Verification of Prostate Conformal Radiotherapy Planning Protocol on an XiO Treatment Planning System

by

Joseph Martinus Steyn

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Supervisor: Dr FCP du Plessis

Co-Supervisor: Prof. WID Rae

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Glossary, Abbreviations and Definitions

Herewith a list of symbols, abbreviations and definitions used in this document.

3D-CRT	three-dimensional conformal radiation therapy / radiotherapy A radiotherapy treatment technique where the beams of radiation to be given as treatment are shaped (collimated) to match the tumour. Both the gantry and collimation of the beam are stationary during the delivery of radiation. Abbreviated in the current literature as CRT.
BTS	Bartlett's Test of Sphericity A test to verify if the correlation-matrix is an identity-matrix, which would show that the variables are unrelated and therefore unsuitable for structure-detection.
CI	conformity-index Ratio of the volume receiving the reference dose to the volume of the target.
CTV	clinical target volume An anatomical-clinical concept. The tissue-volume encompassing a subclinical microscopic malignant disease. This volume must receive an adequate dose of radiation to achieve the aim of the proposed cure or palliation.
DICOM	Digital Imaging and Communications in Medicine
DV	dose-volume The absorbed dose (Gy) given to a specified fractional (percent) volume of tissue such as an organ at risk.
DVH	dose-volume histogram Used in radiation therapy planning, a histogram relates the radiation dose given to a specified tissue-volume.

Focal	Focal™ contouring system (version 4.80.03, 2014, Elekta AB, Stockholm, Sweden) A three-dimensional, radiation therapy CT-simulation planning and dose review system that uses medical images to develop treatment plans and visualize the final planned dose results for cancer patients. Focal/Monaco uses DICOM services to import images, structures, plan and dose and to export images, structures, plan and dose parameters to other vendors.
Gy	Symbol in the International System of Units (SI) for the derived unit of ionizing radiation dose. Defined as the absorption of one joule of radiation energy per kilogram of matter.
GTV	gross tumour volume Gross palpable or visible/demonstrable extent and location of malignant growth. Usually visible on the CT DICOM-images of a cancer patient.
HI	heterogeneity-index Ratio of the highest dose received by 5% to the lowest dose received by 95% of the PTV.
KMO	Kaiser-Meyer-Olkin test A sampling adequacy test showing if the partial correlations among the variables are small or not.
linac	linear particle accelerator A type of particle accelerator that increases the kinetic energy of charged subatomic-particles or ions by subjecting the charged particles to a series of oscillating electric potentials along a linear beamline.
OAR(s)	organ(s) at risk Organs which might be damaged during radiation exposure. In radiation therapy, it most often refers to healthy organs located in the radiation field.

PCA principal component analysis

A set of measurements of correlated variables are converted into a set of values of linearly uncorrelated variables called principal components. The first principal component indicates the largest variance within the dataset.

PTV planning tumour volume

The volume that includes the clinical tumour volume and the margins for the deviation occurring due to patient-setup, organ-movement, etc.

Two volumes were used in this study:
PTV1 refers to the PTV prescribed to receive 27 fractions of 2 Gy each. This is known as the main planning tumour volume.

Also, referred to as the boost-volume, the PTV2 encompasses tumour shrinkage and is smaller than the main tumour volume (PTV1). A dose of 10 fractions of 2 Gy each was prescribed for the treatment of this latter tissue-volume.

QUANTEC Quantitative analysis of normal tissue effects in the clinic

A summary of the available DV-constraints of the organs at risk. These constraints are used to predict the risk of normal tissue injury in competing three-dimensional dose-distributions. This gives an understanding of the trade-off between an expected decrease in toxicity resulting from an improved dose-distribution.

RTOG Radiation Oncology Therapy Group

Siemens Primus linac

Siemens Healthcare GmbH, Erlangen, Germany. The linear accelerator used in this study.

TP treatment planning

The process in which the radiation oncologists, radiation therapist(s) and medical physicist(s) plan the proper external beam radiotherapy treatment technique for a patient with cancer.

TPS	treatment planning software (system) In forward planning (as in the case of 3D-CRT), the system by which a treatment planner simulates the choice and placement of beams onto a patient's DICOM-images to deliver enough radiation dose to a tumour. This while trying to spare the critical organs and minimise the dose to the surrounding, healthy tissue. The system then calculates the required monitor units needed per beam to deliver a prescribed dose to a specific area in the patient, depending on several beam-modifiers and the chosen calculation algorithm.
XiO	XiO® treatment planning software (version 4.80.03, 2014, Elekta AB, Stockholm, Sweden)

Abstract

The evaluation of a prostate three-dimensional conformal radiotherapy (3D-CRT) treatment plan is based on the aims of the specific treatment. An assessment of the plan is therefore performed to reach a certain class of plan-quality.

Several parameters are, however, available for such assessment. Without a standardised protocol, the assessment of a plan for the same tumour volume may therefore differ between treatment planners and take a considerable length of time to complete. To minimise not only the variation in the assessment of prostate 3D-CRT treatment plans, but also to shorten the time needed to do so, a reduced list of prioritised parameters needs to be used for plan-evaluation.

The aim of this study was to find the parameters with the highest covariance within a dataset of prostate 3D-CRT planning parameter-values obtained from several treatment plans. Thereafter the application of these parameters to improve prostate 3D-CRT treatment quality was verified.

To obtain the parameter-data, nineteen different dosimetrists each created a prostate 3D-CRT treatment plan for the target volume and boost volume of the same patient on nineteen XiO treatment planning systems. The data of four physical and eight dosimetric parameters, which are frequently referred to in clinical trials for prostate cancer radiotherapy, were extracted from the plans created.

The factor-loadings of each component of the covariance-matrix of the data were calculated using principal component analysis. Varimax-rotation was used to optimise each parameter's loading. The high loadings (>0,75) not only provided the variables with the highest contribution to variance within the parameter-dataset, but also gave their ranking (prioritisation) in this regard.

The highest contribution to covariance among the dosimetric parameters were shown by the minimum dose, heterogeneity-index, the mean dose and the V_{65} dose-volume constraint of the rectum. The number of beams, the number of opposing beams and the average field-size displayed the highest relation of variance among the physical parameters. These are the

limited list of parameters to be used for plan-evaluation, prioritised in terms of their contribution to treatment plan quality.

As a test for the application of these parameters, four treatment planners made use of these parameters to evaluate and improve twenty prostate 3D-CRT treatment plans which were randomly obtained from various planning sites. The twenty, altered treatment plans were evaluated using eleven dosimetric parameters frequently used in clinical trials.

The use of this list of parameters as an evaluation-protocol for prostate 3D-CRT treatment planning was investigated and verified. The application of these parameters showed that the list can be used as a protocol to evaluate and effectively improve the quality of prostate 3D-CRT treatment plans.

Keywords: Treatment planning, prostate, parameters, principal component analysis

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Conflicts of interest:

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Chapter 1: Introduction

1.1 Epidemiology

Prostate cancer has the highest occurrence rate for any cancer type in males, accounting for 20,2% of the total of new cancer diagnoses worldwide in 2008. In 2011, it accounted for 19,1% of all cancer incidences in South Africa.[1] Due to various social-economic reasons, sub-Saharan African men diagnosed with prostate cancer have demonstrated a high occurrence rate (39%) for a presentation of stage II prostate cancer.[2, 3]

1.2 Routine Variation in Treatment Planning

For radiotherapy treatment, the main aim (objective) is to deliver the prescribed dose to the planning tumour volume (PTV). An equal priority is to give as little dose as possible to the surrounding, normal tissue. This is especially important with regards to the dose to the applicable organs at risk (OARs).[4–7]

A robust treatment plan is essential to deliver a radiotherapy treatment which is of a high quality.[8, 9] A set of specified attributes which are required of the treatment plan will provide an indication to the acceptance of the plan before its clinical use.[10]

Without a verified protocol which enables the complete evaluation of a treatment plan's quality, the process of treatment plan evaluation, in effect, solely depends on so-called "common sense checks" [International Atomic Energy Agency, 2004, p. 220].[11] These checks may lead to an uncertainty in the completion of this process, which may lead to an ambiguous interpretation of the results obtained and, in the worst case scenario, to possible errors.[9, 12] In consequence, these uncertainties demonstrate itself as subtle differences in the quality of the treatment plan.[5, 10, 13] For this reason, the criteria are to be specified and prioritised.[10, 14]

1.3 Quality Assessment of Treatment Plans

Based on the process of treatment planning, a prioritised list can be compiled from both the physical and the dosimetric parameters of the treatment plan.[7, 15]

The physical attributes of a radiotherapy modality serve in the set-up of a treatment plan. Within the treatment planning software (TPS) program, the plan's physical-attributes are set up as the machine-parameters (e.g., the field-size). This set-up is to be used for the delivery of the treatment given as a dose-distribution.[11]

In a dose-volume (DV-) based treatment planning system, such as the XiO (Elekta AB, Stockholm, Sweden), the process of plan-evaluation is based on the characteristics of the dose-volume histogram (DVH).[7] Based on the simulated dose-distribution, a direct correlation to the probable, radiobiological outcome of the tumour and the OARs can be given.[7, 15, 16]

Both the qualitative and quantitative objectives of the treatment must therefore simultaneously be regarded, without the creation of a set of equivocal results.[5]

1.4 The Metrics of Treatment Plan Assessment

The objectives of the radiotherapy treatment serve as the criteria by which the quality of treatment plan are presented, the trade-offs which are embedded in its aims.[5, 17, 18] However, due to its trade-offs, no further clinical benefit can be gained in a treatment plan without the sacrifice of another goal.[14, 19, 20] An optimization-loop for plan-evaluation is thus created.[11]

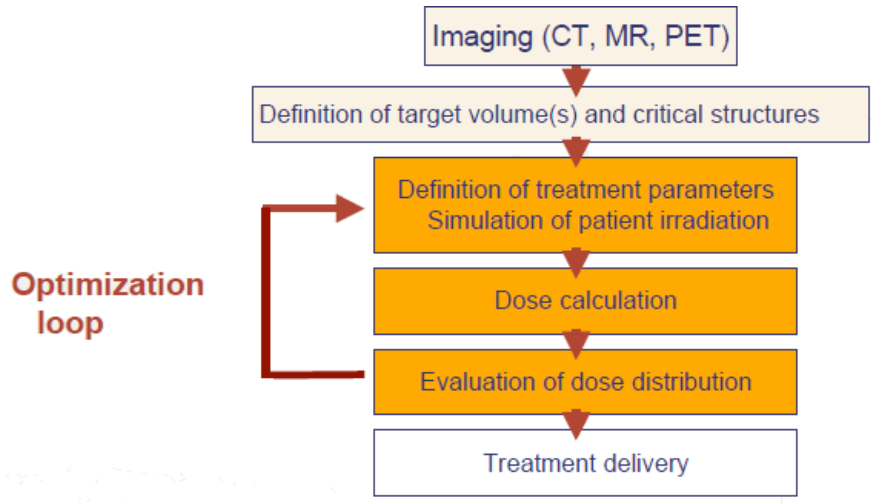

Figure 1: Optimization-loop in treatment planning.[11]

To overcome this overlap, a process of trial and error may be used. An alternative is the use of complex optimization-algorithms.

Any optimization-process requires the identification of a metric - a measure of the prognostic features of the treatment plan.[21, 22] To meet a specific requirement or to be within some tolerance-level, a variation from the quality indicators also needs to be included in the process of optimization.[14] Either way, a number of steps is required for such an optimisation to be performed.[11, 20]

In terms of the multi-objective criteria required for treatment planning, little time can be given for regard to the trade-offs between both the dosimetric and physical criteria of a treatment plan.[4, 14, 20] Any treatment plan thus has a best point of reaching its objectives, after which the plan-quality degrades with an increasing number of alterations performed (see Figure 2 below). There is, however, no guarantee that this end-result is *per se* the best plan.[21]

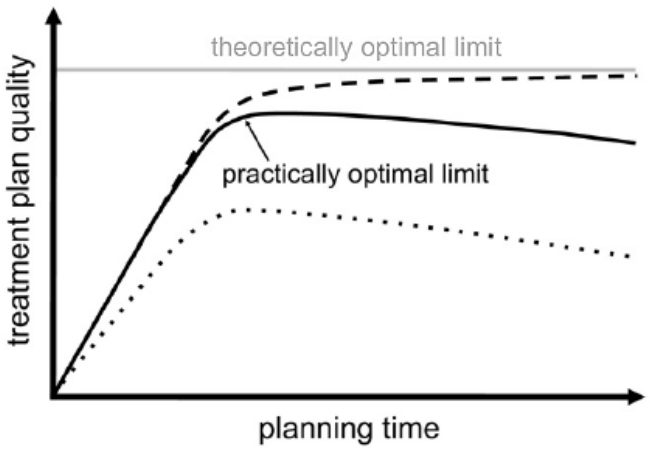

Figure 2: A graph depicting the point of the optimal plan-quality versus practicality (planning-time) during treatment planning.[14]

The optimization-process inherent to treatment planning must therefore aim to distinctly reach a certain class of treatment plan quality and to reduce the inherent process-variations (the so-called “waste”) of the system in as short period time as possible.[4, 10, 18, 22] A shorter process of treatment plan evaluation involving fewer steps is thus needed to reach this optimal limit. A clearly defined, but minimal and prioritised, list of plan-evaluation parameters is therefore required to shorten the process of plan-evaluation.[14, 18, 21]

1.5 Indicators of Treatment Plan Quality

The choice of the evaluation-parameters to be used is based on the following criteria to be met, as given in priority:

- The parameters and its use in evaluating treatment plans should have previously been applied in clinical trials and other studies.[8, 17, 23]
- The parameters must be easily obtainable from the TPS in use.[15, 17]
- The list of parameters should be as short as possible to define the criteria needed to show the quality of the treatment plan.[24, 25]
- A means to obtain the prioritisation of such a list must be acquired. This is usually performed by statistical analysis.[25, 26]

One of the techniques most often used to indicate the prioritisation of the variables within a matrix is principal component analysis (PCA). However, a dataset first needs to be evaluated to indicate whether it is suitable for PCA to be performed.[26, 27]

1.6 Tests Needed Prior to Principal Component Analysis

Six statistical tests can be performed to determine if a dataset is suitable for PCA. These include the test for correlation and covariance, frequency, Spearman-rank correlation, the Bartlett's test of sphericity and the Kaiser-Meyer-Olkin (KMO) sample adequacy test. The latter two tests are especially important for factor-analysis.[26]

If the dataset is confirmed to be suitable to PCA, the extraction of the principal components (also referred to as factors) from this data may commence.[26, 27]

1.7 Principal Component Analysis

The central idea of PCA is to reduce the dimensionality of the data in which a lot of variables are interrelated, while keeping as much as possible of the variance which is present in the original dataset.[27, 28]

The procedure of PCA may be summarized as follows[26–29]:

The variance explained by each principal component is indicated by the eigenvalues of the covariance-matrix of the dataset. By transforming this new set of components, the first few components retain most of the overall variance of the dataset. The user can choose the number of components which sufficiently express the relation of variance between the components. The eigenvector with the highest eigenvalue is then the principal component of the dataset.

The loading of each of the variables within a component indicates the contribution of the individual variable to the component's relation of variance within the dataset. To optimize the loadings of these variables within the principal component, a rotation of these components can be performed. This matrix-rotation, however, depends on whether the components are uncorrelated (orthogonal) to each other or not.

After rotation and the subsequent optimisation, the variables with a very high loading in each component can then be used to demonstrate the overall variance in the dataset.

1.8 The Aim of this Study

From the variation inherent to the creation of treatment plans, this study aims to identify and present the parameters which contributes the most to the variation in the quality of treatment planning for prostate 3D-CRT. These parameters are given as a reduced list of prioritised parameters for the evaluation of prostate 3D-CRT treatment plans. As a final product, the application of this short and prioritised list further aims to improve the quality of prostate 3D-CRT treatment planning to the required clinical, prognostic outcome to be achieved.

1.9 How the Aim was Addressed

The Digital Imaging and Communications in Medicine (DICOM) images of a single, anonymous patient with prostate cancer were sent to nineteen XiO treatment planning systems. The images included the organ-contours and the PTV. Based on the images, nineteen different treatment planners were asked to each create a "best" prostate 3D-CRT treatment plan for

this patient. Afterwards, the data of several evaluation-parameters was extracted from each of these plans.[30]

From principal component analysis and Varimax-rotation, a minimal and prioritised list of parameters for the evaluation of prostate 3D-CRT treatment plans was determined.[27]

Upon request to several treatment planning sites, twenty previously used prostate 3D-CRT treatment plans were randomly obtained. All the personal details in the plans were removed before receipt. The plans were evaluated using only the minimal list of dosimetric parameters. If any of these dosimetric parameters' criteria was not met, only the short list of physical parameters was used to alter the treatment plan to meet the given dosimetric criteria. Eleven dosimetric parameters were then used to evaluate the clinical outcome of these plans and the application of the limited list of prioritised parameters.

