Chapter 8
Proton Therapy for Head and Neck Cancer

V. Budach and A. Thieme

Introduction

Radiation therapy (RT) is a mainstay of treatment for patients with head and neck cancer (HNC). At present, the most common form of RT is external beam photon therapy. The development of intensity-modulated radiotherapy (IMRT) and more recently advanced forms of IMRT such as volumetric modulated arc therapy (VMAT) allowed improvements in dose conformality in target volumes and reduction of high doses in nearby healthy tissues and organs at risk (OARs). This resulted in a drastic reduction of the most common forms of RT-associated toxicity in HNCs such as xerostomia [1–4], and dysphagia [5]. However, technological advances in photon therapy to further optimize the dose distribution are reaching the limits imposed by the physics of photon radiation. In consequence, IMRT's usage of multi-angled radiation fields has led to a redistribution of the integral dose causing alternative toxicities such as fatigue by the low dose bath of the posterior cranial fossa [6]. Therefore, alternative methods of radiation delivery with distinct physical properties are required to further refine the therapeutic index of RT.

For decades, proton therapy (PT) offers attractive options for technological advances in RT, potentially leading to a reduction in treatment-related toxicities or an isotoxic dose escalation through dosimetric advantages over photon therapy. PT is the standard of care for skull-base tumours which are characterized by a challenging tumour location and proximity to critical structures. In recent years, the

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use of PT has expanded to numerous other head and neck disease sites such as nasopharynx, oropharynx, nasal cavity and paranasal sinus, periorbital, and salivary glands including reirradiation.

Physical Properties of Proton Therapy

Dosimetric Benefits of Proton Therapy

Photon and proton beams are different forms of ionizing radiation causing DNA damage in cancer cells. Both are elementary particles with different physical properties and energy deposition profiles in tissue favouring protons for treatment in cancer patients (Fig. 8.1). Photons are electromagnetic packets of energy, which are massless and have an infinite range in patient tissue. In contrast, protons have a physical mass and the range of a proton in patient tissue is a function of its initial energy. A monoenergetic proton beam releases most of the energy in the distal part of its path in a characteristic peak, the so-called Bragg Peak. By using a range of energies a spread out Bragg Peak (SOBP) can be created that allows highly conformal treatment of tumour target volumes. The absence of an exit dose beyond the target volume allows for precise sparing of adjacent OARs. Additionally, the entry portion of the proton beam receives less integral dose compared with a photon beam. In summary, proton beams offer several advantages over photon beams in cancer treatment, including the ability to more precisely spare surrounding healthy tissues and the potential to deliver lower integral doses to the patient.

PT uses passive scattering or active scanning techniques. The passive scattering beam technique was introduced first, using scattering devices to broaden the proton beam and a range-modulation device to create the SOBP. This technique requires patient individualized scattering devices, which are expensive to create and limit the ability of this technique for adaptive planning in case of excessive weight loss of the patient or changes of the anatomy. A more recent form of PT is the active scanning technique which uses magnets to deflect the proton beam. Using this technique, the radiation dose is delivered to the target volume layer by layer with protons of different energies. Inverse planning methods are used to deliver highly conformal doses to the target volume with either single field optimization (SFO) or multifield optimization (MFO) with MFO being generally more conformal than SFO. Intensity-modulated proton therapy (IMPT) takes advantage of MFO with each individual radiation field delivering an inhomogeneous dose to the target volume to minimize radiation exposure of OARs. Comparative HNC treatment plans with IMRT show dosimetric advantages of IMPT (Fig. 8.2). Several recent studies have confirmed the dosimetric advantages of IMPT for unilateral HNCs [8], oropharyngeal carcinoma (OPC) [9], adjuvant RT of OPC [10], and in cases of HNC re-irradiation [11].
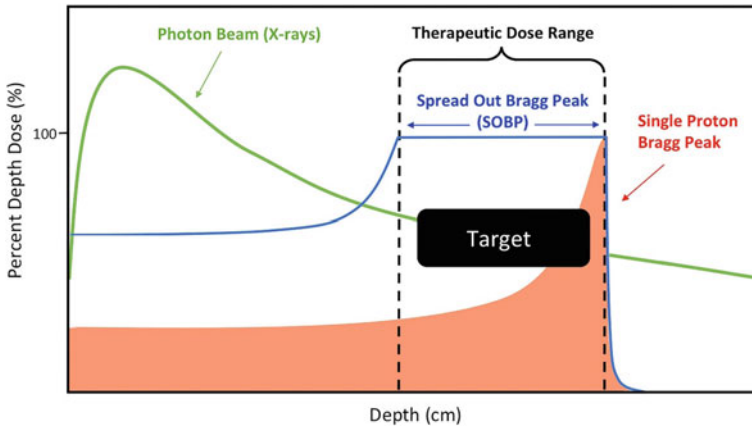
Fig. 8.1 Dose-depth curves comparing photon and proton beams. A single monoenergetic proton beam releases most of its energy in the so-called Bragg Peak (red curve). By variation of the Proton energies, a Spread Out Bragg Peak conformal to the tumour target volume can be created (blue curve). The energy deposition of a photon beam exponentially decreases with depth in the patient tissue and has an infinite range (green curve). [7]

Dosimetric Uncertainties of Proton Therapy for Head and Neck Patients

While the sharp dose fall-off beyond the Bragg Peak is considered to be a primary beneficial property of PT for OAR sparing, it is also the source of significant uncertainties in dose delivery and a possible cause of underdosage in the tumour volume. For instance, proton beams passing the nasal cavity or paranasal sinuses should be avoided due to variable fillings of these structures which can lead to significant distortions of the proton irradiation fields. A general approach for a robust PT treatment plan is the usage of MFO and careful selection of beam angles avoiding heterogeneous tissues. The dose distribution of PT is sensitive to the correct conversion of computed tomography (CT) Hounsfield units to proton stopping power [13, 14], image artifacts and interfraction, and interfield motion [15]. Uncertainties arise at multiple steps of the typical radiation oncology workflow and countermeasures exist (Fig. 18.3). Robust treatment plans that are clinically acceptable can be created when the aforementioned uncertainties are taken into account as part of multi-criteria optimization simulating these uncertainties or combinations thereof [16, 17]. Robust IMPT planning is based on the clinical target volume (CTV) without using margins for a planning target volume (PTV) [18] (Fig. 18.4). Instead of relying on precise proton ranges, robust optimization often relies on the sharp lateral penumbra of proton beams.

