Automation and individualization of radiotherapy treatment planning in head and neck cancer patients
Kierkels, Roel Godefridus Josefina

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 30-09-2019
CHAPTER 1

General introduction, aim and outline of this thesis
1.1 Head and neck cancer

Head and neck cancer (HNC) is the sixth most common cancer worldwide with approximately 700,000 new cases and over 350,000 deaths reported every year [1,2]. In the Netherlands, approximately 3,000 new cases and 900 deaths are reported every year [3]. HNCs are characterized as a heterogeneous type of malignancy that occur in different anatomical sites with varying prognosis. More than 90% are squamous cell tumors, mostly found in the larynx and oral cavity [4]. However, the incidence of oropharyngeal cancer is rising and is increasingly associated with Human Papilloma Virus infection [5]. A large group of patients diagnosed with HNC receive radiotherapy as the primary treatment or as an adjuvant to surgery or in combination with chemotherapy. The aim of radiotherapy is to achieve locoregional tumor control while preventing normal tissue complications. The clearance between tumor control and normal tissue complications is also referred to as the therapeutic window.

With improving overall survival rates of HNC patients the quality of life plays a pivotal role in the management of this disease [6]. Since quality of life is significantly associated with the presence of late radiation-induced complications, minimizing the dose to healthy tissues, to reduce normal tissue complication probabilities (NTCP), is increasingly important. However, designing a treatment plan for HNC patients is complicated due to a relatively large number of healthy organs (e.g. spinal cord, salivary glands and oral cavity) close to the targets. Over the years, numerous critical (sub)volumes have been identified that play an important role in the development of radiation-induced complications during and after treatment. Multivariable NTCP models for many radiation-induced side effects incorporating dose-volume parameters and clinical factors have become available, such as for xerostomia and swallowing dysfunction [7–9].

During the last decades, fundamental technical developments have emerged that have led to substantial improvements of the therapeutic window. A brief outline of hardware and software developments, not only related to HNC radiotherapy, is given in the next section.
1.2 Technological developments - hardware

1.2.1 Photon external beam radiotherapy
The first megavoltage linear accelerator (linac) for curative treatment of cancer was installed in London in 1937 [10]. Since then, beam direction devices, wedges and flattening filters were developed and became the new standard for external beam high energy photon therapy [11]. In the 1950s a variety of linacs with energies ranging from 1 – 15 MeV were installed for clinical use. The following years, the overall stability and performance of linacs increased by computer control and improvements in dosimetry as well as quality assurance. In 1982, Brahme reported the inverse planning problem in intensity modulated radiotherapy (IMRT) [12]. This publication was followed by the work of Källman et al. who reported on dose calculations using multi-leaf collimators (MLCs) [13]. Bortfeld described the first validation of in-field modulation for conformal radiotherapy using a static beam configuration [14]. Currently, state-of-the-art linacs are equipped with dynamic MLCs with leaf width less than 1.0 cm and possibilities of leaf interdigitation and dynamic dose rate possibilities while rotating the gantry. These properties have enabled intensity modulated volumetric arc therapy (VMAT), which became the current standard for HNC photon radiotherapy. Treatment plans for HNC treatment generally consist of two arcs of approximately 360° that deliver the dose within a few minutes as compared to approximately 20 minutes for IMRT. With VMAT not only the number of monitor units decreased but organs at risk (OAR) doses also further decreased, albeit with a larger low dose bath to non-target tissues.

1.2.2 Proton therapy
In parallel, particle therapy was developed starting with the introduction of the cyclotron in the 1930s by Lawrence. The main advantage of proton beams is that the absorbed dose gradually increases with increasing depth and lower speed of the protons, followed by a sharp peak as the protons come to rest and an even sharper fall-off, after which no dose is deposited anymore. This peak is also referred to as the Bragg peak.

