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# SELECTED PROTON THERAPY BIBLIOGRAPHY

## 2008–2017

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# FOREWORD

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

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

**The amount of clinical data on proton therapy is increasing rapidly, making it a challenge to keep up with new findings and advancements. We decided to take advantage of our day-to-day involvement with experienced clinical teams from proton therapy centers worldwide 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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*1. This literary review is a selection of articles about proton therapy and is not intended to be an exhaustive bibliography.*

# REFERENCE WORKS

- **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.**
  *Here are discussed which conditions are 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 HEALTH ECONOMICS

- **Verma V et al. Cost-comparativeness of proton versus photon therapy. PubMed 27506804 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. PubMed 26828647 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. PubMed 27084617 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. PubMed 25641407 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. PubMed 24187330 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 conventional 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. PubMed 24105630 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 disease, 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.*

- **Lundkvist J et al. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. PubMed 16332952 Acta Oncol. 2005;44(8):850-61.**
  *This review article assessed the cost-effectiveness of proton therapy in the treatment of four different cancers: left-sided breast cancer, prostate cancer, head and neck cancer, and childhood medulloblastoma. The results indicated that proton therapy was cost-effective if appropriate risk groups were chosen.*

# PATIENT SELECTION AND CLINICAL TRIALS

- **Delaney AR et al. Using a knowledge-based planning solution to select patients for proton therapy. PubMed 28411963 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 head and neck patients. The authors reported that this 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. PubMed 28068231 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. PubMed 27671784 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", PubMed 22147003, 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", PubMed 20630388, 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 MALIGNANCY

- **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. PubMed 27789564 J Radiat Res. 2017 May 1;58(3):363-371.**
  *Four categories patients i.e. brain, head and neck; thoracic; abdominal, and whole craniospinal irradiation 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. PubMed 28004469 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. PubMed 26636040 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. PubMed 26230629 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. PubMed 25017376 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. PubMed 24122173 Cancer. 2014 Jan 1;120(1):126-33.**
  *This study followed 55 of whom received proton RT and 31 of whom received photon RT for a median of 6.9 years for proton cohort and13.1 years for 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. PubMed 24180282 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. PubMed 23778197 Int J Radiat Oncol Biol Phys. 2013 Sep 1;87(1):46-52.**
  *This 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. PubMed 21236595 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", PubMed 22968191, 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. PubMed 21016799 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", PubMed 19879701, 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-andneck cancer. The results showed the risk was either significantly lower with PT or, at least, did not exceed the risk induced by conventional IMRT.*

- **Chung C.S. et al., "Comparative analysis of second malignancy risk in patients treated with Proton Therapy versus conventional Photon Therapy", Volume 72, Issue 1, Supplement, Page S8, International Journal of Radiation Oncology, Biology. September 1, 2008**
  *Preliminary results here indicate that the use of PT is associated with a significantly lower risk of secondary malignancies compared to RT, even if additional analyses are required given the prolonged latency period for the development of radiation-induced cancers.*

# CLINICAL INDICATIONS

## CENTRAL NERVOUS SYSTEM MALIGNANCIES

- **Holm AIS et al. Functional image-guided dose escalation in gliomas using of state-of-the-art photon vs. proton therapy. PubMed28464742 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. PubMed 28380636 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. PubMed 27673869 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", PubMed 26340383, 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", PubMed 26112360, 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", PubMed 25859843, 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", PubMed 25585890, 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", PubMed 25557901, 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", PubMed 25304948, 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", PubMed 25194666, 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", PubMed 24752878, 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", PubMed 24498590, 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", PubMed 23824106, 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", PubMed 23609202, 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", PubMed 23433794, 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", PubMed 22138457, 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.*

- **Ares C. et al., "Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report", PubMed 19386442, International Journal of Radiation Oncology, Biology, Physics, 2009 November 15, 75(4):1111-8.**
  *Spot-scanning based PT for skull-base chordomas and chondrosarcomas appears to be effective and safe. With target definition, dose prescription and normal organ tolerance levels similar to passive-scattering PT, complication-free, tumor control and survival rates are comparable.*

- **Delaney T.F. et al., "Phase II study of high-dose photon/proton radiotherapy in the management of spine sarcomas", PubMed 19095372, International Journal of Radiation Oncology, Biology, Physics, 2009, 74 (3):732-9.**
  *Radiotherapy for spine sarcomas is constrained by spinal cord, nerve, and viscera tolerance. Negative surgical margins are uncommon, hence low doses are recommended. A Phase II clinical trial evaluated high-dose photon/proton RT for spine sarcomas: local control appears high in patients radiated at the time of primary presentation.*

## OCULAR MALIGNANCIES AND BENIGN CONDITIONS

- **Kim TW et al. Clinical Outcomes of Proton Beam Therapy for Choroidal Melanoma at a Single Institute in Korea. PubMed 28421723 Cancer Res Treat. 2017 Apr 19.**
  *This retrospective study report outcomes oaf choroidal melanoma patients were 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. PubMed 28607957 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", PubMed 26224096, 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 in but the majority of patients avoided enucleation and functional blindness.*

- **Kim J.Y. et al., "Treatment of Retinoblastoma: The Role of External Beam Radiotherapy", PubMed 26446627, 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 orbital bone 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", PubMed 26160531, 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", PubMed 26133249, 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", PubMed 25442038, 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", PubMed 25128597, 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 zone of 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", PubMed 25227498, 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", PubMed 25038910, 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", PubMed 23040219, 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