A further source of uncertainty is the relative biological effectiveness (RBE) of protons which is a factor multiplied by the proton dose to calculate the biological equivalent photon dose. Currently, a homogeneous value of 1.1 for the proton RBE is
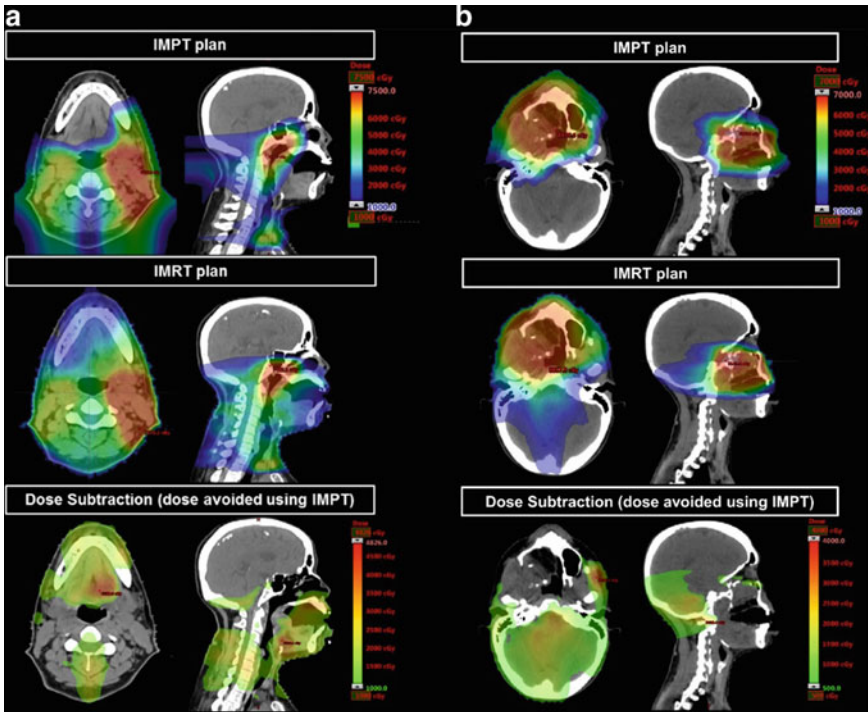
Fig. 8.2 Comparative treatment planning with IMPT and IMRT for two example HNC cases.
(A) definitive RT of a nasopharyngeal carcinoma T1N1, (B) adjuvant RT of an adenoid cystic
carcinoma of the hard palate T4N0. Dose substractions of both cases show a dosimetric advantage
of IMPT compared with IMRT [12]. HNC: Head and neck cancer; IMPT: Intensity-modulated
proton therapy; IMRT: Intensity-modulated radiation therapy; RT: Radiation therapy

used in clinical practice, but there have been studies that suggest a variability of RBE
with higher values close to the Bragg Peak [19]. While the clinical relevance of a
variable RBE is unclear especially in regards to normal tissue toxicity, some treatment
planning systems allow for biological uncertainties optimization by locating higher
RBE values inside the target volume while avoiding OARs.

Take Home Message for Physical Properties of Proton Therapy

- Protons have a different energy deposition profile than photons suitable for cancer treatment.
- Protons have several physical properties that are beneficial for normal tissue sparring: (1) release of most of the energy in the Bragg Peak, (2) steep dose fall-off beyond the Bragg Peak, (3) lower integral dose in the entry path, and (4) a sharp lateral penumbra.
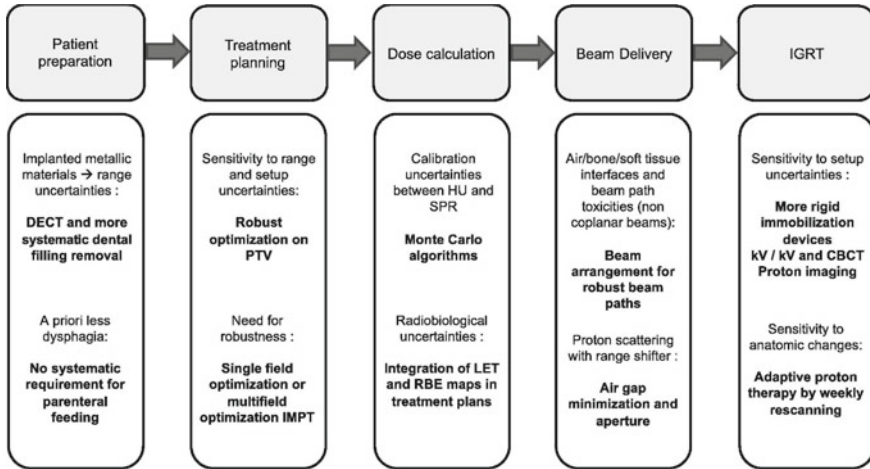
Fig. 8.3 **Causes of uncertainties of proton therapy and possible countermeasures to increase robustness** [20]. CBCT: Cone beam computed tomography; DECT: Dual-Energy computed tomography; HU: Hounsfield Unit; IGRT: Image-guided radiation therapy; IMPT: Intensity-modulated proton therapy; LET: Linear energy transfer; PTV: Planning target volume; RBE: Relative biological effectiveness; SPR: Stopping Power Ratio

- By using a range of energies a spread out Bragg Peak can be created which is highly conformal to the target volume.
- Proton therapy is subject to range uncertainties which can be successfully mitigated with robust optimization of the treatment plan.

Patient Selection for Proton Therapy

While protons, from a physical point of view, have more favourable properties for RT than photons, there is a lack of evidence from randomized controlled trials (RCTs) comparing IMRT vs IMPT and investigating differences in toxicity profiles. The "ALARA" principle states that ionizing radiation should be applied to humans "as low as reasonably possible" motivating the fast introduction of modern photon radiation techniques like IMRT and VMAT into clinical practice, because they allowed for better dose conformity to the target volume and sparing of OARs. Due to the significantly higher costs of PT, the question arises to what extent PT translates into a clinically relevant reduction of toxicities [21].

Alternative evidence-based approaches to RCTs rely on predicting RT related toxicities via Normal Tissue Complication Probability (NTCP) models, to identify patients who benefit most from PT (model-based selection) and to continuously validate this patient selection process (model-based validation).
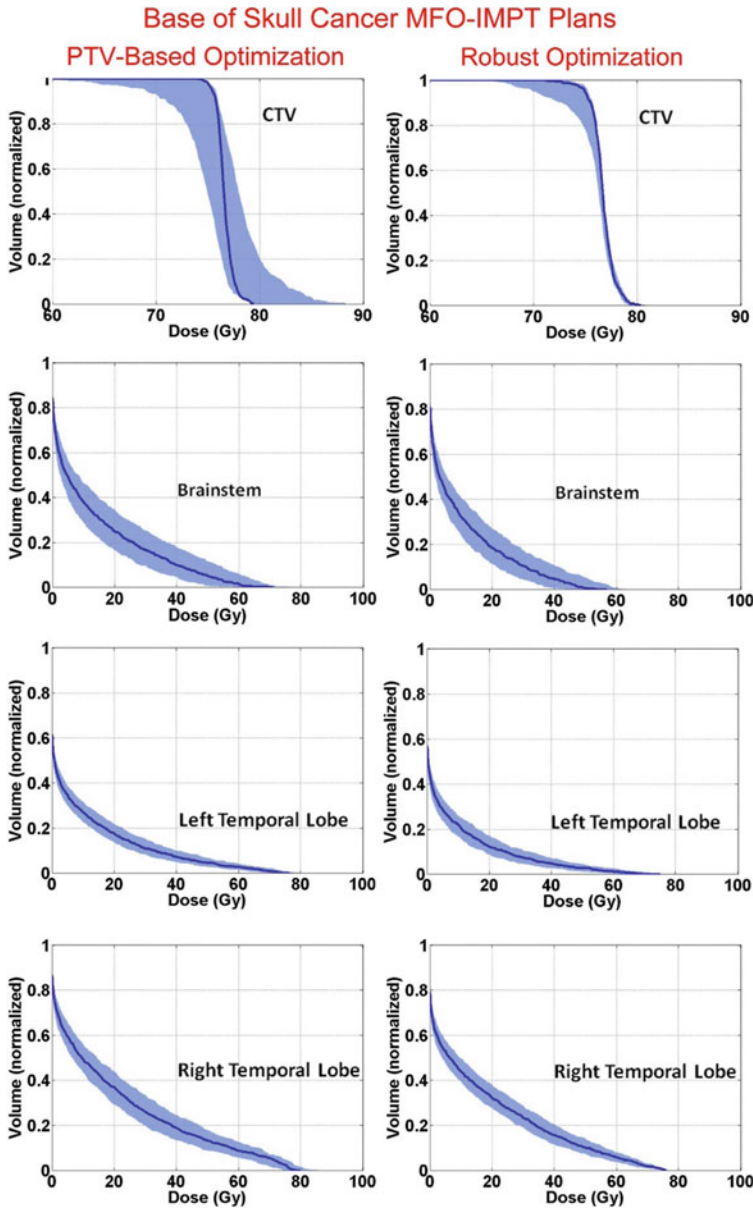
Fig. 8.4 Standard optimization involving a PTV vs robust optimization based on the CTV for a skull base cancer. Nominal DVH curves and DVH bands accounting for proton range uncertainties are shown for a treatment plan without (left column) and with robustness optimization (right column). Smaller variances of DVH bands of CTV coverage for the robustly optimized treatment and benefits in OAR sparing can be observed [17]. CTV: Clinical target volume; DVH: Dosevolume histogram; IMPT: Intensity-modulated proton therapy; MFO: Multifield optimization; OAR: Organ-at-risk; PTV: Planning target volume

