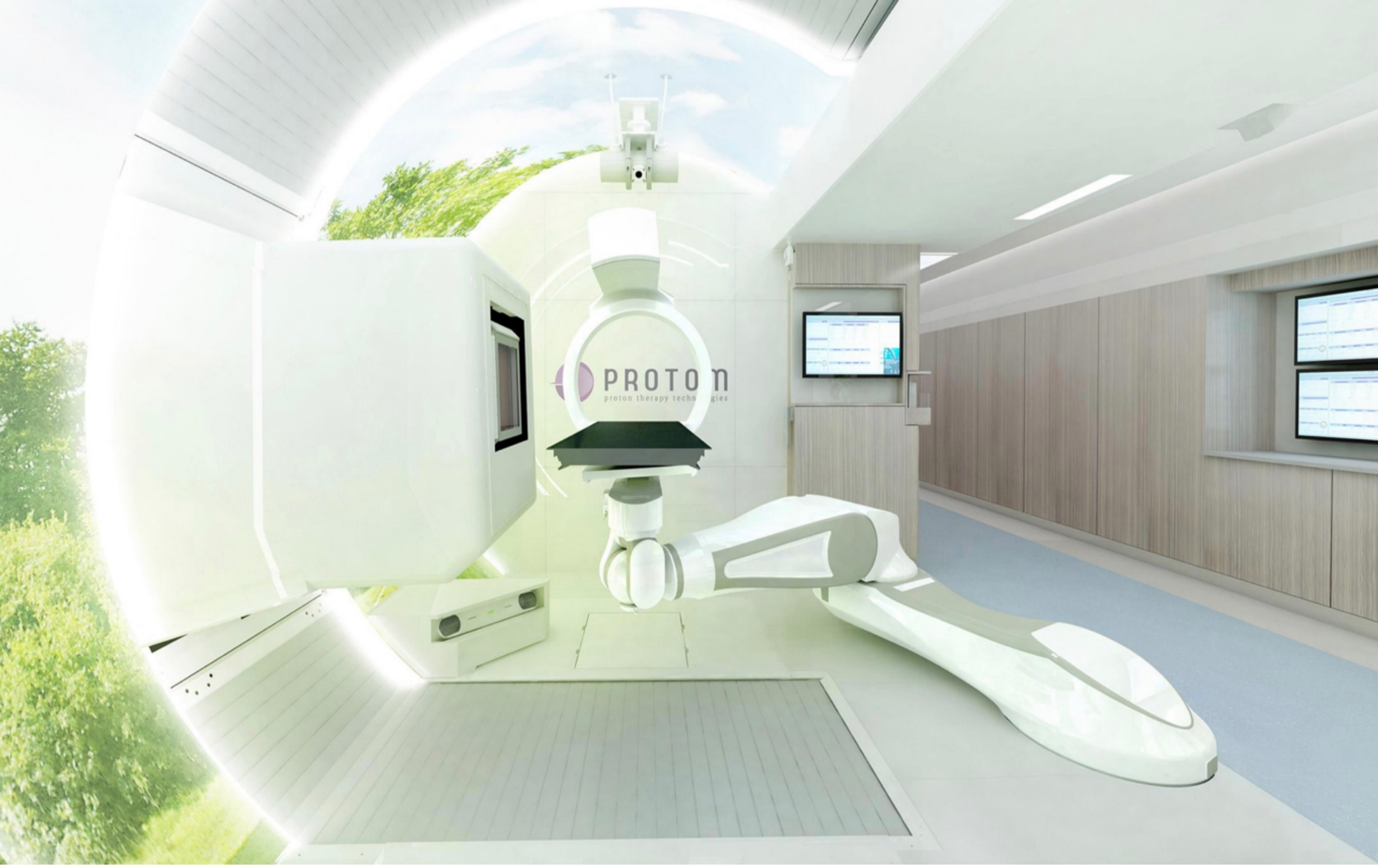

HEAD & NECK CANCERS: TREATMENT WITH PROTON THERAPY

ProTom International | 2019

PROTOM
proton therapy technologies

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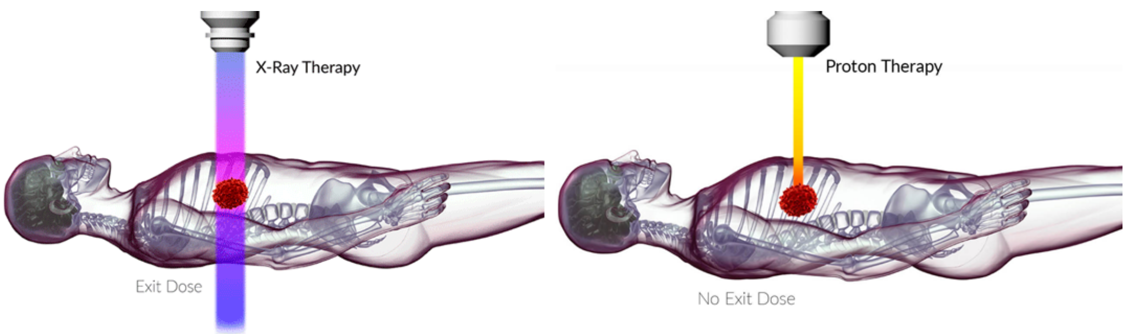
INTRODUCTION: HEAD AND NECK CANCERS AND PROTON THERAPY

Head and neck cancers account for approximately 4% of all cancers in the United States.[1] They include cancers in the pharynx, larynx, oral cavity, throat, lips, mouth, paranasal sinuses and nasal cavity, and salivary glands. These cancers typically begin in the squamous cells that line the mucosal surfaces inside these regions of the body. Because the resulting cancers are often within close proximity to several critical organ structures — such as the brain stem, optic nerves, eyes, and spinal cord — it is imperative to reduce damage to adjacent tissue during treatment.

Proton therapy, or proton beam therapy, is a type of radiation therapy used in the treatment of cancer. Unlike photon-based forms of external beam radiotherapy, proton therapy enables an intense dose distribution pattern, depositing radiation in the precise dimensions of a tumor while eliminating the exit dose and damage to adjacent normal tissue.

