TREATING HEAD AND NECK CARCINOMA WITH PROTON THERAPY

CURRENT PRACTICE, OPPORTUNITIES AND CHALLENGES

Proton Therapy in Practice: Clinical Indications – Head and Neck Tumors

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FOREWORD

Since IBA first started to develop proton therapy solutions, we have focused on collaboration and sharing of information. This culture of cooperation has allowed us to work together with clinical partners to help make proton therapy available to anyone who needs it.

Our purpose is to offer more cancer patients effective treatments, decreased side effects, leading to 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, in order to gather and share information on the use of proton therapy in oncology.

We've compiled this information and written a series of white papers reflecting on 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 the highest level of integrity. While utmost care has been taken to ensure that the information contained in this publication is accurate, complete and unbiased, 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 will help you and your teams learn more about the extraordinary promise of proton therapy, and we hope you will join us in making it accessible to more patients.

We wish you good reading,

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Head and neck cancers refer to a collective group of heterogeneous malignancies that develop in and around oral cavity, oropharynx, larynx, hypopharynx, paranasal sinuses, nasal cavity and salivary glands. Of all head and neck cancers, 90% are squamous cell carcinoma (HNSCC), with histologies including (but not limited to) melanoma, adenocarcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma comprising the remaining 10%. HNSCC is the sixth leading cancer by incidence worldwide and eighth by death. There are 0.5 million new cases a year worldwide. The American Cancer Society estimates that in the United States, approximately 3-5 percent of all cancers will be in the head and neck region. In 2016, an estimated 61,760 people (45,330 men and 16,430 women) will develop head and neck cancer, with an estimated 13,190 deaths (9,800 men and 3,390 women).[1,2,3]

Head and neck cancers are challenging to treat because of the close 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 radiation therapy (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 an improvement in cause-specific survival.[4]

However, even with IMRT, treatment-related toxicity (short and long-term) remains a significant issue. Patients commonly experience dysgeusia, dysphagia, odynophagia, mucositis, xerostomia, pain, nausea, vomiting, and weight loss, some to the point of requiring gastrostomy tube feeding.[5] Proton therapy, owing to the unique physical properties, may lead to improvements in treatment-related toxicity and improvement in quality of life by significantly reducing doses delivered to normal organs or tissue. This paper aims to present the existing clinical outcome data on proton therapy for head and neck cancers.

PATIENT SELECTION

The rapid dose deposition and fall-off seen with proton therapy results in less radiation exposure of adjacent normal tissues, which may lead to therapeutic gains. Proton therapy, when compared to current standard approaches such as photon beam therapy, may lead to gains in areas such as overall survival, disease control, safety, health-related quality of life and other patient outcomes. An increasing emphasis on evidence-based medicine makes it worthwhile to assess the available data that supports proton therapy over other techniques to better guide the physician and patient toward the most appropriate treatment.[6]

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:[7]

- 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.

A recently developed comparative effectiveness model helps clinical decision making in choosing proton or photon

modality for head and neck patients. Based on three levels of evaluation and comparison (i.e. dosimetric, toxicity, and cost-effectiveness level), the model successfully quantified patients for proton or photon treatment choice. A set of threshold values were predetermined by the researchers (e.g. organ at risk (OAR) mean dose, grade 2 toxicity of >10% and total toxicity reduction of 15% or greater) in order for the DVH analysis and NTCP toxicity prediction. In addition, €80,000 was chosen as the acceptable cost per additional QALY for the Markov cost-effectiveness model calculation. This decision making tool helps indicate both clinical outcome benefits and cost-effective benefits in choosing proton therapy.[8]

PROTON THERAPY FOR HEAD AND NECK TUMORS

A) OVERVIEW BENEFITS

Proton particles do not deposit exit dose, which 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 the delivery of aggressive local therapy. Proton therapy for paranasal sinus tumors reported improved local control and survival.[9,10] 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 (81% vs. 64%).[11]

The dosimetric advantage unique to 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.[12,13,14]

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.[15]

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 photonbased techniques (table 1). Figures 1 and 2 illustrate the dose distribution comparison as well as the DVH comparison for a base of tongue tumor treated with IMPT and IMRT. Lomax et al.[16] compared IMRT and IMPT treatment plans of paranasal

