Software Development for Prospective and Retrospective Analysis of Lung Stereotactic Body Radiation Therapy Treatment Planning

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Abstract

Treatment planning in radiotherapy is one of the most important components of the radiotherapy workflow. Dosimetrists must evaluate treatment plans to ensure their conformity to standards and criteria established by protocols and to requirements set by the prescribing radiation oncologists. This evaluation of treatment plans involves a large number of quantitative metrics and qualitative assessments, as well as some subjectivity stemming from the training and experience of the treatment planner. With this in mind, standardizing treatment plan assessment with a tool that can guide the user through the process can be greatly beneficial for reducing the variation of the overall quality of treatment plans created and delivered in a radiation oncology clinic. In addition, a wealth of data is produced daily related to treatment planning but this information is often effectively wasted, as accessing these data is inefficient and time consuming. With a focus on lung SBRT plans, the aim of this project was therefore to develop a software tool for assisting dosimetrists in treatment plan evaluation as well as developing an infrastructure for retrospective data mining of plan data. This was achieved using the Eclipse™ Scripting API (Varian Medical Systems, Palo Alto, CA) platform for software development. The software tool is capable of performing functionalities such as the evaluation of OAR and target constraints, the evaluation of derived plan-specific metrics for lung SBRT and SRS plans, the comparison of structure DVH curves to those of benchmarked plans, the ability to look up DVH coordinates, the rating of plans using quantitative measures, the evaluation of biological metrics, the creation of plan reports and the data mining of historical treatment plan data. This tool offers great promise for optimizing the efficiency of treatment planning as well as increasing the confidence in the quality of treatments planned in a radiation oncology clinic.

Résumé

La planification de traitements en radiothérapie est l'une des étapes les plus importantes dans tout le processus de radio-oncologie. Afin de s'assurer de l'adéquation aux standards et critères prescrits par les différents protocoles et aux critères demandés par les radio-oncologues, les dosimétristes doivent évaluer leurs plans de traitements de manière rigoureuse. Cette évaluation englobe un grand nombre de mesures quantitatives et évaluations qualitatives, ainsi qu'une certaine quantité de subjectivité qui découle de la formation et de l'expérience du planificateur de traitements. Dans cette vague d'idée, standardiser le processus d'évaluation de plans de traitements avec un outil pouvant guider l'usager à travers le processus pourrait grandement bonifier la qualité des plans créés et administrés dans une clinique de radio-oncologie. De plus, malgré la richesse d'informations qui est produite quotidiennement lors de la planification des traitements, ces données sont rarement mises à profit dû au manque d'infrastructure permettant de les accéder de manière efficiente. Avec un accent mis sur les plans de traitements de SBRT du poumon, le but de ce projet était alors de développer un outil informatisé permettant de faciliter la tâche d'évaluation des plans de traitements par les dosimétristes et de concevoir une approche pour l'extraction des données des plans antérieurs. Ce but a été atteint par l'entremise de l'Eclipse™ Scripting API (Varian Medical Systems, Palo Alto, CA) à titre de plateforme de programmation. L'outil conçu comporte de nombreuses fonctionnalités telles que l'évaluation des contraintes liées aux structures cibles et aux organes à risque, l'évaluation de métriques propres aux plans de SBRT du poumon et de SRS, la comparaison des DVHs du plan à ceux de plans historiques, la possibilité d'extraire des coordonnées des graphiques de DVH, la cotation des plans de manière quantitative, l'évaluation d'indices biologiques, la création de rapports et l'extraction de données. En somme, cet outil est très prometteur en matière d'optimisation du processus de planification de traitements et d'augmentation du niveau de confiance en la qualité des traitements de radiothérapie planifiés dans une clinique de radio-oncologie.

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Contribution of authors

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List of abbreviations

AAA – Anisotropic analytical algorithm
AAPM – Association of Physicists in Medicine
API – Application programming interface
BED – Biological effective dose
CI – Conformity index
CPQR – Canadian Partnership for Quality Radiotherapy
CT – Computed tomography
CTCAE – Common Terminology Criteria for Adverse Events
CW – Chest wall
DDI – Dose distribution index
DVH – Dose volume histogram
Dmax – Maximum point dose
Dmean – Mean dose
Dmedian – Median dose
Dstdev – Dose standard deviation
DX – Dose at volume of X
EBRT – External beam radiation therapy
FSU – Functional subunit
HDR – High dose rate
HI – Homogeneity index
ESAPI – Eclipse scripting application programming interface
GTV – Gross tumour volume
GUI – Graphical user interface
ICRU - International Commission on Radiation Units & Measurements
IDE – Integrated development environment
IORT – Intraoperative radiotherapy
ITV – Internal target volume
IMRT – Intensity modulated radiotherapy
LINAC – Linear accelerator
LDR – Low dose rate
MDPD - Maximum dose to prescription dose ratio
MDR – Medium dose rate
MLC – Multileaf collimator
MRI – Magnetic resonance imaging
OAR – Organ at risk
OER – Oxygen enhancement ratio
PDD – Percent depth dose

PET – Positron emission tomography
PITV – Prescription isodose to target volume
PQI – Practice quality improvement
PTV – Planning target volume
RT – Radiation therapy
RVR – Remaining volume at risk
SBRT – Stereotactic body radiotherapy
SRS – Stereotactic radiosurgery
TBI – Total body irradiation
TERMA – Total energy released per unit mass
TG – Task group
TPS – Treatment planning system
TQC – Technical Quality Control
TSEI – Total skin electron irradiation
LINAC – Linear accelerator
QUANTEC – Quantitative Analysis of Normal Tissue Effects
RBE – Relative biological effectiveness
VY – Volume at dose of Y

1. Introduction

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1.1. Cancer

Worldwide, the cancer burden continues to increase with an estimated 14 million new cases in 2012 and a projected number of new cases annually of 21.5 million by 2030[1]. While in Canada cancer is currently the leading cause of death, it is estimated that over the course of this century, this will also be the case on a global scale[2,3]. In fact, it is expected that of the one in two Canadians that will develop cancer in their lifetime, approximately half will die from their cancer[2].

Cancer is defined as the abnormal growth of cells within the body. This uncontrolled cell division can lead to the development of masses that can affect almost any anatomical site. The most common types of cancer reported in Canada are lung, colorectal, breast and prostate cancer[2]. Cancer development is a stochastic process, which encompasses a wide variety of risk factors. Although the exact reason why a given individual may develop cancer is most often unknown, contributing factors may include environmental exposure to various substances (environmental pollutants, radiation or infectious diseases), hereditary and genetic factors, or lifestyle-related factors (sedentary lifestyle, smoking habits, unhealthy diet, etc.)[4].

Amongst other modalities such as surgery, chemotherapy and immunotherapy, radiation therapy, also called radiotherapy, radiation oncology or therapeutic radiology, is an important part of the therapeutic regimen for cancer treatment. In fact, 50% of cancer patients will undergo some form of radiotherapy over the course their prescribed treatment[5,6].

1.2. Radiotherapy

Radiotherapy is defined as the therapeutic use of ionizing radiation. This ionizing radiation interacts with cells within the body by depositing energy potentially resulting in cell death[5]. Radiotherapy can be subdivided into two main categories: external beam radiation therapy (EBRT) and brachytherapy. In EBRT, the source of radiation is produced externally from the patient in the form of beams of photons, protons or

electrons, whereas in brachytherapy the ionizing radiation is emitted from radiation sources that are placed in or on the target volume[7]. Photon EBRT is the most commonly used form of radiotherapy, and typically involves the use of high-energy x-rays that are generally produced by linear accelerators (LINACs).

1.3. Radiotherapy Workflow

Regardless of the type of radiation therapy employed, the radiation oncology treatment workflow typically comprises: *1. The decision to treat*, *2. Radiotherapy simulation*, *3. Treatment planning*, *4. Quality assurance* and *5. Treatment planning and delivery techniques*[8]. The whole process is summarized in Figure 1.1, and further detailed descriptions of each step will follow.

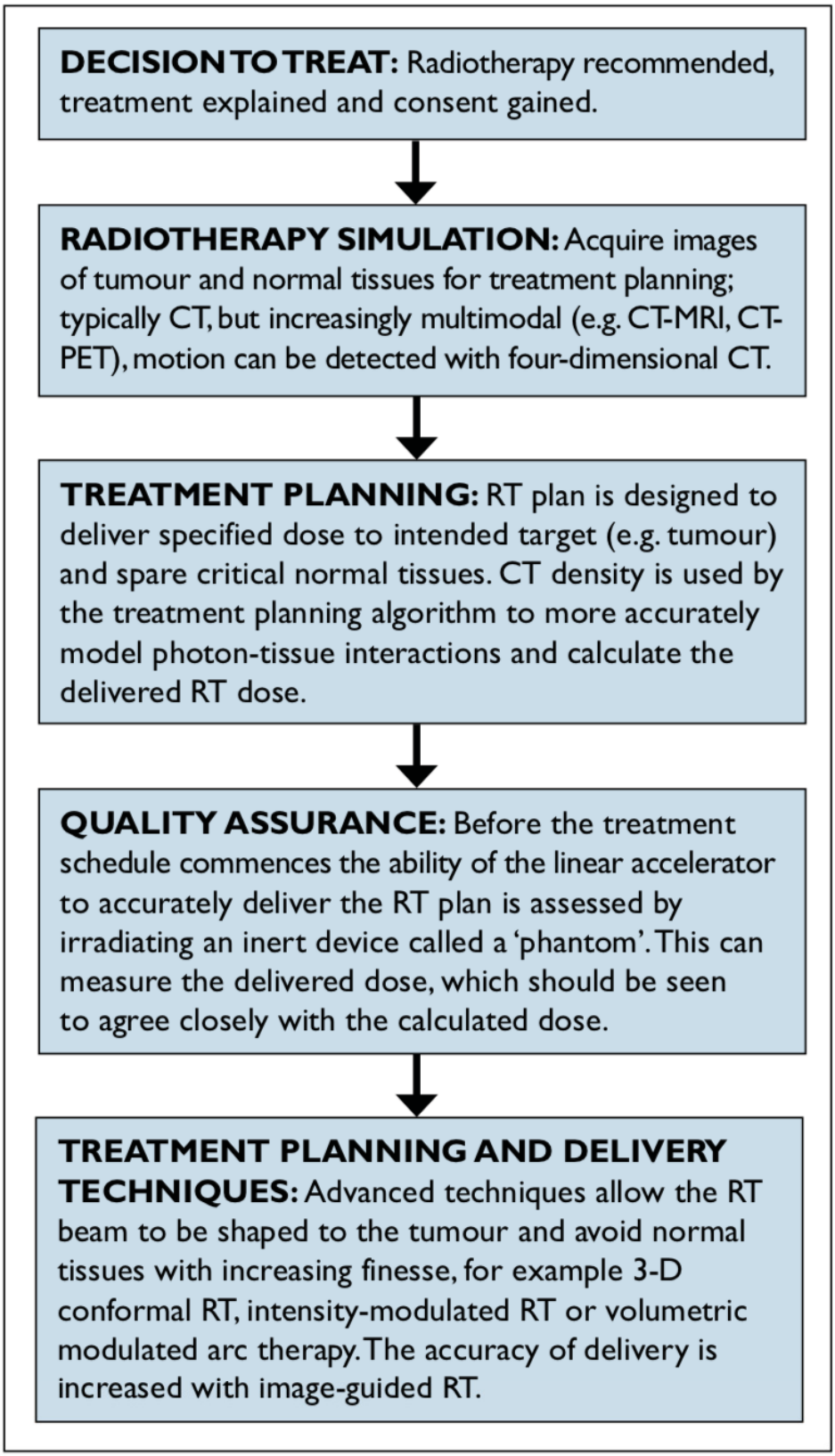

Figure 1.1 Typical radiation therapy treatment workflow. Figure taken from Dahele, 2010[8]

1.3.1. Decision to Treat

The first step of the radiotherapy process after assessing a patient is the decision to treat during which the physician, along with the patient, decides on radiotherapy as the sole treatment modality or as a component of a more complex multi-strategy treatment. Radiation can be prescribed with a curative intent to eliminate the malignancy or in a palliative context to relieve specific symptoms[5]. The decision to use radiation as a treatment option is typically evidence-based and may depend on the cancer type, tumour staging, tumour size and location, health-related aspects of the patient, patient consent, etc.[9,10]

1.3.2. Radiotherapy simulation

Once the radiation treatment has been prescribed, the radiotherapy simulation is performed. Radiotherapy simulation is characterized by the acquisition of 3D anatomical patient data prior to planning the treatment. The gold standard imaging modality currently used for the acquisition of these data is computed tomography (CT), but magnetic resonance imaging (MRI) as well as positron emitting tomography (PET) in combination with CT may also be used. Computed tomography is a highly useful modality, as it allows excellent anatomic and geometric accuracy, and can provide the electron density of the anatomy of use in dose calculations. In fact, the electron density map is an essential element for dose calculations as the delivered dose depends on the type and extent of interaction between the radiation beam and the tissue leading to the energy deposition. These interactions, mainly Compton events, have a probability of occurring that is proportional to the electron density. Electron density can be directly determined from the Hounsfield units provided by the voxels composing a computed tomography acquisition[11]. During the acquisition of the images, the patient must be positioned in the exact treatment position in order to ensure spatial accuracy of the treatment plan. In many cases, patient immobilization is required and is achieved using various external devices and tattoo markers on the skin[12].

1.3.3. Treatment Planning

Treatment planning is the process by which the design of dose delivery is devised. Overall, the main goal of treatment planning is to precisely quantify the dose to the tumour to maximize treatment outcomes while minimizing dose to surrounding organs, or in other words, finding the optimal balance between high tumour control and low normal tissue toxicity[7,13].

Treatment planning in external beam radiotherapy involves many steps that ultimately lead to plan generation and the final transfer of the plan data to the treatment machine[13]. Treatment planning in EBRT requires the determination of the parameters that are necessary to carry out the treatment. These parameters include, amongst others, the target volume, the dose-limiting structures, the treatment volume, the dose prescription, the dose fractionation, the dose distribution, the positioning of the patient, the treatment machine settings, and adjuvant therapies if applicable[7].

For every tentative plan that is generated, treatment plan evaluation is required before it is approved and sent to the treatment machine. This includes verification of the dose distribution in and around the target volume as well as ensuring the fulfillment of different dose constraints. Dosimetrists using specialized treatment planning systems generally carry out the determination of these parameters. A description of these criteria and relevant theory will be presented in *Chapter 2*.

1.3.4. Quality assurance

Quality assurance prior to treatment is important with regards to ensuring that the treatment that has been planned is acceptable and can be correctly delivered. Essentially every step of the radiotherapy chain requires quality control and quality assurance checkpoints. In general, quality assurance in radiotherapy revolves around ensuring that the performance of all of the radiotherapy processes and equipment meet the standard criteria within a certain margin[14]. These standards are generally prescribed by different protocols, such as the Canadian Partnership for Quality Radiotherapy (CPQR) Technical Quality Control (TQC) guidelines or the American Association of Physicists in Medicine

(AAPM) Task Group (TG) reports. In AAPM's report No. 13 – *Physical Aspects of Quality Assurance in Radiation Therapy*, quality assurance is described as "those procedures that ensure a consistent and safe fulfillment of the dose prescription to the target volume, with minimal dose to normal tissues and minimal exposure to personnel"[15]. The four main goals of quality assurance are to reduce the magnitude of uncertainties and errors, reduce the likelihood of errors or accidents, allow a reliable intercomparison between radiotherapy centres and allow improved and more complex treatments[13].

1.3.5. Treatment Planning and Delivery Techniques

After the planning process is completed and the quality of the involved equipment is ensured, the patient is ready to be treated. The patient is first carefully positioned as per during the treatment simulation. Various delivery techniques exist both in brachytherapy and in external beam radiotherapy.

In brachytherapy, the treatment techniques can be classified with respect to the type of implants, the duration of the treatment or the dose rate. In terms of the types of implants, intracavitary implants are those who are placed in cavities of the body in close proximity to the target, interstitial implants are surgically placed within the target, surface implants are placed over the treated area, intraluminal implants are positioned within a lumen, intraoperative implants require surgical positioning within the target during open surgery and intravascular implants are placed within arteries. In terms of treatment duration, an implant can be placed temporarily, for which the implant must be removed after a predetermined time, or permanently, for which the source will remain in place until complete decay. Low dose rate (LDR) brachytherapy ranges between 0.4-2 Gy/h at the dose specification points, medium dose rate (MDR) brachytherapy delivers dose at 2-12 Gy/h and high dose rate (HDR) brachytherapy uses dose rates higher than 12 Gy/h[13].

In EBRT, in addition to conventional radiotherapy techniques whereby 2D planning is used to deliver a single beam of radiation from several directions, more complex techniques exist, such as stereotactic irradiation, total body irradiation (TBI), total skin

electron irradiation (TSEI), intraoperative radiotherapy (IORT), endorectal irradiation, conformal radiotherapy and intensity modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and respiratory gated radiotherapy[13]. Stereotactic radiation is a technique that delivers of high doses of radiation in a small number of fractions by multiple co-planar and non-coplanar beams guided by a set of coordinates. Stereotactic radiation will be further described in *Section 1.5*. TBI involves very large fields of photons or electrons that deliver a uniform whole body dose. TSEI aims to irradiate superficially the entire skin surface of the patient. IORT delivers a radiation dose during a surgical procedure directly to an internal organ, tumour or tumour bed. IMRT is a technique for which the beam intensity is modulated three dimensionally to achieve high dose conformality. IGRT involves the use of imaging prior to or during each treatment fraction, which allows verification of positioning with regards to the treatment plan. Respiratory-gated radiotherapy encompasses techniques for gating the radiation beam synchronously with respiration to allow tighter treatment plan margins[13].

1.4. Radiation therapy health care professionals

Given its complex and multi-stepped nature, many specialized healthcare professionals must be involved in the radiotherapy workflow. Radiation oncologists are physicians who are responsible for the radiotherapy treatment from prescription to follow-up. Medical physicists are scientists that participate in many aspects of the radiotherapy process to ensure safe and accurate delivery of the treatment. Radiation therapists are technologists that are directly involved with the patient at the time of the treatment and carry out treatment simulation, positioning and patient monitoring. Dosimetrists are another sub-group of radiation oncology technologists that are trained to develop personalized treatment plans for each patient. Other professionals involved may include radiation oncology nurses, nutritionists, social workers and others[16].

1.5.Stereotactic Body Radiotherapy

1.5.1. SBRT treatment technique

Stereotactic body radiation therapy (SBRT) is a treatment technique that delivers highly conformal, high dose radiation with a hypofractionated scheme, typically >10 Gy per fraction in less than 5 fractions, which is drastically different to conventionally fractionated radiation therapy that employs daily doses of 1.8-3 Gy per fraction delivered over several weeks[7]. SBRT is achieved by the use of multiple megavoltage beams arranged in rotational and/or static fields. In SBRT, the target is extracranial, contrary to stereotactic radiosurgery (SRS) which relates to the same treatment technique but is a term typically reserved for when the targets are within the brain[17]. SBRT offers a higher cell kill potential when compared to conventional techniques due to the high biological effective doses (BED) it involves (BED >100)[18]. BEDs will be further discussed in *Section 2.6.1.1*.

1.5.2. Treatment planning & plan evaluation in SBRT

Specialized treatment planning is used in SBRT, which results in high dose fall-off beyond the target and very high ablative doses to the target. In order to ensure the safe delivery of this sort of treatment plan, a high level of accuracy in positioning and localisation of anatomy is of utter importance for high targeting accuracy and minimal normal tissue toxicity. In addition to image guidance prior to treatment, frame-based stereotaxy fiducials may be used, which are apposed to non-deformable objects and registered to the target. The patient is therefore carefully positioned according to the stereotactic coordinate system[7].

1.5.3. SBRT for lung cancer

Lung cancer, and in particular non-small-cell lung cancer (NSCLC), is the leading cause of cancer death, with only a 15% 5-year survival rate amongst all NSCLC patients[19]. The standard of care for early stage NSCLC is surgical resection, leading to reasonably high survival rates of 50% to 70%[20]. However, when patients are deemed inoperable, radiotherapy is the next option, which historically was performed using

conventional techniques even though treatment results were inferior to surgical procedures. More recently, SBRT has emerged as an excellent alternative to surgical resection for patients with early stage NSCLC or oligometastatic lesions to the lung, and is increasingly used. The outcomes of the treatment have been found to offer good local control and improved overall survival[20,21].

Standardized treatment regimens for lung SBRT are described in phase II study protocols; RTOG 0236[22] for treatments of 60 Gy in 3 fractions, RTOG 0813[23] for 50 Gy in 5 fractions, and RTOG 0915[20] for 34 Gy in 1 fraction and 48 Gy in 4 fractions. These protocols and their results serve as the basis for treatment and guidance for lung SBRT in our clinic, the Department of Radiation Oncology at the Cedars Cancer Centre of the McGill University Health Centre (MUHC), and across North America in general.

1.6. Thesis objective

1.6.1. Thesis purpose

Radiation therapy treatment planning requires balancing maximal tumour control and minimal normal tissue toxicity in order to ensure optimal outcomes. This, however, can be a challenging task when assessing a plan during the treatment planning process. Many plan evaluation metrics and dose constraints are established by various protocols, but their implementation in the clinical routine can be overwhelming and time-consuming. In addition, with the advent of novel, more complex treatment techniques for EBRT that offer more conformal dose distributions and sharp dose gradients, it is even more so important to have a high level of confidence in the plan quality. With these techniques being increasingly used in the clinic, there is a need for treatment plan evaluation tools to alleviate the workload of medical physicists and dosimetrists. In addition, retrospectively evaluating different plan parameters is an important aspect in analyzing treatment outcomes, which facilitates studies that often become the basis of treatment planning constraints and guidelines.

The purpose of this project can be stated in two different but complementary parts. Firstly, the goal is to develop a user-friendly software tool for dosimetrists that aims to facilitate plan evaluation during the treatment planning process, and secondly, to create a framework for data mining of treatment plans that can quickly provide dosimetric parameters of past plans. In order to limit the scope of this project, these tools will focus on their application for lung SBRT treatment plans, but their use may also be expanded for all types of plans.

1.6.2. Thesis outline

This thesis is divided into six main chapters. Following the introduction in *Chapter 1*, *Chapter 2* reviews the theoretical concepts of treatment planning and treatment plan assessment in external beam radiotherapy. *Chapter 3* describes the methods and materials used to achieve the thesis goals described above. *Chapter 4* presents the main results and presents the current versions of the software tools that were developed in the context of this project. Finally, discussion, conclusions and future recommendations are discussed in *Chapter 5*. A manuscript to be submitted for peer review that resulted from a study performed using the software developed in this project is presented in the Appendix.

1.7. References

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Regardless of the radiotherapy type or delivery technique used, treatment planning prior to treatment delivery is required and represents a major part of the entire radiation treatment workflow. The following chapter will outline important theoretical concepts surrounding treatment planning and treatment plan evaluation of external photon beam radiation therapy. The majority of the information that follows is detailed within Report No.50[1], and its supplements Report No.62[2] and Report No.83[3], from the International Commission on Radiation Units & Measurements (ICRU), which provide widely accepted guidelines for *Prescribing, Recording, and Reporting Photon Beam Therapy*[1–3]. The concepts selected to be presented in this chapter form the basis of many of the functionalities that are incorporated into the software tools developed in the context of this thesis project.

2.1. Volume definitions

ICRU Reports 50, 62 and 83 define two main categories of volumes used for radiotherapy treatment planning: target volumes and organs at risk (OAR). These volumes, or a subset of these volumes, are contoured on the patient's simulation images and serve as structures for dose calculations. In addition, these 3D structures provide a basis for evaluating treatment outcomes. A schematic representation of these volumes is shown in Figure 2.1.

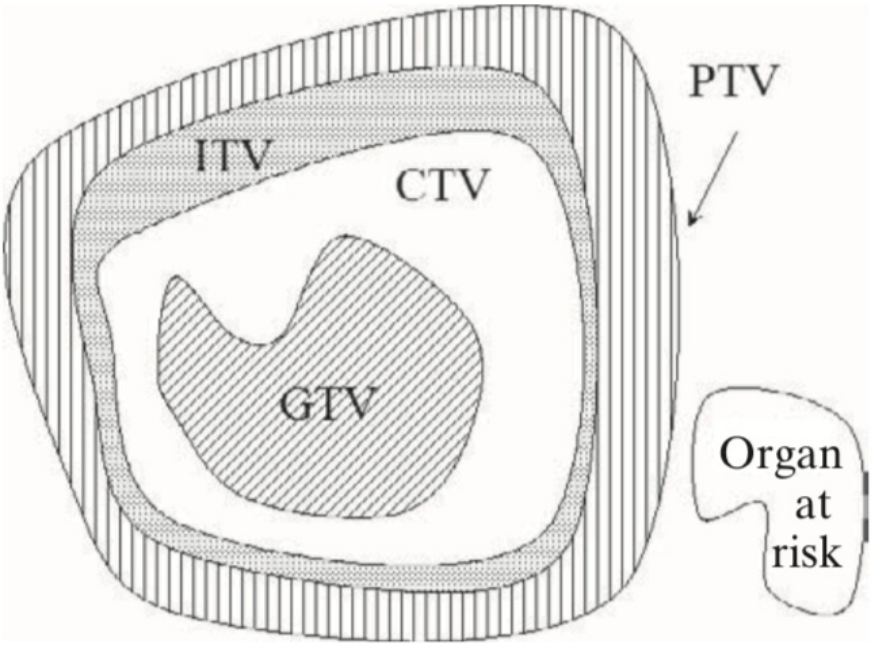


Figure 2.1 - Schematic of target volumes (GTV, CTV, ITV & PTV) and an organ at risk. Figure taken from Podgoršak, 2010[4].

