NTD) is:

\[
NTD_i = \frac{D_i (1 + D_i / (N \frac{\alpha}{\beta}))}{(1 + d_{ref} / \frac{\alpha}{\beta})}
\]

N is the number of fractions, \(\alpha/\beta\) is parameter in the Linear-quadratic model, \(d_{ref}\) is the reference dose used in the standard dose delivery, which is commonly set to 2Gy. \(D_i\) is the dose to the \(i\)th volume bin in the differential dose volume histogram (DVH). For any dose-response calculation in the following biological models, i.e. TCP and NTCP, once they consider the dose-fractionation effect, the dose used should be converted into NTD first.

### 3.3. Tumor response

#### 3.3.1. Tumor Control Probability (TCP)

The tumor control probability (TCP) has a classical sigmoid shape as a function of dose, as shown in Fig. 1-4.

![Dose response of tumor/normal tissue-sigmoid shape](image)

**Fig. 1-4** Dose response of tumor/normal tissue-sigmoid shape

Logit model\(^{35}\) is often applied in this situation. It is used to describe dependencies where
binary (success/failure or complication/no-complication) dependent variables, having been estimated for an observation group, take probability values ranging between 0 and 1. Applying logit transform, shown in Eq. 1.13, the bounded probability value, 0 to 1, turns to unbounded, $-\infty$ to $+\infty$, which allows the use of the general linear regression with the dose as independent variable:

$$P_L = \ln[P/(1-P)]$$  \hspace{1cm} 1.13

The suitable equation has to obey the linearization requirement following logit transform. One possible commonly used expression is:

$$P = \frac{1}{1 + \exp[-4\gamma_{50}(\frac{D}{D_{50}} - 1)]}$$ \hspace{1cm} 1.14

$D_{50}$ is the uniform dose to whole tumor leading to 50% local control. $\gamma_{50}$ is the normalized slope of the dose-response curve at the 50% response level, i.e., $D_{50} \times \partial P(D)/\partial D$. For logistic equation the maximum slope is at 50% response.

Tumor is assumed to have parallel sub-structures which are referred to as tumorlets. The assumption is that for a given patient’s tumor, tumorlets are equally sensitive to radiation and are uniformly distributed. The TCP for single tumorlet with the volume of $v_i$ and dose $D_i$ is:

$$TCP(v_i, D_i) = TCP(D_i)^{v_i}$$ \hspace{1cm} 1.15

In order to sterilize the tumor each tumorlet has to be sterilized. The TCP for whole tumor is, therefore:

$$TCP = \prod TCP(v_i, D_i)$$ \hspace{1cm} 1.16

Combining equations 1.14, 1.15 and 1.16, the expression for TCP may be re-written as:

$$TCP = \prod \left[\frac{1}{1 + \exp[-4\gamma_{50}(\frac{D_i}{D_{50}} - 1)]}\right]^{v_i}$$ \hspace{1cm} 1.17

3.3.2. Equivalent Uniform Dose$^{36}$ (EUD)

Plan evaluation can be also performed based on biologically-weighted dose, rather than prescribed dose related to predicted outcome. The non-uniform dose to tumor can be converted to a uniform dose giving the same biological consequence. The biological
consequence here is referred to as the tumor control which can be specified as clonogen cell survival. Niemierko\(^3\) first proposed the concept of EUD for plan ranking. Later, EUD became the basis for planning optimization to serve as a surrogate for biologically-based optimization. The way in which the EUD concept is implemented connects the surviving fraction after 2 Gy (SF\(_2\)), a common dose per fraction in radiation therapy, to survival at any dose using the linear-quadratic model. Details of the derivation will not be presented here. The final equation used in this report is based on maintaining the same number of fractions. In other words, EUD is the uniform dose delivered in the same number of fractions as the non-uniform dose in a treatment plan, which leads to the same cell kill:

\[
EUD = \frac{N}{d_{ref}} \left[ -\frac{\alpha}{\beta} + \sqrt{\left(\frac{\alpha}{\beta}\right)^2 + 4 \frac{d_{ref}}{N} \left(\frac{\alpha}{\beta} + d_{ref}\right)} \frac{\ln A}{\ln SF_2} \right]
\]

\[
A = \sum_i V_i SF_2
\]

D is the total dose, N is the number of fractions, d is the dose per-fraction (D/N), d\(_{ref}\) is the reference dose (2 Gy per fraction). In this project EUD is used in a similar way to TCP, as a biological index representing the outcome.

3.4. **Normal tissue response**

3.4.1 Power Law

The relation between tissue tolerance and the treated volume became apparent since early days of radiation therapy. The dependence of isoeffective dose on irradiated volume observed in a number of experiments\(^3\) demonstrated that this dependence can be adequately described with a power law relationship between the tolerance dose and the volume irradiated. The expression of the power law was proposed by Jolles:\(^4\)

\[
D_v = \left(\frac{V}{V_0}\right)^{-n} \cdot D_{V_0}
\]

where \(D_{V_0}\) and \(D_v\) are tolerance doses for reference volume \(V_0\) and volume of interest \(V\) respectively; and \(n\) is the exponent which is determined specifically for the tissue of interest. A more comprehensive discussion of \(n\) value will be presented in the next section.
3.4.2. Normal Tissue Complication Probability (NTCP)

Like TCP, the normal tissue complication probability (NTCP) curve is also has the sigmoid shape when plotted as a function of dose (Fig. 1-4). Mathematically, the probit model is the common choice to derive the NTCP. The NTCP can be therefore expressed as:

\[ \text{NTCP}(V, D) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp(-t^2 / 2) \cdot dt \]

\[ t = \left[ D - TD_{50}(V) \right] / \sigma(V) \]

\[ TD_{50}(V) = TD_{50}(1) / (V)^n \]

\[ TD_{50}(V) \] is the tolerance dose 50, the mean value in the Gaussian, which is the dose to partial organ volume V, which will lead to 50% complication rate. \( \sigma(V) \) is the standard deviation of the Gaussian, which is expressed as \( m \times TD_{50}(V) \), where m defines the slope at \( TD_{50}(V) \), see Fig. 1-4. The factor n in equation 1.23 is the dose-volume dependence factor which was introduced in power law (Eq. 1.20) and is discussed below.

Usually the dose to organ is not uniform across the whole volume. The non-uniform dose to organ can be reduced to uniform dose to whole or partial organ by some method. The uniform dose to organ which is called effective dose (\( D_{\text{eff}} \)) has a one-to-one correspondence with the NTCP. This makes the equation for t in Eq. 1.22 look like:

\[ t = [D_{\text{eff}} - TD_{50}(1)] / \sigma(1) \]

The 1 in the bracket means that the parameter values were calculated for the whole organ.

Dose distribution in organs is conventionally expressed as DVH. DVH is complex in shape and its interpretation is not trivial, particularly when a choice between two intersecting cumulative DVH representing competing plans has to be made. The conversion from a non-uniform dose to the uniform dose distribution is designed to reduce the complex DVH into a single step function, which is shown in Fig. 1-5. One popular method of DVH reduction is based on maintaining the maximum dose (\( D_{\text{max}} \)) to organ at a constant, and deriving the partial volume, the so-called effective volume (\( V_{\text{eff}} \)), leading to the same biological consequences:

\[ V_{\text{eff}} = \sum v_i (D_i / D_{\text{max}})^{1/n} \]
The summation is for all the dose bins in the differential DVH. $V_i$ is volume radiated to dose $D_i$, and $D_{\text{max}}$ is the maximum dose in the histogram. The NTCP can be calculated from $V_{\text{eff}}$ and $D_{\text{max}}$ using equations 1.21-1.23.