Proton beams for patient treatment were first suggested in 1946 by Robert Wilson [15]. The years that followed were spent on biological studies and in 1954 the first patient was treated at the Lawrence Berkeley Laboratory [16]. In 1957, the Uppsala University in Sweden treated their first patient and were the first to introduce a spread-out Bragg peak. For a long time, proton therapy remained only available in academic settings limiting the number of patients being treated with proton therapy. Starting in 1990, the Loma Linda University Medical Center in California was the first hospital-based proton center. In 2001, the first commercially available system was installed at the Massachusetts General Hospital [16].
The current state-of-the-art proton therapy uses pencil beam scanning (PBS) techniques which was first described in 1977 [17]. In 1999, intensity modulation methods for proton therapy were further described by Lomax et al. [18]. Intensity modulated proton therapy (IMPT) leads to superior dose distributions as compared to conventional double scattering proton therapy and allows for improved organ sparing close to concave target volumes such as in HNC. IMPT with PBS is the current state-of-the-art technique for treatment of HNC.

1.2.3 Imaging
Radiotherapy moved from a two-dimensional to a three (and even four) dimensional (3D or 4D) era. Anatomical and molecular imaging modalities (computed tomography [CT], magnetic resonance imaging [MRI], positron emission tomography [PET]) are used for the delineation of target volumes and OARs [19]. Volumetric CT imaging is the current standard for treatment planning and dose calculations. These developments have led to more accurate treatments and a substantial reduction of dose to non-target tissues without compromising target coverage as compared to 2D radiotherapy. With the introduction of 3D imaging in combination with intensity modulated radiotherapy (i.e. VMAT and IMPT) the dose distribution can be calculated within a small subvolume of tissue (few mm$^3$). This allows for studies that redistribute the dose away from organ parts that are most sensitive to irradiation [20] or to the metabolically most active tumor region [21].

Moreover, the dynamic nature of patient anatomy requires accurate monitoring of the treatment plan quality over the course of therapy. Therefore, repeated imaging is increasingly applied to get a time-dependent description of the patient and dose distribution, to eventually get a better picture of the delivered dose distribution as compared to the planned dose distribution [22]. Repeated imaging not only includes offline imaging with CT, MR and PET but can also be performed on a daily basis within the treatment room.

1.2.4 On-board imaging
Intensity modulated therapy leads to sharp and connecting dose gradients and therefore requires reproducible immobilization and a geometric description of the patient at each treatment fraction. The introduction of kV cone-beam CT [22] and recently MRI [23] improved accurate and precise radiation delivery to the tumor and minimized dose to the OARs. Cone-beam CT is the current standard on-board imaging modality on linacs and is becoming increasingly available on proton gantries. Due to the sensitivity of protons to anatomical variations on-board MRI has great potential. Therefore, the integration with proton beams is on the research agenda for coming years [24,25].
Chapter 1

1.3 Technological developments - software

1.3.1 3D Conformal treatment planning

Volumetric CT-imaging for treatment planning was an essential condition for the introduction of 3D conformal photon (3DCRT) and proton therapy. Conventional techniques aim to achieve a homogeneous target dose distribution per treatment field, which can be achieved by manually tuning the treatment parameters. For photons, typical parameters include the MLC settings, gantry angles, open or wedge fields, and the individual beam weights. On the other hand, for conventional proton therapy, the conformal beams were delivered with range modulation in conjunction with a double scattering technique. In general, the treatment plan is designed with a forward planning approach requiring manual tuning of these treatment parameters in the treatment planning software. This process may be time consuming and not always result in the ‘most optimal’ treatment plan.

1.3.2 Intensity modulated treatment planning

In contrast to 3DCRT, intensity modulated therapy is characterized by a heterogeneous in-field dose distribution and requires inverse treatment planning optimization. In general, optimization refers to the minimization (or maximization) of an objective function that is subject to a set of constraints. Current IMRT approaches optimize the 2D fluence maps simultaneously (per beam) followed by a direct aperture optimization to e.g. optimize the leaf positions of the MLCs. In a way analogous to IMRT, proton therapy can be used to construct inhomogeneous fields with modulation of the individual Bragg peaks. Since proton beams have varying energy, the intensities of the Bragg peaks can be optimized in 3D space (i.e. across the plane and in depth). In combination with a well-defined beam model, a sophisticated dose distribution can then be created with adequate target coverage and normal tissue sparing. Cozzi et al. investigated the potential benefit and limitations of 3DCRT, IMRT, and IMPT (conventional proton therapy and PBS) in head and neck cancer [26]. They found that intensity modulated treatments substantially decreased the dose to normal tissues, especially for IMPT. This was later confirmed by others [27–29].

