TREATING HEAD AND NECK CANCER WITH PROTON THERAPY
CURRENT PRACTICE, OPPORTUNITIES AND CHALLENGES
Since IBA first started to develop proton therapy solutions, we have focused on collaboration and sharing information. This culture of cooperation allows us to work collectively with clinical partners to make proton therapy available to anyone who needs it.

Our purpose is simply to offer more cancer patients effective treatments, decreased late effects, and a better quality of life.

The amount of clinical data on proton therapy is increasing rapidly, making it a challenge to keep up with new findings and advancements. We decided to take advantage of our day-to-day involvement with experienced clinical teams from proton therapy centers worldwide and gather and share information on the use of proton therapy in oncology.

We have compiled this information in a series of white papers reflecting the latest scientific and clinical advances in proton therapy. The information that follows is the result of our in-depth review of the latest articles published in key scientific journals.

We have undertaken this information-gathering exercise with honesty and ethics. While utmost care has been taken to ensure that the information contained in this publication is correct, unbiased and complete, the reader should be aware that articles have been selected and data interpreted. We encourage you to interpret these data carefully and exercise your own critical and scientific judgment.

The IBA team believes in the benefits of proton therapy for patients and society. This information exemplifies the extraordinary promise of proton therapy, and we hope you will join us in making it accessible to more patients.

We wish you a good reading.
Head and neck cancer refers to a collective group of heterogeneous malignancies that develop in and around oral cavity, oropharynx, larynx, hypopharynx, paranasal sinuses, nasal cavity and salivary glands. 90% of head and neck cancers are squamous cell carcinoma. The remaining 10% has histologies of melanoma, adenocarcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma. Worldwide, head and neck cancer accounted for 4.6% of all cancers, resulting in a total of 874,547 cases and 418,323 deaths in 2018. In 2020, an estimated 53,260 new cases of cancer of the oral cavity and pharynx will be diagnosed in the US and 10,750 people will die from the disease. Incidence rates are more than twice as high in men as in women.

Head and neck cancer is challenging to treat because of the proximity of the tumors to multiple critical normal organs and structures in the region. Multidisciplinary treatment approaches including surgery, radiotherapy and/or chemotherapy are often required, particularly for advanced stage disease. Radiotherapy can be employed as a primary definitive treatment or as an adjuvant to surgery. Intensity-modulated radiotherapy (IMRT) has been an advance for photon-based radiotherapy delivery, reducing toxicity and improving quality of life in the treatment of head and neck cancer, as well as improvement in cause-specific survival.

However, even with IMRT, both short and long-term treatment-related toxicity remains a significant issue. Patients commonly experience dysgeusia, dysphagia, odynophagia, mucositis, xerostomia, pain, nausea, vomiting, and weight loss, with many requiring gastrostomy tube placement for nutritional support.

Protons deposit the bulk of the radiation dose in a highly confined area with minimal to no exit dose. This unique physical property of proton therapy, which results in less radiation exposure to adjacent critical organs and normal tissues, may lead to reduction in treatment-related toxicity and improvement in quality of life.

This paper aims to present the existing clinical outcome data on proton therapy for cancers of the head and neck.

**PATIENT SELECTION**

The physical properties of proton therapy results in more conformal dose distributions, which may result in improved therapeutic gains. The clinical interest lies in the comparative impact of proton beam therapy versus alternatives such as photon beam therapy. The current model policy developed by the American Society for Radiation Oncology (ASTRO) recommends basing patient selection on the added clinical benefit proton therapy offers. This comes down to considering proton therapy in such cases where sparing the surrounding normal tissue is crucial and cannot be adequately achieved with a photon-based approach. The policy provides several non-specific examples:

- The target volume is in close proximity to one or more critical structures and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s).

- A decrease in the amount of dose inhomogeneity in a large treatment volume is required to avoid an excessive dose hotspot within the treated volume to lessen the risk of excessive early or late normal tissue toxicity.

- A photon-based technique would increase the probability of clinically meaningful normal tissue toxicity by exceeding an
integral dose-based metric associated with toxicity.

