On Quality in Radiotherapy Treatment Plan Optimisation

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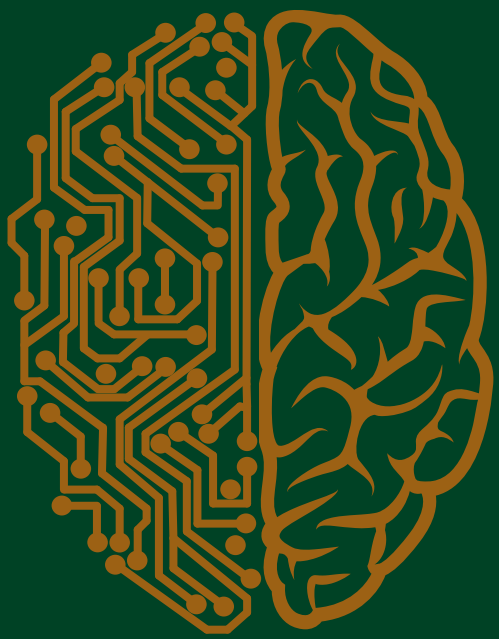
MEDICAL RADIATION PHYSICS | FACULTY OF SCIENCE | LUND UNIVERSITY



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Treatment Plan Optimisation

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LUND
UNIVERSITY

DOCTORAL THESIS

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Abstract

Radiotherapy is one of the essential treatments used in the fight against cancer. The goal of radiotherapy is to deliver a high dose of ionising radiation to the tumour volume and at the same time minimise the effect on healthy tissue by reducing the radiation to critical organs. This contradiction is challenging and has been driving the research and development of the treatments.

Over the last two decades, there has been tremendous technical development in radiotherapy. The rapid increase in computational power introduced treatment plan optimisation and intensity-modulated radiotherapy (IMRT). IMRT made it possible to shape the radiation dose distribution closely around the target volume avoiding critical organs to a higher extent. Rotational implementation of IMRT, e.g. Volumetric Modulated Arc Therapy (VMAT), further improved this “dose shaping” ability.

With these techniques increasing the ability to produce better treatment plans, there was a need for evaluation tools to compare the treatment plan quality. A plan can be judged by how well it fulfils the prescription and dose-volume constraints, ideally based on treatment outcome. In this work, this is denoted Required Plan Quality, the minimum quality to accept a plan for clinical treatment. If a plan does not fulfil all the dose-volume constraints, there should be a clear priority of which constraints are crucial to achieve. On the other hand, if the constraints are easily fulfilled, there might be a plan of better quality only limited by the treatment systems ability to find and deliver it. This is denoted Attainable Plan Quality in this work– the quality possible to achieve with a given treatment system for a specific patient group.

In work described in this thesis, the so-called Pareto front method was used to search for the attainable plan quality to compare different treatment planning systems and optimisation strategies. More specifically, a fall-back planning system for backup planning and an optimiser to find the best possible beam angles. The Pareto method utilises a set of plans to explore the trade-off between target and nearby risk organs. The Pareto plan generation is time-consuming if done manually. The Pareto method was then used in a software that automated the plan generation allowing for a more accurate representation of the trade-off. The software was used to investigate the attainable plan quality for prostate cancer treatments. In the last two publications in this thesis, machine learning approaches were developed to predict a treatment plan closer to the attainable plan quality compared to a manually generated plan.

In the thesis, tools have been developed to help move the treatment plan quality from Required Plan Quality towards the Attainable Plan Quality, i.e. the best quality we can achieve with our current system.

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“I always get to where I’m going by walking away from where I’ve been”

Winnie the Pooh

Table of Contents

Abstract

Radiotherapy is one of the essential treatments used in the fight against cancer. The goal of radiotherapy is to deliver a high dose of ionising radiation to the tumour volume and at the same time minimise the effect on healthy tissue by reducing the radiation to critical organs. This contradiction is challenging and has been driving the research and development of the treatments.

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Summary in Swedish

Målet med strålbehandling är att leverera en tillräckligt hög stråldos för att skada cellerna i en cancertumör utan att skada omkringliggande friska celler. Olika typer av celler är olika känsliga för strålning vilket man måste ta hänsyn till vilket idag görs med datoriserad stråldosplanering. Vid dosplanering provas olika antal strålfält med olika vinklar och intensitet forma stråldosen att täcka tumören utan att spilla över för mycket till frisk vävnad. Känsliga organ kan ibland vara väldigt nära tumören vilket försvårar planeringen och behandling. På senare år har det introducerats nya tekniker där strålfält roterar runt tumören och fältöppningen justeras under tiden. Dessa tekniker kallas för intesitetsmodulerad strålbehandling eftersom strålintensiteten varieras, moduleras, kontinuerligt under behandlingen. Intensitetsmodulerad behandling möjliggör en skarp gräns mellan ett område med hög dos och ett med låg dos. Dosplanering av intensitesmodulering kräver en optimering där en dator söker efter den bästa lösningen för en sorts önskelista som dosplaneraren väljer. I önskelistan anges hur hög stråldos tumören minst ska få och samtidigt hur mycket som friska organ maximalt tillåts få.

Problemet är att dosplaneringsystemet sällan ger exakt det man ber om och därför måste flera gissningar göras för att till slut uppnå önskat resultat. Detta gissande kan ibland vara svårt och ta lång tid och man vet inte om det verkligen är den bästa lösningen. Man behöver också säkerställa att den planerade behandlingen är tekniskt genomförbar. Ett annat problem är att vissa organ rör sig under behandlingen och kan ”putta” tumören ut ur strålfältet.

I de första två arbetena som ingår i den här avhandlingen har metoder utvecklats för att systematiskt utvärdera optimeringens kvalité. Metoden användes sedan för att jämföra plankvalitet från olika optimeraringsmetoder och dosplanerings-system.

I det tredje arbetet har flera tumörrörelsers påverkan av plankavaliten utvärderats och olika stråltyper har undersökts som en lösning.

I det fjärde och femte arbetet har modeller för artificiell intelligens (AI) utvecklats för att lära sig hur en strålplan men bra kvalitet ser ut för att sedan skapa bra planer för nya patienter. I det femte automatiserades metoden från de tidiga arbetena och användes för inlärningen av AI-modellen.

List of original Papers

This thesis is based on studies reported in the following publications, referred to by their roman numerals in the text.

I. **Introducing multiple treatment plan-based comparison to investigate the performance of gantry angle optimisation (GAO) in IMRT for head and neck cancer**
Maria Thor, Hunor Benedek, Tommy Knöös, Per Engström, Claus Behrens, Anna Karlsson Hauer, David Sjöström, Crister Ceberg
Acta oncologica, 2012;51(6):743-51.

II. **Conversion of helical tomotherapy plans to step-and-shoot IMRT plans – Pareto front evaluation of plans from a new treatment planning system**
Kristoffer Petersson, Crister Ceberg, Per Engström, Hunor Benedek, Per Nilsson, Tommy Knöös
Medical Physics, 2011;38(6):3130-8.

III. **The effect of prostate motion during hypofractionated radiotherapy can be reduced by using flattening filter free beams**
Hunor Benedek, Minna Lerner, Per Nilsson, Tommy Knöös, Adalsteinn Gunnlaugsson, Crister Ceberg
Physics and Imaging in Radiation Oncology, 2018;6:66-70.

IV. **Volumetric modulated arc therapy dose prediction and deliverable treatment plan generation for prostate cancer patients using a densely connected deep learning model**
Michael Lempart, Hunor Benedek*, Christian Jamtheim Gustafsson, Mikael Nilsson, Niklas Eliasson, Sven Bäck, Per Munck af Rosenschöld, Lars E. Olsson,*
**Contributed equally to this study*
Physics and Imaging in Radiation, 2021;19:112-119.

V. **Machine-learning assisted treatment-planning based on patient-specific features helps improve plan quality in hypo-fractionated prostate radiotherapy**
Hunor Benedek, Michael Lempart*, Niklas Eliasson, Adalstein Gunnlaugsson, Per Nilsson, Sven Bäck, Tommy Knöös, Crister Ceberg*
**Contributed equally to this study*
Manuscript

The author's contribution

Paper I — I planned the study with the main author, performed all the planning in one of the treatment planning systems (OMP), did the analysis, and wrote the manuscript with the main author.

Paper II — I contributed to the planning of the study, mainly of the Pareto front generation. In addition, I participated in the data acquisition, analysis, and preparation of the manuscript.

Paper III — I lead the planning of the study, assisted in treatment planning, and planned, prepared, and conducted the measurements together with the second author. I also analysed the data together with the second author and was the main author of the publication.

Paper IV — I was shared main author on the publication. Planned the study together with the co-main author. Was responsible for the "generation of deliverable treatment plans" part. I participated in the preparation of the manuscript with a focus on the deliverability part.

Paper V — I was shared main author on the publication. Planned the study and designed the auto planning method. Analysed the data and prepared the manuscript.

Other related publications

Uncertainties in the Evaluation of Treatment Plans
T. Knöös, H. Benedek, C. Ceberg, P. Nilsson, and K. Petersson.
Uncertainties in external beam radiation therapy, J. Palta and T. R. Mackie Eds. Madison, WI: Medical Physics Publishing, 2011, ch. 6, pp. 117-127. (Book chapter)

Strategies for quality assurance of intensity modulated radiation therapy.
H. Benedek, U. Isacsson, M Olevik-Dunder, M. Westermark, P. Hallstrom, J. Olofsson, M. Gustafsson.
8th International Conference on 3D Radiation Dosimetry (IC3DDOSE). Vol. 573 IOP Publishing, 2015. p. 012015. (Paper in conference proceeding)

A selection of preliminary reports

COMPARISON OF IMRT DELIVERY TECHNIQUES AND HELICAL TOMOTHERAPY USING PARETO FRONT EVALUATION,
H. Benedek, M. Thor, P. Engström, C. Ceberg, T. Knöös, A. Karlsson, C. Behrens, Radiotherapy and Oncology, Volume 92, Supplement 1, 2009 p. S86-S87 (10th Biennial ESTRO Conference on Physics and Radiation Technology for Clinical Radiotherapy)

INTRODUCING A NOVEL QUANTITATIVE INDEX FOR THE COMPARISON OF DIFFERENT ADVANCED RADIOTHERAPY METHODS
H. Benedek, P. Engström, T. Knöös, C. Ceberg
Radiotherapy and Oncology, Volume 96, Supplement 1, 2010, p. S75 (ESTRO 29)

THE IMPACT ON THE PLAN QUALITY AND QC RESULTS DUE TO THE CHOICE OF DIFFERENT COLLIMATOR ANGLES IN VMAT FOR PELVIC TUMOURS
H. Benedek, E. Wieslander, T. Knöös, C. Ceberg
Radiotherapy and Oncology, Volume 99, Supplement 1, 2011, p. S497 (11th Biennial ESTRO Conference on Physics and Radiation Technology for Clinical Radiotherapy)

Uncertainties in Plan Evaluation for VMAT Treatment Planning by Choosing Different Collimator Angles.
H. Benedek, E. Wieslander, T. Knöös, C. Ceberg. SU-E-T-470: Medical Physics, 2011;38:3597.

DYNAMYC FLATTENING FILTER FOR FFF BEAMS
H. Benedek, T. Knöös, S. Bäck, C. Ceberg.
Presented at NACP 2014 and the Turku PET Symposium, held in Turku, Finland, May 24-27, 2014

EP-1614: Evaluation of re-optimisation based on AAA-calculated VMAT plan and dose distribution in Eclipse.
A. Haraldsson, H. Benedek, P. Engström, T. Knöös.
Radiotherapy and Oncology, 2014;111:S209-S10.

