Life.
Science.

Bibliography of Proton Therapy Highlights.

Updated in December 2023

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.

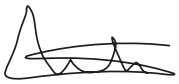
Our purpose is to offer more cancer patients effective treatments, decreased side effects, leading to a better quality of life.

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 and gather and share information on the use of proton therapy in oncology.

In this booklet, we've compiled a list of key scientific publications sorted by indications. 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 hope that you will find this selection of bibliography informative and helpful.



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DISCOVER MORE ABOUT IBA

DISCOVER MORE ABOUT PROTON THERAPY

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This literary review is a selection of articles about proton therapy and is not intended to be an exhaustive bibliography.

Reference Works

■ **Steven J Frank and X. Ronald Zhu. Proton Therapy: Indications, Techniques and Outcomes. 1st Edition. May 21, 2020, Elsevier.**

This book provides up-to-date information on indications for proton therapy and outcomes after proton therapy by disease site, including prostate, head and neck, pediatrics, central nervous system, gastrointestinal, sarcomas, lungs, breast, lymphomas, and gynecologic cancers. The book also discusses technologic advances such as spot scanning and treatment planning systems; radiobiology including DNA damage and repair mechanisms and acute and late effects on normal tissues; and multifield optimized intensity-modulated proton therapy (MFO-IMPT) for optimizing the distribution of linear energy transfer (LET) of proton beams within target volumes and away from critical normal structures.

■ **Bleddyn Jones. Practical Radiobiology for Proton Therapy. January 2018. IOP Publishing Ltd.**

This book blends the relevant physics, biology and medical aspects of this multidisciplinary subject, covering the principles, advantages and potential pitfalls that occur in proton therapy, especially its radiobiological modelling applications. The book provides clear descriptions of useful equations for high LET particle beam applications, worked examples of important clinical situations, and discussion of how proton therapy may be optimized.

■ **Harald Paganetti. Proton Beam Therapy. January 2017. IOP Publishing Ltd.**

Clinical proton therapy has been growing rapidly with currently more than 50 facilities worldwide. This book first evaluates the basics of proton therapy physics and technology and then outlines some of the current physical, biological, and clinical challenges. Solving these will ultimately determine whether proton therapy will continue on its path to becoming mainstream.

■ **Indra J. Das and Harald Paganetti. Principles and Practice of Proton Beam Therapy. By American Association of Physicists in Medicine 2015. Medical Physics Monograph No. 37. Medical Physics Publishing. Inc.**

Proton therapy has been used in radiation therapy for over 70 years, but within the last decade its use in clinics has grown exponentially. This book fills in the proton therapy gap by focusing on the physics of proton therapy, including beam production, proton interactions, biology, dosimetry, treatment planning, quality assurance, commissioning, motion management, and uncertainties.

■ **Charlie Ma C.M. and Lomax T., "Proton and Carbon Ion Therapy", 2012, CRC Press.**

This user guide for proton and carbon ion therapy in modern cancer treatment covers the physics and radiobiology of proton and ion beams, dosimetry methods, radiation measurements, treatment delivery systems, patient setup, target localization and treatment planning for clinical proton and carbon ion therapy. Detailed reports are also given on the treatment of pediatric cancers, lymphomas, and various other cancers.

■ **Paganetti H., "Proton Therapy Physics", 2012, Series in Medical Physics and Biomedical Engineering, Massachusetts General Hospital and Harvard Medical School, Boston, USA.**

"Proton Therapy Physics" covers delivery methods of PT (including beam scanning and passive scattering) and clinical aspects (treatment planning and quality assurance), explores research topics such as biological treatment planning, and offers insight on the past, present, and future of PT from a physics perspective.

■ **Yajnik S., "Proton Beam Therapy: How Protons Are Revolutionizing Cancer Treatment", 2012, Springer.**

Discussed here are the conditions suitable for treatment with PT, how the treatment is delivered, and the current data supporting its use.

■ **Metz J.M. and Thomas R.T. Jr., "Proton Therapy", 2010, Radiation Medicine Rounds, Volume 1, Issue 3.**

This work provides a comprehensive review for practitioners on the current status of PT, its scientific basis and current clinical applications, reviews of the available clinical evidence, discussions of costs and technology development, issues in establishing a PT center, and the future development of PT as a tool in clinical practice.

Cost-Effectiveness and Quality of Life

■ **Brodin NP, et al. Individualized quality of life benefit and cost-effectiveness estimates of proton therapy for patients with oropharyngeal cancer. Radiat Oncol. 2021 Jan 21;16(1):19.**

Proton therapy was more likely to be cost-effective for patients with p16-positive tumors ($234,201/QALY), compared to p16-negative tumors ($516,297/QALY). For patients with p16-positive tumors treated with comprehensive nodal irradiation, proton therapy is estimated to be cost-effective in ≥ 50% of sampled cases for 8/9 patients at $500,000/QALY. The conclusion is that PBT cost-effectiveness varies greatly among oropharyngeal cancer patients, and highlights the importance of individualized decision-making.

■ **Smith GL, Shih YCT and Frank SJ. Financial Toxicity in Head and Neck Cancer Patients Treated With Proton Therapy. Int J Part Ther. 2021 Jun 25;8(1):366-373.**

While cost-effectiveness analysis has been used to assess the value of proton therapy for head and neck cancer, it may not fully incorporate empiric comparisons of patients' and survivors' lost productivity and disability after treatment. A cost-of-illness framework for evaluation could address this gap, thereby more comprehensively identifying the value of proton therapy and distinctly incorporating a measurable aspect of financial toxicity in evaluation. Overall, financial toxicity burdens remain understudied in head and neck cancer patients from a patient-centered perspective.

■ **Mailhot Vega RB, et al. Establishing cost-effective allocation of proton therapy for patients with mediastinal Hodgkin lymphoma. Int J Radiat Oncol Biol Phys. 2022 Jan 1;112(1):158-166.**

A 30-year-old adult with MHL was the base case using 30.6 Gy PT versus IMRT. This study found that PT was not cost-effective in the base case for male ($129K/QALY) or female patients ($196/QALY). A 5-Gy mean heart dose decrease was associated with proton therapy incremental cost-effectiveness ratio<$100K/QALY in 40% of scenarios. Proton therapy may be cost-effective a select minority of patients with MHL based on age, sex, and MHD reduction.

■ **Li G, et al. Intensity-modulated proton radiation therapy as a radical treatment modality for nasopharyngeal carcinoma in China: A cost-effectiveness analysis. Head Neck. 2022 Feb;44(2):431-442.**

A Markov model is used with the assumption that IMPT offered NTCP reduction in long-term dysphagia, xerostomia, and hearing loss, compared to IMRT. Base-case evaluation was performed on T2N2M0 nasopharyngeal carcinoma (NPC) of median age (43 years old). A Chinese societal willingness-to-pay threshold (33558 US dollars/QALY) was adopted. IMPT is cost-effective for average Chinese NPC patients if IMPT provides an NTCP reduction of ≥24%.

■ **Aldenhoven L, et al. Cost-effectiveness of proton radiotherapy versus photon radiotherapy for non-small cell lung cancer patients: Exploring the model-based approach. Radiother Oncol. 2023 Jun:183:109417.**

Dyspnea, dysphagia and cardiotoxicity were the toxicities included in the model calculation. Costs and QALY's were incorporated for grade 2 and ≥3 toxicities separately. Incremental Cost-Effectiveness Ratios (ICERs) were compared to a threshold value of €80,000. PT is not cost-effective for all patients, nor for patient selected on the current NTCP models used in the Dutch indication protocol. PTIndividualized was considered the most cost-effective strategy (ICER: €76,299).

■ **Hiroshima Y, et al. Analysis of the cost-effectiveness of proton beam therapy for unresectable pancreatic cancer in Japan. Cancer Med. 2023 Oct;12(20):20450-20458.**

This study from Japan estimated the incremental cost-effectiveness ratio (ICER) of PBT as a replacement for three-dimensional conformal RT (3DCRT). The effectiveness of PBT and 3DCRT was 1.67610615 and 0.97181271 QALY, respectively. The ICER was estimated to be ¥5,376,915 (US$46,756) per QALY. With the threshold for anti-cancer therapy by the Japanese authority of ¥7,500,000 (US$65,217) per QALY gain, PBT replacing 3DCRT is cost-effective and justifiable as an efficient use of finite healthcare resources.

■ **Bharathi R P, et al. A Systematic Review of the Economic Burden of Proton Therapy in Head and Neck Cancer. Asian Pac J Cancer Prev. 2023 Nov 1;24(11):3643-3653.**

Based on 10 original studies, this systematic review reported that PBT can be cost-effective for HPV-associated tumors and for younger patients. A clinically substantial decrease in toxicities (xerostomia, oral mucositis, dysphagia, and percutaneous endoscopic gastrostomy tube implantation) is necessary for patients to be cost-effective candidates for PBT. Appropriate patient selection is required.

■ **Choi JI, et al. Advances and Challenges in Conducting Clinical Trials With Proton Beam Therapy. Semin Radiat Oncol. 2023 Oct;33(4):407-415.**

Proton therapy has arisen over the past 2 decades with indications grown beyond pediatric, prostate, spine, and ocular tumors. Calls have been growing for high-level evidence to demonstrate the clinical benefit to support its use given its higher cost. This article examined the current status of proton therapy clinical research providing details of completed and ongoing randomized control trials comparing protons and photons, as well as in-depth discussions on challenges and barriers for conducting randomized control trials.

■ **Sher DJ, et al. Cost-Effectiveness Analysis of Intensity Modulated Radiation Therapy Versus Proton Therapy for Oropharyngeal Squamous Cell Carcinoma. Int J Radiat Oncol Biol Phys. 2018 Jul 15;101[4]:875- 882.**

A cost effectiveness comparison based on the Markov model with assumption that PBT led to a 25% reduction in long- term xerostomia, short-term dysgeusia, and the need for gastrostomy tube. The study found that PBT only cost-effective for HPV-positive younger patients who experienced a 50% reduction in both xerostomia and gastrostomy use.

■ **Smith W, et al. Decision analytic modeling for the economic analysis of proton radiotherapy for non-small cell lung cancer. Transl Lung Cancer Res. 2018 Apr;7[2]:122-133.**

An economic analysis comparing proton vs. X-ray radiotherapy for locally advanced non-small cell lung cancer patients based on a toxicity-adjusted, rate-adjusted, risk group-adjusted, and radiosensitivity model. Protons would be expected to recover some cost difference compared to 3DCRT or IMRT, but the current costs favor X-ray therapy.

■ **Verma V, et al. Quality of Life and Patient-Reported Outcomes Following Proton Radiation Therapy: A Systematic Review. J Natl Cancer Inst. 2018 Apr 1;110[4].**

Evaluating quality of life [QOL] and patient-reported outcomes [PROs] is essential to establishing PBT's "value" in oncologic therapy. This systematic review concluded that PBT provides favorable QOL/PRO profiles for select brain, head/ neck, lung, and pediatric cancers; measures for prostate and breast cancers were more modest.

■ **Verma V et al. Cost-comparativeness of proton versus photon therapy. Chin Clin Oncol. 2016 Aug;5[4]:56.**

This review examines PBT health economics studies, evaluating both the design and results. It is recognized that PBT likely will not be the most economical option uniformly for all cancers, rather, subgroups of patients [as stratified for patient, treatment, and tumor characteristics, among others] for various cancers will need to be delineated as those most likely to "economically benefit" from PBT.

■ **Verma V et al. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. Cancer. 2016 May 15;122[10]:1483-501.**

This review article reported that PBT offers promising cost-effectiveness for pediatric brain tumors, well-selected breast cancers, locoregionally advanced NSCLC, and high-risk head/neck cancers. It has not been demonstrated that PBT is cost-effective for prostate cancer or early stage NSCLC. Careful patient selection is absolutely critical to assess cost- effectiveness.

■ **Mailhot Vega RB et al. Establishing Cost-Effective Allocation of Proton Therapy for Breast Irradiation. Int J Radiat Oncol Biol Phys. 2016 May 1;95[1]:11-8.**

Cardiac toxicity due to conventional breast radiation therapy has been extensively reported, and it affects both the life expectancy and quality of life of affected women. Scenarios do exist whereby proton therapy is cost-effective. Referral for proton therapy may be cost-effective for patients with ≥1 cardiac risk factor and in cases for which photon plans are unable to achieve an mean heart dose <5 Gy

■ **Mailhot Vega R et al. Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. Cancer. 2015 May 15;121[10]:1694-702.**

This study developed a Markov model to assess the expected costs and effectiveness for specific radiation doses to the hypothalamus with protons versus photons in pediatric patients. Proton therapy may be more cost effective for scenarios in which radiation dose to the hypothalamus can be spared, but protons may not be cost effective when tumors are involving or directly adjacent to the hypothalamus if there is a high dose to this structure.

■ **Hirano E et al. Cost-effectiveness analysis of cochlear dose reduction by proton beam therapy for medullo blastoma in childhood. J Radiat Res. 2014 Mar 1;55[2]:320-7.**

This study examined the cost-effectiveness of proton beam therapy with cochlear dose reduction compared with con- ventional X-ray radiotherapy for medulloblastoma in childhood. Cost-effectiveness acceptability curve analysis revealed a 99% probability of proton therapy being cost effective at a societal willingness-to-pay value.

■ **Mailhot Vega RB et al. Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. Cancer. 2013 Dec 15;119[24]:4299-307.**

A population of pediatric medulloblastoma survivors aged 18 years was studied who had received treatment at age 5 years and who were at risk of developing 10 adverse events, such as growth hormone deficiency, coronary artery dis- ease, ototoxicity, secondary malignant neoplasm, and death. The study indicated that proton therapy is a cost-effective strategy for the management of pediatric patients with medulloblastoma compared with standard of care photon therapy.

Patient Selection and Clinical Trials

■ **Tambas M, et al. Development of advanced preselection tools to reduce redundant plan comparisons in model-based selection of head and neck cancer patients for proton therapy. Radiother Oncol. 2021 Jul:160:61-68.**

Using data from VMAT plans and volumetric data from delineated targets and OARs, the researchers developed the advanced preselection tools that prevented labor intensive creation of IMPT plans in up to 68% of non-qualifying patients for PT, and no false negative cases, i.e. no patients qualifying for PT would have been incorrectly denied a plan comparison.

■ **Boersma LJ, et al. Model-Based Selection for Proton Therapy in Breast Cancer: Development of the National Indication Protocol for Proton Therapy and First Clinical Experiences.**

The model of Darby et al. (N Engl J Med 2013; 368:987-82) was used for estimation of the relative risk of an acute coronary event (ACE) based on the mean heart dose. Based on a threshold value of a 2% absolute lower risk on ACE for proton therapy compared with photons, 268 breast cancer patients have been treated in the Netherlands with proton therapy between February 2019 and January 2021.

■ **Dutz A, et al. Identification of patient benefit from proton beam therapy in brain tumour patients based on dosimetric and NTCP analyses. Radiother Oncol. 2021 Jul:160:69-77.**

This study used data of 92 patients treated with protons to create VMAT plans for comparison. NTCP differences were calculated for 11 models predicting brain necrosis, delayed recall, temporal lobe injury, hearing loss, tinnitus, blindness, ocular toxicity, cataract, endocrine dysfunction, alopecia, and erythema. If ΔNTCP exceeded a threshold of 10 percentage points for at least one of the side-effects, considering ΔNTCP of all models, 80 patients (87.0%) would have been selected for PBT in this in-silico study, mainly due to predictions of a model on delayed recall (51 patients).

■ **Loizeau N, et al. Optimal allocation of proton therapy slots in combined proton-photon radiotherapy. Int J Radiat Oncol Biol Phys. 2021 Sep 1;111(1):196-207.**

Using a cohort of 45 head-and-neck cancer patients for which IMRT and IMPT plans were previously created, in combination with NTCP models for xerostomia and dysphagia, this study developed methods to optimally assign proton fractions in combined proton-photon treatments to minimize the average NTCP on a population level.

■ **Zientara N, et al. A scoping review of patient selection methods for proton therapy. J Med Radiat Sci. 2022 Mar;69(1):108-121**

This review explored various methods used for selecting cancer patients for proton versus X-ray radiation therapy. Within the 49 articles included for analysis, six different clinical decision-making tools and 14 dose comparison methods were identified. The most commonly reported patient selection tools included the Normal Tissue Complication Probability model, followed by cost-effectiveness modelling and dosimetry comparison.

■ **Tambas M, et al. First experience with model-based selection of head and neck cancer patients for proton therapy. Radiother Oncol. 2020 Aug 5;S0167-8140(20)30715-5.**

This study reported the first experience in model-based selection of HNC patients in the Netherlands. 227 patients were included in this study where 141 (62%) qualified for plan comparison when exceeding any ΔNTCP-thresholds defined in Dutch National Indication Protocol. 80 (35%) patients were eventually selected for proton therapy. The study concluded that model-based selection of patients with HNC for proton therapy is clinically feasible. Approximately one third of HNC patients qualify for protons.

■ **Scherman J, et al. Incorporating NTCP into Randomized Trials of Proton Versus Photon Therapy. Int J Part Ther. Winter 2019;5(3):24-32.**

This study proposed and simulated a model-based methodology to incorporate heterogeneous treatment benefit of proton therapy versus photon therapy into randomized trial designs. Using radiation-induced pneumonitis (RP) as an exemple, ΔNTCP data from treatment plans for photon therapy and proton therapy for patients with locally advanced lung cancer as well as randomly sampled clinical risk factors were included in simulations of trial outcomes.

■ **Ofuya M, et al. Systematic review of methodology used in clinical studies evaluating the benefits of proton beam therapy. Clin Transl Radiat Oncol. 2019 Jul 12;19:17-26.**

This systematic review examined the methodology used in clinical trials that reported PBT benefits. Out of the 219 studies included, prospective studies comprised 89/219 (41%), and of these, the number of randomised phase II and III trials were 5/89 (6%) and 3/89 (3%) respectively. Of all the phase II and III trials, 18/24 (75%) were conducted at a single PBT centre. Research design and/or findings were poorly reported in 74/89 (83%) of prospective studies.

■ **Arts T, et al. The impact of treatment accuracy on proton therapy patient selection for oropharyngeal cancer patients. Radiother Oncol. 2017 Dec;125(3):520-525.**

This study investigated the impact of treatment accuracy on NTCP-based patient selection for proton therapy. For high-precision IMRT (3 mm margin) and high-precision IMPT (3 mm setup/3% range error), most patients were selected for proton therapy based on problems swallowing solid food (51.3%) followed by tube feeding dependence (37.2%), decreased parotid flow (29.5%), and patient-rated xerostomia (7.7%).

■ **Langendijk JA, et al. Clinical Trial Strategies to Compare Protons with Photons. Semin Radiat Oncol. 2018 Apr;28(2):79-87.**

For validation of the added value of protons to improve local control, randomized controlled trials are required. However for the added value of protons to prevent side effects, both model-based validation and randomized controlled trials can be used. Combining these approaches is most efficient and scientifically sound to improve patient selection and the therapeutic window, leading to more cancer survivors with better quality of life.

■ **Bekelman JE, et al. Randomized Trials of Proton Therapy: Why They Are at Risk, Proposed Solutions, and Implications for Evaluating Advanced Technologies to Diagnose and Treat Cancer. J Clin Oncol. 2018 Jul 9:JCO2018777078.**

The National Cancer Institute (NCI) and the Patient-Centered Outcomes Research Institute (PCORI) have made major investments to fund seven randomized clinical trials evaluating the benefits and harms of proton therapy for cancers of the breast, lung, prostate, glioblastoma, esophageal, low-grade glioma, and liver. However, the biggest barrier to enrollment is insurance coverage, and other barriers include disincentives to physician engagement and patient preference.

■ **Delaney AR et al. Using a knowledge-based planning solution to select patients for proton therapy. Radiother Oncol. 2017 Apr 12.**

Using plan-libraries to model and predict organ-at-risk (OAR) dose-volume-histograms (DVH), proton and photon knowledge-based-plans (KBPs) were made and compared for head and neck patients. The authors reported that these knowledge-based DVH-predictions can provide efficient, patient-specific selection for protons, and improve results.

■ **Mishra MV et al. Establishing Evidence-Based Indications for Proton Therapy: An Overview of Current Clinical Trials. Int J Radiat Oncol Biol Phys. 2017 Feb 1;97(2):228-235.**

PBT clinical trials are rapidly expanding. Total 122 ongoing trials with target enrollment of over 42,000 patients. However, observational studies accounted for 21% of trials but 71% (n=29,852) of planned patient enrollment. Studies should be evaluated in terms of comparative effectiveness, as well as incremental effectiveness and value offered by PBT in comparison with conventional radiation modalities.

■ **Blanchard P et al. Toward a model-based patient selection strategy for proton therapy: External validation of photon-derived normal tissue complication probability models in a head and neck proton therapy cohort. Radiother Oncol. 2016 Dec;121(3):381-386.**

192 HNC patients with tumor sites of oropharynx, sinonasal, nasopharynx and parotid glands were analyzed. Apart from the prediction of acute mucositis, the models performed well in predictions of feeding tube, dysphagia, dry mouth, and hypothyroidism. The authors concluded that the study result supports the validity of the model-based approach for selecting treatment for proton therapy.

■ **Grutters J. et al. When to wait for more evidence? Real options analysis in proton therapy. The Oncologist. 2011;16(12):1752-61.**

As it is often unclear whether to adopt a new technology for cancer treatment or to wait for more evidence, a technique originating from financial economics called "real options analysis" can help make this trade-off. Regarding proton therapy, adopt and trial was found to be the preferred option.

■ **Dvorak T., Wazer D.E. Evaluation of potential proton therapy utilization in a market-based environment. Journal of the American College of Radiology. 2010;7(7): 522-8.**

Existing utilization patterns of highly conformal RT were used to estimate that about 1/3 of a patients irradiated annually at the institution could be potentially treated with PT, with an incremental cost of 20% across the entire treated patient population.

Radiation-Induced Secondary Cancers

■ **Indelicato DJ, et al. Second tumor risk in children treated with proton therapy. Pediatr Blood Cancer. 2021 Jul;68(7):e28941.**

This study evaluated the secondary tumor risk based on the data of 1713 children underwent proton therapy. 371 patients were ≤3 years old and 37 patients (2.2%) had tumor predisposition syndromes. The median follow-up was 3.3 years and 549 patients had ≥5 years of follow-up. This study reported that 11 patients developed second tumors; the 5- and 10-year cumulative incidences were 0.8% and 3.1%. Excluding patients with tumor predisposition syndromes, 5- and 10-year rates were 0.6% and 1.7%.

■ **Taylor S, et al. Risk of radiation-induced second malignant neoplasms from photon and proton radiotherapy in pediatric abdominal neuroblastoma. Phys Imaging Radiat Oncol. 2021 Jul 9:19:45-52.**

The risk of radiation-induced SMN was estimated using the concept of organ equivalent dose (OED) for eleven organs (lungs, rectum, colon, stomach, small intestine, liver, bladder, skin, central nervous system, bone, and soft tissues). The risk ratio (RR) between radiotherapy modalities and lifetime absolute risks (LAR) were reported for twenty abdominal neuroblastoma patients historically treated with 3D-CRT that were also retrospectively replanned for IMAT and PBS-PT. This study reported that PBS-PT was associated with the lowest risk of radiation-induced SMN compared to IMAT and 3D-CRT in abdominal neuroblastoma treatment.

■ **König L, et al. Secondary Malignancy Risk Following Proton vs. X-ray Radiotherapy of Thymic Epithelial Tumors: A Comparative Modeling Study of Thoracic Organ-Specific Cancer Risk. Cancers (Basel). 2022 May 13;14(10):2409.**

A modeling study demonstrated significant reduction in secondary malignancy (SM) with the use of PBS relative to both 3DCRT and IMRT for all independent thoracic organs analyzed with the exception of the thyroid gland ($p \leq 0.001$). SM rates per 10,000 patients per year per Gy also resulted in significant reductions with the use of PBS relative to 3DCRT and IMRT for the lungs, breasts, and esophagus ($p \leq 0.001$). The authors concluded that PBS should therefore be considered in patients diagnosed with thymic malignancies, particularly young female patients.

■ **Upadhyay R, et al. Risk of secondary malignant neoplasms in children following proton therapy vs. photon therapy for primary CNS tumors: A systematic review and meta-analysis. Front Oncol. 2022 Aug 12:12:893855.**

A total of 418 second malignant neoplasm (SMN) were seen in 38,163 patients. The median follow-up was 8.8 years. The pooled incidence of SMNs was 1.8% with photons and 1.5% with protons. The most common SMN were gliomas (40.6%) followed by meningiomas (38.7%), sarcomas (4.8%), and thyroid cancers (4.2%). The median latency to SMN for photons and protons were 11.9 years and 5.9 years.

■ **Timlin C, et al. Comparing second cancer risk for multiple radiotherapy modalities in survivors of Hodgkin lymphoma. Br J Radiol. 2021 May 1;94(1121):20200354.**

Using Excess Absolute Risk (EAR) models, this study compared the risk of secondary cancer for Hodgkin lymphoma survivors after either IMRT or PBT radiation treatment. This study found that IMPT decreased the average risk by 40% compared to the IMRT plan, 28% compared to the Volumetric Modulated Arc Therapy plan whereas the 3D Conformal Radiation Therapy plan is equivalent within the uncertainty.

■ **Cartechini G, et al. Proton pencil beam scanning reduces secondary cancer risk in breast cancer patients with internal mammary chain involvement compared to photon radiotherapy. Radiat Oncol. 2020 Oct 2;15(1):228.**

This study compared tangential 3D-CRT and VMAT to PBS proton therapy in terms of secondary cancer risk (SCR) for the lungs and for contralateral breast. The SCR was evaluated with the excess absolute risk (EAR) formalism, considering also the age dependence. This study found that PBS PT was associated to significant SCR reduction in breast cancer patients compared to photon radiotherapy. The benefits are maximized for young patients with both SVC and IMNs involvement.

■ **König L, et al. Secondary Malignancy Risk Following Proton vs. X-ray Treatment of Mediastinal Malignant Lymphoma: A Comparative Modeling Study of Thoracic Organ-Specific Cancer Risk. Front Oncol. 2020 Jul 7;10:989.**

This study used two predication models to estimate secondary cancer risks for 23 mediastinal lymphoma patients treated with active scanning PRT, in comparison with helical photon IMRT re-plans. PRT reported a significant risk reduction in secondary lung, breast, and esophageal cancer compared to IMRT. PRT should be considered for young age and the long natural history of patients.

■ **Jain V, et al. Predicted Secondary Malignancies Following Proton Versus Photon Radiation for Oropharyngeal Cancers. Int J Part Ther. Spring 2020;6(4):1-10.**

This study compared 13 patients with HPV-positive oropharyngeal cancers treated with postoperative radiation alone with IMPT. This study found a significant decrease in the risk of SMNs with IMPT for patients diagnosed at a national median age of 54 years with an average life expectancy of 27 years – 4 excess SMNs per 100 patients could be avoided by treating them with IMPT versus IMRT.

■ **Raptis A, et al. Cancer Risk After Breast Proton Therapy Considering Physiological and Radiobiological Uncertainties. Phys Med. 2020 Jun 18;76:1-6.**

This study analyzed 12 patients plans in free breathing with protons and photons for left breast cancer. This study found that the highest risks were for the lungs (average second cancer risks of 0.31% and 0.12% from photon and proton plans, and concluded that protons have an advantage over the photons with respect to the induction of cancer.

■ **Paganetti H, et al. The Risk for Developing a Secondary Cancer After Breast Radiation Therapy: Comparison of Photon and Proton Techniques. Radiother Oncol. 2020 May 25;149:212-218.**

This study evaluated the dosimetric data from 34 (10 photon-VMAT, 10 photon-3DCRT, 14 pencil beam scanning proton (PBS)) breast cancer patients who received comprehensive nodal irradiation. For the lifetime attributable risk (LAR) for secondary malignancies at age 70, the study found that 3DCRT techniques led to the lowest estimated risks of thyroid and esophageal secondary cancers while PBS demonstrated a benefit for secondary lung and contralateral breast cancer risks, with the highest risks overall associated with VMAT techniques.

■ **Xiang M, et al. Second Cancer Risk After Primary Cancer Treatment With Three-Dimensional Conformal, Intensity-Modulated, or Proton Beam Radiation Therapy. Cancer. 2020 Aug 1;126(15):3560-3568.**

Based on the National Cancer Database, this study analyzed 450,373 pediatric and adult cancer patients in 9 tumor types: head and neck, gastrointestinal, gynecologic, lymphoma, lung, prostate, breast, bone/soft tissue, and brain/CNS, who treated with radiation (33.5% received 3DCRT, 65.2% received IMRT, and 1.3% received PBRT). This study reported no overall difference in the risk of second cancer between IMRT versus 3DCRT. By comparison, PBRT had an overall lower risk of second cancer versus IMRT (P < .0001). Results within each tumor type generally were consistent.

■ **Vogel J, et al. Predicted Rate of Secondary Malignancies Following Adjuvant Proton Versus Photon Radiation Therapy for Thymoma. Int J Radiat Oncol Biol Phys. 2017 Oct 1;99(2):427-433.**

This study assessed the risk of predicted SMNs following adjuvant proton radiation therapy compared with photon radiation therapy after resection of stage II thymic malignancies. SMN risk was calculated based on organ equivalent dose. For patients with thymoma diagnosed at the median national age, 5 excess secondary malignancies per 100 patients would be avoided by treating them with protons instead of photons.

■ **Manem VSK and Dhawan A. Modelling recurrence and second cancer risks induced by proton therapy. Math Med Biol. 2017 Jul 4.**

This study investigated the tumour control probability, relapse time and the corresponding secondary cancer risks induced by proton therapy. This study found that compared with photon therapy, proton therapy markedly reduces the risk of secondary malignancies and for equivalent dosing regimens achieves better tumour control as well as a reduced primary recurrence outcome, especially within a hypo-fractionated regimen.

■ **Tamura M et al. Lifetime attributable risk of radiation-induced secondary cancer from proton beam therapy compared with that of intensity-modulated X-ray therapy in randomly sampled pediatric cancer patients. J Radiat Res. 2017 May 1;58(3):363-371.**

Four categories of patient (brain, head and neck; thoracic; abdominal; whole craniospinal) were selected for this study. Using the dose-volume histograms of PBT and IMXT, the lifetime attributable risks (LAR) were calculated for the same patients. Patients who had undergone PBT, the LAR of PBT was significantly lower than the LAR of IMXT estimated by in silico modeling.

■ **Mizumoto M et al. Long-term follow-up after proton beam therapy for pediatric tumors: a Japanese national survey. Cancer Sci. 2017 Mar;108(3):444-447**

A retrospective observational study of pediatric patients who received PBT in Japan. No malignant secondary tumors occurred within the irradiated field. The 10- and 20-year cumulative rates for malignant secondary tumors were 5% and 13%. The data indicated that PBT has the potential to reduce the risk of late mortality and secondary malignancy.

■ **Eaton BR et al. Secondary Malignancy Risk Following Proton Radiation Therapy. Front Oncol. 2015 Nov 26;5:261.**

Multiple dosimetric studies in varying cancer subtypes have demonstrated that PRT enables the delivery of adequate target volume coverage with reduced integral dose delivered to surrounding tissues, and modeling studies have estimated a significantly reduced risk of radiation-induced secondary malignancy with PRT. Clinical data are emerging supporting the lower incidence of secondary malignancies after PRT compared with historical photon data, though longer follow-up in proton treated cohorts is awaited.

■ **Stokkevåg CH et al. Risk of radiation-induced secondary rectal and bladder cancer following radiotherapy of prostate cancer. Acta Oncol. 2015;54(9):1317-25.**

An elevated risk of radiation-induced secondary cancer has been observed in prostate cancer patients after radiotherapy. This study compared plans of CRT, VMAT and IMPT, and reported that the SC risks for the bladder and rectum when using IMPT were lower or comparable to VMAT. SC risks could be assessed when considering referral of prostate cancer patients to proton therapy, taking also general patient characteristics, such as age, into account.

■ **Stokkevåg CH et al. Estimated risk of radiation-induced cancer following paediatric cranio-spinal irradiation with electron, photon and proton therapy. Acta Oncol. 2014 Aug;53(8):1048-57.**

The treatment plans of six paediatric medulloblastoma patients were analysed with respect to secondary cancer risk following cranio-spinal irradiation, using either electrons and photons combined, or conformal photons, or protons. Using protons decreases the estimated risk of secondary cancer following paediatric CSI compared to conventional photon and electron techniques.

■ **Sethi RV et al. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. Cancer. 2014 Jan 1;120(1):126-33.**

This study followed 86 patients, 55 of whom received proton RT and 31 photon RT, for a median of 6.9 years for the proton cohort and 13.1 years for the photon cohort. The 10-year cumulative incidence of RT-induced or in-field second malignancies was significantly different between radiation modalities (proton vs photon: 0% vs 14%; P = .015).

■ **Fuji H et al. Assessment of organ dose reduction and secondary cancer risk associated with the use of proton beam therapy and intensity modulated radiation therapy in treatment of neuroblastomas. Radiat Oncol. 2013 Nov 1;8:255.**

Plans of PBT, IMRT and CRT for retroperitoneal neuroblastoma were compared and analyzed. With dose-volume analyses of liver, stomach, colon, small intestine, pancreas, and bone, the secondary cancer risks in these organs were calculated using the organ equivalent dose model. Assessments of secondary cancer risk showed that PBT reduces the risk of secondary cancer in most organs, whereas IMRT is associated with a higher risk than CRT.

■ **Chung CS et al. Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiat Oncol Biol Phys. 2013 Sep 1;87(1):46-52.**

This is a retrospective cohort study of 558 patients treated with proton radiation and 558 matched patients treated with photon therapy in the SEER registry. The use of proton radiation therapy was not associated with a significantly increased risk of secondary malignancies compared with photon therapy.

■ **Simone CB et al. Predicted rates of secondary malignancies from proton versus photon radiation therapy for stage I seminoma. Int J Radiat Oncol Biol Phys. 2012 Jan 1;82(1):242-9.**

This study compared photon and proton radiotherapy for stage I seminoma and the predicted rates of excess secondary malignancies for both treatment modalities. This study predicted a reduction of one additional secondary cancer for every 50 patients with a life expectancy of 40 years from the time of radiation treatment with protons instead of photons.

■ **Paganetti H. et al., Assessment of radiation-induced second risks in proton therapy and IMRT for organs inside the primary radiation field. Physics in medicine and biology. 2012;57(19):6047-61.**

Second malignancies in radiation therapy occur mainly within the beam path. Compared to traditional radiotherapy, PT can significantly reduce the risk of developing an in-field second malignancy, depending on treatment planning parameters.

■ **Taddei PJ et al. Risk of second malignant neoplasm following proton versus intensity-modulated photon radiotherapies for hepatocellular carcinoma. Phys Med Biol. 2010 Dec 7;55(23):7055-65.**

This study compared the predicted risk of developing an SMN for a patient with HCC between PBT and IMRT. Risk models predicted absolute lifetime attributable risks of SMN incidence were 11.4% after PBT and 19.2% after IMRT. The results of this study suggest that using proton beams instead of photon beams for radiotherapy may reduce the risk of SMN incidence for some HCC patients.

■ **Yoon M. et al., Radiation-induced cancers from modern radiotherapy techniques: intensity-modulated radiotherapy versus proton therapy, International Journal of Radiation Oncology. Biology. Physics. 2010;77(5):1477-85.**

Comparisons of organ-specific equivalent dose were made to assess the risk of secondary cancer after IMRT and PT in patients with prostate and head-and neck cancer. The results showed the risk was either significantly lower with PT or, at least, did not exceed the risk induced by conventional IMRT.

Most Common Clinical Indications

CENTRAL NERVOUS SYSTEM, SKULL BASE AND SPINE CANCERS

■ **De Leo AN, et al. Vision loss following high-dose proton-based radiotherapy for skull-base chordoma and chondrosarcoma. Radiother Oncol. 2021 May:158:125-130.**

This study included148 chordoma and chondrosarcoma patients and 283 individual eyes with functional vision at baseline who received a minimum 30GyRBE to 0.1cm3 of the anterior optic pathway. With a median follow-up of 4.1 years, 5 eyes in 3 patients developed functional blindness, with 2 patients developing bilateral blindness. The 5-year incidence of vision loss was 2.1%. This study concluded that despite the high radiotherapy dose delivered, the rate of vision loss is low and no events occurred in those who received a maximum dose under 60GyRBE.

■ **Riva G, et al. Particle Radiotherapy for Skull Base Chondrosarcoma: A Clinical Series from Italian National Center for Oncological Hadrontherapy. Cancers (Basel). 2021 Sep 2;13(17):4423.**

This study reported outcomes of 48 patients with skull base chondrosarcoma who underwent particle therapy (67% PT, 33% CIRT). With a median follow-up of 38 months, one local failure (2%) was documented and 3-year local control rate was 98%. One (2%) and 4 (8%) patients experienced G3 acute and late toxicity, respectively. No patients had G3 brain toxicity. No G4-5 complications were reported. The authors concluded that PT and CIRT are effective and safe for skull base chondrosarcoma.

■ **Köthe A, et al. Assessment of Radiation-Induced Optic Neuropathy in a Multi-Institutional Cohort of Chordoma and Chondrosarcoma Patients Treated with Proton Therapy. Cancers (Basel). 2021 Oct 23;13(21):5327.**

Radiation-induced optic neuropathy (RION) is a rare side effect following radiation therapy. A multi-institutional cohort including 289 skull-base cancer patients treated with proton therapy who all received >45 GyRBE to the optic apparatus were analyzed in this study. An overall incidence rate of 4.2% (12) was observed, with chordoma patients being at higher risk (5.8%) than chondrosarcoma patients (3.2%). Older age and arterial hypertension, tumor involvement, and repeated surgeries (>3) were found to be associated with RION.

■ **Kroesen M, et al. Single-institution clinical experience using robust intensity modulated proton therapy in chordoma and chondrosarcoma of the mobile spine and sacrum: Feasibility and need for plan adaptation. Radiother Oncol. 2022 Jan:166:58-64.**

Treatment and acute toxicity data of 17 chordoma and 3 chondrosarcoma patients treated with IMPT were retrospectively evaluated in this study. This study found that treatment plan adaptation was needed in 5 out of 22 (22.7%) plans due to either reduced tumor coverage or increased dose to the OAR. The conclusion is that robust IMPT for chordoma and chondrosarcoma of the mobile spine is feasible and plan adaptations due to anatomical changes were required in approximately 23 percent of treatment courses.

■ **Banfield W, et al. Definitive high-dose, proton-based radiation for unresected mobile spine and sacral chordomas. Radiother Oncol. 2022 Jun:171:139-145.**

Sixty-seven patients with unresected spinal chordomas treated with PBT were evaluated. With a median follow-up of 56.2 months, 5- and 8-year OS were 83.5 % and 65.9%, DFS 64% and 44.1%, LC 81.8% and 63.6%, and distant control 7.4% and 72.5. The most common late side effect was insufficiency fracture. The authors stated that the results of their study continued to support the use of high-dose definitive PBT for this subset of patients, and there was a trend towards better disease-free survival with doses >78 Gy (RBE).

■ **Holtzman AL, et al. The incidence of brainstem toxicity following high-dose conformal proton therapy for adult skull-base malignancies. Acta Oncol. 2022 Aug;61(8):1026-1031.**

This study reported the incidence of brainstem toxicity of 163 patients with skull base chordoma or chondrosarcoma treated with proton therapy. With a median follow-up of 4 years, the 5-year cumulative incidence of grade ≥2 brainstem injury was 1.3%. There was one grade 2, one grade 3, and no grade 4 or 5 events, with all patients recovering function with medical management.

■ **Pahwa B, et al. Proton beam therapy for skull base chordomas: a systematic review of tumor control rates and survival rates. Neurosurg Rev. 2022 Dec;45(6):3551-3563.**

Based on the data from 16 studies involving 752 patients, this review reported outcomes of PBT for skull base chordomas. Eighty percent of the patients showed a positive response to the therapy defined in terms of tumor regression. Five-year LC, OS, and PFS were calculated as 76.6%, 79.6%, and 89%, respectively. The authors stated that PBT has become a growing therapeutic technique that has revolutionized the treatment of skull base chordomas.

Mattke M, et al. Proton and carbon ion beam treatment with active raster scanning method in 147 patients with skull base chordoma at the Heidelberg Ion Beam Therapy Center-a single-center experience. Strahlenther Onkol. 2023 Feb;199(2):160-168.

A total of 147 patients were irradiated with carbon ions (111 patients, 66 GyRBE in 4 weeks) or protons (36 patients, 74 GyRBE in 7 weeks). The median follow-up time was 49.3 months. 41 patients (27.9%) developed a local recurrence. No significant differences between protons and carbon ions were observed regarding LC, OS, or overall toxicity. The 1-year, 3-year, and 5-year LC rates were 97%, 80%, and 61% (protons) and 96%, 80%, and 65% (carbon ions), respectively. The corresponding OS rates were 100%, 92%, and 92% (protons) and 99%, 91%, and 83% (carbon ions).

■ **Tubin S, et al. Proton or Carbon Ion Therapy for Skull Base Chordoma: Rationale and First Analysis of a Mono-Institutional Experience. Cancers (Basel). 2023 Mar 31;15(7):2093.**

This study reported clinical outcomes of 44 patients treated with proton (89%) or carbon ion therapy (11%). At a median follow-up of 34.3 months, 2-, and 3-year actuarial LC rates were 95.5% and 90.9%. The 2-, and 3-year OS and PFS rates were 97.7%, 93.2%, 95.5% and 90.9%, respectively. No grade ≥3 toxicities were observed. There was no significant difference in outcome or side effect profile seen for proton versus carbon ion therapy.

■ **Chhabra CM, et al. linical outcomes and toxicities of 100 patients treated with proton therapy for chordoma on the Proton Collaborative Group Prospective Registry. Radiother Oncol. 2023 Jun:183:109551.**

This study presented efficacy and toxicity outcomes among 100 patients with chordoma treated on the Proton Collaborative Group prospective registry. Locations included base of skull (61%), spine (23%), and sacrum (16%). The 2/3-year LC, PFS, and OS rates are 97%/94%, 89%/74%, and 89%/83%, respectively. Eight patients experienced acute grade 3 toxicities, most commonly pain (n=3), radiation dermatitis (n=2), fatigue (n=1), insomnia (n=1) and dizziness (n=1). No grade ≥4 acute toxicity nor grade ≥3 late toxicities were reported. CNS necrosis is exceedingly low (<1%) despite the high doses of PBT delivered.

■ **Lehrer EJ, et al. Proton and Heavy Particle Intracranial Radiosurgery. Biomedicines. 2021 Jan 3;9(1):31.**

This review provides a comprehensive overview of clinical evidence in the use of particle therapy-based radiosurgery. The vast majority of available data are single institution retrospective studies that utilized protons. While there are theoretical benefits to using particles over photons for intracranial radiosurgical applications, prospective data are needed to validate the safety and efficacy of this treatment modality.

■ **Yang TJ, et al. Clinical trial of proton craniospinal irradiation for leptomeningeal metastases. Neuro Oncol. 2021 Jan 30;23(1):134-143.**

This study reported the outcomes of 24 patients with leptomeningeal metastases (LM) treated with proton craniospinal irradiation (CSI). With the median follow-up was 11 months, two patients experienced grade 4 lymphopenia, grade 4 thrombocytopenia, and/or grade 3 fatigue. The median CNS PFS was 7 months and the median OS was 8 months. Four patients (19%) were progression-free in the CNS for more than 12 months.

■ **Song J, et al. Radiation-induced brain injury in patients with meningioma treated with proton or photon therapy. J Neurooncol. 2021 May;153(1):169-180.**

77 patients (38 proton and 39 photon) were evaluated with a median follow-up time of 2.2 years. This study reported no significant differences in symptomatic adverse events between the two groups: grade ≥ 2 adverse events were seen in 4 (10.5%) patients in the proton group and 3 (7.7%) in the photon group (p = 0.67). Proton therapy was associated with significantly higher rates of T1c+T2 changes on MRI (26.8%) at 2-year compared with 5.3% of photon therapy (p = 0.02), but severe adverse events were uncommon in both groups and survival outcomes were comparable between the two groups.

■ **Liu IC, et al. Proton therapy for adult medulloblastoma: Acute toxicity and disease control outcomes. J Neurooncol. 2021 Jul;153(3):467-476.**

Twenty adults with medulloblastoma (≥ 22 years old) received postoperative proton CSI. This study reported no acute ≥ grade 3 gastrointestinal or hematologic toxicities attributable to CSI. With a median follow-up of 3.1 years, 4-year actuarial local control, disease-free survival, and overall survival rates were 90%, 90%, and 95%, respectively. These data support the standard use of proton CSI for adult medulloblastoma.

■ **Küchler M, et al. Outcome after Radiotherapy for Vestibular Schwannomas – Differences in Tumor Control, Symptoms and Quality of Life after Radiotherapy with Photon versus Proton Therapy. Cancers (Basel). 2022 Apr 18;14(8):2033.**

Based on the data of 261 patients with VS treated with stereotactic radiosurgery/hypofractionated stereotactic radiotherapy (SRS/HFSRT), this study reported at 12 months LC of 99.5% and the hearing preservation rate of 97% with no statistical difference among the groups. The authors concluded that SRS/HFSRT, FRT and FPT for VS showed similar overall clinical and functional outcomes.

■ **Yang JT, et al. Randomized Phase II Trial of Proton Craniospinal Irradiation Versus Photon Involved-Field Radiotherapy for Patients With Solid Tumor Leptomeningeal Metastasis. J Clin Oncol. 2022 Nov 20;40(33):3858-3867.**

Forty-two and 21 patients of non-small-cell lung cancer and breast cancer with LM were randomly assigned to proton craniospinal irradiation (pCSI) and Photon involved-field radiotherapy (IFRT). This interim analysis reported a significant benefit in CNS PFS with pCSI (median 7.5 months) compared with IFRT (2.3 months) (P < .001), and OS benefit with pCSI (9.9 months) versus IFRT (6.0 months) (P = .029). There was no difference in the rate of grade 3 and 4 TAEs (P = .19). The authors concluded that pCSI improved CNS PFS and OS for this subset of LM patients.

■ **Saraf A, et al. Long-term outcomes and late toxicity of adult medulloblastoma treated with combined modality therapy: A contemporary single-institution experience. Neuro Oncol. 2022 Dec 1;24(12):2180-2189.**

This study reported outcomes of 59 adult patients with medulloblastoma treated with proton CSI. The 5-year PFS and OS were 86.5% and 95.8%; 10-year PFS and OS were 83.9% and 90.7%, respectively. Most common grade ≥2 late toxicities were anxiety/depressive symptoms (30%), motor dysfunction (25%), and ototoxicity (22%). Higher posterior fossa radiation dose was associated with increased risk of late toxicity, including worse cognitive dysfunction (P = .05).

■ **Matsuda M, et al. High-dose proton beam therapy versus conventional fractionated radiation therapy for newly diagnosed glioblastoma: a propensity score matching analysis. Radiat Oncol. 2023 Feb 23;18(1):38.**

This study compared the survival outcomes and toxicities of high-dose PBT of 96.6 GyRBE and CRT of 60 Gy using propensity score-matched treatment cohorts. From a total of 235 patients, 26 were selected in each group by propensity score matching. The median OS of the PBT group was 28.3 months and 21.2 months for the CRT group. Radiation necrosis was observed significantly more frequent in the PBT group.

■ **Holtzman AL, et al. Long-term outcomes of fractionated proton beam therapy for benign or radiographic intracranial meningioma. J Neurooncol. 2023 Feb;161(3):481-489.**

This study reported outcomes of 59 (64 lesions) patients with benign intracranial meningioma treated with PBT. With a median clinical and imaging follow-up of 6.3 and 4.7 years, the rates of 5-year actuarial local progression and cumulative incidence of grade 3 or greater toxicity were 6% and 2%. The 5-year actuarial overall survival rate was 87%. The authors concluded that PBT is safe and highly effective therapy for treating benign intracranial meningioma.

■ **Young S, et al. Proton Radiotherapy for Management of Medulloblastoma: A Systematic Review of Clinical Outcomes. Adv Radiat Oncol. 2023 Feb 8;8(4):101189.**

This comprehensive review found moderate grade clinical evidence supporting proton-CSI as the preferred delivery technique for both children and adults with medulloblastoma (MB). Based on 35 original studies (representing an estimated 630-654 unique patients), this review reported that well-designed comparative cohort studies with adequate follow-up have demonstrated superior neurocognitive outcomes, lower incidence of hypothyroidism (23% vs 69%), sex hormone deficiency (3% vs 19%), greater heights, and reduced acute toxicities in patients treated with protons compared to photons. OS (up to 10 years), PFS (up to 10 years), brainstem injury, and other endocrine outcomes were similar to those reported for photon radiation.

■ **Beddok A, et al. Proton therapy for adult craniopharyngioma: Experience of a single institution in 91 consecutive patients. Neuro Oncol. 2023 Apr 6;25(4):710-719.**

This study presented the treatment results of 91 patients with craniopharyngioma received proton therapy after tumor resection (88 patients, 97%), as an adjuvant strategy (64 patients, 70.3%) and for recurrent disease (27 patients, 29.7%). With a median follow-up of 39 months, the 5-year LRFS was 92.0%. Endocrinopathy was the most frequent grade ≥ 2 late toxicity. Four (9.8%) developed visual disorders and 10 (11.3%) symptomatic memory impairment.

