

Faculté des sciences

In silico evaluation of the clinical value of arc proton therapy for brain tumors

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Abstract

Since the beginning of radiotherapy, many improvements were made in order to achieve the perpetual objective of the dose sculpting, for a higher success of treatment with less side effects. As Volumetric Modulated Arc Therapy (VMAT) has improved the clinical potential of photons, the idea of also using an arc with protons in order to improve the quality of the treatments comes naturally and gives birth to Arc Proton Therapy.

The idea is great but before thinking about an implementation in the clinical environment, there is an obligation to see if first, it is possible to achieve and then, if it brings any advantages in order to invest in this technology. This thesis is focused on this second point and aims to show the benefits and limitations of arc proton therapy in the case of a brain tumor by making a comparison with modalities already performed in hospital as VMAT and Intensity-Modulated Proton Therapy (IMPT). This evaluation became possible with the arrival of a new algorithm allowing us to simulate an arc with protons which can be robustly optimized in a treatment planning system, in order to resist to the different uncertainties occurring in radiotherapy. This study consists of the analysis of the dosimetric and robustness metrics, as well as the possibility to reduce the time needed to deliver a fraction of the treatment.

Overall, ArcPT reveals a great potential in the coverage of the target volume and the sparing of the organs at risk, even while some scenarios of errors take place. It also shows that ArcPT could decrease the beam delivery time in comparison to IMPT with some improvements in the delivery technology. Even though, these results are in agreement with the literature already existing in other situations, a lack of patients and the heuristic point of view of the method imply some limitations in this study and more data will be required in order to conclude about the advantages and drawbacks of ArcPT.

Acknowledgments

This thesis is the conclusion of many months of work and now, with a look back on everything that has been done, I realize how much the help of many people is needed to be able to accomplish such a thing.

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Abbreviations

Abbreviations	Definitions
ArcPT	Arc Proton Therapy
BDT	Beam Delivery Time
CI	Conformity Index
CN	Conformity Number
CT	Computed Tomography
CTV	Clinical Target Volume
D	Dose
DNA	Deoxyribonucleic Acid
DVH	Dose Volume Histogram
ELST	Energy Layer Switch Time
EUD	Equivalent Uniform Dose
GTV	Gross Tumor Volume
H&N	Head and Neck
HI	Homogeneity Index
HU	Hounsfield Unit
IMPT	Intensity-Modulated Proton Therapy
IMRT	Intensity-Modulated Radiation Therapy
IQR	Interquartile Range
ITV	Internal Target Volume
LET	Linear Energy Transfer
LQED	Linear Quadratic Equivalent Dose

Abbreviations	Definitions
LKB	Lyman-Kutcher-Birman
LON	Left Optic Nerve
MC	Monte Carlo
MRI	Magnetic Resonance Imaging
MU	Monitor Unit
N/A	Not Available
NKO	Niemierko
NTCP	Normal Tissue Complication Probability
NSCLC	Non-Small Cell Lung Cancer
OAR	Organ at Risk
PBT	Proton Beam Therapy
PET	Positron Emission Tomography
PTV	Planning Target Volume
RBE	Relative Biological Effectiveness
ROI	Region of Interest
RON	Right Optic Nerve
SBRT	Stereotactic Body Radiation Therapy
SFUD	Single Field Uniform Dose
SOBP	Spread Out Bragg Peak
SPArc	Spot-Scanning Proton Arc
SPR	Stopping Power Ratio
TCP	Tumor Control Probability
TPS	Treatment Planning System
VMAT	Volumetric Modulated Arc Therapy

Contents

1	Introduction	1
1.1	Objectives	2
1.2	Structure	2
2	Context	3
2.1	Photons and Protons	3
2.2	Brain anatomy	4
2.2.1	Radiation effects	5
2.3	Radiotherapy workflow	6
2.3.1	Imaging	6
2.3.2	Contouring and prescription	7
2.3.3	Treatment optimization and verification	8
2.3.4	Delivery system	10
2.3.5	Follow-up	13
2.4	Tumor Control and Normal Tissue Complication	13
3	State of the art	14
3.1	Arc proton therapy algorithm	14
3.1.1	Initial algorithm	14
3.1.2	Upgrade version	16
3.2	First prototype	17
3.3	Literature review on ArcPT results	17
3.3.1	Extra-cranial	17
3.3.2	Cranial	19
3.3.3	Summary Table	20
3.4	Uncertainty budget in proton therapy	21
4	Materials and methods	23
4.1	Definitions	23
4.1.1	Dose	23
4.1.2	Linear energy transfer	23
4.1.3	Relative Biological Effectiveness	24
4.1.4	Homogeneity Index	25
4.1.5	Conformity Index and Number	25
4.1.6	TCP and NTCP	25

4.1.7	Beam delivery time	27
4.2	Methodology	27
4.2.1	Heuristic point of view	29
5	Results and discussion	34
5.1	Visualization	34
5.2	Dosimetric outcome	36
5.2.1	CTV	36
5.2.2	OARs	36
5.2.3	Brain and Body	37
5.3	Worst case scenario	38
5.4	Linear Energy Transfer	39
5.5	TCP and NTCP	39
5.5.1	TCP	40
5.5.2	NTCP Brain Stem	41
5.5.3	NTCP Optic chiasm	42
5.6	Homogeneity Index	43
5.7	Conformity index	44
5.8	Beam delivery time	45
6	Discussion	46
6.1	Limitations	47
6.2	Improvements	47
7	Conclusion	49

Chapter 1

Introduction

Over the years, cancer has become one of the main medical concern in the world so that, more than 19 millions persons were diagnosed with cancer in 2020 and nearly half of this number has passed away because of it [1]. However, the five-year survival rate is getting better in most of cancers thanks to progress in medicine [2]. This progress is coming from earlier diagnoses and also better treatments.

This work is focused on the treatment part, especially on external therapy. There was already a lot of improvements since the beginning of radiotherapy. The progress has always followed the desire of a better sculpting of the dose to the tumor with sparing the surrounding healthy tissues. The dose quantifies the energy deposited per unit of mass by ionizing radiation (more precision in section 4.1.1). This improvement was made using different types of radiation, different numbers of beams and different ways of modulating the dose, among others. Photons were the first particles used in radiation therapy, and the dose was initially shaped along the 2D projection of the target volume. Later, in order to improve the treatment, methods such as Intensity-Modulated Radiation Therapy (IMRT) were implemented. In that case, although the dose delivered by each beam is not homogeneous, the overall 3D dose distribution features improve target dose conformity and homogeneity. Finally, Volumetric Modulated Arc Therapy (VMAT) is an upgrade of the IMRT where the gantry is rotating around the patient while the dose is delivered, allowing again a better coverage of the tumor.

On the other hand, there is also a progress made by using particles such as protons or carbon ions. They have the advantage, in comparison with photons, to loose most of their energy at the end of the particle track within a region called the Bragg peak. With pencil beam scanning technique, this is leading to Intensity Modulated Proton Therapy, the equivalent of IMRT for protons.

As VMAT has become the new way of doing radiotherapy, it seems that an equivalent way arises naturally for proton therapy. Here comes the idea of proton arc therapy where the beam is delivering the dose to the patient while the gantry is rotating. It aims at the perpetual goal of a better target coverage and the sparing of the healthy tissues.

1.1 Objectives

The objective of this work is to study the clinical potential of the arc proton therapy in the case of a brain tumor by comparing it with already used techniques in clinical environment (VMAT and IMPT). Criteria such as the coverage of the target, the sparing of the organs, the beam delivery time, the robustness of the plan are evaluated. The ArcPT plans are optimized with the algorithm proposed by G. Liu et al. [3] adapted to RayStation, a treatment planning system. More details will come in chapter 3.

1.2 Structure

This thesis starts with an introduction of the clinical context from a medical physics perspective. This section presents a brief anatomical aspect of the problem, some information about brain anatomy, the characteristics of photons and protons, radiation side effects. Then, a summary of the external therapy workflow will be discussed including the delivery systems that will be compared. Moreover, a context section will explain briefly the deal of radiotherapy.

The third chapter consists in an abstract of the arc proton therapy algorithm implemented and the first prototype developed. Then, a literature survey focused on ArcPT will complete this section.

Chapter 4 introduces the materials and methods used in order to evaluate the benefits and drawbacks of arc proton therapy in comparison with the other delivery systems.

Chapter 5 presents the different results obtained from the simulations of the ArcPT, IMPT and VMAT treatment plans with the metrics introduced in the chapter 4.

Chapter 6 discusses the results obtained in comparison with the literature, as well as the limitations of the study and the heuristic approach of the problem, before giving perspectives of improvements.

The last chapter will resume briefly the different sections of this thesis before finally concluding this work.

Chapter 2

Context

This chapter introduces several key concepts that have been used during the project, including a short comparison between photons and protons, a brief description of brain anatomy, the definition of target volumes, the radiotherapy workflow and the different techniques of therapy that will be compared.

2.1 Photons and Protons

While VMAT is a modality using photons, new delivery systems as IMPT and maybe in the future, ArcPT, use protons. Here is a brief comparison between these particles in order to highlight their differences in radiotherapy.

As the figure 2.1 shows it, there is a huge difference between the depth dose curve of these two ionizing radiations. The proton curve has the advantage to be sharper in depth and with the presence of what is called the Bragg peak. There is less dose deposited along the path and nearly no dose behind the Bragg peak. This is explained by the fact that the energy loss by protons is provided by the stopping power (S) or mass stopping power ($\frac{S}{\rho}$) equations (2.1) where dE is the loss of energy per unit length ds and ρ is the medium density. The stopping power decreases as the square of speed at energies in proton therapy (see the right side of figure 2.1).

$$\frac{S}{\rho} = -\frac{1}{\rho} \frac{dE}{ds} \quad (\text{in } MeVcm^2g^{-1}) \quad (2.1)$$

In other terms, the more a proton slows down, the more it loses energy and slows down quickly, explaining the sharpness of the peak. While, in case of photons, the particles does not slow down but the beam is attenuated, and this is why the dose curve is decreasing slowly with depth. On the left figure, the Spread out Bragg Peak (SOBP) is also visible, which is a combination of different proton beams with different energies and weightings in order to create this flat dose, necessary for the tumor coverage.

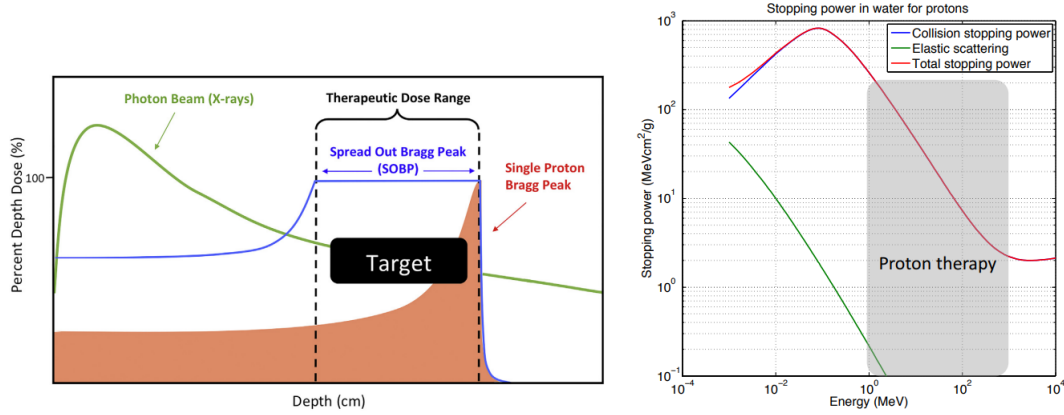


Figure 2.1: Left : Graph of the Percent Depth dose in terms of the depth for photons and protons [4]. Right : Curve of the stopping power in terms of the energy for protons highlighted at the energies of proton therapy.

But, this advantage is also one of the drawback of proton modalities, if there is any uncertainties occurring, the Bragg peak could be located outside of the target volume and likewise for most of the dose. While in the case of photons, even with a shift of the position, a part of the dose will remain in the target. This effect implies that the use of protons in external therapy is more sensitive to position uncertainties than photons and it reminds us the importance of precision in radiotherapy.

2.2 Brain anatomy

As this work is focused on brain tumors, a short introduction to the anatomy is given. A transverse cut of the brain [5] is presented in the figure 2.2 in comparison to the CT-scan of one of our patients. The target volume, the brain stem and the visual system are highlighted. One of the main concerns in radiotherapy will be the sparing of organs, that we call organs at risk (OARs), close to the tumor. They will inevitably receive a dose amount during the therapy process. In our case, the brain stem, the optic nerves, as well as the optic chiasm are the organs that need to be the center of attention.

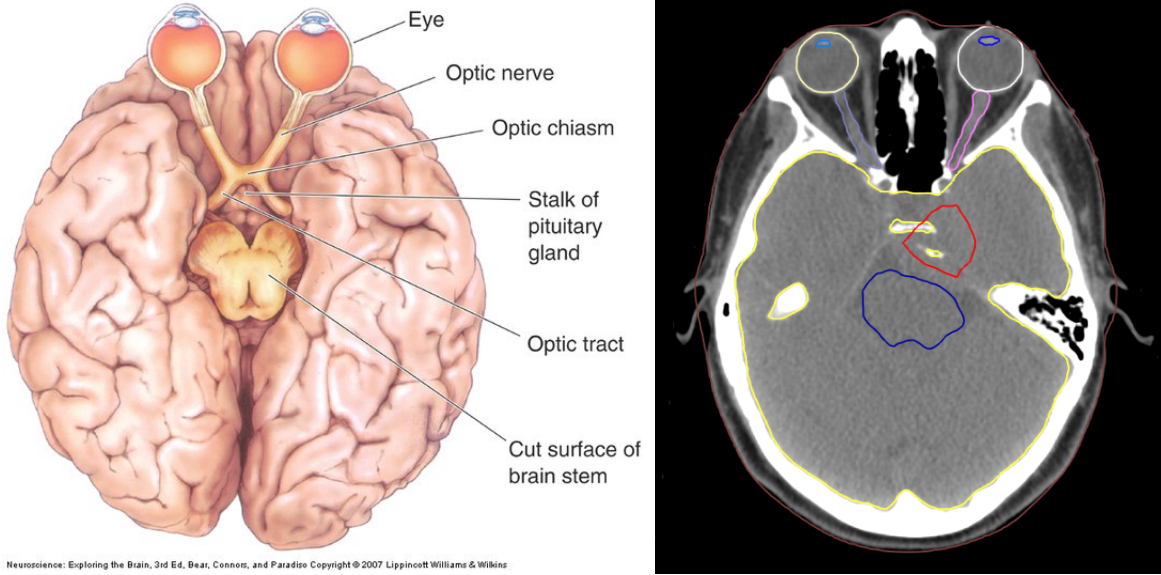


Figure 2.2: Left: Brain anatomy - Transverse cut [5]. Right: CT scan of a patient with the delineation of the ROIs. The brain stem is represented in dark blue, the optic nerves in pink and blue, the brain in yellow, the eyes in white, and finally the target volume in red.

It is also interesting to approach the notion of serial and parallel organs. For serial organs (like the spinal canal), if serious damages happen somewhere in the organ, the whole organ starts to malfunction. Conversely, parallel organs (like liver or lungs) can still ensure their functions even if they are, in part, damaged. This distinction will impact how secondary effects happen after a treatment and will define the clinical goals that have to be fulfilled in radiotherapy. In this work, for serial organs like in the visual system, the objectives are focused on the maximum dose in the volume (D_{max}) or near max dose. For organs in parallel, the focus can be on the percentage X of the volume that receives a certain level of dose ($V_{X\%}$) or the mean dose (D_{mean}) [6].

2.2.1 Radiation effects

It is interesting to see what are the effects of radiation and which level of dose can bring them. The radiation effects can be categorized in 2 parts, deterministic effects which occur generally in a short amount of time with a threshold dose, and stochastic effects with no threshold which mainly concern carcinogenesis and genetic mutations. In this work, we focus on the deterministic effects that can happen in the OARs in a first place, and then on the overall exposition in the body to reduce late effects. According to G. Noël et al [6], there is for example a 50 % risk of blindness after 5 years for a 65 Gy dose in the optical nerves, a 50 % risk of cataract after 5 years for 20 Gy in the lenses or a 5 % risk of complication after 5 years if more than 33 % of the brain volume receives 60 Gy. Considering the quantity of dose involved in external therapy, the secondary effects have to be considered seriously.

2.3 Radiotherapy workflow

The radiotherapy workflow is all the processes, one after the other, that lead to the delivery of the treatment, starting from the imaging of the patient. As mentioned before, the final objective is to eliminate the tumor and to spare the healthy organs, so the different steps in the workflow have to be very precise and accurate in order to avoid as much as possible uncertainties in the treatment delivery which could lead to a failure in the tumor eradication or too much dose in some organs. The figure 2.3 summarizes the workflow process in radiotherapy.

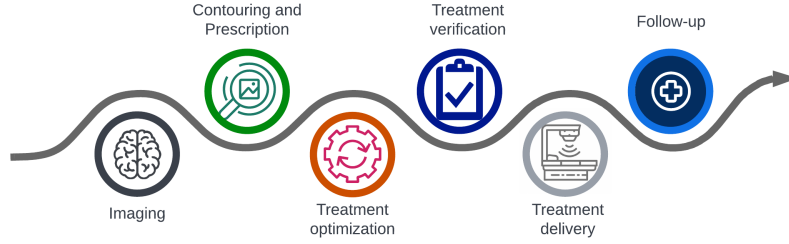


Figure 2.3: Diagram of the radiotherapy workflow.

2.3.1 Imaging

The first step is to get the cartography of the patient's anatomy to have the best description possible of the problem. The main imaging system used in radiotherapy is the CT-scan, which consists of a X-ray tube rotating around the patient, the X-rays are attenuated while crossing the body of the patient, that attenuation can be measured and enables to compute a scan of the anatomy. To gather as much information as possible, the CT-scan can be combined to other imaging systems as positron emission tomography (known as PET scan) or MRI. The CT image is a map of the photon attenuation coefficient in the tissues, it requires a calibration due to the different energies used in imagery and therapy, in order to be used in conventional radiotherapy for the calculation of the dose distribution. The value of a voxel in a CT is given by the Hounsfield Unit (HU) which is linked to the attenuation coefficient by the relation 2.2 :

$$HU = 1000 \times \frac{\mu_X - \mu_W}{\mu_W} \quad (2.2)$$

Where μ_X and μ_W are respectively the attenuation coefficient of the tissue in the voxel and in water. Meanwhile in the case of proton therapy, the stopping power ratio (SPR) has to be estimated from the CT by doing a calibration of the HU to the SPR conversion.