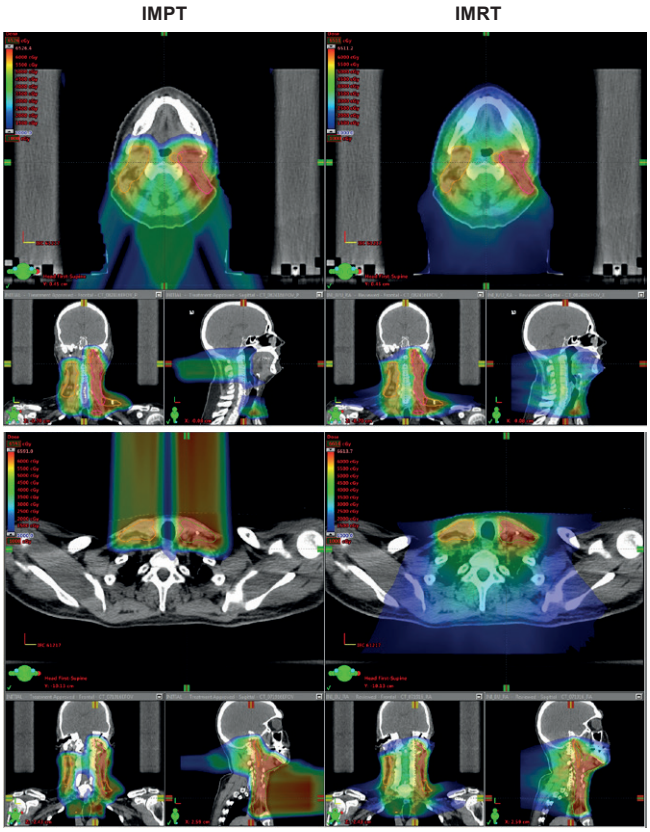

Figure 1: Radiation treatment plans comparing intensity-modulated radiation therapy (right) and intensity-modulated proton therapy (left) for a base of tongue tumor.

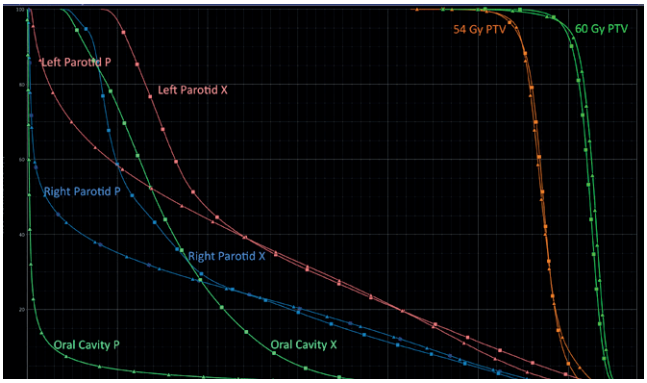

Figure 2: Dose Volume Histogram comparison between IMRT (square and labeled X) and IMPT (triangle and labeled P) for PTV and organs at risk from the treatment illustrated in figure 1. All illustrations courtesy of the Department of Radiation Oncology, University of Pennsylvania.

Table 1: in silico planning comparative studies

			Dose to OARs		
Study	**Disease site**	**Target coverage**	**OAR parameter**	**IMRT**	**IMPT**
Lomax, 2003	paranasal sinus	similar PTV coverage	right eyeball volume≥20Gy	12-88%	20%
		with increased dose constraints to OARs, PTV coverage with IMRT compromised	brainstem volume≥20Gy	13-85%	15%
			noncritical normal tissues≥20Gy	27%	12%
Taheri-Kadkhoda, 2008	nasopharynx	IMPT significantly improved target coverage and conformation	Dmax optic chiasma	23.8Gy	16.1GyE
			Dmax brainstem	58.7Gy	47.3GyE
			Dmean inner ear	36.4Gy	13.1GyE
			Dmean larynx/ esophagus	30.6Gy	14.3GyE
			Dmean oral cavity	44.0Gy	38.1GyE
			Dmean pituitary gland	42.2Gy	34.8GyE
			Dmean parotid gland	40.0Gy	36.3GyE
Muzik, 2008	oropharynx hypopharynx	similar PTV coverage	Dmean spinal cord	10.1-11.4Gy	1.2GyE
			Dmean larynx	37.7-38.4Gy	13.6GyE
			Dmean right parotid	10.3-10.9Gy	0.4GyE
			Dmean non target tissues	5.3-6.0Gy	1.5GyE
Liu, 2010	recurrent nasopharynx	similar PTV coverage	Top of Form	42.5Gy	27.9GyE
			Dmax brainstem		
			Bottom of Form		
			D5 brainstem	19.5Gy	12.8GyE
			Dmax spinal cord	22.91Gy	8.38GyE
			D5 spinal cord	13.62Gy	2.18GyE