![Graph showing dose-volume histogram](image)

**Fig. 1-5.** Two deduction procedures of Dose Volume Histogram (DVH)

The alternative DVH reduction algorithm is based on determining the $D_{\text{eff}}$ to the whole organ that gives the same biological consequences. There are methods explicitly designed to calculate $D_{\text{eff}}$, for example, preferred Lyman method. The $D_{\text{eff}}$ can be also readily calculated from Eq. 1.25 by re-applying the power-law (section 4.1):

$$D_{\text{eff}} = D_{\text{max}} V_{\text{eff}}^n$$  \hspace{1cm} 1.26

The effect of dose-volume dependence has evolved into $D_{\text{eff}}$ calculation. For most organs the value of $n$ falls between 0 and $1^{44}$. Occasionally fitting procedures yield $n>1$, the interpretation of such values is somewhat speculative. If $n=1$, $D_{\text{eff}}$ is simply the mean dose. This means that the mean dose to organ is significantly related to the complication. This kind of organ is referred as having parallel behavior (e.g., lung). In contrast, $n$ can be very close to 0, but never equal to zero. This makes the $D_{\text{eff}}$ approach $D_{\text{max}}$, which determines the complication dominantly. This kind of organ is referred to as serial organ (e.g., spinal cord and optic nerve). After knowing the $D_{\text{eff}}$, the NTCP can also be calculated using $(D_{\text{eff}}, V)$.
using Eqs. 1.21-1.23. (V is the whole volume.)

During computing process in our work, NTCP is calculated by using the following equations, which are transformations of Eqs. 1.21-1.22, providing the same results.

\[
NTCP(D, V) = 0.5 + 0.5\text{erf}(r) \\
r = t / \sqrt{2}
\]

Predicting the treatment outcome in the planning process is the ultimate goal of treatment planning. Biological modeling provides this possibility. Due to insufficient clinical data for all the organs, the models are not well established currently, particularly for conformal and IMRT-type dose distributions. However, with accumulation of clinical data supplemented with 3D dose distributions, the models can be developed and validated. Biologically based treatment plan optimization continues to be explored and will undoubtedly become a clinical reality\textsuperscript{45-47}. 
REFERENCE LIST:


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CHAPTER 2

Internal fiducial markers can assist dose escalation in treatment of prostate cancer:
Result of organ motion simulations

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I. INTRODUCTION:
Dose escalation has been suggested as a means to improve local control in radiation therapy. Normal tissue complications are a limiting factor in dose escalation. Modern dose delivery technologies allow us to conform the dose distribution tightly to the target volume. In clinical practice, the Planning Target Volume (PTV) is usually covered by the 95% isodose surface. Conventionally, the PTV is obtained by adding a margin to the clinical target volume (CTV) that accounts for uncertainties associated with organ motion and day-to-day setup variation. In prostate radiation therapy, one commonly used margin is a 10mm symmetric PTV margin. This is considered sufficient to ensure that the prostate receives an adequate dose. A common modification of this uniform margin is the use of a tighter posterior margin to spare the rectum.

The geometric uncertainty associated with radiation therapy can be divided into two parts: systematic uncertainty and random uncertainty. Systematic uncertainty is carried through the whole treatment and relates to the discrepancies between a CT scan, which is a snap shot of the patient anatomy, and true average positions of specific organs in the body. Also, differences in setup between CT and the treatment room (e.g., different laser alignment), rectal and bladder filling at the time of CT scanning, and other factors may contribute to the systematic uncertainty. Random uncertainty relates to random deviations from the mean position due to internal organ motion, set up error, and other factors.

Use of internal fiducial markers implanted in the prostate, in combination with electronic portal imaging (EPI), provide accurate localization of the prostate. The use of EPI allows several options for accounting for geometric uncertainty. One method of off-line correction performs a single correction of the set-up position, based on averaging the measurements during the first N treatment fractions. A correction for this displacement is applied from the (N+1)th treatment fraction onward to minimize systematic uncertainties. The alternative is to use an on-line protocol that requires repositioning prior to every fraction, providing the deviation in prostate location from the reference CT image is significant (i.e., above a pre-set threshold). This technique reduces both the systematic and random geometric uncertainty for every treatment fraction. However, it increases the burden on radiation therapists who have to
perform image matching, shift the couch, and (optionally) confirm that the residual shift is smaller than the threshold. Whether an on-line or off-line protocol is used, geometric uncertainties are reduced, opening the possibility of reducing PTV margins. In turn, less normal tissue would be irradiated, creating the potential for dose escalation without increasing complication rates.

In this paper, an on-line repositioning protocol using lateral EPI only was tested with the following objectives:

1. To evaluate effects of different PTV margins on dose to CTV and organs at risk without realignment (full uncertainty), and with realignment (reduced uncertainty).
2. To investigate limits for dose escalation achievable with reduced PTV margins and reduced uncertainties

II. METHODS:

A. Treatment planning

This study is focused on three-dimensional conformal radiation therapy of clinically localized intermediate risk prostate cancer, which are patients treated by the prostate field only (i.e. the CTV is defined as the prostate; seminal vesicles and pelvic lymph are assumed to be free of clonogenic tumour cells). The rectum and bladder are considered as critical structures. The original dose prescription was 70Gy/35fractions to the isocenter using 18MV beams.

CT scans of three representative prostate cancer patients were selected. These patients had different prostate volumes: 68cc (large), 55cc (medium), and 40cc (small). The prostate was contoured by the treating radiation oncologist at the British Colombia Cancer Agency - Frasier Valley Cancer Centre (BCCA-FVCC). Both bladder and rectum were contoured as solid organs. Rectum was contoured from the anal verge to the level where it turns into the sigmoid colon. Treatment planning was performed on CadPlan (Varian, Palo Alto, California) for a Varian EX 120 MLC linear accelerator. A set of 3-D uniform margins of 12mm, 9mm, 6mm, 4mm, and 2mm were automatically added to the prostate (CTV) to obtain PTVs.
Two beam arrangements were investigated: a four-field box (4FB) with gantry angles 0, 90, 180, 270°, and a four-field arrangement utilising two lateral and two anterior-oblique fields (4FO), gantry angles 35, 90, 270, 325°. These field arrangements were used for each PTV (figure 2-1). For each beam, an MLC shape was automatically calculated by adding an 8mm margin to the PTV with the leaf edge-contour meeting point set at the middle of the leaf. The 8mm MLC margin is used as a preset in clinic. Usually, in order to cover the entire PTV with the 95% isodose line, the MLC leaf positions are manually adjusted. However, to exclude human factors, manual adjustment was not performed in this study. Instead, we retained the calculated MLC shapes to ensure that the comparison reflects differences in...
This analysis produced 30 (3 patients × 5 margins × 2 beam arrangements = 30) treatment plans. All were planned with the original dose prescription of 70Gy/35fr.

