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TITLE: Individualized robustness in treatment planning for head and neck proton radiotherapy.

INTRODUCTION:

In the last years the use of proton therapy has become one of the most advanced forms of cancer treatment. During the irradiation with protons the total integral dose delivered to the patients is considerably reduced compared to conventional radiotherapy (photons and electrons) [1-3], demonstrating the advantages of this type of treatments. The ability to reduce radiation exposure to adjacent healthy tissue and to spare the tissue behind the tumor almost entirely, make it an optimal treatment for tumors where conventional radiotherapy cannot be accurately applied. Treatments using proton beams are becoming more and more widely used. In Denmark proton therapy is now available at the national Danish Center for Particle Therapy, where the first patient was treated in January 2019 [4].

Worldwide, head and neck squamous cell carcinomas (HNSCC) constitute approximately 7% of all incident cancers. Life-style factors, in particular tobacco and alcohol consumption, are major etiological factors although an increasing number of HNSCC cases are associated with viral infections. This disease is a good example for which large benefits can be gained by introduction of proton radiotherapy.

Radiation therapy is a standard treatment modality for a large fraction (70-80%) of head and neck cancer patients, however side effects of irradiation are unfortunately also prevalent. Most common side effects include xerostomia, loss of taste, and mucositis all of which significantly contribute to decreased quality of life [5]. Proton radiotherapy has the potential of markedly reducing the irradiation of healthy tissues, while maintaining – and possibly even improving – irradiation of the malignancy [6]. Proton radiotherapy for head and neck cancer is used clinically in a number of proton therapy centers worldwide [7], but protocols are still too early and with too few patients for evidence to be established.

An important factor in proton radiotherapy is the geometrical uncertainties and anatomical changes that occur throughout the duration of a radiation treatment course, not least in the case of head and neck cancers. The position of the Bragg peak of a proton beam – where the radiation dose is focused – is highly dependent on the amount and type of tissue in the beam path. Geometrical uncertainties are basically inevitable in radiotherapy, due to the many factors affecting patient positioning over a fractionated treatment lasting up to six weeks with daily radiation sessions. In addition to the "simple" geometrical uncertainties related to daily patient setup on the treatment couch, anatomical changes occur externally when the patient size changes due to weight loss or swelling, and internally in relation to for instance filling of nasal cavities or tumor regression. When changes occur, the tissue in the proton beam path will change accordingly, and the location of the Bragg peak will change. This may change the radiation dose coverage in the patient substantially – in worst cases even fatally – and the projected favorable outcome will no longer be valid.

In photon radiotherapy, the traditional method to overcome uncertainties and small anatomical changes is to add a margin to the treatment field, thus including a leeway for errors into the treatment plan. However, the simple margin method is not valid to account for geometrical uncertainties in proton therapy, as even small errors may result in large dislocation of the Bragg peak [8]. Instead methods are being developed to incorporate expected uncertainties into an inversely optimized treatment plan, which is inherently robust towards these uncertainties – termed robust treatment planning [9]. In the simplest version of robust optimization, a manual selection of beam angles (or other field properties) which are most stable towards variations can be attempted. More advanced robust planning may include automated optimization of beam angles, automated statistical incorporation of uncertainties into the computerized inverse optimization function, and inclusion of multiple criteria for plan evaluation in the optimization process. In such a robust plan, a degree of "smearing" is included, and the dose distribution appears less focused at the planning stage, but is in fact more accurate when accumulated over the fractionated treatment where errors are inevitably present at each treatment day.

Robust planning methods to account for simple geometrical changes are incorporated into commercial treatment planning systems for proton treatment planning, such as the Eclipse TPS from Varian Medical Systems Inc, and the Raystation from RaySearch Laboratories. However, these methods cannot account for more complex anatomical variations. In photon radiotherapy, in the case of large anatomical changes, replanning strategies are used, based on defined tolerances and repeated imaging of the patient at the treatment machine. This has been a field of extensive research over the past years, and solutions are routinely used in the clinic [10,11]. For proton radiotherapy, the use of replanning strategies is in principle still a valid method, and presently it is also the only method available to deal with interfractional anatomical changes. However, owing to the higher sensitivity to variations in proton therapy, the dosimetric effects of even small anatomical changes may be large, and the effects of the variations are less intuitively predictable for proton than for photon radiotherapy. Hence the tolerance levels to trigger a replanning procedure will be lower than for photon therapy, and even with low tolerance levels, the dosimetric effects of allowed changes may in some cases be non-negligible. The procedure of replanning is costly and inconvenient, as it implies the patient showing for an additional CT scan, and the complete process of treatment planning being repeated on the rescan, including delineation, treatment plan optimization and plan assessment and approval. It is therefore desirable to minimize the need for rescanning and plan adaptation.

The use of robust planning for proton radiotherapy to account for more complex changes than simple geometrical errors is only at primitive exploration stage. In this project, we propose to expand the concept of automated robust planning to include robustness towards not only simple geometric errors, but also towards anatomical variations. A generic treatment plan which would include extensive robustness towards both geometrical uncertainties and various types of anatomical changes (rotations, weight loss/gain, swelling, filling/emptying of cavities etc.) would, however, be difficult to make without sacrificing mandatory plan criteria such as target dose coverage or toxicity limit doses for nearby healthy tissues and organs at risk. It is therefore necessary to limit the amount of robustness measures. Previous studies have shown the feasibility of principal component analysis to model and characterize the anatomical variations during the treatment [12,13,14]. We propose to implement an individualized approach by characterizing on an individual basis, the most prominent components of anatomical variation for the specific patient, including primarily robustness towards these components. Individual characteristics can be identified during the first week of treatment based on the daily imaging (cone-beam CT scans) performed in the treatment room for patient setup.