■ **Flechl B, et al. Preservation of Neurocognition after Proton Beam Radiation Therapy for Intracranial Tumors: First Results from REGI-MA-002015. Int J Radiat Oncol Biol Phys. 2023 Apr 1;115(5):1102-1114.**

This study evaluated 123 patients with intracranial tumors treated with protons. At 1-year follow-up, 89.4% of all patients remained stable in their overall cognitive functioning without clinically relevant deterioration. 8.1% presented with radiation-induced brain lesions and exhibited a higher percentage of overall cognitive deterioration without reaching statistical significance. There was no significant correlation of hippocampal doses and memory functioning.

■ **Holtzman AL, et al. Proton Radiotherapy for Skull-Base Malignancies: Imaging Considerations of Radiotherapy and Complications. Oral Maxillofac Surg Clin North Am. 2023 Aug;35(3):469-484.**

This article summarized data of PRT for benign and malignant skull-base tumors including pituitary adenomas, craniopharyngiomas, benign meningiomas, vestibular schwannoma, sinonasal tumors, chordoma and chondrosarcoma. High local control rates and fewer toxicities produced by PRT have been reported. Common complications such as neurocognition, second malignancy, radiation-induced injuries to the brainstem, temporal lobe and optic pathway as well as mitigation strategies were discussed.

■ **Eichkorn T, et al. Analysis of safety and efficacy of proton radiotherapy for IDH-mutated glioma WHO grade 2 and 3. J Neurooncol. 2023 May;162(3):489-501.**

This study reported outcomes of 194 patients diagnosed with IDH-mutated WHO grade 2 (n = 128) and WHO grade 3 (n = 66) glioma treated with proton radiation. With a median follow-up 5.1 years, 5-year OS was 85% for WHO grade 2 patients and 67% WHO grade 3. AEs of 80% grade 1, 7% grade 2, 13% grade 3, and 0% grade 3+ were observed. The authors concluded that these results demonstrated the effectiveness of PRT for IDH-mutated glioma WHO grade 2 and 3.

■ **Qiu XX, et al. Proton radiotherapy in the treatment of IDH-mutant diffuse gliomas: an early experience from shanghai proton and heavy ion center. J Neurooncol. 2023 May;162(3):503-514.**

This study presented results of 52 patients with IDH-mutant diffuse gliomas treated with proton radiation. Tumor classified by WHO grade 2, 3 and 4 were 22, 25 and 5 cases. The median follow-up time was 21.7 months. The 12/24-month PFS and OS rates for the entire cohort were 97.6%/78.4% and 100%/91.0%. No severe acute toxicity (grade 3 or above) was found. Late grade 3 radio-necrosis was developed in one case of oligodendroglioma, WHO grade 3.

■ **Gaito S, et al. Proton Beam Therapy in the Reirradiation Setting of Brain and Base of Skull Tumour Recurrences. Clin Oncol (R Coll Radiol). 2023 Oct;35(10):673-681.**

Based on 12 original studies of PBT reirradiation for brain/base of skull tumor recurrences, this review reported that PBT can provide good local control with acceptable toxicity rates. Reirradiation needs to consider several factors that can increase the risk of toxicities, therefore patient selection is crucial.

■ **Santacroce A, et al. Proton beam radiation therapy for vestibular schwannomas – tumor control and hearing preservation rates: a systematic review and meta-analysis. Neurosurg Rev. 2023 Jul 4;46(1):163.**

This meta-analysis included 8 primary studies with a total number of 587 patients with vestibular schwannomas treated with proton radiation. Overall rate of tumor control was 95.4%. Overall rates of trigeminal nerve preservation, facial nerve preservation and hearing preservation were 95.6%, 93.7% and 40.6% respectively. The authors concluded that PBT achieves high tumor control rates, but does not offer an advantage for facial and hearing preservation compared to most of the currently reported SRS series.

■ **Piperno G, et al. Hypofractionated proton therapy for benign tumors of the central nervous system: A systematic review of the literature. J Pediatr Hematol Oncol. 2023 Oct 1;45(7):e837-e846.**

This systematic review summarized results of patients treated with hypofractionated PT for CNS benign lesions. Twelve original studies were selected including patients treated for base of the skull meningiomas (6 papers), vestibular schwannoma (3 papers) and pituitary adenomas (3 papers). Clinical results were similar to those reported in either photon-based or gamma knife. Long-term toxicity was reported ranging from 2 % to 7 % in patients treated for base of skull meningioma and 1-9 % for schwannoma.

■ **Hug EB, et al. A Review of Particle Therapy for Skull Base Tumors: Modern Considerations and Future Directions. Int J Part Ther. 2021 Jun 25;8(1):168-178.**

A review on proton therapy for skull base tumors including chordoma and chondrosarcoma, pituitary adenoma and acoustic neuroma. Proton therapy for skull base malignancies has been practiced for decades. Protons enable necessary dose escalation to target volumes while pushing the limits of accepted dose tolerances for critical normal structures.

■ **Xu S et al. Comparison of the Effectiveness of Radiotherapy with 3D-CRT, IMRT, VMAT and PT for Newly Diagnosed Glioblastoma: A Bayesian Network Meta-Analysis. Cancers (Basel). 2023 Dec 3;15(23):5698.**

Based on six original studies including 816 glioblastoma multiforme patients, this comprehensive synthesis of data performed by a Bayesian network meta-analysis showed that PT demonstrated the highest probability of being associated with the best OS (SUCRA: 72.6%), followed by VMAT (SUCRA: 66.5%) and IMRT (SUCRA:44.9), whereas 3DCRT was least likely to be the optimal treatment strategy (SUCRA: 26.3%). PT was the most likely regimen yielding a higher PFS with estimated SUCRA values of 78.25%, followed by IMRT with 57%.

■ **Mohan R, et al. Proton Therapy Reduces the Likelihood of High-Grade Radiation-Induced Lymphopenia in Glioblastoma Patients: Phase II Randomized Study of Protons vs. Photons. Neuro Oncol. 2020 Aug 5;noaa182.**

This is a randomized phase II trial that compared the radiation-induced grade 3+ lymphopenia (G3+L), defined as an absolute lymphocyte count (ALC) nadir of <500 cells/μL, for patients of glioblastoma who received PT (n=28) or XRT (n=56), concomitantly with temozolomide. This study found rates of G3+L were lower in PT vs. XRT (P=0.024)). PT reduced brain volumes receiving low and intermediate doses, consequently, reduced G3+L. Sex, baseline ALC and whole brain V20 were the strongest predictors of G3+L.

■ **Bahn E, et al. Late contrast enhancing brain lesions in proton treated low-grade glioma patients: clinical evidence for increased periventricular sensitivity and variable RBE. Int J Radiat Oncol Biol Phys. 2020 Jul 1;107(3):571-578.**

Late radiation-induced contrast enhancing brain lesions (CEBL) on MR images after proton therapy of brain tumors have been observed to occur frequently in regions of high linear energy transfer (LET) and in proximity to the ventricularsystem. This study found 23 out of 110 patients exhibited one or several CEBLs on follow-up MR images, which presented clinical evidence for an increased risk in ventricular proximity and for a proton RBE that increases significantly with increasing LET.

■ **Stross WC, et al. Proton beam therapy utilization in adults with primary brain tumors in the United States. J Clin Neurosci. 2020 May;75:112-116.**

Based on the National Cancer Database, a total of 1,296 patients received PBT between 2004 and 2015 for treatment of their primary brain tumor. High-grade glioma, medulloblastoma, ependymoma, other glioma, other malignant, and other benign intracranial histologies made up 39%, 20%, 13%, 12%, 13%, and 2% of the cohort, respectively. The number of patients treated per year increased from 34 to 300 in years 2004 to 2015.

■ **Dutz A, et al. Neurocognitive function and quality of life after proton beam therapy for brain tumour patients. Radiother Oncol. 2020 Feb;143:108-116.**

This multicenter study reported the neurocognitive function of 62 adult brain tumor patients after PBT. For two years of follow-up time, this study reported that self-reported and objectively measured neurocognition and most other QoL domains remained largely stable. Slight deterioration was associated with tumors located in the left hemisphere and with an increase in relative volume of the anterior cerebellum that received doses of 30-40 Gy(RBE).

■ **Imber BS, et al. Clinical Outcomes of Recurrent Intracranial Meningiomas Treated with Proton Beam Reirradiation. Int J Part Ther. Spring 2019;5(4):11-22.**

This is a retrospective analysis of 16 patients who received PBRT reRT for recurrent meningiomas. The median PBRT dose was 60 Gy(RBE) and the median follow-up was 18.8 months. At last follow-up, 7 intracranial recurrences (44%) and 3 disease-related deaths (19%) were found. Median cohort PFS was 22.6 months, with 1- and 2-year PFS of 80% and 43%, respectively. Overall late grade 3+ toxicity rate was 31%.

■ **Florijn MA, et al. Lower doses to hippocampi and other brain structures for skull-base meningiomas with intensity modulated proton therapy compared to photon therapy. Radiother Oncol. 2020 Jan;142:147-153.**

This study compared IMPT, VMAT and IMRT for skull base meningiomas. For twenty patients, target diameter >3 cm, IMPT plans significantly improved dose conformity to the target volume as compared to plans of VMAT and IMRT. IMPT also allows for a considerable dose reduction in the hippocampi, normal brain and other OARs compared to both non- coplanar VMAT and IMRT, which may lead to a clinically relevant reduction of late neurocognitive side effects.

■ **Baumann BC, Lustig RA, Mazzoni S, et al. A prospective clinical trial of proton therapy for chordoma and chondrosarcoma: Feasibility assessment. J Surg Oncol. 2019 Aug;120(2):200-205.**

Twenty adult patients with non-metastatic chordomas and chondrosarcomas were treated with median dose of 73.8 Gy(RBE) using PBT- only (n = 6) or combination PBT /IMRT (n = 14). The 3-year local control and progression-free survival was 86% and 81%. The authors concluded that the reported local control, survival, and toxicity were favorable following PBT.

■ **Palm RF, Oliver DE, Yang GQ, et al. The role of dose escalation and proton therapy in perioperative or definitive treatment of chondrosarcoma and chordoma: An analysis of the National Cancer Data Base. Cancer. 2019 Feb 15;125(4):642-651.**

This largest retrospective series analyzed 863 patients with chondrosarcoma and 715 patients with chordoma treated with proton or conventional radiation therapy, and found that dose escalation and proton radiotherapy were associated with improved 5-year OS in patients with chondrosarcoma and chordoma.

■ **Eekers DBP, Roelofs E, Cubillos-Mesías M, et al. Intensity-modulated proton therapy decreases dose to organs at risk in low-grade glioma patients: results of a multicentric in silico ROCOCO trial. Acta Oncol. 2019 Jan;58(1):57-65.**

This multicenter planning study compared treatment plans using intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), Tomotherapy (TOMO) and intensity-modulated proton therapy (IMPT) for 25 LGG patients having undergone postoperative radiotherapy. The low dose volume to the majority of OARs was significantly reduced when using IMPT compared to VMAT.

■ **Ryckman JM, Ganesan V, Kusi Appiah A, et al. National practice patterns of proton versus photon therapy in the treatment of adult patients with primary brain tumors in the United States. Acta Oncol. 2019 Jan;58(1):66-73.**

Using National Cancer Database, 73,073 adult patients with primary brain tumors treated with radiation were analyzed (99.4% photon therapy, 0.6% proton therapy). Significant factors for receipt of proton therapy included younger age, highest income quartile, treatment at academic institutions, non-glioblastoma histology.

■ **Thurin E, Nyström PW, Smits A, et al. Proton therapy for low-grade gliomas in adults: A systematic review. Clin Neurol Neurosurg. 2018 Nov;174:233-238.**

This review found that proton treatment plans compared favorably to photon-plans regarding dose to uninvolved neural tissue, but data on long-term survival was limited. Controlled clinical studies are urgently warranted to determine if the potential benefits based on comparative treatment planning translate into clinical benefits.

■ **Jhaveri J, Cheng E, Tian S, Buchwald Z, et al. Proton vs. Photon Radiation Therapy for Primary Gliomas: An Analysis of the National Cancer Data Base. Front Oncol. 2018 Nov 28;8:440.**

Based on the National Cancer Data Base (NCDB), this study found that PBT was associated with improved OS compared to XRT for patients with gliomas, with the median and 5 years survival rates of 45.9 vs. 29.7 months (p = 0.009) and 46.1 vs. 35.5% (p = 0.0160).

■ **Takagi M, Demizu Y, Nagano F, et al. Treatment outcomes of proton or carbon ion therapy for skull base chordoma: a retrospective study. Radiat Oncol. 2018 Nov 26;13(1):232.**

Twenty-four patients, including eleven (46%) receiving PBT and 13 (54%) receiving CIT (Carbon Ion Therapy) reported five- year LC, PFS and OS rates of 85, 81 and 86% respectively. No significant differences were observed in LC rate or incidence of grade 2 or higher late toxicities between patients receiving PBT or CIT.

■ **Petr J, et al. Photon vs. proton radiochemotherapy: Effects on brain tissue volume and perfusion. Radiother Oncol. 2018 Jan 19.**

This study used MRI scanning to compare the structural and hemodynamic changes of healthy brain tissue in the cerebral hemisphere contralateral to the tumor following photon and proton radiochemotherapy. The decrease in perfusion was comparable for both irradiation modalities and proton therapy may reduce brain-volume loss when compared to photon therapy.

■ **Mattke M, et al. High control rates of proton- and carbon ion-beam treatment with intensity-modulated active raster scanning in 101 patients with skull base chondrosarcoma at the Heidelberg Ion Beam Therapy Center. Cancer. 2018 May 1;124(9):2036-2044.**

A total of 101 patients treated with carbon ions (79 patients) or protons (22 patients) to 60 Gy (RBE) at 3 Gy per fraction for carbon ions and 70 Gy (RBE) at 2 Gy per fraction for protons. This study concluded that no significant difference between carbon ions and protons in the therapy of skull base chondrosarcoma could be detected in 1-, 2-, and 4-year local control and overall survival rates.

■ **El Shafie RA, et al. Evaluation of particle radiotherapy for the re-irradiation of recurrent intracranial meningioma. Radiat Oncol. 2018 May 8;13(1):86.**

A retrospective analysis of forty-two patients treated with particle RT (protons (n = 8) or carbon ions (n = 34)) for recurrent intracranial meningioma. In all patients, re-irradiation could be performed safely without interruptions due to side effects. No grade IV or V toxicities were observed. Overall survival after re-irradiation was 89.6% after 12 months and 71.4% after 24 months with a median OS of 61.0 months.

■ **Ahmed SK, et al. Protons vs Photons for Brain and Skull Base Tumors. Semin Radiat Oncol. 2018 Apr;28(2):97-107.**

A systematic review on the role of proton compared to photon therapy in the treatment of adult brain and skull base tumors. Skull base tumors are the agreed-upon indication for PBT given the high radiotherapy doses needed for optimal tumor control in a location containing several radiosensitive structures. For benign tumors or for tumors not requiring dose-escalation, the expected advantage of PBT is decreased risk of long-term radiotherapy related adverse effects.

■ **Combs SE. Proton and Carbon Ion Therapy of Intracranial Gliomas. Prog Neurol Surg. 2018;32:57-65.**

A review on radiation treatment for gliomas. Particle therapy either with protons or with carbon ions, offers the advantage of their distinct physical characteristics and greater relative biological effectiveness. But as to date, there are no convincing data that confirm the superior effects of particle therapy in comparison to advanced photon radiotherapy in patients with either newly diagnosed or recurrent intracranial gliomas.

■ **Atkins KM, et al. Proton Stereotactic Radiosurgery for Brain Metastases: A Single-Institution Analysis of 370 Patients. Int J Radiat Oncol Biol Phys. 2018 Jul 15;101(4):820-829.**

A retrospective study of 815 metastases from 370 patients reported that moderate-dose treated with proton stereotactic radiosurgery (SRS) is well tolerated and can achieve good local control outcomes, comparable to those obtained with conventional photon SRS strategies. Proton SRS remains resource-intensive, future strategies evaluating its selective utility in patients who would benefit most from integral dose reduction should be explored.

■ **Holm AIS et al. Functional image-guided dose escalation in gliomas using of state-of-the-art photon vs. proton therapy.Acta Oncol. 2017 Jun;56(6):826-831.**

Recurrences of glioma are usually local, suggesting the need for higher tumor dose. This study compared standard dose (60 Gy) and dose-escalated plans for seven patients using IMRT, VMAT and IMPT. The results showed that IMPT substantially decreased over-dose volume (61%), boost volume of 30Gy (22%), OAR doses as well as the risk of radionecrosis – being most favorable compared to IMRT and VMAT.

■ **Grosshans D R et al. The role of image-guided intensity modulated proton therapy in glioma. Neuro Oncol. 2017 Apr 1;19(suppl_2):ii30-ii37.**

This review article stated that radiation therapy plays a key role in glioma treatment, improving disease control and oftentimes survival. However, for survivors, either long-term or short-term, radiation-induced cognitive impairments may negatively impact their quality of life. For patients with both favorable and unfavorable prognoses, intensity modulated proton therapy (IMPT) may offer significant, yet unproven benefits.

■ **Wilkinson B et al. Low Levels of Acute Toxicity Associated With Proton Therapy for Low-Grade Glioma: A Proton Collaborative Group Study. Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2S):E135.**

A Proton Collaborative Group Study reported outcomes of 58 WHO grade II glioma patients treated with protons. All side effects under treatment were grade 1 to 2, no grade 3 observed. The most common toxicities being alopecia (81%), dermatitis (78%), fatigue (47%) and headache (40%). The side effects improved over time with statistically significant reductions.

■ **Rotondo R.L. et al., High-dose proton-based radiation therapy in the management of spine chordomas: outcomes and clinicopathological prognostic factors . Journal of Neurosurgery: Spine. 2015 December; 23(6):788-97.**

Spinal chordomas can have high local recurrence rates after surgery with or without conventional dose RT. This paper shows that high-dose proton therapy can be an effective treatment: among patients undergoing surgery, those with primary chordomas undergoing preoperative RT, en bloc resection, and postoperative radiation therapy boost have the highest rate of local tumor control.

■ **Park J. et al. Differential dosimetric benefit of proton beam therapy over intensity modulated radiotherapy for a variety of targets in patients with intracranial germ cell tumors. Radiation Oncology. 2015 June; 10:135.**

Dosimetric measures were performed to compare proton therapy and IMRT for intracranial germ cell tumors arising in various locations of the brain. Compared to IMRT, proton therapy provided superior target volume coverage and saved more normal tissue, with both passive scanning and spot scanning techniques.

■ **McDonald M.W. et al. Proton therapy for atypical meningiomas. Journal of Neuro-oncology. 2015 May; 123(1):123-8.**

This paper reports clinical outcomes of PT in patients with World Health Organization grade 2 (atypical) meningiomas. Fractionated PT was associated with favorable tumor control rates.

■ **Shih H.A. et al. Proton therapy for low-grade gliomas: Results from a prospective trial. Cancer Cytopathology. 2015 May 15;121(10):1712-9.**

This prospective study evaluates the potential treatment toxicity and progression-free survival in patients with low-grade glioma who received treatment with PT. Patients tolerate PT well and only a subset develops neuroendocrine deficiencies.

■ **Hill-Kayser C. and Kirk M. Brainstem-sparing craniospinal irradiation delivered with pencil beam scanning proton therapy. Pediatric Blood Cancer. 2015 April; 62(4):718-20.**

Delivery of craniospinal irradiation (CSI) is a curative approach to recurrent ependymoma but is associated with risks from reirradiation, particularly of the brainstem. PBS PT allows delivery of CSI with sparing of normal tissue and compares favorably to previously described methods using X-rays.

■ **Grosshans D.R. et al. Spot scanning proton therapy for malignancies of the base of skull: treatment planning, acute toxicities, and preliminary clinical outcomes. International Journal of Radiation Oncology. Biology. Physics. 2014 November 1; 90(3):540-6.**

This study describes treatment planning techniques and early clinical outcomes in patients treated with spot scanning proton therapy for chordoma or chondrosarcoma of the skull base. In comparison to passive scattering, treatment plans for spot scanning proton therapy displayed improved high-dose conformality. Clinically, treatment was well tolerated and disease control rates and toxicity profiles were favorable.

■ **Wattson D.A. et al. Outcomes of proton therapy for patients with functional pituitary adenomas. International Journal of Radiation Oncology. Biology. Physics. 2014 November 1; 90(3):532-9.**

This study evaluates the efficacy and toxicity of PT for functional pituitary adenomas (FPAs). Proton irradiation is an effective treatment for FPAs, with hypopituitarism remaining the primary adverse effect.

■ **Delaney T.F. Long-term results of Phase II study of high dose photon/proton radiotherapy in the management of spine chordomas, chondrosarcomas and other sarcomas. Journal of Surgical Oncology. 2014 August; 110(2):115-22.**

Negative surgical margins are uncommon for spine sarcomas, hence adjuvant radiotherapy may be recommended. However, the dose to the tumor may be constrained by the spinal cord, nerves, and visceral tolerance. This study shows that local control with high dose photon/proton RT is high in patients with primary tumors, and late morbidity appears to be acceptable.

■ **Deraniyagala R.L. et al. Proton therapy for skull base chordomas: an outcome study from the university of Florida proton therapy institute. Journal of Neurological Surgery. 2014 February;75(1):53-7.**

Skull base chordoma is a rare, locally aggressive tumor located adjacent to critical structures. Gross total resection is difficult to achieve, and proton therapy has the conformal advantage of delivering a high postoperative dose to the tumor bed. The results obtained in this study are promising in terms of tumor control, and the toxicity profile is acceptable.

■ **Mizumoto M. et al. Reirradiation for recurrent malignant brain tumor with radiotherapy or proton beam therapy. Technical considerations based on experience at a single institution. Strahlentherapie und Onkologie. 2013 August;189(8):656-63.**

Radiotherapy for recurrent malignant brain tumors is usually limited because of the dose tolerance of the normal brain tissue. This study shows that reirradiation for recurrent malignant brain tumor using conventional RT, stereotactic RT or PT was feasible and effective in selected cases.

■ **Chen Y.L. et al. Definitive high-dose photon/proton radiotherapy for unresected mobile spine and sacral chordomas. Spine Journal. 2013 July 1; 38(15):E930-6.**

The purpose of this study is to report the results of high-dose proton based definitive radiotherapy for unresected spinal chordomas. The results support the use of high-dose definitive radiotherapy for patients with medically inoperable or otherwise unresected, mobile spine or sacrococcygeal chordomas.

■ **Brown A.P. et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. International Journal of Radiation Oncology. Biology. Physics. 2013 June 1; 86(2):277-84.**

This report is the first analysis of clinical outcomes for adult medulloblastoma patients treated with proton CSI. Patients treated with PT experienced less treatment- related morbidity than patients treated with conventional RT, including fewer acute gastrointestinal and hematologic toxicities.

■ **Weber D.C. et al. Spot-scanning based Proton Therapy for Intracranial Meningioma: Long-term Results from the Paul Scherrer Institute. International Journal of Radiation Oncology. Biology. Physics. 2012;83(3):865-71.**

In this study about the long-term clinical results of spot scanning proton therapy for intracranial meningiomas, proton-therapy was proved to be a safe and effective treatment modality for patients with untreated, recurrent, or incompletely resected tumors.

OCULAR CANCERS

■ **van Beek JGM, et al. Local tumour control and radiation side effects for fractionated stereotactic photon beam radiotherapy compared to proton beam therapy in uveal melanoma. Radiother Oncol. 2021 Apr:157:219-224.**

Published in the Green Journal, this study compared two cohorts of each 153 patients with uveal melanoma treated with fractionated stereotactic photon-RT (50 Gy in 5 fractions) and PBT (53 Gy in 4 fractions), and reported comparable outcomes from both treatment options. The 5-year local tumor control rates were 96.1% for fSRT and 96.1% for PBR. The enucleation rate is higher in patients treated with fSRT (12.4%) than in patients treated with PBR (5.9%).

■ **Bolling JP, et al. Treatment of Uveal Melanoma With Radioactive Iodine 125 Implant Compared With Proton Beam Radiotherapy. Mayo Clin Proc Innov Qual Outcomes. 2021 Dec 22;6(1):27-36.**

156 patients treated for uveal melanoma either with PBT (n=92) or radioactive iodine 125 implant (RAI) (n=64) were analyzed in this study. With a median follow up of 2.7 years, this study reported no significant difference between RAI and PBT in clinical outcomes except the RAI group had a significantly higher risk of diplopia (P<.001), cataract progression (P<.001), maculopathy (P=.03) and eyelash loss (P=.006), compared with the PBT group.

■ **Hussain RN, et al. Proton beam radiotherapy for choroidal and ciliary body melanoma in the UK-national audit of referral patterns of 1084 cases. Eye (Lond). 2023 Apr;37(5):1033-1036.**

A total of 1084 patients with uveal melanoma were treated between 2004 to 2014. This study found that the common indications for the use of proton treatment in uveal melanoma include small tumors in the posterior pole poorly accessible for plaque treatment (adjacent to the disc), tumors at the posterior pole affecting the fovea and large anterior tumors traditionally too large for brachytherapy.

■ **Hérault J, et al. 30 years of ocular proton therapy, the Nice view. Cancer Radiother. 2022 Nov;26(8):1016-1026.**

A publication by the NICE group presented their 30 years experiences in treating ocular tumors with proton therapy. This article highlighted the fact that 6684 patients treated at the facility between 1991 and 2020. The authors affirmed safety and efficacy of protons in managing ocular tumors achieving excellent tumor control rates (~95%), vision preservation and limited toxicity rates.

■ **Gollrad J, et al. Proton Therapy for 166 Patients with Iris Melanoma: Side Effects and Oncologic Outcomes. Ophthalmol Retina. 2023 Mar;7(3):266-274.**

With a follow-up time of 54 months, this study reported that local recurrence occurred in 2 patients (1.2%), enucleation was 3% (n = 5) and no patient developed metastatic disease. A large-treatment field (full aperture, involving > 10 clock hours) was identified as a risk factor for the development of secondary glaucoma and vision loss.

■ **Eibenberger K, et al. Side Effects of Proton Beam Radiotherapy Treatment on Iris Melanoma. Ophthalmology. 2023 Sep;130(9):958-965.**

This study demonstrated PBR a successful treatment option with a high tumor control rate and low complication profile. 149 eyes of 149 patients were treated with whole PBR (wPBR: n = 51) or segmental PBR (sPBR: n = 98). Tumor recurrence developed in 3 patients (wPBR: 1/51; sPBR: 2/98). Severe side effects such as limbal stem cell failure were found only in the wPBR group (4/51; 7.8%). Secondary glaucoma developed in 31.4% of the wPBR group (16/51) compared with 1.0% in the sPBR group (1/98; P < 0.001).

■ **Thariat J, et al. Single-Masked Randomized Phase 2 Study Assessing 2 Forms of Hypofractionated Proton Therapy in Patients With Large Choroidal Melanomas. Int J Radiat Oncol Biol Phys. 2023 Oct 1;117(2):357-369.**

This randomized phase 2 trial by multiple groups from France reported that 8 x 6.5 Gy scheme is feasible without deteriorating local control and with similar toxicity rates, as compared to the standard 4 x 13 Gy scheme in patients with large uveal melanomas. For the 32 patients in the study, the 2-year local recurrence-free survival rate without enucleation was 79% (95% confidence interval, 65%-96%), similar in both arms.

■ **Espensen CA, et al. Dose-response and Normal Tissue Complication Probabilities After Proton Therapy for Choroidal Melanomas. Ophthalmology. 2020 Jun 20;S0161-6420(20)30572-8.**

With the analysis of 991 patients treated, this study found that macula D2% showed the strongest correlation with visual acuity deterioration, retina D20% was the only variable with clear impact on the risk of developing maculopathy, optic disc D20% had the largest impact on optic neuropathy; cornea D20% had the largest impact on neovascular glaucoma; ciliary body D20% had the largest impact on ocular hypertension.

■ **Santoni A, Thariat J, Maschi C, et al. Management of invasive squamous cell carcinomas of the conjunctiva Treatment of invasive conjunctival carcinoma. Am J Ophthalmol. 2019 Apr;200:1-9.**

This retrospective analysis evaluated the outcomes and management of conjunctival carcinomas and found that irradiation was the only prognostic factor associated with a lower risk for local relapse. Post-operative proton therapy used in squamous cell carcinoma only, was associated with a lower risk for relapse.

■ **Hope-Stone L, Brown SL, Heimann H, Damato B. Comparison between patient-reported outcomes after enucleation and proton beam radiotherapy for uveal melanomas: a 2-year cohort study. Eye (Lond). 2019 Apr 15.**

This study compared differential effects of enucleation and PBT on 115 uveal melanoma patients based on the patient- reported outcomes, and reported that PBT patients reported greater impairments of central and peripheral vision and reading difficulties over 24 months. Patients treated by enucleation experienced greater functional problems at 6 months, which abated at 12 and 24 months.

■ **Thariat J, et al. Proton Beam Therapy for Iris Melanomas in 107 Patients, Ophthalmology. 2018 Apr;125(4):606-614.**

A multi-institute retrospective study reported outcomes of 107 iris melanoma patients treated with protons reported that the cumulative incidence of relapse was 7.5% at 5 years. None of the 107 patients experienced metastases nor died of iris melanoma. Cataracts occurred in 57.4% of patients, secondary glaucoma 7.6%, uveitis 4.7% and hyphema 3.7% of the patients. The study concluded that proton therapy showed efficacy and limited morbidity in iris melanomas.

■ **Thariat J, et al. Cataract Avoidance with Proton Therapy in Ocular Melanomas. Invest Ophthalmol Vis Sci. 2017 Oct 1;58(12):5378-5386.**

The study investigated whether a lens-sparing approach was relevant to avoid cataracts in uveal melanoma patients treated with proton therapy. Having analyzed a cohort of 1696 uveal melanoma patients treated with PT, the study concluded that the lens-sparing approach is feasible and results not only in reduced need for cataract surgery but also in better fundus-based tumor control.

■ **Kim TW et al. Clinical Outcomes of Proton Beam Therapy for Choroidal Melanoma at a Single Institute in Korea. Cancer Res Treat. 2017 Apr 19.**

This retrospective study reports the outcomes of choroidal melanoma patients treated with proton beam 60-70GyE over 5 fractions. The 3-year local progression-free survival, distant metastasis-free survival, and overall survival rates were 95.8%, 95.8%, and 100%, respectively. Grade 3-4 toxicities were observed in four patients (16.7%), including one with neovascular glaucoma.

■ **Mouw KW et al. Analysis of patient outcomes following proton radiation therapy for retinoblastoma, Adv Radiat Oncol. 2017 Jan-Mar;2(1):44-52.**

With the average length of 12.9 years, this study reported longterm outcomes of retinoblastoma patients treated with PBT. PBT provides an opportunity for long-term disease control and functional eye preservation, PBT does not appear to be associated with unexpected late visual, endocrine, or QOL effects.

■ **Willerding G.D. et al., "Neoadjuvant proton beam irradiation followed by transscleral resection of uveal melanoma in 106 cases", British Journal of Ophthalmology, 2016 April; 100(4):463-7.**

This study evaluates the clinical results after neoadjuvant proton therapy followed by transscleral resection of large uveal melanoma. Neoadjuvant proton therapy may help to prevent local recurrence after transscleral resection: additional vitreoretinal surgery was frequently needed but the majority of patients avoided enucleation and functional blindness.

■ **Kim J.Y. et al., "Treatment of Retinoblastoma: The Role of External Beam Radiotherapy", Yonsei Medical Journal, 2015 November; 56(6):1478-91.**

Due to the risk of RT-related secondary cancers in children, EBRT is avoided as much as possible in the treatment of constitutional retinoblastoma. When EBRT is required, proton therapy is one method that can reduce the radiation dose to the adjacent orbitalbone while maintaining an adequate dose to the tumor.

■ **Sikuade M.J. et al. Outcomes of treatment with stereotactic radiosurgery or proton beam therapy for choroidal melanoma. Eye (London). 2015 September; 29(9):1194-8.**

This study shows that the use of stereotactic radiosurgery and proton therapy has proven to be effective to treat large choroidal melanoma of tumors unsuitable for plaque radiotherapy. Over a 10-year period, patients treated with proton therapy retain better vision post-operatively.

■ **Seibel I. et al. Local recurrence after primary proton beam therapy in uveal melanoma: Risk factors, retreatment approaches and outcome. American Journal of Ophthalmology. 2015 June 29; pii: S0002- 9394(15)00372-4.**

This study evaluates the risk factors, recurrence rates, re-treatments, and long-term patient outcomes following PT for uveal melanoma. It is shown that each globe retaining re-treatment approach can result in satisfying local tumor control. In case of early detection of local recurrence, preservation of the globe can be warranted.

■ **Kamran S.C. et al. Outcomes of proton therapy for the treatment of uveal metastases. International Journal of Radiation Oncology. Biology. Physics. 2014 December 1;90(5):1044-50.**

Radiation therapy can be used to treat uveal metastases with the goal of local control and improvement of quality of life. PT is an effective and efficient means of treating uveal metastases, with minor acute adverse effects.

■ **Schönfeld S. et al. Proton beam therapy leads to excellent local control rates in choroidal melanoma in the intermediate fundus zone. American Journal of Ophthalmology. 2014 December; 158(6):1184-91.**

This study evaluates long-term outcomes of PT in the treatment of choroidal melanoma of the intermediate zoneof the fundus and demonstrates the effectiveness of PT in tumor control and preservation of the globe in the analyzed patients.

■ **Mouw K.W. et al. Proton radiation therapy for the treatment of retinoblastoma. International Journal of Radiation Oncology. Biology. Physics. 2014 November 15; 90(4):863-9.**

This study investigates long-term disease and toxicity outcomes for pediatric retinoblastoma patients treated with PT. Long-term follow-up of retinoblastoma patients treated with PT demonstrates that it can achieve high local control rates, even in advanced cases, with many patients retaining useful vision in the treated eye.

■ **Rahmi A. et al. Proton beam therapy for presumed and confirmed iris melanomas: a review of 36 cases. Graefe's Archive for Clinical and Experimental Ophthalmology. 2014 September; 252(9):1515-21.**

This paper reports the clinical features and outcomes of iris melanomas treated by PT. PT appears to be the treatment of choice for the conservative treatment of iris melanomas with excellent tumor control and an acceptable complication rate.

■ **Wang Z. et al. Charged particle radiation therapy for uveal melanoma: a systematic review and meta-analysis. International Journal of Radiation Oncology. Biology. Physics. 2013; 86(1):18-26.**

The present analysis evaluates the efficacy and adverse effects of charged particle therapy (protons, helium ions, or carbon ions) for uveal melanoma. CPT was associated with lower retinopathy and cataract formation rates. Better outcomes may also be possible in terms of local recurrence, retinopathy, and cataract formation rates.

LYMPHOMAS

■ **Tseng YD, et al. Risk of Pneumonitis and Outcomes After Mediastinal Proton Therapy for Relapsed/Refractory lymphoma: A PTCOG and PCG Collaboration. Int J Radiat Oncol Biol Phys. 2021 Jan 1;109(1):220-230.**

Symptomatic pneumonitis, a subacute toxicity, has an incidence of 17% to 24% (≥grade 2) even with IMRT. A total of 85 patients with r/r lymphoma (66% HL, 34% NHL; 46% primary chemorefractory) received thoracic PBT in the consolidation (45%) or salvage (54%) setting. With a median follow-up of 26.3 months among living patients, 11 patients developed symptomatic (grade 2) pneumonitis (12.8%). No grade 3 or higher pneumonitis was observed. The study concluded that PBT for relapsed/refractory lymphoma was associated with favorable rates of pneumonitis compared with historical controls.

■ **Tseng YD, et al. Selection of Mediastinal Lymphoma Patients for Proton Therapy Within the Proton Collaborative Group Registry: Concordance With the ILROG Guidelines. Am J Clin Oncol. 2021 Jun 1;44(6):269-274.**

This study reviewed 56 mediastinal lymphoma patients treated with proton therapy and reported that nearly all treated patients fit the International Lymphoma Radiation Oncology Group consensus recommendations published in 2018 regarding which mediastinal lymphoma patients may most benefit from proton therapy. Mediastinal lymphoma patients treated with proton therapy are typically young with lower mediastinal involvement.

■ **Loap P, et al. Current Situation of Proton Therapy for Hodgkin Lymphoma: From Expectations to Evidence. Cancers (Basel). 2021 Jul 26;13(15):3746.**

Consolidative RT is of prime importance for early-stage Hodgkin lymphoma management since it significantly increases progression-free survival. Proton therapy reduces radiation exposure to several OARs, including cardiac substructures which should significantly reduce late radiation-induced toxicities and secondary cancers. This review examined the current literature and pointed out that the clinical benefits of proton therapy is still uncertain based on the available data which is lack of long term follow-up for late toxicity.

■ **Ntentas G, et al. Proton Therapy in Supradiaphragmatic Lymphoma: Predicting Treatment-Related Mortality to Help Optimize Patient Selection. Int J Radiat Oncol Biol Phys. 2022 Mar 15;112(4):913-925.**

This study identified patients who benefit most from PBT in terms of predicted 30-year absolute mortality risks (AMR30) from radiation-related cardiovascular disease (CVD) and second cancers (SC). Eighty patients with supradiaphragmatic HL treated with PBT were re-planned using optimal photon-RT. Doses and AMR30 from CVD and SC of the lung, breast and esophagus were compared for all patients. This study found that the predicted benefit of PBT is not universal and is limited to certain categories of lymphoma patients with lower mediastinal or axillary disease.

■ **Bates JE, et al. Comparative Effectiveness of Proton Therapy versus Photon Radiotherapy in Adolescents and Young Adults for Classical Hodgkin Lymphoma. Int J Part Ther. 2021 Jul 8;8(3):21-27.**

Ninety-one patients aged 15 to 40 years with stages I and II classical Hodgkin Lymphoma treated with proton therapy (n=48) or photon radiotherapy (n=43) were reviewed in this study. There was no significant difference in 2-year PFS by radiotherapy dose received (≥ 30 Gy, 91%; < 30 Gy, 86%; P = .82), nor by radiotherapy modalities (proton, 94%; photon, 83%; P = .07). However, the authors recommend the use of proton therapy in AYA patients for whom it provides a clear dosimetric benefit.

■ **Patel CG, et al. Systematic Review for Deep Inspiration Breath Hold in Proton Therapy for Mediastinal Lymphoma: A PTCOG Lymphoma Subcommittee Report and Recommendations. Radiother Oncol. 2022 Dec:177:21-32.**

The PTCOG lymphoma subcommittee conducted a systematic review on available dosimetric studies comparing IMPT free breathing (FB) and/or deep inspiration breath hold (DIBH) with IMRT-DIBH, focusing on mean heart dose (MHD), mean lung dose (MLD), and mean breast dose (MBD). Proton with FB or DIBH was superior to IMRT-DIBH in heart, lung, breast, and integral dose, and IMPT with DIBH can further lower doses to lungs and heart. The utilization of proton therapy with DIBH may provide the best opportunity at OAR sparing in mediastinal lymphoma.

■ **Ricardi U, et al. Proton Therapy For Lymphomas: Current State Of The Art. Onco Targets Ther. 2019 Oct 1;12:8033-8046.**

This review evaluated the promising clinical outcomes of proton therapy for Hodgkin lymphoma and Non-Hodgking lymphoma. The outcomes are even more promising for relapsed/refactory disease, despite reports often containing small patient cohorts from a single institute. This review suggested that a careful selection of patients who may benefit from PT, after a proper plan comparison with modern photon therapy, might be a significant step forwards.

■ **Ntentas G, Dedeckova K, Andrlik M, et al. Clinical intensity-modulated proton therapy for Hodgkin lymphoma: which patients benefit the most? . Pract Radiat Oncol. 2019 May;9(3):179-187.**

Twenty-one HL patients were treated with deep inspiration breath-hold pencil-beam scanning (PBS) PBT. PBS significantly reduced the mean dose to the heart, breast, lungs, spinal cord and esophagus, but some high dose measures and hot spots were increased with PBS compared to partial arc volumetric modulated (PartArc) photon RT.

■ **Rechner LA, et al. Life years lost attributable to late effects after radiotherapy for early stage Hodgkin lymphoma: The impact of proton therapy and/or deep inspiration breath hold. Radiother Oncol. 2017 Oct;125(1):41-47.**

This study compared the life years lost (LYL) attributable to late effects after RT for mediastinal Hodgkin lymphoma using IMRT in free breathing (FB) and deep inspiration breath hold (DIBH), and proton therapy in FB and DIBH. The finding is that the lowest LYL was found for proton therapy in DIBH.

■ **Tseng YD, et al. Evidence-based Review on the Use of Proton Therapy in Lymphoma From the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee. Int J Radiat Oncol Biol Phys. 2017 Nov 15;99(4):825-842.**

In this evidence-based review, the committee recommended that in view of the fact that randomized clinical trial data will likely never exist to test the predicted benefits of proton therapy in reducing late toxicities in patients treated for lymphoma, proton therapy should be reasonably considered in appropriately selected lymphoma patients when it can significantly decrease the dose to critical structures.

■ **Hoppe BS et al. Proton therapy patterns-of-care and early outcomes for Hodgkin lymphoma: results from the Proton Collaborative Group Registry. Acta Oncol. 2016 Nov;55(11):1378-1380.**

40 patients were included for analysis and the results show that the 2-year relapse-free survival was 85%, with three recurrence reported, and no grade 3 toxicity occurred. Hodgkin lymphoma young survivors are at great risk of developing chronic morbidities and developing secondary cancer among cancer survivors, these patients may derive considerable benefit with proton therapy.

■ **Sachsman S. et al. Proton therapy in the management of non-Hodgkin lymphoma. Leukemia & Lymphoma. 2015 May; 18:1-5.**

This study reviews a single institution's experience managing patients with non-Hodgkin lymphoma (NHL) treated with PT. PT proved to be a feasible and effective treatment for NHL, with favorable early outcomes.

■ **Rutenberg M.S., Flampouri S., Hoppe B.S. Proton therapy for Hodgkin lymphoma. Current Hematologic Malignancy Reports. 2014 May 20;9(3), 203–211.**

This paper reviews the outcomes of Hodgkin lymphoma treated with PT and discusses the ability of protons to reduce radiation dose to OARs and the impact on the most significant late complications related to the treatment.

HEAD AND NECK CANCERS

■ **Zakeri K, et al. Outcomes and prognostic factors of major salivary gland tumors treated with proton beam radiation therapy Head Neck. 2021 Apr;43(4):1056-1062.**

This study reported clinical outcomes of 68 patients with major salivary gland tumors including the parotid gland (75.0%) and adenoid cystic carcinoma (22.1%) treated by PBT. The 3-year rates of locoregional control, progression-free survival, and overall survival were 95.1%, 80.7%, and 96.1%. This study concluded that the rates of locoregional were high in short-term follow-up.

■ **Bridhikitti J, et al. Oncologic Outcomes for Head and Neck Skin Malignancies Treated with Protons. Int J Part Ther. 2021 Jun 25;8(1):294-303.**

This study reported outcomes of 47 patients with H&N malignancies of the skin (squamous cell, basal cell, melanoma, Merkel cell, angiosarcoma, other) who underwent IMPT for curative intent. The 2-year estimated local recurrence rate, regional recurrence rate, distant metastasis rate, and overall survival were 11.1% , 4.4% , 23.4% , and 87.2%. No patient was reported to have a grade 3 or higher adverse event. The authors conclude that IMPT is safe and effective in the treatment of skin malignancies of the H&N.

■ **Li XZ, et al. Toxicity Profiles and Survival Outcomes Among Patients With Nonmetastatic Nasopharyngeal Carcinoma Treated With Intensity-Modulated Proton Therapy vs Intensity-Modulated Radiation Therapy. JAMA Netw Open. 2021 Jun 1;4(6):e2113205.**

Seventy-seven patients with nonmetastatic NPC received IMPT (n=28) or IMRT(n=49). With a median follow-up time of 30.3 months, IMPT was associated with lower likelihood of grade 2 or higher acute AEs compared with IMRT (P = .01). Only 1 case (3.8%) of a chronic grade 3 or higher AE occurred in the IMPT group compared with 8 cases (16.3%) in the IMRT group (P = .15). Propensity score matching of 48 patients (24 IMPT vs 24 IMRT) showed similar PFS in both groups. Two-year LRFS was 100% in the IMPT group and 86.2% in the IMRT group (P = .08). Three-year OS was 100% in the IMPT group and 94.1% in the IMRT group (P = .42).

■ **Taku N, et al. Proton Therapy for HPV-Associated Oropharyngeal Cancers of the Head and Neck: a De-Intensification Strategy. Curr Treat Options Oncol. 2021 Jun 4;22(6):54.**

This review suggested that IMPT could de-intensifies treatment through dose de-escalation to normal tissues without compromising dose to the primary tumor and involved, regional lymph nodes. Two phase III trials currently underway including the "Randomized Trial of IMPT versus IMRT for the Treatment of Oropharyngeal Cancer of the Head and Neck" and the "TOxicity Reduction using Proton bEam therapy for Oropharyngeal cancer (TORPEdO)" trial are expected to provide prospective, level I evidence regarding the effectiveness of IMPT for such patients.

■ **Lin A, et al. PTCOG Head and Neck Subcommittee Consensus Guidelines on Particle Therapy for the Management of Head and Neck Tumors. Int J Part Ther. 2021 Jun 25;8(1):84-94.**

This consensus guideline examined evidence of proton therapy for nasopharynx, reirradiation, sinonasal, and oropharynx and made recommendations. Proton therapy is an established and safe modality for the treatment of patients with head and neck cancers. The superior dosimetric conformity and organ-sparing capabilities appear to correspond with improved patient outcomes when compared with IMRT. This guideline also provides ongoing including phase III randomized trials comparing proton therapy to IMRT and encourages participation.

■ **Smith GL, et al. Work Outcomes after Intensity-Modulated Proton Therapy (IMPT) versus Intensity-Modulated Photon Therapy (IMRT) for Oropharyngeal Cancer. Int J Part Ther. 2021 Jun 25;8(1):319-327.**

This study compared work outcomes in patients with stage II-IVB oropharyngeal cancer (OPC) received IMPT versus IMRT chemoradiation. Using the work productivity and activity impairment questionnaire at baseline (pre-CRT), at the end of CRT, and at 6 months, 1 year, and 2 years, this study reported an increasing proportion of patients resumed working after IMPT, from 60% (40 of 67) pre-CRT and 71% (30 of 42) at 1 year to 78% (18 of 23) at 2 years (P = 0.025). By 2 years, IMPT demonstrated increasing work and productivity recovery trends(P = 0.06).

■ **Yu NY, et al. Initial Experience with Proton Beam Therapy for Differentiated Thyroid Cancer. Int J Part Ther. 2021 Jun 25;8(1):311-318.**

This study reported outcomes of 14 patients with recurrent, radioactive iodine (RAI) refractory differentiated thyroid cancer (DTC) treated with IMPT. At 8 months, all patients were alive without local-regional failure. Acute grade 3 toxicities were limited to 1 patient with dysphagia, requiring feeding tube placement. Two patients experienced late grade 3 esophageal stenosis requiring dilation. There were no grade 4 or 5 toxicities. The authors suggested that IMPT is a promising treatment for this patient population.

■ **Ebner DK, et al. The Role of Particle Therapy in Adenoid Cystic Carcinoma and Mucosal Melanoma of the Head and Neck. Int J Part Ther. 2021 Jun 25;8(1):273-284.**

This review article examined clinical data available today for particle therapy including proton, carbon ion and neutron for these two radioresistant conditions. Particle therapy appears to improve disease control – proton therapy and carbon-ion therapy provide excellent 5-year LC rates, ranging from 73% to 90% for ACC and 62% to 84% for MM. Consideration for a phase III trial is complicated by disease rarity and consideration of clinical equipoise versus conventional treatment.

■ **Hanania AN, et al. Proton Therapy for Major Salivary Gland Cancer: Clinical Outcomes. Int J Part Ther. 2021 Jun 25;8(1):261-272.**

This study reported clinical outcomes of 72 patients with major salivary gland cancers treated by PBT. Sixty-three patients (88%) received postoperative therapy, and nine patients (12%) were treated definitively. All (99%) but one patient received unilateral treatment With a median follow-up time of 30 months, the two-year LC and OS rates were 96% and 89%. Radiation dermatitis was the predominant grade-3 toxicity (21% [n = 15] of the patients), and grade ≥ 2 mucositis was rare (14%; n = 10 patients). No late grade ≥ 3 toxicities were reported.

■ **Press RH, et al. Clinical Review of Proton Therapy in the Treatment of Unilateral Head and Neck Cancers. Int J Part Ther. 2021 Jun 25;8(1):248-260.**

This review article evaluated the current evidence supporting the use of PBT in unilateral irradiation of head and neck cancers including salivary tumors, cutaneous malignancies, skull base perineural invasion, periorbital tumors, oropharyngeal cancer and reirradiation. This review found compelling reductions in acute toxicities in favor of PBT. Some studies demonstrate impressively low rates of chronic toxicities for optic and orbital structures and a safer path to organ preservation without compromising tumor control rates.

■ **Dagan R, et al. Long-term Outcomes from Proton Therapy for Sinonasal Cancers. Int J Part Ther 2021 Jun 25;8(1):200-212.**

143 patients with nonmetastatic sinonasal cancers treated with primary (18%; n = 26) or adjuvant (82%; n = 117) proton therapy. The 5-year outcomes were LC 80%; neck control 96%; local-regional control 78%; freedom from distant metastases 71%, and overall survival, 59%. Late (G3+) toxicity occurred in 22% (32 of 143), including central nervous system necrosis and vision loss in 6% (9 of 143) and 3.5% (5 of 143), respectively.

■ **Nakajima K, et al. Spot Scanning Proton Therapy for Sinonasal Malignant Tumors. Int J Part Ther. 2021 Jun 25;8(1):189-199.**

62 patients with sinonasal tumors treated with proton radiation. The 2-year LC, progression-free survival, and OS rates of all patients were 92%, 50%, and 76%, respectively. Sixteen grade ≥3 late toxicities were observed in 12 patients (19%), including 11 events resulting in visual impairment; the most common was cataract. There was 1 grade 4 toxicity, and there were no grade 5 toxicities.