sinus cancer, and reported that IMPT was the only method to spare critical structures at all dose levels simultaneously providing acceptable dose homogeneity within the target volume. Taheri-Kadkhoda et al.[17] studied the pharyngeal cancer 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 comparative study on an extensive case in the oropharynx/hypopharynx region recorded significant low dose to OARs.[18] 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.[19] 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 OARs. Of all potential techniques of proton delivery, pencil beam scanning intensity-modulated proton therapy, would offer the biggest advantages in an anatomically-complex site such as the head and neck, leading to a lower probability of radiation-induced side effects.[20]

C) CLINICAL OUTCOMES - LITERATURE REVIEW

The value of protons' dosimetric advantages over photon-based techniques depicted in the in 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.[21] 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 rate of 88%.[22] 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.[23] The latest report from the MGH group on stage III and IV sinonasal squamous cell carcinoma reported 2-year and 5-year local control rates of 80% and overall survival rates of 67% and 47%, respectively.[24]

A Japanese publication of 2004 by Tokuuye et al. 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 local control rates were 44% and 74%, respectively, with > grade 3 treatment-related acute and late toxicity observed in 1 (3%) and 6 (18%) patients, respectively.[25] The authors believed that proton therapy offers high local control rates with fewer toxicities relative to conventional radiation therapy. However, late toxicity was observed in areas of high radiation doses.

In 2008, Resto et al. reported in 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 local control rates, with 5-year local control rates as high as 95% for the complete resection group and 82% for the partial resection group, with an overall survival percentage of 90% and 53%, respectively.[26]

Another study by the Japanese group Zenda et al. 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 with an overall survival 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.[27]

• NASOPHARYNGEAL CARCINOMA (NPC), OROPHARYNGEAL, HYPOPHARYNGEAL AND LARYNGEAL CANCERS

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 overall survival 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.[28]

During the annual 2013 ASTRO meeting, Dr. S. J. Frank presented the results of a study comparing IMRT and IMPT for the treatment of oropharyngeal cancer patients. The study juxtaposed twenty-six patients suffering from oropharyngeal carcinoma that were treated with IMPT against IMRT treated patients extracted from the MD Anderson database. Cases of the two groups were matched on different criteria. The preliminary data suggest that IMPT results in a lower rate of grade 3 dysphagia when compared to IMRT. Additionally, the treatment with IMPT decreased by more than 50% the need for a feeding tube in comparison to IMRT, passing from 48% in IMRT to 20% in IMPT.[29] In 2015, Holliday et al. reported a case-matched control study on NPC patients. The findings show 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, in part, to better dose sparing of the oral cavity.[30]

Toxicity reduction continues to be reported in series of salivary gland tumors, squamous cell carcinoma in the region of the nasopharynx, oropharynx and paranasal sinus. Patients treated with proton therapy experienced less dysphagia, mucositis, xerostomia and dysphagia. Patients were less dependent on opioid pain treatment and gastrostomy tube feeding.[12, 13, 14]

Proton irradiation resulted in excellent local control for advanced primary sphenoid sinus malignancy. Truong et al. reported in 2009 that 2-year local, regional, and freedom from distant metastasis rates were 86%, 86%, and 50%, respectively. The disease-free and overall survival rates at 2 years were 31% and 53%, respectively.[9] Even with high dose 70CGE, proton irradiation achieved local control with acceptable ophthalmological complications for advanced sinonasal cancers.[31]

