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Predicting biological outcome in the radiation treatment of the prostate

Ngcezu, Sonwabile Arthur

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PREDICTING BIOLOGICAL OUTCOME IN THE RADIATION TREATMENT OF THE PROSTATE

Sonwabile Arthur Ngcezu

A research report submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science

Johannesburg, 2006

DECLARATION

I declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

_____

(Signature of candidate)

_____ day of _____ 2006

ABSTRACT

Purpose: A retrospective study was conducted to calculate biological objective functions [Tumor control probability (TCP) for the prostate and normal tissue complication probability (NTCP), in particular for the rectum] for patients treated at Johannesburg hospital during the years 2002 – 2003 for prostate cancer and to correlate these values with observed clinical outcome. Ultimately these results were used to evaluate the effects of dose escalation on tumor control and rectal complications following radiotherapy using conformal external beam radiotherapy.

Methods and materials: To calculate the TCP and the NTCP use was made of BIOPLAN, a PC-based software. This software allows the user to evaluate a treatment plan from the point of view of the biological response of the irradiated tissue, providing at the same time flexibility in the use of models (Poisson Statistics for TCP and Lyman-Kutcher-Burman for NTCP) and parameters. The clinical analysis was based on reports from on treatment review and follow-up visits made by the patients periodically after the treatment. PSA was used as a measure of biochemical failure and correlated with calculated TCP. Also, reported complications were compared to NTCP values calculated by BIOPLAN. The follow-up data were about 2 months to 2.5 years old.

Results: Complications reported after therapy were all less than grade 3 (RTOG) for the patients, which means only mild complications were reported. No patient reported having necrosis, perforation or a fistula for all the prognostic groups. The calculated average NTCP (mild complications) was 36.3 ± 33.3 % and it was 3.9 ± 3.6 % for severe complications. The calculated TCP had an average of 84.3 ± 7.4 % and no biochemical failure was detected on the follow-ups. As the total dose was elevated through 70-Gy, 72-Gy, 76-Gy, and 86-Gy (2 Gy equivalent), the average TCP increased through 76.2 ± 3.8 %, 77.7 ± 2.6 %, 81.5 ± 4 % and 92.5 ± 2.5 %, respectively. The TCP therefore increased about 22 % by increasing prescribed doses from 70 Gy to 86 Gy. The relation between rectal overlap volume and the NTCP was not obvious (scattered).

Conclusions The model predictions gave a reasonable reflection of the reported clinical outcome. A more comprehensive study requires derivation and use of accurate model parameters, and more mature follow-up data.

DEDICATIONS

To my mother, my father, my brothers and sisters, all I do, and what I am is inspired by you.

So this, rightfully belongs to all of you

AMAJWARHA

ACKNOWLEGEMENTS

I would like to thank Prof. Debbie van der Merwe for suggesting this work and for her input. To Dr Kotzen my co-supervisor, I appreciate the help and suggestions you made, especially with the follow-up database. I also want to thank Johannesburg Hospital for letting me use their Planning system and their patient data to do this study. To my friend and colleague, Thulani Nyathi, discussing and talking about this subject has been of great help to me, so thank you 'bro'. A special thanks to Prof. Alan. E. Nahum for letting me use the BIOPLAN software and for the much appreciated help in using the software and in the radiobiology subject. The Wits Ethics committee is also acknowledged for granting ethics clearance for this study.

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1. INTRODUCTION AND AIMS

The aims of the retrospective study were:

- To calculate biological objective functions [Tumor control probability (TCP), for the prostate and normal tissue complication probability (NTCP), in particular for the rectum] that directly determine the clinical outcome of patients treated at Johannesburg hospital during the years 2002 – 2003 for prostate cancer. These factors were calculated using radiobiological models.
- To correlate the calculated TCP and NTCP with observed clinical outcome
- To relate these biological objective functions with the volume of overlap of the target and the rectum.
- To evaluate the effects of dose escalation on tumor control and rectal complications following radiotherapy.

Presently, the evaluation of treatment plans is based on the volumetric distribution of the absorbed dose within the patient. However, it is seldom possible to measure dose distributions directly in patients treated with radiation. Data on dose distributions are almost entirely derived from measurements in water phantoms (which are tissue and muscle equivalent materials), which are usually large enough in volume to provide full scatter conditions for a given beam. These basic data are used in dose calculation systems devised to predict dose distributions in an actual patient. During the treatment planning process the patient is simulated by a 3-dimentional (3D) representation. The dose distribution within the patient is calculated using the electron density distribution provided by the CT slices, to correct for inhomogeneities such as bone and air cavities. Now that the speed of computers has increased dramatically, many treatment planning systems have implemented the 'inverse planning' approach, which uses predetermined criteria as an input and finds the beam configuration that satisfy them the most.

However, to simulate the patient by a tissue equivalent computer program representation is not very accurate clinically since the response of the various organs to radiation

depends on many other factors that are currently not taken into account during treatment planning. Such factors are the volume dependence of organs to radiation, the internal structural organization of the functional sub-units in normal tissue, the density of the clonogenic cells for the targets, the hypoxic cell fraction within the tumor and the fractionation regime. The fractionation regime affects:

- The repair of sublethal damage
- The reassortment of cells within the cell cycle
- The repopulation and
- The reoxygenation of the cells.

In order to take this information into account in the planning of the treatment one needs biological relevant objective functions, which describe the response of tumors and normal tissue to radiation according to their radiobiological characteristics. [1]

As a prevalent malignancy, often presenting with localized disease and therefore lending itself to radiation therapy (RT) during the past 40 years, prostate cancer has presented the opportunity to improve directed therapy by addressing the therapeutic ratio i.e. the benefit in disease outcome over the risk of morbidity. Because this is also a malignancy for which multiple effective treatment methods are available and the option of no therapy is still considered to be a reasonable alternative for at least some patients, it is all the more critical that the hazards of RT, both in terms of tumor recurrence and complications, be seriously considered. Recent technological improvements in treatment planning and delivery systems have given us the tools to improve targeting and thereby increase the total dose.

In practice two main groups of objective functions have been used in radiation oncology, i.e. physical and biological objectives. The most commonly employed objective functions are physical and they often describe the properties of the delivered dose distribution in the target volume and affected normal tissue or organs at risk. Dose volume histograms (DVH) have been in use to quantify these physical objective functions and also to help in treatment optimization. The application of these latter concepts is important for accurate

and precise treatment. It is fundamental that the target volume and the organs at risk are defined with the narrowest possible safety margins in relation to anatomic reference points that are used for setting up the patient for external beam therapy. In principle the target volume should include all the volumes and margins whose dimensions cannot be affected by changing or developing dose planning or treatment techniques (including fixation of the patient).

To this target volume, setup margins may later have to be added depending on the treatment technique and the quality of the treatment unit. It is fundamental that precisely this target volume should be used for dose prescription and reporting, as it is the most relevant one for the treatment outcome. The biological objective function aims at quantifying precisely this quantity, namely the probability that the patient will have the desirable treatment outcome. From this point of view the radiobiological objective function quantifies the patient's quality of life (QOL) after therapy.

To take full advantage of the available technology and to optimize and individualize radiation treatment, one needs tools to assess the patient's clinical outcome of any radiation treatment. That is, one needs tools that quantify the probability of an end point of interest - say, TCP, or NTCP - as a function of the most meaningful characteristics of the irradiated tissue and organs (i.e. their geometry and biology). It is impossible and frankly unfeasible to account for all processes contributing to observed outcomes, however the dominant ones should be identified and modeled. [2]

The main objective of this study was to predict clinical outcome. The study focused mainly on prostate cancer patients, treated at Johannesburg Hospital from 2002 to 2003.

The major challenge in radiation oncology is to maximise normal tissue while delivering sufficient dose to the target volume. The main aim of prostate treatment is to maximize the mean dose to the prostate and its margins and minimize the dose to the rectum and bladder adjacent to and often overlapping the target. This requires the use of dose-volume constraints to the target volume and critical structures. At Johannesburg Hospital for

instance, not more than 25% of the rectum is permitted to receive more than 70-Gy [3]. Violation of this constraint may lead to serious complications (mainly rectal complications).

The analysis was based on the clinical patient data reported from on treatment review and follow-up visits made by patients periodically after the treatment. These data were of use in determining what complication the patients experienced after treatment. Dose volume histograms of the physical dose distribution (from the planning system) were used to calculate the treatment outcome, which was based on the calculation of radiobiological models used to estimate the end-point of radiotherapy treatment (TCP and NTCP).

The effectiveness of dose escalation was also studied. It is a radiobiological fact that higher doses per fraction have a negative effect on the late reacting tissue, but may improve tumor control. Thus, different treatment schedules or dose prescription optimization will/might result in different (preferably better) treatment outcome. The study concentrated on how dose escalation affected the treatment outcome.

Some patients might have received hormone therapy at least for 3 months before radiotherapy or during the course of radiotherapy. This has a direct implication on Prostate specific antigen (PSA) pretreatment levels before and during treatment.

In prostate radiotherapy, the planning target volume (PTV) is not the gross tumor volume (GTV). To effectively deliver the treatment, a margin that takes care of microscopic disease was added to GTV, and the resulting volume is the Clinical target volume (CTV). To the CTV, a margin for the possible anatomical movement of the patient (bladder and rectum relative to prostate) and for differences in setups from different schedules was added, and this defined the PTV. The beams were shaped/blocked to give exact conformation to this PTV. This was to avoid the critical structures (rectum and bladder) thus, allowing the possibility of maximizing the dose to the prostate. The critical organs will always be exposed as there is an overlapping region, which means that part of the rectum and the bladder will be irradiated with high doses as well. Intuitively, the degree

of complications will depend on how much of the rectum is in the overlapping region. Hence, in order to attempt to quantify this complication, the overlap volumes were measured and were related to the TCPs and NTCPs calculated and observed.

To calculate the TCP and the NTCP, use has be made of PC-based software. This software (BIOPLAN) allows the user to evaluate a treatment plan from the point of view of the biological response of the irradiated tissue, providing at the same time flexibility in the use of models and parameters. It requires information on the DVH and can accept a number of different formats (including DVH files from commercial treatment planning systems). BIOPLAN provides tools such as TCP calculations (using the Poisson model), NTCP calculation (using either the Lyman-Kutcher-Burman or the relative seriality models), the ΔTCP method, DVH subtraction, plots of NTCP/TCP as a function of prescription dose, tumor and organs at risk (OAR) dose statistics, Equivalent uniform dose (EUD), individualized dose prescription and parametric sensitivity analysis of the TCP/NTCP models. [1]

2. THEORETICAL BACKGROUND

2.1 Application Of Biological Models To Clinical Data

A methodology for applying biological models to clinical data with the goal of being able to estimate the probability of control or complication in an organ or normal tissue when exposed to non-uniform irradiation is needed.

Several normal tissue complication probability models exist, some of them phenomenological and others of biological nature, that try to describe the response of different types of normal tissue to radiation. With the number of proposed models increasing in time it becomes more important to apply an appropriate methodology to data analysis and model validation. The methodology presented below allowed the retrieval of the model parameter values together with the estimates of their variances and the correlation between them, as well as the calculation of the uncertainty in the model predictions.

The methodology presented here is by no means novel; it simply represents good practice in the analysis of data. A mistaken opinion is that sparse data do not merit so detailed an approach. In fact, when the data are poor, a secure analysis is all the more necessary in order to clarify the degree of confidence one can have in the model's predictions. [4]

The methodology recommended for good practice is as follows:

1. Identify the data together with estimates of confidence limits;
2. Identify one or more models that are to be fit to the data;
3. Perform a fit of the models to the data, for which estimates of the values of the model parameters and their errors (including their correlation) can be derived;
4. Estimate the goodness of fit of the model;

5. Reject models that are inconsistent with the data and either chose a model which best fits the data, or the model that, from a priory considerations, is preferred among the models providing satisfactory fits to the data;
6. From the estimates of the model parameters and their errors, estimate the TCP and NTCP and the confidence limits on the NTCP for any dose distribution of interest. [4]

It should be noted that for this study, a full analysis as presented above was not followed; as it was beyond the scope and aims/objectives.

2.2 Radiobiological Modelling

The radiation oncologist prescribes the treatment in terms of a uniform dose to the target volume accompanied by some sort of constraint on the dose to one or more organs at risk. However, the end points in radiotherapy that are truly of relevance are not dose distributions but the probability of local control, sometimes known as TCP and the NTCP. The aim of treatment is to maximize the TCP while the NTCP remains below some "acceptable" (usually very low) level. Figure 1 illustrates this. [2] [5]

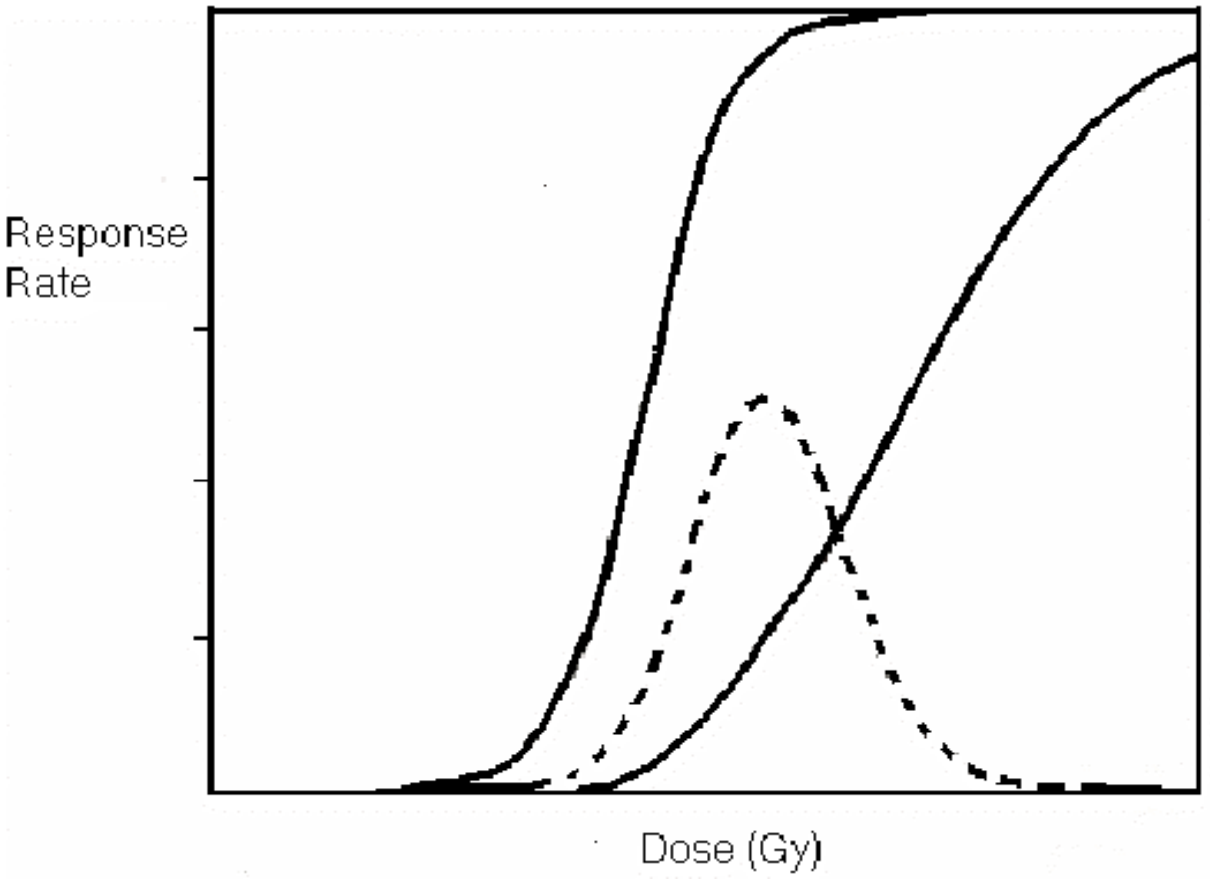


FIGURE 1. Schematic curves illustrating the dose-dependence of TCP (left curve) and NTCP (right curve); the dashed Gaussian-like curve represents the Probability of Complication-Free Control. [2]

