

Faculty of Sciences

Implementation of probabilistic robust optimization with contour propagation uncertainty in adaptive radiotherapy

Thesis submitted for the purpose of obtaining the academic degree of
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Abstract

Background/purpose: Radiotherapy aims to effectively target tumor volumes with adequate doses while preserving nearby healthy cells. It is challenged by the dynamic nature of patient anatomy, leading to significant uncertainties in the position of structures, which impact treatment quality. Traditional approaches, such as using conservative margins to account for positional errors, tend to be overly conservative. Adaptive radiotherapy provides a dynamic approach, adjusting to anatomical changes. However, it requires significant time and resources for frequent re-contouring structures for each optimization phase.

Materials/methods: The use of Deformable Image Registration (DIR) through a neural network significantly speeds up the contouring process. Uncertainties related to these DIRs can be taken into account to form probability maps (PM) of the positions of the structures. We have implemented a *fully probabilistic* optimization method which weights the optimization cost function according to the probability of a setup error (the only error considered in this work) and considers probabilistic masks of structures. We compared the *fully probabilistic* workflow with different optimization methods: classic and worst case and with different structures definition. We also simulate classic non-adaptive workflow.

Results: The classic workflow without optimization shows its limitations by not fulfilling 5 of the 14 constraints/objectives. The structure propagation appears to be validated as it resembles the structures segmented by physicians. The fully probabilistic method appears promising, delivering almost always the lowest doses to organs at risk. However, the tumor itself is not irradiated enough, indicating a need to modify weights, monitor units and indicating the difficulty of weighting constraints for PM targets.

Conclusion: The outcomes confirm the applicability of a neural network in facilitating unsupervised structure propagation. Probabilistic optimization seems to work correctly but should be used with different constraint/objective weights compared to other methods. This is because PM also generate a weighting of dose constraints/objectives.

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Chapter 1

Introduction

Cancer, along with heart disease, is one of the leading causes of premature death [1], with about one in three individuals facing a diagnosis in their lifetime. Tragically, nearly half may succumb to this disease according to the American Cancer Society [2]. Approximately fifty percent of these patients diagnosed with cancer undergo radiotherapy as part of their treatment, often in conjunction with surgery or chemotherapy [3].

The goal of radiotherapy is to deliver therapeutic doses to tumors while minimizing side effects on healthy tissues. Accurately understanding the location of both the organs and the tumor region presents paramount and intricate challenges, essential for the effectiveness of the treatment. This becomes particularly challenging when radiological imaging acquisition and treatment planning do not coincide with the actual treatment time. Managing anatomical variations and uncertainties in treatments introduces significant variability, which can potentially affect the outcomes of the treatment.

1.1 Motivation of the study

The classic Radiotherapy Treatment (cRT) approach involves conducting a planning Computed Tomography (CT) scan prior to the patient's treatment, on which the physicians will delineate the organs at risk and the visible tumor regions. To account for potential anatomical changes during the treatment, two margins, expansion zones, are incorporated around the tumor area. The first margin accounts for non-visible tumor infiltration, it defines the Clinical Target Volume (CTV). The second addresses geometric uncertainties stemming from anatomical changes and potential patient positioning errors that might occur during the treatment, which can extend over several weeks with daily treatment sessions called fractions. It defines the Planning Target Volume (PTV). The treatment plan is then optimized for this anatomical region of the PTV.

However, this strategy of margins has its limits [4, 5]. Anatomical movements are continuous and unpredictable, especially over such extended durations, rendering the margins overly conservative.

Developed 25 years ago, Adaptive Radiotherapy Treatment (ART) involves re-optimizing the treatment plan based on the patient's anatomical changes, captured at certain intervals. Significant variations may prompt offline ART, involving re-

planning with a new CT scan. In areas where anatomy changes rapidly and where organs at risk are radiosensitive, online ART (oART) is used, necessitating daily redelineation and reoptimization of treatment volumes.

The primary challenge of online adaptive radiotherapy (oART) is its time and resource consumption, particularly due to the need for physicians to segment anatomical regions of interest in daily images, making its clinical application difficult. Alternatively, structure propagation using Deformable Image Registration (DIR) can be employed. While promising, this method introduces DIR uncertainties, necessitating physician checks and take approximately 12 minutes by fractions [6].

Neural networks can perform DIR in just a few seconds [7]. Therefore, numerous registrations can be executed, and uncertainties can be directly incorporated into the definition of organs and targets, resulting in probability maps (PM) of structure presence. These PMs can replace the limited concept of binary margins and be directly used in the optimization process.

The innovative approach, recently developed by Luciano A. Rivetti at the University of Ljubljana, leverages DIR with Neural Networks to align structures from the planning CT to match daily-images. It incorporates uncertainties arising from various deformations to generate daily PM for structural positions, which are then directly integrated into a probabilistic robust optimization process. This optimization directly incorporates uncertainty by weighting the optimization based on the probability of different possible scenarios.

1.2 Aim of the project

This master thesis aims to introduce different probabilistic robust optimization concepts, implement them in a Treatment Planning System and compare their performance against two other approaches: (1) non-adaptive cRT and (2) daily online ART optimized with structures delineated by physicians. Additionally, different optimization methods are assessed: (A) classic optimization, (B) robust worst-case optimization, and (C) robust probabilistic optimization.

1.3 Approach

For a patient with a head and neck tumor, we will create a treatment plan and simulate the different fractions as follows:

- Utilize the Deep Learning DIR developed by Luciano A. Rivetti to register the planning CT to the daily CBCT image.
- Use several deformation fields generated by this registration to propagate the structures onto the CBCT, thereby obtaining a probability map of structure presence.
- Create a synthetic CT by correcting the Hounsfield units of the CBCT and check its reliability.

- Generate various treatment plans using the OpenTPS implemented by Luciano Rivetti. These plans will be 21-beams IMRT based on the synthetic CT. The different plans are as follows:
 - **Classic Workflow** : Based on the planning CT and physician-delineated contours. Classic optimization on the PTV.
 - **Online Adaptive Radiotherapy Workflow**: Utilizing the daily synthetic CT and physician-delineated contours. Classic optimization on the PTV.
 - **Online Adaptive Radiotherapy Workflow** with Probabilistic Maps: Based on the daily synthetic CT and contours formed by the probabilistic map with a probability greater than 0.5. Classic optimization on the PTV.
 - **Online Adaptive Radiotherapy** with Robust Worst-Case Optimization: Utilizing the daily synthetic CT and contours formed by the probabilistic map with a probability greater than 0.01. Robust worst-case optimization on the CTV.
 - **Fully Probabilistic Online Adaptive Radiotherapy Workflow**: Based on the daily synthetic CT and contours formed by the entire probabilistic map. Robust probabilistic optimization on the CTV.
- Compare the evolution of dosimetric values for anatomical regions of interest and Target Volume Dose in the context of head and neck treatment. The comparison metrics depend on the organs studied and are based on dose constraints. The following ROIs are typically considered: PTV, Brainstem, Spinal Cord, Parotid Glands, Larynx, Muscles of the Constrictor, Submandibular glands and Esophagus.

1.4 Structure

Chapter 2, *Clinical Context*, discusses the fundamentals of radiotherapy, defines optimization and the steps involved in creating a treatment plan, and introduces the uncertainties encountered during the treatment creation and delivery.

Chapter 3, *State of the Art of Uncertainties Management*, develops the evolution of the managing uncertainties methods. It discusses the current but increasingly criticized margin concept, the more and more widespread offline and online adaptive methods, and the future method that is the subject of this thesis ; probabilistic maps and robust optimization technique.

Chapter 4, *Theoretical Concepts*, addresses the basic concepts necessary for understanding this thesis, which include the concept of dose and some anatomical concepts of the head and neck.

Chapter 5, *Materials and Methods*, explains all the steps that allowed for create and incorporate DIR uncertainties into the optimization of a treatment plan. This begins with multiple DIRs from the CT to the CBCT, creating a probability map of the structures and a synthetic CT. Then, we define the different radiotherapy workflow using various structures and optimization techniques that we will simulate and compare.

Chapter 6, *Results*, analyze the metrics of various structures in order to observe the effects of probabilistic optimization and the PM. Comparison with other workflows.

Chapter 2

Clinical context

Cancer treatments fall into two main categories: systemic (like chemotherapy and immunotherapy) that targets cancer cells throughout the body, and loco-regional (such as surgery and radiotherapy) focusing on specific areas. Surgery is the primary treatment, but over fifty percent of patients receive radiotherapy during their treatment, which offers benefits like non-invasiveness, precision and potential for partial automation thanks to new technologies and the development of artificial intelligence.

This chapter will begin by explaining the basic principles of radiotherapy. Then, it will cover the key points in creating a classic radiotherapy plan, from imaging to optimization. Finally, it will introduce the challenges presented by uncertainties arising during the treatment and its creation.

2.1 Basic principle of radiotherapy

Cells, the fundamental units of life, form tissues and organs in the human body. Each human cell, containing a nucleus with DNA, is vital for organism functions like protein production and cell division. However, when DNA mutations occur, possibly from radiation or replication errors, cells can become unresponsive to biological signals that control growth. These mutated cells, growing uncontrollably, become cancerous, disrupting the body's normal functioning.

Radiotherapy is based on the interaction between energetic particles (mainly photons, protons and electrons) and the atoms that make up the DNA. These particles can have both direct effects, such as damaging DNA strands (single and double), and indirect effects, such as ionization and the creation of free radicals (base and sugar damage). These interactions can lead to alterations in DNA, ultimately resulting in lethal mutations within the cell.

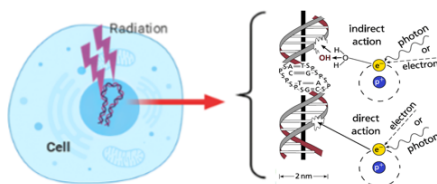


Figure 2.1: Effects of ionizing radiation on Eucaryot cell [8].

Even though cancer cells show a greater radiosensitivity to ionizing radiation, both healthy and cancerous cells undergo similar effects when exposed to radiation. In the context of radiotherapy treatment, the challenge lies in the difficulty of minimizing damage to healthy cells while ensuring a sufficiently high dose to destroy cancerous cells.

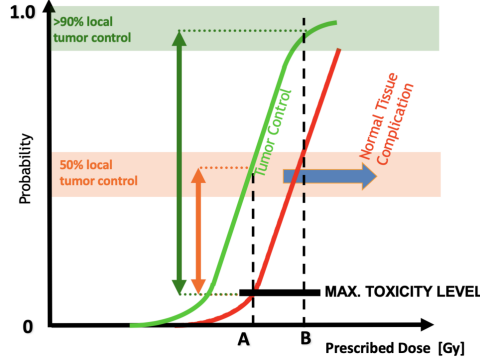


Figure 2.2: Probability of tumor control and normal tissue complication depending on the proscribed dose [9].

To minimize the impact on healthy tissues, it is crucial to precisely define and aim the geometric positions of cancerous cells, even in the presence of uncertainties arising from various anatomical and positional movements.

The choice of particles is a significant consideration when planning radiotherapy. Photons are by far the most commonly used particles in radiotherapy due to their predictable attenuation and cost-effectiveness. Heavier particles such as protons and carbon ions are becoming increasingly widespread due to the fact that they can reduce total energy deposition in the patient. However, the use of heavy particles introduces an additional level of uncertainty compared to photons due to their finite range.

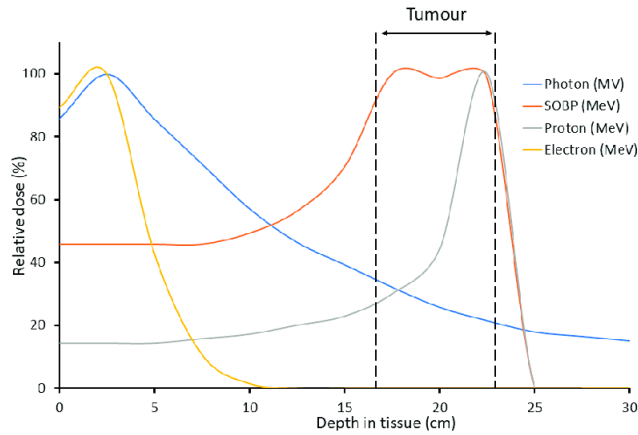


Figure 2.3: Comparison of depth-dose distribution of photons, protons, and electrons relative to a target tumor. A spread-out Bragg peak (SOBP) from several modulated proton beams is also shown [10].

2.2 Radiotherapy Workflow

The radiotherapy workflow encompasses all the sequential processes that culminate in the delivery of the treatment. Classic non-adaptive workflow typically involves pre-treatment imaging, treatment optimization through simulated planning, and a series of identical fractions over a period of 3-4 weeks. This method is the most widespread and simplest methods of treatment because it does not involve additional optimization steps.

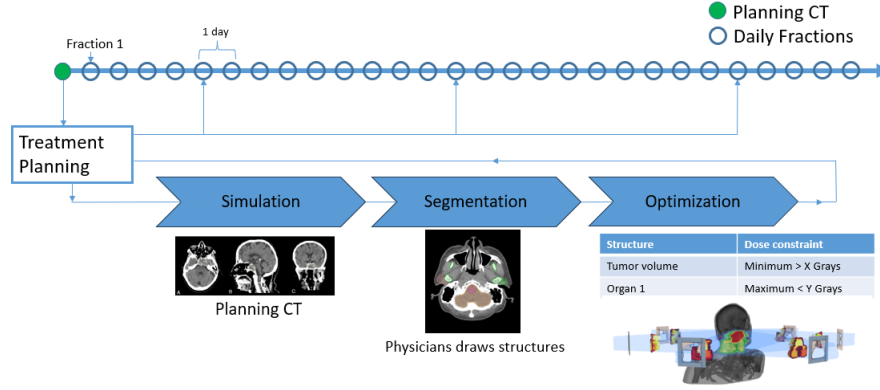


Figure 2.4: Workflow of the classical non adaptive radiotherapy.