Dose distributions of a VMAT plan and an IMPT plan of a representative HNC patient are shown in figure 1.1. The prescription was 70.00 Gy to the primary clinical target volume (CTV) and 54.25 Gy to the elective CTV, delivered in 35 fractions (in 7 weeks) using a simultaneous integrated boost technique. Adequate target coverage (D98≥95%) was achieved and the maximum dose to the spinal cord was <50 Gy, in both plans. The mean dose to the salivary glands, the swallowing muscles, and the oral cavity was minimized as much as possible. The dose-volume histograms illustrate similar CTV coverage between the photon and proton
plan and lower dose to the OARs (parotid gland, oral cavity and integral dose) for the proton plan (figure 1.2). An experienced dosimetrist optimized the plans with conventional physical dose-volume based objective functions. The dosimetric parameters and NTCP values of the VMAT and IMPT plans are given in table 1.1. The following two paragraphs briefly describe different types of NTCP models and objective functions for treatment planning.

**Figure 1.1** Transversal and sagittal cross-section of a CT scan overlaid with the dose distribution of the (a) VMAT plan and (b) IMPT plan.

The thick white and grey contours indicate the planning target volumes and the other thick contours indicate the oral cavity (green), parotid glands (flashy green and purple), and the swallowing muscles (pink to red). The low to high dose is indicated by blue to red colorwash.

**Figure 1.2** Dose volume histograms of the photon plan (solid line) and proton plan (dotted line) as in figure 1.1.
## Table 1.1 Dosimetric parameters and NTCP values

<table>
<thead>
<tr>
<th></th>
<th>VMAT</th>
<th>IMPT</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target dose (Gy)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D$<em>{98}$ CTV$</em>{primary}$</td>
<td>69.7</td>
<td>69.1</td>
<td>-0.6</td>
</tr>
<tr>
<td>D$<em>{50}$ CTV$</em>{primary}$</td>
<td>70.6</td>
<td>70.1</td>
<td>-0.5</td>
</tr>
<tr>
<td>D$<em>{02}$ CTV$</em>{primary}$</td>
<td>71.5</td>
<td>72.4</td>
<td>0.9</td>
</tr>
<tr>
<td>D$<em>{98}$ CTV$</em>{elective}$</td>
<td>53.3</td>
<td>53.4</td>
<td>0.1</td>
</tr>
<tr>
<td>D$<em>{50}$ CTV$</em>{elective}$</td>
<td>69.9</td>
<td>69.4</td>
<td>-0.5</td>
</tr>
<tr>
<td><strong>OAR mean dose (Gy)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral Parotid gland</td>
<td>12.7</td>
<td>7.3</td>
<td>-5.4</td>
</tr>
<tr>
<td>Ipsilateral Parotid gland</td>
<td>28.4</td>
<td>27.5</td>
<td>-0.9</td>
</tr>
<tr>
<td>PCM superior</td>
<td>64.5</td>
<td>64.6</td>
<td>0.1</td>
</tr>
<tr>
<td>PCM medial</td>
<td>48.9</td>
<td>44.2</td>
<td>-4.7</td>
</tr>
<tr>
<td>PCM inferior</td>
<td>37.5</td>
<td>28.8</td>
<td>-8.7</td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>40.7</td>
<td>26.0</td>
<td>-14.7</td>
</tr>
<tr>
<td>Cricopharyngeal muscle</td>
<td>39.3</td>
<td>33.2</td>
<td>-6.1</td>
</tr>
<tr>
<td><em><em>NTCPs</em> (%)</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xerostomia</td>
<td>30.0</td>
<td>24.5</td>
<td>-5.6</td>
</tr>
<tr>
<td>Swallowing problems</td>
<td>31.5</td>
<td>24.4</td>
<td>-7.0</td>
</tr>
<tr>
<td>Tube feeding dependence</td>
<td>29.4</td>
<td>24.0</td>
<td>-5.4</td>
</tr>
</tbody>
</table>

