Advanced treatment planning: robust optimization and proton RBE
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Chapter 7

Discussion
The purpose of this thesis was to investigate how to properly address setup, range and biological uncertainty during treatment planning for head and neck cancer radiotherapy to further improve patient outcomes. Setup uncertainty is relevant for both photon and proton therapy while range and the considered biological uncertainties are relevant for proton therapy, but not photon therapy.

**Setup and range uncertainty**

In chapter 2, the benefit of composite minimax robust optimization for photon volumetric arc therapy (VMAT) in head and neck cancer patients was demonstrated. Two VMAT plans were generated using both planning target volume (PTV)-based and robust optimization for ten head and neck cancer patients. All 20 treatment plans were evaluated on daily acquired cone beam CT (CBCT) scans to simulate actually delivered dose. The results were a small increase in the near-minimum dose (i.e., the dose to 98% of the volume, $D_{98}$) of the clinical target volume (CTV) of 1.5 Gy on average and a reduction in normal tissue complication probability (NTCP) for tube feeding dependence and xerostomia of 0.9% and 2.8% respectively.

An important limitation to the used approach is that the evaluation was based on the CTV. As the analysis was done on the daily anatomy, the calculated dose was taken as an estimate for the actually given dose which only needs to cover the CTV. However, other uncertainties could occur during treatment such as delivery errors and CT calibration errors which are disregarded in this analysis. However, these uncertainties are expected to play a smaller role than the anatomical variation and these uncertainties were present equally for the calculation of the dose for PTV-based optimization and robust optimization so are not expected to influence the conclusions.

The results of chapter 2 clearly show that robust optimization can be beneficial for both target coverage and toxicity prevention. However, there are several practical issues hindering the introduction of robust optimization for photons. Firstly, the optimization time is longer for robust optimization due to the dose calculation on six additional scenario’s which can also reduce plan quality [1]. Secondly, using robust optimization requires training of radiation therapists (RTTs), radiation oncologists and medical physicists to gain familiarity with the new methodology for treatment plan evaluation [2]. Thirdly, comparing target coverage criteria to other centres (e.g. for planning comparison studies) might become more difficult as long as robust optimization is not yet widely adopted.
Because of these current hurdles, the results presented in chapter 2 have not resulted in a wide adoption of robust optimization for photon VMAT in the University Medical Center Groningen. However, robust optimization is applied sparsely in clinical cases where PTV-based optimization results in inadequate target coverage. These cases most frequently occur in esophageal patients which have high motion and high-density gradients and in patients with targets located in the vicinity of metal implants.

In chapter 3, the effect of different setup and range uncertainty settings was tested in ten patients by evaluating treatment plans with different uncertainty settings on weekly verification CTs. Random and systematic setup and range uncertainties were taken into account in a probabilistic dose accumulation. The results substantiate a safe transition to a 2 mm/3% setup and range uncertainty setting which is expected to result in a 6% reduction in total NTCP for xerostomia, tube feeding dependence and dysphagia combined.

A difficulty in interpreting the analysis is the absence of a clear criteria for the actually given dose to the CTV. Typically, a $D_{98}$ of at least 95% of the prescribed dose is required for coverage of the PTV in PTV-based optimization. However, for the actually given dose to the CTV, the criterion cannot be directly translated as small underdosage of the PTV is expected to not result in underdosage of the CTV due to dose blurring in fractionated treatment. In our analysis we chose a $D_{99}$ of 95% to overcome this issue.

The results of this study indicate that the fractionated treatment add to the inherent robustness of proton treatment plans. Four out of ten included patients had received a plan adaptation during clinical delivery but these adaptations were ignored in the analysis. The decision whether or not to adapt treatment plans is based on the calculation of treatment dose on verification CT scans in which fractionation is not taken into account. As a result, plan adaptations are sometimes initiated unnecessarily. Therefore, dose reconstruction of the delivered treatment is ongoing in our clinic to further asses the need for adaptation [3].

