

Exploration of potential parameters that influence when to replan Head and Neck Cancer patients during Radiotherapy

Aixa Xiuhyolotzin Andrade Hernández

Medical Physics Unit, Department of Oncology, Faculty of Medicine

McGill University, Montreal

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science (M.Sc.) Medical Radiation Physics (Thesis), August 2020

©Aixa Xiuhyolotzin Andrade Hernández, 2020

Abstract

The need to modify or “replan” a head and neck cancer patient’s radiotherapy treatment arises when significant anatomical changes occur during their treatment course. While regular patient imaging during treatment can be useful to identify when a patient needs to be replanned, they continue to be treated with the sub-optimal original plans until a new plan is created. For this reason, the ability to predict in advance if and when a patient’s plan will require replanning would be advantageous so that the patient is treated with a more optimized plan throughout their treatment course, improving the overall quality of treatment.

In this thesis, the relationship between clinical variables and the need to replan was investigated. Data from the electronic health records of 490 head and neck cancer patients were used, with special attention paid to patient weight loss and gain throughout treatment.

Weight loss was hypothesized to be a parameter that might be used to represent anatomical changes in patients examined. As a result of a weight time series analysis, it was confirmed that head and neck cancer patients lost weight during their radiotherapy treatment, consistent with the literature (Zhao et al. 2015).

Given its clinical importance, the parameters that influenced weight loss were investigated using a linear regression model. Additionally, the main predictors of when to replan a patient were found to be the 20th to 25th treatment fraction and the weight loss ($p < 0.05$) using a logistic regression model. However, some patients were not replanned even if they lost a significant amount of weight during radiotherapy, which raised the question of whether weight loss was a reliable feature that would accurately represent the anatomical changes in the neck region.

With the motivation to find a predictor that may reflect more accurately the anatomical changes of head and neck cancer patients during radiotherapy, a technique to measure the neck area loss using the set up images from historical head and neck cancer patients was developed. The neck area and weight time series of 18 patients during radiotherapy were

compared and it was found that even if both quantities decreased during the patients' treatments, they did so at different rates. This finding could explain why some patients were not replanned even if they lost a significant amount of weight.

Résumé

La nécessité de modifier ou de “replanifier” les traitements de radiothérapie d’un patient atteint d’un cancer de la tête et du cou survient lorsque des modifications anatomiques importantes se produisent au cours des traitements. Bien que l’imagerie régulière du patient pendant le traitement puisse être utile pour identifier le moment auquel un patient doit être replanifié, il continue à être traité avec les plans d’origine sous-optimaux jusqu’à ce qu’un nouveau plan soit créé. Pour cette raison, la capacité de prédire à l’avance si et quand le plan d’un patient nécessitera une replanification serait avantageuse afin que le patient soit traité avec un plan plus optimisé tout au long des traitements, améliorant ainsi la qualité globale du traitement.

Dans cette thèse, la relation entre les variables cliniques et la nécessité de replanifier a été étudiée. Les données des dossiers de santé électroniques de 490 patients atteints de cancer de la tête et du cou ont été utilisées, une attention particulière étant accordée à la perte et au gain de poids des patients tout au long des traitements.

Notre hypothèse était que la perte de poids était un paramètre pouvant être utilisé pour représenter les changements anatomiques chez les patients examinés. À la suite d’une analyse des séries temporelles chronologiques de poids, il a été confirmé que les patients atteints d’un cancer de la tête et du cou ont perdu du poids pendant leur traitement de radiothérapie, conformément à la littérature (Zhao et al. 2015).

Compte tenu de l’importance clinique du poids des patients, les paramètres qui ont influencé la perte de poids ont été étudiés à l’aide d’un modèle de régression linéaire. Dans ce modèle, les principaux prédicteurs du moment optimal pour replanifier les traitements se sont avérés être notamment la 20^e à la 25^e fraction de traitement et la perte de poids ($p < 0.05$).

Cependant, certains patients n’étaient pas replanifiés même s’ils perdaient une quantité importante de poids pendant la radiothérapie, questionnant ainsi si la perte de poids était

réellement une caractéristique fiable représentant avec précision les changements anatomiques dans la région de la tête et du cou.

Afin de trouver un prédicteur pouvant refléter plus précisément les changements anatomiques des patients atteints de cancer de la tête et du cou pendant les traitements de radiothérapie, une technique pour mesurer la diminution de l'aire dans la région du cou a été développée à partir des images de configuration de patients atteints de cancer de la tête et du cou. Les séries temporelles chronologiques de l'aire dans la région du cou ainsi que du poids de 18 patients durant les traitements de radiothérapie ont été comparées et il a été constaté que même si ces deux quantités diminuaient au cours des traitements, elles le faisaient à des rythmes différents. Cette découverte pourrait expliquer pourquoi certains patients n'ont pas reçu une replanification même s'ils ont subi une importante perte de poids.

Acknowledgments

To all the people from the Radiation Oncology Department, especially those from the Medical Physics Unit that gave me their advice and support throughout these two years.

To my supervisor, John Kildea, who gave me this incredible opportunity to participate in his research group and also provided me advice and support during this journey.

To all the members of my group of research, the Nice Rocks, for their brilliant ideas, great suggestions and advice. Especially to Haley Patrick for her advice, support and for being the most helpful person that I ever have known. Hossein Naseri for our friendship and his participation in the neck area code that I started and he helped to polish it nicely. We made a great team.

To all the people that contributed to my project: Dr. Shenouda, the head and neck cancer expert. Victor Matassa, who taught me the secrets of Aria database and was always willing to help. Farzin Khosrow-Khavar, that provided me with ideas and advice that resulted to be really helpful in my thesis. Marina Faria, that helped me to get DICOM images, despite the tedious activity it was.

To Aditya Kaul, who showed unconditional support every single day, always trying to make me a better person.

To my family: My sister, Malaika, who is always in my heart. My parents, Ángeles and Mariano, who made this possible and have been supporting me all my life. My grandparents, Jorge and Mora who trusted me and supported me in this adventure. My aunts María Clara and Lupita, who have always been for me.

To my friends, Jonathan Yeo, Thierry Lefebvre and Esteban Sepulveda that proved to be a great team during the masters and made my life much happier in Montreal.

To Norma Ybarra, my professor and friend, who showed me support through all the masters.

Contributions of the Author

The author has written all the chapters in this thesis. Chapters 1 and 2 were written based on a literature review performed by the author. In Chapter 3, all the scripts used for mining and processing data from relational databases were created by the author. The data workflow was created by the author, as well as the *weights_project_database*. Only the *neck area* code that was written by the author with the collaboration of Hossein Naseri for the 3D registration between CT and CBCT. Additionally the DICOM images of HNC patients were identified by the author and were downloaded manually from Eclipse with the help of Marina Faria and Hossein Nasser. The results, analysis and conclusions (Chapters 4, 5 and 6) were performed solely by the author. The work done by the author was supervised by John Kildea.

Table of Contents

Abstract	2
Résumé	4
Acknowledgments	6
Contributions of the Author	8
1. Introduction	15
1.1 Overview of Thesis	15
1.2. Radiotherapy	15
1.2.1. Linear quadratic model and fractionation	16
1.2.2. Radiotherapy Treatment Modalities	17
1.2.3. Radiotherapy Treatment Workflow	19
1.2.4. Image-Guided Radiotherapy (IGRT)	21
1.2.5. Adaptive radiotherapy (ART)	22
1.3. Medical Imaging in Radiotherapy	23
1.3.1. Computed Tomography (CT)	23
1.3.2. Cone Beam Computed Tomography (CBCT)	24
1.3.3. Image registration	25
1.3.4. Digital Imaging and Communications in Medicine (DICOM) images	25
1.3.5. Databases in Oncology	26
1.4. Statistics	26
1.4.1. Hypothesis testing	26
1.4.2. Commonly-used statistical tests	27
1.4.3. Statistical learning models	28
1.4.3.1. Linear regression	29
1.4.3.2. Logistic regression	30
2. HNC radiotherapy replanning	32
2.1. Head and Neck cancer	32
2.1.1. HNC treatment	32
2.1.1.1. Surgery	32
2.1.1.2. Chemotherapy	33
2.1.1.3. Radiotherapy in HNC	33
2.1.2. Treatment variations depending on the site location of HNC	34
2.1.3. Secondary effects induced by radiotherapy in HNC patients	34
2.2. Current status and challenges of HNC radiotherapy replanning	35
2.2.1. Anatomical changes during HNC treatment	36
2.2.1.1. When to replan	37
2.2.2. Factors that influence weight loss	38
2.2.3. Challenges for HNC replanning prediction	40
2.2.4. Replanning predictors selection	41

3. Methods	43
3.1. Patient Cohort	43
3.1.1. Radiotherapy plan considerations in the patient's cohort selection	43
3.2. Data Collection	44
3.3. Data processing	45
3.3.1. Considerations for data availability	46
3.3.2. Other considerations to format the data in a useful manner for analysis	46
3.3.3. Calculation of Neck area data	48
3.3.4. Normalization of the neck area and weights data for comparison between patients	52
3.4. Data Storage	53
3.5. Data analysis	55
3.5.1. Univariate analysis between patients replanned and not replanned	55
3.5.2. Multivariate regression models	55
3.5.3. Anatomical changes time series analysis	56
4. Results	58
4.1. Univariate evaluation of replanning	58
4.2. Anatomical changes time series (weight loss) and replanning	62
4.3. Multivariate regression models	65
4.3.1. Anatomical changes predictors (weight loss predictors)	66
4.3.2. Replanning predictors	68
4.4. Area vs weight	70
5. Discussion	74
5.1. Univariate analysis of replanning and anatomical changes	74
5.2. Multivariate analysis of replanning	75
5.3. Area vs weight	77
Conclusions	80
References	81

List of Tables

Table 1.2.5.1. Offline vs Online ART (Green, Henke, and Hugo 2019).	22
Table 1.4.1.1. Treatment modalities that can be used alone or in combination for HNC patients (Yeh 2010).	34
Table 3.4.1. Content of weights_project database tables	54
Table 4.1.1. Frequencies and χ^2 p -values of prescription doses, patients sex, HNC site location, cancer stage and concurrent chemotherapy in patients replanned and not replanned.	61
Table 4.3.1.1. Multivariate linear regression coefficients to predict the patient's relative weight during radiotherapy using the data of 490 HNC patients (2012-2019). Independent variables: Fraction number, prescribed dose, cancer stage, HNC site location, age at the start of the treatment. Multiple $R^2 = 0.2586$. F statistic = 61.59.	67
Table 4.3.1.2. Multivariate linear regression coefficients to predict the patient's relative weight during radiotherapy using 260 HNC (2016-2019). Independent variables: Fraction number, prescribed dose, concurrent chemotherapy and age at the start of the treatment. Multiple $R^2 = 0.1695$. F statistic = 39.73.	68
Table 4.3.2.1 Odds ratio (OR) from multivariate logistic regression model to predict the fraction of replanning. Total number of patients: 490 (2012-2019). Independent variables: Fraction number and normalized weight.	69
Table 4.3.2.2 Odds ratio (OR) from multivariate logistic regression model to predict the fraction of replanning. Total number of patients: 260 (2012-2019). Independent variables: Fraction number, concurrent chemotherapy and normalized weight.	69

List of Figures

Figure 1.3.4.1. Survival curve for cancer cells and normal tissue as a function of the dose delivered. Parameters for cancer cells $\alpha = 0.4 \text{ Gy}^{-1}$ and $\alpha/\beta = 10 \text{ Gy}$. Parameters for normal tissue: $\alpha = 0.22 \text{ Gy}^{-1}$, $\alpha/\beta = 2.5 \text{ Gy}$. The figure was reproduced using the parameters from (Orton 2020.).	17
Figure 1.4.4.4.1. GTV, CTV and PTV structures contoured in a CT image for a malignant neoplasm of the base of tongue.	20
Figure 2.2.4.1 Replanning predictors during radiotherapy that were examined in this thesis research project.	42
Figure 3.3.4.1. Length of the left submandibular gland Δz on the z axis in the plane yz of the patient.	50
Figure 3.4.1. Flowchart of information into the weights_project database.	53
Figure 4.1.1. Proportion of patients replanned and not replanned in groups of total prescribed doses of 60 Gy, 66 Gy and 70 Gy. Total of 490 HNC patients.	58
Figure 4.1.2. (a-d) Proportions of patients replanned and not replanned for patients sex, HNC site location, cancer stage and concurrent chemotherapy. There were considered 490 patients for (a-c) and 260 patients for (d).	60
Figure 4.1.3. Violin plots of the age of the patients replanned and not replanned at the start of their radiotherapy treatment. Total 490 HNC patients.	62
Figure 4.1.4. Box plots of the weight loss of the patients replanned and not replanned at the end of their radiotherapy treatment. Total 490 HNC patients.	62
Figure 4.2.1. Replanning frequency as a function of the fraction number for HNC patients. A total of 201 patients out of 490 patients were replanned. (2012 - 2019)	63
Figure 4.2.2. Median weight series of the 490 HNC patients undergoing radiotherapy who were considered in this thesis project. Number of fractions sampled in 5 fractions increment. (2012 - 2019)	64
Figure 4.2.3. Proportions of HNC site location for replanned and not replanned patients with prescription doses of 60 Gy, 66 Gy and 70 Gy. Total of 490 patients.	65
Figure 4.2.4. Proportions of concurrent chemotherapy patients for replanned and not replanned patients with prescription doses of 60 Gy, 66 Gy and 70 Gy. Total of 260 patients.	65
Figure 4.4.1. Patients replanned and not replanned for 18 HNC patients (2018- 2019).	70
Figure 4.4.2. Median time series of weight and area for 18 patients undergoing radiotherapy. (2018 - 2019). Solid lines represent patients replanned and dashed lines represent patients not replanned.	71
Figure 4.4.3. The value loss at 25 fx and 35 fx for area (green) and weight (purple) of the patients replanned (R) vs not replanned (NR) Total: 18 patients (2018 - 2019).	72

Figure 4.4.4. Differences of relative area and weight (%) during radiotherapy for patients replanned and not replanned. Total: 18 patients (2018 - 2019). 73

Figure 4.4.5. The value of the area and weight at the replanning. Total: 11 patients replanned (2018 - 2019). 73

1. Introduction

1.1 Overview of Thesis

The purpose of this research was to determine if the need to replan a head and neck cancer patient during radiotherapy can be predicted based on available clinical data and images. This thesis describes the search for replanning predictors through the retrospective statistical analysis of radiotherapy data collected from 2012 to Fall 2019 at the McGill University Health Centre in Montreal. Two analyses were used. The first analysis just used basic clinical factors stored in the Electronic Health Records (EHR). The second analysis was created with the additional inclusion of daily imaging and was compared to the first analysis in order to determine if anatomical information provided added value.

This chapter introduces the basic concepts of radiotherapy, it describes the workflow in the clinic and the replanning process and the role of medical imaging in treatment planning. It gives the theoretical background needed to understand the statistical analysis techniques that will be used in the following chapters. Chapter 2 introduces head and neck cancer radiotherapy side effects and describes the current challenges in head and neck treatment planning. Chapter 3 outlines the patient cohort and the methods used in this project to process and analyze the data. In chapter 4 are exposed the results from the analysis described in Chapter 3. Chapter 5 discusses the replanning predictors and compares results with the literature to support the conclusions, which are presented in Chapter 6.

1.2. Radiotherapy

As a result of the interactions of the radiation with matter, some energy can be deposited in the matter, which we refer to as radiation dose (Canadian Nuclear Safety Commission (CNSC) 2020). Ionizing radiation is classified as radiation who has more energy that is required to remove electrons from atoms (World Health Organization (WHO) 2016). The ionizations caused by radiation can damage and potentially kill cells. This is especially true if the ionization modifies a cell's DNA sequence and prevents it from functioning properly.

There are DNA repair pathways, but that they are not always able to fix all the damage. A cell's response to radiation damage may be in the form of apoptosis, in which the cell is programmed to die, or by cell cycle arrest in which the cell stops its duplication and division (Little 2003).

While radiation can cause cancer, it is also highly effective at killing cancer cells. There are two main types of radiotherapy: (1) external beam radiotherapy (EBRT), which uses a radiation source external to the patient's body with the purpose of destroying cancer cells, and (Baskar et al. 2012) (2) brachytherapy, which inserts radioactive material inside the body to achieve the same goal (Canadian Cancer Society - Radiotherapy 2020).

1.2.1. Linear quadratic model and fractionation

Radiation is indiscriminate with regard to cancerous and healthy cells and has the potential to kill both. The goal of radiotherapy, therefore, is to maximize the death of cancer cells while minimizing the damage to healthy ones (Moding, Kastan, and Kirsch 2013). To do this, radiotherapy specialists take advantage of the radiation responses of different tissues. The linear quadratic model is a theoretical approximation to the cell survival curves of normal tissue cells and tumour cells after irradiation. The survival S is a function of the dose delivered in a single fraction D and it is described by the following equation:

$$S(D) = \exp(-(\alpha D + \beta D^2))$$

Where α represents irreversible damage and β the reversible damage. Both parameters depend on the type of tissue (Brenner 2008; van Leeuwen et al. 2018). Typical α/β ratios are on the order of 3 for healthy cells and 10 for tumour cells (Orton 2020). Figure 1.3.4.1 illustrates the survival curve of late reacting normal cells and cancer cells from zero dose to 8 Gy. For low doses, normal tissue survival is greater than the cancer cells survival, while for larger doses, the survival of cancer cells is greater than the normal tissue. In order to reduce the number of surviving cancer cells to 1%, almost 99.5% of normal tissue must be sacrificed and would almost certainly cause severe side effects for the patient. However, there was a much lower dose of 2 Gy where the ratio of cancer cell kill and normal tissue preservation was maximized, and it is this point that fractionation takes advantage of.

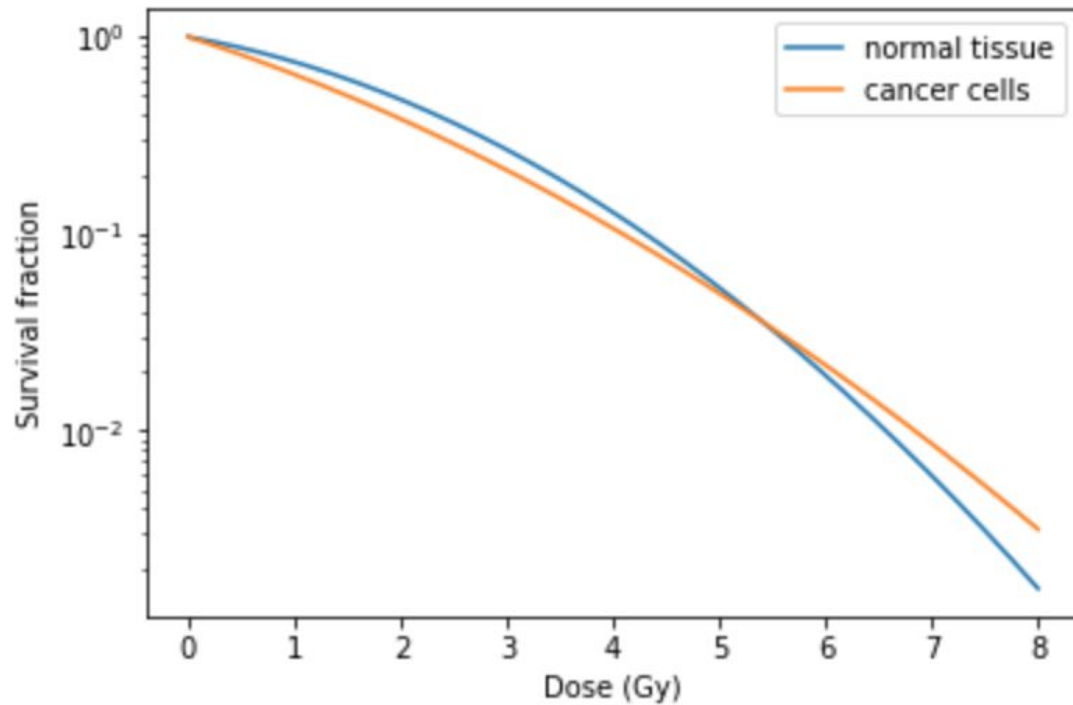


Figure 1.3.4.1. Survival curve for cancer cells and normal tissue as a function of the dose delivered.