Chapter 2: Review of the Literature

2.1 Introduction

Without a protocol for the assessment of radiotherapy treatment planning, several treatment planners will create several different *best* treatment plans for a single patient.[21, 30] To avoid this ambiguity in prostate 3D-CRT treatment plan evaluation, the parameters contributing the most to treatment plan quality thus needs to be calculated and given as a prioritised list for plan-evaluation.[12, 14, 17] The limited list of dosimetric parameters can then be used to evaluate and the limited list of physical parameters can be used to improve the quality of the plans.[8]

2.2 Treatment Plan Set-Up

2.2.1 Radiation Techniques

From the conventional dose of 64-70 Gy given in a fraction size of 1,8 to 2,0 Gy each, a moderate dose escalation of 74 to 78 Gy for low risk (T1-T2a, Gleason score 2-6 and PSA <10 ng/ml) prostate patients, and a dose-escalation of 70-79 Gy for intermediate (T2b-T2c, Gleason score 7 or PSA 10-20 ng/ml) prostate patients, is justified.[31] A total dose of 74 Gy in fractions of 2 Gy each using 3D-CRT is thus acceptable and achievable to provide the prognostic clinical outcome as required for prostate cancer.[32, 33]

As with all the other OARs, the entire rectum needs to be segmented and contoured in all the relevant slices, with pre-defined margins for the clinical tumour volume (CTV). A 4-10 mm margin of peri-prostatic tissue in all directions is recommended to account for microscopic extension, except towards the rectal wall.[34, 35] Should infiltration be suspected, the involved (sentinel) lymph-nodes should also be delineated.[31, 36] Errors in the delineation can be prevented by the inspection of the expected globular form and the recognition of the anatomic structures on magnetic resonance images (MRI).[37–39]

Despite contouring-guidelines, several studies have indicated the inter-observer variation in the margins created for a tumour volume.[9, 36, 40]

Prostate cancer patients are usually treated in the supine position.[31, 41] Many departments make use of the filling and voiding of the bladder and/or bowels prior to treatment, as well

as a knee-rest or other types of immobilization-devices for patient-fixation.[42, 43] A difference in the calculated dose to the bladder and surrounding tissue is observed when the bladder is filled with a contrast-liquid during CT-imaging.[44]

2.2.2 Modification of the Dose-Distribution

Regardless of the stability of the organs with or without fixation, the choice of the number of fields (beams) have a direct impact on the conformity of the dose to the PTV and the dose to the OARs.[45, 46]

While sparing the rectum greatly, the three-field setup provides a considerable increase of the dose to the femoral head-neck regions, while the four-field box-technique (two anterior-inferior-oblique fields and parallel-opposed lateral fields) improves the dose-conformity to the PTV.[47] Less advantage in the dose to the OARs is observed with the box-shape set-up in comparison to the set-up of anterior oblique and lateral fields.[48] An increase in rectal-sparing is achieved when boosted with a six- or seven-field set-up.[9, 49] A more adequate sparing of the critical structures can be obtained with five non-opposing beams than compared to a four-field beam-arrangement.[35, 50] Less dose to the femoral head-neck regions and the rectum is observed with a six-field than with the five-field setup.[47] Both the five- and the six-field arrangement is thus a viable option for use for prostate 3D-CRT. A setup of more than six fields is not recommended for prostate 3D-CRT. With the use of so many beams, more dose is given to the rectum.[51]

Due to treatment techniques becoming more conformed to the PTV with the use of multi-leave collimators (MLCs), the use of wedges is phasing out in the current trend of radiotherapy.[35]

The prescription and/or normalization point of the treatment plan is mostly to the isocentre, which is many times the centre of the PTV in the case of prostate 3D-CRT.[52, 53] Beam-weighting is based on how much each beam must contribute to the target-dose, or on how much dose is incident on the patient.[54]

2.3 Assessment of the Dose-Distribution

2.3.1 The Dose-Volume Histogram

One of the main requirements for reaching a specified clinical, prognostic outcome from radiotherapy treatment is to provide enough dose to the PTV.[31] The International Commission on Radiation Units and Measurements (ICRU) provide the recommendations in this regard.[57, 58, 60] However, the minimum dose-limit given is difficult to achieve in 3D-CRT plans with regard to the dose-conformity to the PTV and the avoidance of the dose given to the surrounding OARs.[37, 56] Compared to this coverage, the mean dose in the PTV is a good representation of the dose to its centre.[53, 54]

The dose-conformation to the PTV has been quantified by various conformity-indices, and the conformity-index (CI) and homogeneity-index (HI) have found wide acceptance in the literature.[15, 46, 55, 57] The CI is given as the ratio of the prescribed isodose volume and the total volume receiving the prescription dose.[58] In the XiO TPS (henceforth referred to as the "XiO") and adjoining Elekta Focal contouring workstation (version 4.80.03) the HI used is given as the ratio of the highest dose received by 5% to the lowest dose received by 95% of the PTV.

The DVH, however, conveys no sense of distance between the iso-surface and the anatomical volumes and very little quantitative volume information about the dose-distribution.[15] A current trend to indicate treatment plan quality is therefore to move away from the use of only the DVH, which is mainly attributed to its inherent inaccuracies and which is propagated into its derivatives (e.g., indices).[7]

An improved conformity and homogeneity of the dose-distribution for prostate treatment can be achieved by radiobiological-optimization. In some treatment planning systems, biological parameters have thus also become incorporated into the indexing of treatment plan quality.[7]

2.3.2 Radiobiological Indicators

Two plans with the same value of equivalent uniform dose (EUD) are assumed to be equivalent. Their biological-effect on the tumour (clonogenic cell survival) will be the same as the one of a homogeneous, absorbed dose.[7]

The relative probabilities of the adverse events of the irradiated tissue do not, however, decide the rankings of plans. The rankings depend on the absolute levels of risk given by the normal tissue complication probability and tumour control probability.[7]

Compared to the biological-optimization by means of the EUD, the main biological indicators used to indicate plan quality on many treatment planning systems are the DV-constraints for OARs.[23] These constraints are much more clearly defined in the optimization-models used in planning.[7, 15]

2.3.3 Dose-Volume Constraints

The outcome of a treatment plan is displayed as a surrogate for the biological outcome of its dose-distribution.[7] An assumption of the DV-constraints is that no tissue-complications will occur if the volume above the tolerance-dose is smaller than the critical volume.[7]

Distinctively different risks are therefore involved with the use of more than one DV-constraint, while a single DV-constraint for an anatomic structure therefore do not create the overall best solution. The use of the QUANTEC DV-constraints as an indication of the risk of radiation-induced complications of the applicable OARs should thus be incorporated into the evaluation of a treatment plan.[7, 23, 59]

Since it is the OAR which usually receives the highest dose in prostate radiotherapy, the dose to the rectum (rectal wall) must be included in the optimization of prostate treatment plans. The V_{50}, V_{60}, V_{65}, V_{70} and V_{75} DV-constraints of the rectum can be used as the guidelines for dose-tolerance, while rectal-complication correlate strongly with the V_{65}, rapidly rising with a dose of >70 Gy given to the rectal wall.[60–63]

The DV-constraints for grade 3+ late complications of the bladder are given by the respective V_{65}, V_{70}, V_{75} and V_{80}.[64]

The DV-constraint for the femoral head-neck regions for a schedule of 2 Gy/fraction is given as 5% of the volume which may not receive more than 60 Gy.[65]

2.4 Statistical Analysis of Treatment Plan Data

The choice as to which statistical technique should be used to obtain a prioritised list of plan-evaluation parameters requires an inference of the problem to be solved.[25] Such a generalized conclusion can be deduced from the combination of instances occurring within the dataset. Inadvertently, these variables should draw a conclusion of the quality of the treatment plan.[66]

2.4.1 Prioritization of the Variables in a Dataset

A list of values for each planning-parameter obtained from several treatment plans creates the matrix of data to be analysed for plan-evaluation.[26, 27] A covariance of these parameters in terms of plan-quality can thus be given based on the variation of the values of a parameter from several treatment plans.[20, 66]

From this matrix of parameter-data, the correlation-matrix, **R**, can be obtained if the characteristics of the sample matrix, **R'**, is required (see Figure 3, p. 25). From the correlation-matrix, the eigenvectors and eigenvalues can be calculated. The eigenvalue of each dimension is then, in combination, the components of the vector-matrix. The components with the highest values (eigenvectors) are resultantly the principal contributors to covariance within the vector-matrix, thus the principal components of the respective dataset.[27]

2.4.2 Prioritization of the Parameter-Data

The sampling-method of deducing a difference with regards to the rest of the population creates the grounds for the evaluation of the variation among the different samples. It is also a means to show the robustness of the sampling-method itself.[27]

An optimization-process strives toward reaching the aims or requirements of a specified project or ideal.[17, 19] In treatment planning, the variables (parameters) can be ranked in an

order of importance with regards to the prioritization of these treatment-goals.[15, 67] Such ranking minimises the possibility for ambiguity in the process treatment plan evaluation.[25]

2.4.3 Tests Preceding Principal Component Analysis

A schematic presentation of PCA is given in Figure 3:

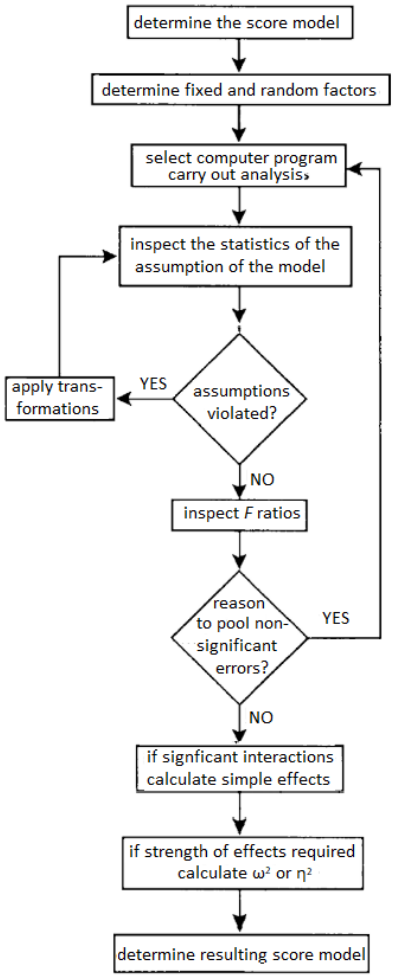

Figure 3: A diagram of the procedure of factor-analysis, including principal component analysis.[68]

Herewith a brief description of each of the six statistical tests required to determine if a dataset is suitable to PCA[26]:

Both the covariance and the correlation of the variables show purely the linear relationship between any of the parameter-datasets given in the horizontal- and the vertical-axis of the matrix. As a scalar, the sign shows the direction of the linear relationship. A strong linear relationship is given in the range of values of ≥0,7 or ≤-0,7.

The covariance of X and Y is the difference between the mean product and the product of the means. If the covariance between two variables is ≥1, then it indicates a very high linear dependency. Should multiple variables indicate a high number of covariance, then the dataset is prone to a high covariation, thus a linear-dependence between all the variables. Regression will then be better suited to indicate the relation between the variables within the dataset.

Correlation is a measure of the strength of the linear relationship between two variables. Independent random variables are uncorrelated, but uncorrelated random variables are not necessarily independent and may be strongly, non-linearly related. The only real assumption is the presence of relation between the variables as represented by the correlation-coefficient. If there are no correlations, then there is no underlying structure.

The frequency-graph, also known as a density-distribution histogram, presents how many of the data-points of a certain parameter which are normalised to a certain value (known as a bin) can be found in a dataset. The can be chosen arbitrarily, based on the population of the dataset. The mean contribution of a parameter to treatment plan quality is best shown if a large part of all the plans' data for that specific parameter falls within the specific criterion. Such a tendency shows little variation within the respective parameter.[25]

The null-hypothesis states that there is no significant difference between the specified populations of data. The Spearman-rank correlation is used to confirm the null-hypothesis between the variables in a dataset and to show the strength and direction of the relationship between any two variables. A high rho-value therefore does not show a strong correlation between the two variables' datasets, but how strong the tendency is for it to be linearly dependent. The lower the rho-value, the less the relation between the data of the two variables. If only single parameters in a semi-ordinal dataset (indicated by the frequency of the data) indicate a linear-relation, then the dataset can be used for PCA.[25, 27, 46]

The Bartlett's test of sphericity compares the observed correlation-matrix to the identity-matrix and shows the overall significance of all correlations within a correlation-matrix. This

comparison is used to show very strong evidence against the null-hypothesis, which shows the redundancy between the variables. This is especially important to PCA, as it is an indication of how many of the principal components contribute substantial amounts of variation. A very low ρ-value therefore shows a dataset with unrelated variables.[26, 27]

The Kaiser-Meyer-Olkin (KMO) test is a more definite measure of the suitability of a dataset to factor-analysis, including PCA. The test compares the size of the observed correlation-coefficients in relation to the magnitudes of the partial correlation-coefficients. This gives the measure of sampling-adequacy. To be able to perform factor-analysis on a dataset, the number of cases should be at least five times the number of variables. A sample is adequate for factor-analysis if the sum-value of the KMO-test is >0,5.[26] However, stronger datasets have been shown to require a smaller sampling-size for adequate accuracy.[26, 27]

2.4.4 Principal Component Analysis

Herewith a short description of the process of PCA and Varimax-rotation.[26, 27, 69]

a) Obtaining the Eigenvalues

The mean is subtracted from each of the data-dimensions of the dataset, providing the average across each dimension. This produces a dataset whose mean is zero.

The covariance is given by

$$cov = \frac{\sum_{i=1}^{n}(X_i - \bar{X})(Y - \bar{Y})}{(n-1)}, \qquad \text{Equation 1}$$

where $\bar{X}$ is the mean of the set and *n* is the order of how many numbers there are in the respective dataset.

Putting this variance into a matrix, Equation 1 is given by

$$C^{n\times n} = \left(c_{ij}, c_{ij} = cov\left(Dim_i, Dim_j\right)\right), \quad \text{Equation 2}$$

where $C^{n\times n}$ is a matric with *n* rows and *n* columns and Dim_x is the x^{th}-dimension.

Using the Caley-Hamilton theorem[27], the matrix *A* of order *n* is given by

$$AC = \lambda C, \quad \text{Equation 3}$$

where λ is an eigenvalue only if there exists a non-zero vector, *C*. Equation 3 then gives

$$(A - \lambda I_n)C = 0, \quad \text{Equation 4}$$

with I_n the identity-matrix with *n* dimensions.

The latter equation has a solution only if the matrix-coefficient is invertible. Since the zero-vector is a solution and *C* is not zero, the characteristic equation is given by

$$det(A - \lambda I_n) = 0, \quad \text{Equation 5}$$

which will provide the eigenvalues of *A* based on the identity-matrix and λ.[27]

To summarise Equation 1 to Equation 5, first the covariance-matrix and then the eigenvectors and eigenvalues of the covariance-matrix are calculated. The eigenvalues (principal components of the dataset) are then ordered in order of significance, thus highest to lowest. Small eigenvalues show a low contribution to the covariance within the dataset. Should some of the eigenvalues be very small, they may be ignored. This reduction makes the matrix of data to consider smaller, which makes the covariance between the variables easier to obtain.

Once the components to be kept are chosen, the original dataset can be obtained in terms of these components. Deriving the new dataset is obtained by taking the transpose of the vector (matrix) and multiplying it on the left of the original dataset, transposed. The data is therefore transformed so that it is expressed in terms of the patterns between these values.

The components are now classified as a combination of the contributions from each line (pattern) of data in terms of the differences and similarities between the variables. The covariance in all the variables accounted for by each factor are the sum of the squared factor-loadings for that factor (column), divided by the number of variables.

It is one of the key advantages of the use of PCA: If the original matrix of eigenvalues and eigenvectors had *n* dimensions and only *p* eigenvectors were selected, the dataset now has fewer dimensions.[26, 27] The factor-loadings are the correlation between the original variables and the components and the key to understanding the underlying nature of a component.[28, 32, 33] These patterns describe the relationships between the data, thus the co-dependency between the variables. The characterization of the data which the eigenvectors perform is of importance for PCA.[26]

b) The Principal Components to Retain

The criteria for choosing the number of principal components to keep is as follows:

- The cumulative percentage of total variation which is chosen, e.g., a cut-off of 70%. This is preferred when one or two components are dominant and can decrease should the sample size increase.[27]
- Historically, an eigenvalue should only be kept if it has a loading greater than one (>1), known as Kaiser's rule.[27] Recently, however, it's been advised to use a cut-off lower than one to allow for sampling-variation. These latter two criteria are therefore subjective in their choice.[26]
- Thirdly, the scree-graph has steep plotted points to the left, which becomes less steep to the righthand-side of the graph. The "elbow" in the graph is taken to be the number of components to be retained. Two or more straight lines formed by the lower eigenvalues define a cut-off at the upper, left-side of the graph.[26, 70]

c) Optimization by Varimax-Rotation

Since the principal components' relation to variance are the sum of the loadings of the variables within them, each variable can be related to the rest of the variables in the sub-space. The difference between these variables can thus be optimised by a sheer turn (rotation) of the matrix by an angle (see Figure 4 below). The sum of the variances of the squared loadings are then maximised within each column. Effectively, the difference between the loadings of the variables within these components are then also maximised (optimised). This while the sum of the variables' loadings within each component will remain the same.

One requirement for matrix-rotation to be performed is to indicate whether the components are orthogonal or oblique to each other. Thus, if the components are correlated or not.[28]

Oblique-rotation is far less common than orthogonal-rotation.[69] In the component-space, oblique-rotations (known as factor-rotations) can take any position, with a general small degree of correlation among the components.[29]

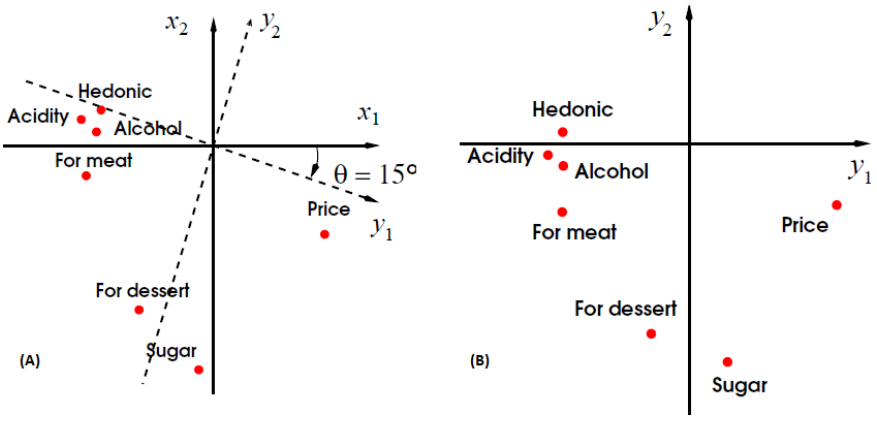

Figure 4: Varimax-rotation of the two principal components (dimensions) of a dataset with seven variables (given by the red dots). (A) Original loadings of the example of variables, with the angle of rotation shown. (B) New loadings of the variables after matrix-rotation was performed.[29]

The Varimax rotation-method may be used for orthogonal rotation, should a simple structure be clear. Assuming uncorrelated components, the five criteria presented by Thurstone for matrix-rotation identifies a simple structure.[28] It states that at least one zero-loading on some

component should be produced on every variable and as many zero-loadings as principal components should be on each component. Each pair of components should have variables with significant loadings on one component and zero-loadings on the other. It should also have a large proportion of zero-loadings on the components, as well as only a few complex variables. Should these criteria be met, a rotation of the component-matrix may be performed.

