Fast re-planning for radiotherapy by using the reference point method

Snel her-plannen voor radiotherapie met behulp van de referentiepunt methode

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Snel her-plannen voor radiotherapie met behulp van de referentiepunt methode

by

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in partial fulfillment of the requirements for the degree of

Bachelor of Science
in Applied Mathematics

at the Delft University of Technology,
to be defended publicly on Wednesday July 13, 2016 at 16.30 AM.

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An electronic version of this dissertation is available at
http://repository.tudelft.nl/.

Contents

Summary

When a patient is diagnosed with cancer, a number of treatments is possible. About half of these patients is treated with radiotherapy. This is a multi-disciplinary field of research, where mathematics, physics and medicine come together. In this thesis the focus will lie on prostate cancer. One of the main problems with this type of cancer is that the organs in the stomach area move, mainly due to volume changes of the bladder. During the treatment, the same treatment plan is used for several weeks, but since these organs move, this plan is not optimal every day. The goal of this thesis is to find a way to make fast optimal plans with the reference point method, such that a new treatment plan can be made every day.

The reference point method is used in multi-objective optimisation where the solution obtained is always Pareto optimal. This means that no objective can be improved without worsening at least one other objective. This is due to the fact that the objectives are conflicting. An objective is for example the mean amount of radiation in the rectum. For the reference point method a reference point and an increasing direction of the reference path are needed. Most of the times it is also necessary to add indifference curves. In those cases a sensitivity parameter is needed as well. The goal is to find a good method to choose these values, such that equally good treatment plans can be calculated with the reference point method as with the time-consuming full method, iCycle.

Several options for choosing a reference point are discussed. First, the reference point is based on the clinically favourable solutions (iCycle solution) of different scans from the same patient. And then the reference point is based on the iCycle solutions from scans of different patients.

The conclusion was that it is best to use the iCycle solution of the planning-CT of the same patient or the mean of iCycle solutions from other patients as reference point. This is also convenient in practice, since almost no prior data for a specific patient is needed in the treatment planning process and the outliers have little influence.

SAMENVATTING

Wanneer een patiënt is gediagnostiseerd met kanker, zijn er meerdere behandelingen mogelijk. Ongeveer de helft van de patiënten wordt behandeld met radiotherapie. Radiotherapie is een multidisciplinair onderzoeksveld waar wiskunde, natuurkunde en geneeskunde samen komen. In dit verslag wordt slechts gekeken naar prostaatkanker. Een van de grootste problemen bij dit type kanker is dat de organen in de buik bewegen, voornamelijk doordat de blaas van volume verandert. Voor de behandeling wordt hetzelfde bestralingsplan gebruikt voor een aantal weken, maar doordat de organen veranderen is dit plan niet elke dag optimaal. Het doel van dit onderzoek is een goede manier vinden om snel optimale plannen te berekenen met behulp van de referentiepunt-methode, zodanig dat elke dag een nieuw behandelingsplan kan worden berekend.

De referentiepunt-methode wordt gebruikt in multi-criteria optimalisatie, waarbij de gevonden oplossing altijd Pareto-optimaal is. Dit betekent dat een doelfunctie niet kan worden verbeterd zonder dat tenminste een andere doelfunctie wordt verslechterd, dit komt doordat de doelfuncties tegenstrijdig zijn. Een doelfunctie is bijvoorbeeld de gemiddelde hoeveelheid straling in de endeldarm. Voor deze methode is een referentiepunt nodig en een stijgende richting van het referentie pad. Meestal zijn ook indifferentiecurven nodig: in deze gevallen wordt er nog een gevoeligheidsparameter toegevoegd. Het doel van dit project is om een goede methode te vinden om deze waardes te kiezen, zodanig dat even goede behandelingsplannen kunnen worden berekend met de referentiepunt-methode als met de huidige tijdrovende methode (iCycle).

Verschillende opties voor het kiezen van een referentiepunt worden bekeken. Als eerste worden manieren van het kiezen van referentiepunten bekeken die gebaseerd zijn op de klinisch geprefereerde oplossingen (iCycle oplossingen) van dezelfde patiënt. En daarna wordt het referentiepunt gebaseerd op de iCycle oplossingen van andere patiënten.

De conclusie is dat het beste is om de iCycle oplossing van de planning-CT van dezelfde patiënt of het gemiddelde van de iCycle oplossingen van andere patiënten als referentiepunt te gebruiken. Dit is ook voordelig in de praktijk, omdat er amper data voor een specifieke patiënt nodig is tijdens het behandelingsproces. Ook hebben de uitschieters weinig invloed.

Preface

I have always had some interest in medicine, which is pretty inevitable since all my family are doctors. I decided however, to do something else and study mathematics, which I really enjoy. When I found out it was possible to combine medicine and mathematics for my bachelor final project I was even more enthusiastic. This resulted in an internship at the Erasmus Medical Center Cancer Institute in Rotterdam. During this internship I did research in improving treatment planning in radiotherapy. This project was in collaboration with the Delft Institute of Applied Mathematics of the Technical University of Delft.

During the project I learned a lot about treatment planning and the mathematics involved. I was delighted by the collaboration between the Erasmus MC and the TU Delft and enjoyed working at the Erasmus Medical Center Cancer Institute. This project wouldn't have been possible without the following people and that's why I would like to give them my thanks. Marleen Keijzer, for all her help with the project, her feedback for my report and for bringing me in contact with the Erasmus MC. Rens van Haveren and Sebastiaan Breedveld for their good support during the project, they were always very helpful and supportive. I would also like to thank Inez Wensing, my fellow student, for always helping me with my problems and thinking along.

Ghiline van Furth
Delft, July 2016

1 INTRODUCTION

Radiotherapy is one of the treatments for cancer patients, which is used for about half of the patients. The malignant cells are controlled or killed by ionizing radiation. Unfortunately it is physically impossible to destroy the tumour without damaging the surrounding organs. The total dose is given in fractions, because healthy tissues recover faster than the malignant cells. So the healthy organs can recover between doses, while the tumour gets destroyed.

The goal is to get a sufficient amount of radiation in the tumour, while minimising the radiation in the surrounding organs. This is a multi-objective optimisation problem. There are multiple objectives which need to be taken into account and multiple constraints.

The goal of this thesis is use the reference point method to obtain equally good treatment plans as with iCycle. In this project the focus lies on prostate cancer. One of the main problems with this type of cancer is the moving of the organs. The organs in the stomach area change a bit of size and position, mainly due to volume changes of the bladder and the rectum. Another issue is to account for the tumour shrinkage during the treatment. Since the radiation is given in fractions, the treatment plan that is optimal for a certain situation will not be optimal for another fraction anymore. The aim is to find a good solution for this problem, such that a new treatment plan is calculated every day. One of the main criteria is that this needs to be calculated very fast (ideally while the patient lies on the treatment table), that is why the reference point method will be used. For this method there is only one optimisation problem that has to be solved to generate a treatment plan, which makes it a very fast method.

For this reference point method a reference point, weight and sensitivity parameter is needed. Several methods of choosing these values will be discussed in this thesis. The solution obtained with the reference point method is always Pareto optimal. This means that no objective can be lowered without worsening at least one other objective. This is due to the conflicting nature of the objectives.

In Chapter 2 a brief introduction of radiotherapy is given, followed by an introduction to multi-objective optimisation (Chapter 3). Then a description of the reference point method is given (Chapter 4) and its implementation in (Chapter 5). In Chapter 6 the results for the reference point method with different reference points based on the same patient are given and in Chapter 7 based on other patients. At last, the conclusion is given in Chapter 8 and the recommendations in Chapter 9.

2
Radiotherapy

When a patient is diagnosed with cancer, a number of treatments is possible. One of these treatments is radiation therapy, or radiotherapy, which is used for about half of the patients somewhere in their treatment. This is a therapy where the tumour cells are controlled or killed by ionizing radiation. This is done by damaging their genetic material, such that these cells can't grow or divide anymore. The goal is to deliver a sufficient amount of radiation to the tumour, while saving the surrounding organs as much as possible. The idea is that the total dose of the radiation is delivered in daily fractions for a certain number of days. This is because healthy cells recover faster than tumour cells, so they get the time to recover while the malignant cells get damaged between doses.

2.1. Treatment

The treatment plan is realized by an external source that irradiates the patient. This form of therapy is called *External Beam Radiation Therapy* (EBRT). The most frequently used source is a linear accelerator, see Figure 2.1. This machine is rotated around the patient, while X-ray beams are transmitted through the *gantry* of this machine. These beams overlap at the tumour to maximise the radiation in the planning target volume and minimise the radiation in the healthy tissues. Because the beam directions and the shapes and intensity profiles of the fields are adjustable, the tumour can be irradiated, while the healthy cells are spared as much as possible.

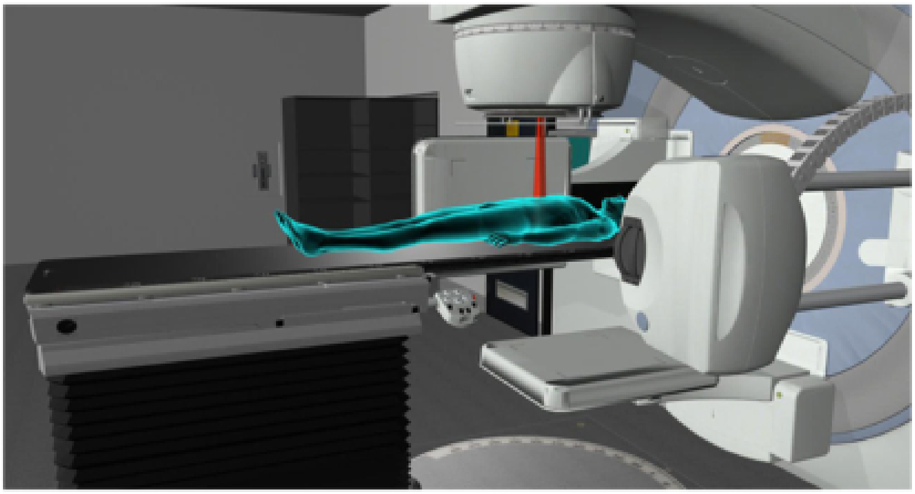

Figure 2.1: A linear accelerator with emitted X-ray beams

2.2. WISH-LIST

For every patient a wish-list is made first. In this list the objectives with their structure, type and priority are given.

Objective	Structure	Type	Priority
f_1	Rectum	EUD_12	1
f_2	Rectum	EUD_8	2
f_3	Rectum	mean	3
f_4	External ring	linear	4
f_5	PTV Shell 5	linear	5
f_6	PTV Shell 15	linear	6
f_7	PTV Shell 25	linear	7
f_8	Vesica Urinaria	mean	8
f_9	Body	mean	9

The first three objectives are all the rectum, which is given three times since the type is different for all three. The external ring is a ring on the surface of the body, this objective controls the entrance dose. This is the dose that is deposited on the edge of the tissue. De tumour is called the PTV (planning target volume), where some rings are delineated around. PTV shell 5, objective f_5, is the ring around the tumour at 5 mm, PTV shell 15 (f_6) at 15 mm and PTV shell 25 (f_7) at 25 mm. This is to realize a steep dose outside of the tumour. The vesica urinaria is the bladder and the objective body is an artificial structure that is added to keep the overall dose as low as possible.

The priority of each objective influences their importance in the minimisation process. The higher the priority, the more importance in minimising the objective, where 1 is the highest priority. The body has the lowest priority, because minimising the overall dose shouldn't happen at the expense of the other objectives.

Each objective also has a type. Objectives f_1 and f_2 are both the equivalent uniform dose (EUD) in the rectum:

$$EUD = \left(\frac{1}{n}\sum_{i=1}^{n} D_i^a\right)^{\frac{1}{a}} \tag{2.1}$$

Each structure is divided in n partial volumes and D_i is the absorbed dose in each partial volume. The difference between f_1 and f_2 is the parameter a, where f_1 has $a = 12$ and f_2 has $a = 8$. The rectum, the bladder and the body are of the type mean:

$$Mean = \frac{\sum_{i=1}^{n} D_i}{n} \tag{2.2}$$

The external ring and the shells around the tumour are of the type linear:

$$Linear = \max_{i=1,\ldots,n} D_i \tag{2.3}$$

2.3. TREATMENT PLANNING

After the wish-list is complete, the treatment plan has to be made. This plan contains information about the total dose, how the dose should be distributed, and the settings of the treatment device and about the physical damage caused by the radiation. Each patient has a unique anatomy, so for each patient a personal treatment plan is generated. This means that it costs a lot of time per patient to make a plan. The goal is to deliver enough ionizing radiation to the tumour, while minimising the radiation in the healthy organs. The entire process of making such a plan is called treatment plan optimisation.

To make a plan, a CT scan (computer tomography scan) is made first, this is a series of 2D images (slices) used to reconstruct a 3D volume image of the patient's interior, see Figure 2.2.