■ **Gamez ME, et al. A Systematic Review on Re-irradiation with Charged Particle Beam Therapy in the Management of Locally Recurrent Skull Base and Head and Neck Tumors. Int J Part Ther. 2021 Jun 25;8(1):131-154.**

A review examined a total of 26 original studies (15 protons, 10 carbon ions, and 1 helium/neon studies) involving a total of 1,118 patients (437 with protons, 670 with carbon ions, and 11 with helium/neon) treated with curative-intent charged particle reRT. 2-year local control rates ranging from 50% to 86% for proton re-RT, and 41% to 92% for carbon ion reRT. Late ≥ G3 toxicities ranged from 0% to 37%, with brain necrosis, ototoxicity, visual deficits, and bleeding as the most common complications. Grade 5 toxicities for all treated patients occurred in 1.4% (n= 16/1118) with fatal bleeding as the leading cause.

■ **Lee A, et al. A Systematic Review of Proton Therapy for the Management of Nasopharyngeal Cancer. Int J Part Ther. 2021 Jun 25;8(1):119-130.**

This review included 9 original studies and reported similar oncologic outcomes of PBT compared to IMRT with 2-year local and regional progression-free survival (LRFS) ranging from 84% to 100%, PFS ranging from 75% to 88.9%, and OS ranging from 88% to 95% in the up-front setting. Four comparison studies reported significantly lower feeding tube rates (20% versus 65%, P = .015; and 14% versus 85%, P < .001) with proton therapy as well as lower mucositis (G2 46% versus 70%, P = .019; and G3 11% versus 76%, P = .0002).

■ **Gunn GB, et al. Proton Therapy for Head and Neck Cancer: A 12-Year, Single-Institution Experience. Int J Part Ther. 2021 Jun 25;8(1):108-118.**

This study reviewed 573 patients treated including oropharynx (33.3%; n = 191), paranasal sinus (11%; n = 63), and periorbital tissues (11%; n = 62) being the most common primary sites. The intent of PT was definitive in 53% (n = 303), postoperative in 37% (n = 211), and reirradiation in 10% (n = 59). At a median follow-up of 2.4 years, the OS, LRC, and DFS at 2 and 5 years were 87% and 75%, 87% and 78%, and 74% and 63%. There were 381 acute grade 3 and 190 late grade 3 unique toxicities across 212 (37%) and 150 (26%) patients, respectively. There were 3 late-grade 4 events across 2 patients (0.3%), 2 (0.3%) acute-grade 5, and no (0%) late-grade 5 events. The authors concluded that the overall results from this prospective study of our initial decade of experience with PT for HNC show favorable disease control and toxicity outcomes.

■ **Cao JZ, et al. Intensity-modulated proton therapy for oropharyngeal cancer reduces rates of late xerostomia. Radiother Oncol. 2021 Jul:160:32-39.**

This study evaluated patients with oropharyngeal cancer (OPC) who received IMRT (n = 429) or IMPT (n = 103). With a median follow-up time of 36.2 months, the proportions of patients with moderate-severe xerostomia were similar in the two groups up to 18 months after treatment. However, moderate-severe xerostomia was less common in the IMPT group than in the IMRT group at 18-24 months (6% vs. 20%; p = 0.025) and 24-36 months (6% vs. 20%; p = 0.01).

■ **Chou YC, et al. Intensity Modulated Proton Beam Therapy versus Volumetric Modulated Arc Therapy for Patients with Nasopharyngeal Cancer: A Propensity Score-Matched Study. Cancers (Basel). 2021 Jul 16;13(14):3555.**

This propensity score matching analysis of 80 NPC patients treated with IMPT and VMAT. At a median follow-up time of 24.1 months, PFS and OS were not statistically different between the two groups but potentially better in IMPT group. The IMPT group had significantly less requirement for nasogastric tube placement and body weight loss during treatment due to the significantly lower mean dose of the oral cavity. However, IMPT increased the grade 3 radiation dermatitis.

■ **Jeans EB, et al. A comparison of acute toxicities and patient-reported outcomes between intensity-modulated proton therapy and volumetric-modulated arc therapy after ipsilateral radiation for head and neck cancers. Head Neck. 2022 Feb;44(2):359-371.**

A cohort of tonsil and salivary gland cancer patients who received ipsilateral curative-intent radiotherapy delivered by IMPT or VMAT were reviewed. This study reported that 40 patients treated with IMPT had decreased dose to multiple OARs and less deterioration in the following patient-report outcomes: pain, swallowing function, dry mouth, sticky saliva, sensory change, cough, speech, feeling ill, and social eating. Physician-reported toxicities demonstrated less oral pain.

■ **Wu PW, et al. Post-Irradiation Sinus Mucosa Disease in Nasopharyngeal Carcinoma Patients Treated with Intensity-Modulated Proton Therapy. Cancers (Basel). 2022 Jan 4;14(1):225.**

This study compared the incidence and severity of chronic rhinosinusitis in NPC patients who were treated with IMPT (n=53) or VMAT (n=54). Sinus mucosal changes were assessed by MRI and CT imaging and endoscopic scoring system. All patients were followed up for 2 years or more. Patients in the IMPT group had a significantly lower incidence and decreased severity of sinus mucosa abnormality than those with VMAT. Better and faster recovery of sinonasal function after radiotherapy in the IMPT group was also observed.

■ **Sheikh S, et al. Proton Beam Therapy for Locally Advanced Head and Neck Tumors: An Analysis of Dosimetric and Clinical Outcomes. Am J Clin Oncol. 2022 Feb 1;45(2):81-87.**

42 patients with locally advanced head and neck tumors treated with PBT were retrospectively analyzed in this study. Compared to VMAT plans, PBT plans showed a significant reduction of the mean dose and max dose to OARs, with the largest reduction mean dose in the contralateral cochlea and parotid glands at 71% and 75%. With a median follow up of 27 months, the OS rate was 44.75% at 4 years and PFS of 73.28% at 2 years. The majority of patients developed grade I dermatitis, mucositis, or both.

■ **Nuyts S, et al. Proton Therapy for Squamous Cell Carcinoma of the Head and Neck: Early Clinical Experience and Current Challenges. Cancers (Basel). 2022 May 24;14(11):2587.**

A significant reduction of toxicities, such as xerostomia, dysgeusia and feeding tube placement has been reported in studies of definitive PT for NPSCC (nasopharynx) and OPSCC (oropharynx). However an increased radiation-induced dermatitis has also reported in the PT groups. In the setting of dose (de-) escalation, adjuvant treatment and reirradiation, there is a paucity of data regarding the benefits of PT. Overall, this review suggests that PT is a promising treatment option for HNSCC, however prospective well-designed investigations comparing PT to IMRT are necessary.

■ **Youssef I, et al. Toxicity Profiles and Survival Outcomes Among Patients With Nonmetastatic Oropharyngeal Carcinoma Treated With Intensity-Modulated Proton Therapy vs Intensity-Modulated Radiation Therapy. JAMA Netw Open. 2022 Nov 1;5(11):e2241538.**

Among the 292 patients with nonmetastatic oropharyngeal cancer of which 272 (93%) were HPV–positive tumors, 58 patients (20%) were treated with IMPT and 234 (80%) with IMRT. With a median follow-up of 26 months, this study reported no significant differences in 3-year OS (97% IMPT vs 91% IMRT; P = .18), PFS (82% IMPT vs 85% IMRT; P = .62), or LRR (5% IMPT vs 4% IMRT; P = .59); however, the incidence of acute toxicities and chronic xerostomia of grade ≥2 was significantly higher for IMRT compared with IMPT.

■ **Held T, et al. Intensity modulated proton therapy for early-stage glottic cancer: high-precision approach to laryngeal function preservation with exceptional treatment tolerability. Radiat Oncol. 2022 Dec 5;17(1):199.**

This study reported outcomes of 15 patients with T1-2N0 glottic cancer. The 1- and 2-year OS and metastases-free survival were 100%. One patient developed local failure and received salvage laryngectomy. The mean number of CTCAE grade I and II overall toxicity events per patient was 4.1. No higher-grade acute or late toxicity was reported. The authors concluded that PT for T1-2N0 glottic cancer resulted in exceptional treatment tolerability with high rates of laryngeal function preservation and promising oncological outcome.

■ **Anderson JD, et al. A Prospective Study of Mucosal Sparing Radiation Therapy in Resected Oropharyngeal Cancer Patients. Int J Radiat Oncol Biol Phys. 2023 Jan 1;115(1):192-201.**

A total of 61 patients with HPV-positive oropharyngeal cancer were treated with mucosal sparing radiation therapy, including 44 (72%) patients with PT and 17 (28%) IMRT. With follow-up time 38 months, the 2-year LC, LRC, DMFS, and OS were 98%, 97%, 98%, and 100%, respectively. There were 6 grade ≥3 events related to treatment. Two IMRT patients required percutaneous endoscopic gastrostomy tube placement during treatment secondary to significant nausea due to dysgeusia.

■ **Singh A, et al. Osteoradionecrosis of the Jaw Following Proton Radiation Therapy for Patients With Head and Neck Cancer. JAMA Otolaryngol Head Neck Surg. 2023 Feb 1;149(2):151-159.**

Of the 122 patients included in this study, 13 (10.6%) developed osteoradionecrosis (ORN) following PRT during a median follow-up time of 40.6 months. The posterior ipsilateral mandible within the radiation field that received the full planned PRT dose was the most involved ORN site. The authors concluded that ORN remains a clinical challenge even in the era of highly conformal PRT.

■ **Fang KC, et al. Acute radiation dermatitis among patients with nasopharyngeal carcinoma treated with proton beam therapy: Prognostic factors and treatment outcomes. Int Wound J. 2023 Feb;20(2):499-507.**

This study reported incidence of acute radiation dermatitis (ARD) of 57 NPC patients treated with PBT. The maximum ARD grade was 1, 2, and 3 in 26 (45.6%), 24 (42.1%), and 7 (12.3%) of the patients, respectively. The results show ARD is a major concern for patients with NPC treated with PBT, especially those with habitual smoking or advanced nodal status.

■ **Lee A, et al. Evaluation of Proton Therapy Reirradiation for Patients With Recurrent Head and Neck Squamous Cell Carcinoma. JAMA Netw Open. 2023 Jan 3;6(1):e2250607.**

This study analyzed 242 patients treated with PT-ReRT. Median follow-up was 12.0 months for all patients and 24.5 months for living patients. Median PT-ReRT dose was 70 GyE for the fractionated cohort and 44.4 GyE for the quad shot cohort. For the fractionated cohort, the 1-year LC was 71.8% and OS was 66.6%. For the quad shot cohort, the 1-year LC was 61.6% and OS was 28.5%. There were a total of 73 grade 3 and 6 grade 4 early toxic effects. There were 79 potential grade 3, 4 grade 4, and 5 grade 5 late toxic effects.

■ **Sethi S, et al. Toxicity with proton therapy for oral and/or oropharyngeal cancers: A scoping review. J Oral Pathol Med. 2023 Aug;52(7):567-574.**

This review included 18 primary studies for analysis focusing on acute toxicities including dysphagia, radiation dermatitis, oral mucositis, dysgeusia and alopecia. The conclusion made in this review is that current evidence supports that proton therapy improves acute toxicity profile compared to photon radiotherapy to treat oral and/or oropharyngeal cancer individuals.

■ **Ng WT, et al. Particle beam therapy for nasopharyngeal cancer: A systematic review and meta-analysis. Clin Transl Radiat Oncol. 2022 Aug 23:37:41-56.**

Twenty-six eligible studies with a total of 1502 patients were included in this review. The pooled OS at 1-year, 2-year and 3-year and 5-year for primary NPC patients who received particle beam therapy were 96 %, 93 %, 90 % and 73 % respectively. The pooled 1-year and 2-year PFS, and LC for these patients were above 90 %. Late toxicity ≥G3 was 20 % or less. The review concluded that particle therapy produced excellent survival outcomes with low toxicity.

■ **Youssef I, et al. Outcomes and Toxicities of Nonmedullary Thyroid Tumors Treated with Proton Beam Radiation Therapy. Int J Part Ther. 2022 Jul 15;9(2):20-30.**

For a cohort of 22 patients with thyroid cancer treated with PBT, with a median follow-up 26 months, 1-year local regional recurrence was 0%, and OS was 90% for all patients. Acute grade 3+ toxicities occurred in 27% of patients, the most frequent being dermatitis (27%). Three patients required a percutaneous endoscopic gastrostomy tube. There were no grade 4+ toxicities. The authors concluded that PBT for thyroid cancer was feasible and effective with minimal toxicities.

■ **Trotter J and Lin A. Advances in Proton Therapy for the Management of Head and Neck Tumors. Surg Oncol Clin N Am. 2023 Jul;32(3):587-598.**

A review article summarized the advances of PBRT as compared to photon-based RT. Clinical evidence has demonstrated promising results of PBRT in the treatment of cancers of the nasopharynx, sinonasal region, and oropharynx as well as in the postoperative and reirradiation settings. Retrospective data suggests that PBRT may be beneficial in decreasing treatment related toxicity and improving patient-reported outcomes, as well as improving disease outcomes.

■ **Bahig H, et al. Long-term outcomes of modern multidisciplinary management of sinonasal cancers: The M. D. Anderson experience. Head Neck. 2023 Jul;45(7):1692-1703.**

This is study retrospectively analyzed 311 patients with sinonasal tumors treated with IMRT or PT. With median follow-up of 75 months, this study reported 10-year LC, regional control, DMFS, PFS, and OS rates were 73%, 88%, 47%, 32%, and 51%, respectively. There was a 13% rate of late grade ≥3 toxicities. The authors concluded that their data demonstrated favorable disease control rate and acceptable toxicity profile.

■ **Walser MA, et al. Clinical outcome after pencil beam scanning proton therapy and dysphagia/xerostomia NTCP calculations of proton and photon radiotherapy delivered to patients with cancer of the major salivary glands. Br J Radiol. 2023 Aug;96(1148):20220672.**

For the 26 patients with salivary gland tumor treated with PBSPT, at a median follow-up time of 46 months, 5 (19%), 2 (8%), 3 (12%) and 2 (8%) patients presented with distant, local, locoregional failures and death, respectively. The estimated 4-year OS and LC were 90% and 90%. Local regional control and distant control were 87 and 77%. Grade 3 late toxicity was observed in 2 (8%) patients. The estimated 4 year late high-grade (≥3) toxicity-free survival was 78.4%.

■ **Sethi S, et al. Toxicity with proton therapy for oral and/or oropharyngeal cancers: A scoping review. J Oral Pathol Med. 2023 Aug;52(7):567-574.**

This review evaluated the toxicity associated with proton therapy for adults with oral and/or oropharyngeal cancer. Based on 18 original studies, this review found improved acute toxicity profile with proton compared to photon-based radiotherapy in dysphagia, radiation dermatitis, oral mucositis, dysgeusia, and alopecia.

■ **Pollock AE, et al. Gross tumor volume margin and local control in p16-positive oropharynx cancer patients treated with intensity modulated proton therapy. Head Neck. 2023 May;45(5):1088-1096.**

This retrospective analysis included 60 patients with p16+ OPC treated with IMPT. The median GTV to CTV expansion was 5 mm. Thirty-three percent of patients (20 of 60) did not have a GTV to CTV expansion. One local failure within the expansion group (3%) was reported at a median follow-up of 17 months. The authors concluded that excellent local control was achieved using IMPT for p16+ OPC independent of GTV expansion. IMPT with minimal target expansions represent a potential harm-minimization technique for p16-positive oropharynx cancer.

■ **Saito T, et al. Proton beam therapy in multimodal treatment for locally advanced squamous cell carcinoma of the nasal cavity and paranasal sinus. Radiat Oncol. 2023 Jun 29;18(1):106.**

This study reported clinical outcomes of 37 patients with locally advanced nasal cavity and paranasal sinus (NPSCC) treated with postoperative PBT or definitive PBT. The median follow-up period was 4.4 years. The 4-year OS, PFS, and LC rates were 58%, 43% and 58% for all patients. The authors concluded that PBT gave favorable outcomes in multimodal treatment for resectable locally advanced NPSCC.

■ **Kim H, et al. Phase II Trial of Combined Durvalumab Plus Tremelimumab with Proton Therapy for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma. Cancer Res Treat. 2023 Oct;55(4):1104-1112.**

This study reported outcomes of 31 recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) patients treated with combined proton therapy and durvalumab plus tremelimumab. With 8.6 months of follow-up, the objective response rate (ORR) was 22.6% (7/31), including one complete response and six partial responses. The median OS was 8.4 months and the median PFS was 2.4 months. Grade 3 or higher adverse events were observed in six patients (19.4%).

■ **Choi JI, et al. Risk of temporal lobe necrosis between proton beam and volumetric modulated arc therapies in patients with different head and neck cancers. Semin Radiat Oncol. 2023 Oct;33(4):407-415.**

This study reviewed 483 patients with various types of head and neck cancer (HNC) and reported that the nasopharyngeal carcinoma (NPC) patients had a higher frequency of temporal lobe necrosis (TLN) compared to non NPC patients (5.6% vs. 0.4%, $p < 0.01$). The frequency of TLN was similar between patients receiving PBT and those receiving VMAT (PBT vs. VMAT: 4.7% vs. 6.3%, $p = 0.76$).

■ **Chiu KW, et al. A systematic review and meta-analysis of osteoradionecrosis following proton therapy in patients with head and neck cancer. Oral Oncol. 2024 Jan:148:106649.**

Osteoradionecrosis (ORN), which is a serious complication and late toxicity of radiotherapy, has been reported in proton therapy. This meta-analysis included 17 original studies and reported the pooled grade ≥3 ORN rate of 0.01. The pooled incidence rate of grade ≥1 ORN was 0.05 and grade ≥2 ORN was 0.03. A previous study showed that the grade ≥3 ORN rate in the IMRT is about 1.5 %. This analysis showed that ORN rate is similar in proton-based radiotherapy and photon-based radiotherapy.

■ **Li XZ, et al. Past, present and future of proton therapy for head and neck cancer. Oral Oncol. 2020 Jul 7;110:104879.**

Head and neck cancer patients are living longer due to epidemiological shifts and advances in treatment options. As such, long-term toxicity from radiation treatment has become a major concern that may be better mitigated by proton therapy. This review examined the evidence of proton therapy in major subsites within the head and neck to facilitate a greater understanding of the full risks and benefits of proton therapy for head and neck cancer.

■ **Jiří K, et al. Proton pencil-beam scanning radiotherapy in the treatment of nasopharyngeal cancer: dosimetric parameters and 2-year results. Eur Arch Otorhinolaryngol. 2020 Jul 4.**

This study reported outcomes of 40 patients treated for nasopharyngeal cancer (NPC) with IMPT. Two-year OS, DFS, and LC were 80%, 75%, and 84%, respectively. Acute toxicity was generally mild with skin toxicity and dysphagia reported as the most frequent acute side effects. The PEG was necessary in four cases (10%). Serious late toxicity (G > 3. RTOG) was observed in two patients (5%) (dysphagia and brain necrosis).

■ **Kitpanit S, et al. Temporal Lobe Necrosis in Head and Neck Cancer Patients After Proton Therapy to the Skull Base. Int J Part Ther. Spring 2020;6(4):17-28.**

234 patients were included in this analysis. This study reported the estimated 2-year TLN rate was 4.6%, and the 2-year rate of any brain necrosis was 6.8%. In comparison to IMRT studies, this study pointed out that the rate of TLN was more frequent in patients receiving proton therapy than IMRT at the same follow-up time. The lack of conformality at the high- dose region with older proton techniques versus IMRT may account for the higher rates of TLN.

■ **Aljabab S, et al. Proton Therapy for Locally Advanced Oropharyngeal Cancer: Initial Clinical Experience at the University of Washington. Int J Part Ther. Winter 2020;6(3):1-12.**

This study reported a favorable toxicity profile of 46 oropharyngeal cancer patients treated with IMPT. This study reported no acute grade 4 or 5 toxicities. 18 patients had percutaneous endoscopic gastrostomy (PEG) tube placement with the majority (14) for prophylactic purpose. The most common grade 3 acute toxicities were dermatitis (76%) and mucositis (72%). The most common late toxicity was grade 2 xerostomia (30%).

■ **Pasalic D, et al. Patient-reported Outcomes, Physician-Reported Toxicities, and Treatment Outcomes in a Modern Cohort of Patients With Sinonasal Cancer Treated Using Proton Beam Therapy. Radiother Oncol. 2020 May 15;148:258-266.**

This study reported physician-assessed toxicities (PATs) and patient-reported outcomes (PROs) of 64 patients treated with PBT. One acute G3 neurologic PAT (blurred vision) was observed and resolved, and no late G3-4 neurologic PATs. No significant changes were noted in PROs from baseline to the chronic period. The 3-year local control, disease-free survival, and overall survival rates were 88%, 76%, and 82%, respectively.

■ **Meijer TWH, et al. Reduced radiation-induced toxicity by using proton therapy for the treatment of oropharyngeal cancer. Br J Radiol. 2020 Mar;93(1107):20190955.**

This review paper examined the outcome reports of oropharyngeal cancer patients treated PBT patients. The prevention of radiation-induced xerostomia and dysphagia and subsequent improvement of health-related quality of life canbe obtained by applying proton therapy. Proton therapy results in lower dose levels in multiple organs at risk, which translates into reduced acute toxicity.

■ **Chuong M, et al. Minimal acute toxicity from proton beam therapy for major salivary gland cancer. Acta Oncol. 2020 Feb;59(2):196-200.**

This multicenter study reported acute toxicities of 105 patients with major salivary gland cancers registered on the Proton Collaborative Group REG001-09 trial. The acute grade 2 or higher toxicity included nausea (1.5%), dysgeusia (4.8%), xerostomia (7.6%), mucositis (10.5%) and dysphagia (10.5%). The study suggests to consider PBT for ipsilateral irradiation for salivary gland cancer because of the considerably lower incidence of acute grade 2 or higher toxicity compared to historical IMRT outcomes.

■ **Lee A, et al. Trends and Disparities of Proton Therapy Use among Patients with Head and Neck Cancer: Analysis from the National Cancer Database (2005-14). Int J Part Ther. Spring 2019;5(4):1-10.**

This analysis found that among the 220,491 patients who received any radiation therapy as part of their initial treatment course, only 417 (0.2%) received proton therapy. The use of protons had a small increase from 0.13% in 2005-06 to 0.41% by 2013-14 (P < .001). The most common primary sites treated with proton therapy were the nasal cavity/nasopharynx and the oral cavity. Most patients had T4 disease.

■ **Azami Y, et al. Proton Beam Therapy for Locally Recurrent Parotid Gland Cancer. Indian J Otolaryngol Head Neck Surg. 2019 Oct;71(Suppl 1):49-54.**

This study from Japan evaluated outcomes of PBT for locally recurrent parotid gland cancer. Ten patients were treated to 70.2 Gy equivalents in 32 fractions. With the median follow-up of 24 months, the study reported that the 1-year overall survival and local control rates were 80 %, and the 3-year overall survival and local control rates were 60 %, and no patient experienced grade 3-5 toxicities.

■ **Yu NY, et al. A Multi-Institutional Experience of Proton Beam Therapy for Sinonasal Tumors. Adv Radiat Oncol. 2019 Jul 16;4(4):689-698.**

Sixty-nine patients with sinonasal tumors underwent curative intent PBT including 42 patients who received de novo irradiation and 27 who received reirradiation. This study reported the 3-year overall survival and freedom from disease progression were 100% and 77.3% respectively for de novo irradiation, and 76.2% and 32.1% for re-RT patients. There were 11 patients with acute grade 3 toxicities. Late toxicities occurred in 15% of patients, with no grade ≥3 toxicities.

■ **Price J, et al. TORPEdO - A Phase III Trial of Intensity-modulated Proton Beam Therapy Versus Intensity-modulated Radiotherapy for Multi-toxicity Reduction in Oropharyngeal Cancer. Clin Oncol (R Coll Radiol). 2020 Feb;32(2):84-88.**

It is a multicenter phase III trial of IMPT versus IMRT for oropharyngeal squamous cell carcinoma, with the primary objective to assess whether IMPT compared with IMRT reduces late treatment-related toxicities in patients who require treatment with concurrent chemotherapy and bilateral neck radiotherapy. Secondary objectives include validation of a biomarker (NTCP model) as a predictor of benefit from IMPT versus IMRT and an assessment of cost-effectiveness.

■ **Rwigema JM, Langendijk JA, Paul van der Laan H, et al. A Model-Based Approach to Predict Short-Term Toxicity Benefits With Proton Therapy for Oropharyngeal Cancer. Int J Radiat Oncol Biol Phys. 2019 Jul 1;104(3):553-562.**

For patients with advanced-stage oropharynx cancer treated with curative intent (PBT, n = 30; IMRT, n = 175), NTCP models were developed, which were then applied to the PBT-treated patients to compare predicted and observed clinical outcomes. This study demonstrates an NTCP model-based approach to compare predicted patient outcomes when randomized data are not available.

■ **Brodin NP, Kabarriti R, Pankuch M, Schechter CB, et al. A Quantitative Clinical Decision-support Strategy Identifying Which Oropharyngeal Head and Neck Cancer Patients may Benefit the Most from Proton Radiation Therapy. Int J Radiat Oncol Biol Phys. 2019 Jul 1;104(3):540-552.**

This study used NTCP models of dysphagia, esophagitis, hypothyroidism, xerostomia and oral mucositis for identifying patients for proton treatment. The QALYs spared by proton RT varied considerably between patients, from 0.06 to 0.84 QALYs. Younger patients with p16-positive tumors who smoked ≤10 pack-years may benefit most from proton therapy.

■ **Park SG, Ahn YC, Oh D, et al. Early clinical outcomes of helical tomotherapy/intensity-modulated proton therapy combination in nasopharynx cancer. Cancer Sci. 2019 Jun 25.**

Ninety-eight nasopharynx cancer patients treated with Tomotherapy (HT) alone or combined HT and intensity-modulated proton therapy. This study reported comparable early oncologic outcomes with more favorable acute toxicity profiles achievable by HT/IMPT combination in treating NPC patients.

■ **Leeman JE, Lee NY, Zhou Y, et al. Endoscopic Resection Followed by Proton Therapy With Pencil Beam Scanning for Skull Base Tumors. Laryngoscope. 2019 Jun;129(6):1313-1317.**

A study compared PBS and IMRT radiation plans in the preoperative and postoperative settings for two patients with advanced skull base tumors following endoscopic resection. The benefits of PBS over IMRT appear greater in the postoperative setting following endoscopic resection with improved sparing of critical organs at risk.

■ **Moreno AC, Frank SJ, Garden AS, et al. Intensity modulated proton therapy (IMPT) - The future of IMRT for head and neck cancer. Oral Oncol. 2019 Jan;88:66-74.**

A review article looked at the development of RT advances. There is a growing awareness of the potential clinical benefits of proton therapy over IMRT in the definitive, postoperative and reirradiation settings given the unique physical properties of protons. Evidence of the clinical translation of dosimetric advantages of IMPT over IMRT has been demonstrated with documented toxicity reductions.

■ **Deshpande TS, Blanchard P, Wang L, et al. Radiation-Related Alterations of Taste Function in Patients With Head and Neck Cancer: a Systematic Review. Curr Treat Options Oncol. 2018 Nov 9;19(12):72.**

Majority of HNC patients undergoing radiotherapy suffer from altered taste function and often complain of inability to taste their food, reduced food intake, and weakness. By using Intensity-Modulated Proton Therapy in HNC patients, the authors anticipate preserving the taste sensation by reducing the dose of radiation to the taste buds.

■ **Endo H, Takayama K, Mitsudo K, et al. Proton Beam Therapy in Combination with Intra-Arterial Infusion Chemotherapy for T4 Squamous Cell Carcinoma of the Maxillary Gingiva. Cancers (Basel). 2018 Sep 15;10(9).**

Thirty patients with T4 squamous cell carcinoma of the maxillary gingiva treated with radiation and chemotherapy. Radiotherapy was using boost PBT for primary tumor and neck lymph node tumors, following photon radiation delivered to the prophylactic area. The 3-year local control and overall survival rates were 69% and 59%, respectively. No grade 3 or higher late toxicities were observed.

■ **Cao KI, et al. Protontherapy of head and neck paragangliomas: A monocentric study. Cancer Radiother. 2018 Feb;22(1):31-37.**

A study reported the outcomes of 10 patients of paragangliomas of the head and neck, rare benign tumours developed close to crucial structures, treated with proton therapy. With a median follow-up of 24.6months, local tumour control rate was 100% and no upper grade 2 acute toxicity. Proton therapy is an effective and well-tolerated treatment modality of skull base paragangliomas.

■ **Blanchard P, et al. Proton Therapy for Head and Neck Cancers, Semin Radiat Oncol. 2018 Jan;28(1):53-63.**

This systematic review detailed the physical properties and dosimetric benefit of proton therapy over advanced photon therapy, and analyzed the published data on the clinical benefit described for each disease site in head and neck cancer, as well as discussing issues of patient selection and cost-effectiveness.

■ **Kim JK, et al. Proton Therapy for Head and Neck Cancer. Curr Treat Options Oncol. 2018 May 9;19(6):28.**

This review summarized the published clinical research, and the authors believe that widespread adoption of proton therapy will elucidate the true value of proton beam therapy and give a greater understanding of the full risks and benefits of proton therapy in head and neck cancer.

■ **Frank SJ, et al. Comparing Intensity-Modulated Proton Therapy With Intensity-Modulated Photon Therapy for Oropharyngeal Cancer(OPC): The Journey From Clinical Trial Concept to Activation. Semin Radiat Oncol. 2018 Apr;28(2):108-113.**

This article describes the process by which a phase III randomized trial was designed to test whether IMPT was truly less toxic for patients with advanced OPC. Outcomes from this trial are expected to better define the value of proton therapy for patients with head and neck cancer.

■ **Leeman J E et al. Proton therapy for head and neck cancer: expanding the therapeutic window. Lancet Oncol. 2017 May;18(5):e254-e265.**

This review article summarized the recent published outcomes of proton therapy for various types of head and neck cancer in an attempt to define the role of PT. The authors pointed out that the clinical benefits of PT in terms of toxicity sparing are becoming increasingly apparent ranging from incremental to substantial in the selected patient groups.

■ **Zhang W et al. Intensity-modulated proton therapy and osteoradionecrosis in oropharyngeal cancer. Radiother Oncol. 2017 Jun;123(3):401-405.**

Comparing mandibular doses and osteoradionecrosis in patients with oropharyngeal cancer after IMRT or IMPT, this study reported both mandibular doses and osteoradionecrosis rates were lower with IMPT. Osteoradionecrosis was significantly associated with higher dose irradiation to mandibular. IMPT minimized excess irradiation of the mandible and consequently reduced the risk of osteoradionecrosis.

■ **Wang L et al. Human papillomavirus status and the relative biological effectiveness of proton radiotherapy in head and neck cancer cells. Head Neck. 2017 Apr;39(4):708-715.**

This study reported that HPV-positive cells were more sensitive to protons and the unrepaired double-strand breaks were more numerous in HPV-positive cells than in HPV-negative cells. Protons killed more cells than XRT at all fraction sizes.

■ **Langendijk JA and Steenbakkers RJ. Optimizing Radiotherapy in HPV-Associated Oropharyngeal Cancer Patients. Recent Results Cancer Res. 2017;206:161-171.**

Given the high survival rates in HPV-positive OPC patients and the high rates of toxicity associated with the concurrent chemoradiation for the locally advanced OPC, the authors advocated the 'de-escalation strategies' which include radiation dose de-escalation based on response to induction chemotherapy, radiotherapy alone without systemic treatment and replace chemotherapy agents. The authors emphasized that IMPT has the highest potential to decrease acute and late toxicities.

■ **Phan J et al. Reirradiation of Head and Neck Cancers With Proton Therapy: Outcomes and Analyses. Int J Radiat Oncol Biol Phys. 2016 Sep 1;96(1):30-41.**

A study reported outcomes of 60 patients who received proton re-irradiation (25% with passive scatter and 75% with IMPT), together with concurrent chemotherapy (73%). The authors concluded that proton therapy can be a safe and effective curative reirradiation strategy, with acceptable rates of toxicity and durable disease control.

■ **McDonald MW et al. Reirradiation of Recurrent and Second Primary Head and Neck Cancer With Proton Therapy. Int J Radiat Oncol Biol Phys. 2016 Nov 15;96(4):808-819.**

61 recurrent patients treated with PBT. The 2-year overall survival estimate was 32.7% and grade 3 and above toxicity were seen 14.7% in acutely and 24.6% late setting. The authors concluded that proton reirradiation with or without chemotherapy, provided reasonable locoregional disease control, survival outcomes and toxicity profiles for an advanced-stage and heavily pretreated population.

■ **Lukens J.N., Lin A. and Hahn S.M. Proton therapy for head and neck cancer. Current Opinion in Oncology. 2015 May;27(3):165-71.**

PT for head and neck cancer is an area of active research, and the subject of heightened scrutiny due to the significant associated cost. This article highlights recent research into proton dosimetry, its clinical benefit relative to other advanced radiotherapy modalities, key safety and cost considerations.

■ **Linton O.R. et al. Proton therapy for head and neck adenoid cystic carcinoma: initial clinical outcomes. Head & Neck. 2015 January;37(1):117-24.**

The purpose of this study is to report outcomes of PT in head and neck adenoid cystic carcinoma. Initial outcomes are encouraging.

■ **Fuji H. et al. High-dose proton beam therapy for sinonasal mucosal malignant melanoma. Radiation Oncology. 2014 July 23;9:162.**

The significance of definitive radiotherapy for sinonasal mucosal melanoma (SMM) is still controversial. This study evaluates the role of high-dose PT in patients with SMM. Findings suggest that high-dose PT is an effective local treatment that is less invasive than surgery but with comparable outcomes.

■ **Holliday E.B., Frank S.J. Proton radiation therapy for head and neck cancer: a review of the clinical experience to date. International Journal of Radiation Oncology. Biology. Physics. 2014 June 1; 89(2):292-302.**

PT has been used for cancer treatment since the 1950s, and both the number of patients and the variety of tumors treated have increased since then. Great interest has been expressed in evaluating whether PT can improve outcomes, especially early and late toxicity, when used in the treatment of head and neck malignancies. This review summarizes the progress made to date in addressing this question.

■ **Frank S.J. 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 October 1; Vol. 87, Issue 2, S144.**

A potential advantage of IMPT over IMRT in the treatment of oropharyngeal carcinoma (OPC) is a decrease in toxicity. This study quantifies the incidence of gastrostomy tube use in OPC patients treated with IMPT and compares it to gastrostomy use in patients treated with IMRT. Preliminary data suggest that IMPT has a lower rate of grade 3 dysphagia.

■ **Gunn G.B. and Frank S.J. Advances in radiation oncology for the management of oropharyngeal tumors. Otolaryngologic Clinics of North America. 2013;46(4):629-43.**

The major benefits of modern radiation therapy in the treatment of oropharyngeal cancer are reduced xerostomia and better quality of life. Treatment-related toxicities must be kept in mind, particularly because most patients are expected to have a high probability of long-term survival after treatment. In this context, IMPT seems to provide additional advantages over IMRT by reducing radiation beam-path toxicities.

■ **Ramaekers B. Protons in head-and-neck cancer: bridging the gap of evidence. International Journal of Radiation Oncology. Biology. Physics. 2013;85(5):1282-8.**

Cost-effectiveness analysis based on normal tissue complication probability models and planning studies proved feasible and informative and enables the analysis of individualized strategies. The increased effectiveness of IMPT does not seem to outweigh the higher costs for all head-and-neck cancer patients. However, when assuming equal survival among both modalities, there seems to be value in identifying those patients for whom IMPT is cost-effective.

■ **Liu W. et al. Effectiveness of robust optimization in intensity-modulated proton therapy planning for head and neck cancers. Medical Physics. 2013; 40(5):051711.**

IMPT is highly sensitive to uncertainties in beam range and patient setup, which are conventionally addressed using geometrically expanded planning target volume (PTV). This paper evaluates IMPT for head & neck cancer and shows that robust optimization based on clinical target volume (CTV) provides significantly more robust dose distributions to targets and organs than PTV-based conventional optimization.

■ **Ramaekers B. et al. Systematic review and meta-analysis of radiotherapy in various head and neck cancers: comparing photons, carbonions and protons. Cancer Treatment Reviews. 2011; 37(3):185-201.**

This study synthesizes and compares available evidence considering the effectiveness of carbon-ion, proton and photon radiotherapy for head and neck cancer.

■ **Van de Water T. 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. The Oncologist. 2011;16(3):366-77.**

Protons have the potential for a significantly lower normal tissue dose, while keeping similar or better target coverage. Scanned IMPT probably offers the most advantage and will allow for a substantially lower probability of radiation-induced side effects.

LUNG CANCER AND OTHER THORACIC CANCERS

■ **Lazarev S, et al. Where are we with proton beam therapy for thoracic malignancies? Current status and future perspectives. Lung Cancer. 2021 Feb:152:157-164.**

This review examines the evolving role of PBT in the treatment of thoracic malignancies and evaluates the data supporting its use. Clinical outcomes data of PBT for early-stage NSCLC, locally advanced stage NSCLC, small cell lung cancer, malignant pleural mesothelioma, thymic malignancies and reirradiation has been summarized in the review. Available prospective investigations are limited by small sample sizes and relatively short follow-up. Comparative data is scarce, making it challenging to draw conclusions about the value of protons over photons.

■ **Gjyshi O, et al. Toxicity and Survival After Intensity-Modulated Proton Therapy Versus Passive Scattering Proton Therapy for NSCLC. J Thorac Oncol. 2021 Feb;16(2):269-277.**

The study included 139 patients of whom 86 (62%) received PSPT and 53 (38%) IMPT. IMPT delivered significantly lower mean radiation doses to the lungs (PSPT 16.0 Gy versus IMPT 13.0 Gy, $p < 0.001$), heart (10.7 Gy versus 6.6 Gy, $p = 0.004$), and esophagus (27.4 Gy versus 21.8 Gy, $p = 0.005$). Consequently, the IMPT cohort had lower rates of grade 3 or higher pulmonary (17% versus 2%, $p = 0.005$) and cardiac (11% versus 0%, $p = 0.01$) toxicities. Six patients (7%) with PSPT and zero patients (0%) with IMPT experienced grade 4 or 5 toxicity. There was also a trend toward longer median OS in the IMPT group (23.9 mo versus 36.2 mo, $p = 0.09$). No difference was found in the 3-year rates of LC, local-regional control and distant recurrences.

■ **Patel NV, et al. Proton therapy for thoracic malignancies: a review of oncologic outcomes. Expert Rev Anticancer Ther. 2021 Feb;21(2):177-191.**

This article reviewed PBT physical properties and treatment techniques for thoracic malignancies and examined the dosimetric advantages and clinical outcomes of PBT for each of the major thoracic malignancies, including lung cancer, esophageal cancer, mesothelioma, thymic cancer, and primary mediastinal lymphoma. Expert opinion: Despite clear dosimetric benefits with PBT in thoracic radiotherapy, the improvement in clinical outcomes remains to be seen.

■ **Shin H, et al. Salvage proton beam therapy for locoregional recurrence of non-small cell lung cancer. Radiat Oncol J. 2021 Mar;39(1):24-32.**

This study retrospectively reviewed 53 patients who received salvage PBT for locoregionally recurrent NSCLC. With a median follow-up time of 15.0 months, 26 patients (49.1%) experienced disease progression, and the 2-year OS, LC, and PFS rate were 79.2%, 68.2%, and 37.1%, respectively. Grade 3 toxicities occurred in 8 patients (15.1%): esophagitis in 2, dermatitis in 3, and pulmonary toxicities in 4.

■ **Chiang JS, et al. Proton beam radiotherapy for patients with early-stage and advanced lung cancer: a narrative review with contemporary clinical recommendations. J Thorac Dis. 2021 Feb;13(2):1270-1285.**

A review article examined data available of proton radiation for early-stage, advanced-stage and recurrent NSCLC, as well as protons in post-operative radiotherapy and SCLC settings. This review also discussed the challenges of proton therapy in treatment for lung cancer.

■ **Boyce-Fappiano D, et al. Single Institution Experience of Proton and Photon-based Postoperative Radiation Therapy for Non-small-cell Lung Cancer. Clin Lung Cancer. 2021 Sep;22(5):e745-e755.**

This study retrospectively evaluated 136 postoperative radiotherapy (PORT) patients (61 PBT, 75 IMRT). Median OS was 76 and 46 months for PBT and IMRT with corresponding 1- and 5-year OS of 85.3%, 50.9% and 89.3%, 37.2% (P = .38). Total toxicity burden was reduced with PBT (P = .017). Rates of cardiac toxicity were 14.7% IMRT and 4.9% PBT (P = .09), rates of ≥ grade 2 pneumonitis were 17.0% IMRT and 4.9% PBT (P = .104). This study concluded that PBT improved cardiac and lung sparing and reduced toxicity compared with IMRT.

■ **Ohnishi K, et al. Long-term outcomes of high-dose (74 GyE) proton beam therapy with concurrent chemotherapy for stage III nonsmall-cell lung cancer. Thorac Cancer. 2021 May;12(9):1320-1327.**

This study reported outcomes of 45 patients with stage III NSCLC treated with PBT of 74 GyE and concurrent chemotherapy. With a median follow-up time of 42.1 months for all patients, the 3- and 5-year OS rates were 63.7% and 38.8%, and the median overall survival was 49.1 months. No grade 4 or 5 acute or late non-hematologic toxicities were observed.

■ **Bayasgalan U, et al. Treatment outcomes of passive scattering proton beam therapy for stage I non-small cell lung cancer. Radiat Oncol. 2021 Aug 18;16(1):155.**

This study retrospectively analyzed 42 patients with stage I NSCLC treated with PBT. At a median follow-up time of 40 months, the 3-year OS rate was 71.8%, LC and PFS was 91.5% and 66.9%, respectively. Thirteen patients experienced disease progression consisting of three local, six regional, and nine distant failures. No grade 4 or 5 toxicities were observed. This study concluded that PSPT for stage I NSCLC using SABR or hypofractionated RT was safe and showed high LC rates.

■ **Kim N, et al. Clinical Outcomes of Pencil Beam Scanning Proton Therapy in Locally Advanced Non-Small Cell Lung Cancer: Propensity Score Analysis. Cancers (Basel). 2021 Jul 13;13(14):3497.**

For a cohort of 219 patients with stage III NSCLC who received definitive concurrent chemoradiotherapy, 25 patients (11.4%) underwent PBSPT and 194 patients (88.6%) underwent IMRT. At a median follow-up of 21.7 months, the 2-year LRC rates were 72.1% and 84.1% in the IMRT and PBSPT groups, respectively (p = 0.287). The rates of grade ≥ 3 esophagitis were 8.2% and 20.0% after IMRT and PBSPT (p = 0.073), respectively, while corresponding rates of grade ≥ 2 radiation pneumonitis were 28.9% and 16.0%, respectively (p = 0.263).

Qiu B, et al. Dosimetry, Efficacy, Safety, and Cost-Effectiveness of Proton Therapy for Non-Small Cell Lung Cancer. Cancers (Basel). 2021 Sep 10;13(18):4545.

In the early-stage NSCLC setting, all of the studies had a small sample size and were single-arm without direct comparison. Proton therapy was promising for locally advanced NSCLC with improved clinical outcomes and reduced toxicity when compared with historical photon therapy data, with lower rates of severe (grade 3) toxicities, although the only RCT reported grade ≥ 3 radiation pneumonitis rate of IMRT, 6.5% versus PSPT, 10.5%. Further study of PBS is ongoing and direct comparison is warranted.

■ **Ma NY, et al. Preliminary Safety and Efficacy of Proton Plus Carbon-Ion Radiotherapy With Concurrent Chemotherapy in Limited-Stage Small Cell Lung Cancer. Front Oncol. 2021 Nov 11:11:766822.**

This study reported outcomes of 25 patients with limited-stage small cell lung cancer treated with combined proton and carbon-ion radiotherapy. The 2-year overall and locoregional progression-free survival rates were 81.7% and 66.7%, respectively. Grade 1, 2, and 3 acute toxicities occurring in 12.0%, 68.0%, and 20.0% of patients, respectively. All grade 3 acute toxicities were hematologically related.

■ **Noh JM, et al. Prospective Study of Proton Therapy for Lung Cancer Patients with Poor Lung Function or Pulmonary Fibrosis. Cancers (Basel). 2022 Mar 11;14(6):1445.**

This study reported results of PBT for 54 patients of inoperable stage I to III NSCLC with poor lung functions (defined as FEV1 ≤1.0 L, or FEV1≤50% predicted or DLco ≤50% or pulmonary fibrosis) due to underlying lung diseases. With a median follow up 19.8 months, this study reported no significant changes in the predicted FEV1 and DLco from baseline to month 7 after PBT treatment. Seven patients (13.0%) who developed grade 3 or higher pulmonary toxicities. The 2-year OS rate was 71.1%.

■ **Hashimoto S, et al. Outcomes of proton therapy for non-small cell lung cancer in patients with interstitial pneumonia. Radiat Oncol. 2022 Mar 21;17(1):56.**

This study reported outcomes of 29 stage I to III NSCLC patients with interstitial pneumonia (IP) treated with PT. With a median follow up of 21.1 months, this study reported grade 3 acute radiation pneumonitis (RP) in one patient and grade 3 late RP in two patients, with no other patients experienced serious toxicities. The 2-year LC, PFS and OS rates were 85%, 30% and 45%.

■ **Hoppe BS, et al. Chemoradiation with Hypofractionated Proton Therapy in Stage II-III Non-Small Cell Lung Cancer: A Proton Collaborative Group Phase 1/2 Trial. Int J Radiat Oncol Biol Phys. 2022 Jul 15;113(4):732-741.**

This study presented outcomes of a prospective multicenter trial with an early closure. Twenty-eight patients with stage II or III unresectable NSCLC were treated with hypofractionated proton therapy at 2.5-4 Gy per fraction to a total 60 Gy(RBE) with concurrent chemotherapy. After a median follow-up of 31 months, the 1- and 3-year OS rates were 89% and 49%; and PFS rates were 58% and 32%, respectively. No acute grade 3 or higher esophagitis occurred. Only 14% developed a grade 3 or higher radiation-related pulmonary toxicity.

■ **Kearney M, et al. Exposure of the heart in lung cancer radiation therapy: A systematic review of heart doses published during 2013 to 2020. Radiother Oncol. 2022 Jul:172:118-125.**

Data of 140 dosimetry studies was analyzed. In the 105 non-SABR studies, the average MHD was similar between IMRT and 3DCRT (10.9 Gy versus 10.6 Gy) and lower with particle beam therapy (proton 7.0 Gy; carbon-ion 1.9 Gy). Active respiratory motion management reduced exposure (7.4 Gy versus 9.3 Gy). In the SABR 35 studies, MHD was 4.0 Gy (0.0-32.4). MHD was lowest for carbon ions (0.5 Gy) compared to other techniques. Active respiratory motion management reduced exposure (2.4 Gy versus 5.0 Gy).

■ **Suh YG, et al. Proton Beam Therapy versus Photon Radiotherapy for Stage I Non-Small Cell Lung Cancer. Cancers (Basel). 2022 Jul 26;14(15):3627**

This study reported clinical outcomes and dosimetry comparison of 289 patients with stage I NSCLC treated with protons (n=112) and photons (n=177). With a median follow-up duration of 27 months, the 2-year PFS and OS rates were 94.0% and 83.0%, respectively. BED ≥125 Gy was significantly associated with improved PFS and OS. Propensity score matching created two groups of 93 patients, who each underwent photon or proton RT, showed that the local PFS and OS did not differ between these two groups.

■ **Volpe S, et al. Hypofractionated proton therapy for non-small cell lung cancer: Ready for prime time? A systematic review and meta-analysis. Cancer Treat Rev. 2022 Nov:110:102464.**

This systematic review evaluated eight studies and 401 patients with early stage NSCLC treated with hypofractionated PBT to a median total dose of 63 Gy(RBE), with a median dose of 6.0 Gy(RBE) per fraction, resulting in a median BED of 105.6 Gy(RBE) to the target volumes. This analysis found that a BED ≥ 105.6 Gy(RBE) consistently provided superior OS, CSS, DFS and LC rates than BED < 105.6 Gy(RBE), however the probability of any late grade ≥ 2 adverse event was almost three-times greater for BED ≥ 105.6 Gy(RBE), with rib fractures being more common in the high dose group.

■ **Yu NY, et al. Cardiopulmonary Toxicity Following Intensity-Modulated Proton Therapy (IMPT) Versus Intensity-Modulated Radiation Therapy (IMRT) for Stage III Non-Small Cell Lung Cancer. Clin Lung Cancer. 2022 Dec;23(8):e526-e535.**

A total of 163 stage III NSCLC patients who received IMPT (n = 35, 21%) or IMRT (n = 128, 79%) were analyzed in this study. This study found no difference in OS, FFDM, and FFLR between the two RT modalities. IMPT provided significant dosimetric pulmonary and cardiac sparing when compared to IMRT. IMPT was associated with a reduced rate of grade ≥3 pneumonitis (HR 0.25, P = .04) and grade ≥3 cardiac events (HR 0.33, P = .08).