The Dosimetric Effect of Prostate Motion in Flattening Filter Free VMAT Treatments Using Extreme Hypofractionation

H. Benedek, M. Ahlström, P. Nilsson, P. Engström, T. Knöös, C. Ceberg. International Journal of Radiation Oncology Biology Physics (2017) 99(2) E637-E638

1 Introduction

"Is this treatment plan as good as it can get? Can the risk organ doses be pushed down a bit more? Do we have time? When is the patient scheduled for treatment start? Ok so that machine does not have VMAT, can we rebook to another machine? Why can't we get VMAT for this patient?"

These are all questions that occur during the dose plan reviews at radiotherapy clinics all over the world. The increased frequency of these types of questions started around 10 to 15 years ago, with the development of Intensity Modulated Radiation Therapy (IMRT). Suddenly the radiation doses could be shaped to avoid critical organs, and at the same time squeezed tighter around the tumour targets. This breakthrough revolutionised radiotherapy. However, this came with some pitfalls, uncertainties, and many challenges. Decades of experience with previous techniques was suddenly less valuable.

The purpose of radiotherapy is to deliver targeted ionising radiation to a tumour volume to kill all cancer cells. Depending on the location and extent of the tumour, nearby healthy organs can be affected by the radiation. These organs at risk (OAR) have, for many years, been the restraining factor for radiotherapy. The amount of radiation given, the absorbed dose, is limited by the sensitivity of adjacent organs. The ultimate goal is to maximise the dose to the tumour area and at the same time minimise the dose to healthy OARs. Depending on the type of organ, either the organ or the tumour has the highest priority. This contradiction between healthy organs at risk and tumours makes radiotherapy, as a whole, a multicriteria problem. The introduction of intensity-modulated techniques has offered a possible solution to this problem.

Before IMRT techniques, the radiotherapy treatment was delivered by a few, typically 5 or less, static beams. The beams were open, block-shaped and covering the whole tumour volume. The intensity modulation in the new techniques is achieved by delivering the dose in several beams which themselves are composed of many small beam segments. By not covering the tumour volume with all the beams and segments, the dose can be shaped to avoid critical organs without compromising the tumour coverage. This benefit, however, comes with a cost.

The first drawback of IMRT techniques is the time-consuming treatment planning process. The dose distribution is composed of several small beam segments. To align these segments to deliver the desired dose, a computerised optimisation is

required. During this optimisation, a treatment planner asks the computerised treatment planning system (TPS) for the desired dose in the target volume and restricts the dose to risk organs, also called inverse planning. The TPS then performs an optimisation based on the planner's input, and presents a mathematically optimal solution. This solution is rarely clinically acceptable, and the planner therefore needs to adjust the input, and run additional optimisations. This trial-and-error process continues until the treatment planner is satisfied with the dose distribution, providing there is still time before the patient is scheduled for treatment. This workflow inevitably results in the plan quality being dependent on the time available for treatment planning. Even if the IMRT plans are better than the conventional ones, there is no guarantee that the plan is as good as possible - *using the available clinical treatment systems* - for each patient. Conventional treatment planning is more straightforward than inverse optimisation. The treatment planner arranges beams to cover the tumour, and adjusts the amount of radiation from each beam to avoid risk organs as much as possible.

Another issue with intensity-modulated techniques is the uncertainty in the actual dose delivery. More and smaller beam segments lead to more complex dose delivery. The different components of a treatment machine work extensively and are put under more stress, (movement of beam collimating components, variations in dose rate and gantry speed) leading to an increased risk of failure during delivery. The calculation of the planned dose also is more uncertain because of the complexity. To verify that every treatment plan can be delivered as calculated by the planning system, every treatment plan is transferred to a patient equivalent phantom geometry which can then be delivered and measured. This verification measurement also adds to the total preparation time of an intensity-modulated treatment.

An increasingly relevant concern with intensity-modulated techniques, covered by this work, is the issue of tumour motion. With a conventional treatment technique, moving tumours are covered providing that the planning margins are sufficient. However, this is not necessarily the case for intensity-modulated methods. Due to the complex composition of smaller beams not covering the whole tumour during the entire treatment, a moving target can be partly or entirely missed. For some cases which have a significant tumour movement within the delivered treatment time, the use of intensity modulation is restricted because the risk of losing tumour coverage is unacceptable. These cases would otherwise benefit significantly from intensity-modulation, so there is a clear benefit in addressing this issue.

1.1 Aims

This work aims to address the three issues: *the time-consuming trial-and-error treatment planning process, the uncertainty in the dose delivery, and the issue of tumour motion*, which can then give answers to the questions described in the opening of this chapter.

To be specific: the aim is to develop methods for unbiased, clinically relevant comparisons of different treatment techniques, beam modalities, treatment strategies and treatment planning systems with consideration of target movement (Paper I, II, and III).

These comparison tools will then be applied to Intensity Modulated Radiation Therapy (IMRT), and Volumetric modulated Arc Therapy (VMAT) treatment planning with a focus on automation and machine learning approaches (Paper IV and V).

The goal is to make intensity-modulation treatment planning less biased, less time consuming, more robust, more accessible to different patient groups, and with an overall higher quality for all patients.

2 Background

2.1 Early development of radiation therapy

The first radiotherapy was delivered to a breast cancer patient in January 1896, less than sixty days after Röntgen's discovery of the X-ray (1). This rapid clinical implementation was done by Emil Grubbé in Chicago (2). A couple of months later, cancer patients were treated for gastric tumours and basal cell carcinoma in France, America, and Sweden. In this very early stage of radiotherapy, the mechanism of X-rays and its effect on healthy tissue were not well understood. Despite the lack of knowledge, the pioneers of X-ray research worked together and implemented new treatment techniques at a remarkable speed. With this rapid development, the harmful effects of radiation quickly became apparent (3). In the first half of the twentieth century, the energy of the X-ray based radiotherapy was limited to 200-500 kilo Volts (kV), so called *ortho-voltage*. These low treatment energies (by today's standards) caused significant side effects for the patients. The inevitable skin toxicity made it very difficult to treat deeply situated tumours. The need for treatment planning to take the harmful effects into account became apparent. Already by this point, the goal became to maximise tumour effect and at the same time limit the harmful effect on the healthy tissue. Treatment planning at this time, however, was very primitive.

The discovery of natural radiation by Henry Becquerel and the discovery of Radium by Marie Curie also led to further advances in radiotherapy. The gamma-rays, as these photons became known, have higher energies (deeper penetration into material), and therefore offered a solution for deep seated tumours. Radium was the only source of gamma-ray in radiotherapy for the first twenty years (1). The radium was encapsulated in some form, and the treatment was delivered with a source to skin distance, (SSD), of a few centimetres. The amount of radium in each capsule was limited to a few grams, which reduced the SSD and resulted in treatment times of up to several hours. To solve the treatment time and SSD issues, a new radiation source was required. The first solution for the limitations of Radium was Cobalt 60 (^{60}Co) (4). The first treatment machine using ^{60}Co as its radiation source was installed in Canada in 1948. With an energy of 1.2 Mega Volts (MV), this therapy machine made it possible to treat deeply situated tumours and limit the dose to risk organs at the same time. This was a revolutionary breakthrough for radiotherapy

and thousands of these machines were sold in the following years, and were widely used for the next 20-30 years.

At the same time as the ^{60}Co machines were installed, a new technology - sprung from radar technology research - was introduced, the linear accelerator (linac). The first medical linear accelerator was installed in 1953 in London. The advantages of linear accelerators were many. The first and most distinct advantage of linacs over ^{60}Co is the lack of a radioactive source. There is no weakening of the beam over time, no required source change and no risk of the source getting stuck in an open position, possibly harming the patient. The second advantage is the higher photon energy. Medical linear accelerators (then and currently) produce X-rays of 4-20MV. This energy range allowed treatment of very deeply situated tumours to absorbed doses of up to 70 Gray (Gy) without exceeding the tolerances to risk organs, (for many tumour types but not all) (5). The third main advantage of linacs is that they can produce and deliver electron beams, meaning that a single machine can treat superficial tumours (with the electron modes) as well as deeply situated tumours (with the photon modes).

2.2 The development of intensity-modulated radiotherapy

Linear accelerators and ^{60}Co coexisted for many years; however, in the 1980s, the linacs started to become the dominant treatment modality in radiotherapy. In the mid-1980s the multi-leaf collimator MLC was commercially introduced, primarily for linacs. The MLC is composed of several thin tungsten blades that together can shape the radiation field to fit the tumour and shield the surrounding healthy organs. The MLC, in combination with computed tomography imaging, (part of the motivation for the 1979 Nobel prize, *"Well-informed observers believe that computer-assisted tomography has introduced a new era in radiation therapy"(6)*), lead to what today is called 3D conformal radiotherapy.

Although the MLC was originally designed to conformally shape radiation beams around targets, this was not what made the most significant impact on radiotherapy. Instead, the MLC had (and still has), a central role in all kinds of intensity modulated radiotherapy.

The first paper describing the dose shaping that later became known as IMRT was written by Brahme et al. in 1982. This paper describes how a rotating beam with a fluence modulated with a unique wedge could form a circular dose distribution (7). In 1988, Brahme published another paper on the subject, introducing a new concept of treatment planning. Brahme describes a method that derives the optimal incident beam dose from the desired dose distribution to the target, in what became known

as inverse optimisation or inverse planning (8). These two ground-breaking papers kickstarted the evolution of IMRT. Within the same year, a second IMRT paper was published by the same group, suggesting a practical way to deliver these shaped dose distributions using moving MLC blades (9).

During the 1990s and early 2000s, several research groups developed the technique of inverse optimisation and the practicalities of delivering IMRT treatments (10-17). By 2003 all radiotherapy departments wanted to have IMRT in their clinic. The two main strategies for IMRT delivery with static (fixed) beam angles, were, (and still are) Dynamic MLC and step-and-shoot MLC. The step-and-shoot IMRT method utilises several small MLC-shapes in every beam. The radiation is stopped while the MLC blades move to shape the next segment. Each segment delivers a small amount of radiation, and the sum of all beamlets results in a shaped dose distribution. During dynamic IMRT delivery, the MLC blades move while the radiation is on. The MLC shapes a narrow slit that slides from one side of the open beam to the other. The opening of this slit can also change during this sliding window delivery, as it is also called. To deliver the best possible treatment, regardless of which technique is employed, several beam angles are required. IMRT in this form results in longer treatment times (10-15 min compared to 2-3min for conventional therapy). This increase in time can be a significant discomfort for patients. The risk of potential problems related to organ and tumour motion also increases with beam delivery time. For these reasons faster treatment techniques were researched.

2.3 Volumetric modulated arc therapy (VMAT)

In 2008 a new type of IMRT technique was described by Karl Otto. This method utilised the rotation of the linac head and gantry, while at the same time the MLC was moving dynamically (18). During all these machine movements, the radiation beam is on. This technique was called Volumetric Modulated Arc Therapy (VMAT) in the paper and later became a general denotation for these kinds of treatments. Shortly after this publication the first patients got treated with VMAT. The most significant advantage of VMAT over static beam IMRT was the delivery time. The beam on times for a single rotation VMAT is about 1min. This results in 10% or less beam-on time compared to IMRT. More and more clinics implemented and treated with VMAT alongside IMRT. Clinics that had not yet started IMRT treatment skipped them entirely and went directly to VMAT treatments (19).

Because of the short treatment times, better plan quality and the fact that conventional c-arm linacs can be used, VMAT is the most common treatment technique at many hospitals today.