Parameters for cancer cells $\alpha = 0.4 \text{ Gy}^{-1}$ and $\alpha/\beta = 10 \text{ Gy}$. Parameters for normal tissue: $\alpha = 0.22$

Gy^{-1} , $\alpha/\beta = 2.5 \text{ Gy}$. The figure was reproduced using the parameters from (Orton 2020).

Fractionated radiotherapy splits the total prescribed dose into small doses distributed in several fractions. Fractionation improves the ratio of cancer to healthy cell kill because it takes advantage of the four R's of radiobiology: The healthy cells have the opportunity of *repopulate*, the cancer cells have time to *redistribute* in the cell cycle (cells in M and G2 phases are more sensitive to radiation than cells in other phases), *reoxygenation* of the tumour cells (the radiation is more more damaging for oxygenated cells) and *repair* of the healthy cells (Pajonk, Vlashi, and McBride 2010).

1.2.2. Radiotherapy Treatment Modalities

There are different techniques, or modalities, used in EBRT. Modern modalities use computers and advanced treatment machines to shape radiation beams based on the morphology of a patient's tumour to achieve better accuracy in the treatment and to reduce the dose to healthy tissues near the tumour. The most common modalities are 3D conformal radiotherapy (3D CRT), Intensity-modulated radiotherapy (IMRT), Volumetric Modulated

Arc Therapy (VMAT) and Tomotherapy (Teoh et al. 2011). All these techniques aim to shape the beam according to the shape of the tumour.

3D CRT uses multi-leaf collimators (MLC) and 3D images of the patient to shape the dose to the tumour while maintaining a relatively uniform dose distribution. Unlike 3D-CRT, IMRT uses the MLC to modulate the beam intensity. This modulation allows for increased sparing of organs at risk (OARs) and can also help deliver a higher dose to the target. However, because of this the dose delivered is not uniform and can lead to hotspots in the patient. For this reason, it is important to check IMRT plans for dose in undesirable locations to avoid causing potentially negative side effects from the radiotherapy (Gomez-Millan, Fernández, and Medina Carmona 2013).

IMRT treatment planning and quality assurance is more complex and computationally intensive than 3D CRT planning. Even though the locoregional control improves with the IMRT technique, it delivers more monitor units (MU) than 3D CRT and leakage through the MLC and the head of the linac may induce secondary malignancies in the patients due to the whole-body dose wash involved (Vallard et al. 2016).

VMAT is the most advanced of the three modalities and is a form of arc therapy in which the MLCs move as the linac gantry moves around a static patient. VMAT has higher efficiency and higher conformal dose distributions than IMRT. Higher efficiency implies less time for dose delivery and less MUs than IMRT. Less toxicity for VMAT patients is also derived from a higher conformity of the treatment (Teoh et al. 2011). Tomotherapy is a subtype of VMAT.

While it is possible to create 3D-CRT plans based on expertise and trial and error (forward planning), the added complexity of moving MLCs in IMRT and VMAT plans necessitates a different approach. Instead of forward planning, modern IMRT and VMAT treatments use an inverse planning approach, in which the treatment planner specifies the requirements of the treatment plan and has a computer try hundreds of possibilities to find the optimum one. Parameters given to the system for this optimization problem include dose constraints, prescription dose for the target, as well as number of beams or arcs.

Both the IMRT and VMAT techniques enable sparing of critical structures in the head and neck region such as the spinal cord and brainstem (Leer 2005). Additionally, both techniques necessitate a well defined structure delineation because the radiation fields will be shaped to the tumour (Leer 2005). A cost function is optimized to obtain the maximum dose to the target while minimizing exposure to organs at risk. Recommended dose constraints to the OARs are used in the optimization process.

In our clinic, VMAT is currently the most used radiotherapy technique for head and neck cancer (HNC). However, IMRT and 3D CRT have historically also been used to treat some HNC patients. Additionally, tomotherapy was used for a large number of patients between 2008 and 2016.

1.2.3. Radiotherapy Treatment Workflow

The radiotherapy treatment workflow starts with acquiring patient images on a special CT scanner called a CT Simulator. Unlike a regular diagnostic CT scanner, the CT Simulator has a flat tabletop, a wider bore, and positioning lasers so the patient can be positioned the same way as they will need to be for treatment. Thermoplastic masks or vacuum bags are examples of common devices fitted to patients at the time of simulation and worn at every fraction in order to immobilize the patients during their radiotherapy treatment and ensure accuracy of the treatment. In addition to any necessary immobilization devices, a set of ball bearings are placed on the patient to mark the origin slice in the CT image that will be used for the patient's positioning during radiotherapy (Beyzadeoglu, Ozyigit, and Selek 2015). The placement of these bearings is marked on the patient with tiny tattoos for reference during the treatment. Images taken at simulation are integrated into the patient's chart in the EHR where they are used to create the treatment plan.

The treatment plan for the patient is designed by one or more dosimetrists, radiation oncologists, and medical physicists depending on the complexity of the case. The treatment planning consists of two stages. The first stage is the contouring of the targets, OARs and relevant structures on the image taken at the CT simulator. In the second stage the dose is calculated and quality assurance checks are performed.

Target structures need to ensure neoplastic tissues that are both visible and invisible in medical images are always included in the region being irradiated and are therefore drawn in three stages. The first stage is the gross tumour volume (GTV), which consists of the tumour volume that is visible to the clinician's eyes. The next stage is the clinical target volume (CTV), which includes the GTV and an external margin that accounts for the potential microscopic spread of the disease (Burnet et al. 2004). Finally, the planning target volume (PTV) is created, which includes the CTV and an additional margin for positioning errors and movement at the treatment machine (Burnet et al. 2004). Sometimes the GTV is not drawn or the GTV and CTV are considered equivalent, usually in cases in which the tumour was removed surgically prior to radiotherapy (eg. breast) or when the disease is well encapsulated in one region without microscopic spread (eg. prostate) (Leer 2005).

An example of a GTV enclosing a malignant neoplasm of the base of tongue, surrounded by the CTV and PTV margins are illustrated in figure 1.4.4.4.1.

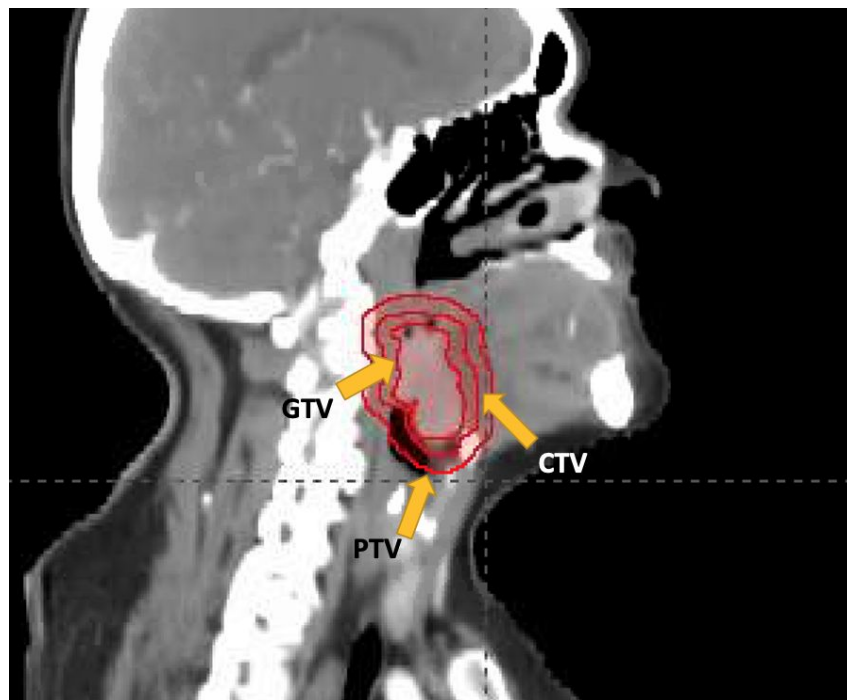


Figure 1.4.4.4.1. GTV, CTV and PTV structures contoured in a CT image for a malignant neoplasm of the base of tongue.

The next stage of the treatment planning process is the designing of the patient's treatment plan and the calculation of the planned dose distribution in the patient that will maximize the dose to the target and minimize the dose to the OARs (Jin et al. 2015). Additionally, the type and modality of the plan will depend on the patient's circumstances and the expertise of the treatment team. In general the dosimetrists will align basic radiation beams and work with the treatment planning software to meet the specifications of the radiation oncologist. Dose gradients are created to spare OARs. The plan has to be approved and go through quality assurance involving medical physicists, dosimetrists, radiation oncologists and radiation therapists before it can be used for treatment.

Finally, the patient is treated according to the treatment plan that was individually planned for their circumstances. Before the delivery of each fraction, the radiation therapists (the staff responsible for delivering the treatment) ensure the patient is set up in the same position as at the CT simulation using a combination of immobilization devices, lasers, and imaging (section 1.2.4). Significant changes in the patient's anatomy could impact the dose to the target and OARs. Thus, the treatment plan will need to be modified to account for the anatomical changes, a step that is also known as a *radiotherapy replan* (Beyzadeoglu, Ozyigit, and Selek 2015). The replan is also performed when the patient's position cannot be reproduced according to the treatment's plan. The request for a replan will be added to the clinical tasks associated with the given patient. Reasons for replanning can include changes in mask or other immobilization device fitting or weight gain or loss (Green, Henke, and Hugo 2019) due to edema or anorexia, respectively. Because a replan can take up to two days to complete, patients continue on their current treatment plans until the modified plan is ready. Any new plans created to treat the same condition are grouped together with the original plan into one course of treatment, which is the total set of treatment plans included in a single radiotherapy treatment.

1.2.4. Image-Guided Radiotherapy (IGRT)

Radiotherapy requires high precision for treatment delivery because failing to deliver the prescription dose to the target could have devastating consequences in the patient. However,

motion of the internal organs, image distortion by the acquisition scanner, and setup errors can all reduce the precision at which radiotherapy can be delivered.

IGRT provides high precision in positioning of the patient that is required for a successful treatment using IMRT and VMAT techniques. One of the most popular imaging modalities for IGRT is cone beam CT (CBCT) because it has better soft tissue contrast than the other on-board imaging techniques. CBCT is generally used to correct for errors in patients positioning before treatment. Additionally, CBCT images can be used to identify anatomical changes in patients.

1.2.5. Adaptive radiotherapy (ART)

Adaptive radiotherapy (ART) is a technique that takes into account the anatomy changes a patient undergoes during treatment and accounts for them as needed (Green, Henke, and Hugo 2019). ART can be performed online or offline. The main characteristics of online and offline ART are compared in table (1.2.5.1) (Green, Henke, and Hugo 2019). Additionally, some centers acquire images more frequently than others. ART requires a solid protocol for replanning and not all replans qualify as ART. In our clinic, no strict protocol for replanning is followed and the replans performed are not considered as ART.

Table 1.2.5.1. Offline vs Online ART (Green, Henke, and Hugo 2019).

Offline ART	Online ART
Uses image from fraction before	Uses image from fraction to be treated
Usually created in the time space between two treatment fractions	Created with the patient positioned for the treatment. It could be before or during a treatment fraction.
Manual image registration, contouring and calculation of the dose	Both images and contours are registered to the adapted plan, a dosimetric threshold is used to decide if the adapted plan will be used instead of the current plan. Inconsistencies are fixed manually.
The replan has the same workflow as a new treatment plan, needs a lot of work to finish it in the expected timeline	Better treatment workflow than offline: Replanning + QA is performed on the treatment room

Less sensitivity than online for anatomical changes	Since the anatomical changes are tracked continuously, the PTV margin is reduced and special attention to internal motion is required.
---	--

In general, ART needs high definition images to map daily IGRT images to the original treatment plan. These are used to identify anatomical changes in the patient and are part of the first step of ART. Depending on the type of ART, the next step may be to select one of the “plan of the days”, adjust the treatment based on the anatomy in the image, or treat the patient with the current plan. If adjusting the treatment, a new plan including new contours and dose calculations is required along with quality assurance (QA). This can either be done rapidly with the patient in the treatment room (online ART) or overnight before the patient returns.

1.3. Medical Imaging in Radiotherapy

Medical imaging is important in radiotherapy to provide anatomical information for diagnostic, treatment planning, and for treatment setup purposes. Many types of medical imaging modalities exist, including Radiography, Computer Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) (Peter 2009). While MRI and PET provide useful functional information for diagnosis (for example, by detecting metastatic lymph nodes (Kim et al. 2016) and can have superior soft tissue contrast, CT is the most common and important modality for treatment planning. This is because in addition to being more inexpensive and much quicker to acquire compared to MRI and PET, it gives a measure of electron density in the tissues (Loeffelbein et al. 2012). The electron density is important in order to calculate and apply heterogeneity corrections during treatment planning.

1.3.1. Computed Tomography (CT)

The acquisition of a CT image includes four important elements: an x-ray source, the object to be imaged, a detector array to measure the attenuation of the x-rays after they pass through the object, and the algorithm that will be used to reconstruct the images. First, a series of

regular radiographic projection images are acquired at many different angles around the object. Next, an algorithm is used to reconstruct the projections to obtain volumetric images used to diagnose and treat radiotherapy patients. Since the first CT scanner was built around 1970, scanners have evolved to reduce the time of scan, optimize the detector array for image acquisition, and improve reconstruction algorithms for better image quality (Bushberg 2020).

In addition to providing 3D anatomical information and soft tissue contrast, one of the most important qualities of CT images are their units for measuring grayscale intensity. These intensity units, called Hounsfield Units (HU) describe the relation between the attenuation of the radiation in a specific tissue μ_t to its attenuation in water μ_{H20} (Toga and Mazziotta 2002). HUs are calculated using the following equation:

$$HU = 1000 \times \frac{\mu_t - \mu_{H20}}{\mu_{H20}}$$

They are usually calibrated to the electron density of the patient scanned (Schneider, Pedroni, and Lomax 1996). As stated above, the electron density is useful to correct heterogeneities in radiotherapy treatment planning (Broder and Preston 2011).

1.3.2. Cone Beam Computed Tomography (CBCT)

CBCT is a type of CT imaging commonly integrated with linear accelerators. Unlike conventional CT, which uses a narrow fan beam and detector array that images a small strip of the body, CBCT uses a cone beam and large flat panel detector that covers a wider area of the body. For both systems, the x-ray source and detector rotate around the stationary patient (Bushberg 2020).

Although the wide collimation aperture of CBCT allows for an entire image to be acquired in one rotation, it also leads to some consequences in the image. Because there are more scattered photons reaching the flat panel in CBCT, the image quality, in particular the soft-tissue contrast, of CBCT images is lower compared to fan-beam CT images (Niu and Zhu 2011).

The CBCT scans can be performed either considering the full beam or half of it. The full-fan geometry is generally used for small anatomic sites such as head and neck, while the half-fan geometry is used for larger anatomic sites such as pelvis, chest and abdomen (Kaliyaperumal et al. 2017).

1.3.3. Image registration

Sometimes it is important to compare two or more medical images to have more information, but it is important when doing so to compare the same thing in each image. In order to do this, it is necessary to line up the anatomy of the two images so that they overlap and match as much as possible. The process that maps one image to the space of a reference image is known as image registration.

There are two main types of registrations: rigid and deformable. The rigid are transformations that conserve the shape of the object. The deformable registrations modify the shape of the object to map the comparison image to the reference image. In both cases, the goal of registration is to find the transformation that best matches the voxel matrix of the comparison image to that of the reference (Tohka 2015). Rigid registrations only allow for rotations and translations of the entire voxel grid, whereas deformable registration allows for rotations, translations and scaling of not only the entire grid, but small sections of the matrix or individual voxels.

In general, although deformable registration is desirable for medical images because the anatomy of patients may change from one image to another, rigid registration is a good approximation in most cases and is easier to perform. For example, the affine registration is a linear transformation that includes scaling, rotations and translation for a fixed body shape (Tohka 2015).

1.3.4. Digital Imaging and Communications in Medicine (DICOM) images

The DICOM format is used in medical informatics to store patient data in a standardized way. Different types of DICOM files exist for different types of information, such as CT, MRI, Ultrasound, and PET images, treatment plans, dose distributions, and image registrations.

Regardless of type, they all store information using DICOM headers, which are dictionaries that codify the information in a format that DICOM readers can translate (Medical Imaging & Technology Alliance, National Electrical Manufacturers Association 2020). When saving 3D images, the DICOM format saves each individual 2D slice of the 3D image as a separate file, which a DICOM reader will read together to generate a 3D image in the viewer.

1.3.5. Databases in Oncology

In medical informatics, relational and non-relational databases are used to store and manage information in the clinic. A relational database is a tool that allows the user to store information in abstract tables that can be joined by common information in the data. Relational databases are used to store the headers from the DICOM images acquired during the patient's treatment. Using the DICOM headers, the relational database can be used to call the DICOM images stored in the Picture Archiving and Communication System (PACS), which is a non relational database (Gregg 2020).

Because radiotherapy clinics have to handle a lot of electronic patient data, it is important to store them in an organized way. An EHR is an example of a relational database that integrates all patient information in a single source. On the other hand, non-relational databases such as the PACS, store image information. Most medical databases have end-user software to make it easy for clinicians to communicate with them.

1.4. Statistics

Statistics are essential to properly interpret the meaning of the data from a study. This section describes the basic theory of hypothesis testing and some statistical tests and statistical models relevant to this thesis.

1.4.1. Hypothesis testing

In clinical studies it is important to determine if two groups of patients with similar characteristics but different treatments have different outcomes. The first step is to define the groups to be compared. The second step is to formulate a null hypothesis and an alternative hypothesis. The alternative hypothesis will state that the outcomes are different while the null

hypothesis states that the outcomes are the same from a statistical point of view. Statistical significance and clinical significance are not the same, if you increase the number of samples, the result will be statistically significant eventually. However, it may not be of clinical significance. On the other hand, a result can have poor statistics and still be clinically significant. The third and last step in determining if two populations are distinct is to test the null hypothesis. The test has to be chosen according to the distribution of the data. The null hypothesis is evaluated according to a parameter α . If the p value (p) is smaller than α , the null hypothesis will be rejected (Harris and Taylor 2003).

1.4.2. Commonly-used statistical tests

The two main statistical tests widely used are parametric and non parametric (Chin and Lee 2008). If we assume that we are working with data that is normally distributed or can be approximated by a normal distribution we can use a parametric test to perform our statistical analysis (Chin and Lee 2008).

One of the most common hypothesis tests is the Student's *t-test*, which compares the mean of two parametric distributions. *t* tests can be used for either one sample or two, and can also be divided into paired and unpaired tests in the case of two samples. In a paired *t*-test, each sample in the first group is compared to its companion in the other group. The two groups are not independent, and often in medicine they involve the same patients at two different time points. In unpaired *t* tests the samples of the two groups are independent from one another, such as when a patient cohort is divided into a treatment and control group. The *t* test assumes that the data are normally distributed. The general expression for the *t* statistic is as follows:

$$t = \frac{\hat{x}_1 - \hat{x}_2}{\left(\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2} \right)}$$

Where $\hat{x}_1$, $\hat{x}_2$ are the means of the group, s_1 , s_2 are the variances, and n_1 and n_2 are the number of samples of the two distributions (Kim 2015).

The *Mann Whitney U test* is the non-parametric analogue of the unpaired *t* test (Nahm 2016). In order to calculate the statistic (*U*), the data are ranked according to the frequency of

appearance. The *Mann Whitney U test* makes no assumptions about the shape of the distributions and takes into consideration the medians of each distribution for the ranking process (Hart 2001).

The *Chi squared χ^2 test* is another example of a non parametric test. Unlike the *Mann Whitney U test*, it is used for categorical data (McHugh 2013). It is commonly used to determine if there is any relation between the frequencies of events observed in different groups. There are two important assumptions when using this test: The groups (in our case groups of patients) are independent, and the categories of the variables considered have to be exclusive between each other (McHugh 2013). The null hypothesis states that there is no relation between the frequencies of events observed in different groups (McHugh 2013). P values are calculated to evaluate the null hypothesis of this test (Harris and Taylor 2003).

1.4.3. Statistical learning models

Statistical models are mathematical expressions that use input data to make predictions about the data. The goal of modelling is to develop a function f to describe the relationship between one or more explanatory variables, X , and the response variable Y in a way that minimizes the random error E that captures the variability in Y that X cannot explain. This expression can be simplified as following:

$$Y = f(X) + E$$

It is important to note that the error in a model can be separated into the error that comes from the algorithm optimization and the error that comes from factors related with the acquisition of the data (the random error) (James et al. 2013). While the error associated with the algorithm can always be optimized to a minimum value, the random error related to data acquisition is irreducible by model optimization and will affect the ultimate performance of the model.