B. Geometric uncertainty simulation

After planning, treatment plans in DICOM format were imported into Matlab via CERR (Computational Environment for Radiotherapy Research). A Monte Carlo code running in the Matlab environment was developed to simulate geometric uncertainties during the treatment on a fraction by fraction basis. This code simulates patient positioning uncertainty and organ motion with the following assumptions: (a) organ deformation and rotation are not considered, and (b) the uncertainty in the positions of the prostate, rectum, and bladder can be described by the same probability density function.

As mentioned above, geometric uncertainty can be separated into systematic and random elements, which are assumed to obey a Gaussian distribution. The overall displacement on a single fraction can be modeled as a sum of systematic and random components. The standard deviations associated with both systematic and random uncertainties used in this simulation were taken from published literature (table 1-1, 1-2). For the treatment without patient realignment, i.e., full uncertainty situation, the standard deviations are taken from van Herk et al. The reduced uncertainty data (i.e. after online correction) are taken from Chung et al. 2.

One history in this simulation is a complete treatment of one virtual patient, having the same anatomy as the planning patient. The systematic error was constant for all the fractions within a virtual treatment history. The random error was re-sampled for every fraction. In all, 200 histories were calculated for each treatment plan, with the calculation time of 6-7 hours on Pentium IV 2.66GHz PC. 200 histories were considered to be sufficient for sampling the geometric error distributions.

C. Dose calculation

To simulate treatment with geometric uncertainty, the static dose distribution can be used to
accurately estimate the dose distribution after a geometric shift. To be precise, the dose distribution should be recalculated for the displaced beams. Nevertheless, the static dose can be applied to generate an expected dose distribution. This issue has been discussed by Craig et al.\(^7\)\(^8\). Considering the fact that high energy beams are used, and that body contour effects are minimal for prostate patients, a reasonable estimate of the error, by review of other publications\(^7\)\(^9\), is less than 0.5% in EUD (equivalent uniform dose) to the CTV. This is an acceptable error for the following analysis. Therefore, superpositions of the static dose distribution are used to calculate the dose distribution when uncertainties are present.

Dose from each fraction was accumulated on a voxel by voxel basis for each organ. For each voxel, dose was biologically normalized. This was achieved by converting the dose to each voxel to normalized total dose (NTD), which is the biologically equivalent dose in 2Gy/fr. NTD is additive by nature, therefore for each voxel, the NTD from all fractions can be summed to obtain an NTD value accumulated over the entire treatment. The conversion formula for dose to a specific voxel from the fraction \(i\) is:

\[
\text{NTD}_i = \frac{d_i[\alpha / \beta + d_i]}{\alpha / \beta + 2\text{Gy}}
\]

\(\alpha\) and \(\beta\) are the parameters in Linear-Quadratic model for a considered organ. This ratio represents sensitivity of a particular organ's response to dose per fraction. The values used in our calculation are shown in table 2-1.

<table>
<thead>
<tr>
<th></th>
<th>(D_{50})</th>
<th>(\alpha / \beta)</th>
<th>(\gamma)</th>
<th>(n)</th>
<th>(m)</th>
<th>(SF_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUD &amp; TCP</td>
<td>66.8Gy</td>
<td>1.5Gy</td>
<td>2.3</td>
<td>-</td>
<td>-</td>
<td>0.65</td>
</tr>
<tr>
<td>Bladder (D_{\text{eff}})</td>
<td>80Gy</td>
<td>3Gy</td>
<td>-</td>
<td>0.5</td>
<td>0.11</td>
<td>-</td>
</tr>
<tr>
<td>Rectum (D_{\text{eff}}) (serial)</td>
<td>80Gy</td>
<td>3Gy</td>
<td>-</td>
<td>0.12</td>
<td>0.15</td>
<td>-</td>
</tr>
<tr>
<td>Rectum (D_{\text{eff}}) (parallel)</td>
<td>56.7Gy</td>
<td>3Gy</td>
<td>-</td>
<td>0.746</td>
<td>0.092</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2-1. Parameters used in biological factors calculation\(^{12\text{-}17}\). The factor \(m\) is associated with the \(n\) value in the literature, describing the steepness of normal tissue complication (NTCP) curve at \(D_{50}\).
D. Plan evaluation

Each plan was evaluated using biological indices and parameters based on dose-volume data. For the prostate, TCP (tumour control probability)\(^{10}\) and the EUD (equivalent uniform dose)\(^{11}\) were calculated. Parameters for TCP calculation were derived from the data set for intermediate risk patients presented in Fowler et al.\(^ {12}\) The following parameter values were obtained for 2Gy/fr treatment schedules: \(D_{50}= 66.84\)Gy and \(\gamma_{50} = 2.32\). In the EUD calculation, an \(SF_2\) (survival fraction after 2Gy) of 0.65 combined with \(\alpha/\beta\) of 1.5Gy, 3Gy, 5Gy, and 10Gy were tested. For critical organs the \(D_{eff}\) (effective dose) was calculated by using the Lyman-Kutcher-Burman (LKB)\(^ {13}\) model with a power law DVH reduction scheme\(^ {14}\). We used the parameter values reported in Emami et al.\(^ {15}\) and Burman et al.\(^ {16}\) to calculate \(D_{eff}\) for bladder. For rectum, two sets of parameters were used, which assume different volume dependence for rectal complications. The first one considers the rectum as a more serial organ with the \(n=0.12\)\(^ {15,16}\), the other assumes a more parallel description, \(n=0.746\)\(^ {17}\). The serial description is assumes that rectal complications are related to the hot spot, while the parallel description assumes complications will be determined by the mean dose to rectum. These parameters are presented in table 2-1. The formulas used in the calculation are shown here, in which \(N\) is fractions, \(V_i\) is the volume of one voxel, \(D_i\) is dose to every voxel, and \(d_{ref}\) is the reference dose, which is always 2Gy in our calculation.

TCP is calculated as follows:

\[
TCP(D_i) = \frac{1}{1 + \exp[-4\gamma_{50}(\frac{D_i}{D_{50}} - 1)]} \tag{1}
\]

\[
TCP(v_i, D_i) = TCP(D_i)^{v_i} \tag{2}
\]

\[
TCP = \prod TCP(v_i, D_i) \tag{3}
\]

where \(D_{50}\) is the dose having 50% probability of local control, and \(\gamma_{50}\) is the normalized slop of TCP vs. Dose curve at 50% of TCP\(^ {10}\). EUD is calculated as follows using the equation for dose-per-fraction effect from Niemierko’s result\(^ {12}\):

\[
EUD = N \frac{d_{ref}}{d_{ref}} \left[ -\frac{\alpha}{\beta} + \frac{\left( \frac{\alpha}{\beta} \right)^2}{2} + 4\frac{d_{ref}}{N} \left( \frac{\alpha}{\beta} + d_{ref} \right) \frac{\ln A}{\ln SF_2} \right] \tag{4}
\]
where $SF_2$ is the cell survival fraction after a dose of 2 Gy. $D_{\text{eff}}$ is calculated as:

$$D_{\text{eff}} = D_{\text{max}} V_{\text{eff}}^n$$

and

$$V_{\text{eff}} = \sum_i v_i (D_i / D_{\text{max}})^{1/n}$$

where $n$ is the volume dependence parameter in normal tissue complication model\textsuperscript{15}.

Simulation results are summarized as Dose Population Histograms (DPH)\textsuperscript{12}. Similar to a DVH, each point on the cumulative DPH represents the number of virtual patients who receive at least a certain dose. The DPH were used in this study to set criteria for the acceptance of dose escalation protocols.

