2021•2022

Faculteit Industriële Ingenieurswetenschappen

master in de industriële wetenschappen: nucleaire technologie

Masterthesis

Implementation of a gEUD-based planning system for prostate cancer

PROMOTOR :

Prof. dr. Brigitte RENIERS

PROMOTOR :

Ms.Sc. Koen TOURNEL

COPROMOTOR :

Ms. Sc. Alexandra JANKELEVITCH

Marte Helsen

Scriptie ingediend tot het behalen van de graad van master in de industriële wetenschappen: nucleaire technologie, afstudeerrichting nucleair en medisch

Gezamenlijke opleiding UHasselt en KU Leuven

2021•2022

Faculteit Industriële Ingenieurswetenschappen

master in de industriële wetenschappen: nucleaire technologie

Masterthesis

Implementation of a gEUD-based planning system for prostate cancer

PROMOTOR :

Prof. dr. Brigitte RENIERS

PROMOTOR :

Ms.Sc. Koen TOURNEL

COPROMOTOR :

Ms. Sc. Alexandra JANKELEVITCH

Marte Helsen

Scriptie ingediend tot het behalen van de graad van master in de industriële wetenschappen: nucleaire technologie, afstudeerrichting nucleair en medisch

UHASSELT KU LEUVEN

Foreword

I got the chance to work together with the Limburgs Oncologisch Centrum (LOC) on implementing generalized Equivalent Uniform Dose (gEUD) based treatment planning in the radiotherapy departments of Ziekenhuis Oost-Limburg (ZOL) Genk and Jessa hospital Hasselt. This was in collaboration with the University of Hasselt. It gave me the chance to get to know the medical nuclear work field. Last year I also did my bacherlor's scriptie for the LOC. Since I was already very interested in what they do, it was honour to be able to work with them again. During this year it was interesting to gain knowledge of gEUD and the possibilities to take into account the biological effects of a dose deposited in the organs by the radiotherapy treatment. Because of this interesting experience I am sure that I want to become a medical radiation physician.

First, I want to thank Ms.Sc. Koen Tournel and Ms.Sc. Alexandra Jankelevitch for the support, feedback and knowledge they gave me during this year. They gave me the guidance and insights I needed to achieve all of this. It was an honour to be able to participate in their research, to work together and to learn from them.

Second, I want to thank my promotor Prof. dr. Brigitte Reniers for the support. I also want to thank drs. ing. Dries Colson for revising my work and giving feedback. The feedback was very useful.

Last, I want to thank some people that are very important to me: my mom, dad and sisters for the motivation and mental support when needed, even when they did not understand what I was talking about, and for the alleviation of the atmosphere in stressful and tough moments; my friends for the support they gave me and for motivating me to get back to work during this whole process of learning and my classmates for the possibility to ventilate if things were stressful and to help when I had a problem.

Index

List of tables

List of figures

Glossary

CTV	clinical target volume
D/V	dose/volume
DVH	dose-volume histogram
EQD2	equivalent dose in 2Gy-fractions
EUD	equivalent uniform dose
gEUD	generalized equivalent uniform dose
IMRT	intensity-modulated radiation therapy
LINAC	linear accelerator
LOC	Limburgs Oncologisch Centrum
LQ	Linear-quadratic model
MLC	multileaf collimator
NTCP	normal tissue complication probability
OAR	organ at risk
PTV	planning target volume
SF	surviving fraction
TCP	tumour control probability
TPS	treatment planning system
VMAT	volumetric modulated arc therapy

Abstract

Currently dose/volume-constraints are the golden standard for optimization of intensity-modulated radiotherapy planning. A possible alternative is using generalized equivalent uniform dose (gEUD)-based constraints which are based on the radiobiological properties of the tissue and a volume parameter a. The implementation of this technique for prostate cancer is studied in cooperation with the Limburgs Oncologisch Centrum (LOC).

An a posteriori study is performed using data of 106 patients to define base-line values for the EUD of all organs and compare with the literature. A planning protocol to recreate or improve identical-quality plans using gEUD is developed. The results are reported both quantitively and qualitatively. An analysis based on NTCP is also performed.

The a posteriori study shows peaked distributions for the gEUD-values of rectum, bladder and target for all volume parameter values and a more smoothed uniform distribution for bowel because of large volume inconsistency between patients. The peaked distributions allows the use of gEUD-constraints. Using these results in a 3-parameter gEUD-plan it is possible to recreate 10/10 treatment plans and improve organ-at-risk (OAR) sparing in 6/10 cases.

gEUD-planning is feasible in case of prostate cancer with building a protocol from a consistent and robust baseline, since the literature values do not agree with the protocol values. The resulting plans show the same or better plan quality.

Abstract – Dutch

Momenteel zijn dosis/volume-constraints de gouden standaard voor optimalisatie van intensiteit-gemoduleerde radiotherapie planning. Een mogelijk alternatief zijn de “generalized equivalent uniform dose”(gEUD)-gebaseerde constraints. Die zijn gebaseerd op radiobiologische eigenschappen van het weefsel en de volume parameter a. Implementatie van deze techniek is bestudeerd voor prostaatkanker, in samenwerking met Limburgs Oncologisch Centrum (LOC).

Een a posteriori onderzoek is uitgevoerd door gebruik van data van 106 patiënten om basiswaarden voor EUD te bepalen voor alle organen en te vergelijken met de literatuur. Er is een planningsprotocol ontwikkeld om plannen met dezelfde of betere kwaliteit te creëren a.d.h.v. gEUD-constraints. NTCP-waarden zijn ook geanalyseerd.

Het a posteriori onderzoek toont een gepiekte verdeling van gEUD-waarden voor rectum, blaas en target voor alle volume parameters en een vloeiende, uniforme verdeling voor darmen door grote volume-inconsistentie tussen de patiënten. Deze gepiekte verdeling maakt gEUD-constaints bruikbaar voor planning. Door gebruik van resultaten in een 3-parameter gEUD-plan was recreatie en verbetering van organ-at-risk(OAR)-sparing mogelijk voor 10/10 en 6/10 plannen.

gEUD-planning kan voor prostaatkanker door het creëren van een protocol vanuit een consistente, robuuste basis aangezien de literatuurwaarden hiermee niet overeenstemmen. De resulterende plannen tonen dezelfde plankwaliteit. Deze gEUD-techniek is niet direct gelinkt aan de biologische effecten voor OAR’s.

1 Preface

The vzw Limburgs Oncologisch Centrum (LOC) is a hospital association and a separate legal entity between the Jessa hospital in Hasselt and ziekenhuis Oost-Limburg (ZOL) hospital in Genk. It is a non-profit organization that manages and operates the radiotherapy services in located in both Jessa hospital as ZOL hospital. [1] in 2021 the LOC treated almost 3000 patients. 480 of them were prostate patients. It is equipped with five up-to-date linear accelerators capable of modern radiotherapy techniques.

In the LOC, like the majority of radiotherapy departments, an inverse-planning technique based on dose/volume-constraints is used for intensity-modulated radiotherapy treatment planning of prostate. Although historically considered as the gold standard, this technique had its disadvantages. The treatment planning system (TPS) used, Varian Eclipse® TPS, is also able to process general generalised equivalent uniform dose (gEUD) based constraints as an alternative in the treatment planning process. This alternative technique is considered a more biologically-based way of treatment planning.

Unlike the dose/volume-constraints these constraints should in theory take into account the biological effect on the organ of the dose deposited in the organ. The question arises if this technique can produce a better treatment plan with more sparing of the Organs At Risk (OAR) and with the same coverage of the target? Radiotherapy treatment planning is a process that is very diverse and tumour, location and patient-dependent. To allow for a consistent study, this thesis focuses on prostate cancer.

This thesis will study the gEUD-based treatment planning to gather knowledge about the practical use of this type of treatment planning and the advantages it could have compared to the planning based on dose/volume-constraints. The prostate is chosen for different reasons: the clear constraints that exist for it; a relatively small variation in size and location of the target; a great number of patients available in the database and very consistent plan quality.

First, a literature study is performed to learn about what gEUD is, where it comes from and to gain knowledge about the state of the art of this gEUD-based treatment planning and the ways this treatment planning technique is currently used. Another goal for this part was to get a starting point that can be used for the actual practical study that will also be executed.

The second part is an a posteriori study that aimed to gain information about gEUD from patient data that was already available in the LOC. The goal was to investigate if a common thread exists by looking into clinical treatment plans. This part of the study will focus on specific OARs, rectum, intestines and bladder, and the target.

Third, a practical study is performed to see what are the possibilities are of the gEUD-based planning in practical cases. The aim is to implement a planning protocol using gEUD-constraints which can replace the existing dose/volume-based protocol and create plans of similar quality. Therefore, the original plan based on dose/volume-constraints will be reconstructed by using gEUD-constraints. Next, an attempt was made to improve the original plans by using gEUD-constraints. This way it should be possible to identify the potential of gEUD-based planning and the possible benefit for patient treatment in the LOC.

Finally, the results found in this study are compared to the values for volume parameter a and gEUD that are found in different sources of literature. The aim of this part is to check

how much biology is present in the practical implementation of this technique and if the assumption of “biology-driven treatment” is really true.

2 Literature study

2.1 Introduction and general framing

In modern radiotherapy inverse planning and optimisation are the standards for planning Intensity Modulated Radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT). In this approach the desired dose constraints on targets and organs-at-risk (OAR) are entered by the user. The system will then try to generate modulated beams for which the calculated dose satisfies the constraints by using an inverse optimization function. It is possible to "steer" this process in a certain direction using a system of cost functions, weights and penalties: depending on the weights/penalties certain solutions of the optimisation function can be favoured. Since conflicting constraints and overlap between targets and OARs can cause major problems, this "steering" is an important part of the process.

Historically, the cost functions used for describing the dose constraints have been Dose Volume Histogram (DVH) based : dose/volume(D/V)-constraints, which means a certain dose on a certain volume for the organ, or maximum constraints for the organs-at-risk or minimum, maximum or mean/median constraints on the targets. To every constraint a weight/penalty is attached, which is transferred into the optimisation process. The advantage is that a well-known metric, such as DVH, is used and the constraints can be defined by points on the curve, which allows for a straight-forward evaluation.

However, this approach also has some disadvantages. By using max or min constraints the optimizer will be forced to "push" dose in or out of very limited volumes which sometimes are irrelevant. Dose/volume constraints are only affecting one specific point on the curve, and not considering the curve as a whole. These dose/volume based cost-functions do not take into account the inherent radiobiological nature of the tumour and normal tissues: organs can be parallel, serial or a combination of both. For a parallel organ the toxicity is a function of a certain dose on a certain volume. The lungs are an example of a parallel organ. The toxicity of a serial organ, the intestine for example, is a function of the maximum dose.

Most of these issues can be solved by using multiple constraints, which means pushing on a lot of points. This will result in a very complicated optimisation process with a great chance on conflicting effects on the optimisation function. As a result of that, the time required for calculation and optimization will be longer. Because more parameters are used it will also be more difficult to produce a consistent method of planning for the entire patient population.

The last few years the approach has shifted to more biologically based cost functions which try to overcome these planning issues. These biological cost functions often find their origin in radiobiological models. Using these in the planning process is referred to as "Biological Optimisation". [2]

However, current planning protocols are well established using the "old" cost functions and the old planning technique. Using these new tools requires good knowledge of their background to be able to use them correctly. It is necessary to recreate the same plan quality using these new tools and investigate if there is still room for improvement. This study will investigate the implementation of these biologically based constraints, specifically for prostate cancer.

In the Limburgs Oncologisch Centrum (LOC) the Varian Eclipse® Treatment Planning System (TPS) is used. Currently, they only use the dose/volume-based cost functions for IMRT/VMAT-plans. This study investigates another possibility also available in Eclipse: (generalized) Equivalent uniform dose (EUD). The first part of this literature study will investigate the system of EUD and gEUD to see why it can be useful to use this way of planning instead of the planning based on physical constraints. After that will be described how gEUD can be used in treatment planning. Next, the literature study will describe the meaning of the gEUD-parameters and will try to identify the parameters that will be needed in the practical part of this thesis, implementing it in the planning system of the hospital.

The definition of EUD is given by formula 1.

$$\mathrm{gEUD} = \left(\sum_{i} v_i \, D_i^a\right)^{1/a} \quad [3] \tag{1}$$

Here: a = volume effect parameter, D = dose, v = partial volume that gets dose D
This equation can be used for both normal tissue and tumours.

The gEUD is defined radiobiological as the dose that, when given homogeneously to a structure, will cause the same radiobiological effect, in terms of tumour control or toxicity, as the given dose distribution. gEUD is equivalent to EUD. It is the same concept but in a more general formula with less parameters. The a-value in this formula can be used for both OARs and target, while for EUD the a is only used for OARs. [4] This addresses an important issue: the toxicity data often is coming from historical data from a time when homogenous irradiation of tissue using a limited number of treatment fields was standard. Currently this is not the case anymore [5] as in IMRT/VMAT the dose distributions to OAR are inherently inhomogeneous because of the use of sharp gradients that allow more tissue sparing. By using EUD the old data can be compared to modern planning results.

gEUD and the a-value are organ specific parameters. Values for a and gEUD can be found in literature. An overview of the values found in literature is given in table 1. The a-value is a dimensionless volume parameter which contains information about the seriality of an organ. If a = 1, then gEUD is equal to the mean dose. This value can be used for organs that have a large volume effect and have a parallel nature. The mid-dose section of the DVH will be affected. This is visualized in figure 1.

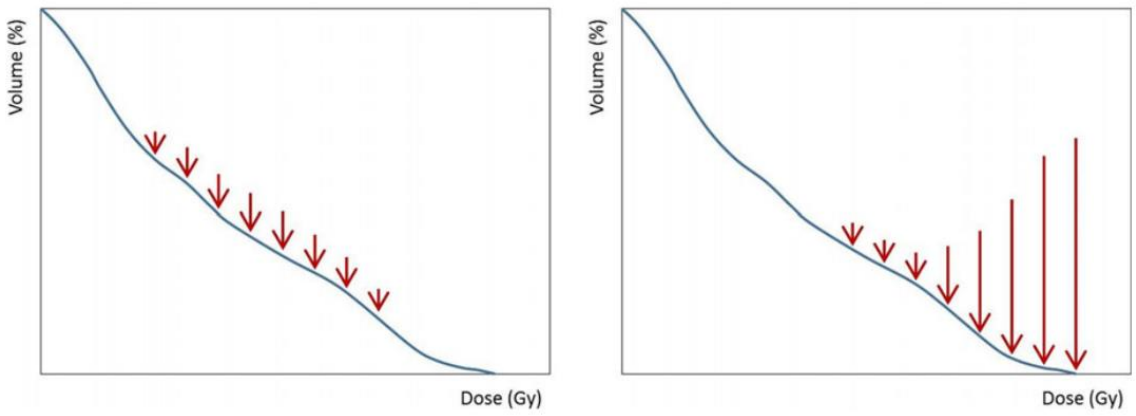


Figure 1: left: a=1, right: a= high value (>10) [6]

A dose can be considered low, middle or high for a value of respectively 0-30%, 30-70% or > 70% of the prescribed dose.

It is important to correctly identify the parallel or serial nature of an organ because there are effects that will occur when an organ is presumed to be serial or parallel but is not. When an organ is presumed to be serial but it is not, then it will not be controlled enough in the low- and mid-dose ranges. When an organ is believed to be parallel but is not, hotspots will be allowed where it should not be allowed. [2] The choice of the value of the volume parameter a is important, and the question will be if it is safe to use only one value in treatment planning, or that multiple values will be necessary.

The gEUD concept can also be linked directly to certain normal tissue complication probability (NTCP) or tumour control probability (TCP) models. For example, in the model of Niemierko *et al.* [7] the EUD is used supplemented by physical objectives.

$$\mathrm{NTCP} = \frac{1}{1+\left(\frac{\mathrm{TD}_{50}}{\mathrm{EUD}}\right)^{\gamma_{50}}} \text{ [8]} \tag{2}$$

$$\mathrm{TCP} = \frac{1}{1+\left(\frac{\mathrm{TCD}_{50}}{\mathrm{EUD}}\right)^{\gamma_{50}}} \text{ [8]} \tag{3}$$

Here: TCD_{50} = tumour dose needed to control 50% of the tumours when irradiated homogenously, TD_{50} = tolerance dose for a 50% complication rate within a specific time interval, γ_{50} = specific parameter for the healthy tissue or tumour of interest, describes the slope of the dose response curve. [8]

Table 1: overview of a- and EUD-values from literature

Literature source	[2]	[9]	[10]	[11]
a-value				
PTV (prostate)	-10	/	-10	-10
Rectum	8	/	6.0	8.33
Bladder	8	/	6.0	2
Intestines	/	/	/	/
EUD-value [Gy] for Eclipse® TPS				
PTV	71.41	80.5	72	/
Rectum	41.30	53.3	35	/
Bladder	45.79	72.9	35	/
Intestines	/	/	/	/

2.2 EQD2 [12]

The dose value for each dose bin in the definition of gEUD given by formula 1 is the equivalent dose in 2Gy-fractions for that bin. The equivalent uniform dose in 2Gy-fractions (EQD2) is an important tool to describe the toxicity of a dose delivered to a specific tissue taking into account the amount of fractions that are used to treat the patient. It allows to compare the patient doses resulting from different fractionation schemes, or in non-homogenous dose regions.

$$\mathrm{EQD2} = \mathrm{n} * \mathrm{d} * \frac{\{\mathrm{d} + (\alpha/\beta)\}}{\{2 + (\alpha/\beta)\}} \tag{4}$$

Here: n = number of 2Gy-fractions, d = dose per fraction

The linear-quadratic model (LQ) is based on calculations of the surviving fraction (SF) of cells in function of the dose D. Other parameters in the function are α and β, they represent the radiosensitivity of the irradiated cells. The α/β-ratio represents the fractionation sensitivity of the cells. [13] This is visualized by figures 2 and 3. Figure 2 shows the practical meaning of α and β and figure 3 visualizes the effect of the α/β-ratio.

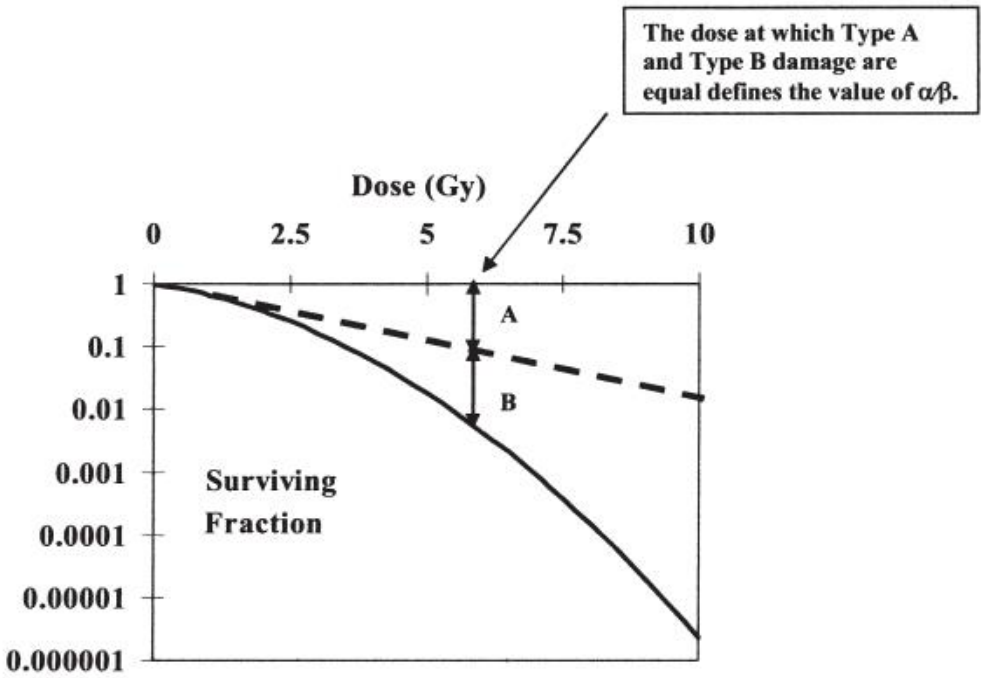


Figure 2: meaning of α, β and α/β-value [14]

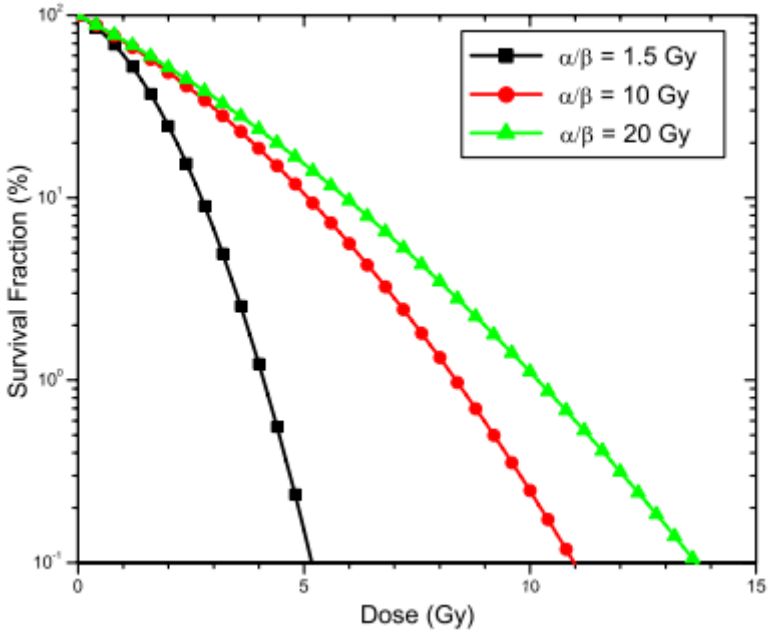


Figure 3: effect of α/β-ratio in LQ model [15]

There is a great number of articles available that estimates the α/β-value of prostate tumours. The values found in these studies differ a lot. C. Schröder *et al.* reports α/β = 3 for OARs and 10 for the target volume. [12] M. van Leeuwen *et al.* states that a prostate tumour has a high sensitivity for fractionation with a α/β of around 4Gy. This source compares 64 other studies to make its conclusion. [13] J.Z. Wang *et al.* found a α/β ratio of 3.1Gy for the prostate target with an uncertainty of 0.5Gy. [16]

2.3 EUD in planning

As mentioned in the introduction, the hospital currently uses dose/volume-constraints based treatment planning. Constraints are added to the DVH. With these constraints The dose is managed within the patient by giving a certain weight to the constraints, as described before.