■ **Bae BK, et al. Clinical Outcomes Following Proton and Photon Stereotactic Body Radiation Therapy for Early-Stage Lung Cancer. Cancers (Basel). 2022 Aug 27;14(17):4152.**

168 patients with early stage of NSCLC were treated by photon SBRT and 34 patients with proton SBRT. Clinical outcomes were comparable between treatment modalities: 5-year LC (90.8% vs. 83.6%, p = 0.602); PFS (61.6% vs. 57.8%, p = 0.370); and OS (51.7% vs. 51.9%, p = 0.475). There was no statistically significant difference in grade ≥ 2 toxicities: radiation pneumonitis (19.6% vs. 26.4%, p = 0.371); musculoskeletal (13.7% vs. 5.9%, p = 0.264); and skin (3.6% vs. 0.0%, p = 0.604).

■ **Li YQ, et al. Proton and Carbon Ion Radiotherapy Decreased Severe Lymphopenia by Reducing Thoracic Vertebra and Aortic Dose in Non-small Cell Lung Cancer versus Intensity Modulated Radiotherapy. Int J Radiat Oncol Biol Phys. 2023 Jul 1;116(3):579-589.**

This study reported lymphopenia differences between IMRT and proton/carbon ion (PCIRT) for NSCLC. With data of 343 patients, the PCIRT group was less likely to develop severe lymphopenia (SRL) (p<0.001). Compared with non-SRL group, SRL group showed significant association with poorer OS, with median survival time of 29.2 vs. 15.0 months (p = 0.046). Thoracic vertebra V5 (p =0.002) and aorta V5 (p =0.026) were identified as independent risk predictors of SRL.

■ **Carrasquilla M, et al. High-Risk Non-Small Cell Lung Cancer Treated With Active Scanning Proton Beam Radiation Therapy and Immunotherapy. Adv Radiat Oncol. 2022 Nov 24;8(2):101125.**

Twenty-nine patients with locally advanced (stage IIB to IIIC, 90%) NSCLC were treated with PBS-PT and immunotherapy. Patients who demonstrated excess respiratory motion (i.e. greater than 1 cm in any dimension noted on the 4DCT simulation scan) were deemed to be ineligible for PBT. A total of 7 grade 3+ late toxicities were observed in 5 patients including pneumonitis (n = 2), pleural effusion (n = 2), lung infection (n = 1), dyspnea (n = 1), and esophageal stricture (n = 1). The majority of patients went on to receive immunotherapy. Two-year progression-free and overall survival was estimated to be 51% and 67%.

■ **Janopaul-Naylor JR, et al. Definitive intensity modulated proton re-irradiation for lung cancer in the immunotherapy era. Front Oncol. 2023 Jan 17:12:1074675.**

This study reported results of 22 patients with recurrent NSCLC received IMPT reirradiation. 1-year OS 68%, LC 80%, PFS 45%, and DMFS 60% were reported, with Grade 3 pneumonitis or dermatitis in two patients, Grade 2 pneumonitis in one patient, and Grade 1 toxicity in seven patients. There were no Grade 4 or 5 toxicities. The authors concluded that definitive IMPT re-irradiation for lung cancer can prolong disease control with limited toxicity, particularly in the immunotherapy era.

■ **Nakamura M, et al. Effects of lymphopenia on survival in proton therapy with chemotherapy for non-small cell lung cancer. J Radiat Res. 2023 Mar 23;64(2):438-447.**

With data of 41 patients with stage III NSCLC who received PBT of 74 GyE with concurrent chemotherapy, this study reported that bone V5-20 and lung V5-50 were significantly correlated with minimum absolute lymphocyte count (ALCmin) and maximum neutrophil/lymphocyte ratio (NLRmax) during PBT. NLRmax was associated with OS, PFS and distant metastasis-free survival (DMFS). The 3-year rates of OS, PFS and DMFS of patients with a low (≤ 6.3) versus high (> 6.3) NLRmax were 73.9% vs 44.4% (P = 0.042), 26.1% vs 5.6% (P = 0.022) and 39.1% vs 5.6% (P < 0.001), respectively.

■ **Chen YL, et al. Efficacy and safety of particle therapy for inoperable stage II-III non-small cell lung cancer: a systematic review and meta-analysis. Radiat Oncol. 2023 May 22;18(1):86.**

This review provided systematic evidence for evaluating the efficacy and safety of particle therapy for inoperable locally advanced NSCLC. Based on 19 studies with a total sample size of 851 patients, the pooled data reported that the OS, PFS, and LC rates at 2 years were 61.3%, 37.9% and 82.2%. The pooled 5-year OS, PFS, and LC rates were 41.3%, 25.3% and 61.5%. The incidence rates of grade 3/4 esophagitis, dermatitis, and pneumonia were 2.6%, 2.6% and 3.4%.

■ **Simone CB 2nd, et al. ASTRO Radiation Therapy Summary of the ASCO Guideline on Management of Stage III Non-Small Cell Lung Cancer. Pract Radiat Oncol. 2023 May-Jun;13(3):195-202.**

Based on the 'Management of Stage III Non-Small-Cell Lung Cancer: ASCO Guideline', this summary document makes recommendations directly related to RT for the practicing radiation oncologist about best practices on the use of RT in the neoadjuvant, adjuvant, and unresectable settings given the current clinical evidence available. Unresectable patients with stage III NSCLC should ideally be managed with combined concurrent chemoradiation using a platinum-based doublet with a standard radiation dose of 60 Gy followed by consolidation durvalumab in patients without progression after initial therapy.

■ **Cortiula F, et al. Proton and photon radiotherapy in stage III NSCLC: Effects on hematological toxicity and adjuvant immune therapy. Radiother Oncol. 2023 Nov 22:190:110019.**

This study reported the incidence of lymphopenia in 271 stage III NSCLC patients treated with IMPT (n=71) vs IMRT (n=200) and concurrent chemotherapy. The incidence of lymphopenia grade ≥ 3 was 67 % and 47 % in the IMRT and IMPT group (P = 0.03). The incidence of anemia grade ≥ 3 was 26 % and 9 % in the IMRT and IMPT group (P = 0.001). IMPT was associated with a lower rate of Performance Status (PS) ≥ 2 at day 21 and 42 after CCRT (13 % vs. 26 %, P = 0.04, and 24 % vs. 39 %, P = 0.02). Patients treated with IMPT had a higher probability of receiving adjuvant durvalumab (74 % vs. 52 %, P = 0.01).

■ **Zou ZW et al. Scanning Beam Proton Therapy (SPT) Versus Photon IMRT for Stage III Lung Cancer: Comparison of Dosimetry, Toxicity, and Outcomes. Adv Radiat Oncol. 2020 Mar 20;5(3):434-443.**

This study reviewed dosimetric data and clinical outcomes of 64 stage III lung cancer patients treated with SPT (34) + IMRT (30). Mean dose to lung, heart, and esophagus was lower in the SPT group, with most benefit in the low-dose region. Esophagitis and dermatitis grades were not different between the 2 groups. Grade 2+ pneumonitis was 21% in the SPT group and 40% in the IMRT group (P = .107). Overall survival and progression-free survival were not different between SPT and IMRT.

■ **Jain V, et al. Updating Photon-based Normal Tissue Complication Probability Models for Pneumonitis in Lung Cancer Patients Treated With Proton Beam Therapy. Pract Radiat Oncol. 2020 May 13;S1879- 8500(20)30102-8.**

Data of 99 patients with LA-NSCLC treated with chemoradiation using PBT was used for analysis to validate if photon- based normal tissue complication probability (NTCP) models fit for predicting radiation pneumonitis in proton therapy. This study presented updated NTCP models that can aid in individualizing selection of the most optimal treatment technique for a particular patient.

■ **Zeng J, et al. Consensus Statement on Proton Therapy in Mesothelioma. Pract Radiat Oncol. 2020 May 24;S1879-8500(20)30117-X.**

This study analyzed 166 NSCLC patients prospectively treated at a single institution with IMRT (103 patients) or PSPT (63 patients). This study reported that 15 of 166 (9%) patients developed severe dermatitis (grade 3). RT technique did not impact RD incidence. The total gross tumor volume (GTV) size was the only non dosimetric variable significantly correlated with severe RD (p = 0.027).

■ **Palma G, et al. NTCP Models for Severe Radiation Induced Dermatitis After IMRT or Proton Therapy for Thoracic Cancer Patients. Front Oncol. 2020 Mar 17;10:344.**

The Particle Therapy Co-operative Group (PTCOG) Thoracic Subcommittee task group provides specific guidelines for the use of proton therapy for mesothelioma. This consensus report can be used to guide clinical practice, insurance approval, and future research.

■ **Wang Z, et al. Lyman-Kutcher-Burman normal tissue complication probability modeling for radiation-induced esophagitis in non-small cell lung cancer patients receiving proton radiotherapy. Radiother Oncol. 2020 May;146:200-204.**

This study developed and tested an NTCP model to predict radiation-induced esophagitis (RE) in NSCLC patients receiving passive-scattering proton therapy (PSPT). For the 328 NSCLC patients treated with PSPT, grade 2-3 RE was observed in 136 (41.5%) patients, and no grade 4-5 RE was reported. The authors concluded that their NTCP model showed good predictive performance, however external validation of the model is warranted.

■ **Hoppe BS, et al. Hypofractionated Proton Therapy With Concurrent Chemotherapy for Locally Advanced Non-Small Cell Lung Cancer: A Phase I Trial From the University of Florida and Proton Collaborative Group. Int J Radiat Oncol Biol Phys. 2020 Jul 1;107(3):455-461.**

This study reported the safety data from the first multicenter phase I trial investigating the use of hypofractionated proton therapy with concurrent chemotherapy for patients with stage II or III NSCLC. Hypofractionated proton therapy delivered at 2.5-3.53 GyRBE/fraction to a dose of 60 GyRBE with concurrent chemotherapy has an acceptable toxicity profile.

■ **McNamara AL, et al. Perspectives on the model-based approach to proton therapy trials: A retrospective study of a lung cancer randomized trial. Radiother Oncol. 2020 Jun;147:8-14.**

Three widely used NTCP models for radiation pneumonitis applied retrospectively to a completed non-small cell lung cancer RCT (NCT00915005). Less than 19% of patients enrolled in the completed trial would have been enrolled in a model-based trial. The uncertainties in NTCP models are the inherent drawback of a model-based approach to clinical trials. NTCP differences between proton and photon therapy treatments may be too small to support a model-based trial approach for specific treatment sites, such as lung cancer.

■ **Brooks ED, et al. Proton therapy for non-small cell lung cancer: the road ahead. Transl Lung Cancer Res. 2019 Sep;8(Suppl 2):S202-S212.**

This review examined the clinical data of PBT for both early stage and locally advanced stage NSCLC, especially analyzing the reasons for the negative results of the only randomized phase II trial. This review pointed out that the greater experience in proton planning and delivery could lead to better outcomes, and such experience is a requisite to achieving desired results. This review confirms potential of protons in reducing toxicity and suggests ways of advancing protons for NSCLC to the next level.

■ **Ohnishi K, et al. Proton Beam Therapy for Histologically or Clinically Diagnosed Stage I Non-small Cell Lung Cancer (NSCLC): The First Nationwide Retrospective Study in Japan. Int J Radiat Oncol Biol Phys. 2020 Jan 1;106(1):82-89.**

Six hundred sixty-nine patients with Stage I NSCLC who received PBT in Japan were retrospectively reviewed to analyze survivals, local control, and toxicities. This study found that the 3-year overall survival (OS) and progression-free survival (PFS) rates for all patients were 79.5% and 64.1%. The incidence of Grade 2, 3, 4, and 5 pneumonitis was 9.8%, 1.0%,0%, and 0.7%, respectively. This study concluded that PBT appears to yield acceptable survival rates, with a low rate of toxicities.

■ **Gjyshi O and Liao ZX. Proton therapy for locally advanced non-small cell lung cancer. Br J Radiol. 2020 Mar;93(1107):20190378.**

A review article assessed data available for proton potential in improving local tumor control and survival while preserving quality of life by reducing treatment-related toxicity. This review pointed out the limitation of evidence that was generated from retrospective or single-institution clinical series, from analyses of national databases and from single-arm prospective studies. There are several ongoing randomized comparative trials.

■ **Kharod SM, et al. Image-Guided Hypofractionated Proton Therapy in Early-Stage Non-Small Cell Lung Cancer: A Phase 2 Study. Int J Part Ther. 2020 Nov 6;7(2):1-10.**

22 patients with T1 to T2 N0M0 NSCLC received image-guided hypofractionated PT including 9 patients (41%) to a total dose of 48 GyRBE in 4 fractions for peripheral lesions, and 13 patients (59%) to 60 GyRBE in 10 fractions for central lesions. With the median follow-up for all patients of 3.5 years, the OS rates at 3 and 5 years were 81% and 49%, respectively. The 3-year local, regional, and distant control rates were 86%, 85%, and 95%, respectively. Four patients experienced in-field recurrences. One patient (5%) developed a late grade 3 bronchial stricture. The study concluded that hypofractionated PT for early-stage NSCLC provides promising local control and long-term survival with a low likelihood of toxicity.

■ **Elhammali A, Blanchard P, Yoder A, et al. Clinical outcomes after intensity-modulated proton therapy with concurrent chemotherapy for inoperable non-small cell lung cancer. Radiother Oncol. 2019 Jul;136:136-142.**

Fifty-one patients treated with IMPT and concurrent chemotherapy, with a median follow-up time of 23.0 months, this study reported the median OS and DFS times were 33.9 months and 12.6 months. The 3-year local control rate was 78.3%. Grade 3 toxicity rate of 18% and no grade 4 or 5 toxicity.

■ **Rice SR, Saboury B, Houshmand S, et al. Quantification of global lung inflammation using volumetric 18F-FDG PET/CT parameters in locally advanced non-small-cell lung cancer patients treated with concurrent chemoradiotherapy: a comparison of photon and proton radiation therapy. Nucl Med Commun. 2019 Jun;40(6):618-625.**

This study evaluated pretreatment and post-treatment F-FDG PET/CT of 18 locally advanced NSCLC patients treated with definitive photon or proton RT. In nine patients treated with photon RT, significant increases in bilateral lung inflammation were noted, but with no significant change in global lung inflammation.

■ **Nakamura N, Hotta K, Zenda S, et al. Hypofractionated proton beam therapy for centrally located lung cancer. J Med Imaging Radiat Oncol. 2019 May 30.**

Thirty-nine patients received hypofractionated PBT for centrally located cT1-2N0M0. This study reported the 2-year PFS and OS rates were 86% and 100% for T1 disease and 56% and 94% for T2 disease. Dyspnoea of grade 3 was noted in one patient (3%), and pneumonitis of grade 2 was noted in four patients (10%).

■ **Zhu HJ, Nichols RC, Henderson RH, et al. Impact of unfavorable factors on outcomes among inoperable stage II-IV Non-small cell lung cancer patients treated with proton therapy. . Acta Oncol. 2019 Mar;58(3):313-319.**

Ninety patients with unresectable stage II-IV (oligometastatic) NSCLC were treated with PBT. The 2-year OS was 52% and 45%, and 2-year PFS was 21% and 44% , for favorable and unfavorable risk patients. This study concluded that most patients treated with PBT for LA-NSCLC have unfavorable risk factors, but these patients had similar outcomes to favorable-risk patients.

■ **Ono T, Nakamura T, Azami Y, et al. Proton beam therapy is a safe and feasible treatment for patients with second primary lung cancer after lung resection. Thorac Cancer. 2019 Feb;10(2):289-295.**

Nineteen patients who were diagnosed with second primary lung cancer after lung resection underwent PBT. The 3-year OS was 63.2% and LC was 84.2%. No grade 4 or 5 toxicities were observed after PBT. The study concluded that PBT is a safe and feasible treatment for second primary lung cancer compared to surgery or X-ray radiotherapy.

■ **Tucker SL, Xu T, Paganetti H, et al. Validation of Effective Dose as a Better Predictor of Radiation Pneumonitis Risk than Mean Lung Dose: Secondary Analysis of a Randomized Trial. Int J Radiat Oncol Biol Phys. 2019 Feb 1;103(2):403-410.**

This retrospective analysis reviewed 203 patients treated with protons or IMRT to 66-74 Gy(RBE) in 33-37 fractions with concurrent carboplatin/paclitaxel. By analyzing the 46 patients experiencing grade ≥2 radiation pneumonitis at a median 3.7 months, this study found that the effective dose (Deff) with n=0.5 (corresponding to root mean squared dose) is a better predictor of RP than MLD.

■ **Kim H, Pyo H, Noh JM, et al. Preliminary result of definitive radiotherapy in patients with non-small cell lung cancer who have underlying idiopathic pulmonary fibrosis: comparison between X-ray and proton therapy. Radiat Oncol. 2019 Jan 28;14(1):19.**

Idiopathic pulmonary fibrosis (IPF) is associated with fatal complications after radiotherapy for lung cancer patients. This study evaluated 30 patients who had underlying IPF treated with definitive RT alone, and found that proton therapy may be helpful to reduce these acute and fatal complications.

■ **Yang P, Xu T, Gomez DR, et al. Patterns of Local-Regional Failure after Intensity-Modulated Radiation Therapy or Passive Scattering Proton Therapy with Concurrent Chemotherapy for Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2019 Jan 1;103(1):123-131.**

This retrospective analysis reviewed 212 patients treated with IMRT and PBT, and reported that no differences in local failure, marginal failure, or regional failure patterns were found for IMRT vs. PSPT. Proton therapy more often required adaptive planning, and the techniques used for adaptive planning did not compromise tumor control.

■ **Mesko S and Gomez D. Proton Therapy in Non-small Cell Lung Cancer. Curr Treat Options Oncol. 2018 Nov 27;19(12):76.**

The most recent randomized comparisons have failed to show significant differences in toxicity and local control between photon and proton therapy. This review pointed out that there may be certain subpopulations in which the benefits of proton therapy are greater, such as central early-stage tumors, previously irradiated tumors, and locally advanced tumors.

■ **Nakajima K, Iwata H, Ogino H, et al. Clinical outcomes of image-guided proton therapy for histologically confirmed stage I non-small cell lung cancer (NSCLC). Radiat Oncol. 2018 Oct 11;13(1):199.**

Fifty-five stage I NSCLC patients were treated with proton for peripherally located tumors 66 Gy (RBE)/10 fractions and centrally located 72.6 Gy(RBE)/22 fractions. The 3-year OS, PFS, and LC rates were 87%, 74%, and 96%. Grade 2 toxicities were radiation pneumonitis in 5 patients (9%), rib fracture in 2 (4%), and chest wall pain in 5 (9%). There were no grade 3 or higher acute or late toxicities.

■ **Yegya-Raman N, Zou W, Nie K, et al. Advanced radiation techniques for locally advanced non-small cell lung cancer: intensity-modulated radiation therapy and proton therapy. J Thorac Dis. 2018 Aug;10(Suppl 21):S2474-S2491.**

PBT can better spare certain OARs such as heart than IMRT, with IMPT providing the greatest dosimetric benefit but potentially requiring additional adjustments for uncertainties associated with beam range and organ motion. PBT may help achieve safer dose escalation, and re-irradiation with PBT appears feasible for carefully selected patients.

■ **Vyfhuis MAL, Rice S, Remick J, et al. Reirradiation for locoregionally recurrent non-small cell lung cancer. J Thorac Dis. 2018 Aug;10(Suppl 21):S2522-S2536**

In the context of definitive retreatment, increasing reRT dose can potentially improve OS and offer a chance of cure, particularly in patients with limited loco-regionally recurrent disease. This review article examined the advanced radiation techniques including IMRT, SBRT and proton approach in reRT setting.

■ **Chang JY, et al. Consensus Guidelines for Implementing Pencil-Beam Scanning Proton Therapy for Thoracic Ma lignancies on Behalf of the PTCOG Thoracic and Lymphoma Subcommittee. Int J Radiat Oncol Biol Phys. 2017 Sep 1;99(1):41-50.**

This consensus provides guidance for implementing PBS for thoracic treatments. IMPT represents the latest advanced proton technology, however, motion uncertainty and tissue density heterogeneity of chest organs can have a significant impact on dose distribution. This consensus guideline lists strategies and steps for clinical pencil-beam scanning IMPT in lung cancer.

■ **Liao Z, et al. Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity- Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2018 Jun 20;36(18):1813-1822.**

This randomized trial compared outcomes of passive scattering proton therapy (PSPT) versus intensity-modulated radiotherapy (IMRT), with concurrent chemotherapy, for patients with locally advanced NSCLC, and concluded that PSPT did not improve dose-volume indices for lung but did for heart. No benefit was noted in radiation-induced pneumonia or local failure after PSPT. Outcomes after both IMRT and PSPT improved over the course of the trial, with a magnitude of improvement in RP greater and statistically more significant in the PSPT arm.

■ **Shusharina N, et al. Differences in lung injury after IMRT or proton therapy assessed by 18FDG PET imaging. Radiother Oncol. 2018 Jan 15.**

This study compared 84 patients post-treatment PET-CT to determine factors predictive for clinically symptomatic radiation pneumonitis either with IMRT or proton modality, and found that despite significantly different dose distributions for IMRT and for protons, the slope of the SUV-dose linear regression line previously shown to be associated with RP did not differ between IMRT and protons.

■ **Jeter MD, et al. Simultaneous Integrated Boost (SIB) for Radiation Dose Escalation to the Gross Tumor Volume With Intensity Modulated (Photon) Radiation Therapy or Intensity Modulated Proton Therapy and Concurrent Chemotherapy for Stage II to III Non-Small Cell Lung Cancer: A Phase 1 Study. Int J Radiat Oncol Biol Phys. 2018 Mar 1;100(3):730-737.**

This study was set to establish the maximum tolerated dose of IMRT or IMPT, both with a SIB, for patients with stage II to IIIB non-small cell lung cancer receiving concurrent chemoradiation therapy. The authors recommended an SIB dose of 72 Gy(CGE) to be used as the highest SIB dose for the planned randomized phase 2 study.

■ **Ono T, et al. Clinical results of proton beam therapy for elderly patients with non-small cell lung cancer. Radiat Oncol. 2018 Feb 5;13(1):19.**

A study of thirty-five T1-T4N0M0 NSCLC patients over 80 years old treated with proton therapy, of which 71% were clinically inoperable, reported that the 3-year overall survival rate was 67.2% and local control rate was 86.5%. Two patients presented with grade 2 pneumonitis, no cases of grade 3 or higher radiation pneumonitis.

■ **Liao Z, et al. Does Proton Therapy Offer Demonstrable Clinical Advantages for Treating Thoracic Tumors?. Semin Radiat Oncol. 2018 Apr;28(2):114-124.**

This review examined the available data with regard to proton therapy for thoracic malignancies and analyzed the unique challenges in translating the dosimetric advantages of proton therapy to clinical benefit for patients with thoracic tumors. To fully realize the potential of particle therapy for thoracic cancer, extensive improvements are needed in all aspects of the treatment process, from planning to patient selection and properly design RCTs.

■ **St James S, et al. Considerations when treating lung cancer with passive scatter or active scanning proton therapy. Transl Lung Cancer Res. 2018 Apr;7(2):210-215.**

A list of additional considerations when using proton therapy to treat lung, compared to treating patients with photon- RT, including accounting for the finite range of protons in the patient, understanding temporal effects, potential dose discrepancies and choosing an appropriate treatment planning system for the task, and differences between passive scattered PT and active scanning PT.

■ **Gomez DR, et al. Proton therapy for early-stage non-small cell lung cancer (NSCLC). Transl Lung Cancer Res. 2018 Apr;7(2):199-204.**

To define the optimal clinical benefit of PT for early stage NSCLC is challenging due to high rates of local control and good tolerance of stereotactic ablative body radiation. PT may be beneficial for complex cases identified as follows: (I) larger tumors (>4 cm); (II) centrally located lesions; (III) tumors that are located in the apex and thus near the brachial plexus; and (IV) cases requiring treatment to multiple sites of disease (e.g., multiple primary tumors).

■ **Shepherd AF. Proton therapy for post-operative radiation therapy (PORT) of non-small cell lung cancer. Transl Lung Cancer Res. 2018 Apr;7(2):205-209.**

Proton has great potential to widen the therapeutic window in patients undergoing PORT as demonstrated in dosimetry studies. A multi-center study randomizing patients to PORT with proton therapy vs. photon therapy with a cardiopulmonary toxicity endpoint would be a good approach to understanding the benefit of proton therapy in patients undergoing PORT.

■ **Chao HH and Berman AT. Proton therapy for thoracic reirradiation of non-small cell lung cancer. Transl Lung Cancer Res. 2018 Apr;7(2):153-159.**

Having examined the clinical data published, this review pointed out that the outcomes from proton reirradiation experiences were largely similar, with median overall survival between 11.1–18.0 months and 1-year overall survival between 47–59%. But there is variability in the incidence and degree of subsequent toxicity experienced. Proton reirradiation should be employed in a discriminating manner for selected patients.

■ **Liao Z and Simone CB 2nd. Particle therapy in non-small cell lung cancer. Transl Lung Cancer Res. 2018 Apr;7(2):141-152.**

This review examined the available clinical data on proton for early stage, locally advanced stage and re-irradiation NSCLC, and analyzed the challenges in translating the dosimetric advantages of proton therapy to clinical benefits for patients with thoracic cancer. The need continues for designing and conducting "smart" proton therapy trials to establish clinical evidence and patient selection criteria.

■ **Badiyan SN, et al. Proton beam therapy for malignant pleural mesothelioma (MPM). Transl Lung Cancer Res. 2018 Apr;7(2):189-198.**

Recent advances in RT have enabled the delivery of radiation therapy as neoadjuvant or adjuvant therapy after an extended pleurectomy and decortication or as definitive therapy for patients with recurrent or unresectable disease. Proton has the potential to deliver high doses of irradiation to the entire effected pleura while significantly reducing doses to nearby organs at risk.

■ **Lee HJ Jr, et al. Proton beam therapy and immunotherapy: an emerging partnership for immune activation in non-small cell lung cancer. Transl Lung Cancer Res. 2018 Apr;7(2):180-188.**

Photon radiation exhibits immunoactivation as well as immunosuppression. Immune cells are very sensitive to radiation and can be eradicated at much lower doses than required to kill cancer cells. In the balance between the proimmunogenic and immunosuppressive effects of radiation on the immune system, proton therapy is apromising modality that can potentially remove components from the immunosuppressive side while adding to the proimmunogenic side.

■ **Rwigema JM et al. Prospective study of proton-beam radiation therapy for limited-stage small cell lung cancer. Cancer. 2017 Jul 5.**

This study prospectively analyzed 30 patients with primary, nonrecurrent LS-SCLC definitively treated with PBT and concurrent chemotherapy. In comparison with the backup IMRT plans, PBT allowed statistically significant reductions in the cord, heart, and lung mean doses and the volume receiving at least 5 Gy but not in the esophagus mean dose or the lung volume receiving at least 20 Gy. Survival and toxicity outcomes are also reported

■ **Chi A et al. Comparison of particle beam therapy and stereotactic body radiotherapy for early stage non-small cell lung cancer: A systematic review and hypothesis-generating meta-analysis.Radiother Oncol. 2017 Jun;123(3):346-354**

This review assessed hypo-fractionated PBT's efficacy relative to that of photon SBRT for early stage NSCLC. PBT was associated with improved overall survival and progression-free survival in the univariate meta-analysis, but not statistically significant after inclusion of operability. PBT was associated significantly lower rates grade 3 and above radiation pneumonitis and chest wall toxicity but higher rib fractures.

■ **Remick J S et al. First Clinical Report of Proton Beam Therapy for Postoperative Radiotherapy for Non-Small-Cell Lung Cancer. Clin Lung Cancer. 2017 Jul;18(4):364-371.**

61 locally advanced NSCLC patients underwent postoperative radiotherapy including 27 patients receiving PBT and 34 IMRT. One-year median overall survival was 85.2% for PBT and 82.4% for IMRT and local recurrence free survival was 92.3% for PBT and 93.3% IMRT. Grade 3 radiation esophagitis was observed in 1 and 4 patients in the PBT and IMRT groups respectively. Grade 3 radiation pneumonitis was in 1 patient in each group. The authors concluded that postoperative PBT for locally advanced NSCLC is well-tolerated and reported similar short-term outcomes when compared to IMRT.

■ **Chang J Y et al. Long-term outcome of phase I/II prospective study of dose-escalated proton therapy for early-stage non-small cell lung cancer. Radiother Oncol. 2017 Feb;122(2):274-280.**

35 patients were treated with 87.5Gy at 2.5Gy/fraction of proton therapy. With the median follow-up 83 months, the study reported the 1, 3, and 5-year overall survival rates were 85.7%, 42.9%, and 28.1%, respectively. Toxicity such as grade 3 dermatitis of 2.9% and grade 3 radiation-induced pneumonitis 2.9% and grade 2 esophagitis (2.9%), rib fracture (2.9%), heart toxicities (5.7%), and chest wall pain (2.9%) were reported. The authors concluded that this long-term follow-up data demonstrated proton therapy with ablative doses is well tolerated and effective in medically inoperable early-stage NSCLC.

■ **Higgins K A et al. National Cancer Database Analysis of Proton Versus Photon Radiation Therapy in Non- Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2017 Jan 1;97(1):128-137.**

Based on the National Cancer Database of stage I-IV NSCLC, a total patients of 243,822 were treated with photon (243,474) and proton (348). With multivariate analysis of all patients, non-proton therapy was associated with significantly worse survival compared with proton therapy. With propensity matched analysis, proton therapy was associated with better 5-year overall survival compared with non-proton radiotherapy.

■ **Kojima H. et al. Preoperative Proton Beam Therapy for Thymoma: A Case Report. Annals of thoracic and cardiovascular surgery. 2016 June; 22(3):186-8.**

This paper assesses the case of a locally advanced thymoma treated with preoperative PT followed by complete surgical resection. The experience suggests that preoperative proton therapy may be an effective modality for reducing tumor size, facilitating complete resection, and preventing toxicity of radiation therapy.

■ **Lee S.U. et al. Ablative dose proton beam therapy for stage I and recurrent non-small cell lung carcinomas: Ablative dose PBT for NSCLC. Strahlentherapie und Onkologie. 2016 June; 192[9], 649–657.**

Authors evaluate the efficacy and safety of ablative dose hypofractionated proton therapy for patients with stage I and recurrent non-small cell lung carcinoma. The studied treatment modality was safe and promising for stage I and recurrent NSCLC.

■ **Wang X.S. et al. Prospective Study of Patient-Reported Symptom Burden in Patients With Non-Small-Cell Lung Cancer Undergoing Proton or Photon Chemoradiation Therapy. Journal of Pain and Symptom Management. 2016 May; 51[5]:832-8.**

Most patients with advanced NSCLC develop radiation-induced symptoms despite careful treatment optimization. This study reports that patients receiving proton therapy have significantly less severe symptoms than those receiving IMRT or 3D conformal RT, even with a significantly higher radiation target dose.

■ **Chang J.Y. et al. Consensus Statement on Proton Therapy in Early-Stage and Locally Advanced Non-Small Cell Lung Cancer. International Journal of Radiation Oncology. Biology. Physics. 2016 May; 95[1]:505-16.**

This consensus report from the PTCOG Thoracic Subcommittee can be used to guide clinical practice and indications for PT, insurance approval, and clinical or translational research directions.

■ **Li H. et al. Reducing Dose Uncertainty for Spot-Scanning Proton Beam Therapy of Moving Tumors by Optimizing the Spot Delivery Sequence. International Journal of Radiation Oncology. Biology. Physics. 2015 November; 93[3]:547-56.**

The aim of this study was to develop and validate a new delivery strategy for reducing the respiratory motion-induced dose uncertainty of spot-scanning PT. The authors concluded that optimizing the delivery sequence can reduce the dose uncertainty, assuming the 4D-CT is a true representation of the patients' breathing patterns.

■ **Pan H.Y. et al. Early experience with intensity modulated proton therapy for lung-intact mesothelioma: A case series. Practical Radiation Oncology. 2015 July-August; 5[4]:e345-53.**

The purpose of this study was to describe our experience implementing IMPT for lung-intact malignant pleural mesothelioma, including patient selection, treatment planning, dose verification, and process optimization. Results showed that IMPT is feasible.

■ **Berman A.T., James S.S. and Rengan R. Proton Beam Therapy for Non-Small Cell Lung Cancer: Current Clinical Evidence and Future Directions. Cancers. 2015 July 2; 7[3]:1178-90.**

Lung cancer is the leading cancer cause of death in the US. Radiotherapy is an essential component of the definitive treatment of early-stage and locally- advanced lung cancer, and the palliative treatment of metastatic lung cancer. Proton therapy has the potential to decrease the toxicity of radiotherapy and subsequently to improve the therapeutic ratio.

■ **Makita C. et al. High-dose proton beam therapy for stage I non-small cell lung cancer: Clinical outcomes and prognostic factors. Acta Oncologica. 2015 March; 54[3]:307-14.**

Evidence has suggested that RT with a lower dose per fraction may be a reasonable option for the treatment of centrally located NSCLC. The aim of this study was to evaluate the safety and efficacy of two PT protocols for stage I NSCLC and to determine prognostic factors. Both high-dose PT protocols achieved high local control rates with tolerable toxicities.

■ **Ohno T. et al. Comparison of dose-volume histograms between proton beam and X-ray conformal radiotherapy for locally advanced nonsmall- cell lung cancer. Journal of Radiation Research. 2015 January. 56[1]:128-33.**

The purpose of this study was to compare the parameters of the dose-volume histogram between PT and conformal RT for locally advanced NSCLC. The number of inadequate X-ray plans increased in cases with advanced nodal stage. This study indicated that some patients who cannot receive RT may be able to be treated using PT.

■ **Chang J.Y. et al. Clinical implementation of intensity modulated proton therapy for thoracic malignancies. International Journal of Radiation Oncology. Biology. Physics. 2014 November 15; 90[4]:809-18.**

This paper reports early experience with IMPT for thoracic malignancies in terms of motion analysis and management, plan optimization and robustness, and quality assurance. IMPT using 4D CT-based planning, motion management, and optimization was implemented successfully and met quality assurance parameters for treating challenging thoracic cancers.

■ **McAvoy S.A. et al. Definitive reirradiation for locoregionally recurrent non-small cell lung cancer with proton beam therapy or intensity modulated radiation therapy: predictors of high-grade toxicity and survival outcomes. International Journal of Radiation Oncology. Biology. Physics. 2014 November 15;90[4]:819-27.**

Intrathoracic recurrence of NSCLC after initial treatment remains a dominant cause of death. IMRT and PT are options for treating recurrent NSCLC, but rates of locoregional recurrence and distant metastasis are high, and patients should beselected carefully to maximize the benefit of additional aggressive local therapy while minimizing the risk of adverse side effects.

■ **Schild S.E. et al. Proton beam therapy for locally advanced lung cancer: A review. World Journal of Clinical Oncology, 2014 October. 10;5[4]:568-75.**

This review examines PT as a component of a combined modality program for locally advanced lung cancers. It is specifically written for non-radiation oncologists who desire greater understanding of this newer treatment modality, and shows that newer forms of radiotherapy such as PT should positively impact the care of lung cancer patients.

■ **Oshiro Y. et al. High-dose concurrent chemo-proton therapy for Stage III NSCLC: preliminary results of a Phase II study. Journal of Radiation Research. 2014 May 25;55(5), 959–965.**

High-dose PT with concurrent chemotherapy is safe to use in the treatment of unresectable stage III NSCLC.

Gomez D.R., Chang J.Y. Accelerated dose escalation with proton beam therapy for non-small cell lung cancer. Journal of Thoracic Disease. 2014 April; 6(4):348-55.

Local tumor control remains challenging in many cases of NSCLC, large or centrally located tumors. Concurrent chemotherapy and radiation can maximize tumor control and survival but a large proportion of patients cannot tolerate this therapy. The energy distribution of protons can be exploited to reduce involuntary irradiation of normal tissue and the resulting side effects.

■ **McAvoy S.A. et al. Feasibility of proton beam therapy for reirradiation of locoregionally recurrent non-small cell lung cancer. Radiotherapy and Oncology. 2013 October; 109(1):38-44.**

Options are limited for patients with intrathoracic recurrence of NSCLC who previously received radiation. This paper reports 5-year experience with the toxicity and efficacy of PT for reirradiation and shows that PT is an option for treating recurrent NSCLC.

■ **Bush D.A. et al. High-dose hypofractionated proton beam radiation therapy is safe and effective for central and peripheral early-stage nonsmall cell lung cancer: results of a 12-year experience at Loma Linda University Medical Center. International Journal of Radiation Oncology. Biology. Physics. 2013 August 1;86(5):964-8.**

High-dose hypofractionated PT achieves excellent outcomes for central or peripheral lung carcinomas. The 70-Gyregimen has been adopted as standard therapy for T1 tumors at Loma Linda. Larger T2 tumors show improved outcomes with higher doses, suggesting that better results could be seen with intensified treatment.

■ **Colaco R.J. et al. Dosimetric rationale and early experience at UFPTI of thoracic proton therapy and chemotherapy in limited-stage small cell lung cancer. Acta Oncologica. 2013 February 26; 52(3):506-13.**

Concurrent chemoradiotherapy is the standard of care in patients with limited-stage SCLC. While treatment with conventional RT is associated with high toxicity rates (particularly acute esophagitis and pneumonitis), this study shows that PT with radical intent was well tolerated, with no cases of acute toxicities and better sparing of lung and esophagus.

■ **Hoppe B.S. et al. Proton therapy with concurrent chemotherapy for non-small-cell lung cancer: technique and early results. Clinical Lung Cancer. 2012 September; 13(5):352-8.**

PT can deliver a more conformal dose distribution than RT and may allow safe dose escalation in stage III lung cancer. Early outcomes are presented here for patients who received mediastinal PT with concurrent chemotherapy for NSCLC, which was associated with acceptable toxicity.

■ **Oshiro Y. et al. Results of proton beam therapy without concurrent chemotherapy for patients with unresectable stage III non-small cell lung cancer. Journal of Thoracic Oncology. 2012 February; 7(2):370-5.**

This study was performed retrospectively to evaluate the outcomes of patients with stage III NSCLC after PT alone. The prognosis of patients with unresectable stage III NSCLC is poor without chemotherapy. Our data suggest that high-dose PT is beneficial and tolerable for these patients.

■ **Koay E.J. et al. Adaptive/Nonadaptive Proton Radiation Planning and Outcomes in a Phase II Trial for Locally Advanced Non-small Cell Lung Cancer. International Journal of Radiation Oncology. Biology. Physics. 2012; 84(5):1093-100.**

Adaptive planning can reduce normal tissue doses and prevent target misses, particularly for patients with large tumors that shrink substantially during therapy. Adaptive plans seem to have acceptable toxicity and achieve same local, regional,and distant control and overall survival as non-adaptive plans, even in patients with larger tumors.

■ **Westover K.D. et al. Proton SBRT for medically inoperable stage I NSCLC. Journal of Thoracic Oncology. 2012; 7(6):1021-5.**

The physical properties of proton beam radiation may offer advantages for treating patients with NSCLC. This study also shows its utility for the treatment of medically inoperable stage I NSCLC patients with stereotactic body radiation therapy (SBRT).

■ **Chang J. et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. The Oncologist. 2011; 117(20):4707-13.**

In this study, authors show that using PT to escalate the radiation dose to the tumor could improve the toxicity of conventional concurrent chemoradiation therapy for stage III non-small cell lung cancer.

■ **Sejpal S. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for nonsmall cell lung cancer. Cancer. 2011; 1; 117(13):3004-13.**

Concurrent chemoradiation therapy, the standard of care for locally advanced NSCLC, can cause life-threatening pneumonitis and esophagitis. Whereas RT often cannot be given at tumoricidal doses without toxicity to proximal normal tissue, higher doses of proton radiation can be delivered with a lower risk of esophagitis and pneumonitis.

BREAST CANCERS

■ **Pasalic D, et al. Proton Accelerated Partial Breast Irradiation: Clinical Outcomes at a Planned Interim Analysis of a Prospective Phase 2 Trial. Int J Radiat Oncol Biol Phys. 2021 Feb 1;109(2):441-448.**

This interim analysis reported acute and late toxicities and cosmetic outcomes after proton-APBI for a total of 100 patients with pTis or pT1-2 N0 (≤3cm) breast cancer after segmental mastectomy. With a median follow-up 24 months, this study reported LC and OS were 100% at 12 and 24 months. There were no acute or late toxicities of grade 3 or higher; no patients experienced fat necrosis, fibrosis, infection, or breast shrinkage. Excellent or good cosmesis at 12 months was reported by 91% of patients and 94% of physicians.

■ **Musielak M, et al. Future Perspectives of Proton Therapy in Minimizing the Toxicity of Breast Cancer Radiotherapy. J Pers Med. 2021 May 13;11(5):410.**

A review article compared the clinical evidence including the parameters of the dose distribution in organs at risk, such as the heart, blood vessels, and lungs, using irradiation techniques including whole breast irradiation and accelerated partial breast irradiation; as well as outcomes data focusing on toxicity. This review concludes that the use of a proton beam is an appropriate approach in the treatment of difficult-to-reach tumor locations. Studies showed a significant reduction in side effects related to cardiac risk events with the use of proton therapy.

■ **Mutter RW, et al. Proton Therapy for Breast Cancer: A Consensus Statement from the Particle Therapy Cooperative Group (PTCOG) Breast Cancer Subcommittee. Int J Radiat Oncol Biol Phys. 2021 Oct 1;111(2):337-359.**

This consensus assessed the data available of proton therapy for breast cancer, provided expert recommendations on indications including regional nodal irradiation, breast reconstruction, partial breast irradiation, whole breast irradiation, bilateral breast cancer, reirradiation; and highlight ongoing trials cost-effectiveness analyses, and key areas for future research.

■ **Choi JI, et al. Proton Therapy for Partial Breast Irradiation: Rationale and Considerations. J Pers Med. 2021 Apr 9;11(4):289.**

A review specifically for PBT partial breast irradiation. This review found that tumor control with PT is excellent, and the toxicities associated with PT PBI are minimal, with cosmetic outcomes improved by the increased recognition to utilize multi-field treatment plans. This review suggested that a subset of patients may benefit most from the use of PT for PBI, such as those with large tumors, limited breast volume, and medial tumor location. In addition, unfavorable anatomy, connective tissue disorders, and prior irradiation may also be considered more strongly for the use of PT for PBI.

■ **LaRiviere MJ, et al. Proton Reirradiation for Locoregionally Recurrent Breast Cancer. Adv Radiat Oncol. 2021 May 9;6(4):100710.**

This study reviewed outcomes of 27 patients treated with proton therapy for local-regional recurrence of breast cancer. With a median follow-up 16.6 months, this study reported acute grade 3 toxicities including dermatitis in 2 patients and breast pain in 2 patients. Grade 2 or higher late toxicities included 6 G2 rib fractures and 1 G2 brachial plexopathy, 1 G3 dermatitis, 1 G3 breast pain, and 1 G4 dermatitis.

■ **Choi JI, et al. Outcomes and toxicities after proton partial breast radiotherapy for early stage, hormone receptor positive breast cancer: 3-Year results of a phase II multi-center trial. Clin Transl Radiat Oncol. 2022 Aug 28:37:71-77.**

This study reports 3-year outcomes of the Proton Collaborative Group phase II trial (PCG BRE007-12) that recruited women ≥ 50 years with node-negative, ER-positive, ≤3cm, IDC or ductal carcinoma in situ undergoing breast conserving surgery followed by PBI. At 35-month median follow-up, all patients were alive, and none had local, regional or distant disease progression. One patient developed an ER-negative contralateral IDC. Seven grade 2 adverse events occurred; no radiotherapy-related grade ≥ 3 toxicities occurred.

■ **Laughlin BS, et al. Proton therapy for isolated local regional recurrence of breast cancer after mastectomy alone. Front Oncol. 2022 Nov 28:12:925078.**

Nineteen patients with locoregional recurrent breast cancer treated with PT. All patients had mastectomy without prior RT. Seventeen patients were treated with PT to the chest wall and comprehensive regional lymphatics (17/19, 90%). With a median follow-up time of 13.4 months, 90% of patients were alive with no LRR or distant recurrence. Late AEs included dermatitis (11% grade 2, 5% grade 3) and lymphedema (5% grade 3). The authors concluded that PT was well-tolerated in the salvage setting with excellent loco-regional control.

■ **Sayan M, et al. Early Toxicity and Patient-Reported Cosmetic Outcomes in Patients Treated With Adjuvant Proton-Based Radiotherapy After Breast-Conserving Surgery. Clin Breast Cancer. 2023 Feb;23(2):176-180.**

This study reported early toxicity and cosmetic outcomes of 21 patients treated with breast-conserving surgery and adjuvant PBT. Grade 2 and 3 dermatitis occurred in 62% and 14% of patients. Grade 2 and 3 pain was reported by 33% and 10% of patients. Median follow-up at the time of cosmetic evaluation was 27 months. Four patients (21%) reported fair cosmetic outcome and 15 patients (79%) reported good or excellent cosmetic outcome. No poor cosmesis was reported.

■ **Sayan M, et al. Reconstructive complications and early toxicity in breast cancer patients treated with proton-based postmastectomy radiation therapy. Front Oncol. 2023 Jan 20:13:1067500.**

This study compared acute toxicities and reconstructive complications in patients treated with proton-based (n = 11)and photon-based PMRT (n = 26). Grade 2 skin toxicity was the most common acute toxicity in both groups (55% and 73% in the proton and photon group, respectively) (p = 0.077). Three patients (27%) in the proton group developed grade 3 skin toxicity. No Grade 4 acute toxicity was reported in either group. Reconstructive complications occurred in 4 patients (36%) in the proton group and 8 patients (31%) in photon group (p = 0.946).

■ **Hong ZS, et al. A retrospective study of adjuvant proton radiotherapy for breast cancer after lumpectomy: a comparison of conventional-dose and hypofractionated dose. Radiat Oncol. 2023 Mar 23;18(1):56.**

Fifty patients were treated with PT using two different regimens following lumpectomy. 14 patients received IMPT to a total dose of 50 Gy in 25 fractions, followed by a 10 Gy 4 fractionated boost to the lumpectomy cavity, while 36 received 40.05 Gy in 15 fractions and SIB 48 Gy to the lumpectomy cavity. Late toxicity occurred in three patients presented grade 1 pneumonitis; one patient graded 2 pneumonitis and two patients rib fracture in hypofractionated group, whereas no patient in the conventional group developed these late toxicities.

■ **Holt F, et al. Proton Beam Therapy for Early Breast Cancer: A Systematic Review and Meta-analysis of Clinical Outcomes. Int J Radiat Oncol Biol Phys. 2023 Nov 15;117(4):869-882.**

This systematic review included 32 studies (1452 early breast cancer patients) treated with adjuvant PBT. The most prevalent severe outcome after scanning PBT was dermatitis which occurred in 5.7% of patients. Other severe adverse outcomes included infection, pain and pneumonitis (each ≤1%). Of the 141 reconstruction events reported, the most prevalent after scanning PBT was prosthetic implant removal (34/181, 19%). 19 locoregional recurrences were reported from 867 patients in 19 studies, 53 distant recurrences were reported from 811 patients in 16 studies.

■ **Lalani N, et al. The Potential of Proton Therapy for Locally Advanced Breast Cancer: Clinical and Technical Considerations. Curr Oncol. 2023 Feb 28;30(3):2869-2878.**

This review presented the rationale of using protons in the setting of locally advanced breast cancer, which is to mitigate treatment related toxicity, especially the cardiopulmonary sequelae. Although data is limited, this review discussed early clinical results which appeared to be promising. Clinical and technical considerations on protons delivery techniques are highlighted, and three ongoing large-scale randomized studies are summarized which will provide comparative evidence to elucidate benefits of PT and guide patient selection.

■ **Gao RW, et al. Postmastectomy Intensity Modulated Proton Therapy: 5-Year Oncologic and Patient-Reported Outcomes. Int J Radiat Oncol Biol Phys. 2023 Nov 15;117(4):846-856.**

127 patients received unilateral conventionally fractionated postmastectomy IMPT. Median follow-up was 4.1 years. Five-year LRC was 98.4% and OS was 87.9%. Acute grade 2 and 3 dermatitis was seen in 45% and 4% of patients. Three patients (2%) experienced acute grade 3 infection, all of whom had breast reconstruction. Three late grade 3 adverse events occurred: morphea (N=1), infection (N=1), and seroma (N=1). There were no cardiac or pulmonary adverse events. Among the 73 patients at risk for postmastectomy RT associated reconstruction complications, seven (10%) experienced reconstruction failure.

■ **Mutter RW, et al. Conventional versus hypofractionated postmastectomy proton radiotherapy in the USA (MC1631): a randomised phase 2 trial. Lancet Oncol. 2023 Oct;24(10):1083-1093.**

This randomized phase 2 study randomized 82 patients to compare conventional fractionated (50 Gy in 25 fractions of 2 Gy) and hypofractionated (40.05 Gy in 15 fractions of 2.67 Gy) proton therapy. Within 24 months of first radiotherapy, complications occurred in six (15%) patients in the conventional fractionation group and in eight (20%) patients in the hypofractionation group (absolute difference 4·9%, p=0·27). After a median follow-up of 39.3 months, non-inferiority of the hypofractionation group could not be established.

■ **Hsieh CC, et al. Radiation-induced skin and heart toxicity in patients with breast cancer treated with adjuvant proton radiotherapy: a comparison with photon radiotherapy. Am J Cancer Res. 2023 Oct 15;13(10):4783-4793.**

The active and inactive (pro-BNP and NT-proBNP) forms of BNP are classically used as biomarkers for diagnosing and monitoring acute and chronic heart failure. This study compared dosimetric data and incidence of toxicity in left breast cancer patients underwent proton-RT (n=24) and photon-RT (n=87). Proton-RT reduced doses to the heart and lungs and was associated with a lower rate of increased NT-proBNP than did photon-RT, however, proton-RT had a higher rate of radiation dermatitis (29%) than did photon RT (11%).

