Curr. Treat. Options in Oncol. (2018) 19: 28
DOI 10.1007/s11864-018-0546-9

Proton Therapy for Head and Neck Cancer

Joseph K. Kim, BS
Jonathan E. Leeman, MD
Nadeem Riaz, MD
Sean McBride, MD, MPH
Chiaojung Jillian Tsai, MD, PhD, MS
Nancy Y. Lee, MD[*]

Address
[*]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1250 1st Avenue, New York, NY, 10065, USA
Email: leen2@mskcc.org

Published online: 9 May 2018

This article is part of the Topical Collection on *Head and Neck Cancer*

Keywords Head and neck neoplasms · Proton therapy · Radiotherapy

Opinion statement

The application of proton beam radiation therapy in the treatment of head and neck cancer has grown tremendously in the past few years. Globally, widespread interest in proton beam therapy has led to multiple research efforts regarding its therapeutic value and cost-effectiveness. The current standard of care using modern photon radiation technology has demonstrated excellent treatment outcomes, yet there are some situations where disease control remains suboptimal with the potential for detrimental acute and chronic toxicities. Due to the advantageous physical properties of the proton beam, proton beam therapy may be superior to photon therapy in some patient subsets for both disease control and patient quality of life. As enthusiasm and excitement for proton beam therapy continue to increase, clinical research and widespread adoption will elucidate the true value of proton beam therapy and give a greater understanding of the full risks and benefits of proton therapy in head and neck cancer.

Introduction

Radiation therapy is an integral treatment modality that is commonly used in the multidisciplinary approach to managing head and neck cancer. In early-stage head and neck cancer, definitive treatment with radiation can result in effective disease control [1]. Radiation therapy is also often used in addition to chemotherapy with the

benefit of organ preservation or as an adjuvant therapy following surgery to help improve overall survival (OS) and locoregional control (LRC) in advanced-stage disease. While the goal of curative intent remains a priority, optimizing the quality of life and minimizing toxicity for each patient remains a challenge due to the potential for significant detrimental effects on functionality (salivation, swallowing, hearing, etc.) and the burden of adverse symptoms following radiation. Over the past few decades, the development of intensity-modulated radiotherapy (IMRT) has had a tremendous impact on the field with innovations in conformity, reductions in toxicity, and critical organ sparing [2]. However, due to the limiting physical properties of the photon beam, IMRT often results in inevitable irradiation of normal healthy tissue at significant doses. The unnecessary irradiation of these normal and critical structures can lead to debilitating acute and chronic toxicity. The patient population of head and neck cancer continues to evolve with a growing proportion of younger patients with HPV-associated oropharyngeal cancer [3]. While there has been treatment success with high rates of disease control with traditional external beam therapy, minimizing treatment-related acute and late complications while improving posttreatment quality of life has become an extremely important goal in managing head and neck cancer [4].

Proton beam therapy (PBT) is a radiotherapy approach that has demonstrated promising results in disease control and treatment outcomes while allowing for a high quality of life in head and neck cancer patients. While proton therapy has been used clinically in the treatment of cancer for decades, its utilization has been limited due to its costly expenses and limited availability. Technological innovations and advances in treatment machines have allowed for increased adoption and affordability of proton therapy [5]. However, interest and excitement regarding proton beam therapy continue to grow with expansion in research and development of proton beam treatment facilities across the world. This chapter aims to summarize the significant trends of proton use and the most recent literature on clinical treatment outcomes, toxicity, optimal patient selection, and limitations of proton radiation therapy for head and neck cancer.

Physics and rationale

Proton therapy is a form of external beam radiation therapy (EBRT) that uses a linear accelerator to generate a concentrated beam of protons directed at a specified target for therapeutic usage. It is the unique physical properties of the proton beam that contributes to its potential for significant therapeutic value. Clinical studies have demonstrated the benefit of proton and the potential advantages and disadvantages when compared to traditional photon therapy (Table 1). At the molecular level, there is a fundamental difference between traditional photon therapy used in IMRT and charged particles such as the proton. In comparison to photons, protons have a heavier mass that leads to a relatively decreased scattering angle and consequently sharper dose distribution with a finite, defined range. Additionally, the majority of the radiation delivered by a monoenergetic proton beam is directed to a concentrated region with sharp distal dose falloff, known as the "Bragg peak." By localizing the Bragg peak to the designated tumor volume, a high dose of radiation is delivered to the tumor with minimal to no exit dose reaching normal, healthy tissue. However, in the clinical context, complex tumor volumes require different energy beams that are combined to form a spread out Bragg peak (SOBP) to cover the tumor volume. The consequence of forming the SOBP is the potential for significant entrance dose and radiation to the skin. However, the minimal to no exit dose is the main dosimetric advantage of proton beam therapy, which allows for high conformality and minimal radiation to normal tissue or critical structures

Table 1. Comparing survival and toxicity outcomes in photon versus proton therapy for head and neck cancer

