Adaptive radiotherapy in head and neck cancer

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2020

Chapter 11

Summary, general discussion, future perspectives and conclusion

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The publications in this thesis are centered around development of adaptive radiotherapy (ART) in head and neck cancer treatment. It includes both development of anatomical adaptive radiotherapy to geometrical changes (Part 1), as well as biological adaptive radiotherapy based on tumor characteristics (Part 2). By tailoring treatment individually, opportunities to improve outcome are created. The following questions were posed:

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

A. How does the primary tumor behave during radiotherapy and what are the implications for adaptive radiotherapy?

B. How do geometrical changes influence the intended dose distribution?

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

A. Which opportunities are available to tailor treatment based on pre-treatment biomarkers?

B. Which molecular biomarkers can be used for biological ART?

These questions were addressed through retrospective analyses (Chapters 4, 5, 6), clinical studies (Chapters 2, 3, 7, 8, 9) and a systematic review (Chapter 10). In the first part of this Chapter, we summarize our work structured by the aims of this thesis. The Chapter is concluded by a general discussion and outline of future perspectives for development of anatomical and biological adaptive radiotherapy in head and neck cancer treatment.

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}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}Zr-Cetuximab uptake was found between patients. Comparison of high uptake regions on the ^{89}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}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}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 divers 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.

General discussion

Anatomical adaptive radiotherapy

Performing anatomical ART during treatment has two aims. The first one is to increase tumor control probability by correcting for deviations from the planned dose distribution or by escalating the radiation dose based on the changing anatomy. The second aim is to decrease OAR dose, either by adapting to the changing anatomy of OARs and surroundings or by decreasing irradiated volumes. Our findings together with available evidence for both aims are discussed in the following paragraphs.

Anatomical ART to increase tumor control probability

Clinical evidence

The ability of anatomical ART to restore the dose distribution with a re-plan and enhance clinical outcome still remains to be determined. Comparative planning studies show that ART has the ability to improve the dose distribution, although not every patient will benefit.[1-6] One of the largest series reported on by Castelli et al.[1], described an in silico study with 37 head-and-neck-cancer patients. Comparison of delivered dose without ART to weekly ART showed an increase of target coverage in the majority of patients, the median D_{98}-CTV increased from 68 Gy to 69.2 Gy. Available evidence of clinical benefit with improved tumor control from ART is sparse. The largest prospective trial comparing standard treatment to ART was performed in nasopharyngeal carcinoma patients in China.[7] In this trial, patients were not randomized, but could choose to receive ART. Two year locoregional control was significantly better in the ART group (97% in 86 ART-patients versus 92% in 43 no-ART-patients, p=0.040), two year overall survival was not significant different (90% versus 82%, p=0.475). However, the non-randomized design introduced confounders, for instance fitter patients are more likely to have chosen the ART group. Chen et al.[8] reported a large retrospective study of head-and-neck carcinoma comparing clinical outcomes of 51 ART-patients to 266 no-ART-patients. The 2-year locoregional control was 88% for ART-patients compared to 79% for no-ART-patients (p=0.01). Another retrospective study comparing 33 ART-patients to 66 matched controlled no-ART-patients with nasopharyngeal carcinoma showed an improved 3-year local progression free survival for patients who had AJCC stage T3-4Nx.[9] Furthermore, two smaller prospective single arm trials reported promising outcomes of patients treated with ART.[10,11]

Although clinical evidence is not available, one could hypothesize, that ART can be used in combination with dose escalation to an adjusted target volume during treatment based on anatomical images. The question which volume to use for such dose escalation is not yet solved, this can either be the entire primary tumor or only a radioresistant sub-volume. The strategy to dose-escalate on the entire primary tumor volume is based on the fact that imaging techniques of sub-volumes might not reflect the actual locations of radioresistant tumor cells that lead to recurrence. By applying ART, dose distributions can be shaped to the changing anatomy and PTV margins might be diminished based on increased accuracy in favor of OAR. On the other hand, toxicity of dose escalation is related to treatment volume and the gain in tumor control could be larger with a focal dose escalation to a smaller radioresistant volume to allow a higher maximum tolerated dose with equal toxicity, thereby making a biological target to guide dose escalation attractive.