2.1.1. Gross tumour volume (GTV)

Four main target volumes are defined and routinely used in treatment planning. The smallest of the group is the gross tumour volume (GTV), which is defined as the "gross palpable or visible/demonstrable extent and location of malignant growth"[1]. In other words, it is the extent of the tumour that can be seen or palpated through imaging or physical examination. It is generally the area of the tumour with the highest cellular density[2].

2.1.2. Clinical target volume – CTV

Including the GTV, the clinical target volume (CTV) is "a tissue volume that contains a demonstrable GTV and/or subclinical malignant disease that must be eliminated"[1]. The CTV is therefore composed of the GTV with an added surrounding area where microscopic or subclinical disease is estimated to be present. CTV volume can also be at a distance from the GTV, for example if lymph node involvement is suspected. The extent of this added region is based on clinical experience for which the treatments and

follow-up evaluations were closely studied[2]. The CTV may also exist without any GTV, for example in cases where the tumour has been resected.

2.1.3. Internal target volume (ITV)

The internal target volume (ITV), also called the internal margin, is an added margin to the CTV "to compensate for expected physiologic movements and variations in size, shape, and position of the CTV during therapy in relation to an Internal Reference Point and its corresponding Coordinate System"[2]. The internal movements of the target can be related to breathing movement, heart beat, swallowing, bladder or rectum fillings, gas or bowel movements, some of which can be controlled whereas others are unavoidable[2].

2.1.4. Planning target volume (PTV)

The planning target volume (PTV) encompasses the internal target volume with an added setup margin. "The planning target volume (PTV) is a geometrical concept, and it is defined to select appropriate beam arrangements, taking into consideration the net effect of all possible geometrical variations, in order to ensure that the prescribed dose is actually absorbed in the CTV".[1] The setup margin accounts for intrafractional and interfractional errors or uncertainties in patient or beam positioning. These uncertainties may be related to patient movement, mechanical uncertainties of the equipment, dosimetric uncertainties, setup errors between simulator and treatment unit or other human-related factors.

2.1.1. Organs at risk (OAR)

Organs at risk (OAR) are anatomical structures that are within or near the irradiated area, and that can be at risk of radiation toxicity[1]. With this in mind, care must be taken to limit the dose delivered in these regions below their tolerances. The tolerance of an OAR depends largely on the functional arrangement of the organ (serial or parallel). Parallel organs (e.g. lung, liver, kidney, etc.) are those for which the functional subunits (FSU), defined as the functional compartments of an organ, work independently. The effect of the radiation will therefore depend on the total dose distribution within the organ. As for serial organs (e.g. spinal cord) the FSUs of the structure are interdependent and damage

to a single component can result in loss of function, meaning that the radiation toxicity is a function of local doses[5]. ICRU Report 50 defines three classes of OARs: Class I, Class II and Class III organs. The first class includes organs for which radiation lesions cause mortality or severe morbidity; Class II organs are those whose radiation lesions result in more moderate to mild morbidity; and the third class comprises those organs for which radiation lesions are mild, transient, and reversible, or result in no notable morbidity[1].

Emami et al.[6] in 1991 were amongst the first to publish normal tissue tolerances, which revolutionized practice and remained throughout the years a widely accepted reference for irradiation tolerances to various organs. The original methods by which these normal tissue tolerances were provided were TD5/5, the 5% risk of a particular outcome at 5 years, and TD50/5, the dose leading to a 50% complication rate at 5 years. Following this paper, many dose-response studies were published, typically based on retrospective analyses. Amongst these papers, the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)[7,8] publications gather a collection of constraints for organs at risk, and act as a follow-up to the data published by Emami *et al.*

2.1.1. Remaining volume at risk (RVR)

The remaining volume at risk (RVR) is defined as the "the imaged volume within the patient, excluding any delineated OAR and the CTVs."[3] It can therefore be described as the difference between the volume of the external contour of the patient and that of the contoured CTV and OAR structures[3].

2.2. Dose-fractionation prescription

The radiotherapy prescription in terms of total dose, fractionation and radiation beam choice depends on a series of variables, such as medical patient-related and physician-related factors, availability of equipment, physical parameters of the treatment beams, and biological factors. A summary of these different variables and their description is presented in Table 2.1. The radiation oncologist must take into consideration all of these factors when deciding on a treatment prescription.

Table 2.1 - Factors influencing the choice of radiation beam and dose prescription in treatment of disease with radiation. Table based on Podgorsak, 2010[9].

Factors	Description
Medical patient-related and physician-related factors	▪ Tumour type and histology ▪ Tumour location in the patient ▪ Location of sensitive structures and healthy tissues in the vicinity of the target ▪ Patient's tolerance of treatment ▪ Any previous radiation treatment ▪ Physician's training and experience
Availability of equipment for diagnostic imaging and dose delivery	
Physical parameters of the radiation beam to be used in treatment	▪ Depth dose characteristics, governed by machine design, beam energy, field size, and other machine parameters ▪ Density of ionization produced in tissue by the radiation beam to be used in treatment
Biological factors produced in tissue by the radiation beam	▪ Relative biological effectiveness (RBE) ▪ Oxygen enhancement ratio (OER)

According to ICRU reports 50 and 62, in conformal radiotherapy, the dose should be prescribed to the *ICRU Reference Point*, which is typically near or at the centre of the PTV, and if possible, at the intersection of the beam axes. The dose at this reference point is referred to as the *ICRU Reference Dose*. When reporting dose, the minimum and maximum dose, along with the *ICRU Reference Dose*, are required to provide a statement regarding the homogeneity of the irradiation[1,2,10].

2.2.1. Fractionation in conventional radiotherapy

In conventional radiotherapy treatments, a total dose of 40-60 Gy is typically prescribed to the target in 1.8 to 3 Gy per fraction over 20 to 30 fractions delivered 5 days a week over the course of several weeks. This way of fractionating treatments allows for differential sparing of normal tissue compared to tumour. This is achieved through a set of four processes known as the four R's of radiotherapy: Repair, Re-oxygenation, Repopulation and Redistribution. Repair refers to that of the sublethal damage to the cells DNA, which increases the survival of normal tissue cells and reduces normal tissue complications. Re-oxygenation of hypoxic cells within the tumour volume between treatment fractions may allow for improved cell kill via the oxygen enhancement effect. Repopulation of normal cells over the course of the treatment regimen means damaged normal cells can repopulate to minimize toxicity of the treatment. Redistribution of cells within the cell cycle may allow tumour cells who are in a more radioresistant phase at a given fraction delivery to transition into a more radiosensitive phase at the time of a subsequent fraction, therefore improving tumour control[11].

2.2.2. Fractionation in stereotactic radiotherapy

As for radio-surgical treatments such as SBRT, the number of fractions is greatly reduced and employs doses as high as 60 Gy in no more than five fractions[12]. The delivery of these high ablative doses in a small number of fractions is possible due to technological advances and the use of a large number of intersecting beams that allow greater conformality therefore minimizing dose to immediate surrounding normal tissues. This makes it possible to practically ignore the classic fractionation paradigm of conventional radiotherapy[13].

2.3. Computerized treatment planning systems (TPS)

In modern radiotherapy, it is difficult to imagine treatment planning without a computerized treatment planning system (TPS) to facilitate the process. A TPS is designed to generate beam shapes and dose distribution in a way that allows optimal

clinical outcomes by sparing OARs while simultaneously achieving target coverage. The software generally includes features for inputting patient data, contouring structures on the patient images, performing dose calculations and allowing treatment plan evaluation. The most important feature of a TPS is the dose calculation algorithm used to correctly model the dose distribution within the patient[4].

2.4. Dose calculation algorithms

Dose calculation algorithms are rapidly evolving due to the constant increase in computer capabilities. Generally speaking, three different dose calculation algorithms exist: correction-based, model-based and Monte Carlo-based algorithms[14,15].

2.4.1. Correction-based techniques

In correction-based algorithms, the dose is determined by applying corrections such as heterogeneity corrections and irregular surface corrections to beam data (percent depth dose (PDD) curves, beam profiles, etc.) that were previously acquired in a homogeneous and flat surface water phantom[4].

2.4.2. Model-based techniques

Model-based techniques, including convolution/superposition algorithms, are used extensively in commercial TPSs. In fact, Eclipse™ (Varian Medical Systems, Palo Alto, CA), the most frequently-used treatment planning system used in our clinic, uses a pencil beam convolution technique called the AAA (anisotropic analytical algorithm). These techniques attempt to simulate dose deposition by representing (1) the total energy released per unit mass (TERMA) in the medium from primary photon interactions and (2) the kernel, which is the energy deposited about a primary photon interaction site[16].

2.4.3. Monte Carlo techniques

Monte Carlo is a stochastic technique where a large number of primary particles are followed to simulate photon transport as well as the transport and energy deposition of electrons generated by photon interactions. Using this method, the random path of

ionizing radiation through a known geometry can be simulated in such a way that it is possible to accurately predict the spatial dose deposition distribution within a patient[12,17]. This dose calculation method is widely considered as the most accurate, but is also the most computationally expensive[16].

2.5. Treatment plan evaluation

Following dose calculation, every treatment plan must be assessed to ensure that it complies with the standards and criteria defined by applicable protocols or specified by the radiation oncologist. The evaluation of the planned dose distribution is qualitative (e.g. isodose distribution inspection) and quantitative (e.g. DVH curves, dose statistics, dose indices, etc.). The tools used for the assessment of treatment plans are described below.

2.5.1. Dose-volume histograms

Dose-volume histograms (DVH) are bi-dimensional graphical representations of the tri-dimensional dose distribution of specific structures in a treatment plan. A DVH represents the relationship between the dose and the volume of an anatomical region. Although the dose-volume histogram is a powerful tool for treatment plan evaluation, its major limitation is that it fails to provide any spatial information, making it impossible for it to be the sole basis of plan evaluation. Two different types of DVH representations exist: differential DVHs and cumulative DVHs. Both types of DVHs can have axes in absolute (Gy for dose and cm^3 for volume) or relative (% of prescription dose or % of structure volume) terms[4,18].

2.5.1.1. Differential

A differential DVH is consistent with the classic mathematical definition of a histogram, where the frequency in terms of voxels on the Y-axis is plotted for each dose bin on the X-axis. The differential form of the DVH indicates the extent of variation of the dose within a structure. Any point on the differential DVH represents the volume of structure that receives a dose within an interval (dose bin). Figure 2.2 depicts typical

differential DVH curves for (a) target volumes where a single peak is centred around the prescription dose and for (b) OAR structures where multiple peaks may exist[4,18].

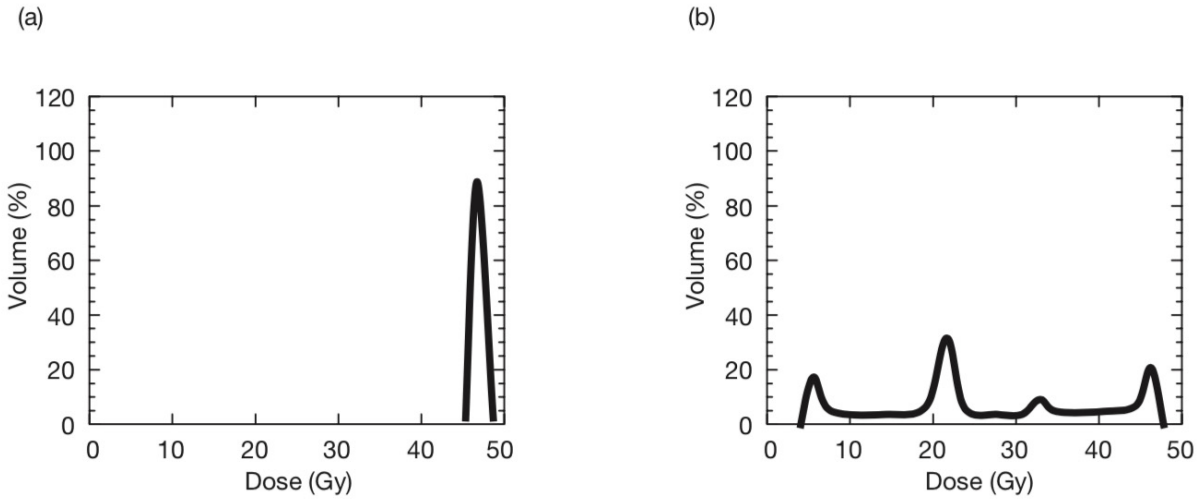


Figure 2.2 – Examples of differential dose volume histograms for (a) a target volume and (b) an OAR. Figure taken from Podgoršak, 2005[4].

2.5.1.2. Cumulative

Cumulative (or integral) DVHs are the most commonly used in treatment planning as they offer a more intuitive way of evaluating the dose distribution[†]. In a cumulative DVH the data is represented as the volume, on the Y-axis, receiving a dose greater than or equal to the dose on the X-axis[4,18]. In other words, each point on this type of DVH indicates the volume that receives the specified dose or higher and can therefore be expressed by:

$$DVH_{cum}(D) = 1 - \frac{1}{V}\int_0^{D_{max}} \frac{dV(D)}{dD} dD \quad (1)$$

Figure 2.3 shows both target volume and OAR structure examples of cumulative DVHs for (a) a realistic example and for (b) a theoretical ideal situation.

[†] For simplicity, every future mention of DVH curves in this thesis refers to that of cumulative DVHs.

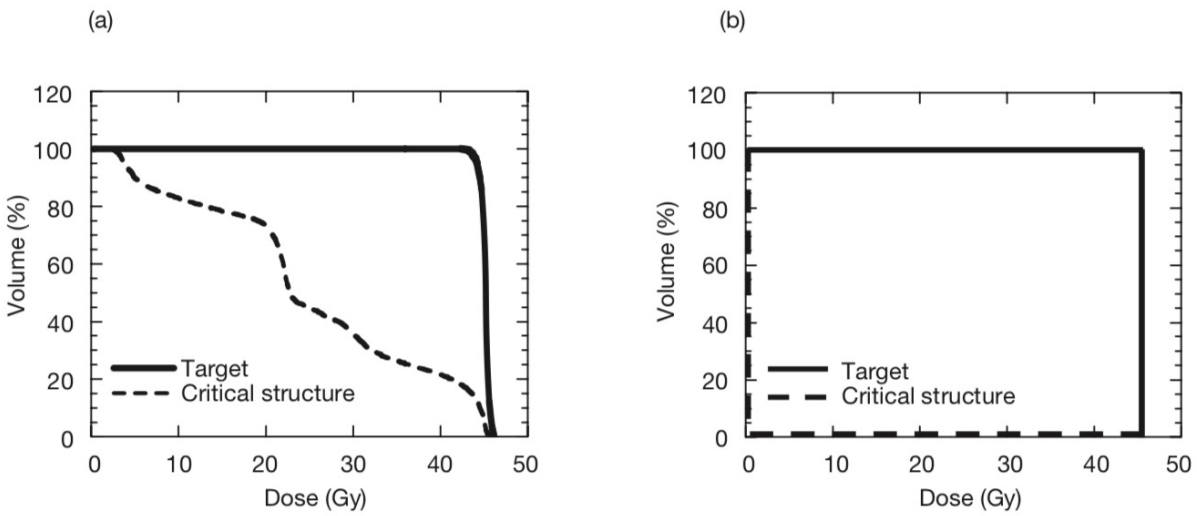


Figure 2.3 - Examples of cumulative DVHs for target and OAR structures where (a) is a realistic representation and (b) is an ideal representation. Figure taken from Podgoršak, 2005[4].

2.5.2. Dose specifications

Quantitative dose-volume values are often used in treatment planning for dose reporting or in plan assessment to verify conformity to dose-volume constraints or prescription indications. In fact, for simplicity, it is often desirable to characterize the dose effect in relevant organs by using a single dose value rather than the complex dose distribution[19]. These include dose statistics (e.g. minimum dose, maximum dose, mean dose, etc.) and dose-volume indices related to points on the DVH curve[20].

2.5.2.1. Dose statistics

The most commonly used dose statistics to evaluate the dose distribution in a structure are the maximum dose, the minimum dose, the mean dose, the median dose and the standard deviation. Unlike DVH curves, these descriptive statistics have the advantage of simplifying the comparison of multidimensional dose distributions through single-valued measurements. However, similarly to the DVH curves, the dose statistics have the same drawback of not providing any spatial information regarding the dose distribution[20].

2.5.2.2. Dose at volume / Volume at dose

The dose delivered to at least X volume (DX% or DXcm3), expressed in Gy or % of the prescription dose, and the volume receiving at least Y dose (VY% or VYGy), expressed in cm^3 or % of the structure volume, are coordinates from the cumulative DVH curve. They are used to express the extent of the radiation dose to a given structure. For example, it is often desirable to report the dose received by at least 95% of the volume (D95%) or the volume irradiated to at least 95% of the prescribed dose (V95%) of the PTV to ensure that the target coverage is adequate.

2.5.3. Isodose distributions

Visual inspection of the dose distribution is typically the first thing performed when evaluating a treatment plan. Although this method is non-quantifiable, visual assessment can allow a treatment planner to quickly identify flaws within a treatment plan. For this purpose, isodose distributions can be visualized on the TPS in order to qualitatively evaluate a treatment plan. Isodose curves are lines representing a perimeter along which the dose is of equal value[20]. For example, Figure 2.4 shows a lung SBRT plan with isodose lines of 30%, 80%, 90%, 100% and 110% (100% being the prescription dose) in the axial view of the thorax. Another useful way to visualize these distributions is with the dose colour wash option available in the Eclipse™ TPS as shown in Figure 2.5. This option is regularly used by dosimetrists. The color wash option displays a color gradient between the isodoses specified on the scale shown on the top-left side of the figure, in this case, between 20.2% and 121.4%.

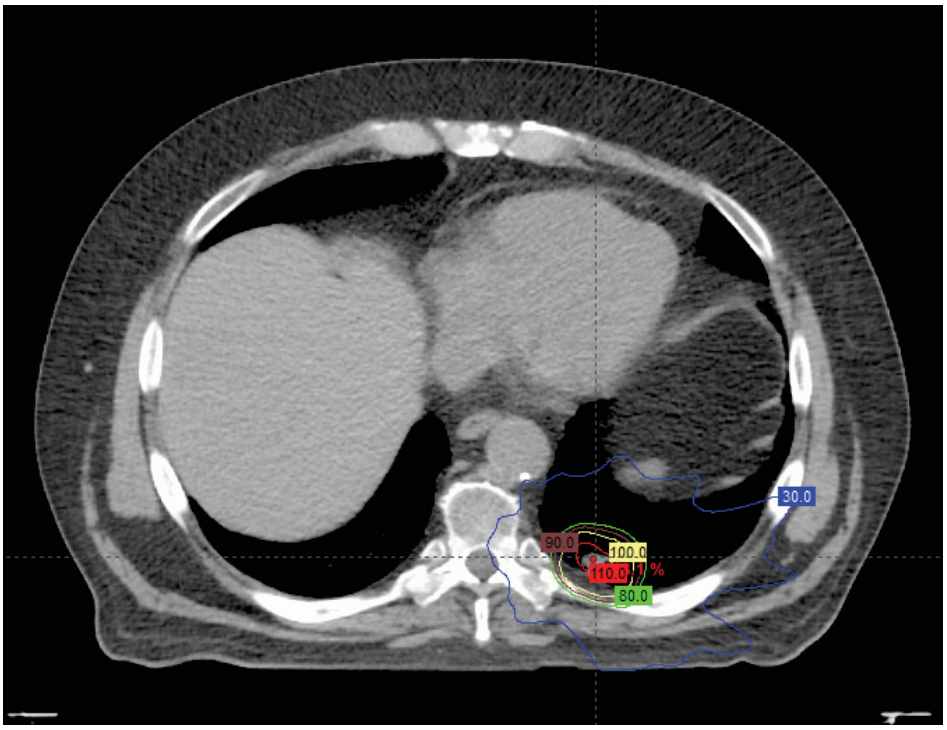


Figure 2.4 – Isodose lines on a lung SBRT treatment plan in the axial view of the thorax.

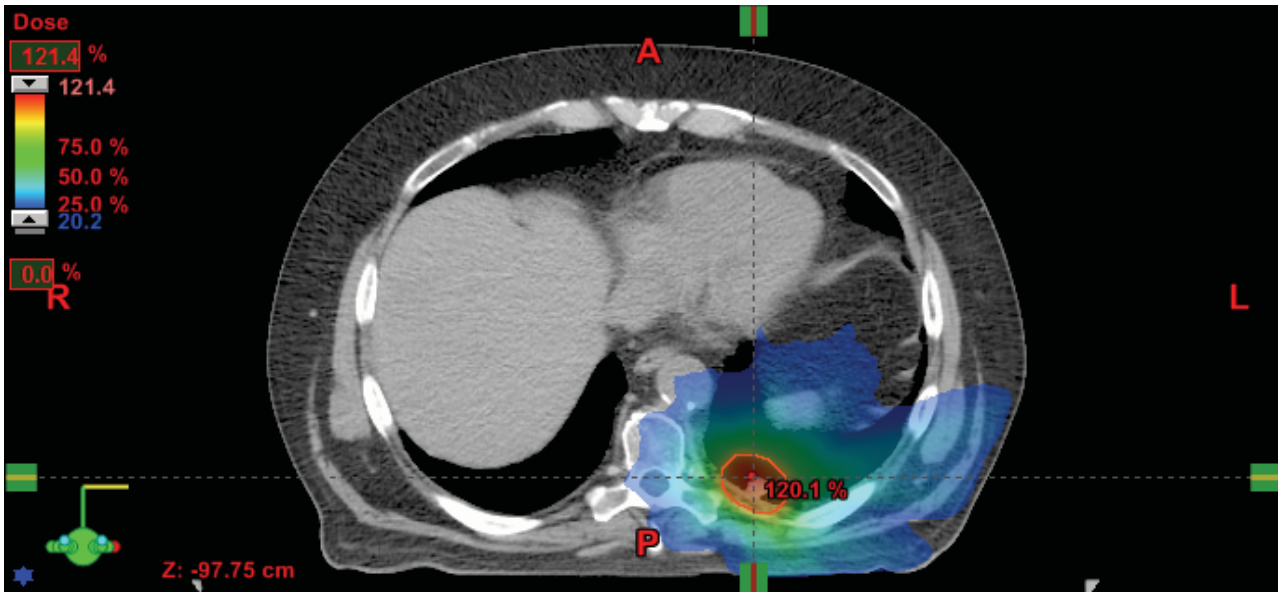


Figure 2.5 - Dose colour wash visualization on a lung SBRT treatment plan.

2.6. Biological models

Although dose-volume indices and isodose distributions are very important in treatment plan evaluation, they give no direct information regarding the biological response of the treatment. Biological indices, on the other hand, offer more comprehensive insight into the expected outcomes and reflect more closely the clinical goals of the radiotherapy[21]. Two examples of these biological models are the biologically effective dose (BED) and the equivalent dose in 2 Gy fractions (EQD2).

2.6.1.1. Biologically Effective Dose - BED

The BED is a dose-response model for which it is possible to convert a physical dose into a "biological dose" that better describes the effect of the radiation on the tumorous or normal tissue[22]. The BED is based on the linear quadratic radiobiological model depicted in Figure 2.6 for which the surviving fraction of cells exposed to radiation is composed of a linear component and a quadratic component, such that it can be expressed by:

$$SF = e^{-(\alpha D + \beta D^2)} . \quad (2)$$

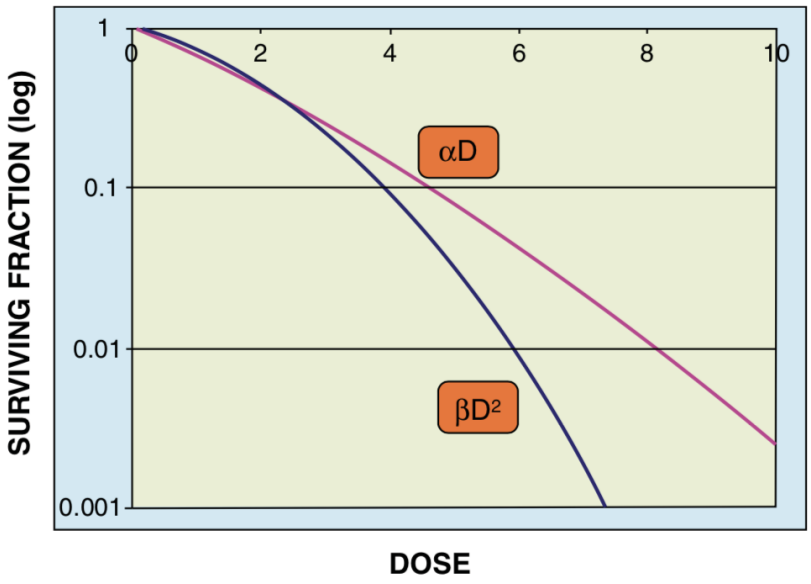


Figure 2.6 - Relation between dose and surviving fraction in the linear-quadratic model. Figure taken from Beyzadeoglu, 2010[23]

In terms of cell kill (E), the equation can be written as:

$$E = n\,(\alpha d + \beta d^2)\,. \tag{3}$$

α and β are radiosensitivity coefficients, n is the number of fractions used, and d is the dose per fraction. The total delivered dose (D) is therefore $D = nd$.