Varimax-rotation gives a simple solution if each component has a small number of loadings and the other variables have near-zero loadings close to the zero-axis (see Figure 4, p. 30).[29]

The maximum variance of the loadings is obtained by rotation, as is given by

$$V = \sum\left(q_{j,l}^{2} - q_{j,l}^{-2}\right)^{2}, \qquad \text{Equation 6}$$

where $q^2_{j,l}$ is the squared loading of the j^{th} variable on the l^{th} component and $q^{-2}_{j,l}$ the mean of the squared loadings.[29]

By rotation, the contribution of the principal components to the relation of variance and the difference in the loading between these latter variables and the rest of the variables have been increased. The variables with a high loading within these latter components have therefore all been increased. Of importance is that, by maximizing the difference between the loading of the variables, it is thus, effectively, an optimization-process for the principal components. The dimensions of the main components linked to certain variables now appear more clearly than the other components of the matrix, and the prioritisation of the variables is therefore more clearly defined.[29]

After rotation, only the variables with a high loading on one component needs to be considered. Depending on the sample size and the number of variables used, a significantly large loading may be considered as >0,40, although a much higher cut-off may be used for more discreet and smaller datasets obtained from a small number of samples.[27] Each component that is retained needs to have at least three variables with a significant loading. Variables that load on a component should all share a mutual concept, while these variables should also measure different constructs within the dataset.[29]

Once matrix-rotation has been performed on the principal components and the variables with the highest loading (priority) have been identified, then the rest of the variables' contribution to variance within the dataset may be ignored. A reduced list of variables, which are prioritised according to their loadings, is then obtained.

d) Software Used for Principal Component Analysis and Varimax-Rotation

The SAS software (version 12.3) can be used to calculate the principal component of the parameters obtained from the PTV1 and PTV2 treatment plans. The Real Statistics Resource Pack add-on software (Release 3.8, Copyright 2013 – 2015, Charles Zaiontz, www.real-statistics.com) can also be used in Microsoft Excel to perform these calculations.

2.5 Summary of the Literature

Based on clinical trials, a 3D-CRT prostate treatment plan can be modified with the use of several physical parameters and the resulting dose-distribution evaluated using several dosimetric parameters.[8, 9, 20, 46] To avoid a possible ambiguity in their use, a minimal list of prioritised parameters is thus needed to perform treatment plan evaluation.[14, 18, 21]

The data of these parameters can be obtained from several treatment plans created for a single patient. Statistical analysis can be used to indicate the variables with the highest contribution to covariance within a dataset.[25] After verifying whether a dataset is suitable for PCA, the principal components of a matrix of data can be calculated by PCA.[26–28] Varimax-rotation can be used to optimize the loadings of the variables.[29] A minimal list of variables prioritised according to their contribution to the covariance within the data-matrix can thus be obtained.

Chapter 3: Methods and Materials

3.1 Introduction

The process which was followed to obtain the limited list of prioritised parameters is given in Figure 5.

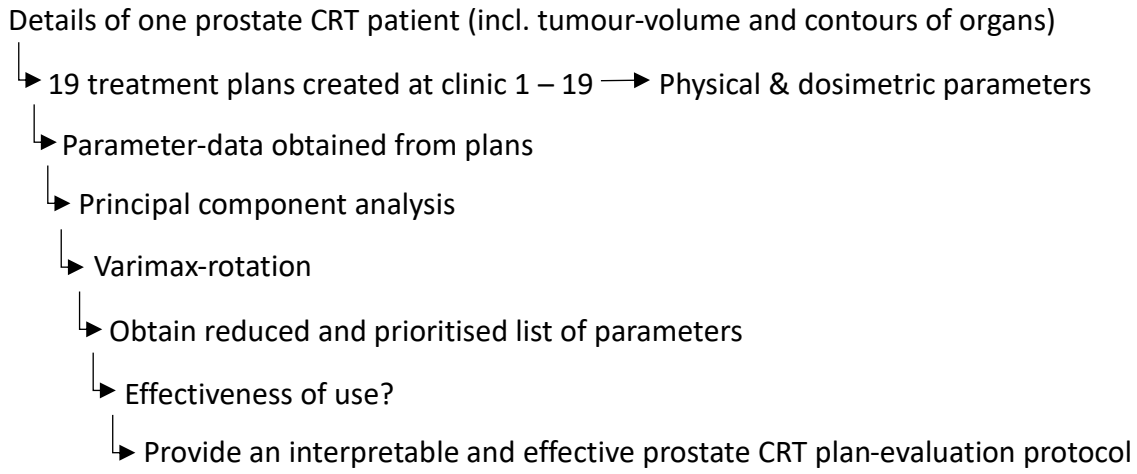

Figure 5: Schematic outlay of methods, procedures and materials used in this study, as performed chronologically.

3.2 Obtaining a Prostate Patient

The *Training Clinic* of the XiO treatment planning software contained the CT DICOM-images of an anonymous *FusionProstate* patient (henceforth referred to as the "prostate patient"). These images displayed the patient's anatomy from the L4-vertebrate of the spinal column to the ischium-section of the pelvis. The contours of the critical organs and the delineation of CTV were also indicated, including the prostate and the proximal seminal vesicles, but not the lymph nodes (see Figure 7, p. 41).[9, 38, 63]

Based solely on this spread of cancer cells, the patient demonstrated a stage T2b or T2c prostate cancer, as is representative of the South African population of men with prostate cancer.[2, 3]

To provide a sufficient scatter of the dose during calculation by the dose-algorithm, an anatomical region of CT-slices of >10 cm was included both superior and inferior to the prostate.[71]

The fused MRI-images confirmed the volume of the CTV and the soft, critical organs.[38]

3.2.1 Delineation of the Treatment Volume

The delineation of the CTV was respected. A margin of 7 mm was added to the CTV to create the PTV. As the OAR receiving the highest dose in prostate 3D-CRT, only a 3 mm margin was added to the CTV in the direction of the rectal-wall, which also accounted for rectal-motion.[43, 45, 50,]

For the treatment plan of the smaller boost-volume, the 7 mm margin was removed from the PTV to allow for possible tumour-shrinkage during irradiation.

The treatment planners were not allowed to alter these volumes, thereby minimising the possibility of user-to-user variation in the contouring of the organs and the delineation of the tumour volume.[9, 36, 40]

3.2.2 Contouring of the Organs at Risk (OARs)

The definite slice-thickness of the DICOM-images created a visible deviation between the contour and the volume of an organ (e.g., air-gaps on the “skin” surface). A minor smoothing of the patient’s outline, bladder, femoral head-neck regions, seminal vesicles, small-bowel and rectum was performed as per the Radiation Therapy Oncology Group (RTOG) contouring-guidelines.[36, 38]

Since the contouring of only the rectal-wall is seldom performed in clinical practice, the full rectum was contoured from the recto-sigmoid junction to the anus.[38, 41]

The bladder was delineated as the outer wall from its dome to the crest, with a section of the PTV covering the base- (inferior) region of the bladder-volume.[38, 41] An unknown contrast-liquid was observed in the bladder of the prostate patient. Since the bladder is usually filled

with urine during treatment, the electron-density of the unknown bladder contents was forced to one (1,00).[44]

The femoral head-neck regions (bilateral femora) were contoured as the top of the hip-joint to the smaller trochanter, with the right femoral head-neck situated slightly closer to the PTV.[9]

No other alterations and/or adjustments were made to the original contouring. Since a CTV is delineated by a radiation oncologist, no smoothing was performed on the edges of this volume.[38]

After the verification of the smoothness of the organ-contours was performed, the MRI-images of the prostate patient were removed from the patient's image-set.

3.2.3 The Prescribed Radiation Dose

The main tumour volume ("PTV1") was to receive a prescribed dose of twenty-seven fractions, given in a fraction size of 2 Gy each. The smaller, boost-volume ("PTV2") was to receive a dose of ten fractions of 2 Gy each. The base-plan of 54 Gy and the boost-plan of 20 Gy thus provided a total dose of 74 Gy to be given to the tumour volume.[9, 32]

3.3 The Export of the Applicable Clinic and Beam Files to Other XiO Treatment Planning Systems

The XiO treatment planning system of Clinic1 (referred to as "XiO-1") was used with eighteen other XiO treatment planning systems (referred to as "XiO-2-19") from various other planning sites. The DICOM-images holding the delineation of the PTV and the contours of the organ-volumes of the prostate patient were transferred from the XiO-1 to the XiO-2-19.

3.4 Treatment Planning Guidelines

At each of the nineteen XiO treatment planning systems used, an individual treatment planner was asked to create a single treatment plan for the treatment of the PTV1 (a base-plan). A second plan was also to be created for the treatment of the PTV2 (a boost-plan).

Three-dimensional conformal radiotherapy treatment was to be performed using a Siemens Primus linear accelerator. Each of the nineteen treatment planners who took part in this study was requested to provide the best base- and boost-plans (see the guidelines given in the Appendix, p. 98).

3.4.1 Treatment Planning

In the treatment plans received, the delineation of the PTV1 and PTV2 and the contouring of the organ-volumes of each plan were evaluated for any alterations made to it by the treatment planner.[40] If altered, the treatment planner was to recreate a plan on the DICOM-images initially sent to the applicable XiO.

Once all the treatment plans were completed and the volumes inspected for changes, the values of the parameters of the treatment plans were retrieved.

3.5 Treatment Planning Parameters Used in this Study

Several parameters for the evaluation of prostate treatment plans are frequently referred to in the literature.[15] A combined summary of the parameters is given in Table 1.

Table 1: The full set of physical and dosimetric parameters initially considered for use in this study [see section 2.2.2 to section 2.3 (pp. 21-22) for a full description of each parameter].

Dosimetric parameters:	**Physical parameters:**
Heterogeneity-index	Number of beams
Conformity-index	Opposing beams
Maximum, minimum and mean dose to the PTV	Average field-size
Dose to 50%, 35%, 25%, 20% and 15% of the rectal volume.	Wedge
Dose to 5% of the volume of each femoral head-neck region.	Gantry-angle
Dose to 50%, 35%, 25% and 15% of the bladder volume	

Clinical trials regard as evaluation-parameters for prostate 3D-CRT, for instance, the DV-constraints of the rectum, bladder and femoral head-neck regions, as well as the maximum, minimum and mean dose to the PTV.[22, 27] Other studies made use of other indices to evaluate prostate 3D-CRT treatment plans.[46, 72] Studies also made use of the influence of the physical parameters on the dose-distribution and thus on treatment plan quality.[9, 46]

The sample size of treatment plans versus parameters indicated that the number of variables had to be lessened if a matrix of parameter-values from the nineteen plans were to be used for statistical analysis.[27] A scrutiny of the application of each of these parameters to prostate 3D-CRT plan-evaluation was performed based on the criteria given in section 2.3 (p. 22).

3.5.1 Obtaining the Parameters from the Treatment Plans

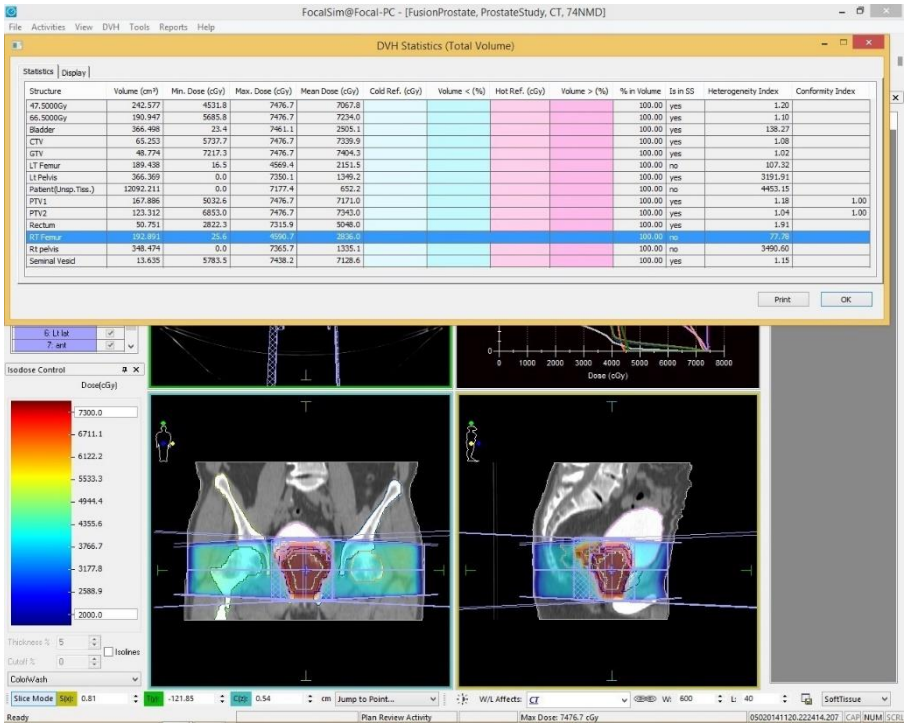

Figure 6: Obtaining the dose- volume of an OAR from the *DVH Statistics* window on the Focal contouring-system.

The *DVH statistics* window of the XiO and Focal is a summary of the DVH. This table shows the planned dose to the contoured organs and the delineated tumour volumes in a treatment plan.[7] The values of the dosimetric parameters were obtained from this table for each plan.

3.5.2 Dosimetric (Biological) Parameters

To determine the possible clinical outcome of a prostate 3D-CRT treatment plan, the following dosimetric parameters were regarded for use:

a) Heterogeneity- and Conformity-Index (abbrev., HI and CI)

The dose-conformity and dose-inhomogeneity in the PTV are to be regarded together for plan-evaluation. However, because of the physical limitations of 3D-CRT, it is difficult to achieve both of these criteria during treatment planning.[45, 46, 51, 52]

Both parameters are often referred to in the literature and are easy to obtain from both the XiO and the Focal. It was thus considered for statistical analysis.

b) Maximum, Minimum and Mean Dose (Abbrev., Max, Min and Mean)

The dose to be given to the PTV must be a maximum of <107% and a minimum of >95% of the prescribed dose.[52, 53] For 3D-CRT and fixed gantry-angles, the conforming of the dose as close as possible to the PTV during treatment planning is a tedious and challenging process, but can mostly be achieved in the pelvic-region.[46] For the mean dose to be given to the PTV, a deviation of >5% from the prescribed dose is unacceptable.[56]

The maximum, minimum and mean dose are straightforward criteria to be met by any 3D-CRT treatment plan. The values of these parameters are easy to obtain from both the XiO and the Focal and were to be used for statistical analysis.

c) Dose-Volume Constraints of the Organs at Risk

The DV-constraints for each OAR were taken as the dose to a percentage of the respective organ-volume[62, 64]

- The V_{65}, V_{70} and V_{75} and V_{80} DV-constraints were respected for the bladder, and the V_{50}, V_{60} and V_{65} for the rectum. Both organs' DV-constraints were obtained from the QUANTEC-data.[16, 62, 64]
- The V_{60} DV-constraint for the bilateral femora was respected, as given in the RTOG 0630 clinical trial.[59]

Regarding the number of samples (treatment plans) versus variables (parameters), the ten DV-constraints given in Table 1 (p. 36) were too many parameters to consider for factor-analysis.[26, 27] The number of parameters therefore had to be made fewer.

The following requirements were evaluated for each, individual DV-constraint:

- More than one DV-constraint of an OAR receiving a certain radiation dose typically correlates with the possibility of tissue-complication(s). If the literature indicates that specific organ-complications strongly correlate with a DV-constraint(s), then only this limit(s) was considered for further use for that OAR.[7, 59]
- Regarding the dose-conformity to the PTV, only a portion of the maximum allowed dose-limit of 79,2 Gy to the PTV was to be received by any OAR. Therefore, all the DV-constraints for a dose of >74 Gy were individually evaluated for further use based on the dose-volume values obtained from the nineteen plans.
- If the average value of a measured dose-volume of the nineteen treatment plans was found to be much less than the given DV-constraint, the specific constraint gave little or no reference to the quality of the plans.[59]

From the above tendencies for the use of DV-constraints in prostate 3D-CRT treatment planning, the following DV-constraints remained for use:

- A series of rectal-complications strongly correlate with the DV-constraint of V_{65}, while the V_{50} is most likely to be exceeded in prostate 3D-CRT.[60] For the dose to each femoral head-

neck region, only one DV-constraint applies and only the highest dose received by the right or the left femoral head-neck was considered.[65]

- Only a small section of the bladder was placed inside the PTV. The bladder was therefore to receive very little (<50 %) of the prescribed dose. No DV-constraint of the bladder was therefore applicable for use in prostate 3D-CRT treatment plan evaluation.

A sumplan is a combination of the treatment plans created for the treatment of the PTV1 (the base-plan) and the PTV2 (the boost-plan). The dose-volumes of each OAR were also obtained for each sumplan (see Table 6, p. 53).

3.5.3 Physical Parameters

A change in any physical parameter of a plan will lead to a change in its dose-distribution. Any other alteration to the dose-distribution is performed electronically (e.g., point of normalization).[54]

The following physical parameters were initially considered for use in this study:

a) Number of Beams (Abbrev. Beams)

Considering the treatment-time and the conformity of the dose to the PTV, as well as the physical limitations of the linac (e.g., collimator), the optimum set-up for a prostate 3D-CRT treatment plan is considered as five or six beams.[35, 50] Due to an increase in the dose to the rectum or bilateral femora, plans which did not contain opposing fields were considered as acceptable.[9, 51]

The number of beams to be used for the treatment of a certain target-site, such as the prostate, is often referred to in the literature. Its value is also easy to obtain from the XiO. This parameter was therefore considered for statistical analysis.

b) Opposing Fields (Abbrev., Opp.)

The use of opposing fields in treatment planning creates an increase in the integral dose in healthy tissue surrounding the prostate's walnut-shape (see Figure 7, p. 41).[9, 73] It is also a parameter which is easy to obtain from the gantry-angle of each beam and was therefore considered for statistical analysis.

c) Average Field-Size (Abbrev., Avg FS)

The set-up of the treatment fields to conform the dose as close as possible to the PTV is crucial. On the XiO TPS, the *Auto-conform* function gives an easy means to conform the collimation to the PTV, but it does not always produce an acceptable dose-distribution.

Figure 7: A prostate 3D-CRT treatment plan created for this study. The four-field box-type of beam set-up is displayed as used for the treatment of the prostate. The DVH is given in the bottom-right window.