Figure 1: Traditional radiation treatment has a relatively high entrance dose and exit dose. Proton therapy has a lower entrance dose and no exit dose.



Because of its unique dose-deposition characteristics, proton therapy is indicated for treating tumors near critical organs and brain tissue, including the treatment of head and neck cancers.

Proton therapy enables radiation oncologists to target tumors with the highest therapeutic radiation dose while sparing nearby critical structures. This improves tumor control, increases the effectiveness of treatment, reduces toxicity, and lessens side effects.[2]

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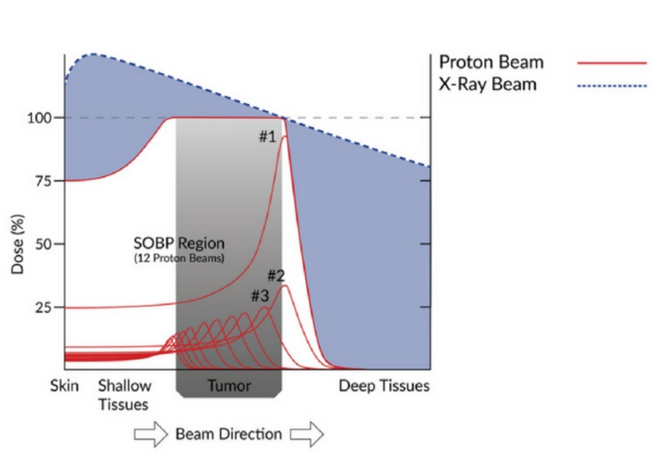
[1] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA: A Cancer Journal for Clinicians 2017; 67(1):7-30.
[2] Holliday EB, Garden AS, et. al. Proton Therapy Reduces Treatment-Related Toxicities for Patients with Nasopharyngeal Cancer: A Case-Match Control Study of Intensity-Modulated Proton Therapy and Intensity-Modulated Photon Therapy. International Journal of Particle Therapy, 2015 2(1), 19-28.