2.4 The treatment planning process

Traditionally the treatment planning process for 3D conformal radiotherapy (nowadays referred to as simply conventional radiotherapy) is a trial-and-error process. The treatment planners try different beam angles, various weighting contributions from each beam and wedging of the fields where available using a computer treatment planning system (TPS). This manual process of optimization of the plan parameters and recalculation of the dosimetry goes on until a satisfactory result is reached, covering the target without overdosing critical risk organs.

Expert treatment planners can go through this process rapidly while it takes longer for inexperienced ones. No matter how skilled the treatment planner might be, the plan quality is limited by the degrees of freedom available. For conventional treatments these freedoms are limited to the few mentioned above (beam angles, wedging and relative contribution to the total delivered dose).

The planning process for IMRT and VMAT is different. The first step is similar to conventional planning, where several beams are distributed around the patient, but for IMRT usually equally distanced. The number of beams usually is larger for IMRT. Next, the clinical goals for target volumes and risk organs are put into a list of goals for the plan in the TPS. These goals become the objectives for the optimisation. The objectives are now prioritised (given relative importance) by the planner, and the automatic optimisation is started. Now the computer attempts to fulfil as many of the objectives as possible. The optimal fluence from each beam is converted to deliverable MLC segments, static or dynamic. The treatment planner now examines the resulting treatment plan and will often find that it is not good enough (according to the requirements of the relevant clinical protocol). To improve the plan the optimisation is re-run with different objectives, sometimes several times (Figure 1).

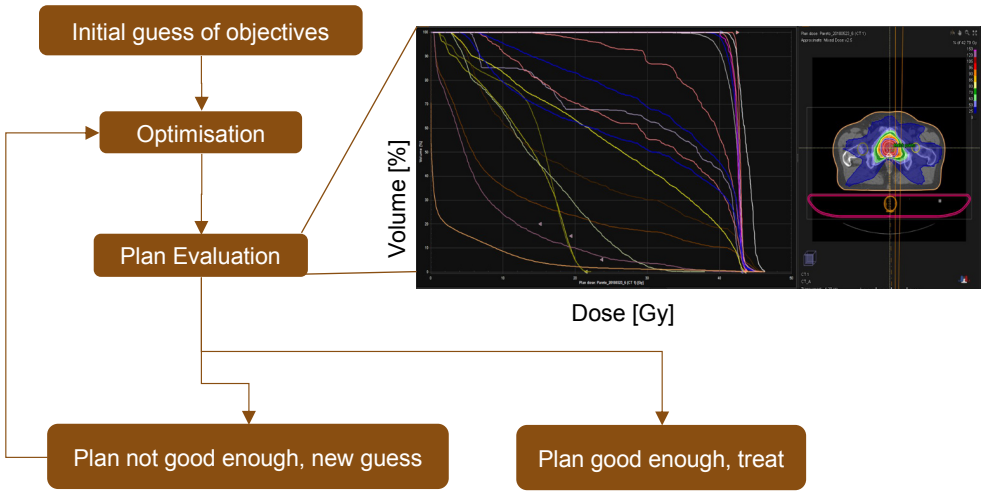

Figure 1.
Illustration of the trial-and-error process involved in treatment planning of intensity modulated radiation therapy treatments (IMRT and VMAT).

For VMAT treatments the process is very similar in principle. The only difference is that the planner chooses the number of rotations, start, and stop angles instead of the fixed beam angles. This means that IMRT and VMAT planning is also a trial-and-error process just like for conventional planning. Because of the infinite number of combinations of different objectives and priorities, the questions remain:

- is the treatment better than before or as good as it could be?
- is the deliverable treatment plan as good as it looks on the computer screen?

The quality of a treatment plan can only be judged by how well it fulfils the prescription (20). A quantitative evaluation of the plan therefore depends on the stated objectives. Prescriptions should be defined for targets as well as OARs with stated importance for each objective - ambiguines importance can lead to individual prioritisation of objectives depending on personal preference. The deliverability of the plan should also be included in quality evaluation, which may not always be the case in the planning process.

3 Optimisation

The basis of the inverse planning, used in both IMRT and VMAT, is an optimisation algorithm. The treatment planning optimisation problem - maximising the target dose and at the same time minimising or even restricting the dose to critical organs - could be set up in a general form to find optimal values for all variable treatment parameters. Because of the many treatment parameters, the search space becomes too large to be practical and the optimisation problem needs to be limited to a few variables. The parameters, for static field IMRT at least, are beam orientation, irradiation geometry, dynamic or static intensity modulation, radiation modality, and beam energy (14). The beam orientation & beam angles are usually set prior to the optimisation but can be included or pre-optimised, (which will be discussed later in this chapter). The parameter left for optimisation are the beam profiles incident at the target. The process starts with an initial guess and then the beam profiles are changed iteratively until an optimal solution is found. The optimal solution is evaluated against an objective function which is a weighted sum of all the dose-volume criteria stated by the user at the start of the optimisation. Two groups of optimisation algorithms are commonly used to determine the optimal beam profiles: deterministic and stochastic.

3.1 Dose volume objectives and objective function

The predominant types of objective used in commercial systems for intensity modulated treatment planning are: dose-volume based, or a combination of dose-volume and dose. Usually, for target volumes the minimum required dose and the allowed maximum dose can be specified in the optimiser. In some systems volume requirements are also allowed for targets, however a strict minimum dose is always required. For risk organs there is naturally no minimum dose requirement, only maximum dose, and maximum dose to a specified volume – dose objectives can also be stated as: Dose, Gray (Gy), to 0% of the volume to specify maximum allowed dose in systems with only dose-volume objectives (see Figure 2). There is usually a weight (or priority factor) that needs to be specified for each dose volume-objective. During the optimisation process the dose distribution from each iteration is evaluated against the weighted sum of all the objective values resulting in a total score value (21). The optimisation algorithms are designed to minimise the

objective value, i.e. the difference between the desired dose and the optimised dose. (21). The optimisation algorithms are designed to minimise the objective value, i.e. the difference between the desired dose and the optimised dose.

Figure 2. Example of setting the dose-volume objectives for PTV in a commercial TPS
Dose-volume objectives set for the PTV in a commercial treatment planning system. In this example, upper means: maximum allowed dose, 43.34Gy or more to 0% of the volume and lower means: at least 42.06Gy to 100% of the volume. The two different objectives have priority 100 and 200 meaning that the lower objective will have be twice as important in the optimisation.

3.2 Optimisation methods

The most common deterministic optimisation method used for IMRT planning is the gradient descent method. To be able to optimise the beam profile for each projection, it is divided into smaller parts called beamlets or beam elements (bixels) (14, 21). All the beamlets that have a projection of the target are included in the optimisation. The patient's 3D volume is also divided into smaller volume elements (voxels). An initial guess of beamlet intensities representing the beam profile, is used to calculate the dose in every voxel of the patient. The difference between the stated objectives and the resulting dose is calculated and then the beamlet intensities are changed. The new "guess" is evaluated in the same way and if it results in a better dose distribution it is retained. The iteration goes on until one of the stop criteria - maximum number of iterations or optimal solution set by the user - is reached. The process can be illustrated by an example (Figure 3).

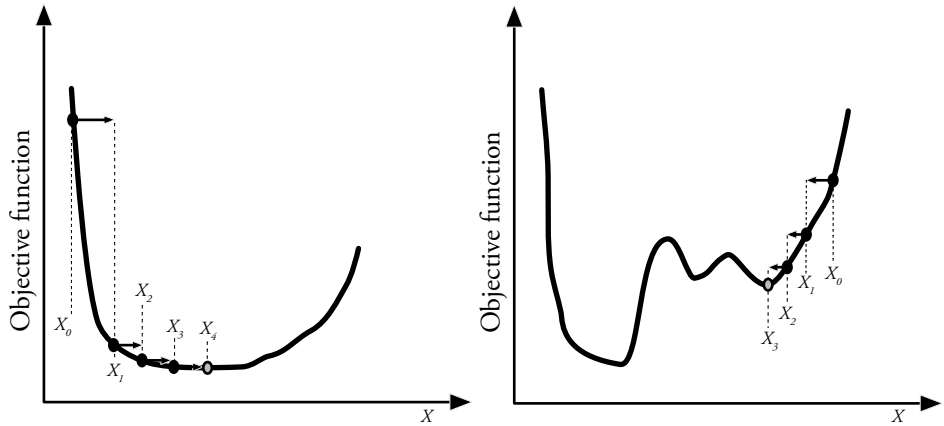

Figure 3. Graphical illustration of the gradient descent method
The graphs in the figure are two examples of objective functions – the measure of how good an optimised treatment plan is, the lower value the better plan – for one adjustable parameter to be optimised, *X, e.g. the intensity of one beamlet of a beam profile.* From the initial guess X_0 the next step is found X_1 by subtracting from X_0 a value, given by gradient at X_0. In this way the gradient of the objective function is followed stepwise until a minimum is reached. In the left example there is only one minimum and the gradient descent optimiser finds the lowest possible value. In the example on the right, there are several minima and because the initial guess is on the right side of the curve, the optimiser gets stuck in a local minimum.

For a given objective function the optimisation starts with an initial guess X_0. From this point, the gradient method calculates its next step X_1 by subtracting from X_0 a value given by the gradient at the point X_0. This is repeated in the same way from X1 to X2, X2 to X3 etc. If the objective function only has one minimum, as in the left graph in Figure 3, the gradient descend algorithm easily finds it and thereby the optimal solution. In the other example, to the right in Figure 3, there are several minima and the initial guess X_0 happens to be on the right side of this objective function curve. In this case the optimisation gets stuck in one of the local minima and a suboptimal solution is found. The gradient method is the fastest, computation wise, of the early algorithms implemented for IMRT planning (14, 22-26). The drawback of the method is, the fact that a sub-optimal solution is likely to be identified if used with dose-volume base objectives (26). To get around this problem other algorithms were developed simultaneously.

The most researched stochastic optimisation technique is simulated annealing (10, 12, 21, 27-29). Annealing is a method used to soften metals by heating them to high temperatures and then quickly cooling them in water. For optimisation the annealing is simulated; the 'temperature' (representing the parameter to be changed during the optimisation), determines the step size in the search area, i.e. the amount that the beamlet intensity is changed in each iteration. The temperature also controls the likelihood that an increase of the objective value will be accepted – the higher the temperature the more likely that a worse solution is temporarily accepted. If many configurations are tested the optimisation can escape the local minima as shown in Figure 3 (right), and the best solution from the tested configurations will be found.

The temperature is lowered as the optimisation progresses leading to smaller steps and less probability of uphill jumps. Stochastic algorithms tend to be slow and to be sure to find the best solution a lot of iterations are required (because steps in the wrong direction are allowed), making it even slower.

The slowest component in both methods is the dose calculation between each iteration. To make the optimisation more practical, simpler, and faster, dose calculation models are used making them less accurate. The beam profile is usually optimised without all treatment machine characteristics meaning that the optimised fluence needs to be converted into a deliverable plan and then a more accurate final dose calculation is required.

3.3 MLC leaf sequencing

To convert the optimised beam profile into a more realistic dose distribution, the characteristics of the MLC need to be added – a process called leaf sequencing or leaf segmentation. Both static (11, 30) and dynamic (31) leaf patterns can be calculated. There are several different physical characteristics of the MLC leaves that need to be modelled. The two most important are the leaf leakage and the tongue-and-groove effect, (these will be discussed in the chapter on deliverability). The discrepancies between optimised fluence and segmented fluence or dose can be significant (32, 33). In Paper I both a static step-and-shoot leaf sequence and a dynamic sliding window sequence was used. In Paper II only a static MLC delivery was used. Depending on where in the IMRT optimisation chain the plan is evaluated, a sub optimal solution could be chosen.