The gEUD-constraints can be seen as a series of dose/volume-constraints. Therefore, the gEUD-constraints are more flexible than the DV constraints.

When the volume parameter a=1 the optimalisation of the planning is based on reducing the mid-dose levels. When the a-parameter goes towards -∞, the gEUD reaches the minimal dose. In practical cases, this value can only go until -40 instead of -∞,. This value can be used for tumour tissue. The a-parameter can also go towards +∞, practically until +40. Here the gEUD reaches a maximal dose and can be used for serial organs. For this a-value is the optimalisation based on reducing the volume that gets a high dose. If a<1 there are small volume effect and the organs are serial organs. The max section will be relevant. When the value a increases >1 the emphasis will shift more to the low dose regions.

The use of gEUD-based planning can potentially have benefit since one single parameter can be used for reporting a non-homogenous distribution of the dose instead of multiple parameters with

dose/volume based planning. As explained before, gEUD is an organ specific parameter. It can take into account the biological response of the organ on the delivered dose in that organ. There also is a more direct link with the results of the radiotherapy treatment than when using physical constraints. The optimization criteria within this planning model are more versatile than the physical optimization criteria.

According to the literature, gEUD-based planning could also results in a better sparing of the organs-at-risk (OARs) although this is not confirmed by all studies. Fogliata *et al.* [6] states that gEUD optimization could spare critical structures without changing the target coverage but that it could also enlarge the inhomogeneity resulting in possible hotspots. They state that a gEUD-objective can be safely used for an a-value from 1 until 5 because it reduces the dose on OARs for every dose level. For an a-value greater than that, they think the decisions should be made case per case because the DVH could be greater or smaller in certain regions depending on the structure. [6] L Widesott *et al.* state that there is not always a better sparing of the OARs by using gEUD-objectives. According to them it is strongly dependent on the anatomy of the patient and on the constraint settings. They opt for a combination of dose/volume and EUD constraints because the EUD has less control over the fine details. Another important constatation is that the profit gained by gEUD-based cost functions is greater for head-and-neck cases than for prostate. [17] The results from the literature show a strong dependence on the anatomy of the patient and the settings of the constraints.

There are possible disadvantages coming with gEUD-constraints. Detailed adjustments on the dose distribution are possible with dose/volume-constraints, but this are not possible with gEUD-constraints.

When only gEUD-based constraints are used, it not possible to do detailed dose management and it can also result in a non-homogenous dose distribution. This are two disadvantages of gEUD-based planning that can be solved by adding some dose/volume-constraints, thus using a combination of both techniques since a balance has to be made between sparing of the OARs and target homogeneity.

It would also be possible to use a gEUD-based constraint as a hard constraint because they have a direct link with the risks and complications. But the definition of EUD accepts a form of freedom in shaping the dose distribution, which means a certain power ove the shape of the DVH is lost using these hard constraints. Some of the recommendations for generating a gEUD-based treatment plan are starting with a dose/volume based treatment plan and improve it by adding gEUD-constraints. [18]

The determination of the weight of the gEUD-cost function is another important issue. Widesott *et al.* propose a formula to determine the ideal weight for the gEUD-objective. This formula is given by formula 5.

$$w = c * (gEUD_{max})^k \text{ [17]} \tag{5}$$

Here: c = a parameter related on the chosen stopping tolerance. k = a value between two other values that depend on the type of tissue. w = the weight

Although the values are TPS-dependant and the Eclipse® TPS was not used in this study, we can make the interpretation that the weights that should be used follow a power-law relation, using a tissue dependant factor k as the exponent. This means that weights should not be applied in a linear way but should be larger for higher $gEUD_{max}$-values.

When using the gEUD-based treatment planning, it is important that sparing of the OARs will not cause an under coverage of the target volume. That is why the minimum dose mostly gets a large weight.

Within the gEUD-based planning, there is a link between de distance between OAR and target and the possibility to reach the desired gEUD-value. If an OAR is placed far from the target, it is relatively easy to gain the desired gEUD-value for a lot of different a-values. The literature also states that a higher a-value will cause a lower target coverage. When the OAR is closer to the target, it is only possible for a smaller range of a-values and a change of a-value will not cause a change of the target coverage. This means that the a-value or weight of the constraint should be re-assessed in cases in which targets and OAR are overlapping in a certain degree. [19]

The cost function of gEUD-based optimalisation is given by equation 6.

$$f_{gEUD} = \omega * H\,(gEUD - gEUD_{max}) * \left(\frac{gEUD - gEUD_{max}}{gEUD_{max}}\right)^2 \qquad (6)$$

Here: w = the weight, H = Heaviside step function given by formula 7.

$$H(gEUD - gEUD_{max}) = \begin{cases} 1, & gEUD > gEUD_{max} \\ 0, & gEUD \leq gEUD_{max} \end{cases} \quad [20] \qquad (7)$$

This means that the gEUD-cost function uses a relative quadratic difference between the actual and the reference gEUD. Once the constraint has been met, this means gEUD < gEUDmax, the cost function goes to zero. This implicates that user intervention is required to check if the constraint can be tightened.

2.4 EUD constraints

Within the Varian Eclipse® TPS, there are several constraints possible: upper gEUD, lower gEUD and target gEUD.

Upper gEUD defines the maximal equivalent uniform dose that a structure or tissue may get. Here the a-value $\in [+0.1; +40]$. For the lower gEUD- constraint the a-value $\in [-40; +1]$, 0 excluded. It defines the minimal equivalent dose the structure must get. The Target gEUD defines the exact equivalent uniform dose that the target volume must receive. Here, the a-value is within the same range as for lower gEUD.

For the ECLIPSE® system of Varian there are some specific sensitivities shown in figure 4 for changing one parameter at a time in a head-and-neck study.

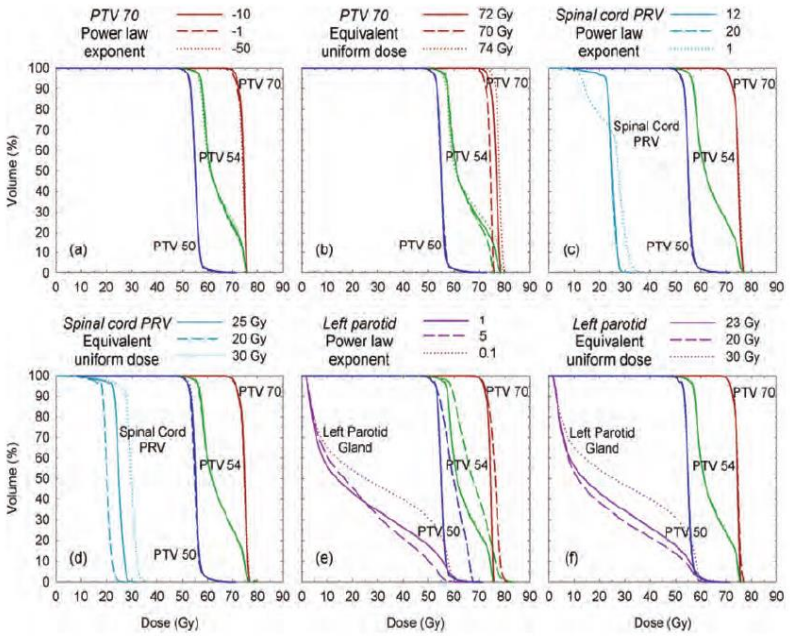


Figure 4: sensitivity of the dose distribution for head-and-neck cancer [2]

The graphs shows that if you change the threshold for the maximum gEUD increases, the DVH shifts uniformly towards the threshold dose.

In other literature, there are a-values given for different organs for treatment of different tumours. These values are given in the table 1. These can be good starting points for the practical part of this thesis.

2.5 Pitfalls of gEUD-planning

There are some issues that can arise when using this gEUD-based planning technique. The first issue is because of the nature of the functions that is used. Biologically based models using more pronounced non-linear functions than dose/volume based functions tend to magnify the effect of any uncertainty in the dose and/or DVH calculations. Therefore, the uncertainties on DVH computations with gEUD will increase. If the uncertainties have a random, and not systematic, nature the gEUD-error will be on the safe side. This means that the EUD of the healthy tissue will be overrated and there will be an underestimation of the target EUD. [2] A second issue is that the EUD is calculated directly from the DVH. Depending on the implementation of the TPS, a DVH may be more than just the straightforward statistics of the voxel doses of an organ. Thus, gEUD computed directly from the dose calculation grid and from the computation of a DVH, such as voxelization, interpolation and volume normalization, affect the computation of the gEUD. Connected to this is also the fact that literature-based gEUD-values are calculated from a EQD2-normalized DVH. Within a TPS-optimisation this is not the case resulting in “different” values. Therefore a conversion has to be performed.

3 Methods and materials

3.1 A posteriori study

An a posteriori study looks at data. In this case previously planned and treated patients were studied and investigated if this data can be used as a premise for the new study. [21]

For this part of the study the treatment plans of 106 prostate cancer patients were used. All patients were diagnosed with grade 1, 2 or 3a tumours without nodal involvement or metastatic disease. The radiotherapy treatment was performed using a 2-arc VMAT technique on a Varian CLINAC® or Truebeam® accelerator using 6, 10 or 15 MV photon beams. A hypofractionation scheme of 20 times 3Gy was used according to a treatment protocol based on one arm of the CHHIP-trial, 60Gy/20fx. [22] The Clinical Target Volume (CTV) was contoured by a radiation oncologist and expanded using margins of 6mm in lateral and 8mm in every other direction. The CTV and the margins form the Planning Target Volume "PTV BST". [23] Full rectum, bladder and bowel were contoured, together with the femoral heads. A rectum and bladder filling protocol was used. The protocol for bladder filling is 250ml of water 15 minutes prior to the CT-scan and treatment and the rectum preparation protocol is a mild laxative 2 hours before the treatment to empty the distal art of the rectum.

The plans were reviewed by a radiation oncologist and were then used for clinical treatment of the patient. The plans were originally optimized using Eclipse® v15.6 and the Photon Optimizer® 15.6.05. [24] On top of this Varian Rapidplan®, in which the result is compared to a model built on a statistically representative subgroup of patients, was used. By using this method, the differences in experience of the planners were minimized and the treatment plans were all meeting up to the department standard for this indication.

The results of planning and optimizing can be visualized in two different ways using a DVH. The Differential DVH, that is used for the numerical data of the patients, represents the volume that receives a dose in the corresponding dose bin while the cumulative DVH represents the volume that receives a dose that is greater than or equal to the value given by the corresponding dose bin. The cumulative DVH is preferred for visual inspection of plan quality, but for computational purposes the differential DVH is preferred like in this study. The cumulative and differential DVH are shown in figures 5 and 6 respectively. The differential DVHs for these clinical plans were exported using the Eclipse® TPS to a numerical file.

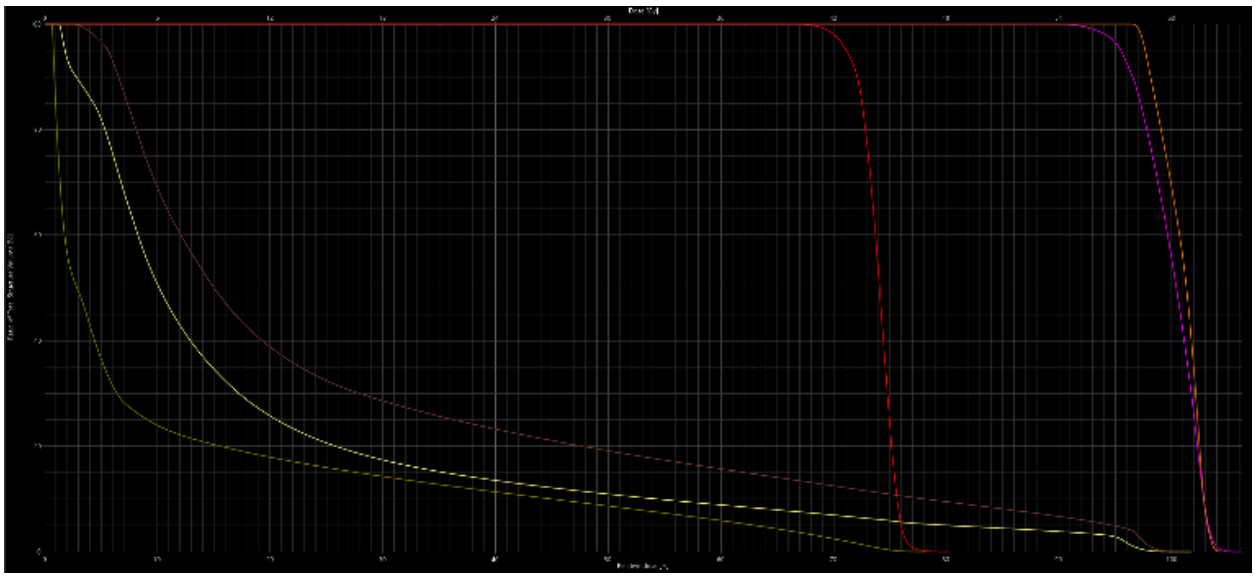


Figure 5: Cumulative DVH

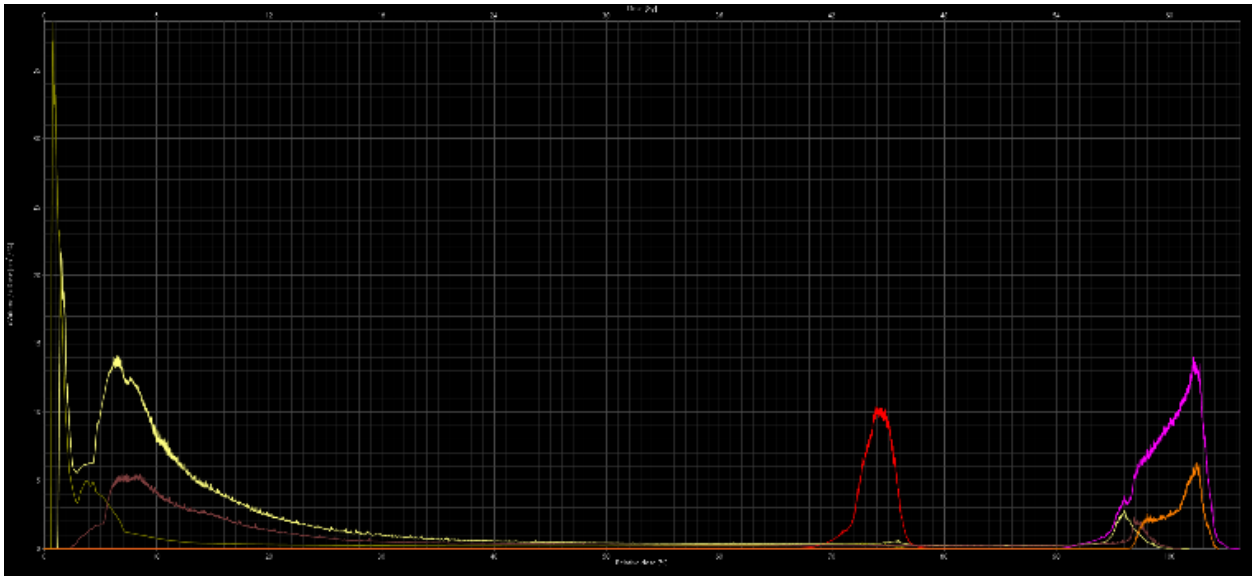


Figure 6: Differential DVH

The raw data file was imported into Microsoft Excel and calculations were executed on the numerical DVHs of each patient. The dose in Gray (Gy) and the dVolume/ddose in cm^3/% are given in the DVH. EUD is defined for Equivalent Dose in fractions of 2Gy (EQD2). Therefore, all data was converted from dose to EQD2 by using formula 8.

$$\mathrm{EQD2} = \mathrm{D} * \left((\mathrm{d}) + \frac{\alpha}{\beta} \right) / \left(2 + \frac{\alpha}{\beta} \right) \tag{8}$$

Here D = the total dose in the selected dose bin, d = the dose per fraction and α/β = a value that shows how resistant a cell is for radiation damage. For the OARs a α/β ratio of 3 is used and 3.5 is

used for the PTV BST, according to the literature as described in part 2.2 of this thesis. The number of fractions was 20 for every patient.

The v*dose^a and v*EQD2^a were also calculated in Gray (Gy) in the Excel file to be able to calculate the EUD-value. This was done with both dose D and EQD2 as shown in formulas 9 and 10.

$$\text{EUD D} = \left(\frac{\text{sum}(\text{v} * \text{d}^{\text{a}})}{\text{V}}\right)^{\text{n}} \tag{9}$$

$$\text{EUD EQD2} = \left(\frac{\text{sum}(\text{v} * \text{EQD2}^{\text{a}})}{\text{V}}\right)^{\text{n}} \tag{10}$$

Besides the EQD2, calculation for dose D is also necessary because the treatment planning system is not able to use EQD2-values. Therefore the dose D is required to be able to compare the values from the literature with the results from planning later on in this study.

Not only dose and d_{volume}/d_{dose} were given, also other specifications such as the volume of the organ and the mean dose that were needed for the calculations. The calculations are performed for rectum, PTV BST, intestines and bladder.

An excel template, as visualized in figure 7, allowed rapid calculation of the EUDs for different values of the volume parameter a for every patient. The EUD-value for a=1 for all organs was compared to the mean dose value reported by the TPS as a benchmark. The EUD-values were calculated for every organ and target for a-values of 0.5, 1, 2, 3, 4, 5, 10, 15, 20 and 30. To examine consistency over the examined patient population, frequency histograms were made with the EUD-values of all the patients using a same value of a. Mean values and standard deviations of these distributions were also calculated. Attachment A gives the EUD-values for all used a-values and all patients for the rectum.

Structure: RECTUM											
Approval Status: Approved											
Plan: PROSTAAT											
Course: C1											
Volume [cm³]: 66.9											
Dose Cover.[%]: 100.0											
Sampling Cover.[%]: 100.0											
Min Dose [%]: 6.4											
Max Dose [%]: 102.5											
Mean Dose [%]: 45.1											
Modal Dose [%]: 11.2											
Median Dose [%]: 39.3											
STD [%]: 28.4				Total dose (Gy)	60						
Equiv. Sphere Diam. [cm]: 5.0				Mean dose (%)	45,10%						
Conformity Index: N/A				Mean dose (Gy)	27,06						
Gradient Measure [cm]: N/A											
Dose Level [Gy]:				V (cm³):	66,9		EUD rectum with D				
RTOG CI:				a	0,5		in Gy	24,19			
Paddick CI:				n	2		in %	40,31			
GI:											
ICRU83 HI:				(alfa/beta) ratio	3		EUD rectum with EQD2				
D99.0% [%]:				Aantal fx	20		in Gy	22,29			
:				dDose (%)	0,1		in %	45,60			

Relative dose [%]	Dose [Gy]	dVolume / dDose [cm³ / %]	EQD2 [Gy]	EQD2 [%]	v*d^a in Gy	v*EQD2^a in Gy	v*d^a in [%]	v*EQD2^a in [%]
0,05	0,03	0	0,018009	0,030025	0	0	0	0
0,15	0,09	0	0,054081	0,090225	0	0	0	0
0,25	0,15	0	0,090225	0,150625	0	0	0	0
0,35	0,21	0	0,126441	0,211225	0	0	0	0
0,45	0,27	0	0,162729	0,272025	0	0	0	0

Figure 7: excel template used for EUD calculations for rectum

3.2 Practical study

3.2.1 Reproduction of original plans using gEUD-based constraints

Ten patients were selected at random from the list of 106 patients that was used to execute the a posteriori research. For these ten patients new plans were created by using the trial-and-error method. EUD-constraints were used instead of the dose/volume-constraints used in the original plans. The goal was to recreate the original plans with these EUD-constraints by planning, optimizing and then inspect the resulting DVH to see where adjustments were needed. This was repeated until the original plan was recreated.

Within the Varian Eclipse TPS there is a possibility to compare the resulting DVHs from two different plans. This tool is used to compare the original plan with the new plan and to decide whether the plan is close enough to the original plan or further adjustments are needed. Also, a script was used to test if the EUD-based plans fulfilled all clinical constraints.

3.2.2 Improvement of plans using gEUD-based constraints

Another plan was created for the same ten patients as for the reconstruction. These plans should have an improved sparing of OARs and similar target coverage. The original and improved plans are compared at the level of clinical constraints and a NTCP evaluation was performed using the Niemerko formula [7] to asses for clinical relevant improvement. Here it should be taken into

account that is a very simple model, that should only be used in a relative way to compare the effect of two plans on the same patients. The resulting DVHs of the improved plans were extracted as numerical data from the TPS and the same EUD-calculations were executed as in the a posteriori study. It was then possible to compare the results of both and investigate where the improved plans were positioned in these results of the a posteriori study.