- The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

Recently developed model-based approaches assist in patient selection, where the potential clinical benefit for protons over photons for each individual patient is estimated based on the reduction in normal tissue complication probability (NTCP). NTCP models for dysphagia, esophagitis, hypothyroidism, xerostomia, oral mucositis and need for feeding tube have been established and validated. Based on a predefined ∆NTCP between the proton and photon plan, the patients benefitting from proton therapy are selected. The feasibility of this model-based selection is clinically proven. Approximately one third of head and neck patients qualify for protons for that these patients have the highest probability to benefit from protons in terms of toxicity prevention.

A) OVERVIEW OF BENEFITS

Proton particles do not deposit exit dose. This allows proton therapy to spare normal tissues distal to the tumor target. This is particularly useful for treating head and neck tumors because of the anatomic constraints encountered in nearly all cancers in this region.

Proton therapy enables delivering aggressive local therapy. Proton therapy dose-intensified treatment for paranasal sinus tumors reported improved local control and survival. A recent meta-analysis also reported that proton therapy was superior to IMRT in both disease free survival (72% vs 50% at 5 years) and tumor control for nasal cavity and paranasal sinus tumours (81% vs 64%).

The dosimetric advantage of proton therapy translates into toxicity reduction. Studies comparing proton versus photon therapy have reported significantly lower rates of acute grade 2 dysphagia, dysgeusia, mucositis and nausea favoring proton therapy. Additionally, proton therapy resulted in prevention of weight loss, lower opioid use, and less gastrostomy tube dependence. Proton therapy provides favorable quality of life and patient-reported outcomes profiles for select head and neck cancer patients.

For recurrent head and neck cancer requiring re-irradiation, proton therapy is able to maximize a focused dose of radiation to the tumor while minimizing dose to surrounding tissues which results in a minimal acute toxicity profile, even in patients who have received multiple prior courses of radiotherapy. Proton therapy is ideally suited for recurrent patients who are at risk of serious complications due to the high cumulative doses to critical structures.

B) DOSIMETRIC COMPARISON

Numerous in silico planning comparative studies on various sites of head and neck cancer reported better dosimetry parameters with proton therapy as compared to photon-based techniques (Table 1). Lomax et al. compared IMRT and intensity modulated proton therapy (IMPT) treatment plans of paranasal sinus cancer, and reported that IMPT was the only method to spare critical structures at all dose levels while simultaneously providing acceptable dose homogeneity within the target volume. Taheri-Kadkhoda et al. studied the nasopharyngeal cancer radiation plans and reported that three-field IMPT has greater potential than nine-field IMRT with respect to tumor coverage and reduction of the integral dose to OARs and non-specific normal tissues. A study on recurrent pharyngeal cancer supported that IMPT exposed the OARs to a significantly lower dose, effectively sparing the brainstem, spinal cord, optic nerve and chiasm, temporal lobes and parotid glands. An extensive review on in silico planning comparative studies for head and neck cancers by van de Water et al. concluded that protons substantially lower the dose to organs at risk (OAR). Of all potential techniques of proton delivery, pencil-beam scanning IMPT would offer the greatest advantages in an anatomically complex site such as the head and neck, leading to a lower probability of radiation-induced side effects.
<table>
<thead>
<tr>
<th>Study</th>
<th>Disease site</th>
<th>Target coverage</th>
<th>OAR parameter</th>
<th>IMRT</th>
<th>IMPT</th>
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<tr>
<td>Lomax, 2003&lt;sup&gt;20&lt;/sup&gt;</td>
<td>paranasal sinus</td>
<td>similar PTV coverage</td>
<td>right eyeball volume≥20Gy</td>
<td>12-88%</td>
<td>20%</td>
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<tr>
<td></td>
<td></td>
<td>with increased dose constraints to OARs, PTV coverage with IMRT compromised</td>
<td>brainstem volume≥20Gy</td>
<td>13-85%</td>
<td>15%</td>
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<tr>
<td>Lomax, 2003&lt;sup&gt;20&lt;/sup&gt;</td>
<td></td>
<td>noncritical normal tissues≥20Gy</td>
<td></td>
<td>27%</td>
<td>12%</td>
</tr>
<tr>
<td>Taheri-Kadkhoda, 2008&lt;sup&gt;21&lt;/sup&gt;</td>
<td>nasopharynx</td>
<td>IMPT significantly improved target coverage and conformation</td>
<td>Dmax optic chiasam</td>
<td>23.8Gy</td>
<td>16.1GyE</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Dmax brainstem</td>
<td>58.7Gy</td>
<td>47.3GyE</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Dmean inner ear</td>
<td>36.4Gy</td>
<td>13.1GyE</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Dmean larynx/ esophagus</td>
<td>30.6Gy</td>
<td>14.3GyE</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Dmean oral cavity</td>
<td>44.0Gy</td>
<td>38.1GyE</td>
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<td></td>
<td></td>
<td></td>
<td>Dmean pituitary gland</td>
<td>42.2Gy</td>
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<td></td>
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<td></td>
<td>Dmean parotid gland</td>
<td>40.0Gy</td>
<td>36.3GyE</td>
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<td></td>
<td></td>
<td></td>
<td>Dmean larynx</td>
<td>37.7-38.4Gy</td>
<td>13.6GyE</td>
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<td></td>
<td></td>
<td></td>
<td>Dmean right parotid</td>
<td>10.3-10.9Gy</td>
<td>0.4GyE</td>
</tr>
<tr>
<td>Liu, 2010&lt;sup&gt;22&lt;/sup&gt;</td>
<td>recurrent nasopharynx</td>
<td>similar PTV coverage</td>
<td>Dmax brainstem</td>
<td>42.5Gy</td>
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<td>D5 brainstem</td>
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<td></td>
<td></td>
<td></td>
<td>Dmax spinal cord</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>D5 spinal cord</td>
<td>13.62Gy</td>
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</table>
The below treatment plan comparison shows IMPT and IMRT for a case of T1N1M0, HPV-positive squamous cell carcinoma of the left oropharynx. The patient received postoperative radiotherapy after surgical resection (transoral robotic resection and left selective neck dissection). Targets included bilateral neck and the left oropharyngeal operative bed. Prescribed 30 fractions, 60 Gy to high-risk elective CTV, and 54 Gy to low-risk elective CTV. DVH’s show equivalent coverage of CTV_60 and CTV_54 between IMPT plan and IMRT plan, however, IMPT achieves superior sparing for Organs at Risk including the contralateral parotid (Dmean 20 vs 8.5 Gy) and the oral cavity (Dmean 22 vs 5 Gy).

![Figure 1. DVH comparison of IMPT and IMRT plans. Equivalent coverage of CTV_60 and CTV_54 between IMPT (triangles) and IMRT (squares). IMPT with superior sparing of the contralateral parotid (pink), Dmean 20 vs 8.5 Gy, and the oral cavity (blue), Dmean 22 vs 5 Gy.](image1)

Figure 1. DVH comparison of IMPT and IMRT plans. Equivalent coverage of CTV_60 and CTV_54 between IMPT (triangles) and IMRT (squares). IMPT with superior sparing of the contralateral parotid (pink), Dmean 20 vs 8.5 Gy, and the oral cavity (blue), Dmean 22 vs 5 Gy.

![Figure 2. Representative image shows superior oral cavity sparing of IMPT compared to IMRT.](image2)

Figure 2. Representative image shows superior oral cavity sparing of IMPT compared to IMRT.

![Figure 3. Representative image shows the superior right parotid gland sparing of IMPT compared to IMRT.](image3)

Figure 3. Representative image shows the superior right parotid gland sparing of IMPT compared to IMRT.

All illustrations courtesy of the Department of Radiation Oncology, University of Pennsylvania.

C) CLINICAL OUTCOMES - LITERATURE REVIEW

The clinical value of proton therapy dosimetric advantages over photon-based techniques depicted in the silico studies is being confirmed by the growing clinical outcome data.

Paranasal sinus and nasal cavity tumors

The Massachusetts General Hospital (MGH) group has substantial experience in proton therapy for nasal cavity and paranasal sinus malignancies. In 1997, a first report on successful treatment for esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation was published by Bhattacharyya et al.24 In 2002, Fitzek et al. published the results of a prospective study of patients with olfactory neuroblastoma or neuroendocrine carcinoma of the sinonasal tract treated by chemotherapy and proton-photon radiation, reporting a 5-year survival rate of 74% and a local control (LC) rate of 88%.26 In 2006, Pommier et al reported a 5-year locoregional control rate of 93% for patients treated with adenoid cystic carcinoma (ACC), via combined photon-proton dose escalation.26 In 2008, Resto et al.27 reported on their retrospective study on 102 patients with locally advanced sinonasal cancers treated with proton therapy either with or without prior surgery. The study indicated that high-dose proton therapy procures excellent LC rates, with 5-year LC rates as high as 95% for the complete resection group and 82% for the partial resection
Researchers from Japan also published promising clinical results. In 2004, Tokuyue et al.\textsuperscript{30} from the University of Tsukuba detailed experiences with thirty-three patients who were treated with either proton alone or in combination with photon, without undergoing prior surgical resection. Overall 5-year survival and LC rates were 44% and 74%, respectively, with > grade 3 treatment-related acute and late toxicity observed in 1 (3%) and 6 (18%) patients, respectively. The authors believed that proton therapy offers high LC rates with fewer toxicities relative to conventional radiation therapy. However, late toxicity was observed in areas of high radiation doses. Another study by the Japanese group Zenda et al.\textsuperscript{31} of the National Cancer Center in Chiba was published in 2011, describing thirty-nine cases of patients with unresectable tumors of the nasal cavity, paranasal sinuses and skull base who were treated with proton therapy. A 49.1% 3-year progression-free rate was noted and with an OS of 59.3%. The most common acute toxicities proved to be mild dermatitis (Grade 2, 33.3%) and there were no severe acute toxicities (Grade 3 or higher, 0%) observed. Five patients (12.8%) did suffer Grade 3 to 5 late toxicities. The authors attest that the clinical profile of proton therapy makes it a promising treatment option for unresectable malignancies of the nasal cavity and in the paranasal area.

In 2019, a multi-institutional study by Yu et al.\textsuperscript{32} reported the outcomes of 69 patients with sinonasal tumors underwent curative intent proton beam radiation therapy (PBRT), including de novo irradiation (42 patients) and reirradiation (27 patients). The study reported the the 3-year OS and freedom from distant metastasis for de novo irradiation of 100% and 84.0% respectively; with re-RT, the 3-year OS and freedom from distant metastasis were 76.2% and 47.4%.

There were 11 patients with acute grade 3 toxicities. Late toxicities occurred in 15% of patients, however no grade ≥3 toxicities. The authors concluded that PBRT may be a safe and efficacious treatment option for patients with sinonasal tumors.

The above studies included some patients treated with a mixed proton-photon technique, were single-institution, and did not directly compare patients treated with proton versus photons. However, the disease outcomes obtained with proton therapy are promising and may reflect potential benefit in an otherwise morbid treatment in a difficult to treat anatomic area.

**Nasopharyngeal carcinoma (NPC)**

In 2004, Chan et al. presented the clinical outcomes of seventeen T4 NPC patients treated with combined proton and photon radiation therapy. At 3 years, the local-regional control rate was 92%, the disease-free survival rate 75% and the OS rate 74%. The late toxicities included one case of radiographic changes in the temporal lobes, one osteoradionecrosis of the mandible and two patients with endocrine dysfunction. The authors concluded that proton radiation therapy combined with photons, whether in combination with chemotherapy or not, resulted in excellent local-regional control in T4 NPC patients.\textsuperscript{33}

In 2015, Holliday et al. reported a case-matched control study on NPC patients, showing that 20% of the IMPT patients required gastrostomy tube (GT) insertion, compared to 65% IMRT patients. The authors concluded that patients with nasopharyngeal carcinoma who are treated with IMPT have decreased rates of GT placement which is likely due to, in part, to better dose sparing of the oral cavity.\textsuperscript{34}

Beddok et al.\textsuperscript{36} also in 2019 reported efficacy and toxicity of proton with photon radiation for locally advanced NPC. This study of 17 patients with previously untreated stages III–IVA NPC, who received a definitive treatment using photon with a proton therapy boost with concurrent chemotherapy, reported 2-, 5- and 10-year local recurrence free rates of 94%, 86% and 86%, respectively. For acute toxicity, one patient was hospitalized for a short period of time (10 days) for dysphagia requiring parenteral nutrition (weight loss of 16%). Two other patients experienced a treatment break of 5 and 6 days due to acute mucositis and middle ear inflammation requiring tympanostomy. Six patients had middle ear inflammation. For late toxicity, this study reported temporal lobe necrosis for six patients on cerebral MRI, one
of them was symptomatic.

Given the results of the comparative toxicity profile suggesting that proton therapy would significantly reduce the need for insertion of a G-tube, proton therapy should be considered for patients receiving curative-intent radiotherapy for nasopharynx cancer.

### Oropharyngeal cancer

In 2016, Sio et al. reported the first comparative results of patient-reported outcomes (PRO) of oropharyngeal cancer treated with IMPT and IMRT. The PRO data was collected and analyzed from 35 patients treated IMPT with chemotherapy and 46 with IMRT with chemotherapy. For the top 5 symptoms, namely, food taste problems, dry mouth, swallowing/chewing difficulties, lack of appetite, and fatigue, changes in taste and appetite during the subacute and chronic phases favored IMPT (all P<.048).

Blanchard et al. conducted another comparative study examining the clinical outcomes of oropharyngeal carcinoma patients treated with IMPT and IMRT. Fifty IMPT and 100 IMRT patients were included. This study reported no statistically significant differences in OS or progression-free survival, however, IMPT was associated with reduced rates of feeding tube dependency and severe weight loss.

In 2017, Zhang et al. reported that mandibular doses were lower for patients treated with IMPT (P<0.001), and osteoradionecrosis rates were lower, as compared to IMRT.

Given the high survival rates in HPV-positive oropharyngeal cancer (OPC) patients, as well as the high rates of toxicity associated with the concurrent chemoradiation for the locally advanced OPC, Langendijk et al. advocated the de-escalation strategies and emphasized that protons would offer more opportunities to decrease the dose to normal tissues in order to prevent radiation-induced toxicities, in which IMPT has the highest potential to decrease acute and late toxicities.

Sharma et al. reported on 64 patients who received postoperative radiotherapy (IMPT versus IMRT) for oropharynx cancer. Patients receiving IMPT had significantly less dose to normal structures, with these dosimetric advantages reflected in higher general as well as head and neck specific quality of life scores.

In 2020, Meijer et al. published a review specifically on the reduced radiation-induced toxicity by using proton therapy for the treatment of oropharyngeal cancer. Proton therapy results in lower dose levels in multiple organs at risk, which translates into reduced acute toxicity while preserving tumor control. In addition to reducing mucositis, tube feeding, xerostomia, distortion of the sense of taste, risk of radionecrosis of the mandible and severe weight loss, proton therapy can improve general well-being by decreasing fatigue and nausea.

Whether IMPT is superior to IMRT in terms of toxicity mitigation and quality of life is currently being investigated via an ongoing phase III randomized trial (Table 2).