Patient selection

The main question to be answered is how to select the appropriate patients who have a clinical benefit of ART. Currently, patient

selection is mainly done ad hoc based on anatomical changes observed during treatment. In **Chapters 2, 3** and **4** we observed that anatomical changes occur in target volumes as well as in OAR during treatment. However, in **Chapter 5**, we showed that patient selection with concern of target volume coverage based on CBCT changes observed by the physician, did not correlate very well to the recalculated deviation from the planned dose distribution. An explanation might be that the negative effect of anatomical changes on the dose distribution is rather limited with the use of 3-5 mm PTV margins, although the risk increases with smaller margins (**Chapters 4** and **5**). Another approach is to select patients based on predictive factors for dose deviation, either pre-treatment or during treatment. In our series of 188 consecutive patients described in **Chapter 5**, factors associated with increased risk of dose deterioration were diverse and depended on the evaluated target volume (low or high dose) and dose parameters (over- or under-dosage). Single strong predictive models were not identified. Besides the lack of strong predictive factors, other aspects add to the complexity of predicting which patient could benefit from ART. Even for evaluation of target volumes only, multiple endpoints (DVH parameters) can be defined, all with their own associated factors. In combination with the relative low number of patients with dose deterioration, it is unlikely that a multifactorial prediction model to select patients for ART based on predictive factors, will become available.

More promising are dosimetric selection tools during treatment, for instance with regular dose recalculation to estimate dose deterioration at the end of treatment. In **Chapter 4** we were able to identify patients with underdosage early during treatment with dose accumulation. Although development of such strategy is attractive, several issues still need to be resolved before wide implementation will be possible. These are discussed in the section Future perspectives.

Anatomical ART to decrease OAR dose

Clinical evidence

Multiple in-silico trials showed a benefit of OAR sparing when ART is applied in patients with head and neck cancer. In a recent review, ART decreases the mean dose to the parotid gland from 0.6 to 6 Gy compared to standard treatment.[1] The maximum dose in the spinal cord improved from 0.1 to 4 Gy.[1] Three clinical studies compared late toxicity between ART and no-ART patients. In the two retrospective studies mentioned above published by Chen et al.[8] and Zhao et al.[9], no difference in late toxicity was observed between ART and no-ART patients. Only the prospective study by Yang et al.[7] showed an improvement in quality of life with ART (n=86) in comparison to no-ART (n=43). However, as mentioned, bias is introduced in this study because patients could choose a treatment arm themselves.[7] Clinical studies investigating the safety and gain of target volume reduction to increase OAR sparing are even more sparse. Schwartz et al.[11] reported on a prospective single arm ART trial in oropharyngeal carcinoma patients with the use of zero PTV margins in adaptive plans. Outcome of the 22 evaluable patients was excellent with 100% local control and 95% regional control at two years.

Patient selection

For improved sparing of OAR, it is not clear yet how to select the appropriate patients for ART. In clinical practice, similar to patient selection to restore target coverage, anatomical changes are the trigger to perform ART. Studies in literature searching for predictive factors are heterogeneous and conclusions ambiguous. Brouwer et al.[12] concluded from a literature review that potential pre-treatment selection criteria to increase parotid gland sparing were tumor location, age, body mass index, planned dose to the parotid glands, the initial parotid gland volume, and the overlap volume of the parotid glands with the target volume. Also for OAR, dosimetric selection

tools seem more promising. McCulloch et al.[13] recently published a model to select patients by fraction 15 with a mean dose deviation over 15% of the planning constraint. They analyzed 10 OAR and found such deviations in 10% of patients, predominantly in the submandibular gland. If a mean dose deviation threshold of 3.5 Gy was set by fraction 15 for the submandibular glands, the need for re-planning could be predicted with 100% sensitivity and 98.7% specificity. A major challenge in the radiation community is to reach consensus on clinically meaningful dose deviations to be used in such models. The principle of using NTCP calculations to interpret dose differences between intended and delivered dose was shown by Heukelom et al.[14] They found the use of NTCP calculations superior to clinical judgment in patient selection for ART. Future requirements of dose accumulation, estimation of delivered dose, interpretation and technical performance of patient selection tools are discussed in the section Future perspectives.

Target volume reduction

Target volume reduction can consist of reducing the PTV margins or of field size reduction following visible shrinkage of macroscopic tumor. Either way, OAR dose is expected to decrease. In fact, we reported an OAR mean dose sparing of approximately 1 Gy/mm PTV shrinkage in **Chapter 4**. Furthermore, reduction of the PTV margin from 5 to 3 mm resulted in a clinical advantage by reducing severity, frequency, and duration of radiation-related toxicity without jeopardizing outcome in a retrospective cohort study of respectively 206 versus 208 head and neck cancer patients.[15] Although preliminary data from Schwartz et al.[11] is encouraging, clinical outcome of reduction beyond 3 mm PTV margin in combination with increased treatment precision with image guidance and ART needs to be validated. Safety of field size reduction following tumor regression also remains to be determined. Based on **Chapter 3**, soft tissue adjustments without clear anatomical borders has a risk of tumor underdosage since regions from which the tumor shrank radiologically might still contain a substantial number of tumor cells. One could hypothesize that these regions need lower radiation doses than visible GTV mid-treatment. A clinical trial using MRI-guided adaptation in a prospective cohort of HPV positive oropharyngeal carcinoma patients studying safety and toxicity is ongoing.[16]