Study	Methodology	*N*	Disease site	Median RT dose	Outcomes	Toxicity
Romesser et al. (2016) [6•]	Retrospective cohort	18 PBT 23 IMRT	Unilateral head and neck salivary glands: 35 parotid 6 submandibular	PBT 66.0 Gy (RBE) IMRT: 66.0 Gy	1-year LRC: 80.0% PBT vs. 95.5% IMRT, $p = 0.473$ 1-year DMFS: 83.3% PBT vs. 93.3% IMRT, $p = 0.662$ 1-year OS: 83.3% PBT vs. 93.3% IMRT, $p = 0.083$	Grade ≥ 2 acute mucositis: 16.7% PBT vs. 52.2% IMRT, $p = 0.019$[a] Grade ≥ 2 nausea: 11.1% PBT vs. 56.5%, $p = 0.003$[a] Grade ≥ 2 dysgeusia: 4.6% PBT vs. 65.2% IMRT, $p < 0.001$[a] Grade ≥ 2 acute dermatitis: 100.0% PBT vs. 73.9% IMRT, $p = 0.019$[a]
McDonald et al. (2016) [7]	Retrospective cohort	14 PBT 12 IMRT 14 PBT to primary and IMRT to neck	17 nasopharynx, 23 nasal cavity/paranasal sinus	PBT: 71.4 Gy (RBE) IMRT: 71.8 Gy	–	G-tube dependent at RT completion: PBT vs. IMRT OR 0.03 (< 0.01–0.15), $p < 0.001$[a] G-tube dependent 1 month after RT: PBT vs. IMRT OR 0.11 (< 0.01–0.61), $p = 0.028$[a] Equivalent morphine dose > baseline at RT completion: PBT vs. IMRT OR 0.09 (0.01–0.57), $p = 0.006$[a]
Patel et al. (2014) [8]	Systematic review/meta-analysis	41 studies: 286 charged particles (helium, proton, carbon, or mixed ions) 1186 photons	Nasal cavity/paranasal sinus	–	PBT vs. photon therapy 5-year disease-free survival: RR 1.44 (1.01–2.05), $p = 0.045$[a] LRC at longest follow-up: RR 1.26	Neurological toxicity: Charged particle therapy 0.20 (0.13–0.31) vs. photon therapy 0.04 (0.02–0.08), $p = 0.0002$[a]

Table 1. (Continued)

Study	Methodology	*N*	Disease site	Median RT dose	Outcomes	Toxicity
					(1.05–1.51), $p = 0.011$[a]	
Holliday et al. (2015) [9]	Retrospective case-matched control	10 IMPT 20 IMRT	Nasopharynx	IMPT: 70 Gy (RBE) IMRT: 70 Gy	At last follow-up: Local failure: IMPT: 0 IMRT: 1 Distant metastasis: IMPT: 1 IMRT: 1	Feeding tube during or after treatment: IMPT 20% vs. IMRT 65%, $p = 0.02$ Grade 3 (G3) acute toxicities: IMPT (5 patients, 9 G3 toxicities) vs. IMRT (18 patients, 30 G3 toxicities), $p = 0.015$[a]
Zhang et al. (2017) [10]	Retrospective cohort	50 IMPT 534 IMRT	Oropharynx	Mandibular dose: minimum, mean, and median mandibular all significantly lower in IMPT group. No difference in maximum mandibular dose between IMPT and IMRT.	–	Mandibular osteoradionecrosis: IMPT 2% (1 grade 1) vs. IMRT 7.7% (12 grade 4, 5; grade 3, 1; grade 2, 23 grade 1) Mean, minimum, and maximum mandibular dose significantly associated with mandibular osteoradionecrosis[a]
Sio et al. (2016) [11]	Retrospective cohort	35 IMPT 46 IMRT	Oropharynx	IMPT: 70.0 Gy IMRT: 70.0 Gy	–	Top 11 MD Anderson symptoms (IMPT vs. IMRT) Subacute food taste: 5.76 vs 7.70, $p = 0.01$ Subacute appetite: 4.68 vs. 6.37, $p = 0.048$ Chronic appetite: 2.12 vs. 4.14, $p = 0.036$ Severe subacute mucus: 16 vs 36, $p = 0.038$
Blanchard et al.	Retrospective case-matched control	50 IMPT 100 IMRT	Oropharynx	–	3-year LRC rate: IMPT 91.0% vs.	3-month post RT (IMPT vs. IMRT):

Table 1. (Continued)

Study	Methodology	*N*	Disease site	Median RT dose	Outcomes	Toxicity
(2016) [12]					IMRT 89.7%, p = 0.96 (5 IMPT local failures, 10 IMRT local failures) 3-year distant control rate: IMPT 97.8% vs IMRT 93.5%, p = 0.30 (1 IMPT distant failure, 7 IMRT distant failure)	Patient-rated xerostomia grade 2–3: OR 0.38 (0.18–0.79), p = 0.009 1-year post RT (IMPT vs IMRT): G-tube or weight loss > 20%: OR 0.23 (0.07–0.73), p = 0.01

[a]Indicates statistical significance

(Fig. 1). The potential for optimal tumor volume conformality has brought attention to the application of proton therapy in various clinical settings.