### Salivary gland cancer

In 2016, Romesser et al. analyzed 41 patients underwent ipsilateral irradiation for major salivary gland cancer including 23 patients treated with IMRT and 18 with PBRT. This study reported that IMRT plans had a greater median maximum brainstem (29.7 Gy vs. 0.62 Gy (RBE), P < 0.001), maximum spinal cord (36.3 Gy vs. 1.88 Gy (RBE), P < 0.001), mean oral cavity (20.6 Gy vs. 0.94 Gy (RBE), P < 0.001), mean contralateral parotid (1.4 Gy vs. 0.0 Gy (RBE), P<0.001), and mean contralateral submandibular (4.1 Gy vs. 0.0 Gy (RBE), P < 0.001) dose when compared to PBRT plans. PBRT had significantly lower rates 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 2020, Chuong et al. published results of the multi-institutional study enrolled on the Proton Collaborative Group REG001-09 trial (NCT01255748). This study evaluated treatment parameters and acute toxicity outcomes of patients with major salivary gland cancers. 105 patients including parotid (N=90) and submandibular gland (N=15) were treated to the median PBRT dose of 66.5 GyE in 33 fractions. This study reported acute grade 2 or higher toxicity included nausea (1.5%), dysgeusia (4.8%), xerostomia (7.6%), mucositis (10.5%) and dysphagia (10.5%). The authors concluded that PBRT should be strongly considered when ipsilateral radiation therapy is indicated for major salivary gland cancer based on a considerably lower incidence of acute grade 2 or higher toxicity in this analysis compared to historical IMRT outcomes.

A current randomized phase II study of proton versus photon radiotherapy for patients receiving unilateral neck radiation (salivary gland, skin or melanoma primary) will assess whether proton therapy reduces the rate of grade 2 or greater...
mucositis (Table 2).

Reirradiation

The largest series by Romesser et al. was published in 2016. The study reported outcomes of 92 patients treated with curative intent reirradiation with PBRT. The actuarial 12-month freedom-from-distant metastasis and OS rates were 84.0% and 65.2%. Acute toxicities of grade 3 or greater included mucositis (9.9%), dysphagia (9.1%), esophagitis (9.1%), and dermatitis (3.3%). The authors concluded that proton re-RT of the head and neck can provide effective tumor control with acceptable acute and late toxicity profiles.

Another study by Phan et al. reported results of proton reirradiation for 60 patients among who 25% received passive scatter proton therapy and 45 (75%) received IMPT. At 1-year, the rates of locoregional failure-free survival, OS, progression-free survival, and distant metastasis-free survival were 68.4%, 83.8%, 60.1%, and 74.9%, respectively. Eighteen patients (30%) experienced acute grade 3 (G3) toxicity, and 13 (22%) required a feeding tube at the end of proton therapy. The authors suggested that proton therapy can be a safe and effective curative reirradiation strategy, with acceptable rates of toxicity and durable disease control.

In 2017, a study from Japan by Hayashi et al. reported outcomes of 34 patients who had recurrent oral cancer treated with protons. One-year and 2-year OS rates were 62% and 42%, respectively. One-year and 2-year LC rates were 77% and 60%. The authors concluded that proton reirradiation combined with chemotherapy improved OS and LC rates compared with other treatment modalities.

In 2019, Dionisi et al. reported outcomes of 17 recurrent NPC patients treated with proton therapy. Acute toxicity was low with no ≥ G3 adverse events. Late events ≥ G3 occurred in 23.5% of patients. Most frequent late toxicity was hearing impairment (17.6%). G2 soft tissue necrosis occurred in two patients. Fatal bleeding of uncertain cause (either tumor recurrence or G5 carotid blowout) occurred in one patient. 18 months OS and LC rates were 54.4% and 66.6%. The authors concluded that the use of modern PT for reirradiation of recurrent NPC patients are encouraging. Favorable LC and OS rates were obtained at the cost of acceptable severe late toxicity.

Two currently accruing trials are comparing outcomes with proton versus photon radiotherapy in the recurrent setting. The first is a non-randomized study comparing locoregional control with protons versus photons (standard or hypofractionated) in patients who previously were irradiated. The other study randomizes patients to stereotactic body radiation therapy (SBRT) versus proton therapy, with a primary outcome of grade 3 or greater toxicity.