The BED represents the total dose required for a given effect when an infinite number of fractions of small doses per fraction are used. Therefore, in the limiting case where d is very small, the cell kill equation becomes:

$$E = n\alpha d = \alpha D = \alpha BED\,, \tag{4}$$

$$BED = \frac{E}{\alpha}. \tag{5}$$

From the initial equation of E the BED can be determined by:

$$BED = \frac{n(\alpha d + \beta d^2)}{\alpha} = nd\left[1 + \frac{d}{(\alpha/\beta)}\right] \tag{6}$$

$$BED = D\left[1 + \frac{d}{(\alpha/\beta)}\right] \tag{7}$$

Therefore, for any type of fractionation scheme, the true biological dose to a certain tissue described by a given α/β ratio can be calculated. The α/β ratio can vary widely for different tumour or normal tissues. However, in the simplified model of the BED, an α/β ratio of 3 Gy is typically assigned for normal tissues and a ratio of 10 Gy is used for tumour volumes[22].

2.6.1.2. Equieffective doses & EQD2

An important aspect of bioeffect modelling is adjusting for different dose and fractionation regimens. An equieffective dose (EQDX) is defined as “the total absorbed

dose delivered by the reference treatment plan (fraction size X) that leads to the same biological effect as a test treatment plan that is conducted with absorbed dose per fraction d and total absorbed dose D"[24]:

$$EQDX_{\alpha/\beta} = D\frac{d+\alpha/\beta}{X+\alpha/\beta} \quad (8)$$

The most commonly used form of equieffective doses is the EQD2 related to conventionally fractionated treatments of 2 Gy per fraction. The EQD2 can be derived from the BED as follows [24]:

$$EQD2 = D\frac{d+\alpha/\beta}{2+\alpha/\beta} \quad (9)$$

$$EQD2 = \frac{BED}{1+\frac{2}{\alpha/\beta}} \quad (10)$$

2.7. Dose indices in stereotactic radiotherapy techniques

Stereotactic radiotherapy plans require a high level of confidence in the treatment planning process due to the high ablative doses employed and the high dose gradients involved. For this purpose, supplementary metrics to the traditional reporting requirements have been proposed to quantify and compare the quality of these plans. These include plan conformity indices, metrics for the dose fall-off outside the target and homogeneity indices[25].

2.7.1. Conformity indices

Conformity indices evaluate how well the prescription conformally covers the PTV. Different definitions for conformity indices exist, but the most common one is the prescription isodose to target volume (PITV), also simply called the conformity index (CI). The PITV is defined as follows[26]:

$$PITV = \frac{V_{PI}}{V_{PTV}} \quad (11)$$

where V_{PI} is the prescription isodose volume and V_{PTV} is the volume of the PTV.

2.7.2. Dose fall-off

Dose fall-off outside of the target can be measured in various ways. The measure of intermediate dose fall-off is typically defined as the $R_{50\%}$, which is the ratio of the 50% prescription isodose ($V_{50\%PI}$) to the volume of the PTV (V_{PTV})[25]:

$$R_{50\%} = \frac{V_{50\%PI}}{V_{PTV}}. \quad (12)$$

In lung SBRT protocols, in order to evaluate dose fall-off, it is also recommended to report the maximum dose (in % of prescription dose) at over 2 cm from the PTV in any direction (D_{2cm})[27].

2.7.3. Homogeneity indices

Homogeneity of the target can be reported as the maximum dose to prescription dose ratio (MDPD), sometimes called the homogeneity index (HI). The MDPD can be calculated as follows [26]:

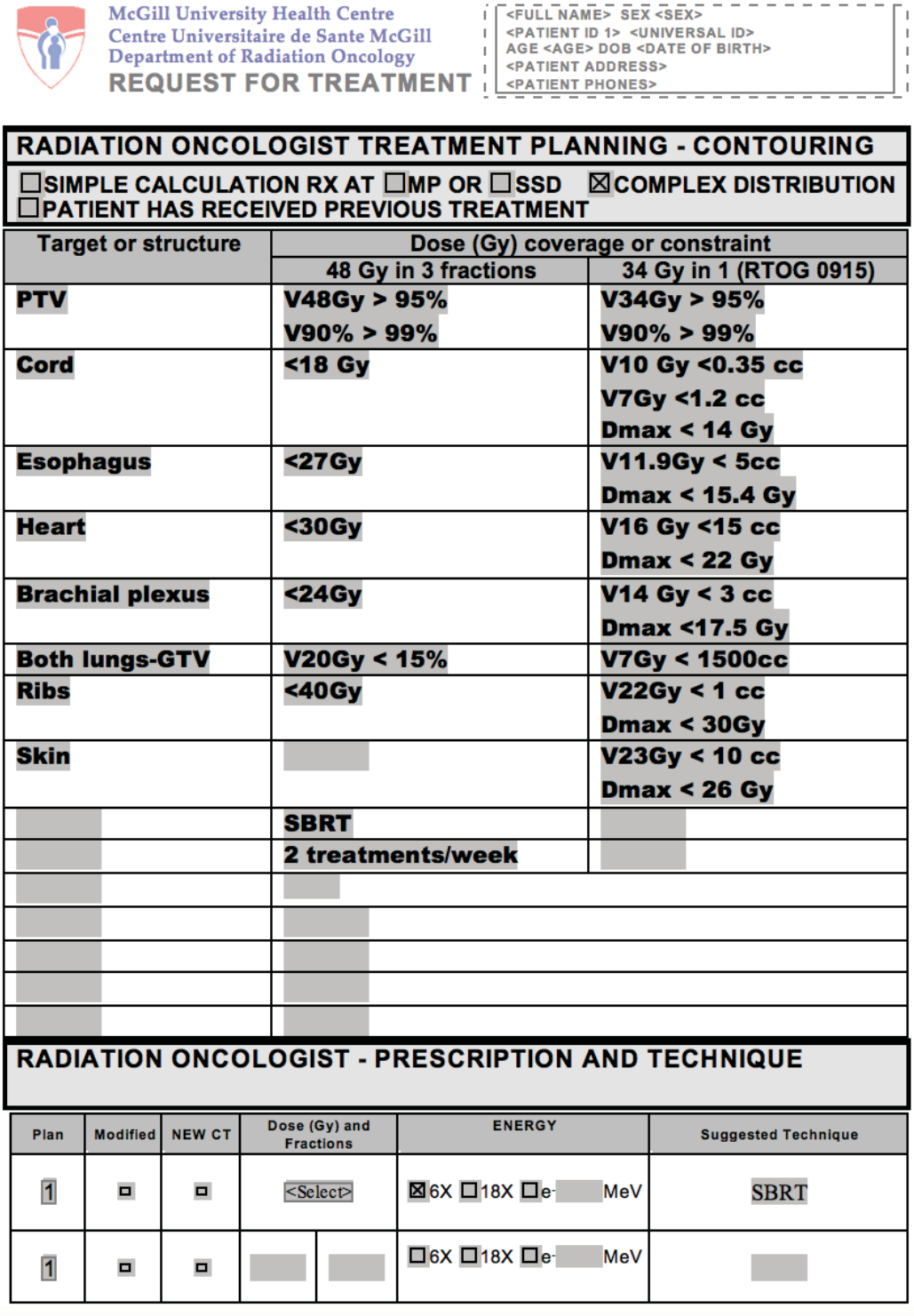
$$MDPD = \frac{D_{max}}{PD}, \quad (13)$$

where $D_{max}$is the maximum dose found in the entire plan and PD is the prescription dose to the target.

2.8. Planning objectives

For each treatment prescribed to a patient in our clinic, the radiation oncologist fills in a "CT planning sheet", which specifies the planning objectives including the prescription, the treatment technique to be used as well as the target and OAR constraints that should

be met. Dosimetrists refer to these CT planning sheets during treatment planning. Templates for the CT planning sheets are available for different anatomical sites and treatment techniques, but the physician may choose to diverge from these templates in some particular cases. An example of a CT planning sheet template for lung SBRT is shown in Figure 2.7.



McGill University Health Centre
Centre Universitaire de Sante McGill
Department of Radiation Oncology
REQUEST FOR TREATMENT

<FULL NAME> SEX <SEX>
<PATIENT ID 1> <UNIVERSAL ID>
AGE <AGE> DOB <DATE OF BIRTH>
<PATIENT ADDRESS>
<PATIENT PHONES>

RADIATION ONCOLOGIST TREATMENT PLANNING - CONTOURING

☐SIMPLE CALCULATION RX AT ☐MP OR ☐SSD ☒COMPLEX DISTRIBUTION
☐PATIENT HAS RECEIVED PREVIOUS TREATMENT

Target or structure	Dose (Gy) coverage or constraint	
	48 Gy in 3 fractions	34 Gy in 1 (RTOG 0915)
PTV	V48Gy > 95% V90% > 99%	V34Gy > 95% V90% > 99%
Cord	<18 Gy	V10 Gy <0.35 cc V7Gy <1.2 cc Dmax < 14 Gy
Esophagus	<27Gy	V11.9Gy < 5cc Dmax < 15.4 Gy
Heart	<30Gy	V16 Gy <15 cc Dmax < 22 Gy
Brachial plexus	<24Gy	V14 Gy < 3 cc Dmax <17.5 Gy
Both lungs-GTV	V20Gy < 15%	V7Gy < 1500cc
Ribs	<40Gy	V22Gy < 1 cc Dmax < 30Gy
Skin		V23Gy < 10 cc Dmax < 26 Gy
	SBRT	
	2 treatments/week	

RADIATION ONCOLOGIST - PRESCRIPTION AND TECHNIQUE

Plan	Modified	NEW CT	Dose (Gy) and Fractions		ENERGY	Suggested Technique
1	☐	☐	<Select>		☒6X ☐18X ☐e- MeV	SBRT
1	☐	☐			☐6X ☐18X ☐e- MeV	

Figure 2.7 - CT planning sheet template example for lung SBRT.

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The goal of this thesis project was to develop a software tool for treatment plan evaluation that would facilitate the workflow of dosimetrists and benefit retrospective analysis of plan cohorts. In this chapter on methods and materials, an overview of the software design specifications and functionalities will be presented along with the motivation behind the different requirements. In addition, technical aspects of the software development process, namely the tools and technologies used, will be described. Finally, the methodology for validation and verification of the software will be discussed.

3.1. Functional requirements

The software design revolved around several specification requirements that were to be included in the final tool. These functionalities are depicted in Figure 3.1 and will be individually described in the following sections.

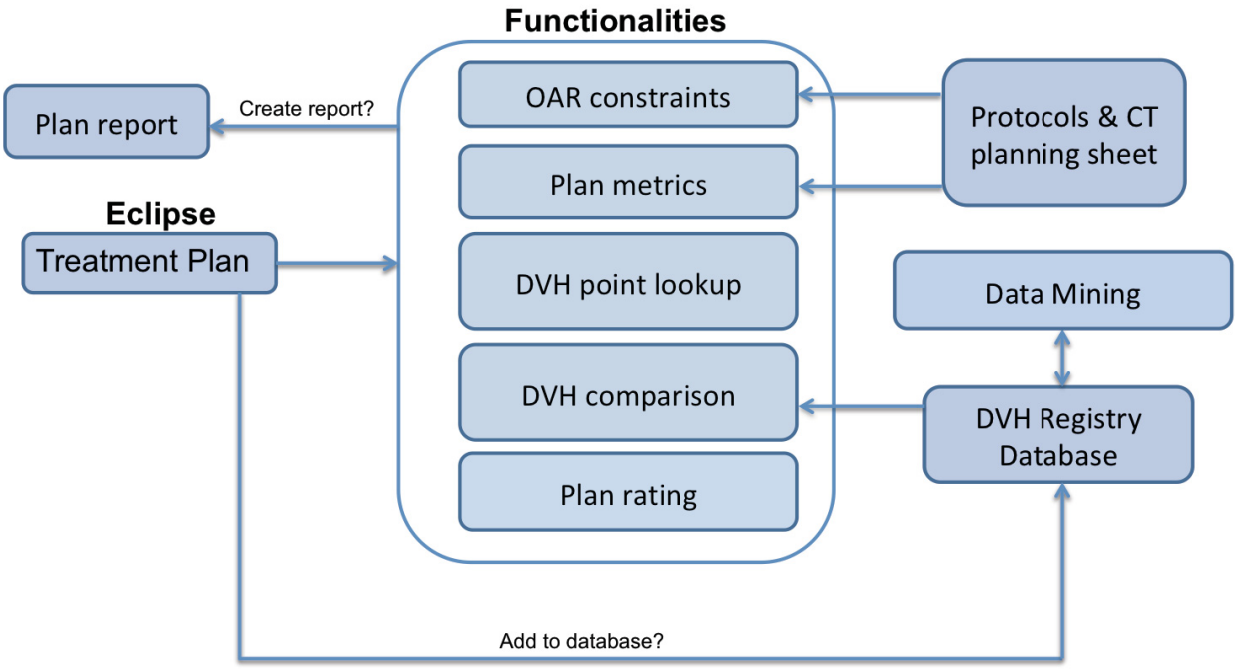

Figure 3.1 – Specification requirements of software

3.1.1. Planning sheet constraints

The first requirement is to permit the user to automatically evaluate if the plan has met the constraints that are established for different treatment techniques and different treatment sites. These constraints are based on the CT planning sheets that are used in our clinic and on various protocols from the literature. The current way dosimetrists evaluate these constraints is by manually looking up points off the DVH curves that are displayed in Eclipse™. Considering that this can be time consuming and error-prone, a solution for a more efficient and intuitive visualization of the prescribed constraints is desired.

3.1.2. Plan-specific metrics

The next requirement is to permit the evaluation of plan-specific metrics. Because this project focused on lung SBRT plans, these metrics are those described by RTOG protocols 0236[1], 0813[2] & 0915[3]. Similarly as for the planning sheet constraints evaluation, the dosimetrists currently need to look up points off the DVH curve, and then further calculate the metric values through various calculations, which can be a very tedious process.

3.1.3. DVH point lookup

The DVH point lookup functionality allows the user to quickly look up a dose at a specified volume or a volume at a specified dose for any structure contained within the plans structure set, without the need to look at the DVH curve.

3.1.4. DVH registry

The purpose of the DVH registry tool is to allow the comparison of the current plan being evaluated to a population of existing similar plans that are contained within the DVH registry database (see *Section 3.2.4*). This allows a quick visual representation of how the current plan compares to past benchmarked plans in terms of the dosimetric distribution within key structures. This is particularly useful for treatment planners having less experience and for whom it may be difficult to interpret the quality of a plan.

3.1.5. QUANTEC

The QUANTEC function evaluates constraints of anatomical structures as specified in the QUANTEC publications by converting the dose values from the plan into EQD2.

3.1.6. Plan rating

Another requirement of the software tool developed is the ability to rate plans in a quantitative manner. The goal of this functionality is to translate an overall quantitative and qualitative evaluation of a plan into a single quantitative value, diminishing the need for subjective assessment. Two different methods were chosen for this purpose. The first is the Dose Distribution Index (DDI)[4] and the second is a cost function based method.

3.1.6.1. Dose Distribution Index – DDI

The Dose Distribution Index (DDI) is a DVH-based plan scoring method developed by Alfonso *et al.*[4] The DDI groups into a single value the dose coverage, the dose conformity, the homogeneity of the target, and the level of sparing of the OARs and the RVR. In order to obtain this value, only the DVH data and the prescription dose are required, which are easily accessible through Eclipse™. The DDI value is a weighted sum of a target coverage component, an OAR sparing component and a RVR sparing component, which makes it also possible to evaluate in a separate manner the impact of each of these key dosimetric goals.

The target coverage component encompasses the dose coverage, the conformity and the homogeneity of the PTV. It is calculated in the following manner:

$$I_T = \left(1 - \left|1 - \left(\frac{\int_0^{D_M} V_T(D)dD}{Dp \cdot PTV}\right) \cdot \left(\frac{D_m}{D_M}\right)\right|\right), \quad (1)$$

where *PTV* is the volume of the PTV, D_p is the prescription dose to the PTV, D_m is the minimum dose to the PTV, D_M is the maximum dose to the PTV and $V_T(D)$ represents the distribution of points on the PTV DVH curve. More simply put, the I_T value represents the ratio between the area under the curve of a given plan and the area under the curve of an ideal plan multiplied by the D_m/D_M ratio accounting for the dose homogeneity. A graphical representation of the I_T index is depicted in Figure 3.2A.

The OAR and RVR sparing follows a similar description. In these cases, an ideal plan consists of a DVH curve with a nearly null area under the curve (see Figure 3.2B). The calculations for respectively the OAR and RVR sparing are as follows:

$$I_o = \frac{1}{N}\sum_{i=1}^{N} w_{Oi}\left(1 - \left(\frac{\int_0^{D_{Mi}} V_{Oi}(D)dD}{Dp \cdot OARV_i}\right) \cdot \left(\frac{D_M}{D_p}\right)\right) \quad (2)$$

and

$$I_R = \left(1 - \left(\frac{\int_0^{D_M} V_R(D)dD}{Dp \cdot RVR}\right) \cdot \left(\frac{D_M}{D_p}\right)\right), \quad (3)$$

where D_M is the maximum dose in each OAR structure involved in the plan, N is the number of OARs considered, $OARV_i$ is the volume of a given OAR, and $V_O(D)$ and $V_R(D)$ are the curves of respectively a given OAR and the RVR. The weighting factors w_{oi} can be chosen as a value between 0 and 1 to account for the relative clinical importance of each OAR considered. The D_M/D_p ratio accounts for the difference between the maximum dose received by the given OAR or the RVR and the prescription dose.

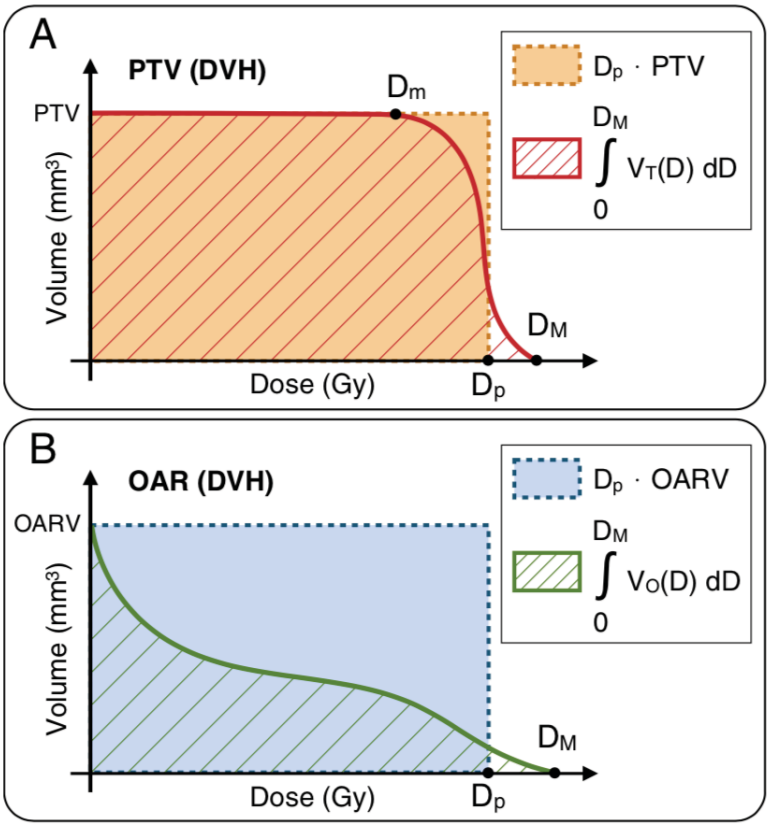

Figure 3.2 – DVH schematics showing the variables included in the formulation of the DDI for A) the I_t component and B) the I_o component. Figure taken from Alfonso et al., 2015[4].

The total DDI index is a weighted sum of I_T, I_O and I_R given by:

$$DDI = \frac{1}{3}\left(w_T I_T + w_o I_o + w_R I_R\right), \tag{4}$$

where w_T, w_o and w_R are weighting factors between 0 and 1 that can be chosen to express the relative priority of each factor. A DDI equal to 1 (or 100%) is given for an ideal plan. Similarly, an I_T of 1 means ideal target coverage, an I_o of 1 is ideal OAR sparing and an I_R of 1 signifies ideal RVR sparing.

3.1.6.2. Cost function

The other plan scoring method that was implemented is based on a cost function, for which a cost of zero is assigned to a plan that meets every constraint both for the OARs and the targets. A cost is assigned to the target coverage and to the OAR sparing, and these costs are added together to provide the final cost. The general form of the cost function is:

$$f = \sum_{n=1}^{N} p_n^T f_n^T + \sum_{n=1}^{N} p_m^{OAR} f_m^{OAR} , \quad (5)$$

where f^T is the objective function of the nth target volume, p^T is the weight assigned to that target, f^{OAR} is the objective function of the mth OAR considered and p^{OAR} is the weight associated to the mth OAR constraint.

The objective function for the OAR is expressed as:

$$f^{OAR} = \frac{1}{N_{OAR}} \sum_{i=1}^{N_T} H(D_i - D_0^{OAR})(D_i - D_0^{OAR})^2 , \quad (6)$$

where N_{OAR} is the number of OARs considered, D_i is the dose or volume value at the specified constraint, D_i^{OAR} is the reference value for that constraint and $H(D_i - D_0^{OAR})$ is the Heaviside step function which can be expressed as:

$$H(D_i - D_0^{OAR}) = \begin{cases} 1, & D_i > D_0^{OAR} \\ 0, & D_i \leq D_0^{OAR} \end{cases} \quad (7)$$

As for the target objective function, the mathematical expression is:

$$f^T = \frac{1}{N_T}\sum_{i=1}^{N_{OAR}}\left[H(D_{low}^T - D_{i-low}^T)(D_{i-low}^T - D_{low}^T)^2 + H(D_{i-high}^T - D_{high}^T)(D_i^T - D_{high}^T)^2\right], \quad (8)$$

where N_T is the number of targets in the plan, $D_{i\text{-}low}{}^T$ is the dose or volume value at the specified lower constraint, D_{low}^T is the lower constraint reference value, $D_{i\text{-}high}{}^T$ is the dose or volume value at the specified higher constraint and D_{high}^T is the higher constraint reference value. The two Heaviside functions in this equation are respectively:

$$H(D_{low}^T - D_{i-low}^T) = \begin{cases} 1, & D_{i-low}^T < D_{low}^T \\ 0, & D_{i-low}^T \geq D_{low}^T \end{cases} \quad (9)$$

and

$$H(D_{i-high}^T - D_{high}^T) = \begin{cases} 1, & D_{i-high}^T > D_0^{OAR} \\ 0, & D_{i-high}^T \leq D_0^{OAR} \end{cases}. \quad (10)$$

3.1.7. Plan report

The plan report tool aims to create a summarized report of the plan evaluation process. This type of report can be stored and reviewed as needed, for example, when discussing a case during patient management rounds. The result of all the different functionalities presented thus far can be grouped into this report.

3.1.8. Data mining

Although large amounts of data are entered daily into a treatment planning system, extracting these data is quite laborious. The ability to perform efficient data mining is very useful for better addressing practice quality improvement (PQI), retrospective studies, or other questions that aim to improve patient care. The goal of this tool was to develop a framework for the efficient extraction of data from past treatment plans. These data include the structures DVH curve data, dose statistics (Dmax, Dmin, Dmean, Dmedian, Dstdev), structure volumes and plan information (prescription dose, prescription isodose, dose per fraction, number of fractions). These data are stored in a database and can be retrieved intuitively with a user-friendly graphical interface.

3.2.Software development tools and technologies

3.2.1. Eclipse™ (Varian Medical Systems, Palo Alto, CA) TPS

Eclipse™ is a multi-modality treatment planning system (TPS) by Varian Medical Systems, Palo Alto, CA. Integrated with the ARIA® oncology information system and Varian delivery platforms, Eclipse™ Version 11 is the main software used for treatment planning in our clinic.

3.2.2. Eclipse™ Scripting Application Programming Interface - ESAPI

One of the interesting features available through Eclipse™ TPS is the Eclipse™ Scripting Application Programming Interface (ESAPI), which was the platform used for software development throughout this project. An Application Programming Interface (API) is a computer science term that describes a tool that provides a set of subroutine definitions that simplifies access to functions within an application, in this case, Eclipse™. In essence, it acts as an interface between the target application and the programmer, by providing intuitive building blocks and abstracting the underlying implementation[5]. A schematic of the Eclipse™ scripting API is depicted in Figure 3.3.