The rectum is usually considered to be the limiting organ for dose escalation. Complication rates have been extensively reported in the literature. For 70Gy in 35 fractions, the probability of rectal grade 2 bleeding, scored with modified RTOG-SOMA scale, is 12%-14%\textsuperscript{1,20}. As an approximation, we assume the patient gets complication is because he received higher dose, which corresponding to the high dose region of DPH curve, namely 12%-14%. Then we consider a more conservative acceptance criterion for dose escalation protocols. For each anatomy, we determine the $D_{\text{eff}}$ on the DPH that corresponds to 20% of patients receiving 70Gy in 35 fractions with a 9mm PTV margin as the acceptable risk level. Between the two beam arrangements, because 4FO always results in a lower $D_{\text{eff}}$ than 4FB, the value from 4FO’s upper 20% was chosen as the criteria. This is justified because it applies more stringent constraints than used in current practice. For the dose escalation protocol to be acceptable, the risk should be lower. For this study, we use the criteria that less than 20% of patients should have a rectum $D_{\text{eff}}$ at this risk level.

\textbf{E. Dose escalation}

After simulating all PTV margins with 70Gy/35fr, two optimum PTV margins, 4mm and 6mm, were chosen for testing possible dose escalation schemes with reduced uncertainty. We
simulated dose escalation to 74Gy/37fr and 78Gy/39fr with the above margins.

F. Potential 3D full correction

In Chung et al’s online correction protocol, only one lateral EPID image is used to correct the AP and SI geometric error. This allows for the imaging to be performed in a reasonable time frame, as said, around 8 minutes. Considering that the lateral shift of prostate should be small compared with AP and SI shifts, that procedure appears reasonable. However, we are still interested in the potential benefits of full 3D correction. To evaluate that quantitatively, we simulated a smaller lateral geometric uncertainty. Instead of 1.1mm and 2.2mm in table 1-2 as the systematic and random lateral uncertainty, we assumed 0.5mm and 1.1mm. This simulation is performed for all three patients with 4mm and 6mm margins, with prescription dose of 74Gy.

III. RESULTS:

A. Full uncertainty vs. reduced uncertainty

The effects of uncertainties were consistent for all three patient anatomies. The data for the large prostate patient are shown as a representative example for 4FB (figure 2-2) and 4FO (figure 2-3) beam arrangements and all PTV margins. The difference between the mean values of the various plan metrics between the different uncertainties is generally minor. However, for reduced uncertainty, dose variation in the population is reduced as shown by smaller error bars.
Figure 2-2. Prostate EUD, bladder $D_{eff}$, and rectum $D_{eff}$ as a function of PTV margin size for the static dose distribution, full uncertainty and reduced uncertainty, with a dose prescription of 70Gy/35fr for the 4FB technique. The narrow slim error bar and the wide thick error bar gives 95% confidence level of full uncertainty and reduced uncertainty simulation.
Figure 2-3. Prostate EUD, bladder D_{eff}, and rectum D_{eff} as a function of PTV margin size for the static dose distribution, full uncertainty and reduced uncertainty, with a dose prescription of 70Gy/35fr for the 4FO technique. The narrow slim error bar and the wide thick error bar gives 95% confidence level of full uncertainty and reduced uncertainty simulation.

The geometric uncertainties introduced in the treatment will blur the dose distribution to reduce the dose at the periphery of the prostate. In addition, critical organs may be overdosed by this blurring effect\textsuperscript{18,19}. The PTV margins of 2mm and 4mm are obviously too small for patients treated with full uncertainty, but may be appropriate for patients treated with reduced uncertainty. With patient realignment, the prostate EUD and TCP may be slightly larger than the static treatment plan results, which is due to the blurring of the hot spots in the center of prostate outweighing the effects of dose decrease in the peripheral region.

B. Dose escalation with patient realignment

Results for all 3 patients are shown in figure 2-4, 2-5, 2-6. As a comparison with current clinical practice, data for a 9mm margin without patient realignment, which has a broad DPH,
are included. This matches the large error bars in previous figures (figure 2-2 and figure 2-3). The steepness of other curves is due to reduced geometric uncertainty. The first row demonstrates $D_{\text{eff}}$ of bladder, indicating that dose escalation with margin reduction will reduce the dose to bladder. Two different rectum complication volume parameters, $n=0.12$ and $n=0.746$, have been considered. The results are shown in the second and third row, and the difference in $D_{\text{eff}}$ is apparent.

![Figure 2-4. Dose Population Histograms (DPH) for the large prostate patient. Different beam arrangements are arranged from left to right. From top to bottom is Bladder $D_{\text{eff}}$, Rectum $D_{\text{eff}}$ with $n=0.12$, and Rectum $D_{\text{eff}}$ with $n=0.746$. The legend gives dose prescription and PTV margin. The risk level, vertical bar, is the lowest upper 20% $D_{\text{eff}}$ between two beam arrangements, for different n value in Rectum $D_{\text{eff}}$.](image-url)
Figure 2-5. Dose Population Histograms (DPH) for the medium prostate patient. Different beam arrangements are arranged from left to right. From top to bottom is Bladder $D_{\text{eff}}$, Rectum $D_{\text{eff}}$ with $n=0.12$, and Rectum $D_{\text{eff}}$ with $n=0.746$. The legend gives dose prescription and PTV margin. The risk level, vertical bar, is intra-patient consistent by using lowest upper 20% $D_{\text{eff}}$ between two beam arrangements, for different $n$ value in Rectum $D_{\text{eff}}$. 
Figure 2-6. Dose Population Histograms (DPH) for the small prostate patient. Different beam arrangements are arranged from left to right. From top to bottom is Bladder $D_{\text{eff}}$, Rectum $D_{\text{eff}}$ with $n=0.12$, and Rectum $D_{\text{eff}}$ with $n=0.746$. The legend gives dose prescription and PTV margin. The risk level, vertical bar, is intra-patient consistent by using lowest upper 20% $D_{\text{eff}}$ between two beam arrangements, for different $n$ value in Rectum $D_{\text{eff}}$.

The DPH for rectum shows that if the rectum is more parallel in its dose-volume response, none of the dose escalation protocols and PTV margins exceeds our threshold risk level for the 4FO beam arrangement. In contrast, the 4FB beam arrangement at 78Gy/39fr with 6mm margin may lead to complication rates exceeding those currently observed. Nevertheless, with the serial model, 74Gy/37fr with 4mm or 6mm margin for both beam arrangements and 78Gy/39fr with 4mm margin for 4FO gave acceptable results. Simulations with all three patient anatomies showed consistent results.

TCP for dose escalation was also calculated. The histogram is shown in figure 2-7. As in figure 2-4 to 2-6, a 9mm PTV margin at 70Gy/35fr without realignment is contrasted with 4 and 6mm PTV margins at 74Gy/37fr and 78Gy/39fr with realignment. With dose escalation
to 74Gy/37fr the TCP increased from ~60% to ~70% for intermediate risk patients, and if the
dose is further escalated to 78Gy/39fr the TCP would be ~80%. Patient realignment should
reduce the uncertainty in the clinical outcome, illustrated by the fact that the width of the
distributions with realignment is narrower than the distribution without alignment.

Figure 2-7. TCP histograms showing all dose escalation schemes. Different beam
arrangements are arranged from left to right. Different patient results are arranged from top to
bottom.