The necessity of dose-conformity to the PTV is defined in the literature. The typical or average treatment field-size is given as a reference to the conformity of the dose to the tumour volume.[36, 40, 45] This parameter is easy to obtain from the *Source data* and was therefore considered for statistical analysis.

d) Wedge

The use of a certain beam-modifying device, such as the physical wedge, may eventually phase out or lose favour among treatment planners.[35] The applicability of a beam-altering device such as a wedge depends on whether most of the treatment plans for a certain target-site make use of it or not.[9]

This parameter is easy to obtain from the *Source data* and was considered for statistical analysis.

e) Gantry-Angle (Abbrev., Gantry)

It is difficult to interpret whether a beam's angle, in relation to the treatment couch, is compromising or contributing to a treatment plan's quality, especially in comparison to a more direct approach to indicate a probable dose-distribution, such as the number of beams or opposing beams.

Although easy to obtain from the *Source data*, the use of this parameter for prostate 3D-CRT planning was therefore not regarded for statistical analysis.

3.6 The Final Sets of Parameters to Be Used for Statistical Analysis

Based on the requirements given in sections 3.5.2 to 3.5.3 (pp. 38-40), eight dosimetric and four physical parameters were kept for use. The final set of parameters used is given in **Error! Not a valid bookmark self-reference.** (p. 43).

Table 2: The final set of dosimetric and physical parameters used in this study.

Dosimetric parameters:	**Physical parameters:**
Heterogeneity- index	Number of beams
Conformity-index	Opposing beams
Maximum dose	Field-size
Minimum dose	Wedge
Mean dose	
V_{50} and V_{65} DV-constraints of the rectum	
V_{60} of the femoral head-neck regions	

The parameter-data obtained from the sumplan of each respective base- and boost-plan is given in Table 6 (p. 53). However, the sumplan-data were not used for statistical analysis due to the following reasons:

- This study evaluates the variance per parameter within the respective dataset. The combination of two plans therefore doubles the size of the vector-subspace during PCA, and thus also the number of principal components. If both plans are simultaneously evaluated by PCA, the multiplication of the number of principal components removes the effectiveness of this statistical technique.
- Since each plan has its own prescription, the base-plan is first created and evaluated, and thereafter the boost-plan is created and evaluated. Evaluation is thus first performed per plan. To evaluate a prostate 3D-CRT sumplan containing two (or more) treatment volumes will remove the possibility of individually evaluating the dose to the PTV1 and the PTV2.
- Only the DV-constraints of the OARs can be evaluated in the sumplan-data.

3.7 Dose-verification with GafChromic Film Placed in An Anthropomorphic Phantom

From the nineteen prostate 3D-CRT treatment plan received, the plan which agreed the most to the criteria given in sections 3.5.2 and 3.5.3 (pp. 38-40) was selected. To measure the given dose-distribution given from this plan by Siemens eight different Primus linacs, a sheet of GafChromic EBT2 film was placed at each linac inside the pelvic-volume of an

anthropomorphic RANDO phantom (phantom number 434) and irradiated.[74, 75] Characterization of the reflection scanner (EPSON V370 Perfection Photo, Seiko Epson Corporation, Suwa, Nagano, Japan) for scanning and the box of 25 sheets of GafChromic EBT2 film (lot # 03181402) was performed and compared to the images obtained from using a EPSON V700 transmission.[76] The gamma-analysis was performed using the DoseLab software (Nathan Childress and U.T. M.D. Anderson Cancer Center, Houston, Tx, USA) in the MATLAB® Compiler Runtime 7.13 (version 4.11, MathWorks, Inc., Natick, Massachusetts, United States).[77] A 3%/3 mm criterion was used for comparison.[71]

3.8 Principal Component Analysis

As given in section 3.6 (p. 42), eight dosimetric and four physical parameters were considered for statistical analysis. The six statistical tests given in section 2.4.3 (p. 25) were used to confirm if each of the four parameter-datasets may be used in PCA. The Real Statistics Resource Pack add-on software (Release 3.8) were used in Microsoft Excel for this purpose.

PCA of the four datasets was performed by the Department of Biostatistics of the University of the Free State using the SAS software (version 12.3). To verify these results, PCA was also performed by using the Real Statistics Resource Pack add-on software.

3.8.1 Tests for the Applicability of the Parameter-Datasets to Principal Component Analysis

The six tests given in section 2.4.3 (p. 25) was used to indicate if any multi-collinearity exists in the data of the parameter-matrix obtained from the PTV1 and PTV2 plans. If the results of the tests indicated no collinearity, the principal components of each dataset were calculated.[25–28]

The covariance and correlation of each dataset were evaluated for the linear relationship between the respective parameters. Values for parameters (line to column) which are >1 show a high covariance.

In summary of the frequency of every parameter in every dataset of the base- and the boost-plans, only the number of sub-plans within the specified group (bin) were categorised as follows:

- Bins given with a prefix of ± show the number of plans with parameter-values within the specified range from the average value of the parameter.
- Bins abbreviated as *OL* show the number of plans with values outside of the limits of a given parameter.
- Bins given as a percentage represent the percentage deviation from the median number of the parameter.

The values of the Spearman-rank correlation between the parameters within a dataset were inspected for a more definite indication of any linear correlation between the parameters.

The size of the result of the Bartlett's test of sphericity was used to indicate the redundancy between the variables in a dataset.

The KMO sum-value of each dataset was used to indicate if the dataset is suitable for factor-analysis. If the sum-value was > 0,5, the test showed an adequate dataset for PCA.

3.8.2 Eigenvectors of the Covariance-Matrix

The covariance-matrix of each parameter-dataset was calculated using Equation 1 and Equation 2 (p. 28). The eigenvectors and eigenvalues of the matrix were then calculated using Equation 5 (p. 28).[26, 27]

3.8.3 Selecting the Number of Components to Retain

The eigenvectors were ranked according to their eigenvalues. Only the components with a significant contribution to the covariance within the dataset were then selected, from which a feature-vector was formed. The significance of the eigenvectors chosen was based on the requirements given in section 2.4.4 b) (p. 29).[26, 27]

3.8.4 Varimax-Rotation

For the Thurstone-criteria to be reached so that Varimax-rotation of each matrix could be performed, the factor-loadings of some of the variables had to be high on some components and the factor-loadings of some of the other variables had to be very low (≤0,1).[28]

The extracted values (factor-loadings) was then further transformed to optimise their contribution to covariance (see section 2.4.4 c), p. 30).[29]

The ratio of the dose prescribed to the PTV1 and the PTV2 is 2,7. To avoid a biased evaluation of the data from the two sub-plans due to ratio of their contribution to the total given dose (54 Gy versus 20 Gy), only the components and its factor-loadings obtained from the parameter data from the base-plans were included for further analysis.

Based on the size of the loadings, a reduced and prioritised list of dosimetric and of physical parameters was obtained. The parameters in each list were ranked in terms of their contribution to the covariance within the respective dataset.[27] The parameters with a high loading (>0,75) were extracted from the list of variables.

3.9 Validation of the Prioritised Parameter List for Its Use in Prostate Conformal Treatment Plan Evaluation

3.9.1 Set-Up of the Test for the Evaluation and Alteration of the Treatment Plans

As per the aim and objective of this study, the list of limited and prioritised parameters is to be used by treatment planners for the evaluation and, if necessary, the subsequent improvement of prostate 3D-CRT treatment plans. The use of the list of parameters therefore had to be validated as when it will clinically be applied.[9]

This section of the study was set to avoid a biased judgement in the use of a treatment plan, as well as to adhere to the ethical requirements and the Protection of Personal Information (PoPI) Act No. 4 of 2013. The treatment plans were therefore received without any detail of the XiO used, the name of the treatment planner who's created the plan, the patient's details and the name of the radiation oncologist responsible for the patient.[6, 12]

To test the suitability of deploying this limited set of parameters as a protocol for prostate 3D-CRT treatment plan evaluation, twenty anonymous prostate plans were randomly obtained.[6, 8] The plans were provided by several planning sites and from various XiO treatment planning systems. All twenty patients have previously been treated according to their respective plans and all the personal detail in the plans was removed before receipt. The variation in the prescribed dose of the plans confirmed that these were previously approved by several radiation oncologists.[31]

Four treatment planners evaluated each treatment plans' dose-distribution in the context of the heterogeneity across the PTV (given by the difference between the V_{60} and V_{65}), the minimum dose (95% of the prescribed dose) and the V_{65} DV-constraint of the rectum (list of parameters obtained as per section 2.4.4, p. 27). The level of the planners' experience in treatment planning for prostate 3D-CRT ranged from 2 to 8 years.[12]

Should the criteria of the treatment plan not meet the latter parameters' criteria, a next alteration of the treatment plan was to be performed by the planner.[15] Only the number of beams, the number of opposing beams and the average field-size were used as needed to improve the dosimetric outcome of the plans.

If a different number of beams was to be used than what the treatment plan previously contained, an alteration of each beam's angle of incidence was expected. Except for the latter three physical parameters, the other physical attributes of the beams in a plan were to be left intact as received.

3.9.2 Re-Evaluation of the Treatment Plans

A one-to-one comparison between the twenty original plans and the respective, altered plans was performed with the use of eleven dosimetric parameters often used in prostate plan-evaluation. This list of parameters was compiled from the eight parameters given in Based on the requirements given in sections 3.5.2 to 3.5.3 (pp. 38-40), eight dosimetric and four physical parameters were kept for use. The final set of parameters used is given in **Error! Not a valid bookmark self-reference.** (p. 43).

Table 2 (p. 43) and several prostate radiotherapy clinical trials.[8, 17, 23] As per section 1.5 (p. 17), a requirement set on each of these parameters was that its value was to be directly obtainable from the DV-based TPS and frequently used in clinical practice, including clinical trials.[6, 9, 46]

The ICRU recommendations for the assessment of the dose to the PTV were used.[52, 53] As per the literature, the DV-constraints of to the rectum were limited to the V_{50} and V_{65}. Per the prescriptions of the plans received (which was included in the plan-data), the DV-constraints of the bladder were limited to the V_{65} and the V_{75}.[59, 62, 64, 65]

Since no other details of the test subject (including the PTV) or of the final plan-evaluation were given, a double-blind study was ensured to verify the effectiveness of the reduced list of parameters.

Table 3: The set of eleven dosimetric parameters used for the re-evaluation of twenty prostate 3D-CRT treatment plans.

Indices:	ICRU criteria:	DV-constraints:
HI	Max dose	Bladder V_{65} and V_{70}
CI	Min dose	Rectum V_{50} and V_{65}
	Mean dose	Bilateral femora V_{60}
		Small-bowel V_{15}

3.10 Summary of the Methods and Materials Used

Nineteen prostate 3D-CRT treatment plans were created by nineteen planners. Each treatment plan held two sub-plans: one for the treatment of the PTV1 (the base-plan) and another for the treatment of the smaller PTV2 (the boost-plan). A dosimetric and a physical parameter dataset were obtained from each of these plans.

The principal components of each parameter-dataset were obtained. Varimax-rotation was performed on the component-matrix for the optimization of the variables' factor-loadings.

From these calculations, a reduced and prioritised list of plan-evaluation parameters for prostate 3D-CRT was obtained.

As a verification for the application of this list, twenty treatment plans were evaluated by four treatment planners using the principal dosimetric parameters. After the evaluation, the plans were altered with the principal physical parameters. Finally, the twenty altered treatment plans created were evaluated using eleven dosimetric parameters (see Table 3, p. 48).

3.11 Ethical Considerations

The information about the clinics and equipment of Equra Health used in this study is not given due to the given company policy.

Ethical approval (see Appendix, p. 98) was obtained before the DICOM-images of the patient were obtained from the study library on the CMS Elekta Training Clinic software.

As per company policy, all patients must sign an informed consent. This consent includes the grant for the use of the detail of their radiotherapy treatment by the personnel of the company, which can be supplied to third parties. All information is to be kept anonymous, with no disclosure of any personal information.

As per approval of this study by the company, all the details of the twenty patients were removed, except for the CT-images, organ-contours, the PTV and the treatment plan. The evaluation of the twenty plans by means of the use of a limited and prioritised list of parameters was performed by radiotherapy personnel of the company (see section 3.9.1, p. 46).

A standard operating procedure of the company provides guidelines for the evaluation of treatment plans. Should the evaluation of the twenty plans have indicated that a plan(s) has failed to deliver the prescribed 3D-CRT treatment, then the administrator of the respective XiO would contact and the necessary information be provided to the respective radiation oncologist.

Chapter 4: Results

4.1 Introduction

The following data was obtained in this study.

4.2 Treatment Plan Data

The two complete datasets of the 15 dosimetric parameters given in Table 1 (p. 36) are given in Table 4 and Table 5 (pp. 51-52). The sumplan of the dose-volumes from the latter two tables is given in Table 6 (p. 53). The physical parameters for the base- and the boost-plans are, respectively, summarised in Table 7 (p. 54).

The data of the final dosimetric and physical parameter datasets obtained from the nineteen XiO treatment planning systems are given in Table 8 (p. 55) for the base-plans and in Table 9 (p. 56) for the boost-plans.

The columns from left to right are as follows:

XiO #	The number of the XiO treatment planning system used.
HI	Heterogeneity-index (variation of the dose over the PTV).
CI	Conformity-index (volume of the PTV to the 95% isodose-line).
Max, min, mean	Maximum, minimum and mean dose to the PTV.
V_{50}, V_{60}, V_{65}, V_{70}, V_{75}	Dose-limit to 50 %, 35 %, 25 %, 20 % and 15 % of the rectal-volume.
Fem h-n	V_{60} dose-limit to 5 % the femoral head-neck regions.
V_{65}, V_{70}, V_{75}, V_{80}	Dose-limit to 50 %, 35 %, 25 % and 15 % of the bladder-volume.

In Table 4 to Table 9 (pp. 51-56), the average (Avg), standard deviation (SD) and median (Med) values are given, where applicable.

Table 4: The dosimetric parameter dataset obtained from nineteen prostate 3D-CRT treatment plans created for the irradiation of the PTV1.

						Rectum (Gy)					Fem h-n (Gy)		Bladder (Gy)			
XiO #	HI	CI	Max (Gy)	Min (Gy)	Mean (Gy)	V_{50}	V_{60}	V_{65}	V_{70}	V_{75}	Left	Right	V_{65}	V_{70}	V_{75}	V_{80}
1	1,05	0,31	54,9	49,1	53,6	36,4	44,9	49,9	51,4	52,4	31,4	32,5	9,6	27,7	34,4	48,8
2	1,04	0,48	55,0	49,7	53,9	37,7	46,6	50,5	51,6	52,4	32,6	33,5	9,9	27,4	30,0	45,8
3	1,05	0,25	54,6	46,5	53,4	33,9	42,0	47,6	49,6	51,0	31,8	33,8	6,7	24,3	28,5	39,7
4	1,04	0,30	54,6	47,8	53,5	35,5	43,6	48,6	50,2	51,4	31,8	33,8	9,1	26,8	29,2	43,7
5	1,04	0,25	54,6	49,0	53,5	34,3	42,4	48,1	49,9	51,2	31,5	34,0	9,7	27,1	30,1	45,3
6	1,04	0,48	55,0	49,7	53,9	37,8	46,9	50,7	51,7	52,5	32,6	33,6	11,3	27,7	30,6	46,5
7	1,04	0,33	54,6	50,1	53,6	35,6	44,1	49,2	50,9	51,9	29,6	31,1	11,4	28,9	31,7	44,4
8	1,05	0,35	54,5	47,8	53,5	44,2	49,1	51,5	52,3	52,9	21,1	22,5	10,9	22,8	30,6	40,5
9	1,03	0,32	54,7	47,3	53,8	40,6	48,3	51,6	52,6	53,2	28,5	28,3	11,3	29,6	32,5	44,9
10	1,04	0,53	55,2	50,0	54,0	39,6	47,9	51,6	52,6	53,2	32,0	32,8	7,0	25,9	29,7	44,8
11	1,06	0,20	55,7	48,6	53,7	37,8	47,4	50,6	51,4	52,0	33,0	34,1	7,6	32,2	35,7	49,4
12	1,09	0,17	55,7	46,1	53,1	34,6	42,7	46,8	48,4	49,6	31,9	33,0	9,3	31,1	35,7	46,8
13	1,06	0,19	55,7	49,7	53,5	46,8	50,1	51,2	51,6	51,9	32,6	33,7	17,3	35,0	41,0	50,9
14	1,05	0,46	54,8	48,3	53,7	35,2	43,5	48,6	50,4	51,6	31,8	32,7	14,3	28,5	31,3	46,3
15	1,04	0,27	54,7	49,7	53,6	34,5	46,3	50,1	51,2	52,0	42,6	44,6	7,1	23,1	27,7	46,9
16	1,06	0,25	55,3	48,6	53,4	35,2	45,8	49,3	50,3	51,1	38,4	39,9	7,4	22,1	29,1	47,0
17	1,05	0,49	55,4	50,7	54,1	38,1	46,7	50,0	51,1	51,8	37,9	37,7	10,0	26,9	34,0	46,4
18	1,33	0,23	56,9	27,5	50,7	35,4	40,7	44,1	46,0	48,1	21,8	25,8	2,3	9,1	16,0	23,2
19	1,09	0,74	58,4	46,9	55,0	33,4	41,7	46,5	48,6	50,7	32,7	35,9	11,0	30,7	36,7	42,1
Avg:	1,067	0,347	55,27	47,52	53,56	37,20	45,30	49,27	50,61	51,63	31,87	33,33	9,64	26,69	31,28	44,39
SD:	0,068	0,147	0,954	5,01	0,79	3,52	2,72	2,00	1,62	1,23	4,90	4,73	3,15	5,37	5,01	5,83
Med:	1,05	0,31	55,0	48,64	53,6	35,6	45,8	49,9	51,1	51,9	31,9	33,6	9,7	27,4	30,6	45,8

Table 5: The dosimetric parameter dataset obtained from nineteen prostate 3D-CRT treatment plans created for the irradiation of the PTV2.