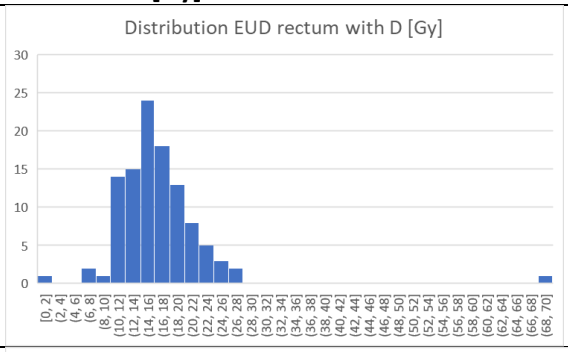
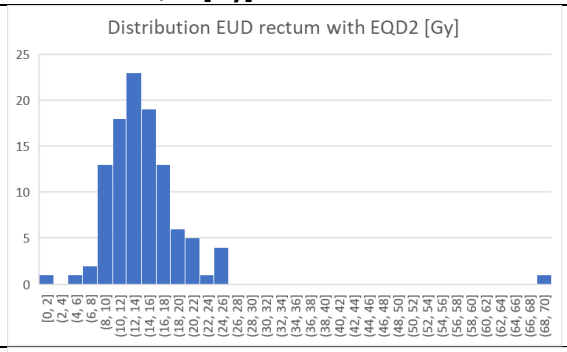
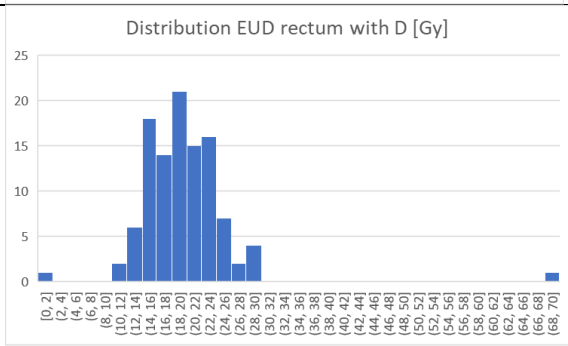
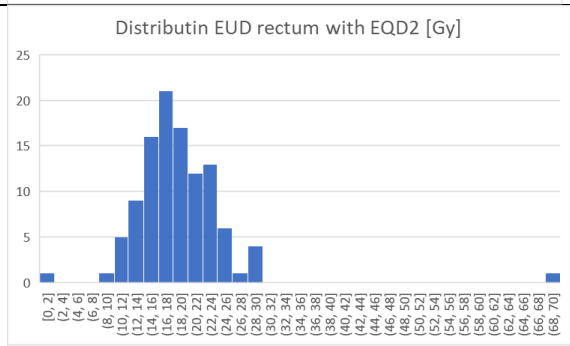
4 Results

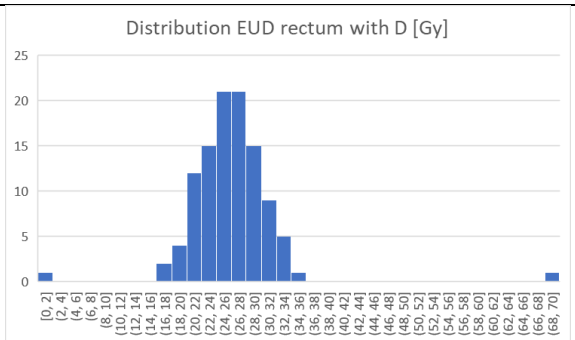
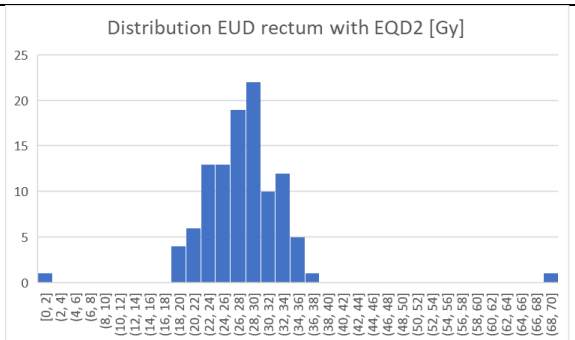
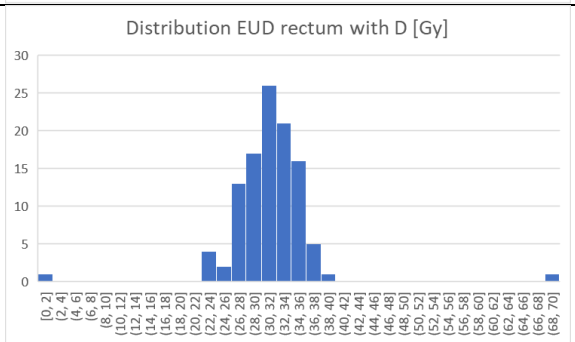
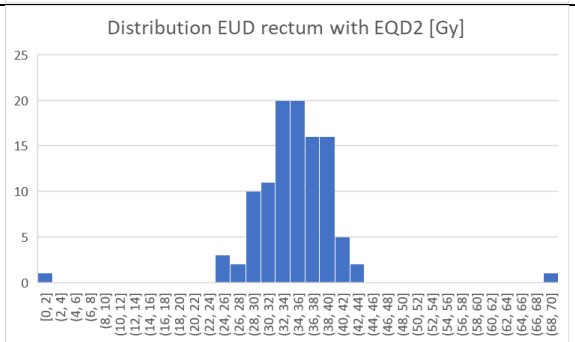
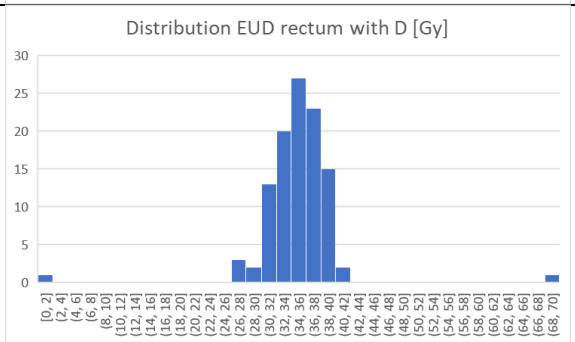
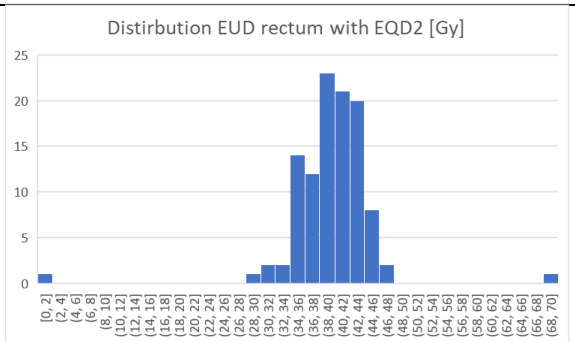
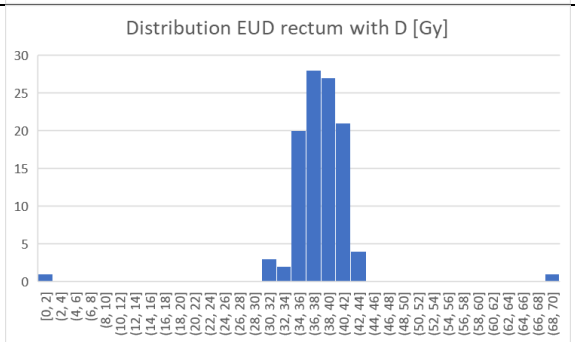
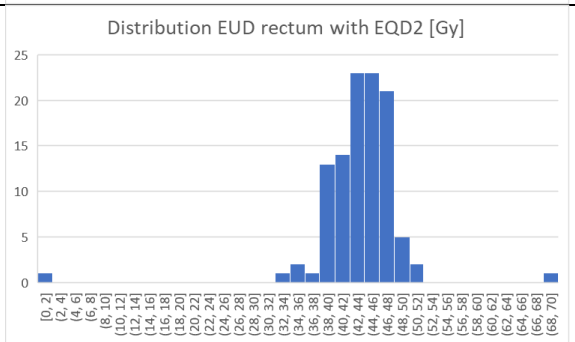
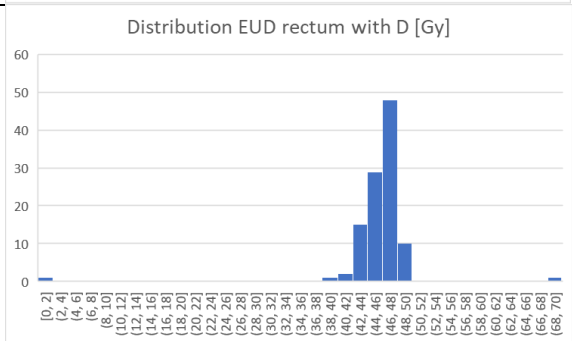
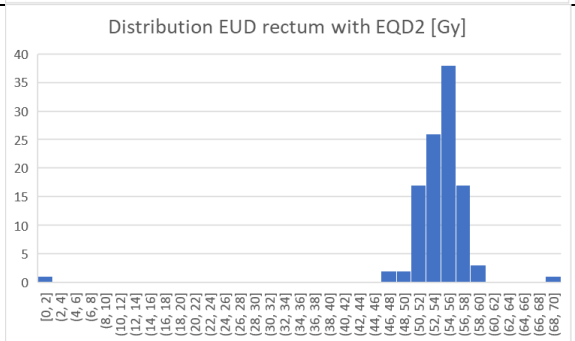
4.1 A posteriori study

The results of the a posteriori study are shown in figures 8, 10, 12 and 14 for respectively rectum, PTV BST, intestines and bladder. For each organ all histograms are scaled and visualized on the same dose axis, therefore two extremum EUD-values are added to the data. The bin width is fixed at 2Gy for the OARs. This is all done to create a clear view of the volume effect for each organ. The axis can differ between different organs.

4.1.1 Rectum

The EUD-values that are added to create the same axis for every plot are 0Gy and 70Gy for the EUD with both dose and EQD2.

	EUD with D [Gy]	**EUD with EQD2 [Gy]**
a = 0.5		
a = 1		

a = 2		
a = 3		
a = 4		
a = 5		
a = 10		

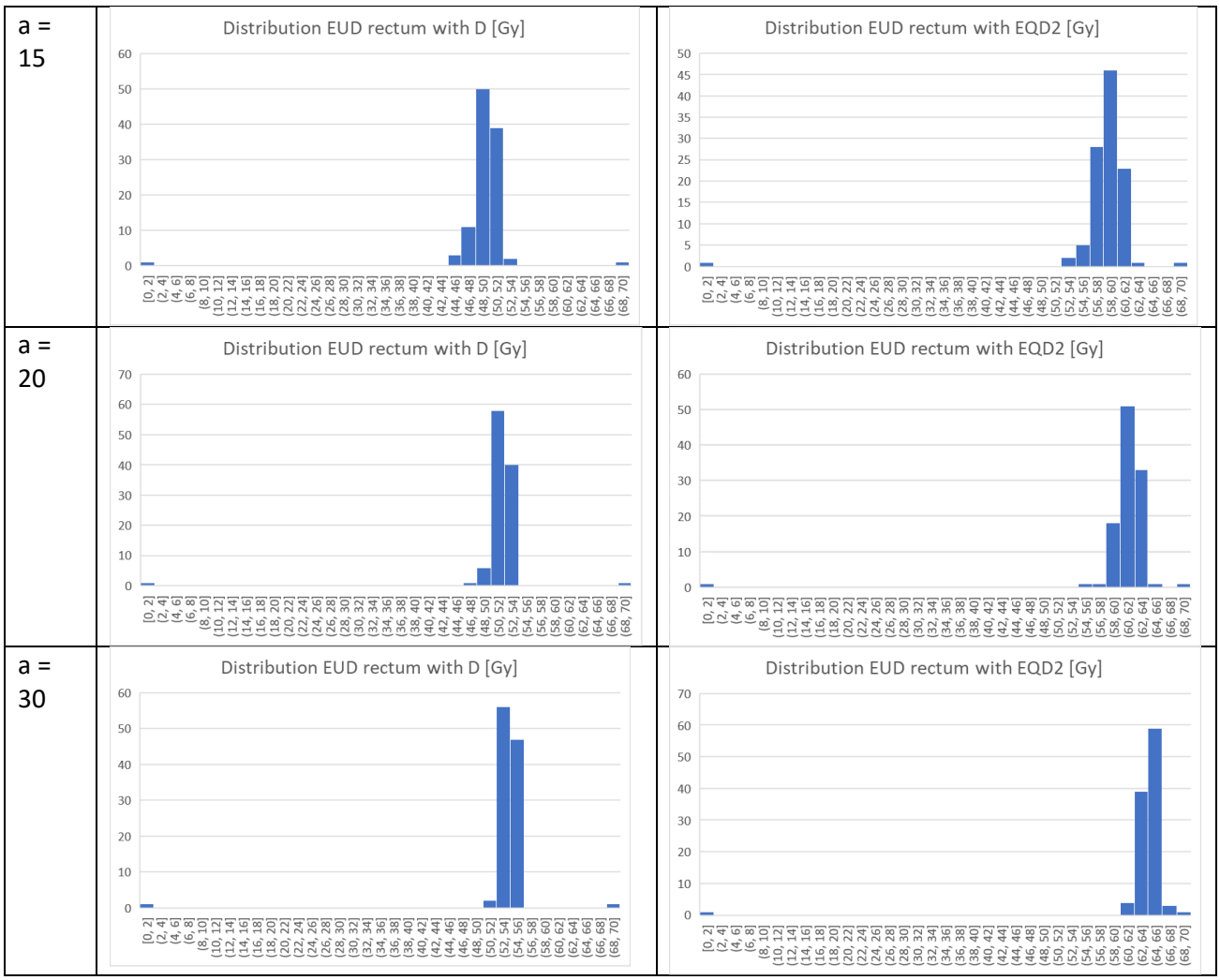


Figure 8: results EUD for a-values for rectum

Since the axis is the same for all plots it is clear that the peak gets finer with an increasing a-parameter and that the peak shifts to the right for both EUD with dose and EQD2. Figure 9 shows that the mean EUD is increasing and the standard deviation is decreasing with increasing value for the volume parameter a, as was indicated by the results of figure 8.

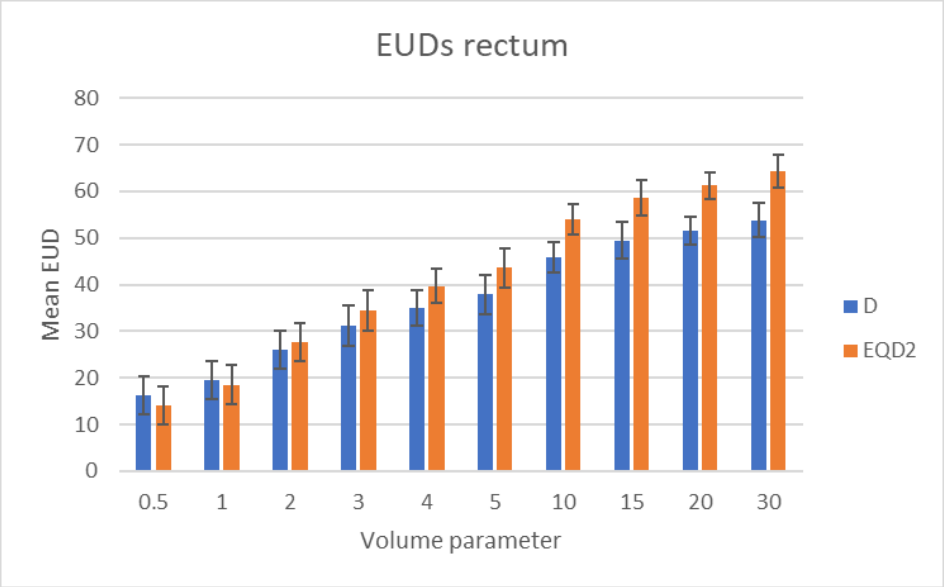
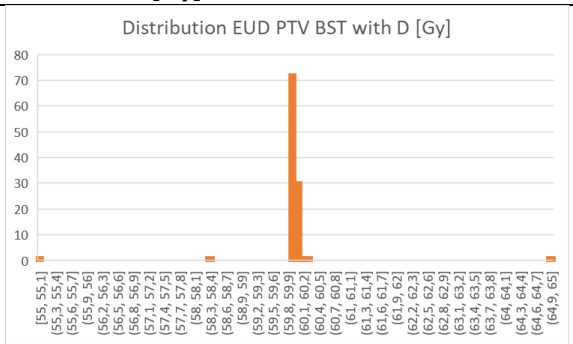
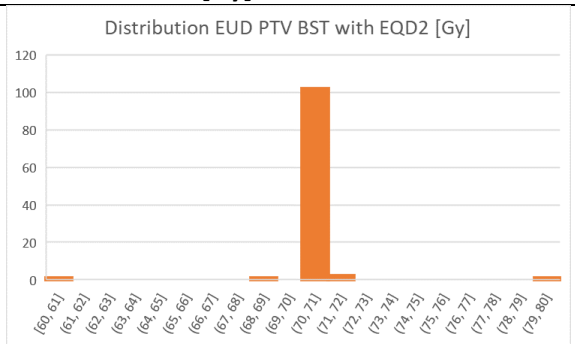
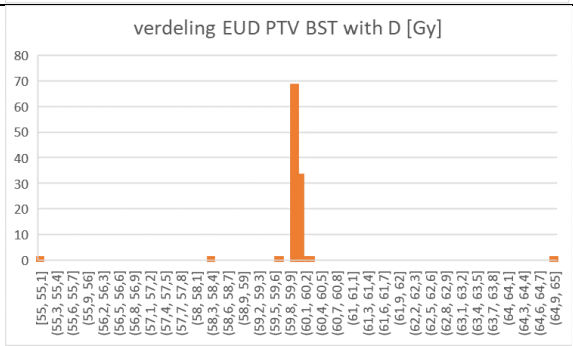
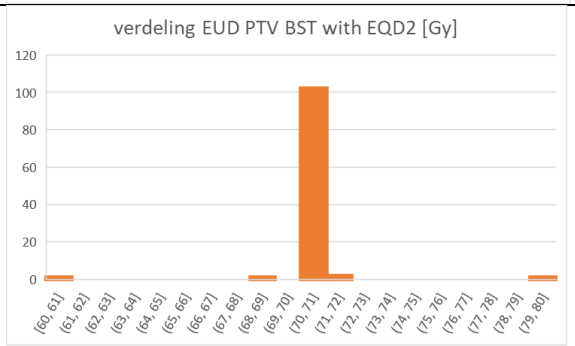


Figure 9: overview mean EUDs for rectum

4.1.2 PTV BST

The EUD-values added to the data for creating the same axis are 55Gy and 65Gy for EUD with D and 60Gy and 80Gy for EUD with EQD2. The bin width is 0.1Gy and 1Gy for EUD with dose and EQD2 respectively.

	EUD with D [Gy]	**EUD with EQD2 [Gy]**
a = 0.5		
a = 1		

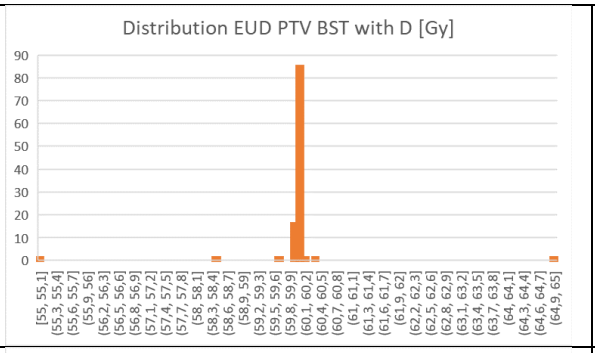
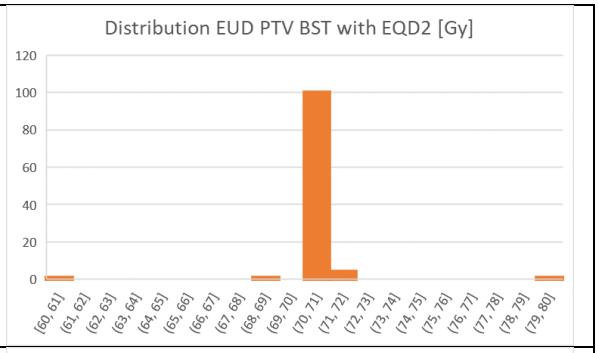
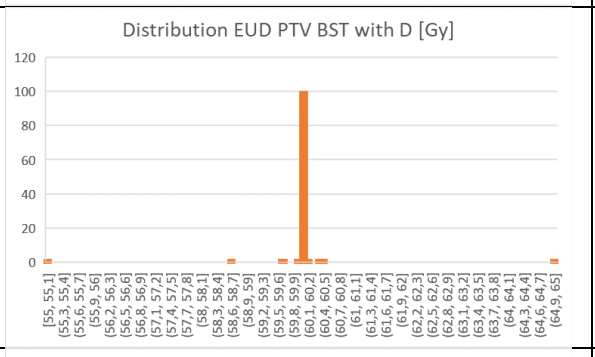
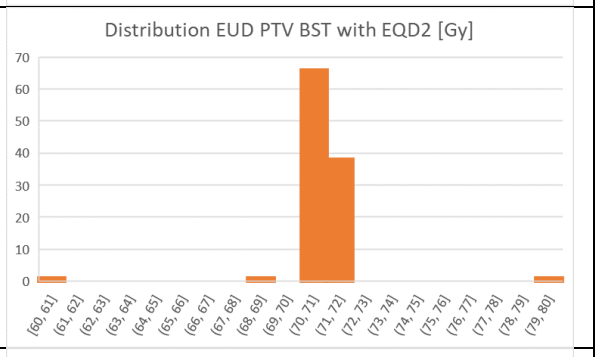
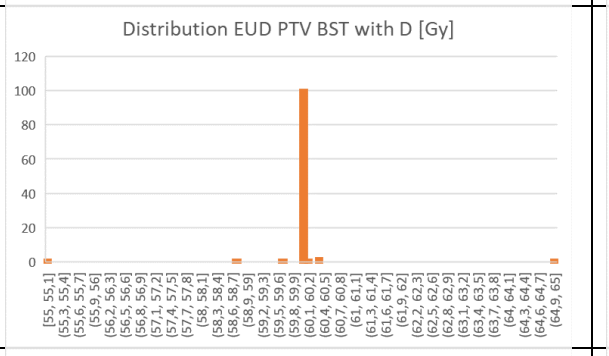
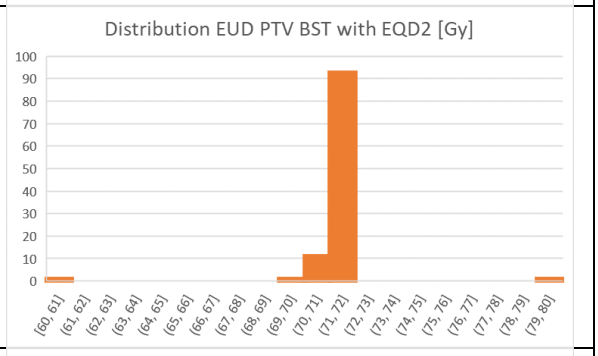
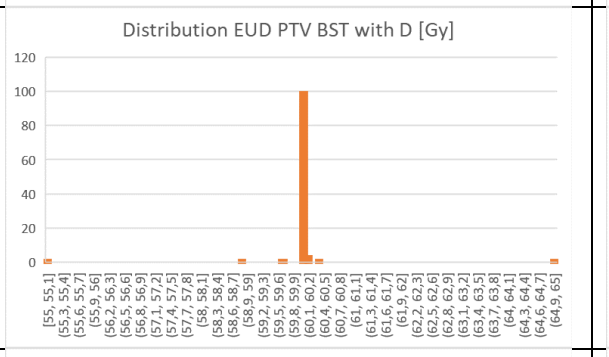
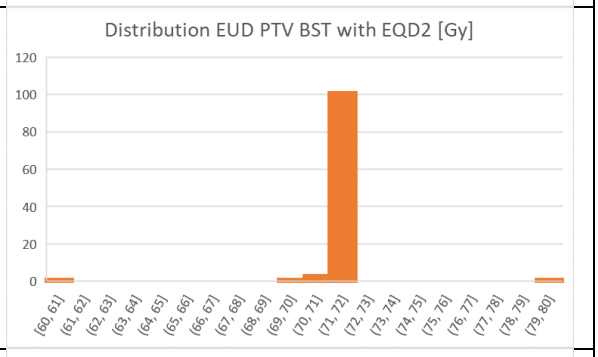
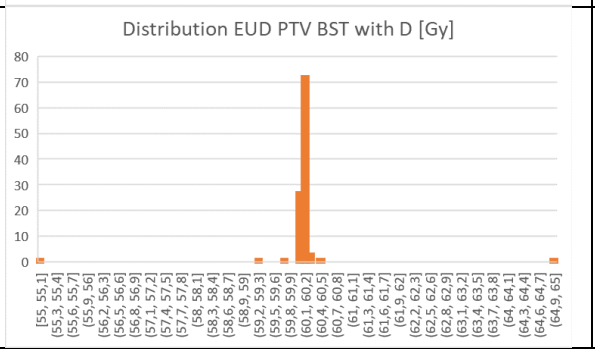
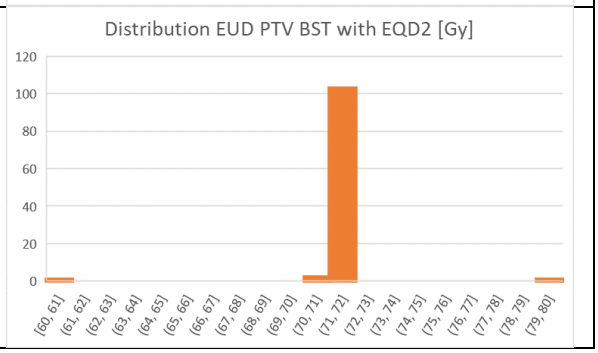
a = 2		
a = 3		
a = 4		
a = 5		
a = 10		

Figure 10: results EUD for a-values for PTV BST

The effect of the a-value on de EUD-distribution for the PTV BST is minimal and found not significant using a student t-test. This is also visualized by figure 11.