Normal Tissue Complication Probability Models for Head and Neck Cancer

RT to the head and neck has various potentially severe acute and late side effects. The relationship between the dose distribution in OARs and the probability to develop RT-related side effects are described by NTCP models. In general, the probability of a side effect will increase with higher doses and larger volumes in the OAR to receive certain doses [22]. Side effects are assessed by medical healthcare professionals (investigator-reported outcomes) preferably in combination with direct reports of the patients (patient-reported outcomes (PROs)). Sophisticated grading scales have been developed for both investigator-reported outcomes such as the Common Terminology Criteria for Adverse Events (CTCAE) [23] and PROs such as the European Organisation for Research and Treatment of Cancer Quality of Life Head and Neck Module (EORTC QLQ-HN43) [24]. Most relevant dose-volume parameters vary from the observed side effect and OARs, e.g. the mean dose to the parotid glands for xerostomia [25], and in some cases may even depend on multiple dose-volumen parameters, e.g. the mean dose to the superior pharyngeal constrictor muscle and the mean dose to the supraglottic area for swallowing dysfunction [26]. The most reliable NTCP models are obtained from prospective clinical trials which are validated in an independent external cohort. Some models improve their predictive performance by considering patient factors (e.g. age) and treatment related factors (e.g. concomitant chemotherapy) which are then called multivariable NTCP models. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) was an effort to accumulate the evidence for dose–response models and dose-volume constraints which was published in 2010 [27]. Since then more NTCP models have been developed which incorporate PROs and/or evaluated modern RT techniques for xerostomia [25, 28–30] (Fig. 8.5), dysphagia and feeding tube dependency [26, 31–33], hypothyroidism [34], laryngeal edema [35], emetogenesis [36] and acute mucositis [33].

Model-Based Approach

The general idea behind the model-based approach is patient selection for either IMPT or IMRT based on an expected reduction of RT-associated toxicities as predicted by NTCP models. A major challenge with this approach is that many NTCP models are based on patient cohorts which received photon therapy with outdated techniques and that their validity for IMPT have not been demonstrated. To this end, existing NTCP models have been verified with external validation cohorts receiving PT. While a drop in the performance of the NTCP models could be noticed, the models demonstrated robustness and generally remained to be valid [37].
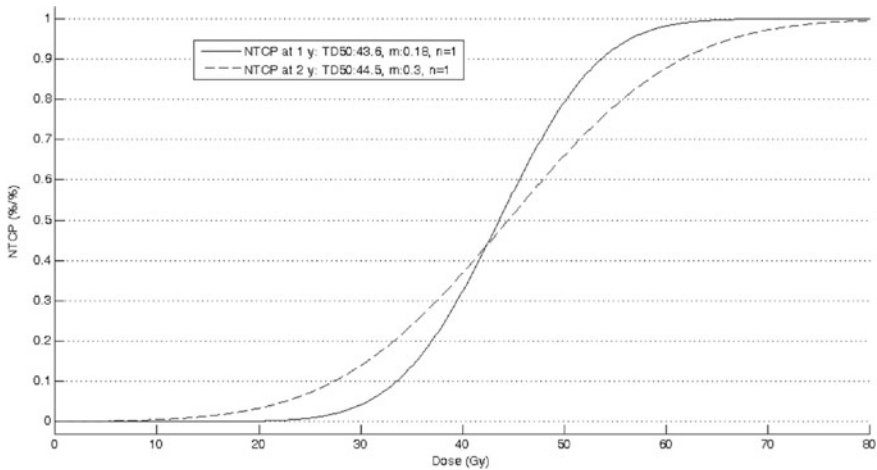
Fig. 8.5 NTCP curve for the parotid gland as function of the mean parotid gland. This curve is based on the objective measurement of the salivary excretion function assessed by quantitive scintigraphy. Complication was defined as a post-RT salivary excretion function ratio of <45%. The solid line represents NTCP after 1 year and dashed line after 2 years. NTCP: Normal Tissue Complication Probability; post-RT: post radiotherapy [29]

The model-based approach works with the following steps (Fig. 8.6):

(1) For every patient in silico planning comparative (ISPC) studies are created and the best photon (VMAT) and proton (IMPT) treatment plans are compared.
(2) NTCP models are used to predict the probability of the most relevant acute and late RT induced side effects for both treatment plans.
(3) It is determined to which extent the difference in dose (Δdose) translates into a large difference in complication probability (ΔNTCP) of acute and late side effects. This step is crucial since not all Δdose translate into ΔNTCP which can be the case in two situations: the VMAT treatment plan is already sufficiently optimized and has a low probability of complication which cannot be significantly improved with IMPT, or 2) both the IMPT and VMAT treatment plans are located at the upper end of the NTCP curve and the Δdose is too small to result into a lower complication probability.
(4) If a predefined threshold for ΔNTCP is reached, e.g. the probability of severe complication is 5% lower with IMPT than with VMAT, the patient is selected for treatment with IMPT (model-based selection).
(5) After treatment, actual complications in patients are observed and NTCP models are validated (model-based validation).

