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Potential benefits of intensity-modulated proton therapy in head and neck cancer

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Chapter 1

General introduction

General introduction

Head and neck cancer and radiotherapy treatment

In the Netherlands, about 44% of all males and 38% of all females will develop cancer during their life time [99]. In 2010, 95,456 new cancer cases were reported of which approximately 3% originated in the head and neck area [82]. Worldwide, cancer of the lip, the oral cavity, the pharynx and larynx accounted for about 5% of all cancer incidences [60].

Radiotherapy, often applied in combination with surgery or chemotherapy, is an important treatment modality for the management of head and neck cancer. Interaction of the ionizing radiation with tissue causes DNA damage and therefore tissue damage due to cell killing. More specifically, an applied dose of 1 Gy (1J/kg) will kill about 30% of the cells when considering a typical mammalian cell line [93]. The main objective of radiotherapy is to optimize the dose to the tumour (sterilizing the tumour cells by administering a dose as high as possible) while avoiding the normal surrounding tissues as much as possible.

In head and neck cancer patients, target volumes are often complex shaped, large and surrounded by various critical and vital structures (e.g. the spinal cord, salivary glands, the hearing organ, the optic structures, the voice producing organ and structures involved in swallowing). Therefore, radiotherapy of the head and neck region is frequently associated with radiation-induced acute and late side effects that adversely affect quality of life [87,89,90,105,130]. Hence, apart from eradication of the tumour, preservation of organ function is of major clinical importance as well.

Most relevant radiation-induced side effects

For head and neck cancer, xerostomia and swallowing dysfunction are the two most important radiation-induced late side effects [47,105]. Xerostomia or oral dryness, is the most frequently reported side effect occurring after radiotherapy of the head and neck region [87,188] and has a significant adverse effect on quality of life [87,105]. The salivary glands that are responsible for a sufficient saliva

production and composition are the parotid, submandibular and sublingual glands (the major salivary glands) and the minor salivary glands lining the oral cavity [42,81,184]. Radiation results in a progressive loss of salivary gland function and therefore in a decrease in saliva output and a change in saliva composition, resulting in the sense of a dry mouth and sticky saliva [38,187]. Furthermore, salivary dysfunction may result in considerable additional problems, including severe oral discomfort, impairment of oral functions (speech, chewing, swallowing) due to insufficient wetting and an increased incidence of caries and mucosal infections [187,188].

More recently, it has been recognised that swallowing dysfunction is also a relevant side effect that adversely affects the quality of life after radiotherapy of the head and neck area [47,105]. This side effect may result in aspiration and may lead to the necessity of feeding through a feeding tube, either through a nasogastric tube or a percutaneous gastrostomy tube (temporarily or even permanently) [52,130]. Anatomic structures that are responsible for a sufficient swallowing function and avoid food from entering the nose and that avoid aspiration, are the muscles lining the pharynx wall, the soft palate, the base of tongue, the more caudally located glottic muscles and the inlet muscles of the oesophagus [33].

It is important to note that the probability of radiation-induced complications markedly depends on the radiation dose to the organs at risk (OARs). Thus, by conforming the radiation dose to the target and simultaneously limiting the dose to the OARs, the severity and incidence of the radiation-induced side effects can be reduced.

Radiotherapy with photons: 3D-CRT and IMRT

Photons have a high penetration power and a large mean free path in tissue: the average path travelled without undergoing any interaction with the traversed material (equal to the reciprocal of the attenuation coefficient, μ [1/cm]) is in the order of the patient's dimension (for 2 MV and 4 MV photons in water, $1/\mu$ equals ~ 20 cm and ~ 30 cm, respectively [97]). As the probability of interaction in tissue is low, many photons pass through the patient without undergoing any interaction

within the patient. When photons do interact with the traversed matter, three main types of interaction take place: photo-electric effect, Compton effect and pair production. The therapeutic photon beam energy ranges from about 0.3 - 20 MeV, therefore interactions of photons with tissue are dominated by the Compton interactions. The depth dose profile of photons is characterized by a steep dose increase just below the surface (due to secondary electron build up at the surface until an equilibrium is reached) that is followed by a nearly exponential dose fall-off with increasing depth, Figure 1.

