AARHUS UNIVERSITY

Project description

Academic title and name: Nadine Vatterodt, MSc.

Project title: Robust optimization for anatomical variations in proton therapy

Background

The medical use of ionizing radiation is one of the three main modalities for cancer treatment besides surgery and chemotherapy. Conventional radiotherapy utilizes high energy photons to irradiate the target and inducing DNA double-strand breaks. However, irradiation is not selectively damaging malignant cells but also healthy tissue. In order to achieve a valuable tumor control probability and a low normal tissue complication probability, a high dose conformity and target coverage with a simultaneous sparing of healthy tissue is the main objective in the planning stage.

For this reason, pencil beam scanning (PBS) particle therapy became one of the most advanced forms of cancer treatment. The use of protons or carbon ions, benefits from the weight and the electrical charge of the particles, resulting in a favorable spatial dose deposition. Photons show a small built-up region close to the patient's surface followed by an approximately exponential decay. In contrast, protons deposit the main dose in a small region at the end of the beam track, called Bragg peak. The small entrance dose and particularly the finite range of protons, i.e., the sharp distal fall-off, allow for excellent sparing of surrounding healthy tissue. In addition, the charged particles provide the possibility of PBS, where the target volume is sculpted by narrow particle beams, i.e., pencil beams, resulting in a high lateral conformity in all depths.

Thanks to the steep dose gradients, proton therapy is an emerging and potentially advantageous treatment modality for malignancies with complex target shapes and proximity to numerous organs at risk), such as the 6th most common cancer worldwide - the head and neck cancer (HNC) [1]. HNC refers to numerous diseases that affect certain regions between the nasal cavity and trachea, while squamous cell carcinomas (HNSCC) show the highest occurrence [2]. The main fraction of HNC patients is treated by radiotherapy with possibility to include surgery or chemotherapy [2]. Since HNCs have a high risk of recurrence, a treatment plan with adequate dose coverage to the target volume is essential. Concurrently, a sparing of the healthy tissue is warranted to obviate short- and long-term toxicities and preserve the healthy functioning of nearby organs. The potential benefit of proton treatment plans addresses this point by effectively reducing dose to surrounding tissues and thus reduces side effects while maintaining - or even improving - an adequate dose to the target volume. Today proton therapy for HNC is already used clinically in a wide range, though it shall be noticed that first randomized clinical trials comparing proton versus photon treatment of HNC are not completed yet [3] [4].

However, proton therapy is not without its drawbacks. First, proton therapy is associated with a larger economical cost than conventional radiotherapy, arising from capital investment and operating costs. Additionally, lower patient capacity for the sake of time-consuming steps of the treatment process, aggravate the financial situation. But above all, the physical properties of protons are not only beneficial but result in a high sensitivity to uncertainties, which may alter the beneficial treatment outcome.

Therefore, the Real-time Adaptive Particle Therapy of Cancer (RAPTOR) initiative was formed to address the optimization of these limitations and to work towards patient specific real-time use in order to release the full potential of proton therapy. The Danish Center for Particle Therapy is one of the 13 beneficiaries, contributing with the present project.

One of the main problems to address are anatomical variations in the head and neck region due to weight loss or swelling, tumor response and nasal cavity fillings introduce interfractional density and volume changes in the patient over time.

Since the range of protons strongly depends on the traversed matter, uncertainties within the beam path or geometrical shifts can lead to misplaced Bragg peaks and hence inadequate tumor volume coverage or excessive overdose to the surrounding tissue, much more pronounced compared to conventional radiotherapy. Thus, the traditional planning target volume concept, i.e., the extension of the clinical target volume (CTV) to fully account for geometrical uncertainties and small anatomical variations, is not sufficient in proton therapy. It was shown for plans with steep in-field dose gradients, that margins can be useful to improve CTV coverage at the edges of the volume, but not in the center [5].