Let us analyze step by step the process of creating the treatment plan.

2.2.1 Imaging

The radiotherapy workflow starts with a 3-dimensional planning Computed Tomography (pCT) scan, where a rotating X-ray tube measures the attenuation of X-rays through the body, creating an anatomical map represented by Hounsfield Units (HU) indicative of tissue photon attenuation ;

$$HU = 1000 \frac{\mu - \mu_{water}}{\mu_{water} - \mu_{air}} \quad (2.1)$$

with μ the linear attenuation coefficient.

The acquisition of the pCT have multiple purpose in radiotherapy: it allows physicians to visualize the patient's anatomy, delineate all anatomical structures, and provides essential data on tissue attenuation, the HU. This data can be used to calculate doses inside the body of the patient and optimise treatment plans.

When treating regions with a high soft tissue density, supplementing CT scans with Magnetic Resonance Imaging or Positron Emission Tomography can be advantageous cause these methods enhance contrast in low-density areas.

2.2.2 Targets volumes & organs at risk

The manual delineation of organs at risk (OARs) and tumor volumes on the pCT is crucial, as it lays the geometric foundation for the entire treatment plan.

When we mention the 'target', we are specifically referring to the tumor regions. The region of the tumor that is visibly identifiable and contoured by the physician

is referred to as the Gross Tumor Volume (GTV). This volume does not account for potential tumor infiltration.

OARs are those situated within or near the irradiation zone, potentially receiving significant doses during treatment. The sensitivity of these organs to radiation varies, as some contain cells more susceptible to damage from radiation than others.

2.2.3 Dose constraints and objectives

For targets volumes, the dose objective is an interval of dose bounded by the minimum dose to ensure effective destruction of cancer cells and the maximum dose to ensure that excessive damage to surrounding tissues is avoided.

For the OARs, dose constraints represent the maximum radiation doses that can be safely administered, and vary depending on the organ's distinct physiological and radiobiological properties. These constraints are determined by institution-specific guidelines but are often derived from statistics and external sources such as the Royal College of Radiologists. Organs are categorized as either serial or parallel, which significantly impacts their tolerance to radiation.

Serial organs, like the spinal cord, fail entirely if any subunit is damaged. Parallel organs, such as the brainstem, require extensive subunit damage for organ failure. This structural difference necessitates varying dose constraints, with serial organs often having stricter limits due to their sensitivity to localized damage.

2.2.4 Gantry

The gantry is a rotating system that can accelerate light particles and directs them towards the treatment target within the patient's body. It comprises a particle accelerator known as a linear accelerator and produces X-rays through the collision of electrons with a typically tungsten target. This rotational capability enables the delivery of radiation from multiple angles for precise treatment.

Radiotherapy employs various techniques to administer the treatment beam from the gantry ; IMRT delivers the dose from specific, discrete angles around the patient. Between each position, the gantry adjusts its intensity, and during the beam delivery, it controls the aperture of its multileaf collimators. These collimators are composed of small blades made of a high-density material, allowing for the shaping of the beam.

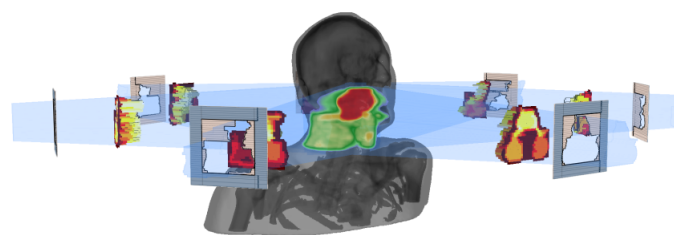


Figure 2.5: Illustration of discrete firing angles in IMRT [11].

On the other hand, Volumetric Modulated Arc Therapy (VMAT) delivers the dose continuously during a 360-degree rotation around the patient, utilizing a single collimator shape for each angle. This approach allows for increasing the entry angles of the beam and thus better distributing the dose in healthy organs.

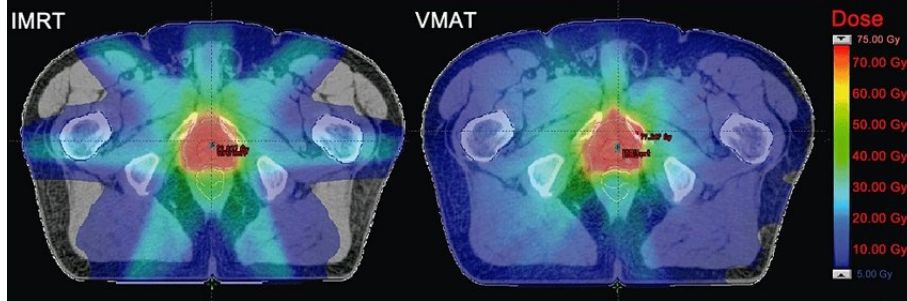


Figure 2.6: Axial colourwash isodose plot for IMRT (left) and VMAT (right) [12]. The 7 discrete beam positions of the IMRT are visible on the dose distribution.

2.2.5 Beamlet

The beam is divided into small units called beamlets. It is the multileaf collimators that enable the opening or closing of these beamlets. For a constant intensity, the longer a beamlet is open, the more its weight is significant.

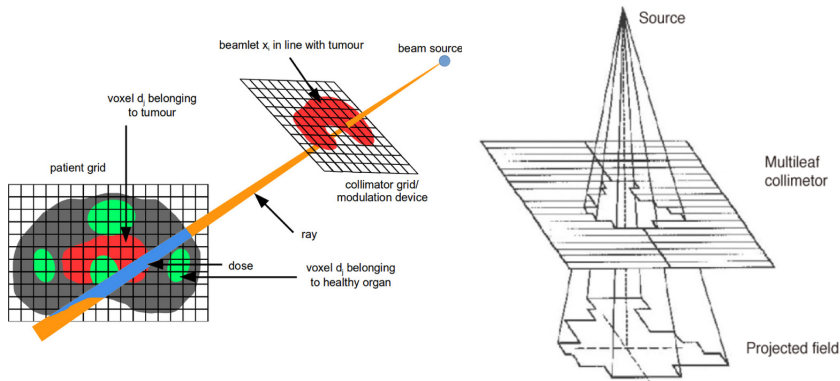


Figure 2.7: Illustration of the multileaf collimator and the beamlets. The left image represents the grid of beamlets, and on the right, the multileaf collimator closing or opening the beamlets [13, 14].

2.2.6 Optimization

Optimisation is the challenge of determining the weight of each beamlet. The weights define the fluence and intensity at each position and moment of rotation around the patient in order to meet the prescribed and limit dose constraints established by the physician. Taking into account the dose constraints, computational iterations are performed to calculate the weights, referred as optimization variables. This process is commonly known as inverse planning.

The attempt to enhance dose coverage in the target area often leads to increased exposure of surrounding normal tissues. The transformation of planning objectives into a mathematical function, commonly referred as the objective function or cost function, is fundamental in evaluating the quality of a treatment plan through a single numerical value. Mathematically, this can be expressed in a general form as follows:

$$\begin{aligned} \min_{\mathbf{w}} \left[f(\mathbf{w}) = \sum_{i=1}^N a_i f_i(\mathbf{d}(\mathbf{w})) \right] \\ \text{s.t. } \mathbf{w} \geq \mathbf{0} \end{aligned} \quad (2.2)$$

with a_i the relative weight factors that define the importance of objective i and f_i is the objective penalty function. The set of uniform beamlet weights constitutes a fluence vector $\mathbf{w} \in \mathbb{R}^{M \times 1}$ which is the optimization variable. A high beamlet weight value indicates that the beamlet is open for a longer duration and delivers more monitor units.

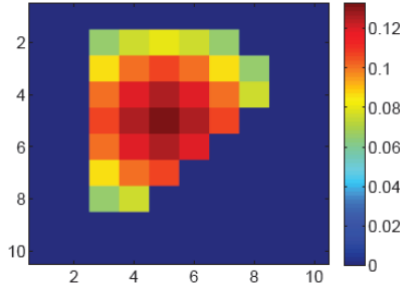


Figure 2.8: Fluence map of a beam containing $N = 10 \times 10$ beamlets [15].

$\mathbf{d} \in \mathbb{R}^{N \times 1}$ is a dose vector, $\mathbf{d}_j$ representing the dose deposited in the voxel j . It is computed by summing the contribution of individual beamlets to the total dose through a matrix multiplication process as

$$\mathbf{d} = \mathbf{P} \cdot \mathbf{w} \quad (2.3)$$

$\mathbf{P} \in \mathbb{R}^{N \times M}$, the dose-influence matrix, holds the elemental impact of each M individual beamlet in the N different voxels j . Additionally, the constraint $\mathbf{w} \geq 0$ ensures the non-negative nature of the fluences, crucial for preserving the physical validity of the solution.

The objective penalty functions typically take the form of asymmetric quadratic functions, penalizing dose distributions that fail to meet constraints.

$$f_i(\mathbf{w}) = \begin{cases} \frac{1}{N} \sum_{j \in \text{ROI}_i} \max \{0, d_j^{\min} - d_j(\mathbf{w})\}^2, & \text{or,} \\ \frac{1}{N} \sum_{j \in \text{ROI}_i} \max \{0, d_j(\mathbf{w}) - d_j^{\max}\}^2. \end{cases} \quad (2.4)$$

The utilization of quadratic dose fidelity terms to measure plan quality presents the advantage that quadratic functions create convex optimization problems that can be computationally resolved efficiently by utilizing gradient descent algorithm. This approach leads to the solution of 2.2 as a global minimum.

The treatment planning system (TPS) generates optimized models for treatment devices and sources, encompassing all design features (e.g., gantry) and beam shaping components (e.g., collimation). One of the primary challenges during the planning optimization phase is the absence of prior knowledge regarding the optimal set of importance weights (a_i in Equation 2.2). Consequently, treatment planners engage in an iterative process, manually adjusting the weights until the treatment plan aligns with clinical endpoints. Due to the iterative nature of this optimization approach, there is no guarantee of achieving a globally optimal solution. Moreover, this iterative approach often leads to time-consuming iterations of the treatment plan. Addressing this issue remains an active area of research. In this context, successful multi-criteria optimization techniques have been developed to explore the optimal trade-offs between planning objectives.

2.3 Uncertainties

In radiotherapy, uncertainties are mainly divided into two categories: systematic and random.

Systematic uncertainties, consistent across multiple treatment sessions, include errors like inaccuracies in treatment planning systems, calibration errors, or consistent patient positioning discrepancies. These errors can be reduced by taking images or correcting the position on the same day.

Random errors vary with each treatment delivery and include factors like setup errors, organ motion, and anatomical changes during treatment. These uncertainties are unpredictable and fluctuate, posing a challenge in management.

2.3.1 Anatomical changes uncertainties

In non-adaptive radiotherapy, the treatment is optimized once using the initial planning CT and is uniformly applied over approximately 30 fractions, with the assumption that the regions contoured by the doctors will maintain their position and volume throughout the treatment course. However, this assumption may not hold true for large-volume tumors and in regions with rapid anatomical changes. If the treatment is effective, the tumor volume should decrease, resulting in anatomical variations. Figure 2.9 illustrates such a significant anatomical change that it displaces the CTV outside the body after 16 fractions.

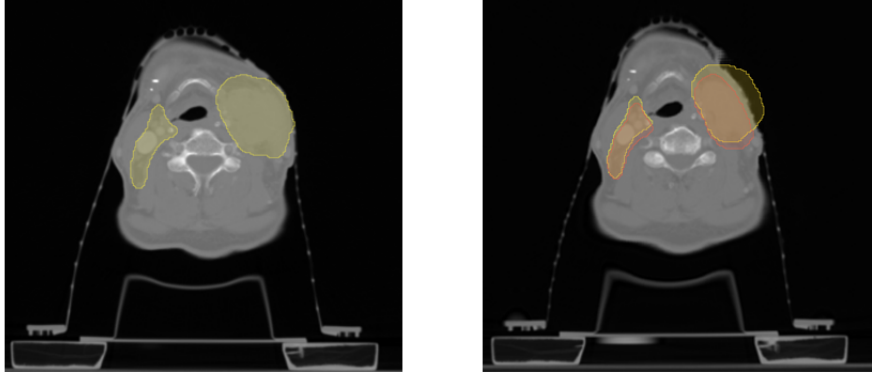


Figure 2.9: Differences of anatomy between the fractions 1 (left) and the fraction 16 (right). The colored regions represent the PTV delineated by the physician in yellow for fraction 1 and in red for fraction 16.

These anatomical changes leads to dose distributions that are no longer adequate with respect to the changing anatomy of the patient. In Arthur Lalonde *et al.* [16], the study shown that out of 10 patients, the effects of anatomical changes without replanning result in underdosage, with 5 patients out of 10 experiencing this in the low-risk Clinical Target Volume (CTV) compared to 2 patients out of 10 in the high-risk CTV.

2.3.2 Positioning uncertainties

Systematic positioning errors remain consistent across all treatment fractions and are typically due to differences in patient positioning during the planning CT scan compared to their usual treatment position. This positioning error results in a shift in the dose distribution for all treatment fractions.

On the other hand, random positioning errors fluctuate between treatment fractions, and relate to day-to-day variations in patient anatomy and positioning. This random error have generally less impact than systematic error because it only blurs the dose.

Chapter 3

State of the art of uncertainties management

External beam radiation therapy inherently involves uncertainties in both treatment preparation and execution, impacting the precision of radiation delivery. Current research in radiotherapy is dedicated to addressing these uncertainties.