■ **Thorpe CS, et al. Acute Toxicities After Proton Beam Therapy Following Breast-Conserving Surgery for Breast Cancer: Multi-institutional Prospective PCG Registry Analysis. Breast J. 2020 Apr 15.**

This is the report of the prospective multi-institutional PCG registry study. 82 patients received PBT and their adverse events (AEs) were recorded prospectively at each institution. Six patients (7.3%) experienced grade 3 AEs (5 with dermatitis, 5 with breast pain). Fifty-eight patients (70.7%) experienced grade ≥2 dermatitis. The study concluded that PBT including regional nodal irradiation after BCS is well-tolerated. Elevated BMI is associated with grade 3 dermatitis.

■ **Wang CC, et al. End-of-Range Radiobiological Effect on Rib Fractures in Patients Receiving Proton Therapy for Breast Cancer. Int J Radiat Oncol Biol Phys. 2020 Jul 1;107(3):449-454.**

This study looked into the possible causes to the high rate of rib fracture that reported in the trial (NCT01340495) which revealed improved dosimetry, favorable disease control, and minimal toxicity, but an increased rib fracture rate of around 7%, as compared to about 1.3% for patients with breast cancer after contemporary external beam radiation therapy. The authors concluded that the increased rib fracture rate is probably associated with the increased LET and RBE at the distal edge of proton beams.

■ **Gabani P, et al. Clinical outcomes and toxicity of proton beam radiation therapy for re-irradiation of locally recurrent breast cancer. Clin Transl Radiat Oncol. 2019 Oct 2;19:116-122.**

This retrospective study analyzed 16 patients with locally recurrent breast cancer who underwent PBT re-irradiation. With the median follow-up time of 18.7 months, this study reported no local failures. Grade 3-4 acute skin toxicity was observed in 5 (31.2%) patients. Four (25%) patients developed chest wall infections during or shortly (2 weeks) after re- irradiation. Late grade 3-4 fibrosis was observed in only 3 (18.8%) patients. Grade 5 toxicities were not observed.

■ **Bekelman JE, et al. Pragmatic randomised clinical trial of proton versus photon therapy for patients with non- metastatic breast cancer: the Radiotherapy Comparative Effectiveness (RadComp) Consortium trial protocol. BMJ Open. 2019 Oct 15;9(10):e025556.**

This is the trial protocol of RadComp. This multi-center trial sets the objective to evaluate whether the differences between proton and photon therapy cardiac radiation dose distributions lead to meaningful reductions in cardiac morbidity and mortality after treatment for breast cancer, hypothesizing that the 10-year estimate major cardiovascular events rate of 3.5% for the proton arm as compared to that of 6.3% of the photon arm.

■ **Jimenez RB, et al. Phase II Study of Proton Beam Radiation Therapy for Patients With Breast Cancer Requiring Regional Nodal Irradiation. J Clin Oncol. 2019 Oct 20;37(30):2778-2785.**

This study evaluated 70 patients. With the median follow-up of 55 months, the study reported that among 62 surviving patients, the 5-year rates for locoregional failure and overall survival were 1.5% and 91%. One patient developed grade 2 radiation pneumonitis (RP), and none developed grade 3 RP. No grade 4 toxicities occurred. PBT for breast cancer has low toxicity rates and similar rates of disease control compared with historical data of conventional RT.

■ **Proton beam therapy reirradiation for breast cancer: Multi-institutional prospective PCG registry analysis. Breast J. 2019 Nov;25(6):1160-1170.**

This study analyzed 50 patients receiving PBT reRT for breast cancer in the prospective Proton Collaborative Group (PCG) registry. Grade 3 AEs were experienced by 16% of patients (10% acute, 8% late). All grade 3 AEs occurred in patients receiving IMN reRT (P = 0.08). At 1 year, LRFS was 93%, and OS was 97%. This study concluded that PBT reRT is well tolerated with favorable local control.

■ **DeCesaris CM, Rice SR, Bentzen SM, et al. Quantification of Acute Skin Toxicities in Patients with Breast Cancer Undergoing Adjuvant Proton versus Photon Radiation Therapy: A Single Institutional Experience. Int J Radiat Oncol Biol Phys. 2019 Aug 1;104(5):1084-1090.**

This study compared the acute radiation dermatitis (RD) and skin hyperpigmentation (SH) after proton or photon radiotherapy, and reported that grade ≥2 RD was in 69.2% versus 29.8% of patients receiving proton and photon therapy respectively (P = 0.002). Rates of grade 3 RD were 5.1% versus 4.3% for proton versus photon radiation (P = .848). There were no significant differences in SH between modalities.

■ **Smith NL, Jethwa KR, Viehman JK, et al. Post-mastectomy intensity modulated proton therapy after immediate breast reconstruction: Initial report of reconstruction outcomes and predictors of complications. Radiother Oncol. 2019 Jun 8;140:76-83.**

Fifty-one women, among whom 42 had bilateral reconstruction, were treated with unilateral IMPT. This study reported that IMPT following immediate breast reconstruction spared underlying organs and had low rates of acute toxicity.Reconstruction complications are more common in irradiated breasts, and reconstructive outcomes appear comparable with photon literature.

■ **Speleers BA, Belosi FM, De Gersem WR, et al. Comparison of supine or prone crawl photon or proton breast and regional lymph node radiation therapy including the internal mammary chain. Sci Rep. 2019 Mar 18;9(1):4755.**

A planning study compared using non-coplanar VMAT or IMPT in supine (S) and prone-crawl (P) position for WBI and LN_IM. This study indicated that radiation-related mortality risk could outweigh the ~8% disease-specific survival benefit ofWB + LN_IM radiotherapy for S VMAT but not P VMAT. IMPT carries the lowest radiation-related mortality risks.

■ **Luo L, Cuaron J, Braunstein L, et al. Early outcomes of breast cancer patients treated with post-mastectomy uniform scanning proton therapy. Radiother Oncol. 2019 Mar;132:250-256.**

Forty-two patients who received mastectomy were treated with adjuvant chest wall and regional nodal proton therapy. With median follow-up of 35 months, there was one local failure, zero regional nodal failure and six distant failures. The3-year rate of locoregional DFS was 96.3% and OS was 97.2%. All patients developed grade 1 or 2 acute skin toxicity but no grade 3 or 4 acute skin toxicity.

■ **Chowdhary M, Lee A, Gao S, et al. Is Proton Therapy a "Pro" for Breast Cancer? A Comparison of Proton vs. Non- proton Radiotherapy Using the National Cancer Database. Front Oncol. 2019 Jan 14;8:678.**

This study compared 871 patients who received PBT and 723,621 who received non-PRT, identified in the national cancer database, and reported that PBT was not associated with OS, including in subsets likely at risk for higher heart doses. In the interim, given the high cost of protons, only well-selected patients should receive PBT unless enrolled on a clinical trial.

■ **Teichman SL, Do S, Lum S, et al. Improved long-term patient-reported health and well-being outcomes of early-stage breast cancer treated with partial breast proton therapy. Cancer Med. 2018 Dec;7(12):6064-6076.**

This cross sectional survey compared patient-reported QoL outcomes among women treated with lumpectomy followed by standard photon whole breast irradiation or partial breast proton irradiation (PBPT). The study reported that PBPT was not only an effective treatment option for early-stage disease, but also significantly improved overall outcomes many years out from treatment, across many domains.

■ **Kammerer E, et al. Proton therapy for locally advanced breast cancer: A systematic review of the literature, Cancer Treat Rev. 2018 Feb;63:19-27.**

This systematic review pointed out that protons decreased mean heart dose by a factor of 2 or 3, i.e. 1 Gy with proton therapy versus 3 Gy with conventional 3D, and 6 Gy for IMRT. Lungs were better spared with proton therapy than with photon therapy. PT reduces mean heart dose in breast cancer irradiation, probably reducing late cardio-vascular toxicity. Large clinical studies will likely confirm a clinical benefit of proton therapy.

■ **Braunstein LZ and Cahlon O. Potential Morbidity Reduction With Proton Radiation Therapy for Breast Cancer, Semin Radiat Oncol. 2018 Apr;28(2):138-149.**

In radiotherapy, the indications for comprehensive nodal irradiation has been expanded and there exists significant interest in employing novel technologies to mitigate cardiac dose while improving target volume coverage. This review summarized the dosimetric evidence and early clinical evidence that supports the efficacy and feasibility of proton radiation in breast cancer.

■ **Ovalle V, et al. Proton Partial Breast Irradiation: Detailed Description of Acute Clinico-Radiologic Effects, Cancers (Basel). 2018 Apr 7;10(4).**

This study reported that accelerated partial breast irradiation with protons results in a very different acute effect profile than standard whole breast irradiation, that visual and mammographic findings showed a clear time-dependent relationship and significant variation between individuals.

■ **Verma V et al. Proton beam radiotherapy as part of comprehensive regional nodal irradiation for locally advanced breast cancer. Radiother Oncol. 2017 May;123(2):294-298.**

This study reported acute toxicity outcomes in breast cancer patients treated with adjuvant PBT. Grades 1, 2, and 3 dermatitis occurred in 23%, 72%, and 5%. Eight percent required treatment breaks owing to dermatitis. Grades 1, 2, and 3 esophagitis developed in 31%, 33%, and 0% patients. The study concluded that PBT displays acceptable toxicity in the setting of comprehensive regional nodal irradiation.

■ **Tommasino F et al. Model-based approach for quantitative estimates of skin, heart, and lung toxicity risk for left-side photon and proton irradiation after breast-conserving surgery. Acta Oncol. 2017 May;56(5):730-736.**

This in silico study re-planned 10 patients of left-side breast cancer who underwent photon irradiation. The findings reported 1) lower toxicity in acute skin NTCP with IMPT compared to IMRT 2) significant heart and lung sparing achieved with IMPT, which resulted in an overall reduction in cardiopulmonary toxicity risk based on NTCP model.

■ **Stick L B et al. Joint Estimation of Cardiac Toxicity and Recurrence Risks After Comprehensive Nodal Photon Versus Proton Therapy for Breast Cancer. Int J Radiat Oncol Biol Phys. 2017 Mar 15;97(4):754-761.**

This study generated proton plans for 41 left-side breast cancer patients who underwent post lumpectomy comprehensive nodal photon irradiation, then evaluated the risks of cardiotoxicity and breast cancer recurrence. The authors reported that proton therapy can reduce the predicted risk of cardiac toxicity. Combined assessment of the risk from cardiac exposure and inadequate target coverage is desirable for rational consideration of competing photon and proton therapy plans.

■ **Verma V et al. Clinical Outcomes and Toxicity of Proton Radiotherapy for Breast Cancer. Clin Breast Cancer. 2016 Jun;16(3):145-54.**

A systematic review examined the current state of proton therapy for breast cancer. The findings included 1) skin toxicity after PBT might be equivalent or better than that of protons 2) the rates of seroma/hematoma and fat necrosis were comparable to those reported in the existing data, 3) PBT offers excellent potential to minimize the risk of cardiac events, keeping the mean heart dose at <1Gy.

■ **Verma V. et al. Clinical Outcomes and Toxicity of Proton Radiotherapy for Breast Cancer. Clinical Breast Cancer. 2016 June; 16(3):145-54.**

This study reviews the current state of proton therapy in the treatment of breast cancer and evaluates its role in the modern era of breast radiotherapy.

■ **Mailhot Vega R.B. et al. Establishing Cost-Effective Allocation of Proton Therapy for Breast Irradiation. International Journal of Radiation Oncology. Biology. Physics. 2016 May; 95(1):11-8.**

Cardiac toxicity due to breast radiation therapy has been extensively reported and affects both life expectancy and QoL. Proton therapy is able to limit the dose to the heart but is a costly treatment modality with limited access. This study uses a cost-effective analysis to help determine which patients may benefit the most from proton therapy referral.

■ **Orecchia R. et al. New frontiers in proton therapy: applications in breast cancer. Current Opinion in Oncology. 2015 November; 27(6):427-32.**

This paper reviews published data on proton therapy in the multimodality treatment of breast cancer so as to provide an overview of the advantages and critical issues relating to this irradiation modality. The authors show that proton therapy is able to optimize the dose to the target and reduce the irradiation of healthy tissues.

■ **Taylor C.W. et al. Exposure of the Heart in Breast Cancer Radiation Therapy: A Systematic Review of Heart Doses Published During 2003 to 2013. International Journal of Radiation Oncology. Biology. Physics. 2015 November; 93(4):845-53.**

Radiation therapy cures many women with breast cancer but can be toxic if the heart is exposed. This systematic review from 2003 to 2013 evaluates radiation doses to the heart from breast cancer radiation and shows that proton therapy delivers the lowest doses.

■ **Farace P. et al. Axillary irradiation omitting axillary dissection in breast cancer: is there a role for shoulder-sparing proton therapy?. The British Journal of Radiology. 2015 October; 88(1054):20150274.**

Axillary radiation therapy and axillary lymph node dissection provide comparable local control and reduced lymphedema, but axillary irradiation could induce toxicity such as shoulder function impairment. Proton therapy shows the potential to spare the shoulder without detrimental increase of the medium-to-low doses to the other normal tissues.

■ **Lin L.L. et al. Proton beam versus photon beam dose to the heart and left anterior descending artery for left-sided breast cancer. Acta Oncologica. 2015 July; 54(7):1032-9.**

The purpose of this study was to compare the dose to the heart, left anterior descending (LAD) artery and lung between proton therapy and radiation therapy for left-sided early stage breast cancer. Proton therapy was associated with lower dose to the LAD, which is the critical structure for late radiation therapy effects, compared to even the most optimized photon beam plan with deep inspiration breath hold and IMRT.

■ **Cuaron J.J. et al. Early toxicity in patients treated with postoperative proton therapy for locally advanced breast cancer. International Journal of Radiation Oncology. Biology. Physics. 2015 June 1; 92(2):284-91.**

Postoperative PT for patients with breast cancer is well tolerated, with acceptable rates of skin toxicity. PT favorably spares normal tissue without compromising target coverage.

■ **Xu N. et al. Can Proton Therapy Improve the Therapeutic Ratio in Breast Cancer Patients at Risk for Nodal Disease?. American Journal of Clinical Oncology. 2014 December; 37(6):568-74.**

Regional node irradiation in patients with invasive breast cancer often results in increased radiation exposure to organs at risk. This study shows that regional node target coverage is inferior with 3D conformal RT compared with either IMRT or 3D conformal RT+PT, with which OARs were exposed to less radiation. PT offers both improved coverage of the regional lymph nodes and decreased dose to the heart, lung, and contralateral normal tissue.

■ **Mast M.E. et al. Whole breast proton irradiation for maximal reduction of heart dose in breast cancer patients. Breast Cancer Research and Treatment. 2014 November, 148(1):33-9.**

IMPT could significantly decrease the dose to the heart and the region of the left anterior descending coronary artery compared to tangential IMRT with breathhold, and could be particularly useful for patients at high risk for major coronary events.

■ **Bush D.A. et al. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. International Journal of Radiation Oncology. Biology. Physics. 2014 November 1; 90(3):501-5.**

This paper is an update of a previous report of a phase 2 trial using PT for partial breast irradiation in patients with early stage breast cancer. PT produces excellent ipsilateral breast recurrence-free survival with minimal toxicity and excellent cosmetic results. The treatment proves to be adaptable to all breast sizes and lumpectomy cavity configurations.

■ **MacDonald S.M. et al. Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial. International Journal of Radiation Oncology. Biology. Physics. 2013 July 1; 86(3):484-90.**

Dosimetric planning studies have described potential benefits for the use of PT for locally advanced breast cancer. This study shows that PT for postmastectomy radiotherapy is feasible and well tolerated. This treatment may be warranted for selected patients with unfavorable cardiac anatomy, immediate reconstruction, or both that otherwise limits optimal radiotherapy delivery using standard methods.

■ **MacDonald S.M. et al. Proton radiotherapy for chest wall and regional lymphatic radiation; dose comparisons and treatment delivery. Radiation Oncology. 2013 March 24; 8[71].**

The delivery of post-mastectomy radiation therapy can be challenging for patients with left-sided breast cancer that have undergone mastectomy. Proton radiation therapy enables delivery of radiation to the chest wall and regional lymphatics, including the internal mammary nodes, without compromise of coverage and with improved sparing of surrounding normal structures.

■ **Jimenez R. et al. Intensity modulated proton therapy for post mastectomy radiation of bilateral implant reconstructed breasts: a treatment planning study. Radiotherapy and oncology: Journal of the European society for therapeutic radiology and oncology. 2013; 107[2]:213-7.**

Delivery of post-mastectomy radiation [PMRT] in women with bilateral implants represents a technical challenge, particularly when attempting to cover regional lymph nodes. IMPT provides improved homogeneity to the chest wall and regional lymphatics with improved sparing of surrounding normal structures. It may also enable women with mastectomy to undergo radiation therapy without the need for delay in breast reconstruction.

■ **Chang J. et al. Phase II trial of proton beam accelerated partial breast irradiation in breast cancer. Radiotherapy and oncology: Journal of the European society for therapeutic radiology and oncology. 2013; S0167-8140[13]00284-3.**

Proton beam accelerated partial breast irradiation [PB-APBI] can be delivered with excellent disease control and tolerable skin toxicity to properly selected patients with early-stage breast cancer. Multiple-field PB-APBI may achieve a high rate of good-to-excellent cosmetic outcomes.

■ **Ares C. et al. Postoperative proton radiotherapy for localized and locoregional breast cancer: potential for clinically relevant improvements?. International Journal of Radiation Oncology. Biology. Physics. 2010; 76[3]:685-97.**

When complex-target irradiation is needed, 3D conformal RT often compromises the target coverage and increases the dose to OARs, and IMRT increases the integral dose. On the other hand, IMPT improves target coverage and reduction of low doses to OARs, potentially reducing the risk of late-toxicity.

LIVER CANCERS

■ **Iwata H, et al. Image-Guided Proton Therapy for Elderly Patients with Hepatocellular Carcinoma: High Local Control and Quality of Life Preservation. Cancers [Basel]. 2021 Jan 9;13[2]:219.**

This study reported the efficacy and safety of image-guided proton therapy [IGPT] for elderly [≥80 years old] hepatocellular carcinoma [HCC] patients. Seventy-one elderly HCC patients were treated using IGPT to a total dose of 66 GyRBE in 10 fractions and 72.6 GyRBE in 22 fractions for central lesions. With the median follow-up 33 months, the 2-year OS and LC were 76% and 88%. No grade 2 or higher radiation-induced liver disease was observed, and only 1 patient developed grade 3 dermatitis.

■ **Dionisi F, et al. Clinical results of active scanning proton therapy for primary liver tumors. Tumori. 2021 Feb;107[1]:71-79.**

Eighteen patients were treated with proton to a total dose 58.05 Gy in 15 fractions with deep breath hold. The median follow-up was 10 months. One-year OS was 63%. A significant correlation between worse OS and patient performance status, vascular invasion, and tumor stages. One-year local control was 90%. No cases of classic radiation-induced liver disease occurred.

■ **De B, et al. Radiation-Associated Lymphopenia and Outcomes of Patients with Unresectable Hepatocellular Carcinoma [HCC] Treated with Radiotherapy. J Hepatocell Carcinoma. 2021 Mar 3:8:57-69.**

This study reviewed 143 HCC patients treated with photon [n=103 [72%]] and proton [n=40 [28%]] and compared the changes in absolute lymphocyte count [ALC]. This study found that proton group had a higher median ALC nadir [0.41 vs 0.32 k/μL, p=0.002] and longer median OS [33 vs 13 months, p=0.002] than photon group. Matched cohort analyses revealed a larger low-dose liver volume in the photon group, which correlated with lower ALC.

■ **Iizumi T, et al. Long-term clinical outcomes of patients receiving proton beam therapy for caudate lobe hepatocellular carcinoma. J Radiat Res. 2021 Jul 10;62[4]:682-687.**

Thirty patients with caudate lobe HCC were treated to a total doses of 55 to 77 [median 72.6] GyRBE. The median follow-up period was 37.5 months. The OS rates at 1-, 3- and 5-year were 86.6%, 62.8% and 46.1%, respectively, and the LC rates of 100%, 85.9% and 85.9%, respectively. No grade 3 or worse adverse events were observed. PBT is effective and safe for the treatment of caudate HCC, should therefore be considered a feasible option for intervention in patients with this disease.

■ **Kim TH, et al. Clinical Effectiveness of Hypofractionated Proton Beam Therapy for Liver Metastasis From Breast Cancer. Front Oncol. 2021 Nov 3:11:783327.**

Seventeen patients with liver metastasis from breast cancer were treated to a total dose of 66 GyE [range, 60-80] in 10 fractions. With a median follow-up time 34.2 months, this study reported that the 3-year freedom from local progression, PFS, and OS rates were 94.1%, 19.6% and 71.7% respectively. The median times of PFS and OS were 7.9 months and 39.3 months. Grade 3 or higher adverse events were not observed.

■ **Kim TH, et al. Proton Beam Therapy for Treatment-Naïve Hepatocellular Carcinoma and Prognostic Significance of Albumin-Bilirubin (ALBI) Grade. Cancers (Basel). 2022 Sep 13;14(18):4445.**

This study reported results of PBT as an initial treatment for 46 treatment-naïve HCC patients. With a median follow-up of 56.5 months, the 5-year freedom from local progression, PFS, and OS rates were 92.7%, 43.3%, and 69.2% respectively. The authors concluded that PBT can produce comparable OS in treatment-naïve HCC patients to other the recommended first-line treatments which are surgical resection, ablative treatments including RFA, and liver transplantation for BCLC 0 or A patients and TACE for BCLC B patients.

■ **Kim K, et al. A phase II trial of hypofractionated high-dose proton beam therapy for unresectable liver metastases. Radiother Oncol. 2022 Nov:176:9-16.**

This study analyzed 46 patients with 49 liver metastases treated by PBT to a total dose of 60 GyRBE in 5 fractions (BED 132 GyE) or 70 GyRBE in 10 (BED 119 GyE). The 1-year freedom from local progression rate in patients with lesion <3 cm was 87.4%, while that was 74.1% in patients with lesion > 3 cm (p = 0.087). One patient developed a grade 2 gastric ulcer. No patients developed grade ≥3 toxicities. The authors concluded that hypofractionated PBT with a BED > 100 GyRBE for liver metastasis is safe and effective.

■ **Kim TH, et al. Clinical Efficacy of Hypofractionated Proton Beam Therapy for Intrahepatic Cholangiocarcinoma. Cancers (Basel). 2022 Nov 12;14(22):5561.**

Forty-seven patients with intrahepatic cholangiocarcinoma (IHCC) treated with PBT to a total mean dose 63.3 GyE (range: 45-80 GyE) in 10 fractions. With a mean follow-up time 18.3 months, this study reported 2-year freedom from local progression, PFS, OS rates, and median time of OS were 86.9%, 16.8%, 42.7% and 21.9 months, respectively; grade ≥ 3 adverse events were observed in four (8.5%) patients. These findings suggest that hypofractionated PBT is safe and could offer a high rate of FFLP and promising OS in patients with inoperable or recurrent IHCC.

■ **Yamaguchi H, et al. Clinical outcomes and factors involved in the local control of proton beam therapy for oligometastatic liver tumors in patients with colorectal cancer. Strahlenther Onkol. 2023 Mar;199(3):304-312.**

Forty-one patients with colorectal cancer liver metastases (63 lesions) treated with PBT to a total dose of 72.6 GyRBE in 22 fractions. The median follow-up period was 27.6 months. The 3-year LC, OS, and PFS rates were 54.9%, 61.6%, and 16.7%, respectively. No grade ≥ 3 AEs were observed. None of the patients experienced liver failure during the acute or late phase.

■ **Cheng PL, et al. Comparison of local ablative therapies, including radiofrequency ablation, microwave ablation, stereotactic ablative radiotherapy, and particle radiotherapy, for inoperable hepatocellular carcinoma: a systematic review and meta-analysis. Exp Hematol Oncol. 2023 Apr 12;12(1):37.**

Based on twenty-six primary studies including 1,809 participants, this review reported that microwave ablation (MWA) (p < 0.001) and particle radiotherapy (p < 0.001) showed better performance of local control compared to RFA, while SABR (p = 0.276) showed a non-significant trend. However, SABR (p = 0.002) and particle radiotherapy (p < 0.001) showed better performance than RFA in HCCs of ≥ 30 mm in size. MWA showed a similar result to RFA while SABR and particle radiotherapy showed a lower survival rate in the 2-, 3-, and 4-year overall survival rates.

■ **Yamazaki H, et al. Particle beam therapy versus photon radiotherapy for extrahepatic biliary cancer-systemic review and meta-analysis. J Radiat Res. 2023 Jun 16;64(Supplement_1):i34-i40.**

A random-effects meta-analysis was conducted based on 9 original studies with a total 1558 patients (seven photon, n = 1488 patients; two PT, n = 70 patients) and data from a proton registry. The 1-, 2- and 3-year OS rates for the photon group, PT group and registry group were 55, 65 and 72%; 26, 38 and 38%; 12, 35 and 18%. The only statistically significant difference is the 1-year OS between the photon group and the registry group. The authors concluded that the efficacy of PT was not superior to that of photon RT during this meta-analysis.

■ **Schiff JP, et al. Ablative radiotherapy for colorectal liver metastases and intrahepatic cholangiocarcinoma. Surgery. 2023 Jul;174(1):108-112.**

For unresectable oligometastases or nonsurgical candidates, SBRT has a growing role with recent randomized phase II trial data indicating a doubling overall survival advantage for ablative SBRT in combination with systemic therapy versus systemic therapy alone. Proton radiation has also been prospectively demonstrated as an effective and safe choice for historically challenging scenarios, and in particular for larger tumors when normal liver sparing is otherwise difficult to achieve.

■ **Iizumi T, et al. Proton beam therapy for hepatocellular carcinoma with bile duct invasion. BMC Gastroenterol. 2023 Aug 3;23(1):267.**

Fifteen patients with hepatocellular carcinoma with bile duct invasion (BDIHCC) treated with PBT. The median follow-up time was 23.4 months. The 1-, 2-, and 3-year OS rates were 80.0%, 58.7% and 40.2%, respectively, and the corresponding LC and PFS rates were 93.3%, 93.3%, and 74.7% and 72.7%, 9.7%, and 0.0%, respectively. Acute grade 3 cholangitis occurred in 1 patient. No grade 4 or higher acute toxicity. Late grade 3 gastric hemorrhage occurred in 1 patient and pleural effusion in 1 patient. No toxicities of grade 4 or higher were observed. The authors concluded that radical PBT is a viable treatment for patients with BDIHCC.

■ **Bush DA, et al. Proton beam radiotherapy versus transarterial chemoembolization for hepatocellular carcinoma: Results of a randomized clinical trial. Cancer. 2023 Nov 15;129(22):3554-3563.**

Patients were randomized to receive PBT (n = 36) or TACE (n = 40). The 2-year OS for PBT versus TACE was similar at 68% (p = .80), however, median PFS was improved for PBT versus TACE (p = .002). LC was improved with PBT versus TACE (p = .003). Days of posttreatment hospitalization were 24 for PBT and 166 for TACE (p < .001). Total mean cost per patient for treatment and posttreatment care revealed a 28% cost savings for PBT. The authors concluded that this data supports the use of PBT as a viable treatment alternative to TACE for patients with HCC within transplant criteria.

■ **Lee SU and Kim TH. Current evidence and the potential role of proton beam therapy for hepatocellular carcinoma. Clin Mol Hepatol. 2023 Oct;29(4):958-968.**

A review article detailed the dosimetric and clinical benefits of PBT in the settings of early, intermediate and advanced stage of hepatocellular carcinoma (HCC). A recent randomized phase III trial demonstrated the non-inferiority of PBT in local tumor control compared to current standard radiofrequency ablation in early-stage HCC. PBT also tended to show more favorable outcomes compared to TACE in the intermediate stage, and has proven effective in-field disease control and safe toxicity profiles in advanced HCC.

■ **Hsieh RCE, et al. Clinical and Dosimetric Results of Proton or Photon Radiotherapy for Large (>5 cm) Hepatocellular Carcinoma: A Retrospective Analysis. Semin Radiat Oncol. 2023 Oct;33(4):407-415.**

This study analyzed 159 patients with >5 cm non-metastatic HCC who underwent definitive radiotherapy using either protons (N=105) or photons (N=54). Proton-treated patients had a significantly higher BED10 (96 vs. 67 Gy, P<0.001) and improved LC (2-year: 88.5% vs. 33.8%, P<0.001), PFS (median 7.4 vs. 3.3 months, P=0.001), and OS (median 18.9 vs. 8.3 months, P<0.001) than those undergoing photon radiotherapy. Patients treated with protons had significantly decreased incidences of radiation-induced liver disease (P=0.007), grade ≥3 UGI bleeding (P=0.001), and grade ≥3 lymphopenia (P=0.003).

■ **Sekino Y, et al. Proton Beam Therapy versus Radiofrequency Ablation for Patients with Treatment-Naïve Single Hepatocellular Carcinoma: A Propensity Score Analysis. Semin Radiat Oncol. 2023 Oct;33(4):407-415.**

Ninety-five patients treated with PBT were analyzed compared to 836 patients treated by RFA as controls. The 1-year, 3-year, and 5-year recurrence-free survival (RFS) rates were 86.6%, 49.5%, and 35.5% in the PBT group and 59.5%, 34.0%, and 20.9% in the RFA group (p = 0.058); the respective OS rates were 97.6%, 77.8%, and 57.1% in the PBT group and 95.1%, 81.7%, and 67.7% in the RFA group (p = 0.16). No grade 3 or higher adverse events in the PBT, but two grade 3 adverse events occurred within 30 days of RFA in the RFA group. The authors concluded that no significant difference between the two treatment options, and PBT can be an alternative for patients with solitary treatment-naïve HCC.

■ **Kim TH, et al. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: a randomized phase trial. J Hepatol. 2021 Mar;74(3):603-612.**

This randomized study compared the outcomes of PBT and radiofrequency ablation (RFA) for patients with recurrent/residual HCC. This study reported the 2-year LPFS rate with PBT vs. RFA was 92.8% vs. 83.2%, a difference of 9.6 percentage points (p <0.001), meeting the criteria for non-inferiority. The most common adverse events were radiation pneumonitis (32.5%) and decreased leukocyte counts (23.8%) for PBT and increased alanine aminotransferase levels (96.4%) and abdominal pain (30.4%) for RFA. No Grade 4 AEs or mortality were noted.

■ **Parzen JS, et al. Hypofractionated proton beam radiotherapy in patients with unresectable liver tumors: multi-institutional prospective results from the Proton Collaborative Group. 2020 Nov 4;15(1):255.**

63 patients (HCC 48% and ICC 40%) received PBT from the registry of the Proton Collaborative Group were analyzed. Thirteen patients (21%) were treated with 5-fraction regimens, 46 (73%) were treated with 15-fraction regimens, and 4 (6%) were treated with 25-fraction regimens. With median follow-up of 5.1 months, the LC rate at 1 year was 91.2% for HCC and 90.9% for ICC. The 1-year LC was significantly higher (95.7%) for patients receiving BED greater than 75.2 GyE than for patients receiving BED of 75.2 GyE or lower (84.6%, p = 0.029). The overall survival rate at 1 year was 65.6% for HCC and 81.8% for ICC.

■ **Kim TH, et al. Phase II Study of Hypofractionated Proton Beam Therapy for Hepatocellular Carcinoma. Front Oncol. 2020 Apr 28;10:542.**

This study reported outcomes of 45 patients including 37 recurrent and/or residual disease treated with PBT to a total dose of 70 Gy equivalent in 10 fractions. No grade ≥3 acute toxicity occurred. The median follow-up duration was 35.1 months, local progression occurred in two patients (8.7%). The 3-year rates of LPFS and overall survival (OS) were 95.2% and 86.4%. The study concluded that hypofractionated PBT showed promising LPFS and OS.

■ **Yoo GS, et al. Comparison of clinical outcomes between passive scattering versus pencil-beam scanning proton beam therapy for hepatocellular carcinoma. Radiother Oncol. 2020 May;146:187-193.**

This study analyzed 103 patients treated with proton therapy including 70 in the passive scattering (PS) and 33 in the pencil-beam scanning (PBS). This study found no significant differences in the rates of OS, in-field local control, extrahepatic progression-free survival, and complete response between the matched groups. There is no significant difference in the toxicity profiles between PS and PBS groups.

■ **Chuong M, et al. Proton beam therapy for liver cancers. J Gastrointest Oncol. 2020 Feb;11(1):157- 165.**

A review article examined the latest utilization of PBT for hepatocellular carcinoma and cholangiocarcinoma, as well as liver metastasis. The dosimetric advantage of PBT over XRT in sparing uninvolved liver from low and moderate doses clearly translates into clinically meaningful benefit for some patients with liver cancer. PBT for HCC has been evaluated over several decades with low rates of toxicity and excellent long-term LC even in patients with large tumors.

■ **Smart AC, et al. Hypofractionated Radiation Therapy for Unresectable/Locally Recurrent Intrahepatic Cholangiocarcinoma. Ann Surg Oncol. 2020 Apr;27(4):1122-1129.**

This study analyzed 66 patients with unresectable intrahepatic cholangiocarcinoma (ICC) who were treated with hypofractionated proton (32 patients) or photon (34 patients) radiation therapy (HF-RT). Median RT dose was 58.05 Gy, all delivered in 15 daily fractions. The 2-year outcomes were 84% LC and 58% OS. On multivariate analysis for OS, compared with photon RT, there was a trend towards improved survival with proton RT (p = 0.05).

■ **Hung SP, et al. Clinical Outcomes of Patients With Unresectable Cholangiocarcinoma Treated With Proton Beam Therapy. Am J Clin Oncol. 2020 Mar;43(3):180-186.**

This study examined 30 patients with unresectable CC treated with PBT to a total dose of 72.6 GyRBE. The 1-year local control, regional control, and distant metastases-free rates were 88%, 86%, and 68%, respectively. The median overall survival and progression-free survival were 19.3 and 10.4 months. Acute skin reactions of Grade III were observed in 7% of patients. Three and two patients had grade III-IV radiation-induced liver disease.

■ **Sekino Y, et al. Proton beam therapy for hepatocellular carcinoma associated with inferior vena cava tumor thrombus. J Cancer Res Clin Oncol. 2020 Mar;146(3):711-720.**

Hepatocellular carcinoma (HCC) with inferior vena cava tumor thrombus (IVCTT) is rare and regarded as an advanced disease stage with poor prognosis. This study reported outcomes of 21 HCC patients with IVCTT treated with proton therapy. For acute toxicities, dermatitis of grade 1-2 was observed in all patients, but no grade 3 or higher late toxicity events were encountered. The OS rates for all patients were 62%, 33%, and 19% at 1, 2, and 3 years, respectively.

■ **Tamura S, et al. A comparison of the outcomes between surgical resection and proton beam therapy for single primary hepatocellular carcinoma. Surg Today. 2020 Apr;50(4):369-378.**

In this study 345 patients with single primary nodular HCC ≤ 100 mm were analyzed, 314 of whom underwent surgical resection (SR) and 31 underwent PBT. The study reported that the median survival time in the SR group was significantly better than in the PBT group (104.1 vs. 64.6 months, p = 0.008) with no difference on the relapse-free survival (RFS) between the two groups. The study concluded that SR may therefore be favorable as an initial treatment for HCC compared to PBT.

■ **Hasan S, et al. Proton beam therapy versus stereotactic body radiotherapy for hepatocellular carcinoma: practice patterns, outcomes, and the effect of biologically effective dose escalation. J Gastrointest Oncol. 2019 Oct;10(5):999-1009.**

With the National Cancer Database for T1-2N0 HCC patients receiving PBT or SBRT, a total of 71 patients received PBT and 918 patients received SBRT were analyzed. The study reported that PBT was associated with longer survival than SBRT, despite being delivered to HCC patients with multiple poor prognostic factors. PBT may also allow for safer BED escalation, which is also independently associated with better outcomes.

■ **Chuong MD, Kaiser A, Khan F, et al. Consensus Report From the Miami Liver Proton Therapy Conference. Front Oncol. 2019 May 31;9:457.**

An International group of 22 liver cancer experts from 18 institutions were brought together to discuss the optimal utilization of PBT for primary and metastatic liver cancer. A consensus is reached among the experts that PBT should be more strongly considered for selected HCC patients including, at least CP-B cirrhosis, high tumor-to-liver ratio, higher number of tumors and prior RT to the liver.

■ **Chadha AS, Gunther JR, Hsieh CE, et al. Proton beam therapy outcomes for localized unresectable hepatocellular carcinoma. Radiother Oncol. 2019 Apr;133:54-61**

Forty-six patients with HCC, Child-Pugh class of A or B, no prior radiotherapy were treated with PBT. Actuarial 2-year LC and OS rates were 81% and 62%. The median OS was 30.7 months. Acute grade 3 toxicities were recorded in 6 (13%) patients. No grade≥3 CTCAE hepatic toxicity or classical RILD was recorded.

■ **Sorin Y, Ikeda K, Kawamura Y, et al. Effectiveness of Particle Radiotherapy in Various Stages of Hepatocellular Carcinoma: A Pilot Study. Liver Cancer. 2018 Oct;7(4):323-334.**

Eighty-three patients with HCC who underwent particle therapy, including proton beam radiation (58) and carbon ion radiation (25), were analyzed. This study concluded that the local control rates after PBT were sufficiently high compared to TACE or sorafenib.

■ **Mizuhata M, et al. Respiratory-gated Proton Beam Therapy for Hepatocellular Carcinoma Adjacent to the Gastrointestinal Tract without Fiducial Markers, Cancers (Basel). 2018 Feb 21;10(2).**

This study reported outcomes of respiratory-gated PBT without fiducial markers for HCC located within 2 cm of the gastrointestinal tract, 40 patients included. 2-year overall survival, progression-free survival, and local tumor control rates were 76%, 60%, and 94%, respectively. One patient (2.5%) developed a grade 3 gastric ulcer and one (2.5%) developed grade 3 ascites retention; none of the remaining patients developed grade >3 toxicities.

■ **Yu JI, et al. Initial clinical outcomes of proton beam radiotherapy for hepatocellular carcinoma (HCC), Radiat Oncol J. 2018 Mar;36(1):25-34.**

A study reported outcomes of 101 HCC patients treated with PBT. Of 78 patients followed for three months after PBT, infield complete and partial responses were achieved in 54 (69.2%) and 14 (17.9%) patients, respectively. The authors concluded that PBT treatment of HCC patients showed a favorable infield complete response rate with acceptable acute toxicity.

■ **Hong TS, et al. Phase II Study of Proton-Based Stereotactic Body Radiation Therapy for Liver Metastases: Importance of Tumor Genotype, J Natl Cancer Inst. 2017 Sep 1;109(9).**

This largest prospective evaluation to date on the efficacy and safety of proton-based stereotactic body radiation therapy (SBRT) for liver metastases, reported that protons were well tolerated and effective even for metastases that were 6 cm or larger. KRAS mutation is a strong predictor of poor LC, stressing the need for tumor genotyping prior to SBRT and treatment intensification in this patient subset.

■ **Lischalk J W et al. Radiation therapy for hepatobiliary malignancies. J Gastrointest Oncol. 2017 Apr;8(2):279-292.**

A review article examining radiotherapy for hepatocellular carcinoma and cholangiocarcinoma. Dose escalation to the tumor with sparing of surrounding normal tissue has yielded notable improvements in efficacy with stereotactic body radiation therapy (SBRT) and hypofractionated proton therapy. Proton therapy is a promising management option for inoperable hepatobiliary cancer.

■ **Oshiro Y et al. Analysis of repeated proton beam therapy for patients with hepatocellular carcinoma. Radiother Oncol. 2017 May;123(2):240-245.**

Japanese researchers reported outcomes of 83 patients treated with definitive repeated PBT. There was no severe acute toxicity, and no radiation-induced liver dysfunction was observed. The median overall survival period from the first PBT was 61months and the 2- and 5-year OS rates were 87.5% and 49.4%. The authors concluded that repeated PBT was well tolerated and safe, even though the liver doses in many patients deviated substantially from well-known critical levels for RILD.

■ **Kimura K et al. Clinical results of proton beam therapy for hepatocellular carcinoma over 5 cm. Hepatol Res. 2017 Feb 14.**

24 patients with hepatocellular carcinoma median tumor size 9cm (ranging from 5 to 18cm) were treated with protons. 2-year local control and overall survival were 87% and 52.4%. No acute or late treatment-related toxicity of Grade 3 or higher other than dermatitis was observed. The authors concluded that proton beam therapy represents a promising modality for treatment of large-volume HCC.

■ **Kim D Y et al. Risk-adapted simultaneous integrated boost-proton beam therapy (SIB-PBT) for advanced hepatocellular carcinoma with tumour vascular thrombosis. Radiother Oncol. 2017 Jan;122(1):122-129.**

41 advanced HCC patients with TVT were treated with proton-boost. The study reported median overall survival of 34.4 months and 2-year local progression free survival of 88.1%. The authors concluded that SIB-PBT is feasible and promising for HCC patients with TVT.

■ **Fukuda K et al. Long-term outcomes of proton beam therapy in patients with previously untreated hepatocellular carcinoma. Cancer Sci. 2017 Mar;108(3):497-503.**

129 patients with HCC treated with proton therapy. This study reported favorable long-term efficacies with mild adverse effect in BCLC stage 0 to C patients, and can be alternative treatment for localized HCC especially when accompanied with tumor thrombi.

■ **Fukumitsu N et al. Proton beam therapy for liver metastases from gastric cancer. J Radiat Res. 2017 May 1;58(3):357-362.**

Liver metastases from gastric cancer is a fatal disease with 5-year survival rate of <10%. This study reported that nine patients were treated with proton therapy and achieved an overall survival rate of 56% at 5 years, with no grade 3 toxicity observed. The authors concluded that proton therapy was a safe treatment and should be considered as an effective local treatment option for patients with liver metastases from gastric cancer.

■ **Bush D.A. et al. Randomized Clinical Trial Comparing Proton Beam Radiation Therapy with Transarterial Chemoembolization for Hepatocellular Carcinoma: Results of an Interim Analysis. International Journal of Radiation Oncology. Biology. Physics. 2016 May; 95(1):477-82.**

The authors report a trend toward improved local control and improved progression-free survival with proton therapy compared to transcatheter arterial chemoembolization (TACE), the 'standard treatment' for unresectable hepatoma.

■ **Hong T.S. et al. Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. Journal of Clinical Oncology. 2016 February; 34(5):460-8.**

To evaluate the efficacy and safety of high-dose hypofractionated proton therapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. High-dose hypofractionated proton therapy demonstrated high local control rates safely, supporting ongoing phase III trials of radiation in both types of tumors.

■ **Fukumitsu N. et al. Proton beam therapy for metastatic liver tumors. Radiotherapy Oncology. 2015 November; 117(2):322-7.**

The purpose of this study was to investigate the safety and efficacy of proton therapy for the treatment of metastatic liver tumors. Proton therapy is a potentially safe and effective treatment for this clinical indication.

■ **Gandhi S.J. et al. Clinical decision tool for optimal delivery of liver stereotactic body radiation therapy: Photons versus protons. Practical Radiation Oncology. 2015 July-August; 5(4):209-18.**

Stereotactic body radiation therapy for liver tumors is often limited by liver dose constraints. When feasible, proton therapy should be considered as a treatment modality of choice to allow maximal liver sparing for dome and central tumors >3 cm and any tumor >5 cm if photon plans fail to achieve adequate coverage or exceed the mean liver threshold.

■ **Schlachterman A. et al. Current and future treatments for hepatocellular carcinoma. World Journal of Gastroenterology. 2015 July; 21(28):8478-91.**

HCC has no definitively curative treatment: many treatment and management modalities exist with differing disadvantages and advantages. This paper systematically discusses the current treatment modalities available for HCC, detailing relevant clinical data, risks and rewards and overall outcomes for each approach.

■ **Ohkawa A. et al. Proton beam therapy for unresectable intrahepatic cholangiocarcinoma. Journal of Gastroenterology and Hepatology. 2015 May; 30(5):957-63.**

Treatment for unresectable intrahepatic cholangiocarcinoma (ICC) has not been established. The aim of this study is to evaluate the outcomes of PT for patients with unresectable ICC. The results suggest that long-term survival can be achieved for patients without distant metastasis.

■ **Kim T.H. et al. Phase I dose-escalation study of proton beam therapy for inoperable hepatocellular carcinoma. Cancer Research and Treatment. 2015 January; 47(1):34-45.**

The purpose of this study is to determine the optimal dose of PT in hepatocellular carcinoma patients (HCC). PT is safe and effective in patients with inoperable HCC, with at least 78 GyE10 of EQD2 needed to achieve sufficient local tumor control.

■ **Dionisi F. and Ben-Josef E. The use of proton therapy in the treatment of gastrointestinal cancers: liver. Cancer Journal. 2014 November-December; 20(6):371-7.**

This article reviews the role of PT in the treatment of primary liver cancer focusing on hepatocellular carcinoma (HCC). The dose-sparing physical properties of protons are of great advantage in the treatment of HCC.

■ **Dionisi F., Widesott L., Lorentini S., Amichetti M. Is there a role for proton therapy in the treatment of hepatocellular carcinoma? A systematic review. Radiotherapy and Oncology. 2014 April; 111(1):1-10.**

This paper reviews the literature concerning the systematic use of PT in the treatment of HCC, focusing on clinical results and technical issues. The literature search was conducted according to a specific protocol in the Medline and Scopus databases by two independent researchers covering the period of 1990-2012.

■ **Lee S.U. et al. Effectiveness and safety of proton beam therapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Strahlentherapie und Onkologie. 2014 Mar 4. 190(9), 806–814.**

This study evaluates the clinical effectiveness and safety of PT in advanced HCC patients with portal vein tumor thrombosis (PVTT). It suggests that PT could improve local progression-free survival, relapse-free survival, and overall survival in advanced HCC patients with PVTT, and that it is feasible and safe for these patients.

■ **Masato A. A phase I study on combined therapy with proton-beam radiotherapy and in situ tumor vaccination for locally advanced recurrent hepatocellular carcinoma. Radiation Oncology. 2013; 8(239).**

This study reports on a prospective phase I study of 'in situ' tumor vaccination using CalTUMP, a newly developed immunoadjuvant, following local PT for HCC to prevent the cancer recurrence. The treatment was feasible and safe in patients with heavily pre-treated HCC.

■ **Ling T.C. et al. Proton therapy for hepatocellular carcinoma. Chinese Journal of Cancer Research. 2012 December; 24(4): 361–367.**

PT has seen an increasing role in the treatment of hepatocellular carcinoma (HCC). This review discusses the physical attributes and rationale for PT in HCC. It also reviews recent literature regarding clinical outcomes of using PT for the treatment of HCC.

■ **Bush D.A. et al. The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: a phase 2 prospective trial. Cancer. 2011; 117 (13): 3053-9.**

PT may provide useful local-regional treatment for hepatocellular carcinoma (HCC). In this study, PT was found to be a safe and effective local-regional therapy for inoperable HCC. A randomized controlled trial to compare its efficacy to a standard therapy has been initiated.

■ **Petersen J. et al. Normal liver tissue sparing by intensity-modulated proton stereotactic body radiotherapy for solitary liver tumours. Acta Oncologica (Stockholm, Sweden). 2011; 5 0(6):823-8.**

Stereotactic body radiotherapy (SBRT) is often the preferred treatment for advanced liver tumors that are out of range of surgical resection or radiofrequency ablation. However, only a minority of patients may be candidates because of the limited radiation tolerance of normal liver and intestine. Due to the favorable depth-dose characteristics of protons, a considerable sparing of normal tissue can be obtained using proton-based SBRT for solitary liver tumors.

■ **Taddei P.J. et al. Risk of second malignant neoplasm following proton versus intensity-modulated photon radiotherapies for hepatocellular carcinoma. Physics in medicine and biology. 2010; 7;55(23):7055-65.**

The purpose of this study was to compare the predicted risk of developing an secondary cancer for a patient with HCC between PBT and IMRT. This study suggests that PT may reduce the risk of second malignant neoplasms compared to photon-based RT for some HCC patients.

PANCREATIC CANCERS

■ **Ogura Y, et al. Factors associated with long-term survival in gemcitabine-concurrent proton radiotherapy for non-metastatic locally advanced pancreatic cancer: a single-center retrospective study. Radiat Oncol. 2022 Feb 10;17(1):32.**

123 patients with locally advanced pancreatic cancer (LAPC) were treated with gemcitabine-concurrent proton radiotherapy (GPT) were reviewed. The study reported a median overall survival of 18.7 months for the total cohort. Cancer at the pancreatic body-tail and those without anterior peripancreatic invasion were independently associated with longer overall survival (P = 0.040 and P = 0.015). The authors concluded that GPT is a promising treatment option for patients with LAPC at the pancreatic body-tail and those with LAPC without anterior peripancreatic invasion.

■ **Kobeissi JM, et al. Proton Therapy in the Management of Pancreatic Cancer. Cancers (Basel). 2022 Jun 4;14(11):2789.**

Although proton treatment plans often showed advantages over photon plans in reducing dose to OARs, the clinical implications were yet to be proven. The key issues remain in range uncertainty and motion management when applying protons for pancreatic cancer. While studies have shown proton therapy is safe and tolerable, non-randomized comparative data have not consistently shown a statistical difference between proton and photon irradiation in terms of oncologic outcomes or toxicity to date, and randomized data so far are lacking.

■ **Rapp CT, et al. Dose-escalated proton therapy with elective nodal irradiation and concomitant chemotherapy for unresectable, borderline resectable, or medically inoperable pancreatic cancer: a phase II trial. J Gastrointest Oncol. 2022 Jun;13(3):1395-1401.**

Fifteen patients received proton therapy delivered 40.5 GyRBE in 18 fractions to the gross disease and elective nodal volumes followed by 22.5 GyRBE as a 10-fraction boost to the gross disease for a cumulative dose of 63 GyRBE over 28 fractions. The 1-year OS rate was 47%. One patient experienced grade 3 nausea requiring cessation of capecitabine, which ultimately resolved by treatment completion. The primary objective of 1-year OS of 75% for this phase II trial was not reached.