Treatment planning

In treatment planning with proton beam therapy, it is important to take advantage of the physical properties of the proton beam (Bragg peak) and the lack of exit dose. The challenge for the planning team and the radiation physician is to choose the shortest and most reliable path for the beams to reach the target. While protons are advantageous over photons in terms of dose homogeneity, proton penetration may encounter worse tissue inhomogeneity issues. Artifacts, such as dental or surgical hardware, can lead to uncertainty in the localization of the Bragg peak and consequently suboptimal treatment delivery with potential for irradiation of normal tissue [5]. Therefore, it is important to avoid choosing a beam path through areas such as the mouth (dental artifacts), hollow organs, and critical structures (e.g., spinal cord, salivary glands). Treatment plans can be further complicated by fluctuations in a patient's anatomy, such as changes in tumor size, patient weight, and daily patient position. Intensive quality assurance as well as reimaging during the treatment is essential to account for all of these technical uncertainties and ensure the integrity of the treatment [13]. Techniques and plans to minimize skin toxicity should also be addressed, such as using three-dimensional conformal passive scattering.

In the head and neck, the complex anatomic geometry and irregularity in target shapes often require more complex proton techniques rather than treatment with uniform or double scattering to successfully treat large tumor volumes [14]. Intensity-modulated proton therapy (IMPT) is an advanced proton technology that can result in treatment plans with remarkable conformality with fewer radiation beams and sparing of normal tissue irradiation via the use of *pencil beam scanning*. Pencil beam scanning uses two pairs of scanning magnets that guide monoenergetic proton beams laterally to a specified spot and intensity that precisely paint the target volume. This technique allows for modulation in both the lateral direction and depth due to variations in proton energies. Individual proton beams that each uniformly cover the entire target

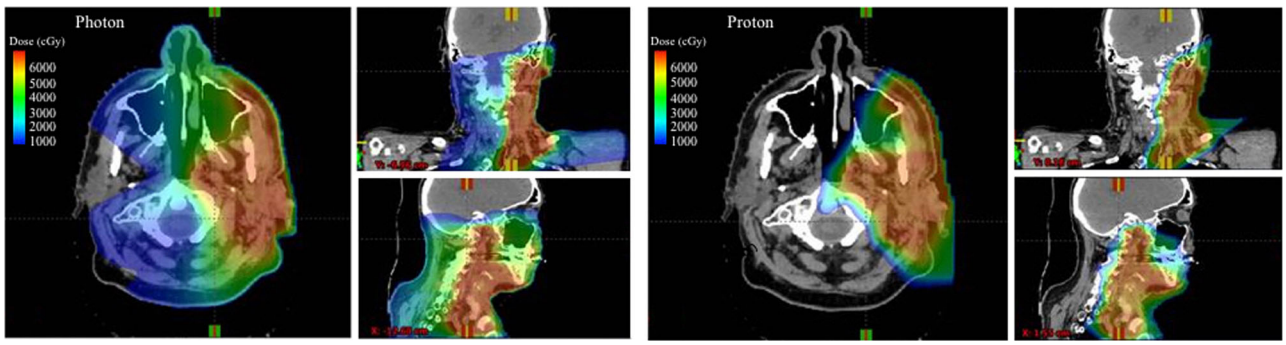

Fig. 1. Comparing photon (IMRT) vs. proton treatment plans for salivary duct carcinoma of the left parotid gland. Photon and proton treatment plans are shown for a salivary duct carcinoma of the left parotid gland. The proton treatment plan demonstrates better sparing of contralateral organs and critical structures in comparison to the photon treatment plan.

volume (single-field optimization) or collectively cover the target volume as a sum (multi-field optimization) can be utilized in planning with IMPT. While multi-field optimization allows for intensity modulation and a high degree of conformality, the uncertainties in proton range and delivery are typically greater in comparison to single-field optimization plans.

Oropharyngeal cancer

In addition to chemotherapy and surgery, radiation is an integral part of the management of oropharyngeal cancer (OPC) in both the definitive and adjuvant settings. Traditionally, IMRT has been a successful treatment option for oropharyngeal carcinoma with reduced toxicities (such as xerostomia). However, with an increasing proportion of young, HPV-positive patients, treatment-related toxicities must be further reduced to ensure optimal quality of life. Due to the nature of the photon, IMRT often results in unnecessary radiation of healthy tissue while proton therapy offers the benefit of sparing irradiation of contralateral oropharyngeal and nasopharyngeal tissue. Proton therapy can be used to reduce the incidental radiation delivered outside of the target volume especially after transoral robotic surgery. In addition to integrating transoral robotic surgery, advancements in de-escalation of radiation dose or volume and alternative systemic chemotherapy agents are being made to optimize the treatment of HPV-positive oropharyngeal cancer patients. The use of proton therapy shows a promising outlook for reducing treatment-related adverse effects and improving long-term quality of life.