The formula for the t-test is given by formula 11.

$$T = \frac{\bar{\bar{X}} - \bar{\bar{Y}}}{S\sqrt{\frac{1}{n} + \frac{1}{m}}} \tag{11}$$

The test itself is executed using the T.TEST function of Microsoft Excel on the two arrays with EUD results for a=0.5 and a=30. It is a two tailed paired t-test.

The result of this test is $8.0144*10^{-39}$. This is the probability that the two data series belong to the same population with the same mean. Using the 95% confidence level this means that the effect on the EUD for the PTV BST is not significant since the probability is smaller than 5%.

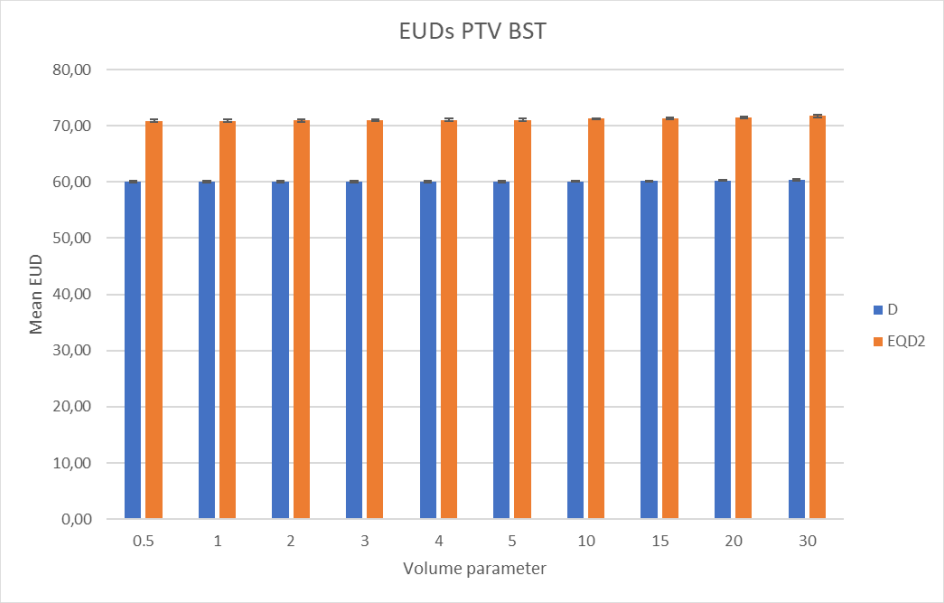
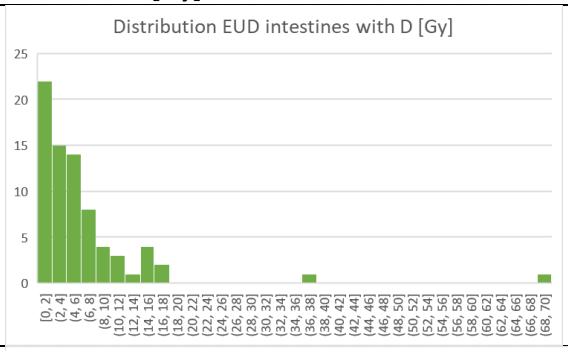
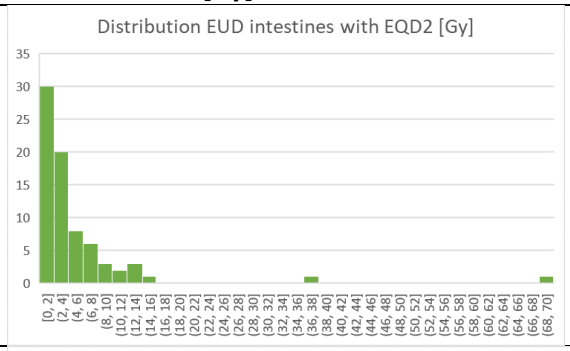
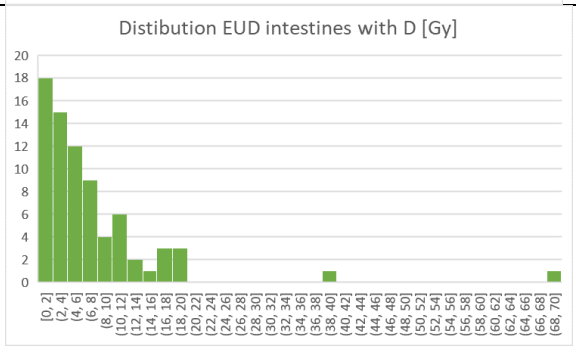
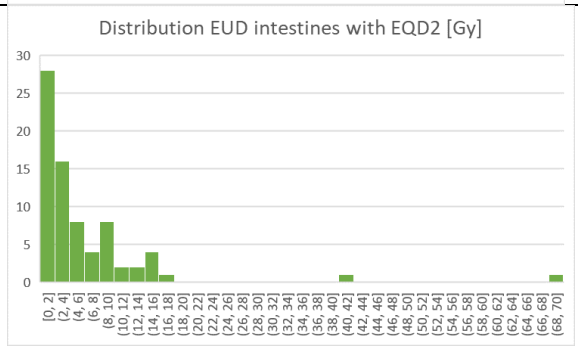


Figure 11: overview mean EUD's for PTV BST

4.1.3 Intestines

EUD-values 0Gy and 70Gy are added for all histograms in figure 12 to create the same axis.

	EUD with D [Gy]	**EUD with EQD2 [Gy]**
a = 0.5		
a = 1		

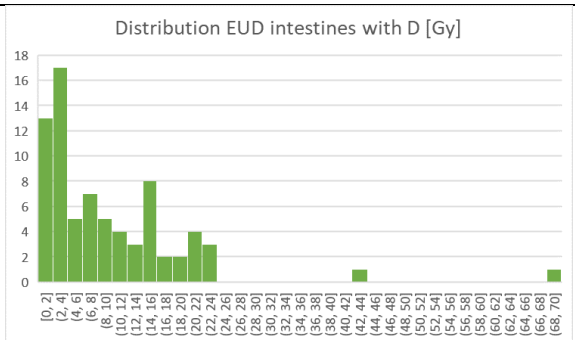
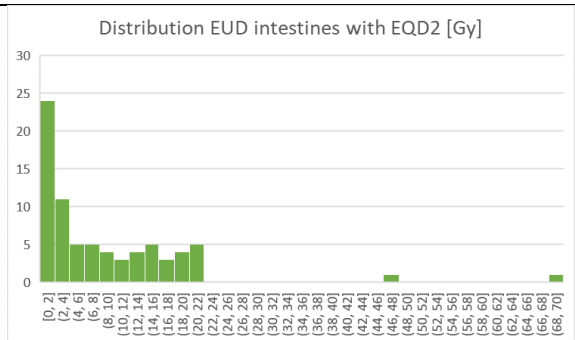
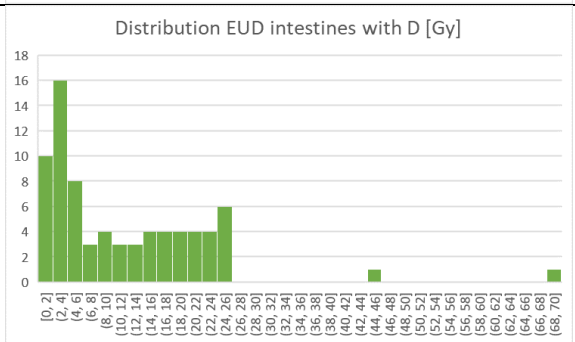
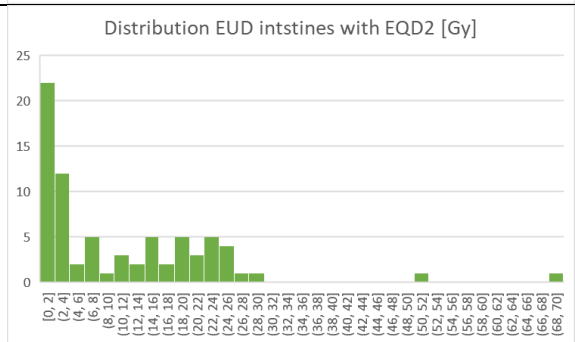
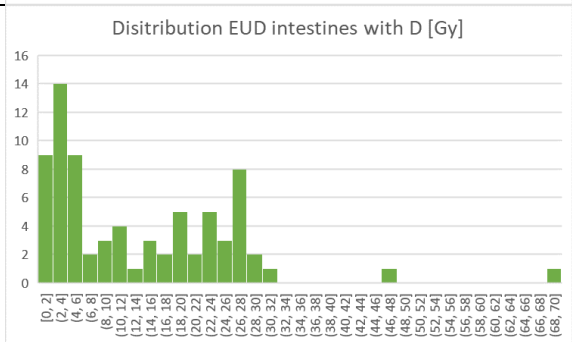
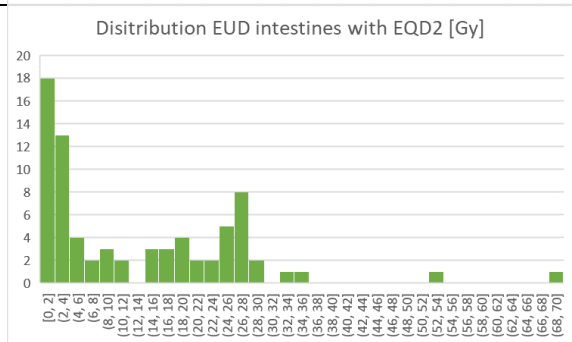
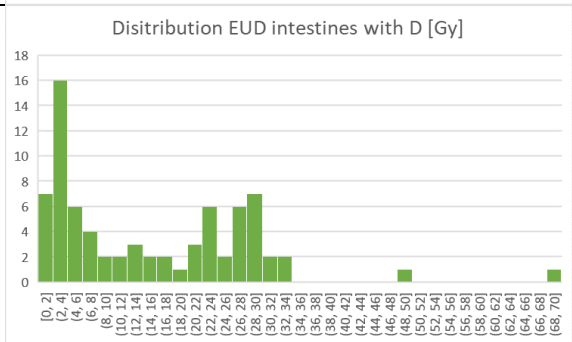
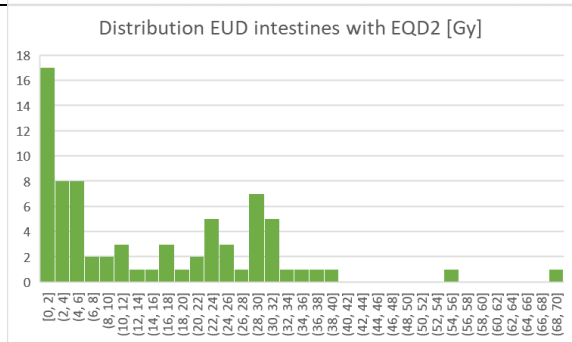
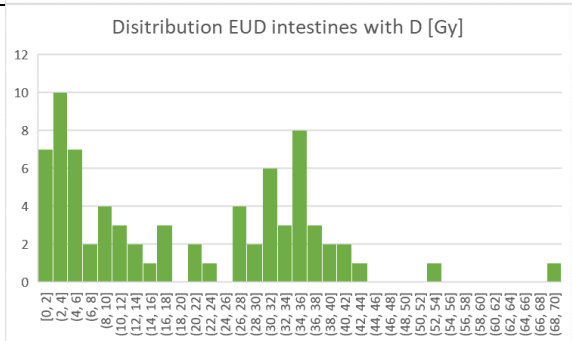
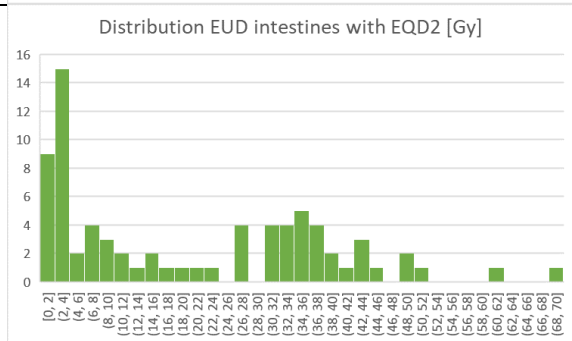
a = 2		
a = 3		
a = 4		
a = 5		
a = 10		

Figure 12: results EUD for a-values for intestines

For a smaller a-parameter there is a finer peak. With a greater a-value, two separate peaks are created. Also, the distribution increases with an increasing a-parameter. This is also visualized in figure 13.

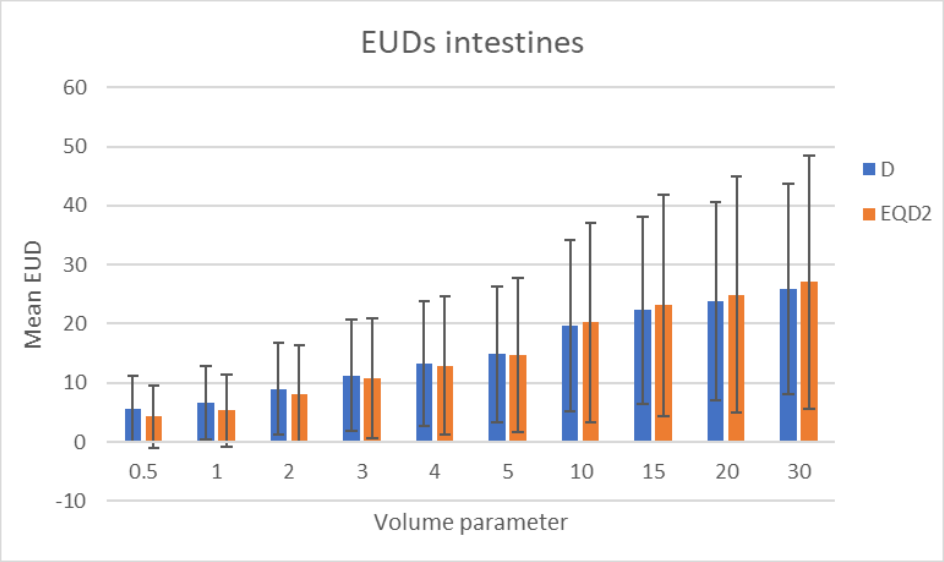
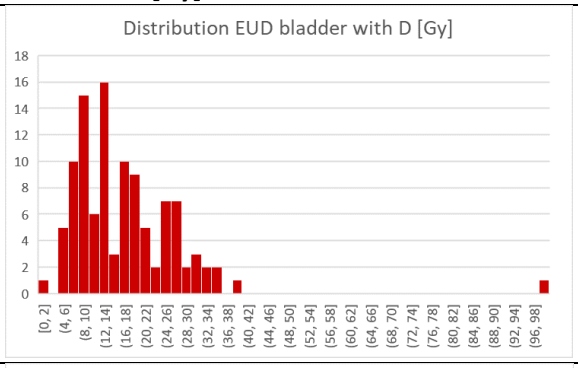
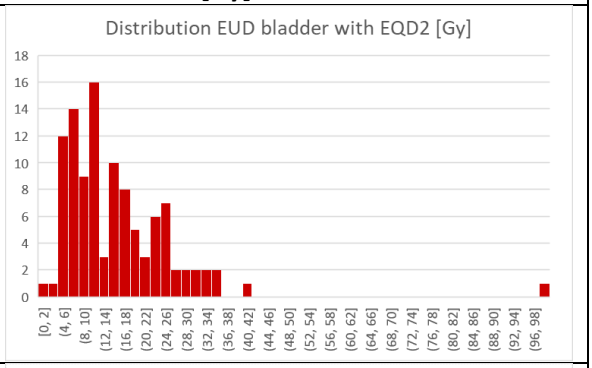
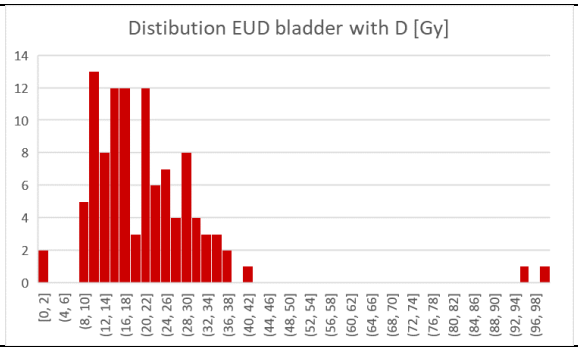
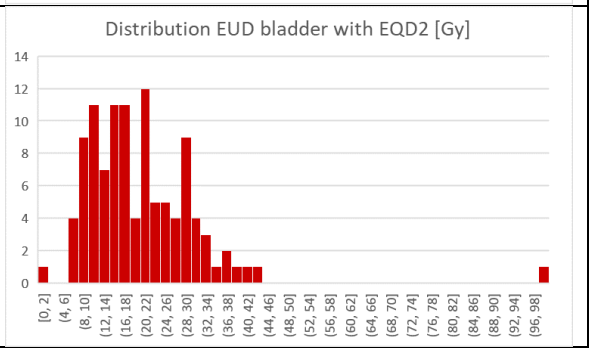
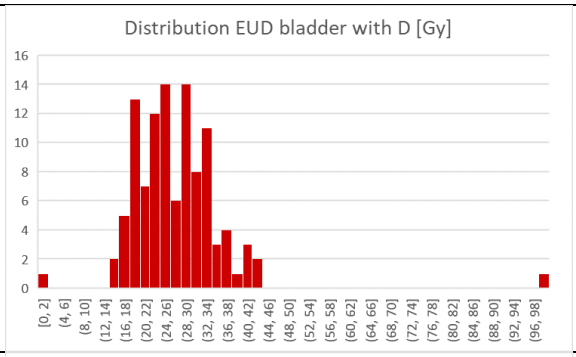
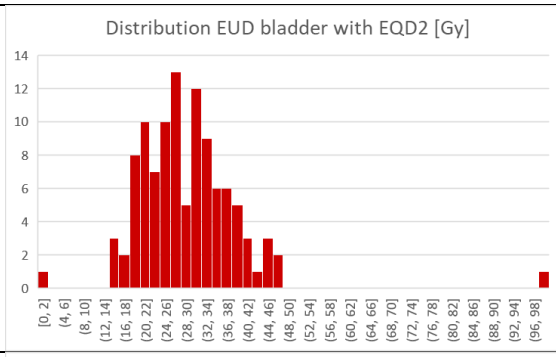
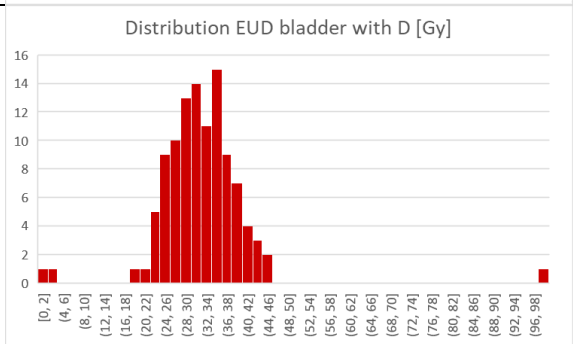
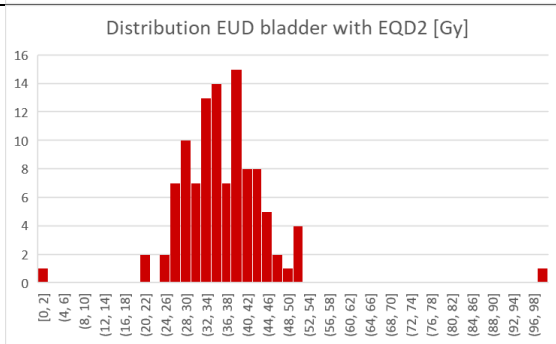
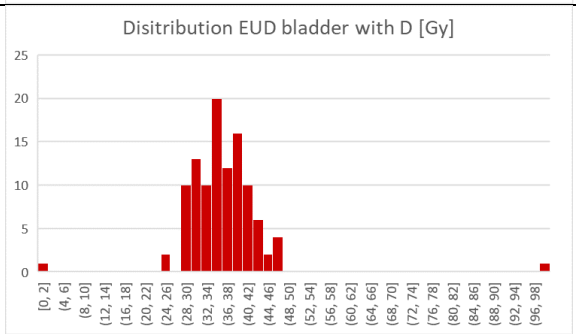
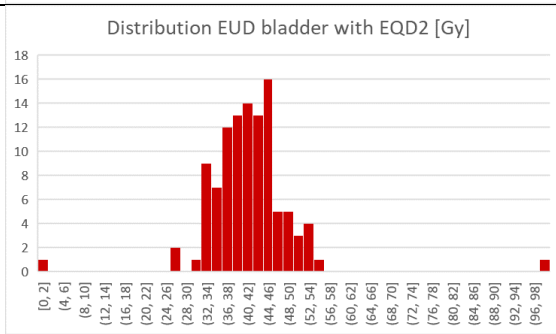
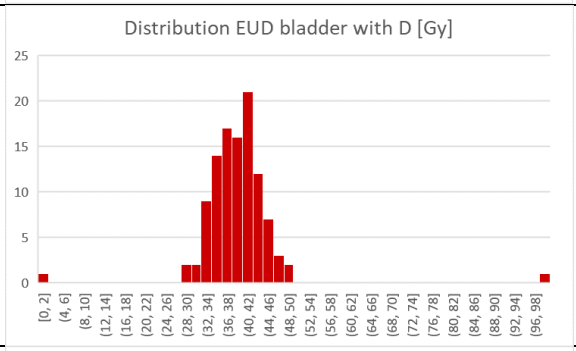
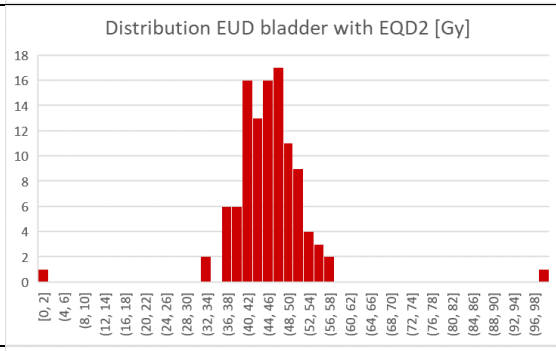
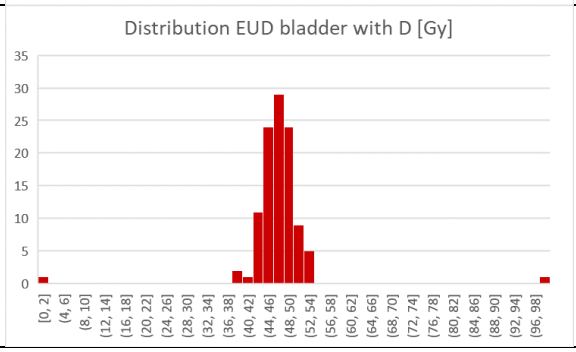
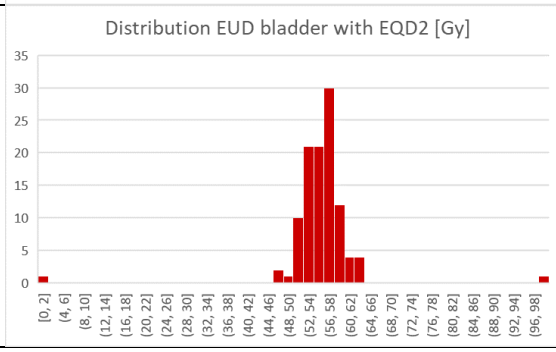