Table 2: literature review summary

Author	Pathology	Study	Outcome	Conclusion
Fitzek et al., 2002	olfactory neuroblastoma neuroendocrine carcinoma	prospective study 19 patients chemotherapy and proton/photon radiation MGH	5-year survival rate, 74% 5-year local control rate, 88%	
Tokuuye et al., 2004	Head and neck malignancy	retrospective analysis 33 patients proton or proton/photon without prior surgery MGH	5-year survival, 44% 5-year local control, 74%	3% acute toxicities 18% > grade 3 late toxicities in areas that received large radiation doses
Chan et al., 2004	NPC	retrospective analysis 17 patients combined proton/photon MGH	3-year local-regional control, 92% 3-year disease-free survival, 75% 3-year overall survival, 74%	photon radiation therapy, whether in combination with chemotherapy or not, results in excellent local-regional control in T4 NPC patients
Resto et al., 2008	locally advanced sinonasal cancer	retrospective analysis 102 patients proton therapy with or without surgery MGH	5-year local control: complete resection group, 95% partial resection group, 82% overall survival: complete resection group, 90% partial resection group, 53%	
Zenda et al., 2011	unresectable tumors of: nasal cavity paranasal sinuses skull base	retrospective analysis 39 patients National Cancer Center Chiba	3-year progression-free, 49.1% 3-year overall survival, 59.3% Most common acute toxicities: mild dermatitis grade 2, 33.3% ≥ grade 3 acute toxicities, 0% grade 3 to 5 late toxicities, 12.8%	promising treatment for unresectable malignancies of the nasal cavity and in the paranasal area
Frank et al., 2013	oropharyngeal cancer	comparison study 26 IMPT patients, 26 IMRT controls MD Anderson	Need for feeding tube: 48% IMRT 20% IMPT	IMPT results in lower rate of grade 3 dysphagia
Truong et al., 2015	advanced primary sphenoid sinus malignancy	retrospective analysis 20 patients University of Texas	2-year local control, 86% 2-year regional control, 86% 2-year freedom from distant metastasis, 50% 2-year disease-free, 31% 2-year overall survival, 53%	brain invasion and involvement of the oropharynx and the anterior cranial fossa are important prognostic factors
Holliday et al., 2015	oropharyngeal cancer	comparison study 10 IMPT, 20 IMRT patients MD Anderson	GT insertion required: 20% IMPT 65% IMRT	decreased rates of GT placement likely partly due to better dose sparing of oral cavity
Grant et al., 2015	salivary gland tumors	retrospective analysis 24 patients protons MD Anderson	grade 2/3 dysphagia: photon group, 27% proton group, 0% grade 2/3 mucositis: photon group, 91% proton group, 46% photon group weight loss, 5.3% proton group weight gain, 1.2%	proton therapy associates with favorable acute toxicity profile
Russo et al., 2016	sinonasal squamous cell carcinoma	retrospective analysis 54 patients stage III IV median dose of 72.8 Gy(RBE) 96% prior surgical resection, 74% elective nodal radiation MGH	2-year and 5-year local control, 80% 2-year overall survival, 67% 5-year overall survival 47%	long-term results show that proton therapy is well tolerated and yields good locoregional control
McDonald et al., 2016	nasopharyngeal and paranasal sinus	comparison study 14 proton, 26 IMPRT patients Winship Cancer Institute		PT with a lower opioid pain requirement at the completion of radiation and a lower rate of gastrostomy tube dependence by the completion of radiation therapy and at 3 months after radiation compared to IMRT

D) ONGOING CLINICAL TRIALS

There are three phase II and III studies registered with Clinicaltrial.gov.

MD Anderson Cancer Center leads a phase II/III randomized trial comparing IMPT and IMRT for oropharyngeal cancer. This study will enroll 360 patients. The primary measure sets the rates and severity of late grade 3-5 toxicity between the two modalities.

MGH leads a phase II study to investigate if proton therapy results in equivalent or improved local control rate with similar or lower toxicity compared to IMRT in treating locally advanced sinonasal malignancy. With 90 patients to enroll, the trial will measure primarily local control at 2 years, and the secondary endpoints including vision preservation, Quality of Life (QoL) and neurocognitive function at 5 years.