Biological adaptive radiotherapy

In the discussion of tailoring radiotherapy to biological tumor parameters we distinguish two approaches. The first is to use biological tissue parameters to select treatment from which the patient is expected to benefit most. The second is to use biological tissue parameters to shape the dose distribution.

Treatment selection

Currently, biological tissue parameters are not widely used to guide treatment choices, but radiation treatment is evolving from one size fits all to individualized treatment. The best known predictive biomarker in head and neck cancer is probably the HPV virus association with squamous cell carcinoma. Because of the better prognosis, several de-escalation strategies are being explored. Recently, two large randomized clinical trials compared radiotherapy with cisplatin to radiotherapy with Cetuximab in patients with HPV-positive oropharyngeal carcinoma.[17,18] Both trials showed that radiotherapy plus Cetuximab had an inferior survival compared to radiotherapy plus cisplatin and concluded that cisplatin in combination with radiation remains the standard of care. The authors hypothesize that the favorable survival outcomes of HPV-positive low-risk oropharyngeal squamous cell carcinoma are in part a function of the type of treatment received, and not merely a reflection of favorable intrinsic tumor biology.[17]

Multi-factorial prediction models could improve prediction of response to therapy. In the example of Cetuximab, an antibody against the epidermal growth factor receptor (EGFR), the expression of EGFR, in combination with accessibility of drug into the tumor might improve estimation of responsiveness. In tumors lacking EGFR expression, response to the targeted drug is not expected regardless of accessibility, while in tumors with an EGFR overexpression, the accessibility of the tumor is expected to be a determining factor in drug uptake. In **Chapter 6**, we demonstrated the possible use of PET imaging with radioactive labeled Cetuximab as a non-invasive way to quantify the uptake of Cetuximab. Furthermore, gene signatures are being developed. For instance, a Chung high-risk expression profile and a negative HPV expression profile were significantly associated with increased risk of local recurrence after chemoradiotherapy in advanced pharynx and oral cavity tumors, independent of clinical factors.[19] Such gene expression profiles are promising to add predictive value in multi-parametric models. Another biomarker expected to be a key component in predictive models is hypoxia. Cells in hypoxic areas may cause tumors to be resistant to radiotherapy and chemotherapy, increase tumor aggressiveness, angiogenesis and metastatic potential.[20,21] Besides hypoxia imaging with PET tracers, alternative non-invasive ways to detect hypoxia are promising, for instance with radiomics built from contrast-enhanced CT features and FDG-PET.[22]

Target delineation

Distinction of radioresistant tumor parts with biomarkers fuels the strategy of focal dose escalation with the aim to improve tumor control without significant increase of toxicity. Such strategy can be applied based on pre-treatment imaging or on imaging acquired during treatment. In **Chapter 8**, we described a clinical trial (rtforce) implementing focal dose escalation to the 50% isocontour of SUV_{max} on pre-treatment FDG-PET. In this trial, the dose in the remainder of the primary target volume is slightly decreased, thereby aiming for equal toxicity. The study is closed and results are expected in 2021. Whether dose escalation strategies indeed are capable of significantly improving outcomes has not been proven yet. The group of Gent reported on the long-term outcome of FDG-PET guided dose painting for treatment of head and neck cancer in comparison to conventional IMRT in a matched case-control study.[23] They included 41 patients from a trial with upfront simultaneous integrated boost with dose painting by contour on the pre-treatment FDG-PET volume, furthermore they included 31 patients from two dose painting by numbers trials adapting to per-treatment changes. These patients were matched on tumor site and T classification with 72 control patients. The 5-year local control rate in the dose-painting patients was 82.3% against 73.6% in the control group (p=.36). There was no difference in regional and distant control, also overall survival was similar. Patients in the dose painting group had increased rates of acute and late dysphagia. However, in the 2 adaptive trials, higher local control and less toxicity was observed. For instance, in the three phase adaptive dose painting trial, 9 out of 10 patients did not have evidence of disease after a median follow up of 3 years.[24] Also, no grade 4 toxicity was observed in the two adaptive trials and all patients could finish treatment without delay. They concluded that applying focal dose escalation based on biological tumor changes during treatment could improve the expected therapeutic gain by reducing high dose volumes compared to pre-treatment biological volumes, thereby preventing an increase of toxicity. Another advantage of mid-treatment adaptation is the possibility to select the appropriate patients on the basis of biological response.