Abbreviations: PCM = pharyngeal constrictor muscle; Dx indicates the dose in the fractional volume x. #NTCP models as in the Dutch National Indication Protocol for Proton Therapy [30]

### 1.3.3 NTCP Models

NTCP models describe the relationship between the absorbed dose to a volume and the complication rate. This relationship is derived by fitting the clinical outcome measures (e.g. patient-rated xerostomia) with sigmoidal shaped functions. Traditional NTCP models are directly based on the biological information and clinical data. The Lyman-Kutcher-Burman (LKB) NTCP model was introduced to describe this relationship with the D$_{50}$ (i.e. the uniform dose that leads to 50% complication rate), a steepness parameter $m$ and a dose-volume parameter of the organ of interest [31]. It is, however, reasonable to presume that complications are related to multiple factors and that traditional biological parameters alone may be insufficient [32]. More recently, developed NTCP models are therefore based on multivariable logistic regression modelling. The linear component of the sigmoidal function can be based on a multitude of factors such as clinical data, dosimetric parameters or genetic data. These NTCP models aim to improve the prediction accuracy as compared to the traditional NTCP models.

An example of such an NTCP model for patient-rated xerostomia was described by Beetz et al. [33]. This NTCP could be estimated by the mean dose to the contralateral parotid gland,
age, and baseline xerostomia score prior to treatment as model parameters. Similarly, the NTCP function of (RTOG) grade 2-4 swallowing dysfunction contained the mean dose to the superior pharyngeal constrictor muscle and the supraglottic larynx [9]. An example of NTCP curves for tube feeding dependence is given in figure 1.3.

To increase the clearance within the therapeutic window, the NTCP should be reduced as much as possible. Therefore, the ‘optimal’ treatment plan should minimize the dose to the OARs described by the NTCP models. More ideally, the NTCP should directly be reduced during the plan optimization process. Objective functions based on multivariable NTCP models are therefore required.

1.3.4 Objective functions
To find the machine parameters that result in the ‘optimal’ distribution of dose, the medical requirements are translated into objective functions and constraints. These functions are then used to guide the inverse planning optimizer through the search space of potential solutions. Often used objective functions in radiotherapy plan optimization are based on measurable physical parameters such as doses and volumes. Typical physical objective functions then calculate the mean-squared deviation from a threshold dose level. Finding the thresholds that lead to the ‘optimal’ solution is an iterative and time-consuming trial-and-error process and highly dependent on the experience of the planner.

It is well known that the relationship between the physical dose and the response to different tissues is non-linear and not described explicitly with these dose-volume based objective functions. Therefore, treatment plan optimization and evaluation has been explored extensively with biological indices that account for dose-response relationships. In the past decades, objective functions based on the tumor control probability (TCP), NTCP, (generalized) equivalent uniform dose ((g)EUD), and more recently also for the relative biological effect (RBE) have been introduced.

The (g)EUD of a non-uniform dose distribution of a certain volume is equal to the uniform dose with the same biologically effect [34]. It uses the physical dose distribution and a tissue-dependent parameter $a$ to describe the tissue properties. Due to its simplicity, the (g)EUD formalism is the most frequently used biologically oriented objective function in current commercially available treatment planning systems. With parameter $a = 1$ for example, the (g)EUD is equal to the mean dose and the optimizer aims to reduce the mean dose of the volume of interest. Although more biologically driven objective functions (i.e. directly based on conventional TCP and NTCP models) have been investigated, their use in the clinic is limited [35].
Källman et al. introduced an algorithm to maximize the probability of complication free tumor control (P+) by optimizing the incident beam profiles and directions [36]. This however, requires the TCP and NTCP to be calculated from a heterogeneous dose distribution delivered to the tumor and healthy tissues with varying sensitivity. Limited information is available about these sensitivities and therefore, direct optimization on complication free tumor control is not standard clinical practice. On the other hand, heterogeneous target doses can be corrected for by hybrid objective functions, combining dose-volume objectives with TCP-based objectives.