The model-based approach has been approved and accepted by the Dutch Health care institute for selection of patients for PT. In the National Indication Protocol Proton therapy (NIPP) the following ΔNTCP thresholds and CTCAE grades are used for patient selection: no ΔNTCP threshold for grade 1 side effects, ΔNTCP $\geq$ 10% for
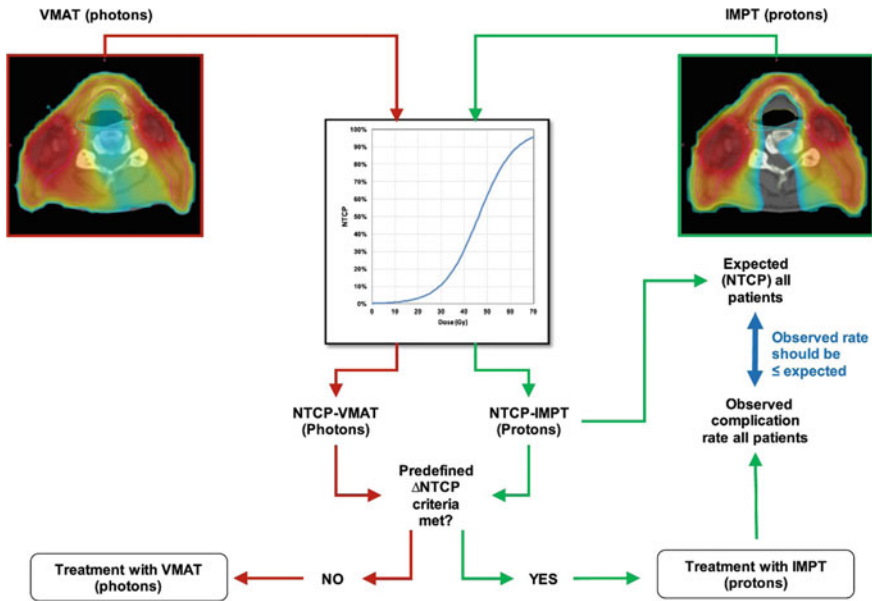
Fig. 8.6 Model-based selection of patients for VMAT or IMPT and validation pipeline. For a patient in silico planning comparative studies for VMAT and IMPT are created and evaluated by NTCP models in regards to their probability of RT-related side effects. If a certain threshold in difference in NTCP (Δ NTCP) is predicted, e.g. a 5% lower probability to develop severe xerostomia with IMPT, the patient is selected for this modality (model-based selection). After treatment, actual complications are observed and compared with NTCP predictions to further validate the process (model-based validation) [38]. IMPT: Intensity-modulated proton therapy; NTCP: Normal Tissue Complication Probability; VMAT: Volumetric modulated arc therapy

grade 2 or ΔNTCP $\geq$ 5% for grade 3 or higher. A further criterion for PT selection is the sum of ΔNTCPs of all grade 2 or higher side effects exceeding the threshold of 15%.

In a first evaluation of the model-based approach by Tambas et al. [39] 35% of patients (n = 221) with HNCs in distinct anatomical loci (oropharynx, larynx, nasopharynx, hypopharynx, oral cavity) and mostly higher stage (stage III/IV 83%) qualified for PT according to the NIPP thresholds. In the sub-group of patients with OPCs the PT qualification rate was with 65% even higher.

Randomized Controlled Trials for Proton Therapy

A RCT is the most scientifically reliable method of hypothesis testing and is considered the gold standard for evaluation of the efficacy of an intervention. There might be situations where a RCT should be preferred over the model-based approach: concerns regarding a decreased tumour control probability; concerns regarding increased side

effects, e.g. due to range uncertainties or an unknown RBE; in healthcare systems that require a RCT for reimbursement.

As pointed out by Widder et al. [40], including patients in a RCT who are unlikely to experience lower toxicity from PT due to a low Δdose and/or ΔNTCP, will only increase the noise and decrease the power of the study. For a particularly costly intervention like PT, even a positive RCT with an unselected patient cohort will provoke questions about patients who benefit most from PT in order to reduce costs in the health care system. In consequence, even in a setting of RCT, patient enrichment by the model-based selection is preferable to generate further evidence of the benefits of PT.

Take Home Message for Patient Selection for Proton Therapy

- Normal Tissue Complication Probability (NTCP) models can be used to estimate the probability of acute and late toxicities associated with photon and proton radiotherapy.
- The model-based approach assumes a clear dose-dependence for RT-related toxicities best described by the NTCP-models, which serve as a selection tool for comparative photon and proton treatment plans.
- The Netherlands consensus for model-based selection implies a reduction of ≥10% and ≥5% for a grade 2 or 3 side effects, respectively, which would qualify the patient for proton treatment.
- With the model-based approach, patient cohorts of randomized controlled trials can be enriched with patients who are likely to profit from proton therapy.

Outcomes After Proton Therapy of Head and Neck Cancers

Skull-Base Chordomas and Chondrosarcomas

Skull-base chordomas and chondrosarcomas are locally aggressive malignancies that belong to the group of sarcomas and are characterized by a close proximity to critical structures. Chordomas are rare malignancies with an incidence <0.1 per 100,000 [41]. Skull-base chordomas mostly arise from the clivus and often become clinically apparent with cranial nerve deficits, sensorimotor deficits, pituitary dysfunction, or hydrocephalus. Without treatment the average overall survival (OS) is short (6–24 months) [42]. Chondrosarcomas comprise a heterogeneous group of slow-growing sarcomas originating from cartilage-producing cells in areas of enchondral ossification and have an incidence of 0.2 per 100,000 [43]. Surgery is the primary treatment, however due to the location a gross total resection often cannot be achieved. In chordomas, surgery alone results in a high local recurrence rate of 58% [44]. Adjuvant

RT is of crucial importance to reach acceptable rates of local control (LC). Since the main site of recurrence is local and the chances of salvage surgery are remote, LC is directly associated with OS. A clear dose–response relationship with LC could be observed. Median PTV doses of <60 Gy, 60 Gy and 66.6 Gy resulted in a 5-year LC of 28% [45], 39% [46] and 50% [47]. Chordomas and chondrosarcomas have a relatively high radioresistance and RT should aim for target volume doses above 70 Gy for best responses. This is especially challenging at the skull-base since the optimal doses exceed the tolerance of proximal neural structures such as the brainstem, spinal cord, and optic nerves and chiasm.

Multiple studies have reported outcomes of PT and skull-base chordomas [48–56] and chondrosarcomas [51, 52, 55, 56]. Munzenrider et al. have published so far results for the largest patient cohort (n = 519) who received 66–83 Gy (RBE) as a combination of photon and proton RT. The median follow-up was 41 months. The 5-year LC and OS was 73 and 80% for chordomas and 98 and 91% for chondrosarcomas. Male chordomas patients had a significantly higher 5-years LC than females (81 vs. 65%, p = 0.035). The following significant toxicities were reported: three (0.8%) patients died from brain stem injury, 8 (2.2%) experienced temporal lobe injury (Fig. 8.7), hearing loss, cranial neuropathy, or endocrinopathy. More recent studies could confirm similar rates for LC [48, 50, 57] and higher grade toxicities [54, 58, 59]. In summary, PT has allowed for dose intensification that resulted in improved clinical outcomes and tolerable toxicity profiles.

Sinonasal Cancers

Sinonasal cancers (SC) are a heterogeneous group and comprise of malignancies from the nasal cavity and paranasal sinuses including the maxillary, ethmoid, frontal, and sphenoid sinuses and the middle ear. SCs are very rare with an incidence of 8.7 per 1.000.000 [61]. The histology is mostly squamous cell carcinomas (SCCs) followed by adenocarcinomas [62]. Risk factors for SCs are occupational exposures, e.g. wood dust, leather dust, formaldehyde, nickel and chromium compounds [63]. After mesothelioma, sinonasal cancers are the second most common malignancies in number of cases associated with occupational exposure [64]. Surgery is the preferred primary treatment of SCs and small tumours with complete gross tumour resection have an excellent prognosis. However, many SCs are detected at a later stage which makes complete resection difficult.