C. Potential 3D full correction
The results of the large patient with 6mm margin and 4FO beam arrangement are shown in
figure 2-8. Other patients and other beam arrangement follow the same trend. Compared with
no lateral correction, the results with additional lateral realignment show that mean value of
TCP increases by ~1% for 4mm margin, and ~2% for 6mm margin. D_{eff} to rectum increases
by ~3Gy, for both rectum parameter settings.
Figure 2-8. Comparison between 2D correction and potential 3D full correction results for large patient with 6mm PTV margin, 4FO beam arrangement and 74Gy prescription dose.

IV. DISCUSSION:

A. Patient selection and geometric uncertainty

This work is intended to investigate the potential of shrinking PTV margins and further dose escalation by using Princess Margaret Hospital’s on-line patient realignment protocol. This study analyzed the process for three representative patients with typical prostate volumes.

Several groups have reported prostate geometric uncertainty values during the treatment. The exact values differ from group to group, presumably because of different treatment protocols (e.g. immobilization devices, rectum / bladder filling instructions). As an example, in Antoni van Leeuwenhoek hospital, patients were treated with full bladder. However, in Wisconsin-Madison, a rectal balloon and 200ml bladder filling were applied, which will reduce the prostate geometric uncertainty comparing with previous one. We chose van Herk et al.'s data is because it most closely resembles our clinical treatment protocol.
B. Dose escalation with reduced margins

In radiation therapy of prostate cancer, bladder complications pose a smaller problem than rectal complications. Our calculations demonstrate that dose to bladder for all three patients' anatomies is not an obstacle for the considered dose escalation schemes.

Due to the risk of increased toxicity, dose escalation using 3D-CRT will be difficult without reducing the PTV margins. A large PTV ensures that the prostate is always irradiated to a high dose. However, a substantial volume of the rectum is also always irradiated to a higher dose. The ensuing toxicity would allow a very narrow window for dose escalation.

These simulations indicate that realignment of the patient position prior to treatment can reduce geometric uncertainty. One advantage is that the dose the patient actually receives is more predictable. This is reflected in the steepness of the cumulative DPH. This complicates the calculation of normal tissue complication probability (NTCP) from our simulation results. As addressed by Bentzen\textsuperscript{24}, the uncertainties during the treatment will cause the dose-response curve to become flatter. When fitting model parameters to describe these curves\textsuperscript{12, 15-17} planned doses to organs are used. These are nominal doses without any uncertainty consideration. If the actual delivered doses and treated volumes were exactly as planned and used for curve fitting, the dose-response curves would have been much steeper.

In our approach, we simulated treatment of each patient with reduced uncertainty. Therefore, although we can quantify the change in effective dose for rectum, we cannot directly translate this into change in NTCP. This is because assumed dose-response curves obtained for patients with reduced geometric uncertainties will exhibit steeper dose dependence, i.e., larger $\gamma_{50}$.

For TCP, we still can use existing parameters. TCP and EUD by definition apply to the CTV. In treatment planning, PTV margins are set to ensure the CTV is contained in the high dose region. The combination of reduced margins and reduced uncertainty does not substantially change doses per fraction to voxels comprising the CTV.

C. TCP model
In our TCP's calculation, $\alpha/\beta = 1.5\text{Gy}$, $D_{50} = 66.84\text{Gy}$ and $\gamma_{50} = 2.32$ from Fowler et al.\textsuperscript{12} (2003) were used. The latest dose response data for prostate cancer were provided by Cheung et al.\textsuperscript{25} (2005). For the intermediate risk prostate cancer, by using ASTRO failure definition, the 5 years data gives $D_{50} = 67.5\text{Gy}$ and $\gamma_{50} = 2.2$ ($p<0.001$), which are very close to the parameters used in this work. Different failure definition's data is also presented in Cheung et al.'s work\textsuperscript{30}. By using CN+2 (prostate-specific antigen rise of $\geq 2\text{ng/ml}$ above current nadir) definition, it gives $D_{50} = 57.8\text{Gy}$ and $\gamma_{50} = 1.4$ ($p=0.023$) for 5 years observation. In order to test our result in different situation, we do the calculation using combination of different $\alpha/\beta$, $D_{50}$, and $\gamma_{50}$. The TCP values were shown in Table 2-2 and Table 2-3.

From Table 2-2 and Table 2-3, the variation of TCP assuming different $\alpha/\beta$ is small, $\sim 2\%$. For specified treatment plan, different $D_{50}$ and $\gamma_{50}$ obviously affects the TCP value. However, even the different parameters were applied, the increase of TCP by using dose escalation with tight PTV margin still substantial.

<table>
<thead>
<tr>
<th>$\alpha/\beta$</th>
<th>70Gy, 9mm</th>
<th>74Gy, 4mm</th>
<th>78Gy, 4mm</th>
<th>74Gy, 6mm</th>
<th>78Gy, 6mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 Gy</td>
<td>0.585</td>
<td>0.683</td>
<td>0.786</td>
<td>0.717</td>
<td>0.814</td>
</tr>
<tr>
<td>3 Gy</td>
<td>0.587</td>
<td>0.689</td>
<td>0.790</td>
<td>0.718</td>
<td>0.815</td>
</tr>
<tr>
<td>10 Gy</td>
<td>0.591</td>
<td>0.696</td>
<td>0.797</td>
<td>0.720</td>
<td>0.817</td>
</tr>
</tbody>
</table>

Table 2-2. Mean value of TCP for different treatment plans using different $\alpha/\beta$. ($D_{50} = 66.84\text{Gy}$ and $\gamma_{50} = 2.32$\textsuperscript{12})

<table>
<thead>
<tr>
<th>$\alpha/\beta$</th>
<th>70Gy, 9mm</th>
<th>74Gy, 4mm</th>
<th>78Gy, 4mm</th>
<th>74Gy, 6mm</th>
<th>78Gy, 6mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 Gy</td>
<td>0.752</td>
<td>0.805</td>
<td>0.857</td>
<td>0.821</td>
<td>0.871</td>
</tr>
<tr>
<td>3 Gy</td>
<td>0.754</td>
<td>0.807</td>
<td>0.859</td>
<td>0.822</td>
<td>0.872</td>
</tr>
<tr>
<td>10 Gy</td>
<td>0.756</td>
<td>0.811</td>
<td>0.863</td>
<td>0.823</td>
<td>0.873</td>
</tr>
</tbody>
</table>

Table 2-3. Mean value of TCP for different treatment plans using different $\alpha/\beta$. ($D_{50} = 57.8\text{Gy}$ and $\gamma_{50} = 1.4$\textsuperscript{25})

D. \textit{Rectum model}

From figure 2-4 to 2-7, if 4mm or 6mm PTV margins are used and dose is escalated to 74Gy/37fr, all DPH for escalated protocols will be well below our defined risk level. This
would be expected to result in significant reduction in rectal bleeding. Additionally, 78Gy/39fr with 4mm PTV margin and the serial model (n=0.12) result in a curve close to the risk level we set, but will lead to a reduced or equivalent risk of rectal complication compared with 70Gy/35fr with 9mm margin and full uncertainty.