■ **Shin H, et al. The Feasibility of Stereotactic Body Proton Beam Therapy for Pancreatic Cancer. Cancers (Basel). 2022 Sep 20;14(19):4556.**

Forty-nine patients with pancreatic cancer (≥80% patients locally advanced unresectable disease) treated with SBPT to a total dose 60 GyRBE in five fractions (n = 42, 85.7%) and 50 GyRBE in five fractions (n = 7, 14.3%). With a median follow-up 16.3 months, the 2-year OS, PFS, and LC rates were 67.6%, 38.0%, and 73.0%, respectively. Grade ≥ 3 gastroduodenal toxicity occurred in three (6.1%) patients

■ **Liu J, et al. Advances in Radiation Oncology for Pancreatic Cancer: An Updated Review. Cancers (Basel). 2022 Nov 22;14(23):5725.**

This review examined studies published in the last 10 years about the advancement of radiotherapy in the treatment of locally advanced pancreatic cancer. Chemoradiation with PBT delivered a total dose 54–67.5 GyE in 25–33 fractions or 45–50 GyE in 10 fractions reported around 26 months median survival time with no grade ≥3 GI toxicity. For LAPC, the current recommended treatment is still standard dose chemoradiation to 54 Gy in 30 fractions or SBRT to 25–33 Gy in 5 fractions.

■ **Ami K, et al. Proton radiotherapy as a treatment strategy to increase survival in locally advanced pancreatic cancer in the body and tail: a retrospective study. Radiat Oncol. 2023 Aug 8;18(1):131.**

200 patients with LAPC were treated with PT to a total dose of 67.5 GyE in 25 fractions and concurrent chemotherapy. The OS rate at 1- and 2-year was 69.6% and 35.4% with a median OS of 18.4 months. The 1- and 2-year LC and PFS rates were 84.3% and 68.0%, and 44.3% and 19.4%, respectively. Acute grade 3 toxicities including gastrointestinal bleeding/ulceration, nausea/vomiting, anorexia, and dermatitis, were observed in 15 (7.5%), 3 (1.5%), 2 (1.0%), and 2 (1.0%) patients, respectively. Late grade 3 gastrointestinal bleeding/ulcer was observed in 14 patients (7.0%), and there was one case (0.5%) of grade 5 toxicity.

■ **Elkhamisy SA, et al. Normo- or Hypo-Fractionated Photon or Proton Radiotherapy in the Management of Locally Advanced Unresectable Pancreatic Cancer: A Systematic Review. Cancers (Basel). 2023 Jul 25;15(15):3771.**

This review included 31 primary studies including CFRT 15, SBRT 10 and PBT 6 for evaluation. The median total dose in the CFRT group was 50.4–59.4 Gy in 25–33 fractions. Total dose 24 Gy to 50 Gy was given in 5 to 8 fractions in the SBRT group. PBT was administered to 50 to 67.5 GyRBE in 25 to 33 fractions. The median OS for the CFRT and SBRT groups was 9.3-22.9 months and 8.5-20 months, respectively. For the PBT group, the median OS was 18.4-22.3 months. Acute toxicity was remarkably less in SBRT compared to CFRT, while in PBT grade 3 or higher acute toxicity was observed more commonly with doses of 67.5 GyRBE or higher.

■ **Lautenschlaeger S, et al. Treatment of primary or recurrent non-resectable pancreatic cancer with proton beam irradiation combined with gemcitabine-based chemotherapy. Strahlenther Onkol. 2023 Nov;199(11):982-991.**

This study reported results of 25 patients with localized nonresectable pancreatic cancer (15 patients) or local recurrent disease (10 patients) treated with chemoradiation using PBT. The median progression-free survival was 5.9 months and median overall survival was 11.0 months. Four grade 3 and 4 acute adverse events were reported.

■ **Raturi VP, et al. Radiobiological Model-Based Approach to Determine the Potential of Dose-Escalated Robust Intensity-Modulated Proton Radiotherapy in Reducing Gastrointestinal Toxicity in the Treatment of Locally Advanced Unresectable Pancreatic Cancer of the Head. Radiat Oncol. 2020 Jun 22;15(1):157.**

This study compared plans of IMPT and IMRT for 9 locally advanced unresectable pancreatic cancer patients and used the NTCP models for predication in reducing GI toxicity risk. NTCP evaluation for the endpoint gastric bleeding of stomach (10.55% vs.13.97%, P = 0.007), duodenum (1.87% vs. 5.02%, P = 0.004), and combined stomach and duodenum (5.67% vs. 7.81%, P = 0.008) suggest reduced toxicity by IMPT compared to IMRT.

■ **Rutenberg MS and Nichols RC. Proton beam radiotherapy for pancreas cancer. J Gastrointest Oncol. 2020 Feb;11(1):166-175.**

A review article examined up to date data of PBT for both resectable and unresectable pancreatic cancer. The clinical outcome data is limited but very encouraging and supports the need for additional trials to fully explore the benefits of PBT. Existing data indicate that PBT combined with chemotherapy in the preoperative, adjuvant, and definitive settings is extremely well-tolerated and allows for the possibility of dose intensification.

■ **Kim TH, et al. Efficacy and feasibility of proton beam radiotherapy using the simultaneous integrated boost technique for locally advanced pancreatic cancer. Sci Rep. 2020 Dec 10;10(1):21712.**

Eighty-one patients with locally advanced pancreatic cancer were treated with PBT simultaneous integrated boost (SIB) technique. With the median follow-up time 19.6 months, OS rates of all patients and of those in groups I (no chemotherapy), II (with maintenance chemotherapy), and III (upfront and maintenance chemotherapy) were 19.3 months, 15.3 months, 18.3 months, and 26.1 months, respectively (p = 0.043). Acute and late grade ≥ 3 toxicities related to PBT were not observed. PBT with SIB showed promising OS with a safe toxicity profile, and combinations of PBT and chemotherapy could improve OS.

■ **Mizumoto T, Terashima K, Matsuo Y, et al. Proton Radiotherapy for Isolated Local Recurrence of Primary Resected Pancreatic Ductal Adenocarcinoma. Ann Surg Oncol. 2019 Aug;26(8):2587-2594.**

Thirty patients had initially undergone surgery but isolated local recurrence occurred. PBT was administered with dose of 67.5 (GyE) in 19 to 25 fractions. This study reported the median OS and PFS were 26.1 and 12.3 months. Four patients (13.3%) experienced acute grade ≥3 gastrointestinal toxicities.

■ **Hiroshima Y, Fukumitsu N, Saito T, et al. Concurrent chemoradiotherapy using proton beams for unresectable locally advanced pancreatic cancer. Radiother Oncol. 2019 Jul;136:37-43.**

Forty-two unresectable locally advanced pancreatic cancer patients were treated with PBT and concurrent chemotherapy. This study reported the 1-year/2-year OS rates were 77.8/50.8% with median survival time of 25.6 months. The 1-year/2-year LC rate were 83.3/78.9% with a median time to local recurrence of more than 36 months. No late adverse effects of grade 3 or higher were observed.

■ **Ng SP and Koay EJ. Current and emerging radiotherapy strategies for pancreatic adenocarcinoma: stereotactic, intensity modulated and particle radiotherapy. Ann Pancreat Cancer. 2018 Aug;1.**

A review article examined the available outcome data of IMRT, SBRT and proton and carbon ion therapy for locally advanced pancreatic cancer. The evidence suggests prolonged survival for patients who receive biological equivalent doses above 70 Gy. The advancements in treatment techniques and imaging modalities have enabled the effective and safe delivery of higher doses of radiation.

■ **Jethwa KR, Tryggestad EJ, Whitaker TJ, et al. Initial experience with intensity modulated proton therapy for intact, clinically localized pancreas cancer: Clinical implementation, dosimetric analysis, acute treatment-related adverse events, and patient-reported outcomes. Adv Radiat Oncol. 2018 Apr 13;3(3):314-321.**

Thirteen patients with localized pancreatic cancer underwent concurrent chemoradiation therapy utilizing IMPT. All patients completed treatment without radiation therapy breaks. No patients experienced grade ≥3 treatment-related AEs. IMPT offered significant reductions in radiation exposure to multiple gastrointestinal organs at risk.

■ **Maemura K, et al. Comparison of proton beam radiotherapy and hyper-fractionated accelerated chemoradiotherapy for locally advanced pancreatic cancer, Pancreatology. 2017 Sep - Oct;17(5):833-838.**

A study compared the clinical outcomes of proton beam radiotherapy and conventional chemoradiotherapy via hyper-. fractionated acceleration radiotherapy after induction chemotherapy in patients with locally advanced pancreatic cancer. There was no statistical significance between the two groups regarding the median time to progression (15.4 months in both) and the median overall survival (23.4 vs. 22.3 months).

■ **Hitchcock K E et al. Feasibility of pancreatectomy following high-dose proton therapy for unresectable pancreatic cancer, World J Gastrointest Surg. 2017 Apr 27;9(4):103-108.**

The study reported that pancreatic resection for patients with initially unresectable cancers was feasible after high-dose proton radiotherapy with a high rate of local control and acceptable surgical morbidity.

■ **Sio T.T. et al. Spot-scanned pancreatic stereotactic body proton therapy: A dosimetric feasibility and robustness study. Physica Medica, 2016 February; 32(2):331-42.**

This paper explores the dosimetric potential of spot-scanned stereotactic body proton therapy (SBPT) for pancreatic cancer, and provides a critical basis for clinical translation of spot size, optimization technique, and OTV expansion for pancreatic SBPT.

■ **Nichols R.C. Jr et al. Proton therapy for pancreatic cancer. World Journal of Gastrointestinal Oncology. 2015 September; 7(9):141-7.**

RT is commonly used to treat pancreatic malignancies although its ultimate utility is compromised by the exquisitely radiosensitive normal tissues surrounding the pancreas. That is why protons appear to be a superior modality for radiation therapy delivery to patients with unresectable tumors or for postoperative RT.

■ **Thompson R.F. et al. A dosimetric comparison of proton and photon therapy in unresectable cancers of the head of pancreas. Medical Physics. 2014 August; 41(8):081711.**

In this study, the authors investigate the potential use of double scattering and PBS PT in limiting dose to critical OARs. Both DS and PBS decreased stomach, duodenum, and small bowel dose in low-dose regions compared to IMRT. However, protons yielded increased doses in the mid to high dose regions.

■ **Nichols R.C. Jr. et al. Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. Acta Oncologica. 2013 April; 52(3):498-505.**

PT may allow for significant sparing of the small bowel and stomach and is associated with a low rate of gastrointestinal toxicity. The favorable toxicity profile associated with PT may allow for radiotherapy dose escalation, chemotherapy intensification, and possibly increased acceptance of preoperative radiotherapy.

■ **Nichols R.C. Jr et al. Protons Offer Reduced Normal-Tissue Exposure for Patients Receiving Postoperative Radiotherapy for Resected Pancreatic Head Cancer. International Journal of Radiation Oncology. Biology. Physics. 2012; 83(1):158-63.**

The potential role for adjuvant PT for resected pancreatic head cancer was assessed in this study. By reducing small bowel and stomach exposure, protons have the potential to reduce the acute and late toxicities of postoperative chemoradiation.

■ **Hong T.S. et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. International Journal of Radiation Oncology. Biology. Physics. 2011;79 (1): 151-7.**

This study shows the safety and feasibility of 1 week of chemoradiation with PT and capecitabine followed by early surgery.

■ **Boimel PJ, et al. Proton beam reirradiation for locally recurrent pancreatic adenocarcinoma, J Gastrointest Oncol. 2017 Aug;8(4):665-674.**

15 patients with locally-recurrent pancreatic cancer treated with PRT. There was a rate of 13% acute ≥ grade 3 toxicities attributed to PRT. The median overall survival (OS) was 16.7 months. The study concluded that PRT was well tolerated, resulted in prolonged clinical outcomes compared to historical controls.

ESOPHAGEAL CANCERS

■ **Nicholas O, et al. The Promise of Proton Beam Therapy for Oesophageal Cancer: A Systematic Review of Dosimetric and Clinical Outcomes. Clin Oncol (R Coll Radiol). 2021 Aug;33(8):e339-e358.**

Based on 32 publications, this review reported that significant benefits with PBT suggested by current literature in terms of toxicity reduction, especially in the postoperative period, with comparable survival outcomes to photon-RT. PBT seemed to reduce dose to organs at risk, especially lung and heart, although not for all reported parameters.

■ **Zhu C, et al. Identifying Individualized Risk Profiles for Radiotherapy-Induced Lymphopenia Among Patients With Esophageal Cancer Using Machine Learning. JCO Clin Cancer Inform. 2021 Sep:5:1044-1053.**

This study analyzed the retrospective data of 746 patients with esophageal cancer treated with photons (n = 500) and protons (n = 246) to determine the pretreatment clinical and radiation dosimetric risk factors of grade 4 radiation-induced lymphopenia (G4RIL). This study found that baseline absolute lymphocyte count and volumes of lung and spleen receiving ≥ 15 and ≥ 5 Gy, were the most important G4RIL risk determinants. The G4RIL risk for an average patient receiving protons increased by 19% had the patient switched to photons.

■ **Sumiya T, et al. The impact of lymphopenia during chemoradiotherapy using photons or protons on the clinical outcomes of esophageal cancer patients. J Radiat Res. 2021 Oct 11:rrab094.**

This study retrospectively review 69 patients with esophageal cancer treated with XRT (n=15) and PBT (n= 54) and concurrent chemotherapy. The study found that the absolute lymphocyte counts (ALC) were significantly higher in PBT group than the XRT group, and a similar trend in the neutrophil-to-lymphocyte ratio (NLR). Dose-volume analysis revealed significant correlations between volumes of the thoracic bones irradiated by 5-50 Gy and minimum ALCs and maximum NLR.

■ **Wang X, et al. Current status and application of proton therapy for esophageal cancer. Radiother Oncol. 2021 Nov:164:27-36.**

This review examined current clinical data that reported protons vs photon-based radiation in reducing postoperative complications, cardiac toxicity, and severe radiation induced immune suppression, in the settings of proton therapy with and without current chemotherapy, as well as reirradiation. This review pointed out that there is still a lack of high-level evidence to support proton therapy in the treatment of esophageal cancer and large randomized trials will be needed to prove the benefits.

■ **Chuong MD, et al. Executive Summary of Clinical and Technical Guidelines for Esophageal Cancer Proton Beam Therapy From the Particle Therapy Co-Operative Group Thoracic and Gastrointestinal Subcommittees. Front Oncol. 2021 Oct 19:11:748331.**

In this guideline document, the dosimetric data and clinical evidence of PBT for esophageal cancer (EC) was summarized and evaluated. The authors concluded that PBT should be strongly considered for tri-modality and nonoperative thoracic EC patients based on retrospective and randomized prospective data that demonstrates clinically meaningful reductions in toxicity compared to XRT. Long-term toxicity and efficacy outcomes of PBT versus XRT are being evaluated in the ongoing NRG-GI006 phase 3 randomized trial (NCT03801876).

■ **Choi JH, et al. A Comparative Analysis of Photon versus Proton Beam Therapy in Neoadjuvant Concurrent Chemoradiotherapy for Intrathoracic Squamous Cell Carcinoma of the Esophagus at a Single Institute. Cancers (Basel). 2022 Apr 18;14(8):2033.**

This study compared the results of 31 patients with locally advanced esophageal cancer treated with neoadjuvant chemoradiotherapy to a median total dose 41.4 Gy using either proton (n = 15) or photon (n = 16). With a median follow-up of 17 months, this study reported no significant differences between the two groups in 2-year OS (67.8% vs. 68.6%, p = 0.867) or 2-year DFS (33.3% vs. 34.5%, p = 0.749). The lungs and heart received significantly less dose in the proton group, however there was no significant differences in short-term postoperative outcomes or lymphocyte count.

■ **Solidum JGN, et al. Proton Beam Therapy for Esophageal Cancer. Cancers (Basel). 2022 Aug 22;14(16):4045.**

A review examined the existing data of PBT for locally advanced esophageal cancer, and reported that current clinical outcome supports that PBT leads to improved disease-related outcomes and reduction in treatment-related AEs. Newer results from ongoing clinical trials will dictate the future utility of PBT versus photon-based RT.

■ **Tokumaru S, et al. Analysis of particle therapy registries based on a unified treatment policy for esophageal cancer. J Radiat Res. 2023 Jun 16;64(Supplement_1):i16-i24.**

Based on data from a registry, clinical outcomes of 174 patients were analyzed in this study. With a median follow-up period 908 days, the 3-year OS rates for stage I, II and III were 84.8%, 60.3% and 42.9%; the 3-year PFS rates for stage I, II and III were 71.9%, 58.3% and 37.0%; and the 3-year LC were 78.4%, 79.8% and 65.2%, respectively. Four patients (2.3%) with ≥Grade 3 cardiopulmonary toxicities were observed. The authors concluded that this study showed lower rates of adverse cardiopulmonary events with particle therapy than photon radiotherapy.

■ **Zhou PX, et al. Efficacy and Safety in Proton Therapy and Photon Therapy for Patients With Esophageal Cancer: A Meta-Analysis. JAMA Netw Open. 2023 Aug 1;6(8):e2328136.**

This meta-analysis showed that photon therapy was associated with poor OS, but no difference in PFS observed between photon and proton groups, based on the 45 original studies included for evaluation. Proton therapy was associated with significantly decreased grade ≥2 radiation pneumonitis and pericardial effusion, and grade ≥4 lymphocytopenia.

■ **Nonaka T, et al. Concurrent chemoradiotherapy using proton beams can reduce cardiopulmonary morbidity in esophageal cancer patients: a systematic review. Esophagus. 2023 Oct;20(4):605-616.**

Based on data from 20 cohort studies, 2 propensity matched analyses and 1 randomized study, this review reported that OS and PFS were better after PBT than after photon-based RT, but the difference was significant in only one of seven studies. The rate of grade 3 cardiopulmonary toxicities was lower after PBT (0-13%) than after photon-based RT (7.1-30.3%). Three of four reports evaluating the absolute lymphocyte counts (ALCs) demonstrated a significantly higher ALC after PBT than after photon-based RT.

■ **Wang X, et al. Incidence and Onset of Severe Cardiac Events After Radiotherapy for Esophageal Cancer. J Thorac Oncol . 2020 Jun 26;S1556-0864(20)30499-8.**

This study analyzed 479 esophageal cancer patients treated with either IMRT or PBT either preoperatively or definitively. G3+ cardiac events occurred in 18% of patients. Pre-existing cardiac disease (p = 0.001) and radiation modality (intensity- modulated RT versus proton beam therapy) (p = 0.027) were significantly associated with G3+ cardiac events. The mean heart dose, particularly of less than 15 Gy, was associated with reduced G3+ events. Furthermore, G3+ cardiac events were associated with worse overall survival (p = 0.041).

■ **Ono T, et al. Proton Beam Therapy Is a Safe and Effective Treatment in Elderly Patients With Esophageal Squamous Cell Carcinoma (ESCC). Thorac Cancer. 2020 Jun 8.**

This study reported results of 54 esophageal cancer patients who are over 75 years old treated with PBT. The five-year overall and cancer-specific survival rates were 56.2% and 71.7%, respectively. The five-year local control rate was 61.8%. There was no grade 3 or higher toxicity, excluding three patients with grade 3 esophageal ulcers.

■ **Manzar GS, et al. Comparative analysis of acute toxicities and patient reported outcomes between intensity- modulated proton therapy (IMPT) and volumetric modulated arc therapy (VMAT) for the treatment of oropharyngeal cancer. Radiother Oncol. 2020 Jun;147:64-74.**

This study compared 46 IMPT and 259 VMAT patients acute toxicities and reported that IMPT was associated with lower PEG-tube placement (p = 0.001) and less hospitalization ≤60 days post-RT (p < 0.001). IMPT was associated with a relative risk reduction of 22.3% for end-of-treatment narcotic use. IMPT is associated with improved patient reported outcomes. Mucositis, dysphagia, and pain were decreased with IMPT.

■ **Jethwa KR, et al. The emerging role of proton therapy for esophagus cancer. J Gastrointest Oncol. 2020 Feb;11(1):144-156.**

This review article discussed the emerging role of PBT for esophageal cancer. Clinical data supports the feasibility, efficacy, and favorable AE profile for curative intent proton-based CRT for esophageal cancer, in addition, suggesting PBT may be associated with improved survival potentially attributable to toxicity reduction, including cardiopulmonary sparing or through a reduction in severe treatment-related lymphopenia which has been associated with disease recurrence and OS. b

■ **Lin SH, et al. Randomized Phase IIB Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for Locally Advanced Esophageal Cancer. J Clin Oncol. 2020 May 10;38(14):1569-1579.**

This randomized trial compared total toxicity burden (TTB) and progression-free survival (PFS) between PBT and IMRT for 145 locally advanced esophageal cancer patients who were randomly assigned to treat with IMRT (72) and with PBT (73). With median follow-up of 44.1 months, this study reported the mean TTB was 2.3 times higher for IMRT (39.9) than PBT (17.4); the mean postoperative complications score was 7.6 times higher for IMRT (19.1) versus PBT (2.5); the 3-year PFS rate (50.8% v 51.2%) and 3-year overall survival rates (44.5% v 44.5%) were similar.

■ **Sato D, et al. Therapeutic results of proton beam therapy with concurrent chemotherapy for cT1 esophageal cancer and salvage endoscopic therapy for local recurrence. Esophagus. 2020 Jul;17(3):305-311.**

This study reported the efficacy of 44 clinical T1 esophageal cancer patients treated with concurrent chemo-proton therapy (CCPT). 43 patients (98%) achieved primary complete response. Among the 44 patients, the 3-year overall survival rate was 95.2%. Five patients (11%) developed local recurrence. The study concluded that CCPT is an effective treatment for cT1 ESCC and careful endoscopic follow-up allows preferable local control with salvage endoscopic treatment.

■ **Gergelis KR, et al. Proton beam radiotherapy for esophagus cancer: state of the art. J Thorac Dis. 2020 Nov;12(11):7002-7010.**

This review discussed the evolution of photon and proton-based radiotherapy techniques, rationale, dosimetric and clinical studies comparing outcomes of photon- and proton-based techniques, ongoing prospective trials, and future directions of PBT as a means of reducing toxicity and improving oncologic outcomes for patients with esophagus cancer.

■ **Ono T, et al. Clinical Results of Proton Beam Therapy for Esophageal Cancer: Multicenter Retrospective Study in Japan. Cancers (Basel). 2019 Jul 16;11(7):993.**

A large retrospective study of 202 patients (90 inoperable patients and 100 patients (49.5%) had stage III/IV cancer) who were treated with PBT in Japan. This study reported that the 3-year and 5-year overall survival rate was 66.7% and 56.3%. The five-year local control rate was 64.4%. There were two patients with grade three pericardial effusion (1%) and a patient with grade three pneumonia (0.5%). No grade 4 or higher cardiopulmonary toxicities were observed.

■ **Garant A, et al. A Comparison of Patient-Reported Health-Related Quality of Life During Proton Versus Photon Chemoradiotherapy for Esophageal Cancer. Pract Radiat Oncol. 2019 Nov;9(6):410-417.**

This study aimed to compare Functional Assessment of Cancer Therapy - Esophagus (FACT-E) questionnaire changes during proton (PRT) or photon (XRT) chemoradiotherapy (CRT) for esophageal cancer (EC). 125 patients completed a baseline and post-treatment FACT-E; 63 received XRT and 62 received PRT. This study found that less mean decline in FACT-E score was observed for PRT vs XRT (p=0.026).

■ **Garant A, Whitaker TJ, Spears GM, et al. A Comparison of Patient-Reported Health-Related Quality of Life During Proton Versus Photon Chemoradiotherapy for Esophageal Cancer. Pract Radiat Oncol. 2019 Jul 13.**

125 patients received preoperative or definitive CRT, including 63 who received XRT and 62 who received PBT. Scores of Functional Assessment of Cancer Therapy - Esophagus (FACT-E) were compared between XRT and PBT groups. This study reported less mean decline in FACT-E score for PBT vs XRT (-12.7 vs -20.6, p=0.026).

■ **Ono T, Wada H, Ishikawa H, et al. Clinical Results of Proton Beam Therapy for Esophageal Cancer: Multicenter Retrospective Study in Japan. Cancers (Basel). 2019 Jul 16;11(7).**

Two hundred and two patients were treated with PBT in four proton therapy centers in Japan. The 3-year and 5-year overall survival rate was 66.7% and 56.3%. The five-year local control rate was 64.4%. There were two patients with grade 3 pericardial effusion (1%) and a patient with grade 3 pneumonia (0.5%). No grade 4 or higher cardiopulmonary toxicities were observed.

■ **Routman DM, Garant A, Lester SC, et al. A Comparison of Grade 4 Lymphopenia With Proton Versus Photon Radiation Therapy for Esophageal Cancer. Adv Radiat Oncol. 2019 Jan 17;4(1):63-69**

Grade 4 lymphopenia (G4L) during radiation therapy (RT) is associated with higher rates of distant metastasis and decreased overall survival. 79 patients received XRT and 65 received PBT were evaluated. This study reported that G4L was significantly higher in patients who received XRT versus those who received PBT (56% vs 22%; P < .01).

■ **Badiyan SN, Hallemeier CL, Lin SH, et al. Proton beam therapy for gastrointestinal cancers: past, present, and future. J Gastrointest Oncol. 2018 Oct;9(5):962-971.**

A review on recent data that PBT for upper GI cancers may decrease acute toxicity and late complications and improve treatment compliance. Given the accruing data showing a strong relationship between clinical outcomes and low dose received by organs at risk, there is a strong rationale to consider PBT, while not all patients likely benefit from PBT.

■ **Haque W, et al. Utilization of neoadjuvant intensity-modulated radiation therapy and proton beam therapy for esophageal cancer in the United States, J Gastrointest Oncol. 2018 Apr;9(2):282-294.**

Based on the National Cancer Database, of 3,138 patients, 1,398 (45%) received 3DCRT and 1,740 (55%) received advanced-RTs (99% IMRT, 1% PBT). The utilization of advanced-RTs is found to be steadily rising in the United States, from 20% in 2004 to 69% in 2013, but with no overall survival differences (P=0.8477).

■ **Prayongrat A, et al. Clinical outcomes of intensity modulated proton therapy and concurrent chemotherapy in esophageal carcinoma: a single institutional experience, Adv Radiat Oncol. 2017 Jun 13;2(3):301-307.**

19 patients with esophageal cancer treated with IMPT to a median dose of 50.4 GyE in 28 fractions concurrently with chemotherapy. Clinical complete response was achieved in 84%. The most common grade 3 acute toxicities were esophagitis and fatigue. Grade 3 esophageal stricture occurred in 1 patient.

■ **Shiraishi Y, et al. Severe lymphopenia during neoadjuvant chemoradiation for esophageal cancer: A propensity matched analysis of the relative risk of proton versus photon-based radiation therapy, Radiother Oncol. 2017 Dec 13. pii: S0167-8140(17)32751-2.**

This study compared the relative risk of radiation-induced lymphopenia between IMRT or PBT in 480 esophageal cancer (EC) patients undergoing neoadjuvant chemoradiation therapy (nCRT), and found that a greater proportion of the IMRT patients (55/136, 40.4%) developed grade 4 lymphopenia during nCRT compared with the PBT patients (24/136, 17.6%, P < 0.0001).

■ **Verma V et al. Advances in Radiotherapy Management of Esophageal Cancer, J Clin Med. 2016 Oct 21;5(10).**

A prime goal of radiotherapy is to minimize not only treatment toxicities, but also postoperative complications and hospitalization. This review article highlighted studies of proton therapy for esophageal cancer that reported promising survivals and fewer complications. Clinical evidence is limited but the authors highlighted the ongoing prospective trials which will define the role of proton therapy for esophageal cancer.

■ **Chuong M.D. et al. Improving Outcomes for Esophageal Cancer using Proton Beam Therapy. International Journal of Radiation Oncology. Biology. Physics. 2016 May; 95(1):488-97.**

Radiation therapy is an essential part of the treatment for esophageal cancer, there is a need to balance the delivery of appropriately high dose to the target while minimizing dose to nearby critical structures, especially the heart and lungs. Technological advancements like IMRT have decreased the risk of heart and lung toxicities, but a growing body of evidence indicates that further risk reductions are achieved with PT.

■ **Makishima H. et al. Comparison of adverse effects of proton and X-ray chemoradiotherapy for esophageal cancer using an adaptive dose volume histogram analysis. Journal of Radiation Research. 2015 May; 56(3):568-76.**

Cardiopulmonary late toxicity is of concern in concurrent chemoradiotherapy (CCRT) for esophageal cancer. The aim of this study was to examine the benefit of proton therapy using clinical data and adaptive dose-volume histogramanalysis. Irradiation dose, volume and adverse effects on the heart and lung can be reduced using protons; hence proton therapy is a promising treatment modality for the management of esophageal cancer.

■ **Lin S H et al. Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer, Radiother Oncol. 2017 Jun;123(3):376-381.**

Compared postoperative outcomes after neoadjuvant chemoradiation with 3DCRT, IMRT and PBT for esophageal cancer patients, the study assessed pulmonary, GI, cardiac, wound healing complications, length of in-hospital stay (LOS), and 90-day postoperative mortality. IMRT and PBT were associated with significantly reduced rate of postoperative complications and LOS compared to 3D, with PBT displaying the greatest benefit in a number of clinical endpoints.

OTHER GASTROINTESTINAL CANCERS

■ **Vaios EJ and Wo JY. Proton beam radiotherapy for anal and rectal cancers. J Gastrointest Oncol. 2020 Feb;11(1):176-186.**

A review article looked at the current status of PBT for anal and rectal cancers. PBT offers appealing potential to reduce toxicity, increase patient compliance, minimize treatment breaks, and enable dose escalation or hypofractionation. However, data on the benefit of PBT for rectal and anal cancer is derived primarily from planning studies for neoadjuvant treatment, therefore unclear about the meaningful differences in acute and late toxicity.

■ **Patel SA et al. Advancing Techniques of Radiation Therapy for Rectal Cancer. Semin Radiat Oncol. 2016 Jul;26(3):220-5.**

A review article looked into advanced radiotherapy technologies and techniques that allow for improved dose conformality to target structures while limiting irradiation of surrounding normal tissue. It reported that dosimetric analyses showed that proton therapy reduced normal tissue exposure compared with 3DCRT and IMRT but it is awaiting clinical evaluation whether this dose reduction will lead to differences in acute or late toxicity.

■ **Ojerholm E. et al. Pencil-beam scanning proton therapy for anal cancer: a dosimetric comparison with intensity-modulated radiotherapy. Acta Oncologica. 2015 Mar 3:1-9.**

Concurrent chemoradiotherapy cures most patients with anal squamous cell carcinoma at the cost of significant treatment-related toxicities. IMRT reduces side effects compared to older techniques, PT offers additional advantages by reducing low dose radiation to important organs at risk.

■ **Plastaras J.P., Dionisi F. and Wo J.Y. Gastrointestinal cancer: non-liver proton therapy for gastrointestinal cancers. Cancer Journal. 2014 November-December; 20(6):378-86.**

Multimodality therapy for gastrointestinal cancers carries considerable risk for toxicity, as they inherently occur amid visceral organs particularly sensitive to radiotherapy. In many sites, local recurrences after chemoradiation pose a particular challenge, and reirradiation in these sites may be done successfully with PT.

■ **Colaco R.J. et al. Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal cancer. Journal of Gastrointestinal Oncology. 2014 February; 5(1):3-8.**

This study compares 3D conformal RT, IMRT and PT plans in patients undergoing neoadjuvant chemoradiation for resectable rectal cancer. By reducing bone marrow exposure, PT may reduce the acute hematologic toxicity of neoadjuvant chemoradiation.

GYNECOLOGIC CANCERS

■ **Anderson JD, et al. Outcomes of Proton Beam Therapy Compared With Intensity-Modulated Radiation Therapy for Uterine Cancer. Int J Part Ther. 2022 Nov 14;9(3):10-17.**

This study reported results of patients with uterine cancer treated with PT (n=22) and IMRT (n=45). When comparing gynecologic-specific subset of PRO-CTCAE, PT was associated with less diarrhea at EOT (P = .01) and at 12 months (P = .24) than IMRT. Loss of bowel control at 12 months was more common in patients receiving IMRT (P = .15). Any patient reporting grade 3+ GI toxicity was noted more frequently with IMRT (31% versus 9%, P = .09). The authors concluded that adjuvant PT is a promising treatment for patients with uterine cancer and may reduce patient-reported GI toxicity as compared with IMRT.

■ **Arians N, et al. Treatment tolerability and toxicity of postoperative proton beam therapy for gynecological malignancies - results of the prospective phase II APROVE-trial. Int J Radiat Oncol Biol Phys. 2023 Jul 15;116(4):825-836.**

This study reported the safety of postoperative PBT in 25 patients with uterine cervical or endometrial cancer. There was no patient developed GI or GU toxicity ≥ grade 3, the treatment tolerability rate was 100%. With a median follow-up time 25.1 months, 7 patients had progressive disease. The authors concluded that postoperative IMPT is a safe treatment option for cervical and endometrial cancer patients with only low-grade acute and late toxicities.

■ **Meixner E, et al. Health-related quality of life and patient-reported symptoms after postoperative proton beam radiotherapy of cervical and endometrial cancer: 2-year results of the prospective phase II APROVE-trial. Radiat Oncol. 2023 Jan 9;18(1):5.**

The same study as above reported QoL significantly (p = 0.036) improved and evened out to comparable norm values 2 years after proton therapy. Treatment caused acute and long-term worsening of pain (p = 0.048) and gastrointestinal symptoms (p = 0.016) for women with endometrial cancer, but no higher-grade CTCAE ≥ 3° toxicity was observed. After 2 years, fatigue had significantly improved (p = 0.030), whereas patients with cervical cancer experienced more often lymphedema (p = 0.017). Scores for endometrial cancer pertaining to sexual activity (p = 0.048) and body image (p = 0.022) had improved post treatment.

■ **Berlin E, et al. Acute and long-term toxicity of whole pelvis proton radiation therapy for definitive or adjuvant management of gynecologic cancers. Gynecol Oncol. 2023 May:172:92-97.**

This study reported outcomes of 23 patients with gynecologic malignancies treated with PBSPRT. 12 (52.2%) patients had uterine cancer, 10 (43.5%) cervical, and 1 (4.3%) vaginal. Median follow up was 4.8 years. 5-year actuarial LC was 95.2%, regional control 90.9%, distant control 74.7% and OS 91.3%. 2 patients (8.7%) had acute G2 GU toxicity, 6 (26.1%) acute GI G2-3 toxicity, and 17 (73.9%) acute G2-4 hematologic toxicity. 3 (13.0%) patients had late G2 GU toxicity, 1 (4.3%) late G2 GI toxicity, 2 (8.7%) late G2-3 hematologic toxicity.

■ **Arians N, et al. Prospective phase-II-study evaluating postoperative radiotherapy of cervical and endometrial cancer patients using protons - the APROVE-trial. Radiat Oncol. 2017 Nov 28;12(1):188.**

The APROVE study is a prospective single-center one-arm phase-II-study, targeting to enroll 25 patients with cervical or endometrial cancer after surgical resection who have an indication for postoperative pelvic radiotherapy who were treated with proton therapy instead of the commonly used photon radiation.

■ **Lin LL et al. Initial Report of Pencil Beam Scanning Proton Therapy for Posthysterectomy Patients With Gynecologic Cancer. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):181-9.**

This study reported acute toxicities of eleven patients with posthysterectomy gynecologic cancer (cervical in 7, vaginal in 1, and endometrial in 3) who received PBS to the whole pelvis. A dosimetric comparison between PBS and IMRT plan was also conducted. The results have demonstrated the clinical feasibility of PBS and the dosimetric advantages.

■ **van de Sande MA et al. Which cervical and endometrial cancer patients will benefit most from intensity-modulated proton therapy?. Radiother Oncol. 2016 Sep;120(3):397-403.**

A dosimetric comparison study that showed IMPT with robust planning reduces dose to surrounding organs in cervical and endometrial cancer treatment compared with IMRT. Especially for the para-aortic region, clinically relevant dose reductions were obtained for kidneys, spinal cord and bowel, justifying the use of proton therapy for this indication.

■ **Hashimoto S et al. Whole-pelvic radiotherapy with spot-scanning proton beams for uterine cervical cancer: a planning study. J Radiat Res. 2016 Sep;57(5):524-532.**

This study compared the dosimetric parameters of whole-pelvic radiotherapy for cervical cancer among plans involving 3D-CRT, IMRT, or SSPT for 10 cervical cancer patients. SSPT can reduce the irradiated volume of the organs at risk compared with 3D-CRT and IMRT, while maintaining excellent PTV coverage.

■ **van de Schoot AJ et al. Dosimetric advantages of proton therapy compared with photon therapy using an adaptive strategy in cervical cancer. Acta Oncol. 2016 Jul;55(7):892-9.**

This dosimetric study compared image guided adaptive proton therapy (IGAPT) with photon-based image-guided adaptive RT (IGART) for 13 cervical cancer patients. Compared to photon-based IGART, IGAPT maintains target coverage while significant dose reductions for the bladder, bowel and rectum can be achieved.

■ **Dinges E et al. Bone marrow sparing in intensity modulated proton therapy for cervical cancer: Efficacy and robustness under range and setup uncertainties. Radiother Oncol. 2015 Jun;115(3):373-8.**

This study evaluates the potential efficacy and robustness of functional bone marrow sparing (BMS) using intensity-modulated proton therapy (IMPT) for cervical cancer, with the goal of reducing hematologic toxicity. The results showed that the potential sparing of functional bone marrow by IMPT for cervical cancer is significant and robust under realistic systematic range uncertainties and clinically relevant setup errors.

PROSTATE CANCERS

■ **Kharod SM, et al. Postoperative or Salvage Proton Radiotherapy for Prostate Cancer After Radical Prostatectomy. Int J Part Ther. 2021 Mar 12;7(4):52-64.**

102 patients were treated with proton radiation after prostatectomy to the prostate bed or to prostate-bed and pelvic-node. With a median follow-up of 5.5 years, the study reported 5-year biochemical relapse-free and distant metastases-free survival rates were 57% and 97% overall. Acute and late grade 3 or higher genitourinary toxicity rates were 1% and 7%. No patients had grade 3 or higher gastrointestinal toxicity. Acute and late grade 2 gastrointestinal toxicities were 5% and 2%.

■ **Kubeš J, et al. Ultra-hypofractionated proton radiotherapy in the treatment of low- and intermediate-risk prostate cancer – 5-years outcomes. Int J Radiat Oncol Biol Phys. 2021 Jul 15;110(4):1090-1097.**

This study reported the 5-year clinical outcomes of 279 patients with low and intermediate risk prostate cancer treated with hypofractionated PBT (36.25 GyE/5 fractions). The 5-year bDFS was 96.9%, 91.7 and 83.5% for the low-, favorable and unfavorable intermediate-risk group, respectively. Late toxicity was: GI: G1-62 patients (22%), G2-20 (7.2%), G3-1 (0.36%); GU: G1-80 (28.7%), G2-14 (5%), no G3 toxicity was observed. PSA relapse was observed in 17 patients (6.1%), lymph node or bone recurrence was detected in 11 patients.

■ **Vapiwala N, et al. A Pooled Toxicity Analysis of Moderately Hypofractionated Proton Beam Therapy and Intensity-Modulated Radiation Therapy in Early Stage Prostate Cancer Patients. Int J Radiat Oncol Biol Phys. 2021 Jul 15;110(4):1082-1089.**

This multi-institutional study compared late toxicity profiles of a total of 1850 patients, including 1282 IMRT and 568 PBT. Overall toxicity rates were low, with the majority of patients experiencing no late GU (56.6%, n=1048) or late GI (74.4%, n=1377) toxicity. No difference was seen in the rates of late toxicity between the groups, with late Grade 3+ GU toxicity of 2.0% vs 3.9%, and late Grade 2+ GI toxicity of 14.6% vs 4.7%, for the PBT and IMRT cohorts respectively.

■ **Agrawal R, et al. Pattern of Radiotherapy Treatment in Low-Risk, Intermediate-Risk, and High-Risk Prostate Cancer Patients: Analysis of National Cancer Database. Cancers (Basel). 2022 Nov 9;14(22):5503.**

With the data from the National Cancer Database, this study reported that the most utilized treatment modality for all PCa patients was IMRT (53.1%). Over the years, a steady increase in SBRT utilization was observed, whereas BT HDR usage declined. IMRT-treated patient groups exhibited relatively lower survival probability in all risk categories. BT, SBRT, and IMRT+BT exhibited similar survival rates. A slightly better survival probability was observed for the PT group across all risk groups.

■ **Choo R, et al. Late Toxicity of Moderately Hypofractionated Intensity-Modulated Proton Therapy Treating the Prostate and Pelvic Lymph Nodes for High-Risk Prostate Cancer. Int J Radiat Oncol Biol Phys. 2023 Apr 1;115(5):1085-1094.**

This study reported the late GI and GU toxicities of 54 patients with high-risk or unfavorable intermediate risk prostate cancer treated with IMPT to a total dose of 67.5 GyRBE to the prostate and 45 GyRBE to pelvic lymph nodes in 25 daily fractions. Median follow-up was 43.9 months. The actuarial rate of late grade ≥2 GI toxicity at both 2 and 3 years was 7.4%. The actuarial rate of late grade 3 GI toxicity at both 2 and 3 years was 1.9%. The actuarial rate of late grade ≥2 GU toxicity was 20.5% at 2 years, and 29.2 % at 3 years. None had grade 3 GU toxicity.

■ **Hasan S, et al. Proton therapy for high-risk prostate cancer: Results from the Proton Collaborative Group PCG 001-09 prospective registry trial. Prostate. 2023 Jun;83(9):850-856.**

Based on the PCG registry data, this is the largest study evaluating outcomes of 605 patients with localized high-risk prostate cancer (HRPC) treated with proton therapy. At a median follow-up of 22 months, the 3- and 5-year freedom from progression were 90.7% and 81.4%, respectively. Five-year metastasis free survival and OS were 92.8% and 95.9%, respectively. No grade 4 or 5 adverse events were reported. There were 23 (5%) grade 2 and 0 grade 3 GI events. The authors concluded that these early outcomes using proton therapy for HRPC were encouraging.

■ **Sosa AJ, et al. Proton therapy for the management of localized prostate cancer: Long-term clinical outcomes at a comprehensive cancer center. Radiother Oncol. 2023 Nov:188:109854.**

This study reported clinical outcomes of 2772 patients with localized prostate cancer including low (LR, n = 640), favorable-intermediate (F-IR, n = 850), unfavorable-intermediate (U-IR, n = 851), high (HR, n = 315), and very high (VHR, n = 116) treated with proton therapy. FFBR rates at 5 years and 10 years were 98.2% and 96.8% for the LR group; 98.3% and 93.6%, F-IR; 94.2% and 90.2%, U-IR; 94.3% and 85.2%, HR; and 86.1% and 68.5%, VHR. Overall rates of late grade ≥ 3 GU and GI toxicity were 0.87% and 1.01%.

■ **Kubeš J, et al. 5-Years Analysis of Effectivity and Toxicity of Ultra-Hypofractionated Proton Radiotherapy in the Treatment of Low- and Intermediate-Risk Prostate Cancer-A Retrospective Analysis. Cancers (Basel). 2023 Sep 15;15(18):4571.**

This study reported clinical outcomes of 853 patients treated with an ultra-hypofractionated schedule (36.25 GyE/five fractions). There were 318 (37.3%), 314 (36.8%), and 221 (25.9%) patients at low (LR), favorable intermediate (F-IR), and unfavorable intermediate risk (U-IR). The whole group of patients reached median follow-up time at 62.7 months. Estimated 5-year bDFS rates were 96.5%, 93.7%, and 91.2% for low-, favorable intermediate-, and unfavorable intermediate-risk groups, respectively. Cumulative late toxicity of G2+ was GI: G2: 9.1%; G3: 0.5%; GU: G2: 4.3%, and no G3 toxicity was observed. PSA relapse was observed in 58 (6.8%) patients.

■ **Bai M, et al. Comparing bowel and urinary domains of patient-reported quality of life at the end of and 3 months post radiotherapy between intensity-modulated radiotherapy and proton beam therapy for clinically localized prostate cancer. Cancer Med. 2020 Nov;9(21):7925-7934.**

This study compared the bowel function (BF), urinary irritative/obstructive symptoms (UO), and urinary incontinence (UI) domains of EPIC-26 collected in 262 patients with T1-T2 prostate cancer receied IMRT (157 patients) or PBT (105 patients). At 3 months post-radiotherapy, the IMRT group had significant and clinically meaningful worsening of BF (-9.3, P < .001). There were no significant or clinically meaningful changes in UO or UI 3 months post-radiotherapy. This study concluded that PBT had less acute decrement in BF than IMRT following radiotherapy.

■ **Barsky AR, et al. Comparative Analysis of 5-Year Clinical Outcomes and Patterns of Failure of Proton Beam Therapy (PBT) versus Intensity-Modulated Radiotherapy (IMRT) for Prostate Cancer in the Postoperative Setting. Pract Radiat Oncol. 2021 Mar-Apr;11(2):e195-e202.**

This case-matched study analyzed 260 prostate cancer patients including 65 treated with PBT and 195 IMRT. At a median follow-up of 59 months, biochemical failure (BF), local failure (LF), regional failure (RF), distant failure (DF), and mortality rates were 45% (n=29), 2% (n=1), 9% (n=6), 9% (n=6), and 2% (n=1) for PBT, and 41% (n=80), 3% (n=5), 7% (n=13), 9% (n=18), and 5% (n=9) for IMRT (all p>0.05). Patterns of failure were qualitatively similar between cohorts. This study concluded that PBT yielded similar long-term disease-related outcomes and patterns of failure to IMRT in the post-prostatectomy setting.

■ **Mishra MV, et al. Patient Reported Outcomes Following Proton Pencil Beam Scanning vs. Passive Scatter/Uniform Scanning for Localized Prostate Cancer: Secondary Analysis of PCG 001-09. Clin Transl Radiat Oncol. 2020 Mar 7;22:50-54.**

This study evaluated patient reported EPIC scores of 304 men with localized prostate cancer enrolled in PCG 001-09 (NCT01255748) including 72 patients receiving PBS and 232 receiving PS/US. The analysis showed differences between PBS and PS/US with regards to two-fold minimally important difference in domain scores changes in urinary function at 12 months i.e. 26.9% and 13.2% of men for urinary QOL (P = 0.01), but no differences for average score declines over time.

■ **Slater JM, et al. Hypofractionated Proton Therapy in Early Prostate Cancer: Results of a Phase I/II Trial at Loma Linda University. Int J Part Ther. Summer 2019;6(1):1-9.**

A cohort of 146 patients with low-risk prostate cancer were treated to 60Gy (RBE) of proton therapy (20 fractions of 3.0 Gy per fraction) in 4 weeks. With the median followup of 42 months, this study reported that acute grade 2 urinary toxicity occurred in 16% of the patients; acute grade 2 or higher gastrointestinal toxicity was seen in 1.7%. No grade 3 gastrointestinal toxicities occurred. The 3-year biochemical survival rate was 99.3% (144/145).

■ **Pedersen J, et al. Cross-modality applicability of rectal normal tissue complication probability models from photon- to proton-based radiotherapy. Oncol. 2020 Jan;142:253-260.**

The data of gastrointestinal morbidities (grade≥2) reported by 1151 prostate cancer patients treated with passive scattering PT and 159 patients treated with 3DCRT were analyzed. This study found that photon-based rectal NTCP models either over- or underestimated the clinically observed gastrointestinal morbidity when used on the proton cohort. Large differences were observed in morbidity predictions between cohorts and modalities, therefore NTCP models should be carefully investigated prior to clinical application.

■ **Mishra MV, et al. Proton beam therapy delivered using pencil beam scanning vs. passive scattering/uniform scanning for localized prostate cancer: Comparative toxicity analysis of PCG 001-09. Clin Transl Radiat Oncol. 2019 Aug 31;19:80-86.**

This study compared PBS toxicity rates with those of PS/US in a prospective multicenter registry, for low-to-intermediate risk patients treated with PS/US (n = 1105) or PBS (n = 238). This study found that acute toxicity grade ≥2 GI in PBS did not significantly differ from that of PS/US (2.9% and 2.1%; P = 0.47), but acute grade ≥2 GU toxicity was significantly higher with PBS (21.9% and 15.1%; P < 0.01). Late grade ≥2 GI and GU toxicities did not differ significantly between groups.

■ **Santos PMG, et al. Comparative toxicity outcomes of proton-beam therapy versus intensity-modulated radiotherapy for prostate cancer in the postoperative setting. Cancer. 2019 Dec 1;125(23):4278- 4293.**

307 men (IMRT, n = 237; PBT, n = 70) were identified, generating 70 matched pairs. The study found that although PBT was superior at reducing low-range (volumes receiving 10% to 40% of the dose) bladder and rectal doses (all P ≤ .01), treatment modality was not associated with differences in acute or late GU/GI toxicities (all P ≥ .05). Five-year grade ≥2 GU toxicity free survival was 61.1% for IMRT and 70.7% for PBT; and 5-year grade ≥3 GU and GI toxicity free survival was>95% for both groups (all P ≥ .05).