THE ADVANTAGE OF PROTON THERAPY OVER TRADITIONAL RADIATION

In the treatment of cancer, radiation therapy works by attacking a cancer cell's DNA, inhibiting growth and reproduction. While advancements in targeting have made the delivery of photon radiation more exact, it can damage nearby healthy tissue and organs. X-rays deposit their energy on the way to, and then beyond, its target, necessitating administration of entry and exit doses.[3] This additional exposure can cause substantial side effects for patients.

Proton therapy, conversely, leaves healthy tissue undisturbed.[4] This distinct advantage comes from the unique behavior of protons as they move through the body. Demonstrated on the Bragg Curve, protons reach a peak near the end of their path. The absorbed dose of radiation increases very gradually with greater depth, rising to its peak when the protons are stopped. Highly charged protons deliver a treatment dose more directly into targeted tissue and tumors than X-rays. In clinical applications, proton therapy can be administered to a precise depth within a patient's body, to a site as small as a few millimeters in diameter — leaving healthy cells unaffected.[5]

Figure 2: The Bragg Peak



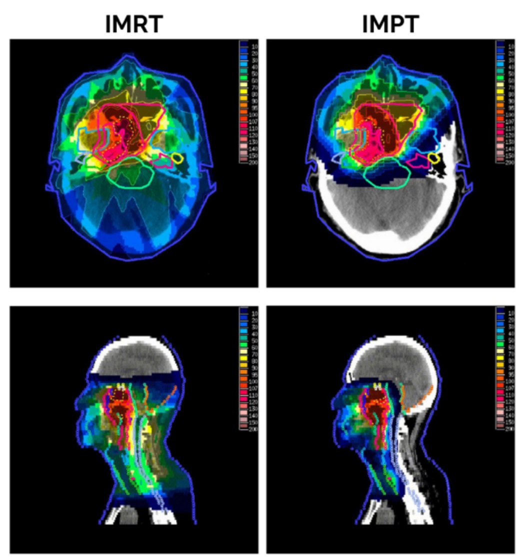
Note: Spread-Out Bragg Peak (SOBP) is defined as the extended uniform dose region in depth formed by the optimal stacking of multiple depth dose curves of pristine peaks of different energies.

[3] Newhauser WD, Zhang R. The physics of proton therapy. Physics in Medicine and Biology. 2015 60(8).
[4] Zhang X, Li Y, et. al. Intensity-Modulated Proton Therapy Reduces the Dose to Normal Tissue Compared With Intensity-Modulated Radiation Therapy or Passive Scattering Proton Therapy and Enables Individualized Radical Radiotherapy for Extensive Stage IIIB Non-Small-Cell Lung Cancer: A Virtual Clinical Study. Int J Radiat Oncol Biol Phys. 2010 June 77(2):357-66.
[5] Welsh J, Gomez D, et. al. Intensity-modulated proton therapy further reduces normal tissue exposure during definitive therapy for locally advanced distal esophageal tumors: A dosimetric study. Int J Radiat Oncol Biol Phys. 2011 81(5): 1336–1342.

In head and neck cancers specifically, proton therapy significantly reduces unnecessary radiation exposure to the spinal cord, auditory canal, and thyroid. By reducing exposure to these critical organs, patients experience less long-term complications and a reduction in the expense of long-term follow-up care following radiation therapy treatment.[6]

Figure 3 shows the difference in radiation exposure between traditional radiation therapy and proton therapy in the treatment of a typical nasopharynx case. In the color washes on the left one can see that with traditional radiation therapy, radiation is delivered to the entire head and neck in the plane of the treatment areas. In the color washes on the right, the dose is focused directly on the nasopharynx areas while sparing normal tissues and critical structures.