In a meta-analysis by Patel et al. [65] a subgroup analysis comprising 16 trials and 539 patients specifically compared PT with IMRT and found a significantly higher disease-free survival (DFS) at 5 years (hazard ratio (HR) = 1.44, 95% confidence interval (CI) = [1.01–2.05], p = 0.045) and locoregional control (LRC) at longest follow-up (HR = 1.26, 95%CI = [1.05–1.51], p = 0.011) in favour of PT.

A large study by Resto et al. [66] comprised 102 patients who received a combination of adjuvant photon RT and PT. The median total dose was 71.6 Gy (range 55.4–79.4 Gy) with a median of 57.1% delivered via protons (range 22.9%–84.8%).
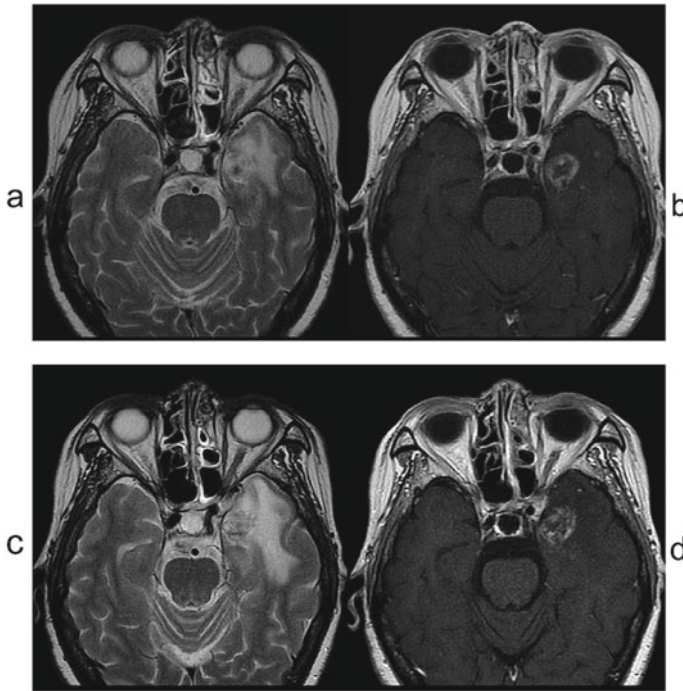
Fig. 8.7 MRI images of a temporal lobe radiation injury induced by proton therapy. An 81-year old woman received proton therapy for adenoid cystic carcinoma of the pterygopalatine fossa and developed temporal lobe radiation injury without symptoms and without requirement of treatment. (a) T2-weighted and (b) contrast-enhanced T1-weighted MRI images 30 months after RT showing marginal enhancement and edema in left temporal lobe; (c) T2-weighted and (d) contrast-enhanced T1 weighted MRI images 36 months after RT showing further development of radiation-induced changes [60]. MRI: Magnetic resonance imaging; RT: Radiation therapy

The study had a median follow-up of 5.1 years. The 5-year LC of patients with complete resection, partial resection and biopsy were 95%, 82% and 87%. The extent of surgical resection was associated with improved OS (p = 0.02), DFS (p = 0.009) and distant relapse (p = 0.03).

In a comparative study by Lewis et al. [67] VMAT and IMPT treatment plans for patients (n = 10) with SCs were created and dosimetric parameters compared (Fig. 8.8). IMPT was superior for dosimetric parameters of the brain (mean, V10, V30), brainstem (max dose/D0.01), ipsilateral cochlea (V30), contralateral cochlea (mean), contralateral lacrimal gland (mean), contralateral parotid (mean), spinal cord (max dose/D0.01) and inferior for the ipsilateral eye (mean) and ipsilateral lens (mean). The secondary malignancy risk with VMAT was 3.35 times higher (95%CI = [1.92,5.89]) than with IMPT. The authors conclude that IMPT better spared OARs not immediately adjacent to the target volume and reduced the risk of secondary malignancies.
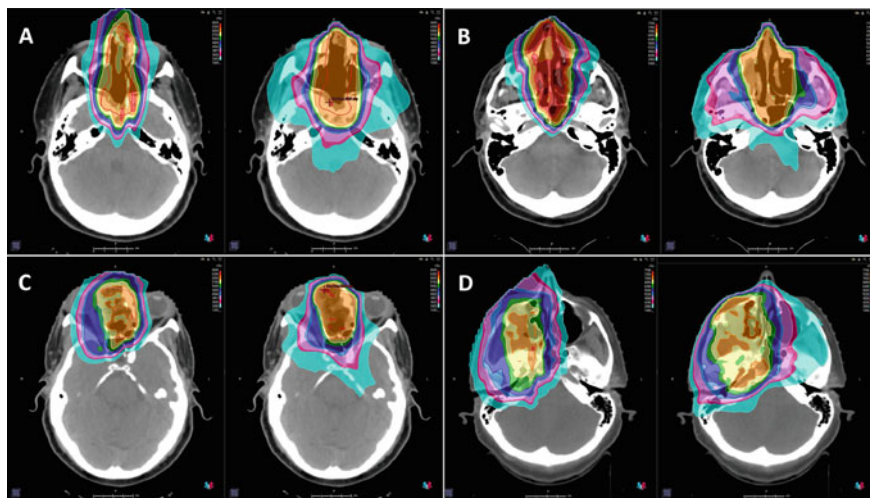
Fig. 8.8 Representative slices of IMPT vs VMAT treatment plans for sinonasal cars. IMPT plans are on the left and VMAT plans on the right of each panel. (A) A high conformality of IMPT and low dose bath of VMAT can be observed; (B) high conformality, but dose hot spots of IMPT in the multiple sinuses; (C) superior ipsilateral eye and lense sparing of VMAT; (D) superior contralateral OAR sparing of IMPT [67]. IMPT: intensity-modulated proton therapy; OAR: organ-at-risk; VMAT: volumetric modulated arc therapy

In a study by Pasalic et al. [68], patients (n = 64) with SCs of mostly advanced stage (T4 disease 46%) and mostly olfactory neuroblastoma as histology (28%) received PT and were evaluated for toxicities by physician-assessed toxicities (PATs) and PROs. The 3-year LC, DFS and OS were 88%, 76%, and 82%. PATs were assessed with CTCAE and PROs with the Xerostomia-Related Quality-of-Life Scale (XeQoLS), MD Anderson Dysphagia Inventory (MDADI), and Functional Assessment of Cancer Therapy (FACT) scales. No late grade 3 or higher PATs were observed. Significant changes in PROs from baseline were observed in the acute and sub-acute phase, but no chronic sequelae.