To mitigate the problem with apparently optimal plans that are challenging to deliver, several groups developed optimisers that directly optimised the MLC patterns (34-39)so sequencing was “built-in”. A different approach, penalising the intensity pattern in the optimisation to find smoother beam profiles was also suggested (34, 40). Some methods used only optimization of the jaws (41). These direct machine parameter or aperture optimisers were attractive for commercial TPS vendors who successfully implemented them (33, 42). The direct machine parameter optimisation methods were found to be superior to fluence based optimisation methods, both in complexity and plan quality in the final dose calculated step. It was for this reason the direct optimisation methods were used in the development and optimisation of Intensity Modulated Arc Therapy (IMAT) techniques (43).

3.4 VMAT optimisation

In a ground-breaking publication, Karl Otto in 2008 presented a method to deliver a conformal IMRT treatment in a single 360° gantry rotation (arc) (18). He proposed a direct aperture optimisation method - MLC leaf positions and dose monitor units (MU) weights are used as optimisation parameters - with an optimisation function based on dose volume constraints. Treatment machine characteristics like maximum leaf travel per gantry angle, gantry rotation speed, and maximum dose rate (output per gantry angle) are used to constrain the optimisation. The optimiser always aims to move the gantry as fast as possible; if this is not possible because the dose rate happens to be insufficient, the gantry slows down. Another innovative approach shown in the publication, was the progressive increase of beam angles with an MLC aperture, called control points. The optimiser starts with a few (6-8) control points and then more are added as the optimisation progresses, thereby increasing the accuracy. The implementation of the VMAT optimiser in Varians treatment planning system, Eclipse (Varian Medical Systems, Palo Alto USA), is very similar to the one presented by Otto (44).

In Paper I two different optimisation methods were used, one fluence optimisation with a dynamic MLC sequence added later and one direct aperture optimiser for step-and-shoot delivery. In paper II the step-and-shoot optimiser was used. In

Papers III and IV, Varian's implementation of Otto's VMAT algorithm was used.

4 Pareto Optimisation

The definition of multicriteria optimisation, also known as Pareto optimisation is: a mathematical optimisation problem involving more than one objective function to be optimised simultaneously. In radiotherapy, there have always been at least two conflicting objectives. With IMRT and VMAT treatment planning these objectives can be optimised (45). What is mathematically optimal in the TPS might not be- - and most likely is not- dosimetrically, or clinically optimal. That is the reason for the trial-and-error process described in chapter 2. In a multicriteria optimisation, there is no one optimal solution where all the objectives are met. Instead, there is a trade-off between mutually conflicting goals. These contradictory objectives are most commonly the doses to the tumour and a nearby risk organ. There can be different priorities between organs and targets depending on the sensitivity of the risk organ. For example, the spinal cord is a sensitive organ, and the tolerance doses are never exceeded because the implications are extremely severe for the patient (e.g. paralysis) (46). Tumours close to the spinal cord have a lower priority and get a dose level that the organ tolerates. An organ that is less sensitive or with a less catastrophic outcome if tolerances are exceeded, is the parotid gland. The parotid glands, one on each side of the mouth, produce saliva. If they are overdosed, the saliva production is impaired with resulting mouth dryness, called xerostomia (47). In the parotid gland case, nearby tumours have higher priority and get the full prescription dose no matter what the parotid receives.

A multicriteria optimisation can reach a state where one of the objectives cannot be improved without worsening another. This is called Pareto optimality. For the two example organs above this could happen for the parotid gland in practice. The treatment planning system always tries to make a mathematically optimal solution based on the objective function which is a result of the user-defined objectives and priorities. This way of optimising always makes a compromise between goals. To handle the multi criteria nature of the optimisation problem, the boundaries of individual objectives need to be found and evaluated against the others. In the pioneering work of Craft et al. optimisers were developed that generated Pareto optimal solutions for several conflicting goals (48, 49). However, with all the physical constraints of the treatment machine not considered during the optimisation, final deliverable plans might not be Pareto optimal in a clinical sense. To visualise the Pareto optimality for a specific patient, two of its conflicting objectives can be plotted, e.g. the x-axis can represent the target underdose and the

y-axis the dose to the selected risk organ. To analyse if a solution is Pareto optimal or not, several solutions, or in this case treatment plans, need to be generated. The optimisation objectives for each plan should be different. It should be noted that the objectives may not be different, only the weights, if the Pareto optimality is evaluated strictly mathematically. This is because the objective function changes is the objectives are changed. The Pareto optimal plans form a boundary between feasible and infeasible solutions. This boundary is called the Pareto front (Figure 4). A larger number of plans give a better representation of the Pareto front. The Pareto plot can be generated with the optimal fluence or the fluence with MLC shapes/motions taken into account, called segmented fluence (50). A substantial difference has been seen between optimal and segmented Pareto fronts (32, 50).

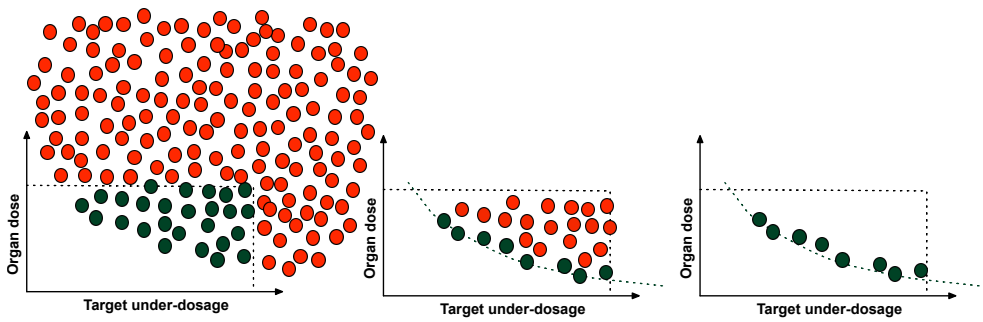

Figure 4. Visualisation of the Pareto front and its generation process.
The plot to the left contains all generated treatment plans. The green ones are clinically acceptable and the red ones are not. In the middle plot, clinically acceptable are filtered out. Green marks the Pareto optimal plans and the red are suboptimal plans. In the right plot only plans on the Pareto front are displayed

In Paper I the clinical Pareto optimality was investigated, meaning that all presented treatment plans are deliverable and have a final dose calculation performed. Pareto fronts were manually generated for two commercial treatment planning systems and linear accelerator vendors. The automatic beam angle optimisation in both systems was also investigated. The study was performed on head and neck cancer patients, and the visualised trade-off was between dose coverage of the planning target volume (PTV) and dose to one of the parotid glands. Paper I demonstrated that the Pareto front method could be used to compare different treatment planning systems, new functionalities, or different machines. Previous studies had shown this method for optimal fluence and segmented fluence but not for deliverable clinical treatment plans (50, 51). It has been argued whether this approach compares apples to oranges and therefore, it is essential to stress the deliverability of the presented treatment plans. If a plan is deliverable with a calculated dose - ideally measured on a phantom – that is what is delivered to the patient no matter what TPS is used. The gantry angle optimisation was found to produce equally good or better plans compared to the equidistant beam arrangement, for both systems. The findings in Paper I

contributed to the clinical implementation of gantry angle optimisation at the Skåne University Hospital.

In Paper II, the same manual multicriteria Pareto front method was used as in Paper I. In Paper II however, the technique was used to evaluate the clinical performance of a fall-back TPS for Tomotherapy. The fall-back TPS was designed to convert Tomotherapy treatment plans into step-and-shoot IMRT plans deliverable on a conventional linac. Pareto fronts for the Tomotherapy system were compared to Pareto fronts generated in the fall-back planning system as well as the clinical TPS at Skåne University Hospital. The optimal number of beam angles and number of segments per beam, was also investigated. Paper II demonstrated that plans generated by the fall-back system were of similar or better plan quality compared to the clinical TPS. The paper also showed that there is no improvement in plan quality if 11 or more beam angles are used.

The advantage of the Pareto front method as a comparative tool is that it is not dependent on human user skills. Therefore, it is unbiased in the sense that the displayed differences rise from the TPS itself, the investigated modality, or functionality. Perhaps the most valuable information provided by the Pareto front method is the free improvement element of the treatment plan quality. This means that in the Pareto fronts there is a rapid improvement of risk organ dose and only a marginal decrease in PTV coverage. At some point, in this work called the “knee”-point, the relationship becomes the opposite; the PTV dose is decreased rapidly with only a minimal dose reduction to the risk organ. This free improvement element can only be visualised by Pareto plots and is strongly dependent on patient anatomy. This information can later be used as input to machine learning approaches.

One of the disadvantages of the Pareto method is that it is incredibly time-consuming, especially for clinically deliverable plans. To generate a sufficient representation of Pareto front hundreds of plans need to be produced. Another disadvantage, for the specific method used in this work, is the lack of information about other trade-offs, which there are for almost all patients, than the two presented in the Pareto plot. One way to mitigate this problem is to always keep the other objectives constant and well under the clinical constraints; this, however, adds to the time needed to generate the Pareto front. To make the method more accessible in a practical sense, there is a need for automation.

4.1 The automated Pareto plan generation software

In Paper V, an in-house developed software for automatic generation of Pareto plans was used. An early version of the working loops in the software was already used in a small study presented at the ASTRO (American Society for Radiation Oncology) conference in 2017 (52). The treatment plans, for both flattening filter

free and flattened beams presented in Paper III, were used as base plans for an automatic Pareto front generation using both Eclipse, (Varian Medical Systems, Palo Alto USA) and RayStation (Ray Search Laboratories, Stockholm Sweden). Pareto fronts from the two systems and two beam modalities were compared. The automation allowed a finer sampling rate of the feasible plans and therefore a more accurate Pareto front was found. This early version of the software had no graphical interface for the visualisation and filtering of suboptimal and clinically unacceptable plans which still had to be done manually, but now for many more plans.

For the Pareto plan generation in Paper V, a graphical user interface was developed for the plan generation but more importantly for the visualisation and filtering of feasible plans. In the plan generation part of the software, the user is given the option to create a base plan from scratch or to use a saved template. Then the objectives that should be included in the Pareto "looping" can be selected with the desired step size and range of the variation; the software runs all the chosen combinations (Figure 5). All the types of objectives available in RayStation can be chosen to be varied in the optimisation. Dose statistics and general information for each plan is saved in text format to a database. There is also an option to include a simple robustness test where the dose is recalculated with a chosen or random isocentre shift.

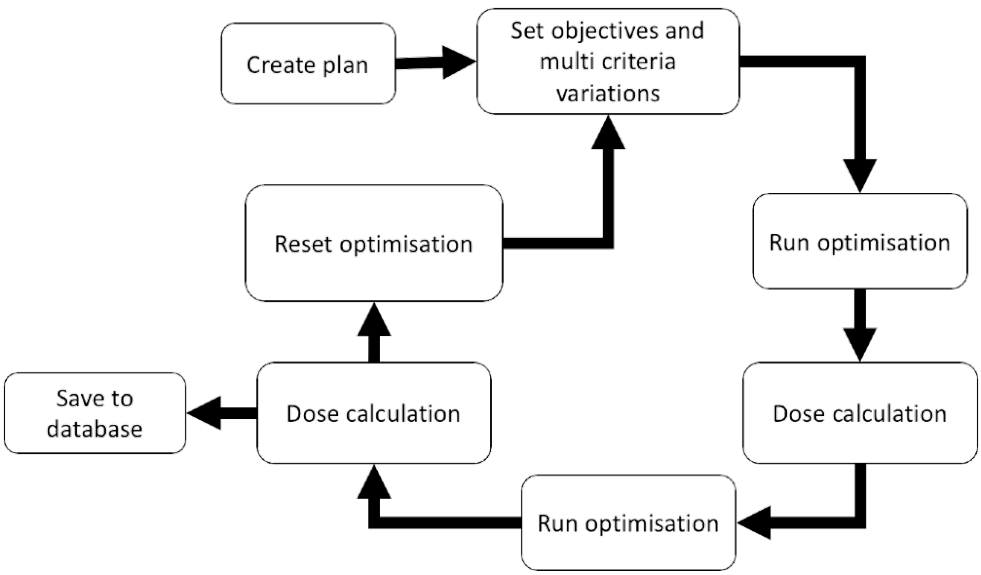

Figure 5. Flow chart of the automatic Pareto plan generation.
In the first step a new treatment plan is created with the desired beam energy and number of rotations, from a template or manually. In the next step the objectives for the starting point plan are set and the ones to be included in the multi criteria optimisation are specified with the desired steps. Then the optimiser is run for a pre-set number of iterations followed by a Collapsed Cone dose calculation; these two steps are repeated. Last, dose volume information is saved to a database and the optimisation is started with the next set of objectives.