Therefore, an alternative tool was developed - the robust treatment planning - to inherently include robustness towards expected uncertainties in the plan optimization. A simple version to improve robustness is the adaption of field properties according to expected uncertainties. For instance, gantry angles perpendicular to organs at risks are selected to reduce the effect of range uncertainties. More advanced approaches may include beam angle optimization in the spot optimization algorithm. Additionally, similarly to error scenarios for patient shifts, over- and undershootings by simple range or density uncertainties can be simulated, and progressive inverse robust optimization strategies or multiple criteria optimizations are increasingly used and already implemented in commercial treatment planning systems.

However, complex anatomical variations cannot yet be mitigated with these approaches. A management for these uncertainties is adaptive radiotherapy using replanning on latest images during the treatment course. While this is routinely used in conventional radiotherapy nowadays, it is still a current research field in proton therapy. Replanning is costly and time-consuming, considering repeated imaging, contouring, plan optimization, and patient specific clinical and physical plan evaluation and verification. This process is much more complex for protons than for photon treatment and in consequence the urgency of replanning must be reduced. This is a competing demand to the requirement of lower thresholds triggering the plan adaptation to account for the increased sensitivity of protons. In addition, the less intuitive dosimetric effects of even small anatomical variations makes tolerance levels hard to predict in proton therapy.

We propose to implement an individualized approach accounting for the most dominant components of anatomical variations for the specific patient. Based on a quantification of the anatomical variations, extracted from daily images of the individual patients, and the respective dosimetric impact, individualization of adaption and progressive robustness strategies are evaluated to identify the best plan quality combined with the highest degree of overall robustness.

Hypothesis

Adaptive treatment planning approaches for head and neck cancer proton therapy giving the best plan quality combined with the highest degree of overall robustness can be identified and categorized for different patient subgroups.

Materials and Methods

All required data and software for realizing the project will be available at Aarhus University Hospital, where supporting physicists and oncologists contribute with extensive experience in treatment planning and evaluation for proton therapy.

Data:

The study will be performed based on CT/PET (computed tomography/positron emission tomography) scans and daily CBCT (cone-beam CT) scans for three groups of head and neck cancer patients; (group a) 24 sinonasal cancer patients who have previously received radiotherapy at the Department of Oncology, AUH, (group b) 20 patients with oropharyngeal cancer who have previously received radiotherapy at Department of Oncology, AUH, and (group c) 80 patients with cancer in different sites of the head and neck region who have previously received proton therapy at the Danish Center for Particle Therapy, AUH.

Permission for use of the described retrospective data sets has been obtained with Region Midt, for previous studies within the aim of this project, and extending permissions will be sought to include the data here. As only retrospective data will be used in the project, there are no relevant ethical considerations for prospective subject inclusion.

Software:

The study will address proton treatment planning with IMPT (Intensity Modulated Proton Therapy with pencil beam spot scanning). Two commercially available treatment planning systems will primarily be used; Eclipse version 16.1 (Varian Medical Systems, Inc), and Raystation version 9B (RaySearch Laboratories), both of which are available to the investigators through existing dedicated research licenses. Both systems include the option of custom-made scripting through application programming interfaces. By this means, the standard robust planning techniques available in the treatment planning systems will be complemented with scripts taylor-made whenever pre-implemented algorithms are not provided.

Deformable image registration (DIR) will be accomplished using the open-source program Elastix as well as the DIR application available in Raystation.

Results including quantitative dose metrics and corresponding biologically effective doses, plus tumor control probabilities and normal tissue complication probabilities calculated using models endorsed by the DAHANCA, will be compared using relevant statistical tests, in the SPSS or similar software.

Study design:

The study builds on a prior PhD study (2018-21), in which patient groups (a) and (b) were investigated dosimetrically with respect to description and quantification of effects of daily anatomical changes. In this study, a method based on principal component analysis (PCA) was developed for modelling daily anatomical changes based on daily CBCT scans. Furthermore, it was shown that for sinonasal cancer, proton treatment was robust for most patients over the entire treatment, but with large daily variations.