Considering the anatomic relationship of the oropharynx to the oral cavity and salivary glands, proton therapy may provide a dosimetric advantage in comparison to photon therapy that virtually eliminates irradiation to critical structures. In a prospective study of 29 patients with locally advanced oropharyngeal carcinoma, Slater et al. reported only three patients with late grade 3 toxicity (11%) and increased locoregional control (5-year LR control, 84%) following treatment with accelerated fractionation using photon therapy and concomitant proton boost [15]. A case-matched analysis by Blanchard and colleagues demonstrated a significant decrease in gastronomy tube dependence (OR 0.53; 95% CI 0.24–1.15) during treatment and grade 3 weight loss (3-month follow-up OR 0.44; 95% CI 0.19–1.0) in patients receiving IMPT for oropharyngeal cancer in comparison to those who received IMRT with no statistical difference in outcomes [12]. Another dosimetric case-matched study of 25 patients treated with IMPT for OPC demonstrated significantly lower mean doses of radiation delivered to the anterior and posterior oral cavity, hard palate, esophagus, and mandible in comparison to IMRT plans for the same group [16]. Further assessments are required to characterize any differences in long-term disease control and toxicity.

Due to the complexity and large volumes often seen in oropharyngeal cancers, IMPT is recommended to enhance homogeneous tumor coverage and contralateral treatment with minimal radiation to adjacent critical structures. In some tumors, such as HPV-positive, node-positive OPC, there is an early response to radiation with subsequent changes in anatomy and volume that may necessitate replanning during the course of treatment. Therefore, after considering the sensitivity of proton beam therapy to anatomic variations,

some clinicians may limit the use of proton beam radiation to the adjuvant setting.

Sinonasal cancer

The application of proton beam radiation in sinonasal cancer is another promising field of research and treatment. While radiation is often used in the postoperative setting with acceptable treatment outcomes, surgery can lead to significant disfiguration in facial anatomy and potential injury to neurovascular structures due to the location of these tumors [42]. In patients with unresectable tumors, treatment with definitive radiation with or without chemotherapy results in discouraging outcomes due to the limiting dose constraints of the surrounding critical structures, such as the optic pathways and brainstem [17]. Several studies have demonstrated better tumor coverage with decreased integral radiation dose when using proton beam therapy in comparison to IMRT or 3D-CRT [18–20]. In a study of 84 patients who received hyperfractionated proton therapy (1.2 Gy [RBE] twice daily) for nonmetastatic sinonasal cancer, local control and overall survival rates were 83 and 68%, respectively at 3 years. On multivariate analysis, continuous local control was a significant predictor of overall survival 15].

In a systematic review and meta-analysis of 41 non-comparative observational studies, Patel and colleagues [8] reported on the clinical outcomes of treatment with charged particle therapy (including helium ions, protons, carbon ions, or mixed charged particles) and traditional photon radiation in patients with paranasal sinus and nasal cavity malignant cancer. There was no significant difference between median doses for the charged particle therapy group and the IMRT group of 60 and 61 Gy, respectively. At 5 years and longest duration of follow-up, charged particle therapy was associated with improved overall survival and disease-free survival in comparison to IMRT. In the subset comparing proton beam therapy versus IMRT, locoregional control at longest follow-up and 5-year disease-free survival were significantly improved in the proton therapy group. There was no difference in toxic effects between the treatment groups besides a higher rate of neurological complications in the charged particle therapy group. However, it is important to note that there may have been reporting bias and referral bias with a significantly greater proportion of charged particle studies that reported treatment-related toxicities and more challenging patients referred for charged particle therapy [8]. Still, this study demonstrates that there are possible benefits and potential for better clinical outcomes by using proton therapy in sinonasal cancer. This study provides high-level evidence that the use of proton therapy in some head and neck cancers is associated with an improvement in survival.

Nasopharyngeal cancer

Radiation with or without chemotherapy is the treatment of choice for nasopharyngeal carcinoma (NPC). However, the complex anatomy of the nasopharynx with close proximity to critical structures, including the pharyngeal constrictor muscles, salivary glands, and brainstem, presents several challenges for the radiation oncologist. IMRT allows for adequate tumor coverage with

good prognosis and decreased radiation delivered to normal critical structures, such as the parotid gland, which leads to reductions in toxicity (xerostomia) and improvements in quality of life [21, 22]. Although IMRT can reduce the dose delivered to specified structures, the nature of IMRT implies an increased dose delivered to nontarget structures along the beam path [23]. Furthermore, some subsets of NPC, such as EBV-negative or previously irradiated, locally recurrent disease, are particularly challenging and difficult to achieve exceptional outcomes with IMRT. Given the dosimetric and physical advantages of using protons, proton beam radiation therapy may be a promising treatment option in some cases of NPC.

In a phase 2 trial of 23 patients treated with combined photon/proton radiation therapy and chemotherapy for stage III/IVB NPC, Chan and colleagues reported 2-year disease-free survival, local control, and overall survival rates of 90, 100, and 100%, respectively. The most common grade ≥ 3 toxicities were hearing loss (29%) and weight loss (38%), and no patients developed grade 3 xerostomia. Additionally, 48% received a gastrostomy tube during the treatment [24]. In a dosimetric comparison of IMPT versus IMRT treatment plans for 29 organs at risk (OAR), Lewis and colleagues reported significant reductions in the mean dose for 13 OAR for proton-based plans [25]. In another study by Chan and colleagues, 17 patients with T4 NPC were treated with proton beam therapy. Local control, progression-free survival (PFS), and overall survival rates were 92, 75, and 74%, respectively. Late toxicities were reported: five patients with radiographical evidence of temporal lobe changes, one patient with mandibular osteonecrosis, and one patient with endocrine dysfunction [26].