Plan generation can be set up to go through a list of patients and run overnight. For each patient in Paper V the plan generation took about 28h for each patient.

When the plan generation is done, the saved information is loaded into the Pareto evaluation part of the software. In Figure 6 some of the layouts and options of the Pareto plot tool are shown. First, all the generated plans are shown, which in this case numbered 800. Each plan is shown as a dot, which can be clicked to show a dose volume histogram (DVH) for that plan. All the goals in the clinical protocol can be chosen to filter acceptable from unacceptable plans. The two conflicting interests to be visualised in the Pareto plot can also be chosen. There is also a choice to only show acceptable plans according to the clinical goals and that are pareto optimal for the desired trade-off. Plans from several sets can be loaded at the same time to allow comparisons. If the robust option was chosen, the static and isocentre moved Pareto fronts can be compared.

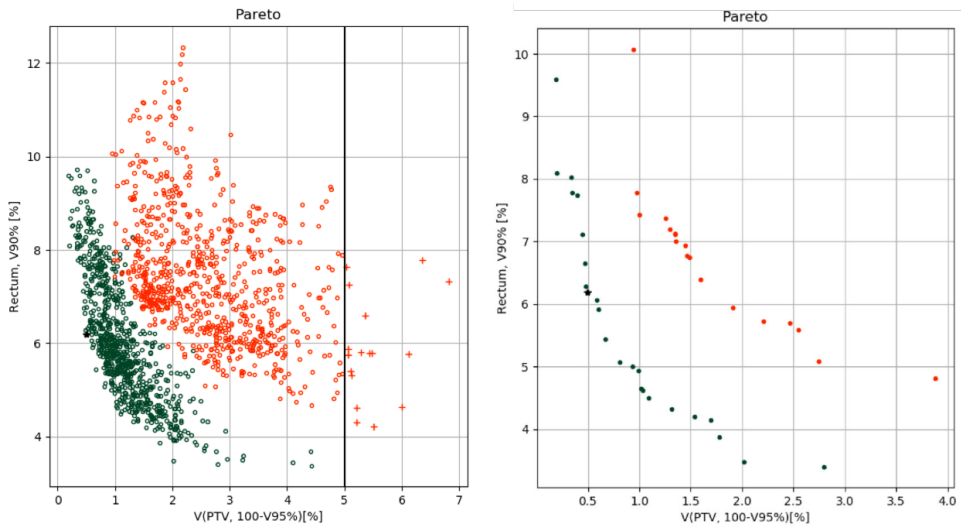

Figure 6. Example of sorting Pareto plan and clinically acceptable plans.
Two sets of autogenerated treatment plans, for two different patients. The left plot shows all the plans, the ones fullfilling the clinical goals are denoted by circles, the ones do not are denoted by plus signs. Pareto optimal plans fullfiling clinical goals are shown as filled circles; only these plans are shown in the right plot.

5 Deliverability

One fundamental concern with all intensity-modulated radiotherapy is whether the delivered treatments are as good as they seem to be in the TPS. The many MLC segments and movements also make it more difficult to intuitively find errors which was the case previously for 3D conformal therapy. The most common strategy to assure the quality of these types of treatment plan is to do a pre-treatment measurement. The most common method is to measure the clinical plan on a dedicated dosimetry phantom and if it passes the quality measurements and checks - it is locked for further editing. As the popularity of intensity-modulated therapy (particularly VMAT) is increasing, the time spent on pre-treatment measuring is becoming untenable. Possible new strategies were presented in 2015 by a working group of the Swedish Society of Radiation Physics (19). These guidelines suggested that an actual measurement is not necessary if all the critical components of a treatment plan are verified otherwise. However, for this to be clinically usable, the treatment plan characteristics should be well established for every patient group where individual plan measurements are not performed. To enable this strategy, plans that deviate from the standard should be caught already at treatment planning. Ideally, this verification also takes tumour motion into account. To make this work, comprehensive benchmarking is needed to classify the standard plans and to optimise the use of the available modalities for each patient. The process of ensuring good agreement between optimised and delivered treatment plan starts by characterising and modelling the treatment machine parameters.

5.1 Treatment machine commissioning

Acceptance testing is performed prior to commissioning the treatment machine for clinical use. The acceptance testing procedure is usually setup by the vendor to demonstrate that the machine satisfies the customer specifications defined during purchase of the equipment. While there may be little room for adjustment of the acceptance test tolerances, the on-site physicists may request slight adjustments to some machine parameters to demonstrate more optimal performance, well inside acceptance test limits. Additional supplementary acceptance tests may be agreed upon between the vendor and clinic to verify optimal performance in specific functionality related to the intended clinical use of the machine.

This ensures better deliverability and treatment quality for a longer period due to normal variations in machine performance.

The next step of commissioning is to measure the characteristics of the treatment machine during clinical treatments and use these parameters for modelling the machine in the TPS. Beam profiles, percental depth doses and output factors for field sizes, defined by the vendor, are used for modelling the beam calculation algorithms. The systems may have different requirements on what is used from the measurements, so it is critical to use the right detector for each measurement and system (44, 53). The physics manuals should state what is important for each parameter, e.g. Eclipse uses the "tails" of a beam profile measurement – the dose under the collimators – for the second source modelling which requires adequate output i.e. use a small ionization chamber. It is also possible to merge measurements with different detectors to ensure the best modelling in each part of the profile or depth dose curves.

For intensity modulated treatment plan optimisation, the modelling of MLC characteristics is the most critical (54, 55). The TPS requires two parameters, determined by the user for their individual machine, to model the MLC: MLC transmission and the Dosimetric Leaf Gap, (DLG) – called Dynamic Leaf Tip in RayStation. The Transmission is the amount of radiation transmitted when all the MLC leaves are closed, measured as described by Arnfied et al. (56). The tips of the MLC leaves are rounded to compensate for the divergence of the radiation beam. Because of these rounded tips the MLC will have a leakage, where the leaves meet. This tip leakage defined as the DLG and is recommended, by Varian, to be measured as described by Losasso et al. in 1998. In RayStation there is an equivalent modelling parameter called *Minimum dynamic tip gap (53).*

For the work described in Papers III-V all treatment plans were made to be deliverable on Varian True Beam linear accelerator. Eclipse was used as the TPS in Paper III, and IV and RayStation in Paper V, (and for the additional study in relation to Paper III) (52). The recommended measurements for DLG and transmission modelling was only used as a starting value and were then tweaked and evaluated using the dynamic fields, e.g. Dynamic chair and C-shape, presented by Van Esch et al. (57, 58), measured with a 2D ion-chamber array.

5.2 Quality Assurance (QA)

The deliverability of all radiotherapy treatment plans depends on the consistency of the treatment machine and the planning system. Comprehensive, government authority regulated, quality assurance (QA) programs are in place at clinics world-wide to ensure safe and accurate treatments. For treatment machines used for IMRT and/or VMAT delivery, the mechanical consistency of the MLC and gantry became

more vital requiring additional QA procedures. It is also necessary to validate that the TPS constantly produces deliverable treatment plans – MLC shapes and moments are physically possible to deliver by the machine with an accurate dose for every patient (19, 54, 58). In Sweden, most radiotherapy clinics have relied on pre-treatment measurements, for every new treatment plan, as an all-in-one QA procedure to verify both IMRT specific machine constancy and TPS performance.

Until recently the Swedish Radiation Safety Authority mandated a measurement for every new treatment field making a phantom measurement for each patient the only available option. Now the mandate has been changed to "verification" and a measurement is no longer needed if all the essential parameters are assured by other means. A working group initiated by *The Swedish Society of Radiation Physics* suggested strategies to implement a non-measurement based QA (19). A flow chart describing the strategies is shown in Figure 7.

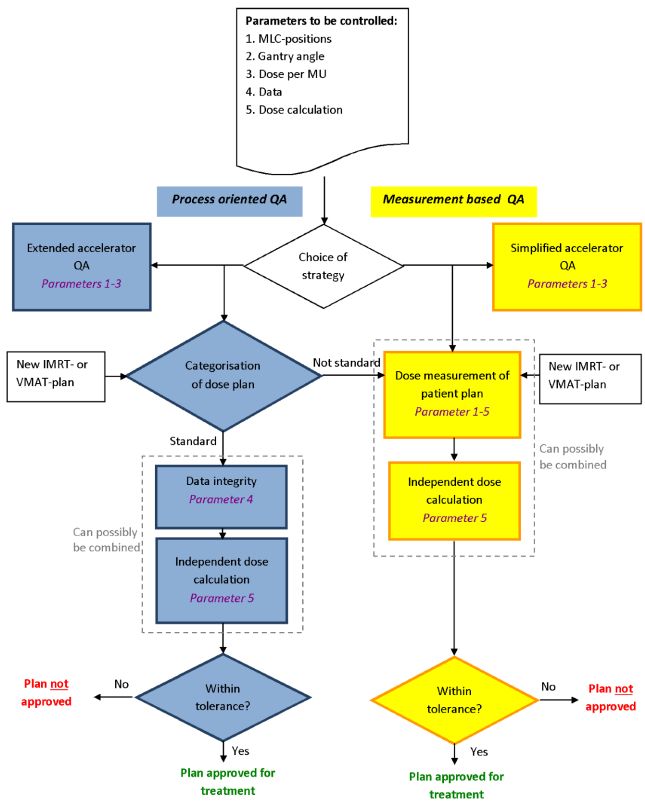

Figure 7. Flow chart of a QA strategy that doesn't always require a patient specific phantom measurement.

The idea of the method is that there are two QA strategies: one QA by measurement based and one process-oriented QA. The measurement QA is as commonly used

today and could be chosen as the only patient specific QA strategy. The process-oriented QA is only assessable if it is validated to ensure consistency of all the parameters essential to the IMRT delivery: MLC-position, gantry angle, dose output, data integrity, and dose calculation. The process-oriented path should only be used for patient groups where there is a well-established planning routine and sufficient experience from measurements. The most difficult step in the process-oriented strategy is to determine if an individual treatment plan should be measured or not. This assessment needs to be based on a quantitative metric that is related to the parameters that are optimised by the TPS. The machine constancy parameters should still be measured on a regular basis - more frequently if process-oriented QA is implemented.

The deliverability of treatment plans evaluated in Papers III-V was verified with a phantom measurement system called Delta 4 (Scandidos AB, Uppsala, Sweden). The Delta 4 phantom has two orthogonal diode-arrays, (p-type diodes), placed in a plexiglass cylinder. The resolution of the arrays is 5mm in the 6 X 6 cm central area and 10 mm in the rest of the area with a total measurement area of 20 X 20 cm. The treatment plan to be measured is recalculated on the phantom geometry and then compared to the measured dose to the phantom. The γ-analysis method was used as a quantitative measure of the difference between measured and calculated dose distribution (59, 60). The evaluation criteria were 3%3mm with a cut of at 15% of the maximum dose in addition profiles of the measured and calculated dose was compared visually.