■ **Kubeš J, et al. Extreme hypofractionated proton radiotherapy for prostate cancer using pencil beam scanning: Dosimetry, acute toxicity and preliminary results. J Med Imaging Radiat Oncol. 2019 Dec;63(6):829-835.**

200 patients with early-stage prostate cancer were treated with IMPT on extreme hypofractionated schedule of 36.25 GyE in five fractions. With the median follow-up of 36 months, this study reported acute toxicity was GI G2-3.5%; GU G2-19%; and no G3 toxicity; late toxicity was GI G2-5.5%; GU G2-4%; and no G3 toxicity. PSA relapse was observed in one patient (1.08%) in the low-risk group and in seven patients (6.5%) in the intermediate-risk group.

■ **Ishikawa H, et al. Particle therapy for prostate cancer: The past, present and future. Int J Urol. 2019 Oct;26(10):971-979.**

Due to a lack of direct evidence, the superiority of particle beam RT over photon beam RT for prostate cancer has not been confirmed in terms of the rates of overall survival or bRFS. The available data reviewed showed that treatment efficacy and toxicity with particle beam RT have consistently been acceptable. Although large-scale randomized study are necessary, but particle beam RT seems a reasonable RT method delivering a high RT dose safely.

■ **Ishikawa H, Tsuji H, Murayama S, Sugimoto M, et al. Particle therapy for prostate cancer: The past, present and future. Int J Urol. 2019 Jul 8.**

Both protons and carbon ions offer advantageous physical properties for radiotherapy, and create favorable dose distributions using fewer portals compared with photon-based radiotherapy. This review examined the results from studies of particle beam therapy for prostate cancer and discuss future developments in this field.

■ **Grewal AS, Schonewolf C, Min EJ, et al. Four-year outcomes from a prospective phase II clinical trial of moderately hypofractionated proton therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2019 Jun 11. pii: S0360-3016(19)30827-2.**

184 men with low to intermediate-risk prostate cancer were treated to 70GyRBE in 28 fractions. Four-year rates of biochemical failure free survival were 93.5%. The 4-year incidence of late grade 2 or higher urologic and gastrointestinal toxicity was 7.6% and 13.6%. One late grade 3 GI toxicity was reported. All late toxicities were transient. IPSS, IIEF and EPIC scores had no significant long term changes.

■ **Dutz A, Agolli L, Baumann M, et al. Early and late side effects, dosimetric parameters and quality of life after proton beam therapy and IMRT for prostate cancer: a matched-pair analysis. Acta Oncol. 2019 Jun;58(6):916-925.**

Eighty-eight patients with localized prostate cancer treated with PBT (31) or IMRT (57) were matched using propensity score. This study reported no significant differences in GI and GU toxicities between both treatment groups except for late urinary urgency, which was significantly lower after PBT (IMRT: 25.0%, PBT: 0%, p = .047). The change of constipation was significantly better at 3 months after PBT compared to IMRT (p = .034).

■ **Holtzman AL, Bryant CM, Mendenhall NP, et al. Patient-Reported Sexual Survivorship Following High-Dose Image-Guided Proton Therapy for Prostate Cancer. Radiother Oncol. 2019 May;134:204-210.**

A study aimed to identify baseline predictive factors that impact long-term erectile function. 676 potent men at base line with localized prostate cancer treated with HD-IGRT (high dose image-guided) protons alone. This study found that baseline response to EPIC Q57 (ability to have an erection) and pre-existing heart disease are two factors enabling prediction of sexual function.

■ **Hoshina RM, Matsuura T, Umegaki K and Shimizu S. A Literature Review of Proton Beam Therapy for Prostate Cancer in Japan. J Clin Med. 2019 Jan 5;8(1). pii: E48.**

A literature review on published works related to PBT for prostate cancer in Japan. This review concluded that PBT can be a suitable treatment option for localized prostate cancer, and despite the favorable results of PBT, future research should include more patients and longer follow-up schedules to clarify the definitive role of PBT.

■ **Ha B, Cho KH, Lee KH, et al. Long-term results of a phase II study of hypofractionated proton therapy for prostate cancer: moderate versus extreme hypofractionation. Radiat Oncol. 2019 Jan 10;14(1):4.**

Eighty-two patients were randomized to the moderate hypofractionated (MHF, 60GyRBE/20f, 54GyRBE/15f, 47GyRBE/10f) group and the extreme hypofractionated (EHF, 35GyRBE/5f) group. At a median follow-up of 7.5 years, this study reported the 7-year BCFFS of 76.2% for the MHF group and 46.2% for the EHF group (p = 0.005). Late GI and GU toxicities did not differ between groups.

■ **Vargas CE, Schmidt MQ Niska JR, et al. Initial toxicity, quality-of-life outcomes, and dosimetric impact in a randomized phase 3 trial of hypofractionated versus standard fractionated proton therapy for low-risk prostate cancer. Adv Radiat Oncol. 2018 Feb 23;3(3):322-330.**

This study compared 38 Gy(RBE) in 5 fractions versus 79.2 Gy RBE in 44 fractions. With the median follow-up 36 months, the study reported low AE rates in both arms, and early temporary differences in genitourinary scores disappeared over time. There were no differences in the EPIC domains of bowel symptoms, sexual symptoms, or bowel ≥G2 toxicities.

■ **Lee HJ Jr, Macomber MW, Spraker MB, et al. Early toxicity and patient reported quality-of-life in patients receiving proton therapy for localized prostate cancer: a single institutional review of prospectively recorded outcomes. Radiat Oncol. 2018 Sep 17;13(1):179**

192 patients of localized prostate cancer treated with protons were followed up for median 1.7 years. The grade 3 toxicity was seen in 5 patients and no grade 4 or 5 toxicity. IPSS score showed no change in urinary function post-radiation. EPIC bowel domain scores declined from 96 at baseline (median) by an average of 5.4 points at 1-year post-treatment, with no further decrease over time.

■ **Royce TJ and Efstathiou JA. Proton therapy for prostate cancer: A review of the rationale, evidence, and current state. Urol Oncol. 2018 Dec 4. pii: S1078-1439(18)30460-5.**

A review examined the dosimetric rationale and theoretical benefit of proton radiation for prostate cancer and the current state of the clinical evidence for efficacy and toxicity, derived from both large claim-based datasets and prospective patient-reported data.

■ **Nakajima K, et al. Acute toxicity of image-guided hypofractionated proton therapy for localized prostate cancer, Int J Clin Oncol. 2018 Apr;23(2):353-360.**

A study reported toxicity of 526 localized prostate cancer patients treated with proton therapy with hypofractionated (HFPT) and conventional fractionated schemes (CFPT). No grade ≥3 acute toxicity was observed. Among acute genitourinary toxicities, grade 2 rates were 15% in CFPT and 5.9% in HFPT (P ≤ 0.001). There were no significant differences in acute gastrointestinal toxicity between the two groups.

■ **Chuong MD, et al. Minimal toxicity after proton beam therapy for prostate and pelvic nodal irradiation results from the proton collaborative group REG001-09 trial, Acta Oncol. 2018 Mar;57(3):368-374.**

This PCG study evaluated toxicity outcomes for non-metastatic prostate cancer patients who received pelvic radiation therapy. 85 received prostate and pelvic radiation therapy exclusively with PBT. Acute grade 1, 2, and 3 GU toxicity rates were 60, 34.1, and 0%. The study concluded that pelvic radiation therapy using PBT experience significantly less acute GI toxicity than is expected using IMXT.

■ **Ho CK, et al. Long-term outcomes following proton therapy for prostate cancer in young men with a focus on sexual health, Acta Oncol. 2018 May;57(5):582-588.**

A study of 254 men ≤60 years old treated with proton therapy alone for prostate cancer including 56% with low-risk, 42% with intermediate-risk and 2% with high-risk disease, reported excellent results with respect to 7-year biochemical control and 5-year erectile function, without clinically significant urinary incontinence 5 years after proton therapy.

■ **Pan HY, et al. Comparative Toxicities and Cost of Intensity-Modulated Radiotherapy, Proton Radiation, and Stereotactic Body Radiotherapy Among Younger Men With Prostate Cancer, J Clin Oncol. 2018 Jun 20;36(18):1823-1830**

A study on younger than 65 years prostate cancer patients treated with IMRT, SBRT and PRT, using the Commercial Claims database, compared the cumulative incidence of urinary, bowel, and erectile dysfunction toxicities by treatment. PRT patients had a lower risk of composite urinary toxicity and erectile dysfunction, but a higher risk of bowel toxicity.

■ **Iwata H, et al. Long-term outcomes of proton therapy for prostate cancer in Japan: a multi-institutional survey of the Japanese Radiation Oncology Study Group, Cancer Med. 2018 Mar;7(3):677-689.**

An analysis based on data from seven PT centers in Japan, including 215, 520, and 556 patients in the low-risk, intermediate-risk, and high-risk groups, reported 5-year biochemical relapse-free survival and overall survival rates in the low-risk, intermediate-risk, and high-risk groups were 97.0%, 91.1%, and 83.1%, and 98.4%, 96.8%, and 95.2%. The incidence rates of grade 2 or more severe late gastrointestinal and genitourinary toxicities were 4.1% and 4.0%.

■ **Ojerholm E and Bekelman JE. Finding Value for Protons: The Case of Prostate Cancer?, Semin Radiat Oncol. 2018 Apr;28(2):131-137.**

Comparing dosimetric data and clinical outcomes, this review concluded that as to date, clinical data suggests no difference between IMRT and PT in urinary side effects or erectile dysfunction. Results vary in rectal toxicity. Acomparative trial has commenced, the Prostate Advanced Radiation Technologies Investigating Quality of Life (PARTIQoL) trial, to investigate if protons add value over IMRT.

■ **Arimura T, et al. Proton Beam Therapy Alone for Intermediate- or High-Risk Prostate Cancer (PCa): An Institutional Prospective Cohort Study. Cancers (Basel). 2018 Apr 10;10(4).**

218 patients with intermediate- and high-risk PCa who declined androgen deprivation therapy (ADT) were treated with PBT, and reported 5-year progression-free survival rate of 97% and 83%, respectively. The rate of grade 2 or higher late gastrointestinal toxicity was 3.9%. Grade 2 or higher acute and late genitourinary toxicities were observed in 23.5% and 3.4% of patients.

■ **Mendenhall N P et al. Comparison of clinical outcomes with IMRT and proton therapy for prostate cancer. J Clin Oncol 35, 2017 (suppl;)**

Presented at the ASCO 2017, this retrospective study compared the clinical outcomes of prostate patients treated with IMRT and PT, and reported that overall survival and freedom from biochemical progression rates were better with PT group in low and intermediate risk groups but similar in the high risk group.

■ **Takagi M, et al. Long-term outcomes in patients treated with proton therapy for localized prostate cancer. Cancer Med. 2017 Oct;6(10):2234-2243.**

1375 consecutive patients of localized prostate cancer were treated with PT. The median follow-up period was 70 months, the low-, intermediate-, high-, and very high-risk groups, 5-year FFBR was 99%, 91%, 86% and 66%. Grade 2 or higher GI and GU toxicities were 3.9% and 2.0%. The study demonstrated favorable biochemical control of PT for high- and very high-risk patients with lower late GU toxicity.

■ **Henderson R H et al. Five-year outcomes from a prospective trial of image-guided accelerated hypofractionated proton therapy for prostate cancer. Acta Oncol. 2017 Jul;56(7):963-970.**

This prospective trial of 215 prostate cancer patients reported 5-year outcomes. Five-year rates of freedom from biochemical were 95.9%, 98.3%, and 92.7% in the overall group and the low- and intermediate-risk subsets. The study concluded that 5-year outcomes showed high efficacy and minimal toxicity of PT for prostate cancer.

■ **Schroeck F R et al. Cost of New Technologies in Prostate Cancer Treatment: Systematic Review of Costs and Cost Effectiveness of Robotic-assisted Laparoscopic Prostatectomy [RARP], Intensity-modulated Radiotherapy[IMRT], and Proton Beam Therapy [PBT]. Eur Urol. 2017 Mar 30.**

49 literatures covering cost and cost-effectiveness of RARP, IMRT and PBT were identified and analyzed. The authors pointed out that the quality of evidence was low for RARP and IMRT, and very low for proton beam therapy. Given the low quality of evidence and the inconsistencies across studies, the precise difference in costs remains unclear.

■ **Bryant C et al. Controversies in proton therapy for prostate cancer. Chin Clin Oncol. 2016 Aug;5(4):55.**

An article reviewed proton therapy dosimetry advantages and disadvantages, existing data on efficacy and toxicity reported by non-comparative cohorts and comparative studies as well as cost effectiveness data. The authors concluded that proton therapy has the potential to improve the therapeutic ratio in the management of prostate cancer by decreasing toxicity and improving disease control.

■ **Habl G et al. Acute Toxicity and Quality of Life in Patients With Prostate Cancer Treated With Protons or Carbon Ions in a Prospective Randomized Phase II Study--The IPI Trial. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):435-43.**

92 patients with localized prostate cancer were randomized to receive either proton therapy (arm A) or carbon ion therapy (arm B) and treated with a total dose of 66Gy (RBE) administered in 20 fractions. The authors concluded that hypofractionated irradiation using either carbon ions or protons results in comparable acute toxicities and QoL parameters.

■ **Bryant C et al. Five-Year Biochemical Results, Toxicity, and Patient-Reported Quality of Life After Delivery of Dose-Escalated Image Guided Proton Therapy for Prostate Cancer. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):422-34.**

1327 men with localized prostate cancer treated between 2006 and 2010 at the proton center. The median follow up was 5.5 years. The 5-year freedom from biochemical progression rates were 99%, 94%, and 74% in low-risk, intermediate- risk, and high-risk patients, respectively. The actuarial 5-year rates of late grade 3 and above gastrointestinal (GI) and genitourinary (GU) toxicity were 0.6% and 2.9%.

■ **Mendenhall N.P. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. International Journal of Radiation Oncology. Biology. Physics. 2014 March 1; 88(3):596- 602.**

Five-year clinical outcomes with image-guided PT for prostate cancer included extremely high efficacy, minimal physician-assessed toxicity, and excellent patient-reported outcomes.

■ **Wisenbaugh E.S. et al. Proton beam therapy for localized prostate cancer 101: basics, controversies, and facts. Reviews in Urology. 2014; 16(2):67-75.**

PT for prostate cancer has become a source of controversy in the urologic community, and the rapid dissemination and marketing of this technology has led to many patients inquiring about this therapy. This article reviews the basic science of the proton beam and examines the literature so that every urologist is able to comfortably discuss this option with inquiring patients.

■ **Hoppe B.S. et al. Erectile function, incontinence, and other quality of life outcomes following proton therapy for prostate cancer in men 60 years old and younger. Cancer. 2012; 15;118(18):4619-26.**

Young men (60 years old) undergoing PT for treatment of prostate cancer have excellent outcomes with respect to erectile dysfunction, urinary incontinence, and other health-related quality of life parameters during the first 2 years after treatment.

■ **Mendenhall N.P. et al. Early outcomes from three prospective trials of image-guided proton therapy for prostate cancer. International Journal of Radiation Oncology. Biology. Physics. 2012; 1; 82(1):213-21.**

Early outcomes with image-guided PT for prostate cancer suggest high efficacy and minimal toxicity, with only 1.9% grade III genito-urinary symptoms and less than 0.5% grade III gastro-intestinal toxicities.

■ **Nihei K. et al. Multi-institutional Phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities. International Journal of Radiation Oncology. Biology. Physics. 2011; 81 (2):390-6.**

PT is theoretically an excellent modality for external beam radiotherapy, providing an ideal dose distribution. However, it is not clear whether PT for prostate cancer can clinically control toxicities. This prospective study has revealed that PT for localized prostate cancer can achieve a low incidence of late grade II or greater rectal toxicities.

■ **Zietman A.L. et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. Journal of Clinical Oncology (ASCO). 2010; 28 (7):1106-11.**

This randomized controlled trial tests the hypothesis that increasing radiation dose delivered to men with early-stage prostate cancer improves clinical outcomes. The results showed superior long-term cancer control compared to conventional- dose radiation. This was achieved without an increase in grade III late urinary or rectal morbidity.

SARCOMAS

■ **Seidensaal K, et al. The role of combined ion-beam radiotherapy (CIBRT) with protons and carbon ions in a multimodal treatment strategy of inoperable osteosarcoma. Radiother Oncol. 2021 Jun:159:8-16.**

This study reported the outcomes of 20 patients with primary (N=18), metastatic (N=3), or recurrent (N=2) inoperable pelvic (70%) or craniofacial (30%) osteosarcoma treated with protons up to 54 Gy (RBE) and a carbon ion boost of 18 Gy (RBE). LPFS, DPFS, PFS and OS were 73%, 74%, 60% and 75% after one year and 55%, 65% 65.3%, 45% and 68% after two years, respectively. No acute toxicities > grade III were observed. One case of secondary acute myeloid leukemia (AML) seven months after CIBRT for recurrent disease and one case of hearing loss.

■ **Worawongsakul R, et al. Proton Therapy for Primary Bone Malignancy of the Pelvic and Lumbar Region - Data From the Prospective Registries ProReg and KiProReg. Front Oncol. 2022 Feb 16:12:805051.**

Eighty-one patients with primary bone malignancy, including Ewing's sarcoma (58%), chondrosarcoma (7.4%), chordoma (24.7%), osteosarcoma (7.4%), and osteoblastoma (2.5%), of the pelvis and lumbar spine treated with PT. With a median follow up of 27.5 months, 2-year and 3-year OS for all patients in this cohort were 88.1 and 68.9%, respectively. 2-year and 3-year LC were 76.5 and 72.9%, respectively. Higher-grade late toxicities were found in seven out of 67 patients (10.4%).

■ **Schmid MP, et al. Particle Therapy in Adult Patients with Pelvic Ewing Sarcoma-Tumor and Treatment Characteristics and Early Clinical Outcomes. Cancers (Basel). 2022 Dec 8;14(24):6045.**

This study reported early outcomes of 21 adult pelvic Ewing sarcoma treated with PT (n=18 primary disease) to a total dose of 45-60 GyRBE and with carbon ion (n=3 recurrent disease). Grade 1-2 skin reactions (n = 16/21) and fatigue (n = 9/21) were the main reported toxicities. After a median follow-up of 21 months, the 2-year LC, DC and OS were 76%, 56% and 86%, respectively.

■ **Guttmann DM et al. A prospective study of proton reirradiation for recurrent and secondary soft tissue sarcoma, Radiother Oncol. 2017 Jul 8.**

Proton reirradiation of recurrent/secondary soft tissue sarcomas is well tolerated. No grade 4-5 toxicities were observed. The 3-year cumulative incidence of local failure was 41%. Median overall survival and progression-free survival were 44 and 29 months, respectively. In extremity patients, amputation was spared in 7/10 (70%).

■ **Demizu Y et al. Particle Therapy Using Protons or Carbon Ions for Unresectable or Incompletely Resected Bone and Soft Tissue Sarcomas of the Pelvis,Int J Radiat Oncol Biol Phys. 2017 Jun 1;98(2):367-374.**

This retrospective study analyzed outcomes of 91 unresectable or incompletely resected pelvic sarcomas who underwent particle therapy with protons (52 patients) or carbon ions (39 patients). All patients received a dose of 70.4 GyRBE in 32 fractions or 16 fractions. The study reported 3-year OS, PFS, and LC was 83%, 72%, and 92%. Late grade ≥3 toxicities were observed in 23 patients.

■ **Demizu Y et al. Proton beam therapy for bone sarcomas of the skull base and spine: A retrospective nationwide multicenter study in Japan. Cancer Sci. 2017 May;108(5):972-977.**

A retrospective, nationwide multicenter study in Japan evaluated the clinical outcomes of PBT for bone sarcomas of the skull base and spine including chordoma, chondrosarcoma and osteosarcoma. The most frequent tumor locations were the skull base and the sacral spine. The study reported the 5-year overall survival, progression-free survival, and local control rates were 75.3%, 49.6%, and 71.1%, respectively, and acute Grade 3 and late toxicities of ≥Grade 3 were observed in 9.4% patients.

■ **Frisch S et al. The Evolving Role of Proton Beam Therapy for Sarcomas. Clin Oncol (R Coll Radiol). 2017 Aug;29(8):500-506.**

This review evaluates current data from clinical and dosimetric trials on the treatment of selected sarcomatous tumours. Proton therapy has been safely applied with encouraging results and advanced techniques such as pencil beam scanning and intensity modulation are increasingly established in proton therapy.

■ **Weber DC 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.**

PT was delivered to 151 (68%) and 71 (32%) chordoma and chondrosarcoma (ChSa) patients. With a mean follow-up of 50 (range, 4-176) months, the estimated 7-year distant metastasis-free- and overall survival rate was 91.6% and 81.7%, and the 7-year high grade toxicity-free survival was 87.2%. PBS PT is an effective treatment for skull base tumors with acceptable late toxicity.

■ **Indelicato DJ et al. A Prospective Outcomes Study of Proton Therapy for Chordomas and Chondrosarcomas of the Spine. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):297-303.**

51 patients with chordoma (n=34) or chondrosarcomas (n=17) of the sacrum (n=21), the cervical spine (n=20), and the thoracolumbar spine (n=10) were treated with external beam proton therapy to a median dose of 70.2 Gy(RBE). High-dose proton therapy controls more than half of spinal chordomas and chondrosarcomas and compares favorably with historic photon data.

■ **Rotondo RL et al. High-dose proton-based radiation therapy in the management of spine chordomas: outcomes and clinicopathological prognostic factors. J Neurosurg Spine. 2015 Dec;23(6):788-97.**

A retrospective review of 126 treated patients treated to a mean dose of 72.4 GyRBE, reported that the 5-year overall survival (OS), local control (LC), locoregional control (LRC), and distant control (DC) for the entire cohort were 81%, 62%, 60%, and 77%, respectively. High-dose proton-based RT in the management of spinal chordomas can be effective treatment.

■ **Ciernik I.F. et al. Proton-based radiotherapy for unresectable or incompletely resected osteosarcoma. Cancer. 2011; 117(19):4522-30.**

A study was undertaken to assess clinical outcomes and the role of PT for local control of osteosarcoma. It was shown that the ability of PT to deliver high radiotherapy doses allows locally curative treatment for some patients with unresectable or incompletely resected osteosarcoma.

PEDIATRIC CANCERS

■ **Jazmati D, et al. Proton Beam Therapy for Children With Neuroblastoma: Experiences From the Prospective Ki-ProReg Registry. Front Oncol. 2021 Jan 20:10:617506.**

44 patients with high-risk (n = 39) or intermediate-risk (n = 5) neuroblastoma were treated with protons. With a median follow-up of 27.6 months, eight patients developed progression including local recurrence (n =1) or distant metastases (n = 7). At three years, the estimated local control, distant metastatic free survival, progression free survival, and overall survival was 97.7, 84.1, 81.8, and 90.9%, respectively.

■ **Indelicato DJ, et al. Proton Therapy for Pediatric Ependymoma: Mature Results from a Bicentric Study. Int J Radiat Oncol Biol Phys. 2021 Jul 1;110(3):815-820.**

386 children with nonmetastatic grade II/III intracranial ependymoma received proton therapy. With the median follow-up of 5 years, the 7-year local control, progression-free survival and overall survival rates were 77.0%, 63.8% and 82.2%. The cumulative incidence of grade 2+ brainstem toxicity was 4%. The second-malignancy rate was 0.8%. The authors concluded that proton therapy offers commensurate disease control to modern photon therapy without unexpected toxicity. The high rate of long-term survival justifies efforts to reduce radiation exposure in this young population.

■ **Gaito S, et al. Skin Toxicity Profile of Photon Radiotherapy versus Proton Beam Therapy in Paediatric and Young Adult Patients with Sarcomas. Clin Oncol (R Coll Radiol). 2021 Aug;33(8):507-516.**

This study reported that among 79 pediatric/young adult patients evaluated, 47.9% (23/48) of XRT patients and 48.4% (15/31) of PBT patients had acute grade 2/3 toxicity. For the late RIST, 17.5% (7/40 with known toxicity profile) of XRT patients and 29.0% (9/31) of PBT patients had grade 1/2 toxicity. This difference of -11.5% in grade 1/2 toxicity between XRT and PBT was not statistically significant (P = 0.25).

■ **Weusthof K, et al. Neurocognitive Outcomes in Pediatric Patients Following Brain Irradiation. Cancers (Basel). 2021 Jul 15;13(14):3538.**

For the 103 pediatric brain tumor patients (proton RT n = 26, photon RT n = 30, surgery n = 47) evaluated in this study, neurocognitive outcomes after RT and surgery showed no significant differences in any neurocognitive domain. Long-term follow up over four years after photon RT showed a decrease in non-verbal intelligence (-9.6%; p = 0.01) and visuospatial construction (-14.9%; p = 0.02). There were no alterations in long-term neurocognitive abilities after proton RT.

■ **Spiotto MT, et al. Proton Radiotherapy to Reduce Late Complications in Childhood Head and Neck Cancers. Int J Part Ther. 2021 Jun 25;8(1):155-167.**

This review compared the efficacy and expected toxicities in proton and photon radiotherapy for childhood cancers and evaluated the benefit of proton radiotherapy in reducing acute and late radiation toxicities, including risks for secondary cancers, craniofacial development, vision, and cognition. This review highlights the benefits of improving the quality of life in cancer survivors, to reduce radiation morbidities, and to maximize efficient health care use.

■ **Yoo GS, et al. Chronological Analysis of Acute Hematological Outcomes after Proton and Photon Beam Craniospinal Irradiation in Pediatric Brain Tumors. Cancer Res Treat. 2022 Jul;54(3):907-916.**

This study reviewed 66 pediatric brain tumor patients who received either proton beam craniospinal irradiation (PrCSI) (n=36) or photon beam craniospinal irradiation (PhCSI) (n=30), and found absolute lymphocyte counts and platelet counts significantly lower in the PhCSI group than in PrCSI group at every timepoint. The rate of grade 3 acute anemia was significantly lower in the PrCSI group than in in the PhCSI group.

■ **Indelicato DJ, et al. Bicentric Treatment Outcomes following Proton Therapy for Non-Myxopapillary High-Grade Spinal Cord Ependymoma in Children. Int J Radiat Oncol Biol Phys. 2022 Feb 1;112(2):335-341.**

Published in the Red Journal, this study reported outcomes of 14 pediatric patients with non-metastatic non-myxopapillary grade II (n=6) and grade III (n=8) spinal ependymoma treated with proton therapy. With a median follow-up of 6.3 years, no tumors progressed; 1 patient developed additional neurologic deficits following radiation, 1 case of grade 2 erectile dysfunction and 2 cases of musculoskeletal toxicity; no patient had developed cardiac, pulmonary, or other visceral organ complications, nor a second malignancy.

■ **Aldrich KD, et al. Comparison of hypothyroidism, growth hormone deficiency, and adrenal insufficiency following proton and photon radiotherapy in children with medulloblastoma. J Neurooncol. 2021 Oct;155(1):93-100.**

For the 118 patients with medulloblastoma who were treated with cranial spinal irradiation and followed for a median of 5.6 years, the study found 31% patients developed hypothyroidism, 66% GHD, and 18% AI. Compared to PBT, XRT was associated with a higher incidence of primary hypothyroidism (28% vs. 6%; p = 0.03). Central hypothyroidism, GHD, and AI incidence rates were similar between the groups.

■ **Vennarini S, et al. Acute Hematological Toxicity during Cranio-Spinal Proton Therapy in Pediatric Brain Embryonal Tumors. Cancers (Basel). 2022 Mar 24;14(7):1653.**

This study evaluated the hematological toxicity of 20 pediatric patients with high-risk medulloblastoma and other rare embryonal brain tumors treated with proton CSI. No serious hematological toxicity was observed, therefore no treatment delayed or discontinued. Leucocytes and neutrophils decreased at the beginning of treatment, but completely recovered at the end of treatment. The authors concluded that CSI with PT was proven to be safe in this setting of pediatric patients.

■ **Yip AT, et al. Post-treatment neuroendocrine outcomes among pediatric brain tumor patients: Is there a difference between proton and photon therapy? Clin Transl Radiat Oncol. 2022 Feb 25:34:37-41.**

This study compared the neuroendocrine outcomes of 112 pediatric primary brain tumor patients treated with XRT(n = 80) or PRT (n = 32). With a median follow-up of 6.3 years for XRT and 4.4 years for PRT, the common endocrinopathies occurred were growth hormone deficiency (26% XRT, 38% PRT) and hypothyroidism (29% XRT, 19% PRT). In CSI cohort, PRT patients had less hypothyroidism (p = 0.045). Sex hormone deficiency developed in 17.1% of the XRT CSI group but did not occur in the PRT CSI group.

■ **Warren EAH, et al. Cognitive predictors of social adjustment in pediatric brain tumor survivors treated with photon versus proton radiation therapy. Pediatr Blood Cancer. 2022 Jun;69(6):e29645.**

This study compared the neurocognitive results of patients who received PRT (n = 38) or XRT (n = 20) at least one year after radiotherapy. This study found that the XRT group performed worse than the PRT group on measures of processing speed (p = .01) and verbal memory (p < .01); however, social outcomes with impairment in peer relations and social skills did not differ by radiation type.

■ **Ruggi A, et al. Toxicity and Clinical Results after Proton Therapy for Pediatric Medulloblastoma: A Multi-Centric Retrospective Study. Cancers (Basel). 2022 Jun 1;14(11):2747.**

This study reported toxicities of 43 children with medulloblastoma treated with PBS-PT. The most common (>30% of patients) acute toxicities were radiation dermatitis (n = 28, 65.1%), pharyngeal mucositis (22, 51.2%), nausea (19, 44.1%), non-preexisting alopecia (17 out of 18 without preexisting alopecia, 94.4%), anorexia (16, 37.2%), and fatigue (15, 34.9%). Seven patients (16.3%) developed hearing impairment at follow-up audiometry, in five cases bilateral, in two cases monoliteral at a median time of 9 months after PT.

■ **Partin RE, et al. Physical function, body mass index, and fitness outcomes in children, adolescents, and emerging adults with craniopharyngioma from proton therapy through five years of follow-up. J Neurooncol. 2022 Sep;159(3):713-723.**

This study evaluated the health outcomes of 94 children with craniopharyngioma treated by protons and reported that BMI and knee extension strength had the largest proportion of participants impaired at both 2 and 5 years (53.2% and 62.3%, respectively). Resting heart rate had the highest proportion of participants not impaired at 2 years but became impaired at 5 years (26.6%).

■ **Chevli N, et al. Renal function in abdominal neuroblastoma patients undergoing proton radiotherapy. Pediatr Blood Cancer. 2023 Jan;70(1):e29981.**

This study retrospectively analyzed the renal function of 30 children with abdominal neuroblastoma treated with chemotherapy, resection of primary tumor, then proton therapy. Median follow-up after PT was 35 months. No patients developed hypertension or renal dysfunction during follow-up. There was no statistically significant change in serum blood urea nitrogen and creatinine clearance between pre-PT and last follow-up.

■ **Peters S, et al. Proton Beam Therapy for Pediatric Tumors of the Central Nervous System-Experiences of Clinical Outcome and Feasibility from the KiProReg Study. Cancers (Basel). 2022 Nov 28;14(23):5863.**

Based on the registry KiProReg, this study evaluated 294 patients treated by PBT for intracranial tumors including 18 tumor and the most frequent ones being ependymomas and medulloblastomas. The 3-year OS of the whole cohort was 82.7%, PFS 67.3%, and LC 79.5%. Seventeen patients developed grade 3 adverse events of the CNS and two patients developed vision loss (grade 4). The authors concluded that PBT produced promising outcomes and long-term side effects were within the expected ranges.

■ **Weber DC, et al. Quality-of-life evaluations in children and adolescents with Ewing sarcoma treated with pencil-beam-scanning proton therapy. Pediatr Blood Cancer. 2022 Dec;69(12):e29956.**

This study investigated the QoL of patients with Ewing sarcoma treated with PBS-PT. With a PEDQOL questionnaire evaluating eight different domains, this study reported that patients with Ewing sarcoma usually recovered well to normal QoL levels 2 years after the end of PT, however, the children rated emotional functioning and body image poorly 2 years after PT.

■ **Mash LE, et al. Superior verbal learning and memory in pediatric brain tumor survivors treated with proton versus photon radiotherapy. Neuropsychology. 2023 Feb;37(2):204-217.**

This study compared verbal learning and memory of survivors of pediatric brain tumor treated with either XRT (n = 29) or PRT (n = 51) using neuropsychological testing on the frequency of encoding, retrieval, and intact memory profiles over one year following radiotherapy. This study reported overall PRT was associated with verbal memory sparing, driven by effective encoding and use of learning strategies.

■ **Vázquez M, et al. Early outcome after craniospinal irradiation with pencil beam scanning proton therapy for children, adolescents and young adults with brain tumors. Pediatr Blood Cancer. 2023 Feb;70(2):e30087.**

This study reported the clinical outcomes and toxicity rates after PBSPT CSI for 71 children and adolescents and young adults (C-AYAs) with CNS tumors. After a median follow-up of 24.5 months, the estimated 2-year local control, distant control, and overall survival were 86.3%, 80.5%, and 84.7%, respectively. Late grade ≥3 toxicity-free rate was 92.6% at 2 years. The authors concluded that excellent tumor control with low toxicity rates was observed in C-AYAs with brain tumors treated with CSI using PBSPT.

■ **Dong M, et al. Efficacy and safety of proton beam therapy for rhabdomyosarcoma: a systematic review and meta-analysis. Radiat Oncol. 2023 Feb 20;18(1):31.**

Based on 11 original studies that reported outcomes of 544 rhabdomyosarcoma (RMS) children and adolescent patients who received PBT, this review reported that the 5-year rates of LC, PFS and OS were 84%, 76% and 82%. Acute and late toxicities were mainly grades 1 to 2 in all studies. The authors concluded that this data has showed that PBT is a feasible, safe, and effective modality for RMS, showing promising LC, OS, PFS, and lower acute and late toxicities.

■ **Merchant TE, et al. Proton therapy and limited surgery for paediatric and adolescent patients with craniopharyngioma (RT2CR): a single-arm, phase 2 study. Lancet Oncol. 2023 May;24(5):523-534.**

94 craniopharyngioma patients were treated with proton therapy. With a median follow-up time of 7.62 years for the whole cohort, this study reported PFS 96.8% and OS 100% at 3 years. At 5 years, necrosis had occurred in two (2%), severe vasculopathy in four (4%), and permanent neurological conditions in three (3%) patients. Compared to historical photon cohort, proton therapy did not improve survival outcomes and severe complication rates were similar. However, cognitive outcomes with proton therapy were improved over photon therapy.

■ **Ioakeim-Ioannidou M, et al. Surgery and Proton Radiation Therapy for Pediatric Base of Skull Chordomas: Long-term Clinical Outcomes for 204 patients. Neuro Oncol. 2023 Sep 5;25(9):1686-1697.**

204 pediatric patients with chordomas were treated by surgery and proton radiotherapy. Median OS and PFS were 26 and 25 years, with 5-, 10-, and 20-year OS and PFS rates of 84% and 74%, 78% and 69%, and 64% and 64%, respectively. 24 (12%) patients developed late toxicities, and 4 (2%) developed secondary radiation-related malignancies. The authors concluded that results of this largest cohort of skull base chordomas demonstrated high-dose PRT following surgical resection is effective with low rates of late toxicity.

■ **Roehrig A, et al. Radiotherapy for Atypical Teratoid/Rhabdoid Tumor (ATRT) on the Pediatric Proton/Photon Consortium Registry (PPCR). J Neurooncol. 2023 Apr;162(2):353-362.**

This study evaluated 68 patients with atypical teratoid/rhabdoid tumors (ATRT) treated with surgery (65% initial gross total resection or GTR), chemotherapy (60% with myeloablative therapy including stem cell rescue) and RT. The study found no difference in LC at 4 years between lower primary dose (50-53.9 Gy) compared to ≥ 54 Gy (p = 0.83). The 4-year OS comparing focal RT with CSI was 54.4% vs 60% respectively (p = 0.944).

■ **Fukushima H, et al. Gastrointestinal bleeding/ulcer among paediatric cancer patients after proton beam therapy. Jpn J Clin Oncol. 2023 Jun 1;53(6):501-507.**

This study analyzed 124 patients who underwent proton therapy with gastrointestinal tract involved in the irradiated field. The study reported gastrointestinal bleeding/ulcer occurred in 4 patients (3.2%), with no death due to the bleeding/ulcer. The authors suggested that upper gastrointestinal irradiation in older children undergoing intensive chemotherapy may increase the risk of developing gastrointestinal complications.

■ **Lassaletta Á, et al. Neurocognitive outcomes in pediatric brain tumors after treatment with proton versus photon radiation: a systematic review and meta-analysis. World J Pediatr. 2023 Aug;19(8):727-740.**

Based on 10 studies including a total 630 patients, this review reported that proton therapy produced significantly higher scores for most analyzed neurocognitive outcomes (i.e., intelligence quotient, verbal comprehension and perceptual reasoning indices, visual motor integration, and verbal memory). No significant differences were found between the two modalities for nonverbal memory, verbal working memory and working memory index, processing speed index, or focused attention.

■ **Grippin AJ, et al. Proton therapy for pediatric diencephalic tumors. Front Oncol. 2023 May 5:13:1123082.**

Tumors arise in the diencephalon including optic pathway/hypothalamic glioma, craniopharyngioma, germ cell tumors, and pituitary adenomas which tend to be low grade tumors but close to the optic nerves, optic chiasm, pituitary, hypothalamus and hippocampi. This review found overall favorable oncologic outcomes and toxicity profile of proton therapy compared to those of photon-based RT.

■ **Hol MLF, et al. Facial deformation following treatment for pediatric head and neck rhabdomyosarcoma; the difference between treatment modalities. Results of a trans-Atlantic, multicenter cross-sectional cohort study. Pediatr Blood Cancer. 2023 Aug;70(8):e30412.**

With data of 173 pediatric head and neck rhabdomyosarcoma (HNRMS) survivors, this study investigated facial deformation caused by these four treatment modalities. All survivors showed significantly reduced facial growth ($p < .001$) and significantly more asymmetric compared to healthy controls, independent of treatment modality ($p \leq .001$). In survivors with a parameningeal tumor, there was significantly less facial deformation in PT when compared to RT ($p = .009$) and surgery+RT ($p = .007$).

■ **Fukushima H, et al. Longitudinal health-related quality of life analysis in childhood cancer survivors after proton beam therapy. Int J Clin Oncol. 2023 Jul;28(7):928-939.**

This questionnaire-based study included 110 childhood cancer survivors who underwent PBT treatment and 41 survivors who did not undergo PBT treatment. This study found that health-related quality of life (HRQoL) tended to be better in the PBT-group than in the noPBT group with CNS or solid tumors. PBT may avoid reduction in HRQoL in terms of the psychosocial functioning for childhood cancer survivors with CNS tumors.

■ **Elkatatny A, et al. The incidence of radiation-induced moyamoya among pediatric brain tumor patients who received photon radiation versus those who received proton beam therapy: a systematic review. Neurosurg Rev. 2023 Jun 24;46(1):146.**

This review found that the incidence of moyamoya syndrome after receiving proton radiation is almost double that of photon-induced moyamoya syndrome. Patients who received PBT for the management of pediatric brain tumors are more likely to develop moyamoya syndrome at the age of less than 5 years. Most patients with proton-induced moyamoya are more likely to be diagnosed within the first 2 years after the completion of their proton beam therapy.

■ **Vennarini S, et al. Clinical Insight on Proton Therapy for Paediatric Rhabdomyosarcoma. J Pediatr Hematol Oncol. 2023 Oct 1;45(7):e837-e846.**

Based on the 21 studies selected for this review including comparative dosimetric (7 studies), outcome (13 studies), and toxicity (14 studies), PT has demonstrated a significant advantage in reducing radiation to OARs, a notable decrease in integral dose, and comparable disease control to well-established photon series, with lower rates of acute and late toxicities in specific RMS sites.

■ **Sienna J, et al. Proton Therapy Mediates Dose Reductions to Brain Structures Associated with Cognition in Children with Medulloblastoma. Int J Radiat Oncol Biol Phys. 2023 Nov 29:S0360-3016(23)08164-6.**

This study evaluated dosimetric and cognitive data from 75 patients with medulloblastoma treated with proton (n=36) and photon (n=39). Significant dose reduction was achieved in the proton group in the brain mean dose and brain D40, the mean doses to the left and right hippocampi, and the mean dose to the left and right temporal lobes, which were found significantly associated to verbal comprehension, processing speed, global IQ scores, perceptual reasoning, and working memory. The authors concluded that proton therapy should be offered to pediatric patients with medulloblastoma.

■ **Yahya N and Manan HA. Neurocognitive impairment following proton therapy for paediatric brain tumour: a systematic review of post-therapy assessments. Support Care Cancer. 2021 Jun;29(6):3035-3047.**

Based on the 13 reports evaluated, this review reported significantly poorer cognitive outcome among patients treated with photon therapy compared with proton therapy especially in general cognition and working memory. Craniospinal irradiation was consistently associated with poorer cognitive outcome while focal therapy was associated with minor cognitive change/difference. The current evidence suggests that PT causes less cognitive deficits compared with photon therapy.

■ **Looi WS, et al. Outcomes following limited-volume proton therapy for multifocal spinal myxopapillary ependymoma. Pediatr Blood Cancer. 2021 Mar;68(3):e28820.**

Twelve pediatric patients with multifocal spinal Spinal myxopapillary ependymoma were treated with limited-volume proton therapy. With the median follow-up of 3.6 years, the five-year actuarial rates of LC, PFS and OS were 100%, 92%, and 100%, respectively. One patient experienced an out-of-field recurrence. One patient developed grade 3 spinal kyphosis and one patient developed grade 2 unilateral L5 neuropathy. Compared with historical reports, this approach using proton therapy improves the therapeutic ratio, resulting in minimal side effects and high rates of disease control.

■ **Bates JE, et al. Visual decline in pediatric survivors of brain tumors following radiotherapy. Acta Oncol. 2020 Aug 7;1-6.**

Radiotherapy-related visual decline is a significant concern in survivors of childhood cancer. This study analyzed 458 children with 875 eyes at risk treated with proton therapy for intracranial malignancy. The actuarial 5-year rate of any visual acuity decline was 2.6%. A dose of approximately 56 GyRBE to 0.1 cm3 results in an approximately 5% risk of visual acuity decline for children with suprasellar or optic pathway tumors, but appears to be safe for children with tumors elsewhere in the brain.

■ **Greenberger BA and Yock TI. The role of proton therapy in pediatric malignancies: Recent advances and future directions. Semin Oncol. 2020 Feb;47(1):8-22.**

This systematic review provides latest outcome data after proton therapy across the common pediatric disease sites. It discusses the main attempts to assess comparative efficacy between proton and photon radiotherapy concerning toxicity, and recent efforts of multi-institutional registries aimed at accelerating research to better define the optimal treatment paradigm for children requiring radiotherapy for cure.

■ **Eaton BR, et al. Long-term Health Related Quality of Life in Pediatric Brain Tumor Survivors Treated with Proton Radiotherapy at <4 Years of Age. Neuro Oncol. 2020 Feb 17;noaa042.**

Fifty-nine children < 4 years old with brain tumors who received PRT were followed for the median 9.1 years (5.5-18 years). This study found that long-term HRQoL among brain tumor survivors treated with proton therapy at a very young age is variable with over a third achieving HRQoL levels commensurate with healthy children.

■ **Kharod SM, et al. Outcomes following proton therapy for Ewing sarcoma of the cranium and skull base. Pediatr Blood Cancer. 2020 Feb;67(2):e28080.**

This study reviewed 25 patients (≤21 years old) with nonmetastatic Ewing sarcoma of the cranium and skull base treated with PBT. This study reported that with the median follow-up of 3.7 years, the 4-year local control, disease-free survival, and overall survival rates were 96%, 86%, and 92%, respectively, with no patient lost. None developed a secondary malignancy.

■ **Thomas H and Timmermann B. Paediatric proton therapy. Br J Radiol. 2020 Mar;93(1107):20190601.**

A review emphasized that PBT is an important therapeutic component in multidisciplinary management in pediatric oncology because of the reduction of radiation related long-term side-effects and secondary malignancy. This review evaluates current data from clinical and dosimetric studies on the treatment of tumors of the central nervous system, soft tissue and bone sarcomas of the head and neck region, paraspinal or pelvic region, and retinoblastoma.

■ **Uezono H, et al. Proton therapy following induction chemotherapy for pediatric and adolescent nasopharyngeal carcinoma. Pediatr Blood Cancer. 2019 Dec;66(12):e27990.**

Seventeen patients with nonmetastatic nasopharyngeal carcinoma underwent PT. With the median follow-up of 3.0 years, the study reported the overall survival, progression-free survival, and local control rates were 100%. Serious late side effects included cataract (n = 1), esophageal stenosis requiring dilation (n = 1), sensorineural hearing loss requiring aids (n = 1), and hormone deficiency (n = 5, including three with isolated hypothyroidism).

■ **Medek S, et al. Practice patterns among radiation oncologists treating pediatric patients with proton craniospinal irradiation. Pract Radiat Oncol. 2019 Nov;9(6):441-447.**

This survey study aimed to assess current practice patterns regarding the vertebral bodies (VB) coverage for pediatric patients undergoing CSI. The practice varies amongst radiation oncologists in respect to target delineation, CTV expansions and modifications for organs at risk. These data suggest the radiation oncology community may benefit from a standardized approach to pediatric proton based CSI.

■ **Doyen J, et al. Outcome and patterns of relapse in childhood parameningeal rhabdomyosarcoma treated with proton beam therapy. Int J Radiat Oncol Biol Phys. 2019 Dec 1;105(5):1043-1054.**

This study reported outcomes of PBT for 46 pediatric patients with parameningeal rhabdomyosarcoma (pRMS). With a median follow-up time of 2.9 years, the estimated 2-year local control (LC), metastasis-free survival (MFS), event-free survival (EFS), and overall survival (OS) were 83.8%, 87.8%, 76.9% and 88.9%. No acute or late local toxicity exceeding grade 3 was observed.

■ **Buszek SM, et al. Patterns of failure and toxicity profile following proton beam therapy for pediatric bladder and prostate rhabdomyosarcoma (B/P-RMS). Pediatr Blood Cancer. 2019 Nov;66(11):e27952.**

19 patients of B/P-RMS were treated with PBT. With a median follow-up of 66.2 months, 5-year overall survival (OS) and progression-free survival (PFS) were 76%. Four patients (21%) experienced disease relapse, all presenting with local failure. Acute grade 2 toxicity was observed in two patients (11%, transient proctitis). Late grade 2+ toxicity was observed in three patients (16%; n = 1 grade 2 skeletal deformity; n = 3 transient grade 2 urinary incontinence; one patient experienced both).

■ **Stokkevåg CH, et al. Normal tissue complication probability models in plan evaluation of children with brain tumors referred to proton therapy. Acta Oncol. 2019 Oct;58(10):1416-1422.**

40 patients treated with PBT were selected for VMAT re-plan. The results showed that reductions in population median NTCP were significant for auditory toxicity (VMAT: 3.8%; PT: 0.3%), neurocognitive outcome (VMAT: 3.0 IQ points decline at 5 years post RT; PT: 2.5 IQ points), xerostomia (VMAT: 2.0%; PT: 0.6%), excess absolute risk of secondary cancer of the brain (VMAT: 9.2%; PT: 6.7%) and salivary glands (VMAT: 2.8%; PT:0.5%).

■ **Bagley AF, Grosshans DR, Philip NV, et al. Efficacy of proton therapy in children with high-risk and locally recurrent neuroblastoma. Pediatr Blood Cancer. 2019 Aug;66(8):e27786.**

Eighteen patients with high-risk (n = 16) and locally recurrent neuroblastoma (n = 2) were treated with PBT. With a median follow-up of 60.2 months, this study reported the five-year progression-free survival (PFS) was 64%, and the five-year overall survival (OS) was 94%. No radiation-related nephropathy or hepatopathy was reported.

■ **Kahalley LS, Douglas Ris M, Mahajan A, et al. Prospective, Longitudinal Comparison of Neurocognitive Change in Pediatric Brain Tumor Patients Treated with Proton Radiotherapy versus Surgery Only. Neuro Oncol. 2019 Jun 10;21(6):809-818.**

93 patients (22 proton CSI, 31 proton focal, and 40 surgery only) received annual neurocognitive evaluations for up to 6 years, including Full Scale IQ (FSIQ), Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Working Memory (WMI), and Processing Speed Index (PSI) scores. In the proton CSI group, WMI, PSI, and FSIQ scores declined significantly, while VCI and PRI scores were stable.

■ **Ludmir EB, Grosshans DR, McAleer MF, et al. Patterns of failure following proton beam therapy for head and neck rhabdomyosarcoma. Radiother Oncol. 2019 May;134:143-150.**

46 patients were analyzed. The five-year OS was 76%, and PFS was 57%. Seventeen patients (37%) experienced relapse, including 7 with local failure (LF). Five-year local control (LC) was 84%. Tumor size greater than 5 cm predicted increased risk of LF, intracranial extension and delayed RT delivery after week 4 of chemotherapy predicted increased risk of relapse.

■ **Lawell MP, Bajaj BVM, Gallotto SL, et al. Increased distance from a treating proton center is associated with diminished ability to follow patients enrolled on a multicenter radiation oncology registry. Radiother Oncol. 2019 May;134:25-29.**

A paper evaluated the factors that affect maximum follow-up time among Pediatric Proton Consortium Registry (PPCR) participants. Among the 333 PPCR patients, loss in average follow up was 0.53 years for patients living outside >121 km from the proton center compared to those living within 121 km. Loss in average follow-up was also associated with Medicaid insurance.