2.3.2 Contouring and prescription

Once the image of the patient is completed, the oncologist will make the delineation of the tumor, called the Gross tumor volume (GTV). He will also follow the guidelines to extend the GTV to the clinical target volume (CTV) to take into account the spread of cancerous cells outside the GTV. He will contour the OARs and finally choose a prescription dose for the target volume allowing to control the tumor and set the maximum dose in the organs in order to avoid as much as possible secondary effects. As the anatomy of every patients are similar, typical guidelines will help in this process. Let's define the target volumes that are going to be encountered in radiotherapy for a brain tumor. The figure 2.4 is a geometrical visualization of these volumes.

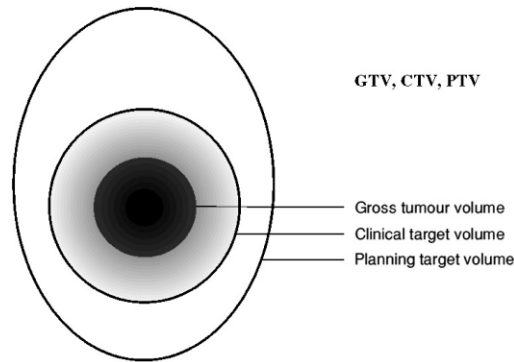


Figure 2.4: visualization of the GTV, CTV and PTV (from [7]).

1. Gross Tumor Volume (GTV) : This is the macroscopic or visible volume of the tumor, delimited by the oncologist based on the CT-scan. The help of other imaging modalities such as MRI or PET-scan allows a better definition of this volume. This is the first target volume, it may not be useful in this work but it helps to define the next target volume.
2. Clinical Target Volume (CTV) : This second volume contains the GTV, extended with a margin that will consider the potential spread of the tumor at a microscopic level, so unseen with an imaging modality. This is the volume that has to be treated correctly in order to cure the patient. Since the spread is not visible with the imaging, the margins are based on previous studies for a given type of cancer and stated in the guidelines. The size of these margins are determined with the probability of tumor cells spreading. Note that there are anatomical barriers in the body through which tumor cells do not pass and so, it can reduce the margins. It is also possible to consider the variations of the position, shape or size of the CTV due to anatomical motions (breathing for example) with an extended volume called Internal Target Volume (ITV).
3. Planning Target Volume (PTV) : In order to take into account the different uncertainties that can happen in radiotherapy (e.g., delineation errors, setup errors or patient movements), the PTV has been created. The PTV is a volume that can be calculated from the CTV to ensure that the CTV receives the dose prescription properly

even though some errors are occurring (separated in two parts, random and systematic errors).

In this thesis, the PTV will not be used as Intensity-modulated proton therapy (IMPT) and therefore ArcPT are very sensitive to uncertainties, because of the characteristics of protons. There is a more effective way to deal with this problem [8], by replacing the geometrical concept of PTV by a method called robust optimization that is going to optimize the treatment in a way that it is already taking into account the set up errors, the range uncertainty and the organs motion (this one does not occur in a brain tumor). This method will be discussed in the optimization section.

2.3.3 Treatment optimization and verification

This part of the workflow is handled by the medical physicists and dosimetrists who create the treatment plan by initially adjusting different variables of the machine such as the number of beams, their positions and directions, by adding a range shifter, for protons, if the depth is too low. The treatment planning is an iterative process where the planner has to adjust the optimization objectives on the Treatment Planning System (TPS) until the optimizer finds a clinically acceptable solution.

When a plan has been robustly optimized, a robust evaluation is done in order to verify the clinical goals while simulating the uncertainties. At this point, the plan consists of the machine parameters and the dose distribution that is supposed to be delivered by the machine, with these parameters. Afterwards, the plan has to be validated before applying it in order to verify if the dose delivered is matching with the simulation and then, check if the plan is achievable by the machine.

Robust optimization

A method used for a robust optimization is the one proposed by the treatment planning system RayStation from RaySearch Laboratories. The TPS simulates the uncertainties and tries to create a plan that can resist to them by using a method called *minimax* optimization [9]. This method computes the worst case scenario of each functions (associated to an objective) that is wanted to be robust. The worst case scenario is the set of errors with which the function gives back the highest value, for several functions. Their worst scenarios are summed together, multiplied by a chosen weight for each function. Finally, the optimization tries to minimize this sum, this can be represented as the following equation :

$$\min_{x \in X} \max_{s \in S} \sum_{i=1}^n w_i f_i(d(x; s)) \quad (2.3)$$

Where w_i are the importance weights, f_i are the optimization functions which depends of the dose distribution $d(x; s)$ (e.g., a certain volume of the ROI should not receive more than a certain dose amount), X is the set of all feasible variables (e.g., spot weights in case of proton therapy) and S is the set of scenarios. The set up uncertainties are seen as a shift of the isocenter on the planning CT, and the range uncertainties as a percentage, the RayStation tool is set out as the following figure 2.5 :

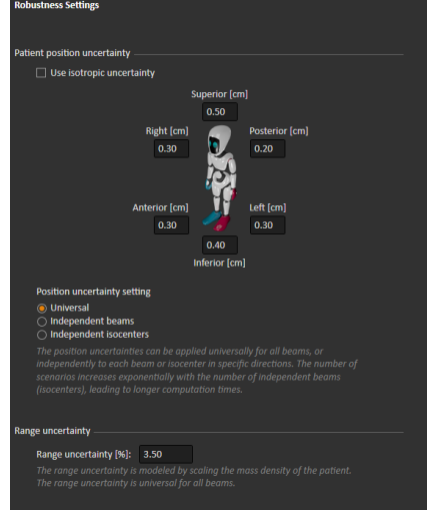


Figure 2.5: Errors settings menu in the RayStation (from [9]).

Dose calculation algorithm

During the treatment planification, the dose has to be calculated in the tissues in order to be able to optimize the plan and to verify it. The types of calculation algorithm that will be discussed in this work are the pencil beam algorithm and the Monte Carlo (MC) algorithm, since these two appear in the process at some point. The main algorithm that is going to be used for this study is the MC Algorithm, it is a mathematical method using random number generator to simulate the generation, transport and interaction of the particles in the patient geometry. This algorithm is a more precise method to predict the dose delivered to the patient but slower because a large number of event N is needed to avoid too much statistic noise ($\sigma = 1/\sqrt{N}$). A visualization is given on the right side of the figure 2.6 where the tracks of the particles simulated are visible.

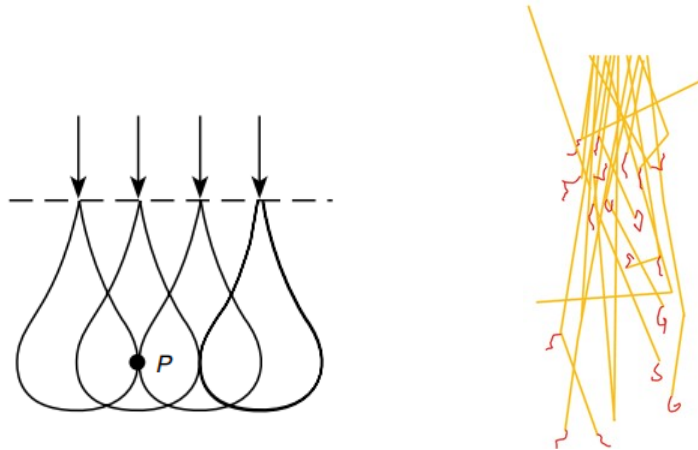


Figure 2.6: Left : visualization of the pencil beam method where the proton fluence is divided in many pencil beam kernels. Right: visualization of the Monte Carlo method where the path of each particle is simulated.

The paths of the particles are reduced in a number of steps, where the particles have a probability to interact, the main interactions for protons are the inelastic collisions with atomic electrons, elastic scattering and inelastic nuclear interactions. The initial position of the particle is sampled because the beam is not a perfect single point and the energy is a distribution sampling around the mean energy value.

The Pencil beam algorithm available in the RayStation TPS consists of a method where the proton fluence is decomposed in multiple pencil beams [10], each of them is associated to the dose distribution around it, calculated with analytical equations. Then, they are all superposed to compute the total dose distribution. A visualization is represented on left side of the figure 2.6. The multiple coulomb scattering is considered as a modulation by a Gaussian with standard deviations depending of the depth, to represent the inhomogeneities along the beam axis. This algorithm can show very similar results to Monte Carlo simulations in case of an homogeneous phantom but the accuracy quickly fades for more complex geometries [11] (especially with lateral inhomogeneities) as the area around the eyes in the case of this work. Therefore, it will be used only in specific situations. The figure 2.7 shows a graph from B. Bednarz et al. [12] that highlights the difference in the Spread Out Bragg Peak when both algorithms are dealing with inhomogeneities.

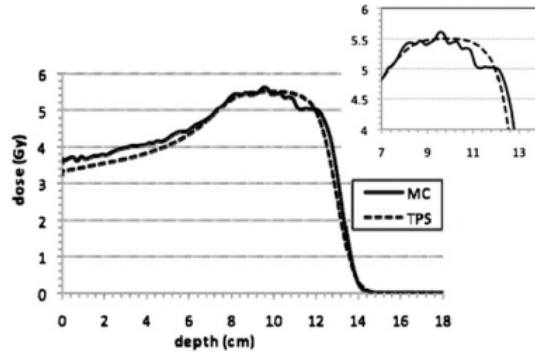


Figure 2.7: Difference in the SOBP simulated in an heterogeneous material with a MC algorithm and a pencil beam algorithm (from [12]).

2.3.4 Delivery system

Once the treatment is planned and verified, it has to be delivered to the patient, in a number of fractions depending of the initial prescription. Accuracy is needed in the positioning of the patient in order to reduce as much as possible the errors. For that purpose, an onboard cone beam CT-scan is performed and the patient position is adjusted if necessary. These scans, although having a lower quality than CT-scan, also allow to follow the evolution of the treatment, the reduction of the tumor volume or organs displacement in the body. As this thesis is dedicated to the comparison between three delivery modalities (VMAT, IMPT and ArcPT), it seems appropriate to give some details about these systems.

VMAT

Volumetric Modulated Arc Therapy uses X-rays created by the collision of electrons, generated in a linear particle accelerator (Linac), with a target (generally tungsten). The dose is delivered during one or multiple arcs that can rotate at 360° around the patient. The use of multileaf collimators and intensity modulated beams allows to reach dose conformity to the target volume and OARs sparing. Modulated intensity consists to separate the field in little elements called beamlets associated to a certain weight which can be achieved by beam attenuators, dose-rate adaptation, multileaf collimators (visualization on the right side in figure 2.8) or beam scanning [13]. The figure 2.8 is a schematic representation of the modulated intensity applied to a target volume.

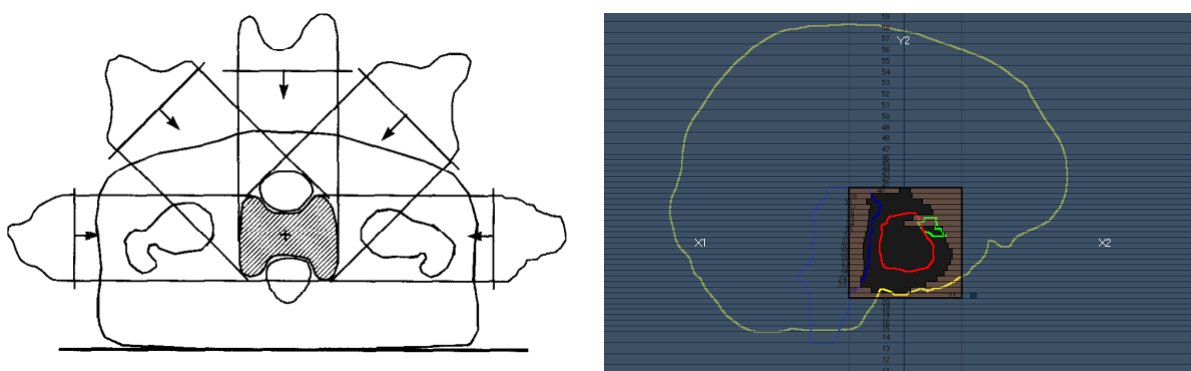


Figure 2.8: Left : Schematic representation of modulated intensity (from [13]). Right: visualization of the multileaf collimators in RayStation TPS.

IMPT

As its name suggests, Intensity-modulated proton therapy use protons as particle for the treatment with the advantages and drawbacks mentioned previously. Protons are accelerated in a cyclotron or a synchrotron up to $2/3$ of the speed of light to propose an energy range between 70 and 250 MeV which corresponds to a minimum of 4cm depth in water. Then, they are guided by magnets to the treatment room of the selected patient. Finally, the pencil beam scanning technology will deliver a thin proton beam ("pencil beam") that is steered with magnets in order to deposit the dose as it shown in figure 2.9. The target volume is divided in energy layers, a high energy is associated to a deeper layer, each layer is then defined as a grid of spots. The beam will reach each of the spots, one after the other with a certain weights in order to reach a high dose conformity in three dimensions in the target.

ArcPT

Arc proton therapy is a new delivery modality that enables to deliver protons like IMPT is doing it, while the gantry is continuously rotating. This system gathers the advantages of IMPT (and protons) and the contribution from an arc configuration as the VMAT modality in classical radiotherapy. One problem of proton therapy is the time to switch energy, it

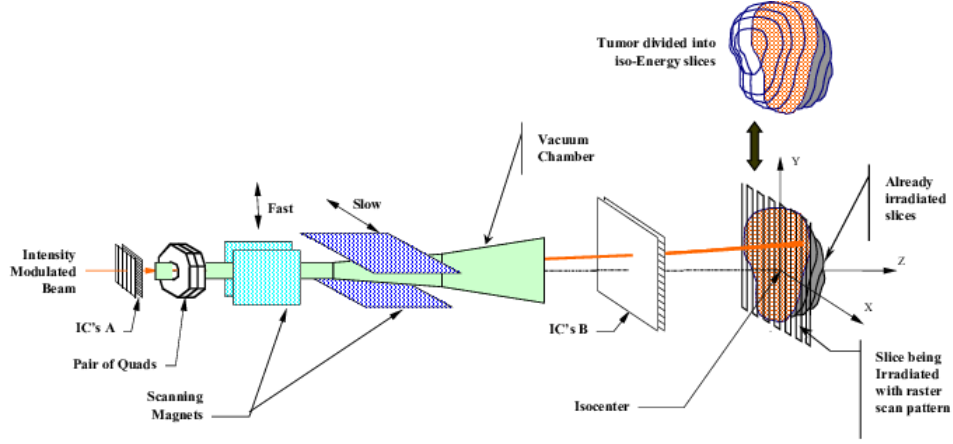


Figure 2.9: Representation of the IBA Proton Pencil Beam Scanning (from [14]). IC : ionization chamber.

needs approximately 0.6 seconds to switch down and 5.5 to switch up (values from first prototype of ArcPT delivery, study presented by X. Li et al. [15]). For IMPT, it is easy to optimize the beam delivery time by sorting the energies in each beam. Conversely, in the case of ArcPT, as there is a lot of angular positions associated to some energy layers, sorting the energy layers in each beams separately will not be enough to decrease significantly the beam delivery time. An optimization of the arrangement of the energy over all the beams, during the rotation of the gantry is necessary to improve the beam delivery time. New algorithms have been developed in the recent years to optimize a treatment plan in proton arc therapy, one of them will be discussed further in the method section.

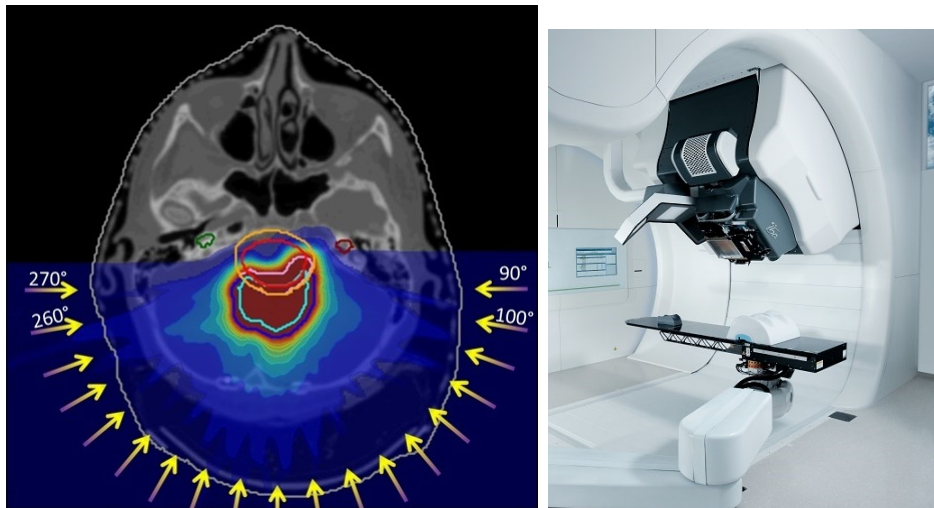


Figure 2.10: Left : Example of a dose distribution in ArcPT with the beam angle range (from [16]). Right: IBA arc proton therapy prototype.

When ArcPT is associated with pencil beam scanning technology, it is called Spot-Scanning Proton Arc (SPArc) Therapy which is the one used for this study, but the term

ArcPT will be commonly used to talk about arc proton therapy in general.

2.3.5 Follow-up

Once the therapy is completed, another CT-scan can be acquired in order to supervise the evolution of the tumor and an appointment with the oncologist is taken in the few months to evaluate patient's health, to check if there is any side effects because of the treatment that have to be managed or if the patient needs any supportive care.