To measure the effect of motion on a treatment plan, the Delta 4 phantom can be connected to a system generating movement in 6 directions called HexaMotion (ScandiDos). The HexaMotion can reproduce motion patterns defined by the user and was used for the verification measurements in Paper III.

5.3 Motion management

Tumour motion, if unaccounted for, can lead to insufficient dose coverage resulting in a worse outcome than expected. Usually, the tumour motion is has been managed by applying a margin e.g. the PTV margin (61). Sufficient margins can account for tumour motion in a static, homogeneous beam, resulting in a dose blurring in the edges of the target. For intensity modulated beams with an inhomogeneous beams profile, the margins may not be sufficient. The tumour motion can interact with the MLC shapes small islands of overdosage and underdosage can occur. This is called the interplay effect (62).

To account for interplay, information about the motion is needed. For periodic motion like breathing, the tumour position can be imaged in several phases. This is usually done with 4DCT. For a more random motion the tumour needs to be

monitored over a longer period usually with an inserted marker. It has been shown that the prostate moves in a random way (63, 64).

In Paper III, two different beam modalities were investigated to manage the prostate motion during hypofractionated radiotherapy. The new hypofractionation scheme reduces the total treatment time from 39 fractions to only 7 (65). However, because of the higher fraction dose, the beam-on time at each treatment is increased. Longer beam-on time increases the risk of prostate movement during the treatment (66). As described in Paper III, this problem is solved by using a flattening filter free (FFF) beam that decreases the beam-on time. The results were verified using a pre-treatment measurement under simulated motion. The plans generated using FFF beams were more robust to prostate motion, compared to beams with flattening filter (FF), and became the clinical standard for hypofractionated prostate treatment at Skåne University Hospital. The knowledge from Paper III will be used in future work to integrate motion management into automated treatment planning. The treatment plans and motion trajectories evaluated in Paper III were reused to generate Pareto fronts for comparison. Pareto fronts were generated for flattened and FFF beams for both Eclipse and RayStation (Figure 8). There was little or no separation between the four Pareto front indicating similar plan quality.

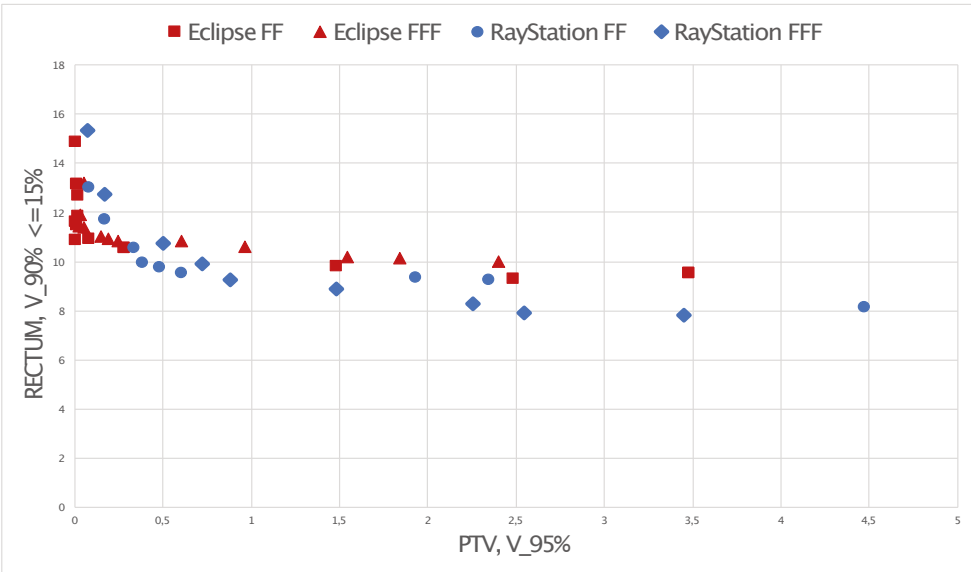

Figure 8.
Pareto fronts for a hypofractionated prostate cancer treatment generated with Eclipse (red) and RayStation (blue), using FF beams (rectangles) and FFF beams (triangles).

Three plans from each Pareto front, (level 1-3 in Figure 12), were then measured with the Delta 4 system, static and with simulated motion Figure 9. The results from the motion measurements confirm the conclusions in Paper III.

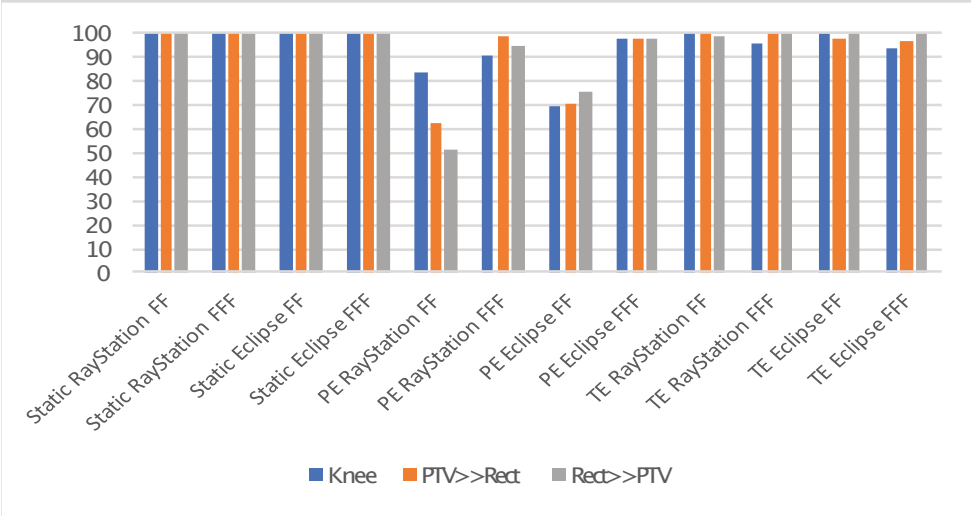

Figure 9.
Gamma pass rates from Delta4 measurements of VMAT plans generated in Eclipse and RayStation, using FF and FFF beams. Plans from three Pareto levels: static phantom and with two simulated motion patterns.

5.4 Multi-Modality

Many of the world's radiotherapy clinics have access to several treatment modalities. These modalities can be somewhat similar or completely different. Some modalities could have different treatment planning systems, others use only a different beam modality. It can be challenging to get the most out of unconventional, specialist machines if the plan comparisons are made on day by day, on-demand basis (Paper II). Other factors, such as hypofractionation can also result in the need to investigate alternative modalities to ensure the plan quality. Ideally treatment plans for every patient could be generated and compared for all available modalities - should be done automatically to work in a clinical routine.

In Paper II the plan quality of two different treatment machines/modalities was evaluated. Additionally, two different TPS are assessed to find the best possible backup plan for Tomotherapy. To ensure deliverability the plans were verified with a pre-treatment measurement. The fall-back planning system, SharePlan (Ray Search Laboratories, Stockholm Sweden) was found to generate treatment plans of adequate quality as backup for Tomotherapy treatments and was used routinely until discontinued.

6 Automated Treatment Planning

About ten years ago, the research on automated treatment planning started to escalate. The promise that IMRT planning would be more or less automatic was not fulfilled, and therefore there was still room for improvement in the automation. Some research groups tackled the problem by navigating the mathematical Pareto fronts during the optimisation process. The plans are evaluated in the optimal fluence step prior to MLC segmentation. The trade-offs can be reviewed, and the desired plan is then made into a deliverable treatment plan (67-69). This approach is implemented in the RayStation multi criteria optimisation module (53). The Pareto generation software used in Paper V, described in chapter 4.1, uses the same principial however not with strictly mathematically Pareto optimal solutions - deliverable plans, verified by measurement, are sorted to form pareto fronts.

Another approach of automation is based on clinical wish lists and multi-criteria optimisation including beam angles and profiles (70, 71). This approach is customisable for each clinic through local wish lists with clinical goals.

One commercially available automated planning tool works with achievable dose volume histograms (DVH). The idea behind this approach is to have a model based on previously delivered plans to predict the achievable DVH therefrom derive the objectives to use in the regular optimisation (44, 72, 73). Note that this approach is model based and not machine learning based.

6.1 AI and Machine Learning Approaches

In recent years, the development of artificial intelligence (AI) has taken huge steps forward. Machine learning (ML), a branch of AI, has promising potential for radiotherapy applications. Commercial vendors and academic research groups are working simultaneously on knowledge-based, machine learning based, automated treatment planning. Knowledge-based in this sense means that the AI searches for similar patients in a database and suggests the clinical plan for that patient. With this approach new patients are planned with the knowledge from previously treated patients. There are several publications on ML based dose predictions for IMRT and only a few for VMAT. Most publications evaluate the predicted dose without converting them into deliverable plans. McIntosh et al. were the first to generate

deliverable VMAT plans based on ML dose predictions using a dose mimicking approach, (similar to the system described in Paper II) (74).

In Paper IV 160 prostate patients were used as training data for a densely connected U-Net trained in 2.5D – three consecutive 2D CT images and their corresponding segmentation are combined into a so called triplet defining 2.5D – and a baseline model in 2D, using an encoder decoder U-Net architecture introduced by Ronneberger et al. (75). Dose predictions from both the 2.5D and 2D model were compared.

A nearest neighbour (NN) search was performed to find the closes match between the dose prediction and one of the clinical dose distributions from the training dataset. The DVH for the dose distribution from the NN patient was compared to the DVH of the predicted dose. The dose volume objectives, used to optimise the from the NN plans, were adjusted so each objective fit the best of the two DVHs, shown in Figure 11 (from Paper IV).

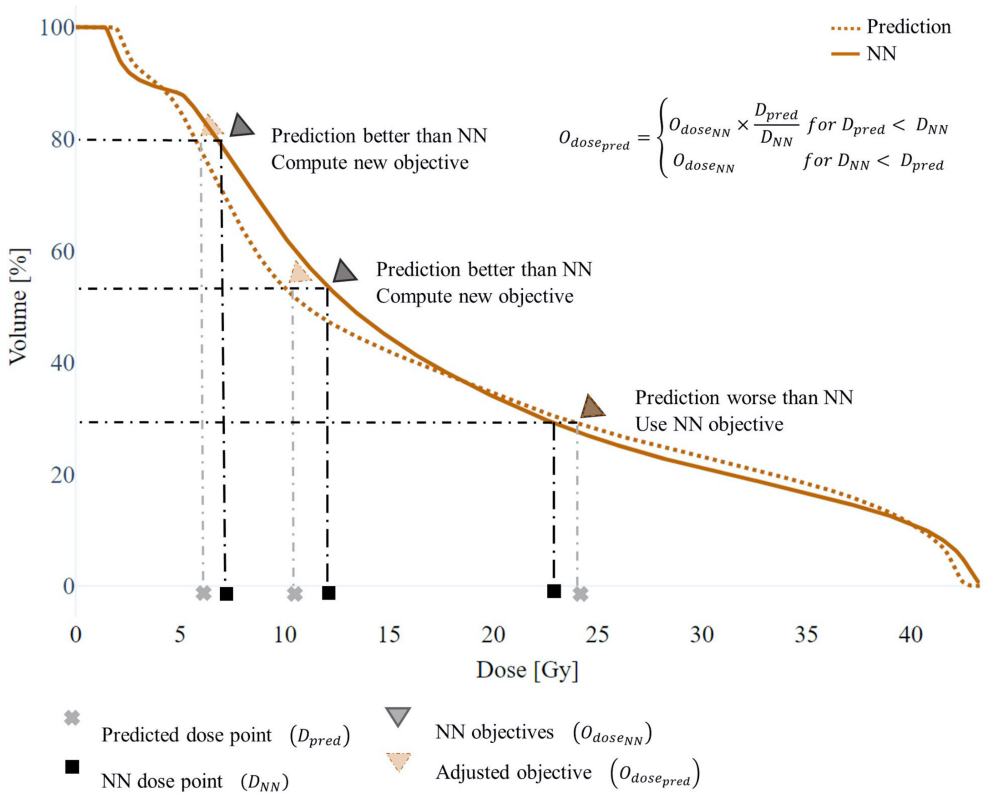

Figure 10. Objectives adjusted to fit the best DVH (figure from Paper IV).

