General introduction

Radiotherapy has a pivotal role in the treatment of head and neck cancer patients [1]. Currently, tumour control and survival have been improved by the combination of radiotherapy with chemotherapy or biological agents (i.e. cetuximab) [2, 3]. The meta-analysis of Pignon et al. [2] showed that the overall survival improved with 6.5% after 5 years when radiotherapy was combined with concomitant chemotherapy. In addition, the addition of cetuximab to radiotherapy resulted in significantly higher rates of locoregional control and overall survival when combined with radiotherapy as compared to that observed after radiotherapy alone [3, 4].

The last decades, the incidence of patients with oropharyngeal cancer related to the human papillomavirus (HPV) is markedly rising [5–7]. This is relevant as patients with HPV-positive tumours that received radiotherapy either or not combined with concurrent chemotherapy showed significantly better prognosis than patients with HPV-negative tumours [8, 9].

The result of this improved survival is that the prevalence of head and neck cancer survivors at risk for radiation-induced side effects is increasing. In general, radiation-induced side effects are distinguished in early and late effects [10]. Early or acute effects emerge during or immediately after the end of therapy, while late side effects develop after latency periods of at least 90 days to years. In contrast to early effects, the majority of late side effects of radiotherapy are considered to be irreversible [10]. Xerostomia is one of the most severe and frequently reported late side effects that has a major influence on quality of life [11–13]. Furthermore, swallowing problems are frequently reported and have a notorious effect on quality of life [13].

Intensity modulated radiotherapy (IMRT) can be applied to conform doses sufficient to eliminate all viable cancer cells within the target region, while sparing organs at risk (OARs) as much as possible. It has been shown that the introduction of IMRT resulted in a significant improvement of the recovery of saliva secretion and a reduction of xerostomia [14–16]. Still, with currently used concomitant chemo-radiation regimens, the limits of acceptable toxicity have been reached with more than half of the patients treated with IMRT suffering from moderate to severe xerostomia 6 months after treatment [17].

Normal tissue complication probability (NTCP) models [18] are used to estimate the probability that patients develop radiation induced side effects. Many types of models that relate dose-volume characteristics to outcome have been proposed in the literature. The Lyman-Kutcher-Burman model was one of the earliest proposed [19, 20], followed by other models that attempt to explicitly model tissue architecture [21–23]. All of these models use information only about fractionation and the dose distribution in a single organ at risk. Since the probability of a complication may be affected also by multiple clinical prognostic factors,
El Naqa et al. were one of the first who proposed other approaches using multivariable logistic regression analysis [24]. Input parameters to these models are usually clinical and dosimetric factors.

The dose to the parotid glands is the most important factor associated to xerostomia-related endpoints [17, 25, 26]. For swallowing problems, the dose to several swallowing structures are of major importance [27].

NTCP and tumour control probability (TCP) models can be applied to optimize the treatment plan, i.e. minimizing the risk for side effects with equal or higher TCP [28]. Furthermore, NTCP and TCP models can be applied to compare different treatment plans and to select patients for more advanced treatments such as adaptive radiotherapy (ART) and proton therapy [29].

A number of uncertainties in the preparation and delivery of radiotherapy exists, which should be minimized to accurately develop and reliably apply NTCP models [30]. Reducing the uncertainties could also lead to smaller treatment margins or smaller robustness parameters in treatment planning, leading to a higher plan quality (i.e. good target coverage with lower dose to the OARs). Dose distributions of IMRT plans are much more sensitive to these uncertainties than 3D-CRT plans, because of the steeper dose gradients in IMRT treatment plans. The most important uncertainties include setup variation, delineation variability, and anatomical variation (variation in shape/position of targets and organs within the patient) [31]. Setup variation in the head and neck area is in the order of 2 mm standard deviation (SD) [32]. Setup variation can be accounted for in position verification protocols, and will be outside the scope of this thesis.

**Variability in delineation**
Variability in the delineation of targets is found to be the largest source of uncertainty (i.e. the weakest link) in head and neck radiotherapy, with standard deviations of 3.4-7.7 mm for CT-based GTV delineation in nasopharynx cancer [33]. Variability in delineation of target volumes and OARs could result in sub-optimal treatment plans with systematic dose errors for all treatment fractions [33, 34]. This may result in inconsistent patient treatments and inconsistent reported dose parameters, with a potential under- or overestimation of the patients’ TCP and NTCP [35].