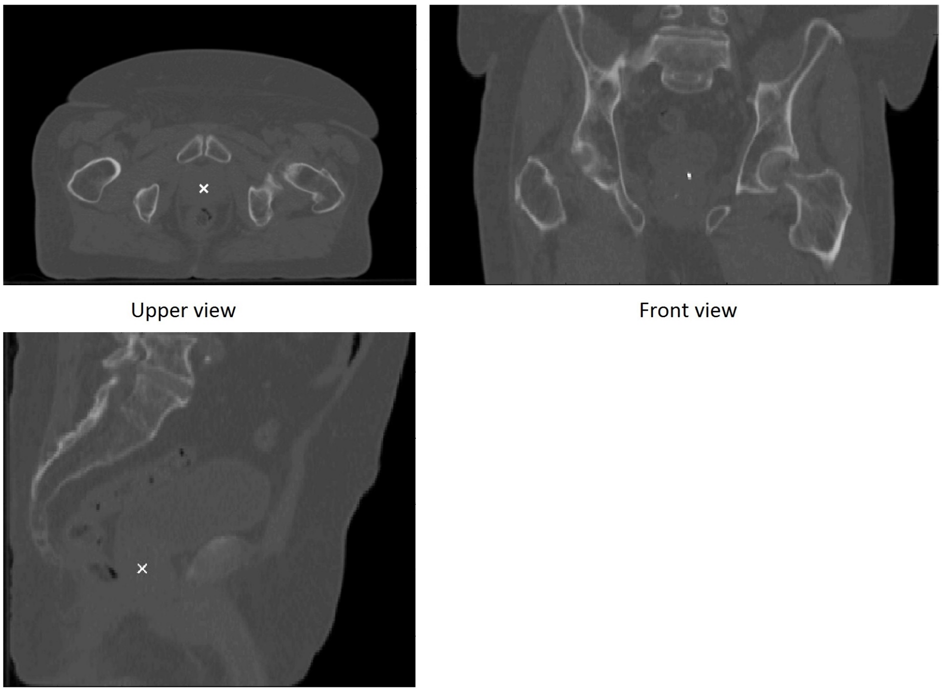

Figure 2.2: Example of CT slices from different views

This way the tumour and the organs at risk can be localized. This is done by delineating around the organs by hand in every slice of the CT scan. An example is shown in Figure 2.3. This process is very difficult and takes a lot of time.

After that, the algorithm iCycle, designed in Matlab by Sebastiaan Breedveld et al. [1], calculates a clinically favourable plan. This program can be used to determine the clinically favourable treatment plan from a CT-scan of the patient. An example of such a plan can be seen in Figure 2.4. As can be seen in the image, the tumour gets the most radiation, but unfortunately the bladder and rectum are irradiated as well. It is physically impossible to have all the radiation in the tumour and save the healthy organs completely. Side-effects in this case can be rectal bleeding, urinal and erection problems. These complications have a big impact on the patient's quality of life, and should be reduced as much as possible.

After this planning process, the treating physician always has to approve the plan before the treatment. Based on historical data, experience and sometimes measurements this physician makes the decision, which is extremely difficult. If the physician concludes that this plan is not good enough the process is done again. If the plan is approved, the patient receives a fraction of the total dose each day, for up to 40 days. This way the healthy tissues can recover between doses.

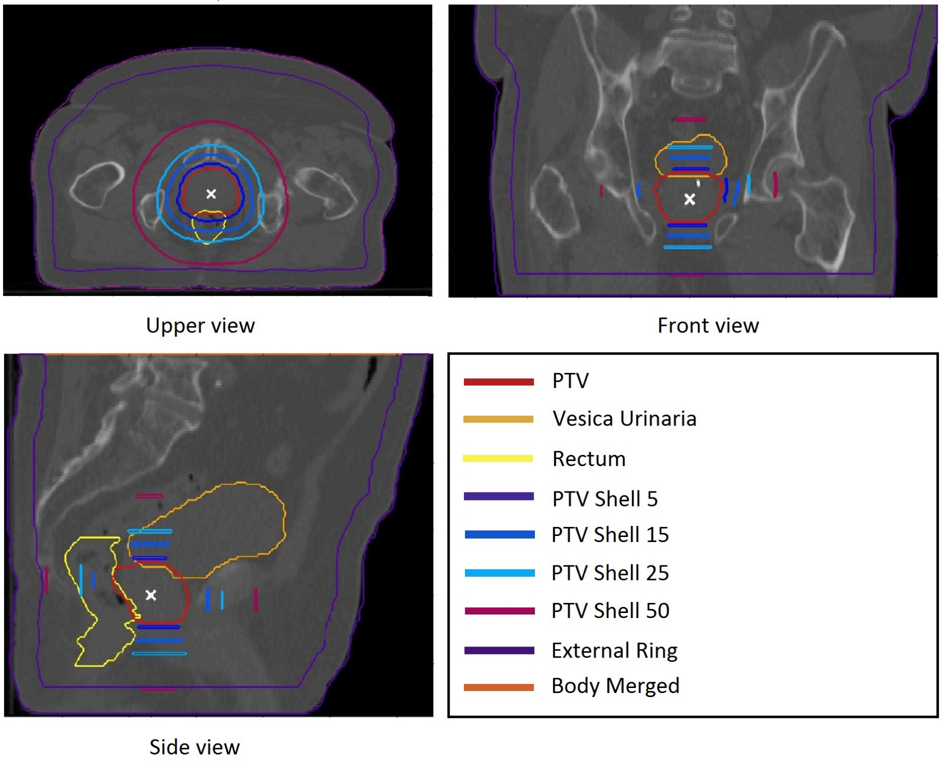

Figure 2.3: Example of CT slices where the tumour and organs at risk are delineated from different views

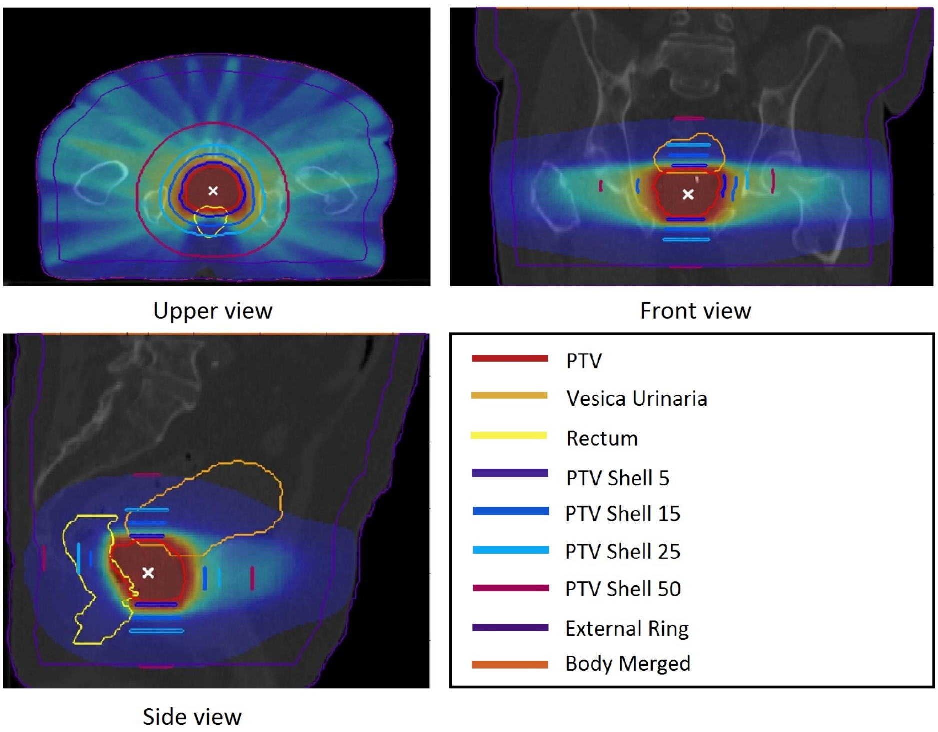

Figure 2.4: Example of CT slices with the treatment plan for a patient from different views

2.4. PROBLEMS

There are still some problems involved with treatment planning. One of them is that the process of calculating a clinically favourable treatment plan can take more than a day. Another problem is that organs always change a bit in size and position, especially in the stomach area where the bladder volume can change from 150 ml up to 800 ml, see Figure 2.5 for the differences in anatomy for a cervical cancer patient. This also influences the position of the organs around, for example that of the rectum. So when a plan is calculated for one position of the organs, it will not be optimal for another position of the organs. Because the same plan is used every day during the treatment period, healthy organs get damaged more. For example, if the bladder gets a lot of radiation because it is partly where the tumour was when the plan was made. This could have big influences on the side-effects for the patient.

Figure 2.5: Example of the different positioning of the bladder (grey contour) and uterus (different colours of contour). The left scan is with an empty bladder and the right scan is with a full bladder.

The ideal situation would be that an optimal treatment plan is calculated every day during the treatment period. Making a CT scan, delineating the tumour and organs, calculating the optimal treatment plan and realizing this plan, all should happen within a few minutes, ideally while the patient lies well positioned on the treatment table. Otherwise, the organs can move again, the patient's comfort decreases, and the treatment room stays occupied for too long.

2.5. AIM OF THIS PROJECT

The aim of this project is to use the reference point method to obtain equally good treatment plans as with iCycle. Since the reference point method generates a treatment plan by solving a single optimisation problem, a new plan can be obtained within a few minutes allowing a clinically favourable plan for each fraction of the treatment. For this method a reference point, weight and sensitivity parameter is needed. The goal is to find a method of choosing these values such that this gives solutions close to the optimal solutions obtained with iCycle.

3

Multi-objective optimisation

3.1. Basic concept

Treatment planning is a multi-objective optimisation problem, where we want to radiate the tumour with a sufficient dose while minimising the radiation in the healthy tissues. This problem can mathematically be formalized as [2]:

$$\begin{aligned} &\text{minimise} && \{f_1(x), f_2(x), \ldots, f_n(x)\} \\ &\text{subject to} && x \in X \end{aligned} \tag{3.1}$$

The variable x is a decision vector where $x = (x_1, x_2, \ldots, x_n) \in \mathbb{R}^n$. This variable determines the intensity of radiation in each beam, so x_i describes the intensities of radiation in beam i. The set X is here the feasible set, so all the possibilities of intensities of radiation. Because there are constraints in the wish-list, the feasible set X is of the form:

$$X = \{x \in \mathbb{R}^n \mid g(x) \leq 0, \; x \geq 0\} \tag{3.2}$$

where $g(x) = [g_1(x), \ldots, g_m(x)]$ is the vector function with all constraints. Thereby the problem is of the type constrained optimisation. The $f_i : \mathbb{R}^n \to \mathbb{R}$ are real valued and convex functions. A function $f : \mathbb{R}^n \to \mathbb{R}$ is convex when:

$$f(ax + (1-a)y) \leq af(x) + (1-a)f(y) \qquad \forall x, y \in \mathbb{R}^n, \forall a \in [0,1] \tag{3.3}$$

For this project, the f_i could for example be the mean amount of radiation in the rectum, see the wish-list in Chapter 2.2. All these functions are real-valued and in most cases conflicting. For example, if the amount of radiation in the rectum is lowered, the amount of radiation in the bladder will increase, in order to ensure that a sufficient dose is given to the tumour. The f_i are called objectives. We denote Y as the set of all feasible outcomes. In case of two objectives we have:

$$Y = \{(f_1(x), f_2(x)) \in \mathbb{R}^2 \mid x \in X\} \tag{3.4}$$

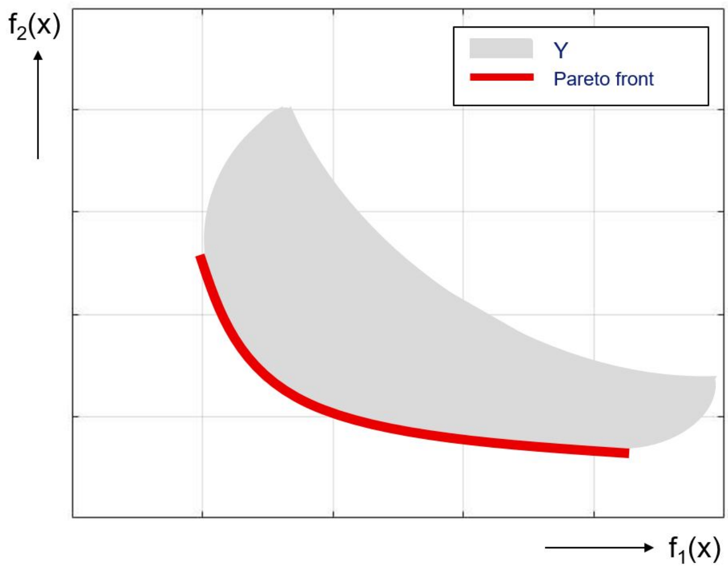

Figure 3.1: An example of a Pareto front for two objectives with its set of feasible solutions Y

3.2. PARETO FRONT

Since the objectives are conflicting there is not just one optimal solution, but there are infinity many optimal solutions to a multi-objective optimisation problem. These solutions are called Pareto optimal, meaning that if you improve one objective, at least one other objective must be deteriorating. All these solutions together are called the Pareto front. As can be seen in Figure 3.1, when one objective is lowered, the other will increase. When there are more objectives the Pareto front becomes a multi-dimensional surface.

Mathematically formalized, a decision vector $x \in X$ is Pareto optimal if there does not exist another vector $x^* \in X$ such that

$$\begin{cases} f_i(x^*) \le f_i(x) & \forall i = 1,...k \\ f_j(x^*) < f_j(x) & \text{for at least one j = 1,...,k} \end{cases} \tag{3.5}$$

The state where it is impossible to improve an objective without worsening another objective is called Pareto-optimality.

4

REFERENCE POINT METHOD

Once this Pareto set (the set of Pareto-optimal solutions) is calculated, it is very difficult to find which Pareto optimal point is clinically favourable as well. The clinically favourable point is where the different f_i's are appropriately weighed, such that the objectives with the highest priority obtain their goal first, and the objectives with lower priority are minimised after. This description is a reformulation of *The reference point method for multi-objective optimisation* [2].

4.1. DESCRIPTION REFERENCE POINT METHOD

One of the methods used in multi-objective optimization is the reference point method. For this method we need a reference point, which is based on the dose distribution of the patient. It doesn't matter if this reference point is feasible or infeasible. We also need a strictly increasing reference path that goes through the reference point. This reference path intersects with the Pareto front in a point, and we call this point the optimal solution, see Figure 4.1.