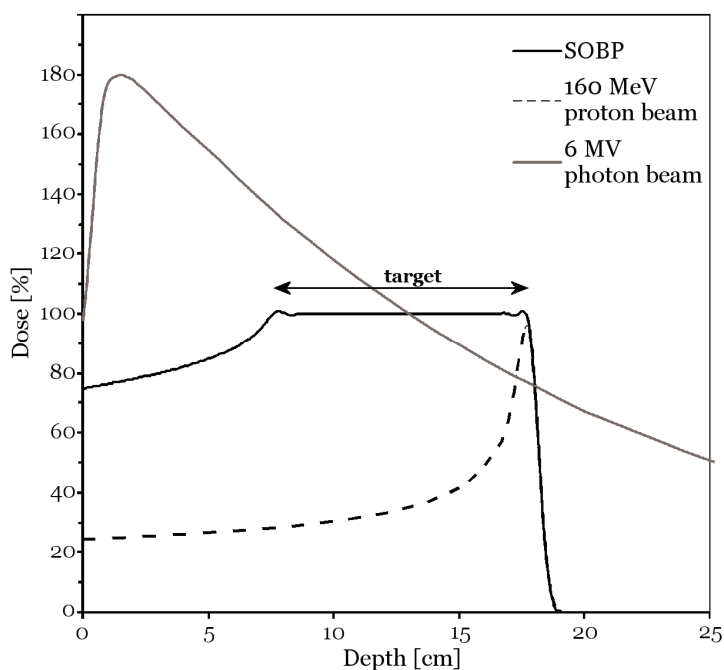


Figure 1. Comparison between the depth dose profiles in water of 6 MV photons and 160 MeV protons with corresponding spread-out Bragg peak (SOBP) that covers the target with a uniform dose. This SOBP is created by shifting the proton range of the 160 MeV beam by placing range shifter plates in the beam (water equivalent material) and simultaneously varying the weights of the shifted proton beams. This specific example clearly displays the benefit of protons regarding the steep dose fall-off distal to the target. Of note is that the entrance dose of the SOBP depends on the extent of the SOBP. As this value can be quite high (typically 80% or higher [66]), in clinical practice multiple proton beams coming from different directions are used to provide good target coverage while reducing the entrance dose to the normal tissues. This also accounts for photon treatment planning techniques.

In the last decade, photon-based radiation delivery techniques, in particular in head and neck cancer, have evolved dramatically. The first radiotherapy techniques were based on 2D-radiography. Nowadays, more advanced techniques are available such as 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), both based on 3D Computed Tomography (CT) imaging [23].

Three-dimensional conformal radiotherapy plans consist of multiple photon beams, irradiating the target from different directions to achieve adequate target coverage. The apertures of these beams are all shaped to match the 3D target volume by using multi-leaf collimators (MLC) or (less sophisticated) customized conformal blocks. Intensity variation across the beam is limited and can be obtained with wedges or patient specific compensators.

Intensity-modulated radiation therapy (IMRT) refers to a radiation technique in which the intensity distribution of the utilized beams is varied (modulated) across the beam. By using several different MLC settings per beam (known as segments) modulation of the beam intensity in the plane perpendicular to the beam direction is possible [17]. Consequently, this technique allows for more degrees of freedom with regard to sparing of OARs, as OARs can be shielded with the MLCs from different beam directions, while simultaneously ensuring adequate target coverage (Figure 2). As a result dose distributions obtained with IMRT are more conformal around the target, whereas those obtained with 3D-CRT exist of relatively large homogeneous high dose regions that enclose the target plus a substantial amount of normal healthy tissue (Figure 2, compare the areas receiving at least 66 Gy).

Radiotherapy with protons

From a physical point of view, protons have an evident advantage over photons. Whereas photons are highly penetrating with a maximum dose near the patient's surface followed by an exponential reduction of the dose with increasing depth, protons have a finite range with a plateau dose that at first slowly, and then rapidly, increases with depth, resulting in a maximum dose near to the end of the

proton beam range, the so-called Bragg peak, which is followed by a rapid drop to nearly zero dose.