Variability in delineation is caused by a number of aspects; limited imaging resolution [36], intra-observer variation (‘observer noise’ and the precision of the delineation tool) [37] and interpretation differences, caused by different guidelines and/or differences with regard to the level of education and frequency of training [38, 39]. More and better quality imaging has become available and CT-slice distance is generally reduced to 2 mm. Also, more and more dedicated software for contouring has become available and education and training sessions are being organised on a regular basis (European training sessions
and delineation meetings at individual departments). For target volumes, international consensus guidelines have been defined to minimize variability in delineation and optimize consistent radiotherapy practice [40, 41]. For OARs however, such guidelines are lacking. The introduction of consensus guidelines are expected to result in reduced interobserver variability [42].

**Anatomical variation during the treatment**

The pre-treatment CT on which IMRT plans are based, is only a snapshot of the patient’s anatomy. Barker et al. [43] were one of the first who reported on variability in shape and position of head and neck targets and OARs within the patient during the course of radiotherapy. The median volume loss on the last day of treatment was 69.5% for the GTV and 28.1% for the parotid glands. The parotid glands also shifted medially over time, the median medial shift of the centre of mass was 3.1 mm at the end of treatment [43]. Robar et al. [44] reported shortly thereafter on the consequences of the anatomic changes for the dose distribution. On average, dosimetric changes were moderate, but for a couple of patients outliers were seen (standard deviation and range of dosimetric changes of the parotid gland were 6 and 15% respectively).

Since 2010, the amount of studies reporting on anatomical and dosimetric changes has increased dramatically [45–65]. Variation in anatomy causes more dose deviations in OARs than in target volumes [66–69]. Not all of the studies reported to what extent anatomical changes translate into dosimetric changes, and for which group of patients this would actually be of clinical relevance. In the study of Chen et al. [67], mean dosimetric changes to the parotid gland mean dose of 10.4 Gy were found, whereas Castadot et al. only reported changes of 0.8 Gy [70]. This pleads for a careful introduction of adaptive radiotherapy since only a selected set of patients would benefit from an extremely labour and resource intensive procedure. Theoretically, adaptive radiotherapy could be fully automated, as Yan et al. introduced in 2005 [71]. The authors predicted that adaptive radiotherapy will become a new treatment standard that will eventually replace the prescheduled treatment plan in routine clinical practice. However, to date and more than 10 years later, online adaptive radiotherapy still remains a future perspective due to its labour and resource intensive nature. Furthermore as yet, no commercial conclusive solution is available for a save and controlled workflow. Therefore, ‘flags’ to select patients for which anatomic changes result in relevant dose deviations need to be established, to be able to select specific patients for an adaptive radiotherapy schedule.
Outline of the thesis

Minimizing the uncertainties in delineation and position and shape of the OARs is expected to result in improved and more general applicable NTCP models. It is of major importance to accomplish generally applicable NTCP models, since these models are essential tools in selecting patients for advanced treatments [29], and in optimizing the treatment plans for every individual patient to guarantee optimal quality of life.

In this thesis, we will focus on variability in delineation and how to minimize its effect on dose in chapters 2, 3 and 4. Chapter 5 and 6 will focus on anatomical variability during the course of treatment and its effect on the dose distribution.

**Chapter 2** reports on the differences between several OAR delineation guidelines, and its effect for dose-volume parameters and corresponding predictions of NTCP models.

**Chapter 3** subsequently shows the variation in delineation of OARs within a guideline, with detailed analysis on sub-regions of the OARs. Causes of interobserver variability and differences between the different sub-regions are discussed.

With the knowledge of Chapter 2 and 3, in **Chapter 4** international consensus guidelines for the delineation of the most important OARs in the head and neck area are presented.

**Chapter 5** reports on a systematic review on anatomic and dosimetric changes of head and neck OARs during the course of radiotherapy. Also, factors related to these changes are studied which could potentially be used to select patients at risk for dosimetric changes of OARs in an adaptive radiotherapy protocol.

Finally, the potential pre-treatment selection parameters identified in Chapter 5 are tested in **Chapter 6** in a cohort of 113 patients. A method to select patients at risk for dosimetric changes of the parotid glands is established, and validated in another, independent patient cohort.

The findings of this thesis are summarized and discussed in **Chapter 7**.
References