Figure 13: overview mean EUD's for intestines

4.1.4 Bladder

In figure 14, the added EUD-values for the axis are 0Gy and 100Gy for both the EUD with dose and EQD2.

	EUD with D [Gy]	**EUD with EQD2 [Gy]**
a = 0.5		
a = 1		

a = 2		
a = 3		
a = 4		
a = 5		
a = 10		

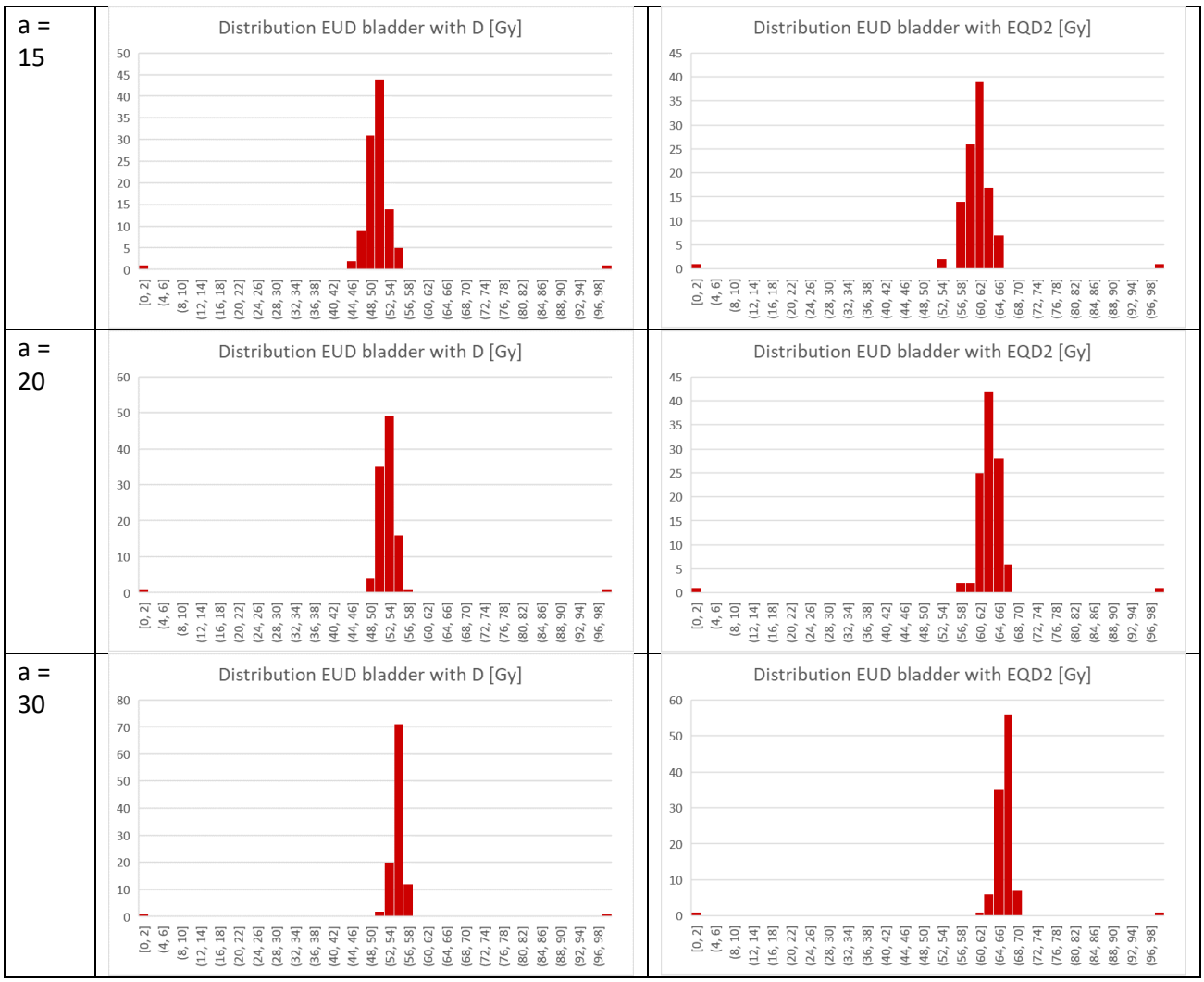


Figure 14: results EUD for a-values for bladder

It is clear that the distribution gets smaller when the a-parameter decreases. A finer peak is created. Besides that, the peak also shifts to the right. The effect of the increasing a-parameter is also visualized in figure 15.

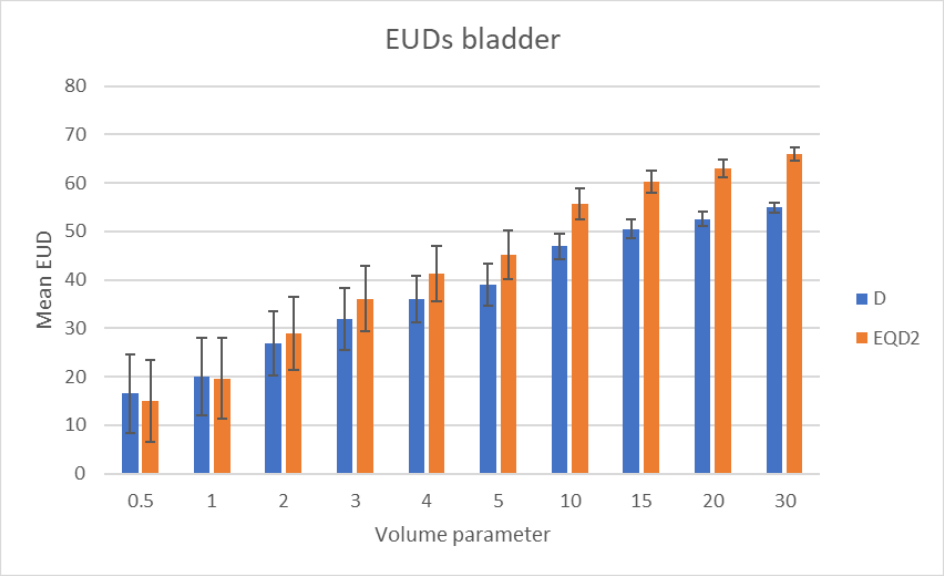


Figure 15: overview mean EUD's for bladder

4.2 Practical study

4.2.1 Reproduction of original plans using gEUD-based constraints

Plans were created for all ten patients with more or less the same result as the original plans. This means that gEUD-constraints were able to create plans that were as good as the plans based on dose/volume-constraints. Figure 16 shows the comparison of the DVHs from the original and reconstructed plan created with a comparison tool of the TPS.

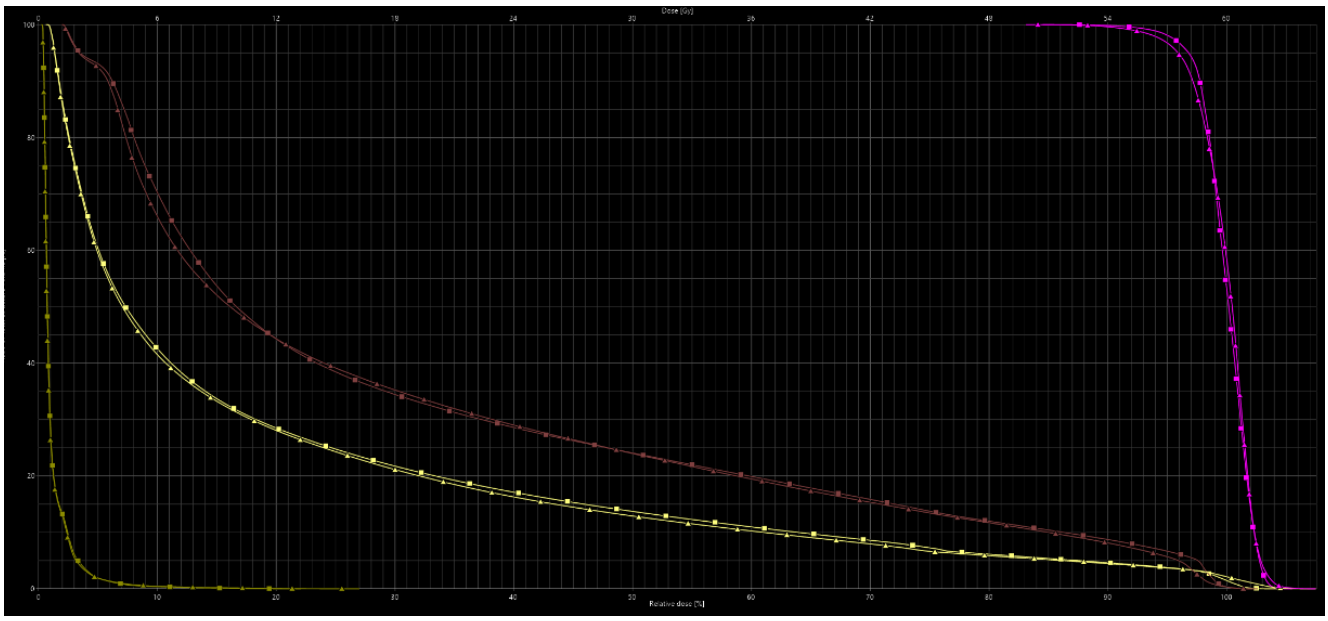


Figure 16: comparison between DVHs of the original (triangles) and EUD based plan (squares) for bladder (yellow), rectum (brown), intestines (olive) and PTV BST (pink)

The complexity of every new plan was checked to see if it was not too complex for the leaves to put this plan into practice with the linear accelerator (LINAC). These results are shown and compared with the complexities of the original plans in table 2.

Table 2: overview complexities reconstructed new plans

	Original plan		**Reconstructed plan**	
	Arc 1	**Arc 2**	**Arc 1**	**Arc 2**
Patient 1	0.206 PASS	0.225 PASS	0.179 PASS	0.187 PASS
Patient 2	0.315 FAIL	0.215 PASS	0.251 PASS	0.233 PASS
Patient 3	0.168 PASS	0.155 PASS	0.173 PASS	0.161 PASS
Patient 4	0.263 PASS	0.235 PASS	0.199 PASS	0.228 PASS
Patient 5	0.189 FAIL	0.163 PASS	0.161 PASS	0.159 PASS
Patient 6	0.222 FAIL	0.158 PASS	0.145 PASS	0.183 PASS
Patient 7	0.251 PASS	0.273 PASS	0.231 PASS	0.231 PASS
Patient 8	0.313 FAIL	0.235 PASS	0.304 FAIL	0.2 PASS
Patient 9	0.278 PASS	0.261 PASS	0.203 PASS	0.199 PASS
Patient 10	0.175 PASS	0.174 PASS	0.154 PASS	0.169 PASS

4.2.2 Improvement of plans using gEUD-based constraints

For some of the patients it was harder to create a treatment plan with a more optimal outcome than for other patients. For four out of the ten patients it was not possible to improve the plan quality. This could indicate that the original plan was already the most optimal way of treating the patient. The result of the improved plan is compared with the DVH of the reconstructed plan in figure 17.

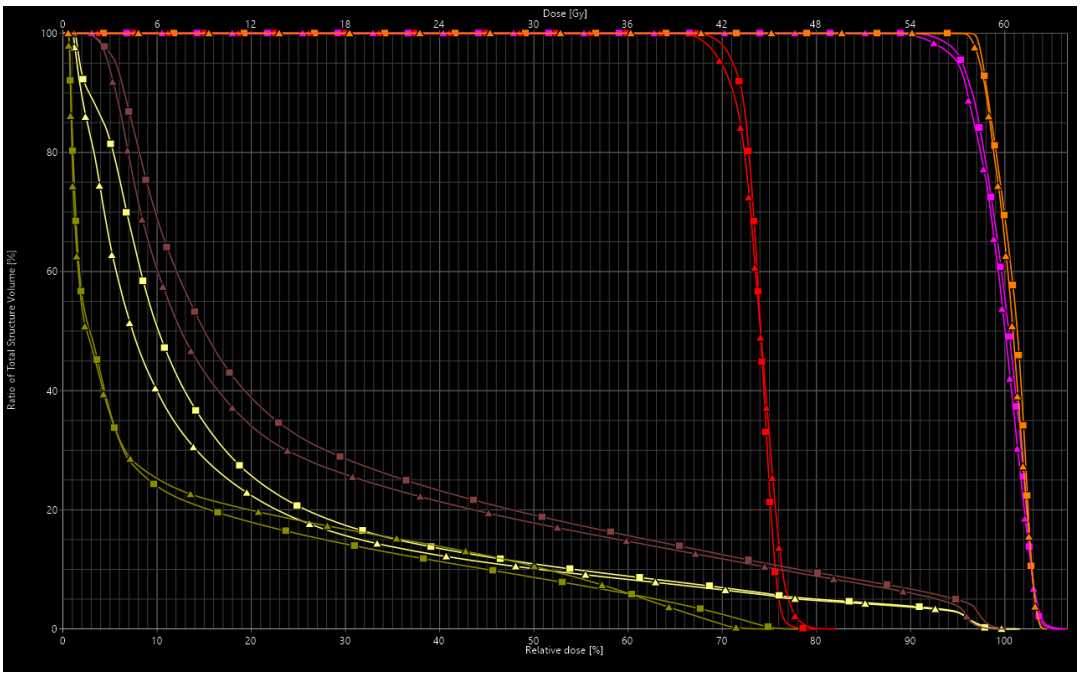


Figure 17: comparison of DVHs for rectum (brown), PTV BST (pink), intestines (olive) and bladder (yellow) from reconstructed (squares) and improved (triangles) EUD based plan

The complexities of the new improved plan are compared with the complexities of the original plan in table 3. Like for the reconstructed plan, this is also done to check that the plans are not too technically challenging to put into practice by using the multileaf collimator (MLC) in the linac. The working principle of a MLC is visualized in figure 18.

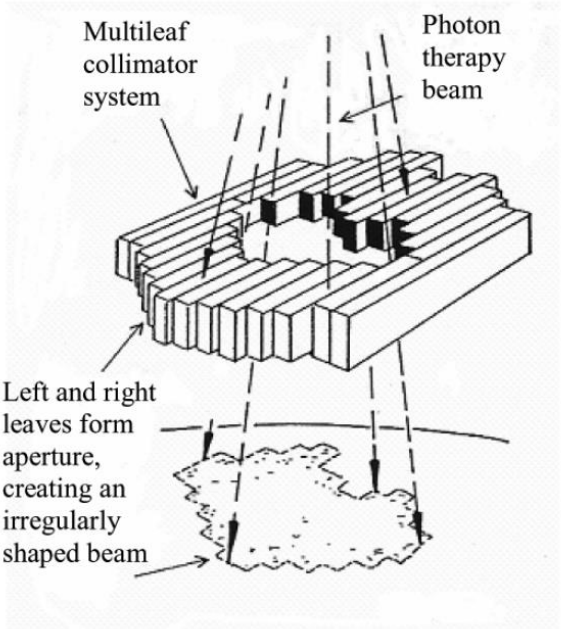


Figure 18: working principle of multileaf collimator in linac [25]

Table 3: overview complexities new improved plans

	Original plan		Improved plan	
	Arc 1	**Arc 2**	**Arc 1**	**Arc 2**
Patient 1	0.206 PASS	0.225 PASS	0.142 PASS	0.189 PASS
Patient 2	0.315 FAIL	0.215 PASS	Not improved	
Patient 3	0.168 PASS	0.155 PASS	Not improved	
Patient 4	0.263 PASS	0.235 PASS	0.273 PASS	0.281 PASS
Patient 5	0.189 FAIL	0.163 PASS	0.171 PASS	0.144 PASS
Patient 6	0.222 FAIL	0.158 PASS	0.205 FAIL	0.179 PASS
Patient 7	0.251 PASS	0.273 PASS	Not improved	
Patient 8	0.313 FAIL	0.235 PASS	0.275 PASS	0.259 PASS
Patient 9	0.278 PASS	0.261 PASS	0.219 PASS	0.194 PASS
Patient 10	0.175 PASS	0.174 PASS	Not improved	

The constraints that are the result of the improved plans are compared with the constraints from the original plan to see whether the plan is improved or not. This comparison is shown in table 4. In the volume constraints the dimension cc is used. This is the equivalent of cm^3.