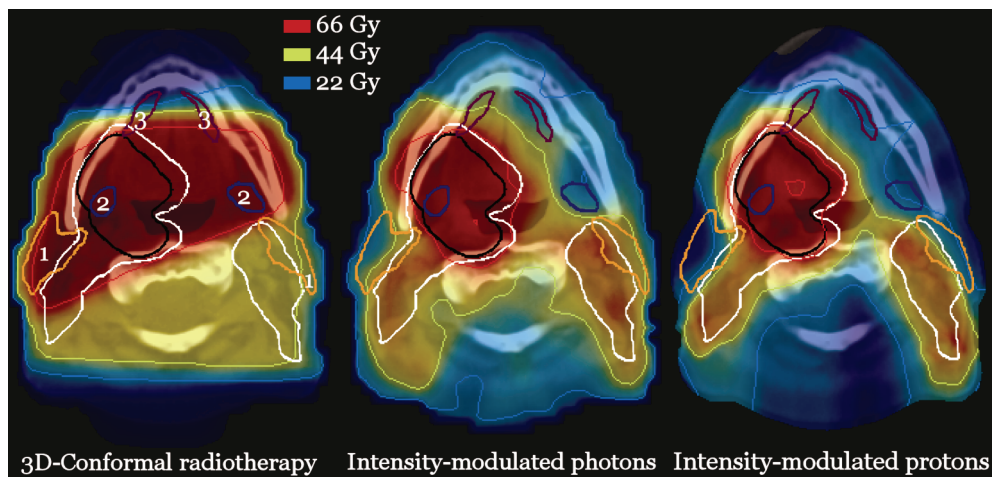


Figure 2. Dose distribution comparison between two different photon techniques and one scanned proton technique. (Adapted from chapter 3, Figure 1.) Contours of the volumes of interest are thickened: elective target volume PTV1 (white contour); boost volume PTV2 (black contour); parotid glands (1); submandibular glands (2); sublingual glands (3).

When positively charged protons pass through matter, three main interactions take place: Coulomb interactions with orbiting electrons of atoms, Coulomb interactions with atomic nuclei and nuclear interactions with atomic nuclei. Therapeutic proton beam energies range from about 85 - 270 MeV [45,66,67] and the gradual loss of energy, is predominantly caused by the Coulomb interaction with orbiting electrons of atoms. The absorbed dose is proportional to the energy lost by the proton in the traversed material, the linear energy transfer (LET) or stopping power that is expressed in MeV per $\text{g} \cdot \text{cm}^{-2}$ and given by the Bethe Bloch formula [13,14]. The stopping power (the mean energy loss per proton as function of the traversed material, dE/dx) depends on the density of the traversed material, its chemical composition and is proportional to the inverse square of the proton's velocity, β (expressed in units of the velocity of light):

$$\frac{1}{\rho} \frac{dE}{dx} \propto \frac{1}{\beta^2} \left(\frac{Z}{A} \right) \quad (1)$$

where ρ , Z and A are the density, atomic number and atomic mass of the traversed material. Therefore, as the particle slows down, the absorbed dose increases. This causes the Bragg peak.

The position of the Bragg peak is energy dependent. By varying the individual proton energies in a proton beam, a spread-out Bragg Peak (SOBP) can be produced that covers the tumour with a uniform dose and minimizes the dose to the normal tissues beyond the tumour (Figure 1).

The Bragg peak effect is characteristic for all charged particle beams and was first discovered by William Henry Bragg in 1904 by recording the ionizations produced in air by alpha particles [21]. Already in 1946, Robert R. Wilson proposed to use protons in radiotherapy and described their potential benefits [193]. However, only recently have protons become more widespread in radiotherapy. Raju suggested three possible explanations for the relatively slow development of proton therapy [149]. The first explanation was the poor experiences with neutrons whose disappointing results slowed down the clinical implementation of other new particle radiotherapy techniques. Second, at the time proton therapy was introduced, radiation oncologists were just beginning to get familiar with photon therapy. Third, during the 1950's and 1960's high-energy physics research was well funded and hence particle accelerators were fully booked with nuclear physics research work, with little available beam time for therapeutic applications. (Of importance is to keep in mind that nuclear physics research work formed the basis for clinical proton beam accelerators and when the fundings for nuclear physics work reduced, accelerators became more available for therapeutic applications.)

In 1954 at the University of California, Berkeley, the first patient was treated with protons and in 1957 proton radiotherapy also started in Europe (at the University of Uppsala, Sweden) [85]. From 1961 patients were also treated with protons at the Harvard Cyclotron Laboratory (a facility that was part of the Harvard University providing irradiation services for physics research and

therapeutic applications). The first hospital-based proton facility, The Loma Linda University Medical Center in California, opened in 1990. During the last decades, an increasing number of hospital-based proton facilities have become available and even more new treatment facilities are under construction. Currently, worldwide 30 proton therapy facilities are operational [139] and by the end of 2011, in total 83,667 patients have been treated with protons.