2.2.1 Tumor control probability (TCP) modelling

It is well know that the dose-response curve has a sigmoid shape. Mathematical functions have been fitted to this curve. However, it is not easy to see how changes in basic parameters such as tumor cell radiosensitivity, inhomogeneities in the dose distribution, variation in tumor volume, in clonogenic cell density etc. can be accommodated by empirical curve-fitting approaches. It is however, possible to develop a TCP model starting from the response of cells to radiation. [2]

a. Basic Cell-Survival Curves

The killing of cells by radiation can be described (from radiobiological experiments) by an expression of the form:

$$S = \exp(-\alpha D - \beta D^2) \qquad (1)$$

Where S is the surviving fraction after a (uniform) dose D of radiation to a population of cells. The parameters α and β characterize the initial slope and degree of curvature, respectively, of the survival curve. This is known as the linear-quadratic (LQ) model of cell killing. [2]

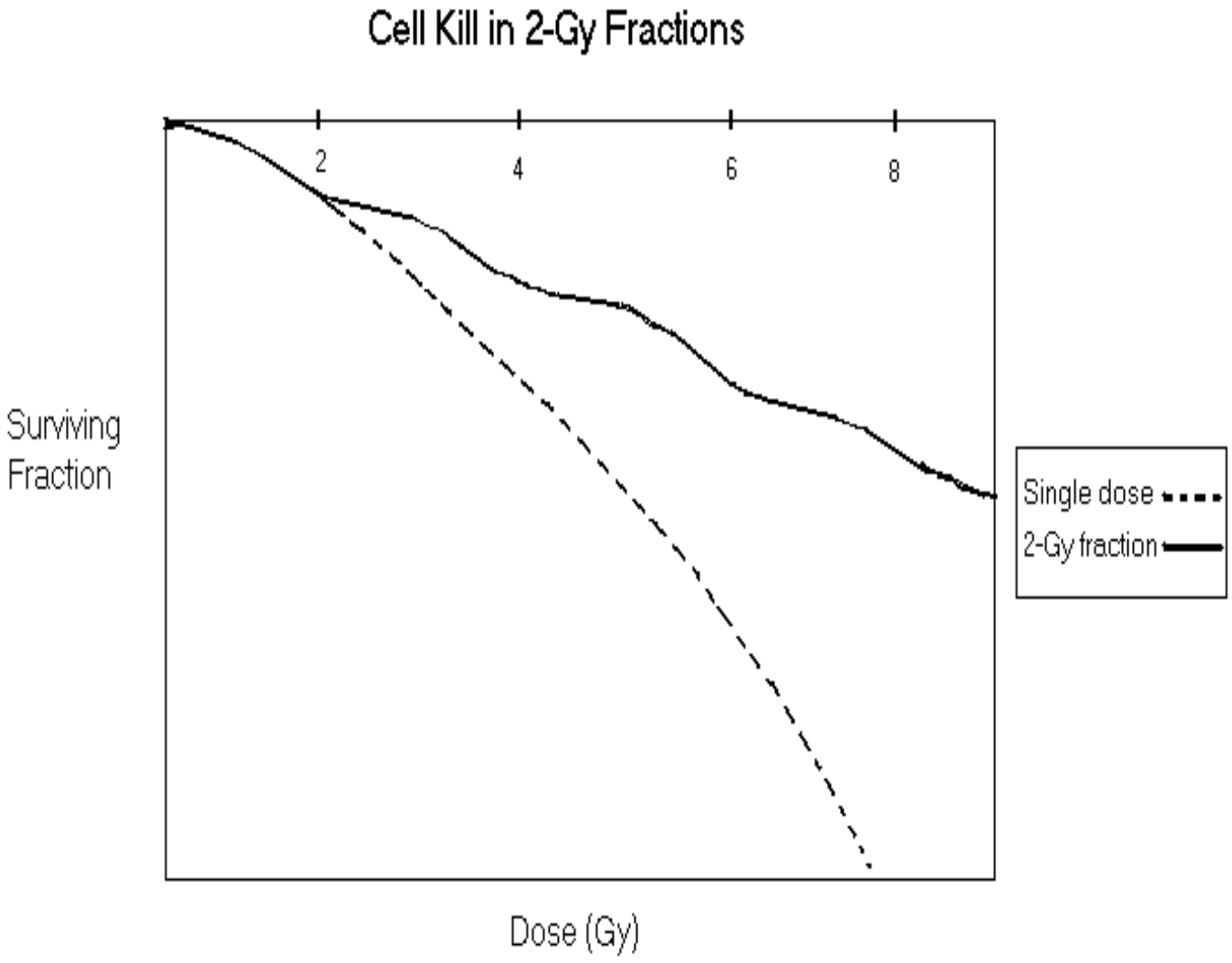


FIGURE 2. Modification of the survival curve to 2 Gy fractions. [2]

When the irradiation is fractionated as is customary in external-beam radiotherapy, for the almost universally adopted 2-Gy (per day) fractionation scheme, the effective slope of the survival curve is very nearly given by the value α alone. Figure 2 illustrates this. Thus one can write:

$$N_s \approx N_o \exp[-\alpha D] \quad (2)$$

N_o is the initial number and N_s the surviving number of clonogenic cells, assumed here to be irradiated uniformly and to have uniform radiosensitivity α (Gy^{-1}): the latter is sometimes donated by α_{eff}. [2]

b. The Poisson Statistics Result

The next step is to incorporate the end point i.e. the eradication of the tumor, into the model. There is considerable radiobiological evidence for the statement that the tumor is only "dead" when every single clonogenic cell (i.e. cells with the potential for uncontrolled division) has been eliminated. Thus the quantity of radiation required is limited to the probability that no single clonogenic cell survives. Equating this with TCP, the Poisson Statistics relation is exploited:

$$TCP = \exp[-N_s] \quad (3)$$

Substituting equation 1 into equation 3 gives

$$TCP = \exp[-N_0 \exp(-\alpha D)] \quad (4)$$

Plotting this expression produces the well-known sigmoid curve. Using a realistic value for the number of initial clonogenic cells of the order of 10^9 and realistic value of α from a to e Gy^{-1} one obtains the family of curves shown in figure 3. [3]

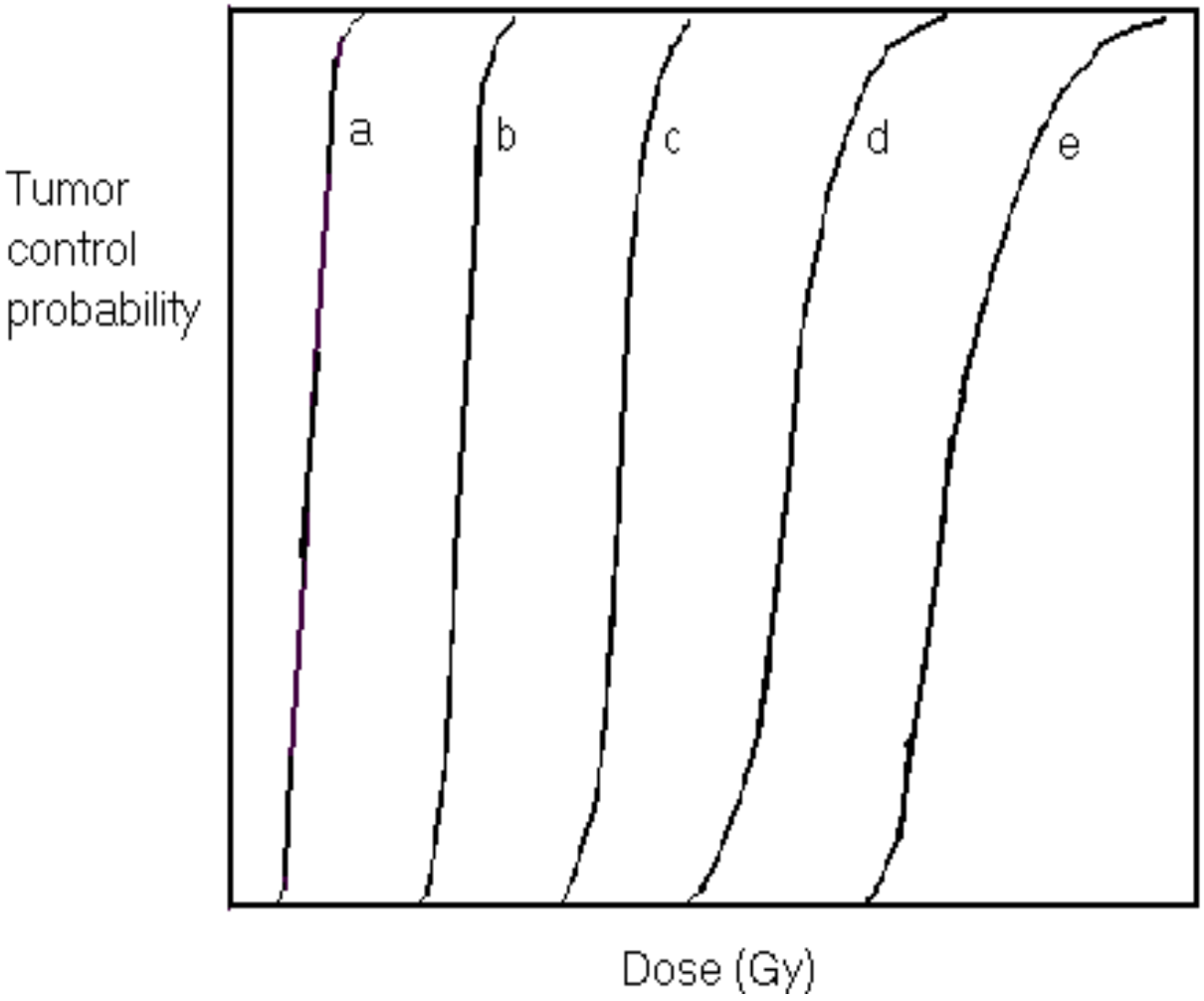


Figure 3. TCP curves from equation 4 for clinically realistic values of $N_o = 10^9$ and α ranging from a to e Gy^{-1}. Note the far from clinically realistic extremely steep slope that results. Note that a > b > c > d > e. [2]

c. Consistency with clinical data

Theoretical models must be compared with clinical data wherever possible. There exist, in the literature, a number of models predicting local control. Despite the limitations associated with such data i.e. uncertainties in dosimetry, inadequate patient numbers, imprecise clinical definition of local control, etc, there are almost no local control curves with slopes as steep as the ones in the figure above. This has led investigators to favor an empirical model to fit these clinical dose-response curves. [2]

Various hypotheses have been advanced over the years to explain the shallowness of the clinically observed local control curves. The explanation that is currently thought to be the most likely is inter-patient heterogeneity in the intrinsic radiosensitivity of the tumor cells i.e the α values. This is in contrast to the possible heterogeneity of radiosensitivity of the clonogenic cells within any one patient's tumor. A very interesting analysis of the clinical dose response has been published by Brenner [2]. Brenner demonstrated that it was possible to explain the wide variations in the dose required to achieve local control for a number of different lesions solely in terms of variation in the number of clonogenic cells, assuming proportionality to the volume of the lesion. The conclusion of his study was that one did not need to invoke any assumptions on the variation in the hypoxic cell fraction with tumor size, for instance. Thus the Brenner analysis lends support to models for TCP based on only two parameters, intrinsic tumor cell radiosensitivity α and clonogenic cell density p_{cl}, that vary with tumor type. However Brenner did not build into his analysis any inter-patient variation in radiosensitivity and as a consequence, the number of clonogenic cells N_o required to fit these clinical data was unrealistically small

The TCP model described here explicitly incorporates inter-patient variation by assuming that α is distributed normally amongst the patient population, with standard deviation σ_α . As one increases the value of σ_α the slope of the dose response curve decreases. [2]

Then the local control can be computed from

$$\overline{TCP}(D) = \sum_l g_i TCP(\alpha, D, N_0) \tag{5}$$

Where TCP (α,D,N_o) is given by equation 4 and a fraction g_i of the patients have α such that

$$g_i \propto \exp\left[-\left(\alpha_i - \overline{\alpha}\right)^2 / 2\sigma_\alpha^2\right] \tag{6}$$

The initial number of cells has been estimated from the product p_{cl} x V_{tgt} with the clonogenic cell density taken to be 10^9.

d. Inhomogeneous dose distribution

The model developed thus far has assumed that all cells receive exactly the same dose. In radiotherapy practice this will never be the case. Thus some way is needed to incorporate dose distributions into the TCP model. The data that is required is the number of clonogenic cells $N_{o,i}$ that receives a dose D_i. This is most conveniently obtained from a DVH generated by a 3D treatment-planning computer. The idea of the DVH is illustrated in the figure below. [2]

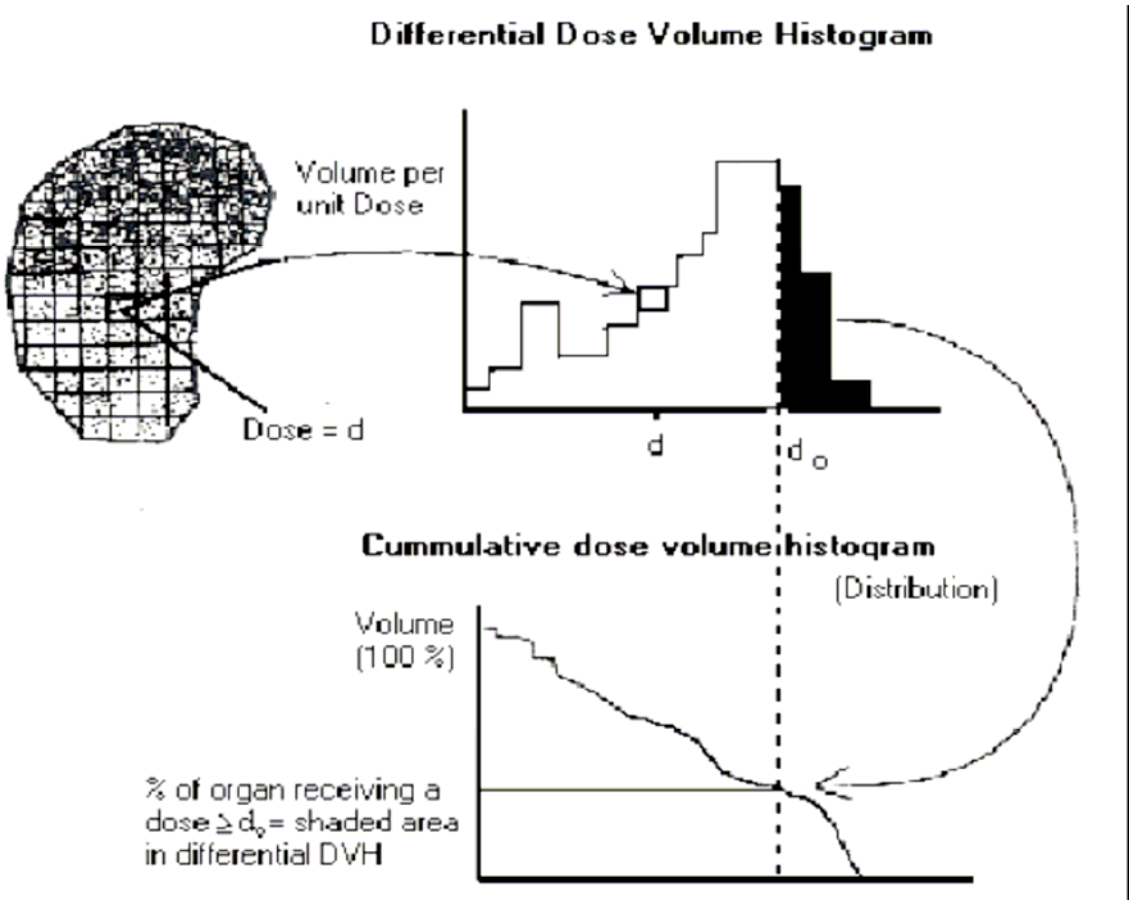


FIGURE 4. Schematic representation indicating how differential and cumulative DVHs are constructed. [2]

