Summary

The three major treatment options for cancer are generally recognized as being surgery, radiotherapy and chemotherapy. Many factors determine which treatment, or combination thereof, is chosen for a specific patient, including the site and stage of the disease, and the patient's biological age, overall health and personal preference. Radiotherapy plays an important role in the treatment of locally advanced head and neck cancer (HNC) and, when combined with chemotherapy, at least as effective as surgical resection for the majority of patients, with the possibility of organ-preservation as an added advantage.

Radiotherapy treatments require the creation of a treatment plan that should result in the delivery of sufficient dose to the tumor, whilst ideally sparing the normal tissues as much as possible. In current clinical practice, treatment plans are often made using computer algorithms with the final plan being obtained through an iterative process in which the resulting improvements get progressively smaller. The quality of the resulting plan, however, strongly depends on the skill of the planner and choices made by the treating physician, which can result in substantial differences between the plans from different planners and radiotherapy departments. This thesis therefore revolves around improving and automating the radiotherapy treatment planning process for HNC.

Treatment planning for HNC is considered a complex and labor-intensive process because this site typically includes a large number of organs-at-risk (OARs) for which the functional outcome after treatment is correlated with the radiation dose. These OARs are generally located in close proximity to the planning target volumes (PTVs) and should therefore be spared from radiation doses as much as possible. The main investigations and findings of the different chapters are summarized below.

During intensity modulated radiotherapy (IMRT), patients are typically treated using multiple static fields that individually deliver inhomogeneous dose distributions, which only when combined lead to sufficient and homogeneous irradiation of the tumor. These inhomogeneous dose distributions are created by moving the leaves of a multileaf collimator (MLC) through the treatment field, which only permits radiation to be delivered through the MLC aperture. During volumetric modulated arc therapy (VMAT) treatments, the treatment field rotates around the patient at the same time as the individual MLC leaves are moved in and out of the field to create different apertures and modulate the treatment beam. The positions and movement of the MLC leaves for IMRT and VMAT treatments are determined during an optimization process in which the planner sets optimization goals for the delineated structures. The optimization algorithms attempt to achieve MLC leaf
configurations that, as far as possible, result in a photon fluence / dose distribution that satisfies the optimization goals. Since the optimal treatment plan is often unknown before starting the planning process for individual patients, these optimization goals should be adjusted regularly during the treatment planning process to achieve high quality plans.

Previous investigations have shown that volumetric modulated arc therapy (VMAT) can lead to plans of similar quality as intensity modulated radiotherapy (IMRT), but with the advantage of offering reductions in delivery time and decreasing monitor unit (MU) requirements. VMAT is therefore increasingly being used for the treatment of HNC. Chapter 2 showed that improvements in plan quality can be obtained by increasing the number of VMAT arcs. Additional arcs increase the number of possible MLC configurations, and these can be exploited to further decrease OAR doses and improve PTV dose homogeneity. This, however, comes at the expense of a longer beam-on time and an increased amount of MUs. It should also be noted that the results discussed in Chapter 2 may be specific to Eclipse, as this treatment planning system (TPS) attempts to generate plans in which the gantry is rotating at maximum speed. Other TPSs allow for a slow-down of the gantry and, if this is fully exploited in the optimization algorithms, increasing the number of arcs may not necessarily improve plan quality.

Automated treatment planning solutions have the potential to both increase the efficiency in modern radiotherapy departments, and to improve resulting plan quality and consistency. Since different treatment planning techniques may lead to varying levels of OAR sparing and PTV dose homogeneity, the trade-offs between these parameters was investigated in Chapter 3. An exponential relationship was found, showing that small decreases in PTV dose coverage and homogeneity may lead to substantial improvements in OAR sparing, and vice versa. This should be taken into account when benchmarking manually and automatically created treatment plans that present varying levels of PTV dose homogeneity, since this may influence the achievable levels of OAR sparing. Despite this, however, there remain differences between major trial groups concerning desirable PTV dose criteria. In Chapter 4, plans were therefore created while satisfying the PTV dose coverage and homogeneity values specified by three different HNC protocols. It was found that using the planning guidelines as specified by the European Organization for Research and the Treatment of Cancer (EORTC) instead of those of the Radiation Therapy and Oncology Group (RTOG) could, on average, improve mean dose values to the salivary glands and swallowing muscles by 7.6Gy and 7.0Gy, respectively. While such mean dose reductions can have a large effect in the anticipated normal tissue complication probability (NTCP) parameters for the respective OARs, no comparison of outcome parameters have as of yet been reported between these trial groups to see if the stricter PTV dose criteria lead to better tumor control.
A technical account of the automatic interactive optimizer (AIO), which was developed as a part of this thesis, is provided in Chapter 5, along with a preliminary investigation of VMAT plan quality using ten HNC patients. AIO was designed to be used in conjunction with the interactive optimization algorithm of the Eclipse TPS. Before AIO was introduced, interactive optimization for HNC was a labor-intensive process, requiring the planner to continuously adapt the position of the dose-volume objectives relative to the dose-volume histogram (DVH)-lines that are displayed during the optimization process. AIO automates the adoptions of the objectives by scanning the optimization window, determining the position of the DVH-lines, and taking over control of the mouse cursor from the user. Automating the positioning of the optimization objectives leads to more consistent and frequent adaptations, ensuring that adequate attempts at sparing are made for all designated OARs throughout the optimization. A more in-depth clinical evaluation of AIO plan quality was provided in Chapter 6 using seventy HNC patients and twenty locally advanced lung cancer (LC) patients. Since the clinically relevant OARs and their doses are different between both groups, the LC patients required a different approach to interactive optimization than HNC. This work demonstrated versatility of the AIO solution. AIO was introduced in clinical practice at the department of radiation oncology of the VU University Medical Center in February 2014 and has since then been used to automatically optimize all clinical HNC treatment plans. This has resulted directly from the research presented in this thesis. We have also shown that AIO typically results in more consistent sparing of the salivary glands and swallowing muscles, while its use improves planning efficiency by allowing the planners to invest their time in other high-value tasks while the treatment plan is being optimized.