Witte et al. combined probabilistic plan optimization to account for geometrical uncertainties with TCP and NTCP-based objective functions [37]. A (modified) LKB NTCP model for rectal wall toxicity was used to derive the complication probability for rectal bleeding and fecal incontinence [38]. They demonstrated a reduction of high dose to the rectum while the dose to the CTV increased [37]. The NTCP is however increasingly derived from multivariable NTCP model. Although used for plan evaluation, direct plan optimization based on these multivariable NTCP models has however not been explored yet. It is expected that the dose to multiple volumes is more optimally distributed with multivariable NTCP-based objective functions, consequently leading to reduced NTCP values.

Traditionally, the dose distribution to target volumes is optimized on the planning target volume (PTV). The PTV is an expansion of the CTV with a margin derived from available recipes and mainly accounts for day-to-day setup errors and geometrical uncertainties. However, these uncertainties can also be considered with robust treatment planning. Currently, two approaches to robust treatment planning have been introduced, including probabilistic optimization and minimax optimization [39,40]. The probabilistic approach optimizes the objective function describing the expected values by sampling a large number of error scenarios from a probability density distribution. This approach has been investigated in IMRT of HNC patients and the authors concluded that probabilistic treatment planning for targets was an efficient tool in the management of uncertainties [41]. However, probabilistic planning remains computationally expensive, limiting its introduction into the clinic. On the other hand, minimax optimization aims to achieve the treatment objectives in the worst-case scenario, requiring only a limited number of perturbed scenarios to be evaluated during optimization [39,42,43]. This technique is gaining interest and is increasingly implemented for IMPT.

Robust optimization can also account for potential proton range uncertainties by adding scenarios in which the Hounsfield numbers of the planning CT were upscaled and downscaled with e.g. 3.0%. These range uncertainties are primarily related to uncertainty in the conversion of Hounsfield numbers to stopping power for protons. To a lesser
extent, the uncertainty is introduced by statistical noise in CT images and because there is no well-defined relationship between tissue properties and Hounsfield numbers [42]. It was shown already that minimax robust optimized IMPT for HNC patients substantially reduces the OAR dose and several NTCPs (e.g. for xerostomia and dysphagia) as compared to PTV-based photon plans and single field optimized proton plans [44,45]. Its potential in HNC photon therapy however, needs further investigation.

1.3.5 Adaptive radiotherapy
To further reduce the OAR dose in HNC radiotherapy, the traditional CTV to PTV margins are increasingly reduced from e.g. 5 mm to 3 mm. Van de Water et al. showed that the average NTCP decreased with approximately 1 %/mm setup uncertainty in IMPT for HNC patients [46]. For VMAT, van Kranen et al. investigated different setup margins and concluded a decrease of approximately 1 Gy/mm margin reduction for the OARs close to the targets [47]. On the other hand, the lymph node CTV can show substantial misalignment (>3 mm) [47]. Therefore, the smaller setup uncertainties require more accurate patient immobilization, more frequent online imaging, off-line plan evaluation and adaptation, and/or more rigorous tolerances on machine delivery.

Currently, the adaptive process is time consuming and requires additional CT imaging, re-contouring, dose calculations and evaluation (with or without mapping and accumulation), and potentially re-planning [48]. In this workflow, deformable image registration (DIR) is a critical component and can be used twofold: (1) to automatically propagate contours from the reference planning CT scan to the evaluation CT scan and (2) to map the dose distribution to the reference (or evaluation) CT scan. Since a DIR optimization is an ill-posed problem, DIR is intrinsically susceptible to errors. The introduction of DIR for dose mapping, and adaptive radiotherapy, into the clinic remains therefore limited and the assessment of DIR errors is needed.