Strictly what is required is the differential dose-volume distribution, dV/dD from which the more familiar cumulative DVH is calculated. Thus one generalizes equation 2 to be:

$$N_s = \sum_{i=1}^{n} N_{0,i} \exp\left[-\alpha, D_i\right] \tag{7}$$

where the summation is carried out over the n bins in the DVH. This expression should also be used in equation 5 in order to take the effect of both dose inhomogeneities and inter-patient α variability into account. A more serious limitation is probably the more implicit assumption that the clonogenic cell density p_{cl} is a constant out to the edges of the tumor or target volume. [2]

For application into BIOPLAN, the complete model has been developed to take the form:

$$\boldsymbol{TCP} = \sum_{\boldsymbol{i}} \boldsymbol{g_i}\left(\sigma_{\alpha}\right) \cdot \boldsymbol{TCP}\left(\boldsymbol{\alpha_i}, \boldsymbol{\beta_i}\right) \tag{8}$$

$$\boldsymbol{TCP}\left(\boldsymbol{\alpha_i}, \boldsymbol{\beta_i}\right) = \prod_{\boldsymbol{j}} \boldsymbol{TCP}\left(\boldsymbol{\alpha_i}, \boldsymbol{\beta_i}, \boldsymbol{D_j}, \boldsymbol{v_j}\right) =$$

$$= \prod_{\boldsymbol{j}} \exp\left[-\boldsymbol{\rho_c} \cdot \boldsymbol{v_j} \cdot \exp\left(-\boldsymbol{\alpha_i} \cdot \boldsymbol{D_j} \cdot \left(1 + {\boldsymbol{d_j}}\Big/{\dfrac{\boldsymbol{\alpha_i}}{\boldsymbol{\beta_i}}}\right) + \boldsymbol{\gamma} \cdot \left(\boldsymbol{T} - \boldsymbol{T_k}\right)\right)\right] \tag{9}$$

$$\boldsymbol{g_i}\left(\sigma_{\alpha}\right) \propto \left({1}\Big/{\sigma_{\alpha} \cdot \sqrt{2\pi}}\right) \cdot \exp\left[{-\left(\boldsymbol{\alpha_i} - \overline{\boldsymbol{\alpha}}\right)^2}\Big/{2 \cdot \sigma_{\alpha}^2}\right] \tag{10}$$

Where:

TCP (equ. 8): Corresponds to the TCP averaged over a population with variability in radiosensitivity (simulated as a Gaussian distribution of α_i values with $\overline{\alpha}$ mean and σ_α standard deviation) where a fraction g_i of patients have α_i radiosensitivity and $\sum_i g_i = 1$. [1]

TCP(α_i, β_i) (equ. 9): Represents the TCP of a patient with radiosensitivity α_i and with a non-uniform tumour dose distribution given by $\{D_j, v_j\}$.

j: Refers to the *j*th-volume (v_j) that receives a dose d_j in each of the *n* fractions ($D_j = d_j$ x *n*).

β: Parameter is allowed to vary over the population of patients such that α/β is always constant.

γ: In order to allow cell proliferation during the course of the treatment, a final term working in the opposite direction to cell-killing has been added; where $\gamma = ln2/T_d$.

T_d: The average doubling time. Defined as the time for tumor volume to double, and is determined by cell cycle time (Tc), the growth fraction (GF) and the rate of cell lose.[5]

T: is the overall treatment time, and

T_k: the time at which proliferation begins after the start of the treatment. [1]

It is possible to avoid the β-term and use instead an effective α value (α_{eff})

$$\alpha_{eff} = \alpha\left(1 + d\left(\beta/\alpha\right)\right) \qquad (11)$$

2.2.2. NTCP modeling

With the introduction of 3D treatment planning systems, it has also become possible to calculate and evaluate the dose distribution not only in the tumor but also in the surrounding organs at risk. A reliable estimation of NTCP based on this 3D dose distribution would greatly facilitate the 3D radiation treatment planning process not only in deciding between rival treatment plans but also in weighing the probabilities of tumor control and complication. This estimation of complication probability has been the subject of numerous publications on various theoretical models. Unfortunately, the proper clinical validation of these models is still lacking for most of the normal tissues. [6]

As 3D conformal radiotherapy is being introduced for a number of tumor sites, measurable clinical complication data become available for several organs. This enables comparison of model predictions with the observed incidence of complication. Before comparing the observed incidence of complications and the model predictions with different parameter values, the reliability of underlying DVHs and of the scoring of NTCPs should be considered carefully.

Several models have been developed for estimating the NTCP, based on the total 3D dose distribution. In the conventional phenomological models, a complex inhomogeneous 3D dose distribution, summarized in a DVH, is converted into a uniform dose distribution for the whole organ, which is estimated to yield the same complication probability as the original treatment plan. This reduction of a complex DVH into a single step DVH is based on a power relation between volume and dose with a volume exponent n. Subsequently, the NTCP can be estimated using a dose effect relationship for homogeneously irradiated whole organ volumes, which are derived from clinical data. The sigmoid dose-effect relation for the whole organ is described by TD50 and a steepness parameter, m. [6]

Recently, models with more biological background have been developed. In these models, it is assumed that the normal tissue consists of functional Sub-Units (FSU) that are responsible for the total organ function. These functional sub-units are defined either structurally or functionally. A local dose effect is used to determine the probability of the destruction of an FSU and the NTCP is assumed to be fully determined by the number or fraction of surviving FSUs in the organ. For organs with serially organized FSUs (e.g. spinal cord and oesophagus) it is required that all FSUs survive in order to avoid complications. For organs with parallel-organized FSUs (e.g. Lung, liver and kidney) the NTCP is determined by the fraction of destroyed FSUs. To take into account inter-patient variability, this fraction is described by a normal distribution. [6]

In both models, the reduction of a multistep DVH, to a single step DVH, i.e. the effective dose for the whole organ, D_{hom} or effective uniform dose (EUD), is a crucial first step for NTCP calculation, since it defines the ranking of the DVHs with respect to the NTCPs. If this step is performed correctly, then a one-to-one relation exists between the D_{hom} or EUD and the NTCP. With respect to the DVH reduction method, the Kutcher model and the parallel FSU model can be classified from simple to more complicated (with more parameters). The relative seriality model (s model), the k-model, the critical element model and the critical volume model are some of the models based on cell survival functions. [6]

Two different models have been implemented in *BIOPLAN*: the Lyman-Kutcker-Burman model (empirical) and the relative seriality model (mechanistic).

a. The Lyman-Kutcher-Burman model

$$\boldsymbol{NTCP} = 1/\sqrt{2\pi}\int_{-\infty}^{t}\exp\left(-x^2/2\right)\quad \boldsymbol{dx} \tag{12}$$

$$t = \frac{D - TD_{50}(v)}{m \cdot TD_{50}(v)} \tag{13}$$

$$TD_{50}(v) = TD_{50}(1) \cdot v^{-n} \tag{14}$$

Where:

$TD_{50}(1)$; is the dose which uniformly delivered over the whole organ will produce a 50% chance of complications.

v; is the fraction of the organ irradiated uniformly.

m; is the steepness parameter.

D; uniform dose to the tumor

n; is the number of voxels

$TD_{50}(1)$, *m* and *n* have been tabulated for different organs and specified end-points, based on the clinical tolerance data. [7] *BIOPLAN* contains a library with some of them, otherwise they can be entered by the user.

In order to incorporate into Lyman's model the more likely situation of a non-uniform irradiation of the critical organ, Kutcher and Burman gave a reduction scheme to reduce the DVH to an effective fractional volume uniformly irradiated to the maximum dose. This reduction model has also been incorporated into *BIOPLAN* to deal with non-uniform dose distributions. [6]

b. The relative seriality model

This model to describe the probability of damage of normal tissue is based on binomial statistics. It accounts for serial and parallel architecture of the FSU. The expression is as follows:

$$NTCP = \left[1 - \prod_{j=1}^{k} \left(1 - NTCP(D_j)^s \right)^{v_j} \right]^{1/s} \qquad (15)$$

This describes the response of the whole organ to an arbitrary dose distribution $\{D_j, v_j\}$ as a function of the response of the whole organ to a homogeneous dose distribution. The number of FSU has been made to coincide with the k bins in the DVH. NTCP(D_j) can be expressed as

$$NTCP(D_j) = 2^{-e^{e \cdot \gamma \cdot \left(1 - \frac{D_j}{D_{50}} \right)}} \qquad (16)$$

It is based on Poisson statistics to describe cell survival.

Where:

s is the relative seriality factor.

v_j defines the jth subvolume.

γ Is the maximum relative slope of the dose-response curve and

D_{50} is the whole organ uniform dose that would produce a 50% complication probability.

BIOPLAN has a library of s, γ and D_{50} values for some critical organs and clinical end points but any other values can be chosen. [6]

c. LQ correction to the physical DVH

Dose heterogeneity in an organ at risk should produce different biological effects with varying fraction sizes as well as total dose. None of the NTCP models given above deal with this fractionation-effect problem, as the parameters in them effectively correspond to a 2 Gy fraction. Thus, the "physical" DVH should ideally be converted to a 2Gy-equivalent DVH before using the models.

Physical doses D delivered with a dose per fraction d can be converted to the 2-Gy equivalent dose D_2 by using the following expression:

$$\boldsymbol{D}_2 = \boldsymbol{D} \cdot \frac{\left(\boldsymbol{\alpha}/\boldsymbol{\beta} + \boldsymbol{d}\right)}{\left(\boldsymbol{\alpha}/\boldsymbol{\beta} + 2\right)} \qquad (17)$$

Equation 17 can be applied to each D_j dose-bin of a DVH. *BIOPLAN* has incorporated the option to apply the equation above to correct the physical DVH for fractionation effects (α/β values are freely selectable by the user). The resulting 2 Gy per fraction equivalent DVH is then used as the input DVH in the NTCP models described above. [6]

2.3. Guidelines For Prostate-Specific Antigen (PSA) Following Radiation Therapy: Biochemical failure

PSA, a serine protease normally produced in the prostate, has become a powerful tool in the care of men with adenocarcinoma of the prostate. Since it is usually elevated when the prostatic epithelium undergoes malignant transformation, it has become useful in the early detection of the disease and in monitoring outcome after treatment. There are many controversies surrounding its use in both areas.

After radiation therapy, the PSA declines slowly and may never reach undetectable levels. Authors have reported using PSA as an end point: "Biochemical" failure has been used widely in the absence of clinical or histopathologic evidence of local persistence or recurrence or demonstrable distant metastasis. Several different definitions of biochemical failure have been used in the literature, which has led to difficulties in deciding if or when a biochemical failure has occurred in an individual patient, and has also made it difficult for physicians and increasingly well-informed patients to interpret reported experiences. [8]

The Board of directors of the American Society for Therapeutic Radiology Oncology (ASTRO) charged a committee to bring resolution to the interpretation of PSA after radiation therapy. A group of investigators who had contributed to the literature on irradiation for prostatic carcinoma met to discuss the role of PSA after irradiation.

Four guidelines were established: [8]

- Biochemical failure is not justification per se to initiate additional treatment. It is not equivalent to clinical failure. It is, however, an appropriate early end point for clinical trials.
- Three consecutive increases in PSA is a reasonable definition of biochemical failure after radiation therapy. For clinical trials, the date of failure should be the

midpoint between the post irradiation nadir PSA and the first of the three consecutive rises (with the PSA taken in 3 or six months intervals) .

- No definition of PSA failure has, as yet, been shown to be a surrogate for clinical progression or survival.
- Nadir PSA is a strong prognostic factor, but no absolute level is a valid cutoff point for separating successful and unsuccessful treatments. Nadir PSA is similar in prognostic value to pretreatment prognostic variables.

Despite these advantages, there are some concerns about the use of PSA testing as the sole determinant of treatment failure. Little is known about the natural history of the irradiated prostate and whether residual or reconstituted normal prostate tissue can manufacture PSA. If it can, then a rising post-treatment PSA may not always signal ongoing disease, and a growing number of men may be unnecessarily subject to antiandrogen therapy. Another issue is whether pretreatment factors such as prostate volume, pretreatment PSA, and Gleason score can influence the level at which PSA stabilizes after treatment. [8]

A clearly defined, biologically based PSA end point could solve some of these problems. Several different end points of PSA response are in use today:

- Nadir PSA (nPSA) levels are widely used as a predictor of treatment success or failure. However, different investigators have chosen different nPSA values as significant end points, ranging from 0.5 to 4.0 ng/ml. These end points generally arise from statistical analyses in which either the survival or freedom from relapse of patients above a certain arbitrarily chosen nPSA level was compared with those below.
- A variant of this was time to nPSA level. At this time however, some investigators suggest that a long time to nPSA level is a favorable sign, while others suggest that a short time to nPSA level is favorable.

- Rising PSA after a period of stabilization is a third marker of treatment success or failure. A perfectly stable PSA after radiation therapy is widely regarded as a favorable sign, indicating either the complete eradication of the prostate cancer or, at the very least, no active tumor growth. A rising PSA is universally regarded as an ominous sign, indicating either local recurrence or distant disease.

Finally, the treatment of prostate cancer is undergoing pronounced changes as a result of new data from clinical trials, correlative studies from the laboratory, and a rapidly evolving understanding of PSA. The consensus statement of September 1996 can only be considered a benchmark from which to seek greater understanding from existing data sets and new investigations. [8]

2.4. Uncertainties in Biological modeling

The reliability of the DVHs of normal tissues, as determined from CT-based planning, is dependent on a number of dose and volume effect related factors. Slice thickness and separation may lead to the partial volume effect and errors in size and position of normal structures. Physiological motion during CT scanning, inter and intra fraction, change of organ shape and position and patient setup deviations during a course of fractionated radiotherapy will have an impact on the reliability of the DVH, based on the planning CT. [6]

2.4.1 The predicted effect of dose non-uniformity

TCP models, which differed only slightly from the one described here, have been applied to the question of the effect on TCP of both inhomogeneities in the target dose distribution and also uncertainities in the absolute absorbed dose determination.
For a group of patients with tumors of exactly the same radiosensitivity i.e. $\sigma_\alpha = 0.0$ even small inhomogeneities in dose have a disastrous effect on the TCP; which implies very steep dose-response curves. The message is that the appreciable inter-patient variability in radiosensitivity indicated clinically for many types of tumors considerably reduces the consequences of even moderate deviations from target dose uniformity. The corollary of this is the conclusion that for certain classes of tumors with steep dose-response slopes, notably in the larynx, only very small uncertainties in the absolute dose determination can be tolerated. [9]

2.4.2 Variation in clonogenic cell density

If the model explained thus far is applied to the DVH of the target volume (the PTV in ICRU 50) then implicitly the assumption is made that the clonogenic cell density is constant over the whole of the PTV i.e. one calculates the number of clonogenic cells at dose D_i, $N_{o,i}$ in Equ. 7 from the product of $V_{o,i}$ and p_{cl}. However, the PTV actually

involves a margin for microscopic spread plus a second margin for geometrically inaccuracies. Thus clearly the assumption of constant p_{cl} is quite unrealistic, the figure 5 below illustrates this point.