Mathematically formalized, we need a reference point $r = (r_1, r_2, ..., r_n)$ and an increasing direction of the reference path $g_1, g_2, ..., g_n$, which results in weights $w = (w_1, w_2, ... w_n) = (1/g_1, 1/g_2, ..., 1/g_n)$. The parametrisation of the reference path is $\gamma(z) = (q_1(z), q_2(z), ..., q_n(z))$ where the q_i $(i = 1, 2, ..., n)$ are strictly increasing. A possible parametrisation, where $g_1, g_2, ..., g_n > 0$, is:

$$\begin{aligned} q_1(z) &= r_1 + g_1 z \\ q_2(z) &= r_2 + g_2 z \\ &\vdots \\ q_n(z) &= r_n + g_n z \end{aligned} \tag{4.1}$$

The optimisation problem becomes:

$$\begin{array}{lll} \text{minimise} & z & \\ \text{subject to} & f_i(x) \le r_i + g_i z & i = 1, 2, ..., n \\ & x \in X & \end{array} \tag{4.2}$$

This is because minimising along the reference path is equivalent with minimising along the variable z. In Figure 4.1 is the optimization problem shown visually. The blue area is the search area for a fixed value of z.

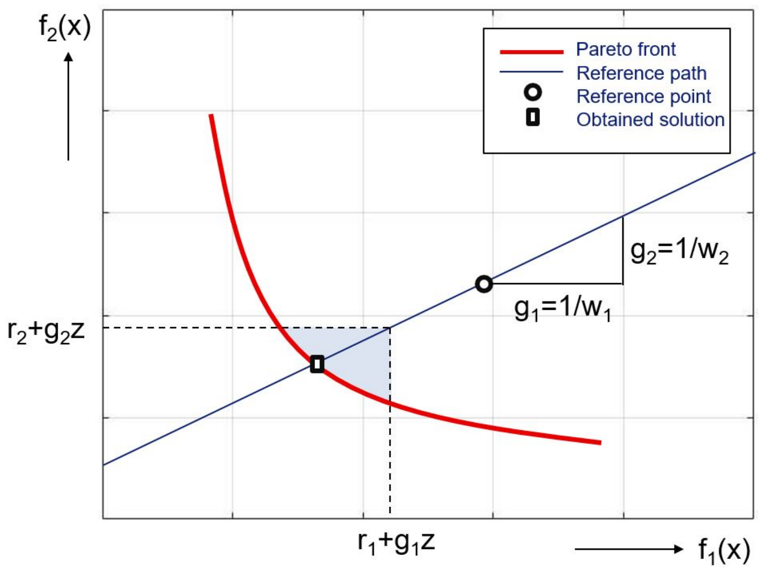

Figure 4.1: An example of the reference point method for two objectives

4.2. INDIFFERENCE CURVES

The solution given by the reference point method is not always clinically optimal. In such cases we can change the indifference curves. In this case we add a sensitivity parameter $\rho = (\rho_1, \rho_2, ..., \rho_n)$ with $\rho_i \geq 0,\ \forall i = 1, ...n$. The minimisation problem becomes:

$$\begin{aligned} \text{minimise} \quad & z + \sum_{i=1}^{n} \rho_i [w_i(f_i(x) - r_i)] \\ \text{subject to} \quad & w_i(f_i(x) - r_i) \leq z \qquad i = 1, 2, ..., n \\ & x \in X \end{aligned} \tag{4.3}$$

or

$$\begin{aligned} \text{minimise} \quad & \max_{i=1,..n} [w_i(f_i(x) - r_i)] + \sum_{i=1}^{n} \rho_i [w_i(f_i(x) - r_i)] \\ \text{subject to} \quad & x \in X \end{aligned} \tag{4.4}$$

where $w_i = 1/g_i, \forall i = 1, ..., n$. The minimisation problems 4.3 and 4.4 are equivalent, but because the functions in Problem 4.3 are differentiable, it is easier to use that formulation. The partial achievement functions

$$s_i(f_i(x)) = w_i(f_i(x) - r_i), \qquad i = 1, ..., n \tag{4.5}$$

are the inverses of parametrisations 4.1. The scalarising achievement function, which is minimised in 4.4, is defined as:

$$S(f_1(x), f_2(x), ..., f_n(x)) = \max_{i=1,...n} [s_i(f_i(x)] + \sum_{i=1}^{n} \rho_i [w_i(f_i(x) - r_i)] \tag{4.6}$$

In the case where $\rho_i = 0,\ \forall i = 1, ...n$, Problem 4.3 is equivalent to Problem 4.2 and the same optimal solution will be obtained. This can easily be seen by filling in $\rho_i = 0$ and $w_i = 1/g_i$ in 4.3 $\forall i = 1, ...n$. In this case the indifference curves are horizontal and vertical lines, but when $\rho > 0$ the indifference curves become lines with an angle, see Figure 4.2. The optimal solution obtained is the point on the Pareto front where its

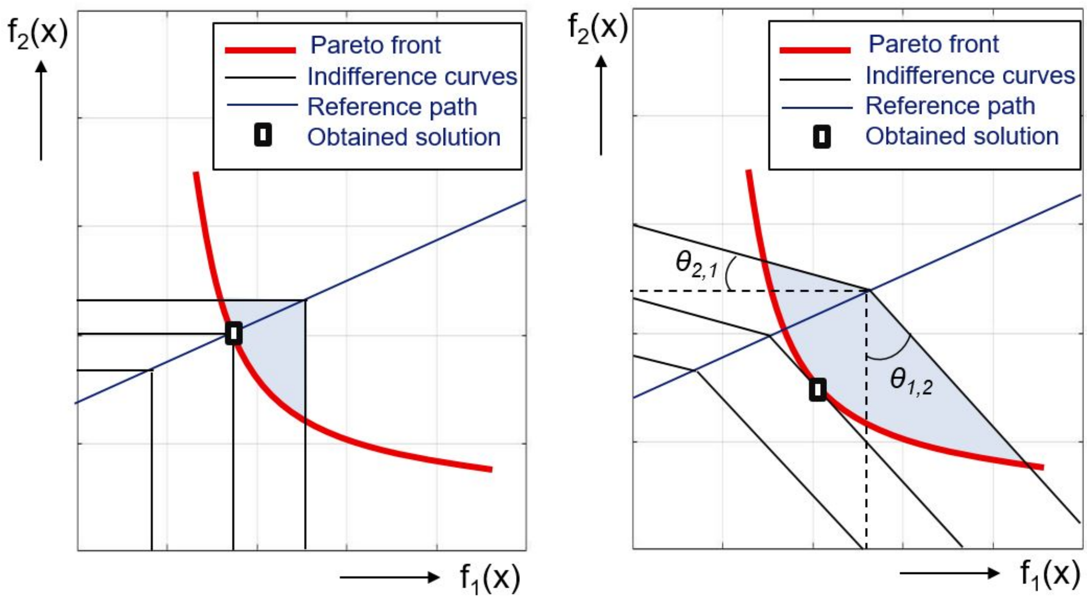

Figure 4.2: Example of the influence of indifference curves for two objectives.
In the left figure $\rho_1 = \rho_2 = 0$, and in the right figure $\rho_1 > 0, \rho_2 > 0$

slope is the same as the slope of the indifference curve. These linear lines make a certain angle $\theta_{i,j}$, which is influenced by the weights and sensitivity parameters:

$$\tan(\theta_{i,j}) = \frac{w_i}{w_j}\frac{\rho_i}{1+\rho_j}$$
$$\Longrightarrow \quad \theta_{i,j} = \tan^{-1}\left(\frac{w_i}{w_j}\frac{\rho_i}{1+\rho_j}\right) \tag{4.7}$$

4.3. PROJECT

The reference point method is a lot faster than iCycle. Because it only solves a single optimisation problem, whereas iCycle solves multiple optimisation problems. For the project the reference point, weights and sensitivity parameters can be chosen. The goal is to find suitable uniform values for these variables such that the solution obtained with the reference point method is (close to) the solution obtained with iCycle. Imagining how these variables influence the solution is very difficult, especially with more objectives. The wish-list for prostate cancer contains nine objectives. This means that there are $9 \cdot 8 = 72$ angles $\theta_{i,j}$ in total. A realistic example is given below.

Objective	Weight	Sensitivity parameter
$f_1(x)$	1	0.5
$f_2(x)$	1	0.5
$f_3(x)$	1	10
$f_4(x)$	1	0.5
$f_5(x)$	1	0.5
$f_6(x)$	1	0.5
$f_7(x)$	1	0.5
$f_8(x)$	1	0.5
$f_9(x)$	1	0.5

$$\Longrightarrow \begin{cases} \theta_{1,2} = tan^{-1}(\frac{1}{1}\frac{0.5}{1.5}) \approx 0.32 \text{ rad} \approx 18° \\ \theta_{1,3} = tan^{-1}(\frac{1}{1}\frac{0.5}{11}) \approx 0.045 \text{ rad} \approx 2.6° \\ \theta_{1,4} = tan^{-1}(\frac{1}{1}\frac{0.5}{1.5}) \approx 0.32 \text{ rad} \approx 18° \\ \vdots \\ \theta_{3,1} = tan^{-1}(\frac{1}{1}\frac{10}{1.5}) \approx 1.4 \text{ rad} \approx 82° \\ \theta_{3,2} = tan^{-1}(\frac{1}{1}\frac{10}{1.5}) \approx 1.4 \text{ rad} \approx 82° \\ \vdots \end{cases}$$

5

Implementation of the reference point method

5.1. Data

For the project there is a lot of data available, that comes from patients with prostate cancer (who have already been treated). The prescribed dose for the prostate was 78 Gray. As mentioned before, this yields unavoidable damage to nearby healthy organs, such as the rectum and bladder. The patient was treated with a plan made by iCycle, and treated with this same plan every day for a few weeks.

This original CT scan on which the plan is based is called *planning-CT*. During the treatment of the patient there were a few more CT scans made, which we call *repeats*. From these CT scans a new treatment plan can be calculated with iCycle or with the reference point method. It is important to notice that these patients were not treated with these plans, since they were treated with the first plan. This plan was only clinically favourable for the spatial properties of the organs in the planning-CT, but not for the following days because of variations in anatomy.

The data used is of ten patients in total, each with a planning scan and multiple repeat scans. For each of these scans a different Pareto optimal plan is calculated with iCycle, we call this plan the *iCycle solution*. This is used as a goal and is attempted to be realized with the reference point method. From each CT scan a solution can be generated with the reference point method and this solution is compared to the iCycle solution of this CT scan. For example, with certain weights, sensitivity parameters and a reference point a solution is found for planning, and this solution is compared to the iCycle solution from planning. If this outcome is similar to the iCycle solution we call the outcome good. To better establish whether solutions are good or bad, a measure system is needed.

5.2. Measure system

To determine the quality of a new plan, the quantity $\triangle_{neg}$ is introduced. This is the negative difference of the iCycle solution f^{iCycle} with the solution obtained f^{RPM}. This means that it only penalizes when objective values of the iCycle plan are lower (better). Equal or lower objective values (compared to the iCycle plan) are thus desired.

$$\triangle_{neg} = \sum_{i=1}^{n} \max(0, f_i^{RPM} - f_i^{iCycle}) \tag{5.1}$$

Sometimes an outcome is also better in a lot of objectives. That is why the quantity $\triangle_{pos}$ is introduced as well. This is the positive difference of the outcome f^{RPM} with the iCycle solution f^{iCycle}.

$$\triangle_{pos} = \sum_{i=1}^{n} \max(0, f_i^{iCycle} - f_i^{RPM}) \tag{5.2}$$

Objective	iCycle solution	RPM solution
f_1	54	57
f_2	36	32
f_3	21	23
f_4	18	18

An example of both quantity's:

5

$$\Longrightarrow \begin{cases} \triangle_{neg} = 5.0 \\ \triangle_{pos} = 4.0 \end{cases}$$

5.3. INFLUENCE OF THE WEIGHTS

The weights influences the steepness of the reference path. A good illustration of what happens if one weight is made bigger or smaller is shown in Figure 5.1. For example, to realize an outcome with a lower objective value for f_2, we need to increase g_2 and thus decrease w_2 (assuming w_1 remains unchanged). The value of objective one gets higher because the objectives are conflicting. This method can be used if there is one specific objective which value has to get lowered. When the Pareto front is on the right side of the reference point this works the other way around.

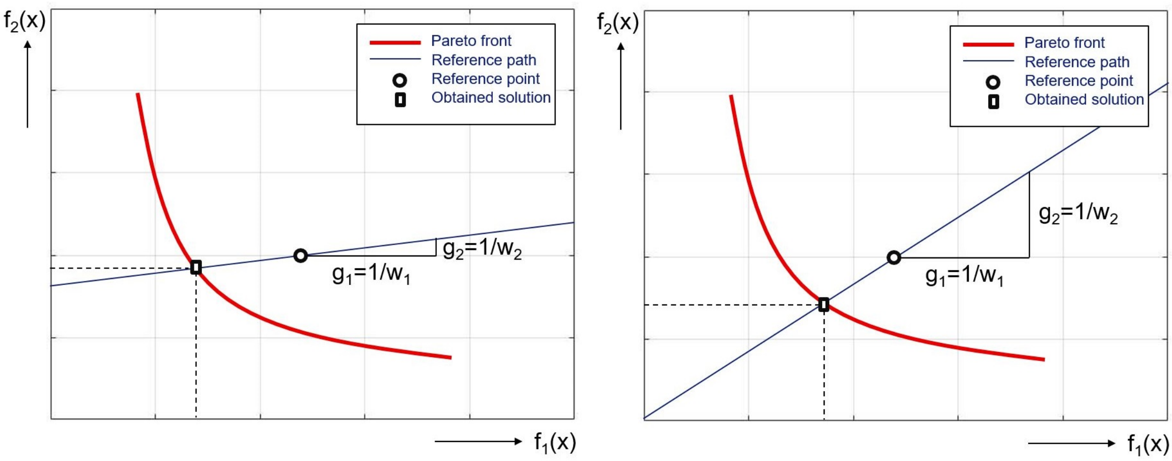

Figure 5.1: Example of the influence of the weights for two objectives

For more objectives the same principle holds. A realistic example with the data of this project is given Table 5.1. For this example the reference point was a lot lower than the iCycle solution, so it is safe to assume that the Pareto front was right of the reference point, meaning that a weight has to be made higher in order for the objective to decrease. Here w_3 is made higher, and a decrease in the value of f_3 can be seen.