						Rectum (Gy)					Fem h-n (Gy)		Bladder (Gy)			
XiO #	HI	CI	Max (Gy)	Min (Gy)	Mean (Gy)	V_{50}	V_{60}	V_{65}	V_{70}	V_{75}	Left	Right	V_{65}	V_{70}	V_{75}	V_{80}
1	1,08	1,00	22,7	19,7	21,8	6,7	8,2	11,4	14,0	16,8	17,0	17,7	2,1	8,6	11,0	17,6
2	1,05	0,19	20,1	18,3	19,8	6,3	7,2	10,2	12,8	15,6	14,9	15,9	1,3	6,6	9,6	13,6
3	1,06	0,16	20,1	16,5	19,7	6,8	7,6	9,4	10,7	13,0	14,1	14,9	1,2	6,2	10,2	13,0
4	1,04	0,19	20,1	18,2	19,8	6,3	7,2	9,6	12,5	15,5	14,9	15,9	1,3	6,4	9,5	13,5
5	1,04	0,13	20,1	18,4	19,8	6,5	7,5	10,6	12,9	15,8	14,6	15,6	1,4	7,3	10,1	13,7
6	1,05	0,50	20,5	18,2	20,0	6,9	8,2	11,6	14,5	16,8	14,5	15,0	1,3	7,1	10,4	13,9
7	1,04	0,01	20,1	18,5	19,8	6,4	7,3	10,1	11,9	15,1	14,7	15,8	1,4	6,9	9,8	13,4
8	1,08	0,33	20,3	16,7	19,7	10,7	11,1	12,5	13,5	15,2	12,1	12,8	2,5	7,6	9,9	12,4
9	1,05	0,24	20,2	18,2	19,8	11,8	12,6	15,1	16,6	17,8	10,6	10,5	2,9	9,2	11,5	14,2
10	1,05	0,15	20,1	17,7	19,7	10,9	12,1	14,8	16,2	17,4	11,5	12,2	1,7	6,7	10,3	13,1
11	1,08	0,44	20,7	18,2	19,9	8,9	11,4	14,4	15,8	17,0	11,8	12,2	1,9	8,9	12,7	15,7
12	1,06	0,37	20,5	18,4	19,0	10,6	15,9	17,7	18,2	18,6	11,9	12,4	1,9	9,4	12,8	15,9
13	1,04	0,32	20,3	18,8	19,9	10,5	16,8	18,4	18,8	19,1	12,3	12,7	1,9	9,3	12,7	15,7
14	1,05	0,00	20,0	17,8	19,6	10,8	11,1	12,6	13,7	15,4	11,4	12,1	2,3	8,1	10,4	12,7
15	1,04	0,17	20,1	18,4	19,8	5,5	6,8	10,8	13,6	16,4	16,2	17,3	1,4	6,8	8,7	14,2
16	1,05	0,20	20,2	17,9	19,8	5,5	6,4	9,6	12,1	15,3	16,2	17,2	1,4	6,6	8,5	14,2
17	1,04	0,57	20,4	19,1	20,0	9,5	10,5	11,1	11,3	11,6	12,1	9,6	2,0	8,6	11,3	15,1
18	1,08	0,23	20,4	16,9	19,6	11,1	14,3	16,1	17,2	18,3	8,6	8,8	1,7	5,3	8,2	12,1
19	1,08	0,74	21,7	18,2	20,3	9,0	10,4	12,9	14,9	16,9	12,2	13,3	2,2	7,6	11,4	13,8
Avg:	1,06	0,310	20,45	18,11	19,88	8,46	10,14	12,57	14,27	16,19	13,24	13,78	1,78	7,54	10,47	14,09
SD:	0,016	0,250	0,66	0,78	0,53	2,212	3,16	2,77	2,32	1,83	2,20	2,62	0,47	1,19	1,36	1,38
Med:	1,05	0,23	20,2	18,2	19,8	8,9	10,4	11,6	13,7	16,4	12,3	13,3	1,7	7,3	10,3	13,8

Table 6: The dosimetric parameter dataset obtained from the sumplan of the nineteen prostate 3D-CRT treatment plans.

	Rectum (Gy)					Fem h-n (Gy)		Bladder (Gy)			
XiO #	V_{50}	V_{60}	V_{65}	V_{70}	V_{75}	Left	Right	V_{65}	V_{70}	V_{75}	V_{80}
1	44,1	54,6	60,3	62,8	67,1	48,3	50,2	12,0	36,0	45,3	66,1
2	45,1	55,5	59,8	61,8	65,2	47,3	49,4	11,2	34,1	39,7	59,2
3	41,4	50,9	57,2	59,5	62,0	45,7	48,6	8,2	30,0	38,5	53,1
4	43,0	52,8	58,2	60,1	62,9	46,5	49,6	10,7	32,8	38,6	57,3
5	41,9	52,1	58,2	60,5	63,9	45,9	49,5	11,1	24,3	40,3	59,4
6	46,2	56,7	60,9	63,2	66,8	46,9	48,6	12,7	35,3	40,6	60,4
7	42,9	53,4	59,2	61,3	64,4	43,8	46,4	13,1	35,6	41,2	58,4
8	55,1	61,1	64,0	65,2	67,0	33,1	35,4	14,3	29,6	40,3	52,9
9	53,3	61,0	64,7	66,3	68,5	38,8	38,6	15,3	37,9	44,0	57,2
10	51,0	59,3	63,7	65,7	68,2	43,3	44,8	10,2	32,1	40,2	55,8
11	46,5	56,5	61,7	64,2	66,8	43,8	45,4	11,5	39,8	48,4	62,1
12	46,8	57,8	63,6	65,8	67,6	43,7	45,3	11,7	40,1	48,3	62,3
13	58,5	65,9	69,1	70,0	70,8	44,8	46,3	19,7	45,8	52,4	66,1
14	46,2	55,5	61,4	63,5	35,5	53,1	44,7	16,9	37,3	41,1	59,3
15	41,2	54,6	59,6	62,8	66,4	58,6	61,7	8,4	30,1	36,4	61,5
16	41,7	53,5	58,0	60,8	64,4	53,8	56,5	8,9	28,2	37,4	61,4
17	47,0	57,7	62,9	66,1	68,7	49,2	49,3	12,2	37,1	44,3	60,9
18	37,9	43,6	47,3	49,4	52,1	28,4	33,0	20,4	23,6	29,4	39,4
19	42,6	52,4	59,1	62,4	66,2	44,9	49,1	13,3	39,4	47,9	55,2
Avg:	45,92	55,52	60,46	62,71	63,92	45,27	46,97	12,73	34,15	41,81	58,32
SD:	5,27	4,70	4,33	4,15	7,90	6,79	6,53	3,40	5,65	5,26	5,85
Med:	45,1	55,5	60,3	62,8	66,4	45,7	48,6	12,0	35,3	40,6	59,3

Table 7: The physical parameter dataset obtained from the nineteen prostate 3D-CRT treatment plans created for the irradiation of the PTV1 (left, a.) and of the PTV2 (right, b.).

a.)

XiO #	Nr. Beams	Opp. beams	Avg FS (cm^2)	Wedge used	Gantry (°)
1	4	4	9,1	Yes	90
2	4	4	7,7	No	90
3	4	4	7,4	No	90
4	4	4	7,7	No	90
5	4	4	7,8	No	90
6	4	4	7,8	No	90
7	4	2	7,6	No	93
8	6	2	9,1	No	90
9	4	2	8,8	No	95
10	4	4	8,0	No	90
11	4	4	8,9	Yes	90
12	4	4	8,9	Yes	180
13	4	4	8,9	Yes	180
14	4	4	8,5	No	90
15	3	2	7,9	Yes	180
16	5	2	7,9	Yes	180
17	3	0	8,7	No	140
18	7	6	8,1	No	90
19	12	12	6,2	Yes	90
Avg:			8,16		112,0
Med:	4	4	8,0	No	90

b.)

Nr. Beams	Opp. beams	Avg FS (cm^2)	Wedge used	Gantry (°)
3	2	8,6	Yes	180
3	2	7,8	Yes	180
3	2	7,6	Yes	180
3	2	8,0	Yes	180
3	2	7,9	Yes	180
3	2	8,1	Yes	180
3	2	7,8	Yes	180
4	4	9,1	No	90
4	2	8,4	No	95
4	4	8,2	No	90
4	4	8,5	Yes	180
4	4	8,8	Yes	180
4	4	8,8	Yes	180
4	4	8,0	No	90
3	2	7,9	Yes	180
5	2	8,1	Yes	180
3	0	8,2	Yes	150
7	6	8,0	No	90
12	12	6,2	Yes	90
		8,11		150,3
4	2	8,1	Yes	180

Table 8: (Left) Final dosimetric parameter dataset from the base-plans. (Right) Final physical parameter dataset from the base-plans.

						Rectum (Gy)		Fem h-n (Gy)				
XiO #	HI	CI	Max (Gy)	Min (Gy)	Mean (Gy)	V_{50}	V_{65}	V_{60}	Beams	Opp.	Avg FS (cm^2)	Wedge used
1	1,05	0,31	54,9	49,1	53,6	36,4	49,9	32,5	4	4	9,1	Yes
2	1,04	0,48	55,0	49,7	53,9	37,7	50,5	33,5	4	4	7,7	No
3	1,05	0,25	54,6	46,5	53,4	33,9	47,6	33,8	4	4	7,4	No
4	1,04	0,30	54,6	47,8	53,5	35,5	48,6	33,8	4	4	7,7	No
5	1,04	0,25	54,6	49,0	53,5	34,3	48,1	34,0	4	4	7,8	No
6	1,04	0,48	55,0	49,7	53,9	37,8	50,7	33,6	4	4	7,8	No
7	1,04	0,33	54,6	50,1	53,6	35,6	49,2	31,1	4	2	7,6	No
8	1,05	0,35	54,5	47,8	53,5	44,2	51,5	22,5	6	2	9,1	No
9	1,03	0,32	54,7	47,3	53,8	40,6	51,6	28,5	4	2	8,8	No
10	1,04	0,53	55,2	50,0	54,0	39,6	51,6	32,8	4	4	8,0	No
11	1,06	0,20	55,7	48,6	53,7	37,8	50,6	34,1	4	4	8,9	Yes
12	1,09	0,17	55,7	46,1	53,1	34,6	46,8	33,0	4	4	8,9	Yes
13	1,06	0,19	55,7	49,7	53,5	46,8	51,2	33,7	4	4	8,9	Yes
14	1,05	0,46	54,8	48,3	53,7	35,2	48,6	32,7	4	4	8,5	No
15	1,04	0,27	54,7	49,7	53,6	34,5	50,1	44,6	3	0	7,9	Yes
16	1,06	0,25	55,3	48,6	53,4	35,2	49,3	39,9	5	2	7,9	Yes
17	1,05	0,49	55,4	50,7	54,1	38,1	50,0	37,9	3	0	8,7	No
18	1,33	0,23	56,9	27,5	50,7	35,4	44,1	25,8	7	6	8,1	No
19	1,09	0,74	58,4	46,9	55,0	33,4	46,5	35,9	12	12	6,2	Yes
Avg:	1,067	0,347	55,27	47,52	53,56	37,20	49,27	33,4			8,16	
SD:	0,016	0,147	0,95	5,01	0,79	3,52	2,00	4,73			0,74	
Med:	1,05	0,31	55,0	48,64	53,6	35,6	49,9	33.6	4	4	8,0	No

Table 9: (Left) Final dosimetric parameter dataset from the boost-plans. (Right) Final physical parameter dataset from the boost-plans.

						Rectum (Gy)		Fem h-n (Gy)				
XiO	HI	CI	Max (Gy)	Min (Gy)	Mean (Gy)	V_{50}	V65	V_{60}	Beams	Opp.	Avg FS (cm²)	Wedge used
1	1,08	1,00	22,7	19,7	21,8	6,7	11,4	17,70	3	2	9,1	Yes
2	1,05	0,19	20,1	18,3	19,8	6,3	10,2	15,88	3	2	7,7	Yes
3	1,06	0,16	20,1	16,5	19,7	6,8	9,4	14,85	3	2	7,4	Yes
4	1,04	0,19	20,1	18,2	19,8	6,3	9,6	15,88	3	2	7,7	Yes
5	1,04	0,13	20,1	18,4	19,8	6,5	10,6	15,62	3	2	7,8	Yes
6	1,05	0,50	20,5	18,2	20,0	6,9	11,6	15,04	3	2	7,8	Yes
7	1,04	0,01	20,1	18,5	19,8	6,4	10,1	15,75	3	2	7,6	Yes
8	1,08	0,33	20,3	16,7	19,7	10,7	12,5	12,76	4	4	9,1	No
9	1,05	0,24	20,2	18,2	19,8	11,8	15,1	10,56	4	2	8,8	No
10	1,05	0,15	20,1	17,7	19,7	10,9	14,8	12,17	4	4	8,0	No
11	1,08	0,44	20,7	18,2	19,9	8,9	14,4	12,21	4	4	8,9	Yes
12	1,06	0,37	20,5	18,4	19,0	10,6	17,7	12,43	4	4	8,9	Yes
13	1,04	0,32	20,3	18,8	19,9	10,5	18,4	12,67	4	4	8,9	Yes
14	1,05	0,00	20,0	17,8	19,6	10,8	12,6	12,13	4	4	8,5	No
15	1,04	0,17	20,1	18,4	19,8	5,5	10,8	17,26	3	2	7,9	Yes
16	1,05	0,20	20,2	17,9	19,8	5,5	9,6	17,23	5	2	7,9	Yes
17	1,04	0,57	20,4	19,1	20,0	9,5	11,1	12,14	3	0	8,7	Yes
18	1,08	0,23	20,4	16,9	19,6	11,1	16,1	8,84	7	6	8,2	No
19	1,08	0,74	21,7	18,2	20,3	9,0	12,9	13,30	12	12	6,2	Yes
Avg:	1,06	0,31	20,45	18,11	19,88	8,46	12,57	13,92	4.2	3.3	8,16	
SD:	0,016	0,250	0,66	0,78	0,53	2,212	2,77	17,6			0,74	
Med:	1,05	0,23	20,2	18,2	19,8	8,9	11,6	13,3	4	2	8,0	Yes

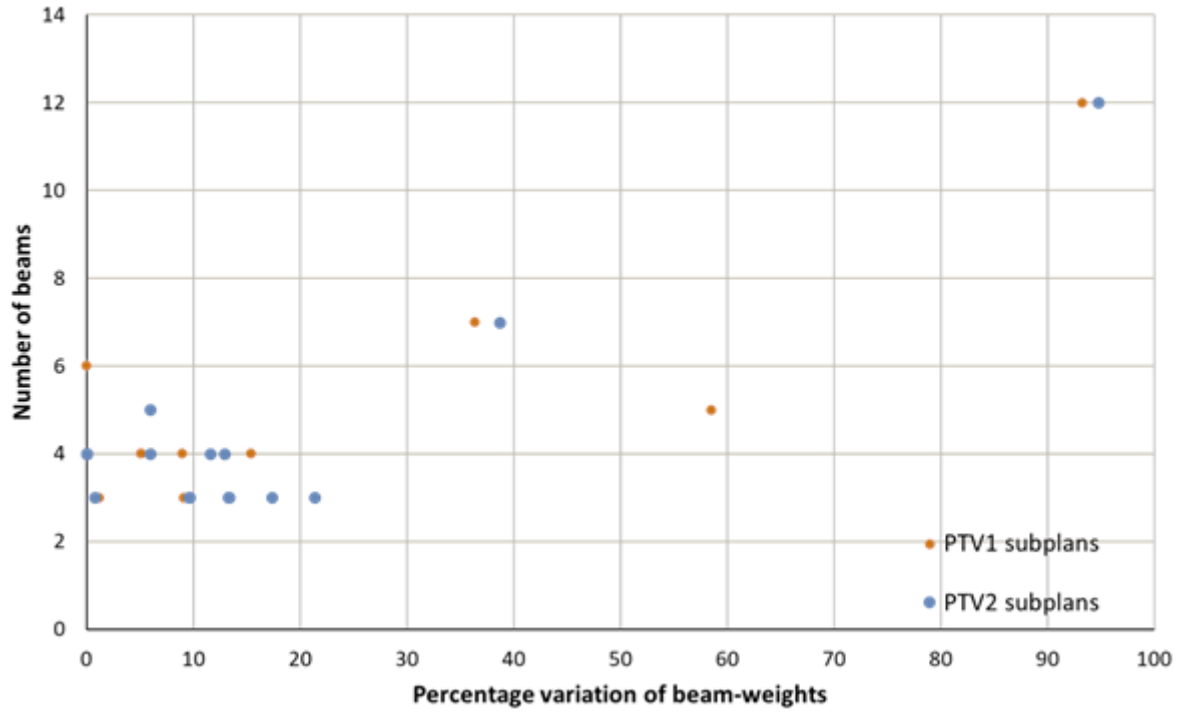

Figure 8: Percentage variation of the beam-weight in a treatment plan versus the number of beams in the base- and the boost-plans.

4.3 Agreement of the Planned and Given Dose-distribution

The variation between the planned and given dose in the plane of the film indicated a 97,0% agreement over a 10 x 10 cm^2 region situated over the prostate, and a 90% agreement in the region between the femoral heads. The agreement between the latter two dose-distributions were found to be within the acceptable tolerance.[56, 78]

4.4 Principal Component Analysis

4.4.1 Tests Preceding to Principal Component Analysis

The results from the following statistical tests performed on the dosimetric and physical parameter datasets for the base- and the boost-plans showed whether these datasets are suitable to PCA or not (see section 2.4.3, p. 25).

a) Covariance and Correlation

The covariance within each of the four parameter datasets are given in Table 10 below to Table 12 (p. 59).

Table 10: Covariance between the values of the dosimetric parameters obtained from the base-plans.

	HI	CI	Max	Min	Mean	V_{50}	V_{65}	V_{60}
HI	1							
CI	0,00	1						
Max	0,03	0,05	1					
Min	-0,30	0,16	-2,01	1				
Mean	-0,04	0,06	0,06	3,23	1			
V_{50}	-0,04	-0,05	-0,57	3,22	0,18	1		
V_{65}	-0,09	0,02	-0,97	6,81	0,78	4,54	1	
V_{60}	-0,10	0,04	0,12	9,89	1,41	-6,39	0,47	1

Table 11: Covariance the values of the dosimetric parameters obtained from the boost-plans.