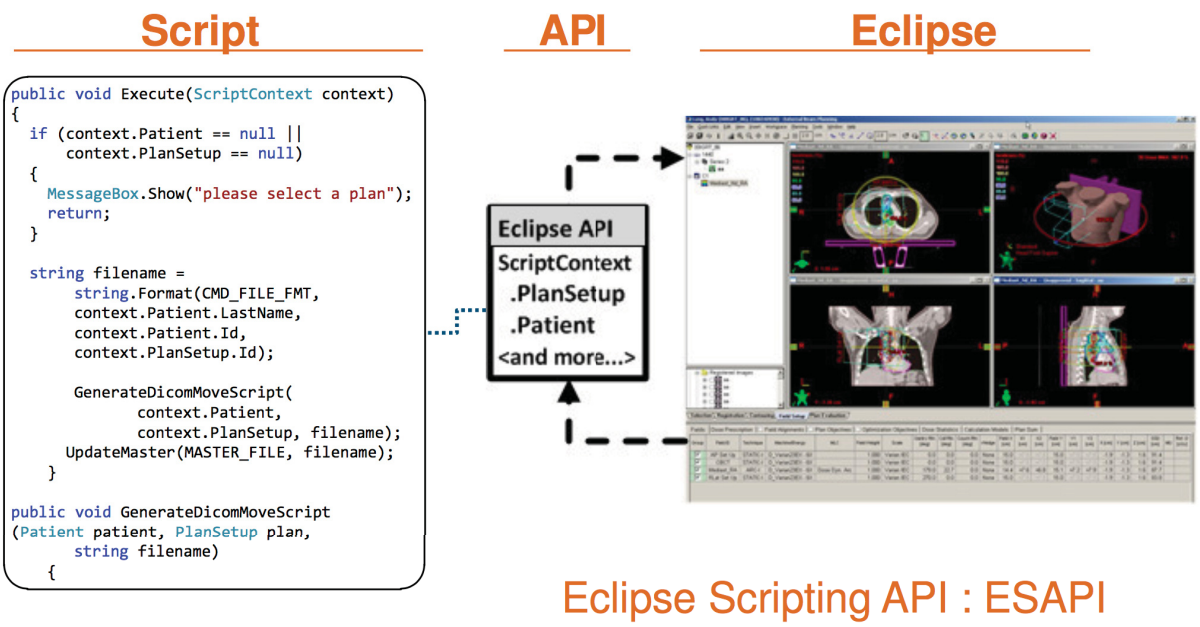

Figure 3.3 - ESAPI Framework schematic. Figure taken from Varian Medical Systems, 2014[5]

ESAPI is therefore a programming interface and software library for Eclipse™. This enables users to develop customized software programs through scripting to access the treatment planning information for a specific need in their clinic or for facilitating research. Treatment planning information that can be accessed through ESAPI Version 11 includes plan, image, dose, structure and DVH information that are stored within the ARIA® oncology database[5].

More specifically, ESAPI comprises a collection of .NET classes, which contain different members, properties and methods. ESAPI includes three main classes, each of which can be divided into sub-classes or objects. The schematic models of each class are shown in Figure 3.4, Figure 3.5 and Figure 3.6. The image class links a patient to different studies/series/images, structure sets encompassing multiple structures, and registration information. The plan class, which was the main class that was exploited for this project, links patients to their courses and plan or plan sums leading to structure sets, dose information and prescription/fractionation values. As for the beam data class, it contains objects such as MLC, applicator, block, compensator, wedge, control point, reference field and external beam information.

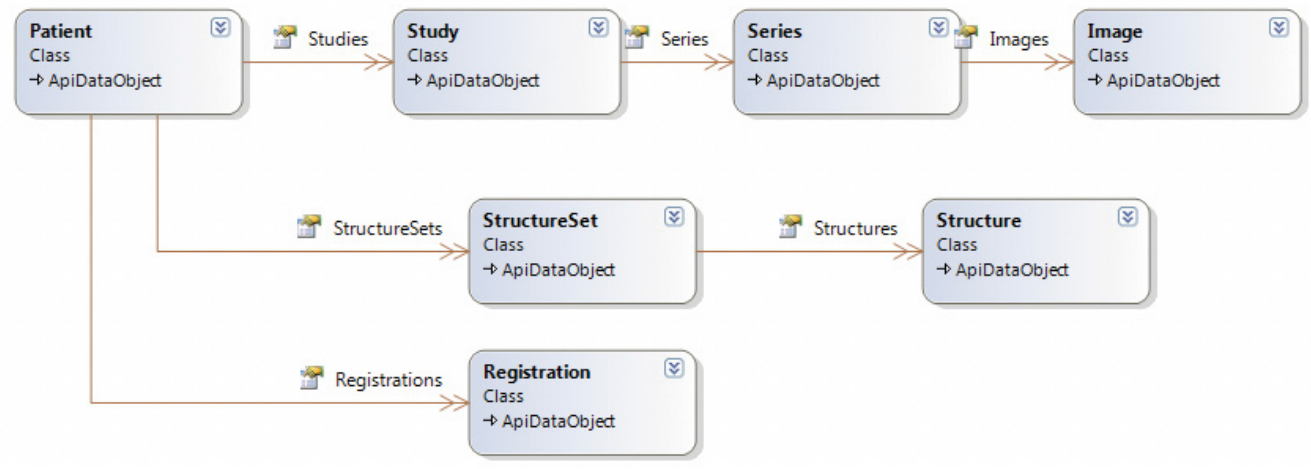

Figure 3.4 - Image class of ESAPI. Figure taken from Varian Medical Systems, 2011[6].

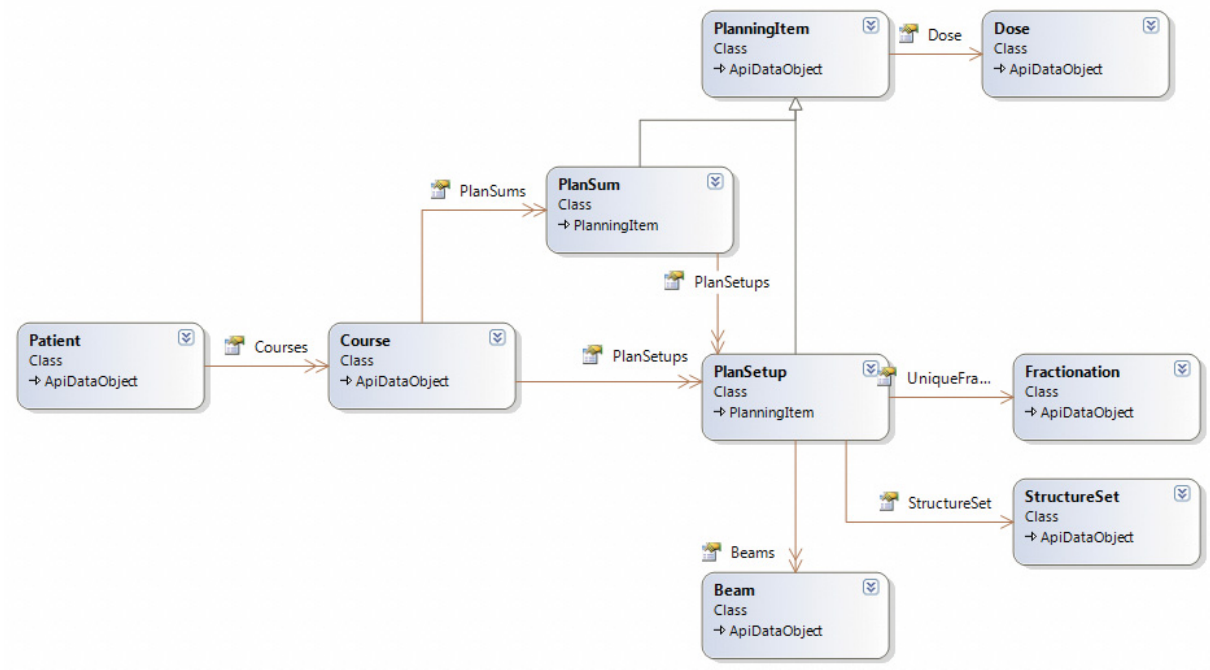

Figure 3.5 - Dose class of ESAPI. Figure taken from Varian Medical Systems, 2011[6].

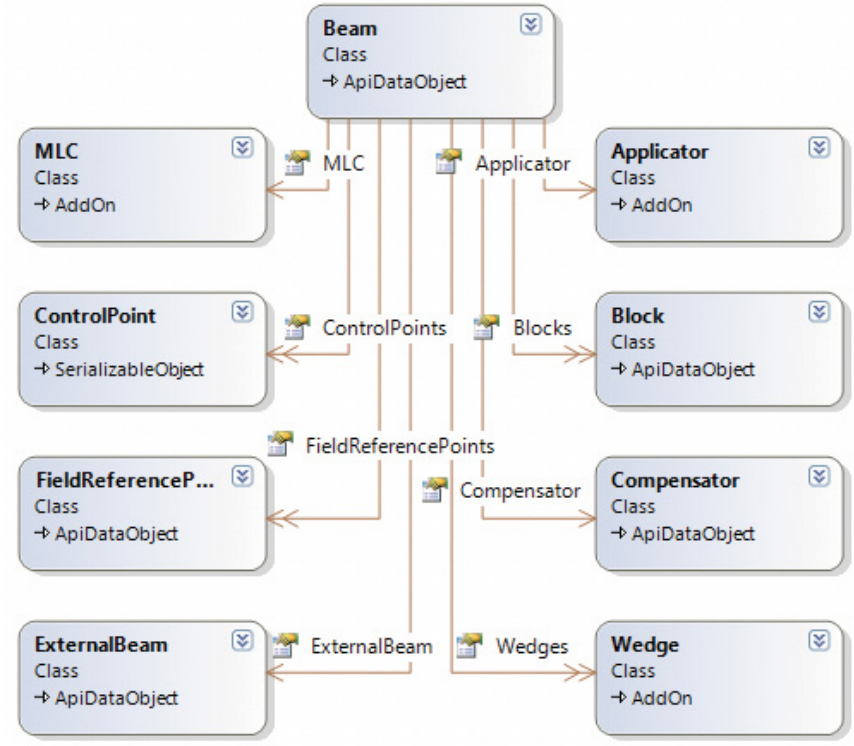

Figure 3.6 - Beam class of ESAPI. Figure taken from Varian Medical Systems, 2011[6].

3.2.3. Programming language & IDE

As recommended by the ESAPI reference guide[6], the programming language used for scripting was C# and Visual Studio was used as the integrated development environment (IDE). In addition, for the graphical user interface (GUI) Windows Forms Applications was used, which is a tool to create interactive Windows-based applications for the .NET framework.

3.2.4. DVH Database

A database system was required in order to store dose-volume information from past plans that would be easily retrieved for comparison with current and future treatment plans. Dr. John Kildea and his team initially developed this MySQL database for a DVH registry web-based software tool[7]. In the context of the current project, the DVH registry was adapted in order to accommodate more in-depth plan information and specific requirements for compatibility with this software tool. A schematic representation of the database infrastructure is presented in Figure 3.7.

The DVH database includes different tables that can be linked as shown by the arrows in Figure 3.7. The patient table is at the top of the database hierarchy and contains a column for the patient ID number, the diagnosis, the sex and the date of birth of the patient. The patients' names are not used in order to maintain anonymity. The patient and the course table are linked through the "PatientSer", which is a simple integer value that is uniquely assigned to each patient. The course table contains the name of the course, and similarly to the "PatientSer", a "CourseSer" that associates each plan to a course. The plan table contains, the name of the plan, which can be matched to a standardized plan name through a dictionary mapping system. It also contains plan information such as the prescription dose, the prescription isodose, the dose per fraction and the number of fractions. The treatment table, linked to the plan table from the "PlanSer", permits to distinguish between the different treatment fractionations. In other words, if needed, the dosimetric information of a particular fraction can be analyzed as well as the original total plan. For each plan or treatment, the structure set is contained within the structures tables. As explained for the plan names, a standard name can be associated with a set of non-standardized structure names through the structure dictionary. The structures table also contains the volume in cm^3, the length (from most inferior to most superior) in cm, the dose coverage, the sampling

coverage, the minimum dose, the maximum dose, the mean dose, the median dose and the standard deviation dose. Each structure for each plan in the database has its set of DVH coordinates within the DVH table. This table has both the absolute (in Gy) and relative (% of prescription dose) doses, with the corresponding volume in both absolute (in cm^3) and relative (% of structure volume) values.

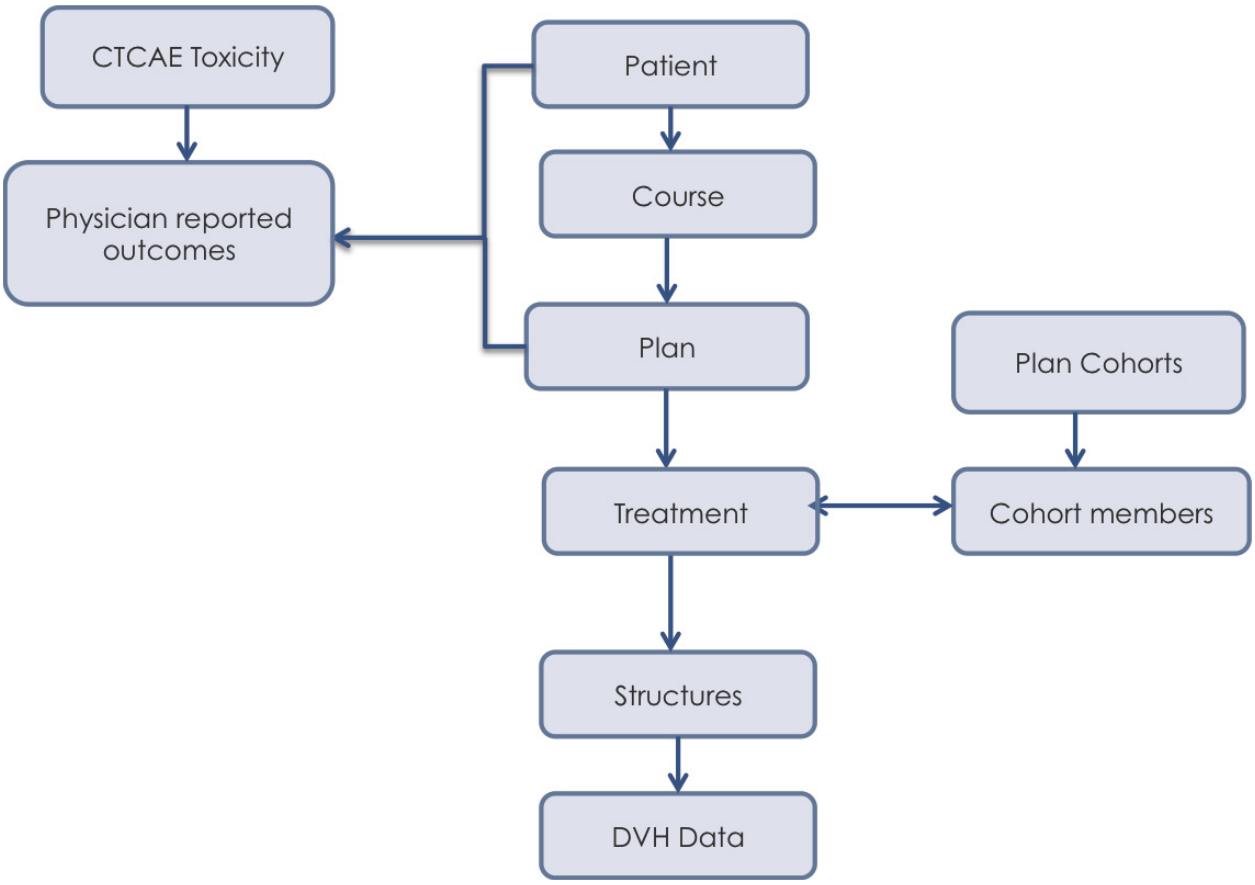

Figure 3.7 – Schematic of the DVH database infrastructure

From this central structure of the database, cohorts of plan can be created in order to create a common link between a set of plans. The plan cohort table contains the name of each of the cohorts created, and the cohort members are indicated in a second table, which contains a list of the "TreatmentSers" that are included in a certain cohort.

Another way of grouping plans is according to the toxicity developed by a certain patient that can be linked to a specific treatment they received. The different radiation toxicities are listed in the Common Terminology Criteria for Adverse Events (CTCAE) toxicity table. The physician reported outcomes table associates the patient and the plan to the toxicity-type and the grade of the toxicity.

3.3. Validation and verification of software tools

The plan evaluation and data mining tools were validated in order to ensure that they met all of the specification requirements described above. In addition, the tools were verified for accuracy of the outputted data through manual comparison of data provided by these tools to that provided by the regular Eclipse™ interface. More specifically, the dose constraints, dose statistics, DVH displays, DVH lookups, plan rating values and data displayed in the report were verified for accuracy through the evaluation of multiple test treatment plans. The validation process was carried out by the author of this thesis and further verified by the thesis supervisor. It is to be noted that because software development is a process of continuous refinement and improvement, it is expected that changes will be required in response to user comments and input in the future.

3.4. References

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4. Results

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In this chapter, the results of this thesis project will be presented. An overview of the two software tools that were developed will be provided, along with a demonstration of their functionalities. For the plan evaluation tool, an example of the assessment of a lung SBRT treatment plan will be shown. For the data-mining tool, an example of a retrospective study on the development of chest wall (CW) pain following lung SBRT will be described.

4.1. Plan evaluation tool

4.1.1. Overview

The plan evaluation tool was designed to facilitate the evaluation of treatment plans by dosimetrists by performing key functions as described in *Section 3.1*. The design of the software was done with great attention to user-friendliness, always keeping in mind the end user, the dosimetrists. The tool is built as a standalone executable meaning that the application can be launched independently of other software. The application can be used on any workstation with an Eclipse™ installation whether accessed through Citrix or otherwise. When initially launched, the user is presented with a window as shown in Figure 4.1, awaiting user input.

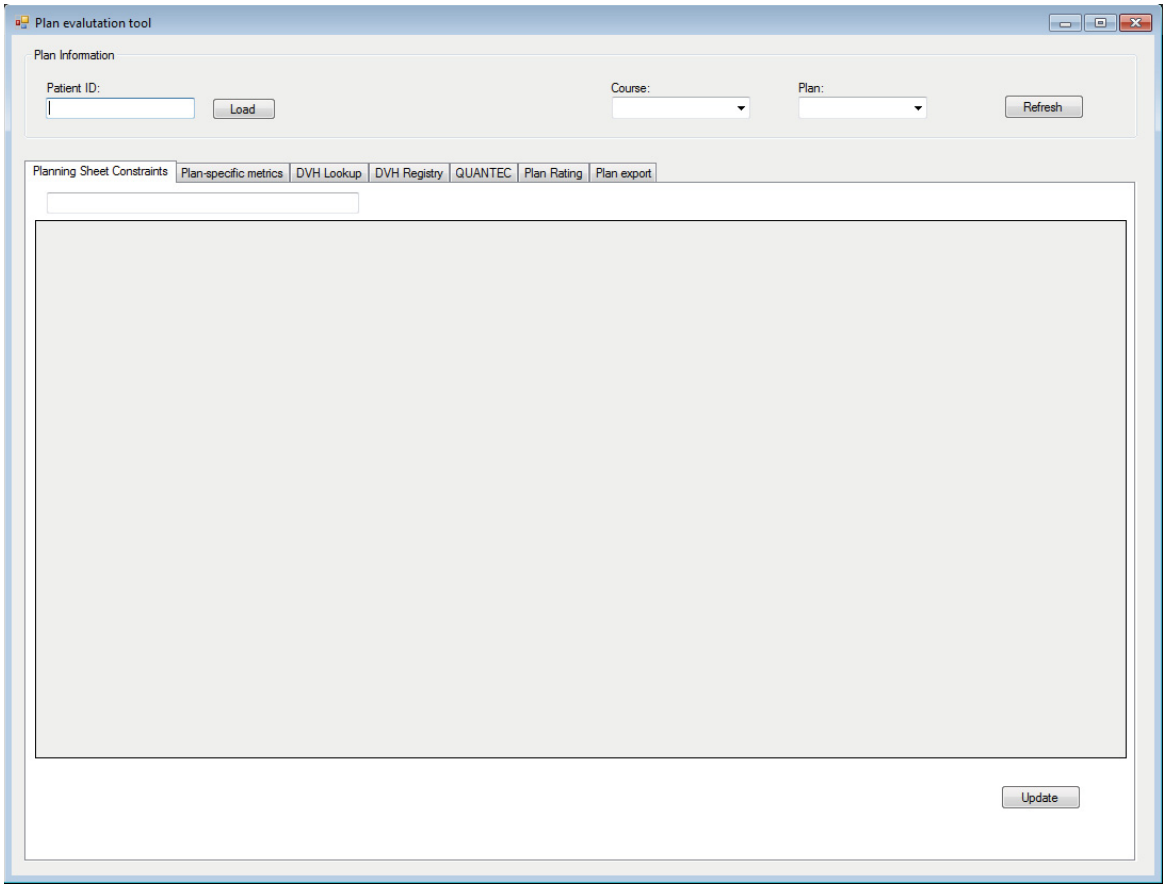


Figure 4.1 - Blank plan evaluation tool awaiting user input

4.1.2. Demonstration – Example: Evaluation of a lung SBRT plan

Once the application is launched, the dosimetrist must type the patient of interest's ID in the text box and click on "Load". This enables the retrieval of the data from the treatment planning system and fills in the combo boxes with the courses and the plans that were created for that patient. The user can then select the course and the plan name that corresponds to the specific treatment plan they aim to evaluate using these combo boxes. In the example shown in Figure 4.2, the patient's ID is "QA_SCRIPT" and the course and plan of interest are respectively named "C1" and "FP1_LT_LUNG". Once the plan name selected, the different tabs performing each a unique functionality can be used. The different tab functions will be presented as they are displayed from left to right.

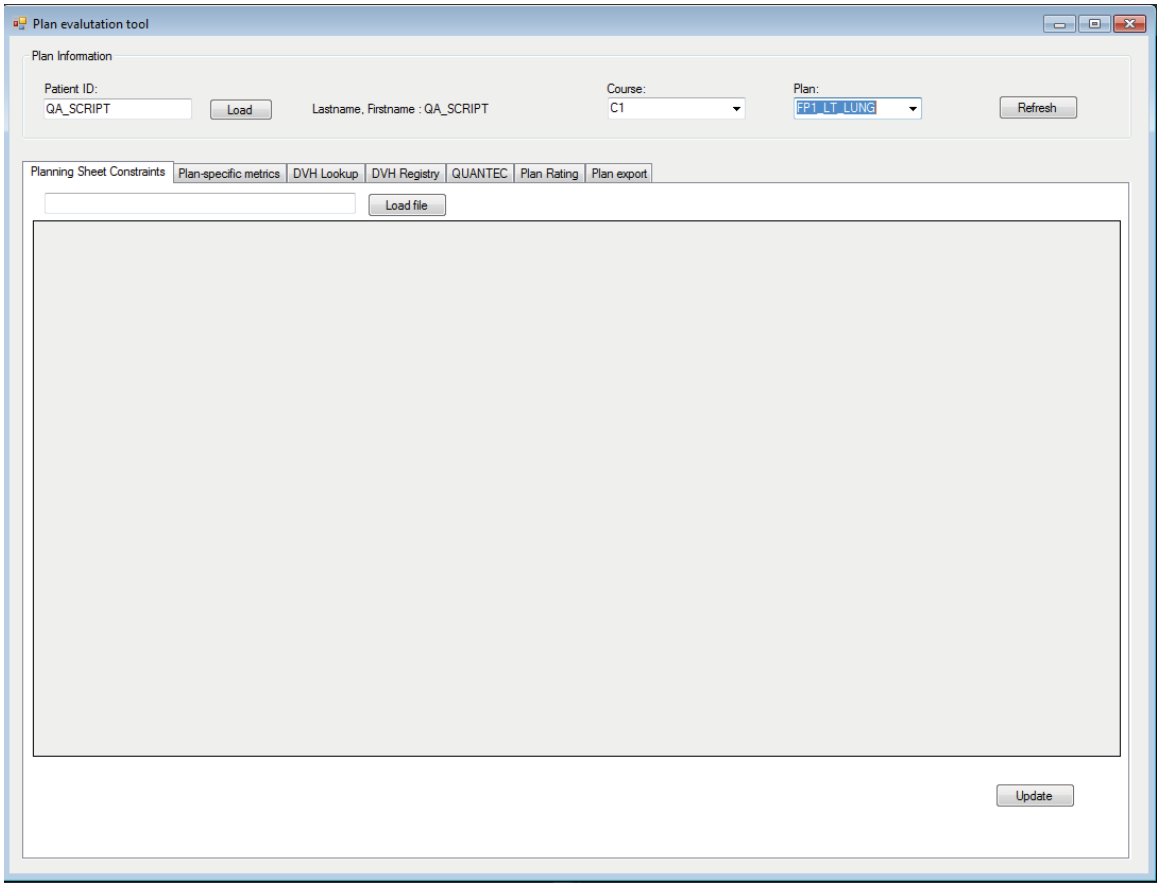
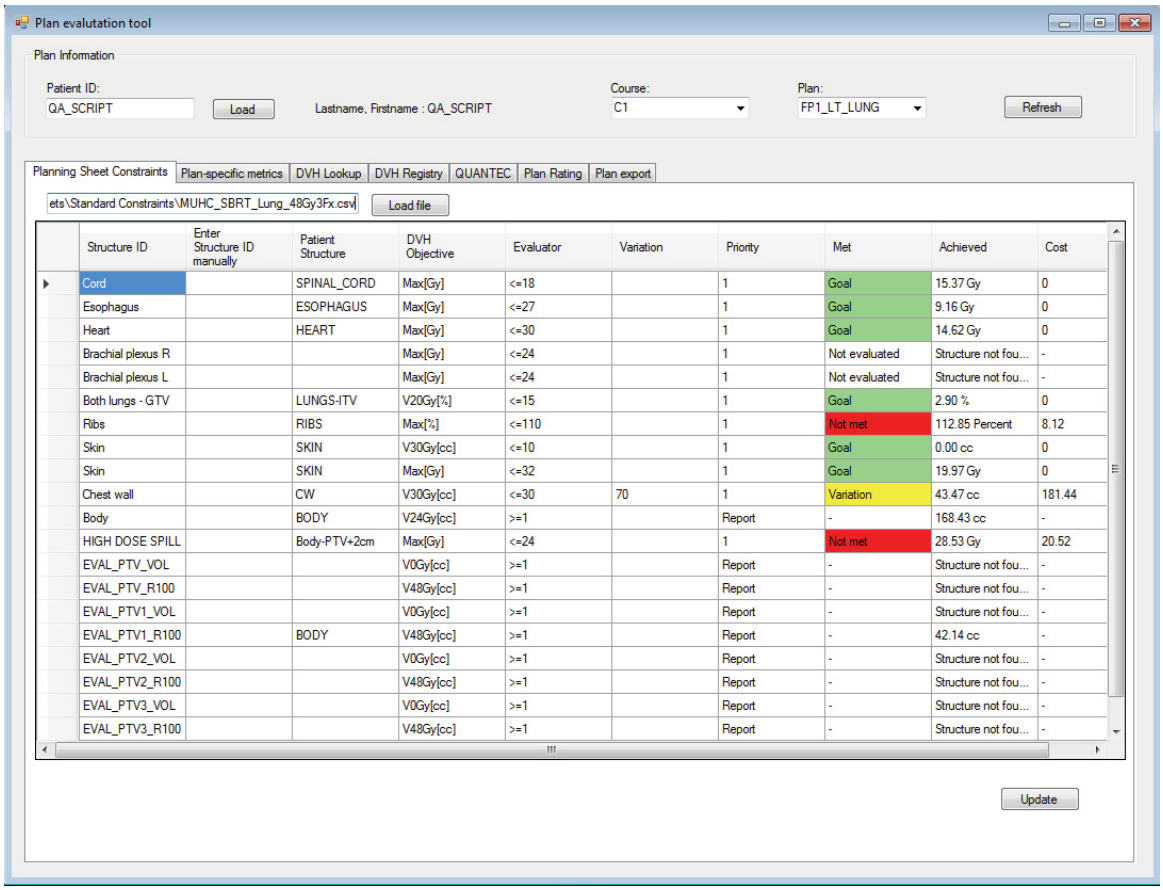