The imaging modality most known for delineation of radioresistant tumor areas is molecular imaging with PET. Several strategies can be followed, in head and neck tumors, these focus on detecting areas with high metabolic turnover (FDG), proliferative activity (FLT) or hypoxic volumes (Nitromidazoles, for example HX4 demonstrated in **Chapter 9**). In **Chapter 10** (review of biological PET-guided adaptive radiotherapy), we concluded that, although all three can be used as patient selection tools during treatment, FDG-PET seems most appropriate to guide target delineation for dose escalation based on signal stability, recurrence data and clinical applicability. This is in line with our analyses of the HX4 signal in **Chapter 9**, showing a correlation of residual hypoxia to prognosis, but the HX4 signal in itself seemed less appropriate for focal target definition due to spatial instability.

Future perspectives

This paragraph discusses future perspectives for implementation of anatomical and biological ART, including patient selection tools, new radiation treatment techniques, biomarker selection and technical implementation issues.

Anatomical ART patient selection tools:
A wish-list for future patient selection tools for anatomical ART includes the following considerations:

1) Daily dose accumulation should be accurate. A key factor in dose accumulation is the use of deformable image registration (DIR) to take anatomical changes into account. Several registration algorithms are available, however, there is currently no consensus how to assess accuracy of resulting deformation vector fields. In a study using anatomical landmarks and implanted tumor markers to evaluate accuracy of B-Spline DIR, a precision of 1.8 mm for normal tissue and 3.3 mm for tumor tissue was found.[25] Additional uncertainties are introduced by (dis) appearing tissue or objects, for instance tumor shrinkage or cavity filling. Biomechanical models, taking relational and intensity data into account, are proposed to mitigate the effect of changing mass.[26,27]

2) Prediction, preferably early during treatment, of the expected delivered dose at the end of treatment should be reliable. False positive patient selection could result in unnecessary re-planning and additional workload, while false negative patients might have decreased tumor control probabilities. Reliable prediction in the early phase of treatment will result in enough remaining fractions to correct dose deviations. It would also be beneficial for the decision process to evaluate possible improvement with an ART step when evaluating predicted dose deviations.

3) Guidelines for thresholds to use for ART patients selection should be developed. Currently, how accumulated dose should be evaluated and thresholds defined still remains unclear. For evaluation of target volume coverage in **Chapter 4** and **5**, we used absolute changes of D_{99} and D_1 as surrogates for under- or over-dosage, but other DVH parameters are used in literature as well, such as $D_{95,}$ D_{98}, Mean dose, Median dose, V_{107}. However, absolute changes do not directly reflect clinical consequences. Translation of dose differences in TCP or NTCP models could be used to quantify probability of tumor control and complications, as we demonstrated in **Chapter 6**. Unfortunately, reliable TCP models for clinical use are not available yet, but decision making in ART would greatly benefit if these were developed. In contrast, NTCP models are widely available in literature, however such models harbor uncertainty and model validation is frequently lacking. In the Netherlands, the Dutch proton therapy platform is pursuing validation of NTCP models to use for model-based patient selection, thereby increasing the

number of applicable NTCP models and creating a nation-wide consensus on their use.[28]

Another issue on which consensus is desirable, is which volumes to compare in the planned versus accumulated dose distribution, i.e. PTV to CTV or CTV to CTV. In **Chapter 5**, we chose to create evaluation target volumes (ETVs) by expanding the CTVs with 2 mm to compare planned PTV doses to accumulated ETV doses. The choice for an evaluation volume in between the CTV and PTV was on the one hand to include geometrical uncertainties such as delineation errors and registration inaccuracies, which are overlooked when evaluating on CTV only. On the other hand to exclude residual setup and inter-fraction anatomical changes, which were already explicitly accounted for in the dose accumulation. Improving standardization of chosen parameters, used thresholds and compared volumes will result in better comparable research to analyze which patients clinically benefit from ART.