Taking the uncertainty in CTV dose criteria and the limited number of patients into account, this research has led to adoption of a 3-mm setup uncertainty setting for robust optimized head and neck cancer proton therapy plans in the UMCG since early 2019.
Biological uncertainty

An important part of this thesis is the investigation of the biological uncertainty of proton therapy. While the setup and range uncertainty setting is actively mitigated in various ways, methods to mitigate the biological uncertainty due to a lower or higher linear energy transfer (LET) and relative biological effectiveness (RBE) are even less clear [4]. Much preclinical research evidence has been generated on the relation between RBE and LET, but the proton therapy community is still uncertain how to use this knowledge in clinical practice [5].

In chapter 4, measurements and independent calculations were done to validate the dose-weighted average linear energy transfer (LET$_d$) calculation of an experimental version of a commercial treatment planning system (TPS). The results were that 90% of the measurement points were within 6%/2 mm of the calculation of the voxel-wise product of dose and LET$_d$ (D·LET$_d$). This type of validation is very important as the LET$_d$ is an important parameter in calculating the additional biological dose in relative biological effectiveness (RBE) models for proton therapy. The LET$_d$ is often calculated in Monte Carlo dose engines, such as the one in our TPS, but these dose engines have been fine tuned to give good agreement to dose measurements. Small changes to the dose engine parameters may have only a negligible effect on dose agreement but a large effect on LET$_d$ agreement, which gives rise to the need for validation of LET$_d$ calculations through measurements and independent calculations as done in this work.

The found uncertainty of 6% is larger than what would typically be accepted of a clinical dose engine. However, since the LET$_d$ is used to calculate the additional biological dose, the required accuracy is lower. A uniform proton RBE of 1.1 is generally accepted in clinical treatment planning indicating that the additional biological dose is approximately 10% of the physical dose. Therefore a 6% uncertainty of the additional biological dose should not translate into clinically unacceptable uncertainties.

A major caveat of comparing LET$_d$ calculations and measurements is in the definition of LET$_d$. Most proton RBE models use the proton LET$_d$, disregarding the secondary particles in their calculation. However, measurement devices do not disregard these particles. Ideally, the spectrum of measurements is compared against the calculated LET$_d$ spectrum. When validating LET$_d$ calculations, extra care must be taken to at least make sure the calculations use scoring settings appropriate for the measurement. In our case, this initially led to a scoring error for the independent dose calculation engine which was not capable of scoring
the secondary particle LET$_d$ using the stopping power approach [6]. LET$_d$ scoring methods are not uniform and the LET$_d$ definition varies among systems and RBE publications [7].

These results give confidence that the available LET$_d$ calculations are accurate enough for clinical practice, but an RBE model is needed to calculate the biologically effective dose (i.e., the RBE-weighted dose ($D_{RBE}$)). There are many different RBE models available, many of which also depend on the fraction dose and $\alpha/\beta$, making it difficult to select which model to use in specific anatomical subsites in clinical practice [8].

In chapter 5, the linearity of the relation between RBE and LET$_d$ was investigated by fitting a RBE model with a linear dependency on LET$_d$ to the clinically relevant dosimetric parameters of 60 patients across three body sites with different prescribed fraction doses. The results showed that the coefficient of agreement ($R^2$) was at least 0.94 for the McNamara and at least 0.87 for the Wedenberg RBE models for $\alpha/\beta$ values between 1 and 10 Gy. Furthermore, the difference between a linear fit and the McNamara RBE model was in the same order of magnitude as the difference between the McNamara and Wedenberg RBE models.

These results indicate that a good representation of an RBE model can be made by approximating the RBE as a linear function of LET$_d$. In doing so, an RBE model is only defined by the slope of the RBE-LET$_d$ relation. Evidence for RBE can thus focus on deriving the slope for different outcomes from clinical data which can then be used to estimate $D_{RBE}$.

In chapter 6, the possibility of deriving the slope of the RBE-LET$_d$ relation was investigated using a simulation based on 100 head and neck cancer patients. From these patients, different dataset sizes were simulated from which NTCP models were generated using both $D$ and $D\cdot$LET$_d$ parameters as independent predictors. Due to lack of variation in beam setup, the LET$_d$ was similar for organs-at-risk among the 100 included patients resulting in a high covariance between $D$ and $D\cdot$LET$_d$ parameters. The required sample size was at least 15,000 patients for all considered toxicities.