2.4 Tumor Control and Normal Tissue Complication

The deal of external therapy is to be able to ensure loco-regional control while maintaining the patient quality of life by limiting radiation induced complication. It can be predicted using models that compute the tumor control probability (TCP) and the normal tissue complication probability (NTCP), the models performed in this work are presented in the section 4.1.6. These two parameters are of course bounded, the situation can be visualized in the figure 5.9, where increasing the probability to cure the tumor with a higher prescribed dose means that more dose is going to be delivered to the organs around and so, the risk of complication is also increasing.

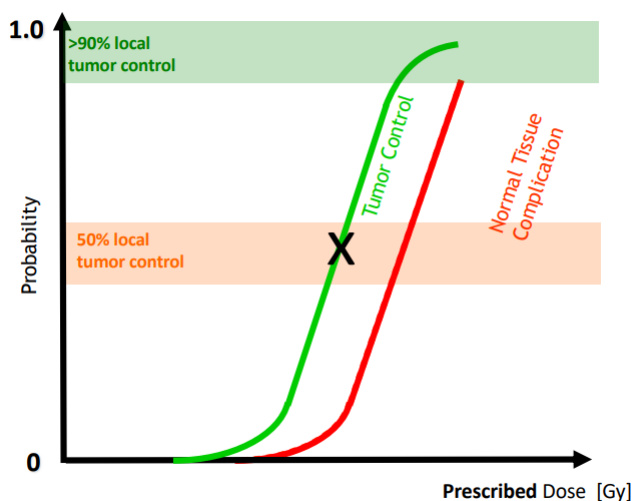


Figure 2.11: Graphic representation of the TCP and NTCP values depending of the prescribed dose.

These parameters depend on things like the number of fractions and many biological characteristics related to the organ or the tissue in question.

Chapter 3

State of the art

This section will first present the algorithm that allows to create an efficient treatment plan in arc proton therapy [17] and its upgraded version [3]. In a second time, it will resume already existing studies and results from works on ArcPT.

3.1 Arc proton therapy algorithm

3.1.1 Initial algorithm

This first algorithm, developed in order to achieve a robust arc proton plan with a decent optimization time, initializes the ArcPT plan the same way as a standard IMPT plan. However, as simply adding more beams would be too much costly in time, the algorithm has to include control point resampling, energy layer redistribution, energy layer filtration, and energy layer resampling. These are going to be explained in the next paragraphs.

Control point resampling The treatment plan is first initialized with a certain number of static beams (called control points), similarly to an IMPT plan, where the energy layers, spot positions and monitor units are optimized. Then, in order to increase the number of beams while keeping a reasonable optimization time, the control points are, one after the other, split in 2 sub-control points around the initial one. So at each steps, there is one more beam position and this is reiterated until the wanted number of control points is achieved. This can be visualized on the figure 3.1.

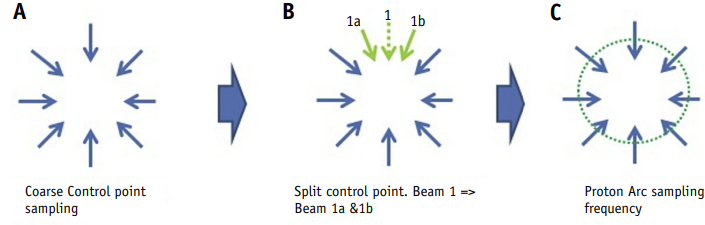


Figure 3.1: Diagram of the splitting steps of the control points for an arc of 360° (from [17]). The new control points are shifted away from the initial position by few degrees before and after.

Energy layer redistribution Once the new sub control points are created, the energy layers are reorganized equitably between them as shown in the figure 3.2, the number of energy layers has to remain constant during the resampling to not increase the optimization time.

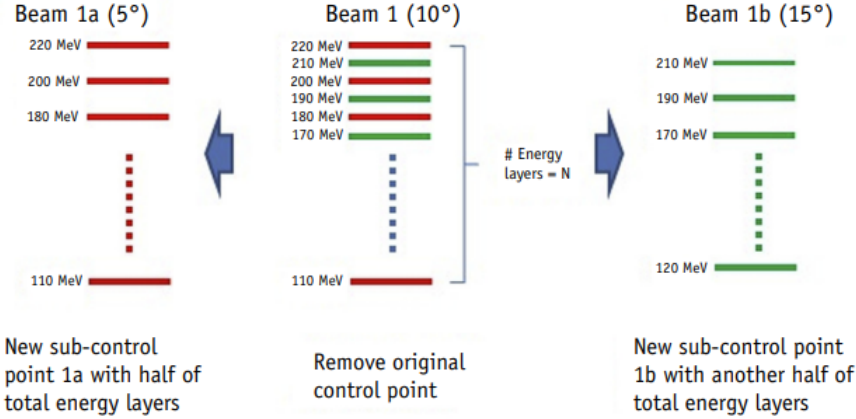


Figure 3.2: Distribution of the energy layers between two sub-control points (from [17]).

The plan is robustly re-optimized at each steps with the energy layers, spot positions and MU weightings distributed from the old control point. It is done with analytical dose calculation algorithm, which are fastest but less accurate methods (fast pencil beam in RayStation), to try to keep the quality of the plan during the process with a low time cost.

Energy layer filtration and resampling As a reminder, the time necessary for a switch of energy layers (ELST) is quite important (5.5s for switch up and 0.6s for switch down) and can induce a long delivery time for a lot of sub-control points. So the number of energy layers is the main factor affecting the beam delivery time, and this is where the filtering become interesting because it will, iteratively, remove the energy layers with a low weighting as long as the plan quality is not affected. Finally, a last energy layer resampling and filtration is performed to return a good quality plan.

3.1.2 Upgrade version

As mentioned in the paragraph just before, the increase of energy is very costly in time, this is due to the magnetic hysteresis effect. An idea to overcome this problem was proposed by G. Liu et al. [3] which consists of a new method to distribute the beams during the splitting process. Instead of having energy layers that are sorted randomly, the algorithm will sort them in a decreasing order until the position of the initial control points where the energy layers will be switch up. This way, the number of energy switch ups will be minimized, as the beam delivery time. The process is explained in the figure 3.3, the energy layers in the control point will be divided in two groups, the high and low energies, separated with the median value. Then, the higher energy layers will be distributed to one of the sub control points (always towards the same size during the whole process) and the lower ones, to the other. This step is reiterated for each splittings of control points until the the final range of the arc is achieved.

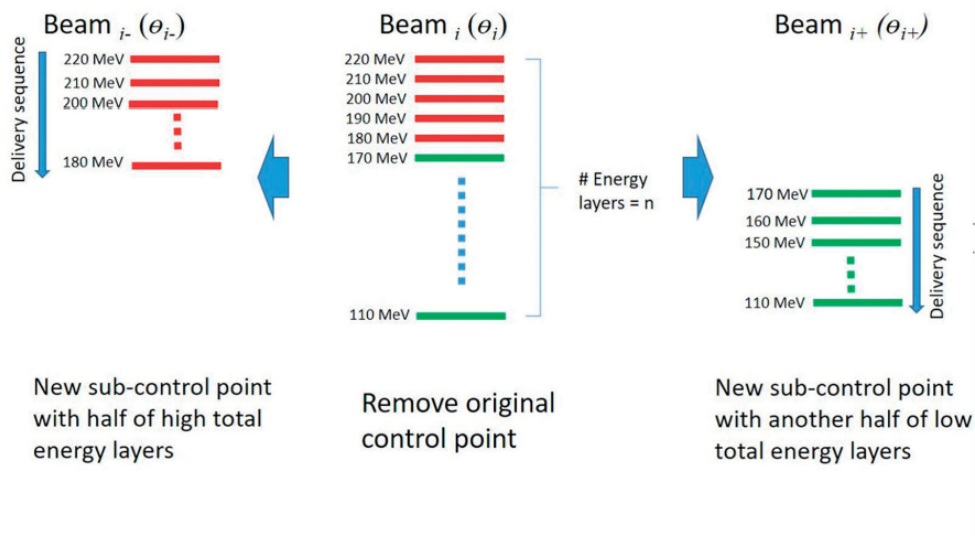


Figure 3.3: Distribution of the energy layers between two sub-control points with the new method (from [3]).

In terms of results, G. Liu et al. [3] compare both of the SParc algorithms with the same plan parameters and show that the new method is able to achieve a dosimetric outcome similar to the previous one (less than 2% of difference) and a similar robustness. As a result of a less number of switch up, it succeed to reduce the beam delivery time of the treatment up to 50 % in cases as prostate, brain, lung and H&N (to give an idea of the magnitude, the beam delivery time was in a range of 300 up to 800 seconds for a number of energy layers between 100 and 220).

3.2 First prototype

ArcPT is a complex delivery system and for this reason, it is really important to know the possibility to achieve a treatment plan while the gantry is rotating with enough accuracy during the whole process. To answer to this problematic, a first study about the potential use of the IBA Proton Dynamic Arc Delivery prototype was proposed by X. Li et al. at Beaumont Health System [15] in order to evaluate the stability and the accuracy of the delivery system for a range of different energies. The treatment plans were made with the energy layer sorted version of the algorithm presented in the section 3.1.2. The study shows that the prototype is able to achieve a position accuracy under 1 mm (with a maximum deviation of $\pm 0.77\text{mm}$) at the isocenter for different energy levels (70 to 227 MeV) while the gantry is rotating. Comparison between the static and rotating mode indicates that the machine has the capacity to maintain a consistent spot size under 1.5 % of difference), a similar square field (under 0.1% maximum), a beam flatness with a difference that does not exceed 0.6 % (except for highest energies, up to 2.2%), a nearly equivalent dose delivered to a ionization chamber (a difference between -0.53% and +1.84%). In terms of quality assurance, the correspondence between the simulated and the measured doses was good, calculated with a gamma index of 98.6% (3% 3mm). In conclusion, this study demonstrates already the potential use of arc proton therapy in clinical environment due to the consistency between static and dynamic mode, and a good matching between the delivered and measured dose. It comforts us into the idea to keep working on this new delivery method and to study its outcome to patients health.

3.3 Literature review on ArcPT results

There are already some studies about the potential outcome of ArcPT in order to improve the plan quality, robustness or beam delivery time and this section will be dedicated to resume and regroup these studies. This section is going to be divided in two, an extra-cranial part focused on studies over tumors in the body and another part focused on studies that are related to brain anatomy.

3.3.1 Extra-cranial

Prostate Cancer : A study of X. Ding et al. (Beaumont)[18] performed on 9 prostate cancer patients, compares IMPT and ArcPT plans created with the first algorithm (explained in section 3.1.1). The evaluation was focused on the OARs sparing, the homogeneity and tumor conformity index (see section 4.1), and the robustness. The results manifest a significant improvement of the dosimetric outcome in the organs at risk in comparison with the IMPT plan, the mean dose was reduced in these organs between 7.32 Gy and 12.86 Gy (prescription : 79.2 Gy) with statistical significance, a similar target coverage, homogeneity index (HI) and conformity index (CI) than IMPT was obtained. The robustness evaluation indicates a similar target coverage with a better OARs sparing. The study also reported a beam delivery time longer for ArcPT, but presented a potential benefit with the consideration of the waiting time between the beams in IMPT.

Non-Small Cell Lung Cancer : X. Li et al. [19] proposed a study on 13 patients affected by a NSCL cancer, the objective was to compare the dosimetric outcome, the robustness and the delivery time of an ArcPT and IMPT robustly optimized plan while the treatment has to deal with a tumor motion (divided in 2 groups, more and less than 5mm). The results indicated that the ArcPT managed to reduce the average dose to the lungs, the heart and esophagus by 1.7 Gy, 0.7 Gy and 1.7 Gy respectively for a prescribed dose of 66 Gy. Both plans achieved robust covering of the Internal Target Volume (ITV) with similar results but ArcPT shows an improvement in the organs under the different scenarios. The beam delivery time was evaluated for different energy layer switch time (ELST). For parameters similar as the ones chosen in this work, they observed a longer delivery time with an arc modality but in case of smaller ELST as 0.2 seconds, the delivery was faster than IMPT. The ArcPT also managed to reduce dose inhomogeneities emerging in the ITV due to the breath motion.

Whole Breast Radiotherapy : A comparison between IMPT and ArcPT on a group composed of 8 patients with a breast cancer was performed by S. Chang et al. [20]. The plans were robustly optimized on an ITV to consider the organs motion. The evaluation was normalized to a prescribed dose of 42.56 Gy, it included the dosimetric outcome with HI and CI, robustness analysis, motion management, beam delivery time and NTCP. The results show for a similar target coverage, an improvement in the organ sparing with ArcPT (Heart D1 : 56.75 cGy lower for example) excepted for the contralateral breast that received a slightly higher mean dose (12.13 cGy vs 18.5 cGy for ArcPT). The NTCP evaluation indicated a potential clinical benefit for the patient. ArcPT plan seemed to mitigate the effect of the uncertainties and the internal body movements by keeping the CI and HI consistent. This study also observed the same results for the beam delivery time as the previous study.

Spine metastasis : G. Liu et al.[21] compared VMAT, IMPT (3 beams) and ArcPT (with version 3.1.1) plans over 7 patients with spine metastasis. The prescription was a dose of 18 Gy in the PTV in a single fraction (Stereotactic Body Radiation Therapy : SBRT). The focus was directed to the plan quality with dosimetric outcome, PTV coverage and CI, and the beam delivery time was also estimated. The robustness of the plan was not in the discussion since the target was a PTV. The results manifest a better coverage of the PTV (95% vs 92.9 % and 92.7% of the prescribe dose for VMAT and IMPT respectively), a reduction of the maximum dose in the spinal cord (10.21 Gy vs 10.96 Gy and 11.07 Gy) and the dose in the lungs. In many other metrics as the mean dose in heart and partial cord, CI and others, there was not significant improvements with ArcPT. In terms of delivery time, the ArcPT could achieve a therapy session 50 % faster than VMAT and could be equivalent to a 3 beams IMPT plan with an ELST of 1 second.

Para-aortic lymph node tumors : The study introduced by J.-E. Ra et al. [22] compared the treatment plans of PBT (proton beam therapy) and ArcPT with passive-scattering, and an IMRT plan prescribed on a PTV (60Gy) over 9 patients. The consideration was on the PTV coverage, CI, HI and OARs sparing with a dosimetric and NTCP evaluation. The comparison shows that ArcPT improved slightly the target coverage, CI and HI in compar-

ison with the proton plan. The arc plan managed to reduce the percentage of the volume receiving 30 % of the prescribed dose in the majority of the organs at risk (1% up to 5% lower) and to reduce significantly the NTCP in the OARs excepted for the Liver, both protons plans were performing better than IMRT overall.

3.3.2 Cranial

Head and Neck cancer : Another study coming from G. Liu et al. [23] compared an ArcPT (planned from 3.1.1) and a 3 beams IMPT plans over 14 patients with a HNC. Both plans were normalized to a prescribed dose of 70 Gy in the CTV, the method first consisted of a plan quality evaluation about the target coverage, the maximum dose in the OARs (brain stem and spinal cord), the HI, CI. The robustness was also analyzed, as well as the delivery efficiency and potential clinical benefits with a NTCP estimation. The ArcPT plan shows a more conformal dose with a slightly better HI and CI, and a lower maximum dose and mean dose in the OARs (Brain stem D1 : 14.2 Gy vs 15.9 Gy for ArcPT and IMPT respectively), theses results are comforted with the NTCP value which reveals a reduction of the mean complication probability in the parotid glands from 36 to 25%. Both plans have a similar robustness for the target coverage but ArcPT performs better in the organs. As it was observed in other studies, the beam delivery time is much more longer for an ELST of 5 seconds (1295s with an arc vs 902s without). Both plans become equivalent in time for an ELST of 0.5 seconds (366s vs 374s for ArcPT and IMPT respectively) .

Whole brain radiotherapy : The study made by X. Ding et al.[24] assessed the potential benefits of spot-scanning proton arc therapy over 8 cases of a whole brain radiotherapy, with IMPT (3 beams) and VMAT as comparison treatment. Protons plans were robustly optimized (3mm and 3.5%) on the CTV (CTV consists of the whole brain parenchyma excepted an avoided region of hippocampus) for a prescribed dose of 30 Gy, the VMAT plan was prescribed on a PTV. The dosimetric outcome in the target and organs, the HI, the robustness and the delivery time were evaluated. The study showed that, for an equivalent target coverage, ArcPT decreased the mean and maximum dose in hippocampus in comparison to other plans. ArcPT was performing better overall, excepted in the lens where IMPT was lower and in the optic nerves and chiasm where VMAT was better. The HI was similar for VMAT and ArcPT, and better than IMPT. The robustness evaluation indicates similar results as in the dosimetric outcome, similar target coverage with an improvement in the organs at risk with ArcPT. The beam delivery time was equivalent with an ELST of 1 second, IMPT was performing better for higher ELSTs and less good for smaller ELSTs.

Skull base chordoma : J. Kiely and B. White [25] proposed a study on a single-energy ArcPT over 6 patients, in comparison with an IMPT and SFUD (single field uniform dose) proton treatment plans. The evaluation was focused on the HI, CI, the organs sparing with the maximum dose in the brain stem, the optic chiasm and nerves, spinal cord, orbits,.. (or mean dose for few organs as cochlea). The results show a similar HI in the target but a slightly better conformity for the ArcPT plan. The ArcPT plan also performs better than SFUD and IMPT in the OARs in 70% of the metrics compared.

3.3.3 Summary Table

The summary table 3.1 resumes the previous studies.