4) Technical issues such as speed, automation, archiving and reporting should be optimized. ART procedures should be fast and mostly automated to limit clinical workload and allow a more generous patient selection. Nowadays, DIR algorithms, contour propagation and dose recalculation engines are generally fast. However, automatic re-contouring harbors uncertainty and visual check of new contours is desirable, especially of areas without clear anatomical borders. Current ART strategies for head and neck cancer use offline re-planning of selected patients. Re-planning may be facilitated by starting a new plan optimization with the objectives and beam parameters from the original plan, although manual tweaking will most likely improve plan quality. Standardization of archiving and reporting will ensure patient safety and facilitate BIG data analyses for correlating image-dose-response data in a clinical utilizable manner.[29]

Proton therapy and MR-Linac treatment

With the development of new radiation treatment techniques, such as MR-guided radiotherapy or intensity modulated proton therapy (IMPT), the use of ART will increase. Proton therapy has different beam characteristics allowing highly conformal dose distributions with reduced dose outside target volumes. However, an IMPT dose distribution is susceptible to range uncertainty, setup uncertainty and anatomical changes. Especially residual anatomical changes after setup correction, such as non-rigid posture changes, weight loss, tumor shrinkage and swallowing, are a risk for disturbing the intended dose distribution. In treatment planning, uncertainties can be taken into account by robust optimization. Such optimization considers dose distributions for a number of uncertainty scenarios and optimizes them to satisfy specified criteria.[30] Frequently, the worst-case scenario is used to guide robust optimization, for instance the minimax worst-case optimization selects the dose distribution corresponding to the worst-case in each step of the process of minimizing the objective function.[31] However, the level of robustness will be a trade off with the dose to surrounding organs at risk and improved tumor control, robustness will cost conformality with an increase of NTCP.[32] In our estimation (**Chapter 6**), the negative effect of uncertainties on the population was less than the worst-case scenario, therefore, completely optimizing the worst-case scenario might not always be necessary. Image guidance will remain indispensable in IMPT to detect patients with substantial anatomical changes. Future perspectives include in-room CT imaging with the possibility of online treatment adaptation in the presence of anatomical changes.[33] By increasing precision in this way, the level of robustness needed is expected to decrease.

The MR-linac, consisting of a linear accelerator with an integrated MR, is in that perspective a

step ahead of proton therapy and already has the ability to adapt the treatment to the anatomy of the day. Together with improved visibility of soft tissue, this enables the use of smaller margins with the aim to reduce OAR dose. The value of MR guided IMRT over CBCT guided VMAT in head and neck cancer still has to be proven. However, the combination of soft tissue visualization with online re-planning is appealing to further refine adaptive radiotherapy with volume reduction following tumor change, although microscopic disease is still not visible.[16] Several improvements are expected making MR-linac treatment for head and neck cancer patients more attractive, examples are:

1. Improved MRI coils specifically for head and neck tumors,
2. Larger maximal field to be able to also treat comprehensive elective neck levels,
3. Reduction of full online plan optimization time to minimize distress during 30-35 treatments in a claustrophobic and noisy environment,
4. Introduction of functional MRI sequences to adapt to biological response patterns on MR.[34,35]

Biomarkers for patient selection and target delineation

Most likely, multi-factorial prediction models will be developed to personalize radiotherapy. Such models combine clinical, pathological and imaging information to determine individual tumor responsiveness to treatment. Analyses of imaging information has recently evolved to the concept of radiomics, meaning the automatic extraction of quantitative features from images by mathematical algorithms. So called radiomics signatures for head and neck cancer are analyzed for their predictive value in themselves, but also for their added value to other predictive factors.[36] Ou et al.[37] found an additional discrimination capability of CT radiomics when added to p16 status, improving prognostic accuracy. In contrast, in a large series of patients with a controlled imaging protocol, addition of CT or PET radiomics to HPV-status and tumor-volume failed to improve prediction of overall survival.[38] An explanation for these conflicting results might be that the radiomics process is complex and harbors uncertainty. The process has several steps, such as image acquisition and reconstruction, image segmentation, features extraction and qualification, analysis, and model building. Each step needs careful evaluation for the construction of robust and reliable models to be transferred into clinical practice.[39]