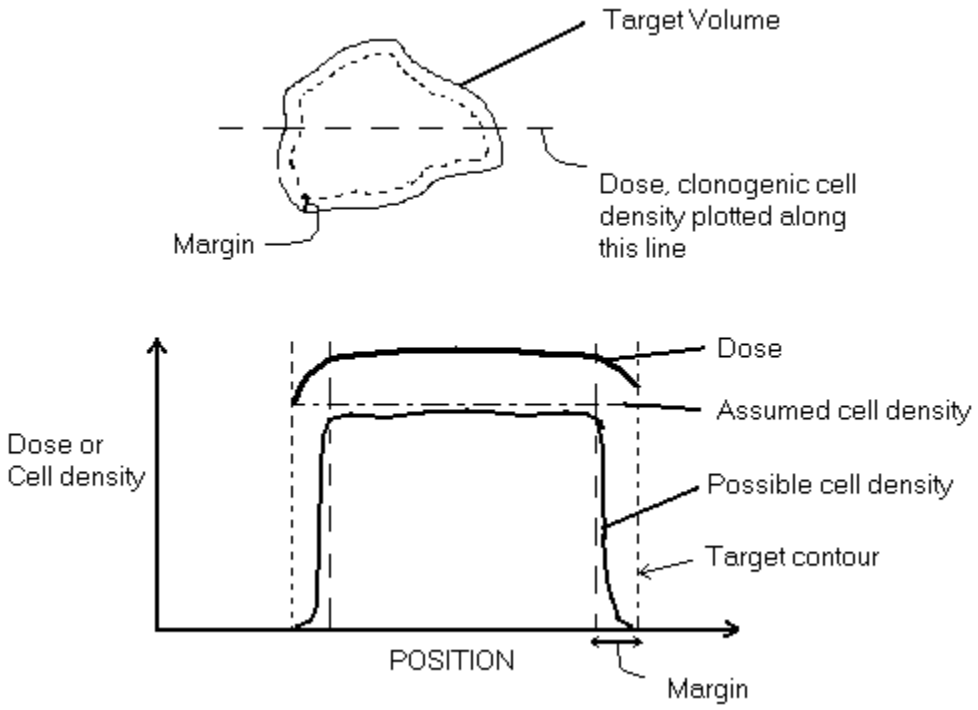


FIGURE 5. Schematic drawing illustrating the problem of the variation of the clonogenic cell density at the edge of the PTV. A hypothetical dose and cell density profile through the center of the PTV is shown.

Whilst there is presently no clinical data on exactly how the cell density does vary throughout a radiotherapy target volume, one can use the model to assess the effect that such variations might have on the predicted TCP. One way of looking at this is to calculate the change in dose D that corresponds to a change in cell density p_{cl} when one requires that the TCP remains unchanged for a given volume element of cells. Taking the clonogenic cell density at the tumor center say, to be $\rho(0)$ and the corresponding quantity at some position r to be $\rho(r)$, then it is straightforward to show that the change in dose at r to yield the same TCP for the same size of volume element is given by

$$-\Delta D = \frac{1}{\alpha}\log_e\left[\frac{p(0)}{p(r)}\right] \qquad (18)$$

where the product α ΔD is proportional to the logarithm of the ratio of cell densities.

Uncertainties in local radiation dose due to setup deviations and organ motion were studied by Kytcher and Mageras for the rectum in 3D conformal prostate treatment [9]. Based on the statistics of a group of 12 patients, the effect of setup deviations and organ motion on the DVH of the rectum for a single patient was described by confidence limit dose volume histograms. [9]

2.4.3 Uncertainties in volume and DVH of rectum and bladder during conformal radiotherapy of prostate cancer

The effects of pattern of changes of rectum and bladder DVHs were studied by Warkentin B. and colleagues [10]; using Tree matched repeat CT scans. DVHs were calculated for all the organs using a three-field technique with an isocentric dose of 80-Gy. To evaluate the DVHs, the high dose volumes and the NTCPs were evaluated.

The variations of total rectum and bladder wall volumes during treatment were 9% and 17% (1 standard deviation), respectively, with no time trend. The variation of total bladder wall was positively correlated with bladder filling variation, indicating a possible overestimation of bladder wall thickness, when the bladder was relatively full. The variation of the high dose (>80%) rectum wall volume was 14% (1 SD) and independent of rectum filling. As a result the variation of the NTCP during treatment was small (on average 3.3 %). [10]

In conclusion, rectum wall DVHs can be determined reliably from CT based planning. However, the drawing of the inner rectum wall is labor intensive and methods need to be developed to generate a DVH of the rectum wall based on information of the outer

contour only, like the approximation of the DVH of the wall by a Dose Surface Histogram. The relative DVH of the bladder wall could not be determined reliably at all. The main reason for this failure was the inability to contour the inner bladder wall consistently. [6]

The success or failure of radiation therapy can depend upon the accuracy with which the dose prescription is fulfilled. For many diseases the required accuracy is not known. In others, the outcome of treatment depends upon tumor doses that do not vary by more than ±5% about the optimum. The establishment of tumor-cure probabilities, optimized time-dose schedules, and radiobiological efficiencies requires that the systematic uncertainties in dosimetry be made considerably smaller than the uncertainties in measuring tumor volume and response. This necessitates that improved accuracy be sought in the dosimetry of high-energy photon and electron beams. [11]

3. EXPERIMENTAL PROCUDURES

3.1 Patient Characteristics

This study was done from records of 41 patients who were treated with 3D conformal radiotherapy for carcinoma of the prostate at Johannesburg Hospital from 2002 to 2003, 37 of whom had post-treatment outcome data. Data collection for these patients was terminated around June 2005.

For patients treated in 2002, 13 were treated as intermediate risk patients with radical intent to 68 Gy (2 Gy per fraction) plus a boost of 8 Gy (2 Gy per fraction) and 5 were treated as high-risk patients to 70 Gy in 2 Gy fractions. Of the patients treated in 2003, 17 were treated as intermediate patients with radical intent to 66 Gy in 2 Gy fractions plus a boost dose of 12 Gy (4 Gy per fraction), and the remaining 8 patients were treated with radical intent to 72 Gy in 2 Gy fractions.

The age range during treatment was 54 – 79 years of age (mean age of 68.3 years) staged at T1 to T4, with a mean stage of II.

3.2 Treatment Simulation, Planning, and Delivery

The patients were treated supine in a personal polyurethane cast extending from the midchest to below the feet. The knees were slightly flexed to relax the lower back and keep the heels together when the cast was made. The patient had three tattoos made in midline (one for midline positioning) and one on either side for anti rotational alignment (one tattoo 10 cm superior and at level of the right lateral tattoo and the other tattoo 10 cm inferior and at level of the left lateral tattoo for anterior-posterior or superior-inferior rotation.) [12]

The patient was CT scanned from the lumbar spine 5 (L5) to the pelvic brim (using 1 cm thickness slices) and then with 0.5 cm thickness slices through the true pelvis, seminal vesicles and the prostate gland to below the ischial tuberosities.

A six-field technique was used with the fields arranged 45 degrees apart. The gantry angles were 45, 90, 135, 315, 270 and 225 degrees. Using the beams eye view (BEV) and the margin options, the aperture blocks were drawn to coincide with the margin of 1.5 cm superiorly, laterally, anteriorly and inferiorly and 0.75 cm (0.8 mm) posteriorly to reduce the volume of the rectum in the treatment fields. Sometimes it was found necessary to use wedges in the lateral fields to prevent a hot spot anteriorly. Figure 6 shows a typical dose distribution obtained from this technique.

The boost was a three-field technique with gantry 0^0, 90^0, and 270^0. Figure 7 shows this field arrangement. This boost treatment was designed to escalate the dose to the GTV and spare the rectum. During the boost treatment, the treated fields were verified daily and positioned away from the rectum, so as to minimize its irradiation.

For the main treatment course the dose prescription was to the mean (average) isodose level of the defined margins (Planning Treatment Volume) according to the ICRU Report 50. For the boost, dose was prescribed to 100 % at the isocenter.

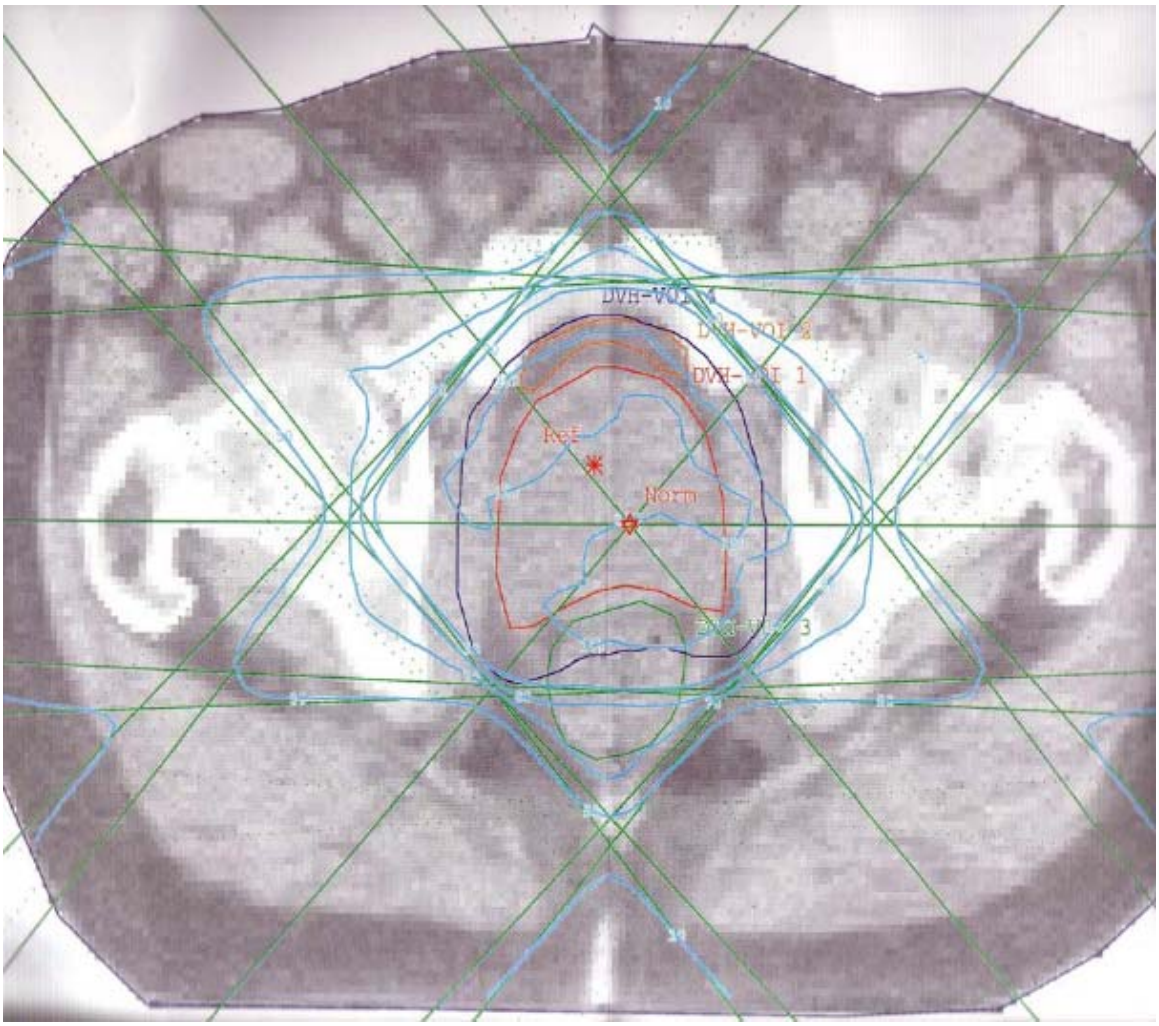


FIGURE 6. A CT slice, showing six conformal fields used as a standard technique in the treatment of radical prostate cancer in Johannesburg Hospital.

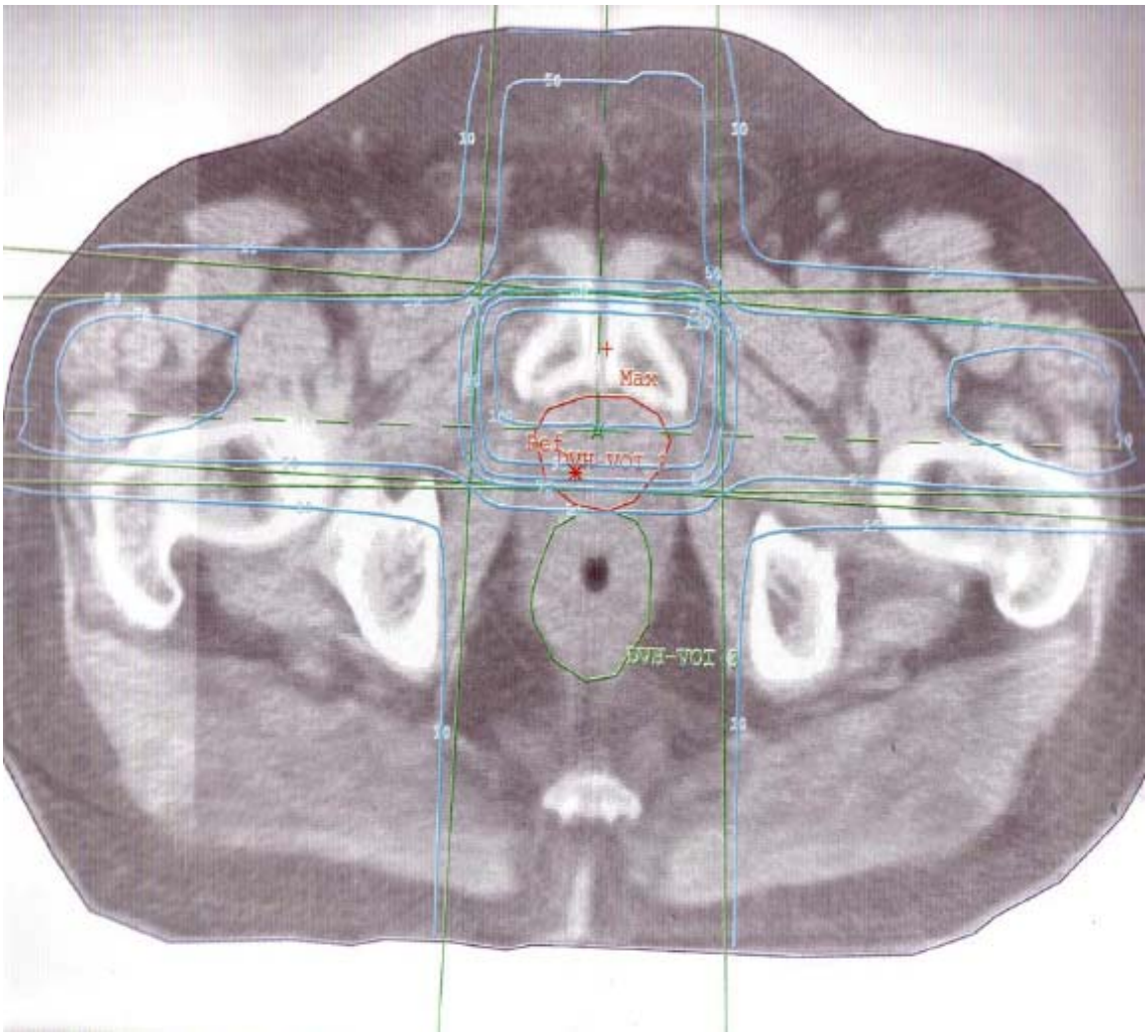


FIGURE 7. A CT slice, showing a three-field booster. Note that the 50 % isodose curve is used as a guide not to overdose the rectum.

3.3 Follow-Up

After treatment, the patient is expected to appear for a follow up consultation every three months, which changes to six monthly after a period of one year. This is to monitor the patient's progress by observing changes in the PSA after treatment and complications resulting from treatment.