Objective	Weights	Outcome
f_1	1	59.9
f_2	1	54.2
f_3	1	21.6
f_4	1	32.4
f_5	1	79.1
f_6	1	67.0
f_7	1	55.8
f_8	1	9.40
f_9	1	4.95

Objective	Weights	Outcome
f_1	1	59.7
f_2	1	53.9
f_3	10	20.5
f_4	1	32.4
f_5	1	79.1
f_6	1	67.0
f_7	1	55.9
f_8	1	9.44
f_9	1	5.02

Table 5.1: A realistic example of the influence of weights

5.4. INFLUENCE OF SENSITIVITY PARAMETER

In this project the sensitivity parameter has to be chosen as well. As described before, the solution found with a sensitivity parameter is where the slope of the indifference curves is equal to the slope of the Pareto front in that point. The angle of the indifference curves $\theta_{i,j}$ is dependent on the weight and the sensitivity parameter. A realistic example with the data can be seen in Table 5.2:

5

Objective	Weights	Sensitivity parameters	Outcome
f_1	1	0.5	59.0
f_2	1	0.5	53.4
f_3	1	0.5	23.6
f_4	1	0.5	20.8
f_5	1	0.5	71.8
f_6	1	0.5	50.8
f_7	1	0.5	40.3
f_8	1	0.5	1.40
f_9	1	0.5	4.81
Objective	Weights	Sensitivity parameters	Outcome
f_1	1	0.5	58.6
f_2	1	0.5	52.7
f_3	1	10	19.0
f_4	1	0.5	31.0
f_5	1	0.5	75.7
f_6	1	0.5	59.3
f_7	1	0.5	49.6
f_8	1	0.5	11.0
f_9	1	0.5	5.07

Table 5.2: A realistic example of the influence of sensitivity parameters

Making ρ_3 higher and keeping the others the same can results in a decrease in the third objective, as shown here.

5.5. SUFFICIENT POINT

Besides a reference point, it is also possible to add a sufficient point $S = (S_1, ..., S_n)$. This means that this point suffices: once the value of the objective f_i is the value of the sufficient point S_i it can stop optimising this objective. So if $S_i = 30$ and our objective f_i has reached the value 30 it will stop and optimise the next objective. Of course, if it can lower this objective for 'free' it will do so (when we can go lower than 30 without making the other objectives higher).

There are multiple options for what can be used as a sufficient point. One is the reference point. But when the iCycle solution is lower than the reference point it will stop optimising and the iCycle solution probably won't be obtained. So this is not really useful. Another option is using the minimum of a lot of iCycle solutions as sufficient point. But in practice this gives the same solutions as using no sufficient point, since this minimum value is almost never obtained. That is why the sufficient point won't be used for this project.

6

REFERENCE POINT METHOD WITH A REFERENCE POINT BASED ON THE SAME PATIENT

First the reference point is based on iCycle solutions of scans from the same patient. There are many different points that can be chosen as a reference point $r = (r_1, r_2, ..., r_9)$. In this chapter a few options are explored and their results given. Only the negative and the positive differences are given, since this gives a good indication of the quality of the method. The full results can be seen in Appendix B and a legend for it in Appendix A. The same weights and sensitivity parameters are used for most of the results. These parameters are chosen because they worked very well in general, they are the result of an iterative trail-and-error procedure. They are:

Objective	**Weight**	**Sensitivity parameter**
f_1	1	0.5
f_2	1	0.5
f_3	1	10
f_4	1	0.5
f_5	1	0.5
f_6	1	0.5
f_7	1	0.5
f_8	1	0.5
f_9	1	0.5

Table 6.1: The weight and sensitivity parameter used for Chapter 6

6.1. THE MEAN FROM ICYCLE SOLUTIONS AS REFERENCE POINT

One option is to take the mean of the iCycle solutions as reference point. For example, the mean of the iCycle solution for repeat scans 2 to 8 can be used as reference point for planning from the same patient. So the first objective of the reference point is the mean of all first objectives of scans 2 to 8, and the second objective is the mean of all second objectives of scans 2 to 8, etc. In Figure 6.1 an illustration of the method is given. The mean of the iCycle solutions is used as reference point, according to:

$$r_i = \frac{\sum_{j=1}^{n} f_i^{\text{scan } j}}{n} \qquad \forall i = 1, ..., 9 \tag{6.1}$$

The full results of this method can be seen in Appendix B.1, but the negative and positive differences are also given in Table 6.2.

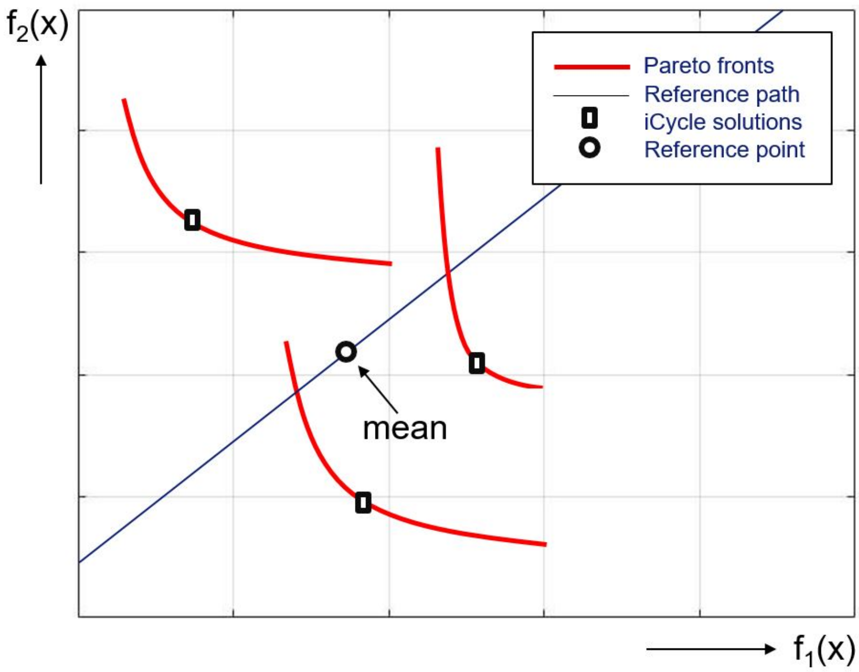

Figure 6.1: An illustration of the mean from the optimal solutions from other scans as reference point for two objectives

	$\triangle_{neg}$	$\triangle_{pos}$
Planning	0.32	11.50
Repeat 2	0.23	8.17
Repeat 3	4.83	0.46
Repeat 4	0.24	5.57
Repeat 5	0.45	9.72
Repeat 6	0.46	12.08
Repeat 7	0.18	3.74
Repeat 8	0.21	0.28

Table 6.2: The results for the mean from the iCycle solutions of other scans as reference point

As can be seen in the results, this method works very well. Almost all solutions have a small negative difference with the iCycle solution from each scan, only Repeat 3 is far away from its iCycle solution. The average of $\triangle_{neg}$ is 0.86 and of $\triangle_{pos}$ is 6.5.

An advantage of this method is that the iCycle solutions of all scans are used in the reference point. A disadvantage is that there are multiple iCycle solutions needed from the same patient before the mean can be calculated. This implies that before the treatment can start, multiple scans have to made and the iCycle solution of all these scans need to be calculated. This would take a lot of time and is dependent on the value of these iCycle solutions. The more solutions there are the better the mean is, but it would also take a lot more time.

6.2. THE ICYCLE SOLUTION FROM A SIMILAR CT SCAN AS REFERENCE POINT

Another method that can be used to determine the reference point is to consider the anatomy of the patient at the moment of the repeat treatment and to compare this to scans of which the optimal solution is known. So if the patient has an appointment for part of the therapy, first a CT scan would be made. Then a doctor or physician would look at the position of the organs of the patient at that moment and look in the database if a previously made scan of this patient is very similar. The iCycle solution of the treatment plan belonging to that scan can be used as reference point to generate a new plan for the new scan.

$$r_i = f_i^{\text{scan } j} \qquad \forall i = 1, \ldots, 9 \tag{6.2}$$

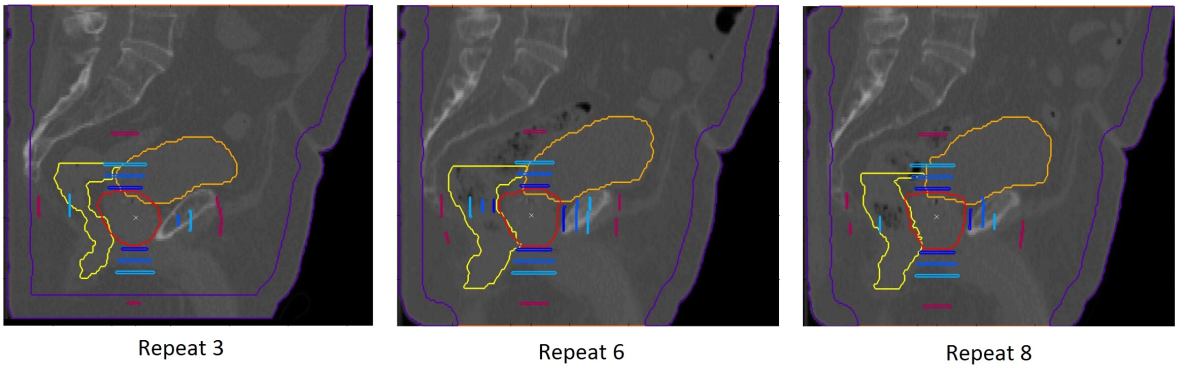

Figure 6.2: The CT scans of repeat 3, repeat 6 and repeat 8 with delineated organs

The CT scans of repeat 3, repeat 6 and repeat 8 from the same patient are pretty similar, as can be seen in Figure 6.2. This means that the iCycle solution of repeat 3 will be used as reference point for repeat 6 and for repeat 8, and the other way around. The results of this strategy, with the parameters chosen as in Table 6.1, for these scans are:

	Reference point	$\triangle_{neg}$	$\triangle_{pos}$
Repeat 3	iCycle solution of repeat 6	0.23	7.14
Repeat 3	iCycle solution of repeat 8	0.23	7.14
Repeat 6	iCycle solution of repeat 3	0.46	12.08
Repeat 6	iCycle solution of repeat 8	0.46	12.08
Repeat 8	iCycle solution of repeat 3	0.21	0.28
Repeat 8	iCycle solution of repeat 6	0.21	0.28

Table 6.3: Results for the optimal solutions of similar CT scans as reference point

As can be seen in Table 6.3, the results for this method are very good. The average of $\triangle_{neg}$ is 0.30 and of $\triangle_{pos}$ is 6.5. It is remarkable that the exact same solutions are obtained for each scan, as can be seen in the complete results in Appendix B.2. This is because the differences in the reference points are not extremely big. Also because the weights and sensitivity parameters have more influence than the reference point.

A drawback of this method is of course that a lot of scans with iCycle solutions are needed before the treatment. This means that it would take a lot of time to generate multiple plans in advance. Also, there is no guarantee that a similar position of organs can be found. This is a big disadvantage of this method.

6.3. A REFERENCE PATH BETWEEN THE MINIMUM AND MAXIMUM POINT OF ICYCLE SOLUTIONS

Another option is to calculate the line between the minimum and maximum points of iCycle solutions and use the weights that cause this line and a point on this line as reference point. So if we have the iCycle solutions from multiple scans of a patient we can calculate the minimum and maximum for each objective. This means that for the first objective the minimum value of all the first objectives from each solution is used as value for the first objective from the minimum point. The same can be done for the maximum point. These points give an indication for the lower bound and upper bound for each objective. The reference point has to be a point on this line, it doesn't matter which one. Since the value of the minimum or maximum point is already known it is easiest to take one of these points as reference point.

$$\begin{aligned} min_i &= \min(f_i^{\text{scan 1}}, f_i^{\text{scan 2}}, \ldots, f_i^{\text{scan } j}) \\ max_i &= \max(f_i^{\text{scan 1}}, f_i^{\text{scan 2}}, \ldots, f_i^{\text{scan } j}) \\ r_i &= min_i \\ w_i &= \frac{1}{max_i - min_i} \qquad \forall i = 1, \ldots, 9 \end{aligned} \tag{6.3}$$

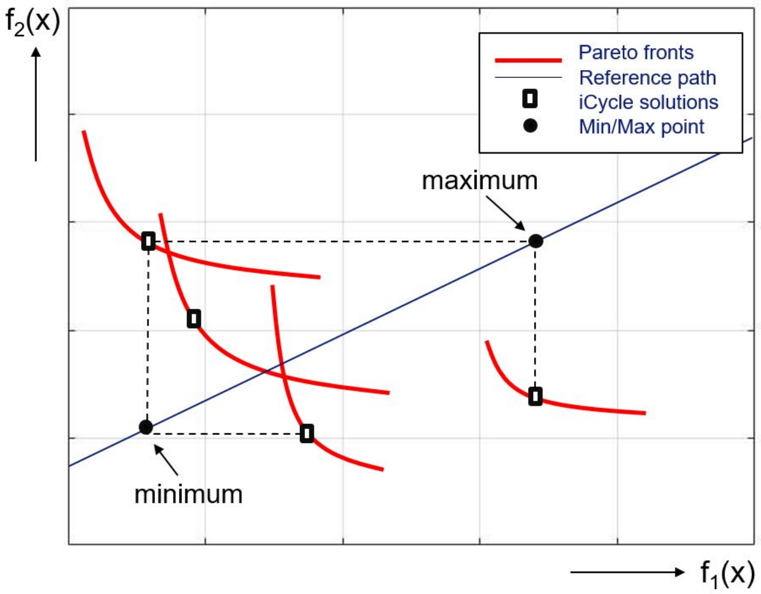

Figure 6.3: An example of the reference path between the minimum and maximum point for two objectives

So in contrast to before, the weight and sensitivity parameter that is used now is:

Objective	Weight	Sensitivity parameter
f_1	0.13	0.5
f_2	0.09	0.5
f_3	0.04	10
f_4	0.13	0.5
f_5	0.17	0.5
f_6	0.10	0.5
f_7	0.18	0.5
f_8	0.09	0.5
f_9	4.06	0.5

Table 6.4: The weights and sensitivity parameters that are used for Section 6.3

The full results can be seen in Appendix B.3, but the negative and positive difference for each scan are:

	$\triangle_{neg}$	$\triangle_{pos}$
Planning	4.08	41.96
Repeat 2	4.64	33.98
Repeat 3	5.10	37.91
Repeat 4	5.16	35.60
Repeat 5	4.96	37.90
Repeat 6	4.61	39.08
Repeat 7	4.38	32.15
Repeat 8	0.21	0.28

Table 6.5: The results for the reference path between the minimum and maximum point of iCycle solutions

Clearly these results are not satisfying, except for repeat 8. The average of $\triangle_{neg}$ is 4.2 and of $\triangle_{pos}$ is 32. So this method obtains solutions that are far from the iCycle solution. Of course these results are for the sensitivity parameter chosen. With different values for the ρ's, different solutions were found. Some of these were better, but some were worse.