Proton beam therapy offers an alternative radiotherapy approach for treating NPC with excellent treatment outcomes and possible reduction in overall toxicity. Future prospective clinical studies are needed to evaluate for neurological toxicity and treatment outcomes in patients with recurrent and T4 disease, locally advanced disease.

Re-irradiation for recurrent head and neck cancer

Several patients who were definitively treated for head and neck cancer will develop recurrence of disease that may require treatment with high-dose re-irradiation in order to achieve effective disease control. Chemotherapy alone may only have a 7- to 10-month median survival benefit, and many patients are not candidates for salvage surgery [27–29]. However, this presents a challenge for the treatment team due to the prior effects following radiation exposure to both the tumor site and the normal tissues.

In a cohort of 206 patients, traditional IMRT re-irradiation for recurrent head and neck disease resulted in suboptimal locoregional control and survival rates at 2 years of 59 and 51%, respectively, with significant grade 3+ toxicity (32% at 2 years, 48% at 5 years) [30]. In comparison, Phan and colleagues reported on a study of 60 patients who received proton beam irradiation for recurrent head and neck cancer (15 passive scattering proton therapy, 35 IMPT). Locoregional failure-free survival, distant metastasis-free survival (DMFS), progression-free survival, and overall survival rates at 1 year were 68.4, 74.9, 60.1, and 83.8%, respectively. Acute grade 3 toxicity was reported in 18 patients (30%), and

feeding tubes were placed in 13 patients (22%) following proton radiation therapy [27]. In a multi-institutional study on proton beam re-irradiation for recurrent head and neck cancer, the 1-year locoregional failure rate was 25.1%, and actuarial distant metastasis-free survival and overall survival rates at 1 year were 84.0 and 65.2%, respectively. The median dose of proton beam radiation therapy received was 60.6 Gy (RBE). Acute grade 3 toxicities included six patients with dysphagia (9.1%), nine patients with mucositis (9.9%), six patients with esophagitis (9.1%), and three patients with dermatitis (3.3%). In comparison to late toxic effects following photon re-irradiation, there were relatively low rates of late toxicity with six cases of grade 3 or four skin complications (8.7%), four cases of grade 3 dysphagia (7.1%), and two cases of grade 5 bleeding (2.9%) [31•].

Although retreating recurrent head and neck disease remains a challenging task, proton beam therapy seems to have a relatively safe toxicity profile in comparison to traditional photon re-irradiation [31•]. Still, the acute and late complications following re-irradiation for recurrent disease remain high with complex adverse effects, such as radiation-induced cutaneous fistula formation, which requires a multidisciplinary approach involving reconstructive surgery. Re-irradiation for recurrent head and neck cancer usually only involves the gross tumor volume without including elective nodal disease or subclinical volumes in order to reduce toxicity. Larger retreatment volumes have also been strongly associated with treatment toxicity and death [27, 32]. While proton beam therapy has demonstrated encouraging toxicity profiles and treatment outcomes, treatment planning in the recurrent setting is highly individualized for each patient due to the heterogeneity in clinical presentation. Since most of the known benefit of proton therapy is based upon the dosimetric advantages and physical properties of the proton, prospective studies are needed in order to further assess for adequate disease control, survival outcomes, long-term toxicity, and costs of proton beam therapy in comparison to traditional radiation treatment modalities.

Limitations of proton beam therapy

The current literature on proton beam therapy is largely confined to comparative dosimetric analyses and retrospective studies at single institutions. Proton beam therapy has a dosimetric advantage compared to photons, which may reduce any unnecessary radiation dose to normal tissues, but organs within the target range will receive the entire dose of proton radiation, and potential toxicities to these structures must be evaluated in order to determine any true clinical advantages of using proton therapy [33, 34]. Some studies have reported possible increased risk for worse toxicities in subsets of patients who received proton beam therapy, such as skin toxicity, temporal lobe necrosis, and neurological complications [6•, 7•, 8]. Further investigations that compare the clinical effectiveness and benefits of proton beam therapy to those of IMRT are necessary, especially in regard to long-term toxicity, patient-reported outcomes, and quality of life. Prospective, randomized controlled studies are also essential to fully understand the risks and benefits of proton beam therapy compared to the current standard of care.

In terms of treatment planning, proton beam therapy is especially sensitive to fluctuations in patient positioning and anatomical changes [35, 36]. Technological advances and excellent quality assurance are required to ensure a safe and effective delivery of treatment for each patient and to minimize any uncertainties.

Future directions

Our current understanding of proton radiation therapy use for head and neck cancer seems to be promising. As the interest in proton beam therapy grows, further clinical research and technological advancements will give more insight into the true value of proton radiation therapy as a therapeutic option in the treatment of head and neck cancer. Furthermore, improvements in proton delivery and automating proton plan adaptation will help establish robust treatment plans and quality assurance system to precisely deliver the radiation dose to the desired target volumes [37•]. Improvements in treatment delivery may also potentially translate to improved clinical outcomes and reduced toxicity-related costs. Efforts to define the optimal patient population will help clarify which patients would most benefit from the application of proton beam therapy.