Periorbital Tumours

Periorbital tumours refer to malignancies in proximity to optic structures, including the nasopharynx, the nasal cavity and paranasal sinuses, and the dura of different histologies. Surgery and adjuvant RT are often indicated in the presence of high risk features like positive resection margins, bone invasion, high-grade disease, positive lymph nodes and/or perineural invasion. Historically, periorbital tumours were treated with orbit exenteration in order to ensure a margin-negative resection. Orbit-sparing RT treatments are an alternative to orbital exenteration which aim to preserve visual function and maintain high rates of LC. The complex anatomy of this region

and the proximity to critical structures such as the globe, cornea, lacrimal gland and duct system, tumours of the periorbital locations are particularly difficult to treat with RT.

In a study by Holliday et al. [69], patients (n = 20) with periorbital tumours were treated with global-sparing surgery and PT. The median radiation dose was 60 Gy (RBE) (range: 50–70 Gy) and 11 patients received concomitant chemotherapy. After a median follow-up of 27 months, LC was 100% (1 regional and 1 distant relapse). Toxicities were graded by CTCAE. There were 3 (15%) occurrences for grade 3 epiphora and 3 (15%) for grade 3 exposure keratopathy (damage to the cornea caused by prolonged exposure to air and instability of the tear film due to incomplete eye lid closure). Patients experiencing these toxicities had a higher maximum dose to the ipsilateral cornea (median 46.3 Gy (RBE) vs. 37.4 Gy (RBE), p = 0.017). Visual acuity decreased in 4 patients (20%).

In the study by El-Sawy et al. [70], patients (n = 14) received treatment for periorbital tumours (lacrimal sac or nasolacrimal duct carcinoma). Globe-sparing treatment was conducted in 10 patients and 4 patients received orbit exenteration. 13 patients received postoperative RT as IMRT (n = 5) or PT (n = 7) (median dose 60 Gy). Globe sparing was successful in all 10 patients after a median follow-up of 27 months. 9 patients (90%) maintained or improved their baseline visual acuity.

Damico et al. (2021) [71] evaluated 17 patients with tumours in paranasal sinuses, nasal cavity, or nasopharynx within 2 cm of the eye and optic apparatus that were treated with passive scatter PT and had comparative VMAT plans available. Median follow-up was 19.7 months. 14 patients received globe-sparing surgery and post operative RT, 3 received definitive RT. PT significantly reduced mean doses to the optic nerves and chiasm, pituitary gland, lacrimal glands and cochlea. Only 1 patient experienced grade 3 late toxicity (hearing impairment). The 18-month cumulative incidence of local failure was 19.1% and 1-year OS was 80.9%.

Additional studies are warranted for this entity to evaluate optimal patient setup, IMPT planning specifications, and dose tolerance limits of OARs.

Salivary Gland Cancer

Malignancies of the salivary glands are rare with incidences varying between 0.05 and 2 per 100.000 [72]. Tumours are mostly adenocarcinomas of the parotid which is the largest salivary gland. The etiology of salivary gland cancer is largely unknown. The primary treatment is surgery followed by postoperative RT for adverse features. Unilateral RT benefits from IMPT versus IMRT due to the absence of the exit dose (Fig. 8.9).

Bhattasali et al. [73] reported on nine patients with unresectable node-negative head and neck adenoid cystic carcinoma (ACC) who received definitive IMPT and concurrent cisplatin. The prescription dose was 70 Gy (RBE) in 33 fractions. Median follow-up was 27 months (range 9.2–48.3 months). 4 patients had complete response
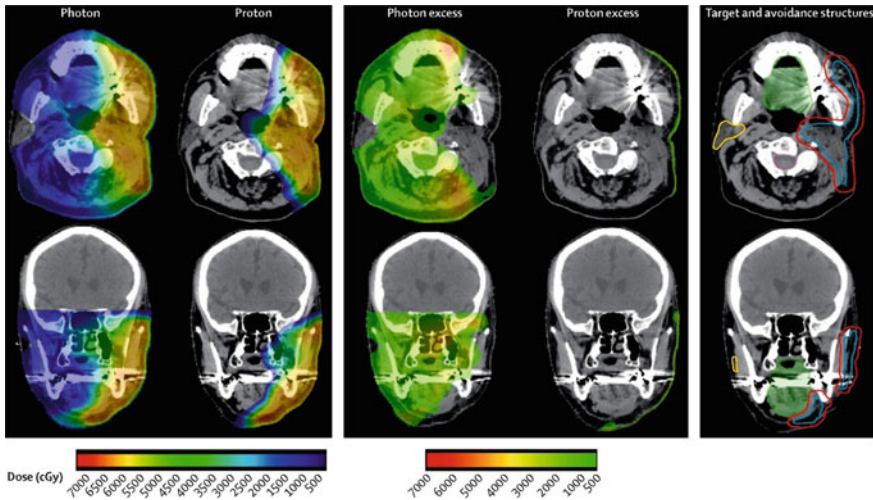
Fig. 8.9 Postoperative RT plans for treatment of a salivary duct carcinoma of the left accessory parotid gland comparing photons and protons. Prescriped dose is 66 Gy (RBE). Dose distributions of photon and proton treatment plans (left), plan differences with excess doses (middle) and contours of target volume and OARs (right) are shown. Color scales are in cGy (RBE) and minimum dose shown is 500 cGy. PT achieves better sparing of midline and contralateral OARs and an increased skin dose can be observed. Colors of contours: Green = oral cavity. Yellow outline = parotid gland. Magenta outline = spinal cord. Blue outline = clinical target volume. Red outline = planning target volume [76]. OARs: Organs-at-risk; RBE: Relative biological effectiveness; PT: Proton therapy; RT: Radiation therapy

(CR), 4 patients partial response (PR) and 1 patient showed progression. 5 patients experienced grade 3 toxicities and one patient grade 4 optic nerve disorder.

In a study by Romesser et al. [74], 41 patients with either major salivary gland cancer or cutaneous SCC were either treated with IMRT (n = 18, 43.9%) or passively scattered PT (n = 23, 56.1%). Gross disease was treated with normofractionated 70 Gy (RBE), close or microscopically positive margin with 66 Gy (RBE), high-risk volumes such as the tumour bed with 60 Gy (RBE). A reduction of grade 2 or greater acute dysgeusia (5.6 vs. 65.2%, p < 0.001), mucositis (16.7 vs. 52.2%, p = 0.019), and nausea (11.1 vs. 56.5%, p = 0.003) in favour of PT was observed.

Zakeri et al. [75] treated 68 patients with major salivary gland tumours with IMPT. Patients with positive margins received 66 to 70 Gy (RBE) and close margins/clear margins with 60 to 66 Gy (RBE) to the postoperative bed. Oncological outcomes were excellent with 3-year rates of LC, progression-free survival (PFS), and OS of 95.1% (95%CI = [89.9%,100.0%]), 80.7% (95%CI = [70.2%,92.7%]), and 96.1% (95%CI = [90.9%,100.0%]). Acute grade 3 dermatitis was observed in 9 (13.2%) patients. One patient developed late grade 3 osteoradionecrosis of the mandible.

Oropharyngeal Cancers

In the study by Tambas et al. [39], evaluating the model-based approach, 65% of OPC patients were predicted to benefit from IMPT. OPC with association of human papillomavirus (HPV) have a rapid increase in incidence. Since this patient cohort has a particularly good prognosis, improvements of late toxicities is one of the most important considerations. Current RCTs use de-escalation protocols for total radiation doses, target volumes, and combinations with systemic treatments to reduce morbidities with the aim to not sacrify oncologic outcomes. PT can provide other measures for a substantial reduction of radiation injury. There is a growing body of studies demonstrating that PT offer unique chances for dose reductions in virtually all organs (Fig. 8.10) and tissues at risk, thereby decreasing acute toxicity and long-term morbidity without compromising the radiation dose to target volumes and oncologic outcome (Table 8.1).