6

6.4. THE MINIMUM POINT OF ICYCLE SOLUTIONS AS REFERENCE POINT

Instead of taking the weights that causes the path between the minimum and maximum point, the weights can be varied as well. So it wouldn't be the path between the minimum and maximum point anymore, but the minimum point would still be the reference point. The method is illustrated in Figure 6.4.

$$r_i = \min(f_i^{\text{scan } 1}, f_i^{\text{scan } 2}, \ldots, f_i^{\text{scan } j}) \qquad \forall i = 1, \ldots 9 \tag{6.4}$$

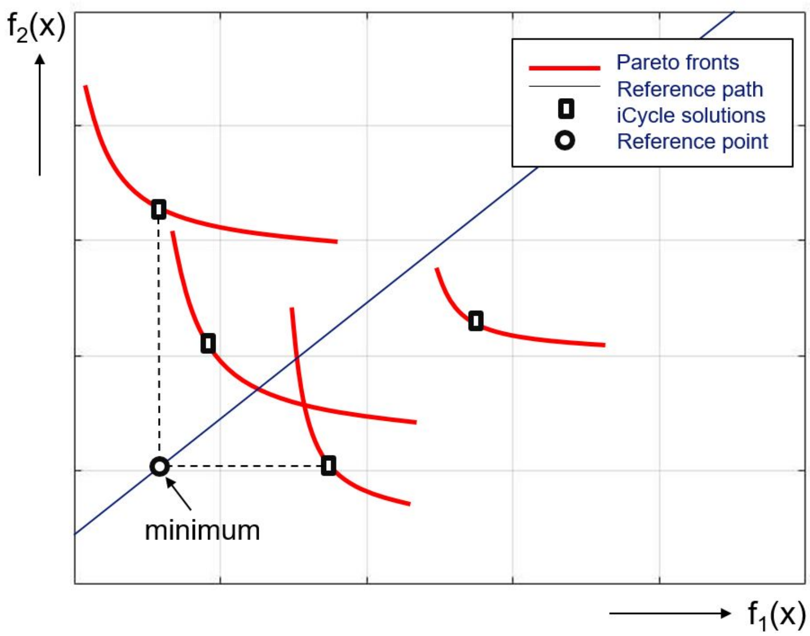

Figure 6.4: An example of the minimum point of iCycle solutions as reference point for two objectives

The results for this method with the weights and sensitivity parameters as in Table 6.1 are:

	$\triangle_{neg}$	$\triangle_{pos}$
Planning	0.33	10.09
Repeat 2	0.18	7.19
Repeat 3	0.23	7.14
Repeat 4	0.24	5.24
Repeat 5	0.39	7.77
Repeat 6	0.40	11.87
Repeat 7	0.18	3.74
Repeat 8	0.21	0.28

Table 6.6: The results for the minimum point of iCycle solutions as reference point

These results are very good for all scans, the complete version can be seen in Appendix B.4. The average of $\triangle_{neg}$ is 0.27 and of $\triangle_{pos}$ is 6.7. A disadvantage is that a several optimal solutions are needed in advance, which costs a lot of time.

6.5. THE iCYCLE SOLUTION FROM PLANNING AS REFERENCE POINT

When the organs change in size and position, the Pareto front changes as well. The clinically favourable solution of the 'old' Pareto front can be used as a reference point for the 'new' Pareto front: the iCycle solution of planning is used as reference point in the reference point method to obtain a solution for a repeat. So the reference point is chosen according to:

$$r_i^{\text{patient } j} = f_i^{\text{planning of patient } j} \qquad \forall i = 1,\ldots,9 \tag{6.5}$$

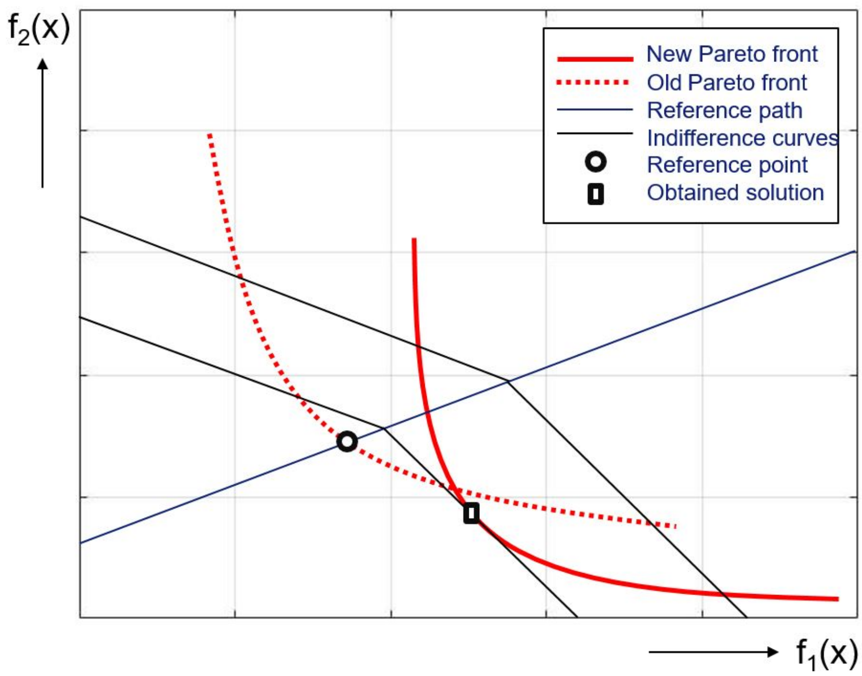

Figure 6.5: Example of the old and new Pareto front for two objectives

In Figure 6.5 the idea of an old and new Pareto front is sketched for two objectives. In this case the old Pareto front is from the moment the planning scan was taken, and the new Pareto front from the moment a repeat scan was taken. So the iCycle solution of planning is used as reference point for a repeat. The negative differences of each scan for each patient are given in Figure 6.6. Not all patients have the same amount of scans and for some scans the same negative difference as another scan was obtained. Hence the difference in points for each patient. A table with all the negative and positive differences is given in Appendix B.5.

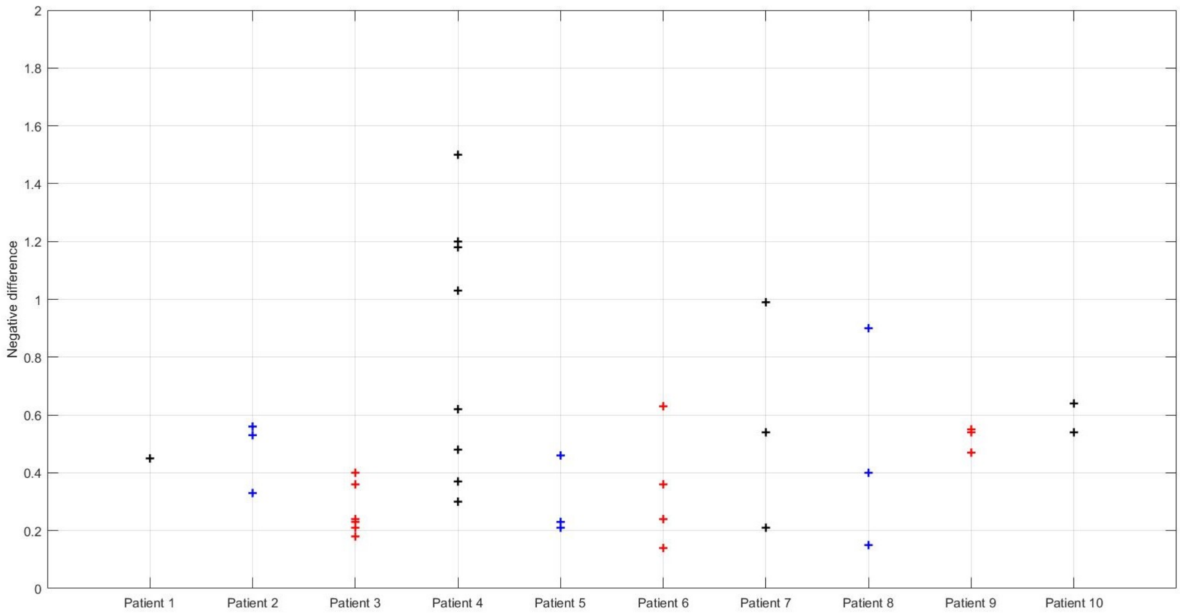

Figure 6.6: $\triangle_{neg}$ for the iCycle solution of the planning-CT of each patient as reference point

These results are very satisfying. Only for patient 4 the negative difference is too high. The advantage of this method is that only the optimal solution of the planning-CT has to be calculated before treatment.

6.6. REVIEW

The results of the methods can be summarized according to the average of the negative and positive differences obtained, see Table 6.7. Of course for some methods more scans were tested, so the comparison is not completely correct.

Reference point	Average of $\triangle_{neg}$	Average of $\triangle_{pos}$
The mean of iCycle solutions	0.86	6.5
The iCycle solution of similar CT scans	0.30	6.5
Reference path between the minimum and maximum point	4.2	32
The minimum of iCycle solutions	0.27	6.7
The iCycle solution of the planning-CT	0.48	8.27

Table 6.7: The average negative and positive difference from each method

It is clear that the reference path between the minimum and maximum point of iCycle solutions gives unsatisfying results. Even though the positive difference is very high, it is most important that the negative difference is very low. The other methods give very similar results.

In usage the method where the iCycle solution of the planning-CT is taken as reference point is best. Since the disadvantage of all other methods is that a lot of iCycle solutions are needed before treatment. The next step is exploring if it is also possible to take a reference path based on the optimal solutions of scans from other patients.

There also must be noticed that for different weights and sensitivity parameters the results could be totally different.

7
Reference point method with a reference point based on other patients

It would be ideal if the optimal solutions from other patients could be used as reference point for a new patient. This way there is a huge database of points that can be chosen from and the tests that have to be done before treatment are none to very few. Different methods of choosing a reference point are discussed here with the negative and positive difference. The complete results are in Appendix C and the legend for it in Appendix A. The weights and sensitivity parameters that is used for all results in Chapter 7 are again:

Objective	**Weight**	**Sensitivity parameter**
f_1	1	0.5
f_2	1	0.5
f_3	1	10
f_4	1	0.5
f_5	1	0.5
f_6	1	0.5
f_7	1	0.5
f_8	1	0.5
f_9	1	0.5

Table 7.1: The weights and sensitivity parameters that is used for Chapter 7

7.1. The mean of iCycle solutions from other patients as reference point

As tested for one patient, the mean of iCycle solutions can be used as reference point. The big disadvantage of that method was that the iCycle solutions of several scans need to be calculated before treatment. So hopefully the mean from iCycle solutions from other patients can be used as reference point for a new patient. This would imply that there are a lot of different solutions that can be used, which would give a more general mean.

$$r_i = \frac{\sum_j f_i^j}{n} \qquad \forall i = 1,...,9, \ \forall j = \text{scan } 1,....,\text{scan } m \tag{7.1}$$

7.1.1. The mean from all other planning-CTs

First only the mean of the original plans (no repeats) is used as reference point for the planning-CT of a new patient. So the mean of the iCycle solutions from the plannings from patients 2 till 10 is used as reference point for the planning-CT of patient 1, and so on. The results are all calculated with the weights and sensitivity parameters as in Table 7.1. As indication of the quality of the method, the negative and positive differences are given, the complete results are given in Appendix C.1.

	$\triangle_{neg}$	$\triangle_{pos}$
Patient 1	0.64	14.26
Patient 2	0.19	1.54
Patient 3	0.35	11.87
Patient 4	0.38	6.93
Patient 5	0.52	5.69
Patient 6	0.65	0.61
Patient 7	0.07	2.37
Patient 8	0.35	0.06
Patient 9	0.76	16.67
Patient 10	0.66	18.37

Table 7.2: The results for the mean of the iCycle solutions of all other planning-CTs as reference point

These results are very rewarding. The average of all negative differences is 0.46 and of all positive differences is 7.48.