A prevalent approach in radiotherapy is the use of margins around target regions, though this conservative method can lead to over or under dosages [4, 5]. Adaptive radiotherapy adjusts the treatment plan daily to suit changes in patient anatomy or tumor size. Additionally, robust optimization introduces uncertainties directly into planning, creating resilient treatment plans against variations in positioning and anatomy.

3.1 Margins

The initial approach to address uncertainties involves adding margins around the visually identifiable and contoured Gross Tumor Volume (GTV). These margins are sized to provide probabilistic coverage of potential uncertainties.

The International Commission on Radiation Units and Measurements (ICRU) recommends defining the Clinical Target Volume (CTV) as the GTV plus a margin to manage sub-clinical microscopic disease spread. In head and neck cancers, the margin GTV-CTV is typically 5 to 10mm [17].

There are three different CTVs based on risk levels: the high-risk CTV includes the macroscopic tumor load, the intermediate-risk encompasses areas with significant microscopic disease, and the low-risk covers regions with potential microscopic tumor spread.

In contrast to the GTV and CTV, which are considered oncological or anatomical concepts, an additional margin is added to the CTV, to account for uncertainties in treatment delivery, forming the Planned Target Volume (PTV). In head and neck cancers, the margin CTV-PTV is typically 2 to 5 mm [17].

The most well-known margin recipe is developed by van Herk *et al.* [18] and characterizes the Clinical Target Volume (CTV) to Planned Target Volume (PTV) margin using two components. The first component is the sum of the variances of systematic uncertainties (Σ^2), and the second component involves the sum of the variances

of random uncertainties (σ^2). The full PTV margin recipe is defined as

$$M_{PTV} = M_{SYST} + M_{RANDOM} = \alpha \sqrt{\sum_{i=1}^N \Sigma_i^2} + \beta \sqrt{\sum_{i=1}^N \sigma_i^2 + \sigma_p^2} - \beta \sigma_p \quad (3.1)$$

$$M_{PTV} = \alpha \Sigma + \beta (\sigma - \sigma_p)$$

with the second formula obtained assuming a spherical perfectly conformal dose distributions and σ_p corresponding to the effect of penumbra ¹. For a confidence interval of 90% of patients and for a dose level of 95% of prescription dose, the recipe become

$$M_{PTV} = 2.5 \Sigma + 1.64 (\sigma - \sigma_p) . \quad (3.2)$$

Sometimes margins called Planning organ at Risk Volumes (PRVs) are also assigned to OARs.

3.2 Offline adaptive radiotherapy

Offline adaptive radiotherapy was first workflow developed to address anatomical changes occurring between treatment fractions. The approach is straightforward: acquiring a new image of the patient before the fractions to verify that the anatomy has not significantly changed and that the treatment remains effective. If such changes are detected, the responsible physician may opt for replanning, which involves acquiring a new CT scan and re-optimizing the treatment to adapt to the altered anatomy and adjust positioning if necessary. This process of replanning is termed 'offline' as it occurs parallel to the ongoing treatment, without the patient's presence and without interfering directly with the treatment sessions.

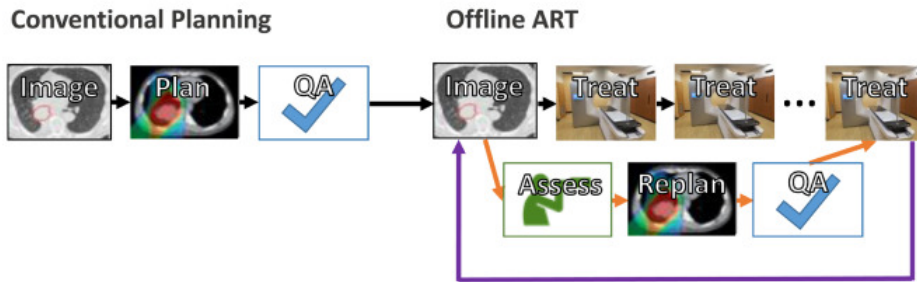


Figure 3.1: Workflow of offline adaptive radiotherapy [19]. QA means for Quality Assurance.

3.3 Online adaptive radiotherapy

Online adaptive radiotherapy (oART) eliminates inter-fractional anatomical positional uncertainties by acquiring new images and adjusting the treatment plan to

¹The penumbra in radiotherapy is caused by the finite width of radiation beams, creating a gradual dose decrease from the maximum within the treatment field to zero outside it.

daily-anatomy with patient remaining on treatment couch.

The workflow of oART begins with an initial planning CT. This CT scan helps the physicians delineate the organs, acquire HU Units data and develop the initial treatment plan to verify the feasibility of meeting the dose constraints. Unlike in classic non-adaptive radiotherapy where the same initial treatment plan developed based on the CT scan is delivered in each fraction, in online adaptive radiotherapy, this initial plan is never executed.

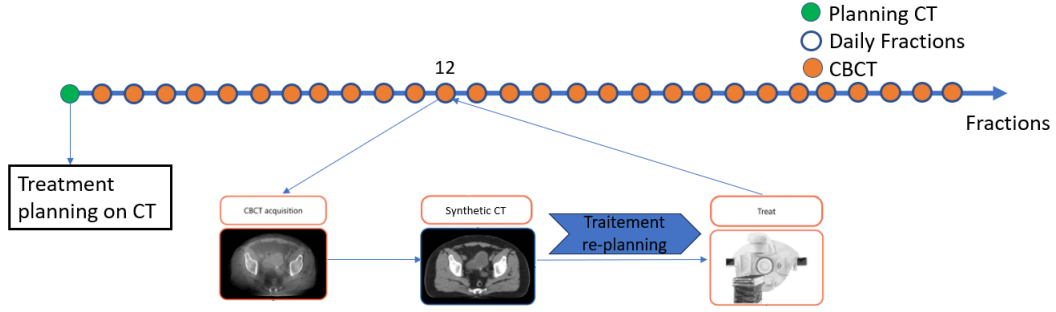


Figure 3.2: Workflow of online adaptive radiotherapy [20].

Let's analyze step by step the process of creating the daily-treatment plan.

3.3.1 CBCT image

Before each treatment fraction in adaptive radiotherapy, a Cone Beam Computed Tomography (CBCT) image of the patient's region of interest is captured. The CBCT utilizes divergent X-rays, forming a cone shape, to generate the image. It contrasts with standard CT imaging, as illustrated in the comparison image provided below.

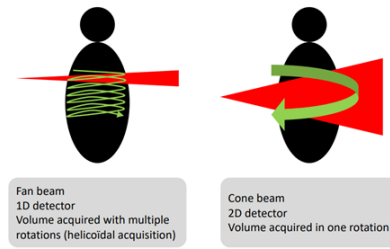


Figure 3.3: Comparaison between CBCT and CT [21].

CBCT has the advantage of being less expensive than CT, easier to install in the treatment room, and capturing the image in a single rotation. However, their cone beam causes significant scatter artifacts, more noise and beam hardening effects. These issues can result in the inaccurate definition of HU and thus tissue density. This limitation prevents it from being used for dose computation.

3.3.2 Using CBCT for planning

The daily acquisition of a CBCT for treatment adaptation poses two challenges: firstly, it is imprecise to simulate doses on the CBCT, and secondly, a rapid daily delineation of the targets and anatomical structures is required. Speed is essential because the patient may be in an uncomfortable position and numerous patients are treated each day.

Daily structure segmentation

Today, structure contouring is directly done by physicians. This results in accurate and reliable structures. However, it requires manual structure delineation, which is often resource- and time-intensive, making this approach challenging to apply in a clinic.

Accelerating the segmentation of structures is therefore one of the main challenges of adaptive radiotherapy.

Current methods rely on the assistance of deformable image registration (DIR) [22], minimizing image similarity metrics such as Sum of Square Differences or Mutual Information, or auto-segmentation [23]. These techniques achieved good performance but are limited by their low speed (some minutes) and specificity to particular problem [24]. In addition, the structures generated by these algorithms must undergo manual review and correction before plan optimization because they are not free from errors and inaccuracies. On average, doctors spend about 5 minutes on this check task [6].

Artificial Neural Networks (ANNs) have transformed image processing with their multi-layered structures that learn from datas. Iteratively, by modifying internal parameters, ANNs can efficiently perform tasks such as image classification and segmentation. The capability of ANNs has led researchers to apply them in image registration, achieving the same accuracy as traditional DIR methods but with the notable advantage of completing the process in seconds [7, 25, 26].

Calibration of Hounsfield units

Given that the CBCT is prone to various artifacts and does not consist of pixel values relative to HU, it is essential to calibrate the CBCT for dose calculation purposes.

Several methods exist and have been extensively validated in clinical settings [27, 28]. A widespread and simple method is the bulk density override, which involves replacing the structures with standard densities like water, air, and bone. Another more developed method involves finding a conversion from the CBCT intensity scale to the planning CT HU intensity scale.

3.4 Probability map for structure presence

A probabilistic approach of structure definition involves creating a gradient around the GTV, designating areas of probable tumor presence with values from 1 (certain

tumor presence) to 0 (no tumor presence). This results in a probability map for a more nuanced representation of tumor and structures.

The creation of probabilistic maps thus allows for a non-uniform prescription of dose. Traditionally, the entire structure had a target of x Grays. With a probabilistic map, we can consider all the infinitesimal volumes of the patient independently and have objectives that depend on the probability of the structure's presence.

In the study conducted by Lena Nenoff *et al.* [29], utilizing CT-CBCT registration, three DIR algorithms - Raystation, Plastimatch Demons, and Plastimatch B-Spline - were compared to improve target structure identification. Voxels consistently identified as target by all three DIRs were categorized into a 100%-target substructure, while those identified by two or one DIRs were classified into 67%-target and 33%-target substructures, respectively, creating a target probability map for each anatomical structure.

In this thesis, we aim to develop a method that is more continuous and robust than this one.

3.5 Robust optimisation

Rather than incorporating treatment errors into a planning margin like classical optimization does, the robust optimization approach integrates them directly into the optimization process. When working with photons, we only consider systematic setup errors, which are a range of possible shifts in the patient's position. By doing so, robust optimization aims to create a treatment plan that is inherently more resilient and effective under various uncertainties.

3.5.1 Statistical framework

Robust optimization explores solutions across a range of *scenarios* - each representing a different realization of the treatment plan with distinct initial error parameters. Mathematically, each scenario is represented by an N-dimensional vector, where N is the number of distinct error sources. These scenarios, seen as data points, lie within a multi-dimensional error space termed the "scenario space." This space encapsulates all conceivable combinations of treatment errors that might occur during patient treatment.

Treatment errors are typically treated mutually independent and each can be modeled using normal probability density functions (PDF), denoted as $\mathcal{N}(0, \Sigma)$.

If we want to select scenarios in a confidence level Q, it can be generated by selecting a specific sub-volume of the scenario space. For instance, by setting Q=90%, we aim to cover 90% of treatment errors. The N-d hypervolume that encompasses Q fraction of the scenario space is defined by the equation:

$$\sum_{i=1}^N \frac{x_i^2}{\Sigma_i^2} \leq \alpha_{N,Q}^2 \quad (3.3)$$

where $x_1, \dots, x_N$ represent the random variables from the N errors distributions. $\alpha_{N,Q}$ is a coverage parameter that sets the integration limit in the scenario space, a property of Gaussian PDFs ; $\alpha_{N,Q}$ value is derived from the inverse-chi-square distribution. For 3D problems, we retrieve the values in the PTV margin recipe, $\alpha_{3,90\%} = 2.50$.

Each dimension of the scenario space S have is therefore of the form :



Figure 3.4: Gaussian density function of a scenario space of a single dimension. The shaded area encompasses 90% of the scenarios.

3.5.2 Robust optimization

With multiple scenarios defined in the space S , each scenario $s \in S$ leads to a unique dose distribution $\mathbf{d}(s)$. The optimization process aims to find a treatment plan that is effective across these various distributions, ensuring optimal dose distribution $\mathbf{d}(s)$ under different possible conditions.

$$\mathbf{d}(s) = \mathbf{P}(s) \cdot \mathbf{w} \quad (3.4)$$

where the geometric uncertainty is modeled with an uncertainty in the dose-influence matrix $\mathbf{P}$.

For worst-case optimization, the strategy focuses on minimizing the objective function in the most unfavorable scenario. This method is expressed as:

$$\begin{aligned} \min_{\mathbf{w}} \max_{s \in S} f(\mathbf{w}, s) \\ \text{s.t. } \mathbf{w} \geq \mathbf{0}. \end{aligned} \quad (3.5)$$

This method thus ensures that, even in the worst possible case of error, the treatment remains of high quality.

In probabilistic optimization, the formulation focuses on minimizing the weighted average of the objective function across different scenarios s and their probability ;

$$\begin{aligned} \min_{\mathbf{w}} \sum_{s \in S} p(s) f(\mathbf{w}, s) \\ \text{s.t. } \mathbf{w} \geq \mathbf{0} \end{aligned} \quad (3.6)$$

with $p(s)$ the probability or importance of scenario s . This optimization method focus on the most probable scenarios, assuming that large variations are less likely

and therefore given less consideration.

By incorporating joint probability into the optimization process, the treatment plan is designed not only to be effective in an ideal scenario but also to be resilient and efficient across a range of probable scenarios, accounting for systematic setup errors.

3.5.3 Robust evaluation

Once we have optimized our treatment plan to meet constraints, it is crucial to assess its quality.

Scenario selection

The robustness of a treatment plan in radiotherapy is defined as its ability to consistently meet clinical objectives and/or constraints despite the presence of uncertainties. The core challenge, therefore, lies in conducting an extensive assessment that considers a broad spectrum of scenarios and offers a reliable level of confidence in the plan's efficacy under varied conditions.