Large prospective, randomized clinical trials will give a direct comparison of proton therapy to modern photon therapy and clarify the risks and benefits of treatment. These studies will elucidate the appropriate patient subsets; assess the impact of proton therapy on patient safety, quality of life, and efficacy; and evaluate the cost-effectiveness of proton beam therapy in comparison to photon therapy [38]. As proton beam therapy becomes more widespread, additional research should also be aimed at the interaction between proton beam therapy and other treatment modalities, such as immunotherapy [39]. Future research on the relationship between proton radiotherapy and immunotherapy can clarify the effects of proton radiation therapy on antitumor immune response and immunogenic cell death. Furthermore, it is important for future direction to focus on the long-term sequelae of proton radiation therapy, such as risk for secondary malignancy following radiation. In an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, Chung and colleagues reported no significant difference in risk for the development of secondary malignancies between proton or photon therapy [40]. Further research regarding the long-term follow-up after proton beam therapy specifically for head and neck cancer is necessary to develop a more comprehensive understanding of the long-term effects of proton radiation therapy. The risk of radiation-induced secondary malignancies is of particular interest due to the differences in proton and photon therapy dose distributions to normal, healthy tissue, which may translate to different long-term consequences. Additionally, a better understanding of the radiobiology and molecular interactions of the proton in various tissues will help optimize target volumes and treatment plans. Proton beam therapy has demonstrated superior dose distribution and reduced radiation doses to organs at risk and nontarget tissues, but additional investigations regarding the optimal dose and fields should be performed to improve therapeutic

approaches with proton beam therapy [34, 41].

According to existing clinical evidence, proton beam therapy has an encouraging future in the treatment of head and neck cancer. The specific role of proton beam therapy will be elucidated as more widespread adoption grows, and the scope of clinical research expands. The overall affordability and effectiveness of proton treatment will also improve as interests in clinical application evolve. It is our responsibility as healthcare providers and medical experts to ensure a high level of integrity in our research and to thoroughly investigate all aspects of proton beam therapy as a therapeutic tool. As clinicians and healthcare providers continue to strive to optimize the standard of care in treating head and neck cancer, proton beam therapy has a reassuring potential to provide excellent treatment outcomes and improve the quality of life for an ever-changing patient population.

Compliance with Ethical Standards

Conflict of Interest

Joseph K. Kim, Jonathan E. Leeman, Nadeem Riaz, Sean McBride, Chiaojung Jillian Tsai, and Nancy Y. Lee declare they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance

1. Thariat J, Bruchon Y, Bonnetain F, Barillot I, Truc G, Peignaux K, et al. Conservative treatment of early glottic carcinomas with exclusive radiotherapy. Cancer Radiother. 2004;8(5):288–96. https://doi.org/10.1016/j.canrad.2004.08.003.
2. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349(22):2091–8. https://doi.org/10.1056/NEJMoa031317.
3. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24–35. https://doi.org/10.1056/NEJMoa0912217.
4. De Felice F, de Vincentiis M, Luzzi V, Magliulo G, Tombolini M, Ruoppolo G, et al. Late radiation-associated dysphagia in head and neck cancer patients: evidence, research and management. Oral Oncol. 2018;77:125–30. https://doi.org/10.1016/j.oraloncology.2017.12.021.
5. Leeman JE, Romesser PB, Zhou Y, McBride S, Riaz N, Sherman E, et al. Proton therapy for head and neck cancer: expanding the therapeutic window. Lancet Oncol. 2017;18(5):e254–e65. https://doi.org/10.1016/S1470-2045(17)30179-1.
6.• Romesser PB, Cahlon O, Scher E, Zhou Y, Berry SL, Rybkin A, et al. Proton beam radiation therapy results in significantly reduced toxicity compared with intensity-modulated radiation therapy for head and neck tumors that require ipsilateral radiation. Radiother Oncol. 2016;118(2):286–92. https://doi.org/10.1016/j.radonc.2015.12.008.

Comparative study of IMRT and PBRT treatment for head and neck cancer. Proton beam radiation demonstrated dosimetric advantages and reductions in acute treatment-related toxicity in comparison to IMRT.