Cancer [study]	ArcPT script and specificity	Modality	Target/Errors	Calculation Algorithm	Dosimetric outcome	Robustness	BDT
Prostate [18] X. Ding et al.	SParc Script 3.1.1	IMPT 2 beams	CTV 5mm 3.5%	N/A	TC, HI, CI similar, better OARs sparing	TC similar Better in OARs	Longer/ Potential with waiting time
NSCLC [19] X. Li et al.	SParc Script 3.1.1	IMPT 3 beams	ITV 5mm 3.5%	N/A	Similar TC Better in OARs	Similar TC Better in OARs	Longer/ Similar with ELST of 0.5s
Breast [20] S.Chang et al.	SParc Script 3.1.1	IMPT	ITV 5mm 3.5%	Monte Carlo	Similar TC Better in OARs and NTCP	Similar TC Mitigate in OARs Better motion management	Longer/ Similar with ELST of 0.5s
Spine metastasis G. Liu et al. [21]	SParc SBRT Script 3.1.2	IMPT 3 beams VMAT	PTV	Pencil beam	Better TC Better sparing for some metrics	/	Similar to 3 beams IMPT with ELST of 1s
Para-aortic [22] J.E. Ra et al.	ArcPT PS	PBT with PS 2/3 beams IMRT	PTV	Pencil beam	Slightly better TC Better in OAR	/	/
H&N [23] G. Liu et al.	SParc Script 3.1.1	IMPT 3 beams	CTV 3mm 3.5%	N/A	Better TC Better in OARs Better NTCP	Similar TC Better in OARs	Longer/ Similar with ELST of 0.5s
Whole Brain [24] X. Ding et al.	SParc Script 3.1.2	IMPT 3 beams VMAT	CTV 3mm 3.5% VMAT: PTV	N/A	Similar TC Better in OARs excepted in lens and ON	Similar TC Better in OARs	Longer/ Similar with ELST of 1s
SB chordoma [25]	ArcPT single-energy	IMPT SFUD	CTV	N/A	Similar HI Better CI Better in OARs	/	/

Table 3.1: Table summarizing the results coming from studies already made on ArcPT. The type of script used was precised, as the other modalities, the calculation algorithm, the target and the robust optimization settings. BDT : Beam delivery time. SParc : Spot-scanning proton arc. PBT: Proton beam therapy. TC : target coverage. HI : Homogeneity index. CI : Conformity index. OAR : Organ at risk. ELST : Energy layer switch time. N/A : Not available. PS : Passive scattering. ON: Optic nerves. SK : skull base. SFUD : single field uniform dose.

Even though the data collected is coming from studies done in specific situations with different parameters, the results were overall along the same line for ArcPT with similar or better target coverage, a similar or better OARs sparing in nominal result and in the

robustness evaluation. The results for the beam delivery time are similar between the different studies, but manifest mitigate results for ArcPT since generally the BDT was longer than IMPT as long as ELST was bigger than 0.5 or 1 second. It only starts to become very interesting for lower values, as 0.2 second, which is not achievable yet, especially for switch ups. This resume comforts us to keep evaluate and improve arc proton therapy in order to achieve its full potential.

3.4 Uncertainty budget in proton therapy

The use of protons in radiotherapy brings the great profit of decreasing the dose deposited in the body in comparison with photons, thanks to the sharpness of the Bragg peak. This benefit is also the source of its main drawback, proton therapy is more sensitive to uncertainties. There is many different uncertainties and it is important to identify where they are coming from and what is their impact. This section will resume the study from H. Paganetti [26] which encompasses the source of uncertainties in proton therapy and the advantages of Monte Carlo dose calculation algorithm in this budget.

- Multiple coulomb scattering : As mentioned in section 2.3.3, analytical algorithms are struggling to predict the effects of the multiple coulomb scattering in very inhomogeneous materials and it will have as consequence a large difference in the final uncertainty in comparison with Monte Carlo algorithms. MC is used as a standard even though there are still physical uncertainties, the uncertainty in a analytical algorithm is then obtained by comparing with the standard model. The study highlights that the uncertainty can be estimated to $\pm 2.5\%$ for analytical algorithm and probably below $\pm 0.1\%$ for MC algorithm.
- Physics : Since MC has been created for high-energy applications, there are uncertainties related to the interpolation with the data or the theoretical models for energies used in clinic. The main element responsible is the mean excitation energy. There are different recommendations made for its value. This range of values (between 10 and 15%) implies an uncertainty estimated at $\pm 1.5\%$.
- CT conversion : A first uncertainty is coming from the imaging of the patient and the calibration of the machine which is estimated at $\pm 0.5\%$. Then, in order to be able to perform proton therapy, the Hounsfield units of the CT-scan which is related to the attenuation factor of photons, have to be converted into stopping power units. This conversion also implies an uncertainty which is smaller with MC algorithm than with analytical algorithm, estimated at $\pm 0.2\%$ and $\pm 0.5\%$ respectively.
- CT resolution : The size of the voxel in the CT image can imply an important uncertainty if there are a lot of heterogeneities, especially in geometries where there is an interface between a low and high density material. A comparison was made with simulations performed on lungs with MC between a CT with a typical resolution in clinic and another one with a better resolution. The study estimated the uncertainty at $\pm 0.3\%$.

- Biological effects : The Relative Biological effectiveness (RBE : section 4.1.3) is the ratio between the photon and another particle doses for a similar biological damage. The dose deposited by different particles will be "normalized" to the dose deposited by photons. A constant value is used in clinical environment while it depends of the dose, the tissue or the energy deposition characteristics which is related to the linear energy transfer (LET : section 4.1.2). The increase of the LET implies an higher RBE, and thus a difference in the biological damage expected at a certain depth. Fortunately, this difference was not observed in tissues such as tumor and so, this has not to be included in the target margin but it has to be considered in the OARs (estimated at 0.8 %).
- Verification : In order to verify the range in vivo, the common method used at the moment is positron emission tomography and it is also a source of uncertainties, mainly due to the cross sections established in physical experiments which are not done in an exactly similar situation as the clinical environment. The uncertainty has been studied with a comparison in a phantom between the results simulated with MC and the measured results. They conclude that more data is needed in order to reduce the uncertainty below 1 mm.

Taking into account the uncertainties from the dose calculation only, considering they are independent between them and without the biological effects, the total uncertainty was finally estimated to $\pm 2.4\%$ and $\pm 2.7\%$ for Monte Carlo and analytical algorithm respectively. The uncertainties not related to the dose calculation (as the error set up, the beam reproducibility, the measurement uncertainty,...) were estimated to a total of 1.2 mm. There are still minor errors that have to be take into account and these values have to be adapted depending of the situation since many elements can influence the uncertainty as the tumor location, the body motion, the treatment plan,...

Chapter 4

Materials and methods

This chapter first presents the tools and metrics used to compare the different delivery modalities based on optimized plans. Then, a section will be dedicated to the method applied to the creation of the plans and the heuristic choices made in order to compare them.

4.1 Definitions

4.1.1 Dose

The dose is a term that has already been mentioned in this thesis. The absorbed dose, commonly called dose, quantifies the amount of energy deposited by ionizing radiation per unit of mass and is expressed in Gray (Gy) where $1\text{Gy} = 1\frac{\text{J}}{\text{kg}}$. It is given by this formula :

$$D = \frac{d\epsilon}{dm} \quad (4.1)$$

Where $d\epsilon$ is the mean energy imparted and dm is the exposed mass of the material.

4.1.2 Linear energy transfer

The Linear Energy Transfer (LET) can be defined as the average energy locally imparted to the media by a charged particle of energy dE_L per unit of distance dl travelled by the charged particle [27].

$$LET = \frac{dE_L}{dl} \quad (\text{in } \text{keV}\mu\text{m}^{-1}) \quad (4.2)$$

In this study, the non restricted dose average LET (LET_d) was calculated, which considers the LET of all the particles including secondary particles. The LET is important to take into consideration since it influences the DNA damage and thus the biological outcome. In the literature, the terms "High LET" and "Low LET" are often used to classify the particles according to their biological effects (see figure 4.1), higher LET producing greater biological damage. Generally, a LET above $10\text{keV}/\mu\text{m}$ is considered as high LET (Neutrons, α and carbon ions). Photons and electrons are thus considered as having low LET (under $2\text{keV}/\mu\text{m}$). Protons can be considered as having intermediate LET.

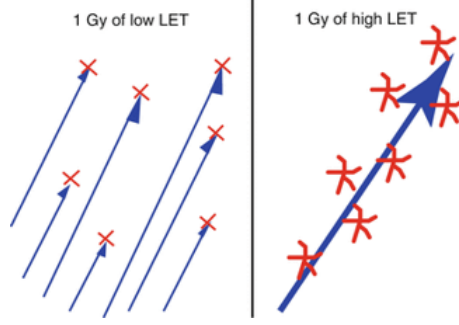


Figure 4.1: Difference between High LET and Low LET particles.

4.1.3 Relative Biological Effectiveness

The dose has already been defined at the beginning of this section, but a further precision is necessary on what is called the relative biological effectiveness (RBE). Different particles do not cause the same damage to DNA for a same energy absorbed, it implies that a correction has to be added. The RBE of a particular radiation is defined as follows : "The ratio between the absorbed dose of a reference radiation D_R (usually X-rays or γ -rays) and the absorbed dose of the particular radiation D_X required to attain the same level of biological effect" (Alpen, 1998) [27].

$$RBE_X = \frac{D_R}{D_X} \quad (4.3)$$

The density of ionization along the particle track influences the RBE. Particles such as α particles and heavy ions have a larger RBE than protons [28]. In the TPS, the RBE for protons was set as $RBE = 1.1$ in the whole body. During the evaluation, the data concerning the dose in the patients was normalized with the RBE and so, for the rest of the thesis, RBE is not going to be mentioned anymore in order to lighten the reading.

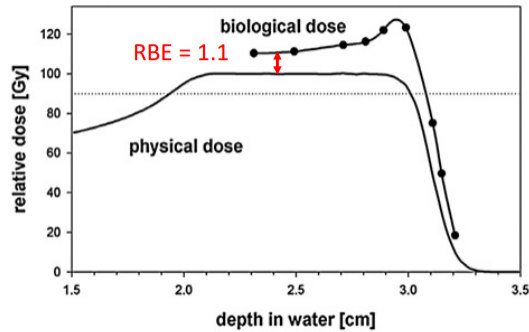


Figure 4.2: Difference between the physical dose and the biological dose in case of protons. The RBE value is highlighted and it can be observed that RBE is not constant all over the SOBP.

In reality, as mentioned in the uncertainty budget in section 3.4, the RBE is not constant all over the body but it increases with the LET. Thus, it is important to calculate the LET distribution in the body to check that the high values are not located into the OARs.

4.1.4 Homogeneity Index

The Homogeneity index (HI) is an evaluation tool that returns a value indicating the uniformity of the dose distribution in the target volume. There is many different formulas proposed in the literature to calculate it. In this case, the most common one is going to be used [29] and is given by the equation 4.4:

$$HI = \frac{D_2 - D_{98}}{D_{50}} \quad (4.4)$$

Where D_2 and D_{98} are the minimum doses present in at least 2% and 98% of the target volume respectively, which represents indeed the near maximum dose and the near minimum dose of the target and D_{50} is the median dose or the prescription dose (65 Gy) in this case. If 2 and 98 percent are used instead of D_{min} and D_{max} , it is because the true maximum and minimum doses are very sensitive to the resolution of the dose grid and the noise in the MC algorithm. A homogeneity index close to 0 means that the dose distribution in the volume considered tends to be perfectly homogeneous. The HI is a good quality indicator and objective measure to help the oncologist in the decision making between different plans[29].

4.1.5 Conformity Index and Number

As the Homogeneity index, the conformity index is another tool used in the radiotherapy literature to define the quality of a treatment plan. CI represents the capacity of the plan to deliver the prescribed dose in the target volume only, without having dose equivalent to the prescription outside the CTV. Of course, it happens because the plan has to be robust with the uncertainties and so, it covers a larger area than the CTV.

$$CI = \frac{V_{T,ref}}{V_{ref}} \quad (4.5)$$

Where $V_{T,ref}$ is the volume of the target covered by the reference dose (usually 95 % of the prescribed dose) and V_{ref} is the volume in the whole body covered by this same reference dose. The conformity number (CN) is the conformity index with an additional term which represents the ratio between the volume of the target V_T and V_{ref} . CN is given by :

$$CN = \frac{V_{T,ref}}{V_T} \times \frac{V_{T,ref}}{V_{ref}} \quad (4.6)$$

The first term gives an insight about the coverage of the target, it should tend to 1. A perfect plan should have a conformity index really close to 1, meaning that only the target is covered by the reference dose.

4.1.6 TCP and NTCP

The Tumor Control Probability and the Normal Tissue Complication has been briefly introduced in the Context chapter. This section is going to resume the two different models used, the Niemierko (NKO) and the Lyman-Kutcher-Birman (LKB) mathematical models

[30] which both present a good fitting with statistical data in the literature. First, the definition of the equivalent uniform dose (EUD) is needed. EUD is the absorbed dose equivalently distributed in the target volume that causes the same number of cancerous cells to survive than the initial absorbed dose [31]. In case of an healthy tissue, the EUD can be seen as the uniform absorbed dose which implies the same amount of biological damage. It is given by the next equation 4.7 :

$$EUD = \left(\sum_{i=1} (V_i D_i^a) \right)^{\frac{1}{a}} \quad (4.7)$$

Where V_i is the partial volume receiving the dose D_i and " a " is a model parameter specific to the tissue or the tumor, its estimation can be found in the literature. For normal tissues, it characterizes the volume effect related to the type of organs (parallel or serial). The factor " a " will determine the behaviour of the EUD. For a large positive number, EUD is close to the max dose, such values are used for serial organs. For values close to 1, the EUD represents the mean dose deposited and is thus used for parallel organs. Finally, a large negative " a " implies that EUD is closer to the min dose and such values are used for the tumors. When calculating NTCP and TCP, the linear quadratic equivalent dose ($LQED_2$) will replace D_i in the previous equation in order to scale the dose, since the TCP and NTCP parameters were calculated for a treatment delivered by fractions of 2 Gy, the $LQED_2$ takes this into account.

$$LQED_2 = D_i \frac{1 + \frac{D_i/n}{\alpha/\beta}}{1 + \frac{2}{\alpha/\beta}} \quad (4.8)$$

Where the ratio $\frac{\alpha}{\beta}[Gy]$ is a factor specific to the tissue that is deduced from survival fraction curves, n is the number of fractions.

Now, the tumor control probability can be defined. In the Niemierko model, TCP is given by the equation 4.9 :

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD} \right)^{4\gamma_{50}}} \quad (4.9)$$

Where TCD_{50} is the dose leading to 50 % of control of the tumor (Gy), γ_{50} is the change in TCP expected for a modification of 1% in dose compared to TCD_{50} . It characterizes the slope of the sigmoid (shown in the figure 5.9). The Normal Tissue Complication is given in the Niemierko model by the equation 4.10 :

$$NTCP = \frac{1}{1 + \left(\frac{TD_{50}}{EUD} \right)^{4\gamma_{50}}} \quad (4.10)$$

Which is very similar to the TCP equation, excepted for one difference, TCD_{50} is replaced by TD_{50} which is the dose leading to 50 % of complication risk. In the other hand, Lyman-Kutcher-Birman proposed the following model :

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{x^2}{2}} dx \quad (4.11)$$

With

$$t = \frac{D_{eff} - TD_{50}}{mTD_{50}} \quad (4.12)$$

Where D_{eff} is the dose that, if given uniformly to the entire volume, will lead to the same NTCP as the actual non-uniform dose distribution and is given by

$$D_{eff} = \left(\sum_{i=1} v_i D_i^{\frac{1}{n}} \right)^n \quad (4.13)$$

With m , the measure of the slope of the sigmoid curve and n which characterizes the volume effects of the organ. D_{eff} corresponds to the EUD if $a = 1/n$. As mentioned before, many of the parameters are specific to the tissue and need to be find by fitting models with data. Here is a table presenting the different parameters with their values for the tumor, the brain stem and the optic chiasm.

Parameters :	a	α/β [Gy]	$TC D_{50}$ [Gy]	TD_{50} [Gy]	γ_{50}	m	n
CTV [32]	-13	10	51.77	/	2.28	/	/
Brain Stem [33],[30]	7	2.1	/	65	3	0.15	0.04
Optic chiasm [34],[30]	25	1.6	/	65	3	0.14	0.25

4.1.7 Beam delivery time

The beam delivery time (BDT) is the time needed for the delivery of a fraction of the treatment and it is also an important factor in external therapy. First, a smaller delivery time allows to treat more patients everyday, meaning a better health care for the population overall. Moreover, reducing the delivery time increases the comfort of the patient, which implies that it is easier for the patient to remain motionless and so, the potential of errors during the delivery is minimized. In proton therapy, the BDT is dependant of the energy layers switching time. As mentioned in chapter 2, it typically takes 0.6 seconds to decrease the energy and 5.5 seconds to increase it [15]. It has also to take into account in case of IMPT, the waiting time between two beams which has been estimated to 55 seconds (this value was obtained from Beaumont and will not be the same for another proton therapy center). In case of ArcPT, the acceleration and the max speed of the rotating gantry are respectively of $0.5^\circ/s^2$ and $6^\circ/s$ (from the IBA prototype in Beaumont, it might be different for the real product and could also vary between different centers).

4.2 Methodology

The simulations have been done on three anonymized patients diagnosed with similar brain tumors, the delineation of the organs was already made by a physician. All plans

were normalized with a dose prescription defined as a median dose (D50) of 65 Gray (RBE) in the clinical target volume. In order to provide a fair comparison, all three plans have been generated in the RayStation using robust optimization even though photons plans are usually done with a PTV. As there is no movements in the brain, a setup error of 3 mm was used in all the directions and the range uncertainty was defined at 2.6% for both proton therapy plans. For ArcPT plan optimization, the SPArc algorithm initially proposed by X. Ding et al [17] was re-implemented with RayStation scripting.

During the splitting of the initials beams to get the final arc, after each creation of a new beam, the dose calculated for the optimization is computed with 30 iterations of an analytical algorithm, called fast pencil beam, in order to keep a reasonable computation time. Once the arc is fully created, a robust optimization of 100 iterations computed with a Monte Carlo algorithm is executed in the continuity of the optimization already done before to get a more precise dose.

The treatment is planned to be delivered in 36 fractions of 1.8 Gy, so the dosimetric outcome is evaluated with the clinical standard goals for a brain tumor in case of a classical fractionation regimen, proposed by G. Noël et al [6], as criteria of comparison. The next table presents these clinical goals, where $D_{0.03}$ is the maximum dose in a volume 0.03 cm^3 of the region of interest (ROI), also called Dose near max and V_{60} is the percentage of the volume at 60 Gy. In addition, the mean dose D_{Mean} in the body and the brain, and the D_{98} and D_{95} of the CTV were also computed.