Two important concepts to keep in mind when creating mathematical models of data are variance and bias. *Bias* is defined as the error associated with modeling a real problem with a mathematical approximation. *Variance* is the error associated with the variability of the model when using data from other datasets. A balance between variance and bias is important because when the model is broad enough to consider variability between datasets, it could

lose reality representation. This is also known as the *bias and variance tradeoff* (James et al. 2013).

Depending on the characteristics of the data, different types of models should be applied. For instance, regression models are useful to predict continuous data, while classification models are useful to predict categorical data (James et al. 2013). The remainder of this section gives a brief overview of two of the most common regression models.

1.4.3.1. Linear regression

Univariate linear regression is a basic model that predicts a variable Y as a function of a single parameter X . The following linear equation is used to describe the relation X and Y :

$$Y(X) = \beta_0 + \beta_1 X$$

Where β_0 is the intercept and β_1 is the slope of the curve. Both β_0 and β_1 are also known as the linear regression coefficients of the model (James et al. 2013). A linear regression algorithm looks to find the coefficients β_0 and β_1 that best describe the data. First, it is important to determine if there is any relation between the two variables. This process is performed by hypothesis t-testing in which the null hypothesis establishes that there is *no relation between X and Y* ($\beta_1 = 0$). If the p - value is small enough, the null hypothesis that there is no relationship between X and Y can be rejected.

Additionally, R^2 is a parameter that measures how well the model approximates a linear curve. The closer R^2 approximates to 1, the better the data fits a line. For physics models the R^2 approximates a lot to one, while for biology and marketing the variations are higher.

Multivariate linear regression is an extension of the univariate linear regression where more explanatory variables are used and is described by the following equation:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_N X_N$$

Where $X_1, \dots, X_N$ are the N parameters considered in the model and $\beta_1 X_1, \dots, \beta_N X_N$ are the multivariate linear regression coefficients. In this case, the null hypothesis considers that

$\beta_1 = \beta_2 = \dots = \beta_N = 0$ and it is proved wrong when at least a regression coefficient is different from zero. Moreover, the F statistic confirms the null hypothesis when it is equal to one. When $F > 1$, at least one of the variables is related to Y (James et al. 2013).

1.4.3.2. Logistic regression

Logistic regression is a type of classification model that is usually used for qualitative or categorical data (James et al. 2013). This makes it a particularly useful model for health care data, which often includes many categorical variables like diagnosis, sex, cancer stage, and more. Perhaps more important is that unlike in linear regression, where the response variable Y is usually a continuous variable, Y in logistic regression is a categorical variable with two possible values. This therefore makes it possible to create models to predict which of two categories an individual will belong to, such as whether or not they develop complications, metastasize, or as in the present study, require a radiotherapy replan.

Consider a logistic regression model with one explanatory variable X . The model estimates the probability $P(X)$ that a given individual will belong to a specific category given the value of the variable X . The probabilities can have any value between zero and one and the variable will be classified according to their highest probability. In a univariate logistic regression, the probabilities are calculated using the sigmoid function as follows:

$$P(X) = \frac{\exp(\beta_0 + \beta_1 X)}{1 + \exp(\beta_0 + \beta_1 X)}$$

Where β_0 and β_1 are the logistic correlation coefficients. Similar to linear regression, statistical tests can be done to evaluate the probability these coefficients are non-zero and assess the quality of fit of the model.

One of the important concepts associated with logistic regression models is the odds ratio. An *odds ratio* (OR) is the ratio of the probability of being classified as category Z (for example, needing a radiotherapy replan) and the probability of not being classified as Z (not needing a replan):

$$OR = \frac{P(X)}{1 - P(X)}$$

To simplify the logistic correlation coefficients to a linear expression, the log function is applied to the odds ratio:

$$\log (OR) = \beta_0 + \beta_1 X$$

For a multivariate logistic regression, the expression is generalized as following:

$$\log (OR) = \beta_0 + \beta_1 X_1 + + \beta_N X_N$$

(James et al. 2013).

The odds ratio is a simple way to compare the probability of something happening to the probability of something not happening. In this thesis, the criterion variable is the replanning and the odds ratio can be interpreted as the ratio of the probability (p) of a patient being replanned and the probability of a patient not being replanned.

$OR = 1 \rightarrow p = 1 - p \rightarrow$ there is no relation between the predictor and the response

$OR > 1 \rightarrow p > 1 - p \rightarrow$ higher probability that the predictor is related to the criterion variable

$OR < 1 \rightarrow p < 1 - p \rightarrow$ lower probability that the predictor is related to the criterion variable

When the predictor is a continuous variable, the odds ratio determines if the probability is higher or lower with an increment in the predictor (Szumilas 2010; Hosmer, Lemeshow, and Sturdivant 2013).

2. HNC radiotherapy replanning

2.1. Head and Neck cancer

Head and neck cancers (HNC) originate in the squamous cells of the mucosa of the upper digestive tract (Haddad 2010) and are classified according to the site in the body they originate from. Common sites include the oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, and major salivary glands (Deschler, Moore, and Smith 2014). Tobacco and alcohol consumption are important risk factors for HNC. HPV is another common risk factor in the development of HNC, especially HPV 16, which is the most common type of virus linked to oropharyngeal cancer (Beynon et al. 2018).

2.1.1. HNC treatment

The head and neck area is a complex area for cancer treatment because it contains many overlapping structures with important basic functions. Accordingly, the treatment for HNC varies depending on the site, type, and stage of cancer. For the squamous cell carcinomas of the head and neck (SCCHN), treatment involves a combination of multiple modalities such as radiation therapy, surgery, and chemotherapy (Yeh 2010). The exact choice of treatment will depend on the location of the neoplasm in the head and neck in order to reduce the probability of treatment significantly impacting the functions of nearby organs or decreasing patient quality of life (Haddad 2010).

2.1.1.1. Surgery

The goal of the surgery in cancer treatment is to remove all neoplastic tissue. However, it is not always possible if the cancer is in an unresectable location. Additionally, because there may be microscopic neoplastic cells in tissues nearby the visible lesion, an excision margin must be defined. This is an additional portion of tissue removed to catch those microscopic deposits. These margins play an important role in determining if a patient needs complementary treatment such as radiotherapy or chemotherapy and to what degree (Homer and Fardy 2016).

2.1.1.2. Chemotherapy

Chemotherapy is the use of cytotoxic drugs that target rapidly dividing cells like cancerous cells. It is a systemic treatment, meaning it circulates throughout the body instead of being localized to one area like surgery or radiotherapy. Because of this, it can also attack healthy cells that replicate quickly, such as skin, bone marrow cells, hair, and intestines, and cause side effects (Airley 2009).

Common chemotherapy drugs for HNC include cisplatin, fluoropyrimidines, taxanes, and cetuximab (Airley 2009). Chemotherapy can also be delivered as an induction or consolidation therapy. Induction chemotherapy is the use of chemotherapy as the primary treatment modality to cure disease, as opposed to consolidation or maintenance chemotherapy which ensures a patient stays in remission once a primary treatment has succeeded. Depending on the cancer, an induction treatment may result in a partial response or total response (cancer elimination) of the disease to the treatment (Airley 2009). Chemotherapy can also be applied together with radiation therapy or surgery in order to obtain better outcomes and prevent the recurrence of the disease. The combination of chemotherapy and radiotherapy is usually called concurrent chemoradiation.

2.1.1.3. Radiotherapy in HNC

External beam radiotherapy is the standard treatment for SCCHN. As mentioned before, it can also be combined with other modalities such as surgery and chemotherapy for a better prognosis of the patient. Radiotherapy is usually either delivered post-surgery to remove the remaining microscopic disease, or it is used with chemotherapy alone to reduce the radiation side effects on OARs and to prevent metastatic lesions. Depending on the area of the head and neck, the radiotherapy treatment varies in prescribed dose, fractionation scheme, radiation fields set up and the technique used (Yeh 2010).

2.1.2. Treatment variations depending on the site location of HNC

Due to the complex nature of the head and neck area, the choice of treatment modality used to treat HNC depends on the site location of the tumour, the stage of the lesion and must take into account individual characteristics of the tumour and the patient (Yeh 2010). Table 1.3.5.1. shows which treatment modalities are commonly used and in what combination for several HNC sites. One thing to note is that chemotherapy is usually only used for advanced diseases and/or inoperable tumours (Yeh 2010).

Table 1.4.1.1. Treatment modalities that can be used alone or in combination for HNC patients (Yeh 2010).

<i>HNC site location</i>	<i>Radiotherapy</i>	<i>Surgery</i>	<i>Chemotherapy</i>	<i>Brachytherapy</i>
Paranasal sinuses	Yes	Yes	Inoperable	
Nasal Cavity	Preferred	Small and superficial lesions		
Oral cavity	Yes	Yes	Advanced stage	
Nasopharynx	Yes	Difficult	Advanced stage	
Oropharynx and soft palate	Yes	Yes	Advanced stage	
Tonsillar region (oropharynx)	Yes	Yes		
Base of the tongue (oropharynx)	Yes	Yes	Advanced stage (inoperable)	
Oropharyngeal wall	Yes	Yes		
Hypopharynx	Yes	Yes		
Larynx	Yes	Yes	Advanced stage (inoperable)	
Salivary glands	Yes	Yes		
Thyroid gland	Yes	Yes		Yes

2.1.3. Secondary effects induced by radiotherapy in HNC patients

Head and neck patients are prone to developing side effects that impact the quality of their lives. Even before treatment, tumour growth may affect essential bodily functions like the ability to chew, swallow, and taste food (Larsson, M., Hedelin, B. and Athlin, E. 2003).

Furthermore, irradiation to organs such as the parotid and larynx has a negative impact on basic functions such as swallowing, chewing, and speaking (Haddad 2010).

Because important OARs are usually close to HNC targets, radiotherapy side effects are very common. Radiotherapy side effects may be temporary or permanent, and can include pain, swelling of the mucosa (mucositis), decreased saliva production, dry mouth (xerostomia), problems swallowing (dysphagia), nausea, and loss of taste (van der Laan et al. 2015).

Muzumder et al (2019) describe the acute toxicities observed in a cohort of 164 patients treated with radiotherapy where 56.7% were treated with concurrent chemotherapy. 89% of the patients developed mucositis, 98.5% dysphagia, 54.7% aspiration, 93.2% dermatitis, 31.8% nausea, 47.9% vomiting, 50% anorexia, 87.2% weight loss and 89.2% pain. *Muzumder et al* also showed that most HNC patients develop mucositis and dysphagia by the third week of their radiotherapy treatment. Additionally, mucositis was also found to be the leading cause of interruption of the patient's treatment (Muzumder et al. 2019).

All the side effects combined with stress, low self esteem and depression can cause nutrition problems and weight loss during radiotherapy, which in turn can lead to immunosuppression and higher mortality in these patients (Larsson, M., Hedelin, B. and Athlin, E. 2003).

2.2. Current status and challenges of HNC radiotherapy replanning

In the literature, HNC replanning is less studied than weight loss, with a lot of studies reporting a new ART strategy or reporting on how patients benefit from it, rather than studying the factors associated with replanning. This section summarizes the current research on tracking and predicting anatomical changes in patients to determine the factors that determine replanning.

Radiotherapy dose distributions are conformal to the target. Thus, significant anatomical changes in the neck region impact the accuracy of the radiotherapy treatment delivery and the treatment plan has to be adapted accordingly. As mentioned in section 1.5.3, weight loss is a

very common side effect in radiotherapy linked to anatomical changes of HNC patients. Additionally, because of location, *shrinkage of tumours or swelling of organs* in response to treatment impacts the anatomy in the treatment beam more than other cancers.

2.2.1. Anatomical changes during HNC treatment

The impact of tumour shrinkage on patient positioning errors is quantifiable with imaging and has been found to be non-negligible. For example, a study by Hou *et al* (2016) of 217 nasopharyngeal cancer patients found significant mean anterior-posterior (AP) positioning errors of $2.9 \pm 1.1 \text{ mm}$ for the target volume when patients had weight loss equal or lesser than 5% of the initial weight. This setup error increased to $3.6 \pm 1.5 \text{ mm}$ for patients with weight loss higher than 5% and even exceeded 5.0 mm in 16% of patients (Hou et al. 2016). For head and neck cancers, the extension margins added to the CTV vary from 3.0 mm to 5.0 mm (Chen et al. 2011).

The main predictors of replanning are *tumour changes* and the *weight loss*, but many studies investigate as well the shrinkage of the parotids as a measure of the volume loss in the neck region (Schwartz and Dong 2010; Barker et al. 2004; Loo et al. 2011). Additionally, many studies are performed in small cohorts due to lack of automatization of the process and problems of data availability. Most studies are performed with patients having standard prescription doses (60 Gy, 66 Gy and 70 Gy delivered in 2 Gy/fx)

One study by Schwartz and Dong (2010) investigated the online adaptive radiotherapy of 22 oropharyngeal patients who completed radiotherapy in late stages of oropharyngeal cancer. All patients needed to be replanned at least once and eight (36%) were replanned twice. The median fraction at which the first replan occurred was 16, at which point both the CTV and parotids had shrunk on average by 4% and 15% respectively. Total mean shrinkage by the end of treatment was 15% for the CTV and 26% for the parotids (Schwartz and Dong 2010).

Baker *et al* (2004) and Loo *et al* (2011) found that weight and parotid volume decreased during radiotherapy treatment. Loo *et al* (2011) reported a mean volume loss of 350 ml ranging from 289 ml to 428 ml, when measuring the skin contour limited by the length of the target volume. Baker *et al* (2004) reported a GTV median volume loss of 1.8% per day and

69.5% at the end of the treatment. Additionally, *Baker et al* (2004) measured the shift of the center of mass of the parotid glands during radiotherapy. They found that the parotid shifts were highly correlated to weight loss. The median weight loss was greater than 6% at the end of the treatment (Barker et al. 2004; Loo et al. 2011).

The high correlation between parotid shifts and weight loss found by *Barker et al* (2004) may be an indication that the volume loss in the neck area is somehow linked to total weight loss (Barker et al. 2004). However, taking into account that patients may have different body fat distributions, their total weight loss may not represent accurately the volume loss in the neck. This is why the correlation between weight loss and neck area loss will be investigated in this thesis.

Because of these anatomical changes, replanning HNC patients to adapt their treatment plans according to their individual weight loss and tumour response can improve the overall quality of their treatments (Gensheimer and Le 2018). Studies suggest that for patients in late stages, some sort of replanning improves the survival of the patients (L. Zhao et al. 2011). However, different institutions have different criteria for replanning and consensus is lacking in the literature on what are the best predictors.

Additionally, *Ma et al* (2014), found that the weight loss has a greater impact than the tumour shrinkage in the dose distribution of the treatment plan. (Ma et al. 2014)

2.2.1.1. When to replan

The time of replanning is as important as the predictors, given that a prediction of when to replan is the tool that would allow us to improve the clinical workflow. In this section the studies of *Brown et al* (2016) and *Guide et al* (2016) are described regarding their predictions of the time of replanning in HNC radiotherapy treatments of duration of 7 and 6 weeks, respectively (Brown et al. 2016; Guidi et al. 2016).

Brown et al (2016) studied 21 oropharyngeal and node positive nasopharyngeal patients with a total prescription dose of 70 Gy in 35 fractions and concurrent chemotherapy. Patients were

imaged daily with CBCT and imaged a second time with a CT to identify if they needed a replan. From those 21 patients only 5 were replanned (4.5% from the total number of patients). The reason for replanning was that the dose planned for the brachial plexus was surpassing the constraints. At the time of the second CT, the median weight loss of the patients was 10.3%. Patients imaged a second time with CT, were grouped in replanned and not replanned. The median fraction in which the second CT was acquired was 22 (10-25). Additionally, replanned patients had an earlier CT and the median fraction for replanning was significantly different between patients replanned and not replanned. Other anatomical changes were measured at the time of the second CT, such as 42.8% volume loss of the largest node and a volume loss of 20.3% and 21.7% for both parotid glands (Brown et al. 2016).

Guidi et al (2016) used a machine learning approach to predict the time of replanning during radiotherapy. They tracked the volume of the parotid during radiotherapy for 90 patients at four different institutions. The total prescription dose for those patients was 66 Gy in 33 fractions in the tumour and 54 Gy in the lymph nodes. The decision of when to replan was based on clinician perspective. Their software predicted that most patients were not receiving good treatment at the 5th week of radiotherapy. Additionally the volume loss of the parotid after 6 weeks was $23.7 \pm 8.8\%$ (Guidi et al. 2016).

Even though the definition of when a patient has to be replanned was specific to each clinic, the decision for replanning was correlated to visible anatomical changes occurring at least two weeks before the end of treatment. However, the volume estimation at the time of replanning had statistical deficiency given that it was based on a really small dataset. Overall, the time of replanning needs more studies before it can be determined accurately (Brown et al. 2016; Guidi et al. 2016).

2.2.2. Factors that influence weight loss

While weight loss is one of the reported causes of replanning, it is not a perfect predictor. If the effects of weight loss are more evident in the abdominal region rather than in the neck region, a HNC patient may not need a replan. Weight loss instead may indicate eating

problems that decrease quality of life and should be handled accordingly. For this reason, many studies have examined possible predictors of weight loss during radiotherapy with and without considering the relation to replanning.

According to *Lonbro et al* (2016); chemotherapy in addition to radiotherapy can increase the weight loss of the patients. Additionally, different studies report different HNC site locations associated with weight loss. *Lonbro et al* (2016); reported that pharyngeal and oral cavity cancer increased the probability of weight loss ($\geq 5\%$) when compared to glottic cancer (laryngeal cancer). *Ghadjar et al* (2015); reported the weight loss of patients from oral cavity, oropharynx, hypopharynx and larynx. *Zhao et al* (2015); classify oropharyngeal and oral cavity as moderate predictors for weight loss (*Lonbro et al.* 2016; *Ghadjar et al.* 2015; *Zhao et al.* 2015).

Both *Cacicedo et al* (2015) and *Lonbro et al* (2016); reported higher weight loss for advanced stages of cancer (III and IV) than for cancer earlier stages (I and II). *Zhao et al* (2015); reported cancer stage as a strong predictor of weight loss (*Cacicedo et al.* 2014; *Lonbro et al.* 2016; *Zhao et al.* 2015). A higher body mass index (BMI) at the start or before treatment was reported to be related to greater weight loss during radiotherapy (*Lonbro et al.* 2016; *Zhao et al.* 2015). However, the height of patients was not systematically recorded at our clinic and consequently, the BMI data was not considered for this thesis work.

A common practice to analyze weight loss during radiotherapy is the use of a 5% weight loss threshold to classify and compare patients (*Ghadjar et al.* 2015; *Lonbro et al.* 2016; *Cacicedo et al.* 2014). On the other hand, other studies reported the use of univariate and multivariate analyses as well as observational studies (*Zhao et al.* 2015).

Most studies seem to predict the total weight loss during radiotherapy rather than reporting the weight loss as a function of time. Additionally, they report the absolute change of weight in kg, which makes it difficult to compare time series patients of different BMIs and adds significant error bars to their studies (*Cacicedo et al.* 2014; *Lonbro et al.* 2016).

Another observation from the literature is that weight loss studies were performed in cohorts with a greater number of men than women (Cacicedo et al. 2014; Lønbro et al. 2016; Ghadjar et al. 2015). This may be due to the fact that around 74% of HNC cases are men and only 26% are women (Siegel, Miller, and Jemal 2020), but the relation between weight loss and sex will also be investigated in this thesis.

Across the various retrospective studies reported in the literature and mentioned in this thesis, the maximum number of patients analyzed in a single institution was 476 by *Ghadjar et al* (2015). This shows that in general the number of HNC patients treated in a single clinic is relatively small for statistical analysis, which is a limitation for a study that involves so many predictors. On the other hand, the review from *Zhao et al* (2015); involves the results from a total 6,159 patients. Even though the review has the limitation of not being able to use the statistical power to analyze the predictors for all of the patients in a single shot, it can help to point out which results are consistent across the treatments that different institutions apply (Zhao et al. 2015; Ghadjar et al. 2015; Lønbro et al. 2016; Cacicedo et al. 2014).