	HI	CI	Max	z	Min	Mean	V_{50}	V_{65}	V_{60}
HI	1								
CI	0,00	1							
Max	0,01	0,08	1						
Min	0,00	0,04	0,22		1				
Mean	0,00	0,05	0,05		0,20	1			
V_{50}	0,01	0,03	-0,06		-0,36	-0,30	1		
V_{65}	0,01	0,03	0,13		0,03	-0,34	4,69	1	
V_{60}	-0,01	-0,05	0,29		0,51	0,46	-4,86	-4,47	1

In the PTV1 dosimetric parameter dataset, the minimum dose indicated a high covariance to the maximum dose, the mean dose, the V_{50} and V_{65} DV-constraints of the rectum and the V_{60} DV-constraint of the femoral head-neck regions. The mean dose and the V_{60} DV-constraint

indicated a high covariance, as well as the V_{50} and V_{65} DV-constraints. The V_{50} and V_{60} DV-constraints also indicated a high covariance.

The V_{50} and V_{65} DV-constraints indicated a high covariance in the PTV2 dosimetric parameter dataset, as well as the V_{50} DV-constraint of the rectum and the V_{60} DV-constraint of the femoral head-neck regions.

Table 12: Covariance between the values of the physical parameters obtained from the a.) base-plans and the b.) boost-plans.

a.)	Beams	Opp.	Avg FS	Wedge
Beams	1			
Opp.	4,75	1		
Avg FS	4,75	-0,75	1	
Wedge	0,31	-0,75	0,04	1

b.)	Beams	Opp.	Avg FS	Wedge
	1			
	4,75	1		
	4,75	-0,71	1	
	-0,12	-0,71	-0,09	1

The correlation between the parameters in the parameter-datasets are given in Table 13 below to Table 15 (p. 60).

Table 13: Correlation-matrix of the values of the eight dosimetric parameters obtained from the base-plans.

	HI	CI	Max	Min	Mean	V_{50}	V_{65}	V_{60}
HI	1							
CI	-0,17	1						
Max	0,57	0,38	1					
Min	-0,97	0,23	-0,44	1				
Mean	-0,83	0,59	-0,04	0,86	1			
V_{50}	-0,17	-0,09	-0,18	0,19	0,07	1		
V_{65}	-0,72	0,08	-0,54	0,72	0,53	0,68	1	
V_{60}	-0,35	0,07	0,03	0,44	0,40	-0,40	0,05	1

Table 14: Correlation-matrix of the values of the eight dosimetric parameters obtained from the boost-plans.

	HI	CI	Max	Min	Mean	V_{50}	V_{65}	V_{60}
HI	1							
CI	0,46	1						
Max	0,63	0,71	1					
Min	-0,29	0,31	0,46	1				
Mean	0,32	0,52	0,83	0,52	1			
V_{50}	0,29	0,07	-0,05	-0,22	-0,27	1		
V_{65}	0,25	0,07	0,07	0,02	-0,25	0,80	1	
V_{60}	-0,22	-0,13	0,17	0,27	0,36	-0,89	-0,65	1

Table 15: Correlation-matrix of the values of the four physical parameters obtained from a.) the base-plans and the b.) boost-plans.

a.)	Beams	Opp.	Avg FS	Wedge
Beams	1			
Opp.	0,93	1		
Avg FS	-0,51	-0,42	1	
Wedge	0,31	0,32	0,11	1

b.)	Beams	Opp.	Avg FS	Wedge
	1			
	0,93	1		
	-0,49	-0,41	1	
	-0,13	-0,18	-0,29	1

b) Frequency

The frequency of the data in the base-plan parameter-dataset is given in Table 16 (p. 61) and the frequency of the boost-plan parameter-dataset is given in Table 17 (p. 61).

Although the data in all four datasets appears to be mostly grouped into a single bin, it should be noted that the bins given were deliberately made large enough to encompass all the data within the respective dataset. Despite the size and the scale of the bin, no parameter in any of the four datasets could be placed in only one bin. A relative distribution in the data of each parameter, in each dataset, was thus observed.

Table 16: Frequency-distribution of the dosimetric parameter dataset obtained from the base- (PTV1) and the boost-plans (PTV2), grouped as bins: a.) HI, b.) CI, c.) maximum dose, d.) minimum dose, e.) mean dose, dose to f.) 50% of the rectum, g.) 25% of the rectum and h.) 5% of the femoral head-neck region.

a.)	HI	
Bin	PTV1	PTV2
± 0,1	15	14
± 0,2	1	0
± 0,4	2	5

b.)	CI	
Bin*	PTV1	PTV2
>0,4	6	4
0,3→0,4	5	1
0,2→0,3	6	6

c.)	Max	
Bin	PTV1	PTV2
-1,0	1	3
-2,0	10	14
OL	1	2

d.)	Min	
Bin	PTV1	PTV2
-0,5	0	1
-1,0	0	1
OL	19	17

e.)	Mean	
Bin	PTV1	Bin
-0,5	14	± 1
-1,0	4	± 2
OL	1	0

f.)	V_{50}	
Bin	PTV1	PTV2
± 1	8	2
± 2	3	5
± 4	4	12

g.)	V_{65}	
Bin	PTV1	PTV2
± 1	8	1
± 2	7	4
± 4	3	9

h.)	V_{60}	
Bin	PTV1	PTV2
± 1	9	0
± 2	3	10
± 4	4	6

*Range given for actual values.

Table 17: Frequency-distribution of the physical parameter dataset obtained from the base- (PTV1) and the boost-plans (PTV2), grouped as bins: a.) Number of beams, b.) number of opposing beams, c.) average field-size and d.) wedge.

a.)	Beams		b.)	Opp.		c.)	Avg FS		d.)	Wedge	
Bin	PTV1	PTV2	Bin	PTV1	PTV2	Bin	PTV1	PTV2	Bin	PTV1	PTV2
3	1	9	0	1	1	≤5%	9	9	Used	7	14
4	14	7	2	4	10	≤10%	4	4	Not used	12	4
≥5	4	3	4	12	6	>10%	6	6			

a) Spearman-Rank Test

The rho-value of each dosimetric parameter dataset obtained from the base- and the boost-plans are, respectively, given in Table 18 below and Table 19 (p. 62).

Table 18: Rho-values from the Spearman-rank test performed on the values of the dosimetric parameters obtained from the base-plans.

	HI	CI	Max	Min	Mean	V_{50}	V_{65}	V_{60}
HI	1							
CI	0,14	1						
Max	-0,28	0,16	1					
Min	-0,34	0,31	-0,11	1				
Mean	0,68	0,49	0,14	-0,23	1			
V_{50}	0,31	0,50	0,39	-0,03	0,62	1		
V_{65}	0,27	0,39	0,08	0,08	0,37	0,71	1	
V_{60}	-0,21	0,02	0,23	0,07	-0,36	-0,31	-0,39	1

Table 19: Rho-values from the Spearman-rank test performed on the values of the dosimetric parameters obtained from the boost-plans.

	HI	CI	Max	Min	Mean	V_{50}	V_{65}	V_{60}
HI	1							
CI	-0,41	1						
Max	-0,06	0,36	1					
Min	-0,06	0,50	-0,10	1				
Mean	0,38	0,41	0,65	-0,03	1			
V_{50}	-0,25	0,23	0,19	-0,04	0,12	1		
V_{65}	-0,23	0,22	0,22	-0,04	0,13	1,00	1	
V_{60}	0,20	0,13	-0,32	0,18	-0,05	-0,61	-0,62	1

Only the V_{50} and V_{65} DV-constraints of the rectum in the boost-plans indicated a perfect degree of association between the two variables. The rest of the variables showed a poor correlation to each other.

The rho-values of the physical parameter dataset obtained from the base- and the boost-plans are given in Table 20.

Table 20: Rho-values from the Spearman-rank test performed on the values of the physical parameters obtained from the a.) base- and the b.) boost-plans.

a.)	Beams	Opp.	Avg FS	Wedge
Beams	1			
Opp.	0,16	1		
Avg FS	-0,52	0,10	1	
Wedge	-0,19	0,27	-0,32	1

b.)	Beams	Opp.	Avg FS	Wedge
	1			
	-0,50	1		
	0,29	-0,25	1	
	-0,44	0,35	-0,30	1

b) Bartlett's Test of Sphericity

The results of the Bartlett's test of sphericity performed on the values of the dosimetric and physical parameters from the base- and the boost-plans are summarised in Table 21 below.

Table 21: Outcome of the Bartlett's test of sphericity performed on the four parameter datasets.

	PTV1		PTV2	
	Dosimetric	Physical	Dosimetric	Physical
ρ-value	$9{,}60\times10^{-59}$	$2{,}85\times10^{-10}$	$7{,}11\times10^{-59}$	$4{,}01\times10^{-13}$

The very low ρ-value of all four datasets given in Table 21 above indicate that the variables within each dataset are unrelated to one another.

c) Kaiser-Meyer-Olkin Test

The value of the KMO-test for each dataset is given in the final column of Table 22 and Table 23. The lowest KMO-value of all four datasets is >0,62. The number of samples to variables were large enough for each dataset to be suitable for factor-analysis.[26]

Table 22: The Kaiser-Meyer-Olkin test performed on the respective dosimetric parameter datasets obtained from the nineteen plans.

	HI	CI	Max	Min	Mean	50%	25%	5%	Sum:
	PTV1 (base-plan)								
KMO:	0,649	0,733	0,445	0,767	0,691	0,556	0,689	0,297	0,629
	PTV2 (boost-plan)								
KMO:	0,518	0,731	0,621	0,536	0,783	0,614	0,614	0,762	0,653

Table 23: Outcome of the Kaiser-Meyer-Olkin test performed on the respective physical parameter datasets obtained from the nineteen plans.

	Beams	Opp.	Avg FS	Wedge	Sum:
	PTV1 (base-plan)				
KMO:	0,700	0,846	0,642	0,317	0,696
	PTV2 (boost-plan)				
KMO:	0,713	0,837	0,653	0,646	0,717

In summary of the six tests performed on the four datasets, the covariance of a few parameters in the PTV1 and PTV2 dosimetric and physical parameter datasets were shown to be high. No two variables indicated a perfect correlation in the four datasets, and no variable in any of the datasets indicated values which could all be placed into one bin. The Spearman-rank test indicated two variables with a perfect association, and the Bartlett's test of sphericity indicated unrelated variables in each of the datasets. The datasets are thus all heterogeneous and can be used in PCA.

4.4.2 Principal Components

The eigenvalues given in Table 27 (p. 66) provide a summary of the eigenvectors given in Table *24* below to Table 26 (p. 66).The eigenvalues (components) were calculated and ranked according to their contribution to the overall variance within the respective dataset.

The scree-graph (scree-plot) of the components of every dataset is given in Figure 9 (p. 67).

Table 24: Eigenvectors of the dosimetric parameter dataset obtained from the base-plans.

					Rectum		Fem h-n
HI	CI	Max	Min	Mean	50%	25%	5%
0,493	-0,010	-0,132	0,179	0,274	0,052	0,361	-0,706
-0,137	0,449	-0,548	-0,344	0,537	-0,224	0,061	0,136
0,252	0,420	-0,426	0,483	-0,388	0,284	0,133	0,310
-0,497	0,070	0,087	0,015	-0,245	-0,201	0,798	-0,062
-0,435	0,314	-0,187	-0,042	-0,345	0,105	-0,405	-0,618
-0,159	-0,498	-0,469	0,458	-0,008	-0,525	-0,149	-0,018
-0,423	-0,308	-0,164	0,197	0,388	0,709	0,077	0,031
-0,184	0,419	0,460	0,605	0,396	-0,191	-0,140	0,001

Table 25: Eigenvectors of the dosimetric parameter dataset obtained from the boost-plans.

					Rectum		Fem h-n
HI	CI	Max	Min	Mean	50%	25%	5%
0,122	-0,432	0,568	0,268	-0,120	-0,476	0,019	0,404
0,317	-0,366	0,010	-0,724	-0,378	0,259	-0,023	0,174
0,451	-0,347	0,036	0,210	-0,055	-0,047	-0,222	-0,759
0,338	-0,016	-0,732	0,055	-0,052	-0,515	-0,116	0,257
0,503	-0,150	-0,030	0,151	0,624	0,375	0,337	0,241
-0,339	-0,448	-0,144	0,044	0,328	0,210	-0,692	0,174
-0,261	-0,421	-0,327	0,435	-0,437	0,327	0,398	0,037
0,362	0,397	0,108	0,377	-0,386	0,385	-0,431	0,273

Table 26: Eigenvectors of the physical parameter dataset obtained from the a.) base- and b.) the boost-plans.

a.)

HI	CI	Max	Min
0,589	0,019	0,564	0,578
0,610	0,067	0,154	-0,775
-0,490	0,470	0,705	-0,205
0,202	0,880	-0,400	0,156

b.)

HI	CI	Max	Min
0,628	0,089	-0,226	0,740
0,605	0,176	-0,409	-0,660
-0,487	0,427	-0,750	0,133
-0,051	-0,882	-0,468	0,008

Table 27: Percentage contribution to the covariance in each parameter dataset by each of the matrix-components (the eigenvalues).

Component	Dosimetric, PTV1	Physical, PTV1	Dosimetric, PTV2	Physical, PTV2
1	48,02%	60,21%	38,47%	59,57%
2	24,07%	27,15%	34,37%	29,14%
3	16,33%	8,84%	14,26%	9,83%
4	7,20%	3,80%	6,37%	1,46%
5	3,28%		3,92%	
6	0,82%		1,54%	
7	0,27%		0,74%	
8	0,02%		0,32%	

4.4.3 Varimax-Rotation

The unrotated factor-matrix for the PTV1 and PTV2 dosimetric and physical parameter datasets are respectively given in Table 28 and Table 29 (p. 67-68). The optimized loadings are summarised in Table 30 and Table 31 (pp. 68-69).

From Table 30 (p. 68), the first component in both the dosimetric and the physical parameter data contribute the most to the covariance within the dataset. The factor-loadings in the first component therefore need to be given a higher regard than the factor-loadings in the second component of each parameter-dataset (see section 2.4.4 c), p. 30).[26, 27]

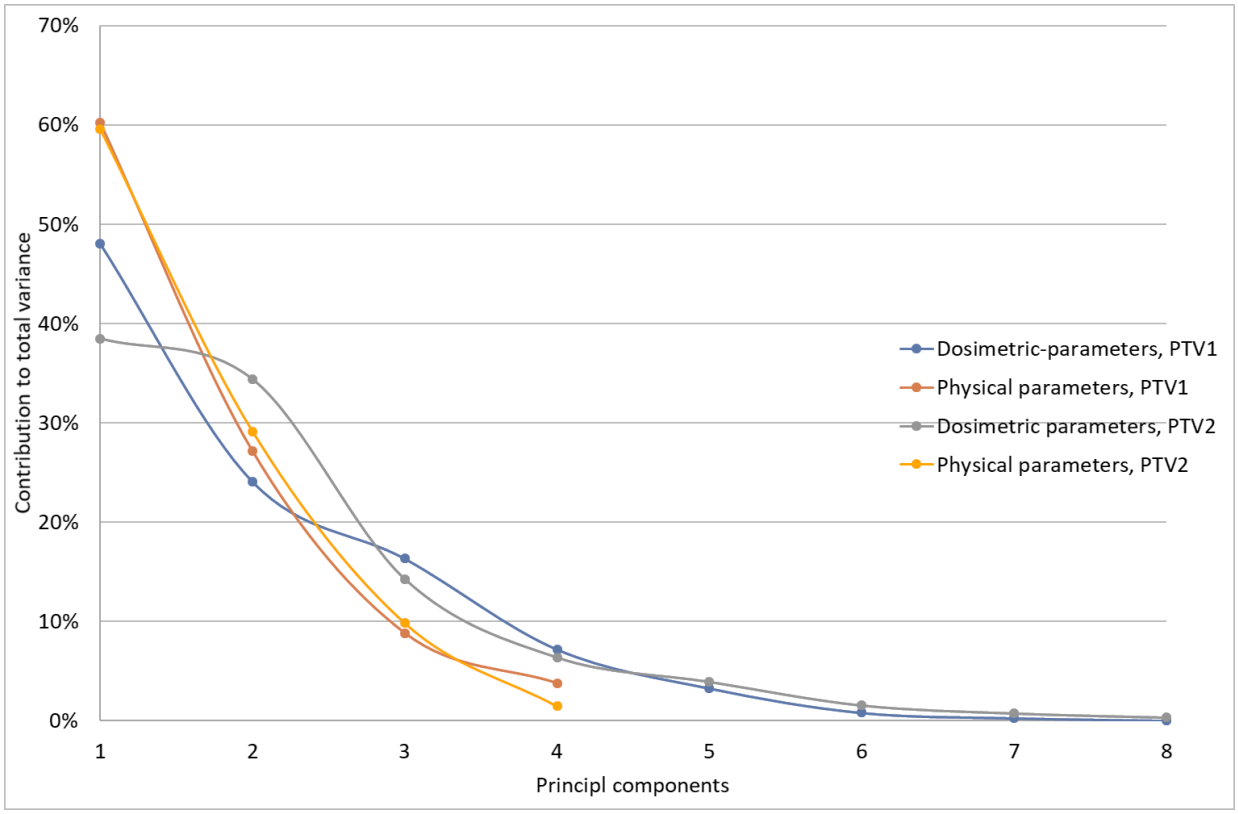

Figure 9: Scree-graph of the components' contribution to the overall variance in each of the four parameter-datasets.

Table 28: Unrotated factor-matrix of the principal components of the a.) dosimetric and the b.) physical parameter dataset obtained from the base-plans.

a.)

Component:	1	2	3
HI	0,751	0,549	-0,154
CI	-0,673	0,621	-0,164
Max	-0,116	0,946	-0,175
Min	-0,864	-0,205	0,199
Mean	-0,862	0,435	-0,058
Rectum V_{50}	-0,755	-0,280	-0,437
Rectum V_{65}	-0,920	-0,237	-0,075
Fem h-n V_{60}	-0,350	0,333	0,836

b.)

	1	2
Beams	0,962	-0,091
Opp,	0,939	-0,003
Avg FS	-0,956	0,198
Wedge	0,292	0,955

Table 29: Unrotated factor-matrix of the principal components of the a.) dosimetric and the b.) physical parameter dataset obtained from the boost-plans.

a.)

Component:	1	2	3
HI	0,406	-0,609	0,650
CI	0,890	-0,332	0,000
Max	0,942	-0,279	0,123
Min	0,634	0,167	-0,727
Mean	0,966	-0,056	-0,036
Rectum V_{50}	-0,318	-0,897	-0,090
Rectum V_{65}	-0,113	-0,834	-0,483
Fem h-n V_{60}	0,433	0,863	0,076

b.)