Figure 4.2 - User must enter patient's ID, then chooses course name and plan name

4.1.2.1. Planning sheet constraints

The first tab named "Planning Sheet Constraint" evaluates and displays the agreement of the treatment plan in terms of the achievement of the OAR constraints and target constraints for that plan. The constraints are contained in modifiable spreadsheets on a shared hard drive and are based on the "CT planning sheet" templates that are typically provided by the physician as described in *Section 2.8*. By clicking on the "Load file" button, the user can select from a collection of spreadsheets contained in the "Standard Constraints" folder and choose the one that is appropriate for the plan of interest. In the example shown in Figure 4.3, "FP1_LT_LUNG" is a lung SBRT plan treated with 48 Gy in 3 fractions. The spreadsheet named "MUHC_SBRT_Lung_48Gy3Fx.csv" was therefore selected by the user. In the first column, the standard name of the structure evaluated is written. The third column indicates, if found, the corresponding structure name as written in the plan. The software is programmed to find structures that are named according to a list of aliases that are specified within the spreadsheet templates. In the case where the structure indicated in this column is not the correct one, or if the desired structure was not found, it is possible to manually type the appropriate structure name in the second column and click on "Update". The fourth column shows the metric that is to be evaluated, with the corresponding constraint value in the fifth column. If a variation around this evaluator is acceptable, a value will be shown in the "Variation" column. The priority values indicate the level of importance of each constraint and are used as the weighting factors in the plan rating cost function as seen in *Section 3.1.6.2*. If "Report" is indicated, there is no constraint associated with the structure, but the value of the metric is simply evaluated for reporting purposes. The "Met" column shows along with colour coding whether the evaluated constraint has been met ("Goal"), not met ("Not met") or within the tolerated variation ("Variation"). The "Achieved" column indicates the value of the evaluated metric in the current plan. Finally, the last column shows the cost of each constraint that is not met, as per the cost function presented in *Section 3.1.6.2*.



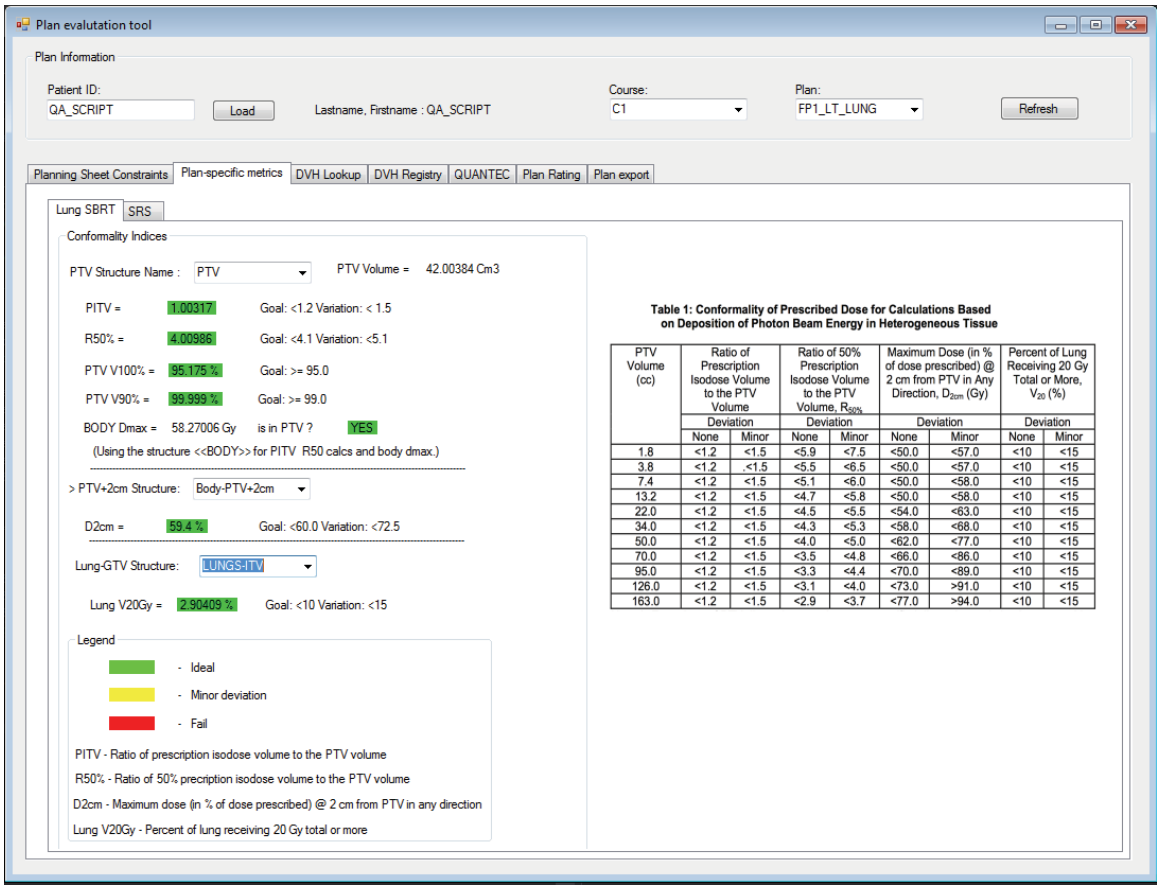
Structure ID	Enter Structure ID manually	Patient Structure	DVH Objective	Evaluator	Variation	Priority	Met	Achieved	Cost
Cord		SPINAL_CORD	Max[Gy]	<=18		1	Goal	15.37 Gy	0
Esophagus		ESOPHAGUS	Max[Gy]	<=27		1	Goal	9.16 Gy	0
Heart		HEART	Max[Gy]	<=30		1	Goal	14.62 Gy	0
Brachial plexus R			Max[Gy]	<=24		1	Not evaluated	Structure not fou...	-
Brachial plexus L			Max[Gy]	<=24		1	Not evaluated	Structure not fou...	-
Both lungs - GTV		LUNGS-ITV	V20Gy[%]	<=15		1	Goal	2.90 %	0
Ribs		RIBS	Max[%]	<=110		1	Not met	112.85 Percent	8.12
Skin		SKIN	V30Gy[cc]	<=10		1	Goal	0.00 cc	0
Skin		SKIN	Max[Gy]	<=32		1	Goal	19.97 Gy	0
Chest wall		CW	V30Gy[cc]	<=30	70	1	Variation	43.47 cc	181.44
Body		BODY	V24Gy[cc]	>=1		Report	-	168.43 cc	-
HIGH DOSE SPILL		Body-PTV+2cm	Max[Gy]	<=24		1	Not met	28.53 Gy	20.52
EVAL_PTV_VOL			V0Gy[cc]	>=1		Report	-	Structure not fou...	-
EVAL_PTV_R100			V48Gy[cc]	>=1		Report	-	Structure not fou...	-
EVAL_PTV1_VOL			V0Gy[cc]	>=1		Report	-	Structure not fou...	-
EVAL_PTV1_R100		BODY	V48Gy[cc]	>=1		Report	-	42.14 cc	-
EVAL_PTV2_VOL			V0Gy[cc]	>=1		Report	-	Structure not fou...	-
EVAL_PTV2_R100			V48Gy[cc]	>=1		Report	-	Structure not fou...	-
EVAL_PTV3_VOL			V0Gy[cc]	>=1		Report	-	Structure not fou...	-
EVAL_PTV3_R100			V48Gy[cc]	>=1		Report	-	Structure not fou...	-

Figure 4.3 - Planning sheet constraint tab showing the agreement of OAR and target constraints

4.1.2.2. Plan-specific metrics

The next tab aims at evaluating plan specific metrics. As the main focus of the thesis was treatment planning of lung SBRT plans, a section was specifically designed for the evaluation of metrics relevant to these plans as shown in Figure 4.4. The user selects the PTV of the plan and the software calculates the PITV, the $R_{50\%}$, the V100% and V90% of the PTV, as well as the Dmax of the PTV. The definitions of these metrics are presented in *Section 2.5.2* and *Section 2.7* of this thesis. Additional metrics such as the D2cm, the maximum dose of the region beyond 2 cm from the PTV, and the lung V20Gy are also computed when the user selects the appropriate structures from the combo boxes. The table on the right is taken from the RTOG 0915 protocol and shows the criteria for conformity of the different metrics that are evaluated in this section. Again, colour coding

is used to indicate whether these criteria are met or not. In this example, all of the metrics are shown in green, meaning that they all meet the constraints.



PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV Volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (Gy)		Percent of Lung Receiving 20 Gy Total or More, V_{20} (%)	
	Deviation		Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	.<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	>91.0	<10	<15
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	>94.0	<10	<15

Figure 4.4 - Plan specific metrics tab for lung SBRT plans

A similar approach was also developed to evaluate SRS treatments as shown in Figure 4.5. This section was added because of the particularity of these treatments, which do not contain the true prescription dose within the treatment plan data in Eclipse™ since most of the treatment planning is performed on an SRS-specific system. Therefore, a text box was included to accommodate the need to manually specify the prescription dose, which is an important parameter in the calculation of the PITV and the MDPD. Once the structure of the PTV is selected and the prescription dose is entered, these metrics are calculated as defined in *Section 2.7*.

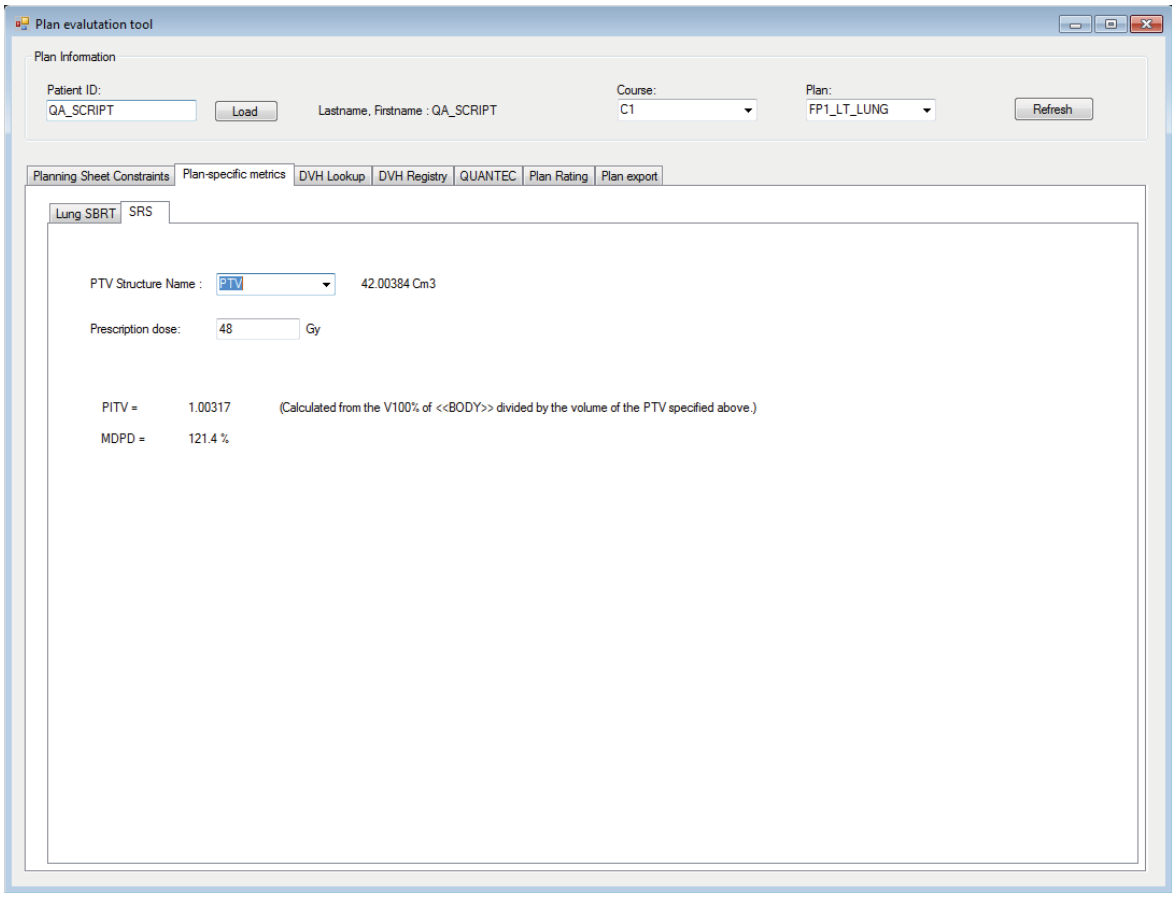


Figure 4.5 – Plan specific metrics tab for SRS plans

4.1.2.3. DVH lookup

The next tab is the DVH lookup. This enables the user to lookup the exact value of any point off the DVH curve of any structure contoured in the treatment plan. More specifically, the user can specify a dose value (in absolute or relative terms) in order to get the corresponding volume, or specify a volume value (in absolute or relative terms) to get the corresponding dose. In the example shown in Figure 4.6, the CW was selected to lookup up the relative volume of CW receiving over 30 Gy and the relative dose that is received by at least 50% of the CW volume. In the lower section of this tab, DVH statistics for the selected structure are shown including the maximum dose, the minimum dose, the mean dose, the median dose and the standard deviation. The "Add to report" buttons permit the user to save the value of the lookup to the PDF report that will be described in *Section 4.1.2.7*.

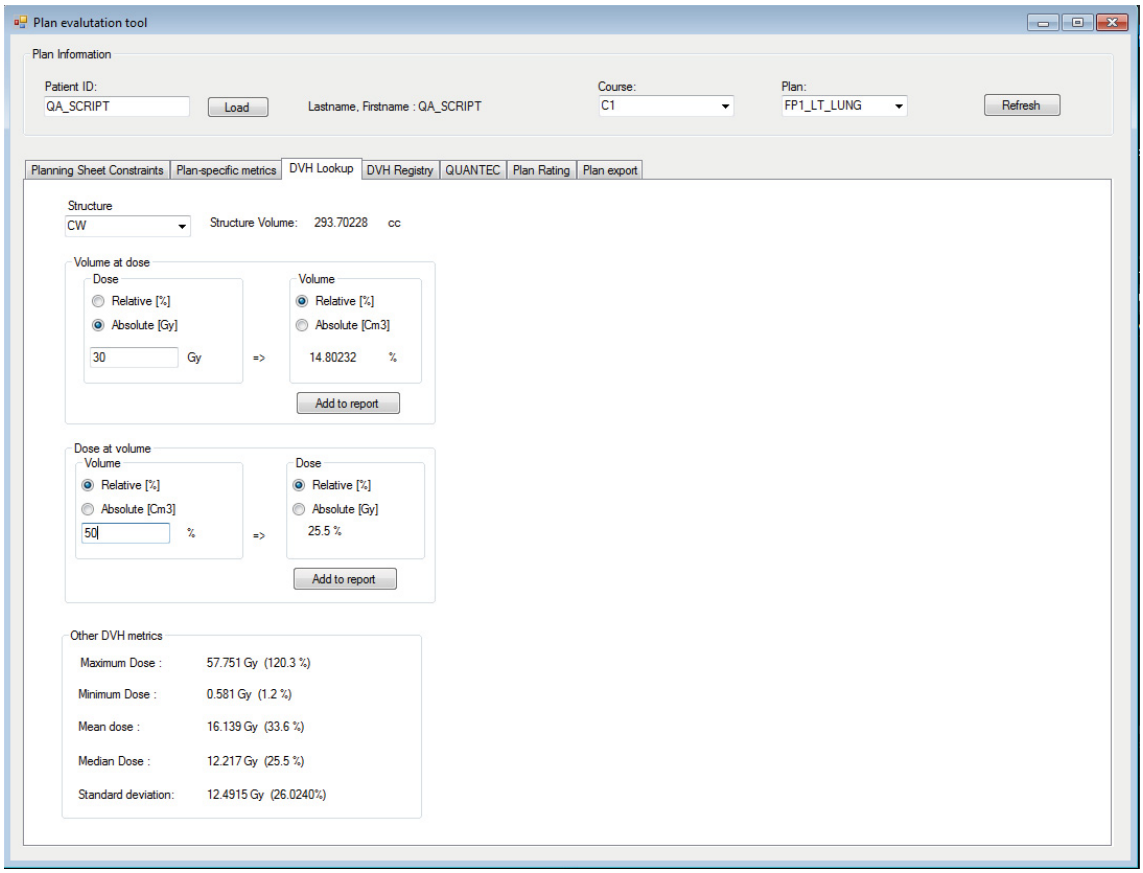


Figure 4.6 - DVH lookup tab

4.1.2.4. DVH registry

In the "DVH registry" tab, the user can compare their plan to previous plans of the same type in terms of DVH curves of different key structures. In the example shown in Figure 4.7 and Figure 4.8, the user is comparing the CW DVH of their plan to the population of CW DVHs that are entered in the registry database with "SBRT_LUNG" as a standard plan name. In the first "Average/Stdev" window shown in Figure 4.7, the blue curve represents the CW DVH in the loaded plan, the green and the orange curve represents respectively the mean and the median of the CW DVH data in the database and the two mint coloured curves represent the upper and lower standard deviation of the population.

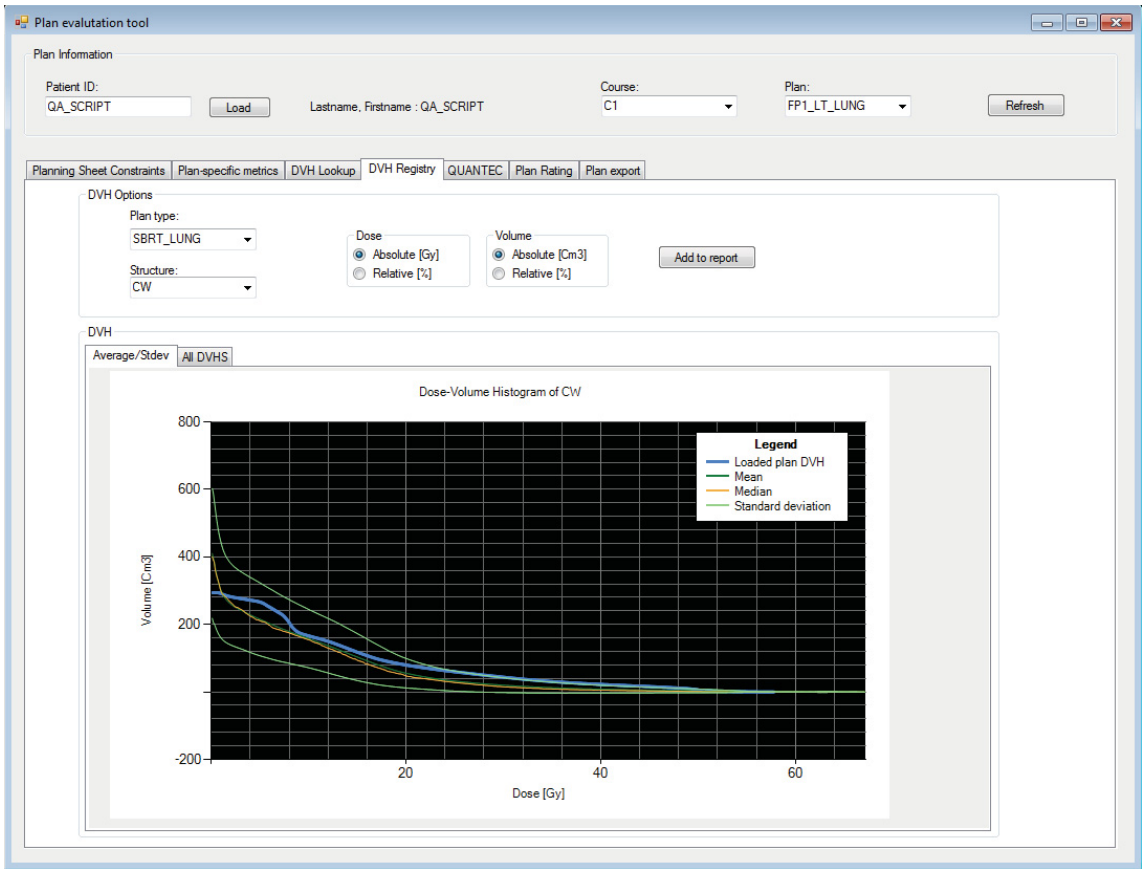


Figure 4.7 – DVH registry tab. The blue CW DVH curve of the loaded plan is compared to the median (orange), mean (green) and standard deviation (mint) of the plans in the registry database

In Figure 4.8, for the "All DVHs" tab, a similar DVH comparison can be made, but this time all of the individual curves contained in the database are plotted (in magenta) against the DVH of the current plan (in blue). It is to be noted that these DVH curves can be plotted with either relative or absolute axes. In addition, these graphs can be added to the PDF report by clicking on the "Add to report" button.