2.2.3. Challenges for HNC replanning prediction

Regardless of the method used for radiotherapy replanning, it remains a time consuming process that requires many clinical resources. In the literature, the decision of when to replan was found to be correlated to anatomical changes such as weight loss, tumour and parotid shrinkage, occurring at least 2 weeks before the end of treatment (Brown et al. 2016; Guidi et al. 2016). A prediction of when to replan radiotherapy would thus be useful to reduce the workflow of the clinic as well as the costs of replanning and potentially improve the treatment of patients.

In general, small HNC cohorts were found in the literature for the investigation of weight loss and tumour shrinkage. The use of small cohorts leads to poor statistics in the study of replanning variables.

The role of data collection for research purposes is often underestimated. Some of the challenges that are faced in the Radiation Oncology environment are the patient's privacy

which makes the data unavailable to researchers, the low quality of the data and the lack of standardization of the data. Those characteristics also limit the possibility to share data between institutions to increase the repository, which is always useful for statistical analysis and the implementation of machine learning algorithms. Small datasets make it difficult to compare data between institutions and to study cohorts of many patients that share common characteristics (Lustberg et al. 2017).

A limitation of using weight loss during radiotherapy as a replanning predictor, is that it may not be representative of the volume changes in the neck region. Thus, there is a need to find a parameter that shows the volume loss in the neck. In this thesis, it is proposed the neck area parameter, that measures the change in the area in a single slice in the neck during radiotherapy. This parameter will be evaluated and compared to the weight loss to measure the track the proportional neck changes during radiotherapy.

2.2.4. Replanning predictors selection

There is still a lot of work to do to improve statistics regarding replanning predictors. Based on our understanding of the literature, we decided to examine the following factors: Anatomical changes during radiotherapy such as *weight and area loss*, the HNC site location, the stage of the cancer, the presence of concurrent chemotherapy appointments during radiotherapy, the radiotherapy information such as prescription dose and treatment fraction and patients demographics such as sex and age at the start of the treatment. Those parameters were integrated into a single dataset as illustrated in figure 2.2.4.1.

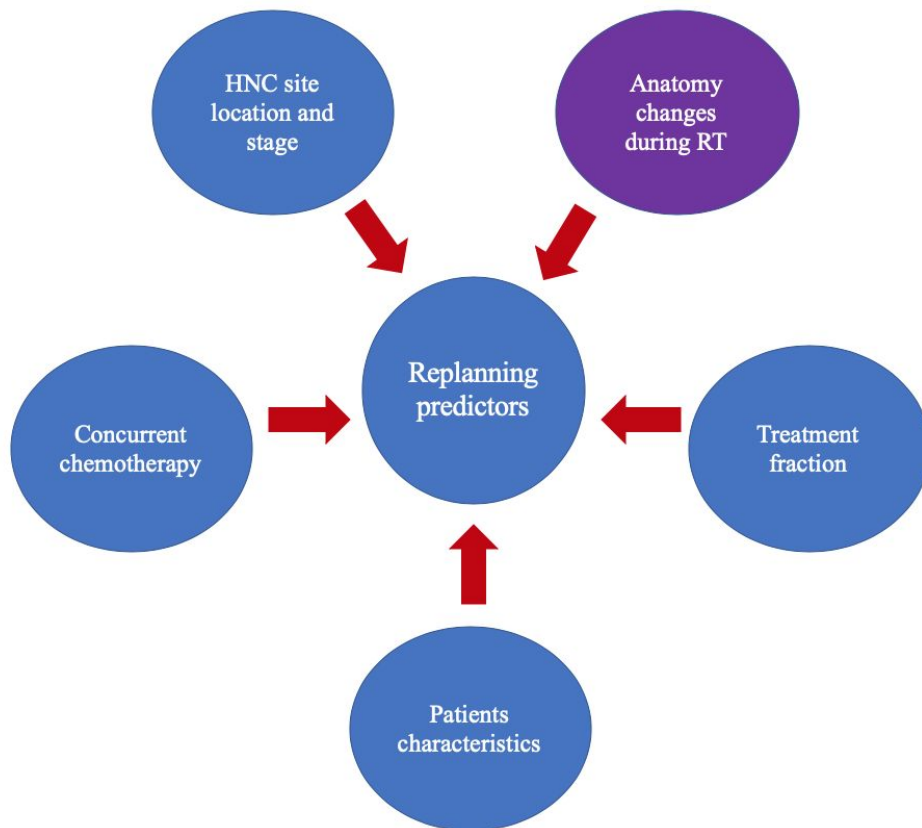


Figure 2.2.4.1 Replanning predictors during radiotherapy that were examined in this thesis research project.

3. Methods

This thesis describes a retrospective study involving head and neck cancer patients treated with radiotherapy at the McGill University Health Centre (MUHC). Within the radiotherapy department, the radiotherapy treatment information is stored and managed using the Aria Oncology Information System from Varian Medical Systems (Palo Alto, California), the PACS information system and other repositories developed for local use. The steps followed for the patients' data collection, processing, storing and analysis will be described in this chapter.

3.1. Patient Cohort

The cohort used in this study consisted of 490 HNC patients that completed radiotherapy treatment between 2012 and Fall 2019. Patient data was eligible for inclusion in this study if the patients were diagnosed with cancer disease in the head and neck area and they were treated with external beam radiation therapy with prescribed dose to the targets of 60 Gy, 66 Gy and 70 Gy delivered in 2 Gy/fx. Another requirement for these patients was to have weight data available during their radiotherapy treatment.

The data were grouped in sub cohorts when the data was available only for specific periods of time. For example, chemotherapy data were only available from 2016 to 2019, and a subcohort of 260 patients was created accordingly.

Additionally, a subcohort of just 18 patients was created for a pilot study to examine anatomical changes in the neck. The 18 patients used for this study were randomly selected from the patients treated in 2018 and 2019 with the requirement that they were in the initial cohort and that they were all prescribed a dose of 70 Gy.

3.1.1. Radiotherapy plan considerations in the patient's cohort selection

For data homogeneity, only one radiotherapy course of treatment (labelled C1) was considered. This was fundamental in the hypothesis that patients receiving a second treatment course could be more affected than the patients with only one course because they had

received prior radiation. Additionally, only the first replan was analyzed given that only a few patients had a second replan.

Initially, the following standard fractionations used in the MUHC for HNC radiotherapy treatment were considered: 2 Gy/ fx delivered in 20 fx, 30 fx and 33 fx for a total prescribed dose of 70 Gy, 66 Gy, 60 Gy and 50 Gy.

At the MUHC, the prescription dose of 70 Gy (2Gy/fx) is usually used for patients that are treated by radiotherapy and for whom no surgical resection is performed. Chemotherapy is used for advanced diseases (stage III and IV). The predominant cancer site location for this prescription dose is oropharyngeal cancer because the clinicians try to avoid surgery to preserve the vocal cords.

Additionally, the prescription dose of 60 Gy or 66 Gy (2 Gy/fx) has been used for HNC patients characterized by a positive external margin and extranodal extension in the lymph nodes. Radiotherapy treatment for this prescription is usually combined with surgery and concurrent chemotherapy is used depending on the stage of cancer.

Furthermore, the 50 Gy (2 Gy/fx) prescription dose has been used for laryngeal cancer of early stage (T1), which is treated mostly by Radiotherapy. Chemotherapy is rarely used for these cancer conditions. Given the fact that the patients of 50 Gy total prescribed dose were hardly ever replanned during their treatments, this group of patients was not included in the further analysis.

Moreover, patients that received hyperfractionation (1.8 Gy/fx) and fractionation schemes different from 2 Gy per fraction in 30, 33 and 35 fractions were not considered for this study.

3.2. Data Collection

For the purpose of this project, data from the patient's treatment stored in the *Aria* database and the *AEHRA* (Automatic Electronic Health Record Auditing) database, previously created for data centralization for radiation oncology quality assurance at the MUHC, were required;

(Joseph et al. 2014) and DICOM images stored in the institutional PACS. As the reader can infer, the data from relational databases were obtained using the SQL language, while the DICOM images were accessed through Varian's Eclipse software.

In this thesis, the *Aria* database was used to gather information about the radiation treatments, weight's data, demographics of the cohort, diagnosis, stage of cancer and CBCT image data. The treatment radiation data included the dates of the treatment, course of the treatment, plan information, treatment fraction and prescribed dose. The image data consisted of the filenames and dates of the CBCT images acquired during radiotherapy for treatment positioning. The data were gathered for all 490 patients with the exception of the CBCT image data that were only available for non Tomotherapy patients.

The AEHRA database was useful for two things: First, to identify which diagnosis codes belong to the HNC classification. Second, to identify which patients in the cohort had radiotherapy with concurrent chemotherapy. The chemotherapy data were only available from 2016 onwards.

Additionally, CBCT images of 18 HNC patients acquired during their radiotherapy treatment were identified and downloaded from Eclipse as DICOM files. Their respective treatment plan data, CT images, structure files and image registration files were also obtained in DICOM format. The DICOM files would be used as the input for the neck area script, which was built to track cross sectional changes in the neck. Details about this script are described in this chapter.

3.3. Data processing

The radiation oncology department of the MUHC offers a wide variety of data. However, the data needed for the project was not in the expected format and it required the mining and processing of the information described in this section.

3.3.1. Considerations for data availability

The weight data come from nutrition appointments programmed according to each patient's individual needs. As a consequence, the weights were not acquired for every single day of treatment. Due to the sparse nature of weight data, the frequency of the weights data and the spacing between days were examined to determine the best way to approach the problem.

On the other hand, the CBCT images were acquired twice per week according to institutional protocol. This information was verified on extraction from the Aria database.

Additionally, a common timeline for both images and weights data was investigated. The data had to be grouped to reduce the number of missing data points. A potential way to pair the weight's data with the CBCT data was to group the data by week. However, if the treatment starts on a day other than Monday, the treatment can be extended by an "extra week".

To avoid having different treatment durations for the same prescription dose, the better option available was to group the data in samples of 5 fractions that would be the equivalent of one week if the treatment started on Monday. This measure would also assure that the treatment data were distributed evenly and the patients were compared at periods of their treatment in which they received the same amount of dose. If we consider a daily fraction, there were five fractions a week delivered for every patient. This structure also allows unifying the weight's data and CBCT data. On average, patients have two data points every five fractions from the CBCT data, and only one data point from the weight's data.

3.3.2. Other considerations to format the data in a useful manner for analysis

The following considerations were taken into account for preprocessing each patient's data in a useful way for analysis:

- *Concurrent chemotherapy*: The HNC patients were grouped in two categories: "chemo" and "no chemo". In the "chemo" category patients had at least one concurrent chemotherapy appointment registered. The chemotherapy cycle was

assumed to be administered during the appointment. Concurrent chemotherapy was a factor that was observed to contribute to anatomical changes in the patients so it was important to consider.

- *HNC site location:* At the MUHC, diagnosis is classified according to the International Classification of Diseases, Tenth Revision (ICD-10) codes (World Health Organization (WHO) 2019). The HNC site location was derived from the anatomy location of the disease. This classification was performed under the motivation of analyzing the data by the irradiated area. Patients with oral cavity, oropharyngeal, laryngeal, hypopharyngeal, major salivary glands, nasal cavity and nasopharyngeal cancer were found. Given that diagnosis is related to the patient and not to the radiation treatment, one patient could have more than one diagnosis in their record. From the 490 patients' cohort, nine patients belonged to two categories of diagnosis and stage and one of them belonged to three. All of these patients were considered in the analysis.
- *Stage of cancer:* The stage of the cancer was an important parameter because it is a determinant in the treatment modality selection and in the treatment plan. Just the summary stage was used for the analysis because the TNM classification has too many variants that divided the data into too many subgroups that did not have statistical significance. For the same reason as for diagnosis, 12 patients had two stages and one had three. All were considered in the analysis.
- *Sex:* The sex of the HNC patients was extracted from the Aria database without the need for further processing. The motivation to include this parameter was to analyze the potential relation of sex in the anatomical changes of HNC patients.
- *Age at the start of the treatment:* The possibility of different responses to the treatment in HNC patients according to their age was interesting to analyze. The age of the patients was obtained at the start of their treatment.
- *Replanning:* Due to the lack of standardization of plan names, a *Plan_Replan* classification that unified the nomenclature of all the treatment plans was created. The first digit of the *Plan_Replan* classification corresponds to the number of the *Plan* and the second digit corresponds to the number of the *Replan*. These parameters were defined by the treatment course in question. Additionally, a binary classification was added to identify if patients were *replanned or not* during their treatments.

- Fraction of replan: Binary classification that has one in the fraction in which the patients were replanned and zero otherwise.
- *Weights at the fraction of replan*: This classification was performed to identify a potential threshold for the weights at the time of the replanning.

3.3.3. Calculation of Neck area data

As mentioned in chapter 2, the replanning of head and neck cancer patients is usually due to the neck anatomy changing from what it was at the time the planning CT was taken. While this is usually associated with weight loss, we recognized that not all patients will lose weight in the head and neck region in the same way and that weight alone may not sufficiently predict the need to replan a patient. For this reason, we conducted a small pilot experiment where we calculated the cross-sectional area of patients' necks over the course of treatment using daily CBCT images.

The code to calculate *neck areas* was written in Python using the Pydicom, OpenCV, Pandas, OS, Scipy and Numpy libraries (Andrade and Naseri 2020). The script uses CT images, CBCT images, beam geometry, structure and registration DICOM files as input and returns the calculation of the patient's neck area at the same position over the course of their treatment as output.

The input DICOM files are the following:

- *CT DICOM files*: One CT volumetric image consists of many files where every file represents a slice of the volume. A CT image is of great importance because the treatment plan was created on these images. There are as many CT images as treatment plans.
- *CBCT DICOM files*: They also represent a CBCT volumetric image. The CBCT images were acquired twice a week on average and they were used to verify the patient's positioning during RT treatment. On every fraction, the CBCT was registered to the CT of their corresponding treatment plan.

- *Registration (RE) DICOM file*: The CBCTs were registered to the CT images during the patient's treatment and the image was stored in the PACS system in DICOM format. The registration sequence contains the frame of reference of the affine transformation that maps two images. For this project, the rotation matrix was assumed to be equal to the identity because rotation could be absorbed on the slice thickness.
- *Structure (RS) DICOM file*: This file contains the volumetric coordinates of the structures contoured by the clinician for the treatment plan. Since they are associated with the treatment plan, the frame of reference used was the same as the CT. The coordinates are defined in *mm*. In particular, there were used the coordinates of the submandibular gland structure to locate the neck in the 3D volume.
- *Beam geometry (RP) DICOM file*: This file contains the data of all the beams used in the treatment plan. This file was only used to obtain the isocenter coordinates in the CT frame of reference.

To understand the process, it is important to remember that there is one CT image per plan, there is at least one treatment plan per patient and there may or may not be a replan for each patient. This results in more CBCT than CT images for a single patient. In turn, every CBCT image accounts for one treatment fraction. The workflow of the *neck area* code for a single patient and fraction is summarized in the following steps:

1. *Load input images*: The script reads both CT and CBCT volumetric images and stores them in a 3D $512 \times 512 \times n$ grayscale matrix, where n is the number of axial slices along the superior-inferior axis. It also identifies if the patient was replanned or not and the treatment fraction number. The z axis is in the direction of the patient's height and the 3D volume can be seen as a collection of 2D arrays at different points on the patient's height. Each point represents an axial slice of the patient.
2. *Registering the CBCT to the CT*: Using the registration file, the script next registers the CBCT and CT images to the same coordinate system. To do this, the CBCT and CT meshes are first converted from pixels to mms to match the units of the affine transformation stored in the registration file. Then, the CBCT matrix is translated into three dimensions to align with the CT. While the affine transformation also includes a

rotational component, the rotation is negligible and therefore ignored in this project. Thus, only the translation in x, y and z axis is considered. Also, to map from one reference frame to another is necessary to transform the pixels to mm using the pixel spacing. This is to account for the difference in field of views between CT and CBCT images.

3. *Selecting a neck slice in the CT frame of reference:* Because CBCT and CT files do not have tags to identify an appropriate slice in the middle of the neck, we used the structures drawn by clinicians on the planning CT image to identify a suitable neck region. After investigating, we chose to use the z-coordinate of the center-of-mass of the submandibular gland contour to select the slice to be used for area calculations. of interest in the registered CBCT image. In figure 3.3.4.1 the contour of the left submandibular gland cross section in the yz plane can be seen. This point was selected because of its location in the neck with little interference from the shoulders. Δz is the length of the submandibular glands on the z axis. The coordinates of the middle point $\Delta z/2$ of the submandibular glands will be used to select a slice in the z axis.



Figure 3.3.4.1. Length of the left submandibular gland Δz on the z axis in the plane yz of the patient.

4. *Obtaining the body contour of the region of interest at the level of the neck:* Once the appropriate slice was identified in the registered CBCT, the 2D cross section was extracted using a thresholding technique using the OpenCV2 library (OpenCV 2020). The function `cv.findcontours` identifies shapes based on pixel intensity and the body contour is selected as the one with the maximum length.
5. *Obtain the area of the body contour:* The area of the neck at the selected location is calculated with the `cv2.moments(cnt)` function from the OpenCV library that uses the center of mass of the contour to find the area.

This process was used to calculate neck areas for a pilot investigation of 18 patients (11 replanned, 7 not replanned). Neck areas were calculated for all CBCTs for all patients. On average, each patient had 14 CBCT images taken over the course of treatment. The output data were stored in the *weights_project* database.

3.3.4. Normalization of the neck area and weights data for comparison between patients

Having data from various different sources, there was a need for data integration. Luckily, the radiotherapy treatment parameters were common to the CBCT images data and relational data. The fusion of the data was thus performed for every patient and it required the normalization of the parameters.

The two parameters that were investigated to track the anatomical changes of patients during their radiotherapy treatments are the patient's weights and the area in a region of interest in the neck.

As mentioned before, the first step in the data integration was to sample the patients' weights and the CBCT images every 5 fractions, and to unify and homogenize the number of the time-series data points per patient. Another step for the integration of the data was the normalization of the data points to the first value, allowing determination if the variables increased or decreased their value during the patient's treatment.

For the CBCTs, the data normalization of the replanned patients was straightforward since all the patients were imaged on the first day, following the MUHC protocol. However, there was an extra normalization needed for replanned patients. In that case, there were two treatment plans and the data points from the second treatment were normalized to the last data point of the first treatment.

In the case of the weights data, there was the challenge of patients not weighted during their first five fractions of radiotherapy treatment. To account for the missing data points, patients' weight was tracked backwards to 15 days before their start of the treatments. This step was based on the assumption that patients' weight may not vary significantly before radiotherapy treatment. However, there were patients with no weights registered 15 days before radiotherapy or during their first 5 fractions. In this case, the first weight available was taken as the first weight of the treatment.

Additionally, linear interpolation was used to fill the missing values for patients in which their weights data were sparse even after the five fractions sampling.

For both CBCTs and weights, the data points were normalized for every patient, and the data points acquired between five fractions were averaged to obtain the same number of points for both parameters.

3.4. Data Storage

Since the project's data were distributed across various sources, we created the *weights_project* database in order to gather and store the processed data for analysis. The *weights_project* database was created using Python and MySQL and is securely mounted on a Linux server within the department. The database has raw data and mined data, cleaned and processed from the *Aria* and *AEHRA* databases and relational data obtained from DICOM image processing.

A local repository in the MUHC network was created to temporarily store the CBCT images for the 18 plans examined in neck area study. To trace the files to their origin, the names of the folders storing the files were arranged to have information about the plan or replan and fraction number.

Finally, the *neck_area* table was created in the *weights_project* database to store the output of the neck area script. The flowchart of the complete process of the creation of the *weights_project* database is illustrated in figure 3.4.1.