Clinical local control was assessed (or determined) by measuring the PSA, which was the biochemical measure to determine local control (hence TCP). The ASTRO definition of biochemical failure (BF) was adopted to determine outcome for this study. According to this definition, biochemical failure (BF) was indicated by three consecutive rises in PSA after the nadir. Side effects (complications) were reported by patients on these follow up visits. These could be early or late complications, depending on how long after the treatment the patient continued to attend these follow up visits. So a retrospective review of these records was used to assess the (NTCP) following the treatment. For the analysis, the Modified Radiotherapy and Oncology group (RTOG) system was adopted to grade complications. This information was correlated to the calculated Biological objective functions calculated by the BIOPLAN software and the overlap volume to critical structures.

3.4 Drawing Of Treatment Margins And Overlap Volume

The success of treatment can be affected by any of the steps in the radiotherapy management of cancer including imaging, simulation, immobilization, treatment planning, and treatment delivery.

In the treatment planning stage defining or drawing of treatment and critical volumes is a challenging and important stage. This has a direct implication on the treatment outcome. Underestimation of the treatment volume (or the cancer) by the doctor could mean a number of cancer cells has might be left untreated and this could result in re-growth and hence treatment failure. Drawing target volumes is also limited, since interest is not only on visible disease (structures visible on the CT for example) but also on microscopic disease, movement of the structures within the patient and the day-to-day differences in-patient set up. Hence treatment margins are defined accordingly.

If it were possible, only the diseased area would be targeted, but this is impossible, thus normal tissue will always be irradiated. A number of techniques are used to minimize the treatment of these dose-limiting organs. The task at hand is to limit the dose to these organs at risk to below tolerance and give as much dose to the target volume as possible. This is possible only if the doctor accurately defines these critical volumes (for if this is not done, an organ at risk might be treated to above tolerance). Volume definition is critical also because treatment plans are evaluated based on the DVHs calculated by the planning system, and these are directly influenced by volume definition and drawing.

3.4.1 Drawing target volume and treatment margins [13]

The International Commission on Radiation Units and Measurements (ICRU) Report 50 has given the radiation oncology community a language for the methodology used in image-based 3D planning for defining the known tumor, suspected microscopic spread, and marginal volumes necessary to account for setup variations and organ and patient motion. Due to limitations and practical issues when using Report 50 methodology, the ICRU published a supplement to Report 50 (ICRU Report 62) to formulate more accurately some of the definitions and to take into account the consequences of the advances made over time. [13]

Presented in the figure below, is the schematic diagram depicting volume definition according to the ICRU Report 50

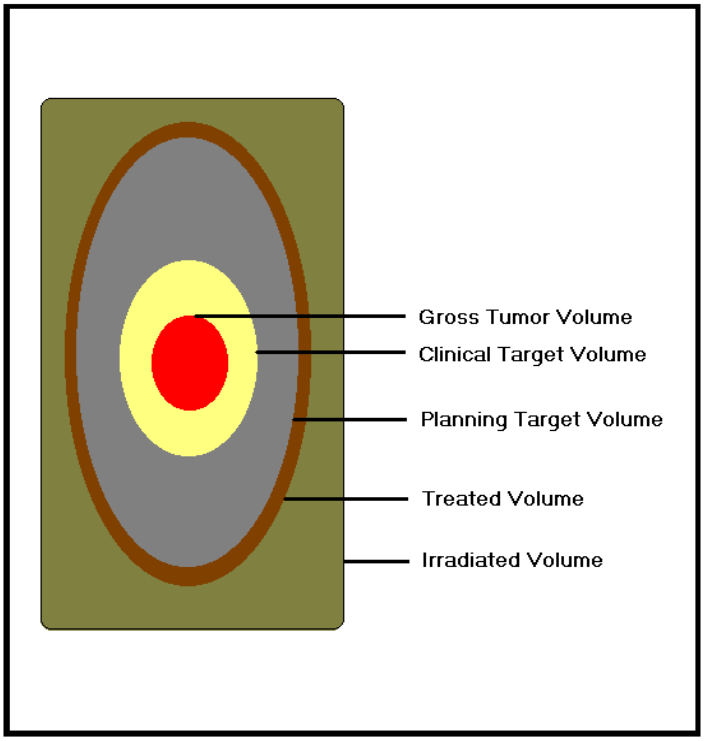


FIGURE 8. Schematic illustration of the boundaries of the volumes defined by ICRU 50.

3.4.2 Clinical target volume (CTV), and planning target volume (PTV)

The ICRU Report 50 definition of target volume is separated into three distinct boundaries:

1. Visible tumor- Gross Tumor Volume
2. Region to account for uncertainties in microscopic tumor spread- Clinical Target Volume , and
3. A region to account for positional uncertainties - Planning Target Volume

The GTV; The GTV is the gross demonstrable extent and location of the malignant growth. It consists of the primary tumor and possibly metastatic lymphadenopathy or other metastases. The GTV almost always corresponds to those parts of the malignant growth where the tumor cell density is the highest.

The CTV; the CTV is the tissue volume that contains a GTV and/or subclinical microscopic malignant disease. In specifying the CTV, the physician must consider microextensions of the disease near the GTV, and the natural avenues of spread for that particular disease and site including lymph node, perivascular, and perineural extensions.

The PTV; The PTV is the geometrical concept used for treatment planning, and is defined to select appropriate beam sizes and beam arrangements, to ensure that the prescribed dose is delivered to the CTV. To avoid significant deviation from the prescribed dose in any part of the CTV, one must add margins to the CTV for variation in tissue position, size, and shape, as well as for variations in patient position and beam position, both intrafractionally and interfractionally. This leads to the concept of PTV.

For planning in Johannesburg hospital the PTV was defined by the internal margin and was used to define the personalized conformal prostate shielding blocks. Beam shaping blocks were drawn using the beams-eye-view option for all the six fields. A schematic diagram to illustrate this is shown in figure 9.

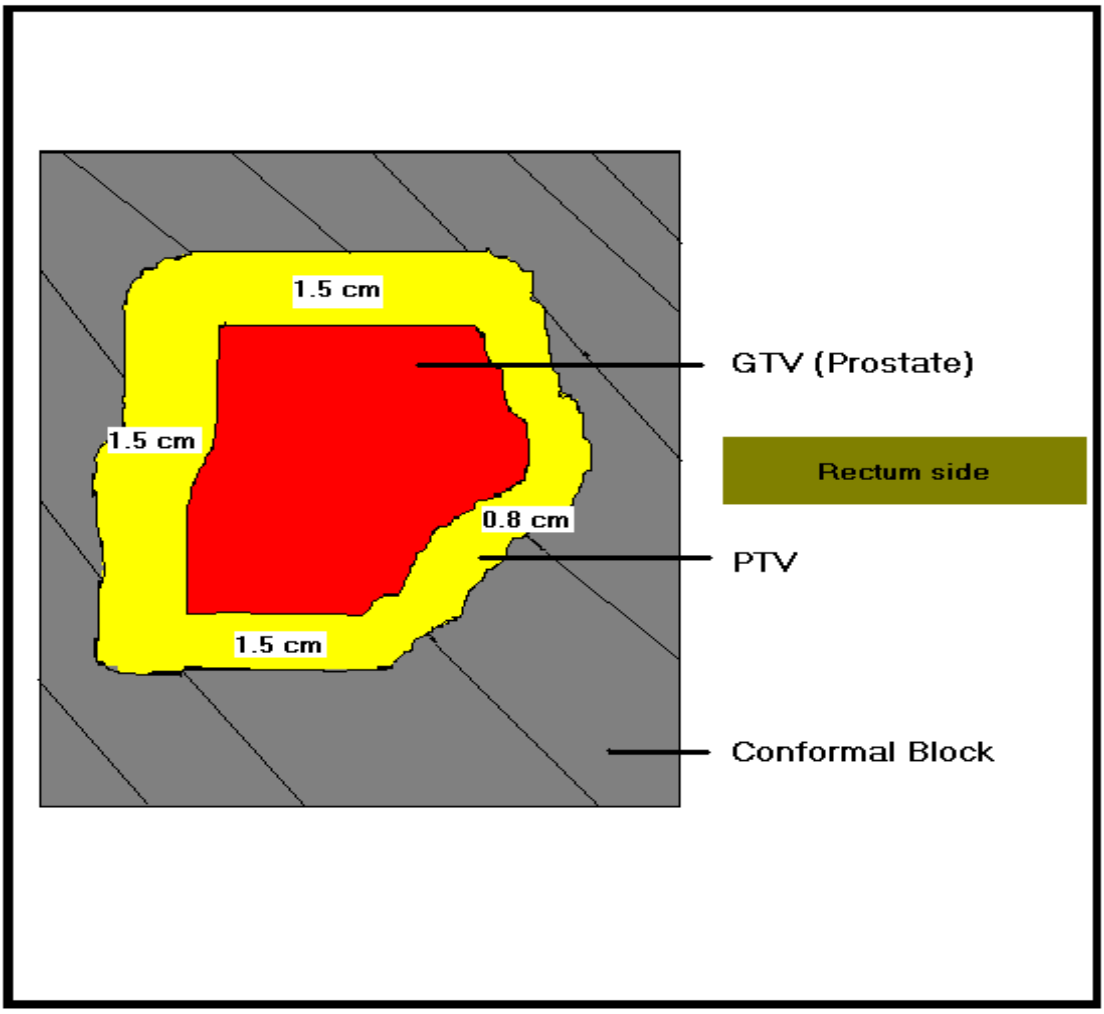


FIGURE 9. Diagram showing a typical conformal block defining the treatment field and indicating the size of the margins allowed on all sides of the GTV. The margin is 1.5 cm all around the GTV but only 0.8 cm over the rectum side.

The distances indicated the PTV's outer boundary. The PTV or block boundary is drawn at 1.5 cm from the GTV boundary all around the prostate itself except posterior, were the margin is at 0.8 cm from the GTV. This is thought to minimize the dose to the rectum when using this technique. [13]

3.4.3 Drawing the overlap volume

The overlap volume in this study was the volume of the rectum that coincided with the planning target volume. This was defined on the Helax TMS for the purpose of a DVH estimation by demarcating it on every CT slice where the volumes intercepted each other, as illustrated in figure 10 below.

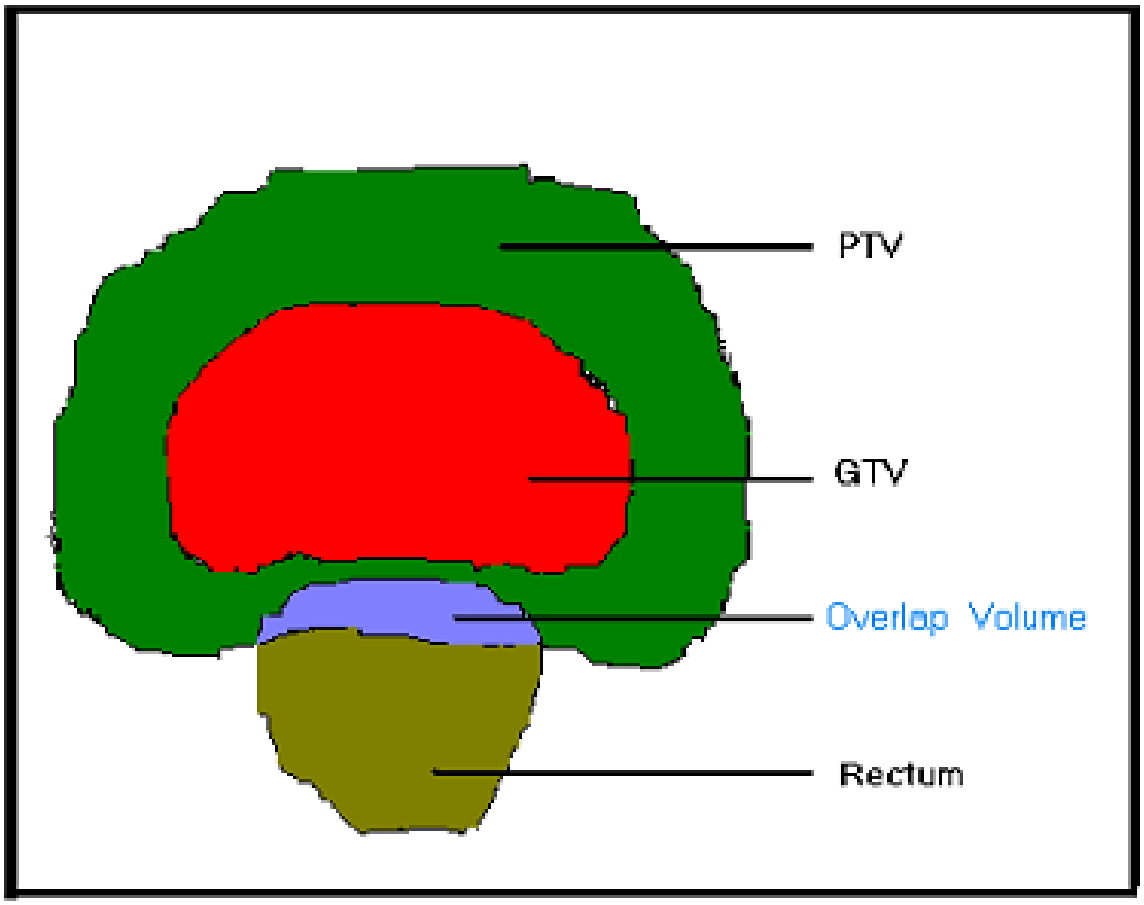


FIGURE 10. This diagram depicts the overlap volume defined by the intersection of the rectum and the PTV.

After all the volumes had been drawn, the plan was sent for recalculation. Dose Volume Histograms for the GTV, Margins (PTV), Rectum, Bladder, and Overlap Volume were calculated.

3.5 DVH Data Transporting And Calculation Of Biological Objective Functions Using BIOPLAN

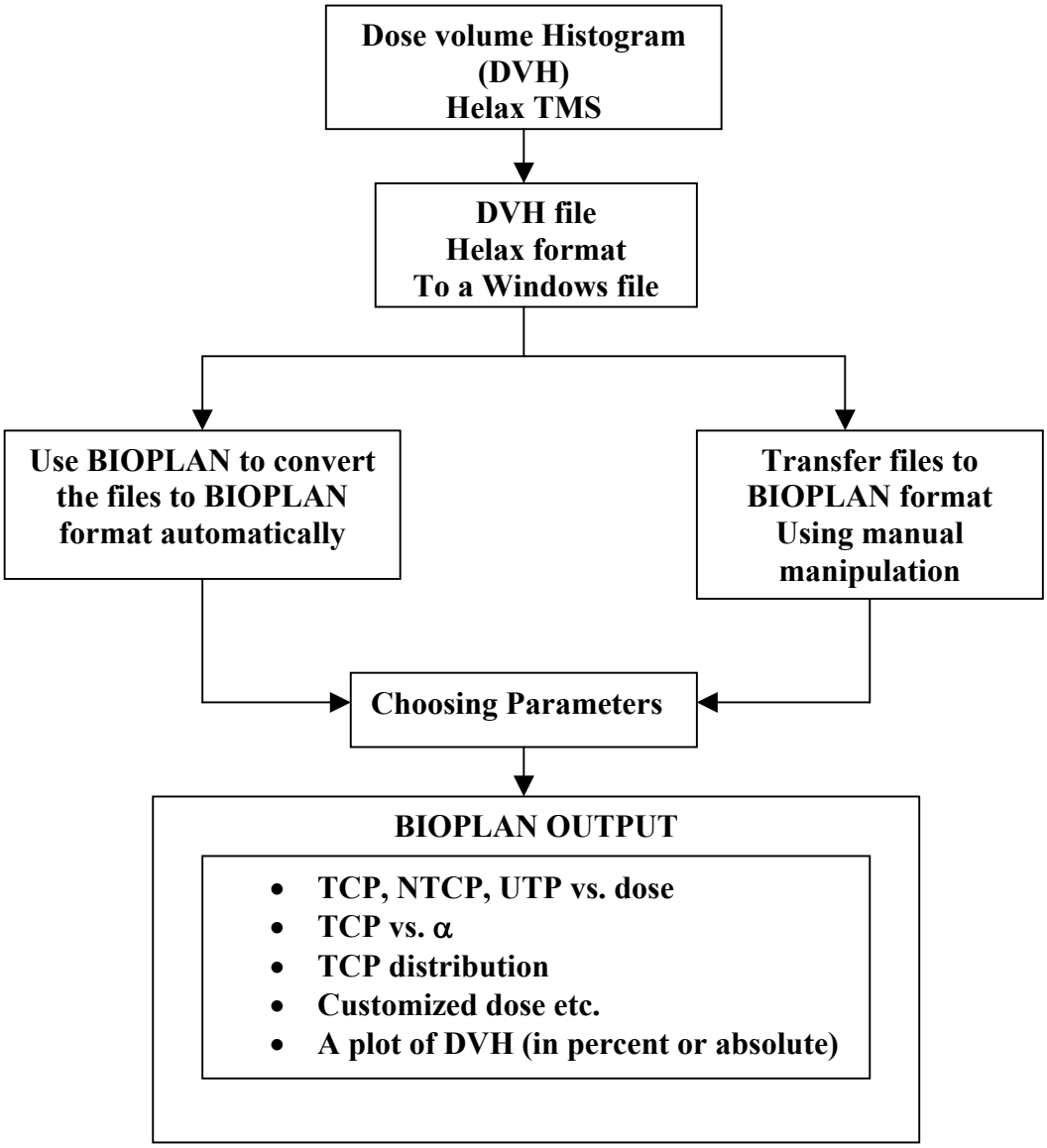


FIGURE 11. Flow chart indicating the flow of data execution in BIOPLAN calculations.