Improving the selection of radio-resistant patients and sub-volumes can be expected from the addition of functional MR to PET imaging biomarkers. MR sequences considered are diffusion weighted MR (DW-MR), which relies on the free and random diffusion of water molecules, and dynamic contrast enhanced MR (DCE-MR), which signal is related to perfusion and permeability of the tumor microenvironment.[40] From a review published by Leibfarth et al.[41], it was concluded that a higher increase in apparent diffusion coefficient (DW-MR) during therapy seemed related to a better outcome, this might be attributed to reduced cellularity in the tumor caused by treatment-induced cell death. In a series of 35 head and neck cancer patients, early intra-treatment changes of FDG-PET, DW and DCE MR-derived parameters were compared.[42] The authors reported that all three were predictive of ultimate response to chemoradiation, however, the optimal timing for assessment with FDG-PET parameters (week 1) differed from MR parameters (week 2). Evaluation of signal correlation and spatial overlap of different imaging biomarkers was done in several small series and although correlations between signals were found, spatial overlap between signals was only partial.[40,43-45] Different functional imaging modalities are likely to be complimentary and a combination could provide multi-parametric tumor assessment with

increased accuracy to define the radio-resistant sub-volume. It is unknown if the union or overlap of different imaging modalities might be a better strategy as compared to a single modality for the purpose of dose escalation.[45] The development of combined PET-MR scanners may facilitate the use of multi-modality imaging, allowing acquisition of multiple modalities at one scan session. Moreover, as mentioned, it is expected that functional imaging will be implemented in MR-linac treatment to allow in-room response monitoring during treatment in the future.[34,35]

Implementation of biological ART

Besides selection of appropriate patients and imaging to define radioresistant sub-volumes, several issues remain. First of all the level of dose escalation. Several dose escalation studies are ongoing, either based on pre-treatment imaging or with implementation of adaptive radiotherapy into the treatment scheme. In the coming years, results of these trials will provide more insight in the value and toxicity of dose escalation in head and neck cancer. Also the optimal timing to implement biological ART is yet to be determined, although most authors recommend the second week of treatment. At this timepoint, therapy associated inflammation of the mucosa is still limited and there is enough time left to profit from treatment adaptation. Whether a second adaptation is useful, for instance in the fourth week of treatment, remains questionable.

Implementation of biological adaptive radiotherapy requires a dedicated workflow for image registration, (re)delineation, (re)planning and dose summation. Similar to implementation of anatomical ART, DIR methods should be validated and accurate. Delineation of sub-volumes visualized on imaging can be done manually, with thresholds or with advanced automatic algorithms. Especially during treatment, with decreasing signal to noise ratio and tumor uptake approaching the background level, advanced algorithms can aid delineation accuracy of residual uptake. Although developments in radiotherapy techniques and treatment delivery facilitate inhomogeneous treatment planning, several choices can be made. For instance: dose painting by contour or dose painting by numbers, how to deal with diffusely dispersed sub-volumes, can proton or MR-guided plans improve treatment, should the radiation dose be changed in voxels with appearing or disappearing imaging signals during treatment, similarly, how to deal with orphan and newborn voxels when delineations are manually adjusted mid-treatment and last but not least, should the objective function in later phases be adjusted to correct sub-optimal dosimetric results in earlier phases. Furthermore, applying dose accumulation of heterogeneous dose distributions and dealing with anatomical changes during such treatments is a challenging puzzle.

General conclusion

This thesis focuses on individual tailoring of treatment to enlarge the therapeutic window by contributing to the development of both anatomical and biological adaptive radiotherapy. We showed that although anatomical changes occur in primary target volumes, anatomical ART to correct delivered target dose is only expected to result in clinical benefit in a minority of patients. Development of patient selection tools should focus on interpretation of dose difference between intended and delivered dose distributions, both for target volumes as for OAR. Decrease in OAR dose can be achieved with smaller PTV margins or field size reduction during treatment, however, because of the risk of underdosing microscopic disease, safety of such approaches should be evaluated in clinical trials. In this thesis we evaluated several ways to use biomarkers to individualize treatment, both for treatment selection as well as target delineation. For treatment selection, multi-factorial prediction models are warranted, combining clinical, pathological and imaging

information to determine individual tumor responsiveness for personalized radiotherapy. Biological PET-guided ART early during treatment based on biological response and delineation of radioresistant sub-volumes is a promising strategy to improve outcome.