A case-matched analysis by Blanchard et al. [77] evaluated patients with IMPT (n = 50) and IMRT (n = 1000). 20% of patients received unilateral irradiation. It
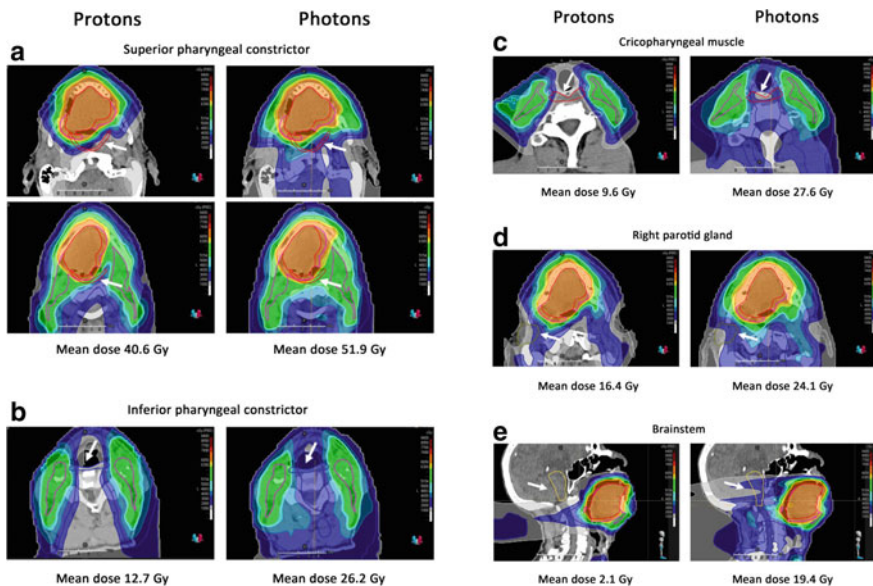
Fig. 8.10 Comparison of proton and photon treatment plans of a patient with cT4N0M0 OPC. Patient is 47 years old and receives chemoradiotherapy with 70 Gy (RBE) for HPV-positive OPC involving the base of the tongue, tongue and floor of the mouth. (A) Mean dose to the superior pharyngeal constrictor is 40.6 Gy for protons vs 51.9 Gy for photons; (B) Mean dose to the inferior pharyngeal constrictor is 12.7 Gy for protons versus 26.2 Gy for photons; (C) Mean dose to the cricopharyngeal muscle is 9.6 Gy for protons vs 27.6 Gy for photons; (D) Mean dose to the right parotid gland is 16.4 Gy for protons vs 24.1 Gy for photons; (E) Mean dose to the brainstem is 2.1 Gy for protons vs 19.4 Gy for photons [87]. HPV: Human papillomavirus; OPC: Oropharyngeal cancer; RBE: Relative biological effectiveness

Table 8.1 Selection of proton studies for oropharyngeal cancer. Modified from Blanchard et al. [12]

References	Study type	Site/Stage (percentage)/edition	Technique (dose)	Comparison with IMRT	CCT	Patients (n)	Follow-up (median)	Outcomes	Toxicity
Slater et al. [84]	Retro	OPC/ II (10.3%) III (27.6%) IV (62.1%)/ AJCC 4th	Cobalt (50.4 Gy) + PSPT boost (25.5 Gy RBE)	No	No	29	28 mo	5 y: LRC 88%, DFS 65%	2 y actuarial incidence of grade ≥3 16%
Gunn et al. [85] Blanchard et al. [77] Sio et al. [81]	Pro	OPC/ I (2%) III (18%) IVA (74%) IVB (6%)/ N/A	IMPT (70 Gy RBE)	Yes	Yes	50	30 mo	3 y: LRC 91%, OS 94.3%	Reduced use of gastrotomy tube or severe weight loss at 3 mo and 1 y; less subacute impairment of quality of life
Takayama et al. [86]	Pro	OC/ III (24%) IVA (73%) IVB (3%)/ UICC 7th	Photon (36 Gy) + PSPT boost (28.6–39.6 Gy RB), no surgery	No	Yes	33	43 mo	3 y: LC 86.6%, RC 83.9%, OS 87%	No grade ≥3 osteonecrosis
Manzar et al. [78]	Pro	OPC/ N/A (1.3%) I (1%) II (2.3%) III (7.5%) IVA (80.3%) IVB (5.6%) IVC (2.0%)/ AJCC 7th	VMAT/IMPT (70 Gy RBE definitive, 60–66 Gy RBE adjuvant)	Yes	Yes	305	12 mo (IMPT) and 30 mo (VMAT)	1 y: OS 92.6%	IMPT had lower feeding tube placement, less hospitalization during 60 days post-RT and less narcotic use

(continued)

Table 8.1 (continued)

References	Study type	Site/Stage (percentage)/edition	Technique (dose)	Comparison with IMRT	CCT	Patients (n)	Follow-up (median)	Outcomes	Toxicity
Bagley et al. [79]	Retro	OPC/ III (20%)/ IV (80%)/ AJCC 7th	IMPT (median 69.3 Gy RBE)	No	Yes	69	N/A	N/A	Significant improvement of xerostomia-related PROs at 10 wks post-RT

AJCC: American Joint Committee on Cancer; CCT: concomitant chemotherapy; IMPT: Intensity-modulated proton therapy; IMRT: Intensity-modulated radiation therapy; LC: Local control; LRC: Locoregional control; mo: Month; N/A: Not available; OC: Oral cancer; OPC: Oropharyngeal carcinoma; OS: Overall survival; Pro: Prospective study; PSPT: Passive scattered proton therapy; RBE: Relative biological effectiveness; RC: Regional control; Retro: Retrospective study; UICC: Union for International Cancer Control; wks: weeks; y: Year

could be demonstrated that IMPT significantly decreased the necessity for feeding tube placement during treatment (odds ratio (OR) = 0.53; p = 0.011) and resulted in a significant reduction of the composite endpoint of grade 3 weight loss or feeding tube placement at 3 months (OR = 0.44) and 1 year (OR = 0.23; p < 0.05). There was no difference in OS or PFS between the study arms.

Several studies have evaluated PROs and could demonstrate the benefits of PT, including significant reductions in mucositis, xerostomia, dysgeusia, nutrition, dental problems, fatigue, and physical function [78–81].

The largest PROs study to date is a comparative analysis by Manzar et al. [78] reporting PATs and PROs of patients receiving IMPT (n = 46) or VMAT (n = 259) with either 70 Gy (RBE) definitively or 60–66 Gy (RBE) postoperatively. In the cohort receiving unilateral RT (n = 44), significant improvements for IMPT could be identified in PROs including dry mouth, sticky saliva, and taste (p < 0.05). Improvements in PATs could be observed for IMPT in regards to mucositis, pain, weight loss, and fatigue, while VMAT induced less mucosal infection and dermatitis. IMPT was associated with a relative risk reduction of 22.3% for narcotic use at the end of treatment. Feeding tube dependency within 30 days of RT was significantly lower among patients treated with IMPT (19.6% versus 46.3%, OR = 0.27, 95%CI = [0.12,0.59], p = 0.001). Additionally, a significantly lower rate of acute hospitalization was observed in the IMPT-arm (OR = 0.21, 95%CI = [0.07,0.6], p = 0.009). No difference in the 1-year OS could be detected between the study-arms (VMAT 91.3% vs IMPT 92.6%, p = 0.98).