Table 4: comparison quality of plans

	Constraints		**Original plan**		**Improved plan**	
Patient 1	PTV BST	D99[%] ≥ 90 [%]	93.36 [%]	PASS	91.02 [%]	PASS
		D95[%] ≥ 95 [%]	96.4 [%]	PASS	94.59 [%]	FAIL
		D50[%] ≤ 100 [%]	100.33 [%]	PASS	100.49 [%]	PASS
		D5[%] ≤ 105 [%]	102.66 [%]	PASS	104.37 [%]	PASS
		Dmax[%] ≤ 107 [%]	106.27 [%]	PASS	109.06 [%]	FAIL
	Rectum	V60[Gy] ≤ 1 [cc]	0.32 [cc]	PASS	0.02 [cc]	PASS
		V50[Gy] ≤ 22.2 [%]	10.74 [%]	PASS	9.95 [%]	PASS
		V40[Gy] ≤ 37.7 [%]	19.06 [%]	PASS	17.81 [%]	PASS
		V30[Gy] ≤ 56.7 [%]	25.71 [%]	PASS	24.2 [%]	PASS
		V26[Gy] ≤ 68.2 [%]	28.45 [%]	PASS	26.88 [%]	PASS
		V20[Gy] ≤ 85.2 [%]	33.4 [%]	PASS	31.76 [%]	PASS
		Dmean[cc] ≤ 30 [Gy]	18.8 [Gy]	PASS	17.81 [Gy]	PASS
	Intestines	V58.5[Gy] ≤ 1 [cc]	0 [cc]	PASS	0 [cc]	PASS
		V41[Gy] ≤ 17 [cc]	0 [cc]	PASS	0 [cc]	PASS
		V36[Gy] ≤ 195 [cc]	0 [cc]	PASS	0 [cc]	PASS
	Bladder	V63.6[Gy] ≤ 1 [cc]	0 [cc]	PASS	0 [cc]	PASS
		V60[Gy] ≤ 5 [%]	1.67 [%]	PASS	0.11 [%]	PASS
		V49[Gy] ≤ 25 [%]	6.15 [%]	PASS	5.93 [%]	PASS
		V41[Gy] ≤ 50 [%]	9.42 [%]	PASS	9.44 [%]	PASS
		V31[Gy] ≤ 60 [%]	13.27 [%]	PASS	13.21 [%]	PASS
Patient 4	PTV BST	D99[%] ≥ 90 [%]	93.99 [%]	PASS	91.57 [%]	PASS
		D95[%] ≥ 95 [%]	96.77 [%]	PASS	94.99 [%]	FAIL
		D50[%]≤ 100 [%]	100 [%]	PASS	100.02 [%]	PASS
		D5[%] ≤ 105 [%]	102.91 [%]	PASS	103.33 [%]	PASS
		Dmax[%] ≤ 107 [%]	104.84 [%]	PASS	106.64 [%]	PASS

	Rectum	V60[Gy] ≤ 1 [cc] V50[Gy] ≤ 22.2 [%] V40[Gy] ≤ 37.7 [%] V30[Gy] ≤ 56.7 [%] V26[Gy] ≤ 68.2 [%] V20[Gy] ≤ 85.2 [%] Dmean[cc] ≤ 30 [Gy]	0.21 [cc] 8.42 [%] 13.25 [%] 18.59 [%] 21.01 [%] 25.5 [%] 16.56 [Gy]	PASS PASS PASS PASS PASS PASS PASS	0 [cc] 7.96 [%] 12.75 [%] 17.79 [%] 20.1 [%] 24.26 [%] 15.29 [Gy]	PASS PASS PASS PASS PASS PASS PASS
	Intestines	V58.5[Gy] ≤ 1 [cc] V41[Gy] ≤ 17 [cc] V36[Gy] ≤ 195 [cc]	0 [cc] 1.96 [cc] 3.58 [cc]	PASS PASS PASS	0 [cc] 1.12 [cc] 4.16 [cc]	PASS PASS PASS
	Bladder	V63.6[Gy] ≤ 1 [cc] V60[Gy] ≤ 5 [%] V49[Gy] ≤ 25 [%] V41[Gy] ≤ 50 [%] V31[Gy] ≤ 60 [%]	0 [cc] 1.62 [%] 5.07 [%] 7.6 [%] 10.88 [%]	PASS PASS PASS PASS PASS	0[cc] 0.01 [%] 4.6 [%] 6.87 [%] 9.79 [%]	PASS PASS PASS PASS PASS
Patient 5	PTV BST	D99[%] ≥ 90 [%] D95[%] ≥ 95 [%] D50[%] ≤ 100 [%] D5[%] ≤ 105 [%] Dmax[%] ≤ 107 [%]	92.99 [%] 96.68 [%] 100.23 [%] 102.8 [%] 106.19 [%]	PASS PASS PASS PASS PASS	89.81 [%] 93.79 [%] 100.64 [%] 104.62 [%] 109.12 [%]	FAIL FAIL PASS PASS FAIL
	Rectum	V60[Gy] ≤ 1 [cc] V50[Gy] ≤ 22.2 [%] V40[Gy] ≤ 37.7 [%] V30[Gy] ≤ 56.7 [%] V26[Gy] ≤ 68.2 [%] V20[Gy] ≤ 85.2 [%] Dmean[cc] ≤ 30 [Gy]	0.39 [cc] 13.66 [%] 17.43 [%] 22.5 [%] 24.99 [%] 29.82 [%] 18.98 [Gy]	PASS PASS PASS PASS PASS PASS PASS	0.02 [cc] 12.92 [%] 17.01 [%] 21.67 [%] 23.85 [%] 27.84 [%] 17.64 [Gy]	PASS PASS PASS PASS PASS PASS PASS
	Intestines	V58.5[Gy] ≤ 1 [cc] V41[Gy] ≤ 17 [cc] V36[Gy] ≤ 195 [cc]	0 [cc] 0 [cc] 0 [cc]	PASS PASS PASS	0 [cc] 0 [cc] 0 [cc]	PASS PASS PASS
	Bladder	V63.6[Gy] ≤ 1 [cc] V60[Gy] ≤ 5 [%] V49[Gy] ≤ 25 [%] V41[Gy] ≤ 50 [%] V31[Gy] ≤ 60 [%]	0 [cc] 3.78 [%] 16.49 [%] 21.43 [%] 27.17 [%]	PASS PASS PASS PASS PASS	0 [cc] 0.28 [%] 15.27 [%] 20.13 [%] 26.39 [%]	PASS PASS PASS PASS PASS
Patient 6	PTV BST	D99[%] ≥ 90 [%] D95[%] ≥ 95 [%] D50[%]≤ 100 [%] D5[%] ≤ 105 [%] Dmax[%] ≤ 107 [%]	93.8 [%] 96.79 [%] 100.17 [%] 102.75 [%] 105.53 [%]	PASS PASS PASS PASS PASS	92.1 [%] 95.54 [%] 100.55 [%] 103.01 [%] 105.96 [%]	PASS PASS PASS PASS PASS
	Rectum	V60[Gy] ≤ 1 [cc] V50[Gy] ≤ 22.2 [%] V40[Gy] ≤ 37.7 [%] V30[Gy] ≤ 56.7 [%] V26[Gy] ≤ 68.2 [%] V20[Gy] ≤ 85.2 [%] Dmean[cc] ≤ 30 [Gy]	0.18 [cc] 10.93 [%] 17.18 [%] 24.05 [%] 26.99 [%] 32.27 [%] 18.68 [Gy]	PASS PASS PASS PASS PASS PASS PASS	1.01 [cc] 10.86 [%] 16.8 [%] 24.15 [%] 27.46 [%] 33.28 [%] 18.65 [Gy]	FAIL PASS PASS PASS PASS PASS PASS
	Intestines	V58.5[Gy] ≤ 1 [cc] V41[Gy] ≤ 17 [cc] V36[Gy] ≤ 195 [cc]	0 [cc] 0 [cc] 0 [cc]	PASS PASS PASS	0 [cc] 0 [cc] 0 [cc]	PASS PASS PASS

	Bladder	V63.6[Gy] ≤ 1 [cc] V60[Gy] ≤ 5 [%] V49[Gy] ≤ 25 [%] V41[Gy] ≤ 50 [%] V31[Gy] ≤ 60 [%]	0 [cc] 1.45 [%] 5.86 [%] 8.97 [%] 13.22 [%]	PASS PASS PASS PASS PASS	0 [cc] 0.22 [%] 5.31 [%] 7.96 [%] 11.67 [%]	PASS PASS PASS PASS PASS
Patient 8	PTV BST	D99[%] ≥ 90 [%] D95[%] ≥ 95 [%] D50[%]≤ 100 [%] D5[%] ≤ 105 [%] Dmax[%] ≤ 107 [%]	91.42 [%] 96.29 [%] 100.1 [%] 103.16 [%] 106.15 [%]	PASS PASS PASS PASS PASS	90.79 [%] 95.37 [%] 100.28 [%] 103.81 [%] 107.66 [%]	PASS PASS PASS PASS PASS
	Rectum	V60[Gy] ≤ 1 [cc] V50[Gy] ≤ 22.2 [%] V40[Gy] ≤ 37.7 [%] V30[Gy] ≤ 56.7 [%] V26[Gy] ≤ 68.2 [%] V20[Gy] ≤ 85.2 [%] Dmean[cc] ≤ 30 [Gy]	0.36 [cc] 8.85 [%] 17.64 [%] 26.33 [%] 30.23 [%] 37.31 [%] 20.83 [Gy]	PASS PASS PASS PASS PASS PASS PASS	0.55 [cc] 8.32 [%] 16.34 [%] 24.55 [%] 28.19 [%] 34.55 [%] 19.13 [Gy]	PASS PASS PASS PASS PASS PASS PASS
	Intestines	V58.5[Gy] ≤ 1 [cc] V41[Gy] ≤ 17 [cc] V36[Gy] ≤ 195 [cc]	0 [cc] 0 [cc] 0.18 [cc]	PASS PASS PASS	0 [cc] 0.07 [cc] 0.45 [cc]	PASS PASS PASS
	Bladder	V63.6[Gy] ≤ 1 [cc] V60[Gy] ≤ 5 [%] V49[Gy] ≤ 25 [%] V41[Gy] ≤ 50 [%] V31[Gy] ≤ 60 [%]	0 [cc] 3.96 [%] 13.93 [%] 18.62 [%] 25.05 [%]	PASS PASS PASS PASS PASS	0 [cc] 0.76 [%] 13.95 [%] 18.98 [%] 25.45 [%]	PASS PASS PASS PASS PASS
Patient 9	PTV BST	D99[%] ≥ 90 [%] D95[%] ≥ 95 [%] D50[%] ≤ 100 [%] D5[%] ≤ 105 [%] Dmax[%] ≤ 107 [%]	91.7 [%] 95.17 [%] 100.29 [%] 102.63 [%] 106.97 [%]	PASS PASS PASS PASS PASS	90.41 [%] 94.68 [%] 100.45 [%] 103.77 [%] 108.81 [%]	PASS FAIL PASS PASS FAIL
	Rectum	V60[Gy] ≤ 1 [cc] V50[Gy] ≤ 22.2 [%] V40[Gy] ≤ 37.7 [%] V30[Gy] ≤ 56.7 [%] V26[Gy] ≤ 68.2 [%] V20[Gy] ≤ 85.2 [%] Dmean[cc] ≤ 30 [Gy]	0.92 [cc] 13.44 [%] 19.31 [%] 25.8 [%] 28.89 [%] 35.01 [%] 20.34 [Gy]	PASS PASS PASS PASS PASS PASS PASS	0.3 [cc] 12.95 [%] 18.85 [%] 25.15 [%] 28.04 [%] 33.3 [%] 19.17 [%]	PASS PASS PASS PASS PASS PASS PASS
	Intestines	V58.5[Gy] ≤ 1 [cc] V41[Gy] ≤ 17 [cc] V36[Gy] ≤ 195 [cc]	0 [cc] 3.57 [cc] 5.87 [cc]	PASS PASS PASS	0[cc] 6[cc] 8.3 [cc]	PASS PASS PASS
	Bladder	V63.6[Gy] ≤ 1 [cc] V60[Gy] ≤ 5 [%] V49[Gy] ≤ 25 [%] V41[Gy] ≤ 50 [%] V31[Gy] ≤ 60 [%]	0 [cc] 4.38 [%] 17.62 [%] 24.41 [%] 32.94 [%]	PASS PASS PASS PASS PASS	0 [cc] 0.3 [%] 17.5 [%] 24.4 [%] 33.18 [%]	PASS PASS PASS PASS PASS

The resulting DVHs are also turned into numerical data and the same EUD-calculations as in the a posteriori study were performed on these numerical data. The results of these EUD-calculations are given in table 5.

Table 5: EUD-values for improved plans

		Patient 1	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 8**	**Patient 9**
a=0.5	With dose [Gy]	6.9	7.2	15.2	7.4	15	20.7
	With EQD2 [Gy]	5.65	5.62	13.43	5.91	13.25	18.85
a=1	With dose [Gy]	11.0	10.2	19.5	11.0	19.4	24.3
	With EQD2 [Gy]	10.27	9.08	19.25	10.04	18.94	23.93
a=2	With dose [Gy]	19.2	17.2	27.5	18.6	27.1	30.6
	With EQD2 [Gy]	20.45	18.02	29.88	19.56	29.27	32.89
a=3	With dose [Gy]	25.6	23.4	33.1	24.8	32.6	35.2
	With EQD2 [Gy]	28.4	25.91	37.18	27.41	36.54	39.23
a=4	With dose [Gy]	30.3	28.2	37.0	29.5	36.5	38.5
	With EQD2 [Gy]	34.23	31.94	42.18	33.35	41.6	43.68
a=5	With dose [Gy]	33.7	31.9	39.8	33.0	39.4	41.0
	With EQD2 [Gy]	38.63	36.55	45.78	37.9	45.31	46.93
a=10	With dose [Gy]	43.1	42.0	47.0	42.8	46.8	47.5
	With EQD2 [Gy]	50.5	49.05	54.95	50.31	54.91	55.37
a=15	With dose [Gy]	47.3	46.4	50.1	47.2	50.1	50.3
	With EQD2 [Gy]	55.77	54.58	58.89	55.85	59.12	59.08
a=20	With dose [Gy]	49.7	49.0	51.8	49.8	51.9	52.0
	With EQD2 [Gy]	58.76	57.7	61.13	59.01	61.56	61.22
a=30	With dose [Gy]	52.4	51.8	53.8	52.5	54.0	53.8
	With EQD2 [Gy]	62.09	61.13	63.69	62.54	64.38	63.71

These EUD-values from the improved plans can be used to calculate the NTCP- and TCP-value according to formulas 2 and 3.

The results can give a good indication of the clinical impact of this improvement although it is a very simple model. The EUD used in this formula is the EUD in Gray [Gy] with EQD2. The values for TD_{50} , TCD_{50} and γ_{50} are described by Sang Won *et al.* [26] and shown in table 6.

Table 6: values TD50, TCD50 and y50 for prostate and OARs [26]

	γ_{50}	**a**	**TD_{50}**	**TCD_{50}**
Prostate	1.0	-10	/	28.34
Rectum	4	8.33	80	/
Bladder	4	2	80	/

The results of these NTCP-calculations are compared to the NTCP-values of the original plans in table 7.

Table 7: comparison NTCP-values for bladder and rectum

		EUD original plan [Gy]	NTCP original plan	EUD improved plan [Gy]	NTCP improved plan
Patient 1	Rectum	54.38	0.176	52.59	0.157
	Bladder	21.09	0.005	20.45	0.004
Patient 4	Rectum	53.05	0.162	51.13	0.143
	Bladder	19.41	0.003	18.02	0.003
Patient 5	Rectum	56.24	0.196	53.7	0.169
	Bladder	31.64	0.024	29.88	0.019
Patient 6	Rectum	54.49	0.177	54.97	0.182
	Bladder	20.93	0.005	19.56	0.004
Patient 8	Rectum	53.43	0.166	52.91	0.161
	Bladder	29.91	0.019	29.27	0.018
Patient 9	Rectum	56.2	0.196	54.9	0.182
	Bladder	33.81	0.031	32.89	0.028

A paired two-tailed t-test is performed for both rectum and bladder for the EUD- and NTCP-values of the original and improved plans. This is done by using the T.TEST function in excel. The result of this t-test gives the probability that the two data series have the same mean. The results of these t-tests are given by table 8.

The T-test is executed by using data-analysis pluging. The α-value used is 0.05, this means that there is a 95% confidence level. The results are given by table 8. These results show that there is not a significant difference for the EUD-value for the rectum and for the NTCP-value for the bladder since the value is greater than 0.05. For the NTCP of the rectum and the EUD of the bladder the difference is significant. This also shows that it is not straightforward to judge clinical impact from the changes in the DVH.

Table 8: results of paired, two-tailed t-test for EUD- and NTCP-value of rectum and bladder

	Paired, two-tailed t-test for EUD-values	Paired, two-tailed t-test for NTCP-values
Rectum	0.287699972	0.049210766
Bladder	0.001847983	0.824038131

The constraints were met for the PTV BST. Since the constraints for PTV BST were the same for reconstruction and improvement as for the original plan the TCP-values are not calculated for the target.

4.2.3 Practical results

The trial-and-error method that is used for this means that constraints are given to the optimizer and a plan is created. By looking at the resulting DVH and compare it with the original plan using the comparing tool of the TPS could be seen where the DVH should be modified to reconstruct the original DVH. This resulted in a clear link between the regions of the DVH and the a-values that are

needed to effect that region. To push on a certain region of the DVH, the constraint that is pushed on should have the correct a-value.

A constraint with a=1 effects the whole DVH. This is because this is the main EUD that is adjusted with that a-value. A constraint with a low value, a = 0.5 is used in this research, effects the low-dose region and a high a-value, a = 10 is use here, effects the high-dose region of the DVH. This is shown in figures 19, 20 and 21.

In figure 19 the constraint for a-value 0.5 is pushed from 5Gy to 1Gy. In figure 20 the constraint for a=1 is pushed from 10Gy to 6Gy and in figure 21 the constraint for a-value 10 is pushed from 45Gy to 40Gy.

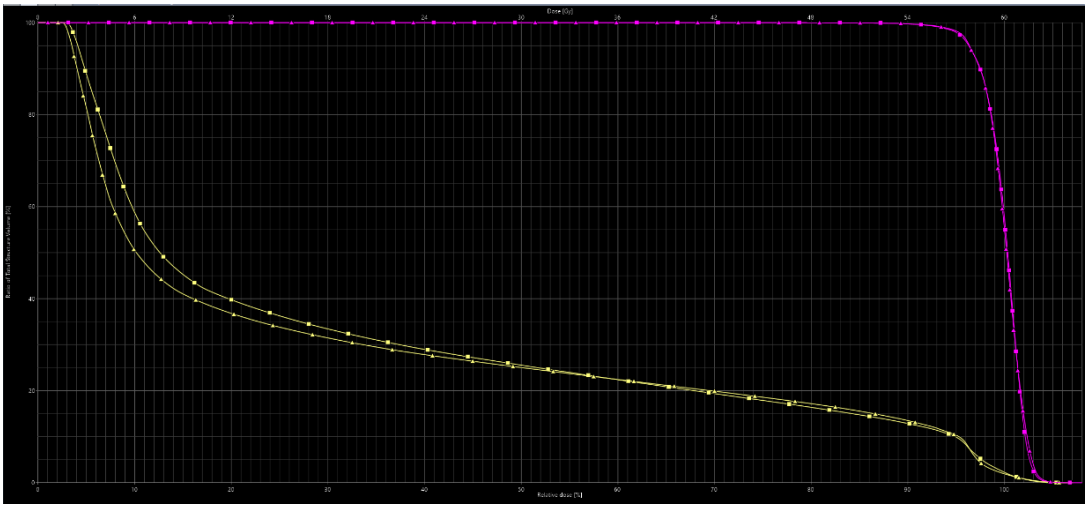


Figure 19: effect of pushing from reference of 5Gy (squares) to 1Gy (triangles) on constraint with a=0.5

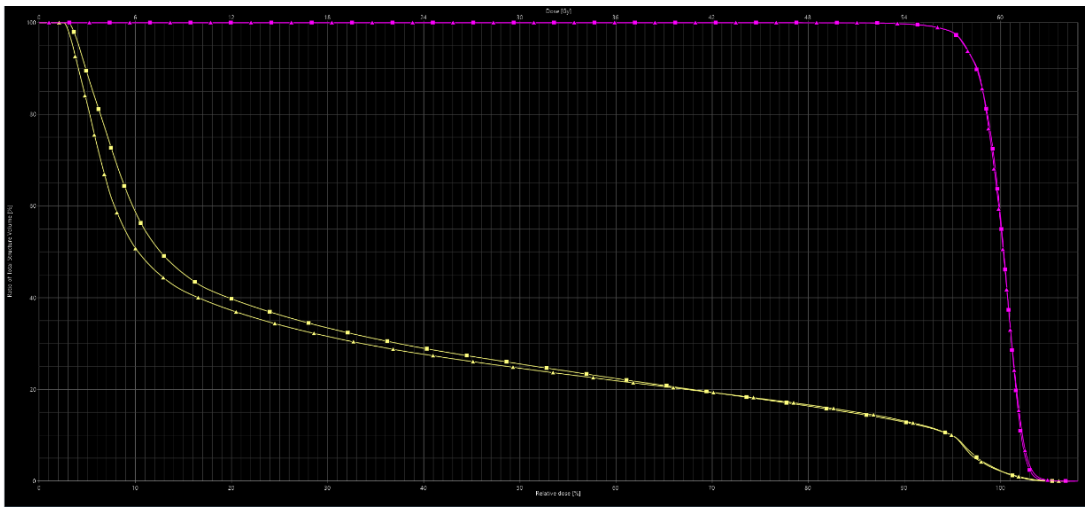


Figure 20: effect of pushing from reference of 10Gy (squares) to 6Gy (triangles) on constraint with a=1

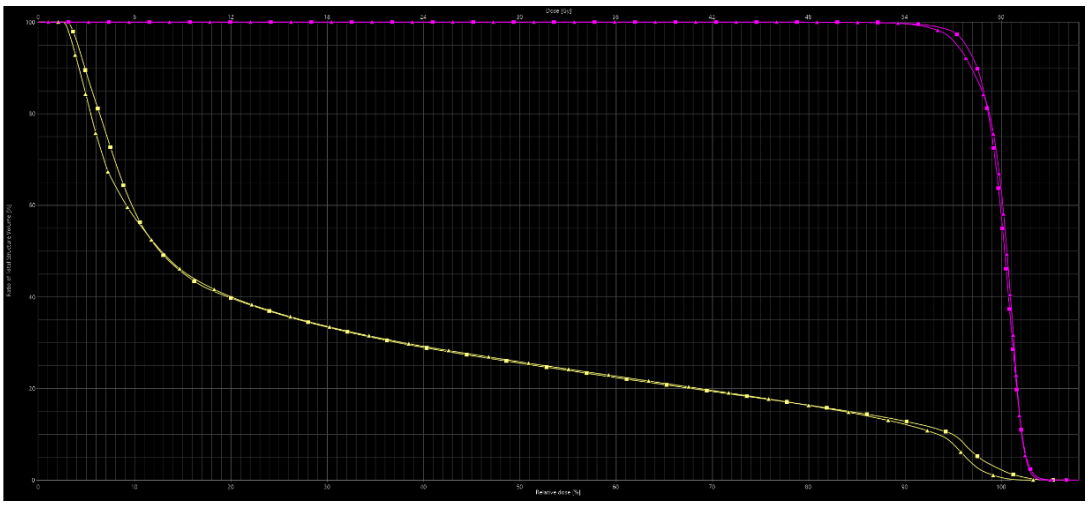


Figure 21: effect of pushing from reference of 45Gy (squares) to 40Gy (triangles) on constraint with a=10

Another result of this practical study is the effect of a somewhat changed a-value. These effects are visualized in figures 22 and 23. They show the effect of respectively slightly decreasing and increasing the a-value of the constraint. The constraint of the reference DVH, indicated with the squares in both figures, is 5Gy for an a-value of 0.5. The a-value is changed to 0.4 and 0.6 in figures 22 and 23 respectively. These DVHs are indicated by triangles. Figures 24 and 25 visualize the effect of a somewhat changed a-value for the constraint 40Gy with a=10. In figure 24 the a-value decreased from 10 to 9 and for figure 25 this a-value changed from 10 to 11.