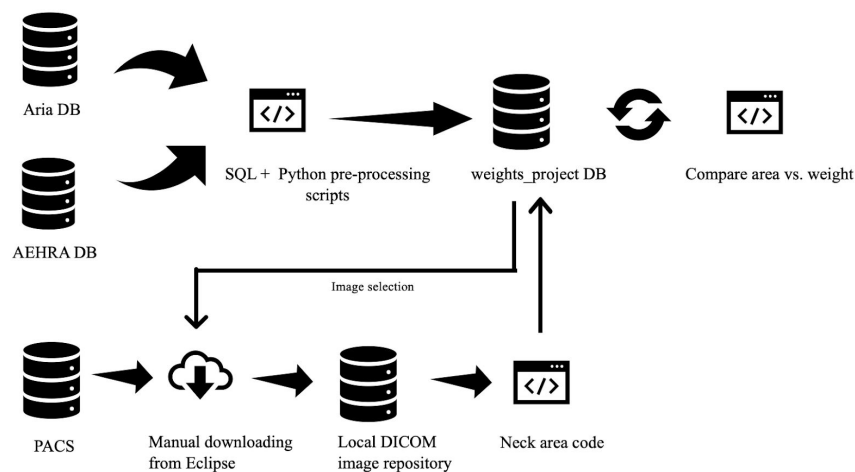


Figure 3.4.1. Flowchart of information into the *weights_project* database

Table 3.4.1. Content of weights_project database tables

<i>Table name</i>	<i>Content</i>
Area_weight_integration	Contains the area of a region of interest of the neck and the patients' weight integrated data from 18 HNC patients ready to be analyzed. (2018 - 2019)
CBCT_images	CBCT images names from RT HNC patients (data from 2016 - 2019) <i>*Input table</i>
Diagnosis categories	HNC cancer categories by cancer site location <i>*Input table</i>
Diagnosis categories catalogue	Dictionary between the ICD-10 HNC diagnosis codes and HNC categories <i>*Input table</i>
Neck_area	Neck area of a region of interest of the head and neck (for 18 HNC patients) (2018 - 2019) <i>*Input table</i>
PatientId catalogue	Dictionary of PatientId to anonymous ID (for 490 HNC patients) <i>*Input table</i>
Patient_age	Patients age at the start of their radiotherapy treatment (for HNC patients 2012 - 2019) <i>*Input table</i>
Replanning_predictors	Contains the weights processed data from 490 HNC patients ready to be analyzed. (2012 - 2019) <i>*Output table</i>
Replanning_predictors_chemo	Contains the weights processed data from 260 HNC patients ready to be analyzed. Includes concurrent chemotherapy information (2016 - 2019) <i>*Output table</i>
RT_plan_data	RT plan data: specifies prescribed dose, plan and replan of HNC patients (2012 - 2019) <i>*Input table</i>
RT_treatment_dates	RT treatment plan dates by fraction number and plan (for HNC patients from 2012 - 2019) <i>*Input table</i>
Weights_data	Patients' weights (for HNC patients from 2012 - 2019) <i>*Input table</i>

3.5. Data analysis

In addition to descriptive statistics like mean, median and standard errors, various statistical tests and models were used to compare the replanned and non-replanned populations. This section outlines these tests and models.

3.5.1. Univariate analysis between patients replanned and not replanned

A univariate exploratory analysis was performed to explore which factors may be related to the replanning. Continuous and categorical variables for replanned and not-replanned patients were compared. Each subcategory of the HNC site location, the presence of concurrent chemotherapy, patient sex and cancer stage variables were compared proportionally between replanned and not-replanned patients. Additionally, a χ^2 test was used to verify that the relation between the categories and the replanning was statistically significant.

On the other hand, the distributions of the patients' age and total weight loss were compared between replanned and not-replanned patients using the Mann Whitney U test. For this work, the null hypothesis stated that there was no difference between replanning distributions.

Both the χ^2 and Mann Whitney U tests were performed using the Scipy package from Python.

3.5.2. Multivariate regression models

Multivariate linear and logistic regression models were chosen to find the predictors of the anatomical changes (weight loss) and when to replan a patient.

There were two models of linear regression and logistic regression: The first model included all 490 patients without adjuvant-chemo data, and the second model included only the 290 patients from when chemo data were available. From all the variables considered in the models, only the relative weight was considered continuous while the rest of the variables were considered categorical. The models were calculated using the linear model function *lm*

from the R statistical package. Also, the 95% confidence intervals (CI) were calculated for each of the coefficients considered in the models.

The models were runned several times to find the best combination of variables that would produce statistically significant regression coefficients. In the case of the linear regression model, the R^2 parameter was also used to choose the best model. The variable sex was excluded from all the final models because it was not found to be statistically significant in either the univariate or multivariate models ($p > 0.05$).

Since the weight was the only parameter from which we had enough information to understand which parameters affect the anatomical changes during radiotherapy, *a linear regression model* was created to predict the relative changes in the weight. For the 490 patients cohort, the independent variables were HNC site location, cancer stage, prescription dose and patients age. In the 260 subcohort, the HNC site location, cancer stage were replaced by the presence of concurrent chemotherapy. Even though age was not found to be correlated to the replan in the univariate analysis, it was used in the linear model to see if it had any relation with the weight loss.

On the other hand, *the logistic regression models* were used to find the predictors of the *time of replanning*. The fraction number at the time of replan was modeled using a binary variable, which had the value of one, only if the patient was replanned at that fraction, and zero otherwise. The independent variables were the weight loss (%) during radiotherapy, the treatment fraction and the presence of concurrent chemotherapy.

3.5.3. Anatomical changes time series analysis

The preprocessing of the data facilitated the construction of time series of neck area and weight to track anatomical changes during radiotherapy. Medians, means, and standard error were calculated to represent the data relative weight of the patients sampled in 5-fraction increments. In particular, time series for each prescription dose were created.

First, the weight time series were compared to the replanning fraction. Afterwards, a pilot study compared neck area and weight to identify if the weight represents accurately the anatomical changes in the neck. Mann Whitney U tests were performed to determine if the replanned and not-replanned patients' time series were significantly different at each fraction for both area and weight. Additionally, differences between area and weight at each fraction were computed for all patients. Finally, the relative changes in the neck area and patient's weight were compared.

4. Results

4.1. Univariate evaluation of replanning

To begin, a preliminary exploratory analysis comparing characteristics between patients who were and were not replanned was conducted to identify potential factors that may have influenced the choice to replan. These characteristics included HNC site location, the presence of concurrent chemotherapy, patient sex, patient age and cancer stage. Although these factors are not directly related to the anatomical changes associated with replanning, they may have played an indirect role.

Patients were classified according to their prescription dose in the 60 Gy, 66 Gy and 70 Gy groups. The majority (58%) of patients were prescribed 70 Gy, compared to 60 Gy (18%) and 66 Gy (24%). Interestingly, the 70 Gy prescription also had the highest proportion of patients replanned (50%), equal to those not replanned, compared to the proportion of patients replanned in the 66 Gy (32%) and 60 Gy (24%) prescriptions. Figure 4.1.1. shows the proportions of patients replanned and not replanned as a percentage of the total population of 490 HNC patients. Additionally, differences in the prescription dose between patients replanned and not replanned were confirmed statistically significant by a χ^2 test ($p < 0.005$).

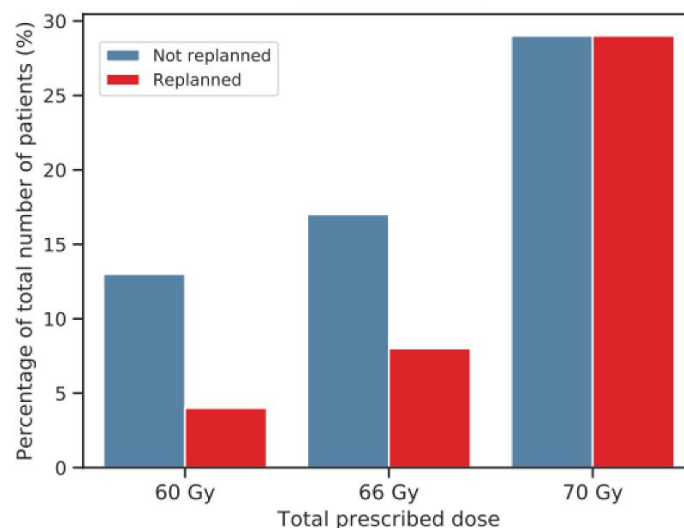


Figure 4.1.1. Proportion of patients replanned and not replanned in groups of total prescribed doses of 60 Gy, 66 Gy and 70 Gy. Total of 490 HNC patients.

Figure 4.1.2 shows the proportions of patients replanned and not replanned according to sex (a), HNC site location (b), cancer stage (c) and concurrent chemotherapy (d). Additionally, table 4.1.1 complements the figures 4.1.1 and 4.1.2 (a - d) with the frequency counts and p - values from χ^2 tests comparing the number of patients replanned and not replanned of each variable.

The relation between patients sex and replanning is not statistically significant (NS) as shown in table 4.1.1 and figure 4.1.2 a). Also, a dominance of male HNC patients is preserved in the data with 71% of male patients in the main cohort.

On the other hand, HNC site location does have a statistically significant impact on the replan ($p < 0.005$) as shown in table 4.1.1 and figure 4.1.1. b). They also show that oropharyngeal cancer is the only cancer category which incidence increases (124%) in the patients replanned compared to the not replanned patients. Nasopharyngeal cancer incidence remains equal but is proportionally higher for replanned patients, while the rest of HNC site location proportionally decreased in replanned patients.

Cancer stage is also significantly different ($p < 0.05$) between replanned and not replanned patients (table 4.1.1 and figure 4.1.2 c. In both groups, advanced stages (III and IV) are dominant over early stages (I and II). Undefined stages (X) are the second more common stage after stage IV. Stages (IV and X) are the only two categories that increased their incidence in replanned patients compared to not replanned patients.

Moreover, the relation between the concurrent chemotherapy and replan is shown in (table 4.1.1 and figure 4.1.2 d). A limitation of this study was to have the information from chemotherapy appointments only for 260 patients from 2016 to 2019. From the graph, it can be observed that patients replanned, more often received chemotherapy. Moreover, the relation between chemotherapy and replanning is statistically significant ($p < 0.005$).

Figure 4.1.3 illustrates the distribution of the patient's age at the start of the treatment. Figure 4.1.4 shows the total weight loss distribution at the end of the treatment. Mann–Whitney U tests were performed to compare age and weight loss of replanned and not replanned patients.

Both patients replanned and not replanned seem to have similar age distributions ($p = 0.30$). The median age at the start of the treatment is around 63 ± 11 years for both distributions.

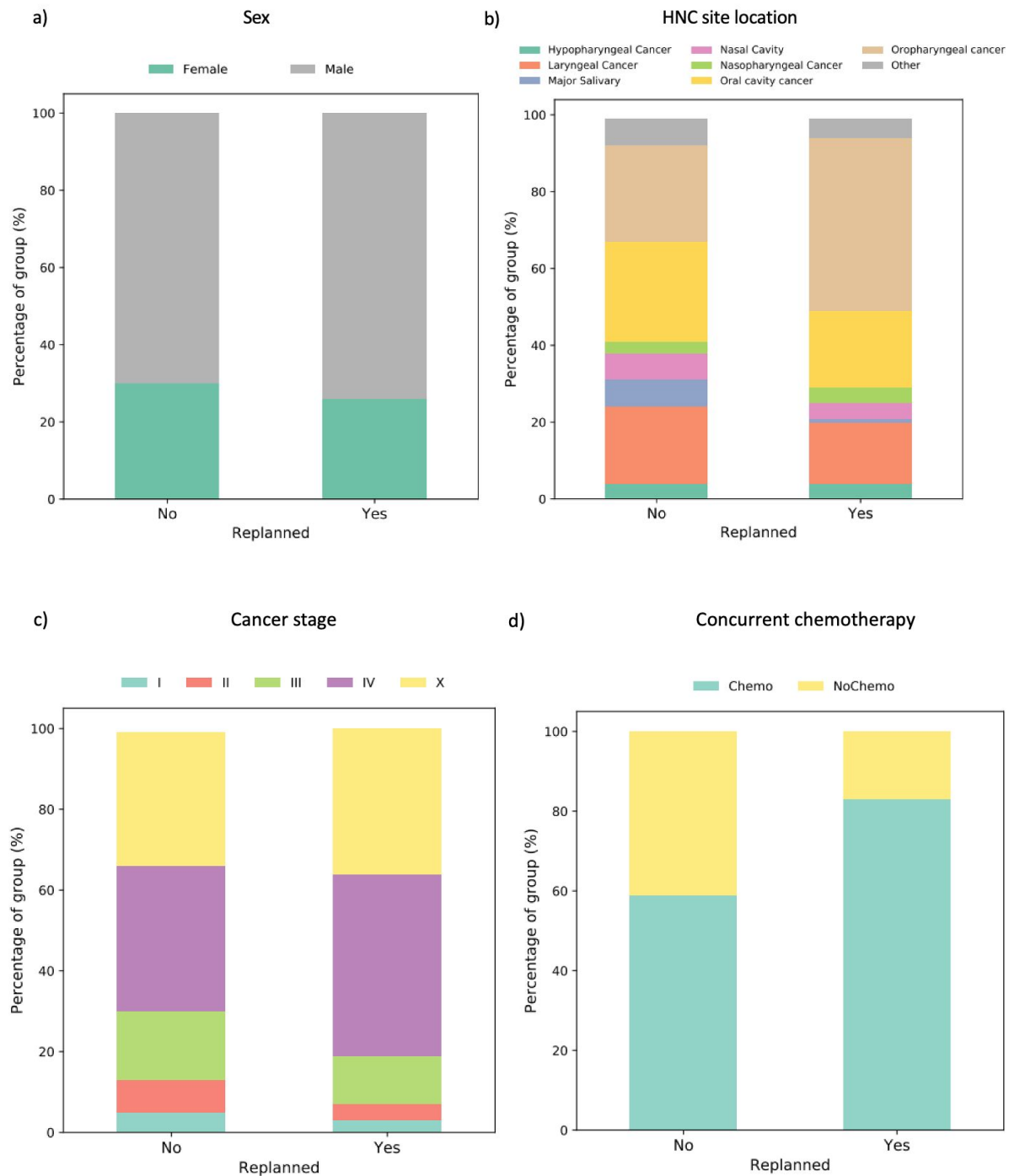


Figure 4.1.2. (a-d) Proportions of patients replanned and not replanned for patients sex, HNC site location, cancer stage and concurrent chemotherapy. There were considered 490 patients for (a-c) and 260 patients for (d).

Table 4.1.1. Frequencies and χ^2 p -values of prescription doses, patients sex, HNC site location, cancer stage and concurrent chemotherapy in patients replanned and not replanned.

	All N=490	Replanned N=201	Not replanned N=289
Prescription dose P < 0.005			
60 (Gy)	86 (18%)	21 (10%)	65 (22%)
66 (Gy)	120 (24%)	38 (19%)	82 (28%)
70 (Gy)	284 (58%)	142 (71%)	142 (49%)
Sex P = 0.32 (NS)			
Female	141 (29%)	53 (26%)	88 (30%)
Male	349 (71%)	148 (74%)	201 (70%)
HNC site location P < 0.005			
Hypopharyngeal	19 (4%)	8 (4%)	11 (4%)
Laryngeal	92 (19%)	33 (16%)	59 (20%)
Major salivary	25 (5%)	3 (1%)	22 (8%)
Nasal cavity	29 (6%)	8 (4%)	21 (7%)
Nasopharyngeal	18 (4%)	9 (4%)	9 (3%)
Oral cavity	117 (24%)	40 (20%)	77 (27%)
Oropharyngeal	168 (34%)	93 (46%)	75 (26%)
Other	33 (7%)	11 (5%)	22 (8%)
Stage P < 0.05			
I	22 (4%)	6 (3%)	16 (6%)
II	33 (7%)	8 (4%)	25 (9%)
III	76 (16%)	25 (12%)	51 (18%)
IV	198 (40%)	92 (46%)	106 (37%)
X	173 (35%)	74 (37%)	99 (34%)
	All N=260	Replanned N=76	Not replanned N=184
Chemo P < 0.005			
Yes	171 (66%)	63 (83%)	108 (59%)
No	89 (34%)	13 (17%)	76 (41%)

On the other hand, weight loss was significantly different for replanned and not replanned patients ($p < 0.005$). The median weight loss was 6.26 ± 4.54 (%) for patients replanned, while it was 4.69 ± 4.60 (%) for patients not replanned.

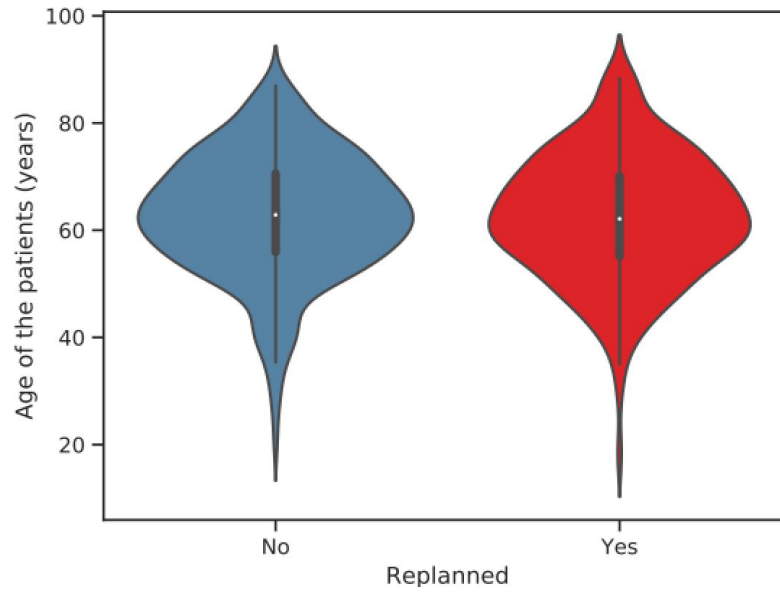


Figure 4.1.3. Violin plots of the age of the patients replanned and not replanned at the start of their radiotherapy treatment. Total 490 HNC patients.

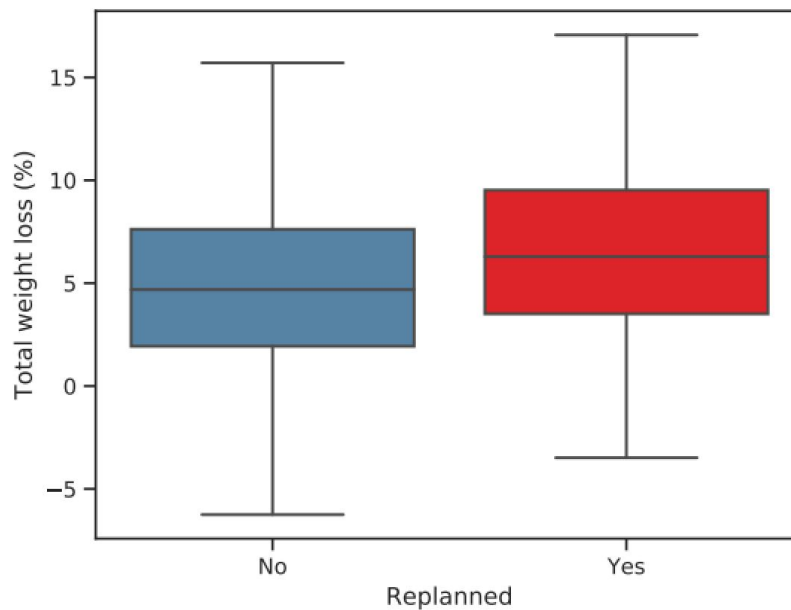


Figure 4.1.4. Box plots of the weight loss of the patients replanned and not replanned at the end of their radiotherapy treatment. Total 490 HNC patients.

4.2. Anatomical changes time series (weight loss) and replanning

Unlike other variables, weight loss was found to have a direct relation to the replanning since the changes in the weight are known to cause visible anatomical changes in the patients.

Now, the replanning fraction was investigated with the purpose of identifying the time in which the replanning occurred within each group. Differences in the time of replan between groups follow from differences in treatment durations. Since there were daily fractions delivered for most patients, the treatment was approximately three days longer for the 66 Gy and one week longer for the 70 Gy group in comparison to the 60 Gy group. In figure 4.2.1 the replanning frequency can be observed as a function of fraction number for each of the prescribed dose groups. The number of replans peaked at 25 and 30 fractions for the 70 Gy group. For the 60 Gy group, the replans occurred earlier, peaking at the 25th fraction. Finally, for the 66 Gy group, the replans peaked in the 20th to 25th fraction. Thus, most of the replans occur two weeks before the end of the treatment. No replans occur during the last week of the treatment because the new treatment plan may not be processed on time.