The adjusted set of objectives are combined with the predicted dose and the VMAT segment from the NN plan. This merge is then run through the last step of the Eclipse optimiser to adjust the MLC segments to fit the dose prediction. The resulting deliverable plans were compared to the ground truth and were also measured with the Delta 4 system. The entire workflow can be seen in Figure 12 (from Paper IV).

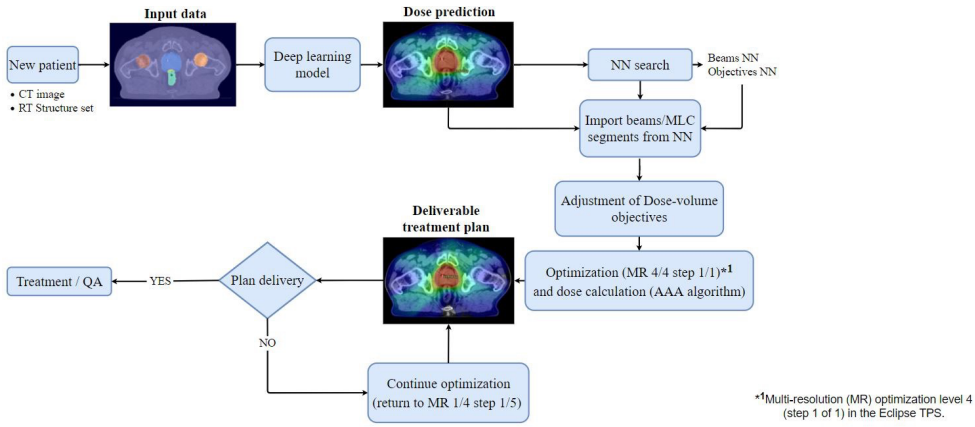

Figure 11. The suggested treatment planning workflow to transform a deep learning dose prediction into a deliverable treatment plan (figure from Paper IV).

In Paper V, Pareto front based automated treatment planning is used to explore the achievable rectum and femoral head doses during hypofractionated prostate cancer. The Pareto automated software (chapter 4.1) generated 800 treatment plans for each patient by systematically varying the objectives using the optimiser and dose calculation of a commercial TPS. This "swarm" of plans are then sorted so that only the ones that fulfil the clinical dose criteria and Pareto optimal ones are left. The clinical dose-volume criteria were evaluated for the CTV, PTV, rectum, femoral heads, and the body contour for four regions of the pareto front (Figure 13). The achieved dose-volume criteria were compared to manually generated treatment plans for the same patients.

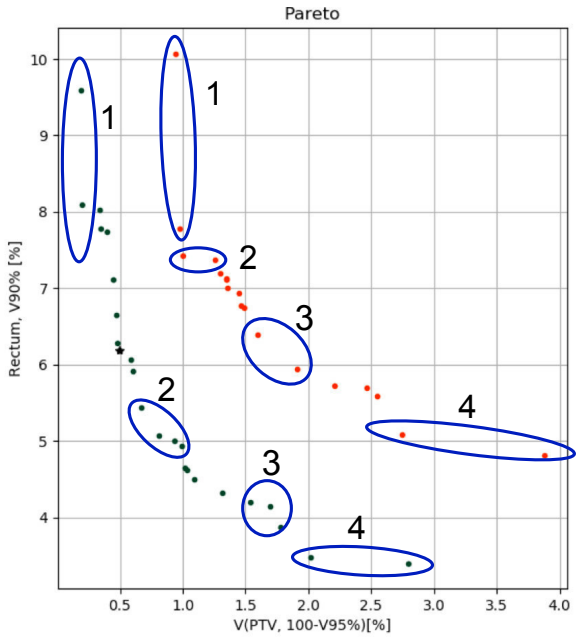

Figure 12. Pareto front from two different patients with the examples of the four Pareto levels circled. The four Pareto levels that were evaluated and compared to the manual plans in Paper V were: 1 (PTV>rectum), 2 (Knee), 3 (PTV<rectum), and 4 (PTV<<rectum). The circled areas are examples of the different Pareto levels' positions.

The Pareto plans were also used as training data for two different machine learning algorithms. One algorithm, a k-nearest neighbour algorithm (KNN) and a deep neural network-based autoencoder (DA). The KNN algorithm was trained with patient specific features derived from the delineated structures and the DA was trained on the CT images. For a new patient the ML, the two algorithms combined, searches for the closest matched patient in the database and suggests optimisation objectives to generate a Pareto front. Only the Pareto optimal objectives are proposed, not the hundreds of plans required to create the training data. With this method almost every possible solution is gone through, making it likely to find the optimal plan for the entire system. ML Pareto fronts generated for four test patients were compared to a Pareto front generated by the Pareto software. The significance of the difference between the Pareto fronts was evaluated with a 2D Kolmogorov-Smirnov test described by Peacock (76).

A potential correlation between achievable rectum PTV doses and the volume of the overlap between the PTV and the rectum was also investigated. The achievable rectum V90%, V75%, and V65% as a function of the overlapping volume was evaluated for the three first pareto levels. An F-test was used to test the significance of the slope of the linear regression model. A level of significance of $\alpha = 0.05$ was used. The overlap dependence of the V95% for PTV was likewise studied.

7 Evaluating treatment plan quality

The quality of a treatment plan can only be judged by how well it fulfils the prescription and, if available, OAR dose requirements. The plan should also be achievable considering the deliverability parameters described in chapter 5. There should be no additional dose calculation or plan conversion step required for the evaluated plans.

For a manual optimisation workflow, the first step in the assessment of the plan quality is done after the first round of optimisation (see Figure 1). In the optimisation module of a modern TPS, dose information is presented in several ways: a DVH and a visualisation of the dose distribution on a CT slice of the patient (typically displayed with a colour wash or with isodose lines). To navigate the 3D dose distribution, individual CT slices can be displayed in succession. The DVH also contains markers for the selected dose volume objectives giving the user feedback about how well they are set and if they are contributing to the optimisation or not.

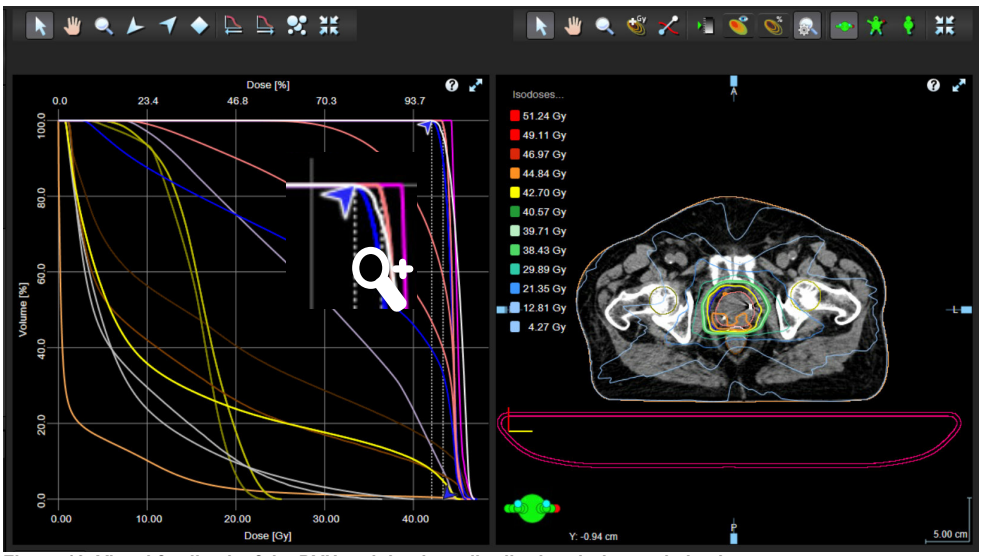

Figure 13. Visual feedback of the DVH and the dose distribution during optimisation.
To the left: DVH with dose volume objectives marked. The minimum dose objective for the PTV is fullfiled and no longer contributes to the optimisation. To the right: Dose distribution displayed as isodose lines on a CT slice of the patient.

The dose-volume objective for the PTV in Figure 14 is touching the DVH curve for the PTV. This indicates that the objective is completely (or almost completely) fulfilled, and therefore no longer contributing to the optimisation. This is also indicated by a very small objective value displayed by the TPS. To achieve better target coverage in this case, the planner needs to ask for higher dose. This assessment only gives information about how well the resulting plan of an optimisation fulfils the chosen optimisation objectives. An evaluation of how well the clinical dose-volume constraints are fulfilled is also needed. This can be done by evaluating each dose-volume constraint achievement manually from the DVH, or from the dose statistics list. In some TPS the clinical constraints can be defined and automatically evaluated, with a green light displayed in the user interface (UI) if fulfilled and a red light if not fulfilled. Because spatial information gets lost in a DVH representation of the dose it is essential to also evaluate the 3D dose distribution on the CT images (20).

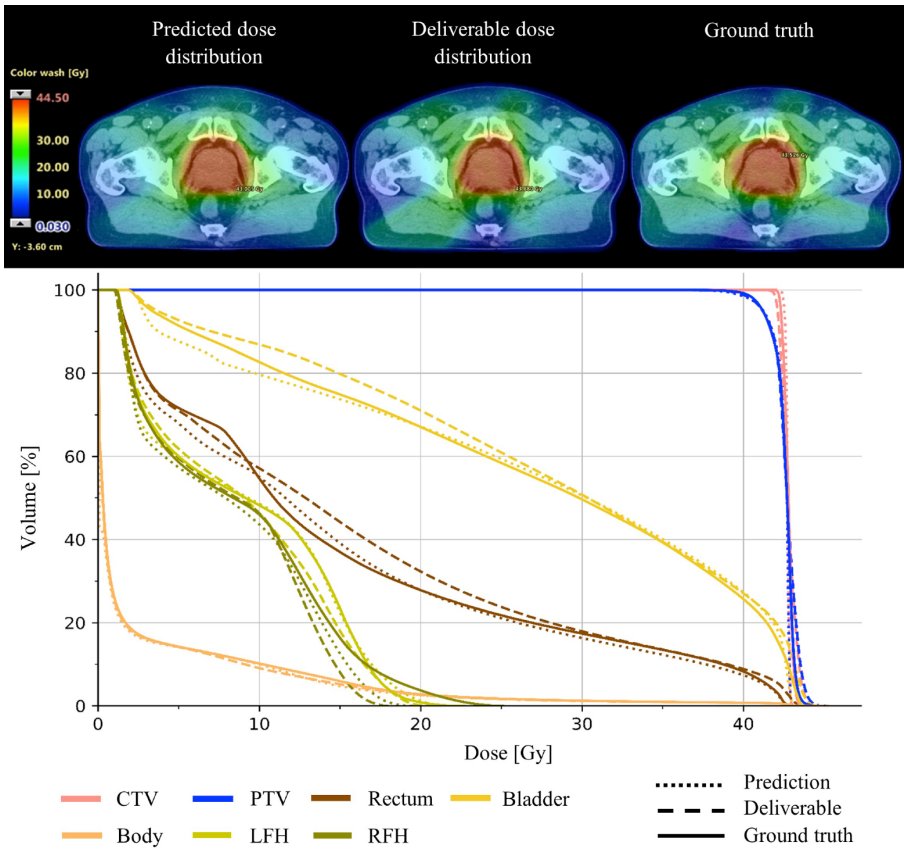

Figure 14. Traditional visualisation of a plan comprison.
Top panel: Side-by-side comparison of three different treatment plans for the same patient. Lower panel: DVH comparison of the three plans (figure from Paper IV).