As 15,000 patients was a lower-bound estimate and is more than can be acquired in a reasonable time frame for a prospective data study, deriving RBE models in this way was deemed unfeasible. Other methods are required for investigating the RBE-LET$_d$ slope in clinical patients. These methods need to either result
in lower covariance between $D$ and $D \cdot \text{LET}_d$ or be able to investigate the local biological effect in patients treated with proton therapy.

**Recommendations for mitigating biological uncertainty in clinical practice**

The studies described in the chapters of this thesis mark important steps towards more active consideration of the effects of biological uncertainty for clinical patients. Below some practical considerations are shared how these tools can be used now or in the near-future to mitigate biological uncertainty in clinical practice.

The biological uncertainty caused by an increase in RBE is present at the distal edge of the spread-out Bragg peak. As such, a common strategy to reduce the potential maximum $D_{\text{RBE}}$ is to treat high dose targets with multiple beams to spread out this effect [9]. While such rules adequately decrease the area where high $D_{\text{RBE}}$ occurs, the $D_{\text{RBE}}$ at the area where each beams distal edge overlaps is still equally high (figure 1). If a particular organ-at-risk needs to be spared in particular, care needs to be taken that no proton beams stop in that organ-at-risk.

The $\text{LET}_d$ is a physical property of the protons delivering the dose. Therefore, evaluating the $\text{LET}_d$ directly has unclear clinical translation without dose.

**Figure 1: Example of $\text{LET}_d$ and $D \cdot \text{LET}_d$ evaluation**

A brain tumor (red) treated with two proton therapy beams coming from the posterior and left side. Images display the isodose line of the $D_{\text{RBE}}$ calculated with a uniform RBE of 1.1 (a), proton $\text{LET}_d$ (b) and the $D \cdot \text{LET}_d$ (c). The 20 Gy$_{\text{RBE}}$ isodose line from image a is projected onto the other distributions as a white line.
When interpreting the LET\textsubscript{d} of a clinical plan, the distribution contains much information which is of clinical relevance as the highest values of LET\textsubscript{d} occur in regions where the dose is clinically irrelevant (figure 1b). The region of most interest is that where the LET\textsubscript{d} is increasing and the dose is decreasing. The clinically relevant regions can be identified much easier by evaluating the D\cdot\text{LET}\textsubscript{d} (figure 1c) which scales linearly with the additional biological dose (i.e., \(D_{\text{RBE}} - D\)) when a linear RBE model is used. Therefore, evaluating the D\cdot\text{LET}\textsubscript{d} distribution visually, using a dose-volume histogram (DVH) or dosimetric parameters may be more practical than doing so with the LET\textsubscript{d} distribution.

Nevertheless, if the average LET\textsubscript{d} is to be calculated for a region-of-interest, this needs to be carefully performed. Taking the voxel average of the LET\textsubscript{d} does not retain the dose weighting of the LET\textsubscript{d}. Instead, to calculate the LET\textsubscript{d} of a region-of-interest, the averaging needs to be done dose-weighted. To do so, the voxel values need to be multiplied with dose, averaged over the voxels in the region-of-interest and divided by average dose of the region-of-interest (i.e., average D\cdot\text{LET}\textsubscript{d} is divided by average dose).

As the D\cdot\text{LET}\textsubscript{d} provides information where the D\textsubscript{RBE} is highest it can be used to differentiate the effectiveness of treatment planning approaches in reducing the D\textsubscript{RBE} to organs-at-risk. However, an RBE model is needed to estimate the actual increase in D\textsubscript{RBE} in these structures. Due to the differences in available RBE models and the uncertainty in the \(\alpha/\beta\) value on which they depend, a pragmatic solution might be to derive a lower and higher estimate of the D\textsubscript{RBE}. From the results of chapter 6, we can see that the RBE-LET\textsubscript{d} slope varies between 0.03 and 0.10 (keV/\(\mu\)m\(^{-1}\)) for \(\alpha/\beta\) values between 1 and 10 Gy. An example of a low and high estimate of the D\textsubscript{RBE} is shown in figure 2, where the D\textsubscript{RBE} is calculated using the Unkelbach RBE model and the McNamara model with an \(\alpha/\beta\) value of 2 Gy. Ultimately, decisions how to treat patients are made in a multi-disciplinary team which makes it important to evaluate the data in a way similarly to dose distributions with which the entire treatment team is already familiar.