Several evaluation strategies have been developed in Sterpin *et al.* [30] and some of them will be discussed here.

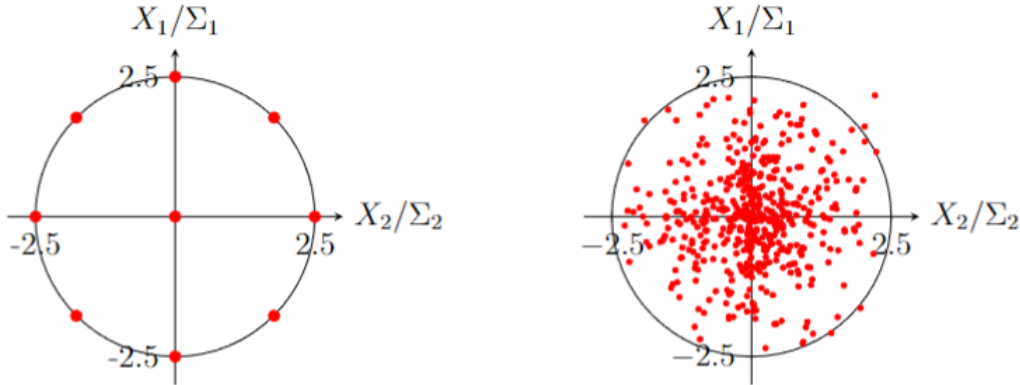


Figure 3.5: Illustration of scenario selection methods in a 2D slice of an N-dimensional iso-probability hypersphere composed of two error dimensions 1 and 2. Each dot represents a selected scenario, and the hypersphere encompasses 90% of all possible scenarios. In the left figure, Good practice scenario selection with the nominal case in the center. On the right figure, the Statistically sound dosimetric selection sampling.

1. Nominal scenario evaluation Nominal scenario evaluation assesses a dose plan based on the original, unmodified geometry. This approach yields a single value, lacking the capacity to reflect any variations in results. Despite its limitation in capturing variability, this method remains intuitive and is easily understood, aligning closely with current clinical practices.

2. Good practice scenario selection A strategic approach might be to focus on the extremes. This means prioritizing scenarios that represent the worst-case

errors. The rationale behind this choice is the assumption that an extreme error, in either dimension, will have a more significant impact on the treatment's efficacy than more moderate errors. It is also common to select the nominal case where there is no error in either dimension.

Its relative simplicity and ease of calculation, due to the small number of scenarios considered. It provides clear parallels to classical planning techniques that use margins, as it essentially substitutes the CTV to PTV margin with a systematic setup error of comparable magnitude. However, a significant drawback of this method is that it represents only a coarse sampling of the uncertainty space. As a result, the confidence intervals it provides are not as precise or reliable as those obtained through more advanced methods that consider a broader range of uncertainties.

3. Statistically sound dosimetric selection In this method, scenarios are sampled in a Gaussian manner within the N-dimensional space of different errors in the scenario space. We then assess the confidence interval in the dose space related to these scenarios. The primary advantage of this method is its statistical robustness, stemming from the evaluation of a large fixed number of scenarios (enough to reduce statistical noise). Notably, the method does not require more extreme scenarios for increased dimensions, even at a fixed confidence level. However, this also results in a more time-consuming process.

Dose reporting metrics

Once the evaluation scenarios are selected, it becomes possible to indicate the associated uncertainty in the evaluation. An example of such an evaluation notation could be "nominal $\langle \min, \max \rangle$ ". In this format, the dose metric evaluated in the nominal scenario is reported first, followed by the minimum and maximum values observed across the selected scenarios. Alternatively, the mean or the median of the scenarios can be used instead of nominal. This method provides a clearer picture of the potential range of outcomes, reflecting the inherent uncertainties in the treatment plan.

Chapter 4

Theoretical concepts

In this chapter, we will explore the technical concepts essential for understanding this thesis.

4.1 Photon Dose

Photons are energy quanta associated with electromagnetic waves. They are considered to have zero mass and neutral charge.

4.1.1 Dose definition

The absorbed dose, more commonly referred to simply as dose, is the amount of energy deposited per unit of mass by ionizing radiation.

Given an ionizing radiation beam irradiating an element of a material with volume dV , density ρ , and mass $dm = \rho \cdot dV$. Let dE be the energy deposited in this element by the beam, the absorbed dose D is then defined as

$$D = \frac{dE}{dm} = \frac{dE}{\rho \cdot dV}. \quad (4.1)$$

The value is expressed in J/kg or the SI unit Gray [Gy]. Soft tissue density is approximately 1.04 g/cm³ and bone density between 1.9 for cortical and 1.03 for marrow.

4.1.2 Interaction photon - matter

Due to their neutral charge, photons ionize matter indirectly by interacting with electrons. In contrast, charged particles like protons and electrons lose their energy in matter through multiple energy transfer interactions.

In radiotherapy, the potential for acceleration of photons typically have an energy range between 4 and 18 MeV. Depending on their energies, photons are subject to various types of interactions ; the photoelectric effect involves photons colliding with and ejecting electrons from atoms, potentially causing photon emission from electron transitions. X-rays scatter at specific angles based on their interaction with atoms, altering their wavelengths. Collisions with photons can be elastic (Rayleigh scattering, with no energy loss) or inelastic (Compton scattering, where the photon

transfers energy to the target). Additionally, high-energy photons can generate particle-antiparticle pairs in certain mediums.

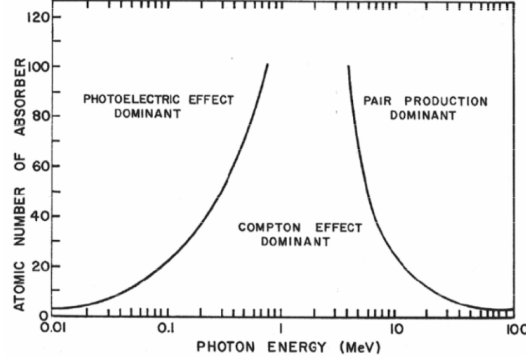


Figure 4.1: Predominance of photon-matter interactions based on the energy of the photon in MeV and the atomic number, Z , of the material or tissue [31].

Although the effects are predominant depending on the energy, it's still possible for certain interactions to occur at an unexpected energy level.

In considering a photon beam, the photons within it are either deflected or transformed into another form of energy, leading to what is termed beam attenuation and follow an exponential rule:

$$I(x) = e^{-\mu x} \quad (4.2)$$

$$\text{with } \mu = \mu_{PE} + \mu_{Compton} + \mu_{Pair}, \quad (4.3)$$

$$\text{and } \mu = \frac{\rho N_A \sigma}{m_A} \quad (4.4)$$

with x the depth in the homogeneous matter, μ the attenuation coefficient of the matter, N_A the Avogadro number and m_A the molar mass of the medium.

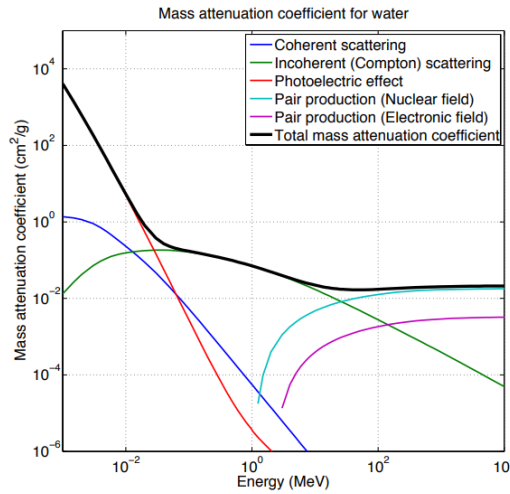


Figure 4.2: Evolution of the composant of the mass attenuation coefficient [21].

4.1.3 Depth dose curve

Photons exhibit a dose deposition in matter following the formula referenced as 4.2 and illustrated in Figure 2.3. However, prior to this, photons undergo a build-up region (creation of electronic equilibrium) upon entering the material. Due to this exponential dose deposition, achieving a dose distribution as precise as that attainable with heavy particles, like protons, is challenging.

4.2 Head and neck anatomy

The regions most commonly affected by tumors, in order of frequency, are: the tongue (25%), the larynx (16%), the tonsils (15%), and salivary glands such as the parotids (7%) [32].

To understand the challenges faced when attempting to optimize a dose distribution, particularly when the tumor region is close to a radiosensitive area, it is instructive to introduce anatomical concepts.

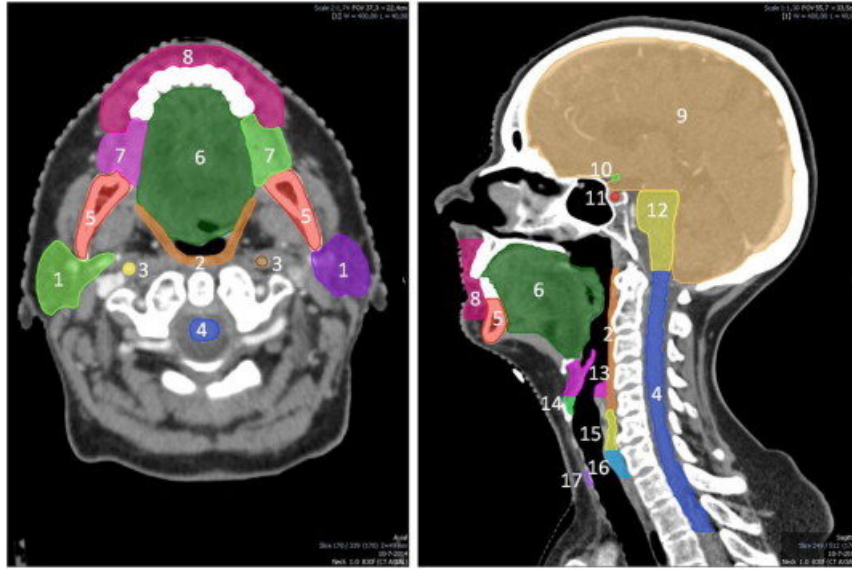


Figure 4.3: Axial (left) and sagittal (right) view of the consensus delineations of the parotid glands (1), pharyngeal constrictor muscles (2), carotid arteries (3), spinal cord (4), mandible (5), extended oral cavity (6), buccal mucosa (7), lips (8), brain (9), chiasm (10), pituitary gland (11), brainstem (12), supraglottic larynx (13), glottic area (14), crico-pharyngeal inlet (15), cervical esophagus (16) and thyroid (17) [33].

Chapter 5

Materials and methods

In this section, we will walk through, step by step, the stages involved in creating a treatment plan for an adaptive radiotherapy workflow with different optimization methods.

5.1 Patient data

The experiments conducted in this research involved a head and neck patient who underwent radiation therapy. The dataset include 33 fractions. Patient received a re-planning in fraction 24, which was optimized based on images taken on the day of fraction 13.

We had access to the planning CT and day-to-day CBCTs with, for both, segmentations executed by a specialized radiation oncologist.

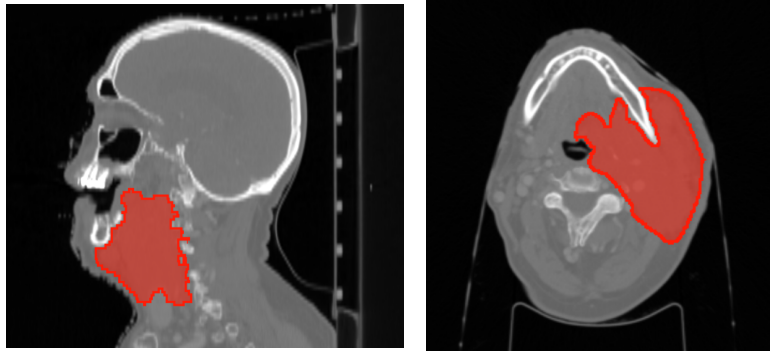


Figure 5.1: Sagittal (left) and transverse (right) anatomical view of a head and neck patient. High risk CTV colored in red.

The low-risk CTV is included within the high-risk CTV.

5.2 Creation of the sCT and structure propagation

Let us quickly recall the context. The workflow for online adaptive radiotherapy begins with a planning CT scan (pCT), on which physicians delineate OARs and tumor volumes. On the day of the treatment fraction, a 3D Cone Beam CT (CBCT) image is acquired of the patient in the treatment position (same as CT).

In subsection 3.3.2, we observed that using CBCT as a substitute for CT for treatment planning is not feasible due to its inferior quality and lack of accurate HU values. Additionally, the CBCT lacks the physician-made segmentations present in CT scans. To address these issues, one solution is the creation of a synthetic CT (sCT) by combining the CBCT’s daily anatomy, the CT’s HU values, and the physician’s drawn CT segmentations. Figure 5.2 outlines the steps involved in constructing this sCT.