The Technische Universität Dresden is conducting a study looking into proton re-irradiation for patients with head and neck cancer in a previously (> 50 Gy) irradiated field. The trial will measure late toxicity as the primary endpoint, as well as survival and QoL as the secondary endpoints.

Title	Type	randomized	comparative	PI	endpoint	No. subject
Re-irradiation of Recurrent Head and Neck Cancer	phase II			Technische Universität Dresden	toxicity, tumor control	50
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	phase III	yes	yes	MD Anderson	toxicity	360
Intensity-Modulated or Proton Radiation Therapy for Sinonasal Malignancy	phase II			MGH	local control, regional control, survival, QoL, neurocognitive functions	90

E) THE EXPERT'S PERSPECTIVE

Dr. Alexander Lin, Director of Clinical Proton Operations, Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania

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 contains 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 after 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 untreatable 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 beginning to emerge, 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 early 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 larger, prospective 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 proton therapy is the newest development in proton radiation, giving us the greatest capabilities to deliver and limit high 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.”

BIBLIOGRAPHY

1. https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet#q4
2. http://www.rtanswers.org/treatmentinformation/cancertypes/headneck/facts/
3. Siegel, RL, Miller, KD & Jemal, A. 'Cancer statistics, 2016', Pubmed 26742998CA: *A Cancer Journal for Clinicians*, 2016, vol. 66, no. 1, pp. 7-30.
4. Nutting, CM, et al. 'Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial', Pubmed 21236730, *The Lancet Oncology*, 2011, vol. 12, pp. 127–136.
5. Frank, SJ. 'Intensity modulated proton therapy for head and neck tumors: gilding the lily or holy grail?', Pubmed 27084621, *International Journal of Radiation Oncology, Biology, Physics*, 2016, vol. 95, no. 1, pp. 37-39.
6. Gragoudas, ES, Munzenrider, JE, Lane, AM & Collier, JM. 'Eye', in Delaney, TF & Kooy, HM (eds.), *Proton and Charged Particles Radiotherapy*, 2008, Lippincott Williams & Wilkins, Philadelphia, PA., pp. 151-161.
7. https://www.astro.org/Practice-Management/Reimbursement/Model-Policies.aspx
8. Cheng, Q, Roeloffs, E, et al. 'Development and evaluation of an online three-level proton vs photon decision support prototype for head and neck cancer - Comparison of dose, toxicity and cost-effectiveness', Pubmed 26924342, *Radiotherapy and Oncology*, 2016, vol. 118, no. 2, pp. 281-285.
9. Truong, MT, Kamat, UR, et al. 'Proton radiation therapy for primary sphenoid sinus malignancies: treatment outcome and prognostic factors', Pubmed 19536762, *Head & Neck*, 2009, vol. 31, no. 10, pp. 1297-1308.
10. Dagan, R, Bryant, C, et al. 'Outcomes of sinonasal cancer treated with proton therapy', Pubmed 27084655, *International Journal of Radiation Oncology, Biology, Physics*, 2016, vol. 95, no. 1, pp. 377-385.
11. Patel, SH, Wang, Z, et al. 'Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis', Pubmed 24980873, *The Lancet Oncology*, 2014, vol. 15, no. 9, pp. 1027-1038.
12. Romesser, PB, Cahlon, O, 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', Pubmed 26867969, *Radiotherapy and Oncology*, 2016, vol. 118, no. 2, pp. 286-292.
13. Grant, SR, Grosshans, DR, et al. 'Proton versus conventional radiotherapy for pediatric salivary gland tumors: Acute toxicity and dosimetric characteristics', Pubmed 26232128, *Radiotherapy and Oncology*, 2015, vol. 116, no. 2, pp. 309-315.
14. McDonald, MW, Liu, Y, et al. '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', Pubmed 26922239, *Radiotherapy and Oncology*, 2016, vol. 11, p. 32.
15. Romesser, PB, Cahlon, O, et al. 'Proton beam reirradiation for recurrent head and neck cancer: multi-institutional report on feasibility and early outcomes', Pubmed 27084656, *International Journal of Radiation Oncology, Biology, Physics*, 2016, vol. 95, no. 1, pp. 386-395.
16. Lomax, AJ, Goitein, M & Adams, J. 'Intensity modulation in radiotherapy: photons versus protons in the paranasal sinus', Pubmed 12559516, *Radiotherapy and Oncology*, 2003, vol. 66, no. 1, pp. 11-18.
17. Taheri-Kadkhoda, Z, Björk-Eriksson, T, et al. 'Intensity-modulated radiotherapy of nasopharyngeal carcinoma: a comparative treatment planning study of photons and protons', Pubmed 18218078, *Radiotherapy and Oncology*, 2008, vol. 3, p.4.
18. Muzik, J, Soukup, M & Alber M. 'Comparison of fixed-beam IMRT, helical tomotherapy, and IMPT for selected cases', Pubmed 18491552, *Medical Physics*, 2008, vol. 35, no. 4, pp. 1580-1592.
19. Liu, SW, Li, JM, et al. 'A treatment planning comparison between proton beam therapy and intensity-modulated x-ray therapy for recurrent nasopharyngeal carcinoma', Pubmed 21045280, *Journal of X-ray Science and Technology*, 2010, vol. 18, no. 4, pp. 443-450.
20. van de Water, TA, Bijl, HP, et al. 'The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature', Pubmed 21349950, *The Oncologist*, 2011, vol. 16, no. 3, pp. 366-377.
21. Bhattacharyya, N, Thornton, AF, et al. Successful treatment of esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation. Results in 9 cases', Pubmed 9006501, *Archives of Otolaryngology – Head & Neck Surgery*, 1997, vol. 123, no. 1, pp. 34-40.