References

1. Castelli J, Simon A, Rigaud B, et al. Adaptive radiotherapy in head and neck cancer is required to avoid tumor underdose. Acta Oncol. 2018;1267-70.
2. Schwartz DL, Garden AS, Shah SJ, et al. Adaptive radiotherapy for head and neck cancer – dosimetric results from a prospective clinical trial. Radiother Oncol. 2013;106:80-4.
3. Dewan A, Sharma S, Dewan A, et al. Impact of adaptive radiotherapy on locally advanced head and neck cancer – A dosimetric and volumetric study. Asian Pac J Cancer Prev. 2016;17:985-92.
4. Jensen AD, Nill S, Huber PE et al. A clinical concept for interfractional adaptive radiation therapy in the treatment of head and neck cancer. Int J Radiat Oncol Biol Phys. 2012;82:590-6.
5. Olteanu LA, Berwouts D, Madani I, et al. Comparative dosimetry of three-phase adaptive and non-adaptive dose-painting IMRT for head and neck cancer. Radiother. Oncol. 2014;111:348-53.
6. Capelle L, Mackenzie M, Field C, et al. Adaptive radiotherapy using helical tomotherapy for head and neck cancer in definitive and postoperative settings: initial results. Clin Oncol. 2012;24:208-15.
7. Yang H, Hu W, Wang W, et al. Replanning during intensity modulated radiation therapy improved quality of life in patients with nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2013;85:e47-54.
8. Chen AM, Daly ME, Cui J, et al. Clinical outcomes among patients with head and neck cancer treated by intensity-modulated radiotherapy with and without replanning. Head Neck. 2014;36:1541-6.
9. Zhao L, Wan Q, Zhou Y, et al. The role of replanning in fractionated intensity modulated radiotherapy for nasopharyngeal carcinoma. Radiother Oncol. 2011;98:23-7.
10. Kataria T, Gupta D, Goyal S, et al. Clinical outcomes of adaptive radiotherapy in head and neck cancers. Br J Radiol. 2016;89:20160085.
11. Schwartz DL, Garden AS, Thomas J, et al. Adaptive radiotherapy for head and neck cancer: initial clinical outcomes from a prospective trial. Int J Radiat Oncol Biol Phys. 2012;83:986-93.
12. Brouwer CL, Steenbakkers RJ, Langendijk JA et al. Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in head and neck organs at risk during radiotherapy proved information to help? Radiother Oncol. 2015;115:285-94.
13. McCulloh MM, Choonik L, Rosen BS, et al. Predictive models to determine clinically relevant deviations in delivered dose for head and neck cancer. Prac Radiat Oncol. 2019;9:e422-e431.
14. Heukelom J, Kantor MR, Mohamed ASR, et al. Differences between planned and delivered dose for head and neck cancer, and their consequences for normal tissue complication probability and treatment adaptation. Radiother Oncol. 2019;S0167-8140(19)33027-0
15. Navran A, Heemsbergen W, Janssen T, et al. The impact of margin reduction on outcome and toxicity in head and neck cancer patients treated with image-guided volumetric arc therapy (VMAT). Radiother Oncol. 2019;130:25-31.
16. Bahig H, yan Y, Mohamed ASR, et al. Magnetic resonance based response assessment and dose adaptation in human papilloma virus positive tumors of the oropharynx treated with radiotherapy (MR-adaptor): An R-ideal stage 2a-2b/Bayesian phase II trial. Clin Transl Radiat Oncol. 2018;13:19-23.
17. Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or Cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open label randomized controlled phase 3 trial. Lancet 2019;393:51-60.
18. Gillison ML, Trotti AM, Harris J et al. Radiotherapy plus Cetuximab or cisplatin in human papillomavirus-positive