Different ways of describing the rectal architecture lead to different results. The data from Burman et al.\textsuperscript{15,16} (n=0.12) point towards serial behaviour for rectum, i.e., volume effect is weak. When we realign the patient before treatment, we always put the same area of rectum in the radiation field, resulting in the consistent irradiation of the same area of rectum (if changes in the shape of the rectum are ignored). Rectal complications predicted for these reproducible irradiation conditions may be prohibitive for dose escalation to 78Gy/39fr and margin of 6mm. However, some recent studies\textsuperscript{26-29} have found more pronounced volume effects for rectum. This has been also confirmed by Cheung et al.'s recent data\textsuperscript{17}. Cheung et al. obtained n=0.746, clearly demonstrating strong volume effects typical of parallel organs. If this is the case, reduced PTV margins would mean reduced rectum volume in the radiation field and a more significant decrease in risk of complication compared to the serial model, which is sensitive to hot spots.

The results of our simulations show that irrespective of whether the rectum has more serial structure or more parallel structure; we can escalate the dose to 78Gy/39fr with a 4mm PTV margin with decreased or equal rectal complication probabilities.

\textit{E. Potential 3D full correction}

The increase of TCP with 3D patient realignment is easily understood, because the prostate is well confined to the high dose volume. The increase of the rectum $D_{\text{eff}}$ is less obvious. This results from the fact that the rectum will not often be displaced to a region were it may receive a lower dose. In other words, the hot spot is at the same location. This increase in $D_{\text{eff}}$ may also be related to the assumptions made. In our calculations prostate repositioning automatically implies rectum repositioning. In real life, due to the independent motion of prostate and rectum, the hot spot in rectum will be blurred. Figure 2-8 shows that in $D_{\text{eff}}$ calculation, with the model assumptions, the effect of hot spot is greater than the irradiated
volume when 2D and 3D corrections are compared.

From a biological view, there is little potential benefit to increasing the local control by 2% with the cost of raising the $D_{eff}$ to rectum by 3Gy. On the other hand, considering the extra work-load of lateral geometric uncertainty correction, correction of lateral geometric uncertainty may provide little clinical benefit.

**F. 4FB vs. 4FO**

From figure 2-4 to 2-6, the 4FO technique is systematically better than the 4FB technique, with a lower $D_{eff}$ to rectum. This is because the oblique beam arrangement spares the rectum better than the box-shaped dose distribution. This result is consistent with Bedford et al.'s study\textsuperscript{30}.

Examining the static dose distributions of the two techniques (figure 2-1), the 4FO leads to larger lateral coverage of the 95% isodose line. This happens to be beneficial for the realignment procedure described, which corrects the SI and AP geometric uncertainty but not the lateral uncertainty. The wide lateral 95% isodose line allows large lateral uncertainty without substantial underdosing of the CTV. We can conclude that dose escalation magnifies the difference between these two beam arrangements, and that 4FO is superior to 4FB, since it leads to a lower dose to rectum and fairly good local control. The 4FO may be recommended for patient realignment strategies, which corrects for SI and AP uncertainties only, due to its wide isodose coverage.

**V. CONCLUSION:**

We conclude from our simulation of organ movement in prostate radiation treatment that if on-line patient realignment is applied with 3D-CRT, we can decrease the PTV margin to 4mm and escalate the dose from 70Gy/35fr to 78Gy/39fr with 4FO beam arrangement. This is expected to be associated with less rectal bleeding and a 20% increase of local control.

**VI. ACKNOWLEDGEMENTS:**

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REFERENCE LIST:


CHAPTER 3

PTV margin for dose escalated radiation therapy of prostate cancer with daily on-line realignment using internal fiducial markers: Monte Carlo approach

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A version of this chapter will be submitted to Physics in Medicine and Biology in 2005.
I. INTRODUCTION:

Planning target volume (PTV) margins are conventionally added to the clinical target volume (CTV) to account for uncertainties associated with organ motion and day-to-day setup variation. These margins can be uniform or asymmetric depending on organ motion and risk of toxicity in organs surrounding CTV. For radiation therapy of prostate cancer patients there appears to be a certain degree of variation between cancer centers regarding the PTV definition (bunch of refs). Commonly, the margin is of the order of 1 cm with a smaller posterior margin to achieve better rectal sparing. A more generic approach was suggested by Van Herk, who proposed to link the PTV margin with systematic and random errors. 

Various methods to improve tumour targeting were suggested. Patient realignment is adequate if inter-fraction motion is considerable, but intra-fraction motion is not as significant, e.g., prostate. This is in contrast to gating, when intra-fraction motion is significant, e.g., lung. Realigning the patient allows us to reduce the PTV margin while keeping CTV adequately covered, spare normal tissues and potentially escalate the dose.

In our previous work, we tested PTV margins from 2 to 12 mm using three real patient anatomies and full (no realignment) or reduced (daily on-line realignment) uncertainties. An on-line realignment using fiducial marker implanted in prostate in combination with daily EPI prior to every fraction was simulated. We assumed that lateral images only were taken to localize the prostate. Of all the considered margins 4 and 6 mm margins were deemed acceptable for dose escalation up to 74 or 78Gy while keeping rectal toxicity at the level associated with larger PTV and full uncertainties.

In this paper we extend this study to ensure that these smaller margins will be applicable to a larger group of patients. We also specifically address importance of dose-volume effects in rectum for dose escalation with patient realignment. This topic has become debatable recently as evidence pointing towards more parallel behaviour for rectal toxicity accumulates in contrast to previously assumed serial behaviour. There also appears difference in volume dependence for various grades of rectal toxicity.
II. METHODS:

A. Treatment planning

The emphasis of this study is whether we can safely exploit tighter than conventional PTV margins to escalate dose to prostate in three-dimensional conformal radiation therapy. The CTV was defined as the prostate; seminal vesicles and pelvic lymph nodes were not included. The rectum and bladder are considered organs at risk (OAR). CT scans of 20 prostate cancer patients were randomly selected. Prostate was contoured by the treating radiation oncologist in BCCA-FVC. Both bladder and rectum were contoured as solid organs. Rectum was contoured from anal verge to level where it turns into sigmoid colon. Treatment planning was performed on Eclipse (Varian) for a Varian EX 120 MLC linear accelerator. 3D uniform margins of 10mm, and 5mm were automatically added to prostate (CTV) to obtain PTVs. In this paper, 10mm margin, prescription dose of 70Gy/35fx and without patient realignment was referred as Reference Plan. The treatment plan with 5mm margin, 78Gy/39fx with patient realignment was called Escalated Plan.

The beam arrangement was four-field, utilising two lateral and two anterior-oblique fields (4FO), gantry angles 35, 90, 270, 325°. The MLC leaf positions were manually adjusted to cover the entire PTV with the 95% isodose surface. All the treatment plans were checked for acceptability for clinical use criteria by a senior medical physicist in BCCA.

B. Organ motion simulation and dose calculation

Organ motion simulation was described in detail in our previous work. In brief, a Monte Carlo code running in Matlab environment was developed to simulate geometric uncertainties during the treatment on a fraction by fraction basis. This code simulates organ motion with the following assumptions: (1) organ deformation and rotation are not considered, and (2) relative positions between prostate, rectum, and bladder do not change. The standard deviations associated with both systematic and random uncertainties used in this simulation are shown in Table 1-1 and 1-2. 200 histories were calculated for each treatment plan, with the calculation time of 6-7 hours on Pentium IV 2.66GHz PC. The static dose distribution was used to calculate the dose distribution after a geometric shift. Dose from
each fraction was accumulated on a voxel by voxel basis for each organ\textsuperscript{9,10}. For each voxel, dose was biologically normalized to NTD (normalized total dose)\textsuperscript{11}.