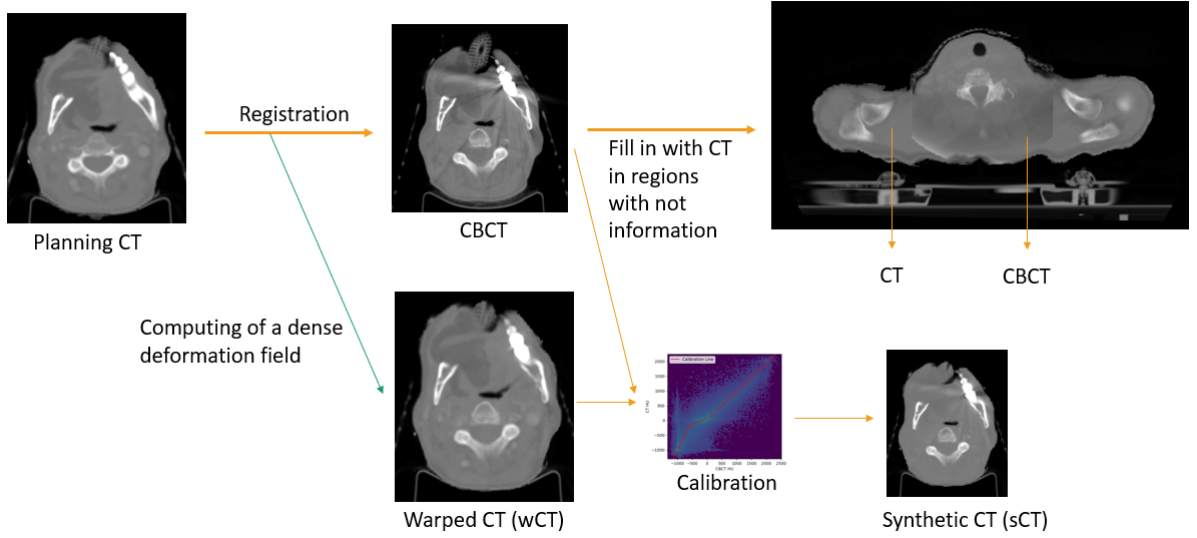


Figure 5.2: Steps involve in the creation of the synthetic CT.

The two technical steps involve registration between the CBCT and CT, resulting in the creation of a warped CT (wCT), and the calibration of HU between the CBCT and the warped CT. Registration also allows for the propagation of structures from the pCT to the wCT. These steps will be elaborated upon in the following sections.

5.2.1 Image registration

A registration is a geometrical transformation that identifies a set of translation vectors creating voxel-to-voxel correspondence between two images. In this case, the pCT and the CBCT. This collection of vectors is known as a dense deformation field (DDF).

In the study conducted by Luciano Rivetti *et al.* [7], Neural Networks (NN) were employed to generate a distribution of DDF. The NN was trained using a dataset consisting of 220 pairs of images (CT and CBCT) obtained from seven patients with their respective structures designed by oncologists.

For the inference, NN incorporate dropout layers, meaning that several neurons are randomly, based on a predefined probability ($p = 0.5$ here), removed from the network (see Figure 5.3). This unique property allows the generation of different configurations of the same network, generating different inferences for the same input and allowing for the acquisition of a distribution of possible outputs.

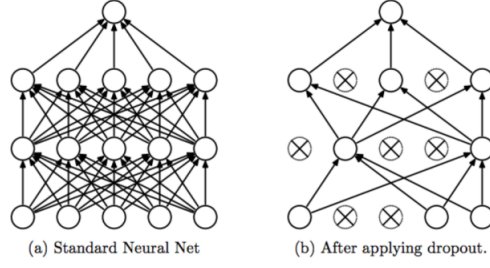


Figure 5.3: Comparison of a standard Neural Network (a) against one possible configuration of the same network using Drop Out (b) [7].

Image 5.4 shows an example of DDF created with this method.

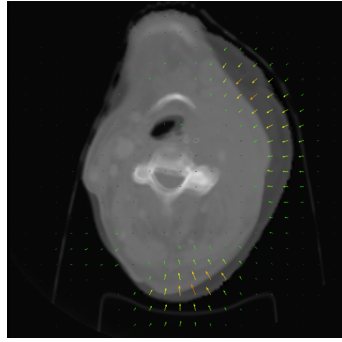


Figure 5.4: The representation of the dense deformation field (DDF) over an overlay of a CT image and CBCT. The CT is placed on the CBCT with a lower grey level. The vectors indicate the DDF.

By creating 100 DDFs with the dropout layers, we then take the mean and apply the deformation to the pCT. This creates the warped CT (wCT).

Generating 100 DDFs here is not of interest, as it is even time-consuming compared to just one. However, this has a statistical purpose, which is to assess the uncertainty of the registration.

5.2.2 Structure propagation

The 100 generated DDFs can be applied to the structures present on the pCT, thereby generating 100 different structures on the wCT. These structures are all binary and can be used to construct a probabilistic map of the structure's presence. For instance, if all 100 structure in the wCT include a voxel within the structure, this voxel will have a probability of 1 of belonging to the structure. Conversely, if a voxel appears in only one registration, its probability of belonging to the structure is 0.01.

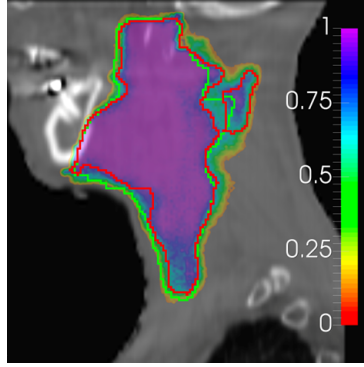


Figure 5.5: Example of probabilistic map. In this example, we compare the B-Spline method in red, the physician contouring in green and the non-binary probabilistic map in rainbow.

This non-binary mask can be used in various ways to define the structures. We will use both the complete probability map and the binary-transformed probability map by setting a threshold of 0.01 or 0.5.

5.2.3 Calibration

Now that we have transformed our CT into a wCT, it's feasible to find a linear transformation of the Hounsfield units from this wCT to the CBCT. Several calibration processes exist, but we have decided to use a voxel-to-voxel mapping method using calibration curves. This calibration process is used by *RayStation* [34]. To do this, we plot the Hounsfield units (proportional to the pixel values in both images) of the CBCT against those of the CT, resulting in a calibration plot.

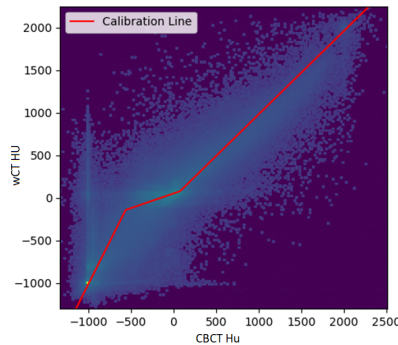


Figure 5.6: Plot of CT HUs against CBCT HUs.

Utilizing the calibration line on our plot, we map all pixel values of the CBCT to correspond with the values indicated by this calibration line. This calibration allows us to provide valid Hounsfield Units (HU) in the CBCT, thus enabling dose calculations on this new synthetic CT.

5.2.4 Extention of the sCT

CBCTs are often cropped outside the field of interest since his field of view is limited. This poses a challenge for conducting dose calculation on these images, as it becomes

difficult to accurately simulate particle displacement throughout the entire region of interest.

To address this, we will overriding the regions from the wCT that are not present in the CBCT.

5.3 Validation of the sCT

To verify that the sCT has the necessary HU for dose calculation, we conducted a comparison of the dose distribution in the sCT and the wCT. The method and the results are detailed in the Appendix A.

Our results falls within the same range as those obtained in Emilia Palmér *et al.* (2017) [35] and Iva Bratova *et al.* (2019) [36]. The variations in patient-specific absorbed dose calculations between sCT and wCT images were found to be minor and considered to be within the clinically acceptable tolerance range. Consequently, it can be concluded that sCT exhibits comparable HU to wCT, thus validating its suitability for dose calculation purposes.

5.4 Treatment plan

In this section, the methodology for generating and simulating treatment plans across different workflows is discussed. The focus is on exploring and evaluating various approaches to radiotherapy planning for their effectiveness and applicability.

5.4.1 Treatment planning system

In this study, we will utilize the OpenTPS developed by UCLouvain and IBA, Luciano A. Rivetti developed the photon dose calculation module. This open-source TPS optimizes dose distributions using medical imaging and dose constraints, adjusting parameters like irradiation times, energies, field sizes, and fluence patterns to customize the treatment to the patient’s requirements.

The TPS is configured to operate in IMRT with the following settings:

- Number of Gantry positions : 21
- Gantry Angles: $n \cdot \frac{360}{21}$ for $n \in \mathbb{N} \cap [0, 20]$
- Dose Resolution: [1.5, 1.5, 3] mm
- Dose Engine Algorithm: Collapse Cone Convolution

The patient received VMAT treatments, and the constraints were specifically designed for these gantry use. Achieving such excellent results in IMRT is very challenging. Therefore, we opted to use 21 beam positions in our IMRT. Although this approach may not be common in practice, the clinical intent remains the same as a VMAT treatment.

5.4.2 Constraints and objectives

The dose limits, as provided by the physician, are summarized in Table 5.1. For certain dose constraints, it is important to adjust the weight of the constraints. This adjustment is particularly relevant when the tumor's location is close to organs at risk, making it challenging to adhere to the specified dose constraints.

Re-planning in fraction 24 is of great importance because the patient changes position at that moment, and a new CT scan along with its structures is reconstructed. The weights of the constraints were iteratively tested on the cRT. These constraints were retained for the other methods, allowing for an intrinsic comparison. The idea is also to understand if we can adjust robust and classical optimizations in the same way.

Structure	$a<F24$	$a>F24$	Dose limits
PTV _{high risk}	5	10	Min >70.46
PTV _{low risk}	5	10	Min >59.9
Brainstem	3	3	Max <54Gy
SpinalCord	3	6	Max <43Gy
SpinalCord_PRV05	10	20	Max <48Gy
Cavity_Oral	1	1	Max <40Gy
Parotid_L	1	10	Mean <26Gy
Parotid_R	1	1	Mean <26Gy
Larynx	1	1	Mean <30Gy
Musc_Constrict	1	1	Mean <50Gy
Esophagus	1	1	Mean <34Gy
Glnd_Thyroid	1	1	Mean <49Gy
Bone_Mandible	1	1	Max <70Gy
Out_of_organ	30	20	Max <50Gy

Table 5.1: Table of constraints for patient HN_01 before and after Serie24. "Out_of_organ" structure representing the area of interest excluding other structure to prevent hotspots. *Abbreviation:* $a<F24/a>F24$ mean constraint weights before/after the replanning in fraction 24.

The "Out_of_organ" structure is an artificial structure composed of the entire region of interest minus the structures created to avoid hotspots in areas where no dose constraints are imposed. It create a dose falloff along the edges of the targets.

5.4.3 Optimization methods

The TPS is programmed to support three distinct optimization methods, with varying cost functions for each: one classic and two robust approaches.

If a binary mask is considered, we utilize the objective penalty functions, which vary depending on whether the constraint involves a maximum or minimum dose requirement :

$$f_i(\mathbf{w}, s) = \begin{cases} \frac{1}{N} \sum_{j \in \text{ROI}_i} \max \{0, d^{\min} - d_j(\mathbf{w}, s)\}^2, & \text{or,} \\ \frac{1}{N} \sum_{j \in \text{ROI}_i} \max \{0, d_j(\mathbf{w}, s) - d^{\max}\}^2. \end{cases} \quad (5.1)$$

When a non-binary mask is considered, the objective penalty functions include a weighting term that defines the probability of the presence of a structure t in voxel j , $p_{t,j}$. For a scenarios s , equation then takes the form :

$$f_i(\mathbf{w}, s) = \begin{cases} \frac{1}{N} \sum_{j \in \text{ROI}_t} p_{t,j} \left(\max \{0, d^{\min} - d_j(\mathbf{w}, s)\} \right)^2, & \text{or,} \\ \frac{1}{N} \sum_{j \in \text{ROI}_t} p_{t,j} \left(\max \{0, d_j(\mathbf{w}, s) - d^{\max}\} \right)^2. \end{cases} \quad (5.2)$$

Equations 5.1 and 5.2 are examples of cost functions for target.

1. Classic Nominal optimization

The classic optimization on the nominal case is the simplest approach. It directly optimizes beamlet weights $\mathbf{w}$ in 2.3. This approach is applied to the nominal case, meaning it does not consider error scenarios, as uncertainties in position are already accounted for in the CTV-PTV margin. The equations implemented in the TPS are as follows:

$$\min_{\mathbf{w}} \left[f(\mathbf{w}) = \sum_{i=1}^N a_i f_i(\mathbf{w}) \right]. \quad (5.3)$$

For classic optimization, only binary masks will be used; therefore, penalty functions will be as equation 5.1.

2. Robust optimization

The uncertainty set S is chosen to cover a region of scenario space within a selected 90% confidence interval, resulting in $\alpha_{3,90\%} = 2.5$. We will only consider here the systematic setup errors distributed as a Gaussian of standard deviation $\Sigma = 0.8\text{mm}$ in the three spatial directions. This lead to a a total of $2.5 \times 0.8 = 2\text{mm}$, corresponding to the PTV margin used in classic optimization.

17 scenarios are considered during optimizations process: the nominal case, 12 cases $(x\pm, y\pm, z\pm)$ with 1 mm setup errors, and 2 mm setup errors.

In practice, the process for determining the worst-case scenario starts with calculating the 3D dose distribution matrix for the nominal case within the patient. Then, this matrix is translated according to the different scenarios, and for each scenario, the total cost function is calculated.

Cause we consider scenarios, we have the following cost function

$$f(\mathbf{w}, s) = \sum_{i=1}^N a_i f_i(\mathbf{w}, s). \quad (5.4)$$

Robust Worst-case optimization

The worst case is identified as the scenario with the highest cost function. Once this worst-case scenario is determined, optimization is performed on the weights focused on this specific case.

Simply translating the dose distribution matrix is an effective approximation that avoids the need to recalculate the entire dose distribution for each scenario.

Considering the pre-defined set of uncertainty scenarios S . Minimax is implemented as

$$\min_{\mathbf{w}} \max_s f(\mathbf{w}, s) \quad (5.5)$$

$$\text{s.t.} \begin{cases} \mathbf{w} \geq 0, \\ s \in S. \end{cases} \quad (5.6)$$

Here, we will use two different types of mask so equations 5.1 and 5.2.

