Adaptive radiotherapy in head and neck cancer

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Chapter 1

General introduction and outline of the thesis

Introduction

Head and neck cancer

Head and neck cancer refers to a heterogeneous group of malignancies originating from the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, nasal cavity, paranasal sinuses or orbit. Radiation therapy is an important modality in organ preserving treatment of these cancers. In early stage head and neck cancer, single modality treatment is the mainstay, while patients with loco-regional advanced disease require multimodality treatment with a combination of radiation therapy with surgery and/or systemic chemo- or targeted- therapy. Unfortunately, the outcome of curative intended treatment remains suboptimal. Especially in locally advanced tumors, loco-regional failure remains a major problem.[1] Furthermore, toxicity of radiotherapy is substantial, for instance xerostomia and dysphagia can be burdensome and affect quality of life. In search for better treatment outcomes, tailoring treatment individually is being explored, for instance by tailoring therapy to pre-treatment predictive markers or by individual adaptation of the radiation treatment plan during treatment (ART) based on observed anatomical deformations or biological tissue parameters.

Another development in head and neck cancer treatment is the introduction of intensity modulated proton therapy (IMPT). Comparative planning studies show potential benefit of IMPT in the risk of side effects such as xerostomia and dysphagia.[2,3] Clinical data is expected from an ongoing randomized clinical trial comparing proton to photon treatment for stage III/IV oropharyngeal tumors.[4] The benefit is likely to differ on an individual patient level.[5] In the Netherlands, a model based approach has been developed to select patients for treatment with proton therapy.[6] Such an approach translates absolute dose differences in clinical effect and, depending on the model, multiple factors can be taken into account. Patients are deemed eligible for proton treatment if individually applied NTCP models predict a clinically relevant reduction of toxicity.

Radiation therapy

In the last decades, precision of radiation treatment has increased. Improvements have especially been made in target volume delineation, treatment planning and setup verification for treatment delivery. Target volume delineation is typically done on a CT scan to provide the treatment planning system with the anatomy and tissue density for dose calculation. First, a gross tumor volume (GTV) is contoured consisting of the visible tumor based on clinical examination and imaging. To decrease inter-observer variation, co-registration of MRI and/or PET has been introduced.[7,8] Next, the high-risk clinical target volume (CTV) is derived from the GTV by applying a margin to account for the likely presence of microscopic tumor extensions. Furthermore, a low-risk CTV is contoured consisting of areas where a low tumor cell density is assumed, for instance in draining neck lymph nodes levels. Recently, extended guidelines have been published how to derive such CTVs, as well as delineation guidelines for organs at risk (OAR).[9-11] However, the difficulty remains that microscopic disease is not visualized on currently available imaging modalities and little is known about the behavior of the CTV during treatment.

To account for target delineation errors and other geometrical uncertainties such as tumor displacement, tumor deformation and setup errors, the CTV is expanded with a safety margin to the planning target volume (PTV). Subsequently, the radiation dose is prescribed to the PTV in the treatment planning system. Modern external beam photon radiotherapy treatment plans are designed with advanced

planning and delivery techniques such as intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) to create conformal treatment plans. Intensity modulated treatment planning for proton therapy (IMPT) is more complex due to a different susceptibility to uncertainties by causing a shift of Bragg peaks. The effect of uncertainties such as range and set up errors, can be checked with error scenarios and can be taken into account in treatment planning by robust optimization.

During treatment, image guided setup correction strategies are applied, for instance with daily cone beam CT (CBCT) scans. These CBCTs are registered with the planning CT to determine the setup error and to apply a couch correction before treatment is delivered. However, even with online setup correction, residual errors have to be expected due to anatomical deformations. Examples of such deformations include changes in shoulder position or neck flex, decrease in neck diameter due to weight loss or tumor deformations in case of response or edema.