ROI	Clinical goals
Brain Stem	$D_{0.03} < 54 \text{ Gy}$
Optic chiasm	$D_{0.03} < 54 \text{ Gy}$
Optic nerves (LON and RON)	$D_{0.03} < 54 \text{ Gy}$
Eyes (Left and Right)	$D_{0.03} < 10 \text{ Gy}$
Brain	$V_{60} < 33\%$
Brain	D_{Mean}
Body	D_{Mean}
CTV	D_{95} and D_{98}

A robustness evaluation was then performed for the 3 plans to assess and compare their dosimetric performances. A set of 42 different scenarios were calculated with the same parameters as the robust optimization ones, the focus has been placed on the nominal result and the worst case scenario. In addition, the HI, CI and CN were also calculated for a bunch of scenarios to have another view on the robustness of the plans. A LET distribution was computed for both proton therapy plans using MCsquare with OpenTPS. Finally, the TCP was evaluated for the target volume, and the NTCP for the optic chiasm and the brain stem.

4.2.1 Heuristic point of view

Beam positions

Beam arrangement was selected for each modality to provide the best plan quality, while avoiding to harm as much as possible the brain stem and optic chiasm. The VMAT plans have been made according to the local clinical guidelines in the case of a brain tumor, which consists here of five arcs organized as follows (cw and ccw are the abbreviations for clockwise and counter-clockwise) :

Arc	1	2	3	4	5
Couch angle	0°	30°	60°	330°	300°
Gantry angle	178-182°	182-358°	358-182°	2-178°	178-2°
Rotation	ccw	cw	ccw	cw	ccw

On the other hands, the IMPT and ArcPT plans have been made following a more heuristic approach that is going to be stated immediately, with the help of the figure 4.3 for the visualization and the comprehension. The beams of the IMPT plans have been placed to avoid crossing through the brain stem and the optic nerves avoiding any useless overdose. A choice of two beams have been finally made because of the orientations remaining. A lower beam delivery time and a better sparing of the closest organs in this set up was observed, they are aiming from the left and the right on the transverse cut.

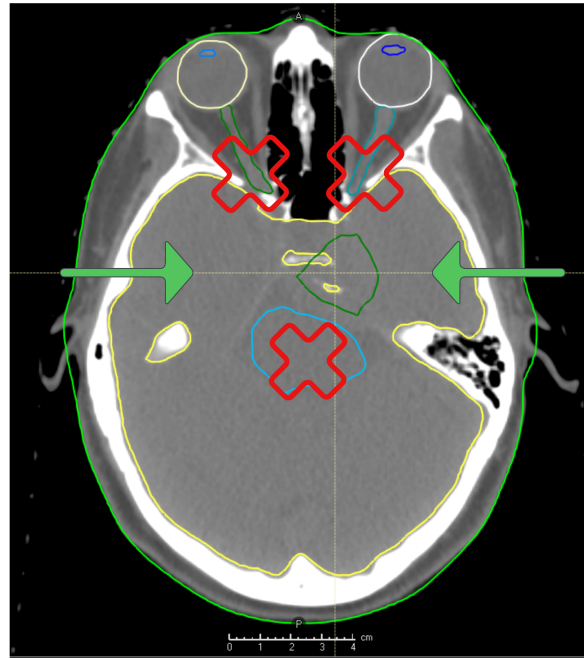


Figure 4.3: Overview of the beam positions in the IMPT plan, green arrows representing the orientation of the beams and the red crosses, the organs that are avoided.

In the ArcPT case, as there is a longer optimization time and starting from a low number of beams (between 2 and 8) that is increasing along the process, a little change at the beginning can become huge at the end. So, there is no more place for intuition and it becomes difficult to adjust the plan as desired. ArcPT is a new modality and there is no guidelines existing to create a treatment plan, many attempts were performed in order to maximize its potential in this situation despite the constraints and the followings heuristic choices have been made for this purpose. Even though, in the case of an arc, it could have been possible to go through the organs because the dose is spread over a larger area than in IMPT, the angle range still avoids the OARs. However, this decision was taken for other reasons.

First, the eyes area is a place full of inhomogeneities, the density varies a lot over a small distance. Since the robust optimization is computed in a first place with an analytical algorithm before being completed with the Monte Carlo algorithm, the switch from one to the other is complicated because the analytical algorithm struggles with inhomogeneities as mentioned before. Indeed, huge differences in the dose distribution were observed with beams positioned too close to these inhomogeneities to a point where the plans were hardly degraded.

Secondly, the algorithm creating the ArcPT plan, sorts the energy layers in a way that the energies are decreasing angle after angle, with a switch up after a number of control points chosen before. Therefore, as the energy decreases, the distance between the skin and the target is increasing which means that the position of the Bragg Peak shifts towards the brain stem for posterior beams. Then, it becomes difficult to match the energy layers and beam angles in an optimal way. In the attempts of doing a full arc around the patient without any constraints for the OARs, the optimizer tends to decrease to zero the weights of the energy layers of the beams behind the brain stem because of this situation.

To avoid these problems, the final choice was directed to a double arc plan which can be seen as a single one with a big step at a certain point. The arcs were located at the same place as the IMPT beams while trying to take a large range of angle as it can be seen on the figure 4.4.

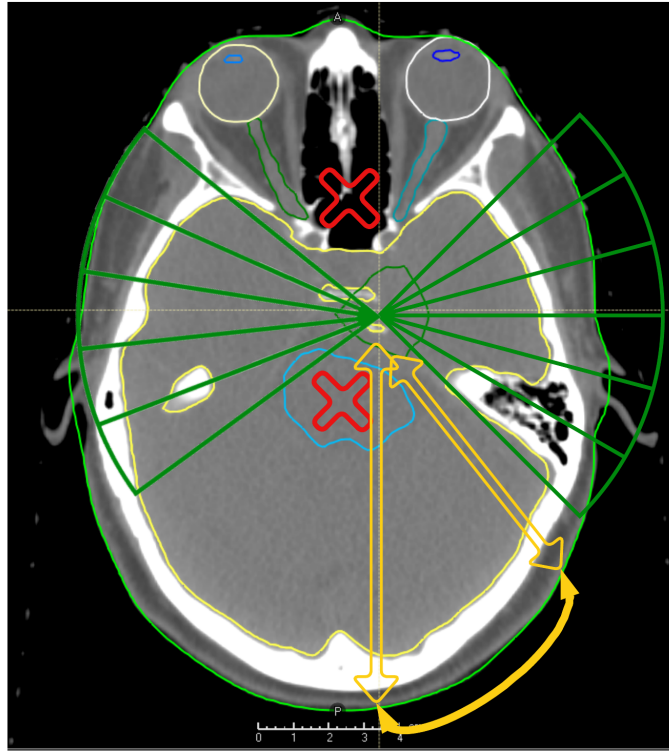


Figure 4.4: Overview of the arc positions in ArcPT plan, green arcs representing the range of angles covered by the arcs, red crosses are the area of inhomogeneity and the brain stem, and the yellow lines highlight the increase of depth behind the brain stem.

Finally, the angles of the IMPT and ArcPT plans were defined as follows :

		Patient 1	Patient 2	Patient 3
ArcPT	Arc 1	50-120°	70-120°	70-110°
	Arc 2	255-295°	240-290°	220-290°
IMPT	Beam 1	100°	90°	90°
	Beam 2	280°	270°	270°

Objective values

During the optimization process, the values of the objective functions and their weightings are editable and allow to constrain the beams to deliver the dose as wanted. To make a consistent comparison, the values and weightings were chosen in a first place to respect the strict main objectives to cover 99% of the CTV at 95% of the prescribed dose and avoid hot spots. Then for the VMAT and IMPT plans, the dose objectives in the OARs were progressively decreased or the weighting values were increased as long as the plans were respecting the main goals. However, in the ArcPT plan, this was not possible because of the duration of the algorithm and the impossibility to change the values during the optimization, so the starting objectives were the ones from the best IMPT plan. The figure 4.5 resumes the process used during the optimization of the IMPT and VMAT plans.

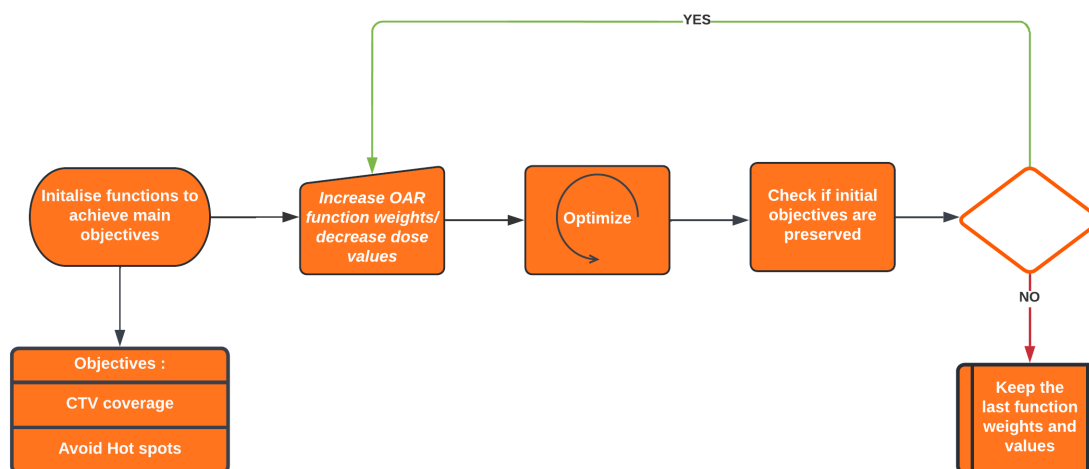


Figure 4.5: Flowchart of the optimization process performed during the treatment planification of VMAT and IMPT.

Hot spots

Another difficulty has been encountered while planning the last two patients, huge hot spots tend to appear in the dose distribution, even without any considerations for the OARs. It seems it was due to the tumor volume which was much smaller than in the first patient (8.98 vs 2.96 and 2.34 cm^3). In order to achieve a good quality plan, an idea was to increase the number of distal and proximal layers in the margin of the target since it can help in the target coverage [35] and moreover, to avoid hot spots. The target margins were then increased in the RayStation parameters. The visualization of this modification is presented in the figure 4.6.

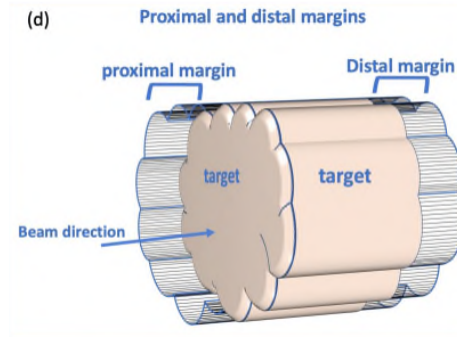


Figure 4.6: visualization of the proximal and distal margins (from [35]).

Chapter 5

Results and discussion

In this chapter, the results obtained by following the methods introduced previously will be presented. The dosimetric outcome, the target coverage, the robustness and the beam delivery time are going to be analyzed and discussed in order to extract the different advantages and drawbacks. Paired T-test is a common way in the literature to compute the statistical significance between different modalities but 3 patients are certainly not enough to represent a normal law, this section gives a preliminary study of the potential of ArcPT and the statistical significance will not be discussed. Therefore, more patients will be needed to validate the results.

5.1 Visualization

Before going any further in the evaluation, here is a first visual comparison between the ArcPT, IMPT and VMAT plans with their beam positions in order to have a first look on the situation. It can be already observed in the figure 5.1 and 5.2 that the arc implies a dose distributed in a bigger area than IMPT but the dose is lower overall. The VMAT plan on the other hand deposits much more dose overall in the patient.

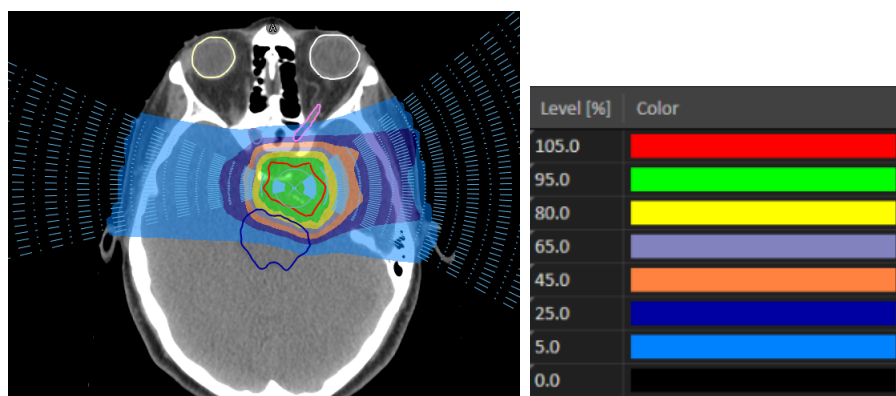


Figure 5.1: Left : Dose distribution on the transverse cut of the brain of the first patient with ArcPT (two arcs and 72 beam positions). Right : Color scale associated to the dose level in percent of the prescribe dose.

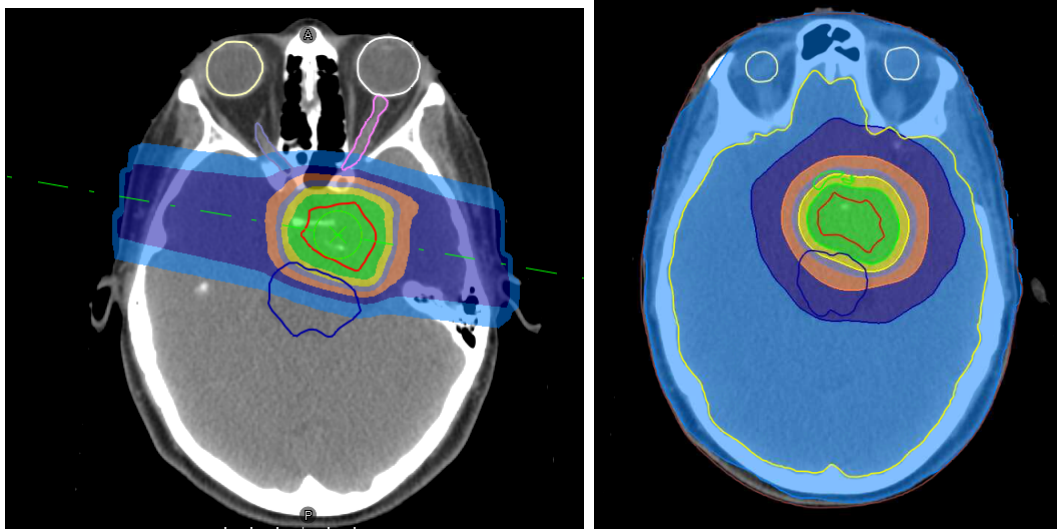


Figure 5.2: Dose distribution on the transverse cut of the brain of the first patient. Left : IMPT plan with two beams. Right: VMAT plan.

Another way to compare the plans is to pay attention on the dose volume histogram (DVH). For example, on the figure 5.3, there is the DVH related to the ArcPT, IMPT and VMAT plans of the first patient presented previously. We can see in red, that the ArcPT curve seems to be sharper than the IMPT one, this implies that the homogeneity of the target coverage will be better in this case. The green curve shows also a potential sparing of the optic chiasm by the ArcPT plan. The blue and yellow lines also reveal that the photon plan induces more dose overall in the brain stem and in the body in comparison to the photon plans. Then it becomes more difficult to get any further information, so a deeper evaluation is necessary.

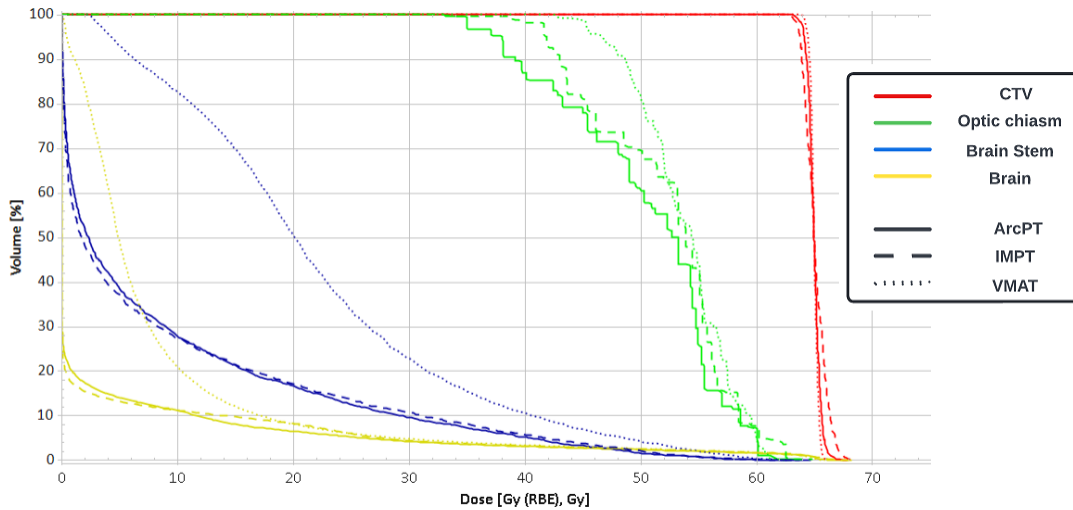


Figure 5.3: Dose Volume Histogram between ArcPT, IMPT and VMAT of the first patient.

5.2 Dosimetric outcome

This section focuses to the dosimetric outcome comparison and the potential benefit of arc proton therapy. The results of ArcPT will be compared two by two with the IMPT and VMAT plans with the mean results over the 3 patients and they will be presented in tables, one for the CTV as shown in the figure 5.4, one for the OARs and finally one for the body and the brain. The differences between the plans have been highlighted to facilitate the reading, a positive value in case of the CTV and a negative value in case of the OARs imply an improvement. All of the dose distributions on CT, the DVHs and the dosimetric outcome tables specific to each patient and each modality are presented in the Annex (section 7).

5.2.1 CTV

The dosimetric evaluation will first start with the CTV coverage, the focus is on the minimum dose present in 95 % and 98 % of the target volume.

D50 = 65 Gy (36 x 1,8 Gy)						
ROI	Clinical Goals	ArcPT (Gy)	IMPT (Gy)	Δ (Gy)	VMAT (Gy)	Δ (Gy)
CTV	D98	63.94	63.31	0.63	64.18	-0.24
CTV	D95	64.17	63.60	0.56	64.37	-0.21

ArcPT is doing better

Figure 5.4: Dosimetric outcome in the CTV for a prescribed median dose of 65 Gy in the CTV.