7. McDonald MW, Liu Y, Moore MG, Johnstone PA. Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. Radiat Oncol.

2016;11:32. https://doi.org/10.1186/s13014-016-0600-3.
8. Patel SH, Wang Z, Wong WW, Murad MH, Buckey CR, Mohammed K, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. Lancet Oncol. 2014;15(9):1027–38. https://doi.org/10.1016/S1470-2045(14)70268-2.
9. Holliday EB, Garden AS, Rosenthal DI, Fuller CD, Morrison WH, Gunn GB, et al. Proton therapy reduces treatment-related toxicities for patients with nasopharyngeal cancer: a case-match control study of intensity-modulated proton therapy and intensity-modulated photon therapy. Int J Part Ther. 2015;2(1):19–28. https://doi.org/10.14338/ijpt-15-00011.1.
10. Zhang W, Zhang X, Yang P, Blanchard P, Garden AS, Gunn B, et al. Intensity-modulated proton therapy and osteoradionecrosis in oropharyngeal cancer. Radiother Oncol. 2017;123(3):401–5. https://doi.org/10.1016/j.radonc.2017.05.006.
11. Sio TT, Lin HK, Shi Q, Gunn GB, Cleeland CS, Lee JJ, et al. Intensity modulated proton therapy versus intensity modulated photon radiation therapy for oropharyngeal cancer: first comparative results of patient-reported outcomes. Int J Radiat Oncol Biol Phys. 2016;95(4):1107–14. https://doi.org/10.1016/j.ijrobp.2016.02.044.
12. Blanchard P, Garden AS, Gunn GB, Rosenthal DI, Morrison WH, Hernandez M, et al. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer—a case matched analysis. Radiother Oncol. 2016;120(1):48–55. https://doi.org/10.1016/j.radonc.2016.05.022.
13. Yeh BK, Georges RH, Zhu XR, Palmer MB, Amin MV, Cheung JP, et al. Adaptive replanning is required during intensity modulated proton therapy for head-and-neck cancers. Int J Radiat Oncol Biol Phys. 84(3):S56–S7. https://doi.org/10.1016/j.ijrobp.2012.07.354.
14. Ahn PH, Lukens JN, Teo BK, Kirk M, Lin A. The use of proton therapy in the treatment of head and neck cancers. Cancer J. 2014;20(6):421–6. https://doi.org/10.1097/PPO.0000000000000077.
15. Slater JD, Yonemoto LT, Mantik DW, Bush DA, Preston W, Grove RI, et al. Proton radiation for treatment of cancer of the oropharynx: early experience at Loma Linda University Medical Center using a concomitant boost technique. Int J Radiat Oncol Biol Phys. 2005;62(2):494–500. https://doi.org/10.1016/j.ijrobp.2004.09.064.
16. Holliday EB, Kocak-Uzel E, Feng L, Thaker NG, Blanchard P, Rosenthal DI, et al. Dosimetric advantages of intensity-modulated proton therapy for oropharyngeal cancer compared with intensity-modulated radiation: a case-matched control analysis. Med Dosim. 2016;41(3):189–94. https://doi.org/10.1016/j.meddos.2016.01.002.
17. Snyers A, Janssens GO, Twickler MB, Hermus AR, Takes RP, Kappelle AC, et al. Malignant tumors of the nasal cavity and paranasal sinuses: long-term outcome and morbidity with emphasis on hypothalamic-pituitary deficiency. Int J Radiat Oncol Biol Phys. 2009;73(5):1343–51. https://doi.org/10.1016/j.ijrobp.2008.07.040.
18. Mock U, Georg D, Bogner J, Auberger T, Potter R. Treatment planning comparison of conventional, 3D conformal, and intensity-modulated photon (IMRT) and proton therapy for paranasal sinus carcinoma. Int J Radiat Oncol Biol Phys. 2004;58(1):147–54.
19. Lomax AJ, Goitein M, Adams J. Intensity modulation in radiotherapy: photons versus protons in the paranasal sinus. Radiother Oncol. 2003;66(1):11–8.
20. Hoppe BS, Stegman LD, Zelefsky MJ, Rosenzweig KE, Wolden SL, Patel SG, et al. Treatment of nasal cavity and paranasal sinus cancer with modern radiotherapy techniques in the postoperative setting—the MSKCC experience. Int J Radiat Oncol Biol Phys. 2007;67(3):691–702. https://doi.org/10.1016/j.ijrobp.2006.09.023.
21. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol. 2011;12(2):127–36. https://doi.org/10.1016/S1470-2045(10)70290-4.
22. Kuang WL, Zhou Q, Shen LF. Outcomes and prognostic factors of conformal radiotherapy versus intensity-modulated radiotherapy for nasopharyngeal carcinoma. Clin Transl Oncol. 2012;14(10):783–90. https://doi.org/10.1007/s12094-012-0864-5.
23. Rosenthal DI, Chambers MS, Fuller CD, Rebueno NC, Garcia J, Kies MS, et al. Beam path toxicities to non-target structures during intensity-modulated radiation therapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2008;72(3):747–55. https://doi.org/10.1016/j.ijrobp.2008.01.012.
24. Chan A, Adams JA, Weyman E, Parambi R, Goldsmith T, Holman A, et al. A phase II trial of proton radiation therapy with chemotherapy for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 84(3):S151–S2. https://doi.org/10.1016/j.ijrobp.2012.07.391.
25. Lewis GD, Holliday EB, Kocak-Uzel E, Hernandez M, Garden AS, Rosenthal DI, et al. Intensity-modulated proton therapy for nasopharyngeal carcinoma: decreased radiation dose to normal structures and encouraging clinical outcomes. Head Neck. 2016;38(Suppl 1):E1886–95. https://doi.org/10.1002/hed.24341.
26. Chan AW, Liebsch LJ, Deschler DG, Adams JA, Vrishali LV, McIntyre JF, et al. Proton radiotherapy for T4 nasopharyngeal carcinoma. J Clin Oncol. 2004;22(14_suppl):5574. https://doi.org/10.1200/jco.2004.22.90140.5574.
27. Phan J, Sio TT, Nguyen TP, Takiar V, Gunn GB, Garden AS, et al. Reirradiation of head and neck cancers with proton therapy: outcomes and analyses. Int J Radiat