Adaptive Radiation Therapy

In the quest to further improve accuracy and decrease toxicity, adaptive radiotherapy (ART) is explored to allow a more individualized dose delivery. The aim of ART, as defined by Yan et al.[12] in 2005, is 'to customize each patient's treatment plan to patient-specific variation by evaluating and characterizing the systematic and random variations through image feedback and including them in adaptive planning'. Systematic errors are errors that are identical at each fraction throughout the treatment, in contrast to random errors which differ from fraction to fraction and cancel out on average.[13] ART to account for anatomical deformations will mainly be applied to correct systematic errors or progressive changes such as weight loss, tumor regression or changing OAR. Furthermore, ART can be applied to exploit changes in biological tissue parameters.

1. Anatomical ART

In head and neck cancer, ART has primarily been introduced to correct the treatment plan for non-rigid anatomical changes. These changes can occur during the course of treatment, either in target volumes or OAR. In this thesis, the focus will be on the change of the primary target volume and its consequences. Literature on volumetric and positional changes of the primary target volume during treatment mainly reports a gradual decrease of the GTV with a shift of the GTV center of mass.[14-15] Due to these changes, treatment plans based on pre-treatment imaging could deteriorate. Several authors investigated differences between planned and delivered doses. Reported results on actual delivered doses calculated on repeat imaging to target volumes are controversial.[16-26] Some studies reported target volume underdoses,[16-21] others found no difference [22-24] and a few reported target volume overdoses[20,25,26]. Multiple factors may contribute to these apparent conflicting results, such as the limited number of patients included in these studies (10-37 patients), definition and location of the target volumes, variability in planning techniques and proximity of dose gradients, different dose accumulation methods and time points used, choice in compared volumes and DVH parameters. Dose deterioration in OAR is studied most for parotid glands and spinal cord. Castelli et al.[16] concluded in a recent review that the difference between mean planned and delivered doses without ART ranged in literature from -1 Gy to 6 Gy, with 85% of studies showing an increase in parotid gland dose. For spinal cord, maximum dose increased from -0.1 Gy to 3.8 Gy.[16]

Clear guidelines on how to identify patients who could benefit from ART during treatment are not available and patient selection remains therefore challenging. In clinical practice, patients are generally selected at the discretion of the physician, often considering gross deformations visualized with image guidance techniques. ART moreover, is labor intensive. Frequently,

new imaging is acquired to re-plan the radiation treatment. Alternatively, adjustment of delineated volumes and re-planning is performed on the original planning CT. The balance between availability of resources and benefit of ART would be improved with accurate patient selection of those in need to correct dose deterioration.

Implementation of ART for anatomical deformations may also create opportunities to adjust the dose distribution after tumor regression, for instance by reducing treatment volumes. However, field size reduction following tumor regression assumes that microscopic disease in the CTV behaves congruent with changes in the visible GTV, otherwise such strategy could pose risk on coverage of microscopic disease and tumor control.

2. Biological ART

In recent years, the possibility of tailoring radiotherapy to biological tissue parameters has emerged. Most likely, not all patients will benefit from the same treatment, for example due to inter- and intra-tumor heterogeneity and patient related factors. Biological tumor characteristics are explored for their predictive value, either before or during treatment. Pre-treatment for instance, markers predicting response to systemic treatment with either cisplatin or Cetuximab could assist in patient selection for combined modality treatment.

During treatment, biological aspects in the tumor can change even more rapidly and dramatically compared to volumetric changes.[27] With biological ART these changes can be used to discriminate between responders and non-responders, with the aim to adapt the treatment plan accordingly, for example by adjusting the radiotherapy dose. The goal of this strategy is to enlarge the therapeutic ratio, by improving loco-regional control with treatment intensification in radio-resistant parts of the tumor, and/or by decreasing side effects in responders with treatment deintensification. Imaging biomarkers are being selected that can predict response early during treatment as well as identify sub-volumes to guide radiation treatment. Molecular imaging with positron emission tomography (PET) is a promising technique to provide such biomarkers; it is suitable for both quantitative imaging as well as determination of spatial distribution with different tracers. Potential applications include imaging of metabolism, hypoxia or proliferation.[28-30] However, it is currently insufficiently clear which biological parameters provide the most relevant information, which patients will benefit most, and how the results from imaging should guide treatment decisions.