■ **Ludmir EB, Mahajan A, Paulino AC, et al. Increased Risk of Pseudoprogression among Pediatric Low-Grade Glioma Patients Treated with Proton versus Photon Radiotherapy. Neuro Oncol. 2019 May 6;21(5):686- 695.**

Pseudoprogression (PsP) is a recognized phenomenon after radiotherapy (RT) for glioma. This study evaluated 83 pediatric low-grade glioma (LGG) patients treated with IMRT (39%) and PBT (61%), and found that 37% patients scored PsP including IMRT patients (25%) and PBT patients (45%). PsP should be considered when assessing response to RT in LGG patients within the first year after RT.

■ **Gross JP, Powell S, Zelko F, et al. Improved neuropsychological outcomes following proton therapy relative to x-ray therapy for pediatric brain tumor patients. Neuro Oncol. 2019 Apr 17. pii: noz070.**

This study analyzed 125 children who received XRT or PBT and had post-treatment neuropsychological evaluation including intelligence (IQ), attention, memory, visuographic skills, academic skills, and parent-reported adaptive functioning. PBT was associated with higher full-scale IQ (p=0.048) and processing speed (p=0.007) relative to XRT, with trend toward higher verbal IQ (p=0.06) and general adaptive functioning (p=0.07).

■ **Huynh M, Marcu LG, Giles E, et al. Are further studies needed to justify the use of proton therapy for paediatric cancers of the central nervous system?. Radiother Oncol. 2019 Apr;133:140-148.**

Having analyzed the available data of PBT for paediatric cancers of the central nervous system (CNS), this review concluded that current evidence supports PBT effectiveness and potential benefits in reducing the incidence of late-onset toxicities and second malignancies. For stronger evidence, it is highly desired for future studies to improve current reporting.

■ **Journy N, Indelicato DJ, Withrow DR, et al. Patterns of proton therapy use in pediatric cancer management in 2016: An international survey. Radiother Oncol. 2019 Mar;132:155-161.**

This survey study presented the data from 40 participating centers (participation rate: 74%), a total of 1,860 patients treated in 2016 (North America: 1205, Europe: 432, Asia: 223). More than 30 pediatric tumor types were identified, mainly treated with curative intent: 48% were CNS, 25% extra-cranial sarcomas, 7% neuroblastoma, and 5% hematopoietic tumors.

■ **Lavan NA, Saran FH, Oelfke U and, Mandeville HC. Adopting Advanced Radiotherapy Techniques in the Treatment of Paediatric Extracranial Malignancies: Challenges and Future Directions. Clin Oncol (R Coll Radiol). 2019 Jan;31(1):50-57**

A review article examined reports on pediatric organ motion, in anticipation of the increasing application of advanced radiotherapy techniques in pediatric radiotherapy. Misappropriation of target margins could result in disease recurrence from geometric miss or unnecessary irradiation of normal tissue, organ motion and deformation increase the complexity of defining safety margins.

■ **Jaramillo S, Grosshans DR, Philip N, et al. Radiation for ETMR: Literature review and case series of patients treated with proton therapy. Clin Transl Radiat Oncol. 2018 Nov 7;15:31-37.**

Embryonal tumors with multilayered rosettes (ETMRs) are aggressive tumors that typically occur in young children. Seven patients were treated with PBT and the median OS was 16 months (range 8-64 months), with three patients surviving36 months or longer. The study concluded that the outcomes of patients with ETMR treated with proton therapy are encouraging compared to historical results.

■ **Huynh M, Marcu LG, Giles E, et al. Current status of proton therapy outcome for paediatric cancers of the central nervous system - Analysis of the published literature. Cancer Treat Rev. 2018 Nov;70:272-288.**

This review analyzed 74 papers published from year 2000 onwards, and found proton therapy provides survival and tumor control outcomes comparable to photon therapy. Reduced incidence of severe acute and late toxicities was also reported including reduced severity of endocrine, neurological, IQ and QoL deficits.

■ **Bielamowicz K, Okcu MF, Sonabend R, et al. Hypothyroidism after craniospinal irradiation with proton or photon therapy in patients with medulloblastoma. Pediatr Hematol Oncol. 2018 May;35(4):257-267.**

This study reviewed ninety-five patients (54 XRT and 41 PBT) treated with CSI who had baseline and yearly follow-up for thyroid studies. Hypothyroidism developed in 46.3% who received XRT vs. 19% in the PBT group (HR =1.85, p=.14). The study concluded that PBT in patients with medulloblastoma was associated with numerically lower but not significantly lower risk of hypothyroidism.

■ **Ojerholm E and Hill-Kayser CE. Insurance coverage decisions for pediatric proton therapy. Pediatr Blood Cancer. 2018 Jan;65(1).**

Despite unfavorable language in coverage policies, real-world decisions were eventual approval in >99% of cases. Payers appear to have largely accepted the current level-of-evidence for pediatric PBT, but all parties spend significant time and resources on appeals. Streamlined approval processes could align incentives among stakeholders.

■ **Vogel J, et al. Proton therapy for pediatric head and neck malignancies. Pediatr Blood Cancer. 2018 Feb;65(2).**

69 pediatric patients were treated with PT for head and neck malignancies. Grade 3 oral mucositis, anorexia, and dysphagia were reported to be 4, 22, and 7%, respectively. Actuarial 1-year freedom from local recurrence was 92% and the actuarial 1-year overall survival was 93% in the entire cohort. This study demonstrated low rates of acute toxicity.

■ **Ventura LM, et al. Executive functioning, academic skills, and quality of life in pediatric patients with brain tumors post-proton radiation therapy.J Neurooncol. 2018 Mar;137(1):119-126.**

This study investigated the role of executive functioning (EF) in academic skills and health-related quality of life (HRQoL) in sixty-five children treated with PRT, and reported relatively intact intelligence, academics, attention, EF, and school HRQoL, but were at risk for reduced processing speed. Overall results compare favorably to XRT outcomes reported in the literature.

■ **Paulino AC, et al. Ototoxicity and cochlear sparing in children with medulloblastoma: Proton vs. photon radiotherapy. Radiother Oncol. 2018 Jan 17.**

The study compared ototoxicity rates between 84 children diagnosed with medulloblastoma treated with either passively scattered protons (n = 38) or photons (n = 46). Mean cochlear dose was lower in proton group, but had similar grade 3 and 4 ototoxicity rates i.e. grade 3 and 4 ototoxicity was seen in 9.3% and 9.9% ears, 17.3% and 20.9% ears with protons and photons respectively.

■ **Mokhtech M, et al. Early outcomes and patterns of failure following proton therapy for nonmetastatic intracranial nongerminomatous germ cell tumors. Pediatr Blood Cancer. 2018 Jun;65(6):e26997.**

This study of 14 children with nonmetastatic NGGCT were treated with PT after induction chemotherapy. At a median follow-up of 2.8 years, all patients were alive with no local recurrences. Three-year progression-free survival was 86%. This study suggested that the high conformality of PT does not compromise disease control and yields low toxicity.

■ **Hall MD, et al. Risk of Radiation Vasculopathy and Stroke in Pediatric Patients Treated With Proton Therapy for Brain and Skull Base Tumors. Int J Radiat Oncol Biol Phys. 2018 Jul 15;101(4):854-859.**

This study analyzed 644 pediatric patients with central nervous system and skull base tumors treated with proton therapy, and reported that the 3-year cumulative rates of any vasculopathy and serious vasculopathy were 6.4% and 2.6%, respectively. Seven children (1.2%) experienced a stroke with permanent neurologic deficits; 4 required revascularization surgery.

■ **Bavle A, et al. Meta-analysis of the incidence and patterns of second neoplasms after photon craniospinal irradiation in children with medulloblastoma. Pediatr Blood Cancer. 2018 Aug;65(8):e27095.**

This meta-analysis reviewed six studies with total 1,114 patients with MB, after CSI, and reported the 10-year cumulative incidence was 6.1% for all SNs (excluding skin cancer and leukemia), 3.1% for SBNs (benign), and 3.7% for SMNs (malignant). 40% of SNs occurred outside the target central nervous system field, with a majority in areas of exit RT dose. Studies are needed to determine whether the use of proton therapy, which has no exit RT dose, is associated with a lower incidence of SNs.

■ **Ladra MM, et al. Proton therapy for central nervous system tumors in children. Pediatr Blood Cancer. 2018 Jul;65(7):e27046.**

Up-to-date clinical outcomes of proton therapy for pediatric CNS malignancies are summarized in this review. The authors highlighted the capability of protons to decrease radiation exposure for children is regarded as an important advance in pediatric cancer care, particularly for central nervous system (CNS) tumors.

■ **Haas-Kogan D, et al. National Cancer Institute Workshop on Proton Therapy for Children: Considerations Regarding Brainstem Injury. Int J Radiat Oncol Biol Phys. 2018 May 1;101(1):152-168.**

Reports of brainstem necrosis after proton therapy have raised concerns over the potential biological differences among radiation modalities. A workshop was organized including twenty-seven physicians, physicists, and researchers from 17 institutions with expertise to discuss this issue. The workshop concluded that the established guidelines allow for safe delivery of proton radiation.

■ **Weber DC, et al. Proton therapy for pediatric malignancies: Fact, figures and costs. A joint consensus statement from the pediatric subcommittee of PTCOG, PROS and EPTN. Radiother Oncol. 2018 Jun 21.**

This review by the three organizations assessed the data available about PT for a range of pediatric CNS and non-CNS tumors. Through almost all dosimetric and model based evaluation, clinical outcomes for PT should be favorable with an improved QOL, organ function, development with a reduction in the risk of SMNs.

■ **De B, et al. Early Axial Growth Outcomes of Pediatric Patients Receiving Proton Craniospinal Irradiation. J Pediatr Hematol Oncol. 2018 Jun 8.**

58 patients who received p-CSI were reviewed including spinal target volumes of whole vertebral body (WVB) in 67% and partial vertebral body (PVB) in 33%. This study reported that WVB patients had significantly greater reduction in heightz-score versus PVB patients (P=0.004) but no difference in Cobb angle change (P>0.05).

■ **Kralik SF, et al. Radiation-Induced Large Vessel Cerebral Vasculopathy in Pediatric Patients With Brain Tumors Treated With Proton Radiation Therapy. Int J Radiat Oncol Biol Phys. 2017 Nov 15;99(4):817-824.**

75 consecutive pediatric patients with primary brain tumors were treated with proton radiation therapy. RLVCV was present in 5 of 75 (6.7%) patients. The incidence of vasculopathy in this study was less than that of a photon series, which reported 6 of 32 (19%). This study emphasized that radiation-induced large vessel cerebral vasculopathy may occur in pediatric patients with brain tumors treated with PBT.

■ **Antonini TN et al. Attention, processing speed, and executive functioning in pediatric brain tumor survivors treated with proton beam radiation therapy. Radiother Oncol. 2017 Jun 24.**

Survivors treated with PBRT may exhibit relative resilience in cognitive domains traditionally associated with radiation late effects. Attention, processing speed, and executive functioning remained intact and within normal limits for survivors treated with focal PBRT.

■ **Weber DC et al. Pencil beam scanned protons for the treatment of patients with Ewing sarcoma. Pediatr Blood Cancer. 2017 Jun 19.**

This study reported the outcomes of patients with Ewing sarcoma treated with pencil beam scanned protons. The 5-year actuarial rate of LC, distant metastasis-free survival, and OS were 81.5%, 76.4%, and 83.0%, and the 5-year actuarial rate of grade 3 toxicity-free survival was 90.9%. The outcomes of children and adolescents and young adults with EWS are good and PT was well tolerated with few late adverse events.

■ **Shen CJ et al. Socioeconomic factors affect the selection of proton radiation therapy for children. Cancer. 2017 Jun 27.**

Of 12,101 children (age ≤ 21 years) in the National Cancer Database who received radiotherapy between 2004 and 2013, 8% received proton therapy. This proportion increased between 2004 (1.7%) and 2013 (17.5%). Patients with higher median household income with private/managed care were more likely to receive proton therapy than patients with Medicaid or no insurance. Improving access to proton therapy in underserved pediatric populations is essential.

■ **Indelicato DJ et al. Clinical outcomes following proton therapy for children with central nervous system tumors referred overseas. Pediatr Blood Cancer. 2017 May 24.**

This study conducted by the Jacksonville proton group is to report patient outcomes of U.K. children referred for proton therapy. 166 U.K. children with approved CNS tumors were treated with proton therapy. The authors concluded that disease control does not appear compromised, toxicity is acceptable, and improvement in long-term function is anticipated in survivors owing to the reduced brain exposure afforded by proton therapy.

■ **Farace P et al. Supine craniospinal irradiation in pediatric patients by proton pencil beam scanning. Radiother Oncol. 2017 Apr;123(1):112-118.**

This study reported methods and techniques for performing PBS CSI effectively. Special methods included 1) supine patient position 2) field-junctions via the ancillary-beam technique 3) lens-sparing by three beam whole brain irradiation 4) applied a movable snout and beam splitting technique to reduce the lateral penumbra for dose reduction to kidney.

■ **Sato M et al. Progression-free survival of children with localized ependymoma treated with intensity-modulated radiation therapy or proton-beam radiation therapy. Cancer. 2017 Jul 1;123(13):2570-2578.**

This retrospective study reported outcomes of 79 children of localized intracranial ependymomas treated with IMRT(38) and PRT (41). Patients treated with PRT were younger, gross total resection (GTR) was achieved more frequent in the PRT group versus the IMRT group. The 3-year PFS rates were 60% and 82% with IMRT and PRT (P = .031). The authors concluded that GTR was the only prognostic factor for PFS, and PRT produced comparable 3-year PFS.

■ **Takizawa D et al. A comparative study of dose distribution of PBT, 3D-CRT and IMRT for pediatric brain tumors. Radiat Oncol. 2017 Feb 22;12(1):40.**

For 6 cases of ependymoma and 6 germinoma, plan comparison showed that PBT significantly reduced the average dose to normal brain tissue compared to 3D-CRT and IMRT in all cases. The effects are higher in the cases of larger tumors and for tumors located at the periphery of the brain.

■ **Odei B et al. Patterns of Care in Proton Radiation Therapy for Pediatric Central Nervous System Malignancies. Int J Radiat Oncol Biol Phys. 2017 Jan 1;97(1):60-63**

The USA National Cancer Database showed that 4,637 pediatric patients received radiation treatment from 2004 to 2012, among whom 267 were treated with PBT. PBT use increased with time from <1% in 2004 to 15% in 2012. However, children from higher-income households and with private insurance were more likely to be treated with PBT. As we continue to demonstrate the potential benefits of PBT in children, efforts are needed to expand the accessibility of PBT for children of all socioeconomic background and regions of the country.

■ **Tamura M et al. Lifetime attributable risk of radiation-induced secondary cancer from proton beam therapy compared with that of intensity-modulated X-ray therapy in randomly sampled pediatric cancer patients. J Radiat Res. 2017 May 1;58(3):363-371.**

A group of Japanese researchers compared the lifetime attributable risk of secondary cancer (LAR) induced by proton therapy and IMRT in pediatric patients. The paper reported that for categories of brain, head and neck, thoracic, abdominal and whole craniospinal irradiation, the LAR of PBT was significantly lower than IMRT.

■ **Wray J. et al. Proton Therapy for Pediatric Hodgkin Lymphoma. Pediatric Blood & Cancer.2016 September; 63(9):1522-1526.**

Compared to photon RT, proton therapy reduces the radiation dose to OAR, which is expected to translate into less long-term morbidity. Proton therapy for pediatric Hodgkin lymphoma shows no short-term severe toxicity and yields similar short-term control to recently published large multi-institutional clinical trials.

■ **Ares C. et al. Pencil beam scanning proton therapy for pediatric intracranial ependymoma. Journal of Neurooncology. 2016 May; 128(1):137-45.**

Data indicate the safety and effectiveness of proton therapy in this study assessing the clinical outcomes and late side effects of pencil beam scanning proton therapy delivered to children with intracranial ependymoma.

■ **Leiser D. et al. Tumour control and Quality of Life in children with rhabdomyosarcoma treated with pencil beam scanning proton therapy. Radiotherapy and Oncology. 2016 May; pii: S0167-8140(16)31116-1.**

This paper assesses the clinical outcomes in children with rhabdomyosarcoma (RMS) treated with pencil beam scanning PT. PBS proton therapy led to excellent outcomes, with minimal late non-ocular toxicity and good QoL.

■ **Kahalley L.S. et al. Comparing Intelligence Quotient Change After Treatment With Proton Versus Photon Radiation Therapy for Pediatric Brain Tumors. Journal of Clinical Oncology. 2016 April; 34(10):1043-9.**

This paper compares long term IQ change in pediatric patients with brain tumors treated with proton therapy or RT.It remains unclear if proton therapy results in clinically meaningful cognitive sparing that significantly exceeds that of modern radiation therapy protocols. Additional long-term data are needed.

■ **Laprie A. et al. Paediatric brain tumours: A review of radiotherapy, state of the art and challenges for the future regarding protontherapy and carbontherapy. Cancer Radiothérapie. 2015 December; 19(8):775-89.**

Brain tumors are the most frequent radiation therapy indications in paediatrics, with frequent late toxic effects on cognitive, osseous, visual, auditory and hormonal systems. Both proton therapy and carbon ion therapy show promising results, with the benefit of decreasing late effects without altering global survival.

■ **Eaton B.R. et al. Use of proton therapy for re-irradiation in pediatric intracranial ependymoma. Radiotherapy and Oncology. 2015 August; 116(2):301-8.**

This paper reports disease control, survival and treatment-associated toxicity with the use of proton therapy for re-irradiation of intracranial ependymoma. Proton therapy appears safe and efficacious for this specific indication of treatment.

■ **Grant S.R. et al. Proton versus conventional radiotherapy for pediatric salivary gland tumors: Acute toxicity and dosimetric characteristics. Radiotherapy and Oncology. 2015 August; 116(2):309-15.**

This retrospective study evaluates acute toxicity profiles and dosimetric data for children with salivary gland tumors treated with adjuvant photon/electron-based radiation therapy or proton therapy. Proton therapy was associated with a more favorable acute toxicity and dosimetric profile. Continued follow-up is needed to identify long-term toxicity and survival data.

■ **Mailhot Vega R. et al. Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. Cancer. 2015 May 15; 121(10):1694-702.**

Proton therapy may prove to be cost effective if chronic medical complications can be avoided. This paper is the first evidence-based guide for identifying children with brain tumors who may benefit the most from proton therapy with respect to endocrine dysfunction: proton therapy proves to be more cost effective when the hypothalamus can be spared.

■ **Lucas J.T. Jr. et al. Proton therapy for pediatric and adolescent esthesioneuroblastoma. Pediatric Blood Cancer. 2015 March 27; 71(2), e30793.**

Esthesioneuroblastoma of the paranasal sinus comprises less than 3% of tumors in pediatric and adolescent patients. The collective adult literature indicates a critical role for radiotherapy in attaining cure, yet pediatric outcome data is limited. This study shows that PT provides excellent locoregional disease control even in patients with locally advanced disease and intracranial extension.

■ **Mizumoto M. et al. Proton beam therapy for pediatric ependymoma. Pediatrics International. 2015 March 6; 57(4), 567–571.**

The aim of this study is to evaluate the efficacy of PT for pediatric patients with ependymoma. Proton beam therapy for pediatric ependymoma is safe, does not have specific toxicities, and can reduce irradiation of normal brain tissue.

■ **Weber D.C. et al. Tumor control and QoL outcomes of very young children with atypical teratoid/rhabdoid tumor treated with focal only chemoradiation therapy using pencil beam scanning proton therapy. Journal of Neuro-oncology. 2015 January; 121(2):389-97.**

The aim of this analysis is to assess the early clinical results of PBS PT in the treatment of young children with non- metastatic atypical teratoid/rhabdoid tumor of the central nervous system. PBS PT is proven to be an effective treatment for those patients, with manageable acute toxicity.

■ **McGovern S.L. et al. Outcomes and acute toxicities of proton therapy for pediatric atypical teratoid/rhabdoid tumor of the central nervous system. International Journal of Radiation Oncology. Biology. Physics. 2014 December 1; 90(5):1143-52.**

Atypical teratoid/rhabdoid tumor (AT/RT) of the CNS is a rare cancer primarily affecting children younger than 5 years old. This paper is the largest report of children with AT/RT treated with PT, and preliminary survival outcomes in this young pediatric population are encouraging compared to historic results.

■ **Indelicato D.J. et al. Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy. Acta Oncologica. 2014 October; 53(10):1298-304.**

PT offers superior low and intermediate radiation dose distribution compared with photon RT for brain and base of skull tumors. This article investigates the tolerance of the pediatric brainstem to PT and shows that the utilization of current national brainstem dose guidelines is associated with a low risk of brainstem toxicity in pediatric patients. For posterior fossa tumors, particularly after aggressive surgery, the study suggests more conservative dosimetric guidelines should be considered.

■ **Bishop A.J. et al. Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. International Journal of Radiation Oncology. Biology. Physics. 2014 October 1; 90(2):354-61.**

This paper compares PT with IMRT for pediatric craniopharyngioma in terms of disease control, cyst dynamics and toxicity.

■ **Song S. et al. Proton beam therapy reduces the incidence of acute haematological and gastrointestinal toxicities associated with craniospinal irradiation in pediatric brain tumors. Acta Oncologica. 2014 September; 53(9):1158-64.**

This paper compares the acute toxicity of PT craniospinal irradiation (CSI) to that of conventional RT CSI in children with brain tumors: the incidence rates of thrombocytopenia and diarrhoea were lower with PT than with RT, and one month after treatment, the recovery from leukopenia and thrombocytopenia was better in patients treated with PT.

■ **Rombi B. et al. Proton radiotherapy for pediatric tumors: review of first clinical results. Italian Journal of Pediatrics. 2014 September 26; 40:74.**

PT has been used safely and effectively for medulloblastoma, primitive neuro-ectodermal tumors, craniopharyngioma, ependymoma, germ cell intracranial tumors, low-grade glioma, retinoblastoma, rhabdomyosarcoma and other soft tissue sarcomas, Ewing's sarcoma and other bone sarcomas. Other possible applications are emerging. The main advantage of PT is the sparing of intermediate-to-low-dose to healthy tissue.

■ **Greenberger B.A. et al. Clinical outcomes and late endocrine, neurocognitive, and visual profiles of proton radiation for pediatric low-grade gliomas. International Journal of Radiation Oncology. Biology. Physics. 2014 August 1; 89(5):1060-8.**

Primary low-grade gliomas are common brain tumors of childhood, and many of them require radiation therapy as definitive treatment. Increased conformality could decrease the incidence and severity of late effects. PT appears to be associated with good clinical outcomes, especially when the tumor location allows for increased sparing of the left temporal lobe, hippocampus, and hypothalamic-pituitary axis.

■ **Hoppe B.S. Involved-node proton therapy in combined modality therapy for hodgkin lymphoma: results of a phase 2 study. International Journal of Radiation Oncology. Biology. Physics. 2014 August 1; 89(5):1053-9.**

This study describes the early clinical outcomes of a prospective phase 2 study of consolidative involved-node PT as a component of combined-mode therapy in patients with stages I to III Hodgkin lymphoma with mediastinal involvement.

■ **Moteabbed M. et al. The risk of radiation-induced second cancers in the high to medium dose region: a comparison between passive and scanned proton therapy, IMRT and VMAT for pediatric patients with brain tumors. Physics in Medicine and Biology. 2014 June 21; 59(12):2883-99.**

The incidence of second malignant tumors is a clinically observed adverse late effect of radiation therapy. This study aims to evaluate the risk of second cancer incidence for pediatric patients with brain/head and neck tumors and compare passive scattering and pencil beam scanning PT, IMRT and VMAT.

■ **Petrovic A. et al. Proton therapy for uveal melanoma in 43 juvenile patients: long-term results. Ophthalmology. 2014 April. 121(4):898-904.**

This study examines the metastatic and survival rates, eye retention probability and visual outcomes of juvenile patients after PT for uveal melanoma. It is shown that metastatic and survival rates are significantly better for juvenile than for adult patients.

■ **Ladra M.M. and Yock T.I. Proton radiotherapy for pediatric sarcoma. Cancers. 2014 March; 6(1): 112–127.**

Radiotherapy plays an integral role in the local control of pediatric sarcomas, which often arise adjacent to critical structures and growing organs. PT shows either equivalent or improved outcomes, and lower toxicity for soft tissue sarcoma compared to RT. For bone and cartilaginous sarcomas, a clearer advantage exists for PT due to its ability to increase total dose while respecting adjacent structures.

■ **MacDonald S.M., et al. Proton radiotherapy for pediatric central nervous system ependymoma: clinical outcomes for 70 patients. Neuro Oncology. 2013 November; 15(11):1552-9.**

Ependymoma is treated with maximal surgical resection and localized radiotherapy. Minimizing unnecessary exposure to radiation is of paramount importance for young children. PT spares healthy tissue outside the target region, and outcomes for children treated with PT compare favorably with the literature.

■ **Jimenez R. et al. Proton radiation therapy for pediatric medulloblastoma and supratentorial primitive neuroectodermal tumors: outcomes for very young children treated with upfront chemotherapy. International Journal of Radiation Oncology. Biology. Physics. 2013; 87(1):120-6.**

Upfront chemotherapy followed by 3D PT presents good disease early outcomes for very young children with medulloblastoma or supratentorial primitive neuroectodermal tumor.

■ **Suneja G. et al. Acute toxicity of proton beam radiation for pediatric central nervous system malignancies. Pediatric Blood & Cancer. 2013; 60(9):1431-6.**

PT appears to be well tolerated in pediatric patients with CNS malignancies. Acute toxicity can be managed with supportive care.

■ **Kumar R.J. et al. Breast cancer screening for childhood cancer survivors after craniospinal irradiation with protons versus x-rays: a dosimetric analysis and review of the literature. Journal of Pediatric Hematology/Oncology. 2013; 35(6):462-7.**

Early screening for breast cancer may be unnecessary after craniospinal irradiation with PT, whereas it should be considered with X-ray therapy, given doses to the breast that approach the Children's Oncology Group-recommended threshold.

■ **Rombi B. et al. Spot-scanning proton radiation therapy for pediatric chordoma and chondrosarcoma: clinical outcome of 26 patients treated at paul scherrer institute. International Journal of Radiation Oncology. Biology. Physics. 2013; 86(3):578-84.**

Spot-scanning PT shows excellent clinical outcomes with acceptable rates of late toxicity in pediatric patients with chordoma or chondrosarcoma of the skull base or axial skeleton.

■ **Rombi B. et al. Proton radiotherapy for pediatric Ewing's sarcoma: initial clinical outcomes. International Journal of Radiation Oncology. Biology. Physics. 2013; 82(3):1142-8.**

This study presents preliminary clinical outcomes including late effects on pediatric Ewing's sarcoma patients treated with PT. This treatment modality was well tolerated with few adverse events.

■ **Zhang R. et al. Comparison of risk of radiogenic second cancer following photon and proton craniospinal irradiation for a pediatric medulloblastoma patient. Physics in Medicine and Biology. 2013; 58(4):807-23.**

Pediatric patients who received radiation therapy are at risk of developing side effects such as radiogenic second cancer. PT confers lower predicted risk of second cancer than RT for pediatric medulloblastoma patients receiving craniospinal irradiation.

■ **Amsbaugh M.J. et al. Proton therapy for spinal ependymomas: planning, acute toxicities, and preliminary outcomes. International Journal of Radiation Oncology. Biology. Physics. 2012 August 1; 83(5):1419-24.**

PT offers a powerful treatment option in the pediatric population, where adverse events related to radiation exposure are of concern. This study reports acute toxicities and preliminary outcomes for pediatric patients with ependymomas of the spine treated with PT at the MD Anderson Cancer Center.

■ **Armstrong F.D., Holtz Children's Hospital. Proton-Beam Radiation Therapy and Health-Related Quality of Life in Children With CNS Tumors. JCO 2012 42 1248. Journal of Clinical Oncology (ASCO). 2012; Vol. 30, as 10.1200/JCO.2012.42.1248.**

Children treated for CNS tumors with conventional RT or cranial radiation therapy (CRT) are at high risk of neurocognitive impairment or dysfunction. Delaying CRT or reducing dose of CRT in adjuvant chemotherapy was associated with better long-term cognitive function. Proton therapy represents an alternative to photon radiotherapy, which may now offer the next step with respect to both survival and long-term neurocognitive functioning.

■ **Cotter S.E. et al. Proton radiotherapy for solid tumors of childhood. Technology in cancer research and treatment. 2012; 11(3):267-78.**

The increasing efficacy of pediatric cancer therapy has produced many long-term survivors who now struggle with serious morbidities mostly related to radiation therapy. PT holds great promise to drastically reduce these treatment- related late effects in long term survivors by reducing dose to normal tissue.

■ **Cotter S.E. et al. Proton radiotherapy for pediatric bladder/prostate rhabdomyosarcoma: clinical outcomes and dosimetry compared to intensity modulated radiation therapy. International Journal of Radiation Oncology. Biology. Physics. 2011 December 1; 81(5):1367-73.**

This paper reports the clinical outcomes of 7 children with bladder/prostate rhabdomyosarcoma treated with PT and compares PT plans with matched IMRT plans, with an emphasis on dose savings to reproductive and skeletal structures. PT provides significant dose savings to normal structures compared to IMRT and is well tolerated in this patient population.

■ **MacDonald S.M. et al. Proton radiotherapy for pediatric central nervous system germ call tumors: early clinical outcomes. International Journal of Radiation Oncology. Biology. Physic. 2011; 79:121-129.**

This paper reports early clinical outcomes for children with CNS germ cell tumors treated with PT and compares dose distributions for IMRT, 3D-CPT and IMPT with PBS for whole-ventricular irradiation with and without an involved-field boost. Preliminary disease control with PT compares favorably to the literature and dosimetric comparisons demonstrate the advantage of PT over IMRT for whole-ventricle radiation, with superior dose distributions and fewer beam angles.

REIRRADIATION

■ **Simone CB, et al. Proton Reirradiation: Expert Recommendations for Reducing Toxicities and Offering New Chances of Cure in Patients With Challenging Recurrence Malignancies. Semin Radiat Oncol. 2020 Jul;30(3):253-261.**

This review article evaluated clinical data up-to-date on proton reirradiation for local and regional recurrence. As photon reirradiation can be associated with considerable risks of high grade acute and late toxicities, protons offer significant advantages for reirradiation. In select patients, PT is often the best modality for delivering reirradiation. IMPT offer increased dose conformality and even further advantages over photon therapy in the setting of reirradiation.

■ **Barsky AR, et al. Proton beam re-irradiation for gastrointestinal malignancies: a systematic review. J Gastrointest Oncol. 2020 Feb;11(1):187-202.**

A systematic review assessing for reports of proton reirradiation for recurrent or second primary GI cancers. 7 included studies reported on proton-beam re-irradiation for the following disease sites: esophageal (n=2), pancreas (n=1), liver (n=2), rectal (n=1), and anal (n=1). Local control rates, with variable follow-up, ranged from 36-100%. There were 2 acute (esophagopleural fistula in esophageal cancer, small bowel perforation in pancreatic cancer) and 1 late (esophageal ulcer in esophageal cancer) grade 5 toxicities, all due to progressive disease.

■ **Verma V, et al. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation, Radiother Oncol. 2017 Oct;125(1):21-30.**

This review assessed clinical outcomes and toxicity profiles by evaluating available evidence regarding PBT reRT. Fourteen original investigations across central nervous system (CNS) (n=6), head/neck (H&N) (n=4), lung (n=2), and gastrointestinal (n=2) malignancies were analyzed.

Proton Therapy Utilization and Future Development

■ **Marcus D, et al. Charged Particle and Conventional Radiotherapy: Current Implications as Partner for Immunotherapy. Cancers (Basel). 2021 Mar 23;13(6):1468.**

A review article discussed the possible synergy of radiotherapy and immunotherapy, and the theoretical basis that charged particle RT (PRT) may enhance tumor immunogenicity compared to conventional RT due to its unique biological and physical properties. The review also examined the available evidence supporting a favorable immunogenicity profile of PRT.

■ **Vidal M, et al. Future technological developments in proton therapy - A predicted technological breakthrough. Cancer Radiother. 2021 Oct;25(6-7):554-564.**

This article presents an overview of on-going technical developments and innovations that the authors felt most important today, as well as those that have the potential to significantly shape the future of proton therapy. This review discussed the developments in the accelerator field, in transport and spatial resolution achievable with pencil beam scanning, or conformation of collimation, proton arc therapy and adaptive PT, as well as FLASH proton therapy.

■ **Bishop AJ, et al. Young Adult Populations Face Yet Another Barrier to Care with Insurers: Limited Access to Proton Therapy. Int J Radiat Oncol Biol Phys. 2021 Aug 1;110(5):1496-1504.**

Young adult patients (n = 68/143, 48%) were significantly less likely to receive initial approval compared with pediatric patients (n = 139/141; 99%) (P < .001). Given the decades of survivorship of YA patients, PBT is an important tool to reduce late toxicities and secondary malignancies. Insurance denials and subsequent appeal requests result in significant delays for YA patients.

■ **Lee SU, et al. Patterns of Proton Beam Therapy Use in Clinical Practice Between 2007 and 2019 in Korea. Cancer Res Treat. 2021 Oct;53(4):935-943.**

A total of 54,035 patients had been treated with some form of RT, of whom 5,398 received PBT (10.0%). Among all types of cancer, PBT use in liver cancer has been steadily increasing from 20% in 2008-2009 to 32% in 2018-2019. Prostate cancer has been continuously decreasing from 20% in 2008-2009 to <10% in 2018-2019. Male sex, very young or old age, stage I-II disease, residency in non-capital areas, a definitive setting, a curative treatment aim, enrollment in a clinical trial, re-irradiation and insurance coverage were significantly associated with the receipt of PBT (all p < 0.05).

■ **Tambas M, et al. Current practice in proton therapy delivery in adult cancer patients across Europe. Radiother Oncol. 2022 Feb:167:7-13.**

This survey study reported findings of current practice of proton therapy for adult cancers in Europe. 19 out of 22 centers from all 13 countries where PT is available participated in the survey. 4233 adult patients are currently treated across Europe annually, of which 46% consists of patients with central CNS, 15% HNC, 15% prostate, 9% breast, 5% lung, 5% gastrointestinal, 4% lymphoma, 0.3% gynaecological cancers. Lack of evidence for PT and reimbursement issues are the most reported reasons for not treating specific tumor types with PT.

■ **Burnet NG, et al. Estimating the percentage of patients who might benefit from proton beam therapy instead of X-ray radiotherapy. Br J Radiol. 2022 May 1;95(1133):20211175.**

This paper presents experts' opinions on benefits of PBT and the level of provision for PBT utilization in the UK. The most reliable figure for percentage of radical radiotherapy patients likely to benefit from PBT was at 4.3%. The biggest estimated potential benefit was from reducing toxicity, median benefit to 15%, followed by dose escalation median 3%. Head and neck cancer is considered to benefit most from both reducing toxicity and dose escalation. Both CNS and lung cancer are also identified as potentially benefitting large numbers of patients, however clinical evidence is lacking.

■ **Santos A, et al. The Role of Hypofractionation in Proton Therapy. Cancers (Basel). 2022 May 2;14(9):2271.**

A review examined the reported data of hypofractionation with PBT. Over 50 published manuscripts were included for analysis. The most common treatment regions reported were prostate, lung and liver, making over 70% of the reported results. Hypofrationated PBT has been reported also for intracranial, breast and retroperitoneal sarcoma. 90% data was published since 2010, among which 36 reports published in the past 5 years making over 60% of the total reported data. This shows a significant and growing interest in the field of hypofractionation with PBT.

■ **Chen Z, et al. Proton versus photon radiation therapy: A clinical review. Front Oncol. 2023 Mar 29:13:1133909.**

This review summarized comparative clinical outcomes between proton and photon radiotherapy. 63 interventional comparative studies were presented in this analysis, including 6 randomized studies (1 prostate, 3 lung, 1 esophagus, 1 adult CNS) and 57 non-randomized reports (8 prostate, 3 breast, 9 lung, 8 esophagus, 7 head and neck, as well as 4 adult and 18 pediatric CNS cancers). The evidence of value is not definitive and further demonstration of the clinical benefit of proton therapy will depend on the findings of ongoing and future comparative randomized clinical trials.

■ **Yan S, et al. Global democratisation of proton radiotherapy. Lancet Oncol. 2023 Jun;24(6):e245-e254.**

This review summarized the current situation of proton therapy in clinical use, technology development, patient access and social benefits, suggesting that high costs of a proton facility is the main reason hindering its expansion. This review also highlighted the future direction towards affordable proton therapy in standard treatment rooms. In addition to further clinical research, the authors called for engagement of different stakeholders including regulatory bodies and international agencies for the global expansion and democratization of proton therapy.

■ **Mazzola GC, et al. Patients' needs in proton therapy: A survey among ten European facilities. Clin Transl Radiat Oncol. 2023 Aug 22:43:100670.**

This is a qualitative analysis of a recent survey took place in 10 PT centers in Europe. Nine centers treat from 100 to 500 patients per year. Pediatric patients accounted for 10-30%, 30-50% and 50-70% of the entire cohort for 7, 2 and 1 center, respectively. The most frequent tumors treated in adult population were brain tumors, sarcomas and head and neck carcinomas.

■ **Velalopoulou A, et al. FLASH proton radiotherapy spares normal epithelial and mesenchymal tissues while preserving sarcoma response. Cancer Res. 2021 Sep 15;81(18):4808-4821.**

This study reported that FLASH proton radiotherapy (F-PRT) of the C57BL/6 murine hind leg produced fewer severe toxicities leading to death or requiring euthanasia than standard proton therapy (S-PRT) of the same dose. RNAseq analyses of murine skin and bone revealed pathways upregulated by S-PRT yet unaltered by F-PRT. F-PRT reduced skin injury, stem cell depletion, and inflammation, mitigated late effects including lymphedema, and decreased histopathologically detected myofiber atrophy, bone resorption, hair follicle atrophy, and epidermal hyperplasia.

■ **Mascia AE, et al. Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases: The FAST-01 Nonrandomized Trial. JAMA Oncol. 2023 Jan 1;9(1):62-69.**

A single-transmission proton beam delivering 8 Gy in a single fraction at a dose rate ≥40 Gy/sec was used for patients with bone metastases. 10 patients with 12 metastatic sites were irradiated and 8 patients were evaluated with a median follow up of 4.8 months. Pain relief was recorded in 67% patients including 50% a complete response (no pain). Adverse events were mild. This study concluded that proton FLASH was clinically feasible.

■ **Atkinson J, et al. The current status of FLASH particle therapy: a systematic review. Phys Eng Sci Med. 2023 Jun;46(2):529-560.**

This comprehensive review summarized literatures of electron-FLASH, in vitro and in vivo studies of proton- and carbon-FLASH therapy, and the first human study of proton-FLASH. The possible mechanisms of FLASH effect was discussed including hypoxia, DNA repair and response and immune modulation. This review pointed out the current major issues of developing FLASH with particle therapy including the lack of stringent verification of dosimetry and solid reporting on beam characteristics, doses administered and quality control.

■ **Iturri L, et al. Proton FLASH Radiation Therapy and Immune Infiltration: Evaluation in an Orthotopic Glioma Rat Model. Int J Radiat Oncol Biol Phys. 2023 Jul 1;116(3):655-665.**

This study reported the potential immune response generated by proton-FLASH using a single dose 25 Gy at a dose rate of (257 ± 2 Gy/s) in an orthotopic glioma rat model. Proton FLASH-RT spared memory impairment and induced a similar tumor infiltrating lymphocyte recruitment.

■ **Shukla S, et al. Ultra-High Dose-Rate Proton FLASH Improves Tumor Control. Radiother Oncol. 2023 Sep:186:109741.**

This study reported that proton-FLASH (>60 Gy/s) was more effective in reducing tumor burden and decreasing tumor cell proliferation compared conventional proton irradiation (<0.05 Gy/s) based on a mouse model of NSCLC. Proton-FLASH was more efficient in increasing the infiltration of cytotoxic CD8+ T-lymphocytes inside the tumor while simultaneously reducing the percentage of immunosuppressive regulatory T-cells (Tregs) among T-lymphocytes.

■ **Paganetti H, et al. Roadmap: proton therapy physics and biology. Phys Med Biol. 2021 Feb 26;66(5):10.1088/1361-6560/abcd16.**

This review presents the roadmap for proton therapy development, which includes further research in advancing dose shaping capabilities, high degrees of freedom in dose delivery, optimizing pencil beam scanning, and understanding the biological effects of proton differ from photon radiation. This roadmap highlights the current state and future direction in proton therapy categorized into four different themes, "improving efficiency", "improving planning and delivery", "improving imaging", and "improving patient selection".

■ **Hughes JR and Parsons JL. FLASH Radiotherapy: Current Knowledge and Future Insights Using Proton-Beam Therapy. Int J Mol Sci. 2020 Sep 5;21(18):6492.**

A review summarized FLASH radiotherapy research conducted to date and the current theories explaining the FLASH effect, with an emphasis on the future potential for FLASH proton beam therapy. The FLASH effect has been confirmed in many studies in recent years, both in vitro and in vivo, with even the first patient with T-cell cutaneous lymphoma being treated using FLASH radiotherapy. A promising FLASH delivery method is via proton beam therapy, as the dose can be deposited deeper within the tissue.

■ **Ning MS, et al. Three-Year Results of a Prospective Statewide Insurance Coverage Pilot for Proton Therapy: Stakeholder Collaboration Improves Patient Access to Care. JCO Oncol Pract. 2020 Apr 17;JOP1900437**

This insurance coverage study is conducted with a statewide self-funded employer (n = 186,000 enrollees), incorporating a value-based analysis and ensuring preauthorization for appropriate indications. This study found that appropriate access to proton therapy does not necessitate overuse or significantly increase comprehensive medical costs. Objective evidence-based coverage polices ensure appropriate patient selection.

■ **Grau C, et al. Particle therapy in Europe. Mol Oncol. 2020 Jul;14(7):1492-1499.**

A review article looked at the status of clinical utilization of particle therapy such as protons or heavier ions in Europe. The authors suggested that particle therapy holds great promise to improve the therapeutic outcome of cancer patients treated with this modality, however, there is an urgency to produce high quality clinical evidence. The collaboration across institutions and countries is needed to secure evidence-based implementation of particle therapy.

■ **Mendenhall WM, et al. Insurance Coverage for Adjuvant Proton Therapy in the Definitive Treatment of Breast Cancer. Int J Part Ther. Fall 2019;6(2):26-30.**

Among 131 insured patients, 96 patients (73%) had policies that "covered" PT. It was found that insurance "coverage" for PT was not associated with final approval nor was lack of "coverage" associated with denial. The only parameter that significantly influenced approval was insurance type combined with potential coverage with ultimate approval rates ranging from 54% to 100%.

■ **Burnet NG, et al. Proton beam therapy - perspectives on the National Health Service England clinical service and research programme. Br J Radiol. 2020 Mar;93(1107):20190873.**

A review on proton therapy situation in the UK. Since the first proton therapy center opening in Manchester in 2018, by September 2019, 108 patients had started treatment, 60 pediatric, 19 teenagers and young adults, and 29 adults. The review highlighted the vision of building a research capability including translational pre-clinical biological and physical studies; cellular processes of DNA damage response; targeted drugs and immunomodulatory agents and the ultra-high dose rate FLASH irradiation.

■ **Waddle MR, et al. Photon and Proton Radiation Therapy Utilization in a Population of More Than 100 Million Commercially Insured Patients. Int J Radiat Oncol Biol Phys. 2017 Dec 1;99(5):1078-1082.**

This study examined the changes in the use of radiation therapy, specifically proton beam radiation therapy, among adult and pediatric patients over a 11-year period. The greatest increase in utilization was of IMRT for prostate cancer,growing from 3.5% to 64.0%. For all patients, advanced technology (SBRT and PBRT) use was very low at <2%, versus 22% for IMRT.

■ **Weber DC, et al. Profile of European proton and carbon ion therapy centers assessed by the EORTC facility questionnaire.Radiother Oncol. 2017 Aug;124(2):185-189.**

This survey of 15 centers in 8 countries evaluated the human, technical and organizational resources of particle centers in Europe. The average number of patients treated per year and per particle center was 221. All centers treated routinely chordomas, chondrosarcomas, brain tumors and sarcomas but rarely breast cancer. The majority of centers treated pediatric cases with particles.

■ **Baumann BC, et al. Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer. JAMA Oncol. 2019 Dec 26;6(2):237-246.**

1483 adult patients with nonmetastatic, locally advanced cancer treated with concurrent chemoradiotherapy were matched with 391 PBT and 1092 photon-based therapy. Proton chemoradiotherapy was associated with a significantly lower relative risk of 90-day adverse events of at least grade 3 (P=.002), 90-day adverse events of at least grade 2 (P=.006), and decline in performance status during treatment (P<.001). There was no difference in disease-free or overall survival.

■ **Chhabra AM, et al. Prioritization of Proton Patients in the COVID-19 Pandemic: Recommendations From The New York Proton Center. Int J Part Ther. Spring 2020;6(4):38-44.**

The recent COVID-19 pandemic, especially in the United States has made the very challenge of safely balancing a patient's risk of contracting COVID-19, while under active radiation treatment, against their risk of cancer progression. The New York Proton Center established an internal algorithm that considers treatment-related, tumor-related, and patient-related characteristics for a patient prioritization process to triage incoming patient referrals for PBT.

■ **Shih HA, et al. ACR-ASTRO Practice Parameter for the Performance of Proton Beam Radiation Therapy. Am J Clin Oncol. 2020 Mar;43(3):149-159.**

The American College of Radiology (ACR) and the American Society for Radiation Oncology (ASTRO) have jointly developed the practice parameter which is to serve as a tool in the appropriate application of this evolving technology. It addresses clinical implementation of proton radiation therapy, including personnel qualifications, quality assurance standards, indications, and suggested documentation. It is to guide technical use of proton therapy to focus on the best practices.

■ **Sha ST, et al. Trends, Quality, and Readability of Online Health Resources on Proton Radiotherapy. Int J Radiat Oncol Biol Phys. 2020 May 1;107(1):33-38.**

This study examined the quality and readability of the Internet for online health resources (OHR) about proton radiotherapy (PRT). This study found that the volume of search on "proton therapy" increased by an average of 2.0% each year for the last 15 years, however PRT websites require reading levels much higher than currently recommended, making PRT OHR less accessible to the average patient.

■ **Jefferson T, et al. Hadrontherapy for cancer. An overview of HTA reports and ongoing studies. Recenti Prog Med. 2019 Dec;110(12):566-586.**

Hadron therapy often refers to proton therapy (PBT) and carbon ion therapy (CIRT). These are not new technologies but have been subject to assessment by several Health Technology Assessment (HTA) agencies over the past years. This review paper summarized the evidence findings from most recent HTA reports and provided a description of currently ongoing clinical studies.

■ **Seidensaal K, et al. Active-Scanned Protons and Carbon Ions in Cancer Treatment of Patients With Cardiac Implantable Electronic Devices: Experience of a Single Institution. Front Oncol. 2019 Aug 22;9:798.**

A study examed if ionizing radiation influenced the function of cardiac implantable electronic devices (CIED's) leading to malfunctions with potentially severe consequences. 31 patients (22 received carbon ion and 10 proton) were analyzed, among whom 3 patients had an implantable cardioverter-defibrillator (ICD) and 28 patients had a pacemaker at the timeof treatment. This analysis reported that treatment of CIED-patients with protons and carbon ions was safe without any incidents.

■ **Ning MS, Gomez DR, Shah AK, et al. The Insurance Approval Process for Proton Radiation Therapy: A Significant Barrier to Patient Care. Int J Radiat Oncol Biol Phys. 2019 Jul 15;104(4):724-733.**

1753 patients considered for PBT and entered the insurance process were analyzed. Approval rates by Medicare and private insurance were 91% and 30% on initial request. This study concluded that despite an 87% ultimate approval rate for PBT, the insurance process is a resource-intensive barrier to patient access associated with significant time delays to cancer treatment.

■ **Hu M, Jiang L, Cui X, et al. Proton beam therapy for cancer in the era of precision medicine. J Hematol Oncol. 2018 Dec 12;11(1):136.**

A general review on PBT inlcuding dosimetric advantage, clinical data on PBT for ocular tumor, skull base, paraspinal tumors (chondrosarcoma and chordoma), and unresectable sarcomas, reirradiation and pediatrics, as well as the expanded applications as treatment for malignancies of head and neck, lung, liver, breast and prostate.

■ **Li X, Liu G, Janssens G, et al. The first prototype of spot-scanning proton arc treatment delivery. Radiother Oncol. 2019 Aug;137:130-136.**

This paper reported the first prototype of spot-scanning arc treatment (SPArc) delivery on IBA Proteus®One. The brain SPArc plan with similar or superior plan quality was delivered in 4 mins compared to total 11 mins for the clinical treatment of the three-field IMPT plan.

■ **Diffenderfer ES, et al. Design, Implementation, and in Vivo Validation of a Novel Proton FLASH Radiation Therapy System. Int J Radiat Oncol Biol Phys. 2020 Feb 1;106(2):440-448.**

This paper reported the effect of FLASH proton versus standard dose rate PRT on tumors and normal tissues in mice. Dose rates of 78 ± 9 Gy per second and 0.9 ± 0.08 Gy per second for the FLASH and standard PRT were delivered. FLASH-PRT decreases acute cell loss and late fibrosis after whole-abdomen and focal intestinal RT, whereas tumor growth inhibition is preserved between the 2 modalities.

Web References

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- **PubMed:** www.ncbi.nlm.nih.gov/pubmed
- **Particle Therapy Co-Operative Group:** www.ptcog.site
- **PCG:** www.pcgresearch.org
- **EPTN:** www.estro.org/Science/Activities/EPTN
- **PPCR:** www.pediatricradiationregistry.org

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