7.1.2. THE MEAN FROM ALL OTHER SCANS

The results for the mean of all the planning-CTs are very good. Here the mean of the iCycle solutions of all the scans from other patients is used as reference point. So the mean of all iCycle solutions from patient 2 up to 10 is calculated and used as reference point for all the scans from patient 1. The negative differences per patient are shown in Figure 7.1, all results are given in Appendix C.2.

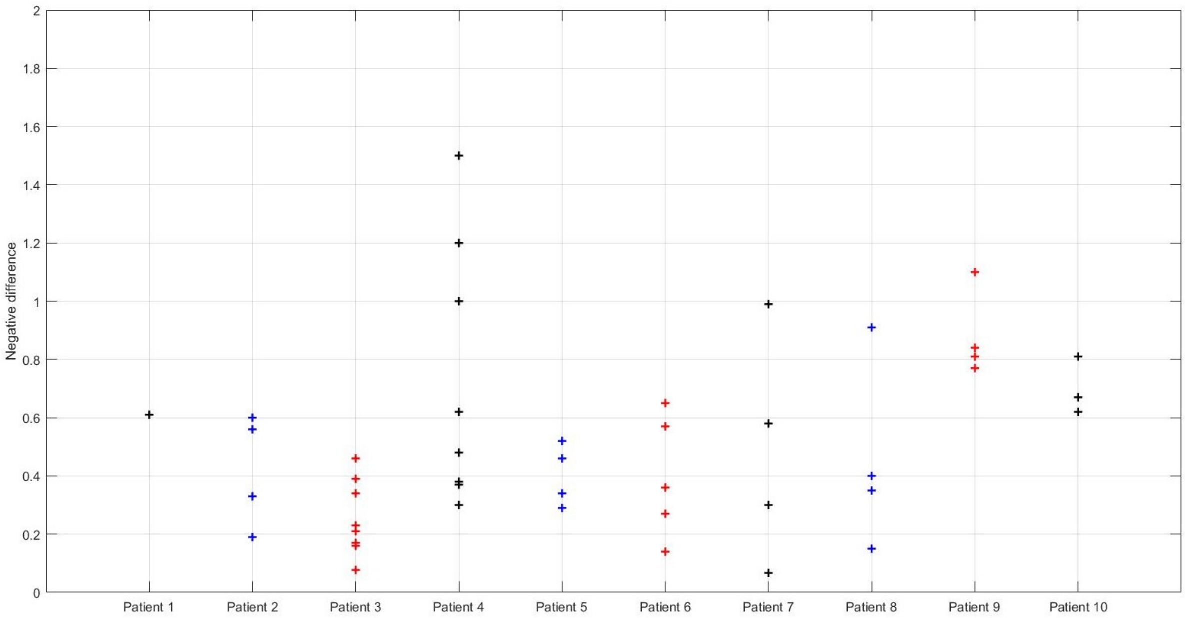

Figure 7.1: $\triangle_{neg}$ for the mean of all iCycle solutions from other scans as reference point

The average of all negative differences is 0.54, which is just a little higher than in §7.1.1.

The advantage of this method is that it takes all patients into account, and gives a general reference point. The outliers are averaged with the other points.

7.2. THE MINIMUM OF OPTIMAL SOLUTIONS FROM OTHER PATIENTS AS REFERENCE POINT

Another option is taking the minimum from the optimal solutions from other patients as reference point. This worked well when the minimum was taken of iCycle solutions of the same patient, so hopefully it works better when the minimum is taken of iCycle solutions of other patients.

7.2.1. THE MINIMUM FROM ALL OTHER PLANNING-CTS

First only the minimum of all plannings from other patients is taken as reference point. The results are from the weights and sensitivity parameters as in Table 7.1, the complete results are given in Appendix C.3.

	$\triangle_{neg}$	$\triangle_{pos}$
Patient 1	0.61	13.67
Patient 2	0.19	1.54
Patient 3	0.33	10.09
Patient 4	0.38	6.93
Patient 5	0.52	5.69
Patient 6	0.65	0.61
Patient 7	0.07	2.37
Patient 8	0.35	0.06
Patient 9	0.76	16.67
Patient 10	0.59	17.50

Table 7.3: The results of the minimum from all plannings as reference point

These results are very satisfying, the average of all negative differences is 0.45 and of all positive differences 7.75.

7.2.2. THE MINIMUM FROM ALL OTHER SCANS

Now the minimum of all scans from other patients is taken. The results are from the weights and sensitivity parameters as given in Table 7.1. This was tested for every scan from each patient, the results are given in the Figure 7.2.

The average of all negative differences is 0.56, which is comparable to that in §7.2.1. The disadvantage of this method is that the outliers have a big influence on the reference point.

7

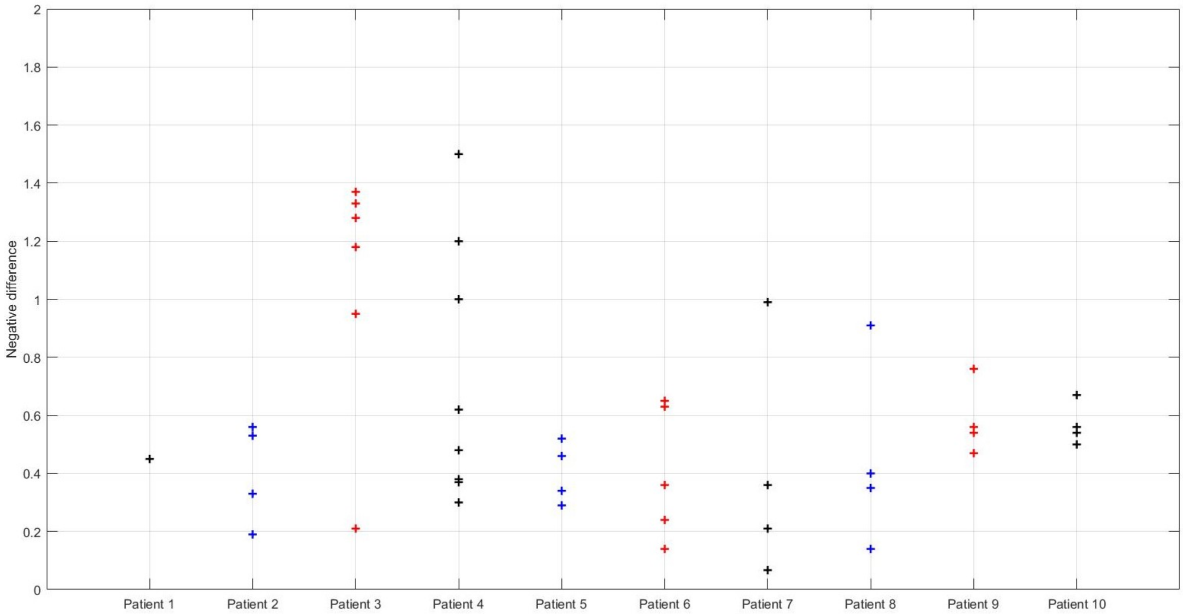

Figure 7.2: $\triangle_{neg}$ for the minimum of all iCycle solutions from all other scans as reference point

7.3. REVIEW

The results from all methods are really similar. The negative differences differ not much from each other, so the difference in reference point doesn't have a lot of influence.

All methods are comparable in usage as well, since none or one iCycle solutions of the patient have to be calculated before treatment. Furthemore, the outliers are averaged with the mean, but have a big influence on the minimum. This is a disadvantage of the method where the minimum is used as reference point.

8 CONCLUSION

The main goal of this project was to find a way such that equally good results are obtained with the reference point method as with iCycle. Hence to find a good way to choose the reference point, weights, and sensitivity parameters. Important is that little prior data should be needed for a specific patient in the planning process.

In Chapter 6 and 7 a few methods of choosing a reference point are discussed. There was already stated that it is inconvenient to use a reference point based on multiple iCycle solutions of scans from the same patient. But using only the iCycle solution from the planning-CT is accepted. Using the iCycle solutions of scans from other patients as the reference point is convenient, since the database that can be used is very big.

There can be concluded that using the iCycle solution from the planning-CT or taking the mean of iCycle solutions of scans from other patients give equally good results. These methods are most also convenient in practice and outlines have a small influence. These results were sometimes also a lot better than the iCycle solutions.

By an iterative process of trial-and-error there was concluded that the best weights and sensitivity parameters are:

Objective	Weights	Sensitivity parameters
f_1	1	0.5
f_2	1	0.5
f_3	1	10
f_4	1	0.5
f_5	1	0.5
f_6	1	0.5
f_7	1	0.5
f_8	1	0.5
f_9	1	0.5

There can also be concluded that the weight and sensitivity parameter have more influence on the outcome than the reference point. Hence the indifference curves have most influence.

To summarize, using the mean from iCycle solutions from other patients or using the iCycle solution from the planning-CT are both very good methods. They give very satisfying results and are convenient in practice.

9

Recommendations

For further research a few suggestions can be made. First of them is that the parameters should be optimized. Now they were chosen by an iterative process of trial-and-error, so there could be better values for the weights and sensitivity parameters. Another option that can be explored is if it is possible to obtain one reference point that works on all patients. Then the same point can be used, and there won't have to be a new one calculated each time. And of course this method should be tested on a lot more patients. Even though the results were satisfying for these patients, there is a chance that they won't be for other patients.

One of the big problems with fast re-planning is also the delineating of the tumour and organs at risk. This takes about two hours to delineate, and about two hours to check if everything is done correctly. With the reference point method a new optimal plan can be calculated within a minute with a computer with strong computing power, but if the delineating takes so long there is no point in doing this. Another problem is checking if a plan is correct. This also takes a lot of time and should happen a lot faster. These are big subjects that more research needs to be done in, before every day planning can be done in reality.

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A

APPENDIX

The results in the appendix can also be coloured in such a way that easily can be seen whether an outcome is good or bad. The following colour system is used:

(red) if the value of this objective is more than 0.5 above the iCycle value
(green) if the value of this objective is between 0.5 above and 0.5 below the iCycle value
(yellow) if the value of this objective is more than 0.5 below the iCycle value
For example:

iCycle solution	Solution obtained with the reference point method
54.2	57.6
36.1	32.5
21.8	23.4
18.1	18.3

Of course it is better when an outcome is more than 0.5 below the optimal point. But when one objective is very low that often results in a disadvantage for other objectives, due to the conflicting nature. This is why the colour yellow is used instead of green.

B

Reference point method with a reference point based on the same patient

The weights and sensitivity parameters that are used for the results in Appendix B are:

Objective	Weight	Sensitivity parameter
f_1	1	0.5
f_2	1	0.5
f_3	1	10
f_4	1	0.5
f_5	1	0.5
f_6	1	0.5
f_7	1	0.5
f_8	1	0.5
f_9	1	0.5

Table B.1: The weights and sensitivity parameters that are used for Appendix B, except for B.3

Objective	Weight	Sensitivity parameter
f_1	0.1254	0.5
f_2	0.0917	0.5
f_3	0.0351	10
f_4	0.13	0.5
f_5	0.1719	0.5
f_6	0.1042	0.5
f_7	0.1763	0.5
f_8	0.0901	0.5
f_9	4.0609	0.5

Table B.2: The weights and sensitivity parameters that are used for Appendix B.3

B

B.1. THE MEAN FROM ICYCLE SOLUTIONS AS REFERENCE POINT

Patient 3	Planning	
iCycle solution	Reference point	Outcome
60,13	59,95	60,07
54,52	54,47	54,48
20,42	22,92	20,74
31,20	31,78	30,77
77,93	77,40	75,56
65,82	63,99	61,17
54,65	52,85	50,79
8,24	14,01	8,15
5,10	5,02	5,10
Δ_{neg} = 0.32	Δ_{pos} = 11.50	

Patient 3	Repeat 2	
iCycle solution	Reference point	Outcome
58,64	60,16	58,61
52,67	54,74	52,66
18,74	23,16	18,96
31,20	31,78	30,82
77,23	77,50	75,69
62,73	64,43	59,36
51,88	53,24	49,26
11,45	13,56	11,22
5,06	5,02	5,07
Δ_{neg} = 0.23	Δ_{pos} = 8.17	

Patient 3	Repeat 3	
iCycle solution	Reference point	Outcome
59,10	60,09	59,27
53,41	54,63	53,60
19,54	23,04	19,92
31,15	31,79	32,56
75,91	77,69	76,66
62,01	64,54	63,55
51,87	53,24	52,25
16,21	12,87	15,78
5,07	5,02	5,03
Δ_{neg} = 4.83	Δ_{pos} = 0.46	

Patient 3	Repeat 4	
iCycle solution	Reference point	Outcome
60,25	59,93	60,21
54,69	54,45	54,65
20,25	22,94	20,46
30,40	31,90	29,29
76,47	77,61	75,45
62,61	64,45	60,84
52,24	53,19	50,98
16,00	12,90	15,67
5,12	5,01	5,15
Δ_{neg} = 0.24	Δ_{pos} = 5.57	

Patient 3	Repeat 5	
iCycle solution	Reference point	Outcome
58,54	60,17	58,45
52,80	54,72	52,74
19,68	23,02	20,01
31,17	31,79	29,47
77,06	77,53	75,52
63,19	64,37	59,76
52,49	53,16	49,59
11,01	13,62	11,11
5,00	5,03	5,03
Δ_{neg} = 0.45	Δ_{pos} = 9.72	

Patient 3	Repeat 6	
iCycle solution	Reference point	Outcome
57,57	60,31	57,45
51,16	54,95	51,07
16,01	23,55	16,39
31,20	31,78	29,38
76,95	77,54	74,82
64,02	64,25	59,43
53,65	52,99	50,33
10,30	13,72	10,37
4,87	5,05	4,89
Δ_{neg} = 0.46	Δ_{pos} = 12.08	