C. Biological factor calculation

Each plan was evaluated for both local control and toxicity in OAR. This was done by calculating biological indices, TCP\textsuperscript{12,13} and NTCP\textsuperscript{5,6}, as well as reducing DVH for OAR. For all the critical organs, D\textsubscript{eff} (isoeffective dose to whole volume) was calculated using power-law based algorithm\textsuperscript{14,15}. This requires use of a parameter, n, describing strength of volume effect. Three possible values reported in literature, which assume different volume dependence for rectal complications, with n=0.12\textsuperscript{6}, n=0.24\textsuperscript{4} and n=0.746\textsuperscript{3} were considered. All the parameters used in calculation were listed in Table 2-1. After all 200 simulations were completed for all 20 patients the data were summarized as dose-population histograms (DPH)\textsuperscript{1}.

D. Plan evaluation

The rectum is considered to be the limiting organ for dose escalation. For 70Gy/35fx, same as our Reference plan, the probability of rectal grade 2 bleeding, scored with modified RTOG-SOMA scale, is 12%-14\%\textsuperscript{7,17}. To be on conservative side, we strengthen the acceptance criteria for dose escalation protocols. For single treatment plan of each anatomy, we designate D\textsubscript{eff} on the DPH which corresponds to 20\% of patients having Reference plan as the acceptable risk level. For the dose escalation protocol to be acceptable, less than 20\% of patients should have a rectum D\textsubscript{eff} at this risk level. In terms of crossover, the location on DPH plot should be equal or less than 20\%.

III. RESULTS:

A. Tumour control

All 4000 (20 treatment plan × 200 histories = 4000) virtual patients’ TCP are shown in Fig. 3-1. The Escalated Plan provides TCP with the mean of 0.817 and standard deviation of 0.011. In comparison, the Reference Plan gives the mean of 0.609 and standard deviation of 0.014.
Fig. 3-1 TCP histograms showing Escalated Plan and Reference Plan for all patient simulations.

B. Rectal complications

The typical DPH curves for single patient's simulation are shown in Fig. 3-2. The vertical axis is the percentage of all 200 histories and the horizontal axis is the $D_{eff}$. Reference Plan (70Gy with 10mm margin and full uncertainty) leads to a broad distribution in $D_{eff}$. In contrast, DPH for the Escalated Plan (78Gy with 5mm margin and reduced uncertainty) is steep. If one DPH was fully 'contained' in another – the preference from clinical perspective would be trivial. However, quite often, the DPH cross over at one point. In the region that $D_{eff}$ larger than at the point of crossing, Escalated Plan always gives lower dose to rectum comparing with Reference Plan, and vice versa. The point at which two DPH cross strongly depends on the value of the parameter $n$, used in $D_{eff}$ calculation. If the point of crossing corresponds to $D_{eff}$ of little clinical consequence, i.e., rectal toxicity, then Escalated protocol would be superior and safer compared to the Reference Plan.
Fig. 3-2 Rectal Dose Population Histograms (DPH) for one of the 20 patients (n=0.746). The Reference Plan curve has broad spread out, and the Escalated Plan is steeper. Beyond the crossing, the Escalated Plan gives lower dose than the Reference Plan, and vice versa.

Fig. 3-3 shows the relationship between location of crossing, represented as vertical axis value of crossing for each patient, and the static $D_{\text{efr}}$ with 70Gy prescription dose for each patient as an index. As was addressed above, $D_{\text{efr}}$ will change with n value. The graph shows the proportion of patients who would benefit if they were treated with the escalated dose, smaller margin and patient realignment, compared to the treatment with full uncertainty. As stated above, if the point of crossing falls on clinically inconsequential $D_{\text{efr}}$ we can assume that no patient will be put under higher risk of rectal toxicity compared to the Reference Plan. From the graph, the dose escalation protocol works well by reducing dose to a large proportion of patients with large $D_{\text{efr}}$, if we assume rectum behaviour is more parallel, i.e., $n=0.746^3$ or $n=0.24^4$. However, if more serial behaviour is assumed, $n=0.12^6$, some of the virtual patients have shown no obvious improvement.
Fig. 3-3 The location of crossing on DPH curve for each patient under different $n$ values. It was shown as percentage in population. $X$ index is the static $D_{\text{eff}}$ of the Reference Plan.

C. Look-up table for static $D_{\text{eff}}$ vs. realistic $D_{\text{eff}}$

Look-up graphs for the relation between the $D_{\text{eff}}$ from the planning DVH and the realistic doses to patient accounting for geometric uncertainty in treatment are shown in Fig. 3-4, 3-5, and 3-6. The three possible parameters describing strength of volume effects were modeled for two prescription doses. The median dose and 95% confidence limit derived from 200 histories are shown for all considered patients. Variation in planned $D_{\text{eff}}$ comes from patient anatomy differences. These graphs provide us with the relation between what we saw in treatment planning system and what is really delivered to a patient. For some patients due to their anatomical features the spread-out distribution in $D_{\text{eff}}$ with full uncertainties the toxicity risk levels are not reached. Presumably the worst case is when systematic error is large and during the actual treatment, larger than planned rectal volume is always present in the field. These graphs also clearly show how potential benefits of applying tighter PTV margins and escalating the dose depend on assumed strength of volume effects.
Fig. 3-4 Static $D_{\text{eff}}$ of the Reference Plan vs. the blurred $D_{\text{eff}}$ of the Reference Plan (Left) and the Escalated Plan (Right). $n=0.12$. The blurred $D_{\text{eff}}$ were shown by median value and the 95% confidence level.
Fig. 3-5 Static $D_{eff}$ of the Reference Plan vs. the blurred $D_{eff}$ of the Reference Plan (Left) and the Escalated Plan (Right). $n=0.24$. The blurred $D_{eff}$ were shown by median value and the 95% confidence level.
IV. DISCUSSION:

A. Patient anatomy

For dose to critical organ among population there are two factors which contribute to the dose variation. One is the geometric errors which will ‘blur’ dose distribution for a single patient, another one is patient’s anatomy. Some patients would receive higher doses to critical organ because of the relative position of critical organ and prostate. This can be offset to some extent by choosing alternate beam arrangement, e.g., six-field vs. four-field. In clinical practice, plan acceptance depends on dose distribution calculated for the planning CT. In this study we calculated look-up plots which allow us to estimate more realistic dose variation when uncertainties are full (no realignment) and reduced (patient realigned prior to every
fraction). These look-up plots can be used to identify patients who may be suitable for dose escalations without excess risk of rectal complications.

B. Rectal complication

In our study, we considered gastro-intestinal (GI) complications only. Genito-urinary (GU) complications were omitted. That is because GU complications are difficult to analyse, bleeding may come from bladder or urethra, which goes through the PTV (prostate). For rectal complication, we use $D_{\text{er}}$ as our evaluation scale. $D_{\text{er}}$ was got by deduct rectal DVH into one number which tells the biological effective dose to rectum. In this procedure an n factor was introduced as saw in Methods part, which describes the rectum volume dependent. Larger the n value, more parallel it is, and vice versa. However, this value makes it’s hard to get any judgemental conclusion, since we have to assign a proper n for rectum and analysis the consequence later.