Figure 3: Comparative treatment planning for nasopharyngeal carcinoma (Areas shown in red have the highest radiation dose while those in blue have a lower dose. Areas in gray receive no radiation.)



Source: Taheri-Kadkhoda Z, Björk-Eriksson T, Nill S, et al. Intensity-modulated radiotherapy of nasopharyngeal carcinoma: a comparative treatment planning study of photons and protons. Radiat Oncol. 2008 3:4.

[6] Diwanji TP, Mohindra P, et. al. Advances in radiotherapy techniques and delivery for non-small cell lung cancer: benefits of intensity-modulated radiation therapy, proton therapy, and stereotactic body radiation therapy. Transl Lung Cancer Res. 2017 Apr;6(2):131-147.

INDICATIONS FOR USE

Sparing normal tissue and improving quality of life is important for all patients. But when the patient's cancer is located near or in critical organ structures or sensitive tissues, radiation oncologists must take special care to spare healthy structures and preserve their vital functions. The treatment of such tumors benefits significantly from the increased dosing and precision administration of proton therapies.

Proton therapy is most often used in pediatric cancer cases and in adults who have well-defined tumors in or near organs such as the brain, head, neck, or the spine. It is also used to treat tumors for which complete removal cannot be achieved by surgery.[7]

Tumor sites of the head and neck area that benefit from proton therapy include:

- Nasopharynx
- Nasal cavity and paranasal sinus
- Oropharyngeal
- Parotid
- Periorbital
- Base of skull chordomas and chondrosarcomas
- Recurrences of cancer in the head and neck, previously treated with other forms of radiation

While the focus of this paper is the use of proton therapy to treat cancers of the head and neck, it is important to note that other tumors in the head (intracranial lesions such as low-grade gliomas, grade III gliomas, recurrent glioblastoma, meningiomas, ependymomas, medulloblastomas, pineoblastomas, supratentorial PNET, germ cell tumors) also benefit tremendously from proton treatments.[8]

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[7] American Cancer Society. "External Beam Radiation Therapy." https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/radiation/external-beam-radiation-therapy.html. Accessed 22 Feb. 2019.
[8] Steneker M, Lomax A, Schneider U. Intensity modulated photon and proton therapy for the treatment of head and neck tumors. Radiotherapy and Oncology. 2006 Aug. 80(2): 263-267.

BENEFITS

External beam radiation therapy to the head and neck is associated with acute and late toxicity. Complications and side effects may affect patients from the time of treatment through the many years following. Proton therapy, conversely, has been shown to increase patient quality of life measures during and after treatment by limiting out-of-field doses, thereby reducing or eliminating side effects.[9]

During treatment

Common side effects of traditional radiation therapy include mucositis (which can lead to malnutrition through severe pain and difficulty when swallowing), xerostomia, and dysgeusia. These conditions can then lead to hospitalization and treatment interruptions,[10] which may adversely affect disease outcomes.[11] Additional treatment-related benefits of proton therapy include a 50% reduction in the need for a feeding tube during treatment as compared to those treated with traditional radiation therapy.[12],[13],[14]

Following treatment

In addition to dosimetric gains, proton therapy has been linked to more positive toxicity-related outcomes — contributing to better quality of life after treatment. While even the most advanced forms of radiation therapy still cause grade-3 side effects in many patients, proton therapy has been shown to decrease these side effects while increasing patient quality of life outcomes when compared to radiation therapy.[15] Many patients report