	1	2
Beams	0,952	-0,171
Opp,	0,937	-0,058
Avg FS	-0,937	0,284
Wedge	0,612	0,789

Table 30: Factor-matrix after rotation of the principal components of the a.) dosimetric and the b.) physical parameter dataset from the base-plans.

a.)

Component:	1	2	3
HI	0,974	-0,038	-0,088
CI	-0,259	0,008	-0,887
Max	0,494	0,133	-0,748
Min	-0,982	0,063	-0,006
Mean	-0,858	0,107	-0,464
Rectum V_{50}	-0,245	-0,892	0,075
Rectum V_{65}	-0,795	-0,503	0,144
Fem h-n V_{60}	-0,421	0,754	-0,016

b.)

	1	2
Beams	0,884	0,235
Opp.	0,903	0,290
Avg FS	-0,854	0,297
Wedge	0,089	0,965

Table 31: Factor-matrix after rotation of the principal components of the a.) dosimetric and the b.) physical parameter dataset for the boost-plans.

c.)

Component:	1	2	3
HI	0,214	-0,716	0,606
CI	0,556	-0,608	0,010
Max	0,791	-0,575	0,039
Min	0,592	-0,026	-0,782
Mean	0,882	-0,248	-0,032
Rectum V_{50}	-0,595	-0,743	-0,154
Rectum V_{65}	-0,459	-0,699	-0,350
Fem h-n V_{60}	0,635	0,658	0,115

d.)

	1	2
Beams	0,970	0,086
Opp.	0,936	0,180
Avg FS	-0,747	0,469
Wedge	-0,090	-0,952

The factor-loadings of the PTV1 dosimetric parameter data given in Table 30 (p. 68) indicate four variables with a very high loading in the first component. These were the minimum dose, the HI, the mean dose and the V_{65} DV-constraint of the rectum. The mean dose, however, indicated a very low factor-loading in the second component and was therefore not included for further use. The factor-loadings of the PTV1 physical parameter data indicate a very high loading on the number of beams, the number of opposing beams and the average field-size.

4.4 Validation of the Prioritised Parameter List for Prostate Conformal Treatment Plan Evaluation

The difference between the original and the altered treatment plans delivered a new set of values for each dosimetric parameter, as obtained from each altered treatment plan. For each parameter the average value of the percentage difference between the original and altered treatment plan is given in Table 32 (p. 70). A negative value shows a decrease in the average value of the specific parameter and a positive value an increase of its average value in respect of the requirement (criterion) set by the respective parameter.

Table 32: Percentage difference between the original and altered treatment plans based on eleven dosimetric parameters given in Table 3 (p. 47).

						Bladder		Rectum		Fem h-n	Small-bowel
Parameter	HI	CI	Max	Min	Mean	V_{65}	V_{70}	V_{50}	V_{65}	V_{60}	V_{15}
% diff.	-3,0	40,8	0,4	16,5	-0,1	6,5	3,3	-4,2	5,9	3,4	-7,8

4.5 Summary of the Results

The dosimetric and physical parameter-data of the nineteen treatment plans created for this study was obtained and analysed.

The six statistical tests given were used to indicate whether each dataset is suitable for PCA. From PCA, the principal component of the dosimetric parameter dataset indicated four variables with a very high (>0,75) loading, namely the minimum dose, the HI, the mean dose and the V_{65} DV-constraint of the rectum. The physical parameter dataset indicated three variables with a very high loading, namely the number of beams, the number of opposing beams and the average field-size. This created the minimal list of prioritised parameters used for the evaluation of prostate 3D-CRT treatment plans.

This list of parameters was used to evaluate and improve twenty prostate plans which randomly obtained. The evaluation of the altered plans displayed a delivery of more dose to the PTV, less dose to the small bowel and slightly more dose to the rectum, bladder and femoral head-neck regions.

Chapter 5: Discussion

5.1 Introduction

Herewith a discussion of the results obtained.

5.2 The Treatment Plan Data

One treatment plan was received with the normalisation-point situated on the isocentre, while the other plans were normalized to the centre of the PTV1.[54] The size of the original PTV1 and PTV2 was also altered by the treatment planner.[9, 36, 38, 40] The treatment planning site was therefore asked to re-create the base- and the boost-plan. The plan's parameter data was then added to the data of the other 18 plans.

The use of a predefined protocol for prostate 3D-CRT can be seen in the physical set-up of several of the treatment plans received, especially for the treatment of the PTV1. E.g., thirteen of the nineteen base-plans made use of the four-field, box-type arrangement of the beams (see Table 7, p. 54).

5.2.1 Dosimetric Parameter Data

The datasets given in Table 4 and Table 5 (pp. 51-52) can be summarised as follows:

The dose-conformity to the PTV and the boost-volume is very low (34,7% and 31,3%, respectively), while the HI is close to unity in both datasets (1,066 and 1,056, respectively). It is therefore evident that the uniform spread of the dose in the PTV is of a higher importance in planning for prostate 3D-CRT than the conforming of the dose to the treatment volume.[5] One of the main contributors to this distribution of dose outside the PTV is the 1 cm MLC leave-width of the Siemens Primus linac.[5, 55, 78] The base-plans have a 42,2% variation in the values of the CI, with an even higher variation (79,9%) in the values of this parameter in the boost-plans' data. The correlation between the CI and the average field-size is low in both the base- (0,381) and the boost-plans (0,146). The agreement of the alignment of the field-size collimation to the PTV is therefore not linearly correlated, indicating an individual selection

of the collimation required considering the shape of the PTV and the use of the chosen number of beams.

The number of beams and opposing beams do not have a linear agreement with the dose-conformity.

The base-plan with a twelve-fields beams-arrangement shows a conformity of 74% of the prescribed dose given to the PTV (see Figure 10 below). Even though this conformity is higher than the rest of the plans, the dose-distribution of this plan was not necessarily an improvement in respect of the other plans and parameters, as shown by the minimum dose of 46,9 Gy (86,9%) and the maximum dose of 58,4 Gy (108,1%) in the base-plans (see Table 4, p. 51).

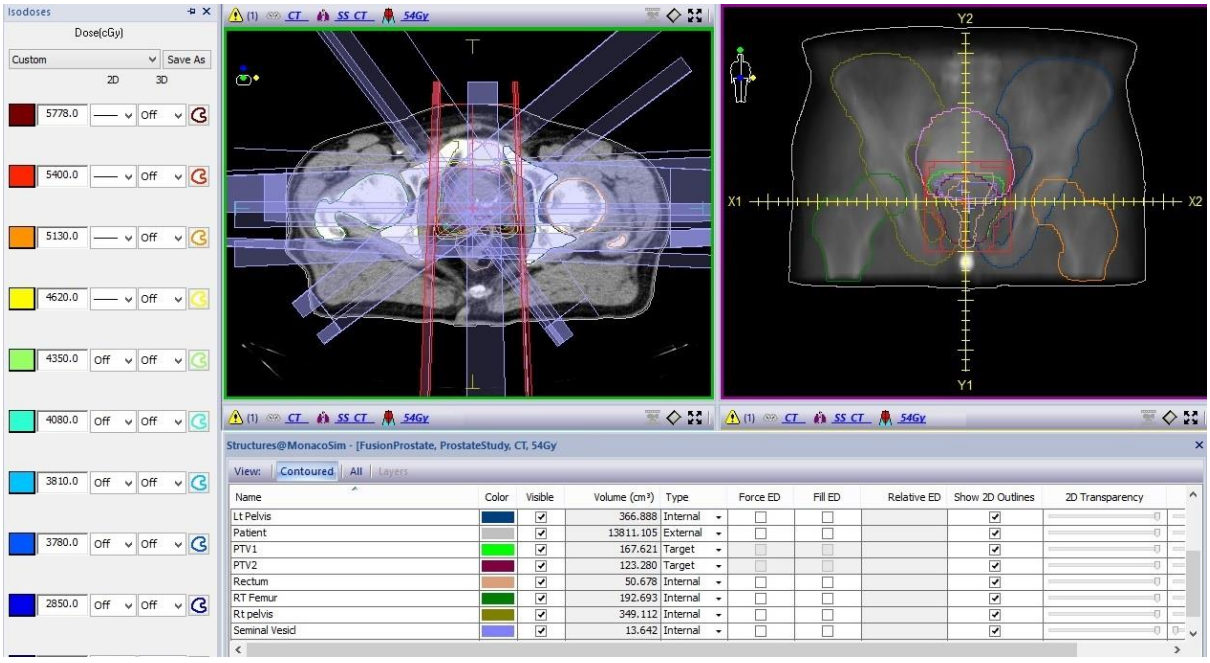

Figure 10: Prostate 3D-CRT treatment plan with a twelve-field beam arrangement.

Two plans exceed the maximum dose limit (21,4 Gy) and only two other plans comply to the minimum dose-limit (19,0 Gy) in the PTV2 dosimetric parameter data. All the base-plans had a mean dose <5% from the prescribed dose, despite no compliance to the minimum dose-limit of 51,3 Gy.

Of the three OARs used in this study, the rectum receives the highest dose in both the base- and the boost-plans. The V_{50} DV-constraint of the rectum shows a high variation in both the base- and the boost-plans (9,6% and 26,2%, respectively). The V_{50} DV-constraint shows the highest variation of any OAR in the boost-plans (31,2%).

The dose to any specified volume of the bladder was found to be much less than the given dose-tolerance (e.g., 14,8% of the V_{65} DV-constraint of the bladder).

The tendency for the base- and boost-plans which shows a very low minimum dose is for the rectum to receive a very high dose. This is due to the partial overlap of the rectum by the PTV and a shift of dose to the areas of low-density (gas) within the contents of the rectum.

In contrast to the expected, the number of beams does not show a linear agreement with the dose to the rectum or to both femoral head-neck regions.

The average dose to the V_{50}, V_{60}, V_{65} and V_{70} dose-volumes of the rectum are, respectively, 45,9 Gy, 55,5 Gy, 60,5 Gy and 62,7 Gy. As given in the literature, the V_{50} and the V_{65} DV-constraints indicated the least difference between the dose received and the dose-tolerance of the given rectal-volume.[56, 84]

The femoral head-neck regions both received <80% of the tolerance-dose.

Since only a small section of the bladder was included in the PTV1 (see section 3.2.2, p. 34), the V_{80}, V_{75}, V_{70} and V_{65} showed a dramatic decrease in the dose per volume received. E.g., the average of the V_{80} for the nineteen plans was 72,9% of the tolerance-dose, and the V_{65} for the nineteen plans was 19,6% of the tolerance-dose. Since none of the dose-values of the bladder's DV-constraints were >75% of the given tolerance-dose, all the constraints of the bladder were discarded for statistical analysis.

5.2.2 Physical Parameter Data

The data of the physical parameters given in Table 7 (p. 54) can be summarised as follows:

The physical parameter datasets show a higher variation for each parameter than the dosimetric parameter data given in Table 4 and Table 5 (pp. 51-52).

The average variation between the physical parameters is 56,4% and 12,6% in the base- and the boost-plans, respectively. For the boost-plans, it is 61,9% versus 18,4%.

Thirteen of the nineteen base-plans (68,4%) made use of the four-field, box-type beam-arrangement. Some of the plans which made use of >4 beams had two opposing fields. Ten of the nineteen (10/19) plans received displayed a similar beam-arrangement in both the base- and the boost-plans.

In contrast to the expectation, the number of beams did not correlate with the dose to the rectum in both the base- (-0,16) and the boost-plans (0,315) (see section 2.2.2, p. 21).

In contrast to the expectation, the correlation between the average field-size and the number of beams was R^2 = -0,504 and the correlation between the average field-size and the opposing beams was R^2 = -0,422. This variation depends on the shape and size of the PTV, as well as the width of the multi-leave collimators (MLCs). The width of an MLC in the Siemens Primus linac is 1 cm, thus the coverage of the walnut-shaped PTV by the prescribed dose is a challenge for the setup of a prostate 3D-CRT treatment plan.

The wedge as a beam-modifying device was used in seven of the base-plans and eight of in the boost-plans. No conclusion could thus be made from these results on the preference to its use in prostate 3D-CRT.

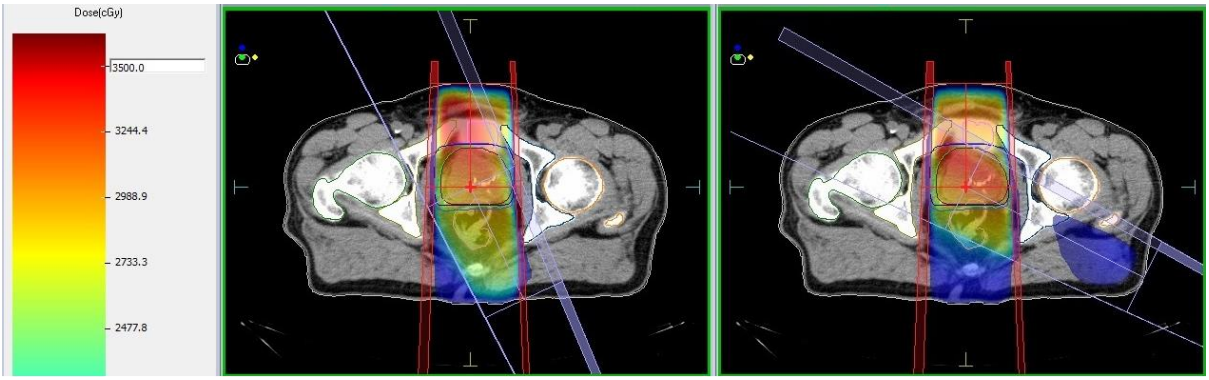

Figure 11: Difference in the dose-distribution due to the angle between the two beams. Left.) 155° and right.) 117°.

The ratio of the opposing beams to the number of beams is of importance to prostate CRT (see section 2.2.2, p. 21 and section 5.2.1, p. 71). Despite the spread of the dose around the PTV, this ratio is 0,083 in the base-plans and 0,742 in the boost-plans. Thus, the smaller the PTV, the more likely is the use of non-opposing beams.

The maximum angle between the two adjoining beams in a simple two-beam arrangement provides the difference in the dose-distribution given in Figure 11 (p. 74). The spread of more dose away from the PTV by the second beam at a gantry-angle of 117° is obtained compared to this beam placed at an angle of 155°.

From the above, the maximum gantry-angle between any two adjoining beams in a treatment plan is related to the delivery of less dose to the PTV. In the nineteen plans, consisting of a range of a three-field to a twelve-field beam-arrangement, the average value of the maximum angle between any two adjoining beams in a treatment plan is greater in the boost-plans (155°) than in the base-plans (117°). In Figure 8 (p. 57), the average beam-weight versus the number of beams indicate no linear relationship as expected. Plans containing opposing fields did, however, indicate a tendency for the opposing fields to be equal in the dose per beam.[73]

Although planning was performed for the same patient and the tendency for certain planning sites were to make use of only a certain type of beam-arrangement, it is clear from the data received that a substantial variation within the data of all the physical parameters exists.[28]

5.2.3 Summary of the Treatment Plan Data

As expected, little variation is displayed by the data of the dosimetric parameters between the nineteen plans. However, regarding the set-up of a prostate plan, the variation between the plans obtained from sites which are not treatment planning centres is more pronounced compared to the plans obtained from planning centres. This variation is also more visible in the data of the physical parameters. This is most likely due to a conformed protocol or a class-solution for prostate 3D-CRT in many planning sites.[22]

It is clear from both the dosimetric and the physical parameter datasets in Table 8 and Table *9* (pp. 55-56) that no two parameters used in this study display a linear relationship between them. Regression-analysis was therefore not suitable for identifying the parameters which contribute the most to variation within the dataset.

5.3 Principal Component Analysis

5.3.1 Tests for the Applicability of the Parameter-Datasets to Principal Component Analysis

a) Covariance and Correlation

From Table 10 and Table 11 (p. 58), the dosimetric data obtained from the base-plans display a high covariance (>50%) in the following parameters:

- The HI and the maximum, minimum and mean dose.
- The CI and the mean dose.
- The maximum dose and the V_{65} of the rectum.
- The minimum and mean dose.
- The minimum dose and the V_{65} of the rectum.
- The mean dose and the V_{65} of the rectum.
- The V_{65} and V_{50} DV-constraints of the rectum.

From Table 12 (p. 59), the following parameters display a high covariance (>50%) in the dosimetric data obtained from the boost-plans:

- The HI and maximum dose.
- The CI and maximum and mean dose.
- The maximum and mean dose.
- The maximum and minimum dose.
- The minimum and mean dose.
- The V_{65} and V_{50} DV-constraints of the rectum.
- The V_{50} and V_{65} DV-constraints of the rectum.
- The V_{50} DV-constraints of the rectum and the V_{60} DV-constraint of the femoral head-neck.

From Table 13 and Table 14 (p. 59), the following physical parameters display a high correlation (>50%) in the data obtained from the base-plans:

- The number of beams and opposing beams.

- The number of beams and the average field-size.

From Table 15 (p. 60), the following physical parameters display a high correlation (>50%) in the data obtained from the boost-plans:

- The number of beams and opposing beams.

Since the covariance of the parameters is calculated within a vector-subspace, it is difficult to visualise the simultaneous change of a parameter in the matrix simply by observing each of the datasets given in Table 4 to Table 7 (pp. 51-54).

b) Frequency

Some of the dosimetric parameters given in Table 8 and Table 9 (pp. 55-56) demonstrate a visible trend (grouping) within the two sub-plans' data (see Table 16 and Table 17, pp. 61). The HI and the maximum, minimum and mean dose all mostly display a similar grouping. The CI and the DV-constraints, in contrast, shows one grouping in the base-plans and another, but different, grouping in the boost-plans. In the physical parameter datasets, only the average field-size shows a similar grouping in the two sub-plans' data.

Based on the irregularity of the grouping (or range) of dosimetric and physical parameter-values, the frequency of the parameters do not all deliver the same variation and thus not a frequent score.[25]

c) Spearman-Rank Test

From Table 18 (p. 62), the following pairs of dosimetric parameters show a high (>50%) rho-value in the data of the base-plans:

- The HI and the mean dose.
- The CI and the V_{50} DV-constraint of the rectum.
- The V_{50} DV-constraint of the rectum and the mean dose.
- The V_{50} and V_{65} DV-constraints of the rectum.