1.3.6 Automated treatment planning
Last decade, automated and semi-automated treatment planning methods have been increasingly described in literature including, lexicographic ordering optimization [49,50], and multicriteria optimization (MCO) methods that facilitate decision making [43,51] amongst others. MCO is used to semi-automatically create a radiotherapy treatment plan which strives for Pareto-optimality. A Pareto optimal solution is required in order to guarantee that no criterium can be improved without a sacrifice in another. With MCO, a library of Pareto optimal plans is created through which the user can navigate to a clinically favorable plan through continuously interpolation of these library plans. Previous studies have demonstrated the potential of MCO with navigation for prostate and stereotactic lung treatment planning [52,53]. MCO with navigation for HNC has been described in this thesis.
Fully automated approaches to treatment planning are generally based on a database of previous plans, or those that aim to mimic the iterative tuning process of the dosimetrist. Recently, machine learning based automated treatment planning has been introduced [54]. This method requires a database of dose distributions of previously treated patients and features from CT images and their respective contours. With this algorithm, the dose distribution can be predicted for novel patients and mimicked into a deliverable dose distribution. The last step, the dose mimicking part (voxel-based and dose volume histogram based mimicking), was previously introduced by Fredriksson and aimed to automatically improve upon a reference dose distribution [55]. This mimicking algorithm has great potential to more efficiently achieve the ‘most optimal’ treatment plan. Fredriksson only evaluated the algorithm for photon therapy in a phantom. In this thesis we extended the mimicking algorithm to achieve automated robust proton treatment planning given a reference photon dose distribution for HNC patients.

More information on recent innovations of intensity modulated treatment planning automation can be found in a recently published review by Hussein et al. [56].

1.4 Outline of this Thesis

The reduction of radiation-induced complications plays a pivotal role in (HNC) radiotherapy research. In addition to dose-volume evaluations, treatment plan quality is increasingly scored by NTCP values. The NTCPs can potentially be reduced by:
- (semi-) automated treatment planning, optimizing directly on NTCPs to avoid treatment planner subjectivity and level of experience;
- adaptive radiotherapy to monitor the treatment plan quality (and adapt the plan if needed) during the fractionated treatment course;
- proton therapy, to benefit from the physical properties of the Bragg peak.

The clinical implementation of these tools and therapies is resource intensive. Therefore, more efficient workflows and automation of processes are needed. The aim of this thesis was to introduce and evaluated different algorithms that contribute to the efficiency in radiotherapy treatment planning considering multivariable NTCP models, deformable image registration for adaptive workflows, and patient selection for proton therapy. The presented work has extensively been evaluated in HNC patients but is expected to be applicable to other treatment sites. The following research topics are addressed:
1.4.1 Assessing the potential of multicriteria optimization with navigation in head and neck cancer
The investigated MCO is a semi-automated treatment planning procedure and only requires manual navigation of the Pareto front to achieve the appropriate clinical treatment plan. HNC radiotherapy is however characterized by many OARs close to the target, which may complicate navigation due to the complexity of the multi-dimensional Pareto front. Therefore, in chapter 2, we investigated the potential of MCO with navigation for IMRT in HNC and compared the MCO plans with the ‘dosimetrist-optimized’ reference plans.

1.4.2 Introducing treatment plan optimization with multivariable NTCP models
Traditional objective functions are related to physical dose-volume parameters and calculate the weighted mean-squared deviation from a threshold value. However, the response to dose is described by TCP and NTCP functions. Increasingly, externally validated multivariable NTCP models become available for different endpoints. For example, the NTCP model for tube feeding dependence 6 months after therapy depends on T-classification, baseline weight loss, treatment modality, and four dosimetric variables (figure 1.3) [57]. To benefit from this coherence of dose and clinical parameters, in chapter 3, we investigated the application of multivariable NTCP models as objective function for IMRT planning in HNC patients. The method was evaluated using Pareto-based automated treatment planning, with the advantage that the search for a threshold value for the OARs was omitted because the optimizer directly minimized the NTCP.