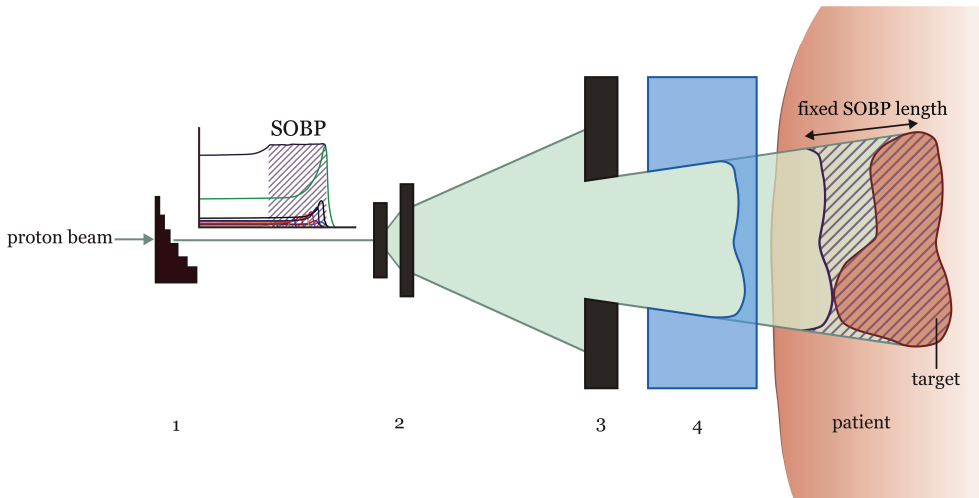


Figure 3. Sketch of the beam elements of a typical passive scattering system. The proton pencil beam coming from the accelerator is first scattered before entering the patient: 1. The range shifter wheel creates the spread-out Bragg peak (SOBP); 2. The double scattering system spreads the beam laterally; 3. The patient specific collimator shapes the beam to the lateral edge of the target; 4. The patient specific range modulator shapes the beam to the distal edge of the target volume. The purple arced region indicates the volume receiving a high uniform dose (prescribed dose), corresponding to the plateau region of the SOBP. As the length of the SOBP is fixed and conformed to the distal edge of the target volume, this technique does not provide good dose conformity proximal to the target. *Illustration by R. van Deijk.*

Nowadays, protons can be delivered by two different techniques: passive scattering and the more sophisticated active scanning technique [67]. With scattered protons each single beam delivers a uniform dose to the target. As the length of the SOBP is fixed for each field and conformed to the distal edge of the target, this technique does not provide good conformity to the proximal target side

as illustrated in Figure 3. However, with scanned protons, a single field can deliver highly non-uniform dose distributions to the target and multiple non-uniform scanned proton beams can be combined to deliver a more uniform dose to the target. This is referred to as intensity-modulated proton radiotherapy, IMPT. Moreover, the length of the SOBPs is not fixed, providing more degrees of freedom with regard to OAR-sparing and target dose coverage (Figure 4). This latter scanned proton technique is used in the treatment planning comparison studies performed in this thesis (chapters 4 - 7), in which proton therapy is compared with photon therapy. The main objective of this thesis is to investigate the potential clinical benefits of scanned proton therapy for head and neck cancer regarding sparing of OARs involved in xerostomia and swallowing dysfunction and thereby reducing normal tissue complication probabilities.

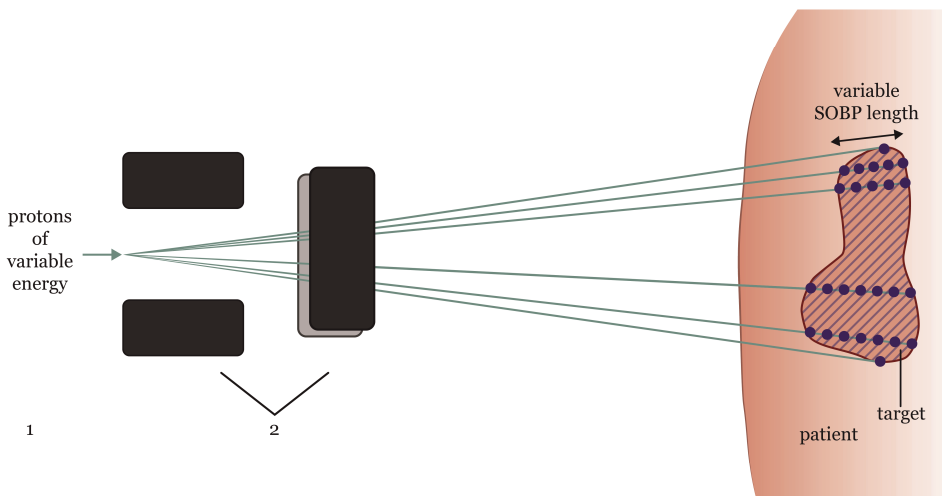


Figure 4. Sketch of the basic beam elements of a typical active scanning system. The patient is irradiated with the proton pencil beam directly coming from the accelerator: 1. The variable proton beam energy (to adjust the depth of the individual Bragg peaks, the so called spots) is created by changing the energy of the beam upstream or by dynamically adding material (so called range shifter plates) in the beam; 2. Magnets are used to deflect the beam in and out of the plane. This technique allows placement of individual Bragg peaks (spots, as indicated by the purple circles) and vary their weights in such a way to create a SOBPs within the target. The length of the spread-out Bragg peak (SOBPs) is not fixed and the high dose region is only present within the target volume (purple arced area). *Illustration by R. van Deijk.*

Proton versus photon penumbra

The proton beams used for the scanning technique have a relatively small cross section and are referred to as proton pencil beams. When entering the tissue the beam has a certain width that gradually increases as protons are laterally scattered in the medium they traverse. Deeper penetrations correspond to more scattering and thus broader beams.