The first thing the table shows is that there is an improvement on the CTV coverage with ArcPT in comparison to IMPT (an extra 0.63 Gy in the D98 and 0.56 Gy in the D95), this could already be seen on the DVH on the figure 5.3 as it was mentioned before. However, this improvement is not enough in comparison to the VMAT plan which is the one performing better (0.24 Gy and 0.21 Gy lower in D98 and D95 for ArcPT). Thus, there is a potential improvement from IMPT to ArcPT in the tumor coverage.

5.2.2 OARs

Afterwards, a focus on the organs at risk is made in order to know the sparing potential of the plans, the outcome is presented in the figure 5.5.

D50 = 65 Gy (36 x 1,8 Gy)						
ROI	Clinical Goals	ArcPT (Gy)	IMPT (Gy)	Δ (Gy)	VMAT (Gy)	Δ (Gy)
BrainStem	D0,03cc	46.58	48.04	-1.47	51.81	-5.23
Chiasm	D0,03cc	48.79	49.12	-0.33	47.62	1.17
Eye_L	D0,03cc	0.04	0.04	0.00	8.48	-8.44
Eye_R	D0,03cc	0.07	0.05	0.02	7.31	-7.24
LON	D0,03cc	27.72	29.01	-1.29	32.00	-4.28
RON	D0,03cc	16.96	16.72	0.23	28.93	-11.98

	ArcPT is doing better
--	-----------------------

Figure 5.5: Dosimetric outcome in the OARs for a prescribed median dose of 65 Gy in the CTV.

Overall, the ArcPT plan seems to better spare the organs around the tumor as the results in brain Stem, the optic chiasm and the left optic nerve (LON) show it (1.47 Gy, 0.33 Gy and 1.29 Gy lower for the brain stem, the chiasm and the LON respectively in comparison to IMPT). For organs that are localized further of the CTV as the eyes, both protons plan seems to perform similarly with a difference close to zero, but they both outperform the VMAT plan (8.44 Gy and 7.24 Gy lower for both eyes in ArcPT). In the other hand, VMAT improves the dose in the optic chiasm which is an organ close to the CTV in the patients (especially in the second patient where the chiasm were partially included in the CTV), since the photon plans does not have to take into account the range uncertainty errors, it is eventually easier to spare really proximate organs.

5.2.3 Brain and Body

Finally, the mean dose in the brain and the body are evaluated and the results are presented in the figure 5.6.

D50 = 65 Gy (36 x 1,8 Gy)						
ROI	Clinical Goals	ArcPT (Gy)	IMPT (Gy)	Δ (Gy)	VMAT (Gy)	Δ (Gy)
Brain	V60 < 33%	1.29 (%)	1.3 (%)	-0.01 (%)	1.35 (%)	-0.06 (%)
Brain	Mean Dose	3.37	3.30	0.07	7.49	-4.12
Body	Mean Dose	1.04	1.03	0.01	2.51	-1.47

	ArcPT is doing better
--	-----------------------

Figure 5.6: Dosimetric outcome in the body and the brain for a prescribed median dose of 65 Gy in the CTV.

In the case of the mean dose in the brain or body, there is no significant differences in the comparison between ArcPT and IMPT but these two delivery systems are doing better than the photon plan as expected (the mean dose in the brain and the body are reduced by 4.12 Gy and 1.47 Gy respectively in comparison to VMAT). It is the consequence of the way protons and photons interact with matter, protons allowing to have a lower dose delivered on the path of the beam (Bragg Peak curve). The percentage of the volume at 60 Gy is similar in the 3 modalities and well below the clinical objective.

5.3 Worst case scenario

In order to have a better insight of the robustness of the plan, we compared the worst case scenario of ArcPT, IMPT and VMAT plans. Of course, these scenarios are very unlikely to happen and are only used to see which plan, while the worst situation is occurring, was performing better. The dosimetric outcome is presented in the table in the figure 5.7.

Worst scenario comparison						
ROI	Clinical Goals	ArcPT (Gy)	IMPT (Gy)	Δ (Gy)	VMAT (Gy)	Δ (Gy)
CTV	D98	63.19	62.85	0.34	63.61	-0.42
CTV	D95	63.62	63.34	0.29	63.88	-0.26
BrainStem	D0,03cc	57.77	58.49	-0.72	60.03	-2.26
Chiasm	D0,03cc	55.70	56.66	-0.96	53.49	2.21
Eye_L	D0,03cc	0.12	0.07	0.05	9.19	-9.07
Eye_R	D0,03cc	0.22	0.07	0.15	8.77	-8.55
LON	D0,03cc	41.63	44.01	-2.38	44.31	-2.68
RON	D0,03cc	30.15	33.61	-3.47	35.67	-5.53
Brain	V60 < 33%	1.47 (%)	1.54 (%)	-0.07 (%)	1.49 (%)	-0.02 (%)
Brain	Mean Dose	3.78	3.70	0.08	7.88	-4.10
Body	Mean Dose	1.07	1.06	0.01	2.51	-1.44

ArcPT is doing better

Figure 5.7: Overall Worst case scenario evaluation between the 3 plans.

The results obtained in the dosimetric outcome of the worst case scenario are quite similar to what have been seen for the nominal results. The ArcPT plan is still doing better than IMPT to cover the target (an increase of 0.63 Gy in the D98 and 0.56 Gy in the D95 for ArcPT) and VMAT is still the best one for this criteria (0.42 Gy and 0.26 Gy higher for D98 and D95 respectively for the VMAT). Overall, the ArcPT plan is still doing better in the OARs, especially in the brain stem with a reduction of 0.96 Gy and 2.26 Gy in comparison to IMPT and VMAT plans. Even in the worst case scenario, the ArcPT plan still manages to perform well indicating robustness against setup errors and range uncertainties.

5.4 Linear Energy Transfer

The LET distribution was also computed on the 3 patients, the results are presented with a LET Volum Histogram between IMPT and ArcPT plans focused on the CTV, the brain stem and the chiasm.

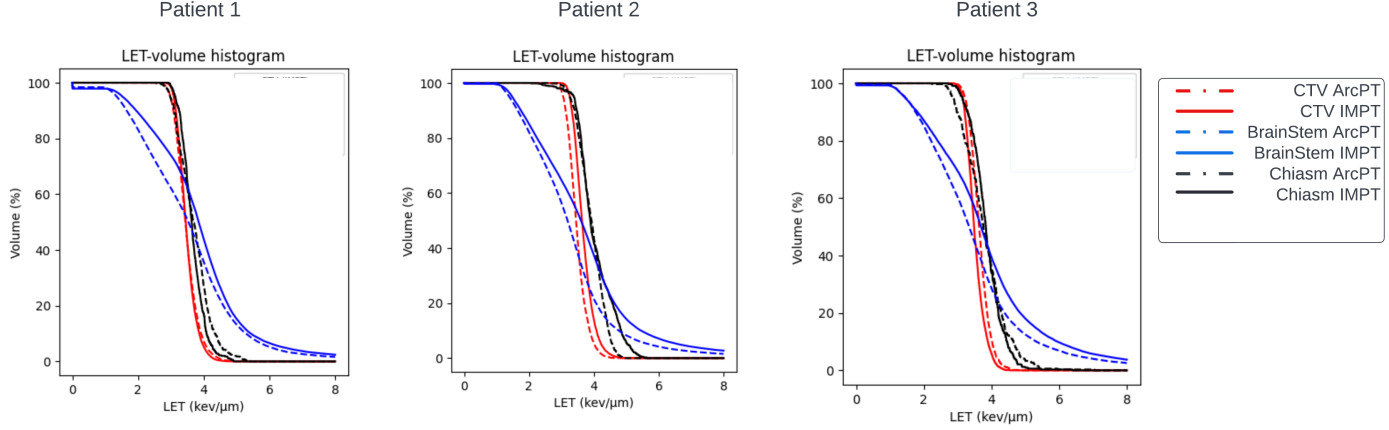


Figure 5.8: Linear energy transfer distribution in the CTV, brain stem and optic chiasm in the 3 patients. The solid lines represent the IMPT plans and the dashed lines, the ArcPT plans.

The LET volume histograms show that the ArcPT plans tend to decrease the LET distribution in the brain stem in each patient which means a potential lower toxicity in this organ. In the optic chiasm, the situation is a little bit trickier, the max LET seems to be lower in patient 2 with ArcPT and higher in the other cases, while the LET is slightly lower in the major part of the volume. In the other hand, the LET distribution in the CTV seems to be quite similar in both plans.

5.5 TCP and NTCP

This section discusses the Tumor Control Probability and the Normal Tissue Complication Probability for the brain stem and the optic chiasm. The results will be presented in box plots for each region of interest and for the 3 patients. In the box plots, the orange line represents the median value, the box regroups the lower to upper quartile values of the data and the whiskers show the percentile 5 and the percentile 95, the values lower than p5 or higher than p95 are presented with circles out of whiskers.

5.5.1 TCP

The figure 5.9 presents the results of each patient separately for the ArcPT, IMPT and VMAT plans obtained with the two different models. The TCP was computed for a set of error scenarios and the box plot form is also used to show the robustness over TCP.

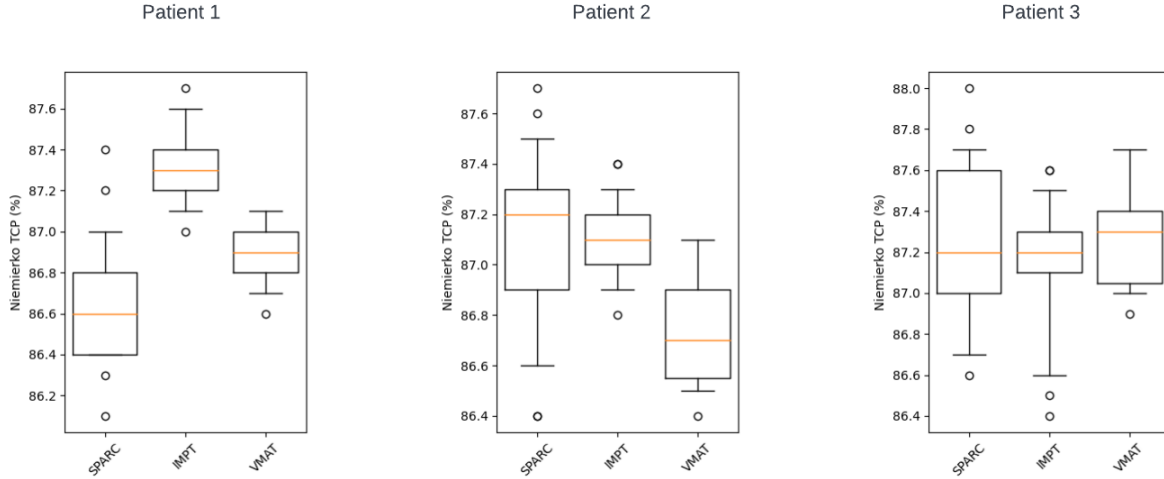


Figure 5.9: Box plots of the TCP distribution related to the error scenarios for each patient.

The data show mitigate results, as in the first patient, the ArcPT plan is lower than the two other plans ($86.6\% \pm 0.281$ vs $87.3\% \pm 0.162$ and $86.6\% \pm 0.148$) but seems to perform well in the other patient with a similar median value with IMPT ($87.2\% \pm 0.323$ and $87.2\% \pm 0.365$ for ArcPT vs $87.1\% \pm 0.148$ and $87.2\% \pm 0.317$ for IMPT). The higher TCP value in the first patient is not in agreement with the dosimetric outcome, it comes probably from an overdose in the CTV (the max dose in the CTV is higher up to 1 Gy) which has implied a higher gEUD (63.53 Gy vs 63.97 Gy for ArcPT and IMPT) and therefore, a higher TCP. Moreover, the IMPT plan seems more robust with a smaller Interquartile Range (IQR) overall.

5.5.2 NTCP Brain Stem

In the same way as previously, the NTCP box plots of the brain stem are presented in the figure 5.10 :

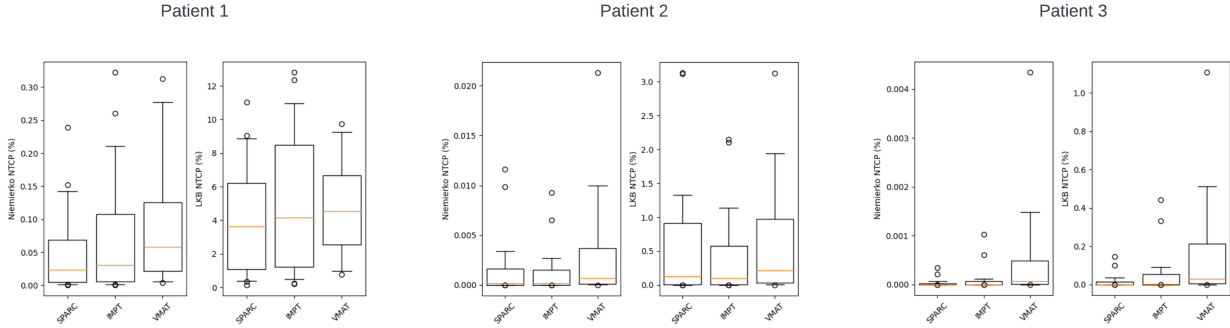


Figure 5.10: Box plots of the NTCP distribution in the brain stem related to the error scenarios for each patient.

In the brain stem, we can see that in general, the probability of complication is very low in this situation, the Niemierko model shows NTCP values close to 0% and the LKB model shows values a little bit higher but there is no median values exceeding 10%. In this situation, the ArcPT plan presents slightly lower median values as it can be seen in the table 5.1 where the best values were colored in green. It also performs better than the other plans in terms of robustness as the IQR in the box plots of the figure 5.10 indicates it. The results in the NTCP evaluation seems to be in agreement with the dosimetric outcome.

	ArcPT		IMPT		VMAT	
	NKO [%]	LKB [%]	NKO [%]	LKB [%]	NKO [%]	LKB [%]
Patient 1	0.023 ± 0.057	3.62 ± 3.08	0.03 ± 0.08	4.15 ± 3.9	0.058 ± 0.096	4.52 ± 2.83
Patient 2	$10^{-4} \pm 2.7 \cdot 10^{-3}$	0.127 ± 0.831	$10^{-4} \pm 2 \cdot 10^{-3}$	0.104 ± 0.593	$6 \cdot 10^{-4} \pm 5.6 \cdot 10^{-3}$	0.216 ± 0.889
Patient 3	$7 \cdot 10^{-7} \pm 7 \cdot 10^{-5}$	$8 \cdot 10^{-4} \pm 0.032$	$2.5 \cdot 10^{-6} \pm 2 \cdot 10^{-4}$	0.003 ± 0.0987	$7 \cdot 10^{-5} \pm 1.1 \cdot 10^{-3}$	0.031 ± 0.293

Table 5.1: NTCP median values and standard deviations in the brain stem for Niemierko and LKB models.

5.5.3 NTCP Optic chiasm

The results of the NTCP calculated in the optic chiasm are displayed in the figure 5.11 :

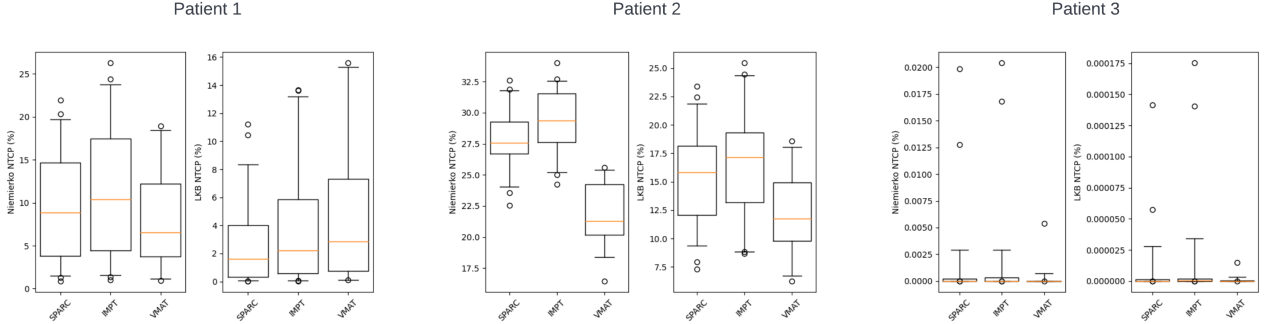


Figure 5.11: Box plots of the NTCP distribution in the chiasm related to the error scenarios for each patient.

The values show that a complication in the chiasm is more likely to happen in comparison to the brain stem (up to 30%). In this case, VMAT is performing better, especially in the second patient ($21.27\% \pm 2.7$ vs 27.56 ± 2.43 and 29.39 ± 2.58 for ArcPT and IMPT respectively) where the chiasm was partially localized in the CTV, the VMAT plan better manages the sparing of very close OARs since it delivers a more homogeneous dose (with less random hot spots) to the target and does not have to take into account additional uncertainties in comparison to protons. Otherwise, the ArcPT plan decreases the probability of complication in comparison to the IMPT plan (e.g. with NKO model, $8.84 \pm 6.4\%$ and $27.56 \pm 2.43\%$ vs $10.37 \pm 7.84\%$ and $29.39 \pm 2.58\%$ for ArcPT and IMPT respectively in patient 1 and 2) and with a smaller IQR overall for both models as it can be seen on the table 5.2. Again, the results from the NTCP evaluation tend to be in agreement with the dosimetric outcome.

	ArcPT		IMPT		VMAT	
	NKO [%]	LKB [%]	NKO [%]	LKB [%]	NKO [%]	LKB [%]
Patient 1	8.84 ± 6.4	1.61 ± 3.26	10.37 ± 7.84	2.21 ± 4.45	6.54 ± 5.85	2.84 ± 5.12
Patient 2	27.56 ± 2.43	15.81 ± 4.26	29.39 ± 2.58	17.1 ± 4.77	21.27 ± 2.7	11.76 ± 3.82
Patient 3	$6.6 \cdot 10^{-6} \pm 4.2 \cdot 10^{-3}$	$1.4 \cdot 10^{-7} \pm 2.8 \cdot 10^{-5}$	$1.3 \cdot 10^{-5} \pm 4.7 \cdot 10^{-3}$	$2.2 \cdot 10^{-7} \pm 4.05 \cdot 10^{-5}$	$4.2 \cdot 10^{-7} \pm 1.3 \cdot 10^{-3}$	$4.3 \cdot 10^{-7} \pm 3.7 \cdot 10^{-6}$

Table 5.2: NTCP median values and standard deviations in the optic chiasm for Niemierko and LKB models.