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[9] Sharma S, Zhou O, Thompson R, et. al. Quality of Life of Postoperative Photon versus Proton Radiation Therapy for Oropharynx Cancer. International Journal of Particle Therapy. 2018 5(2): 11-17.
[10] Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 2003 66:253-62.
[11] Cox JD, Pajak TF, Marcial VA, et al. Interruptions adversely affect local control and survival with hyperfractionated radiation therapy of carcinomas of the upper respiratory and digestive tracts. New evidence for accelerated proliferation from Radiation Therapy Oncology Group Protocol 8313. Cancer 1992; 69:2744-8.
12 NCBI "Cancer Statistics, 2017." https://www.ncbi.nlm.nih.gov/pubmed/28055103. Accessed 22 Feb. 2019.
[13] Sakthivel V, Ganesh KM, et. al. Second malignant neoplasm risk after craniospinal irradiation in X-ray-based techniques compared to proton therapy. Australas Phys Eng Sci Med. 2019 Feb 6.
[14] Ardenfors O, Dsu A, Lillhök J, et. al. Out-of-field doses from secondary radiation produced in proton therapy and the associated risk of radiation-induced cancer from a brain tumor treatment. Physica Medica: European Journal of Medical Physics. 2018 Sep; 53: 129-136.
[15] Mock U, Georg D, et. al.. 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; 58:147–54.

maintaining the quality of life they enjoyed pre-diagnosis — continuing at their jobs, going to the gym, and spending time with their families.[16]

Proton therapy's unique ability to leave surrounding healthy tissue relatively undisturbed contributes to a number of benefits to individuals with head or neck cancers. These include reduced damage to the eyes and optic nerves, preservation of sight, reduced damage to the auditory structures, preservation of hearing, and reduced dry mouth, which can cause permanent tooth loss and difficulty eating, resulting in malnutrition.[17,18,19]

Patients treated with proton therapy report significantly less head and neck pain, fewer problems with xerostomia, and lower rates of post-treatment dental problems than those treated with IMRT.[20] Proton therapy has also been linked to increased preservation of sensations, secretions, taste, and range of motion.[21]

Late effects

Of concern to long-term cancer survivors are secondary malignancies — at present, 17-19% of primary-malignancy survivors develop a new cancer in the months or years following radiation or chemotherapy treatment.[22]

While out-of-field doses of photon therapy can increase a patient's risk of developing secondary cancers later in life, proton therapy has been found to reduce the lifetime risk of radiation-induced brain cancer to approximately 0.01%.[23]

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[16] C. Bryant, T.L. Smith, R.H. Henderson, et. al. Five-Year Biochemical Results, Toxicity, and Patient-Reported Quality of Life Following Delivery of Dose-Escalated Image-Guided Proton Therapy for Prostate Cancer. Int J Radiat Oncol Biol Phys. 2016 95(1):422-34.
[17] Steneker M, Lomax A, Schneider U. Intensity modulated photon and proton therapy for the treatment of head and neck tumors. Radiother Oncol. 2006 80(2):263-267.
[18] Taheri-Kadkhoda Z, Björk-Eriksson T, Nill S, et al. Intensity-modulated radiotherapy of nasopharyngeal carcinoma: a comparative treatment planning study of photons and protons. Radiat Oncol. 2008 3:4.
[19] Chao KSC, Deasy JO, Markman J, et al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys. 2001 49(4):907-916.
[20] Bernier J, Cooper JS, et. al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005 27:843–50.
[21] Pearlstein KA, Wang K, Amdur RJ. Quality of Life for Patients With Favorable-Risk HPV-Associated Oropharyngeal Cancer After De-intensified Chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2019 Mar 1;103(3):646-653.
[22] Morton LM, Onel K, et. al. The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults. Am Soc Clin Oncol Educ Book. 2014 e57–67.
[23] Ardenfors O, Dsu A, Lillhök J, et. al. Out-of-field doses from secondary radiation produced in proton therapy and the associated risk of radiation-induced cancer from a brain tumor treatment. Physica Medica: European Journal of Medical Physics. 2018 Sep; 53: 129-136.

Additionally pencil-beam scanning proton therapy has been shown to effectively reduce tumor recurrence for skull-base low-grade chondrosarcomas and chordomas.[24]

Taken in sum, these benefits provide significant increases to quality of life measures at all lengths of follow-up.