Deflections of protons from their primary beam path caused by multiple Coulomb interactions with electrons are small, as protons are much heavier than electrons (about 1830 times heavier). However, nuclei are much heavier than electrons and therefore do have a significant effect on the primary proton beam path. More specifically, nuclear interactions produce a dose halo as seen at the end of the proton range (Figure 5), caused by scattered primary protons and secondary protons that have a large range (though smaller than the primary proton range). Therefore, the least sharp penumbra (the lateral 80-20% dose fall-off) of a proton pencil beam occurs at the end of its range and equals about 3 % of the proton range [66]. Thus, the lateral penumbra of a proton beam with a range of 160 mm, could be ~5 mm. This value is smaller than the penumbra of a photon beam that typically equals 6 – 9 mm for energies varying from 4 to 20 MV [66]. Compared to photons, the penumbra of protons is narrower up to a certain penetration depth, i.e. about 17–18 cm (depending on the used proton energy) [66,85].

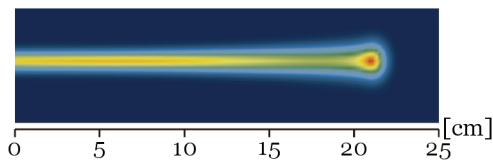


Figure 5. Cross section of a narrow 177 MeV proton pencil beam, displaying the effect of multiple Coulomb scattering on the beam. Deflections of protons from their primary beam path caused by multiple coulomb interactions with electrons are small, however nuclei interactions do significantly deflect protons form their beam path. The latter interactions produce a dose halo of primary scattered protons and secondary knocked-out protons as seen at the end of the proton range.

Goitein reported that great care should be taken to optimize the proton penumbrae and that Gaussian beam sizes should be at the most 10 mm full width at half maximum (FWHM) in air at isocenter [69]. However, producing narrow proton beams remains a challenge. During the last decade, in addition to the gantry available at the Paul Scherrer Institute (PSI) in Switzerland, multiple proton therapy facilities allowing for gantry-based¹ scanned proton therapy, have been developed or are under construction [139]. Since 2008, Massachusetts General Hospital uses gantry-based proton beam scanning equipment that is commercially available. In their initial clinical implementation they used broad pencil beams of ≥ 20 mm FWHM at the isocenter in water [103]. At the Heidelberg Ion Therapy Center, since 2009, gantry-based proton therapy is available with a beam size of 10 mm FWHM [94] (however this is not specified as whether this is in air/water or at isocenter). With the current gantry at PSI, ~ 8 mm FWHM in air can be achieved [116], but this is without the effect of the range shifter plates used to modulate energy and which degrade the beam size considerably. However, with the second-generation gantry that is under development at PSI, at least similar spot sizes in air and improved spot sizes in the patient can be achieved that will result in smaller beam sizes. Therefore, in this thesis we also investigate the influence of a reduced proton pencil beam spot size for the IMPT technique, regarding a potential improvement in sparing of the organs at risk (chapter 5).

The effect of density inhomogeneities

As protons have a well-defined finite range in tissue and a steep distal fall-off, they are more sensitive to density heterogeneities than photons. Density inhomogeneities affect the proton dose distribution by

1. affecting the proton range distal to the density inhomogeneity (e.g. protons will lose more energy in traversing bone than in traversing water, resulting in variable ranges of the individual protons) and

¹ In contrast to the horizontal fixed beams that were previously only available, gantry-based proton therapy allows the beam to be directed to the patient from any direction in the plane of rotation of the gantry.

2. by causing perturbations due to differences in scattering between adjacent tissues with different composition and densities (e.g. bone adjacent to air or soft tissue).

Those effects can spread out the Bragg peak and thereby degrade the Bragg peak [66,115].

As patient's tissues are inhomogeneous, it is hard to avoid all inhomogeneous regions. Therefore, accurate dose models that can approximate the effects of such density inhomogeneities are essential and a prerequisite for proton therapy. In clinical practice, awareness of the potential problems caused by such density inhomogeneities and techniques to avoid those effects is of importance. However, the effectiveness of protons used in regions that include density inhomogeneities have been proven by the positive clinical results as obtained for skull base chordomas and chondrosarcomas, both concerning anatomic regions that include many bone-soft tissue and/or bone-air interfaces [5,79,133].