5.6 Homogeneity Index

The homogeneity index is a great tool to highlight the capacity of a treatment plan to cover the target correctly. The HI was calculated for different scenarios of uncertainty in order to give an idea of the robustness of the plan to achieve the target objectives with the potential errors. The results of the HI for IMPT, VMAT and ArcPT in every patient are presented in box plots in figure 5.12 where the median values are the orange lines.

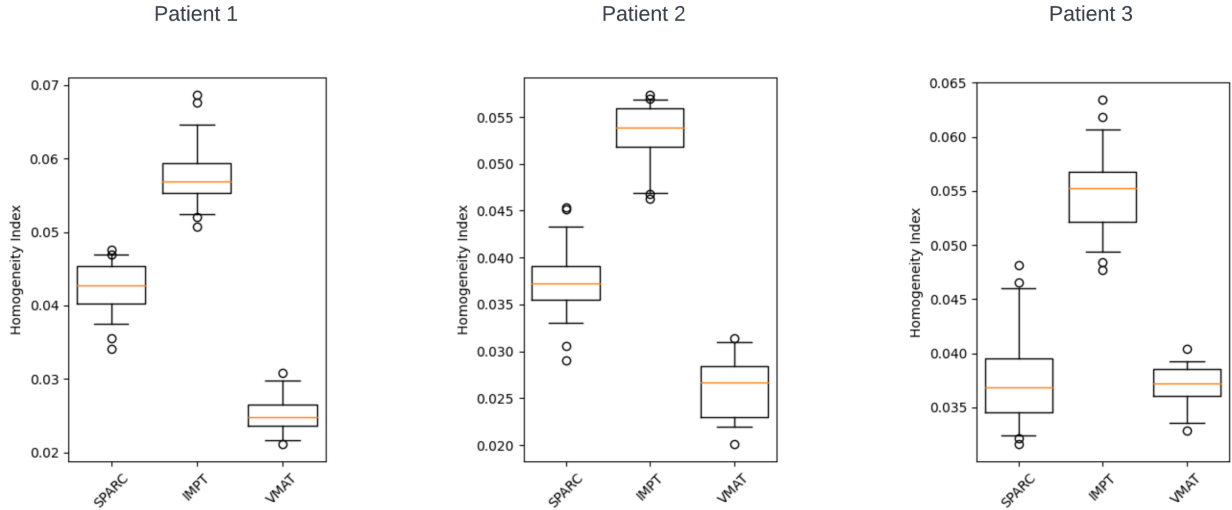


Figure 5.12: Box plot of the homogeneity index with ArcPT, IMPT and VMAT plans for the 3 patients.

As the figure shows it, for the 3 patients, the ArcPT plan has a median homogeneity index closer to zero each time in comparison to IMPT, meaning that the treatment delivers a more homogeneous dose in the target (the median values are 0.0569, 0.0538 and 0.0552 vs 0.0427, 0.0372 and 0.0368 respectively for the IMPT and the ArcPT plans). Moreover, this is the case no matter the scenario of errors occurring to the plan as the boxes of ArcPT are entirely lower than IMPT ones. Proton therapy applied with the help of an arc seems to increase the robustness in comparison to IMPT concerning the homogeneity in the target volume. As it could have been expected with the dosimetric results in the CTV, VMAT is the modality which is delivering the most homogeneous dose to the target (HI median values: 0.0248, 0.0267 and 0.0372).

5.7 Conformity index

As the HI, the conformity Index and Number were calculated among a bunch of scenarios of set up errors and range uncertainties. The CI is presented in box plots (figure 5.13) for each patient, where the median values are the orange lines. In order to not overload the figure, only the median values of the CN are presented and compared to the CI values.

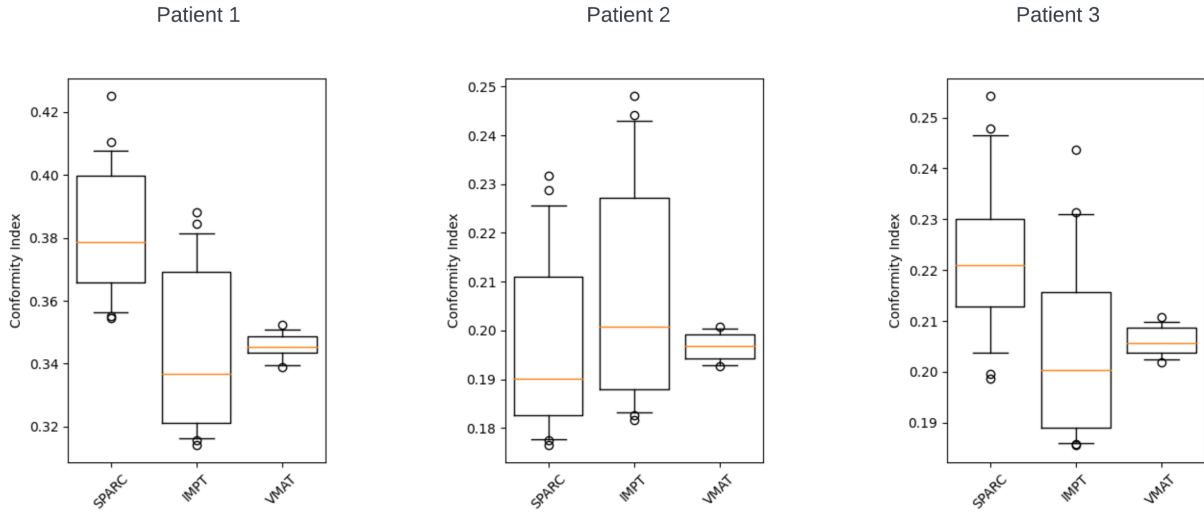


Figure 5.13: Box plot of the conformity index with ArcPT, IMPT and VMAT plans for the 3 patients.

The box plots in figure 5.13 indicate that ArcPT performs well overall, with median values (0.379, 0.19 and 0.221 for the patient 1, 2 and 3 respectively) closer to 1 in comparison to IMPT (0.337, 0.201, 0.2) and VMAT (0.345, 0.197, 0.206). We can also see that the values are higher overall in the first patient because of a bigger tumor volume for the same errors settings. The Conformity Number evaluation manifests a very good coverage of the target in general, since there is no significant difference between the median CI and CN values (ArcPT : 0.378, 0.19, 0.221 ; IMPT : 0.337, 0.201, 0.2 ; VMAT : 0.345, 0.197, 0.206). VMAT is the most robust plan in order to maintain a good conformity with a much smaller IQR, partially due to the fact that there is no range uncertainty to consider with photon plans. However, on that point, ArcPT manages to improve the robustness in comparison to IMPT with a smaller IQR in the 3 patients.

5.8 Beam delivery time

The beam delivery time for ArcPT and IMPT in every patients are presented in the figure 5.14 with some extra information about the number of energy layers, initial beams and switch ups.

	Patient 1		Patient 2		Patient 3	
Delivery system	ArcPT	IMPT	ArcPT	IMPT	ArcPT	IMPT
Energy Layers	72	35	68	30	72	33
Initial beams	2 x 3	2	2 x 3	2	2 x 3	2
Switch up	5	/	5	/	5	/
Delivery time (s)	119,2	27,8	113	24,1	118,8	25,8

Figure 5.14: Beam delivery time and number of energy layers for IMPT and ArcPT plans in the 3 patients.

While the ArcPT plans take around 2 minutes to be delivered, the IMPT plans take only about 25 seconds but that is without taking into account the waiting time of 55 seconds between the beams. Since the IMPT plans are only composed of 2 beams, IMPT is still delivering the treatment faster (~ 80 seconds) than ArcPT but, that increase in time is acceptable if there is advantages in return, as the dosimetric outcome or the LET distribution. Indeed, the ArcPT plans duration are more similar to IMPT plans with 3 beams. The BDT of the ArcPT could have been lower because, as mentioned in the table 5.14, it consists of 5 switch ups which are time consuming. Initiate the plans with a lower number of beams could reduce the final BDT but it would result in a deterioration of the plan quality.

Chapter 6

Discussion

The results obtained in this study tend to show potential benefits in the use of ArcPT. It seems that ArcPT is able to take advantage of proton therapy such as a lower mean dose in the brain and the body, a better sparing of the organs at risk located quite far from the target. It also benefits of the advantages of using an arc since a better coverage of the target than IMPT was observed (but VMAT is still performing better on that point) and also a better sparing of the important OARs such as the chiasm and the brain stem, comforted by the NTCP evaluation. Likewise, ArcPT improves the homogeneity index and the conformity index of the IMPT plan with less variations under uncertainties. While scenarios of uncertainties are occurring, the ArcPT is still performing well in terms of robustness, even taking the worst case scenario. ArcPT also manages to decrease the LET distribution in the brain stem which is great in order to reduce potential toxicities in this OAR. These results are in agreement with the literature available for the moment for different contexts, these studies were resumed in the table 3.1.

On the other hand, the ArcPT delivery seems to take a little bit longer than IMPT with the actual machine characteristics. Data coming from the literature shows similar results. However, the studies also indicate that the beam delivery time becomes similar between the two modalities for lower energy layer switch times (0.5s or 1s depending of the study) and for values even lower, ArcPT can become faster which comfort us in the possibility to improve the beam delivery time in the future.

The radiotherapy workflow is going through many different steps which imply uncertainties. From the patient imagery with the resolution of the machine, the delineation of the organs and the tumor or the image conversion. Passing by the uncertainties of the dose calculation due to the physics to the accuracy of the delivery system and the positioning errors of the patients. A majority of them are included in the optimization process with the set up errors and the range uncertainty. They are evaluated with the robustness and the one that are not included in it, have a minor impact in comparison. Therefore, the biggest uncertainty concern in this study is more related to the heuristic process than to physical uncertainties.

6.1 Limitations

There are some limitations in this study implying that we should take with care the results given above, the main objective was a preliminary study in order to have an idea of the behaviour of the ArcPT plan and to discuss it. First, 3 patients are surely not enough to make a strict conclusion about the efficiency of the plan to be able to improve the dosimetric outcome or the beam delivery time, even more as this work is restricted to a particular case of brain tumor. The results could be totally different in other organs and ArcPT could be endowed with qualities that could become very interesting in very specific cases.

Another limitation comes from the fact that ArcPT was planned with the IMPT plan as a starting point and was not initialized with its own objective functions. It means that, the weights or the values could be not perfectly adapted to this modality and we could expect better results if we had the possibility to optimize the ArcPT plans with more strict objectives.

Afterwards, there is also a limitation based on the heuristic point of view of the evaluation of the plans. Despite the method established in order to make the most fair comparison, the plans are sensitive to the initial conditions, little details can have an impact in the final optimized plan. It even become a bigger issue in the case of ArcPT since the splitting beam and optimization time is very long (several hours), and the possibility to adjust parameters during this process is null, so trying to observe the variation in the final results by changing initial settings requests the creation of a whole new plan each time and this is strongly time-consuming. We have to remind that in a clinical environment, it is not possible to allow so much time on creating plans, looking at the final results and restarting if necessary, and also this search of the "best possible" plan was made in a framework of an evaluation study and are the results of a long time period of thinking for each patient. The creation of detailed guidelines to create a treatment plan will be inevitable if one day, the ArcPT technology has to be integrated to the clinical routine, and this work suggests some ideas as a result of the observations made while trying to achieve the best possible plan.

6.2 Improvements

A first place of innovation could be the delivery system itself with the decrease of the energy layer switch time, especially in the switch ups. This could first improve the delivery time of the therapy and then, it could allows us to get rid of the limitation in the ArcPT script which implies sorted energy layers. Indeed, the energy resampling could be applied in a different way, it could erase the necessity of decreasing the energy layers during the rotation of the gantry and it would add more flexibility to the algorithm that could improve the quality of the plans.

Another place of potential amelioration is the optimization algorithm. A decrease of the optimization time could bring benefits like the possibility to create, evaluate and compare plans faster and so, the possibility of a study on a larger scale (an algorithm from RaySearch is now available in our RayStation version and can be a first direction to study). This will also lead to an easier access in clinical environment, as a treatment planification which takes too much time could not be included in the radiotherapy workflow. Moreover, it would allow to imagine a more complex treatment plan, even the eventuality of many arcs, as it already exists with VMAT and it has shown great results with photons. This would also need an improvement of the delivery time.

Heuristic choices take a big part of the plan optimization. A first possibility of improvement is the creation of a consistent planification method for ArcPT that could be included in a clinical workflow, in order to try to get the best out of this technique in terms of plan quality and delivery time without losing too much time on the process. A method has been proposed by S. Wuyckens (MIRO, UCLouvain) in her paper "Treatment Plan Optimization in Arc Proton Therapy: Theory, Algorithms and Benchmarks" (article in revision) to counter this issue with an optimization algorithm in order to choose the tradeoff between BDT and plan quality at the end of the process instead of tuning the parameters ourselves at the beginning of the process.

Chapter 7

Conclusion

As VMAT has improved radiotherapy, it comes naturally that ArcPT can become the new way of doing proton therapy and so, studies on the potential benefits of such a delivery system are needed before expecting a clinical implementation.

After a brief introduction of the brain anatomy and the differences between photons and protons, this thesis goes through the radiotherapy workflow in order to present some clinical backgrounds and to give a wider view on the whys and wherefores of the study. The optimization algorithm which allows us to create an ArcPT plan was presented and followed by a literature review of results already observed in other contexts. Once all the required information was settled, we introduced the methods and the metrics used during this work in order to evaluate the quality and efficiency of ArcPT.

This preliminary study compared dosimetric, LET, beam delivery time and robustness performances of VMAT, IMPT, and ArcPT plans for the treatment of a brain tumor. The results obtained show a potential improvement with a better target coverage, some benefits in the OARs sparing, as a lower dose and LET distribution. Moreover, ArcPT kept the advantages of the use of protons in comparison of photons with less dose deposited in the brain and the body overall. In the other hand, ArcPT reveals a little longer delivery time than IMPT which is acceptable in return of plan quality and it can be improved in the future.

Overall, the results obtained in this study were in agreement with the literature available for the moment. However, additional patients will be required to conclude on the advantages and limitations of the new ArcPT modality. Furthermore, the plan quality will probably continue to improve with the future innovations in ArcPT optimization algorithms. The results and the potential improvements comfort us in the idea that one day, arc proton therapy could fit in the radiotherapy workflow for cancer treatment.

Personally, if I had the possibility to go further in this study, I would first work on more patients in order to extend the results already obtained and to validate them. Then, I would probably use the script proposed by the RayStation TPS to make a comparison with the one used in this work in order to observe some potential improvements. Finally, I would try to work on a new script in order to overcome the limitations that restricted me in the planification process, and that could lead to an improvement of the ArcPT plans.

Annexes

Caption

The dose distribution on the CT-scans of the patients and the DVHs for the each delivery modalities are displayed in the next paragraphs. In order to not overload this section, the same caption is used for all the figures and is presented in the figure 7.1.

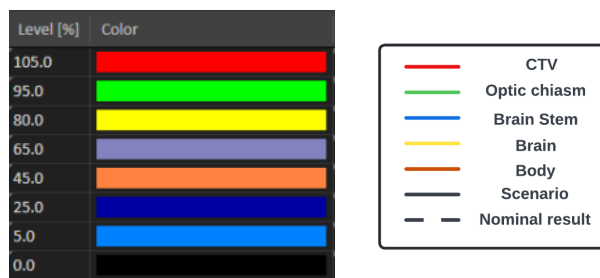


Figure 7.1: Left : Color scale associated to the dose level [% of the prescribed dose].
Right: Caption of the different ROIs associated to a line color for the DVHs.

Patient 1

Dosimetric outcome

Patient 1 : Nominal result						
ROI	Clinical Goals	ArcPT (Gy)	IMPT (Gy)	Δ (Gy)	VMAT (Gy)	Δ (Gy)
CTV	D98	63,9	63,51	0,39	64,27	-0,37
CTV	D95	64,1	63,79	0,31	64,47	-0,37
BrainStem	D0,03cc<54Gy	59,65	60,61	-0,96	61,61	-1,96
Chiasm	D0,03cc<54Gy	58,72	58,88	-0,16	59,45	-0,73
Eye_L	D0,03cc<50Gy	0,02	0,02	0	9,22	-9,2
Eye_R	D0,03cc<50Gy	0,01	0,03	-0,02	7,48	-7,47
LON	D0,03cc<54Gy	24,09	24,5	-0,41	41,57	-17,48
RON	D0,03cc<54Gy	20,66	19,56	1,1	32,12	-11,46
Brain	Mean Dose	3,74	3,89	-0,15	8,23	-4,49
Body	Mean Dose	1,34	1,39	-0,05	3,41	-2,07

ArcPT is doing better

Figure 7.2: Dosimetric outcome in patient #1

ArcPT

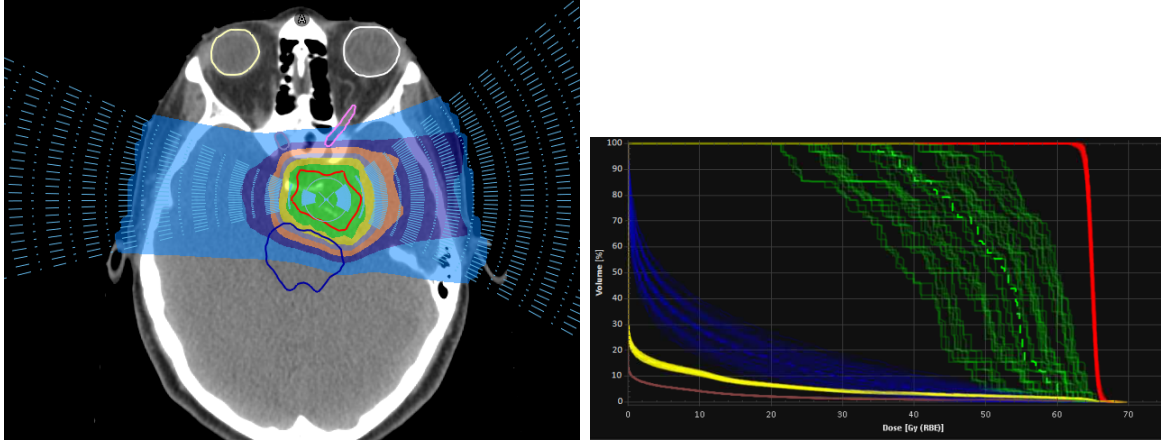


Figure 7.3: Left : Dose distribution of ArcPT in the CT. Right: DVH for all scenarios, the dashed line is the nominal result.