The value of the parameter describing strength of volume effects, $n=0.12^6$, reported by Burman et al. was obtained from the TD5/5 and TD50/5 data given by Emami et al. $^5$. Because of lacking clinical evidence for partial organ tolerance doses expert opinion was used. In Burman et al. said it formulated as: ‘To determine the volume dependence parameter, $n$, for organs with insufficient data, a best clinical estimate was made by a group of investigators.’ Therefore, $n=0.12$ originates from professional opinion rather than dose-volume based clinical data.

The $n=0.746^3$ reported by the M.D. Anderson hospital group, was based on clinically observed complications and planning DVH. The study group was 128 patients, but they excluded patients with hemorrhoids to obtain the above n factor, a further reduction to 84 patients. The prescription dose was same for all patients: 46Gy with a 4-field box technique followed by a 6-field arrangement to boost the total target dose to 78Gy.

The latest data, $n=0.24^4$ is given by multi-centre study performed in Italy (ref). The patient population is 547, and different prescription doses were used, ranging from 64Gy to 79.2Gy. Presently, this is the most broadly based study both in terms of sample size and
variation in dose-volume distributions.

From the clinical regression data, it appears that the rectum behaviour is not that serial as we long believed, n=0.12. Some hints for this fact are provided by some clinical practice using 3DCRT. Memorial Sloan-Kettering Cancer Center\textsuperscript{16} reported: with prescription dose of 81Gy and a 1.0cm margin PTV, except at the prostate–rectum interface where a 0.6 cm margin was used, the rectal G2 complication rate is about 16.5%, slightly higher than 15%. In M.D. Anderson\textsuperscript{17}, 78Gy prescription dose with a larger margin, ‘the block edge was placed 1.25–1.5 cm around the CTV in the anterior and inferior directions and 0.75–1.0 cm in the posterior and superior directions’, were used. The rectal G2 complication rate was 21%.

According to Italian’s multi-centric analysis data for rectum (n=0.24)\textsuperscript{4}, dose escalation with patient realignment not only improves the local control but gives lower probability of rectal complication, see Fig. 3-1.

V. CONCLUSION:

Prescription dose, for patient treated with prostate fields only, can be escalated from 70Gy/35fx to 78Gy/39fx with shrink the 3D PTV margin from 10mm into 5mm if we use patient repositioning by EPID and internal fiducial markers. Currently available data support more parallel response for rectal bleeding. If this is confirmed, further escalation might be achievable. Obtained look-up plots for static D\textsubscript{eff} vs. realistic D\textsubscript{eff} by considering geometric uncertainty in treatment were generated. They can be used for more informed clinical decision process for plan evaluation and acceptance.

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REFERENCE LIST:


CHAPTER 4

Project summary and future work

Dose escalation has been proposed as a way to improve local control in cancer patients undergoing radiation therapy with a curative intent. The obvious limitation on dose escalation is normal tissue response and the resultant radiation-induced toxicity in organs at risk. New technologies in planning and dose delivery have paved way to improved conformal treatment. However, conformal dose delivery require accurate and verifiable patient positioning. For specific sites, for example lung and prostate, uncertainties associated with setup and organ motion lead to PTV margins of the order of a centimeter. The internal fiducial makers combined with EPID provide the possibility of reducing the systematic and random geometric uncertainty, which potentially allows us reducing the PTV margin added to CTV. The direct consequence of this is that one can attempt dose escalation while maintaining or even reducing the normal tissue complication rates.

In the first step of this project, 3 patients with different prostate volumes were studied. A set of five (2, 4, 6, 9 and 12 mm) PTV margins was assigned to each anatomy. Daily organ motion simulation was performed and, from the biological factor evaluation, the best margins, 4mm and 6mm, which have lower rectum $D_{eff}$ and adequate prostate dose, were derived. Then, a dose escalation to 74Gy/37fr and 78Gy/39fr was tested with these margins. Using rectal $D_{eff}$ DPH to compare the results with the original prescription dose 70Gy/35fr, the possibility of dose escalation protocol was established.

In the second step, 20 anatomies of prostate patients were tested by comparing the current treatment protocol: 70Gy/35fr with 10mm PTV margin and no geometric uncertainty control, with the dose escalation protocol: 78Gy/39fr with 5mm PTV margin and geometric uncertainty control. The margin and prescription dose used in escalation protocol were derived by interpolating results from the 1st step. The final results show that with the help of fiducial marker and EPID, we can reduce the PTV margin for prostate cancer patient to 5mm and increase the dose to 78Gy/39fr. With this prescription dose we expect a 20% increase in
local control comparing with 70Gy/35fr, and a lower rectal complication rate.

Specific methods were developed in the process of implementation of this project. These include organ motion simulation method with rigid body assumption, and biological factor calculation from fractionating dose with voxel registration. We plan to use these in our future work.

The rectal dose-volume behavior affects the normal tissue complication estimation in our work, which still is an issue in radiobiological modeling. Derivation of radiobiological parameters for rectum is a part of our future work. These parameters have to be separately derived for situations when patients are treated with and without realignment. Uncertainties have been shown to affect dose-response behavior. In particular, the slopes of dose-response curves for both complication rates and tumor control may change if uncertainties are reduced. Currently used radiobiological parameters were obtained based on clinical data predating 3D conformal radiation therapy. Use of these parameters in treatment planning will lead to results that misrepresent reality. Currently proposed biologically based inverse optimization for IMRT will also suffer similar setback. Constraints, penalty functions and expected treatment outcomes based on old technology data will lead to suboptimal fluence maps. Therefore, derivation of parameters and their comparison is the key to the success of future study. The proposed study includes:

1. Dose-response for reference group with no realignment.
   Currently there are dose-volume data available for approximately 250 prostate cancer patients treated to 70-74Gy in 35-37 fraction. The collected follow-up data include local failures, GU and GI complications. This real clinical data can be used to establish radiobiological parameters for patient population treated with no realignment and 1cm PTV margin.

2. Bootstrap analysis of the data.
   The clinical data described in item 1 can be used to evaluate uncertainties associated with radiobiological parameters. Using look-up graphs obtained in this study (Fig. 3-4, 3-5,
and 3-6), one may use bootstrap technique to estimate the impact of population-associated uncertainties on radiobiological parameters.

3. Comparative study of imaging modalities.
New image guided radiation therapy (IGRT) modalities will be installed in our center in the near future. The new technology will include the use of fiducial marker with EPID, ultrasound on-line correction system, a Linac with a kV imager. This will provide a better control of dose delivery leading to a more predictable dose to the patient. We will quantify residual uncertainties in prostate positioning depending on the modality used, and their effect on dose-volume distributions.

4. Outcomes data for patients treated with realignment.
IGRT Patients' information will be documented for outcomes study. Comparative study of radiobiological parameters for patient populations described in item 1 and those treated with realignment will be performed. This part of the project depends on how many patients will be treated with realignment. It is very possible that the sample size will be limited and the follow-up will be of the order of three years by the time this project is completed.

5. Impact of radiobiological parameters on IMRT optimization
After deriving the normal tissue complication parameter in previous steps, biological modeling can be incorporated into the IMRT inverse planning process. The cost function and penalty rules used in that process will be upgraded from dose point information to dose-biological response predicting the treatment outcome directly.
REFERENCE LIST:


