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## Adaptive radiotherapy in head and neck cancer

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## Summary

### **Part 1A: Tumor behavior during radiotherapy and implications for ART**

In this thesis, tumor behavior of the primary target volume during treatment is studied in **Chapter 2 and 3**. To follow tumor variability on daily CBCT, small fiducial markers were implanted at the edge of the macroscopic tumor since CBCT soft tissue contrast is insufficient to distinguish tumor boundaries adequately. In **Chapter 2**, quantification of oropharyngeal tumor shape changes showed that the extent of tumor variation depended on sub-localization and tumor volume, 3D-vectors were highest in base of tongue and bulky tumors. Different marker patterns were observed, the majority of patients had a stable or inward time trend, but outward time trends were also observed. Furthermore, within patients, markers could behave differently, showing an inhomogeneous pattern of in- and outward moving markers during treatment. Such tumor variability may be related to actual increase or decrease of tumor volume, however, weight loss, fluid shift within the body, alteration in muscle mass and fat distribution, will also play a role. The observed outward marker motion might pose risk for underdosage since this soft tissue variability is currently not accounted for in standard setup margins and correction protocols based on the assumption of rigid body motion. On the other hand, patients with a shrinking tumor might benefit from mid-radiation therapy re-delineation to reduce toxicity.

To analyze if adaptive field size reduction based on GTV shrinkage is safe, we compared variation of implanted fiducial markers at the edge of the GTV with GTV behavior on MRI in **Chapter 3**. In patients with oropharyngeal tumors treated with (C)RT, marker and MRI surface positions were compared pre-treatment and in week 3 and 6 of treatment. We found that GTV surface

displacement in time derived from MRI was larger than derived from fiducial markers. The MRI-GTV shrank faster than the surrounding tissue represented by the markers. We showed that adapting to primary tumor GTV shrinkage on MRI mid-treatment is potentially not safe since at least part of the GTV is likely to resolve instead of actually shrink.

### **Part 1B: Effect of geometrical changes on dose distribution**

Intended dose distribution, based on pre-treatment imaging, can be influenced during treatment by geometrical changes in the volumes itself or in surrounding anatomy. How robust coverage is to geometrical changes depends on chosen planning margins and the applied setup correction protocol. In **Chapter 4 and 5**, the effect of non-rigid setup errors are evaluated with a methodology based on CBCT. A B-spline CBCT-CT deformable registration was applied to recalculate the dose distribution after online patient positioning from alignment of bony anatomy. The daily dose was recalculated on a modified CT (planning CT deformed to daily CBCT following online positioning), for all fractions accumulated in the original planning CT and compared to the intended dose distribution. **Chapter 4**, investigates loss of target coverage from anatomy changes as a function of applied PTV margins (5/3/0 mm) in oropharyngeal cancer patients. Anatomical changes were predominantly observed in elective lymph node regions and parotid gland volumes. Margin reduction improved OAR sparing with approximately 1 Gy/mm at the expense of target coverage in a subgroup of patients. Patients at risk of underdosage could be identified early in treatment, at fraction 10, with dose accumulation. Adaptive intervention using average anatomy modeling substantially improved coverage in the majority of cases. From this work we can conclude that clinically used PTV margins create rather robust treatment

plans for target coverage, furthermore, single adaptive intervention has the potential to correct the majority of dose deteriorations.

In **Chapter 5**, dose deterioration in target volumes due to anatomical deformations is assessed in a large series of consecutive head and neck cancer patients treated with curative intent. Decrease of near minimum dose ( $D_{99}$ ) more than 1 or 2 Gy occurred respectively in 16% and 5% of patients. Increase of near maximum dose ( $D_1$ ) was less frequent and was respectively found in 4% (1 Gy) and 2% (2 Gy) of patients. Factors associated with deterioration of  $D_{99}$  were higher baseline weight and BMI, weight gain early in treatment and smaller PTV margins. Factors associated with deterioration of  $D_1$  were higher baseline weight and T-stage. The sensitivity of patient selection with CBCT for detection of dosimetric changes was low. We concluded that large dose deteriorations in target volumes occur in a minority of patients, although the risk increases with smaller margins. Clinical prediction based on patient characteristics or changes on CBCT is challenging and other selection tools, such as dosimetric, seem warranted to identify patients in need for ART.

Susceptibility to geometrical uncertainties is larger in treatment with proton therapy compared to photon therapy. Proton therapy has different beam characteristics allowing highly conformal dose distributions, but in case of uncertainties, a disturbance of the intended dose distribution can occur due to a shift of Bragg peaks. In **Chapter 6**, the effect of geometrical uncertainties, as well as range uncertainties, is modeled with error scenarios in patients with both a VMAT and an in-silico PTV based IMPT treatment plan. In this uncertainty analyses, 8 scenarios were recalculated on the original planning CT, i.e., 6 scenarios for geometrical errors with isocenter shifts and 2 for range errors

by scaling of the range (IMPT) or CT density (VMAT). The aim of this work was to assess the clinical effect of uncertainties on the population. To this aim, dose differences between nominal and error scenarios were translated to changes in tumor complication probability (TCP, 2 models) and normal tissue complication probability (NTCP, 15 models). Evaluation was done for both random and systematic shift errors. The effect of random shift errors was negligible for all TCP or NTCP endpoints, for systematic errors VMAT plans were more robust than IMPT plans. Although individual scenarios revealed risk of plan deterioration in IMPT, the population effect on TCP and NTCP was limited. From this work we concluded that TCP and NTCP models make it possible to consider the clinical effect of uncertainties on the population.

### ***Part 2A: Evaluation of pre-treatment biomarkers to tailor treatment.***

The possibility of tailoring radiotherapy to biological tissue parameters is researched to improve outcome. Most likely, not all patients will benefit from the same treatment and predictive biomarkers could assist in patient selection to individualize treatment schemes to enhance the therapeutic ratio. **Chapter 7**, describes the use of Zirconium-89 ( $^{89}\text{Zr}$ ) labeled Cetuximab PET-CT imaging in patients with advanced head and neck cancer as a possible strategy to differentiate between responders and non-responders. A large variation in  $^{89}\text{Zr}$ -Cetuximab uptake was found between patients. Comparison of high uptake regions on the  $^{89}\text{Zr}$ -Cetuximab PET-CT images with high uptake regions on FDG images revealed only minor overlap. Furthermore, comparison of uptake in groups with low or high EGFR expression on pathology showed a significant difference in the mean and peak standard uptake value between groups, however, not in tumor to background ratio. We concluded that  $^{89}\text{Zr}$ -Cetuximab PET-CT imaging can discriminate between high or

low uptake and provides additional information compared to FDG-PET or EGFR expression, however, further research is necessary to show a link between  $^{89}\text{Zr}$ -Cetuximab uptake and treatment outcome.

Another approach to improve outcome based on pre-treatment biomarkers is to take biological tissue parameters into account in radiation treatment planning. In **Chapter 8**, a randomized controlled trial called Artforce (Adaptive and innovative Radiation treatment FOR improving Cancer treatment outcome) is described. This multi-center trial was designed to improve outcome by redistribution of the radiation dose to the metabolically most FDG-PET avid part of the tumor, while simultaneously sparing normal tissues. Patients are randomized between standard radiotherapy to 70 Gy in 35 fractions and adaptive radiotherapy combined with dose redistribution through dose-painting based on pre-treatment 50% FDG-PET uptake. In the experimental arm a heterogenous dose distribution is created, aiming to deliver a maximum dose of 84 Gy in 2% of the high FDG uptake volume with a mean of 77 Gy in this volume, together with a minimum dose of at least 64 Gy and a mean dose of 68 Gy in the remainder of the primary tumor PTV. Final results of the trial are expected in the fall of 2021.

### **Part 2B: Exploration of molecular markers for biological ART**

In the search for biomarkers to improve treatment outcome, the presence of hypoxia is considered, both as a prognostic factor, as well as a target for dose redistribution. **Chapter 9** investigates the value of molecular imaging with HX4-PET in this respect. Both static uptake pre-treatment and in week 2, as well as change of HX4 uptake early during treatment were evaluated. In week 2, detection of an increase of hypoxic volume or the presence of more than 20% residual hypoxia compared to baseline were associated with a significantly worse prognosis. Evaluation of

spatial stability showed a rather low correlation coefficient between the location of the hypoxic volume at baseline and at week 2 PET. We concluded that the change of HX4 uptake measured with PET early during treatment can be considered as a prognostic factor. With such models patients with a worse prognosis can be selected for treatment intensification or hypoxia targeting, although the HX4 signal in itself seems less appropriate due to spatial instability to use for focal target definition.

In **Chapter 10**, a systemic review of biological PET guided adaptive radiotherapy for dose escalation in head and neck cancer is presented. A structured literature search was done to select clinical trials including patients with a PET performed during treatment used to develop biological adaptive radiotherapy by i) delineation of sub-volumes suitable for adaptive re-planning, ii) in silico adaptive treatment planning or iii) treatment of patients with PET based dose escalated adaptive radiotherapy. Nineteen articles were selected, 12 analyzing molecular imaging signal during treatment and 7 focusing on biological adaptive treatment planning (two clinical trials). Based on this review, the most attractive strategy is selecting patients with radio-resistant sub-volumes in the second week of treatment. Whether a second adaptation is useful, for instance in the fourth week of treatment, is questionable, especially since PET signals are weak around this time. Patient selection tools are diverse and hypoxia, proliferation or metabolism could all be used in predictive models. Based on signal stability, recurrence data and clinical applicability, FDG-PET seems most appropriate to guide target selection for dose escalation. Whether such biological adaptive strategies result in improved local control, survival parameters or toxicity profiles remains unclear, and will require prospective clinical trials before biological adaptive radiotherapy can be applied in standard clinical practice.