Clinical Efficacy of Proton Therapy to Patients with Cancers of the Head and Neck

An ideal treatment modality for patients with head and neck cancers, proton therapy provides both dosimetric and clinical advantages for treating tumors near critical structures. Its improved dose targeting allows nearby organs such as the salivary glands, larynx, and esophagus, to be spared from treatment dosing. This superior method of dosing, along with reducing toxicity, also decreases the risk of recurring or secondary radiation-related cancers.

Notable studies published in recent years have shown proton therapy's potential in treating head and neck cancers.

The paper *Reduced acute toxicity and improved efficacy form intensity-modulated proton therapy (IMPT) for the management of head and neck cancer,*[25] published in the journal *Chinese Clinical Oncology*, provides an overview of the research. The paper examines the existing evidence on toxicity, treatment outcomes, and survival rates of patients treated with IMPT. The authors report on the ability to target the tumor with precision, and decreased side-effects including reduced malnutrition, and gastrostomy tube dependence and improved patient-reported outcomes. The paper highlights the primary advantages of using proton beam therapy for the treatment of head and neck cancers:

> "Cancers in the head and neck area are usually close to several critical organ structures. Traditional external-beam photon radiation therapy unavoidably exposes these structures to significant doses of radiation, which can lead to serious acute and chronic toxicity. Intensity-modulated proton therapy (IMPT),

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[24] Weber DC, Malyapa R, Albertini F, et. al. Long term outcomes of patients with skull-base low-grade chondrosarcoma and chordoma patients treated with pencil beam scanning proton therapy. Radiother Oncol. 2016 Jul 120(1):169-74.
[25] McKeever MR, Sio TT, Gunn GB, et. al. Reduced acute toxicity and improved efficacy from intensity-modulated proton therapy (IMPT) for the management of head and neck cancer. Chin Clin Oncol. 2016 Aug;5(4):54.

however, has dosimetric advantages that allow it to deposit high doses within the target while largely sparing surrounding structures”.

The paper concludes that IMPT is safe and effective treatment for head and neck tumors:

> “IMPT eliminates the unnecessary radiation delivered to proximal organs and structures associated with IMRT and seems to be associated with improved [patient reported outcomes] PROs during the first 3 months after treatment, decreased gastrostomy tube dependence, and lower rates of grade ≥3 toxicity while resulting in equivalent or improved effectiveness for tumors at a variety of anatomical subsites of the head and neck.”

Oral Cavity

Lip and oral cavity cancer is characterized as a disease in which malignant cells form in the lips or mouth. Tobacco and alcohol use are known to increase the risk of cancers of the oral cavity. Treatment of the soft tissue, in which oral cavity cancers often begin, makes it difficult to avoid unwanted radiation to the jaw bone — increasing the risk of infection and fracture of the mandible.[26]

A comparative review of patients treated with IMRT to patients treated with IMPT found that, for patients with oropharyngeal cancer, proton therapy led to significantly reduced treatment doses to the mandible compared with IMRT.[27]

Pharynx and Larynx

Cancers that develop in the throat can affect the pharynx, voice box (larynx), or tonsils. It most frequently starts in the cells that line the inside of the throat. Throat cancer can also affect the epiglottis.

One recent study considering longer-term quality of life outcomes followed patients with oropharyngeal cancer for a full year. Participants were either treated with intensity modulated radiation therapy (IMRT) or pencil beam scanning proton therapy (PBS). Findings indicate proton therapy increases head- and neck-specific, as well as general, quality of life measures.[28] Patients treated with proton therapy reported significantly less head and neck

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[26] Zhang W, Zhang X, Yang P, er. al. Intensity-modulated proton therapy and osteoradionecrosis in oropharyngeal cancer. Radiother Oncol. 2017 Jun;123(3):401-405.
[27] Zhang W, Zhang X, Yang P, er. al. Intensity-modulated proton therapy and osteoradionecrosis in oropharyngeal cancer. Radiother Oncol. 2017 Jun;123(3):401-405.
[28] Sharma S, Zhou O, Thompson R, et. al. Quality of Life of Postoperative Photon versus Proton Radiation Therapy for Oropharynx Cancer. International Journal of Particle Therapy. 2018

pain, fewer problems with xerostomia, and lower rates of post-treatment dental problems than those treated with IMRT.