BIOPLAN is computer software for the biological evaluation of treatment plans, and has been developed using Visual Basic version 3.0. BIOPLAN requires DVHs in ASCII

format, a file for each volume or structure. The files from Helax were converted into BIOPLAN format either manually or using tools provided by BIOPLAN to do this automatically. Figure 11 indicates the flowchart to process or calculate biological objective functions from Helax TMS input files.

3.5.1 DVH data transporting and file preparation

DVH data for the GTV, PTV, Rectum, Bladder, and overlap volumes were transported for each patient via ftp to a networked LANTISTM (Local area network therapy information system) computer. In the process, each DVH was given a file name and the data points were converted into absolute values of dose and volume. To serve as meaningful input to BIOPLAN, these files were converted to BIOPLAN format either by manual manipulation or automatically, by BIOPLAN itself.

3.5.2 Calculating biological objective functions

DVH files give only physical data about a treatment plan. To initiate biological calculations, model parameters were chosen. BIOPLAN has default parameter values for most critical structures and for the prostate. In particular, the default α/β ratio for the prostate is 10 Gy^{-1} although it is known to be much smaller than this (= 1.5 Gy^{-1}). For this study and for consistency, all default values from BIOPLAN were used for the calculations. The default parameters used are given in table 1 below. The α/β ratio of 1.5 Gy^{-1} was also used in the calculation to compare with TCP and NTCP resulting from the default α/β value.

Tissue	Parameter	Type of complication	Value
Tumor (Prostate)	α/β	-	10-Gy
	α	-	0.292-Gy^{-1}
	SD of α	-	0.07
	Cell density	-	1.1 X 10^{7} cm^{3}
		-	
Organ at risk (Rectum)	m	Mild (as defined by RTGO)	0.064
		Perforation, necrosis, fistula	0.15
	n	Mild (as defined by RTGO)	0.203
		Perforation, necrosis, fistula	0.12
	TD50	Mild (as defined by RTGO)	56
		Perforation, necrosis, fistula	80

TABLE 1. This table gives default values of the parameters used in BIOPLAN calculations.

Calculations for prostate tumours were done ignoring effects of proliferation, as it is a very slow (approximately has T_d = 40 days) growing tumor. Thus for all the calculations, proliferation is not taken into account. [1] After the selection of the appropriate parameters for the prostate and the rectum, the software was commanded to do all the calculations.

4. RESULTS

4.1 Follow-Up Results

As mentioned previously, follow-up review of the patient after treatment is part of the holistic cancer management program. After treatment review is of paramount importance since it serves as a feedback or report on the response of the treated area or quality of life of the patient after treatment. The quality of life of the patient is measured against optimum tumor control with complications (morbidity) kept as low as possible. Thus, follow-up reviews should quantify tumor management based on tests done on the patient and reports by the patient of any problems encountered after irradiation.

For this study special attention was given the measure of tumor control (PSA levels, indicating biochemical control for the prostate) and rectal complications reported by the patient after treatment noting that the reviews were at least 2 months to about 2.5 years after treatment.

The ASTRO guidelines for biochemical failure (Three consecutive rises in PSA after radiotherapy) were adopted for this study. 100 % biochemical control was obtained in this sample.

Reported complication probabilities are graded according to the modified RTOG morbidity scale. Table 2 gives an indication of complications for each grade. [13]

Grade	Description
1	Mild diarrhea, mild cramping, bowel movement 5/day, slight rectal discharge or bleeding
2	Moderate diarrhea and colic, bowel movement 5/day, excessive rectal mucus or intermittent bleeding
3	Obstruction or bleeding requiring surgery, coagulation procedure, or transfusion
4	Necrosis, perforation, fistula

TABLE 2. Modified RTOG morbidity scale for late rectal toxicity. [13]

Complications reported after therapy were all less than grade 3 (RTOG) for the patients, which means only mild complications were reported. No patient reported having necrosis, perforation or fistulae for all prognostic groups.

4.2. Tumor Control Probability

4.2.1 Tabulated results

Table 4 below shows all the BIOPLAN calculated biological objective functions for the patients included in the study. Some of the patients had no follow-up. A column of the absolute GTV volumes and Overlap volumes per patient is included

As mentioned in the methods, default parameters were used in the calculations of these biological functions unless otherwise stated.

Two columns are shown for the NTCP results, one predicts severe complications (perforation, necrosis, fistula) to the rectum while the second shows the probability of mild complications.

All the doses used in these results were converted to 2Gy (ID2) equivalent dose.

Patient No.	GTV Volume (ccm)	Overlap Volume (ccm)	TCP (%) α/β = 10	TCP (%) α/β = 1.5	NTCP (Proc/nect) (%)	NTCP (mild) (%)
1	64.37	2.40	90	99.7	4.20	69.30
2	102.72	68.50	92.4	99.7	1.70	7.50
3	78.94	8.03	90.8	99.2	3.30	49.90
4	114.41	0.79	90.5	99.3	0.50	0.10
5	76.03	3.06	89.7	99.2	1.50	7.50
6	100.21	11.95	89.4	99.0	5.10	78.60
7	121.50	15.06	90.6	99.7	4.60	61.90
8	83.41	3.48	91.9	99.2	1.90	18.20
9	75.52	19.37	92.8	99.4	3.90	47.90
10	84.14	6.09	90.7	99.1	2.40	21.30
11	78.50	1.22	93.5	99.2	4.30	77.10
12	84.36	12.30	93.4	99.1	0.90	0.90
13	111.05	5.95	95.9	99.0	1.80	10.30
14	142.85	18.78	97.1	99.4	4.10	55.30
15	47.08	12.79	97.1	99.4	0.40	0.00
16	124.43	17.86	86.1	99.9	7.70	89.80
17	54.06	10.15	80.7	100.0	3.90	27.40
18	75.68	5.76	86.2	99.9	4.20	50.60
19	101.26	4.50	80	99.9	0.50	0.00
20	110.67	19.44	71.1	99.9	4.70	43.60
21	99.01	11.47	85.5	99.9	2.90	18.60
22	70.82	11.20	81.9	99.9	5.00	48.40
23	85.19	2.65	80.7	100.0	6.80	83.20
24	88.46	16.88	80	99.9	6.80	80.60
25	98.65	18.11	80.6	100.0	16.90	99.30
26	92.51	4.23	82.1	100.0	8.10	86.70
27	110.94	14.94	84.8	99.9	2.70	19.30
28	108.03	23.30	80.1	99.0	1.30	3.50
29	58.87	15.62	74.4	100.0	3.40	21.50
30	102.93	0.40	71.2	100.0	0.80	0.10
31	79.40	6.62	81.2	100.0	16.70	99.10
32	57.74	2.00	78.1	100.0	0.20	0.00
33	45.67	5.24	75.9	100.0	3.60	18.60
34	113.62	4.96	74.2	100.0	4.80	41.20
35	46.22	9.65	78.9	100.0	1.90	1.00
36	94.53	2.72	75.2	100.0	5.50	64.80
37	90.64	4.95	75.4	100.0	7.20	79.80
38	55.05	8.94	77.9	100.0	1.80	0.80
39	53.8	4.92	78.2	100.0	2.40	5.30
40	23.29	3.52	82.2	100.0	1.60	0.90
41	43.68	2.04	79.3	100.0	1.30	0.70

TABLE 3. Table of results calculated by BIOPLAN.

4.2.2 TCP vs dose (dose escalation)

Figure 12 shows a graphs of the calculated TCP as a function of the prescribed dose for a α/β=10. This effectively summarizes the dose escalation results calculated from BIOPLAN.

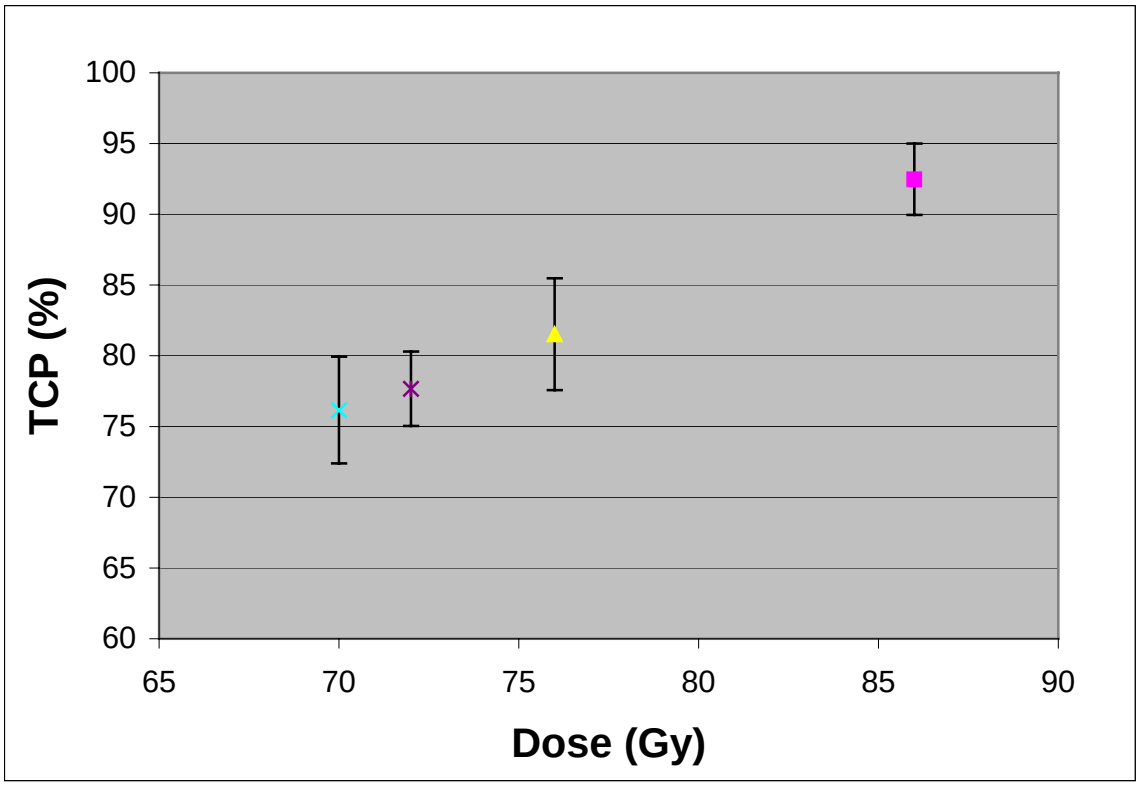


FIGURE 12. Graph showing how the calculated TCP varied with prescribed dose.

4.2.3 TCP vs mean dose to tumor

The schematic diagram below shows how the TCP varied with the mean dose to the target volume or GTV.

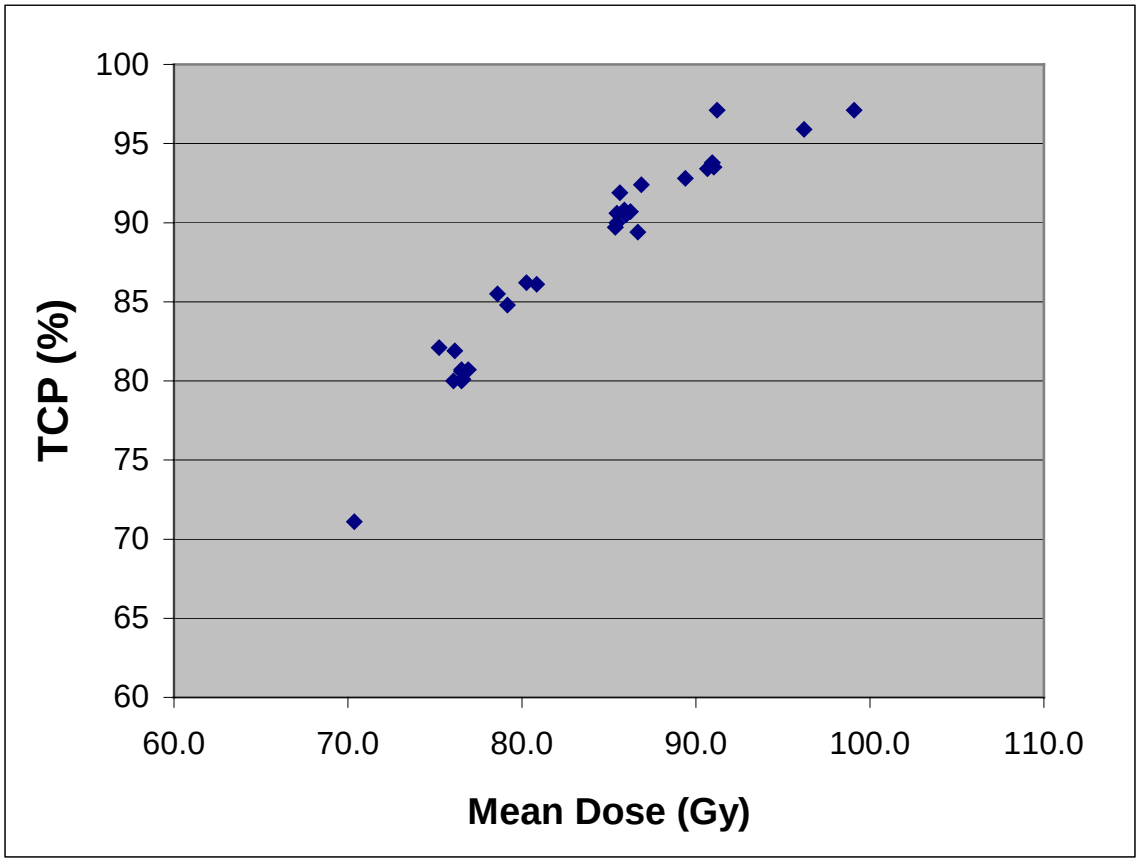


FIGURE 13. Tumor control probability plotted against mean dose to the GTV.

4.2.4 TCP vs GTV

Figures 14 show how the calculated TCP varied with GTV volume.