**Future perspectives**

The role of robust optimization for photons warrants further investigation. The main drawbacks of robust optimization for photons are expected to decrease over time as increase in computing power reduces the optimization time and all radiotherapy personnel gains experience with robust optimization concepts due to its use in proton therapy. In particular the inclusion of additional robustness scenarios has the potential to improve photon treatment planning in the vicinity of metal implants and in thoracic targets. Currently, metal implants
need to be avoided when using intensity modulated radiotherapy (IMRT) to prevent overmodulation near the implant which results in treatment plans that are not robust to inaccurate implant density or movement.

The robustness setup uncertainty setting could potentially be further reduced from 3.0 mm to 2.5 or even 2.0 mm for head and neck cancer proton therapy. More daily proton therapy dose calculations are required to substantiate the hypothesis that random errors wash out potential underdosage due to anatomical variation to a degree where a smaller setup uncertainty setting adequately covers the target. Automated daily dose accumulation using CBCT based synthetic CT might provide the required evidence for this as machine learning improves the synthetic CT quality enough so they can be used to accurately calculate the daily dose of proton therapy plans through the entire course of treatment [9].

Validation of LET$_d$ algorithms is required before LET$_d$ calculations are used to make clinical decisions. The process of validating LET$_d$ calculations is time consuming and new tools need to be developed to make measuring LET$_d$ in routine periodic quality assurance (QA) processes feasible.

There is a need for more uniform reporting of LET in scientific writing and presenting. The recent review by Kallholm et al. already provides valuable information for researchers, editors and reviewers on what parameters should be included on the LET calculation of any publication. The EPTN currently has a
working committee which may provide clearer guidelines on the best practice of reporting and displaying LET in the near future.

To better investigate the relation between RBE and LET\textsubscript{d} using toxicity, a clinical trial where patients are treated using different planning approaches could differentiate between the risk of higher physical dose and the risk of higher LET\textsubscript{d}. Such an approach could result in a dataset with dose and D-LET\textsubscript{d} parameters with lower covariance from which it would be much more feasible to derive an RBE model. Another approach could be to use imaging to measure the local biological effect of proton therapy dose and LET\textsubscript{d}. One such attempt was able to make an NTCP model predicting the chance of developing contrast enhancing brain lesions after proton therapy based on the voxel location, the dose and the D-LET\textsubscript{d} [11]. Functional imaging such as diffusion weighted imaging (DWI) magnetic resonance imaging (MRI) for brain white matter or prostate-specific membrane antigen (PSMA)-positron emission tomography (PET) for salivary glands could potentially be used to evaluate the biological damage on a voxel-level on a continuous scale [12,13].

LET\textsubscript{d} optimization is being thoroughly researched and will allow users to add objectives on the LET\textsubscript{d} distribution similarly to dose objectives. Doing so will potentially result in lower LET\textsubscript{d} in organs-at-risk and higher LET\textsubscript{d} in targets. Another interesting development is the introduction of proton arc therapy. By treating continuously over a range of angles the distal edges are spread out across a much larger region. When combined with LET\textsubscript{d} optimization, proton arc therapy could potentially greatly reduce enhanced RBE in organs-at-risk, but many simulations of this do not yet include range uncertainty in the robust optimization which could limit these results.

It is likely that tools to evaluate and manipulate LET\textsubscript{d} and RBE distributions will be available before much more is known about the RBE-LET\textsubscript{d} relation or the accuracy of RBE models [14]. More clinical data is becoming available and novel imaging techniques are promising in investigating the RBE in clinical patients. The interest in the biological effects of proton therapy is growing, but many challenges still lie ahead in assessing and mitigating the biological uncertainty.
Chapter 7

References