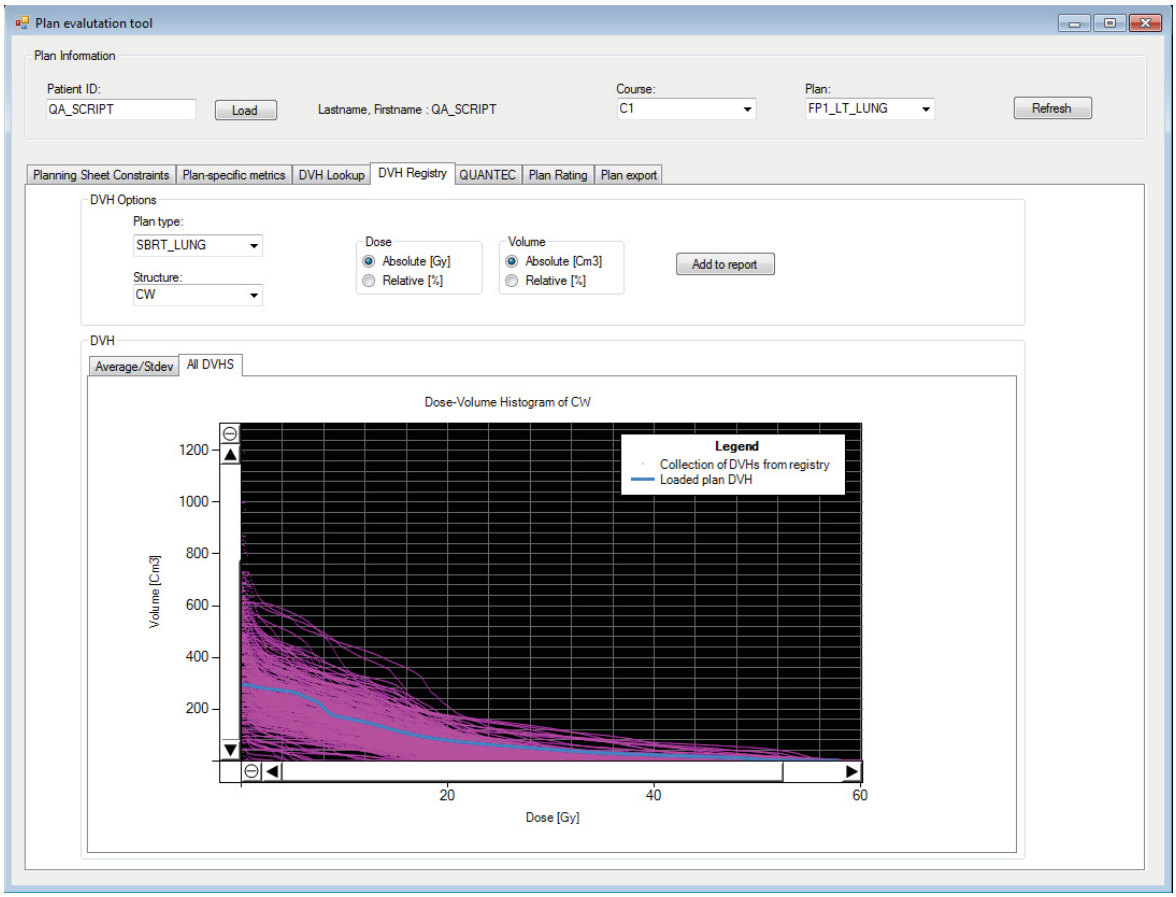
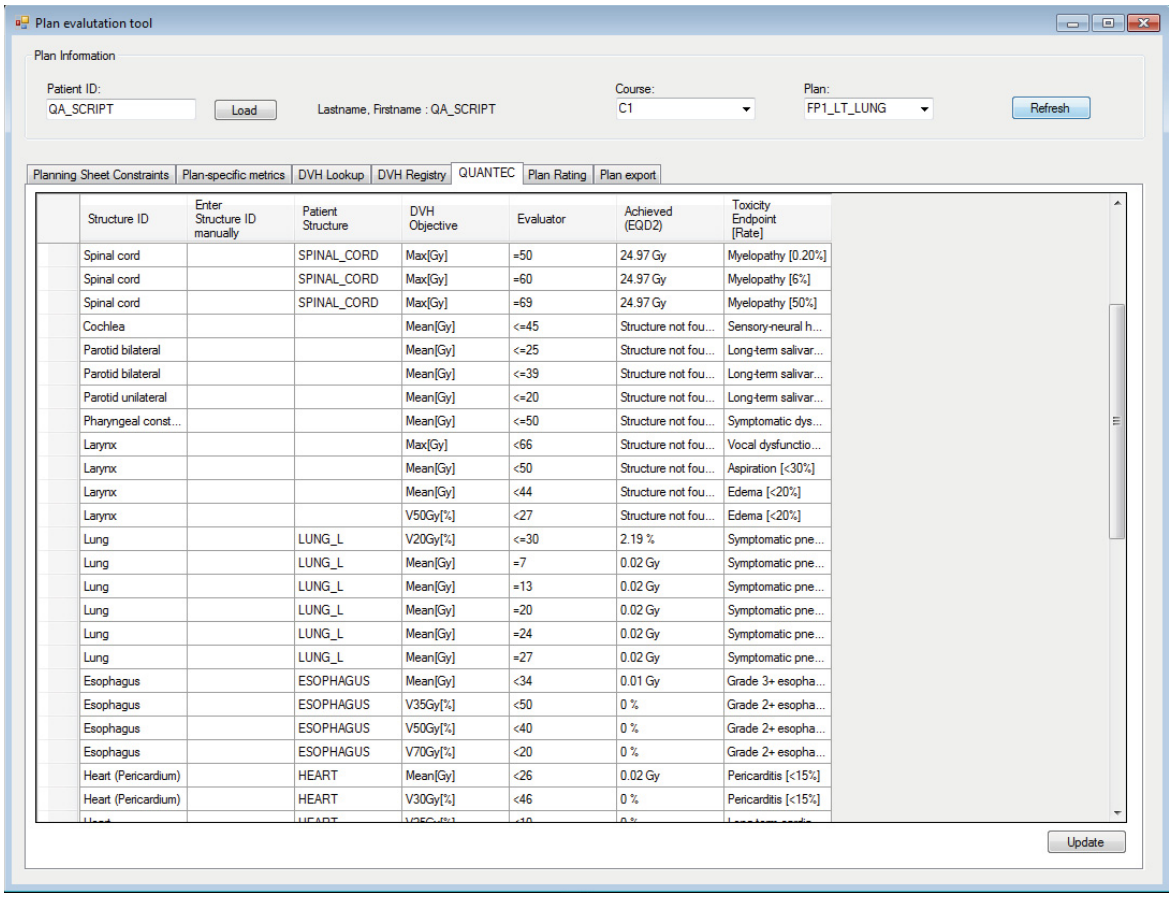


Figure 4.8 – DVH tab. The CW DVH curve of the loaded plan is compared to the individual curves contained within the registry database

4.1.2.5. QUANTEC

Following the "DVH registry" tab is the "QUANTEC" tab, which evaluates and displays the anatomical constraints defined in QUANTEC. These constraints are displayed in a similar manner to the planning sheet constraints. In this section, however, the achieved value is translated into an EQD2 value in order to be able to compare it to the evaluator value, which is defined for 2 Gy fractions. In addition, in the last column, information regarding toxicity related to each of the listed structures is defined with an approximate rate of occurrence.



Structure ID	Enter Structure ID manually	Patient Structure	DVH Objective	Evaluator	Achieved (EQD2)	Toxicity Endpoint [Rate]
Spinal cord		SPINAL_CORD	Max[Gy]	=50	24.97 Gy	Myelopathy [0.20%]
Spinal cord		SPINAL_CORD	Max[Gy]	=60	24.97 Gy	Myelopathy [6%]
Spinal cord		SPINAL_CORD	Max[Gy]	=69	24.97 Gy	Myelopathy [50%]
Cochlea			Mean[Gy]	<=45	Structure not fou...	Sensory-neural h...
Parotid bilateral			Mean[Gy]	<=25	Structure not fou...	Long-term salivar...
Parotid bilateral			Mean[Gy]	<=39	Structure not fou...	Long-term salivar...
Parotid unilateral			Mean[Gy]	<=20	Structure not fou...	Long-term salivar...
Pharyngeal const...			Mean[Gy]	<=50	Structure not fou...	Symptomatic dys...
Larynx			Max[Gy]	<66	Structure not fou...	Vocal dysfunctio...
Larynx			Mean[Gy]	<50	Structure not fou...	Aspiration [<30%]
Larynx			Mean[Gy]	<44	Structure not fou...	Edema [<20%]
Larynx			V50Gy[%]	<27	Structure not fou...	Edema [<20%]
Lung		LUNG_L	V20Gy[%]	<=30	2.19 %	Symptomatic pne...
Lung		LUNG_L	Mean[Gy]	=7	0.02 Gy	Symptomatic pne...
Lung		LUNG_L	Mean[Gy]	=13	0.02 Gy	Symptomatic pne...
Lung		LUNG_L	Mean[Gy]	=20	0.02 Gy	Symptomatic pne...
Lung		LUNG_L	Mean[Gy]	=24	0.02 Gy	Symptomatic pne...
Lung		LUNG_L	Mean[Gy]	=27	0.02 Gy	Symptomatic pne...
Esophagus		ESOPHAGUS	Mean[Gy]	<34	0.01 Gy	Grade 3+ esopha...
Esophagus		ESOPHAGUS	V35Gy[%]	<50	0 %	Grade 2+ esopha...
Esophagus		ESOPHAGUS	V50Gy[%]	<40	0 %	Grade 2+ esopha...
Esophagus		ESOPHAGUS	V70Gy[%]	<20	0 %	Grade 2+ esopha...
Heart (Pericardium)		HEART	Mean[Gy]	<26	0.02 Gy	Pericarditis [<15%]
Heart (Pericardium)		HEART	V30Gy[%]	<46	0 %	Pericarditis [<15%]

Figure 4.9 - QUANTEC constraint evaluation tab

4.1.2.6. Plan rating

The "Plan rating" tab shown in Figure 4.10 and Figure 4.11 allows the quantification of the plan quality according to two different methods: the DDI and the cost function (see *Section 3.1.6.1* and *Section 3.1.6.2*). For the DDI rating, the user can select which structures correspond to an OAR by clicking on the arrows to move the structures to the "Selected OARs" list box. Once the list of OAR structures is completed, by clicking on "Calculate" the rating for the OARs will be determined. For the rating of target conformity, the user simply selects the PTV from the combo box. The overall rating, defined as the average of the OAR index and the target index, appears in the lower section of the window. It is to be noted that the RVR component from the original formulation of the DDI (see *Section 3.1.6.1*) was excluded from the tool as it was found

to have a low impact on plan evaluation. As mentioned in the previous chapter, a 100% rating indicates a theoretically ideal plan.

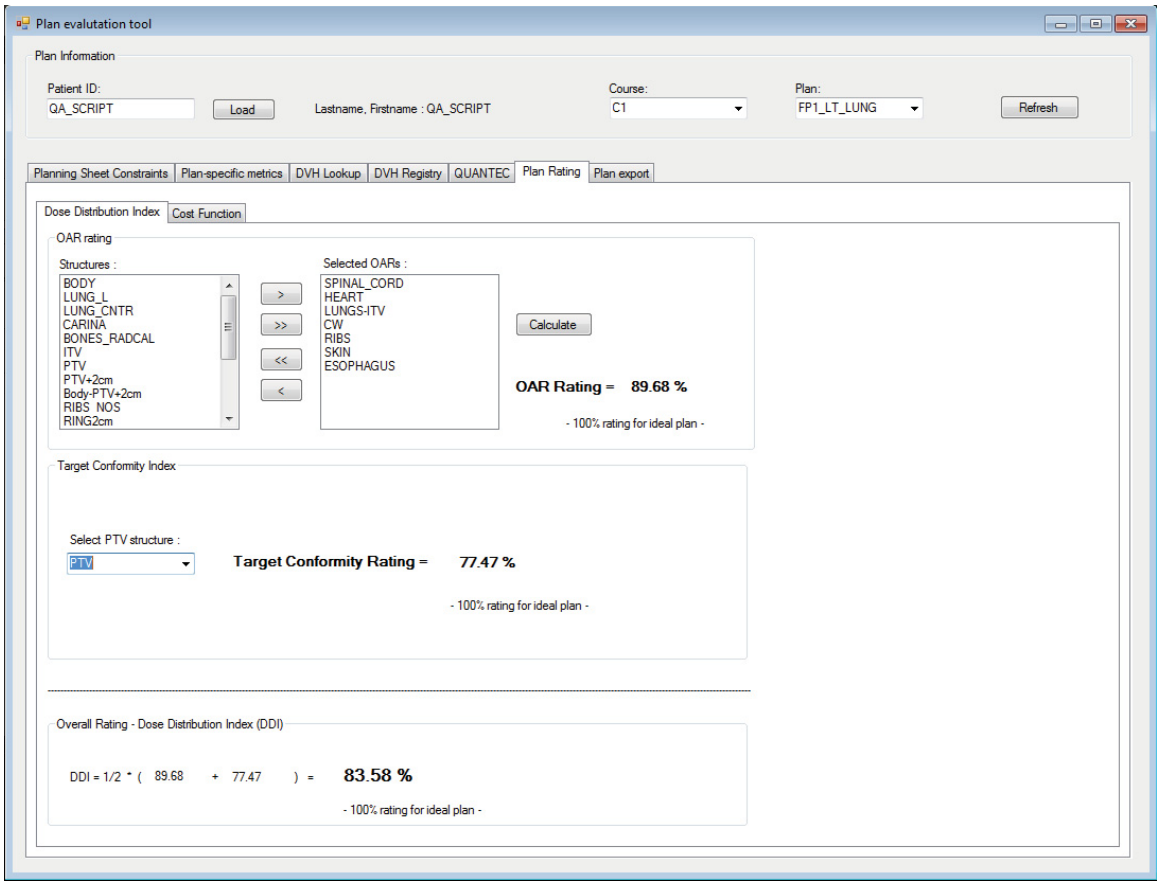


Figure 4.10 - DDI plan rating tab

The plans can also be rated using a cost function as described in *Section 3.1.6.2*. As shown in Figure 4.11, the user must specify the structure corresponding to the PTV as well as the desired conformity criteria for the PTV, which will be taken into account in the cost calculation. This can be specified in terms of dose or volume. The default input is V95% to V107%, but this can be modified as desired. The overall OAR cost shown in this tab is the sum of the individual costs of each OAR that is displayed in the last column of the spreadsheet in the "Planning sheet constraints" tab. The overall cost is displayed in the lower section of the tab and corresponds to the sum of the target cost and the OAR cost.

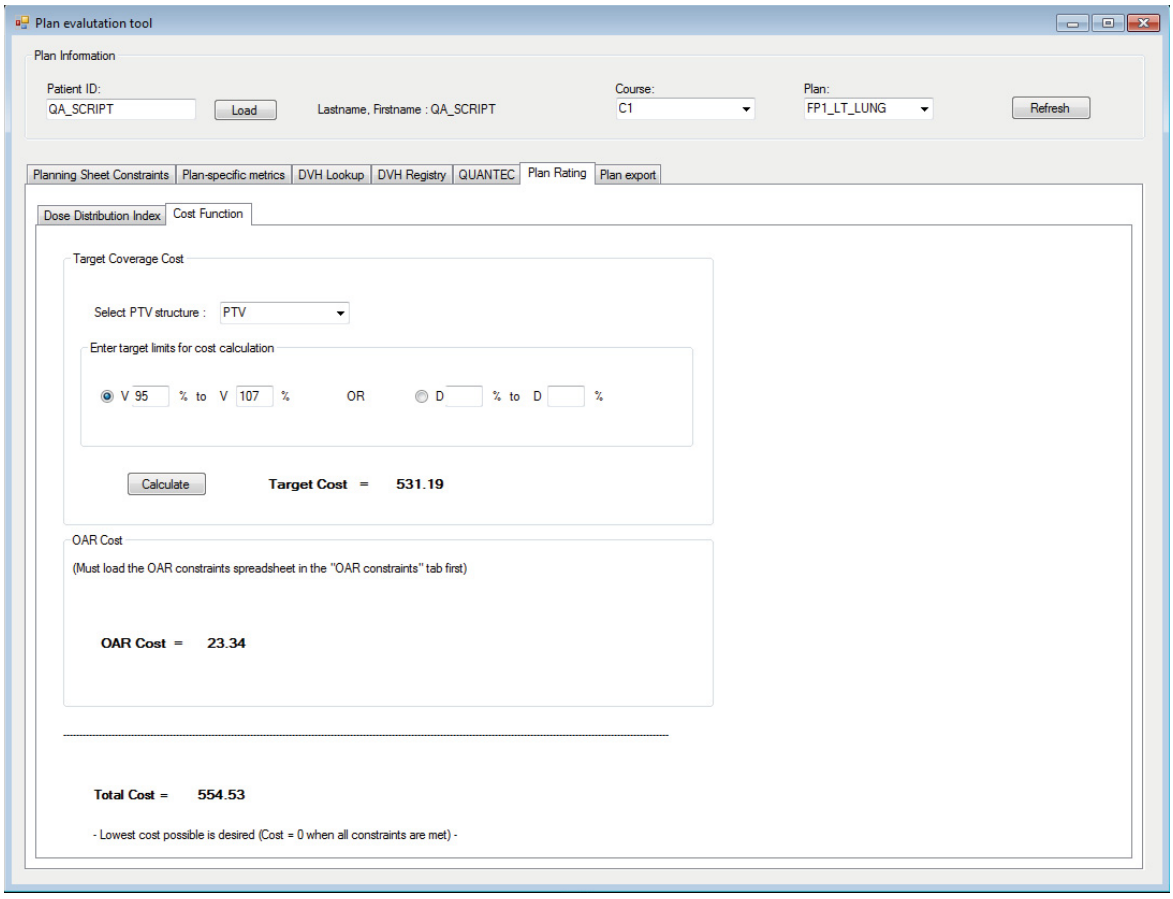


Figure 4.11 - Cost function plan rating tab

4.1.2.7. Plan exporting

The final functionality of the plan evaluation software tool is the possibility to export the plan to the DVH registry database in order for it to be used for future population analyses or to export the plan evaluation information to a PDF report format. The tab shown in Figure 4.12 shows the two buttons that can perform these functionalities. An example of a generated four-page PDF report is shown in Figure 4.13, Figure 4.14, Figure 4.15 and Figure 4.16. On the first page of this report, a summary of the patient and plan information is presented with the patient's name, ID and birthdate, as well as the plan name and prescription. Below this information is a list of the structures contoured on the simulation image with a summary of their volume, mean dose, minimum dose, maximum dose and near maximum dose (D0.3cc). In the first section of the second page is the table containing the OAR constraints that were evaluated in the "Planning

constraints" tab. Below this section is a table containing the plan specific metrics which, in this case, are the lung SBRT metrics. The DVH lookups for which the user selected to "Add to report" are then displayed. In this case, only two were added, but there can be as many as desired. The third page contains the DVH graphs from the DVH registry tab that were added to the report by the user. In this example, only the CW DVHs were added. On the fourth page, the QUANTEC constraint evaluation is shown, with below, the plan rating calculations and results.

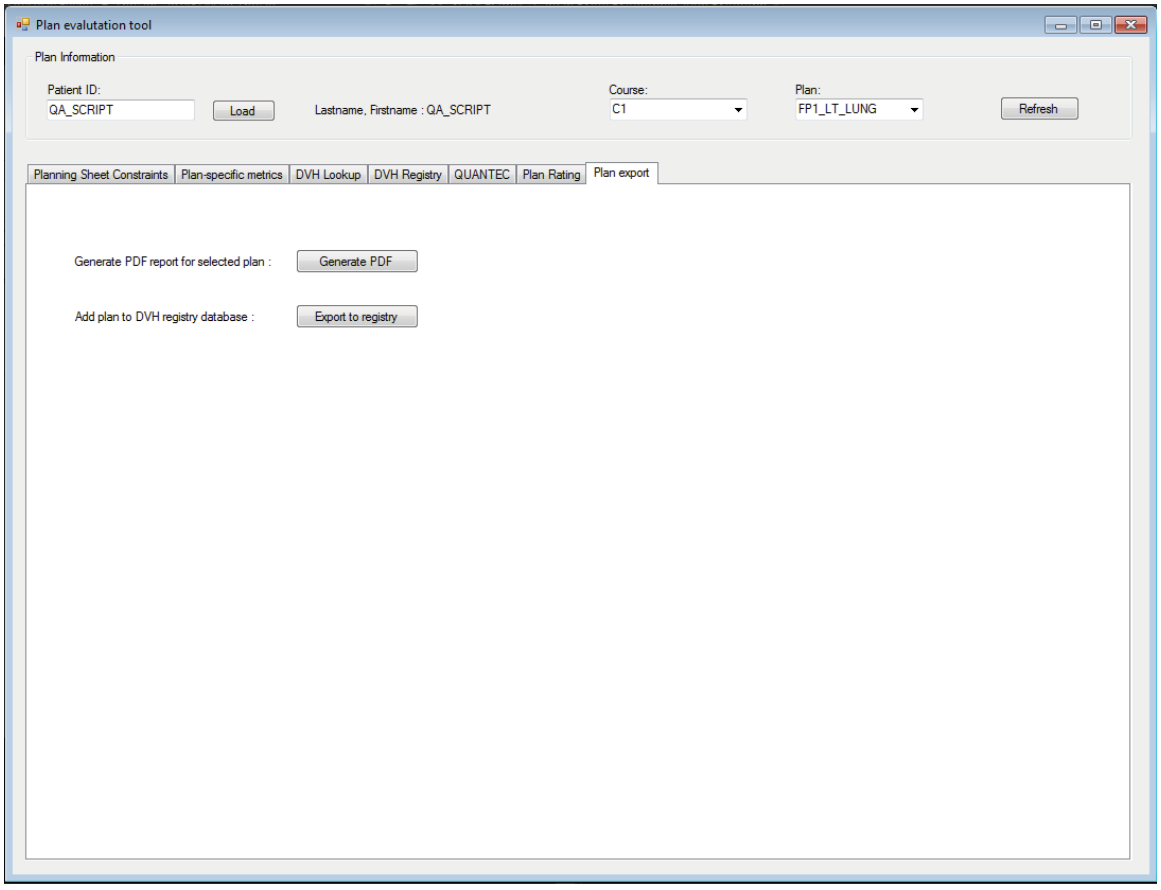


Figure 4.12 - Plan export options (PDF report and/or add to registry database)

Lastname, Firstname (ID: QA_SCRIPT) Generated 2/26/2018 11:54 AM

Lastname, Firstname
ID: **QA_SCRIPT**

Birthdate: **10/24/1930 (age 87)**

PlanID: **FP1_LT_LUNG**
Total prescribed dose: **48 Gy**
Number of fractions: **3**

CT_12_MAY_2016

Image CT_12_MAY_2016 taken 2/6/2018 2:45 PM

Structures

Structure ID	Volume [cc]	Mean Dose [Gy]	Min Dose [Gy]	Max Dose [Gy]	Near Max Dose (D0.3cc) [Gy]
BODY	40594.48	1.10	0.00	58.27	57.74
SPINAL_CORD	85.61	1.55	0.00	15.37	13.78
LUNG_L	1501.28	4.36	0.04	58.24	57.57
LUNG_CNTR	1708.99	0.84	0.06	8.11	7.24
HEART	808.74	3.65	0.30	14.62	14.08
CARINA	22.40	0.32	0.13	0.67	0.61
ESOPHAGUS	32.68	2.26	0.02	9.16	8.39
LUNGS-ITV	3208.46	2.33	0.04	54.97	53.36
BONES_RADCAL	1400.28	1.41	0.00	54.03	50.46
ITV	14.08	53.18	48.53	58.27	57.66
CW	293.70	16.14	0.58	57.75	55.47
PTV	42.00	50.98	42.56	58.27	57.66
RIBS	125.56	9.20	0.17	54.17	50.50
SKIN	1457.31	0.36	0.00	19.97	17.27
PTV+2cm	338.38	24.62	1.14	58.27	57.66
Body-PTV+2cm	40270.83	0.90	0.00	28.53	26.87
RIBS NOS	125.60	8.63	0.17	48.97	47.07
RING2cm	274.85	19.13	1.14	47.75	44.31
LUNG_LT NOS	1477.08	3.47	0.04	49.77	48.24
optPTV_edge	28.12	49.87	42.37	56.78	54.27
optPTV_center	0.32	57.56	55.99	58.27	56.73
HighDoseSpill	40297.45	0.90	0.00	28.56	26.88
R50	168.26	37.23	22.65	58.27	57.66
R100	40.84	51.12	44.52	58.27	57.66

Figure 4.13 - Page 1 of PDF report

Lastname, Firstname (ID: QA_SCRIPT) Generated 3/9/2018 11:02 AM

Planning Sheet Constraints

Structure ID	Patient Structure	DVH Objective	Evaluator	Variation	Priority	Met	Achieved	Cost
Cord	SPINAL_CORD	Max[Gy]	<=18		1	Goal	15.37 Gy	0
Esophagus	ESOPHAGUS	Max[Gy]	<=27		1	Goal	9.16 Gy	0
Heart	HEART	Max[Gy]	<=30		1	Goal	14.62 Gy	0
Both lungs - GTV	LUNGS-ITV	V20Gy[%]	<=15		1	Goal	2.90 %	0
Ribs	RIBS	Max[%]	<=110		1	Not met	112.85 Percent	8.12
Skin	SKIN	V30Gy[cc]	<=10		1	Goal	0.00 cc	0
Skin	SKIN	Max[Gy]	<=32		1	Goal	19.97 Gy	0
Chest wall	CW	V30Gy[cc]	<=30	70	1	Variation	43.47 cc	181.44
Body	BODY	V24Gy[cc]	>=1		Report	-	168.43 cc	-
HIGH DOSE SPILL	Body-PTV+2cm	Max[Gy]	<=24		1	Not met	28.53 Gy	20.52
EVAL_PTV1_R100	BODY	V48Gy[cc]	>=1		Report	-	42.14 cc	-

Plan Metrics -- Lung SBRT

Constraint	Measure	Goal/Variation	Value
PITV	Prescription isodose volume / PTV volume	Goal: <1.2 Variation: < 1.5	1.00317
R50	50% rescription isodose volume / PTV volume	Goal: <4.1 Variation: <5.1	4.00986
PTV V100%	Volume of PTV receiving the prescription dose or higher	Goal: >= 95.0	95.175 %
PTV V90%	Volume of PTV receiving the 95% of the prescription dose or higher	Goal: >= 99.0	99.999 %
Body Dmax	Maximum dose to the whole body	Maximum dose must be in PTV	YES
Low Dose Spillage	Maximum dose from 2cm and away from PTV	Goal: <60.0 Variation: <72.5	59.4 %
Lung V20Gy	Volume of lung receiving 20Gy or more	Goal: <10 Variation: <15	2.90409 %

DVH Lookups

Structure	Reference Value	Lookup Value
CW	30 Gy	14.80232 %vol
CW	50 %vol	25.5 %dose