Robust Probabilistic optimization

Probabilistic optimization utilizes an objective function that sums up weighted contributions based on the probability of scenario occurrence $s \in S$, $p(s)$;

$$\min_{\mathbf{w}} \left[\mathcal{E}(\mathbf{w}) = \sum_{s \in S} p(s) f(\mathbf{w}, s) \right] \quad (5.7)$$

$$\text{s.t.} \begin{cases} \mathbf{w} \geq 0, \\ s \in S. \end{cases}$$

An additional penalty term is added to the objective function that minimizes the standard deviation over the scenarios:

$$\min_{\mathbf{w}} \left[(1 - \lambda) \mathcal{E}(\mathbf{w}) + \lambda \sqrt{\sum_{s \in S} p(s) (f(\mathbf{w}, s) - \mathcal{E}(\mathbf{w}))^2} \right] \quad (5.8)$$

$$\text{s.t.} \begin{cases} \mathbf{w} \geq 0, \\ s \in S \end{cases}$$

where λ is a user-defined parameter that determines the importance of the standard deviation term in the objective function [37].

Given that all uncertainty sources are assumed to be independent of one another, $p(s)$ is calculated as the product of the probabilities associated with each individual uncertainty. In the case of this study, we only consider uncertainties related to the setup.

5.4.4 Treatments workflows

We will simulate treatment plans and apply them to thirty fractions for the patient. Here are the different treatment methods that will be employed:

Method Name	Setup uncertainty	Structures	Target	Optimization	Image for optimization
cRT	2mm margin	CT Physician structures	PTV	Classic	Planning CT
oaRT	2mm margin	CBCT Physician structures	PTV	Classic	sCT
oaRTDIR	2mm margin	PM>0.5	PTV	Classic	sCT
oaRTDIR-WC	Robust optimization	PM>0.01	CTV	Robust: Worst case	sCT
paRTCBCCT	Robust optimization	PM	CTV	Robust: Probabilistic	sCT

Table 5.2: Different treatment methods for a H&N patient. *Abbreviations:* PM = Probability map coming from the DIR structure propagation, "PM > x" means only the elements of the PM greater than x, resulting in a binary mask and WC = Worst case.

5.4.5 Evaluation method

To evaluate our plan, we will employ the 'Statistically Sound Dosimetric Selection' method. This involves sampling randomly 50 setup error scenarios from the 3-dimensional scenario space. Same 50 are use for every different methods. Calculate the 50 corresponding doses and report them as 'Nominal [Q1 - $1.5 \times \text{IQR}$, Q3 + $1.5 \times \text{IQR}$]', providing a range that encapsulates the variability in dosimetric outcomes due to these setup errors. Q1 and Q3 represent the first and third quartiles, respectively, while IQR refers to the interquartile range.

We will take the structures contoured by the physician as the evaluation structures, since we assume they are the gold standard.

5.5 Dose analysis

Dose analysis is performed using evaluation metrics, which differ from the dose constraints used for optimization. Dose constraints for optimization are easier to implement in a TPS and are more conservative than dose evaluation metrics. Here are the metrics we will use:

Structure	Dose Metrics
CTV _{high risk}	$D95 \geq 0.95 D_{prescr}$
CTV _{low risk}	$D95 \geq 0.95 D_{prescr}$
Brainstem	$V54Gy < 0.03cc$
Brainstem	$D2cc < 54 Gy$
SpinalCord	$V54Gy < 0.03cc$
SpinalCord	$D2cc < 54 Gy$
Parotid_L	Mean $< 26Gy$
Parotid_R	Mean $< 26Gy$
Larynx	Mean $< 30Gy$
Musc_Constrict	Mean $< 50Gy$
Esophagus	Mean $< 34Gy$
Glnd_Thyroid	Mean $< 49Gy$
Glnd_Thyroid	$V50 < 70\%$
Bone_Mandible	$2\% < 70Gy$
Out_of_organs	Max $< 50Gy$

Table 5.3: Evaluation Metrics. "Out_of_organ" structure representing the area of interest excluding other structure to prevent hotspots. *Abbreviation:* CTV = Clinical Target Volum, D95 = Dose received by the 95 most irradiated percent of the volume, VxGy = Volume in cubic centimeters [cc] that received at least xGy, 2% = Dose received by the 2 most irradiated percent of the volume.

We will plot these metrics for each method and each fraction, observing their evolution over time.

A dashed red line will always correspond to the prescribed or objective dose.

We also define the pass rate, which is a value between 0 and 1 representing the proportion of times, out of the 50 samples, that the dose satisfies the constraint/objective. If this value equals 1, it means that the plan is totally robust and continues to meet the clinical constraints/objectives despite uncertainties, for a certain confidence interval of 0.9.

Chapter 6

Results

In this chapter, we will analyze the results obtained from treatment simulations of a head and neck cancer patient according to five different workflows: classic non-adaptive radiotherapy workflow, online daily adaptive radiotherapy using classical optimization with the physician-defined structures, online daily adaptive radiotherapy using classical optimization with the probability map greater than 0.5 coming from DIR structure propagation uncertainty, online daily adaptive radiotherapy with robust worst-case optimization on the probability map greater than 0.01 coming from DIR structure propagation uncertainty, and online daily adaptive radiotherapy with probabilistic optimization on the probability map resulting from DIR structure propagation uncertainty.

6.1 Metrics analyse

We will begin by discussing the dose received in the high-risk CTV. Then, we will examine the bone mandible and the parotid glands. Finally, the pass rate in the other structures will also be analyzed.

All results are present in the [Appendix B](#).

The dose constraints and weights are the same for the 5 methods, implying that the differences can come from the adaptation, the optimizations method and structures.

It is important to note that the structures used for evaluation are those one contoured by the doctors on the daily-CBCT, which are considered the most accurate. This has an effect on the evaluation because only the oaRT method possesses the same structures for both optimization and evaluation.

For reasons of timing, we simulated only one out of every three fractions. In this way, simulating all five methods takes a week and a half.

6.1.1 Target

Let us start by analysing the high-risk CTV. It is called CTV_6996, cause 69.96 is the dose constraint, measured in grays.

We start by analyzing the D50, which is the dose received by the 50 most irradiated percent of the volume. It should always reach the value of the prescribed dose.

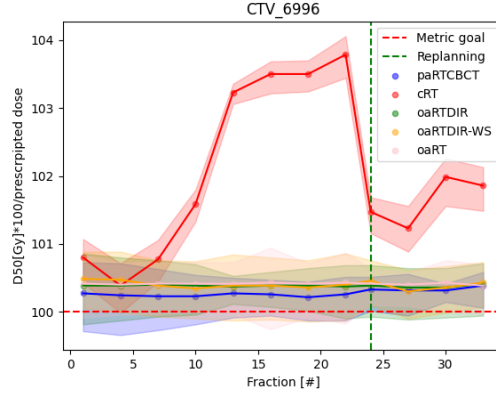


Figure 6.1: Dose received by the 50% most irradiated portion of the CTV (D50[Gy]). *Abbreviations:* cRT = classic non-adaptive radiotherapy workflow, oaRT = online adaptive radiotherapy using classical optimization with the physician structures, oaRTDIR = online adaptive radiotherapy using classical optimization with the probability map > 0.5 coming from DIR structure propagation, oaRTDIR-WS = online adaptive radiotherapy with robust worst case optimization on the probability map > 0.01 coming from DIR structure propagation and paRTCBCT = online adaptive radiotherapy with probabilistic optimization on the probability map coming from DIR structure propagation.

All methods allow for the fulfillment of the D50 constraint by being close to the 100% of the dose constraint. The workflow in cRT is the only one that shows a trend towards higher values over time, which is corrected during reoptimization.

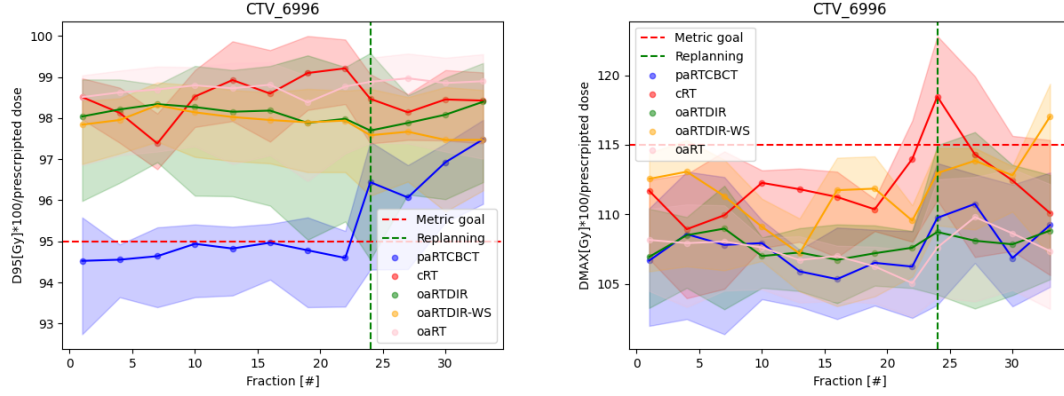


Figure 6.2: Dose received by the 95% most irradiated portion of the CTV (D95) normalized to the dose constraint (left) and maximum dose received by the target (right). *Abbreviations:* cRT = classic radiotherapy workflow, oaRT = online adaptive radiotherapy using classical optimization with the physician structures, oaRTDIR = online adaptive radiotherapy using classical optimization with the probability map > 0.5 coming from DIR structure propagation, oaRTDIR-WS = online adaptive radiotherapy with robust worst case optimization on the probability map > 0.01 coming from DIR structure propagation and paRTCBCT = online adaptive radiotherapy with probabilistic optimization on the probability map coming from DIR structure propagation.

- **cRT** : The dose in the target shows an increasing trend, even leading to an overdose in the nominal case in fraction 24. The evolution is not surprising because there is no adaptation before replanning ; there is no monitoring of the patient's anatomy, so the treatment is given on an anatomy that is increasingly different from the initial anatomy on which the plan was optimised. The evolution also logically follows that of the D50. This is not supposed to happen in fraction 24 because it is precisely the replanning fraction. This can be explained by the fact that the image for replanning is done in fraction 13 and applied only in fraction 24, so the anatomy may have changed. Another explanation is the setting of poor constraints, which then leads to a suboptimal dose distribution. The dose is not regular, which can be explained by the fact that the workflow is not adaptive and therefore strongly influenced by random inter-fraction errors.
- **oaRT** : Dose very regular. It is not possible to obtain a better dose distribution than the one optimize and evaluate according to the daily physician's contours. The patient did not experience any major anatomical changes during treatment, so we decided to reduce the PTV margin to 2mm, as it seemed sufficient to account for intra-fraction uncertainties [38, 39, 40].
- **oaRTDIR-WS** : The worst-case scenario, which depicts the setup error leading to the most adverse dose distribution, is taken into account for optimization. Therefore, the optimization is conservative. The dose distribution is close to the one of oaRTDIR meaning that the worst case is close to the nominal one.
- **oaRTDIR** : The optimization on the PM >0.5 , following the same trend as the

oaRT, seems to say that $PM > 0.5$ corresponds quite well to the CTV. This also mean that the structure propagation developed here with the neural network seems validated.

The dose being slightly lower may indicate that the 0.5 threshold value is perhaps too low (a higher threshold leads to a smaller volume, which avoids the real edges of the structure and results in the central region being better irradiated). However, the difference of less than one percent is too small to draw conclusions.

- **paRTCBCT** : The paRTCBCT is under-dosed for 76 % of the evaluated cases. The nominal case (represented by the darker line) only experiences an under-dosage of 0.5%, which is relatively low.

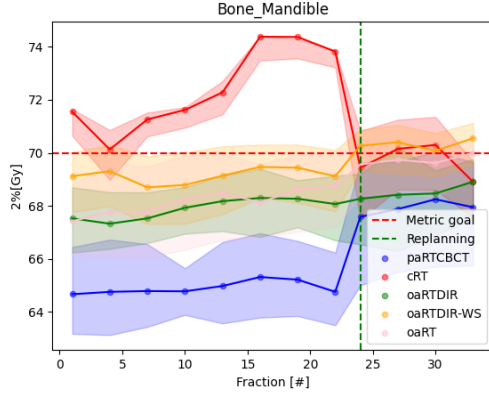
One reason for the under-dosage observed in the paRTCBCT method might be linked to the optimization constraints, which were initially optimized for cRT using the planning CT, and thus not optimized for this new method. It would be beneficial to refine the weights associated with the constraints or adjust the beam monitor unit in order to achieve doses that meet the constraints and objectives.

Another reason for under-dosing is the consideration of the complete probabilistic map for optimization. The probabilistic target map is larger than the CTV, but the region with a probability of 1 is smaller than the actual CTV. Thus, a region smaller than the CTV has the same dose constraint as the CTV. Regions with a lower probability have a lower dose constraint.

Furthermore, the high weight applied to the dose falloff constraints (weight of the Out_of_organ structure) has a notable impact. This weighting prompts the optimizer to reduce the dose in regions of the PM that have a low probability. This effect becomes even more evident when the weight value is reduced from 30 to 20 before re-planning, allowing the method to begin fulfilling the constraint more effectively.

6.1.2 Bone mandible

Any dose analysis in an organ must be done knowing the pass rate of the 50 samplings of the dose delivered to the target. Otherwise, a method can be judged better than another by delivering 0 gray in an organ but never reaching the constraint dose in the target.



Methods	PassRate of CTV_6996
cRT	1.00
oaRT	1.00
oaRTDIR	0.98
oaRTDIR-WS	1.00
paRTCBCT	0.24

Figure 6.3: Dose received by the two percent of the volume of the mandibular bone receiving the highest dose (left) and pass rate of the target (right). *Abbreviations:* cRT = classic non-adaptive radiotherapy workflow, oaRT = online adaptive radiotherapy using classical optimization with the physician structures, oaRTDIR = online adaptive radiotherapy using classical optimization with the probability map > 0.5 coming from DIR structure propagation, oaRTDIR-WS = online adaptive radiotherapy with robust worst case optimization on the probability map > 0.01 coming from DIR structure propagation and paRTCBCT = online adaptive radiotherapy with probabilistic optimization on the probability map coming from DIR structure propagation.