1.4.3 Improving treatment planning efficiency with NTCP models for swallowing dysfunction and tube feeding dependence incorporated in the IMRT optimizer
The dosimetric parameters of an NTCP model dictate the priority of objectives during the plan optimization process. Due to the relatively large number of OARs in the head and neck region, the dose that is steered away from one OAR may end up in another OAR. Finding the dose distribution that results in the lowest NTCP is therefore challenging. In chapter 4, we assessed the potential of multivariable NTCP-based plan optimization (as described in chapter 3) using NTCP models for grade 2-4 swallowing dysfunction and tube feeding dependence 6 months after intensity modulated photon therapy. With the latter, four different dose-volume parameters were captured into one NTCP-based objective, substantially simplifying the optimization process.

1.4.4 Introducing a dose mimicking and reducing algorithm for automated treatment planning
NTCP models are increasingly used to select the preferred treatment modality per patient (e.g. photon or proton therapy) and requires a treatment plan comparison, which is a time-consuming task and may greatly benefit from automation. Therefore, in chapter 5, we...
developed and evaluated a dose mimicking and dose reduction algorithm to automatically create a robust IMPT plan from a reference photon dose distribution and the target and OARs contours. We evaluated the automatically generated plans against the 'dosimetrists-optimized' IMPT plans by means of NTCP values for moderate to severe xerostomia, grade 2-4 swallowing problems and tube feeding dependence.

1.4.5 Assessing deformable image registration uncertainties in the context of adaptive radiotherapy

DIR is an important tool for adaptive radiotherapy. The accuracy of DIR depends on the used algorithm and imaging data. Especially in image regions with little contrast, most DIR algorithms lack accuracy. In order to use DIR for dose mapping and accumulation the errors should be identified. Several methods to assess the DIR errors are available but are generally based on user input (e.g. anatomical landmarks or contours) and time consuming. Furthermore, those methods can only be used in image regions with clear contrast and not in the regions with little contrast, where the DIR errors are probably larger. Automated, quantitative, and case-specific DIR evaluation methods are therefore required. In chapter 6, we introduced and implemented a framework to automatically assess the DIR error. The method is evaluated against synthetically generated ‘ground-truth’ deformation vector field acquired from the radiotherapy planning CT scan and an evaluation CT scan acquired near the end of treatment.

**Figure 1.3** NTCP model for tube feeding dependence 6 months after IMRT of head and neck cancer patients.

NTCP curves are shown given the following fixed variables: T3-4 tumor classification, Dmean = 64.5 Gy of the superior pharyngeal constrictor muscle (PCM), Dmean = 37.5 Gy of the inferior PCM (PCM INF), Dmean = 12.7 Gy of the contralateral parotid gland, and Dmean = 39.3 Gy to the cricopharyngeal inlet muscle (values extracted from the VMAT plan in figure 1.1). The dotted lines indicate different ΔNTCPs at a ΔDose of 10 Gy.
1.4.6 Assessing the impact of robust treatment plan optimization for VMAT using dose mapping and accumulation

Robust treatment planning accounts for setup errors (and range uncertainties in proton therapy) during the optimization process. Robust plan optimization is fundamental to proton therapy but not fully explored in HNC VMAT. Therefore, in chapter 7, we assessed the efficiency of minimax robust VMAT planning in 10 HNC patients. The robustly optimized VMAT plans were compared with VMAT plans that were optimized on the traditional PTV. For each plan, the plan quality was assessed with dose calculations (and mapping and accumulation) on daily-acquired CBCTs and weekly acquired evaluation CT scans. In addition, the effect of a plan adaptation (after three weeks of treatment) on the accumulated dose distribution was investigated.

A summarizing discussion of the work and the future perspectives are presented in chapter 8. The different optimization strategies for photon and proton therapy as presented throughout the thesis were applied to the case as presented in chapter 1 (figure 1.1-2) and discussed.
1.5 References


1. General introduction, aim and outline of this thesis