Figure 4.14 - Page 2 of PDF report

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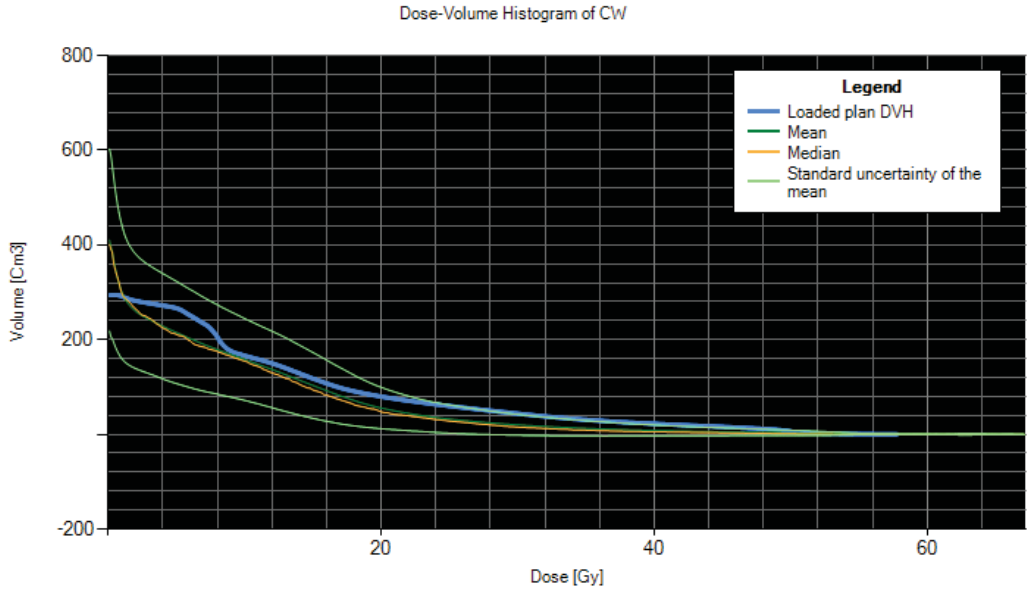
DVH Registry Graphs



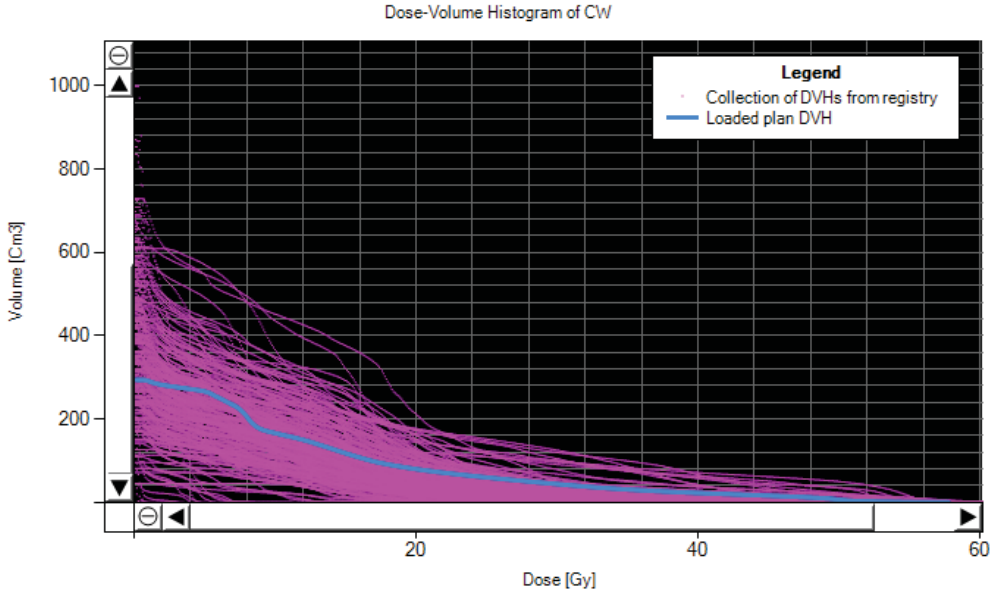


Figure 4.15 - Page 3 of PDF report

Lastname, Firstname (ID: QA_SCRIPT) Generated 2/26/2018 11:54 AM

QUANTEC

Structure ID	Patient Structure	DVH Objective	Evaluator	Value	Toxicity [Rate]
Spinal cord	SPINAL_CORD	Max[Gy]	=50	24.97 Gy	Myelopathy [0.20%]
Spinal cord	SPINAL_CORD	Max[Gy]	=60	24.97 Gy	Myelopathy [6%]
Spinal cord	SPINAL_CORD	Max[Gy]	=69	24.97 Gy	Myelopathy [50%]
Lung	LUNG_L	V20Gy[%]	<=30	2.19 %	Symptomatic pneumonitis [<20%]
Lung	LUNG_L	Mean[Gy]	=7	0.02 Gy	Symptomatic pneumonitis [5%]
Lung	LUNG_L	Mean[Gy]	=13	0.02 Gy	Symptomatic pneumonitis [10%]
Lung	LUNG_L	Mean[Gy]	=20	0.02 Gy	Symptomatic pneumonitis [20%]
Lung	LUNG_L	Mean[Gy]	=24	0.02 Gy	Symptomatic pneumonitis [30%]
Lung	LUNG_L	Mean[Gy]	=27	0.02 Gy	Symptomatic pneumonitis [40%]
Esophagus	ESOPHAGUS	Mean[Gy]	<34	0.01 Gy	Grade 3+ esophagitis [5-20%]
Esophagus	ESOPHAGUS	V35Gy[%]	<50	0 %	Grade 2+ esophagitis [<30%]
Esophagus	ESOPHAGUS	V50Gy[%]	<40	0 %	Grade 2+ esophagitis [<30%]
Esophagus	ESOPHAGUS	V70Gy[%]	<20	0 %	Grade 2+ esophagitis [<30%]
Heart (Pericardium)	HEART	Mean[Gy]	<26	0.02 Gy	Pericarditis [<15%]
Heart (Pericardium)	HEART	V30Gy[%]	<46	0 %	Pericarditis [<15%]
Heart	HEART	V25Gy[%]	<10	0 %	Long term cardiac mortality [<1%]

DDI Plan Rating
OAR Index (Io) : 89.68 %
Target Conformity Index (It) : 77.47 %

Total rating: 83.58 %

Cost Function Plan Rating
OAR Cost: 23.34
Target Coverage Cost: 531.19

Total cost: 554.53

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Figure 4.16 - Page 4 of PDF report

4.2. Data mining tool

4.2.1. Overview

Similar to the plan evaluation tool, the data mining tool is a standalone executable that can be launched from any workstation that runs Eclipse™. This tool aims to facilitate retrospective analyses of treatment planning data by allowing simple data extraction. For this purpose, two main steps are required: first, loading the data to the registry database, and second, selecting the data required for analysis.

4.2.2. Demonstration

4.2.2.1. Entry to database

In order to load the data to the database, a list of the patients IDs, course IDs, plan IDs, the type of the plans ("planning CT" or "CBCT") and the fraction number must be provided in a .CSV spreadsheet. The five columns must be filled in as shown in Figure 4.17 for which two example plans are entered. A fraction number "0" is entered for a planning CT. This spreadsheet is then loaded using the software tool as shown in Figure 4.18. The user can then choose to rename the structures and the plans according to the standardized naming dictionaries from the database. Cohorts can also be created in order to group plans for a particular study. For example, as shown in Figure 4.18 these plans are to be added to an existing cohort named "CW pain study".

DB_Insert_Demo

	A	B	C	D	E	F
1	QA_SCRIPT	C1	FP1_LT_LUNG	Planning CT	0	
2	QA_FLOYD	C1	FP1_LLUNG	Planning CT	0	
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						

Figure 4.17 - Example of spreadsheet listing the plans to be added to the database.

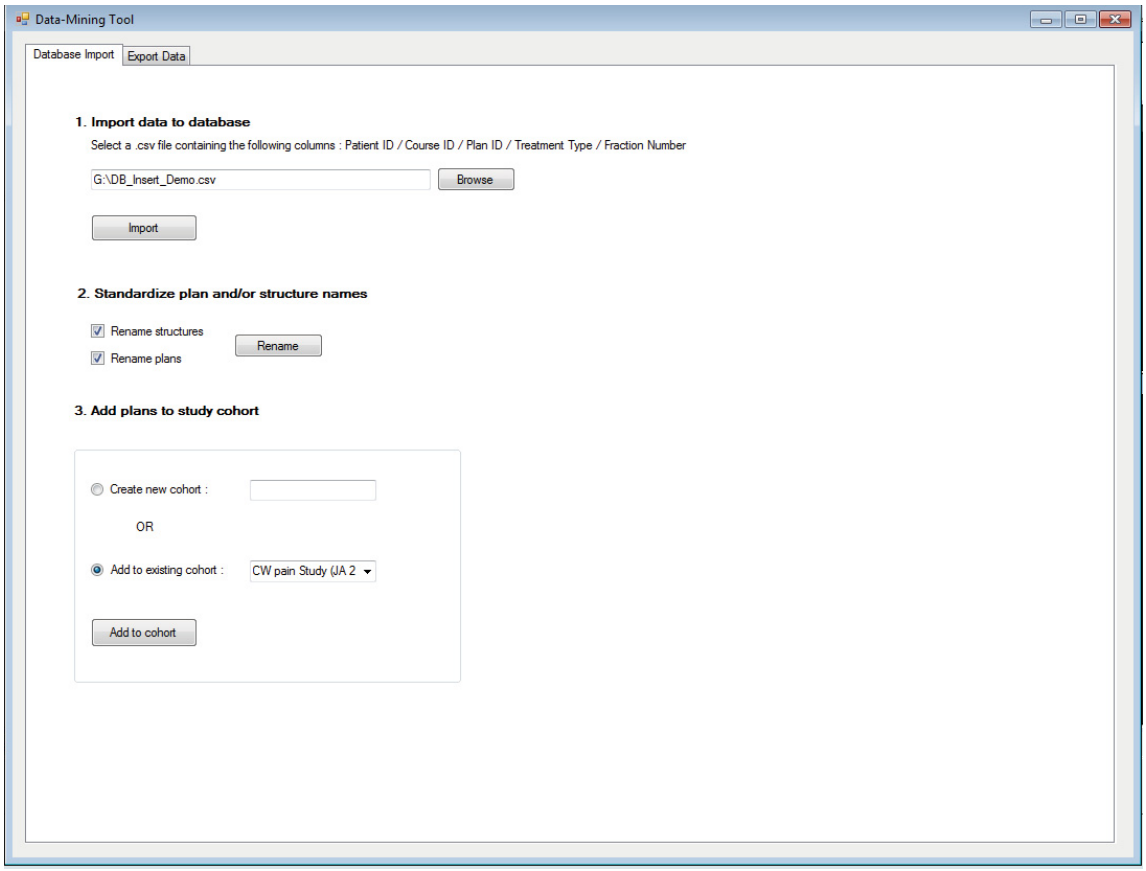

Figure 4.18 – Tab for data entry into the database.

4.2.2.2. Data extraction

Once the plans are entered into the database, it is possible to extract data from them. Using filtering options, the plans from which these data are extracted are chosen. For example in Figure 4.19, only data from lung SBRT planning CT plans treated with 48 Gy in 3 fractions in the CW pain study cohort will be extracted. The type of data to extract is then chosen from the options in the lower section of the tab. In this example, dosimetric CW data including the maximum dose, V30Gy, V40Gy, V50Gy, D1cm^3, D2cm^3 and D5cm^3 will be exported to spreadsheets. This is in fact what was used for the lung SBRT chest wall pain study that is discussed in *Section 4.2.3* and for which the manuscript is presented in the Appendix of this thesis.

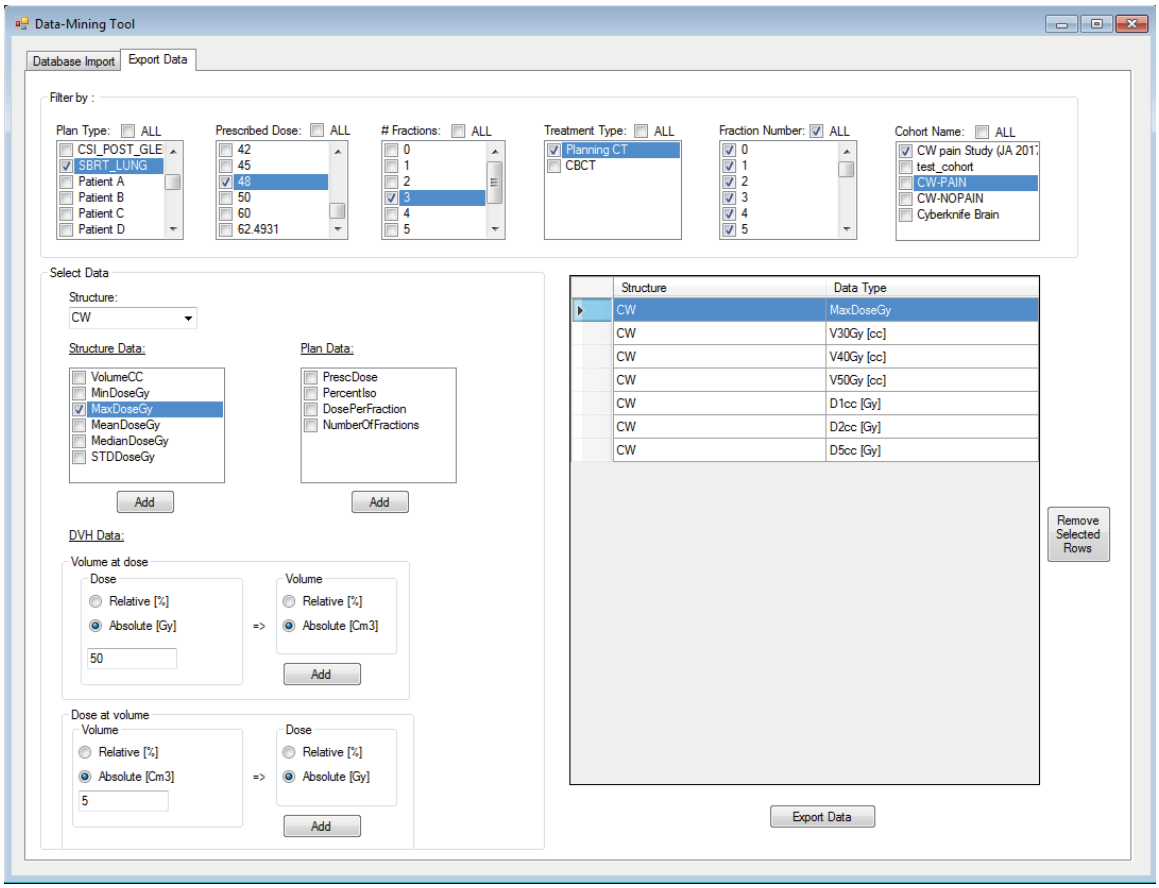

Figure 4.19 – Tab for data extraction showing the filtering options and the selection of the data of interest

Once the selected structures and data type are selected, the user can click on the "Export Data" button, which prompts the user to select a location to store the output files. An output file is created for each structure and data type pair chosen by the user and is named according to the following nomenclature: "StandardStructureName_DataType _Date.csv". The output files are in the form of CSV files and indicate the patient ID, course name, the plan name, the structure name and the data type of interest. For example, shown below in Figure 4.20 is the CSV file for the V30Gy values in cm^3 of the CW in for a test cohort composed of two plans.

CW_V30Gy [cc]_4-Apr-2018

	A	B	C	D	E
1	Patient ID	Course ID	Plan ID	Structure ID	V30Gy [cc]
2	QA_SCRIPT	C1	FP1_LT_LUNG	CW	43.4742
3	QA_FLOYD	C1	FP1_LLUNG	CW	30.5777
4					
5					
6					
7					

Figure 4.20 - Ouput example of data mining tool. CW V30Gy (cm^3) of test cohort.

4.2.3. Chest wall (CW) pain study example

As previously mentioned, the data mining tool enables efficient data collection for retrospective analysis of treatment plans. For example, dose-outcome retrospective studies that require analysis of large amounts of dosimetric data can greatly benefit from such a tool. In this perspective, a retrospective study on the investigation of dosimetric predictors of chest wall (CW) pain following lung SBRT in 48 Gy in 3 fractions was performed, for which this data mining tool was used to gather the data. This data included the volume of the PTV, the volume of the overlapping region between the CW the PTV, and the CW V30Gy, V40Gy, V50Gy, Dmax, D1cm^3, D2cm^3 and D5cm^3, of 135 different treatment plans. The manuscript resulting from this study is presented in the Appendix.

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In this chapter, we will discuss the results in terms of the benefits and the limitations of the software tools developed for this project. Conclusions will then be made by presenting a summary of the thesis and future work that can be done in line with the work completed thus far.

5.1. Discussion

Many software tools have been proposed for general quality assurance of treatment plans for prescription checks, control point checks, beam checks, etc. such as the Plan Checker Tool created by Covington *et al*[1]. On the other hand, few applications have been developed that focus specifically on the dosimetric evaluation of treatment plans as the treatment planning is being performed.

In 1994, Drzymala *et al*. published on integrated software tools for the evaluation of treatment plans, which aimed at presenting a graphical plan evaluation tool that provides assessment of dose statistics, biological models and plan figures of merit for treatment

planning. Although having a similar goal as this thesis project, the portability of their tool was lacking as the installation of the software involves a programmer to write a software bridge between the TPS and the tool. More recently, Song *et al.*[2] proposed an automated treatment plan quality control tool for IMRT plans which amongst other functionalities evaluates dosimetric endpoints and criteria for assessing IMRT plan quality. However, this tool was designed to function through their in-house IMRT re-planning system, and not directly with the commercial TPSs, which limits the scope of its use. Another plan evaluation tool developed by Zhao *et al.*[3] coined "SABER" incorporated biological parameters and retained spatial dose information for an enhanced assessment of treatment planning. Similarly to the other tools mentioned previously, the integration of such a tool in the clinical workflow may be difficult, as DICOM-RT exports from the treatment planning system are required in order to perform the evaluation of a plan. In 2010, Olsen *et al.*[4] used ESAPI to develop software tools aiming to automate various steps of treatment planning. In terms of automating treatment plan evaluation, similar to this thesis project, their software is capable of comparing dosimetric aspects of the treatment plan (OAR constraints, PTV coverage, plan conformality, etc.) to the physician-specified treatment planning orders. In addition, the use of ESAPI in their software development allows a seamless integration of the tool and eliminates the need for exporting or manipulating the treatment plan data. However, unlike the solution presented in this thesis, there is no use of previous treatment plan data for comparison with the current treatment plan being evaluated.

It is believed that the proposed plan evaluation tool developed in the context of this thesis is the first of its kind using API scripting for easy integration with the Eclipse™ TPS, that is capable of assessing dosimetric objectives and constraints, grading the plans as well as comparing the dosimetry of past plans in a single graphical user-friendly stand-alone software.

As for data mining, ESAPI scripts have been developed by Varian collaborators[5] to extract dosimetric information from plans within the Aria database. These scripts, however, lack intuitive user interfaces and are not designed to batch process specified lists of plans. The tool developed for this project addresses these issues by offering a

user-friendly way to mine data from a large number of plans. In addition, the ability to store the extracted data on a network database facilitates the organization of the data for analysis.

5.1.1. Project benefits

5.1.1.1. Plan evaluation tool

The assessment of the quality of treatment plans in radiotherapy involves a variety of quantitative metrics and qualitative assessments. Common metrics, standards and criteria exist in our clinic, but their implementation can vary. In fact, much of the decision-making pertaining to treatment planning involves subjectivity that may depend on the training and past experience of the treatment planner. With this in mind, standardizing treatment plan assessment with a tool that can guide the user through the evaluation of various metrics can be greatly beneficial for reducing the variation of the overall quality of treatment plans created and delivered in our clinic. The software tool developed in the context of this thesis addresses this challenge in a way that can enrich the experience of treatment planning and the confidence in the quality of the outputted plans.

Beyond the standardization of treatment planning, the plan evaluation tool greatly contributes to the efficiency of the treatment planning process. As described in the *Results* section, *Chapter 4*, many processes that are typically evaluated in a manual manner are made more automatic with only a limited need for user input. In fact, although the Eclipse™ treatment planning software alone provides all the data necessary for treatment plan assessment, the traditional methods for identifying these data, calculating metrics and comparing the results to standards are not always user-friendly and can be very time-consuming. The grouping of the majority of the steps of treatment plan evaluation into a single user-friendly tool that is integrated and communicates directly with the existing treatment planning system can greatly reduce the amount of time required to complete a treatment plan.

Another advantage of our plan evaluation tool is its ability to compare with past data. In fact, each treatment plan produced in our clinic carries a vast amount of useful data that is otherwise "wasted" due to the previous lack of a framework for easily exporting and storing these data. This aspect is efficiently handled by the plan evaluation tool, which allows DVH visualization of historical plans and allows the dosimetrist to easily export their treatment plans to the registry at the moment they are created.

5.1.1.2. Data mining tool

In order to fully benefit from the wealth of data contained in treatment planning, it is necessary to be able to store, access and retrieve these data in an efficient manner. This is what the data mining tool allows. For the CW pain study presented in the Appendix, 135 plans were analyzed in order to investigate several different predictors of this SBRT-related toxicity. By using the DVH registry database to store these plans and the data mining tool to retrieve the values of the different predictors, the amount of time required for data collection was greatly reduced. In fact, data collection is amongst the most difficult and time-consuming challenges when carrying out such a study.

5.1.2. Limitations

5.1.2.1. Plan evaluation tool

Some limitations of the treatment plan evaluation tool pertain to the inflexibility or the inaccessibility of certain information using the ESAPI framework. In fact, because ESAPI is continuously being adapted and improved, there are some treatment planning data stored in Eclipse™ TPS that cannot easily be retrieved using it. In addition, we are currently using Eclipse™ Version 11, and therefore have access to the corresponding version of ESAPI, which is not the latest and most up-to-date version. The consequence of this on the plan evaluation tool is that the user input must be increased, which limits the automation of the treatment planning assessment. For example, it is not possible to know the name of the structure to which the dose is prescribed using ESAPI, which makes it necessary for the user to specify the target structure in the plan evaluation tool for the evaluation of certain metrics.

5.1.2.2. Data mining tool

A notable limitation of the data mining tool is the lack of standardization in the naming of plans and structures by dosimetrists, radiation oncologists and physicists in Eclipse™. When creating new structures or plans, the TPS requests the user to enter a name using free text boxes. As a result, this creates a wide range of variability in the naming of structures and plans that may relate to the same concept. Although standard nomenclature is suggested, it is difficult to implement and is rarely enforced in clinical practice. In order to address this inevitable issue that is present in all of our historical data, mapping dictionaries were created in order to associate non-standard names to standard names. However, this method is imperfect and requires, in some cases, a great deal of manual quality assurance to ensure that the associated standard names are correct.

5.2. Conclusion

5.2.1. Thesis summary

The goal of this thesis project was to develop a software tool for assisting dosimetrists in treatment plan assessment as well as developing a framework for retrospective data mining of plans. These goals were achieved and two unique software tools were developed. The tools provide various functionalities including the evaluation of OAR and target constraints, the evaluation of derived plan-specific metrics for lung SBRT and SRS plans, the comparison of structure DVH curves to those of benchmarked plans, the ability to look up DVH coordinates, the rating of plans using quantitative measures, the evaluation of biological metrics, the creation of plan reports and the data mining of historical treatment plans.

5.2.2. Future Work

Both of the software tools developed over the course of this project have the great advantage of being flexible and can easily be adapted for future improvements. This is in fact an important aspect to consider as the field of radiation oncology and medical

physics is constantly evolving. For example, OAR constraints and other plan metrics that are widely accepted today may be completely different in a few years years.

The plan evaluation tool will soon be implemented into the clinical routine of our institution. Once implemented, feedback from the users will be incorporated to ensure it is well adapted to the needs of our clinic. As for the data mining tool, it is currently available for researches in our department to efficiently collect data for their respective studies.

5.3. References

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2. Song T, Li N, Zarepisheh M, et al. An Automated Treatment Plan Quality Control Tool for Intensity-Modulated Radiation Therapy Using a Voxel-Weighting Factor-Based Re-Optimization Algorithm. *PLoS One*. 2016;11(3):e0149273. https://doi.org/10.1371/journal.pone.0149273.

3. Zhao B, Joiner MC, Orton Colin G, Burmeister J. "SABER": A new software tool for radiotherapy treatment plan evaluation. *Med Phys*. 2010;37(11):5586-5592. doi:10.1118/1.3497152

4. Olsen L, Robinson C, He G, et al. Automated radiation therapy treatment plan workflow using a commercial application programming interface. *Pract Radiat Oncol*. 2014;4(6).

5. Varian Developor. variandeveloper.com. Accessed March 3, 2018.

Appendix

Chest Wall Pain Following Stereotactic Body Radiation Therapy to the Lung Using 48 Gy in 3 Fractions: A Search for Predictors

Julia Albers, William Parker, John Kildea, Catherine Pembroke, Sergio Faria

Abstract

Purpose: Chest wall (CW) pain is an uncommon but bothersome late complication following lung stereotactic body radiation therapy (SBRT). Despite numerous studies investigating predictors of CW pain, no clear consensus has been established for a CW constraint. In addition, the majority of these publications have limitations including analysis of a mix of patients treated with different dose and fractionation regimens, less than 6-month follow-up times and analysis of patients treated without heterogeneity correction during dose calculation. The aim of our study was to investigate factors related to CW pain in a homogeneous group of patients treated at our institution.