The present study is based on four specific research tasks, progressively contributing to the overall aim of establishing the ideal individualized robust treatment planning approach, as described below.

Q1: *Global and local analysis of anatomical variations, and correlation with dosimetric variations*.
For all three patient groups, the PCA method (previously developed in the group) will be used to identify modes of anatomical variation on both population basis and individually. The model results will be analyzed spatially to determine potential anatomical regions in the patients which are more prone to vary from day to day (such as nasal cavity, swallowing structure, shoulders). In a subset of the patients for which there are clearly distinguishable localized anatomical variations, recalculations of daily doses on CBCT scans will be performed. Correlation between localization of anatomical variations and dosimetric variations will be performed to make a priority ranking of location of anatomical variation.

Q2: *Development of treatment plan optimization strategy with anatomical robustness*.
Based on the model results from Q1, three different strategies for including global anatomical robustness from first week CBCT scans in treatment plan optimization will be developed and tested. The strategies include optimization with an average CBCT, with all five CBCTs, and with an ensemble of virtual CBCTs generated from the PCA model parameters. The generated optimized plans will be compared based on physical dosimetric parameters as well as robustness in the remaining part of treatment fractions.

Q3*: Optimization with spatially confined anatomical robustness measures*.
The results from Q1 and Q2 will be combined to perform robust optimization considering only local anatomical variations. Optimization strategies will be compared for various degrees of localizations included successively according to priority ranking (single localization up to global variations), on both population level (prior to treatment) and individual level (based on first week CBCT scans). The resulting plans will be compared based on physical dosimetric parameters as well as robustness in the remaining part of treatment fractions.

Q4: *Individualization of adaption and anatomical robustness strategy*.
Individualized robust treatment planning and adaptation based on identified modes of variations are compared for four different approaches of increasing complexity; (I) a standard robust optimization for geometrical uncertainties performed on an planning CT, (II) an approach considering the planning CT and the primary five cone beam CT scans with a global anatomical robustness optimization (from Q2) (3) a localized anatomical robustness, including population and individual prominent modes of variations as robustness parameters (from Q3), and (4) an initial robust optimization considering

population-based modes of variation combined with a weekly progressively adapted robustness optimization considering individual modes of variation from the daily CBCT scans.
The plan quality of the derived treatment plans is compared using standard dose volume metrics. Dose recalculation on CBCT scans and on CT scans performed in the course of the treatment allow for an evaluation of overall robustness of all four approaches.
Based on these dose and robustness comparisons, the approaches giving the best plan quality combined with the highest degree of overall robustness are identified and categorized for patient subgroups.

Personnel

This applicant will carry out the tasks of the research plan (enlisted above) from 1 to 4 with the contribution from local experienced oncologists to ensure proper assessment and evaluation of patient anatomies and treatment plan quality together with the overall supervision of Professor of Medical Physics at Aarhus University Stine Sofia Korreman, and associate Professor of Radiation Oncology at Danish Center for Particle Therapy Kenneth Jensen.

A parallel PhD study will be carried out by a dosimetrist at the DCPT, who will investigate workflow issues, efficacy and practical aspects of implementation of adaptation strategies for head and neck cancer proton therapy.

Expected results and impact

The study is expected to demonstrate that the concept of automated robust planning can be enhanced to include robustness towards anatomical variations for head and neck cancer proton therapy by the characterization of the most prominent components for an individual patient based on initial daily images performed for patient setup.

Consequently, clinical protocols for head and neck cancer treated with proton radiotherapy can be implemented at DCPT with confidence regarding geometrical setup and robustness towards anatomical variations.

The results and developed methods will be relevant and applicable for other particle therapy centers worldwide and, furthermore, expandable to other patient groups.

Referencer

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