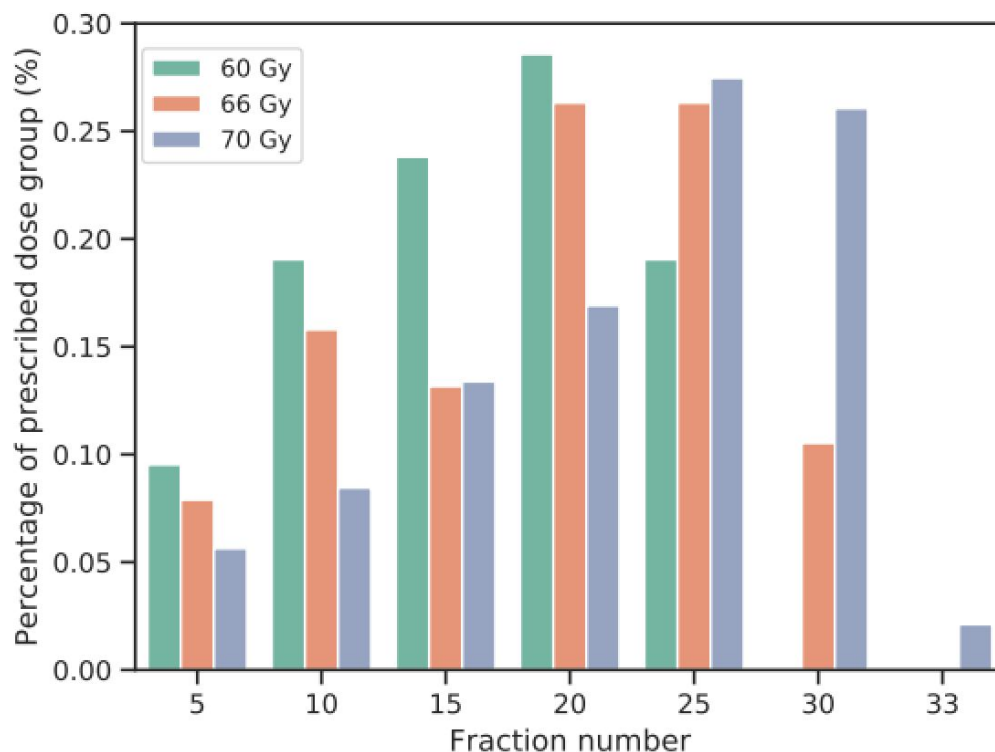


Figure 4.2.1. Replanning frequency as a function of the fraction number for HNC patients. A total of 201 patients out of 490 patients were replanned. (2012 - 2019)

In figure 4.2.2, the median weight series of patients replanned and not replanned from the 60 Gy, 66 Gy and 70 Gy groups is presented. The total number of HNC patients considered for this graph was 480. Every point in each curve represents the median weight acquired every five fractions. The dashed lines represent the not replanned patients while the solid lines

represent the replanned patients. This graph confirms that the patients lost weight during radiotherapy for patients with prescription doses of 60 Gy, 66 Gy and 70 Gy.

The median weight loss also changed between patients replanned and not replanned for different prescription doses. The 66 Gy group had a clear weight loss threshold around 4% between patients replanned and not replanned, while other groups did not. The 60 Gy group median weight loss was above 4% for both replanned and not replanned patients. Finally, the replanned and not replanned patients from the 70 Gy group, had over 4% weight loss during treatment. The fact that no threshold was found for the 70 Gy group is surprising given that this group has the highest proportion of replanned patients. The overlap between standard errors is observed even at the 25 fractions in which the higher cases of replan were observed.

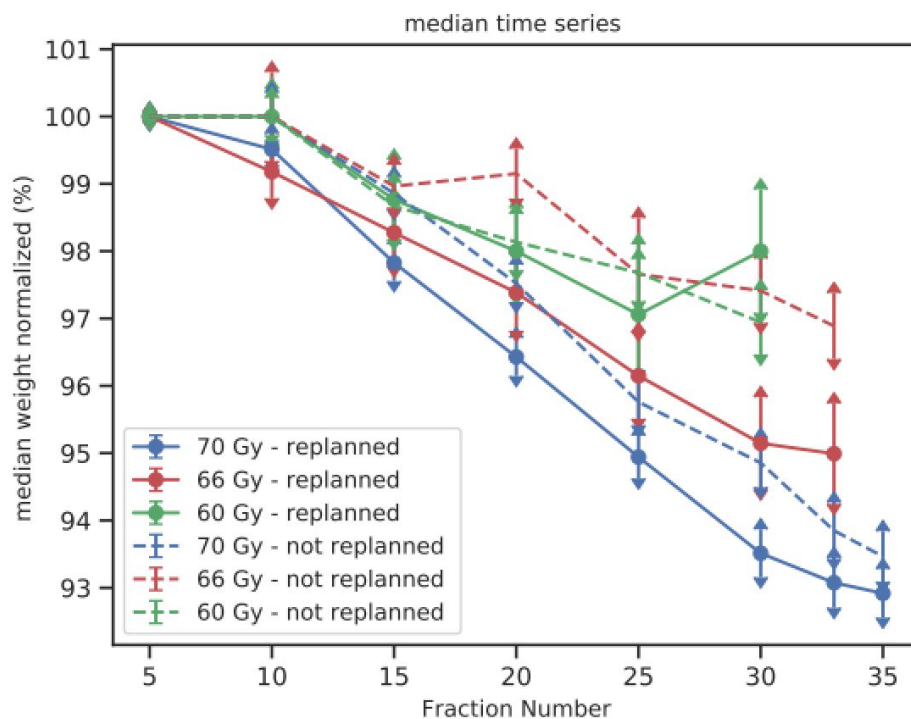


Figure 4.2.2. Median weight series of the 490 HNC patients undergoing radiotherapy who were considered in this thesis project. Number of fractions sampled in 5 fractions increment. (2012 - 2019)

Additionally, the 70 Gy group has a visibly greater proportion of oropharyngeal, laryngeal and nasopharyngeal cancer patients (figure 4.2.3) and concurrent chemotherapy patients (figure 4.2.4), which may be a possible explanation for patients losing more weight for this prescription dose than others.

A higher incidence of chemotherapy patients in the 60 Gy group for patients replanned when compared to not replanned (figure 4.2.4) could also help to explain why the patients of the 66 Gy group had a clear threshold of 4% weight loss for replanning.

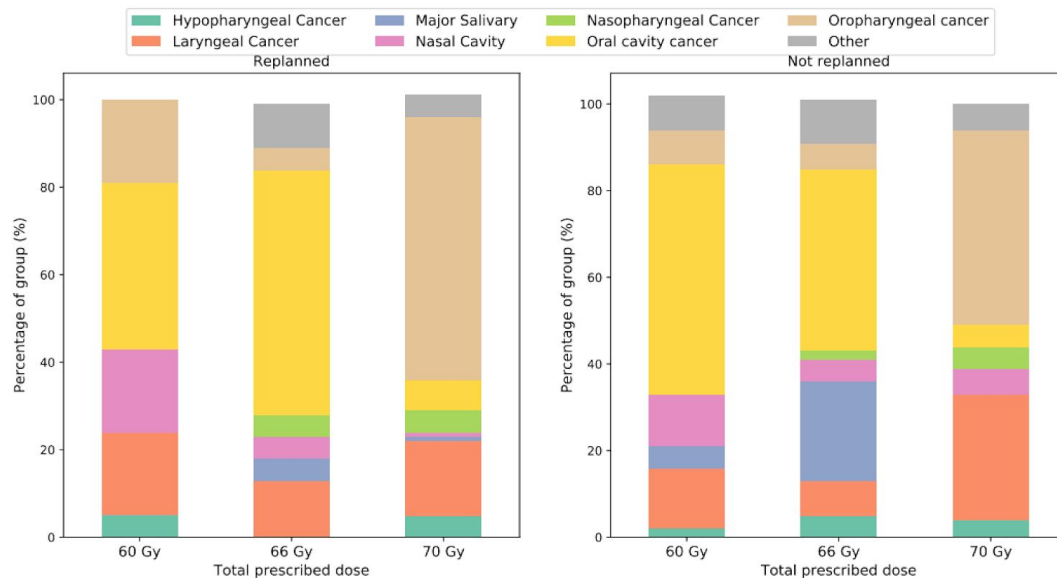


Figure 4.2.3. Proportions of HNC site location for replanned and not replanned patients with prescription doses of 60 Gy, 66 Gy and 70 Gy. Total of 490 patients.

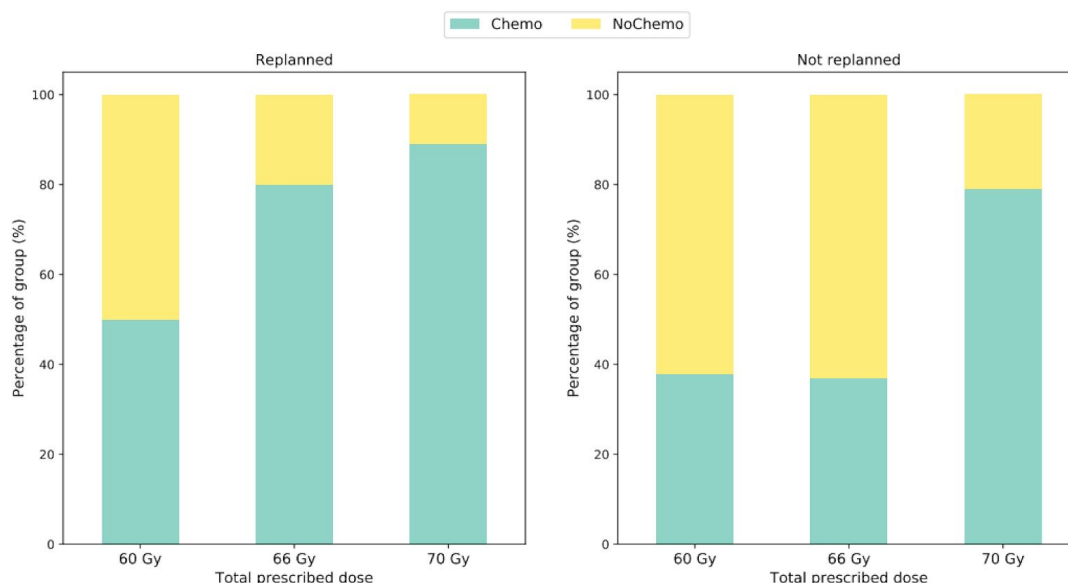


Figure 4.2.4. Proportions of concurrent chemotherapy patients for replanned and not replanned patients with prescription doses of 60 Gy, 66 Gy and 70 Gy. Total of 260 patients.

4.3. Multivariate regression models

The previous sections studied weight loss and replanning using univariate statistics. However, these two phenomena depend on more than one variable and using a multivariate model allows us to identify stronger predictors over weaker predictors.

4.3.1. Anatomical changes predictors (weight loss predictors)

The predictors of weight loss during radiotherapy were investigated using a multivariate linear regression model, where the regression coefficients were used to determine the magnitude of the correlation.

In table 4.3.1.1 can be observed the coefficients obtained from the 490 patients multivariate linear regression model. The following observations are derived from this model:

- The weight decreases as a function of the fraction number. At the 25th fraction patients lose around 3.65% more weight than the patients at fraction 5.
- The 70 Gy group lost more weight when compared to the 66 Gy group, while the 60 Gy negative coefficient was not statistically significant.
- Patients at cancer stages II, III and IV lose more weight than the patients at cancer stage I
- The nasopharyngeal, oropharyngeal and major salivary glands cancer are correlated to negative changes in the weight compared to hypopharyngeal cancer. Other HNC categories are not statistically significant.
- The age at the start of the treatment has a small positive contribution to the weight changes.

In table 4.3.1.2 the coefficients obtained from the multivariate linear regression model to calculate the weight changes for 260 HNC patients with chemotherapy data available can be observed. The confidence intervals from table 4.3.1.2 have a wider range than table 4.3.1.1. The difference in accuracy can be due to the higher number of patients used in the model of table 4.3.1.1. It is important to mention that when the chemotherapy data were available, the stage of cancer and HNC site location were not statistically significant ($p > 0.05$) and they were removed from the model.

Table 4.3.1.1. Multivariate linear regression coefficients to predict the patient's relative weight during radiotherapy using the data of 490 HNC patients (2012-2019). Independent variables: Fraction number, prescribed dose, cancer stage, HNC site location, age at the start of the treatment.
Multiple $R^2 = 0.2586$. F statistic = 61.59.

	Coefficients	CI 2.5	CI 97.5	P value
(Intercept)	99.83%	98.84%	100.82%	< 0.005
Fraction number (compared to 5 fx)				
10 fx	-1.02%	-1.49%	-0.56%	< 0.005
15 fx	-1.59%	-2.05%	-1.13%	< 0.005
20 fx	-2.52%	-2.99%	-2.06%	< 0.005
25 fx	-3.65%	-4.11%	-3.18%	< 0.005
30 fx	-4.54%	-5.00%	-4.07%	< 0.005
33 fx	-5.16%	-5.65%	-4.66%	< 0.005
35 fx	-5.98%	-6.53%	-5.43%	< 0.005
Total prescribed dose (compared to 66 Gy)				
60 Gy	0.30%	-0.13%	0.72%	0.172
70 Gy	-0.85%	-1.23%	-0.46%	< 0.005
Cancer Stage (compared to stage I)				
Stage II	-1.28%	-2.06%	-0.51%	< 0.005
Stage III	-1.10%	-1.79%	-0.42%	< 0.005
Stage IV	-1.03%	-1.67%	-0.39%	< 0.005
Stage X	-0.87%	-1.54%	-0.21%	< 0.005
HNC site location (compared to oral cavity)				
Hypopharyngeal	0.31%	-0.39%	1.01%	0.390
Laryngeal	0.06%	-0.38%	0.50%	0.798
Major salivary	0.93%	0.29%	1.57%	< 0.005
Nasal cavity	0.37%	-0.23%	0.97%	0.222
Nasopharyngeal	-1.21%	-1.94%	-0.48%	< 0.005
Oropharyngeal	-0.91%	-1.36%	-0.47%	< 0.005
Other	0.08%	-0.49%	0.65%	0.774
Start age	0.03%	0.02%	0.04%	< 0.005

The following observations are derived from table 4.3.1.2:

- The negative contributions to the weight associated to the radiotherapy fraction number are present in this model and they are consistent to the 490 patients model.
- Patients with chemotherapy appointments lose more weight than those without chemotherapy appointments.

The contributions of the prescribed dose and the patient's age to the weight changes were consistent with the previous model.

Table 4.3.1.2. Multivariate linear regression coefficients to predict the patient's relative weight during radiotherapy using 260 HNC patients (2016-2019). Independent variables: Fraction number, prescribed dose, concurrent chemotherapy and age at the start of the treatment.

Multiple $R^2 = 0.1695$. F statistic = 39.73.

	Coefficients	CI 2.5	CI 97.5	P value
(Intercept)	100.32%	98.68%	101.95%	p < 0.005
Fraction number (compared to 5 fx)				
10 fx	-1.18%	-2.15%	-0.22%	p < 0.005
15 fx	-1.34%	-2.30%	-0.37%	p < 0.005
20 fx	-2.23%	-3.20%	-1.27%	p < 0.005
25 fx	-3.68%	-4.65%	-2.72%	p < 0.005
30 fx	-4.58%	-5.54%	-3.61%	p < 0.005
33 fx	-5.43%	-6.46%	-4.41%	p < 0.005
35 fx	-6.82%	-7.98%	-5.67%	p < 0.005
Total prescribed dose (compared to 66 Gy)				
60 Gy	-0.76%	-1.61%	0.08%	0.073
70 Gy	-1.50%	-2.16%	-0.85%	p < 0.005
Chemo (Compared to no chemo)	-2.35%	-2.94%	-1.76%	p < 0.005
Start age	0.03%	0.01%	0.06%	p < 0.005

Finally, interaction terms between chemotherapy, HNC categories and stage of cancer may be interesting to revise but they were not statistically significant to be considered in the model.

An important observation from both models, is that the confidence intervals for weight are overlapped from fraction 15 to 35 which makes it difficult to determine a weight loss threshold at every fraction.

4.3.2. Replanning predictors

The odds ratio (OR) obtained from a multivariate logistic regression model were used to find the predictors of the time of replanning.

Table 4.3.2.1, shows the odds ratio (OR) from a multivariate logistic regression of 490 patients that predicts the fraction of replanning. The 25th fraction has the highest odds ratio of all the fractions (compared to fraction 5). This result agrees with the higher numbers of replans found in the 66 Gy and 70 Gy (Figure 4.2.1). Additionally, the odds ratio of the weight loss are greater than one, which confirms that the probability of replanning increases

with each unit (%) of weight loss. Table 4.3.2.2, shows the odds ratio (OR) of a multivariate logistic regression of 260 patients that predicts the fraction of replanning. This model includes the concurrent chemotherapy variable. Since the replanned patients have higher odds than the patients not replanned ($p < 0.05$), the concurrent chemotherapy is also a predictor of replanning.

Table 4.3.2.1 Odds ratio (OR) from multivariate logistic regression model to predict the fraction of replanning. Total number of patients: 490 (2012-2019). Independent variables: Fraction number and normalized weight.

	OR	CI 2.5	CI 97.5	P value
(Intercept)	0.027	0.015	0.045	$p < 0.005$
Fraction number (compared to 5 fx)				
10 fx	1.549	0.776	3.212	0.223
15 fx	2.044	1.066	4.126	$p < 0.05$
20 fx	2.704	1.451	5.362	$p < 0.005$
25 fx	3.393	1.839	6.689	$p < 0.005$
30 fx	2.401	1.263	4.835	$p < 0.005$
33 fx	0.185	0.042	0.594	$p < 0.05$
35 fx	0.000	0.000	0.000	0.968
Weight loss (%)	1.067	1.031	1.104	$p < 0.005$

Table 4.3.2.2 Odds ratio (OR) from multivariate logistic regression model to predict the fraction of replanning. Total number of patients: 260 (2012-2019). Independent variables: Fraction number, concurrent chemotherapy and normalized weight.

	OR	CI 2.5	CI 97.5	P value
(Intercept)	0.006	0.001	0.019	$p < 0.005$
Fraction number (compared to 5 fx)				
10 fx	2.088	0.564	9.856	0.295
15 fx	3.093	0.929	13.963	0.090
20 fx	5.467	1.802	23.700	$p < 0.05$
25 fx	6.829	2.291	29.404	$p < 0.005$
30 fx	3.014	0.909	13.648	0.098
33 fx	0.483	0.058	3.139	0.448
35 fx	0.000	0.000	104.131	0.977
Chemo (Compared to no chemo)	2.280	1.265	4.419	$p < 0.05$
Weight loss (%)	1.054	1.010	1.095	$p < 0.05$

4.4. Area vs weight

Since overall weight loss may not accurately reflect weight changes in the head and neck region, we also investigated how neck size changes during radiotherapy treatment for a subcohort of 70 Gy prescription patients.

Of the 18 patients examined, 11 were replanned and 7 were not, as shown in figure 4.4.1. No patients were replanned before the 15th fraction. Most replans occurred at the 25 fraction, similar to what was seen in the larger cohort.

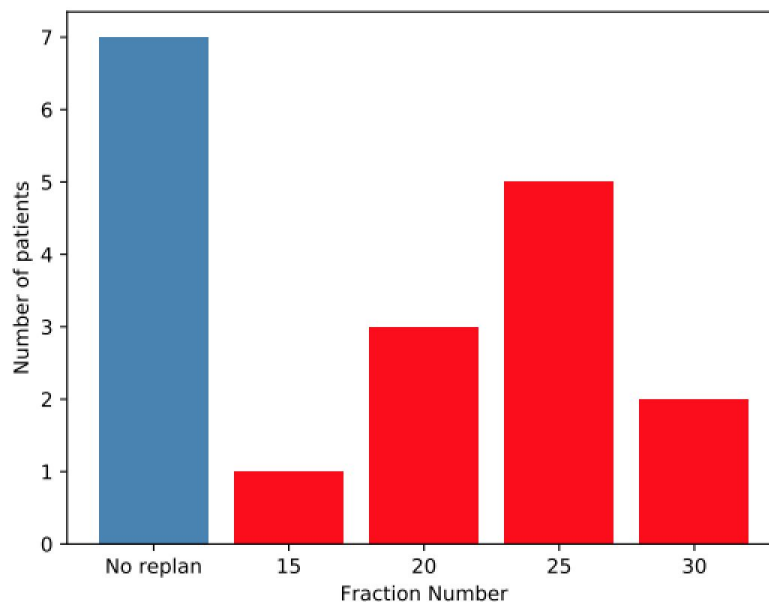


Figure 4.4.1. Patients replanned and not replanned for 18 HNC patients (2018- 2019).