oropharyngeal cancer (NRG Oncology RTOG 1016): a randomized, multicenter, non-inferiority trial. Lancet 2019;393:40-50.
19. De Jong MC, Pramana J, Knegjens JL et al. HPV and high-risk gene expression profiles predict response to chemoradiotherapy in head and neck cancer, independent of clinical factors. Radiother Oncol. 2010;95:365-70.
19. Muz, B, de la Puente P, Azab F, et al. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia (Auckl) 2015;3:83-92.
20. Nordsmark, M, Bentzen, SM, Rudat V, et al. Prognostic value of tumor oxygenation in 397 head and neck tumors after primary radiation therapy. An international multi-center study. Radiother.Oncol. 2005;77:18–24.
21. Crispin-Ortuzar M, Apte A, Grkovski M, et al. Predicting hypoxia status using a combination of contrast-enhanced computed tomography and [18F]-Fluorodeoxyglucoses positron emission tomography radiomics features. Radiother Oncol. 2018;127:36-42.
22. Berwouts D, Madani I, Duprez F, et al. Long-term outcome of 18F-fluorodeoxyglucose-positron emission tomography-guided dose paiting for head and neck cancer: matched case-control study. Head Neck 2017;39:2264-75.
23. Berwouts D, Olteanu LA, Duprez F, et al. Three-phase adaptive dose-painting-by-numbers for head-and-neck cancer: initial results of the phase I clinical trial. Radiother Oncol. 2013;107:310-6.
24. Mencarelli A, van Kranen S, Hamming-Vrieze O et al. Deformable image registration for adaptive radiotherapy of head and neck cancer: accuracy and precision in the presence of tumor changes. Int J Rad Oncol Biol Phys. 2014;90:680-687.
25. Qin A, Ionascu D, Liang J, et al. The evaluation of hybrid biomechanical deformable registration method on a multistage physical phantom with reproducible deformation. Radiat Oncol. 2018;13:240.
26. Zhong H, Chetty IJ. Caution must be exercised when performing deformable dose accumulation for tumors undergoing mass changes during fractionated radiation therapy. Int J Radiat Oncol Biol Phys. 2017;97:182-3.
27. Langendijk JA, Lambin P, de Ruysscher D, et al. Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model based approach. Radiother Oncol. 2013;107:267-73.
28. Bibault JE, Zapletal E, Rance B, et al. Labeling for Big Data in radiation oncology: The Radiation Oncology Structures oncology. PLoS One 2018;13:e0191263.
29. Mohan R, Das IJ, Ling CC. Empowering Intensity Modulated Proton Therapy Through Physics and Technology: An Overview. Int J Radiat Oncol Biol Phys. 2017;99:304-16.
30. Frederiksson A, Forsgren A, Hardemark B. Minimax optimization for handling range and setup uncertainties in proton therapy. Med Phys. 2011;38:1672-84.
31. Van de Water S, van Dam I, Schaart DR, et al. The price of robustness: impact of worst-case optimization on organ at risk dose and complication probability in intensity-modulated proton therapy for oropharyngeal cancer patients. Radiother Oncol. 2016;120:56-62.
32. Bernatowicz K, Geets X, Barragan A, et al. Feasibility of online IMPT adaptation using fast, automatic and robust dose restoration. Phys Med Biol. 2018;63:085018.
33. Corradini S, Alongi F, Andratschke N, et al. MRI-guidance in clinical reality: current treatment challenges and future perspectives. Radiat Oncol. 2019;14:92.
34. Kupelian P, Sonke JJ. Magnetic resonance-guided adaptive radiotherapy: a solution to the future. Semin Radiat Oncol. 2014;24:227-32.
35. Leijenaar RT, Carvalho S, Hoebers FJ, et al. External validation of a prognostic CT-based radiomic signature in oropharyngeal squamous cell carcinoma. Acta Oncol. 2015;54:1423-9.
36. Ou D, Blanchard P, Rossellini S, et al. Predictive and prognostic value of based radiomics signature in locally advanced head and neck cancers patients treated with concurrent chemoradiotherapy or bioradiotherapy and its added value to human papilloma status. Oral Oncol 2017;71:150-5.
37. Ger RB, Zhou S, Elgohari B et al. Radiomics features of the primary tumor fail to improve prediction of overall survival in large cohorts of CT and PET-imaged head and neck cancer patients. PLoS One. 2019;14:e0222509.
38. Rizzo S, Botta F, Raimondi S, et al. Radiomics: the facts and the challenges of image analysis. Europ Radiol Exp. 2018;2:36.

39. Subesinghe M, Scarsbrook AF, Sourbron S, et al. Alterations in anatomic and functional imaging parameters with repeated FDG PET-CT and MRI during radiotherapy for head and neck cancer: a pilot study. BMC Cancer 2015;15:137.
40. Leibfarth S, Winter RM, Lyng H et al. Potentials and challenges of diffusion-weighted magnetic resonance imaging in radiotherapy. Clin Transl Radiat Oncol. 2018;13:29-37.
41. Wong KH, Panek R, Dunlop A, et al. Changes in multimodality functional imaging parameters early during chemoradiation predict treatment response in patients with locally advanced head and neck cancer. Europ J Nucl Med Mol Imag. 2018;45:759-67.
42. Bird D, Scarsbrook AF, Sykes J, et al. Multimodality imaging with CT, MR and FDG-PET for radiotherapy target volume delineation in oropharyngeal squamous cell carcinoma. BMC Cancer 2015;15:844.
43. Dirix P, Vandecaveye V, De Keyzer F, et al. Dose painting in radiotherapy for head and neck squamous cell carcinoma: value of repeated functional imaging with 18F-FDG PET, 18F-Fluoromisonidazole PET, diffusion weighted MRI and dynamic contrast enhanced MRI. J Nucl Med. 2009;50:1020-7.
45. Teng F, Aryal M, Lee J, et al. Adaptive boost target definition in high-risk head and neck cancer based on multi-imaging risk biomarkers. J Radiat Oncol Biol Phys 2018;102:969-77.