It should be noted that the anatomic structures in the skull base area are less prone to density heterogeneity variations (in between different radiotherapy treatment fractions) than the anatomic structures in the more caudally located parts of the head and neck area (i.e., the oral cavity region including the tongue and possible air cavities). Density inhomogeneities are common in this more caudal region of the head and neck area, and the size and shape of some may vary from day to day. Therefore, especially for this anatomic region, awareness of density inhomogeneities and avoidance of those regions is of importance to improve treatment plan robustness.

In this thesis, the influence of density inhomogeneities is investigated by comparison of IMPT plans using beams that traverse regions with density inhomogeneities, with more advanced IMPT plans, using beams that avoid those regions (chapter 6).

Relative biological effectiveness of protons

The actual biological impact of a given dose of radiation can vary between radiation beams (proton or photon beams) and depends on multiple factors,

including the energy deposition pattern on a microscopic scale. To take into account the differences in biological impact of dose deposited by different radiations, the so called relative biological effectiveness (RBE) is used. The RBE of a specific radiation (tested beam) is defined as the ratio of the dose of the reference radiation beam (e.g. photons, as reference irradiation the photons resulting from ^{60}Co decay are taken) to that of the tested beam, required to cause the same biological level of effect. Therefore, the RBE of protons is defined as the ratio of the dose given with the reference radiation (photon D_{photons}), required to cause an equivalent biological level of effect compared to the given proton dose (D_{protons}):

$$RBE_{\text{protons}} = \frac{D_{\text{photons}}}{D_{\text{protons}}} \quad (2)$$

Physical dose distributions obtained with photons and protons are expressed with the unit Gy. The RBE-weighted proton dose values, however, are expressed in Gy(RBE) i.e. the physical proton dose in Gy multiplied by the RBE of protons.

Generally the RBE depends on various parameters, including the LET, the dose per fraction, the specific endpoint, the considered tissue and the environment of the irradiated tissue. For protons, various RBE values have been measured in different studies [136]. RBE values (determined at mid SOBP) obtained from in vitro studies ranged from 0.9 - 2.1 (mean value 1.2). However, in vivo data results were somewhat lower, RBE values (mid SOBP) ranged from 0.7 – 1.6 (mean 1.1). Nevertheless, Paganetti et al. [136] report that using a generic RBE of 1.1 is reasonable, as currently implemented in clinical practice and also recommended by the ICRU Report 78 [85]. However, it should be noted that locally increased RBE values were reported near the end of the SOBP (the initial few millimetres of the declining distal edge) and this can yield an elongation of the RBE-weighted proton range by ~1 to 2 mm [85,136]. Therefore, such effects should be taken into account in treatment planning, especially when single field treatments are applied and when OARs are distal to the Bragg peak.

As an RBE of 1.1 is used in clinical practice and recommended, in this thesis a constant RBE value of 1.1 for protons has also been assumed.

Potential advantages of proton therapy in head and neck cancer treatment

As in head and neck cancer patients the target volumes are generally large and complex and surrounded by many OARs, the main objective of radiotherapy (sterilizing the tumour while avoiding the normal surrounding tissues as much as possible) cannot be easily achieved. Hence, severe and late radiation side effects often occur, in particular when radiation is combined with chemotherapy.

As previously described, the superior beam properties of protons allow for a better target dose conformity than can be achieved with the currently used photon technique. These superior properties can be translated into clinical benefits using two different strategies: First, protons can be used to escalate the tumour dose providing possibilities to improve local tumour control without increasing the dose to the healthy surrounding tissue and the consequent increase of the risks for radiation-induced side effects. This strategy may be particularly useful when tumour dose escalation is expected to improve local tumour control and when the prescribed photon dose is limited by surrounding OARs. Second, protons can be used to reduce the normal tissue dose while keeping a similar target dose. In this case, tumour control is expected to be similar to the results obtained with photons, while radiation-induced side effects will most likely be reduced as the probability and severity of radiation-induced side effects strongly depend on dose and volume irradiated.

Patient data for radiation treatment planning

For calculation of the absorbed radiation dose in a patient, information about the anatomy of the patient is necessary (target and OAR volumes). Additionally, knowledge about the attenuation properties of the tissues is needed. This information is obtained from computed tomography scans (CT scans). CT scan data are expressed in units of relative photon absorption coefficients, referred to as Hounsfield Units (HUs). To be able to calculate the dose distributions for photon based treatments, the HUs are converted to electron densities [9], whereas for proton based treatment planning, conversion from HUs to proton stopping powers relative to water is required [157].