Figure 4.4.2 shows the median weight and area loss at each time point over the course of radiotherapy for replanned and not replanned patients. The median area of the patients replanned is lower than the area of the patients not replanned. In summary, the patients lose area more rapidly than the weight at the start of the treatment until their stabilization from the 25th fraction to the end of their treatment. The difference in slope from area and weight suggests that the area value is more sensitive to the anatomical changes in the neck area.

Additionally, figure 4.4.3 illustrates with detail the distribution of the weight and area loss at the 25th to the end of their treatment at the 35th fraction. The values at the 25th fraction are important given that most replans occur at this fraction of the treatment.

From figures 4.4.2 and 4.4.3 there can be observed that the values of the weights for the non replanned and replanned patients are overlapping under the uncertainties at each fraction, which agrees with the global behaviour observed in figure 4.2.2.

In order to compare the distributions at different points of the patients treatment, Mann Whitney U tests were used to compare the replanned and not replanned distributions for area and weight. In the case of the area, the difference between distributions was statistically significant ($p < 0.05$) for all the fractions with the exception of 10 and 15. In the case of the weight the difference between distributions was not statistically significant from the 10 to 33 fractions. However, even if the distributions were significantly different, they still have certain overlap that implies that there is no threshold value for either of weight and area that could be used as ground truth for the replanning.

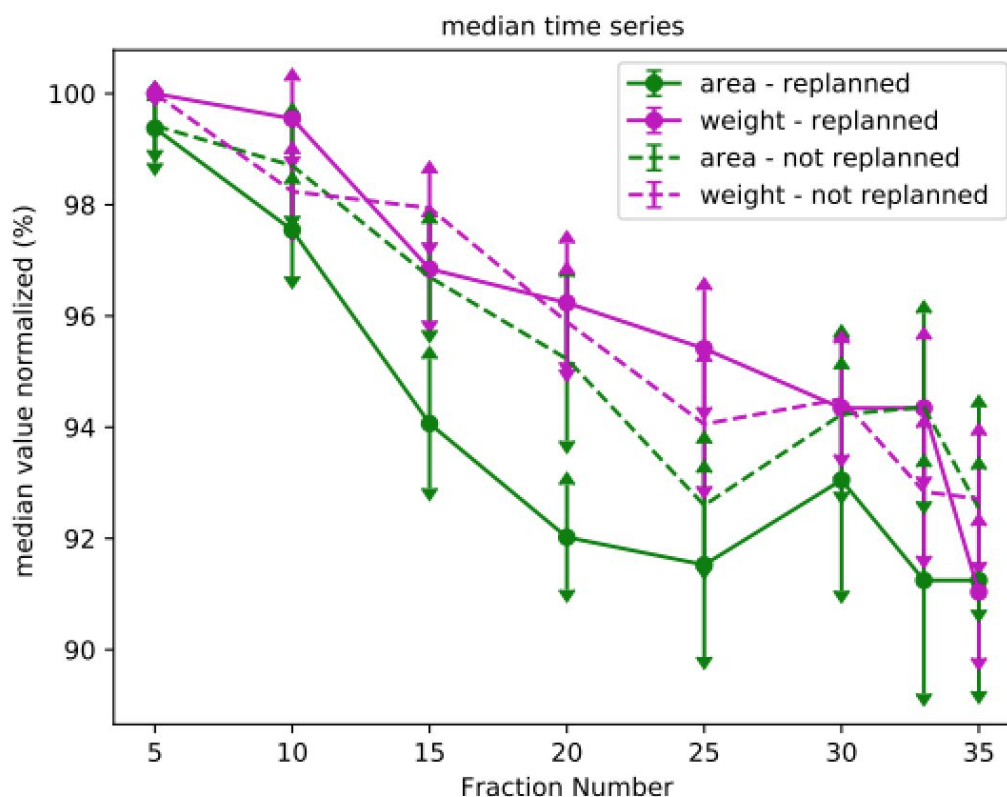


Figure 4.4.2. Median time series of weight and area for 18 patients undergoing radiotherapy. (2018 - 2019). Solid lines represent patients replanned and dashed lines represent patients not replanned.

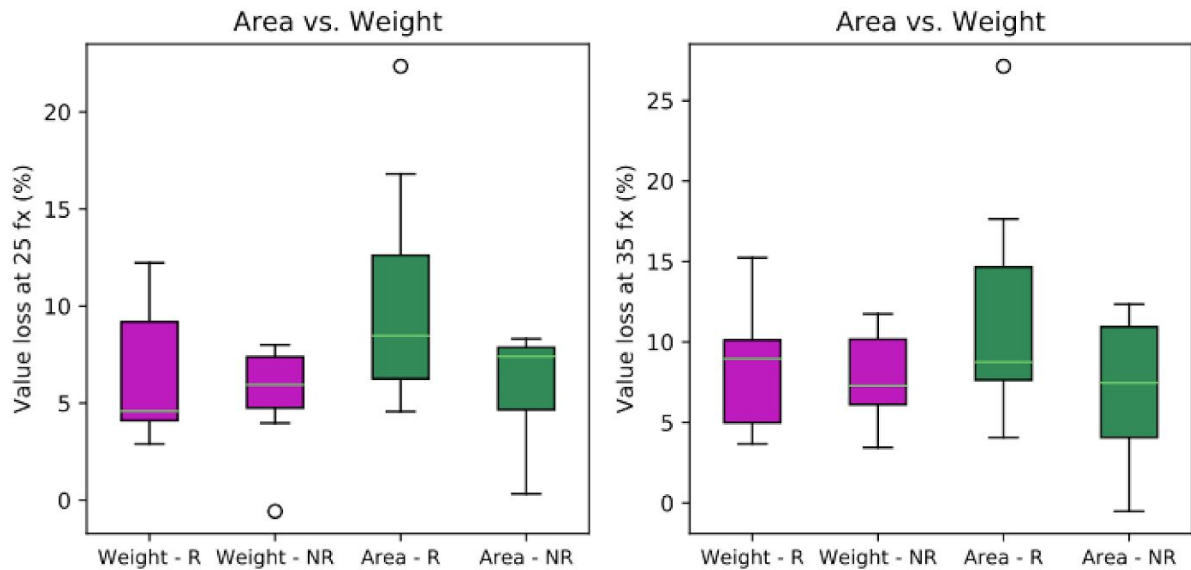


Figure 4.4.3. The value loss at 25 fx and 35 fx for area (green) and weight (purple) of the patients replanned (R) vs not replanned (NR) Total: 18 patients (2018 - 2019).

As seen in figures 4.4.2 and 4.4.3, the area and weight trends are not equivalent. Figure 4.4.4 shows the normalized area - normalized weight difference at every 5 fraction increments for patients replanned and not replanned. When area is equal to weight, the value is zero. As we can observe, most medians are below zero, which means that area is smaller than weight at every fraction. Thus area is decreasing at a faster rate than weight as we previously saw in figure 4.4.2. Moreover, we can see that for replanned patients, the difference between area and weight is even more abrupt, which could explain why some patients were replanned even if they lost a significant amount of weight.

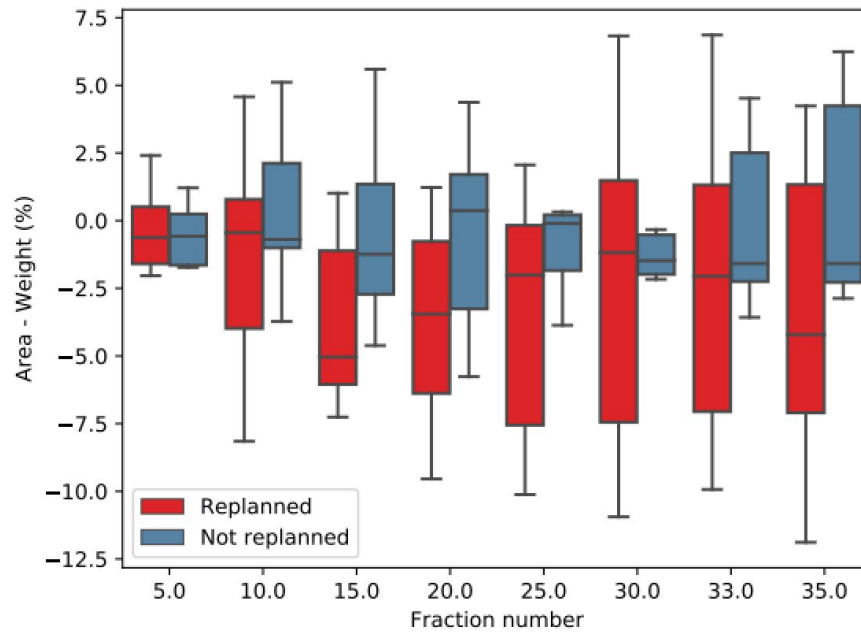


Figure 4.4.4. Differences of relative area and weight (%) during radiotherapy for patients replanned and not replanned. Total: 18 patients (2018 - 2019).

In figure 4.4.5 the normalized values of the area and weight at the fraction of replanning are shown. The median neck area at the 25 fraction could be used as a threshold for replanning in future work.

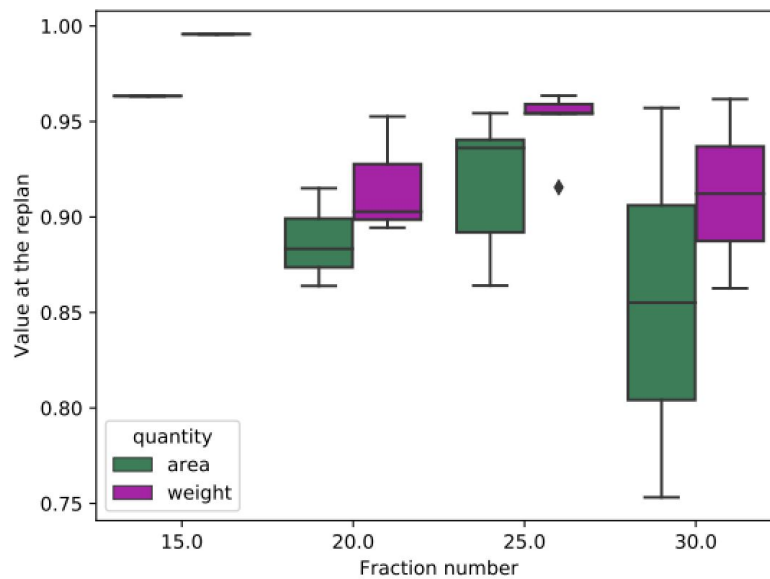


Figure 4.4.5. The value of the area and weight at the replanning. Total: 11 patients replanned (2018 - 2019).

5. Discussion

5.1. Univariate analysis of replanning and anatomical changes

For the purpose of this work, the treatment fraction numbers give information about two variables considered in this study: the cumulated dose received by the patient and the time measured from the start of the treatment. Since all plans were standard fractionation (2 Gy/fx), all three groups had received the same radiation dose at each timepoint, the only difference, dose wise, is that some groups ultimately had more time points. Shorter overall treatment could explain why earlier replans occurred for the 60 Gy group compared to the 66 Gy and 70 Gy groups. Also, no replans occurred for the last fractions of the treatment for any prescription dose. This is likely due to the fact that the workload of replanning is not justified for a few fractions. The main prescription dose differences reside in the HNC site location and the use of concurrent chemotherapy.

For our cohort, most replannings were performed two weeks before the end of the treatment for all prescription doses, which also matches with literature findings (Brown et al. 2016; Guidi et al. 2016). The peak of the replans occurred at the 25th fraction for 70 Gy, 20th-25th fractions for 66 Gy and 20th fraction for 60 Gy. *Brown et al* (2016) found that the median fraction at which replanning occurred was at the 22nd fractions for a 70 Gy prescription dose, which falls approximately within the same timeline as our result (Brown et al. 2016). Additionally, Guidi et al (2016) found that patients with a prescribed dose of 60 Gy required a replan from the 4th week of treatment (or 15th-20th fraction according to our timeline), which also agrees with our result (Guidi et al. 2016).

In our work, weight loss was observed during radiotherapy for patients from all prescription doses. At the same time, weight loss was found to be correlated to the presence or absence of replanning (χ^2 test, $p < 0.005$), results that agree with findings in the literature (Gensheimer and Le 2018; Ma et al. 2014). Additionally, patients of different prescription doses lost weight at different rates during radiotherapy. In particular, patients from the 70 Gy group had a higher weight loss rate compared to other prescription doses. Moreover, the replans were

more common for the 70 Gy than the 60 Gy or 66 Gy patients. Thus, the greater rate of replanning in the 70 Gy group may be related to the higher median weight loss rate in this group.

Some factors that may explain a greater weight loss of patients within the 70 Gy group are the presence of more patients with oropharyngeal and nasopharyngeal cancer than in the other groups. The oropharyngeal and nasopharyngeal cancer sites have been found to be associated with greater weight loss than other cancer sites (Ottosson et al. 2013; Zeng et al. 2016). Moreover, the presence of a higher number of concurrent chemotherapy patients may be related to a higher rate of weight loss in the 70 Gy group. Studies from the literature have shown that chemotherapy is a weight loss predictor (Ghadjar et al. 2015).

We confirmed univariate correlations (χ^2 test, $p < 0.05$) between the replanning and the following variables: HNC site location, cancer stage and concurrent chemotherapy. This is not surprising because all of these variables have been shown to be predictors of weight loss (Zhao et al. 2015) and weight loss has been found to be a predictor of replanning. HNC site location determines the irradiated region (Yeh 2010), and patients develop more or less weight loss depending on the affected organs (Muzumder et al. 2019; Grundmann, Mitchell, and Limesand 2009). Cancer stage also determines the use of concurrent chemotherapy for advanced diseases (Yeh 2010). Likewise, concurrent chemotherapy contributes to both weight loss and treatment response (Ghadjar et al. 2015; Iqbal et al. 2017), which are relevant for replanning (Gensheimer and Le 2018).

The presence of concurrent chemotherapy in most replanned patients in the 66 Gy group may also explain why it was the only group with a clear difference in median weight loss between patients replanned and not replanned.

5.2. Multivariate analysis of replanning

The *multivariate linear regression model* was useful to confirm that the weight loss decreased during radiotherapy, given that the linear regression coefficient decreases with the more fractions the patient receives. It also confirmed that the weight loss depends on multiple

variables and it was useful to identify which parameters have stronger correlations to weight loss.

The linear models also confirmed that the patients with 70 Gy prescription dose lose more weight than the patients with 66 Gy ($p < 0.005$), behaviour that was observed in the univariate analysis. When comparing linear regression coefficients from patients in different stages, patients in early stages (I), were observed to lose more weight than patients in later stages (II, III and IV). Similar behaviour has been observed by *Lonbro et al* (2016) when comparing early stages (I - II) to late stages (III- IV) (Lønbro et al. 2016). Additionally, the linear model shows that oropharyngeal and nasopharyngeal cancer patients lose more weight than patients with oral cavity cancer.

The linear regression coefficients for the age at the start of the treatment were statistically significant in the two linear models. However, they were too small to be clinically significant, which explains why age was not relevant for replanning in the univariate analysis.

An interesting observation is that when the chemotherapy variable was considered, the cancer stage and HNC location did not remain statistically significant. This suggests that chemotherapy is a stronger predictor of weight loss than cancer stage and HNC location.

The multivariate linear regression models give a rough approximation of the patient's weight during radiotherapy. However it is not possible to use them to obtain accurately the patient's weight at each fraction as indicated in the wide confidence intervals of the regression coefficients and the low $R^2 (< 0.3)$ value. This may be due to the variability of the weights data, that come from patients' weight not being acquired in a systematic way. Also, there are other variables such as stress and self esteem of patients that impact their weight that we are not considering (Larsson, M., Hedelin, B. and Athlin, E. 2003). The two linear models had similar performance, even though they considered different variables. Also a bigger dataset could help to improve the statistics of the models.

The logistic regression model was useful to find the main predictors of replanning ($p < 0.05$): the treatment fraction (because each treatment fraction adds dose to the patient), the weight

loss and the presence of concurrent chemotherapy. Whereas concurrent chemotherapy is expected to have an impact on the tumour response (Iqbal et al. 2017), it is not commonly referred to as a predictor of replanning. However, studies have shown that concurrent chemotherapy can have an indirect impact on the replanning. For example, *Ma et al* (2014) found greater variations in the parotid volume in patients undergoing concurrent chemotherapy treatment (Ma et al. 2014).

Additionally, the 20th - 25th fraction had the highest probability of replanning of all fractions (compared to fraction 5), behaviour that also was observed in the univariate analysis. This timeline is associated with a median weight loss of 4%, which is consistent with the 4.4% weight loss at the 21st fraction reported as a predictor of replanning by *Ma et al* (2014) (Ma et al. 2014).

A bigger dataset would have been useful for the logistic regression model, because the fraction of replan was modeled as a binary variable assigning the value of one only if the patient was replanned in a certain fraction. Thus, the ratio of ones to zeros is smaller for the fractions with less replans, worsening the statistics.

The fact that all 70 Gy patients lost almost the same relative amount of weight during radiotherapy, can be explained by the presence of a high number of patients of oropharyngeal cancer and concurrent chemotherapy for both replanned and not-replanned patients. Additionally, the residual variability of the weight loss likely contributed to the ambiguity of the replanning decision. Accordingly, we asked ourselves why some patients were replanned and others not. This could have two possible explanations:

- Weight loss does not accurately reflect change in the head and neck region.
- Replanning is not standardized

5.3. Area vs weight

To evaluate these two possibilities, we created a new parameter to analyze the changes on a localized region of the neck, the neck area. Studies in the literature use different approaches to track anatomical changes, for example, the volume of the parotid has been used for this

purpose (Barker et al. 2004; Loo et al. 2011). Additionally, *Loo et al* (2011) measured the volume enclosed in the target volume.

The important differences between neck area and weight throughout radiotherapy are that the neck area decreases at a faster rate than the weight until it is stabilized at the end of the treatment. For most cases, the median neck area was smaller than the median weight. For the replanned patients the difference between neck area and weight was larger than for not-replanned patients. Thus, the differences between weight and neck area confirm the explanation that says that the weight loss does not accurately represent changes in the head and neck region.

Nevertheless, overlapping of the median neck area of replanned and not-replanned patients was also observed in this small study. It becomes visible even at the 25th fraction that was most frequently replanned. The difference between the neck area of patients replanned and not replanned is too small to determine a neck area threshold for replanning. This behaviour suggests that our second guess is correct and the replanning is not standardized. In other words, there are some patients who lost a similar amount of neck area as the replanned patients but they were not replanned for any reason.

A standardization in the replanning process would be useful to provide assurance that all patients will receive an updated treatment plan if needed. There are, however, a few challenges for replan standardization. The most important of these is that in our clinic, there are no reliable tools that allow clinicians to measure the anatomical changes of patients during radiotherapy.

In this work, the weight and the neck area were proposed as two potential parameters that could be used for anatomical change tracking. When the weight was compared to the neck area during radiotherapy, there were found discrepancies that suggest that the weight is not a good parameter to track anatomical changes. That leaves the neck area as the best option to track anatomical changes.

However, the neck area code, as written for this thesis project, is just a prototype and needs to be optimized before any clinical implementation. The software is adapted for a local repository of DICOM images and the next step would be to adapt it to leverage data from the PACS system and from the Aria database. Eclipse scripting could be a potential solution but it has not been investigated within the scope of this project. Another important point to consider is that the software would have to be used at the treatment room for which an appropriate interface would be needed.

As a starting point for standardization, the median neck area at the 25th fraction could be used as a threshold for replanning. Patients that lose neck area beyond 6 % would have to be replanned. The neck area study could also be extended to the 490 patients to improve the statistics. Once replanning is standardized, a prediction of replanning could be made based on the neck area parameter's performance at the start of treatment.

6. Conclusions

In our cohort, the main predictors of replanning were identified as the 20th - 25th treatment fraction and the weight loss. Chemotherapy was also found to be a predictor of replanning but it could have an indirect effect on the replanning because of its strong correlation with weight loss. Other predictors of weight loss were HNC site location and cancer stage but the correlation was not statistically significant when chemotherapy was considered.