AIM OF THE STUDY:

- Reduce the need for plan adaptation

    - Increase robustness of IMPT plans for head and neck cancer patients towards anatomical variations.

MATERIALS AND METHODS:

All data and software necessary for carrying out the project will be available at Aarhus University Hospital, and participating physicists and oncologists are experienced in treatment planning and evaluation for proton therapy.

Data:

CT (computed tomography) and PET (positron emission tomography) scans for treatment planning from 20 head and neck cancer patients who have previously received radiotherapy at the Department of Oncology at Aarhus University Hospital will be used to perform the studies. For quantification of anatomical variations, and for plan adaptation and replanning, the stored daily cone-beam CT (CBCT) scans for the same patients will be used.

A sample size of 20 is sufficient in this scenario to give an estimated statistical power of around 70-90%. This estimate is based on mean changes in doses for relevant organs at risk for head and neck cancers – a treatment course based on repeat CT scans from Elstrom et al, Acta Onc 2010. The standard deviations of the changes are on the same order of magnitude as, or up to approximately twice, the reported changes.

The results – physical dose metrics and corresponding biologically effective doses – will be compared using relevant statistical tests, in the SPSS or similar software. As only retrospective data will be used in the project, there are no relevant ethical considerations for prospective subject inclusion.

Software:

Treatment planning will be performed primarily in two treatment planning systems; Eclipse version 13.7 (Varian Medical Systems, Inc), which is available to the investigators through an existing dedicated research license, and Raystation (RaySearch Laboratories), which will be acquired in a stand-alone research license for the purposes of this project. Both systems include the option of custom made scripting through application programme interface.

For the performance of deformable image registration, the Velocity software (Varian Medical Systems, Inc) will be used.

The study will be performed using proton treatment planning with IMPT (Intensity Modulated Proton Therapy with beam spot scanning) performed retrospectively for 20 head and neck cancer patients previously treated at Aarhus University Hospital. Commercially available treatment planning systems will be used (see description below in the section Materials and Feasibility), employing the standard robust planning techniques available in the treatment planning systems, complemented with scripts taylor-made for the parts of this study for which pre-implemented algorithms are not available.

The study falls in three parts – three specific research questions – with a progression towards the overall aim of identifying the optimal method for performing individualized robust treatment planning.

It is expected that the methods developed in this study will be generalizable and can be translated to other patient groups treated with proton radiotherapy.

Q1. Quantification of dosimetric effects of anatomical variations.

Method: Proton plans will be generated with and without use of the robust planning technique available in the treatment planning system for simple geometric errors. Errors and anatomical variations will first be simulated by manipulation of the original CT planning scans. Manipulations will include translations, rotations and artificial mimicking of weight loss and gain, filling and emptying of nasal cavity. Recalculation of the radiation dose by delivery of the original treatment plan will be performed on the manipulated scans, and changes in doses to target and organs at risk will be quantified. Secondly, recalculation of dose will be performed on CT scans actually performed for the patients during the course of the treatment. Such extra CT scans are typically performed when large anatomical variations are seen on cone-beam CT scans, above certain tolerances for which it is expected that the dose distribution will be substantially altered, and a plan adaptation must be made.

Recalculation of the dose distribution based on the original plans performed with and without robustness for simple geometric variations will be compared to quantify the extent to which the available standard robustness methods can account for the more complex anatomical variations seen during the course of a treatment.

Q2. Analysis and categorization of components of anatomical variations.

Method: The cone-beam CT scans performed on days of treatment (for setup purposes) will be used to quantify the variations for each patient. Deformable image registration will be performed between the cone-beam CT scans and the treatment planning CT scan, resulting in a deformable vector field map for each registration. The vector field maps for each patient are averaged and an average anatomy is created by deformation of the treatment planning CT scan with this average deformation map. The differences between the average anatomy and each day anatomy (differences between each deformation field and the average map) are quantified for each patient using a principal component analysis, giving the most prominent modes of variation. Geometrical and physiological interpretation of the modes of variation will be performed by visual inspection of the scans and the corresponding deformation fields.

The modes of variation and their interpretation are compared with the recalculated dose distributions (results from the first research question Q1) for each patient, to identify which modes of variation are most prone to result in large dosimetric changes.

Q3. Robust treatment plan optimization based on first week imaging.

Method: Based on the first five days cone-beam CT scans, an average deformation map is generated, and a principal component analysis is performed for these first five scans to identify the three most prominent modes of variation. Individualized robust treatment planning based on the first five days variations is compared for three different approaches of increasing complexity; (1) The treatment planning CT scan is deformed with the average deformation map for the first five days, and a treatment plan is optimized on that deformed CT scan using standard robust optimization for geometrical uncertainties, (2) a treatment plan is optimized based on a series of scans including the initial treatment planning scan and the first five cone-beam CT scans, with and without standard robust optimization, and (3) a treatment plan is optimized with individual robustness using the three most prominent modes of variation as robustness parameters. The treatment plans produced in the three approaches are compared for plan quality using standard dose volume metrics. The doses are furthermore recalculated on CT scans performed during the course of treatment to test for overall robustness for all three approaches.

Based on the dose and robustness comparisons, the approach giving the best plan quality combined with the highest degree of overall robustness is identified.

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EXPECTED RESULTS AND IMPACT:

- Based on the results of this study, it is expected that clinical protocols for proton radiotherapy for head and neck cancer can be set up at DCPT with confidence regarding geometrical setup and robustness towards anatomical variations.
- The results and developed methods will be relevant and applicable to head and neck cancer patients treated with proton therapy at other centers in the world, and to other patient groups treated with proton therapy.

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