IMPT

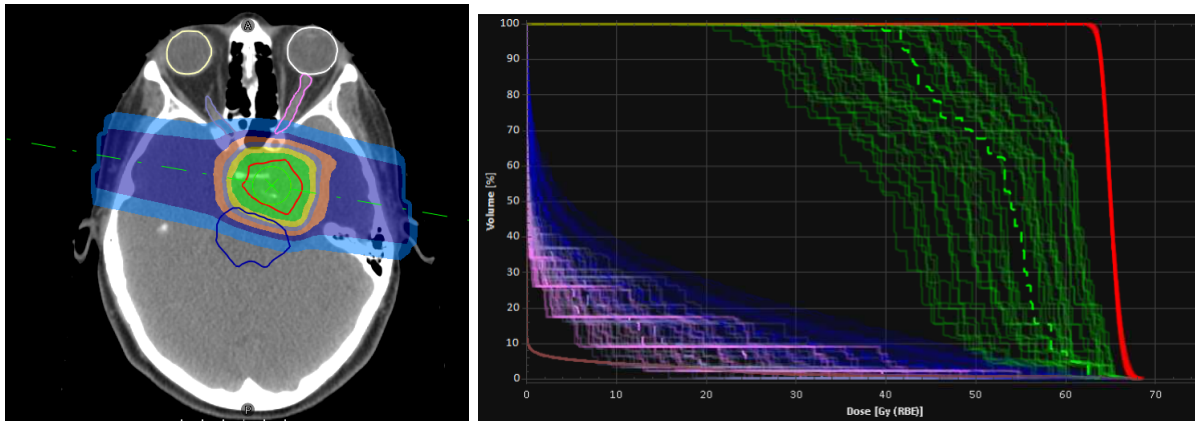


Figure 7.4: Left : Dose distribution of IMPT in the CT. Right: DVH for all scenarios, the dashed line is the nominal result.

VMAT

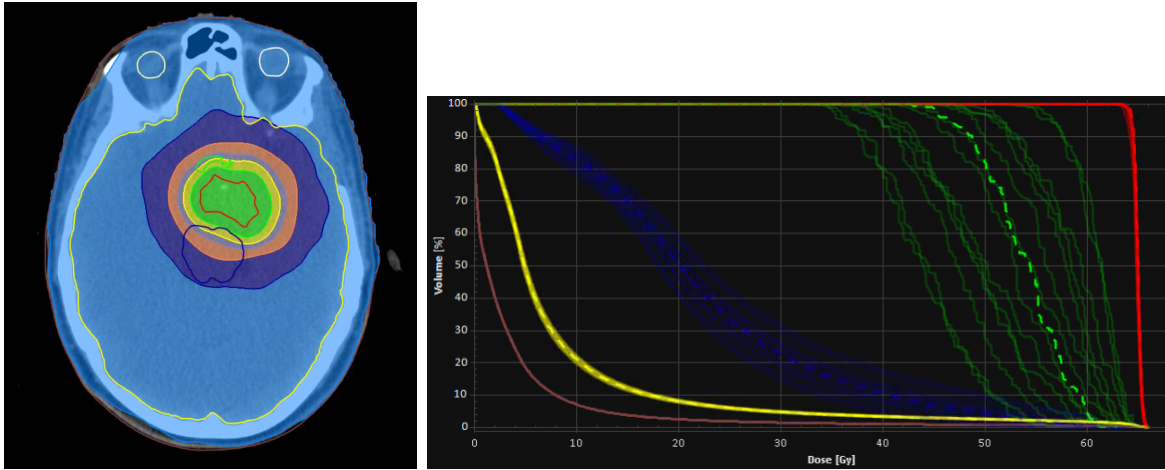


Figure 7.5: Left : Dose distribution of VMAT in the CT. Right: DVH for all scenarios, the dashed line is the nominal result.

Patient 2

Dosimetric outcome

Patient 2 : Nominal result						
ROI	Clinical Goals	ArcPT (Gy)	IMPT (Gy)	Δ (Gy)	VMAT (Gy)	Δ (Gy)
CTV	D98	64,09	63,24	0,85	64,26	-0,17
CTV	D95	64,25	63,6	0,65	64,5	-0,25
BrainStem	D0,03cc<54Gy	47,96	49,71	-1,75	50,67	-2,71
Chiasm	D0,03cc<54Gy	65,59	66,17	-0,58	64,36	1,23
Eye_L	D0,03cc<50Gy	0,09	0,08	0,01	10,7	-10,61
Eye_R	D0,03cc<50Gy	0,09	0,04	0,05	8,9	-8,81
LON	D0,03cc<54Gy	28,61	30	-1,39	25,13	3,48
RON	D0,03cc<54Gy	13,25	13,88	-0,63	25,74	-12,49
Brain	Mean Dose	3	2,71	0,29	6,74	-3,74
Body	Mean Dose	0,83	0,77	0,06	2	-1,17

ArcPT is doing better

Figure 7.6: Dosimetric outcome in patient #2

ArcPT

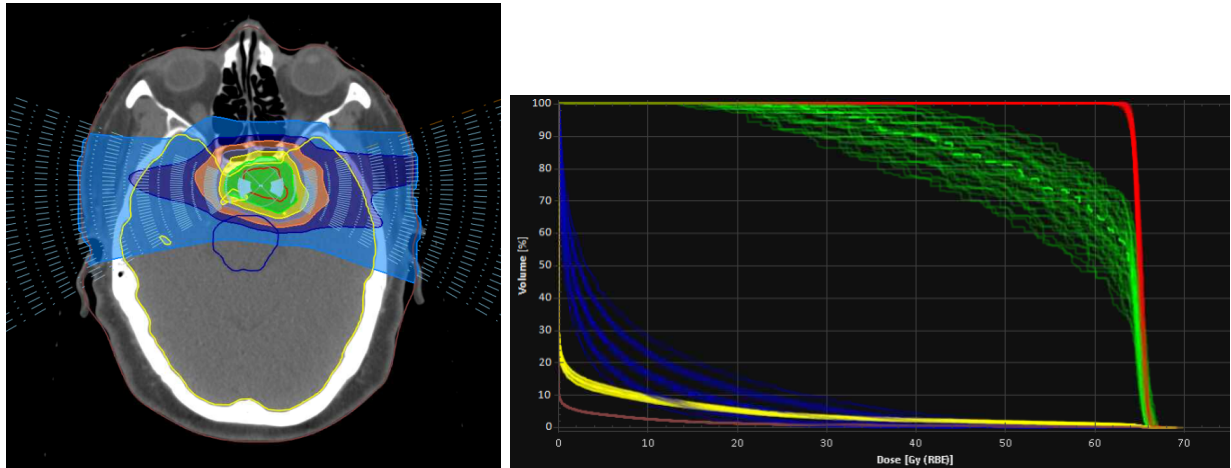


Figure 7.7: Left : Dose distribution of ArcPT in the CT. Right: DVH for all scenarios, the dashed line is the nominal result.

IMPT

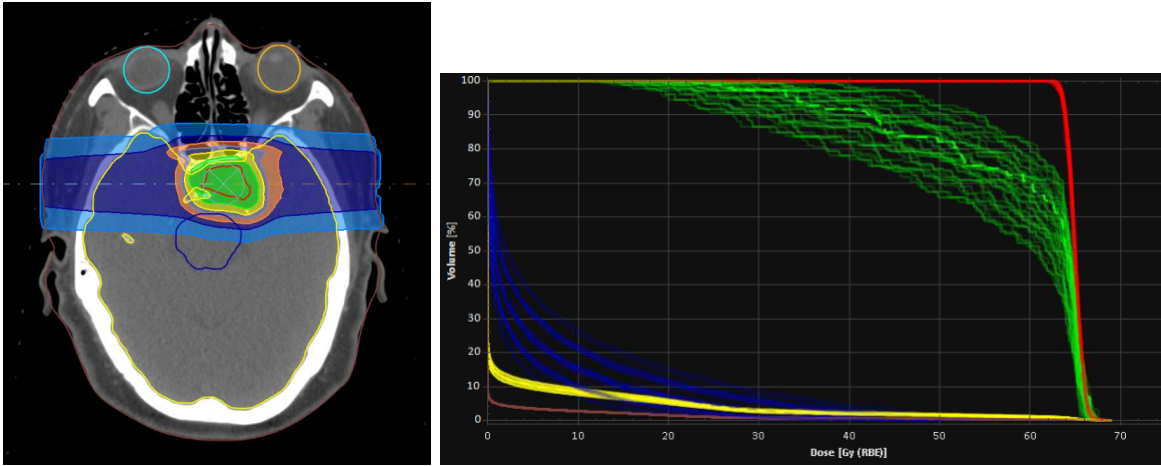


Figure 7.8: Left : Dose distribution of IMPT in the CT. Right: DVH for all scenarios, the dashed line is the nominal result.

VMAT

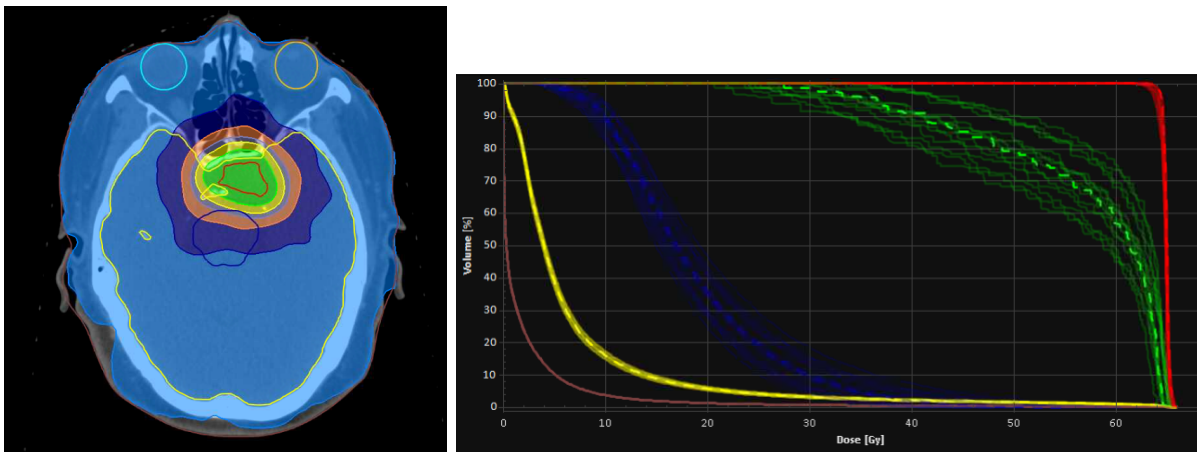


Figure 7.9: Left : Dose distribution of VMAT in the CT. Right: DVH for all scenarios, the dashed line is the nominal result.

Patient 3

Dosimetric outcome

Patient 3 : Nominal result						
ROI	Clinical Goals	ArcPT (Gy)	IMPT (Gy)	Δ (Gy)	VMAT (Gy)	Δ (Gy)
CTV	D98	63,83	63,18	0,65	64,01	-0,18
CTV	D95	64,15	63,42	0,73	64,15	0
BrainStem	D0,03cc<54Gy	32,12	33,81	-1,69	43,15	-11,03
Chiasm	D0,03cc<54Gy	22,05	22,31	-0,26	19,04	3,01
Eye_L	D0,03cc<50Gy	0,01	0,03	-0,02	5,53	-5,52
Eye_R	D0,03cc<50Gy	0,1	0,07	0,03	5,54	-5,44
LON	D0,03cc<54Gy	30,45	32,53	-2,08	29,3	1,15
RON	D0,03cc<54Gy	/	/	/	/	/
Brain	Mean Dose	/	/	/	/	/
Body	Mean Dose	0,94	0,93	0,01	2,11	-1,17

ArcPT is doing better

Figure 7.10: Dosimetric outcome in patient #3

ArcPT

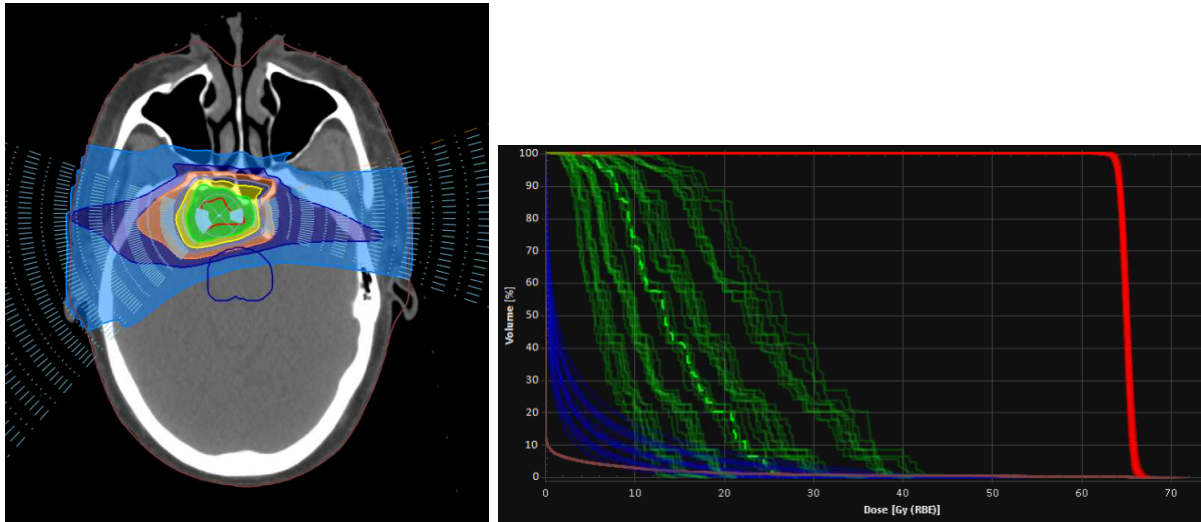


Figure 7.11: Left : Dose distribution of ArcPT in the CT. Right: DVH for all scenarios, the dashed line is the nominal result.

IMPT

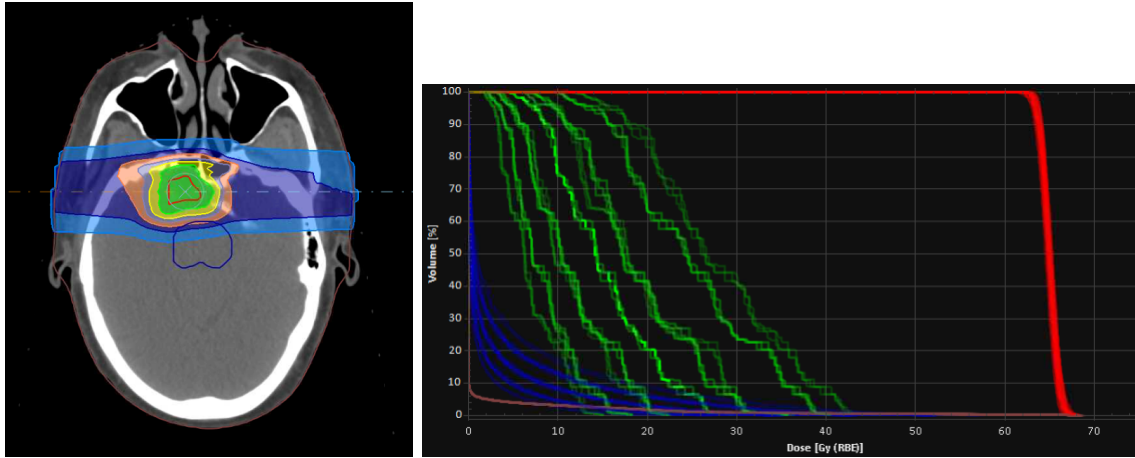


Figure 7.12: Left : Dose distribution of IMPT in the CT. Right: DVH for all scenarios, the dashed line is the nominal result.

VMAT

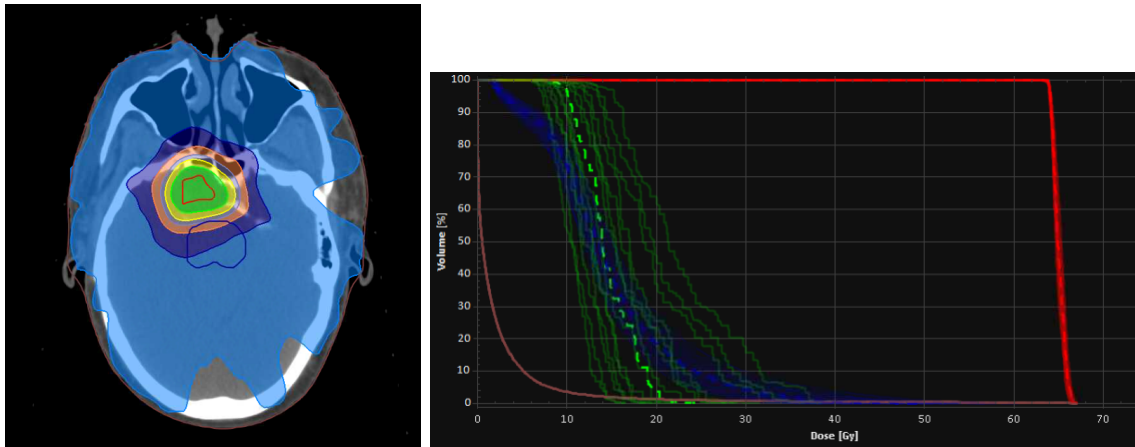


Figure 7.13: Left : Dose distribution of VMAT in the CT. Right: DVH for all scenarios, the dashed line is the nominal result.

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