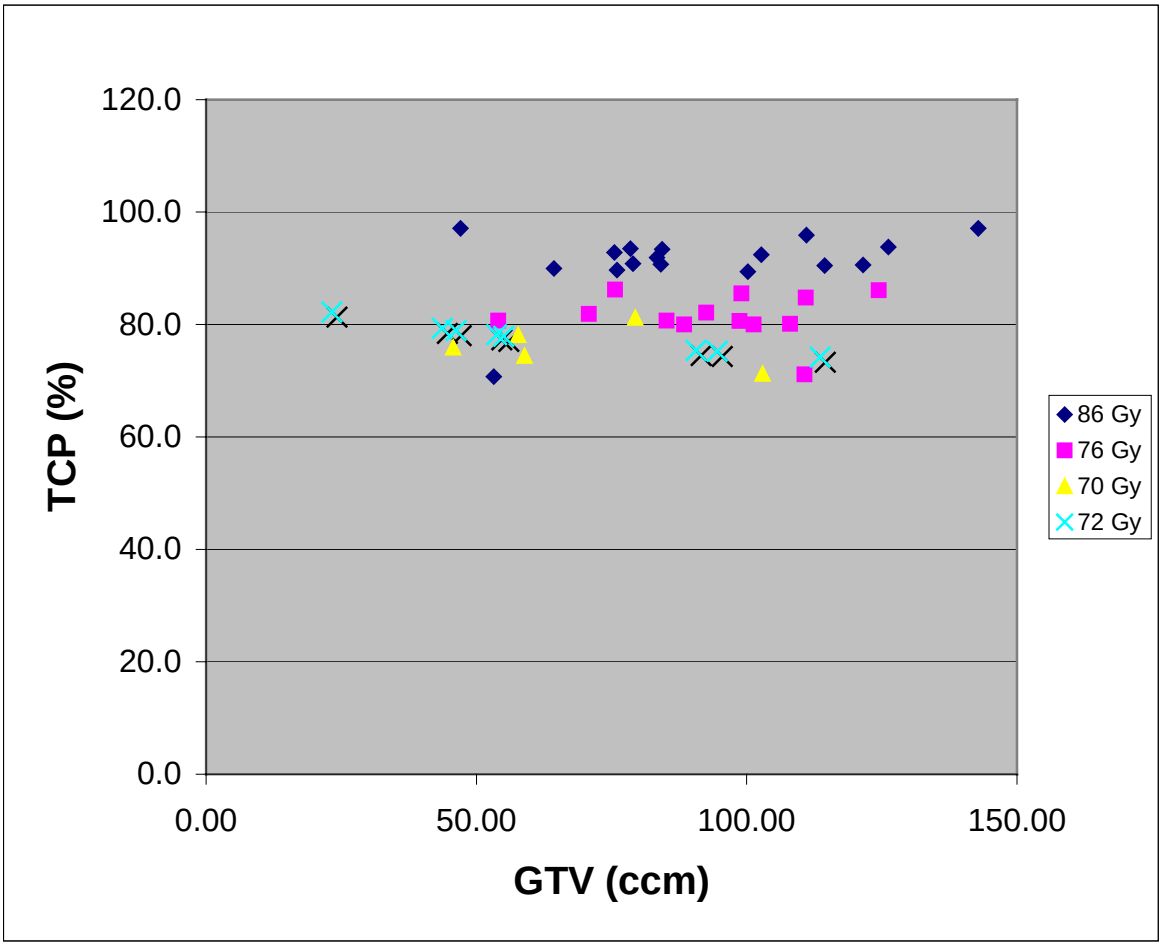


FIGURE 14. TCP vs PTV volume for all dose prescriptions.

4.3 Normal Tissue Complication Probability

NTCP depends on a number of factors, but in this case only the dependence of rectal NTCP on dose and overlap volume was studied.

4.3.1 Effects of dose escalation on rectum complications

The effect of dose escalation on predicting rectal complications (NTCP) is shown in the figures below. The first graph depicts the change in NTCP with dose for severe rectal complications and the second graph show it for mild conditions.

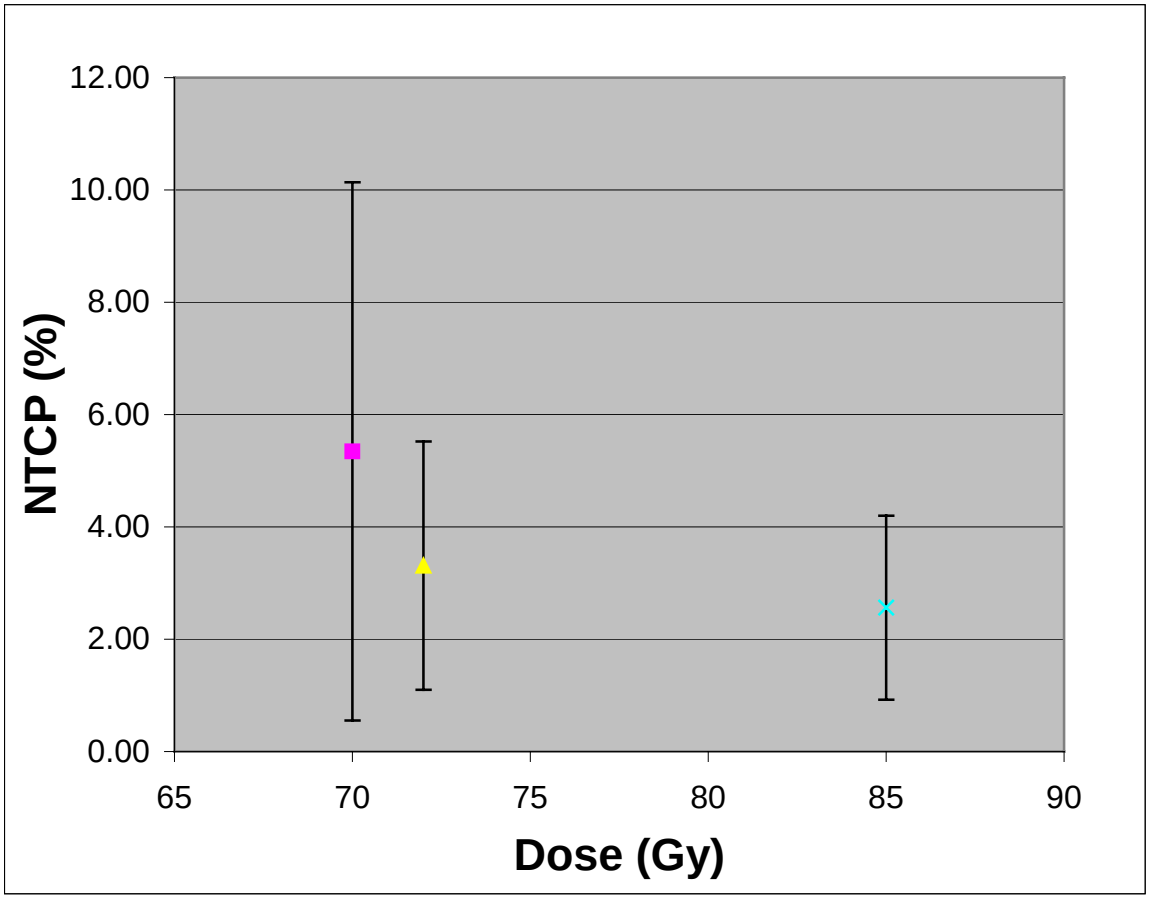


FIGURE 15. NTCP plotted against prescribed dose for severe conditions.

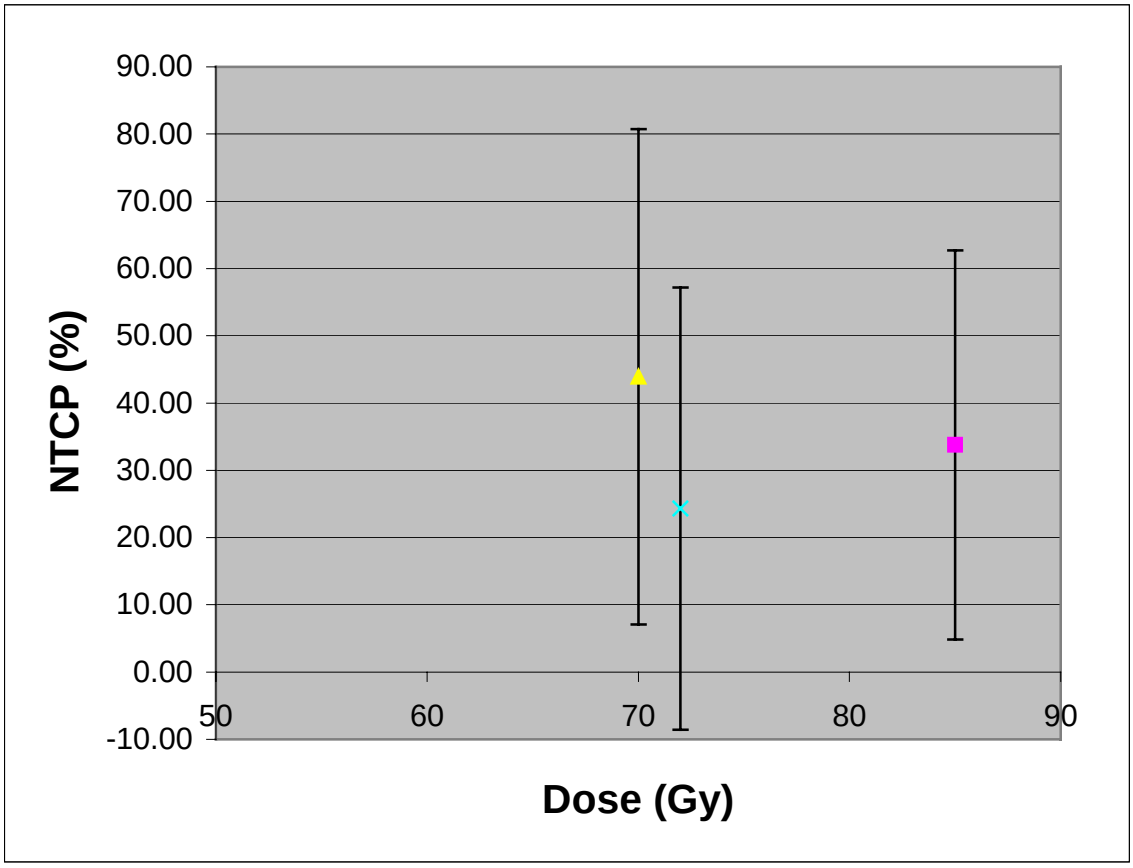


FIGURE 16. NTCP vs dose for mild complications

4.3.2 Effects of increased volume of overlap on rectum complications

A graph of calculated NTCP against volume of overlap is shown. This graph shows four series, which represent dose prescription regimes. The diagram shows how NTCP for equal overlap volumes changes with dose as well as how overlap volume changes affect the NTCP at a certain dose level.

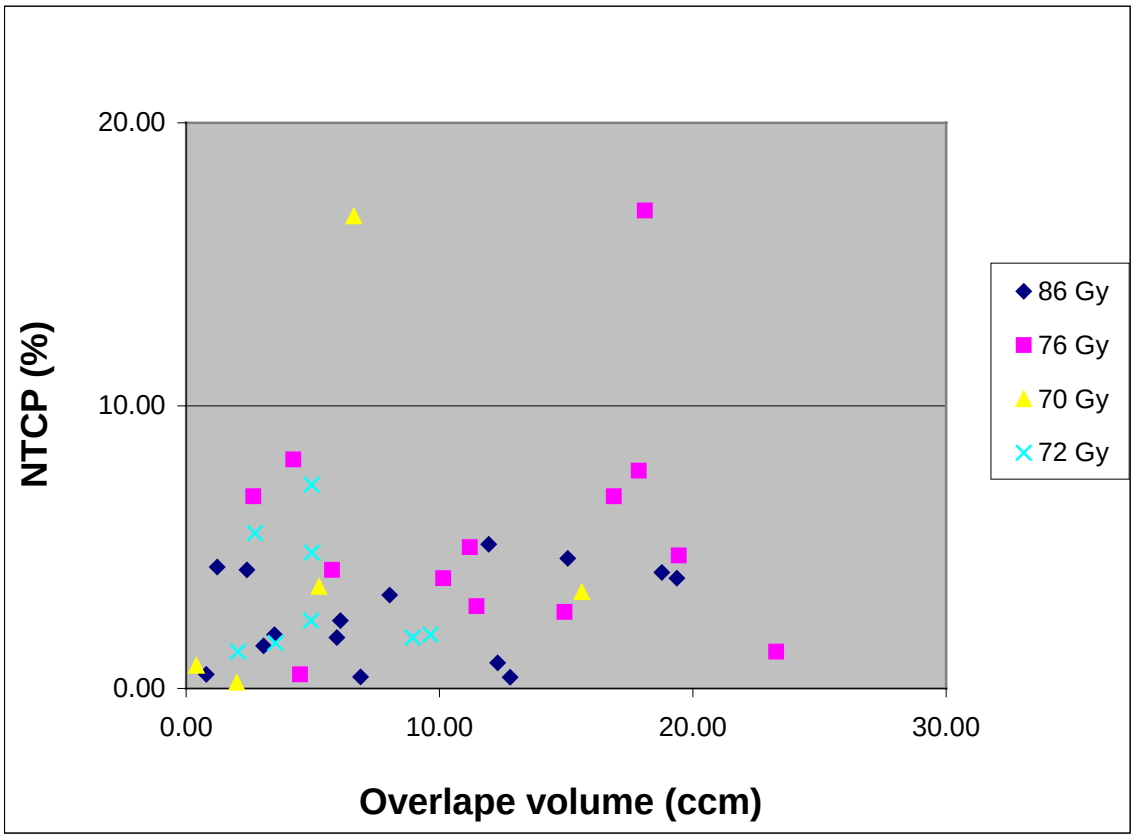


FIGURE 17. The change in NTCP (%) with changing overlap volume.

5. DISCUSSION

5.1 Follow-Up Data

Patients were stratified into three risk groups on the basis of pretreatment PSA level, Gleason score, and American Joint Commission on Cancer (AJCC) T stage; low risk (stage T1-T2 and Gleason score =6 and PSA =10 ng/mL); intermediate risk, stage T1-T2 and Gleason score 7 or PSA 10.1–20 ng/mL; and high risk, PSA =20 ng/mL or Gleason score =8. Patients with T3/T4 disease are classified as high-risk patients. [14]

Nonrandomized clinical trials of 3D-CRT for prostate cancer have suffered from methodologic problems, including small sample sizes, use of different definitions of biochemical failure, selection bias, a mixed range of treatment doses, and short follow-up time.

For this study, the small sample size of 37 patients was the major limiting factor. This was compounded by short-term follow-up, which introduced big statistical uncertainties in the study.

As mentioned above, short follow-up times are a major problem in such studies. Periodical follow-ups after treatment for this study are from a few months to about 2 years. This is problematic in this particular analysis because the accuracy of determining TCP and biochemical failure is very dependent on the maturity of the data. Biochemical failure as defined in section 2.3, is time dependent. So the study is limited by this immaturity of the clinical data. Most rectal complications develop at least 3 years after treatment. For a complete and accurate analysis, at least 5 years is the time frame recommended [15]. Thus the follow up results of this study were analyzed with this limitation in mind.

The benefit of dose escalation is known to be most apparent in patients with intermediate-risk features.[14]

From our follow up data, the results suggest that for all our 37 patients, the aim of treatment – Biochemical control – was achieved. For all patients, no 3 consecutive rises in PSA were found, which suggests local control. But this high success in local control may be attributed to small sample size and the short time of follow up data.

Rectal complications reported on the last day of follow-up for all patients suggested only mild or minor complications. According to the RTOG grading system, the reported complications are of grade 3 or less.