Summary

The clinical data reported has demonstrated proton therapy promising clinical efficacy and the benefits of toxicity reduction, which are becoming increasingly apparent ranging from incremental to substantial in the selected patient groups. Moreno et al. claimed that IMPT is analogous to IMRT and the future of IMRT for head and neck cancer. Blanchard et al. pointed out that proton therapy is a standard of care for base of skull tumors and is an option for periorbital tumors according to NCCN guidelines. The use of proton therapy is expanding for other head and neck tumor sites including nasopharynx, oropharynx, nasal cavity and paranasal sinuses, skin, and salivary gland, or to reirradiation. Novel forms of proton therapy such as IMPT, and technical improvements in dose modeling, patient setup, image guidance and radiobiology, will help further enhance the benefits of proton therapy.

DI ONGOING CLINICAL TRIALS

There are 4 currently recruiting phase II or III clinical trials registered with clinicaltrials.gov that are directly comparing proton to photon-based radiation, which are described in the text above and included in the below Table 2.
<table>
<thead>
<tr>
<th>Title</th>
<th>Type</th>
<th>Randomized</th>
<th>Comparative</th>
<th>PI</th>
<th>Endpoint</th>
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<td>II</td>
<td>yes</td>
<td>yes</td>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>number of patients with grade 2 or greater acute mucositis</td>
<td>132</td>
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<td>Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck</td>
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<td>yes</td>
<td>yes</td>
<td>MD Anderson Cancer Center</td>
<td>Rates and Severity of Late Grade 3-5 Toxicity. Time Frame: 90 days to 2 years post radiation therapy Progression-Free Survival (PFS). Time Frame: 3 years</td>
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<td>Stereotactic Body Radiation Therapy or Intensity Modulated Radiation/Proton Therapy in Treating Patients With Recurrent Head and Neck Cancer</td>
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<td>yes</td>
<td>yes</td>
<td>MD Anderson Cancer Center</td>
<td>Compare rates of grade 3 or higher toxicity; LFFS, PFS, LC and OS at 2 years between the two modalities Compare PRO and QoL measures</td>
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<td>no</td>
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<td>ocoregional recurrence-free at 12 months</td>
<td>88</td>
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Treating Head and Neck Cancer with Proton Therapy |

Dr. Lin. “We are starting to observe and report that patients obtain cure while maintaining patient safety.” Clinical results potentially deliver the higher doses of radiation needed to treatable with standard techniques, proton therapy can offer excellent post-treatment quality of life. For cancers that are not treatable with standard techniques, proton therapy can minimize long-term toxicity, ensuring potential. By reducing normal tissue exposure to radiation, proton therapy has tremendous potential. It is here that proton therapy may be beneficial. “The head and neck region contain many vital organs that perform critical everyday functions. Often, these organs are located very close to areas that require treatment with radiotherapy. For many patients who are cured, they live long-term with the side effects of treatment, often with a negative impact on functions such as speech, swallowing, and general quality of life. For other patients, there are limitations on how much radiation can be safely delivered, limiting the odds of obtaining a cure. It is here that proton therapy has tremendous potential. By reducing normal tissue exposure to radiation, proton therapy can minimize long-term toxicity, ensuring excellent post-treatment quality of life. For cancers that are not treatable with standard techniques, proton therapy can potentially deliver the higher doses of radiation needed to obtain cure while maintaining patient safety.” Clinical results supporting these potential benefits are now emerging, says Dr. Lin. “We are starting to observe and report that patients who are treated with proton therapy for cancers of the oropharynx are maintaining/recovering taste, appetite and saliva production at rates far greater than those treated with standard radiation techniques. We expect that these benefits will translate into long-term gains for patients with respect to function and quality of life. We believe that these results should be confirmed through currently accruing, randomized studies, and we are committed to ensuring that the gains seen with proton therapy are clear and generalizable to the medical community. Our ultimate goal is a shared mission amongst patients and providers alike; to help better the lives of our patients”.