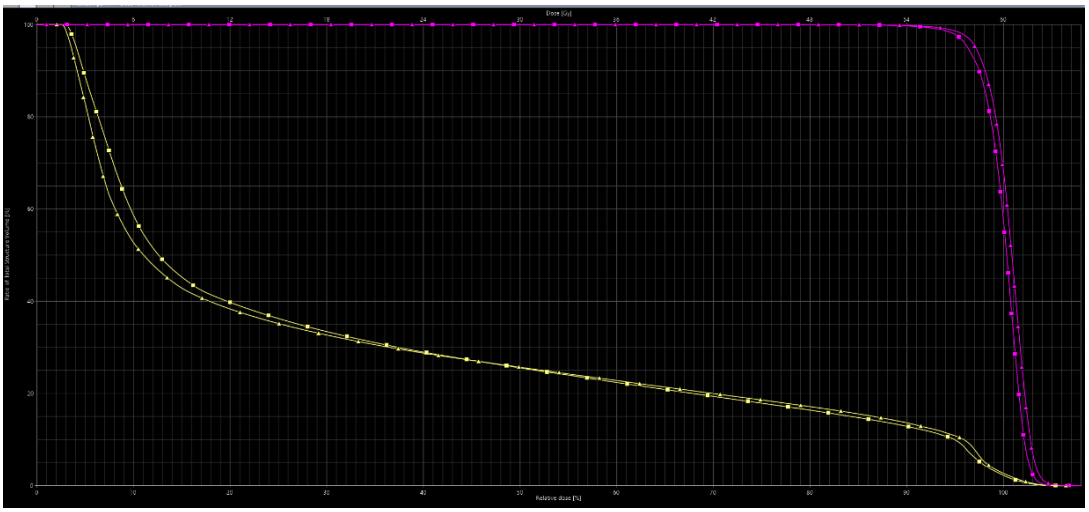


Figure 22: effect of slightly decreasing a-value from reference of 0.5 (squares) to 0.4 (triangles)

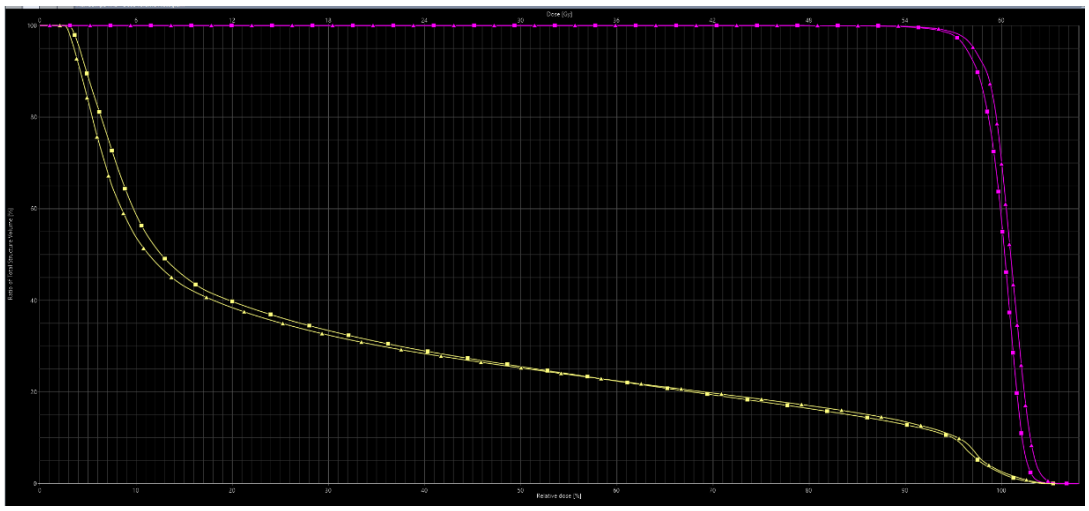


Figure 23: effect of slightly increasing a-value from reference of 0.5 (squares) to 0.6 (triangles)

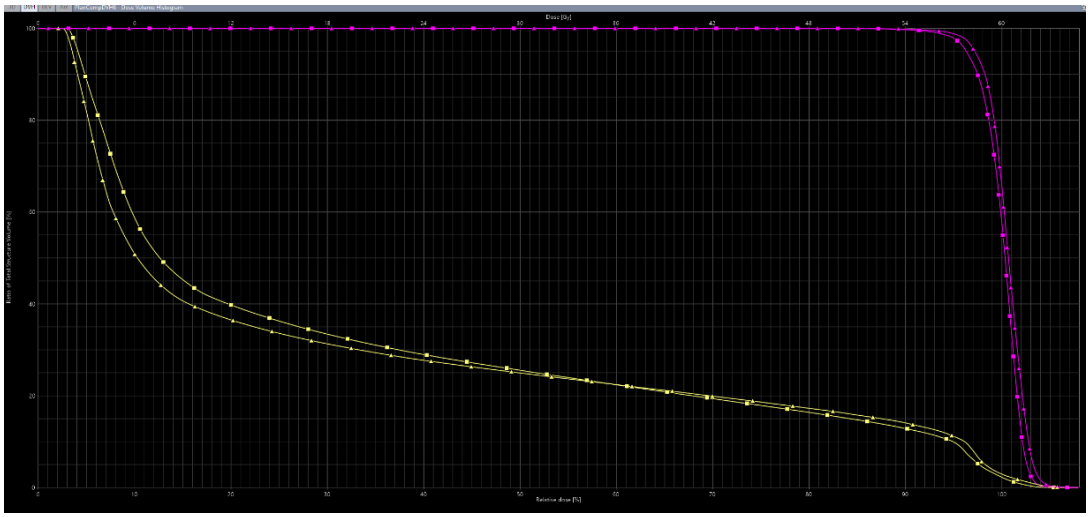


Figure 24: effect of slightly decreasing a-value from reference of 10 (squares) to 9 (triangles)

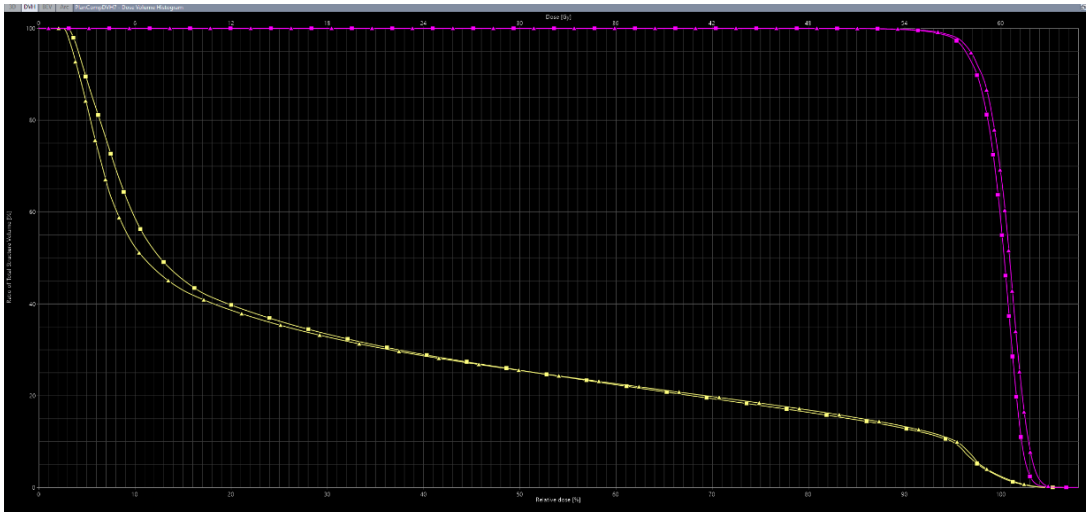
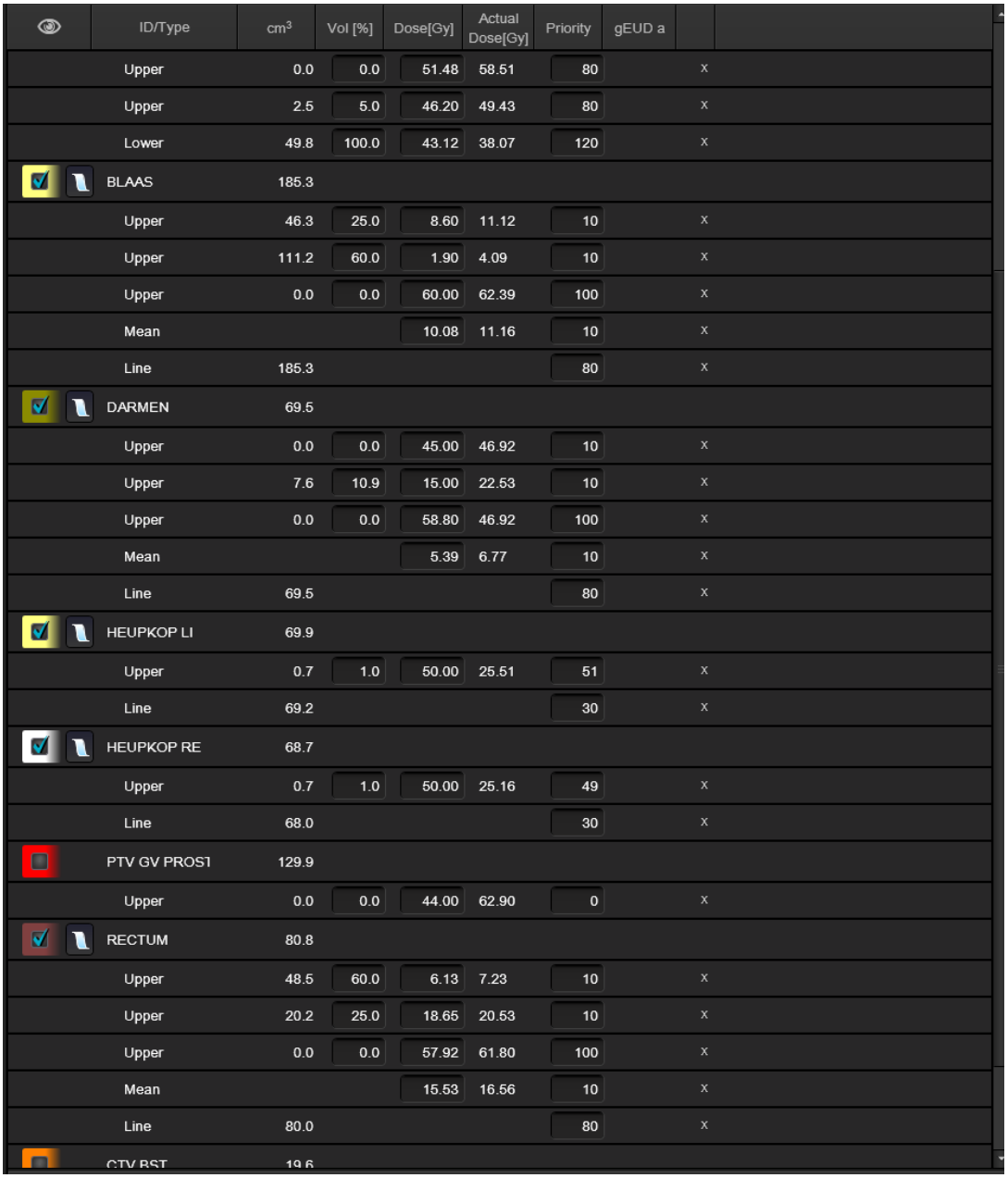


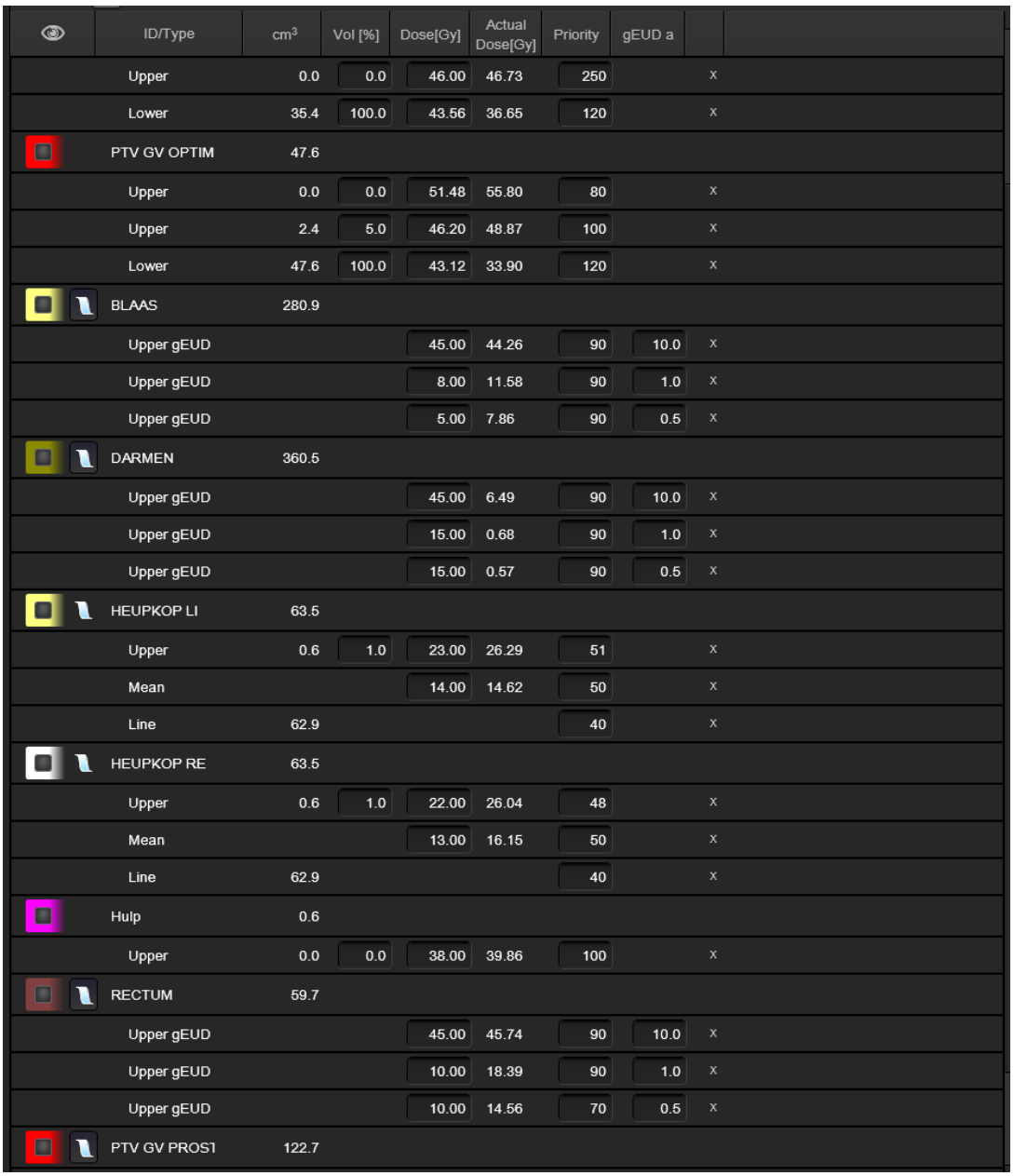
Figure 25: effect of slightly increasing a-value from reference of 10 (squares) to 11 (triangles)

For the treatment planning that uses dose/volume-constraints around four constraints were needed for the OARs to create the treatment plan. By using gEUD-constraints this number of constraints is reduced to around three constraints. An example of the used constraints is shown by figures 26 and 27. The constraints for the PTV BST were not adjusted during the planning of the new plans, only the weight of the constraints was sometimes adjusted to push more on the minimum constraint.



ID/Type	cm³	Vol [%]	Dose[Gy]	Actual Dose[Gy]	Priority	gEUD a	
Upper	0.0	0.0	51.48	58.51	80		x
Upper	2.5	5.0	46.20	49.43	80		x
Lower	49.8	100.0	43.12	38.07	120		x
BLAAS	185.3						
Upper	46.3	25.0	8.60	11.12	10		x
Upper	111.2	60.0	1.90	4.09	10		x
Upper	0.0	0.0	60.00	62.39	100		x
Mean			10.08	11.16	10		x
Line	185.3				80		x
DARMEN	69.5						
Upper	0.0	0.0	45.00	46.92	10		x
Upper	7.6	10.9	15.00	22.53	10		x
Upper	0.0	0.0	58.80	46.92	100		x
Mean			5.39	6.77	10		x
Line	69.5				80		x
HEUPKOP LI	69.9						
Upper	0.7	1.0	50.00	25.51	51		x
Line	69.2				30		x
HEUPKOP RE	68.7						
Upper	0.7	1.0	50.00	25.16	49		x
Line	68.0				30		x
PTV GV PROST	129.9						
Upper	0.0	0.0	44.00	62.90	0		x
RECTUM	80.8						
Upper	48.5	60.0	6.13	7.23	10		x
Upper	20.2	25.0	18.65	20.53	10		x
Upper	0.0	0.0	57.92	61.80	100		x
Mean			15.53	16.56	10		x
Line	80.0				80		x
CTV BST	19.6						

Figure 26: example of constraints for OARs for an original plan



ID/Type	cm³	Vol [%]	Dose[Gy]	Actual Dose[Gy]	Priority	gEUD a	
Upper	0.0	0.0	46.00	46.73	250		x
Lower	35.4	100.0	43.56	36.65	120		x
PTV GV OPTIM	47.6						
Upper	0.0	0.0	51.48	55.80	80		x
Upper	2.4	5.0	46.20	48.87	100		x
Lower	47.6	100.0	43.12	33.90	120		x
BLAAS	280.9						
Upper gEUD			45.00	44.26	90	10.0	x
Upper gEUD			8.00	11.58	90	1.0	x
Upper gEUD			5.00	7.86	90	0.5	x
DARMEN	360.5						
Upper gEUD			45.00	6.49	90	10.0	x
Upper gEUD			15.00	0.68	90	1.0	x
Upper gEUD			15.00	0.57	90	0.5	x
HEUPKOP LI	63.5						
Upper	0.6	1.0	23.00	26.29	51		x
Mean			14.00	14.62	50		x
Line	62.9				40		x
HEUPKOP RE	63.5						
Upper	0.6	1.0	22.00	26.04	48		x
Mean			13.00	16.15	50		x
Line	62.9				40		x
Hulp	0.6						
Upper	0.0	0.0	38.00	39.86	100		x
RECTUM	59.7						
Upper gEUD			45.00	45.74	90	10.0	x
Upper gEUD			10.00	18.39	90	1.0	x
Upper gEUD			10.00	14.56	70	0.5	x
PTV GV PROS1	122.7						

Figure 27: example of constraints for OARs for a reconstructed plan

5 Discussion

The focus of this study is the clinical implementation of the (radio)biologically based gEUD-concept in the optimization and treatment planning of prostate cancer. For a successful implementation it is important that two basic conditions are met. First, the plans the study is based on should be planned consistently. Second, the existing plans should also be consistent for at least certain values of the volume parameter a. The first condition is important to reduce differences in plan quality because of variations in plan experience of the planner. It is also important that the plans are optimized to the limit, meaning that all constraints are pushed as far as possible, to allow comparison of plans planned using the new and old technique.

This condition is fulfilled in this study because the RapidPlan®-library was used. This allows for plan comparison against a large (200pt) database of reviewed plans. The Rapidplan®-model used was constructed in two steps. First, a reviewed library (set of patients) was used and the planners used the model and tried to improve the plans beyond the initial model. Next, the second group of patients was also inserted into the model, improving the model. All patients from our cohort were planned using this tighter second model and can be considered “optimal” to the department standards of the LOC.

The second condition is important because it allows to optimize in the same way for every case. An implementation of the technique can be considered more successful if it results in a fixed number of parameters, in this case the volume parameter “a” and the corresponding gEUD, which can be employed for the majority of the patient population. This minimizes trial-and-error and necessity of tweaking. It also allows for a well-defined planning protocol.

Looking at the data of the a posteriori study can be deducted that for the PTV, Rectum and bladder the distribution of the gEUD-values are peaked and have a limited variance. For rectum and bladder the distribution will decrease for an increasing volume parameter and the peak will also shift to the right. This means that the starting EUD-values for these organs increase for an increasing a-value. For the PTV BST the effect of the changing volume parameter is minimal and not significant. This is also confirmed by the statistical t-test. This indicates that an gEUD-based optimalisation is possible and a same a- and EUD-value can be used for every patient making planning very efficient. The shape of the distribution does not show a large dependence of the volume parameter “a”. This means that different gEUD-cost functions could be combined in the optimisation without losing the advantage of using fixed values for the population. For the intestines no clear peak was observed and the distribution of the gEUD-values was more uniform. The explanation for this is that there is a great difference in volumes for the intestines for the different patients. This would suggest that a fixed parameter in the optimisation is not possible, and every different patient will require a different EUD-value that has to be searched with the trial-and-error method. The results show that the patient cohort can be used to base the next step of the implementation on.

The practical study showed that the clinical dose/volume-based plans can be reconstructed by using gEUD-constraints and that the number of required constraints can be reduced from four to three. It was shown that gEUD-cost functions with parameters of respectively 0.5, 1 and 10 are sufficient to reproduce the plans. Besides, it has to be considered that the original plans also uses a “line”-constraint resulting from the Rapidplan® library. This type of constraint results from the RapidPlan® library and is a combination of several dose/volume-constraints. This suggests that even a larger reduction would be obtained when not using the RapidPlan® initially. By looking at the number of D/V-constraints in the used CHIPP-protocol this would suggest a reduction from seven and five constraints to three for respectively rectum and bladder.

However, the gEUD-value that belongs to that constraint was still found by using the trial-and-error method. The starting gEUD-values were 10, 15 and 45 for the three constraints respectively but were then changed during the optimalisation**.** It was also not possible to connect these values to the results of the a posteriori study. A first reason is that for the calculation of gEUD a conversion of the dose to EQD2 is necessary. The DVH during optimisation cannot be scaled to EQD2, so there will always be a non-linear offset between the values. A second reason is that it is unclear how gEUD as a cost function in the optimizer can be related to the theoretical definition of gEUD used in this study. As was discussed in part 2.5 this can be a source of uncertainty.