A study by Bagley et al. (2020) [79] evaluated patients (n = 69) treated for OPC with IMPT in regards to PROs for xerostomia using the Xerostomia-Related QoL Scale (XeQoLS). Greatest xerostomia-related impairment was recorded at 6 weeks on treatment, followed by a 49% improvement 10 weeks after RT. PROs improved subsequently but remained above baselines after 2 years. Late xerostomia PRO scores were correlated with the mean oral cavity dose (p = 0.038), baseline score (p = 0.001), stage (p = 0.008) and N status (p = 0.006).

The current evidence in support of PT, particularly the benefits as assessed by PROs, warrants further investigation via RCTs: The "Randomized Trial of IMPT versus IMRT for the Treatment of Oropharyngeal Cancer of the Head and Neck" (NCT01893307) is a non-inferiority phase II/III RCT comparing IMPT with IMRT for OPC [82]. The primary endpoint is PFS at 3 years, with secondary endpoints of PATs and PROs. The "TOxicity Reduction using Proton bEam therapy for Oropharyngeal cancer (TORPEdO)" trial is a multicenter, phase III RCT of IMRT versus IMPT for OPC [83]. The primary endpoints are PROs as physical toxicity composite score, and feeding tube dependency or severe weight loss at 12 months after treatment.

Nasopharyngeal Cancers

Nasopharyngeal cancers (NPC) are chemoradiosensitive, and, therefore, RT plays a crucial role in both the definitive and adjuvant settings. This particular region

includes critical neurological structures that can be affected by the high doses of RT which can result in hearing impairment, optic neuropathy, or temporal lobe necrosis [88]. Several studies demonstrated improved target volume coverage and reduced dose to OARs with IMPT vs IMRT and helical tomotherapy [89, 90]. Studies with clinical evidence on oncological outcomes and toxicities after PT are summarized in Table 8.2.

A phase II study by Chan et al. [91] evaluated patients (n = 23) with stage III-IVB NPCs treated with PT. Prescribed dose was 70 Gy (RBE) in 35 fractions. The chemotherapy regimen consisted of 3 cycles of concurrent cisplatin (100 mg/m2) on days 1, 22, and 43 followed by adjuvant cisplatin (80 mg/m2) on day 1 and fluorouracil (1,000 mg/m2/d) on days 1 through 4 every 4 weeks for 3 cycles. Toxicity was graded with CTCAE. At a median follow-up of 28 months, none of the patients had local or regional relapse. 2-year DFS and OS were 90% and 100%. Grade 3 hearing impairment was present in 29% and weight loss in 38% of patients. 48% of patients required feeding tube placement during treatment.

Lewis et al. [92] published a study for a cohort of 10 NPC patients treated with platinum-based concurrent chemoradiation using IMPT (prescribed dose of 70 Gy (RBE) in 33 fractions) and treatment plan comparison with IMRT. Median follow-up of this study was 24.5 months (range, 19–32 months). 2-year LRC and OS were excellent with 100% and 88.9%. Acute grade 3 toxicity dermatitis (n = 4) and acute grade 3 mucositis (n = 1) were reported. No patient experienced late grade 3 or higher toxicities. The dosimetric comparisons revealed significant differences in OAR mean doses in favour for IMPT in 13 out of 29 evaluated OARs.

A 2:1 case-matched analysis with patients (n = 20) receiving IMRT for NPC found a significantly lower rate of feeding tube placement with IMPT (20% vs. 65%; p = 0.02) [93].

Beddok et al. [94] analyzed patients (n = 17) with stages III–IVa NPC, who received a definitive treatment with a combined photon and proton-boost therapy and concurrent chemotherapy. Patients with stage III and IVa were 12% and 88%. The prescribed doses were 70–78 Gy (RBE). Median follow-up was 98 months. After 2-,5- and 10-years LRC was 94%, 86% and 86% and OS 88%, 74%, and 66%. Three patients (17.6%) developed distant metastasis. Late grade 3 toxicities were observed in regards to hearing loss (n = 4, 23.5%) and osteroradionecrosis (n = 1, 5.9%). One patient died from necrosis-induced nasopharynx bleeding.

Take Home Message for Outcomes after Proton Therapy of Head and Neck Cancers

- Skull base tumours: Proton therapy is the standard of care and allowed for dose intensification resulting in improved clinical outcomes and tolerable toxicity profiles.

Table 8.2 Selection of proton studies for nasopharyngeal carcinoma. Modified from Blanchard et al. [12]

References	Study type	NPC stage (percentage)	Technique (dose)	Comparision with IMRT	CCT	Patients (n)	Follow-up (median)	Outcomes	Toxicity
Chan et al. [91]	Pro	III (N/A) IVB (N/A)	PSPT (70 Gy RBE, upper neck only)	No	Yes	23	28 mo	2 y: LRC 100%, DFS 90%, OS 100%	Grade ≥3: Hearing loss 29%
Lewis et al. [92] Holliday et al. [93]	Pro	II (22%) III (56%) IVA (22%)	IMPT (70 Gy RBE)	Yes	Yes	10	24 mo	2y: LRC 100%, OS 88.9%	Less gastrostomy tube in IMPT patients compared to IMRT (p = 0.02)
Beddok et al. [94]	Retro	III (12%) IVA (88%)	PSPT + 3DRT/IMRT (70–78 Gy RBE cummulative)	No	Yes	17	98 mo	2 y: LRC 94%, OS 88%	Grade ≥3: Hearing loss 23.5%, Osteoradionecrosis 5.9%, Nasopharynx bleeding 5.9%

CCT: Concomitant chemotherapy; IMPT: Intensity-modulated proton therapy; IMRT: Intensity-modulated radiation therapy; LRC: Locoregional control; mo: Month; N/A: Not available; NPC: Nasopharyngeal carcinoma; OS: Overall survival; Pro: Prospective study; PSPT: Passive scattered proton therapy; RBE:Relative biological effectiveness; Retro: Retrospective study; y: Year

- Periorbital tumours: Proton therapy is part of orbit-sparing multidisciplinary concepts, and further studies are warranted to find optimal parameters and dose constraints for IMPT.
- Salivaryry gland cancer: Proton therapy delivers excellent oncological outcomes and favourable toxicity profiles for unilateral radiation.
- Oropharyngeal cancers: Competitive dose planning studies showed protons offering unique chances for dose reductions in virtually all organs-at-risk with the possibility of toxicity reduction without dose de-escalation in the target volumes. Toxicity reduction is of particular importance in HPV-positive patients with a good prognosis. Randomized phase III trials comparing IMPT with IMRT are underway.
- Nasopharyngeal cancers: Proton therapy offered dosimetric advantages at critical neurological structures and excellent oncological outcomes.

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