From Table 19 (p. 62), the following pairs of dosimetric parameters show a high (>50%) rho-value in the data of the boost-plans:

- The CI and the minimum dose.
- The maximum and the mean dose.
- The CI and the V_{50} DV-constraint of the rectum.
- The V_{60} DV-constraint of the femoral head-neck regions and the V_{50} and V_{65} DV-constraints of the rectum.

Only a few parameters displayed a correlation to each other. The assumptions of the parametric-data therefore do not fulfil the requirements needed to merely draw a conclusion from the linear correlation between the parameter-values within a dataset.[25]

The number of beams and the average field-size in the PTV1 parameter dataset (see Table 20, p. 63) show a high rho-value. In the PTV2 data, the number of beams and opposing beams show a high rho-value.

Only the data from the boost-plans display a very high possibility of a linear-dependency between any two parameters, namely the V_{50} and the V_{65} DV-constraints of the rectum.

d) Bartlett's Test of Sphericity

When comparing the correlation-matrix to the identity-matrix, the results of the Bartlett's test of sphericity are given in Table 21 (p. 63). The results show a very strong evidence against the null-hypothesis. In any of the four parameter datasets, no multi-collinearity exists between any of the parameters. The possibility of a purely linear relationship between any of the parameters within the datasets therefore do not exist. In effect, the identity-matrix will therefore show vectors which are orthogonal to each other. This requirement for PCA is therefore met by all four of the parameter-datasets.

e) Kaiser-Meyer-Olkin Test

The sampling-ratio was 2,38 for the eight dosimetric parameters and 4,8 for the physical parameters. Despite these low sampling-ratios, the sum-value of the KMO-test performed on the dosimetric parameter datasets shows an adequate sampling-ratio (0,629 and 0,653, respectively) (see Table 22 and Table 23, p. 64). The KMO-test performed on the physical parameter dataset shows a slightly higher sampling-adequacy (0,696 and 0,717, respectively). All four parameter-datasets thus indicate a sufficient KMO measure for PCA to be performed.[27]

5.3.2 Principal Components

The values given in Table 27 (p. 66) and the scree-graph given in Figure 9 (p. 58) provide enough proof that the three main (principal) components in the dosimetric parameter data and two main components in the physical parameter data from the base-plans provide a sufficient indication of the covariance within the respective dataset[26, 27]:

- The first three components of the dosimetric parameter data accounts for 88,2% and 87,1% of the covariance within the respective vector-matrix. The first two components of the physical parameter data accounts for 87,4% and 88,7% of the overall covariance within the respective vector-matrix.
- The values of the three components are also above the “elbow-region” of the graph for both the PTV1 and the PTV2 dosimetric parameter datasets (see Figure 9, p. 67).[70] The area above the lower “elbow-region” of the scree-graph displays the same tendency as in Table 27 (p. 66).
- Two components of the physical parameter datasets are above the elbow-region. The two principal components contribute >72,8% to the overall variance within the respective vector-subspace of the boost-plans.
- The components of both the dosimetric and the physical parameter datasets also met Kaiser’s criterion (thus above the 10% line on the scree-graph).

Considering the percentage contribution to the covariance by each component, as well as its position on the scree-graph, three components were therefore retained in each of the dosimetric parameter datasets and two components in the physical parameter datasets.

5.3.3 Varimax-Rotation

Within each principal component, some of the parameters' loadings shows a marginal difference in the contribution by the variables to the overall variation given by the component (see Table 28 and Table 29, pp. 67-68). One of the three components of each dataset also had significant loadings and the other two components had less significant loadings. These requirements of the Thurstone-criteria for Varimax-rotation to be used was therefore met by all the datasets.[28] The second and third components were therefore discarded for further use.

In the dosimetric parameter dataset, the evaluation of a prostate 3D-CRT plan can be prioritised as the minimum dose, the HI, the mean dose and the V65 DV-constraint of the rectum.

Except for the wedge, all the variables in the physical parameter dataset from both the base- and the boost-plans show a high loading. For improving treatment plan quality, prioritisation must therefore be given to the number of opposing beams, the number of beams, as well as the average field-size.

5.4 Validation of the Prioritised Parameter List for Prostate Conformal Treatment Plan Evaluation

From the results given in Table 32 (p. 70), the values of the first five parameters (HI, CI, maximum, minimum and mean dose) display collectively an overall increase in the dose given to the PTV. This is especially clear in the dose-conformity (given by the CI) and the minimum dose, which both relate to a higher dose given to the PTV (see Table 8 and Table 9, pp. 55-56). Since the result of a higher confinement of dose to the PTV leads to a higher success rate in the patient's clinical outcome, this higher dose to the PTV is a positive outcome from the use of the limited list of prioritized parameters.[37]

The average increase in the dose to the bladder, to the rectum and to the femoral head-neck regions is 3,0%. In contrast, a significant decrease (-7,8%) in the dose to the small-bowel is observed. The decrease in the dose to the small-bowel from the use of the reduced list of parameters is thus also a positive, clinical outcome for the patients.

From the above, the application of the limited list of prioritised parameters to evaluating prostate 3D-CRT plans has indicated the clinical shortcomings of the plans. This especially in the dose to the PTV. Based on these results, each plan could also be altered to improve its quality.

From the feedback received from the treatment planners after the twenty plans were altered, the use of only the three given dosimetric parameters to evaluate a prostate plan was experienced as unusual compared to the standard means of evaluating plans with several other parameters to also consider.

The planners also indicated that a by-product of the application of this list of evaluation-parameters was that less time was needed for the initial plan-evaluation by the planner.[12] The point where practicality meets optimality was therefore reached sooner compared to the time which was needed in the standard practice of treatment planning previously used (see Figure 2, p. 16).[4, 14] Considering the iterative optimisation of a treatment plan (see section 1.4, p. 15), this was a huge boost for the evaluation and the alteration of several plans in the same length of time needed to evaluate, alter and manually optimise a single plan.[18, 21, 22, 51]

The definition and effectiveness of the reduced number of prioritised parameters in the evaluation and improvement of the outcome of the final treatment plans showed the robustness of this list of parameters.[4, 15, 18]

5.5 Limitations of the Study

Some of the following alterations to this study may be considered for future investigation.

The delineation of the tumour volume has a very large influence on the outcome of any treatment plan, especially on the dose to the OARs. This also holds true for the values of the plan-evaluation parameters.[38]

This study may also be performed for other tumour sites and treatment modalities, especially for other modalities which are often used, such as intensity-modulated radiotherapy.

Although the XiO does not provide the biological-optimisation of a treatment plan, this optimization-regime is a consideration worth exploring for a limited list of prioritised parameters.[7]

A parameter which may be included as a plan-evaluation parameter in future studies for the prostate is the dose to the small-bowel.[36, 62]

Chapter 6: Conclusion

6.1 Introduction and Aim

Without the use of a minimal list of prioritised parameters, several different treatment plans will be created for a single patient. This is due to a variation in the number and priority of the metrics by which the quality of a plan is evaluated.[13, 22]

This aim of this study was to obtain and verify the use of a short list of parameters which can be ranked and used as a protocol to evaluate and improve the quality of prostate 3D-CRT treatment plans.

6.2 The Principal Components

In the data obtained from the nineteen prostate 3D-CRT plans created for this study, no linear-correlation was shown between the parameters. This tendency indicated heterogeneous datasets, a requirement for factor-analysis. The sampling-adequacy of the parameter-data obtained from the nineteen treatment plans was enough to indicate that the dataset is suitable for PCA to be used.[26, 27]

Based on its contribution to the overall covariance within each dataset, only the first principal component of both dosimetric and physical parameter datasets were considered. The rotated and optimised factor-loadings of the parameters in each component were used to give the priority of the parameters for plan-evaluation.[29, 69]

The parameters contributing the most (>0,75) to the covariance in the quality of the prostate 3D-CRT treatment plans are presented as a limited list of ranked priority. The prioritised dosimetric parameters are the

- minimum dose,
- heterogeneity-index,
- mean dose to the PTV, and the
- rectum's V_{65} DV-constraint.

The prioritised physical parameters are the:

- number of opposing beams,
- number of beams. and the
- average field-size.

6.3 Application of the Principal Components to Plan-Evaluation

The process used to obtain and verify the use of the limited list of prioritised parameters as a treatment plan evaluation protocol for prostate 3D-CRT were performed and completed. With an application of the list to the several plans, the altered plans indicated an increase of 16,5% of the minimum dose and a 40,8% higher conformance of the dose to the PTV. A decrease of 7,8% in the dose to the small intestine and a 3,0% increase in the dose to the rectum, bladder and femoral head-neck regions were observed.

6.4 In Retrospect: The Use of a Short, Prioritised List of Parameters

Considering that such a list for plan-evaluation is intended for use by a treatment planner, this method of knowledge-based evaluation not only holds promise as a protocol to improving decision-making support-systems in radiation oncology in the future, but also holds promise to dramatically decrease the time needed for plan-evaluation.

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Table of Figures

Summary of the Study

Problem and Objective

Several studies have found that different treatment plans will be created for a single patient by different planners or institutions due to a variation in the number and priority of the metrics by which the quality of a plan is evaluated.[13, 22] A minimal list of prioritised parameters is therefore needed to evaluate three-dimensional conformal radiotherapy (3D-CRT) treatment plans create for a specific tumour-site.[11, 15]

The aim of this study was to obtain a short list of prioritised parameters which can be used to evaluate and improve prostate 3D-CRT treatment plans. Such a list should evaluate the dose given to the PTV and the dose to the OARs. It should also aim to minimise the fluctuations most likely to be included in the set-up of the treatment plan.[10, 14, 22]

Methodology

Nineteen treatment plans were created for the same prostate patient on nineteen XiO treatment planning systems by nineteen planners. The 3D-CRT treatment was to be given to the main planning target volume (PTV) and thereafter to the smaller boost-volume. A dosimetric and a physical parameter dataset were obtained from each of the two sub-plans created.

The principal components of each parameter-dataset were obtained using principal component analysis (PCA), and the loadings of the variables (parameters) were optimised using Varimax-rotation. From the variables with the highest loading in the principal component of each dataset, a minimal list of prioritised plan-evaluation parameters was obtained.[26–28]

Twenty plans which were randomly obtained were evaluated using only the selected list of prioritised dosimetric parameters. The plans were then improved by using only the list of prioritised physical parameters. Afterwards a set of eleven dosimetric parameters was used to evaluate the outcome of the altered plans.

Results

No linear-correlation was found between any of the dosimetric and physical parameters in the two sets of sub-plans, which indicated heterogeneous datasets. From PCA and subsequent Varimax-rotation it was shown that the minimum dose, the heterogeneity-index, the mean dose and the V_{65} DV-constraint of the rectum, as well as the number of beams, the number of opposing beams, and the average field-size provided the highest contribution to the variance within the respective vector-subspaces. These parameters created the minimal and prioritized list of parameters to be used for plan-evaluation.

In the twenty plans which were altered by the application of this minimal list of parameters, more dose was delivered to the PTV. A higher conformity-index and minimum dose, a 3,5% dose-escalation of the dose to the rectum, bladder and bilateral femora and 7,8% less dose to the small-bowel was demonstrated by the plans.

Conclusion

Given the increase of the dose to the PTV and less dose to the small intestine, the application of a limited and prioritised list of plan-evaluation parameters will improve the decision-based support in prostate CRT treatment planning. In consequence, the use of only a few parameters will also minimise the time needed in which to optimise a prostate 3D-CRT treatment plan.

Acknowledgements

My sincere appreciation to everyone who's been involved in this study. There are too many to thank individually. I would, however, like to give my thanks especially to the following people and/or institutions:

- This work was supported by the Medical Research Council of South Africa in terms of the MRC's Flagships Awards Project [SAMRC-RFA-UFSP-01-2013/HARD],
- To my supervisor and co-supervisor: For the many discussions, your advice and the endless patienc. I am indebted to you. Thank you very much for giving me the chance to perform this research, and for guiding me in reaching its goal,
- To Dr. J. Raubeheimer: My thanks to you for deciphering to me the usefulness and application of PCA,
- To Equra Health. Thank you for the chance to perform this study and for the use of the equipment at all the clinics,
- To the personnel of Clinic1: My thanks to you for all the help and the countless words of encouragement.

- To my family, the lifeline which kept me going through everything and who had to endure all the challenges:

  Thank you for believing in me, for keeping my perspective on the finish-line, and for all your prayers and advice,

- To my sons:

  My love for you is stronger than my will to breath. Never give up, never let go of our Saviour's hand, and always finish strong.

- To my wife:

  You are the core of my determination, the pulsating heart which has kept me going throughout this study. I know I can't return the time this took from us, but my hope is that

the experience and knowledge gained from it will not only enrich our lives but will pave the way for greater things yet to come. My love to you and our children.

We make plans. God plans outcomes.

Daniel 2:20

Appendix

The final version of the guidelines to the treatment planners for the participation in this study (see section 3.4, p. 35) and the letter of approval from the ethics committee of the University of the Free State (see section 3.11, p. 49) are given in the appendix. All references to Clinic1 have been removed.

Radiotherapy Planning Protocol on an XiO Treatment Planning System"
Joseph Steyn [Medical physicist, Equra Health]

The updated guidelines consist of two sections: one for the medical physicist (MP), and one for the treatment planning radiotherapist (RTT). Please see below for details.

Prostate CRT planning guidelines – MP

Please allow your local CMS/Elekta XiO® treatment planning system (TPS) to comply with the following requirements:

1. Add the clinic onto your local XiO® TPS(s).
1. Next, add the *ProstateStudy* (Patient ID: *FusionProstate*) patient in the clinic patient directory on your local XiO® TPS. Should you do step 1, step 2 will not be needed as the study patient is already in the Patient directory of the latter clinic.
2. After the treatment plan is created as per below, the created conformal radiotherapy (CRT) prostate plan needs to be exported and sent to the researcher.

Prostate CRT planning guidelines – RTT

The following guidelines must be followed when planning the prostate conformal radiotherapy
(CRT) treatment:

1. Only use the *ProstateStudy* (Patient ID: *FusionProstate*) patient added onto your XiO® TPS. Your MP will direct you to the correct patient.

a. The MRI DICOM-images have been removed from this patient and only the CT-slices will be available for use.
b. The CT-density table of the clinic was already attributed to this patient. Please ensure that this conversion file is chosen under Patient File Maintenance (Edit → CT to ED Conversion File). Please ask your local MP for assistance herewith

2. The physical parameters to be followed for treatment planning are as follows:
   a. This CRT treatment is to be performed at the clinic indicated. Therefore, planning should only be done using this clinic on your XiO® TPS.
   b. The patient is prescribed a dose of 54 Gy to be given in 27 fractions to the main planning target volume given as PTV1. A boost-volume treated with 20 Gy in 10 fractions then needs to be added for a total dose of 74 Gy in 37 fractions. This is the total radiotherapy treatment prescription to be given.
   c. 6 MV and/or 15 MV beams may be used.
   d. Any number and arrangement of beams may be used. (Please do note: This is not an IMRT patient.)
   e. As in Equra Health's protocol, the recommendations of the International Commission on Radiation Units and Measurements (ICRU) report 50 and 62 are to be followed:
      i. The prescription point is to be on the isocentre.
      ii. The planning target volume (PTV) is already on the treatment plan.
      iii. A minimum of 95% and a maximum of 107% of the prescribed dose should cover the PTV. Any dose lower or higher than this range will be regarded as cold or hot spots, respectively.
   f. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) tolerance-dose limits are to be followed for the OARs given below. These are as follows:
      i. Rectum: 50 Gy < 50 %; 60 Gy < 35 %; 65 Gy < 20 %; 75 Gy < 15 %.
      ii. Bladder: 65 Gy < 50 %; 70 Gy < 35 %; 75 Gy < 25 %; 80 Gy < 15 %.
      iii. Femoral heads: 60 Gy < 5 %.

3. The choice for a best CRT prostate plan is made according to the treatment planning team. This includes the radiation therapist performing the treatment planning, as well as the medical physicist (if available).

Thank you for your kind participation in this study, which will hopefully allow improved and more efficient treatment of CRT prostate patients at Clinic1.

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Letter of approval from the Ethics Committee of the University of the Free State.

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS UV

Research Division
Internal Post Box G40
☎(051) 4052812
Fax (051) 4444359

E-mail address: StraussHS@ufs.ac.za

Ms H Strauss

2014-07-30

REC Reference nr 230408-011
IRB nr 00006240

MR JM STEYN
P O BOX 263209
THREE RIVERS
1935

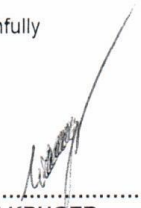
Dear Mr Steyn

ECUFS NR 118/2014
MR JM STEYN **EQURA HEALTH**
PROJECT TITLE: VERIFICATION OF PROSTATE CONFORMAL RADIOTHERAPY PLANNING PROTOCOL ON AN XIO TREATMENT PLANNING SYSTEM.

1. You are hereby kindly informed that the study was approved at the Ethics Committee meeting held on 22 July 2014.
2. Committee guidance documents: Declaration of Helsinki, ICH, GCP and MRC Guidelines on Bio Medical Research. Clinical Trial Guidelines 2000 Department of Health RSA; Ethics in Health Research: Principles Structure and Processes Department of Health RSA 2004; Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Second Edition (2006); the Constitution of the Ethics Committee of the Faculty of Health Sciences and the Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines.
3. Any amendment, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.
4. The Committee must be informed of any serious adverse event and/or termination of the study.
5. All relevant documents e.g. signed permission letters from the authorities, institutions, changes to the protocol, questionnaires etc. have to be submitted to the Ethics Committee before the study may be conducted (if applicable).
6. A progress report should be submitted within one year of approval of long term studies and a final report at completion of both short term and long term studies.

7. Kindly refer to the ETOVS/ECUFS reference number in correspondence to the Ethics Committee secretariat.

Yours faithfully



.....
PROF WH KRUGER
CHAIR: ETHICS COMMITTEE

Cc Dr FCP du Plessis

Declarations

I, Joseph Steyn, declare that the master's research dissertation or interrelated, publishable manuscripts / published articles that I herewith submit to the University of the Free State, is my independent work and that I have not previously submitted it for a qualification at another institution of higher education.

I, Joseph Steyn, hereby declare that I am aware that the copyright is vested in the University of the Free State.

I, Joseph Steyn, hereby declare that all royalties as regards intellectual property that was developed during the course of and/or in connection with the study at the University of the Free State, will accrue to the University.

Joseph Steyn