For the improvement of the plans the same number of constraints and the same a-values for the constraints were used as used for the reconstruction. The results show that even with limited experience in planning it was possible to have an, although limited, clinical impact on 60% of the plans. This is shown by the relatively calculation and comparison of the NTCP-values out of the gEUD-results. A statistical paired t-test is performed. The result of this showed that the improvement is significant, with a 95% confidence level, for both rectum and bladder based on the calculated NTCP-values. Based on the EUD-values the difference is only significant for the rectum and not for the bladder. Although a limited model was used, this shows the extra advantage of the use of gEUD in evaluating plan quality. Improvement was not possible for every patient. We have to note that the RapidPlan-model already pushed the plan to the limit based on the dose/volume-constraints.

6 Conclusion

6.1 A posteriori study

This study showed that for successful implementation of gEUD-based treatment planning a sample is needed that is contoured and planned in a consistent way. Performing an a posteriori analysis of existing treatments is necessary to investigate if gEUD-based planning is possible, and if a clear planning protocol can be developed. It was shown that for rectum and bladder the distribution of the gEUD-values for different values of the volume parameter a were peaked. This means that optimizing based on fixed values and parameters should be possible.

Since for the PTV there was no dependence on the volume parameter, could argued if a gEUD-constraint is useful, especially since there is less control on min/max values.

The results for the intestine again show the need for consistency in contoured volume: because of the large variation, there are no clear guidelines to contouring the intestine, gEUD-optimization would need much more trial-and-error.

6.2 Practical study

Since it was possible to reconstruct all plans using the gEUD-constraints, it can be concluded that this way of planning results in the same quality of treatment planning as the dose/volume based plans.

It is shown that this approach can also result in treatment plans with more sparing of the OARs in 60% of the cases without increasing the technical complexity of the plans. Although this improvement is not always clinically relevant or significant it must be noted that the original plans were created using the RapidPlan® Library, and were already of very high quality. Also, this study was executed with minimal experience in treatment planning. When this is performed by a more experienced person, the results could possibly be even better.

Besides the numerical results there are also important practical results. As the figures showed, an a-value around 0.5 mostly affects the low-dose region of the DVH. A constraint with a=1 affects the whole DVH. A constraint with a high a-value affects mostly the high-dose region of the DVH. This was described in the literature but it was not expected to be this straightforward and obvious. This can clearly be attributed to the consistency of the base-data set. It shows that when starting from a clear, well-defined protocol gEUD-implementation is not that difficult.

The effect of small changes in the a-values in is rather small. This means that the exact a-value of the constraint is not the most important factor for creating a good treatment plan using this EUD constraints for the OARs.

When using EUD constraints, less constraints are required to accomplish a plan with the same quality, this means that it can reduce plan time while maintaining plan quality and increasing overall efficiency.

6.3 How biological is biological way of planning?

The values used in the practical study to reconstruct and improve the original plan by using the gEUD-constraints are 0.5, 1 and 10 for the volume parameter a for all OARs. The values for EUD differ from patient to patient but were around 5, 10 and 40Gy. When these results are compared with the results from the literature that are given by table 1 can be concluded that there a large differences between them.

Although it is based on biological principles, gEUD-planning does not import the biology straight into the TPS. It does offer an extra tool in the planning toolbox that can help shape the dose distribution and DVH into a shape that is relevant to toxicity. Also, the link between gEUD and NTCP can help in evaluating the clinical effect of different plans. The advantage of using fixed values also makes the planning process more robust.

However, because of the need for a consistent protocol and the theoretical background, gEUD-based planning will have a steeping learning-curve. The gEUD-values cannot be read directly from the DVH, and a good understanding of the volume parameter a is necessary. This is why mixing the D/V and gEUD approach to gain experience will be a preferred way to go for most radiotherapy departments.

6.4 Possibilities for new additive research

In the future the number of patients this method is tested on could be increased for a better result and the planning could also be done by several different people to minimize the effect of a difference in experience. This could be an important factor to exclude. This study can also be expanded to other types of cancer and therefore other OARs. It will probably be not as effective for every indication, depending on how “peaked” the gEUD-distributions are. For the moment, this technique is being implemented to allow more low-dose sparing of lung tissue in the treatment of esophagal cancers at the LOC.

References

[1] “Limburgs Oncologisch Centrum,” Limburgs Oncologisch Centrum, [Online]. Available: https://www.jessazh.be/web/loc/over-loc. [Accessed 5 June 2022].

[2] X. A. Li, M. Alber, J. O. Deasy, A. Jackson, K.-W. Ken Jee, L. B. Marks, M. K. Martel, C. Mayo, V. Moiseenko, A. E. Nahum, A. Niemierko, V. A. Semenenko and E. D. Yorke, “The Use and QA of biologically related models for treatment planning: Short report of the TG-166 of the therapy physics committee of the AAPM,” 2012.

[3] K. Senthilkumar and K. J. Maria Das, “Comparison of biological-based and volume-based intensity-modulated radiotherapy plans generated using the same treatment planning system,” *Journal of Cancer Reserch and Therapeutics,* 2018.

[4] J. Z. Wang, N. A. Mayr and W. T. C. Yuh, “Behind EUD,” *Acta Oncologica,* vol. 47, no. 5, pp. 971-972, 2009.

[5] B. Emami, J. Lyman, A. Brown, L. Coia, M. Goitein, J. E. Munzenrider, B. Shank, L. J. Solin and M. Wesson, “Tolerance of normal tissue to therapeutic irradiation,” *I. J. Radiation Oncology, Biology and Physics,* vol. 21, no. 1, pp. 109-122, 1991.

[6] A. Fogliata, S. Thompson, A. Stravato, S. Tomatis, M. Scorsetti and L. Cozzi, “On the gEUD biological optimization objective for organs at risk in Photon optimizer of Eclipse treatment planning system,” *Journal of Applied Clinical Medical Physics,* vol. 19, no. 1, pp. 106-114, 2018.

[7] A. Niemierko, “Reporting and analyzing dose distributions: a concept of equivalent uniform dose,” *The International Journal of Medical Physics Research and Practice,* vol. 24, no. 1, pp. 103-110, 1998.

[8] S. Rana and C. Y. Cheng, “Radiobiological Impact of Planning Techniques for Prostate Cancer in Terms of Tumor Constrol Probability and Normal Tissue Complication Probability,” *Annals of Medical and Health Sciences Research ,* vol. 4, no. 2, pp. 167-172, 2014.

[9] B. Ruiz and Y. Feng, “Clinical and radiobiological evaluation of a method for planning target volume generation dependent on organ-at-risk exclusions in magnetic resonance imaging-based prostate radiotherapy,” *Pysics and Imaging in Radiation Oncology,* vol. 8, pp. 51-56, 2018.

[10] Q. Wu, R. Mohan, A. Niemierko and R. Schmidt-Ullrich, “Optimization of intensity-modulated radiotherapy plans based on the equivalent uniform dose,” *Radiation Oncology Biol. Phys.,* vol. 52, no. 1, pp. 224-235, 2002.

[11] S. Rana and K. Rogers, “Radiobiological Impact of Acuros XB Dose Calculation Algorithm on Low-Risk Prostate Cancer Treatment Plans Created by RapidArc Technique,” 2012.

[12] C. Schröder, I. Stiefel, S. Tanadini-Lang, I. Pytko, E. Vu, M. Guckenberger and N. Andratschke, “Re-irradiation in the torax - An analysis of efficacy and safety based on accumulated EQD2 doses,” *Radiotherapy and Oncology,* pp. 56-62, 2020.

[13] M. van Leeuwen, A. L. Oei, J. Crezee, A. Bel, N. A. P. Franken, L. J. A. Stalpers and H. P. Kok, “The alfa and beta of tumoers: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies,” 2018.

[14] R. Dale, “Use of the Linear-Quadratic Radiobiological Model for Quantifying Kidney Response in Targeted Radiotherapy,” *Cancer Biotherapy & Radiopharmaceuticals,* vol. 19, no. 3, 2004.

[15] S. F. C. O'Rourke, H. McAneny and T. Hillen, “Linear quadratic and tumour control probability modelling in external beam radiation,” *Mathematical Biology,* vol. 58, pp. 799-817, 2009.

[16] J. Z. Wang, M. Guerrero and X. Allen Li, “How low is the alpha/beta ratio for prostate cancer?,” *international Journal of radiation and oncology,* 2003.

[17] L. Widesott, L. Strigari, M. C. Pressello, M. Benassi and V. Landoni, “Role of the parameters involved in the plan optimization based on the generalized equivalent uniform dose and radiobiological implications,” 2008.

[18] S. K. Patnaikuni, R. R. Jain, S. M. Saini, R. M. Chandola, S. K. Azad, M. Back, A. Sinha and V. Choudhary, “Effective Use of Generalized Equivalent Uniform Dose-Based Optimization on Dose-Volume Objectives in Volumetric Modulated Arc (VMAT) Radiation Therapy for Prostate Cancer,” *Journal of Dental and Medical Sciences ,* vol. 12, no. 9, pp. 48-56, 2018.

[19] A. Foglia, S. Thompson, A. Stravato, S. Tomatis, M. Scorsetti and L. Cozzi, “On the gEUD biological optimization objective for organs at risk in Photon Optimizer of Eclipse planning system,” 2017.

[20] M. Battestini, M. Schwarz, M. Krämer and E. Scifoni, “Including Volume Effects in Biological Treatment Plan Optimization for Carbon Ion Therapy: Generalizes equivalent Uniform Dose-Based Objectives in TRiP98,” 2022.

[21] “Oxfords Learner's dictionaries,” Oxford University Press, 2022. [Online]. Available: https://www.oxfordlearnersdictionaries.com/definition/english/a-posteriori. [Accessed 17 May 2022].

[22] “The Institute of Cancer Research,” The Institute of Cancer Research, [Online]. Available: https://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/clinical-trials/chhip. [Accessed 23 May 2022].

[23] D. Dearnaley, I. Syndikus, H. Mossop, V. Khoo, A. Birtle, D. Bloomfield, J. Graham, P. Kirkbride, J. Logue, Z. Malik, j. Money-Kyrle, J. M O'Sullivan, M. Panades, C. Parker and H. Patterson, “Conventionel versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, hase 3 CHHiP trial,” *The Lancet Oncology,* pp. 1047-1060, 2016.

[24] “Varian,” Varian Medical Systems, [Online]. Available: https://www.varian.com/. [Accessed 30 May 2022].

[25] H. E. Romeijn, R. K. Ahuja, J. F. Dempsey and A. Kurmar, “A Column generation approach to radiation therapy treatment planning using aperture modulation,” *Society for Industrial and Applied Mathematics,* vol. 15, no. 3, pp. 838-862, 2005.

[26] K. Sang Won, C. Jin Beom, K. Jae Sung, K. In Ah, E. Keun Yong, S. Changhoon, L. Jeong Woo, K. Jin Young and S. Tae Suk, “Optimal planning strategy among various arc arrangements for prostate stereotactic body radiotherapy with volumetric modulated arc therapy technique,” *Radiology and Oncology,* 2017.

Attachments

A collected EUD values for all a values and all patients for the rectum

	a = 0,5	a = 0,5	a = 1	a = 1	a = 2	a = 2	a = 3	a = 3	a = 4	a = 4
patiëntnummer	EUD D [Gy]	EUD EQD2 [Gy	EUD D [Gy]	EUD EQD2 [Gy]	EUD D [Gy]	EUD EQD2 [Gy	EUD D [Gy]	EUD EQD2 [Gy]	EUD D [Gy]	EUD EQD2 [Gy
11257	24,19	22,29	27,09	26,5	32,01	33,7	35,71	39,06	38,52	43,09
19465	11,51	9,45	14,85	13,56	21,57	22,29	26,99	29,31	31,07	34,61
28613	19,33	17,42	23,1	22,56	29,5	31,53	34,2	38,06	37,65	42,78
40167	21,1	19,01	24,33	23,44	29,74	31,09	33,8	36,84	36,88	41,15
43714	14,25	12,52	18,8	18,22	26,35	28,19	31,74	35,33	35,62	40,43
57121	16,55	14,43	20,12	19,2	26,7	28,01	31,56	34,38	35,05	38,98
60629	20,86	19,06	24,55	24,34	31,01	33,75	35,85	40,54	39,37	45,3
61085	15,24	13,07	18,64	17,83	25,78	27,92	31,55	35,64	35,76	41,07
78018	13,23	10,87	16,05	14,67	22,45	23,66	28,12	31,34	32,51	37,1
87104	10,17	8,1	12,97	11,7	19,8	20,91	25,9	28,86	30,57	34,83
88958	13,46	11,21	16,57	15,35	23,25	24,6	28,89	32,16	33,17	37,74
93896	13,17	10,74	15,85	14,25	21,76	22,49	27,09	29,79	31,34	35,45
124188	17,02	14,92	20,56	19,92	27,55	29,88	33,03	37,33	37,01	42,58
144034	15,15	13,05	18,75	17,86	25,72	27,44	31,14	34,7	35,12	39,96
147761	21,44	18,62	23,31	21,52	27,45	28,29	31,56	34,67	35,1	39,78
154959	18,35	16,45	22,21	21,81	29,12	31,5	34,22	38,44	37,88	43,34
155857	15,4	13,32	18,98	18,35	26,38	28,85	32,27	36,76	36,54	42,29
164470	17,3	15,29	21,09	20,35	27,74	29,42	32,64	36,03	36,2	40,82
182903	11,84	9,78	15,16	14,11	22,39	23,81	28,32	31,52	32,69	37,09
188308	7,86	6,3	11,37	10,43	19,01	20,06	25,22	27,95	29,88	33,87
200846	15,93	13,91	19,77	18,99	26,69	28,58	32	35,85	35,94	41,11
201038	16,7	14,68	20,49	19,72	27,26	29,04	32,35	35,93	36,07	40,9
202562	14,52	11,97	17,07	15,45	22,82	23,57	27,98	30,6	32,03	36
228686	18,09	15,87	21,31	20,59	27,92	30,24	33,28	37,6	37,21	42,81
228699	12,05	10,08	15,63	14,73	23,14	24,75	29,09	32,49	33,42	38,06
242512	14,58	12,29	17,76	16,51	24,21	25,42	29,51	32,62	33,55	38
247039	12,42	10,18	15,39	14,14	22,14	23,54	28,06	31,48	32,58	37,37
250008	14,41	12,71	18,91	18,6	26,93	29,38	32,7	36,94	36,75	42,17
251730	13,34	11,48	17,54	16,61	24,67	25,85	29,88	32,72	33,71	37,79
260537	15,37	12,97	18,3	17,01	24,57	25,88	29,88	33,13	33,93	38,51
270516	17,98	15,89	21,52	20,74	27,98	29,69	32,83	36,24	36,36	40,99
306350	14,77	12,75	18,48	17,88	26,06	28,53	32,05	36,51	36,35	42,08
327395	19,06	16,81	22,18	21,24	28,17	29,85	32,93	36,44	36,48	41,24
328929	22,29	20,38	25,58	25,1	31,23	33,35	35,5	39,49	38,7	43,98
333702	14,62	12,22	17,51	16,17	23,8	25,09	29,25	32,52	33,45	38,04
334168	14,91	12,92	18,89	17,84	25,51	26,35	30,22	32,56	33,68	37,19
354510	21,63	18,99	23,76	22,27	28,31	29,47	32,51	35,85	35,99	40,83
358054	15,07	12,78	18,21	17,19	25,03	27	30,81	34,87	35,14	40,55
358799	18,1	15,87	21,37	20,42	27,56	29,25	32,47	36,07	36,17	41,28
364172	16,85	14,36	19,64	18,23	25,39	26,42	30,26	33,1	34	38,11
365554	25,61	24,18	28,83	29,07	34,31	37,32	38,36	43,17	41,33	47,29
372301	14,62	12,37	17,82	16,77	24,65	26,48	30,4	34,28	34,72	39,89
400874	19,89	17,69	23	22,27	29,1	31,26	34	38,08	37,63	42,95
406252	16,1	13,98	19,67	18,84	26,52	28,36	31,85	34,57	35,77	40,77
427062	11,83	10,01	15,74	15,16	23,92	26,1	30,21	34,2	34,67	39,83
445122	11,02	8,61	13,25	11,31	18,34	18,15	23,28	24,81	27,44	30,32
457597	13,71	11,73	17,56	16,7	24,82	26,37	30,33	33,61	34,33	38,81
483871	18,72	17,28	23,47	23,67	30,96	34,03	36,1	41,02	39,7	45,83
495610	19,64	17,68	23,19	22,86	29,91	32,61	35,04	39,69	38,75	44,63
593799	12,29	10,2	15,57	14,6	22,92	24,68	29,03	32,69	33,53	38,43
594574	13,43	11,25	16,8	15,48	23,14	24,03	28,38	30,9	32,3	36,14

	a = 5	a = 5	a = 10	a = 10	a = 15	a = 15	a = 20	a = 20	a = 30	a = 30
patiëntnummer	EUD D [Gy]	EUD EQD2 [Gy]	EUD D [Gy]	EUD EQD2 [Gy	EUD D [Gy]	EUD EQD2 [Gy]	EUD D [Gy]	EUD EQD2 [Gy	EUD D [Gy]	EUD EQD2 [Gy]
11257	40,7	46,24	47,13	55,34	50,33	59,68	52,24	62,2	54,42	65,02
19465	34,2	38,71	43,04	50,38	47,27	55,9	49,77	59,12	52,61	62,76
28613	40,26	46,33	47,4	55,89	50,66	60,18	52,55	62,63	54,67	65,41
40167	39,27	44,49	46,14	53,92	49,46	58,32	51,42	60,86	53,64	63,71
43714	38,5	44,23	46,26	54,38	49,75	58,86	51,74	61,39	53,95	64,18
57121	37,66	42,47	44,97	52,4	48,52	57,1	50,63	59,81	53,02	62,82
60629	41,99	48,75	48,74	57,44	51,6	61,08	53,2	63,1	54,94	65,33
61085	38,85	45,01	46,77	55	50,13	59,21	52	61,55	54,04	64,12
78018	35,86	41,44	44,89	52,93	48,86	57,92	51,1	60,73	53,56	63,82
87104	34,13	39,35	43,7	51,47	47,96	56,86	50,39	59,94	53,09	63,35
88958	36,4	41,92	45,08	53,05	48,93	57,94	51,12	60,7	53,54	63,76
93896	34,67	39,83	43,95	51,82	48,18	57,2	50,6	60,26	53,28	63,66
124188	39,95	46,41	47,57	56,15	50,82	60,26	52,64	62,55	54,62	65,07
144034	38,11	43,88	46,13	54,36	49,74	59	51,8	61,64	54,09	64,59
147761	37,98	43,7	46,03	54,16	49,62	58,74	51,65	61,33	53,91	64,2
154959	40,6	46,94	47,77	56,33	50,93	60,42	52,73	62,75	54,74	65,35
155857	39,66	46,28	47,58	56,24	50,88	60,35	52,7	62,62	54,67	65,09
164470	38,88	44,44	46,3	54,41	49,76	58,91	51,77	61,45	53,98	64,22
182903	35,96	41,24	44,58	52,12	48,36	56,87	50,5	59,56	52,87	62,54
188308	33,42	38,38	43,11	50,76	47,52	56,39	50,06	59,63	52,91	63,26
200846	38,91	45,02	46,8	55,24	50,27	59,7	52,25	62,23	54,44	65,04
201038	38,87	44,63	46,47	54,71	49,94	59,25	51,96	61,87	54,23	64,79
202562	35,18	40,18	44,03	51,82	48,17	57,16	50,58	60,24	53,27	63,67
228686	40,13	46,6	47,67	56,29	50,91	60,4	52,72	62,71	54,72	65,24
228699	36,66	42,2	45,19	53,07	48,94	57,81	51,07	60,49	53,42	63,45
242512	36,65	42,08	45,15	53,23	49,04	58,31	51,31	61,28	53,88	64,64
247039	36,01	41,77	45,13	53,32	49,1	58,29	51,33	61,09	53,77	64,16
250008	39,69	45,95	47,25	55,59	50,48	59,7	52,3	62,01	54,31	64,57
251730	36,62	41,65	44,72	52,39	48,52	57,36	50,75	60,26	53,28	63,52
260537	37,02	42,57	45,41	53,49	49,21	58,37	51,38	61,15	53,81	64,25
270516	39,02	44,58	46,35	54,41	49,76	58,89	51,75	61,46	53,99	64,35
306350	39,5	46,1	47,51	56,22	50,87	60,44	52,73	62,79	54,76	65,35
327395	39,17	44,85	46,51	54,53	49,83	58,81	51,74	61,23	53,85	63,89
328929	41,16	47,38	47,95	56,57	51,07	60,66	52,87	62,98	54,87	65,54
333702	36,64	42,17	45,17	52,99	48,89	57,67	51	60,3	53,3	63,19
334168	36,34	40,8	44,03	51,37	47,88	56,57	50,22	59,67	52,93	63,23
354510	38,77	44,65	46,56	54,9	50,07	59,39	52,06	61,92	54,26	64,72
358054	38,37	44,72	46,79	55,43	50,39	59,98	52,4	62,53	54,61	65,33
358799	38,98	44,87	46,67	55,05	50,16	59,56	52,16	62,12	54,37	64,94
364172	36,87	41,92	44,84	52,48	48,57	57,49	50,81	60,54	53,44	64,23
365554	43,54	50,32	49,43	58,18	52,04	61,62	53,54	63,6	55,23	65,86
372301	37,94	44	46,27	54,43	49,78	58,78	51,72	61,19	53,83	63,79
400874	40,34	46,54	47,52	55,92	50,69	60	52,49	62,29	54,47	64,83
406252	38,7	44,63	46,55	54,86	50,04	59,35	52,03	61,89	54,24	64,7
427062	37,91	43,92	46,19	54,3	49,7	58,69	51,66	61,14	53,8	83,84
445122	30,81	34,73	40,72	47,61	45,52	53,82	48,37	57,52	51,65	61,82
457597	37,33	42,69	45,32	52,99	48,89	57,53	50,93	60,1	53,19	62,93
483871	42,33	49,3	49,1	58,1	51,99	61,81	53,62	63,89	55,4	66,17
495610	41,47	48,22	48,52	57,34	51,44	61,18	53,23	63,31	55,06	65,62
593799	36,86	42,66	45,53	53,59	49,27	58,29	51,37	60,94	53,69	63,87
594574	35,34	40,2	43,97	51,6	48,03	56,79	50,38	59,75	52,98	63,02