Another longer-term study examined proton therapy's role in the treatment of oropharynx cancers. Researchers supplementally treated 29 study participants with protons. Side effects of treatment were drastically reduced when compared to patients treated with only photon therapy. After only three months, proton therapy was shown to significantly reduce rates of feeding tube dependency and drastic weight loss. Further, the 2- and 5-year locoregional control rates were 93% and 84% respectively, while treatment showed to be well tolerated with late grade 3-toxicities reported in only three patients.[29]

Paranasal sinuses and nasal cavity

There are unique challenges for the treatment of paranasal sinuses and nasal cavity carcinomas. Due to tumor location, surrounding neurological structures are at risk for high doses of treatment radiation. Possible side effects from this integral radiation include hearing impairment, optic neuropathy, or temporal lobe necrosis.

Clinical data published by the M.D. Anderson Cancer Center at the University of Texas indicates treatment of nasopharyngeal carcinomas with proton therapy provides substantial benefits over IMRT.[30] Locoregional control and overall survival at 2 years was 100% and 89%, respectively.

Further, in a dosimetric comparison between treatment IMPT plans and theoretical IMRT plans in this study, 87% of cases showed proton therapy to be more advantageous for organs at risk. Other non-comparative observational studies of paranasal sinus and nasal cavity patients indicate an improved overall survival rate for patients treated with proton therapy compared to IMRT.[31] Moreover, disease-free survival rates are significantly higher for patients treated with proton therapy.

Salivary glands

Recent findings are also supportive of proton therapy use for tumors of the salivary glands. Proton therapy allows for greater sparing of normal tissue without sacrificing target

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[29] Moreno A, Frank S, et. al. Intensity modulated proton therapy (IMPT) – The future of IMRT for head and neck cancer. Oral Oncology. 2018 Jan 88:66-74.
[30] Moreno A, Frank S, et. al. Intensity modulated proton therapy (IMPT) – The future of IMRT for head and neck cancer. Oral Oncology. 2018 Jan 88:66-74.
[31] Moreno A, Frank S, et. al. Intensity modulated proton therapy (IMPT) – The future of IMRT for head and neck cancer. Oral Oncology. 2018 Jan 88:66-74.

coverage when irradiating the ipsilateral neck. This dosimetric advantage means significantly lower rates of treatment-related toxicity including dysgeusia, mucositis, and nausea.[32]

CONCLUSION

Because it targets tumors with precision, proton therapy gives radiation oncologists a promising option in treatment planning for head and neck cancer patients.

This seems particularly relevant, as the United States continues to witness a rapid rise in incidences of HPV-related oropharyngeal cancers.[33] The Centers for Disease Control and Prevention estimates that more than 90% of sexually active men and 80% of sexually active women will be infected with at least one type of HPV during their lifetime.[34] Around one-half of these infections are with a high-risk HPV type[35], which can cause cancer.

The dosimetric advantages proton therapy offers can reduce treatment-related toxicity and provide potential dose escalation while protecting surrounding healthy tissues and organ structures from integral doses. As research on proton therapy continues to emerge, it is likely that proton therapy will be established as a standard of care for the management of head and neck cancers.

[32] Romesser PB, Cahlon O, Scher E, 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.
[33] National Cancer Institute. Head and Neck Cancers" https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet. Accessed 22 Feb. 2019.
[34] National Cancer Institute. Head and Neck Cancers" https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet. Accessed 22 Feb. 2019.
[35] National Cancer Institute. Head and Neck Cancers" https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet. Accessed 22 Feb. 2019.

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