- cRT** : The dose in the mandibular bone is the highest and, above all, too high for the dose constraint. This can be explained by the fact that the PTV is formed to be conservative and there is no adaptation.
 The significant D50 indicates that the dose distribution seems to exceed the limits of the CTV structure, leading to significant dosing outside the CTV and thus in nearby regions. The mandibular bone is, in fact, located in contact with the CTV.
 This dose is also increasingly higher before replanning. Despite this unacceptable dose delivered to the mandible, cRT allows achieving 100% PassRate in the CTV.
- oaRT & oaRTDIR** : Both methods obtain very similar results, further showing that the DIR structures are similar to those drawn by the physician.
 The overlapping doses indicate that there is no sign of a poorly weighted probability map.
- oaRTDIR-WS** : Optimization on the worst-case scenario allows for a good dose rate and therefore a good dose for the most distant scenarios.
 Since we optimize on the worst-case scenario, it is not surprising to see a higher average dose than with other optimization methods.
- paRTCBCT** : Despite a low pass rate, the probabilistic method is not far from the dose constraints in the target, less than 0.5%. In the mandibular bone, the dose is relatively low, below 4 Gray compared to other methods, which represents 6%.

Increase 0.7% Monitor Unit increase 0.5% of the dose in the target and thus allow to have a better passrate. If we do that, we continue to have a best dose in the Mandibule than other methods.

6.1.3 Parotids

Both parotids have dose limits of 26 Gy, but one can be irradiated up to 30 Gy if the other remains below 26 Gy. Since the tumor region is in the left part of the jaw, the left parotid is more irradiated than the right.

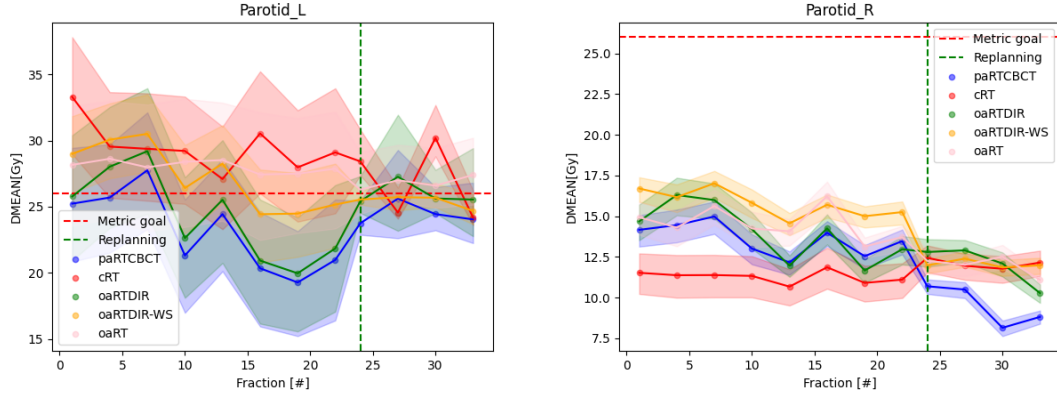


Figure 6.4: Mean dose received by the left parotid (left) and pass rate of the target (right). *Abbreviations:* cRT = classic non-adaptive radiotherapy workflow, oaRT = online adaptive radiotherapy using classical optimization with the physician structures, oaRTDIR = online adaptive radiotherapy using classical optimization with the probability map > 0.5 coming from DIR structure propagation, oaRTDIR-WS = online adaptive radiotherapy with robust worst case optimization on the probability map > 0.01 coming from DIR structure propagation and paRTCBCT = online adaptive radiotherapy with probabilistic optimization on the probability map coming from DIR structure propagation..

The overall reduction of the dose for adaptive methods can be explained by the fact that the left parotid gland is close to the CTV, and therefore, when tumor cells are destroyed through irradiation, the target volume is decreased, leading to a reduction in irradiation of the neighboring organs. This is not the case for cRT, which always maintains the same PTV.

The methods cRT and oaRTDIR-WS are the only ones to stay below 30 Gy in the nominal case. The paRTCBCT method appears to be the most interesting, having a pass rate of 0.82.

The right parotid shows interesting results: it seems that the adaptive methods were able to distribute more dose in this parotid. This is not negative and is even maybe a positive sign, indicating that the methods took advantage of this less irradiated region to find another path to reach the target volume.

6.1.4 Other structures

The other structures are included in Appendix B. Table 6.1 summarizes the pass rates for all the structures.

Structures	cRT	oaRT	oaRTDIR	oaRTDIR-WS	paRTCBCT
Brainstem-D2cc	1.0	1.0	1.0	1.0	1.0
SpinalCord-V45[cc]	0.86	1.0	1.0	1.0	1.0
SpinalCord-D2cc	1.0	1.0	1.0	1.0	1.0
Parotid_L-DMEAN[Gy]	0.18	0.1	0.58	0.52	0.82
Parotid_R-DMEAN[Gy]	1.0	1.0	1.0	1.0	1.0
Larynx-DMEAN[Gy]	0.58	0.68	0.52	0.93	0.58
Musc_Constrict-DMEAN[Gy]	0.98	1.0	1.0	0.99	1.0
Esophagus-DMEAN[Gy]	0.0	1.0	0.73	0.96	0.73
GlnD_Thyroid-DMEAN[Gy]-49	1.0	1.0	1.0	1.0	1.0
GlnD_Thyroid-V50[%]	1.0	1.0	1.0	1.0	1.0
Bone_Mandible-2%[Gy]	0.29	0.96	1.0	0.79	1.0
Cavity_Oral-DMEAN[Gy]	1.0	1.0	1.0	0.98	1.0
CTV_6996-D95[Gy]	1.0	1.0	0.98	1.0	0.25
CTV_5940-D95[Gy]	0.87	0.7	0.34	0.67	0.16

Table 6.1: Pass rate of dose constraints for structures using different methods. *Abbreviations:* cRT = classic non-adaptive radiotherapy workflow, oaRT = online adaptive radiotherapy using classical optimization with the physician structures, oaRTDIR = online adaptive radiotherapy using classical optimization with the probability map > 0.5 coming from DIR structure propagation, oaRTDIR-WS = online adaptive radiotherapy with robust worst case optimization on the probability map > 0.01 coming from DIR structure propagation and paRTCBCT = online adaptive radiotherapy with probabilistic optimization on the probability map coming from DIR structure propagation.

Although the constraints were optimized for cRT, this method is on par with paRTCBCT in terms of the number of structures not meeting the dose constraint (Pass Rate < 0.9).

The fact that none of the methods pass all the constraints with a dose rate of at least 0.9 clearly shows that the weights associated with the constraints have not been rigorously defined.

Chapter 7

Conclusion and perspectives

The effective creation of probabilistic structure maps, formed by the uncertainties of structure presence in multiple DIRs from a neural network, has already been validated in Luciano A. Rivetti *et al.* [7] but has been included in treatment plans for the first time. This technological advance is corroborated by the similarity in dose distributions between the oaRT and oaRTDIR methods, which confirms the efficient propagation of the DIR structures. This progress signifies a substantial leap towards an unsupervised method of structure propagation, offering the potential for considerable time and resource savings in each fraction of the treatment process.

The successful implementation of probabilistic optimization in OpenTPS represents a significant advancement in treatment planning. By integrating probabilistic structure maps into the optimization, this approach enables the weighting of structure voxels in the objective function based on their individual presence probabilities. And thus, the doses constraints are weighted. This provides an alternative to the classical optimization approach that uses the conservative PTV, where each target voxel is assigned equal weight.

By integrating joint probability into the optimization process, the treatment plan is designed to be effective not only in an ideal scenario but also to be resilient and efficient across a range of probable scenarios, taking into account positioning errors. This ensures that the treatment remains accurate and effective even in the presence of uncertainties.

paRTCBCT appears to have the capability to reduce the dose in OARs that are close to target volumes. Conceptually, paRTCBCT should perform better than a classical approach as it takes into account the uncertainties in the presence of structures. However, it is currently challenging to understand how to optimize and define weights for constraints and objectives. The weight associated with the dose falloff constraints needs to be more carefully considered to avoid under-dosage in regions where the PM has low probabilities.

The cRT workflow, which does not involve re-optimization, appears to have some limitations with certain organs at risk over time. This is evident despite the patient not undergoing significant anatomical changes during the treatment period.

The time consumed for probabilistic optimization and dose calculation is lengthy, so improving the efficiency of OpenTPS is a primary avenue for enhancement. The frequency of plan adaptation can also be questioned if the calculation time remains long. It's worth considering whether to adapt every three fractions, as done in this work, or even on a weekly basis. This approach is suggested in the paper by Mislav Bobić *et al.* [6] and appears to be a good alternative that reduces the clinical workflow.

Numerous research studies have attempted to include other uncertainties, such as those arising from tumor infiltration, by creating PM as well [37, 41]. A new research direction would be to try to merge several PM, weighting the value of each voxel, thus allowing for the incorporation of numerous uncertainties into robust optimization. For proton therapy treatments, the integration of range uncertainties must also be included in the optimization phases.

Another research avenue is the inclusion of constraint weights in optimization. Multi-variable optimization should be able to optimize both the beamlets and beam parameters, as well as the weights associated with each constraint.

Appendix A

Validation of the synthetic CT

A.1 Method

In order to verify that the sCT possesses the requisite HU for use in dose calculation, we will start by optimize a treatment plan on our TPS, using the wCT as the reference image. During optimization, the TPS selects a dose-influence matrix $\mathbf{P}$, incorporates the dose constraints provided by the physician, and attempts to optimize the value of the beamlets weight ($\mathbf{w}$) so that $\mathbf{d}$, the dose matrix, meets the constraints.

$$\mathbf{d} = \mathbf{P} \cdot \mathbf{w} \quad (\text{A.1})$$

Here $\mathbf{P}$ and $\mathbf{d}$ do not depend on a scenario, as the optimization is not robust. The optimization was performed with the constraints present in the Table 5.1. Structures are binaries mask delinearized by oncologist doctors.

Next, we use the same beamlet weight values to calculate the dose distribution inside the sCT.


$$\mathbf{d}_w = \mathbf{P}_w \cdot \mathbf{w}_w \quad \mathbf{d}_s = \mathbf{P}_s \cdot \mathbf{w}_w$$

w and s mean respectively for wCT and sCT.

By employing this method, we ensure that any differences in dose distributions are solely attributable to the images used, and consequently, to their respective Hounsfield Units (HU).

A clinical metric to expresses the difference in dose as a function of structure's constraints and is inspired by the method used in Iva Bratova *et all* (2019) [36], dose difference normalized (DDN) is,

$$\text{DDN} = (d_w - d_s) \frac{100}{d_{prescr}} \quad (\text{A.2})$$

We will analyze four regions of interest: the high-risk PTV, the low-risk PTV and both the left and right parotid glands. The specific selection of these regions is

not of primary importance, as the goal is simply to evaluate anatomical areas within the image, regardless of their specific nature.

We will conduct this analysis on patient HN_01. This patient exhibits minimal anatomical variation across different treatment fractions. This is crucial because, as mentioned earlier, the registration forming the sCT is not error-free and not unique. Therefore, it's important to use sCT and wCT images that are as closely matched as possible, ensuring that any dose differences arise solely from HU discrepancies and not from differing anatomies.

A.2 Results

The following boxplot contain the DDN across regions of interests for 33 fractions. The similarity between the dose distributions of the sCT and the wCT increases as the mean gets closer to zero.

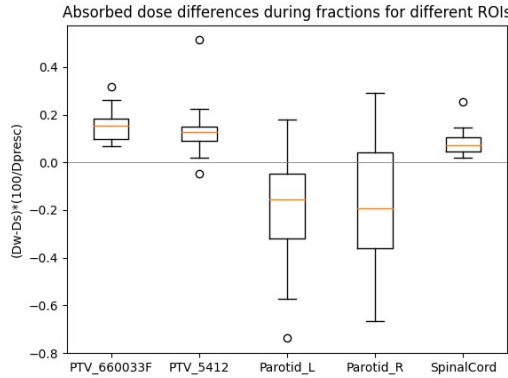


Figure A.1: Boxplot of absorbed dose difference normalized $DDN = (d_w - d_s) \frac{100}{d_{presc}}$ across various fractions for different regions of interest.

The results for the DDN (left in A.1) all fall within a maximum of 0.8 from the origin, indicating less than a 1% dose difference between sCT and wCT. Each point represents a voxelwise difference, but our focus is not on individual points; rather, it's on their average. Therefore, the most significant average value in the left plot, being approximately 0.2%, is negligible. The average DDN across the Regions of Interest is 0.00058 with a standard deviation of 0.149.

Negative values indicate that the dose calculated from wCT is higher than that from sCT. The averages are three times less than zero out of five for DDN. There appears to be no general trend between the doses calculated with sCT and wCT, suggesting that the differences are random.