Materials and Methods: 122 patients treated with SBRT were analyzed. All patients were treated with the same SBRT regimen of 48 Gy in 3 fractions, seen for at least 6 months of follow-up, and planned with heterogeneity correction. CW pain was scored according to CTCAE v3.0. Patient (age, sex, diabetes, osteoporosis), tumour (volume of PTV, PTV/CW overlapping volume) and CW dosimetric parameters (V30Gy, V40Gy, V50Gy, D1cm^3, D2cm^3, D5cm^3, Dmax) were collected. The correlation between CW pain (Grade $\geq$ 2) and the different parameters was evaluated using univariate and multivariate logistic regression.

Results: Median follow-up was 18 months (6-56). 12/122 patients developed CW pain of any grade (7 with Grade 1, 3 with Grade 2 and 2 with Grade 3 pain). In univariate analysis, only V30Gy (p=0.034) and the volume of the overlapping region between the

PTV and the CW (p=0.038) significantly predicted CW pain, but these variables were later proved non-significant in multivariate regression.

Conclusions: Our analysis could not find any correlation between the studied parameters and CW pain. Considering our present study and the wide range of differing results from the literature, a reasonable conclusion is that a constraint for CW pain is yet to be defined.

Introduction

Stereotactic body radiation therapy (SBRT) has emerged as an appropriate alternative to surgical resection for patients with early stage non-small cell lung cancer (NSCLC) or oligometastatic lesions to the lung[1]. In fact, local control with SBRT has been found to be similar to surgery but with less toxicity, mainly because of its non-invasive nature[2]. Furthermore, numerous single-institutional series and phase II studies investigating lung SBRT have demonstrated high local control rates of 70–90% with an acceptable risk of severe toxicity of less than 10%[1–5].

However, early reports of lung SBRT demonstrated unique toxicity events that have not been previously seen with conventionally fractionated thoracic radiotherapy. In particular, chest wall (CW) toxicity, for which symptoms may not be apparent until six months after SBRT, has been only more recently described with varying incidences[6]. CW toxicity includes a spectrum of clinical findings including rib fracture (symptomatic or asymptomatic), skin changes (from erythema to ulceration) and CW pain believed to be neuropathic and not related to rib fracture. Despite these known complications, there are no clear dose constraints for the CW, particularly related to CW pain. Bothersome CW pain unrelated to rib fracture is an uncommon but important side effect that can occur after SBRT and that may significantly affect the patient's quality of life. The majority of publications to date on predictors of CW pain after SBRT have limitations including studies with analysis of a mix of patients treated with different dose and fractionation regimens[7–15], short follow-up times (less than 6 months) that do not account for the latency of toxicity[9,12,13,15–18], analysis of patients treated with SBRT planned without

appropriate heterogeneity correction making it impossible to know the true dose received by the CW[11–13,16], or analysis of a small cohort of patients (less than 100 cases)[4,13–15,18,19].

In this article, we report on our institutional experience with CW pain and the search for dose constraints for the CW as an organ at risk in a group of patients treated with SBRT with the same dose and fractionation, with at least 6 months of follow-up, planned with appropriate heterogeneity correction and without any special dose constraint to the CW at the initial treatment planning.

Materials & Methods

Inclusion criteria

Patients treated at our institution by SBRT to the thorax due to any peripheral lung tumour (primary or metastatic) between January 2007 and June 2016 were reviewed for this study. Peripheral lung tumours were defined as located beyond 2 cm of the central bronchial tree. Amongst these patients, only those with a clinical follow-up longer than six months were considered to account for the latency of CW pain onset, which typically is of a median greater than 6 months[6,19]. In addition, in order to ensure a homogenous cohort, only patients that received our institutional "standard" dose for peripheral lesions of 48 Gy in 3 fractions and planned with heterogeneity correction were included. With these criteria considered, 122 patients treated for 135 lesions were analyzed. All patients were planned and treated without contouring the CW or any specific CW avoidance criteria. This study was approved by the research ethics board of our institution.

Treatment planning & delivery

A 4DCT was acquired (3 mm slice separation) for each patient, from which the internal target volume (ITV) was contoured. The treatment planning was carried out using Eclipse™ (Varian Medical Systems, Palo Alto, CA) treatment planning system with the use of the superposition-convolution algorithm with heterogeneity correction. Patients were treated either with volumetric modulated arc therapy (VMAT) or conventional static fields for which 5 to 7 static fields were used with the multileaf

collimators positioned to shape the fields. A free breathing CT was used for dose calculation and contouring of non-target structures. The dose prescription to the planning target volume (PTV), defined as the ITV + 5 mm isotropic margin, and the constraints to the organs at risk were based on the RTOG 0236 protocol[20]. A cone beam CT (CBCT) was acquired prior to each fractionation to verify patient positioning. The treatment planning and treatment delivery characteristics are summarized in Table A-1.

Table A-1 – SBRT 48 Gy in 3 fractions treatment characteristics, constraints and standard procedure

3D-CRT	
Dose Prescription	Dose normalized to 100% at center of mass of the PTV (COM_{PTV}) 95% of PTV covered by prescription isodose surface
Dose Planning Procedure/Calculation Algorithm	Forward planning using Eclipse™ (Varian Medical Systems, Palo Alto, CA)/ Superposition-convolution algorithm with heterogeneity correction
Beam Type	6 MV photon
Target Volume Definition	ITV: drawn from 4DCT using maximum intensity projection protocol PTV: ITV +5mm isotropic margin
IGRT (Image-Guided Radiotherapy)	CBCT before each fraction
Plan Verification	Independent monitoring unit check using RadCalc® (LifeLine Software, Inc., Tyler, TX)
Organ	**Constraints**
PTV	V48Gy > 95%
Spinal cord	D_{max} < 18 Gy (6 Gy/fr)
Oesophagus	D_{max} < 27 Gy (9 Gy/fr)
Heart	D_{max} < 30 Gy (10 Gy/fr)
Brachial Plexus	D_{max} < 24 Gy (8 Gy/fr)
Both lungs - GTV	V20Gy <15%

Follow-up and CW pain grading

All patients were seen for a follow-up at 1-2 months after completion of the SBRT, and every 4-6 months thereafter. The charts of all eligible patients were reviewed and CW pain was retrospectively graded by two physicians according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for pain[21]. Accordingly, Grade 1 is defined as mild pain that does not interfere with function, Grade 2 is moderate pain where the pain or analgesics interfere with function without interfering with activities of daily life (ADL), Grade 3 is severe pain with pain or analgesics severely interfering with ADL, and Grade 4 is described as disabling pain.

CW definition

The CW was contoured retrospectively for each patient and defined as a 2 cm expansion from the visceral pleural surface as illustrated in Figure A-1; a similar definition to what was previously described by Dunlap *et al.*[13], but with a 2 cm expansion instead of 3 cm. The posterior limit of the CW contour finished at the border of the vertebral bodies and the anterior limit at the sternum or manubrium. The CW was contoured not more than 1-2 cm above and below the PTV.

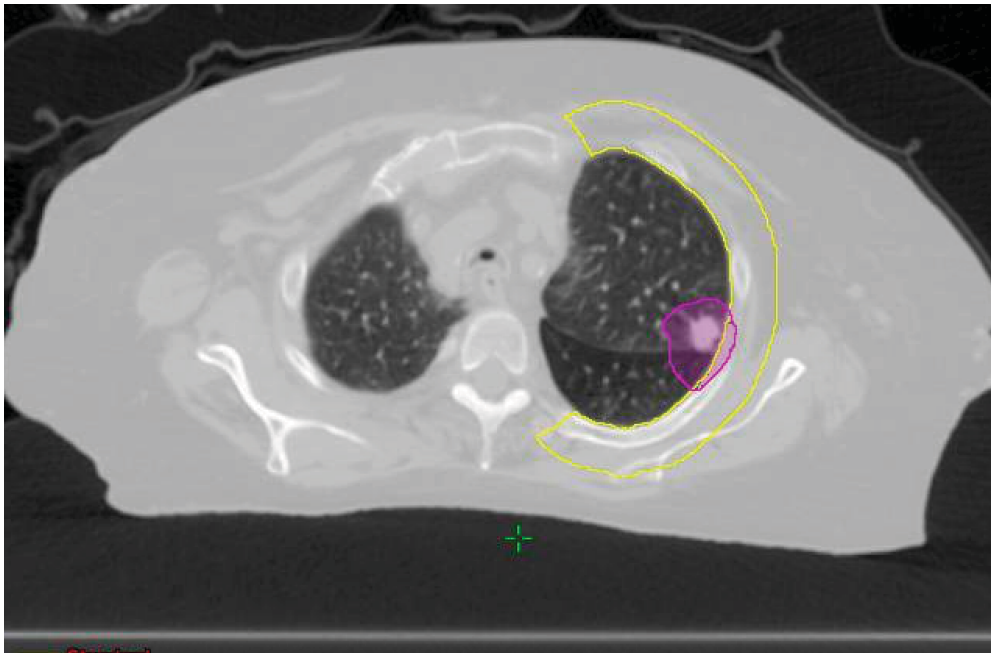

Figure A-1 - The CW region is defined by the yellow C-shaped contour. The PTV is shown in magenta, involving the chest wall.

Data Collection

Using the electronic medical records and Eclipse™ (Varian Medical Systems, Palo Alto, CA) treatment planning system, various patient, tumour and dosimetric parameters were gathered. The patient parameters included the age, sex, and the presence of diabetes or osteoporosis at the time of consultation. The tumour parameters extracted were the volume of the PTV and the volume of the overlapping region between the PTV and the CW, both in cm^3. The dosimetric parameters were the V30Gy, V40Gy, V50Gy, D1cm^3, D2cm^3, D5cm^3 and maximum point dose (D_{max}) of the CW, all in absolute values.

Data Analysis

Data analysis and data correlation were carried out using the SAS® 9.4 (SAS Institute Inc., Cary, NC) statistical software. To verify the correlation between the patient, tumour and dosimetric parameters and CW pain (Grade ≥ 2), logistic regression analysis was performed using both univariate and multivariate models. A *p* value of 0.05 or less was considered for statistical significance. The univariate analysis was performed for each of the aforementioned parameters and the statistically significant factors from the univariate analysis were used as predictors in the multivariate regression.

Results

Patients & CW pain

Table A-2 summarizes the patient and tumour characteristics of the study cohort. 122 patients treated for 135 lung lesions (113 primary lung cancer and 22 pulmonary metastases) met the inclusion criteria of the present analysis. The median age was 71 years with half of the patients being female. Six patients (5%) were previously diagnosed with osteoporosis and 18 (15%) with diabetes at the time of consultation. Median follow-up time was 18 months (range, 6-56 months), and 12 of the 122 patients (10%) expressed CW pain of any grade at a median of 6 months (range, 2-25) with 7 (6%) patients reporting Grade 1 CW pain, 3 (2%) patients Grade 2 and 2 (2%) patients Grade 3. Of the 5 patients with Grade ≥ 2 pain, 4 reported CW pain on at least two consecutive visits, and

the other was not seen in another follow-up after the first report of CW pain. Six patients presented rib fractures, half of whom also had CW pain that seemed unrelated to the rib fracture. Typically, the patients with CW pain complained of persistent burning-type pain radiating through the CW around the area where they received the treatment. The pain was generally controlled with opioid pain medication such as fentanyl patches and/or hydromorphone, and in some cases lasted for weeks.

Table A-2 – Patient and tumour characteristics of the study cohort

Patient characteristics		
Patients	122	100%
Age median (range)	71	(44-90)
Female	61	50%
Osteoporosis	6	5%
Diabetic	18	15%
Tumour characteristics		
Total number of lesions	135	100%
Primary lung cancer	113	84%
Pulmonary metastasis	22	16%
Cases of pain	13	10%
Grade 1	8	6%
Grade 2	3	2%
Grade 3	2	1%
Cases of rib fracture	6	4%
Duration of follow-up (range)	Mean: 19.9 mo	(6-56 mo)
	Median: 18.0 mo	

Correlation of dosimetric/tumour/patient parameters with CW pain

Median, mean and the standard deviation of each of the analyzed CW dosimetric parameters separated by toxicity are shown in Table A-3. Mean values of the CW dose-volume histograms (DVH) were computed for all patients who presented CW pain Grade ≥ 2 and for all those without reported CW pain or Grade 1 CW pain as shown in Figure A-2. The shaded envelopes around each curve indicate the standard deviation of the respective data set. Logistic regression was performed to estimate odds ratios and evaluate the correlation between the characterizing parameters and CW pain (Grade ≥ 2). The odds ratios and *p* values for both the univariate and multivariate analyses are shown in Table A-4. The univariate analysis results demonstrate that only the V30Gy (p=0.0339) and the overlapping volume between the CW and the PTV (p=0.0376) are of statistical significance in terms of correlation with CW pain. Dosimetric variables such as V40Gy, V50Gy, D1cm^3, D2cm^3, D5cm^3 and PTV volume as well as clinical parameters, such as age, osteoporosis and diabetes all failed to show any statistical significance. The overlapping volume and the V30Gy of the CW were then used in a multivariate model for further analysis of correlation with CW pain. For this purpose, multivariate logistic regression including these two parameters as predictors was performed. Considering a *p* value of 0.05 or less for statistical significance, none of the parameters remained predictive for CW pain after multivariate analysis.

Table A-3 - CW dosimetry mean, median and standard deviation by toxicity

	All tumours (n=135)			Pain (Grade ≥ 2) (n=5)			No pain (Grade ≤ 1) (n=130)		
	Median	Mean	StdDev	Median	Mean	StdDev	Median	Mean	StdDev
Dmax (Gy)	55.4	52.1	9.7	55.8	55.8	2.2	55.4	51.9	9.9
D1cm^3 (Gy)	51.7	47.6	10.7	53.8	53.9	1.9	51.7	47.3	10.8
D2cm^3 (Gy)	50.1	45.5	10.9	52.5	52.5	2.3	49.7	45.3	11.0
D5cm^3 (Gy)	43.7	41.1	10.7	49.2	48.5	54.5	43.3	40.8	10.8
V30Gy (cm^3)	18.7	23.1	21.4	39.4	45.1	31.6	18.2	22.3	20.4
V40Gy (cm^3)	7.0	9.8	12.1	15.7	21.2	19.4	6.9	9.4	11.5
V50Gy (cm^3)	2.0	3.9	6.8	3.6	9.9	12.8	1.8	3.7	6.3
PTV volume (cm^3)	28.2	33.8	24.7	50.8	53.6	35.05	28.1	33.1	23.9
Overlapping volume (cm^3)	1.2	2.6	4.2	3.1	7.2	9.2	1.1	2.5	3.7

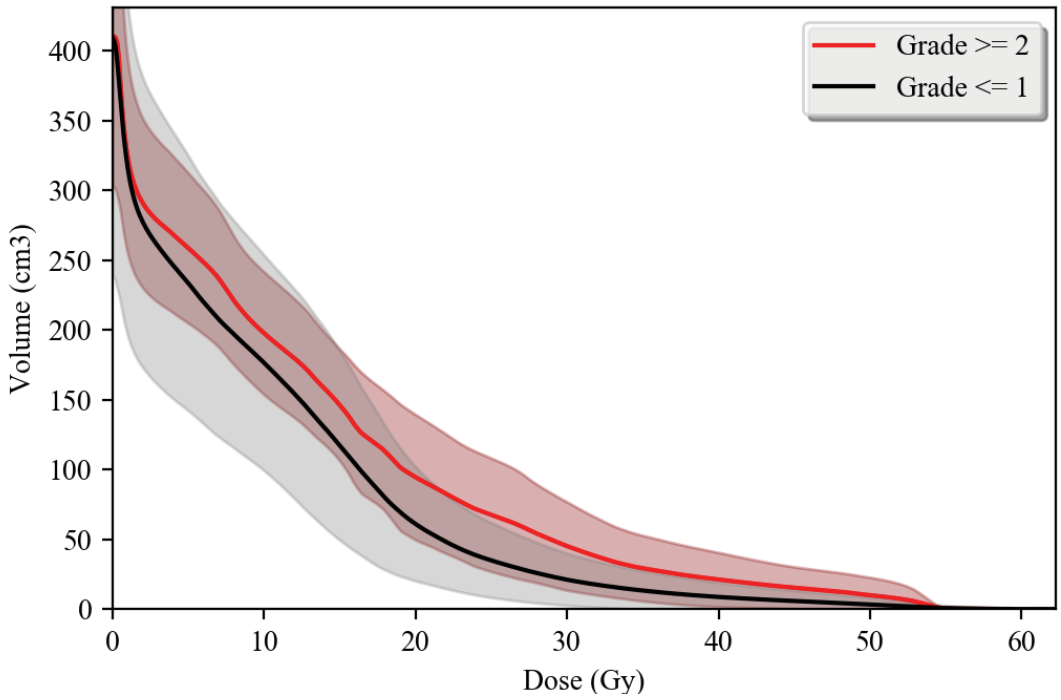

Figure A-2 - Mean DVH curves with shaded standard deviation envelopes for patients with (Grade ≥ 2) and without (Grade ≤ 1) CW pain

Table A-4 - Univariate logistic regression results for all patient, tumour and dosimetric parameters considered and multivariate results combining the CW V30Gy and the overlapping volume between the CW and the PTV

Univariate analysis		
Factor	**OR (95% CI)**	***p* value**
V30Gy	1.030 (1.002-1.059)	0.0339
V40Gy	1.042 (0.999-1.087)	0.0581
V50Gy	1.064 (0.992-1.141)	0.0840
D1cm^3	1.139 (0.923-1.406)	0.2248
D2cm^3	1.131 (0.939-1.362)	0.1963
D5cm^3	1.106 (0.966-1.266)	0.1430
Dmax	1.073 (0.904-1.274)	0.4189
PTV volume	1.024 (0.997-1.052)	0.0862
Overlap vol. CW/PTV	1.130(1.007-1.267)	0.0376
Age	1.064 (0.952-1.188)	0.2744
Diabetes	1.662 (0.175-15.764)	0.6582
Osteoporosis	6.250 (0.586-66.633)	0.1291
Sex	0.667 (0.108-4.122)	0.6628
Multivariate analysis		
V30Gy	1.022 (0.981-1.064)	0.2963
Overlap vol. CW/PTV	1.057 (0.894-1.249)	0.5146

Discussion

CW pain is widely recognized as an important adverse effect of SBRT and has been the subject of multiple studies since 2010[6–19,22–27]. Symptoms can range from mild and transient to severe and chronic. In some cases, pain may remain incompletely relieved despite aggressive medical management. The exact pathophysiology of CW pain is not well understood, however, it is thought to be caused by injury to the intercostal nerves resulting in neuropathic pain[6].

Interestingly, the reported incidences of CW pain after SBRT vary widely ranging from 8%[14] to 46%[26]. Furthermore, the incidence for Grade 3 CW pain ranges from 0%[17,19] to 28%[13]. These large ranges suggest that the assessment of CW pain needs to be improved and perhaps routinely done in a prospective way. Our findings are in the lower range of these brackets with 10% of our cohort that developed CW pain of any grade and only 1% with Grade 3 pain.

Dunlap *et al.*[13] have the merit of being among the first to analyze predictors of CW toxicity including CW pain and rib fracture, and to suggest a CW constraint for lung SBRT. In 2010, they reported a retrospective review of 60 patients treated by SBRT in two different institutions, with total doses varying from 21 Gy to 60 Gy given in 3 to 5 fractions and with constraints for organs at risk according to the RTOG 0236 protocol. They did not mention whether heterogeneity correction was used during treatment planning. The CW was not designated as a constrained structure for the original treatment plans. They were the first to suggest contouring the CW volume similarly as in our present study, an approach which has also been reproduced by different groups[8,10,13,19]. They reported a surprisingly high 28% rate of Grade 3 CW pain. The authors suggested that, to reduce the risk of CW toxicity without compromising tumour coverage, the CW volume receiving over 30 Gy (V30Gy) in 3 to 5 fractions should be limited to 30 cm^3. It is to be noted that this suggestion practically eliminates the use of SBRT with 3-5 fractions in any case where the PTV overlaps the CW and is ultimately unrealistic.

Mutter *et al.*[9] performed a similar exercise reviewing 126 patients that received SBRT with doses varying between 40 Gy to 60 Gy also given in 3 to 5 fractions. Again, the CW was not a constrained structure during the treatment planning. In spite of similar dose and fractionation compared to the Dunlap *et al.*[13] study, they found "only" 15% of Grade 3 CW pain, although still a much higher rate then in our study. In their analysis, rather than 30 cm^3, a CW volume over 70 cm^3 receiving more than 30 Gy was significantly correlated with Grade ≥ 2 CW pain. The drawbacks of these two important studies are the mix of different number of fractions from 3 to 5 in the same analysis, the inclusion of patients with follow-up times less than 6 months and the possible lack of appropriate heterogeneity correction, which we believe are non-negligible factors.

A few other early studies also had the same limitation of mixing different dose/fractionation schemes in the same analysis. One of which is the study published in 2011 by Andolino *et al.*[12] reviewing 347 cases treated with doses varying from 18 to 72 Gy in 3 fractions and with only some cases corrected for inhomogeneity. They reported that the maximum point dose to the CW should be limited to 50 Gy and that the V40Gy should be kept below 5 cm^3. Also in 2011, Bongers *et al.*[11] reported on a large cohort of 500 patients treated with 60 Gy in 3, 5 and 8 fractions where the risk factors found to be associated with CW toxicity were the tumour size, the PTV volume and the distance of the tumour from the CW, but dosimetric variables were not analyzed. Creach *et al.*[10] reviewed 140 patients treated with either 54 Gy in 3 fractions or 50 Gy in 5 fractions, planned with heterogeneity correction and concluded that the relative volume of CW receiving over 30-40 Gy should be minimized.

With the same objective of studying CW pain after SBRT, Stephans *et al.*[19] reported a retrospective review of 48 patients for which all received the same prescription of 60 Gy in 3 fractions as per the RTOG 0236 protocol, but also without heterogeneity correction at the time of treatment planning. Median follow-up was 18.8 months (range, 5.6-30.7). Contrary to the previous studies mentioned above, albeit a more similar incidence as in our study, they did not find any Grade 3 CW pain in their cohort in spite of giving 60 Gy in 3 fractions. Patient characteristics such as age, diabetes, hypertension, peripheral

vascular disease, smoking or body mass index were not predictive for CW toxicity. However, tumour size and CW dosimetry were correlated to late CW toxicity (CW pain and rib fracture). In their review, they found that restricting the CW V30Gy<30 cm^3 and V60Gy<3 cm^3 should result in a risk of late CW toxicity of less than 15%.

More recently, in 2016, Murray *et al.*[16] reviewed 192 patients all receiving the fractionation scheme of 55 Gy in 5 fractions. Similarly to our study, they focused on CW pain of Grade 2 or higher and found an incidence of 10.9%, for which the tumour size and the D1cm^3 were significant predictors. However, it is unclear whether heterogeneity correction was used during treatment planning, and the inclusion of patients in the study was not limited by a minimum follow-up time, which ranged from 0.3 to 45 months.

Also in 2016, Thibault *et al.*[8] reported on their institutions experience with rib fracture and CW pain following 48-60 Gy in 4 to 5 fractions. 289 lesions from 239 patients were reviewed. The median follow-up was 21.0 months and 16% experienced CW pain. Dose calculation was performed with heterogeneity correction and, similarly to the previous studies, target coverage was not compromised to spare the CW. However, unlike all other publications mentioned above, they reported that in their cohort no clinical or dosimetric factors were found to be predictive of CW pain.

In our present study, we solely focused on patients receiving 48 Gy in 3 fractions with heterogeneity correction and with a minimum follow-up of 6 months, and we also could not find any correlation between CW pain and the studied dosimetric variables, particularly the V30Gy as suggested by many groups[9–11,13–15,17–19]. Despite the average DVH curves differing between the cases with and without CW pain of Grade ≥ 2 as seen in Figure A-2, our statistical analysis showed that this difference is not significant, at least in the V30Gy to V50Gy region. Although our study has the same limitation as others of being retrospective, the merits of our study are that all of our 122 patients received the same dose and fractionation, were treated with heterogeneity correction and were followed for at least 6 months.

The published studies have raised multiple possible predictive factors for CW pain including dosimetric factors such as total dose, dose per fraction, maximum dose to the CW or rib, CW V30Gy to V70Gy, size of the PTV, and patient related factors such as female gender, location of the tumour in the chest, age, body mass index (BMI), but they have not been consistent. The most commonly reported predictor for CW pain remains the V30Gy, perhaps because it was the first one to be suggested. The wide range of results from the literature may be due to differences in study design and factors such as differences in SBRT dose prescriptions (total dose and number of fractions), difficulties and differences in evaluating or scoring CW pain, retrospective assessment of CW pain, and different follow-up intervals.

CW pain (Grade $\geq$ 2) is an infrequent SBRT-related toxicity and is less concerning than CW pain after thoracotomy for which some reports mention incidences of more than 50% of patients still taking pain medication one year after surgery[28]. Considering the wide range of differing results from the literature and the lack of significant predictors found in our current study, a reasonable conclusion is that an ideal constraint for the avoidance of CW pain is yet to be defined.

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