Additionally, a new parameter was proposed to measure the changes in the neck area. Given the limited amount of neck area data available in this preliminary study, the neck area loss parameter was only used to test if the weights data can be used as a measure of the anatomy changes in the neck region. The weight and neck area were found to decrease at different rates during radiotherapy. The differences between weight and neck area loss were more evident for replanned patients, which suggested that weight was not an accurate or sufficient representation of the anatomical changes in the head and neck region.

However, neither the weight nor the neck area had a clear threshold for replanning, which means that some patients were not replanned even if they lost a significant amount of weight or area. As a consequence, the current data cannot be used to identify and classify replanned and not replanned patients until the replanning process is standardized. In particular, a threshold of a 6% neck area loss from the start of the treatment could be implemented in the replanning workflow as a first approach to standardize replanning. This threshold could be optimized by improving the statistics with a bigger dataset and a dosimetric impact analysis would be required. Overall, replanning standardization would be useful to formulate predictions of when to replan radiotherapy for head and neck cancer patients.

References

- Airley, Rachel. 2009. *Cancer Chemotherapy: Basic Science to the Clinic*. John Wiley & Sons.
- Andrade, Aixa, and Hossein Naseri. 08-2020. "HNC Project - Neck Area." Github: McGillMedPhys/HNC_project. 08-2020. https://github.com/McGillMedPhys/HNC_project.
- Barker, Jerry L., Adam S. Garden, K. Kian Ang, Jennifer C. O'Daniel, He Wang, Laurence E. Court, William H. Morrison, et al. 2004. "Quantification of Volumetric and Geometric Changes Occurring during Fractionated Radiotherapy for Head-and-Neck Cancer Using an Integrated CT/linear Accelerator System." *International Journal of Radiation Oncology*Biology*Physics* 59 (4): 960–70.
- Baskar, Rajamanickam, Kuo Ann Lee, Richard Yeo, and Kheng-Wei Yeoh. 2012. "Cancer and Radiation Therapy: Current Advances and Future Directions." *International Journal of Medical Sciences* 9 (3): 193.
- Beynon, Rhona A., Samantha Lang, Sarah Schimansky, Christopher M. Penfold, Andrea Waylen, Steven J. Thomas, Michael Pawlita, et al. 2018. "Tobacco Smoking and Alcohol Drinking at Diagnosis of Head and Neck Cancer and All-Cause Mortality: Results from Head and Neck 5000, a Prospective Observational Cohort of People with Head and Neck Cancer." *International Journal of Cancer. Journal International Du Cancer* 143 (5): 1114–27.
- Beyzadeoglu, Murat, Gokhan Ozyigit, and Ugur Selek, eds. 2015. *Radiation Therapy for Head and Neck Cancers: A Case-Based Review*. Springer, Cham.
- Brenner, David J. 2008. "The Linear-Quadratic Model Is an Appropriate Methodology for Determining Isoeffective Doses at Large Doses Per Fraction." *Seminars in Radiation Oncology*. <https://doi.org/10.1016/j.semradonc.2008.04.004>.
- Broder, Joshua, and Robert Preston. 2011. "Imaging the Head and Brain." *Diagnostic Imaging for the Emergency Physician*. <https://doi.org/10.1016/b978-1-4160-6113-7.10001-8>.
- Brown, Elizabeth, Rebecca Owen, Fiona Harden, Kerrie Mengersen, Kimberley Oestreich, Whitney Houghton, Michael Poulsen, Selina Harris, Charles Lin, and Sandro Porceddu. 2016. "Head and Neck Adaptive Radiotherapy: Predicting the Time to Replan." *Asia-Pacific Journal of Clinical Oncology* 12 (4): 460–67.
- Burnet, Neil G., Simon J. Thomas, Kate E. Burton, and Sarah J. Jeffries. 2004. "Defining the Tumour and Target Volumes for Radiotherapy." *Cancer Imaging: The Official Publication of the International Cancer Imaging Society* 4 (2): 153–61.

Bushberg. 2020. *Essn Physics Medical Imag 4e (int Ed)*. Lippincott Williams & Wilkins.

Cacicedo, Jon, Francisco Casquero, Lorea Martinez-Indart, Olga del Hoyo, Alfonso Gomez de Iturriaga, Arturo Navarro, and Pedro Bilbao. 2014. "A Prospective Analysis of Factors That Influence Weight Loss in Patients Undergoing Radiotherapy." *Chinese Journal of Cancer* 33 (4): 204–10.

Canadian Cancer Society - Radiotherapy. 2020. Canadian Cancer Society. Accessed July 27, 2020. <https://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/radiation-therapy/internal-radiation-therapy/?region=on>.

Canadian Nuclear Safety Commission (CNSC). 2020. "Radiation Doses." <Http://nuclearsafety.gc.ca/eng/resources/radiation/introduction-to-Radiation/radiation-Doses.cfm>. Accessed July 27, 2020.

Chen, Allen M., D. Gregory Farwell, Quang Luu, Paul J. Donald, Julian Perks, and James A. Purdy. 2011. "Evaluation of the Planning Target Volume in the Treatment of Head and Neck Cancer with Intensity-Modulated Radiotherapy: What Is the Appropriate Expansion Margin in the Setting of Daily Image Guidance?" *International Journal of Radiation Oncology, Biology, Physics* 81 (4): 943–49.

Chin, Richard, and Bruce Y. Lee. 2008. "Analysis of Data." *Principles and Practice of Clinical Trial Medicine*. <https://doi.org/10.1016/b978-0-12-373695-6.00015-6>.

Deschler, Daniel G., Michael G. Moore, and Richard V. Smith. 2014. "Quick Reference Guide to TNM Staging of Head and Neck Cancer and Neck Dissection Classification." *American Academy of Otolaryngology-Head and Neck Surgery Foundation, Alexandria, VA*.

Gensheimer, Michael F., and Quynh-Thu Le. 2018. "Adaptive Radiotherapy for Head and Neck Cancer: Are We Ready to Put It into Routine Clinical Practice?" *Oral Oncology* 86 (November): 19–24.

Ghadjar, Pirus, For the Swiss Group for Clinical Cancer Research (SAKK), Stefanie Hayoz, Frank Zimmermann, Stephan Bodis, David Kaul, Harun Badakhshi, et al. 2015. "Impact of Weight Loss on Survival after Chemoradiation for Locally Advanced Head and Neck Cancer: Secondary Results of a Randomized Phase III Trial (SAKK 10/94)." *Radiation Oncology*. <https://doi.org/10.1186/s13014-014-0319-y>.

Gomez-Millan, Jaime, Jesús Romero Fernández, and Jose Antonio Medina Carmona. 2013. "Current Status of IMRT in Head and Neck Cancer." *Reports of Practical Oncology and Radiotherapy : Journal of Greatpoland Cancer Center in Poznan and Polish Society of Radiation Oncology* 18 (6): 371–75.

Green, Olga L., Lauren E. Henke, and Geoffrey D. Hugo. 2019. "Practical Clinical Workflows for Online and Offline Adaptive Radiation Therapy." *Seminars in Radiation Oncology* 29 (3): 219–27.

Gregg, William. 2020. "Archiving, Chapter 9: Databases for Medical Image Archives." *Society for Imaging Informatics in Medicine*. 2020. https://siim.org/page/archiving_chapter9.

Grundmann, O., G. C. Mitchell, and K. H. Limesand. 2009. "Sensitivity of Salivary Glands to Radiation: From Animal Models to Therapies." *Journal of Dental Research* 88 (10): 894–903.

Guidi, G., N. Maffei, B. Meduri, E. D'Angelo, G. M. Mistretta, P. Ceroni, A. Ciarmatori, et al. 2016. "A Machine Learning Tool for Re-Planning and Adaptive RT: A Multicenter Cohort Investigation." *Physica Medica: PM: An International Journal Devoted to the Applications of Physics to Medicine and Biology: Official Journal of the Italian Association of Biomedical Physics* 32 (12): 1659–66.

Haddad, Robert I. 2010. *Multidisciplinary Management of Head and Neck Cancer*. Demos Medical Publishing.

Harris, Michael, and Gordon Taylor. 2003. *Medical Statistics Made Easy*. CRC Press.

Hart, A. 2001. "Mann-Whitney Test Is Not Just a Test of Medians: Differences in Spread Can Be Important." *BMJ*. <https://doi.org/10.1136/bmj.323.7309.391>.

Homer, J. J., and M. J. Fardy. 2016. "Surgery in Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines." *The Journal of Laryngology and Otology* 130 (S2): S68–70.

Hosmer, David W., Jr., Stanley Lemeshow, and Rodney X. Sturdivant. 2013. *Applied Logistic Regression*. John Wiley & Sons.

Hou, Wei-Hsien, Chun-Wei Wang, Chiao-Ling Tsai, Feng-Ming Hsu, and Jason Chia-Hsien Cheng. 2016. "The Ratio of Weight Loss to Planning Target Volume Significantly Impacts Setup Errors in Nasopharyngeal Cancer Patients Undergoing Helical Tomotherapy with Daily Megavoltage Computed Tomography." *Radiology and Oncology*. <https://doi.org/10.1515/raon-2016-0047>.

Iqbal, Muhammad Shahid, Cheng Chaw, Josef Kovarik, Shahzeena Aslam, Aaron Jackson, John Kelly, Werner Dobrowsky, and Charles Kelly. 2017. "Primary Concurrent Chemoradiation in Head and Neck Cancers with Weekly Cisplatin Chemotherapy: Analysis of Compliance, Toxicity and Survival." *International Archives of Otorhinolaryngology* 21 (2): 171–77.

James, Gareth, Daniela Witten, Trevor Hastie, and Robert Tibshirani. 2013. *An Introduction to Statistical Learning: With Applications in R*. Springer, New York, NY.

Jin, L., R. Wang, S. Jiang, J. Yue, T. Liu, X. Dou, K. Zhu, et al. 2015. "Dosimetric and Clinical Toxicity Comparison of Critical Organ Preservation with Three-Dimensional Conformal Radiotherapy, Intensity-Modulated Radiotherapy, and RapidArc for the Treatment of Locally Advanced Cancer of the Pancreatic Head." *Current Oncology*. <https://doi.org/10.3747/co.23.2771>.

Joseph, Ackeem, J. Seuntjens, C. Freeman, W. Parker, and J. Kildea. 2014. "An Analysis of the Effectiveness of Automated Pre-, Post-and Intratreatment Auditing of Electronic Health Records." *Department of Medical Physics and Radiation Oncology*.

<http://www.patientsafetyinstitute.ca/en/toolsResources/Research/studentships/Documents/2013-2014%20CPSI%20Studentships/Ackeem%20Joseph%20CPSI%20Final%20Report%202014.pdf>.

Kaliyaperumal, Venkatesan, C. Jomon Raphael, K. Mathew Varghese, Paul Gopu, S. Sivakumar, Minu Boban, N. Arunai Nambi Raj, K. Senthilnathan, and P. Ramesh Babu. 2017. "Study of Variation in Dose Calculation Accuracy Between kV Cone-Beam Computed Tomography and kV Fan-Beam Computed Tomography." *Journal of Medical Physics / Association of Medical Physicists of India* 42 (3): 171–80.

Kim, Sungheon Gene, Kent Friedman, Sohil Patel, and Mari Hagiwara. 2016. "Potential Role of PET/MRI for Imaging Metastatic Lymph Nodes in Head and Neck Cancer." *AJR. American Journal of Roentgenology* 207 (2): 248–56.

Kim, Tae Kyun. 2015. "T Test as a Parametric Statistic." *Korean Journal of Anesthesiology* 68 (6): 540.

Laan, Hans Paul van der, Hendrik P. Bijl, Roel J. H. M. Steenbakkens, Arjen van der Schaaf, Olga Chouvalova, Johanna G. M. Vemer-van den Hoek, Agata Gawryszuk, et al. 2015. "Acute Symptoms during the Course of Head and Neck Radiotherapy or Chemoradiation Are Strong Predictors of Late Dysphagia." *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology* 115 (1): 56–62.

Larsson, M., Hedelin, B. and Athlin, E. 2003. "Lived Experiences of Eating Problems for Patients with Head and Neck Cancer during Radiotherapy." *Journal of Clinical Nursing* 12 (4): 562–70.

Leer, J. W. H. 2005. "What the Clinician Wants to Know: Radiation Oncology Perspective: Monday 3 October 2005, 08: 45--10: 45." *Cancer Imaging: The Official Publication of the International Cancer Imaging Society* 5 (Spec No A): S1.

Leeuwen, C. M. van, A. L. Oei, J. Crezee, A. Bel, N. A. P. Franken, L. J. A. Stalpers, and H. P. Kok. 2018. "The Alfa and Beta of Tumours: A Review of Parameters of the Linear-Quadratic Model, Derived from Clinical Radiotherapy Studies." *Radiation Oncology* 13 (1): 96.

Little, J. B. 2003. "Principal Cellular and Tissue Effects of Radiation." *Holland-Frei Cancer Medicine*.

Loeffelbein, Denys J., Michael Souvatzoglou, Veronika Wankerl, Axel Martinez-Möller, Julia Dinges, Markus Schwaiger, and Ambros J. Beer. 2012. "PET-MRI Fusion in Head-and-Neck Oncology: Current Status and Implications for Hybrid PET/MRI." *Journal of Oral and Maxillofacial Surgery: Official Journal of the American Association of Oral and Maxillofacial Surgeons* 70 (2): 473–83.

Lønbro, Simon, Gry Bjerg Petersen, Jens Rikardt Andersen, and Jørgen Johansen. 2016. "Prediction of Critical Weight Loss during Radiation Treatment in Head and Neck Cancer Patients Is Dependent on BMI." *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer* 24 (5): 2101–9.

Loo, H., J. Fairfoul, A. Chakrabarti, J. C. Dean, R. J. Benson, S. J. Jefferies, and N. G. Burnet. 2011. "Tumour Shrinkage and Contour Change during Radiotherapy Increase the Dose to Organs at Risk but Not the Target Volumes for Head and Neck Cancer Patients Treated on the TomoTherapy HiArt™ System." *Clinical Oncology*. <https://doi.org/10.1016/j.clon.2010.09.003>.

Lustberg, Tim, Johan van Soest, Arthur Jochems, Timo Deist, Yvonka van Wijk, Sean Walsh, Philippe Lambin, and Andre Dekker. 2017. "Big Data in Radiation Therapy: Challenges and Opportunities." *The British Journal of Radiology* 90 (1069): 20160689.

Ma, L., W. Yao, S. Xu, F. Zhou, B. Liu, G. Ren, L. Feng, B. Qu, and C. Xie. 2014. "Replanning Criteria and Timing Definition for Parotid Protection-Based Adaptive Radiation Therapy in Nasopharyngeal Carcinoma." *International Journal of Radiation Oncology*Biophysics*. <https://doi.org/10.1016/j.ijrobp.2014.05.1597>.

McHugh, Mary L. 2013. "The Chi-Square Test of Independence." *Biochemia Medica: Casopis Hrvatskoga Drustva Medicinskih Biokemicara / HDMB* 23 (2): 143–49.

Medical Imaging & Technology Alliance, National Electrical Manufacturers Association. 2020. "DICOM Standard." Part 1: Introduction and Overview. National Electrical Manufacturers Association.

Moding, Everett J., Michael B. Kastan, and David G. Kirsch. 2013. "Strategies for Optimizing the Response of Cancer and Normal Tissues to Radiation." *Nature Reviews. Drug Discovery* 12 (7): 526–42.

Muzumder, Sandeep, Nirmala Srikantia, Avinash H. Udayashankar, Prashanth Bhat Kainthaje, and M. G. John Sebastian. 2019. "Burden of Acute Toxicities in Head-and-Neck Radiation Therapy: A Single-Institutional Experience." *South Asian Journal of Cancer* 8 (2): 120–23.

Nahm, Francis Sahngun. 2016. "Nonparametric Statistical Tests for the Continuous Data: The Basic Concept and the Practical Use." *Korean Journal of Anesthesiology* 69 (1): 8–14.

Niu, Tianye, and Lei Zhu. 2011. "Scatter Correction for Full-Fan Volumetric CT Using a Stationary Beam Blocker in a Single Full Scan." *Medical Physics* 38 (11): 6027–38.

OpenCV. 2020. "Contours in OpenCV." OpenCV. 2020. https://docs.opencv.org/trunk/d4/d73/tutorial_py_contours_begin.html.

Orton, Colin. 2020. "Fractionation: Radiobiological Principles and Clinical Practice." *Oncohemakey*. 2020. <https://oncohemakey.com/fractionation-radiobiological-principles-and-clinical-practice/>.

Ottosson, Sandra, Björn Zackrisson, Elisabeth Kjellén, Per Nilsson, and Göran Laurell. 2013. "Weight Loss in Patients with Head and Neck Cancer during and after Conventional and Accelerated Radiotherapy." *Acta Oncologica* 52 (4): 711–18.

Pajonk, Frank, Erina Vlashi, and William H. McBride. 2010. "Radiation Resistance of Cancer Stem

Cells: The 4 R's of Radiobiology Revisited. *Stem Cells* 28 (4): 639–48.

Peter, Jörg. 2009. "Medical Imaging Modalities — An Introduction." *Advanced Imaging in Biology and Medicine*. https://doi.org/10.1007/978-3-540-68993-5_10.

Schneider, U., E. Pedroni, and A. Lomax. 1996. "The Calibration of CT Hounsfield Units for Radiotherapy Treatment Planning." *Physics in Medicine and Biology* 41 (1): 111–24.

Schwartz, David L., and Lei Dong. 2010. "Adaptive Radiation Therapy for Head and Neck Cancer—Can an Old Goal Evolve into a New Standard?" *Journal of Oncology* 2011 (August). <https://doi.org/10.1155/2011/690595>.

Siegel, Rebecca L., Kimberly D. Miller, and Ahmedin Jemal. 2020. "Cancer Statistics, 2020." *CA: A Cancer Journal for Clinicians* 70 (1): 7–30.

Szumilas, Magdalena. 2010. "Explaining Odds Ratios." *Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Académie Canadienne de Psychiatrie de L'enfant et de L'adolescent* 19 (3): 227–29.

Teoh, M., C. H. Clark, K. Wood, S. Whitaker, and A. Nisbet. 2011. "Volumetric Modulated Arc Therapy: A Review of Current Literature and Clinical Use in Practice." *The British Journal of Radiology* 84 (1007): 967–96.

Toga, Arthur W., and John C. Mazziotta. 2002. *Brain Mapping: The Methods*. Academic Press.

Tohka, J. 2015. "Rigid-Body Registration." *Brain Mapping*. <https://doi.org/10.1016/b978-0-12-397025-1.00299-2>.

Vallard, Alexis, Jean-Baptiste Guy, Sylvie Mengue Ndong, Nicolas Vial, Romain Rivoirard, Pierre Auberdiac, Benoîte Méry, et al. 2016. "Intensity-Modulated Radiotherapy or Volumetric-Modulated Arc Therapy in Patients with Head and Neck Cancer: Focus on Salivary Glands Dosimetry." *Head & Neck*. <https://doi.org/10.1002/hed.24398>.

World Health Organization (WHO). 2016. "Ionizing Radiation, Health Effects and Protective Measures." *World Health Organization (WHO)*. April 29, 2016. <https://www.who.int/news-room/fact-sheets/detail/ionizing-radiation-health-effects-and-protective-measures>.

World Health Organization (WHO). 2019. "International Statistical Classification of Diseases and Related Health Problems 10th Revision." *ICD-10 Version:2019*. 2019. <https://icd.who.int/browse10/2019/en>.

Yeh, Shyh-An. 2010. "Radiotherapy for Head and Neck Cancer." *Seminars in Plastic Surgery* 24 (2): 127–36.

Zeng, Qi, Lu-Jun Shen, Xiang Guo, Xin-Ming Guo, Chao-Nan Qian, and Pei-Hong Wu. 2016.

“Critical Weight Loss Predicts Poor Prognosis in Nasopharyngeal Carcinoma.” BMC Cancer 16 (February): 169.

Zhao, Jin-Zhi, Hong Zheng, Li-Ya Li, Li-Yuan Zhang, Yue Zhao, and Nan Jiang. 2015. “Predictors for Weight Loss in Head and Neck Cancer Patients Undergoing Radiotherapy: A Systematic Review.” Cancer Nursing 38 (6): E37–45.

Zhao, Liang, Qiuyan Wan, Yongqiang Zhou, Xia Deng, Congyin Xie, and Shixiu Wu. 2011. “The Role of Replanning in Fractionated Intensity Modulated Radiotherapy for Nasopharyngeal Carcinoma.” Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology 98 (1): 23–27.