Patient 3	Repeat 7	
iCycle solution	Reference point	Outcome
59,98	59,97	59,92
54,52	54,47	54,47
21,71	22,73	21,87
29,83	31,98	29,17
76,47	77,61	76,15
61,89	64,55	60,89
51,07	53,36	50,18
19,34	12,43	18,57
4,97	5,03	5,00
Δ_{neg} = 0.18	Δ_{pos} = 3.74	

Patient 3	Repeat 8	
iCycle solution	Reference point	Outcome
65,55	59,17	65,57
62,06	53,40	62,09
44,49	19,48	44,57
37,52	30,88	37,46
81,73	76,86	81,79
71,49	63,18	71,42
56,74	52,55	56,59
13,79	13,22	13,80
5,00	5,03	5,00
Δ_{neg} = 0.21	Δ_{pos} = 0.28	

B.2. THE ICYCLE SOLUTION FROM A SIMILAR CT SCAN AS REFERENCE POINT

Patient 3	Repeat 3	
iCycle solution	Reference point	Outcome
59,10	57,57	59,02
53,41	51,16	53,34
19,54	16,01	19,75
31,15	31,20	28,95
75,91	76,95	74,74
62,01	64,02	60,24
51,87	53,65	50,68
16,21	10,30	15,56
5,07	4,87	5,08
Δ_{neg} = 0.23	Δ_{pos} = 7.14	

Patient 3	Repeat 3	
iCycle solution	Reference point	Outcome
59,10	65,55	59,02
53,41	62,06	53,34
19,54	44,49	19,75
31,15	37,52	28,95
75,91	81,73	74,74
62,01	71,49	60,24
51,87	56,74	50,68
16,21	13,79	15,56
5,07	5,00	5,08
Δ_{neg} = 0.23	Δ_{pos} = 7.14	

Patient 3	Repeat 6	
iCycle solution	Reference point	Outcome
57,57	59,10	57,45
51,16	53,41	51,07
16,01	19,54	16,39
31,20	31,15	29,38
76,95	75,91	74,82
64,02	62,01	59,43
53,65	51,87	50,33
10,30	16,21	10,37
4,87	5,07	4,89
Δ_{neg} = 0.46	Δ_{pos} = 12.08	

Patient 3	Repeat 6	
iCycle solution	Reference point	Outcome
57,57	65,55	57,45
51,16	62,06	51,07
16,01	44,49	16,39
31,20	37,52	29,38
76,95	81,73	74,82
64,02	71,49	59,43
53,65	56,74	50,33
10,30	13,79	10,37
4,87	5,00	4,89
Δ_{neg} = 0.46	Δ_{pos} = 12.08	

Patient 3	Repeat 8	
iCycle solution	Reference point	Outcome
65,55	59,10	65,57
62,06	53,41	62,09
44,49	19,54	44,57
37,52	31,15	37,46
81,73	75,91	81,79
71,49	62,01	71,42
56,74	51,87	56,59
13,79	16,21	13,80
5,00	5,07	5,00
Δ_{neg} = 0.21	Δ_{pos} = 0.28	

Patient 3	Repeat 8	
iCycle solution	Reference point	Outcome
65,55	57,57	65,57
62,06	51,16	62,09
44,49	16,01	44,57
37,52	31,20	37,46
81,73	76,95	81,79
71,49	64,02	71,42
56,74	53,65	56,59
13,79	10,30	13,80
5,00	4,87	5,00
Δ_{neg} = 0.21	Δ_{pos} = 0.28	

B.3. A REFERENCE PATH BETWEEN THE MINIMUM AND MAXIMUM POINT OF ICYCLE SOLUTIONS

B

Patient 3	Planning	
iCycle solution	Reference point	Outcome
60,13	57,57	60,30
54,52	51,16	54,93
20,42	16,01	24,64
31,20	29,83	22,48
77,93	75,91	71,53
65,82	61,89	52,92
54,65	51,07	41,01
8,24	10,30	8,36
5,10	4,87	4,80
Δ_{neg} = 4.80	Δ_{pos} = 41.96	

Patient 3	Repeat 5	
iCycle solution	Reference point	Outcome
58,54	57,57	58,86
52,80	51,16	53,36
19,68	16,01	23,55
31,17	29,83	21,75
77,06	75,91	71,34
63,19	61,89	52,54
52,49	51,07	40,66
11,01	8,24	11,23
5,00	4,87	4,73
Δ_{neg} = 4.96	Δ_{pos} = 37.90	

Patient 3	Repeat 2	
iCycle solution	Reference point	Outcome
58,64	57,57	59,04
52,67	51,16	53,32
18,74	16,01	22,32
31,20	29,83	22,88
77,23	75,91	72,21
62,73	61,89	53,14
51,88	51,07	41,39
11,45	8,24	11,20
5,06	4,87	4,75
Δ_{neg} = 4.64	Δ_{pos} = 33.98	

Patient 3	Repeat 6	
iCycle solution	Reference point	Outcome
57,57	58,54	57,75
51,16	52,67	51,63
16,01	18,74	19,82
31,20	29,83	21,63
76,95	75,91	71,37
64,02	61,89	52,65
53,65	51,07	41,35
10,30	8,24	10,45
4,87	4,97	4,62
Δ_{neg} = 4.61	Δ_{pos} = 39.08	

Patient 3	Repeat 3	
iCycle solution	Reference point	Outcome
59,10	57,57	59,43
53,41	51,16	54,04
19,54	16,01	23,69
31,15	29,83	20,59
75,91	75,91	70,45
62,01	61,89	51,91
51,87	51,07	40,58
16,21	8,24	16,03
5,07	4,87	4,74
Δ_{neg} = 5.10	Δ_{pos} = 37.91	

Patient 3	Repeat 7	
iCycle solution	Reference point	Outcome
59,98	57,57	60,17
54,52	51,16	54,93
21,71	16,01	25,49
29,83	30,40	21,48
76,47	75,91	71,96
61,89	62,01	52,90
51,07	51,87	41,44
19,34	8,24	18,95
4,97	4,87	4,70
Δ_{neg} = 4.38	Δ_{pos} = 32.15	

Patient 3	Repeat 4	
iCycle solution	Reference point	Outcome
60,25	57,57	60,55
54,69	51,16	55,22
20,25	16,01	24,50
30,40	29,83	21,67
76,47	75,91	71,16
62,61	61,89	52,62
52,24	51,07	40,95
16,00	8,24	16,07
5,12	4,87	4,83
Δ_{neg} = 5.16	Δ_{pos} = 35.60	

Patient 3	Repeat 8	
iCycle solution	Reference point	Outcome
65,55	57,57	65,57
62,06	51,16	62,09
44,49	16,01	44,57
37,52	29,83	37,46
81,73	75,91	81,79
71,49	61,89	71,42
56,74	51,07	56,59
13,79	8,24	13,80
5,00	4,87	5,00
Δ_{neg} = 0.21	Δ_{pos} = 0.28	

B

B.4. THE MINIMUM POINT OF ICYCLE SOLUTIONS AS REFERENCE POINT

Patient 3	Planning	
iCycle solution	Reference point	Outcome
60,13	57,57	60,12
54,52	51,16	54,53
20,42	16,01	20,66
31,20	29,83	31,28
77,93	75,91	75,74
65,82	61,89	61,59
54,65	51,07	51,07
8,24	10,30	8,15
5,10	4,87	5,10
Δ_{neg} = 0.33	Δ_{pos} = 10.09	

Patient 3	Repeat 5	
iCycle solution	Reference point	Outcome
58,54	57,57	58,45
52,80	51,16	52,73
19,68	16,01	19,91
31,17	29,83	30,12
77,06	75,91	75,85
63,19	61,89	60,32
52,49	51,07	50,00
11,01	8,24	11,13
5,00	4,87	5,05
Δ_{neg} = 0.39	Δ_{pos} = 7.77	

Patient 3	Repeat 2	
iCycle solution	Reference point	Outcome
58,64	57,57	58,61
52,67	51,16	52,65
18,74	16,01	18,92
31,20	29,83	31,15
77,23	75,91	75,82
62,73	61,89	59,65
51,88	51,07	49,56
11,45	8,24	11,15
5,06	4,87	5,08
Δ_{neg} = 0.18	Δ_{pos} = 7.19	

Patient 3	Repeat 6	
iCycle solution	Reference point	Outcome
57,57	58,54	57,48
51,16	52,67	51,09
16,01	18,74	16,39
31,20	29,83	29,44
76,95	75,91	74,90
64,02	61,89	59,51
53,65	51,07	50,40
10,30	8,24	10,17
4,87	4,97	4,88
Δ_{neg} = 0.40	Δ_{pos} = 11.87	

Patient 3	Repeat 3	
iCycle solution	Reference point	Outcome
59,10	57,57	59,02
53,41	51,16	53,34
19,54	16,01	19,75
31,15	29,83	28,95
75,91	75,91	74,74
62,01	61,89	60,24
51,87	51,07	50,68
16,21	8,24	15,56
5,07	4,87	5,08
Δ_{neg} = 0.23	Δ_{pos} = 7.14	

Patient 3	Repeat 7	
iCycle solution	Reference point	Outcome
59,98	57,57	59,92
54,52	51,16	54,47
21,71	16,01	21,87
29,83	30,40	29,17
76,47	75,91	76,15
61,89	62,01	60,89
51,07	51,87	50,18
19,34	8,24	18,57
4,97	4,87	5,00
Δ_{neg} = 0.18	Δ_{pos} = 3.74	

Patient 3	Repeat 4	
iCycle solution	Reference point	Outcome
60,25	57,57	60,21
54,69	51,16	54,65
20,25	16,01	20,46
30,40	29,83	29,29
76,47	75,91	75,45
62,61	61,89	60,84
52,24	51,07	50,98
16,00	8,24	15,67
5,12	4,87	5,15
Δ_{neg} = 0.24	Δ_{pos} = 5.24	

Patient 3	Repeat 8	
iCycle solution	Reference point	Outcome
65,55	57,57	65,57
62,06	51,16	62,09
44,49	16,01	44,57
37,52	29,83	37,46
81,73	75,91	81,79
71,49	61,89	71,42
56,74	51,07	56,59
13,79	8,24	13,80
5,00	4,87	5,00
Δ_{neg} = 0.21	Δ_{pos} = 0.28	

B

B.5. THE ICYCLE SOLUTION FROM THE PLANNING-CT AS REFERENCE POINT

Patient	Scan	$\triangle_{neg}$	$\triangle_{pos}$
Patient 1	Repeat 2	0.46	12.42
Patient 1	Repeat 3	0.48	12.69
Patient 1	Repeat 4	0.46	11.97
Patient 1	Repeat 5	0.46	12.07
Patient 1	Repeat 6	0.48	12.43
Patient 1	Repeat 7	0.46	11.98
Patient 1	Repeat 8	0.48	12.47
Patient 1	Repeat 9	0.48	11.99
Patient 1	Repeat 10	0.45	12.24
Patient 2	Repeat 2	0.33	0.86
Patient 2	Repeat 3	0.56	12.60
Patient 2	Repeat 4	0.53	11.28
Patient 3	Repeat 2	0.24	7.95
Patient 3	Repeat 3	0.23	7.14
Patient 3	Repeat 4	0.24	5.57
Patient 3	Repeat 5	0.36	9.55
Patient 3	Repeat 6	0.40	11.87
Patient 3	Repeat 7	0.18	3.74
Patient 3	Repeat 8	0.21	0.28
Patient 4	Repeat 2	0.37	4.17
Patient 4	Repeat 3	1.18	3.35
Patient 4	Repeat 4	1.03	3.19
Patient 4	Repeat 5	0.62	3.83
Patient 4	Repeat 6	0.48	4.02
Patient 4	Repeat 7	0.30	1.50
Patient 4	Repeat 8	1.50	1.70
Patient 4	Repeat 9	1.20	3.05
Patient 5	Repeat 2	0.46	0.18
Patient 5	Repeat 3	0.21	5.52
Patient 5	Repeat 4	0.23	5.96
Patient 6	Repeat 2	0.63	14.66
Patient 6	Repeat 3	0.14	0.14
Patient 6	Repeat 4	0.24	5.32
Patient 6	Repeat 5	0.36	8.24
Patient 7	Repeat 2	0.99	0.02
Patient 7	Repeat 3	0.21	4.91
Patient 7	Repeat 4	0.54	11.88
Patient 8	Repeat 2	0.15	1.76
Patient 8	Repeat 3	0.90	0.24
Patient 8	Repeat 4	0.40	9.86
Patient 9	Repeat 2	0.54	13.94
Patient 9	Repeat 3	0.47	11.11
Patient 9	Repeat 4	0.55	13.02
Patient 10	Repeat 2	0.64	15.34
Patient 10	Repeat 3	0.54	12.56
Patient 10	Repeat 4	0.54	15.48

C

Reference point method with a reference point based on other patients

The weights and sensitivity parameters that are used for the results in Appendix C are:

Objective	Weights	Sensitivity parameters
f_1	1	0.5
f_2	1	0.5
f_3	1	10
f_4	1	0.5
f_5	1	0.5
f_6	1	0.5
f_7	1	0.5
f_8	1	0.5
f_9	1	0.5

Table C.1: The weights and sensitivity parameters that are used for Appendix C

C.1. THE MEAN FROM OTHER PLANNING-CTS AS REFERENCE POINT

C

Patient 1	Planning	
iCycle solution	Reference point	Outcome
57,95	61,12	58,00
51,54	55,75	51,62
14,48	21,51	14,97
29,76	34,82	24,13
75,03	79,32	74,42
57,47	67,15	54,29
48,03	55,41	43,21
10,22	17,41	10,25
4,29	4,72	4,26
Δ_{neg} = 0.64	Δ_{pos} = 14.26	