In addition to CT scan data, data acquisition with Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) also become more widely available. These important imaging data will help to define and improve the accuracy of target and OAR volume definition on the CT scan.

Target and organ at risk definition

To be able to analyze the dose received by the targets and the relevant organs at risk, these structures should be defined (delineated) in the CT scan that is used for treatment planning. A number of authors reported on the existence of inter- and intra-observer variability in delineation of target volumes and OARs [64,78,151,156]. Minimizing these inconsistencies in volume definition will help improve adequate reporting and interpreting of radiation treatment results. Therefore, for treatment planning, it is recommended to use guidelines to delineate those structures to improve consistent delineation. For head and neck cancer patients, delineation guidelines already exist for target volume delineation [72,73], however they do not yet exist for OARs related to xerostomia and swallowing dysfunction. Therefore, in this thesis (chapter 1) we performed an anatomical analysis to developed guidelines for delineation of the OARs involved, or potentially involved, in salivary dysfunction and xerostomia that eventually permit unambiguous reporting of dose-volume effect relationships for these OARs. Additionally, guidelines for delineation of the OARs involved, or potentially involved, in swallowing dysfunction have also been recently developed [33].

In general, for primary radiotherapy of head and neck cancer with curative intent, two planning target volumes (PTVs) are defined, referred to as PTV2 and PTV1. PTV2 refers to the planning target volume enclosing the primary tumour and the involved lymph nodes, receiving the highest dose (the boost). PTV1 refers to the planning target volume enclosing the areas that are at risk for the development of metastases, the lymph node regions. These regions are electively irradiated to improve tumour control. Typically, when a sequential boost technique (lymph node region irradiation is followed by primary target irradiation) is applied, the prescribed doses to PTV2 and PTV1 are 70 Gy in 35 fractions and 46 Gy in 23

fractions, respectively. When a simultaneous integrated boost technique is used (i.e. the PTV₂ and PTV₁ are irradiated at the same time), the prescribed doses are typically 70 Gy and 54 Gy respectively, delivered in 35 fractions.

Normal tissue complication probability models

When comparing treatment plans, it is interesting to know whether the differences in dose distributions result in a difference in complication probability. This, unfortunately, cannot be determined directly from the differences in the dose distributions. Normal tissue complication probability (NTCP) models, however, can translate the differences in dose distribution into expected differences in toxicity.

Various NTCP models exist that are generally related to the irradiation of specific tumour sites, as treatments of different tumour sites with radiotherapy involve the irradiation of different OARs. For head and neck cancer, existing models mainly focus on xerostomia. More specifically, models have been developed that describe a relation between the dose administered to the parotid and/or submandibular salivary glands and xerostomia-related endpoints [86,128,164]. Semenenko et al. developed a model based on multi-institutional toxicity data that predicts the probability of a reduction of salivary flow to below 25% of the baseline flow at ≤ 6 months after radiotherapy [164]. The mean dose to both parotid glands was used as the only predictive factor. Murdoch-Kinch et al. [128] investigated the relation between the dose to the submandibular glands and submandibular salivary flow. Their model predicts the probability of a reduction in stimulated submandibular salivary flow below 25% of the baseline level (per gland) at 12 months after radiotherapy [128].

The two previously mentioned models only use one input parameter and are based on objective measures of salivary output. In other words, the used endpoint only relates the dose distribution in one specific OAR to the function of that specific OAR. However, to reduce the probability of patient-rated xerostomia – a subjective endpoint that is clinically more relevant but more complex – sparing only one salivary gland might not be sufficient enough. This was illustrated by the findings of Jellema et al. [86]. They showed that patient-rated xerostomia was significantly

associated with both the mean parotid gland dose and the mean submandibular gland dose. Hence, a NTCP model as developed by Jellema et al. [86] is based on patient-rated scores and more than one input parameter. The model predicts the probability of moderate to severe patient-rated xerostomia at 6 months after radiotherapy, based on the mean dose to both parotid glands and both submandibular glands [86].