Oncol Biol Phys. 2016;96(1):30–41. https://doi.org/10.1016/j.ijrobp.2016.03.053.
28. Forastiere AA, Metch B, Schuller DE, Ensley JF, Hutchins LF, Triozzi P, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. J Clin Oncol. 1992;10(8):1245–51. https://doi.org/10.1200/JCO.1992.10.8.1245.
29. Salama JK, Vokes EE, Chmura SJ, Milano MT, Kao J, Stenson KM, et al. Long-term outcome of concurrent chemotherapy and reirradiation for recurrent and second primary head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2006;64(2):382–91. https://doi.org/10.1016/j.ijrobp.2005.07.005.
30. Takiar V, Garden AS, Ma D, Morrison WH, Edson M, Zafereo ME, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: outcomes and analyses. Int J Radiat Oncol Biol Phys. 2016;95(4):1117–31. https://doi.org/10.1016/j.ijrobp.2016.03.015.
31.• Romesser PB, Cahlon O, Scher ED, Hug EB, Sine K, DeSelm C, et al. Proton beam reirradiation for recurrent head and neck cancer: multi-institutional report on feasibility and early outcomes. Int J Radiat Oncol Biol Phys. 2016;95(1):386–95. https://doi.org/10.1016/j.ijrobp.2016.02.036.
Large, multi-institutional study on re-irradiation of recurrent head and neck cancer using proton beam therapy. Proton radiation therapy was able to demonstrate acceptable acute and late toxicities and tumor control.
32. De Crevoisier R, Bourhis J, Domenge C, Wibault P, Koscielny S, Lusinchi A, et al. Full-dose reirradiation for unresectable head and neck carcinoma: experience at the Gustave-Roussy Institute in a series of 169 patients. J Clin Oncol. 1998;16(11):3556–62. https://doi.org/10.1200/JCO.1998.16.11.3556.
33. van de Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature. Oncologist. 2011;16(3):366–77. https://doi.org/10.1634/theoncologist.2010-0171.
34. Cozzi L, Fogliata A, Lomax A, Bolsi A. A treatment planning comparison of 3D conformal therapy, intensity modulated photon therapy and proton therapy for treatment of advanced head and neck tumours. Radiother Oncol. 2001;61(3):287–97.
35. Ahn PH, Ahn AI, Lee CJ, Shen J, Miller E, Lukaj A, et al. Random positional variation among the skull, mandible, and cervical spine with treatment progression during head-and-neck radiotherapy. Int J Radiat Oncol Biol Phys. 2009;73(2):626–33. https://doi.org/10.1016/j.ijrobp.2008.10.007.
36. Kraan AC, van de Water S, Teguh DN, Al-Mamgani A, Madden T, Kooy HM, et al. Dose uncertainties in IMPT for oropharyngeal cancer in the presence of anatomical, range, and setup errors. Int J Radiat Oncol Biol Phys. 2013;87(5):888–96. https://doi.org/10.1016/j.ijrobp.2013.09.014.
37.• Kurz C, Nijhuis R, Reiner M, Ganswindt U, Thieke C, Belka C, et al. Feasibility of automated proton therapy plan adaptation for head and neck tumors using cone beam CT images. Radiat Oncol. 2016;11:64. https://doi.org/10.1186/s13014-016-0641-7.
A study aimed to improved quality assurance and treatment adaptation using cone beam CT imaging for proton radiation therapy in head and neck cancer. Automated system was able to reduce overdosing for high-dose and low-dose PTV regions.
38. Ramaekers BL, Grutters JP, Pijls-Johannesma M, Lambin P, Joore MA, Langendijk JA. Protons in head-and-neck cancer: bridging the gap of evidence. Int J Radiat Oncol Biol Phys. 2013;85(5):1282–8. https://doi.org/10.1016/j.ijrobp.2012.11.006.
39. Gameiro SR, Malamas AS, Bernstein MB, Tsang KY, Vassantachart A, Sahoo N, et al. Tumor cells surviving exposure to proton or photon radiation share a common immunogenic modulation signature, rendering them more sensitive to T cell-mediated killing. Int J Radiat Oncol Biol Phys. 2016;95(1):120–30. https://doi.org/10.1016/j.ijrobp.2016.02.022.
40. Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiat Oncol Biol Phys. 2013;87(1):46–52. https://doi.org/10.1016/j.ijrobp.2013.04.030.
41. Palm A, Johansson KA. A review of the impact of photon and proton external beam radiotherapy treatment modalities on the dose distribution in field and out-of-field; implications for the long-term morbidity of cancer survivors. Acta Oncol. 2007;46(4):462–73. https://doi.org/10.1080/02841860701218626.
42. Dagan R, Bryant C, Li Z, Yeung D, Justice J, Dzieglewiski P, et al. Outcomes of sinonasal cancer treated with proton therapy. Int J Radiat Oncol Biol Phys. 2016;95(1):377–85. https://doi.org/10.1016/j.ijrobp.2016.02.019.