Patient 6	Planning	
iCycle solution	Reference point	Outcome
61,66	60,70	61,55
56,24	55,23	56,14
19,98	20,90	19,91
37,21	33,99	36,89
81,40	78,61	81,49
68,69	65,91	69,15
59,54	54,13	59,64
11,17	17,30	11,15
4,27	4,72	4,26
Δ_{neg} = 0.65	Δ_{pos} = 0.61	

Patient 2	Planning	
iCycle solution	Reference point	Outcome
64,73	60,36	64,42
60,42	54,77	60,13
28,71	19,93	28,56
44,44	33,19	44,64
83,04	78,43	82,83
75,30	65,17	75,16
59,25	54,16	58,90
14,55	16,93	14,48
4,90	4,65	4,88
Δ_{neg} = 0.19	Δ_{pos} = 1.54	

Patient 7	Planning	
iCycle solution	Reference point	Outcome
63,70	60,48	63,27
59,17	54,91	58,77
26,31	20,20	26,10
41,04	33,57	40,25
82,90	78,45	82,54
77,75	64,90	77,82
61,59	53,90	61,52
12,39	17,17	12,30
4,40	4,71	4,38
Δ_{neg} = 0.07	Δ_{pos} = 2.37	

Patient 3	Planning	
iCycle solution	Reference point	Outcome
60,13	60,87	60,13
54,52	55,42	54,54
20,42	20,85	20,75
31,20	34,66	30,69
77,93	79,00	75,44
65,82	66,23	61,07
54,65	54,67	50,64
8,24	17,63	8,14
5,10	4,63	5,09
Δ_{neg} = 0.35	Δ_{pos} = 11.87	

Patient 8	Planning	
iCycle solution	Reference point	Outcome
63,43	60,51	63,48
59,16	54,91	59,21
32,55	19,50	32,54
39,17	33,77	39,12
81,83	78,57	81,84
72,76	65,46	72,96
59,70	54,11	59,74
20,30	16,29	20,30
2,98	4,86	2,98
Δ_{neg} = 0.35	Δ_{pos} = 0.06	

Patient 4	Planning	
iCycle solution	Reference point	Outcome
60,58	60,82	60,62
54,86	55,38	54,93
18,36	21,08	18,63
29,47	34,85	27,08
76,62	79,15	76,19
57,81	67,12	56,50
48,26	55,38	45,91
28,60	15,36	28,15
5,94	4,54	5,94
Δ_{neg} = 0.38	Δ_{pos} = 6.93	

Patient 9	Planning	
iCycle solution	Reference point	Outcome
58,40	61,07	58,49
52,30	55,67	52,44
15,90	21,35	16,44
31,20	34,66	27,59
76,40	79,17	75,02
60,69	66,80	55,01
51,47	55,03	45,92
17,38	16,61	16,96
4,27	4,72	4,23
Δ_{neg} = 0.76	Δ_{pos} = 16.67	

Patient 5	Planning	
Optimal solution	Reference point	Outcome
59,85	60,90	59,88
54,10	55,47	54,16
17,72	21,15	17,97
28,43	34,97	26,99
75,06	79,32	75,20
58,29	67,06	57,30
48,44	55,36	47,88
31,36	15,06	28,65
4,88	4,65	4,93
Δ_{neg} = 0.52	Δ_{pos} = 5.69	

Patient 10	Planning	
Optimal solution	Reference point	Outcome
57,56	61,16	57,48
51,00	55,81	50,98
13,65	21,60	14,22
31,20	34,66	28,33
78,71	78,91	75,08
67,30	66,06	60,99
55,77	54,55	50,32
12,68	17,13	12,77
5,72	4,56	5,73
Δ_{neg} = 0.66	Δ_{pos} = 18.37	

C.2. THE MEAN OF ALL OTHER SCANS AS REFERENCE POINT

Patient	Scan	$\triangle_{neg}$	$\triangle_{pos}$
Patient 1	Planning	0.64	12.26
Patient 1	Repeat 2	0.60	14.37
Patient 1	Repeat 3	0.63	14.74
Patient 1	Repeat 4	0.62	14.17
Patient 1	Repeat 5	0.61	12.25
Patient 1	Repeat 6	0.64	14.54
Patient 1	Repeat 7	0.61	14.07
Patient 1	Repeat 8	0.62	14.48
Patient 1	Repeat 9	0.63	14.10
Patient 1	Repeat 10	0.61	14.36
Patient 2	Planning	0.19	1.54
Patient 2	Repeat 2	0.33	0.86
Patient 2	Repeat 3	0.56	12.63
Patient 2	Repeat 4	0.60	12.76
Patient 3	Planning	0.34	10.09
Patient 3	Repeat 2	0.23	8.17
Patient 3	Repeat 3	0.17	5.95
Patient 3	Repeat 4	0.16	3.90
Patient 3	Repeat 5	0.39	7.77
Patient 3	Repeat 6	0.46	12.08
Patient 3	Repeat 7	0.08	1.85
Patient 3	Repeat 8	0.21	0.28
Patient 4	Planning	0.38	6.93
Patient 4	Repeat 2	0.37	4.17
Patient 4	Repeat 3	1.18	3.30
Patient 4	Repeat 4	1.03	3.19
Patient 4	Repeat 5	0.62	3..83
Patient 4	Repeat 6	0.48	4.02
Patient 4	Repeat 7	0.30	1.50
Patient 4	Repeat 8	1.50	1.70
Patient 4	Repeat 9	1.20	3.05
Patient 5	Planning	0.52	5.69
Patient 5	Repeat 2	0.46	0.18
Patient 5	Repeat 3	0.29	6.18
Patient 5	Repeat 4	0.34	6.73
Patient 6	Planning	0.65	0.61
Patient 6	Repeat 2	0.57	15.18
Patient 6	Repeat 3	0.14	0.14
Patient 6	Repeat 4	0.27	6.48
Patient 6	Repeat 5	0.36	9.03
Patient 7	Planning	0.07	2.37
Patient 7	Repeat 2	0.99	0.01
Patient 7	Repeat 3	0.30	5.93
Patient 7	Repeat 4	0.58	13.33
Patient 8	Planning	0.35	0.06
Patient 8	Repeat 2	0.15	1.75
Patient 8	Repeat 3	0.91	0.24
Patient 8	Repeat 4	0.40	9.85
Patient 9	Planning	1.06	18.66
Patient 9	Repeat 2	0.84	16.16
Patient 9	Repeat 3	0.81	13.51
Patient 9	Repeat 4	0.77	15.53
Patient 10	Planning	0.67	18.37
Patient 10	Repeat 2	0.67	15.97
Patient 10	Repeat 3	0.81	16.23
Patient 10	Repeat 4	0.62	17.67

C.3. THE MINIMUM FROM OTHER PLANNING-CTS AS REFERENCE POINT

C

Patient 1	Planning	
iCycle solution	Reference point	Outcome
57,95	57,56	58,01
51,54	51,00	51,63
14,48	13,65	14,94
29,76	28,43	24,36
75,03	75,06	74,28
57,47	57,81	54,42
48,03	48,26	43,67
10,22	8,24	10,12
4,29	2,98	4,27
Δ_{neg} = 0.61	Δ_{pos} = 13.67	

Patient 6	Planning	
iCycle solution	Reference point	Outcome
61,66	57,56	61,55
56,24	51,00	56,14
19,98	13,65	19,91
37,21	28,43	36,89
81,40	75,03	81,49
68,69	57,47	69,15
59,54	48,03	59,64
11,17	8,24	11,15
4,27	2,98	4,26
Δ_{neg} = 0.65	Δ_{pos} = 0.61	

Patient 2	Planning	
iCycle solution	Reference point	Outcome
64,73	57,56	64,42
60,42	51,00	60,13
28,71	13,65	28,56
44,44	28,43	44,64
83,04	75,03	82,84
75,30	57,47	75,16
59,25	48,03	58,90
14,55	8,24	14,48
4,90	2,98	4,88
Δ_{neg} = 0.19	Δ_{pos} = 1.54	

Patient 7	Planning	
iCycle solution	Reference point	Outcome
63,70	57,56	63,27
59,17	51,00	58,77
26,31	13,65	26,10
41,04	28,43	40,25
82,90	75,03	82,54
77,75	57,47	77,82
61,59	48,03	61,52
12,39	8,24	12,30
4,40	2,98	4,38
Δ_{neg} = 0.07	Δ_{pos} = 2.37	

Patient 3	Planning	
iCycle solution	Reference point	Outcome
60,13	57,56	60,12
54,52	51,00	54,53
20,42	13,65	20,66
31,20	28,43	31,28
77,93	75,03	75,74
65,82	57,47	61,59
54,65	48,03	51,07
8,24	10,22	8,15
5,10	2,98	5,10
Δ_{neg} = 0.33	Δ_{pos} = 10.09	

Patient 8	Planning	
iCycle solution	Reference point	Outcome
63,43	57,56	63,48
59,16	51,00	59,21
32,55	13,65	32,54
39,17	28,43	39,12
81,83	75,03	81,84
72,76	57,47	72,96
59,70	48,03	59,74
20,30	8,24	20,30
2,98	4,27	2,98
Δ_{neg} = 0.35	Δ_{pos} = 0.06	

Patient 4	Planning	
iCycle solution	Reference point	Outcome
60,58	57,56	60,62
54,86	51,00	54,93
18,36	13,65	18,63
29,47	28,43	27,08
76,62	75,03	76,19
57,81	57,47	56,50
48,26	48,03	45,91
28,60	8,24	28,15
5,94	2,98	5,94
Δ_{neg} = 0.38	Δ_{pos} = 6.93	

Patient 9	Planning	
iCycle solution	Reference point	Outcome
58,40	57,56	58,49
52,30	51,00	52,44
15,90	13,65	16,44
31,20	28,43	27,59
76,40	75,03	75,02
60,69	57,47	55,01
51,47	48,03	45,92
17,38	8,24	16,96
4,27	2,98	4,23
Δ_{neg} = 0.76	Δ_{pos} = 16.67	

Patient 5	Planning	
iCycle solution	Reference point	Outcome
59,85	57,56	59,88
54,10	51,00	54,16
17,72	13,65	17,97
28,43	29,47	26,99
75,06	75,03	75,20
58,29	57,47	57,30
48,44	48,03	47,88
31,36	8,24	28,65
4,88	2,98	4,93
Δ_{neg} = 0.52	Δ_{pos} = 5.69	

Patient 10	Planning	
iCycle solution	Reference point	Outcome
57,56	57,95	57,53
51,00	51,54	51,03
13,65	14,48	14,20
31,20	28,43	28,79
78,71	75,03	75,24
67,30	57,47	61,07
55,77	48,03	50,82
12,68	8,24	12,29
5,72	2,98	5,74
Δ_{neg} = 0.59	Δ_{pos} = 17.50	

C.4. THE MINIMUM FROM OTHER SCANS AS REFERENCE POINT

Patient	Scan	$\triangle_{neg}$	$\triangle_{pos}$
Patient 1	Planning	0.48	12.14
Patient 1	Repeat 2	0.46	12.42
Patient 1	Repeat 3	0.48	12.69
Patient 1	Repeat 4	0.46	11.97
Patient 1	Repeat 5	0.46	12.07
Patient 1	Repeat 6	0.48	12.43
Patient 1	Repeat 7	0.46	11.98
Patient 1	Repeat 8	0.48	12.47
Patient 1	Repeat 9	0.48	11.98
Patient 1	Repeat 10	0.45	12.24
Patient 2	Planning	0.19	1.54
Patient 2	Repeat 2	0.33	0.86
Patient 2	Repeat 3	0.56	12.60
Patient 2	Repeat 4	0.53	11.32
Patient 3	Planning	1.37	23.53
Patient 3	Repeat 2	1.18	18.30
Patient 3	Repeat 3	1.33	19.42
Patient 3	Repeat 4	0.95	14.79
Patient 3	Repeat 5	1.28	20.85
Patient 3	Repeat 6	1.18	22.15
Patient 3	Repeat 7	1.18	14.84
Patient 3	Repeat 8	0.21	0.28
Patient 4	Planning	0.38	6.48
Patient 4	Repeat 2	0.37	4.17
Patient 4	Repeat 3	1.18	3.35
Patient 4	Repeat 4	1.03	3.19
Patient 4	Repeat 5	0.62	3.83
Patient 4	Repeat 6	0.48	4.02
Patient 4	Repeat 7	0.30	1.50
Patient 4	Repeat 8	1.50	1.70
Patient 4	Repeat 9	1.20	3.05
Patient 5	Planning	0.52	5.69
Patient 5	Repeat 2	0.46	0.18
Patient 5	Repeat 3	0.29	6.18
Patient 5	Repeat 4	0.34	6.73
Patient 6	Planning	0.65	0.61
Patient 6	Repeat 2	0.63	14.66
Patient 6	Repeat 3	0.14	0.14
Patient 6	Repeat 4	0.24	5.32
Patient 6	Repeat 5	0.36	8.24
Patient 7	Planning	0.07	2.37
Patient 7	Repeat 2	0.99	0.01
Patient 7	Repeat 3	0.21	4.91
Patient 7	Repeat 4	0.36	9.46
Patient 8	Planning	0.35	0.06
Patient 8	Repeat 2	0.14	1.73
Patient 8	Repeat 3	0.91	0.24
Patient 8	Repeat 4	0.40	9.86
Patient 9	Planning	0.76	16.67
Patient 9	Repeat 2	0.54	13.94
Patient 9	Repeat 3	0.47	11.11
Patient 9	Repeat 4	0.56	13.67
Patient 10	Planning	0.56	17.15
Patient 10	Repeat 2	0.67	15.54
Patient 10	Repeat 3	0.54	12.56
Patient 10	Repeat 4	0.50	16.92