Chapter 7 benchmarked VMAT plans for HNC created by RapidPlan against their manually optimized counterparts. RapidPlan is a commercial knowledge-based planning (KBP) solution developed by Varian Medical Systems (Palo Alto, USA). By using a model that correlates the geometric and dosimetric features of a library of previously created patient plans, RapidPlan can predict the achievable OAR DVHs for individual patients. These predictions can be used as input for the subsequently performed optimization process, thereby reducing the need for iterative adjustments to find optimal placement of the optimization objectives. For most OARs, RapidPlan improved mean dose values over the manually optimized plans, although model size and composition could influence these results. In addition, dosimetric outliers in the model library, e.g. plans that provide sub-optimal OAR sparing compared to the bulk of the model, may reduce the accuracy of the DVH predictions. Chapter 8 therefore investigated the effect on plan quality when including
varying numbers of dosimetric outliers, in the form of plans in which no attempt was made to spare the salivary glands), to a 70-patient HNC model. These particular RapidPlan models were found to be robust against such outliers, up to 20 of which (out of a total of 70 plans) could be included in the library before affecting the quality of the resulting plans.

KBP solutions can also be used to provide quality assurance (QA) of plans, for example by comparing the achieved OAR doses with the doses that were predicted by the KBP model based on the patient's geometric features. This application was discussed in Chapter 9, where the accuracy of OAR dose predictions from a ninety patient RapidPlan HNC model were evaluated by comparing the predicted and achieved mean OAR doses for a twenty patient evaluation group. Excellent linear correlations were found between these parameters for all included OARs, although it was noted that the OAR dose predictions were less accurate in the high and low dose regions. As suggested in this chapter, KBP solutions could provide clinical trials a fast and patient specific method to evaluate whether submitted plans are deemed of sufficient quality.

The aforementioned investigations can be viewed as traditional treatment planning studies, in which different planning techniques are benchmarked using the same set of evaluation patients. This ensured that the results were not influenced by potential differences between the selected patients. Based on such studies, preferred techniques are often introduced in the clinic. However, the controlled environment in traditional planning studies makes it uncertain whether the predicted gains have been successfully translated into routine clinical practice. To investigate this, Chapter 10 provided a longitudinal evaluation of routine clinical HNC plans delivered at the department of radiation oncology at the VU University Medical Center over the past decade. For four different periods, 30 patients were selected. Each period was characterized by a distinct approach to radiotherapy dose delivery and /or treatment planning. The transition from the first period (including manually optimized IMRT plans from 2005-2008 solely attempting parotid gland and spinal cord sparing), to the last period (automatically optimized VMAT plans from 2014-2015 that attempted sparing of the parotid glands, submandibular glands, oral cavity and a large number of swallowing muscles) was associated with substantial gains in OAR sparing. These gains neither degraded PTV dose homogeneity values, nor did they increase dose deposition in the remainder of the body volume. Since different patients were included in the different periods, statistical corrections were used to account for inevitable geometric differences between the groups.
Finally, proton therapy has often been suggested for the treatment of HNC because the steep dose fall-off after the proton beams’ dose maximum (the Bragg-peak) offers the potential to improve OAR sparing over conventional photon techniques. The critical positioning of the Bragg-peak, however, may also make proton plans less robust for errors in patient positioning and range uncertainties (i.e., errors in Hounsfield density of the planning CT-scan). Chapter 11 therefore investigated OAR sparing and plan robustness for different single- and multi-field optimized proton plans and compared these with VMAT photon plans. Plan robustness was evaluated by introducing ±3mm setup errors and ±3% range uncertainties to the plans and evaluating the resulting V95% and V107% values for the clinical target volumes. Multi-field optimized plans resulted in improved OAR sparing over single-field optimized proton plans and VMAT plans, but they were also less robust.

Different methods to achieve high quality IMRT and VMAT treatment plans for HNC were investigated in this thesis. Exploring optimal plan quality for individual patients has generally been limited to well-equipped and staffed, modern radiotherapy institutes. The advent of automated planning, however, may also facilitate the widespread creation of optimal plans in radiotherapy institutes that have fewer resources.