22. Fitzek, MM, Thornton, AF, et al. 'Neuroendocrine tumors of the sinonasal tract. Results of a prospective study incorporating chemotherapy, surgery, and combined proton-photon radiotherapy', Pubmed 12173330, *Cancer*, 2002, vol. 94, no. 10, pp. 2623-2634.

23. Pommier, P, Liebsch, NJ, et al. 'Proton beam radiation therapy for skull base adenoid cystic carcinoma', Pubmed 17116822, Archives of Otolaryngology – *Head and Neck Surgery*, 2006, vol. 132, no. 11, pp. 1242-1249.

24. Russo, AL, Adams, K-JA, et al. 'Long-Term Outcomes After Proton Beam Therapy for Sinonasal Squamous Cell Carcinoma', Pubmed 27084654, *International Journal of Radiation Oncology, Biology, Physics*, 2016, vol. 95, no. 1, pp. 368-376.

25. Tokuuye, K, Akine, Y, et al. 'Proton therapy for head and neck malignancies at Tsukuba', Pubmed 14762662, *Strahlentherapie und Onkologie*, 2004, vol. 180, no. 2, pp. 96-101.

26 Resto, VA, Chan, AW, et al. 'Extent of surgery in the management of locally advanced sinonasal malignancies', Pubmed 17902164, *Head & Neck*, 2008, vol. 30, no. 2, pp. 222-229.

27. Zenda, S, Kohno, R, et al. 'Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses', Pubmed 20961697 *International Journal of Radiation Oncology, Biology, Physics*, 2011, vol. 81, no. 5, pp. 1473-1478 - Epub 2010 Oct 18.

28. Chan, AW, Liebsch, LJ, et al. 'Proton radiotherapy for T4 nasopharyngeal carcinoma' *Journal of Clinical Oncology*, 2004, ASCO Annual Meeting Proceedings., vol. 22, no. 14S, Abstract 5574.

29. Frank, SJ, Rosenthal, DI, et al. 'Gastrostomy tubes decrease by over 50% with Intensity Modulated Proton Therapy (IMPT) during the treatment of oropharyngeal cancer patients: a case –control study', *International Journal of Radiation Oncology, Biology, Physics*, 2013, vol. 87, no. 2, S144.

30. Holliday, E, Garden, A, 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', *International journal of particle therapy*, 2015, vol. 2, no. 1, pp. 19-28.

31. Weber, DC, Chan, AW, et al. 'Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons', Pubmed 17050017, *Radiotherapy and Oncology*, 2006, vol. 81, no. 3, pp. 243-249.

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