Unfortunately, data with regard to the more recently recognised, important radiation-induced side effect, swallowing dysfunction, is scarce. Currently, predictive models for radiation-induced swallowing dysfunction are under development. In a multicenter prospective cohort study, Christianen et al. [34] investigated the relation between the dose to OARs involved in swallowing and the probability of swallowing dysfunction at 6 months after radiotherapy. Later on, in the same multicenter study, they investigated which dose-volume histogram (DVH) parameters and other parameters are most important to predict the probability of swallowing dysfunction at 12, 18 and 24 months after radiotherapy [32]. The results showed that at 6 months after radiotherapy, grade 2-4 swallowing dysfunction was best predicted by a model that uses the mean dose to the superior pharyngeal constrictor muscle (PCM) and the mean dose to the supraglottic larynx [34]. At 12 and 18 months after radiotherapy, a model based on the mean dose in the PCM superior and the PCM medius was most predictive for the probability of grade 2-4 swallowing dysfunction and at 24 months after radiotherapy only the mean dose to the PCM superior was most predictive [32].

Clinical studies

Radiotherapy treatment techniques have been improved and allow better conformation of the high dose region to the PTV, while OARs can be spared more adequately. As in head and neck cancer, radiation-induced xerostomia is the most frequently reported grade 2 or more side effect significantly affecting quality of life [87], radiation oncologists have mainly focussed on reducing the probability of xerostomia and, for this purpose, mainly focussed on reducing the dose to the parotid glands [95,146,186].

Clinical studies indicated that compared with 2D and 3D-CRT radiotherapy, IMRT significantly reduces the parotid gland dose, resulting in higher flow rates after treatment and/or lower rates of xerostomia contributing to an improved quality of life [54,95,146,186]. However, sufficient sparing of the parotid glands with IMRT below the threshold cannot be achieved in all patients. Furthermore, sparing the parotid glands alone does not always translate into a reduced probability of patient-rated xerostomia [95,146]. Moreover, in a prospective trial Kam et al. [95] compared parotid gland sparing IMRT with 2D-RT in nasopharyngeal cancer. Despite the fact that IMRT reduced the parotid gland dose significantly, corresponding to an increased flow rate compared with 2D-RT, no differences were found between the two arms with regard to patient-rated xerostomia [95]. Similar results were found by Pow et al. [146]. These discrepancies may be explained by the fact that parotid gland sparing alone may not be sufficient enough to reduce the probability of patient-rated xerostomia, reflecting the need to enhance sparing of other salivary glands. Therefore, further dose reductions in all relevant salivary glands by using more advanced radiotherapy techniques, like proton therapy, can help to reduce the probability of patient-rated xerostomia and thereby improve quality of life during and after radiotherapy treatment.

The physical properties of protons allow further improvement of the dose distribution. However, clinical studies concerning head and neck cancer patients treated with proton therapy are scarce. Moreover, most clinical studies that use protons to treat head and neck cancers, use mixed photon-proton techniques: protons are only used during part of the radiation treatment course [145,167,175]. Furthermore, reviews on the added value of protons over photons mainly focus on the role of protons in terms of treatment efficiency (by reporting on local tumour control and overall survival), rather than on potential benefits of protons with regard to radiation-induced side effects [20,30,106,162].

Aims of this thesis

In summary, compared with advanced photon techniques, advanced proton techniques have the potential to improve the therapeutic ratio, i.e. to reduce the probability of radiation-induced side effects while maintaining similar or increased tumour control. The main objective of this thesis is to investigate the potential clinical benefits of scanned proton therapy in radiotherapy for head and neck cancer with regard to sparing of organs at risk and reducing normal tissue complication probabilities.

As (1) clinical data with regard to the potential benefits of protons focussing on radiation-induced side effects are scarce and (2) as an *in silico* planning comparison study is one of the first and necessary steps in the development of emerging radiation techniques that allows for a comparison of dose distributions between the current standard and new radiation techniques, this thesis focuses on *in silico* planning comparison studies. In addition, by using the differences in dose distributions as input for existing NTCP models, the potential clinical benefits of protons regarding improvement of the therapeutic ratio can be estimated.

The specific aims are:

1. To define delineation guidelines for organs at risk involved in radiation-induced salivary dysfunction and xerostomia allowing consistent delineation of relevant organs at risk.
2. To review the literature on *in silico* planning comparative studies published so far that compared proton therapy with photon therapy to treat head and neck cancers and to determine the optimal approach to use protons.
3. To compare the dose distributions as obtained with intensity-modulated proton therapy with those obtained with advanced photon therapy techniques and to determine if differences in dose distribution translate into clinical benefits in terms of the risk of salivary dysfunction and xerostomia.

4. To determine the additional value of using a reduced spot size for intensity-modulated proton therapy with regard to salivary gland sparing.
5. To investigate whether a more advanced, split-beam geometry for intensity-modulated proton plans could further improve sparing of the salivary glands and improve avoidance of regions with density heterogeneities.
6. To evaluate the value of intensity-modulated proton therapy in sparing the anatomical structures involved in the development of radiation-induced swallowing dysfunction.