To evaluate how changing a certain plan parameter affects the treatment plan quality a more systematic and unbiased assessment is required.

In Paper I, the Pareto optimisation method described in chapter 4 was used to compare the change in quality of head and neck cancer treatments plans when introducing a beam angle optimiser. Pareto fronts were generated for two different TPS, Varian Eclipse and Oncentra Master Plan (OMP) (Nucletron BV), with and without beam angle optimisation, totalling four fronts per patient. The two TPS use different approaches to optimise the beam angles. Eclipse used a two-step method, first selecting beam angles depending on the relative position of the targets and OAR, and then slightly adjusting the beam angles during the regular IMRT optimisation. OMP only performed the second step of beam angle optimisation. The trade-off used in the Pareto fronts was the one between underdosed PTV and the mean dose of one of the parotid glands. There was a clear separation between the beam angle optimised Pareto front and the equidistant control front for Eclipse but not for the OMP front. The conclusions were that beam angle optimisation might be better for Eclipse and the equivalent in OMP, however, beam angle optimisation resulted in more acceptable treatment plans for both systems. The differences of the Pareto fronts were not quantified.

In Paper II, the Pareto front was used to evaluate the performance of a commercial fall-back TPS for Tomotherapy treatments of head and neck, and prostate cancer. The plan quality of the fall-back plans was compared with the plan quality of the clinical TPS as well as the original Tomotherapy plans. The quality of the fall-back plans was found to be comparable to the plans from the clinical system.

All the plans in both Papers I and II were generated manually, making it tremendously time consuming. To make the Pareto method useful on a day-to-day basis, automatic plan generation is needed. The number of plans needed to represent a Pareto front was investigated by Craft and Bortfeld in 2008. They concluded that N+1 plans, where N is the number of objectives, is sufficient to form a Pareto front (67). Their conclusions considered fluence based treatment plans which indicates that the manual method using a commercial TPS, additional plans would be required for a sufficient representation.

In Paper V automated Pareto front generation was used, allowing a search for optimal plans in a wider range. The automation was thus used to achieve a better representation of the Pareto front instead of decreasing the required pan generation time. With a better representation of the Pareto front, the achievable quality of a treatment system (TPS and treatment machine combination) can be explored.

To be able to improve the overall plan quality of a particular system, the quality evaluation must be split into two categories:

- Required Plan Quality – the minimum quality to accept a plan for clinical treatment.
- Attainable Plan Quality – the quality possible to achieve with a given treatment system for a certain patient group (close to the physical limits of the system).

To assess if a plan has reached the required plan quality dose-volume statistics are compared to the clinical dose-volume constraints (mentioned in the introduction to this chapter). If any of the dose-volume constraints are easily achieved and the user doesn't continue the optimisation, the attainable plan quality will not be reached. This was most clearly demonstrated in Paper V for the femoral heads – the maximum dose to the femoral heads for the Pareto generated plans were significantly reduced compared to manually generated plans.

Current dose-volume constraints are derived from studies done decades ago, evaluating end points and the effect of the radiation as understood at the time (5, 77, 78). There is also a lack of data considering doses given with IMRT techniques or with unconventional fractionation, that are not in the single fraction dose range of 1.8-2Gy. Recently, studies investigating other, less severe endpoints and hypofractionation have been published (79-82). In order to improve plan quality, it is essential for radiotherapy clinics to continually update their local dose-volume constraints based on these kinds of studies.

To evaluate the attainable plan quality, a systematic approach is needed and should be done for each patient category and treatment system. In Paper V the attainable plan quality was explored for hypo-fractionated prostate cancer treatment with optimised doses calculated with RayStation for Varian TrueBeam linacs. It was shown that under the above circumstances there is room for improvement regarding the required plan quality, with the aim to get closer to the attainable plan quality.

The strive to close the gap between required and attainable plan quality can be helped even without automation available in clinical routine. In Paper V a significant overlap dependence was shown for the achievable rectum doses. If this dependence is known in advance by the planners, they can work towards this goal, thus creating plans which are closer to the attainable plan quality.

8 Discussion

Evaluating treatment plan quality is not a trivial task. There is always a compromise between at least two conflicting objectives, sometimes more. Systematically exploring and visualising this trade-off can help find the range of attainable plan qualities for a given system. A comparison of this range is more suitable than a plan-by-plan comparison when evaluating different TPS or optimisation strategies.

In Paper I and II, the Pareto front method first described by Ottosson et al. (50) was used to evaluate the performance of, respectively, I: beam angle optimisers in commercial TPSs, and II: the performance of a fall-back TPS. In these early studies, all the plans were generated manually. As a result, both the optimisation and dose calculations took longer time than would be the case today. For these reasons, the Pareto fronts presented in these papers might not be as close to the attainable quality than if they were created automatically as in Paper V. The main conclusions are still as valid but less relevant now because VMAT is replacing IMRT.

No measure or statistical test was used to quantify the separation between Pareto fronts, which might have changed the conclusion about the beam angle optimiser in Eclipse in Paper I. In Paper II, the conclusion was that the fall-back planning system generates plans comparable to plans developed by the clinical system. This conclusion would probably be confirmed with a statistical test. However, despite the limitations discussed, the Pareto front method was less user-biased than a plan-by-plan comparison. For example, suppose two treatment plans from two different Pareto levels, in Figure 12, are compared. In that case, the difference is because of optimisation priorities and not because of a difference between the compared treatment planning systems.

In Paper III, the plan quality of VMAT plans with FF beams and FFF beams were compared by evaluating their dose-volume statistics. There was no clinically significant difference in plan quality between FF and FFF plans. Pareto fronts based on the treatment plans from Paper III were generated and compared in a smaller study, Figure 9. The Pareto fronts visually confirmed the comparable plan quality found in Paper III, however, no direct quantitative measure was used.

As described in this work, Pareto fronts can be used for example in implementation or benchmarking of new techniques. However, automation is required for this to be of practical use considering a typical clinical workflow.

In Paper V, an automated Pareto front generation software was developed. The automation allowed for an extensive scale search for achievable Pareto optimal treatment plans. About 2% of the 800 generated plans were on the pareto front. The low yield of pareto optimal plans indicates that a manual approach is unlikely to find the true Pareto front. In Paper V an ML approach was described to recreate the Pareto fronts. The ML model successfully generated Pareto fronts for four test patients. It should be noted again that the Pareto optimality evaluated in this manner might not be Pareto optimal in the mathematical sense. However, all the presented plans were instead *deliverable* in the sense that they had dose calculated for realistic, dynamic MLC control points (because a validated clinical TPS vas used for optimisation). To evaluate deliverable plans is desirable and also recommended by an international review on plan quality by Hernandez et al. (83).

The evaluation of dose-volume criteria of Pareto optimal plans, compared to manually generated plans, showed a statistically significant reduction in rectum doses without a significant loss of PTV dose coverage. There was also a significant decrease of the maximum dose to the femoral heads for the automated plans. The study was set up to include only plans that fulfil all the dose-volume constraints, meaning that all plans fulfilled the required plan quality (chapter 7). The automated Pareto plans demonstrated that the attainable plan quality was not reached, most clearly for the femoral head doses. To avoid an ambiguous approach based on personal preference, stricter dose-volume constraints, with clear priorities (20, 83) could drive the manual planning towards the attainable plan quality. There is a need for continuous improvement of both dose-volume constraints and in treatment planner skills (84).

There is a large number of publications demonstrating the potential of artificial intelligence and machine learning to improve plan quality, but only a few specifically considering VMAT, e.g. (74, 85-88). Transforming the ML predicted dose into deliverable plans is even more uncommon (86).

In Paper IV a deep learning model was developed to predict VMAT dose distributions for hypofractionated prostate treatments. A novel planning workflow was used to transform the predicted dose into a deliverable treatment plan. The model training was done with patients previously treated between 2018 and 2019. By restricting the inclusion to more recent years, the trained model performed better predictions. This illustrates a potential problem with including too many patients in a training dataset – treatment plans from several years ago are most likely of inferior quality compared with today's standards. It is also remarkable that so few have evaluated deliverable ML based treatment plans. There is a resemblance to the fluence based vs segmented IMRT plan evaluations discussion from a decade ago.

8.1 Conclusions

The Pareto front method was successfully used to compare and evaluate different treatment planning systems and optimisation strategies by assessing the target vs OAR trade-off. However, with the lack of automation, the technique is impractical (c.f. Paper I-II).

The physical and mechanical limitations of conventional photon radiation therapy machines regarding plan quality are about to be reached. This, however, does not mean that this limit can always be "found" with the current planning systems or strategies. Artificial intelligence brings promising results in the strive for better plan quality, however sometimes overlooking the physical limitations of the treatment machines, ML dose predictions can and should be converted into deliverable treatment plans. Automation of the Pareto front method helps find the limits, Attainable Plan Quality, for a specific system (c.f. Paper IV-V).

Evaluating treatment plan quality is not a trivial task and will always be subject to bias and personal preference. However, by knowing the limits of a treatment system, the Attainable Plan Quality and modelling of correlations between patient characteristics, e.g. rectum PTV overlap, can map out the achievable quality for each patient. (c.f. Paper V).

Deliverability for moving targets can be improved by choosing and evaluating different beam modalities, for example, FF vs. FFF beams for moving targets (c.f. Paper III). Even if a shorter beam on time may not shorten the treatment time slot, it should be considered as an easily attainable method to improve deliverability.

If all the information mentioned above is available at treatment planning, the answerers to the question in the introduction could be:

– *"Is this treatment plan as good as it can get?"*– "For the current trade-off situation, yes! *You can navigate the Pareto plans to see."*

–*" Can the risk organ doses be pushed down a bit more?" – "Yes, but then the target dose will decrease by this amount."*

8.2 Future perspectives

Ongoing work with the Pareto software involves integrating the movement patterns used in Paper III to directly account for motion in the initial plan generation. The software is also updated to include the Eclipse optimiser in the workflow. The aim is to use Pareto optimal plans generated with the Pareto software as training data for the ML model in Paper IV, considering motion and deliverability (possibly plan complexity).

The Pareto software has only been tested for prostate cancer. The plan generation can be set up or other treatment sites. The number of plans needed increases for every trade-off included. For head-and-neck cancer, with many organs close to the target, several thousand plans are required. It would be helpful information.

The correlation between rectum overlap and achievable dose could be used to assess which patients require prostate rectal spacers to reach the required plan quality. This feature, linear regression models, could be used as information in ML training. Other patient-specific features cloud also be investigated for correlation with organ doses.

It would be valuable to verify the trained ML models in a multi-institutional study. For example, several models could be trained for each clinic with their own treatment plans, one trained with all the plans, and one trained with automatically generated Pareto optimal plans. The Pareto optimal Plans should be roughly the same for clinics with the same treatment setup. Such study could clarify the importance of training data for ML models predicting dose distributions, particularly if predictions are made deliverable, which they should.

All work presented in this thesis was done on photon radiotherapy, mainly delivered with c-arm linacs. However, to further explore the attainable plan quality, the concept should be widened to assess the limits of all available treatment machines and modalities.

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Publications