5.2 Tumor Control Probability

5.2.1 TCP vs dose (dose escalation)

Because radiotherapy is a local therapeutic modality, the emphasis has long been on developing methods to affect better local control. In the case of prostate cancer, the current prevailing hypothesis centers on delivering higher doses to the gland. The necessary technology for treatment planning, delivery, and target localization to support this has recently become available.

It is very important to note that the calculations with these models do not take care of all clinical characteristics of the tumor. For instance, the model does not give provision for the fact that patients can be classified in different prognostic groups. As a result, the models give results representative of grouping only and will not show the dependence of dose escalation on any prognostic grouping of patients.

TCP vs prescribed dose normalized to 2-Gy per fraction equivalent was calculated for four different dose prescriptions. The calculated TCP were arrived at after making a

number of assumptions in the calculation chain, which determine the level of accuracy for the results. The effects of tumor proliferation are not taken into account in the calculation, which underestimates the fact that the tumor is growing as it is treated. This is because the prostate tumor is very slow growing, and its growth was considered negligible.

The model also ignored any oxygenation effects. Changes in tumor local control probability (TLCP) vs. total dose curves have been shown to deviate from sigmoidal curves when hypoxic fractions are not included in the model for TCP. [16]

It is also important to note that, the α/β ratio of 10-Gy was used for the calculation as this choice was made because BIOPLAN suggested this value for the prostate and that the results obtained with this value were comparable to clinical outcomes. This value is in marked contrast to α/β of less than 3-Gy, suggested in the recent analyses [17] [18]. For comparison, an α/β of 1.5-Gy was also used. All other parameters were taken as given in BIOPLAN, thus these might have a significant contribution in the uncertainty associated with such results

The results showed the general trend that the TCP increased with increasing the total dose to the gland. The calculated TCP had an average of 84.3 ± 7.4 %. As the total dose was elevated through 70-Gy, 72-Gy, 76-Gy, and 86-Gy, the average TCP increased through 76.2 ± 3.8 %, 77.7 ± 2.6 %, 81.5 ± 4 % and 92.5 ± 2.5 %, respectively. The TCP increased about 22 % by increasing prescribed doses from 70 Gy to 86 Gy.

5.2.2 TCP vs GTV

It is important to note that in this analysis, the CT volume was probably an over estimation of true volume. In Johannesburg, the whole organ (prostate) is targeted and not just the tumor, so the planned volume (GTV) does not strictly conform to the actual tumor. This would require magnetic resonance spectroscopy (MRS) imaging, which would make visible the tumor within the prostate gland. The initial PSA gives a more accurate indication of tumor volume, which is why it is such an important prognostic

factor. Another prognostic factor that may be interesting to compute is the PSA density i.e. PSA/Volume. It may be of interest to try to incorporate these parameters into the models.

The present model predicted a decreasing probability of achieving complication free tumor control with increasing tumor size and increasing volume of normal tissue irradiated. As mentioned above the TCP is expected to vary with the target volume. In general, the TCP should decrease as the tumor volume increases, as long as the tumor dose remains unchanged. This is because more cells have to be destroyed with the same tumor dose. The results shown in figure 14 show no apparent variation of TCP with GTV for the 86 Gy, 76 Gy and 70 Gy dose prescriptions. Even when the GTV increased three fold, the TCP showed no major change. It has been shown from other studies that the TCP at constant doses does not always decrease with increasing volume [19]. But, for the 72 Gy prescription, it showed that the TCP decreases when the GTV increases. The decrease is from around 82 % to about 74 % when the volume increases about 5 times its initial value.
This last result suggests that as the tumor volume increases, high doses are to be delivered order to maintain the same level of local control.

5.2.3 TCP vs mean dose

Dose escalation translates to increasing the mean dose delivered to the GTV. Increases in the mean dose to the tumor predicted better control of the tumor. The TCP changes faster for lower doses but as the mean dose increased the TCP increased further, but the rate at which TCP increased, decreased. This trend continued until a threshold was reached where the TCP remaind more or less the same even if the mean dose increased. This threshold indicated that dose escalation increased TCP only up to a point above which there would be no more theoretical gain from increasing the dose.

5.3 NTCP

It is very important to note that for a number of normal tissues, the incidence and severity of late complications are not only dependent on radiation dose and irradiated volume, but on a number of other factors as well. For example, for late rectum complications, patient-related factors such as hypertension, diabetes, previous surgery, vascular disease, adjuvant chemotherapy, homone manipulation prior to radiotherapy and previous bowel disease may predispose the rectum to radiation injury. Furthermore, late side effects seem to be correlated to acute side effects as well.

5.3.1 NTCP vs dose

Dosimetric, anatomic, and clinical factors correlate with late rectal toxicity after three-dimensional conformal radiotherapy for prostate cancer. (The models used for the study do consider these factors in the calculation but not all e.g. the effects of hypoxia and chemotherapy to treatment outcome are not included in the calculation.)

Dose-volume constraints used in evaluating and accepting plans are meant to give the best result to the patient. A dose volume constraint is used to ensure that treatment objectives are met, achieving optimum control and keeping complications low. For this study, mild conditions are expected with high probability. But serious complications are expected to be less than 5 %, because of the initial dose volume constraint used.

Figure 15 shows NTCP vs delivered dose was calculated for severe complications. There are three dose regimes of 70 Gy, 72 Gy and 85 Gy. The results showed that the average NTCP was 3.9 ± 3.6 %, which is within the accepted 5 %.

The effects of dose escalation were not apparent in this graph. The graph predicts that increasing the prescribed dose did not alter the NTCP significantly. The reason might be that for all plans, if a volume more than 25 % of the PTV received doses more than 70 Gy

then that plan would be rejected. Thus this dose-volume constraint controls the level of morbidity and control after RT not the prescribed dose.

The calculated average NTCP (for mild complications) was 36.3 ± 33.3 %. There was no trend showing of increasing NTCP as the dose increases.

5.3.2 NTCP vs overlap volume

The rationale for 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) is that safe dose escalation to tumors may be achievable if the volume of adjacent normal tissue exposed to high radiation doses can be kept within acceptable limits. To understand these limits in terms of dose and volume, many studies have been performed to estimate the risk of normal-tissue complications as a function of the dose distribution to tissue summarized in the form of a dose–volume histogram (DVH). Although the DVH does not retain spatial information (i.e., which part of the organ is exposed to which dose), it nonetheless provides considerable information regarding the dose–volume characteristics of the treatment plan. [7]

Dose volume histogram analysis clearly indicates a volume effect on the probability of developing late rectal complications. The dose and the volume behave as continuous interrelated variables, because both the absolute and the percentage of rectal volume correlate significantly with late toxicity across a range of doses. Studies show that the risk of developing late rectal complications grows exponentially as a more absolute volume of the rectum is irradiated to a defined dose. [7]

For “solid” organs, such as liver, lung, and parotids, use of a DVH based on the entire volume encompassed by the outer contour of the organ makes sense as a way of summarizing the dose–volume distribution. However, for “hollow” organs, such as rectum and bladder, the contents of the organ are irrelevant to the risk of complications that may occur as a result of radiotherapy (RT). For this reason, the dose–wall histogram

and dose–surface histogram (DSH) have been proposed as alternatives to the DVH for such organs. [7]

These results showed scattered data for all dose regimes. This suggested that the irradiation of a bigger rectum volume does not increase the chances of rectum complications.

At first glance, the notion that NTCP models based on the DWH would better describe the risk of rectal toxicity than do models based on the DVH seems intuitively clear because of the irrelevance of the dose received by the rectal contents. However, the DWH assessed from the planning CT is not necessarily an accurate representation of the true dose distribution to rectal wall during treatment. Numerous studies have demonstrated that considerable variation may occur in the shape and position of internal organs, including rectum, during the course of RT for prostate cancer. This variation is largely caused by interfractional differences in rectal and bladder filling over the course of treatment. In addition, the DVH and DWH have fairly similar shapes. Therefore, whether NTCP modeling based on the DWH (especially a semiauto-contoured DWH) would in fact be more accurate than NTCP modeling based on the DVH is not immediately obvious. [7]

Some studies have shown that for each of the models, the fit to the late rectal bleeding data was slightly improved when the analysis was based on the rectal DWH instead of on the DVH. Thus, the use of DVH instead of DWH might have an influence on the results and relationships between dose and volume.

5.4 A Comparison Of Calculated To Clinical Follow-Up Results

Dose-volume constraints used to keep the incidents of complications within specified levels, at least for a given period of time, are a useful tool in radiotherapy to co-evaluate a treatment plan.

The constraint used in this study to keep severe rectal complications to 5 % within a 5-year period to maintain local control within acceptable levels was used. In order to achieve such results, the plans were passed on the condition that at least not more that 25 % of the rectal volume would recieve 70 Gy or more.

Our calculated results (from BIOPLAN) showed a high percentage of severe rectal complications being maintained within the 5 % NTCP level (section 4.3.1). This showed that our calculations were within clinical acceptable results. This gives strong support to the success of the treatment regimes used. Such agreement between modeled and expected results validated the models and to a certain accuracy, the parameters used.

Mild rectal complications were also calculated. These were found to be highly probable and were expected to increase with increasing prescribed dose. With the follow-up data reported in this study, an agreement to calculated results was found (section 4.3.1). An analysis done on patient files revealed that a high percentage of mild (not serious) complications were reported from follow-ups as per the calculated NTCPs. This in general, shows that the models gave results related and close to the clinical ones. The modeled results on dose escalation showed the increase in TCP with dose (section 4.2.2). This was the case for all the patients in this study. But clinically, the significance of dose escalation on Low and high-risk patients is not expected. Gains in TCP are expected only for intermediate patients as the dose is increased. This is because the models used in this study did not take care of differences in prognostic grouping in its calculation.

6. CONCLUSIONS

- The use of BIOPLAN to predict biological outcome from DVH data exported from the Helax TMS at Johannesburg was successful.

- Dose escalation has been found to improve local control. The calculation does not classify different patients according to their factors clinical prognostic. It has been found that dose escalation is not beneficial for all prognostic groups. Some studies have shown that dose elevations improve local control (Biochemical control) for intermediate risk groups only; no improvements are reported for low and high risk groups. The model therefore predicted an increased TCP with dose escalation for all patients groups.

- The TCP vs tumor dose study showed no variation in TCP with GTV size (tumor size) for three dose regimes, which was not expected. A clear decrease in TCP with increased target volume was observed for only one dose regime. Use of GTV alone therefore was inadequate to accurately predict TCP.

- The NTCP vs dose results confirmed that if not more than 25 % of the rectal volume receive more than 70-Gy then grade 3 or more complications will be within 5 % But mild conditions (less than or equal to grade 3) can go up to a NTCP of 100 %.

- This study did not show any increase in rectal complication as the overlap volume (rectal wall) was increased. This was unexpected since an increase in rectal irradiation should translate to an increase in complications.

- Mature follow-up data is a requirement for studies of prostate cancer, however the ability to correlate physical and biological objective functions with current technology, is encouraging.

- With the improvement/maturity of our clinical data and the increased number of prostate cases, a proper study can be done. This includes the derivation of model parameters fitted from our clinical data. This would improve the predictive value of these models.

- Perhaps a more realistic dose wall histogram (DWH) tool might be used for future analysis, instead of the dose volume histograms (DVH).

- The TCP model described here is mathematically very simple and yet it is a reasonably complete description of the process of tumor eradication by irradiation, excluding proliferation and re-oxygenation effects. The main limitations in its use are lack of clinical data on radiosensitivity and clonogenic cell density. Thus the absolute values of TCP (and for NCTP) predicted must be treated with caution.

7. REFERENCES

1. Sanchez-Nieto, B. and Nahum, A.E. BIOPLAN: A software for the biological evaluation of radiotherapy treatment plans. Medical Dosimetry 25 (20), 2000, pp. 1-19.

2. Nahum, A.E. Modelling tumor control probability and consequences for treatment planning. ESTRO Teaching Course on "Conformal radiotherapy in Practice", 1998.

3. Fiorino, C. Sanguineti, G. Cozzarini, C. Fellin, G. Foppiano, F. Menegotti, L. Piazzolla, A. Rectal dose volume constraints in high-dose radiotherapy of localized prostate cancer. Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 4, pp. 953-962, 2003.

4. Stavrev, P. Niemieko, A. Stavreva, N. Goitein, M. The Application of biological models to clinical data. Physica Medica, Vol XVII, No. 2, 2001, pp. 001-0013.

5. Panayiotis Mavroidis.(2001) determination and use of radiobiological response parameters in radiation therapy optimization A doctoral Dissertation 2001 Division of Medical radiation physics

6. Lebesque J.V. Normal tissue complication probability models. ESTRO Teaching Course on "Conformal radiotherapy in Practice". (1998)

7. Susan, L. Lei, Dong. Rex, Cheung. Johnson, J. Mohan, R. Eugene, H. Huang, 0846730629H. Liu, H. Howard, D. Thames Kuban, D. Comparing of rectal dose wall histogram vs dose volume histogram for modeling the late incidence of late rectal bleeding after radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 5, 2004, pp. 1589–1601

8. Consensus statement: guidelines for PSA following radiation therapy American Society For Therapeutic Radiology and Oncology Consensus Panel, Int. J. Radiation Oncology Biol. Phys., Vol. 37, No. 5, 1997, pp. 1035-1041.

9. Webb, S. and Nahum, A.E. A model for calculating tumour control probability in radiotherapy including the effects of inhomogeneous distribution of dose and clonogenic cell density. Phys. Med. Biol. 38, 1993, pp. 653-66.

10. Warkentin, B. Stavrev. P. Stavreva, N. Field, C. Fallone, B. G. A TCP-NTCP estimation module based on known models, parameter sets and DVHs. Cross cancer institute, edmonton ab.

11. Task Group 21, Radiation Therapy Committee. A protocol for the determination of absorbed dose from high-energy photons and electron beams, Medical Physics, Vol. 10, No. 6, 1983 pp. 741-771

12. Nutting, M.C, Khoo S.V, Walker V, Mcnair H, Beardmore C, Norman A. and Dearnaley D.P. A randomised study of the use of a customised immobilisation system in the treatment of prostate cancer with conformal radiotherapy Radiother. Oncol, 2000, pp. 54 1-9

13. Skwarchuk, M.W. Jackson, A. Zelefsky, M.J. Venkatraman, E.S. Cowen, D.M. Levegr¨Un, S. Burman, C.M. Fuks, Z. Leibel, S.A. And Ling, C.C. Late rectal toxicity after conformal radiotherapy of prostate cancer (i): multivariate analysis and dose response. Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 1, 2000, pp. 103–113.

14. Symon, Z. Griffith, K.A. Mclaughlin, P.W. Sullivan, M And. Sandler, H.M Dose escalation for localized prostate cancer: substantial benefit observed

with 3d conformal therapy. Int. J. Radiation Oncology Biol. Phys., Vol. 46, No. 4, 2000, pp. 823–832.

15. Dr Kotzen J. optimising the therapeutic ratio. Radiation oncology Witwatersrand. Internal communication 2003.

16. Nahum, A. Chapman, J. Dose-escalation strategies for increasing prostate local control: how clinically proven hypoxia radically changes the picture. Radiation Oncology department, Copenhagen University Hospital.

17. Henk, B. and Marion, P. R. Van Gellekom. How low is the α/β ratio for prostate cancer? Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 4, 2003, pp. 1116–1121.

18. Jian, Z. Wang, X. Allen, L. I. Cedric, X. And Steven, J. Dibaise, M.D. The low α/β ratio for prostate cancer: what does the clinical outcome of HDR brachytherapy tell us? Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 4, 2003, pp. 1101–1108.

19. Webb, S. Optimum parameters in a model for tumour control probability including interpatient heterogeneity. Phys. Med. Biol. Vol 39, No. 11, 1994, pg. 1895-1914.