In summary, both anatomical and biological ART are promising techniques to create opportunities for increase of tumor control and/or decrease of toxicity by increasing precision of radiation treatment and allowing margin reduction or dose (de-)escalation. However, many questions remain before wide clinical implementation will be fact. This thesis addresses outstanding issues to accelerate implementation of adaptive radiotherapy in head and neck cancer.

Outline of this thesis

This thesis centers around individual tailoring of treatment to enlarge the therapeutic window by contributing to the development of both anatomical and biological adaptive radiotherapy. In the first part, the impact of geometrical change is studied and implications for anatomical ART are evaluated. In the second part, opportunities to adjust treatment based on biomarkers is addressed. The specific aims explored in this thesis were:

- To understand geometric tumor behavior during radiotherapy and implications for ART.
- To quantify the effect of geometrical changes

on the delivered dose distribution.
- To evaluate use of pre-treatment biomarkers to tailor treatment.
- To explore molecular biomarkers as a target for biological ART.

Part 1: Geometrical changes during treatment: effects on delivered dose distribution and implications for ART

In ***Chapter 2***, tumor shape variability during the course of radiation therapy is quantified based on the position of gold markers that are implanted at the edge of the visible tumor. Markers are identified on planning CT and daily CBCT after bony anatomy registration. Daily marker movement, time trends and response patterns are investigated.

In patients with visible tumor response mid-treatment, ART with field size shrinkage could be beneficial to reduce OAR dose, but is only safe if the tissue containing microscopic disease surrounding the GTV is shrinking together with the GTV. To answer this question, fiducial markers at the edge of the GTV are used as a surrogate and are compared to GTV changes on MRI in ***Chapter 3***.

Treatment planning is typically performed with 3-5 mm PTV margins. In ***Chapter 4*** we investigate loss of target coverage due to anatomy changes as a function of applied PTV margins. We evaluate at which margins treatment plans become sensitive for deformations and if a single intervention with an average anatomy, derived from CBCT from the first 10 fractions, effectively mitigates discrepancies.

Chapter 5 describes dose deterioration in target volumes due to anatomical changes of 188 consecutive head and neck cancer patients treated with curative intent. In this study, planned dose is compared to actual delivered dose and predictive factors for dose deterioration are evaluated. Furthermore, dosimetric patient selection is compared to clinical selection of patients for ART based on visual changes on CBCT.

In proton therapy, setup and range uncertainties can compromise the dose distribution by causing a shift of Bragg peaks, thereby creating cold and hot spots. In ***Chapter 6***, we introduce a method to evaluate the clinical effect of these uncertainties on the population using tumor control probability and normal tissue complication probability models. The effect of uncertainties in proton therapy is compared to the effect in photon therapy in this Chapter.

Part 2: Biomakers to tailor treatment: patient selection, target definition and opportunities for ART

To improve outcome, predictive biomarkers are investigated to identify which patients benefit from which treatment. For instance, in patients with irresectable head and neck cancer, radiotherapy is frequently combined with either cisplatin or Cetuximab and treatment could be individually tailored if predictive markers for cisplatin or Cetuximab treatment efficacy would be available. ***Chapter 7*** describes the use of Zirconium-89 labeled Cetuximab PET-CT imaging in patients with advanced head and neck cancer as a possible theragnostic strategy.

Another approach to improve outcome 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 aims to improve

outcome by redistribution of the radiation dose to the metabolically most FDG-PET avid part of the tumor measured pre-treatment, while simultaneously sparing normal tissues.

Chapter 9 investigates the prognostic value of HX4-PET imaging in patients treated with definitive chemoradiotherapy. Both static uptake pre-treatment and in week 2, as well as a change of HX4 uptake early during treatment are correlated to outcome. Furthermore, the spatial stability of the HX4 signal is evaluated to consider its use for focal target definition in biological adaptive radiotherapy.

In ***Chapter 10***, a systemic review of biological PET guided adaptive radiotherapy for dose escalation in head and neck cancer is presented. In the development of biological dose adaptation during radiotherapy, many aspects of the procedure remain ambiguous. Patient selection, tracer selection for detection of radio-resistant sub-volumes, timing of adaptive radiotherapy, workflow and treatment planning aspects are discussed in a clinical context.

Chapter 11 provides a summary, general discussion, future perspectives and conclusion.

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