Appendix B

Results of the metrics for the different structures

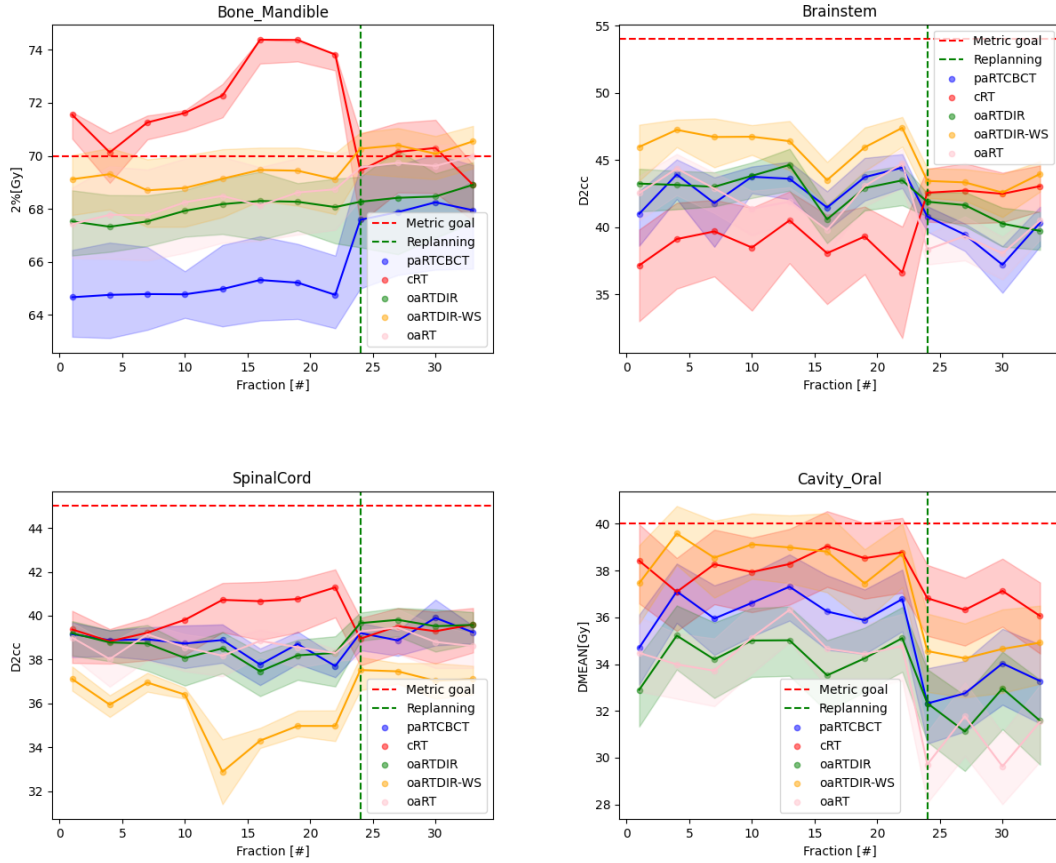


Figure B.1: Metric values for the mandible bone, brainstem, spinal cord, and oral cavity. *Abbreviations:* cRT = classic non-adaptive radiotherapy workflow, oaRT = online adaptive radiotherapy using classical optimization with the physician structures, oaRTDIR = online adaptive radiotherapy using classical optimization with the probability map > 0.5 coming from DIR structure propagation, oaRTDIR-WS = online adaptive radiotherapy with robust worst case optimization on the probability map > 0.01 coming from DIR structure propagation and paRTCBCT = online adaptive radiotherapy with probabilistic optimization on the probability map coming from DIR structure propagation.

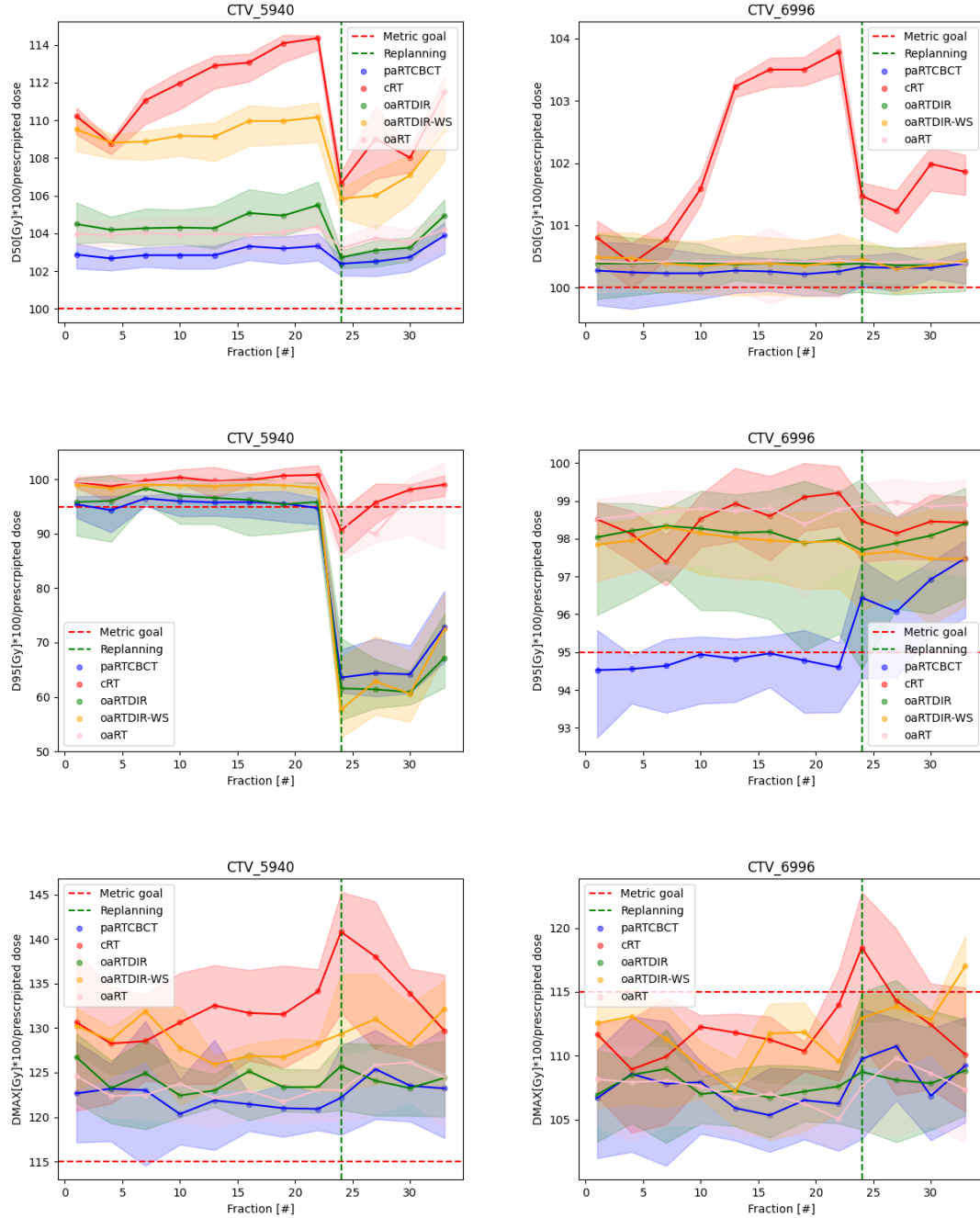


Figure B.2: Dose metrics in the CTV targets. *Abbreviations:* cRT = classic non-adaptive radiotherapy workflow, oaRT = online adaptive radiotherapy using classical optimization with the physician structures, oaRTDIR = online adaptive radiotherapy using classical optimization with the probability map > 0.5 coming from DIR structure propagation, oaRTDIR-WS = online adaptive radiotherapy with robust worst case optimization on the probability map > 0.01 coming from DIR structure propagation and paRTCBCT = online adaptive radiotherapy with probabilistic optimization on the probability map coming from DIR structure propagation.

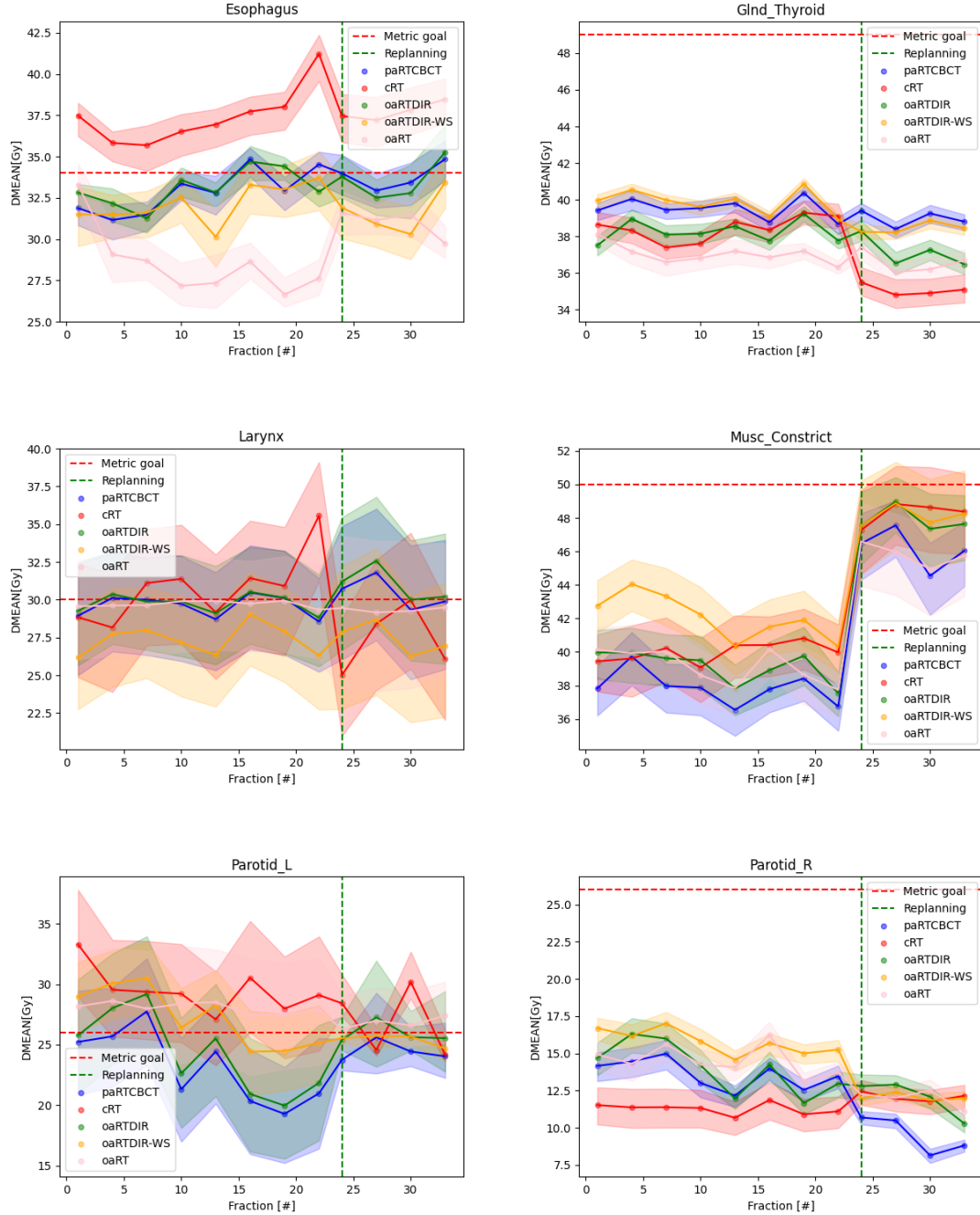


Figure B.3: Dose metrics for the Esophagus, Thyroid Gland, Larynx, Constrictor Muscle, and Left and Right Parotids. *Abbreviations:* cRT = classic non-adaptive radiotherapy workflow, oaRT = online adaptive radiotherapy using classical optimization with the physician structures, oaRTDIR = online adaptive radiotherapy using classical optimization with the probability map > 0.5 coming from DIR structure propagation, oaRTDIR-WS = online adaptive radiotherapy with robust worst case optimization on the probability map > 0.01 coming from DIR structure propagation and paRTCBCT = online adaptive radiotherapy with probabilistic optimization on the probability map coming from DIR structure propagation.

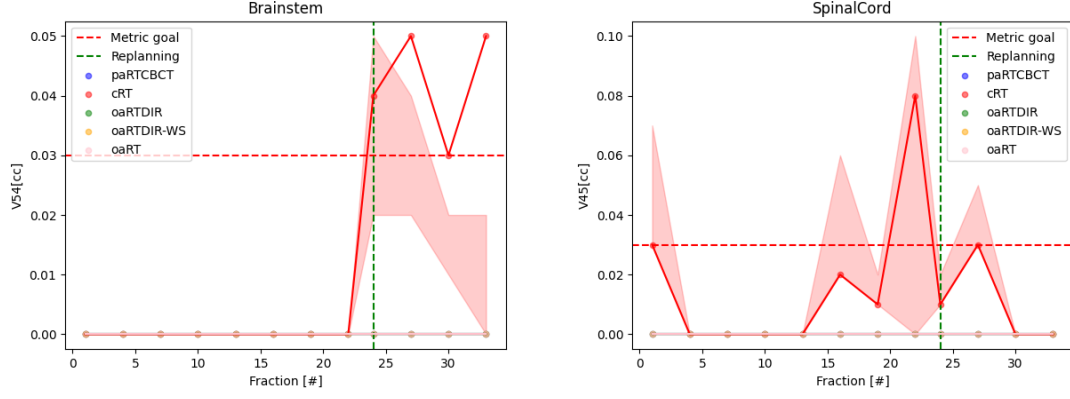


Figure B.4: Dose metrics for the brainstem and the spinal cord. *Abbreviations:* cRT = classic non-adaptive radiotherapy workflow, oaRT = online adaptive radiotherapy using classical optimization with the physician structures, oaRTDIR = online adaptive radiotherapy using classical optimization with the probability map > 0.5 coming from DIR structure propagation, oaRTDIR-WS = online adaptive radiotherapy with robust worst case optimization on the probability map > 0.01 coming from DIR structure propagation and paRTCBCT = online adaptive radiotherapy with probabilistic optimization on the probability map coming from DIR structure propagation.

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