THE EXPERT’S PERSPECTIVE

Dr. Alexander Lin
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At the Perelman School of Medicine of the University of Pennsylvania, Dr. Alexander Lin is the Chief of the Head and Neck Cancer Radiotherapy Section and the Medical Director of the Roberts Proton Therapy Center. He is an NIH-funded clinical investigator, with a focus on the multidisciplinary management of head and neck cancers, the integration of novel radiotherapy techniques (such as proton therapy) in the cancer treatment paradigm, and the use of novel radio-sensitizers to improve disease outcomes. Dr. Lin’s proton research program has focused on the integration of proton therapy in the context of a multidisciplinary treatment approach, with the goal of improving patient outcomes beyond what is currently observed with standard radiotherapy approaches.

THE PRESENT

Radiotherapy is a well-established, curative treatment modality for patients with head and neck cancer. For patients with early stage disease, it is often the only treatment needed, while for those with more advanced cancers, radiotherapy is used in conjunction with chemotherapy, or after surgical resection. Dr. Lin addresses challenges specific to standard head and neck radiation and cites specific scenarios in which proton therapy may be beneficial. “The head and neck region contain many vital organs that perform critical everyday functions. Often, these organs are located very close to areas that require treatment with radiotherapy. For many patients who are cured, they live long-term with the side effects of treatment, often with a negative impact on functions such as speech, swallowing, and general quality of life. For other patients, there are limitations on how much radiation can be safely delivered, limiting the odds of obtaining a cure. It is here that proton therapy has tremendous potential. By reducing normal tissue exposure to radiation, proton therapy can minimize long-term toxicity, ensuring excellent post-treatment quality of life. For cancers that are not treatable with standard techniques, proton therapy can potentially deliver the higher doses of radiation needed to obtain cure while maintaining patient safety.” Clinical results supporting these potential benefits are now emerging, says Dr. Lin. “We are starting to observe and report that patients who are treated with proton therapy for cancers of the oropharynx are maintaining/recovering taste, appetite and saliva production at rates far greater than those treated with standard radiation techniques. We expect that these benefits will translate into long-term gains for patients with respect to function and quality of life. We believe that these results should be confirmed through currently accruing, randomized studies, and we are committed to ensuring that the gains seen with proton therapy are clear and generalizable to the medical community. Our ultimate goal is a shared mission amongst patients and providers alike; to help better the lives of our patients”.

THE FUTURE

Dr. Lin believes that the technology for proton beam radiation will continue to advance and enhance its capabilities. “There are numerous developments currently in process to improve our ability to deliver proton radiation more accurately and efficiently. Pencil beam, intensity-modulated proton therapy is the most advanced form of proton radiation delivery available today, giving us the greatest capabilities to deliver sufficient doses of radiation to areas of cancer involvement, while minimizing doses to normal organs. It is currently the standard approach for the majority of our patients receiving proton therapy at Penn Medicine. Other advances in imaging and quality assurance will allow us to further advance the field of cancer care and improve patient outcomes.” The role of proton therapy will furthermore continue to grow along with advances in other fields of oncology, concludes Dr. Lin. “Proton therapy is a highly potent and effective treatment for patients who require radiotherapy. However, we realize that cancer care is complex, and often requires a multidisciplinary approach, with the best results coming from combining other treatments such as surgery and/or chemotherapy with radiotherapy. No single treatment is likely to be a universal cure for patients with aggressive and advanced forms of cancer. For the patients whom we routinely treat with radiation, we believe that proton therapy will help them achieve better results, not only during the course of their treatment, but also for the years after they have put their cancer diagnosis behind them. For other patients who currently do not routinely receive radiotherapy as part of their treatment regimen, we are just starting to scratch the surface of the potential of radiation, and proton therapy to be able to unleash the power of a patient’s own immune system to fight their cancer when used in combination with novel drugs targeting the immune system. I believe that it is important that all cancer physicians (whether they are surgeons, medical oncologists, or radiation oncologists) and their patients...
should have the ability to receive a careful evaluation by a specialist in proton radiotherapy, and for those in which there is a compelling necessity, to have access to proton treatment to obtain the best possible results."
REFERENCES


NOTES
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Tomorrow, our unique and open culture of sharing will further strengthen the clinical and patient communities we have always cared for. Working collectively, we will achieve our goal which is to offer cancer patients access to effective treatments with decreased side effects and better quality of life.

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