- **Hoppe BS et al. Proton therapy patterns-of-care and early outcomes for Hodgkin lymphoma: results from the Proton Collaborative Group Registry. PubMed 27579554 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", PubMed 25669925, 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", PubMed 24842407, Current Hematologic Malignancy Reports, 2014 May 20.**
  *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 CANCER

- **Leeman J E et al. Proton therapy for head and neck cancer: expanding the therapeutic window. PubMed 28456587 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. PubMed 28549794 Radiother Oncol. 2017 Jun;123(3):401-405.**
  *Compared mandibular doses and osteoradionecrosis in patients with oropharyngeal cancer after IMRT or IMPT, this study reported both mandibular doses and osteoradionecrosis rates were 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. PubMed 28039958 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 did XRT at all fraction sizes.*

- **Langendijk JA and Steenbakkers RJ. Optimizing Radiotherapy in HPV-Associated Oropharyngeal Cancer Patients. PubMed 27699537 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. PubMed 27325480 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. PubMed 27788954 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", PubMed 25811343, 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", PubMed 25646551, 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", PubMed 25056641, 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", PubMed 24837890, 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", PubMed 23910474, 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", PubMed 23273998, 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", PubMed 23635259, 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", PubMed 20817407, 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", PubMed 21349950, 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.*

- **Chan A. and Liebsch N., "Proton radiation therapy for head and neck cancer", PubMed 18493920, Journal of surgical oncology, 2008, 97(8):697-700.**
  *Conventional RT can be associated with significant acute and long-term treatment-related toxicities in the treatment of head & neck tumors. Superior dose localization properties of proton radiation therapy allow smaller volumes of normal tissue to be irradiated than is feasible with any photon technique, and initial clinical experience with PT appears promising.*

## LUNG CANCER AND THORACIC MALIGNANCIES

- **Rwigema JM et al. Prospective study of proton-beam radiation therapy for limited-stage small cell lung cancer. PubMed 28678434 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. PubMed 28545956 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. PubMed 28162946 Clin Lung Cancer. 2017 Jul;18(4):364-371.**
  *61 locally advanced NSCLC patients underwent postoperative radiotherapy including 27 patients received PBT and 34 IMRT. One-year median overall survival were 85.2% for PBT and 82.4% for IMRT and local recurrence free survival were 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. 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. PubMed 28139305 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. PubMed 27979443 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", PubMed 26356685, 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", PubMed 27282279, Strahlentherapie und Onkologie, 2016 June.**
  *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", PubMed 26891607, 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", PubMed 27084663, 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", PubMed 26460997, 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", PubMed 25572666, 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", PubMed 26147335, 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", PubMed 25291076, 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", PubMed 25368341, 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", PubMed 25260491, 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", PubMed 25220718, 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 be selected 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", PubMed 25302161, 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", PubMed 24864278, Journal of Radiation Research, 2014 May 25.**
  *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", PubMed 24688779, 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", PubMed 24016675, 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", PubMed 23845845, 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-Gy regimen 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", PubMed 23438357, 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", PubMed 22264659, 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", PubMed 22157368, 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", PubMed 22543217, 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", PubMed 22551902, 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", PubMed 21437893, 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", PubMed 21264827, 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 CANCER

- **Verma V et al. Proton beam radiotherapy as part of comprehensive regional nodal irradiation for locally advanced breast cancer. PubMed 28457577 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. PubMed 28281862 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. PubMed 28244411 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. PubMed 26995159 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.", PubMed 26995159, 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", PubMed 27084617, 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", PubMed 26371777, 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.", PubMed 26530753, 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?", PubMed 26153903, 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", PubMed 25789715, 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", PubMed 25754632, 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?", PubMed 23466577, 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", PubMed 25266130, 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", PubMed 25084608, 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", PubMed 23523326, 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", PubMed 23521809, 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", PubMed 23647751, 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", PubMed 23891102, 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?", PubMed 19615828, 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 CANCER

- **Lischalk J W et al. Radiation therapy for hepatobiliary malignancies. PubMed 28480067 J Gastrointest Oncol. 2017 Apr;8(2):279-292**
  A review article examines 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 caner.*

- **Oshiro Y et al. Analysis of repeated proton beam therapy for patients with hepatocellular carcinoma. PubMed 28366501 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. PubMed 28198132 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. PubMed 28034460 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. PubMed 28012214 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. PubMed 27974509 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", PubMed 27084661, 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", PubMed 26668346, 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", PubMed 26385268, 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", PubMed 25703530, 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", PubMed 26229392, 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", PubMed 25376272, 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", PubMed 25381830, 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", PubMed 25415681, 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", PubMed 24560761, 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", PubMed 24589917, Strahlentherapie und Onkologie, 2014 Mar 4.**
  *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", PubMed 24131485, 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", PubMed 23359779, 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", PubMed 21264826, 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", PubMed 21767180, 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", PubMed 21076199, 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.*

- **Sugahara S. et al. "Proton-beam therapy for hepatocellular carcinoma associated with portal vein tumor thrombosis", PubMed 20013087, Strahlentherapie und Onkologie, 2009 December, 185(12):782-8.**
  *The prognosis of patients with advanced hepatocellular carcinoma with portal vein tumor thrombosis is extremely poor, as effective treatment options are limited. This paper shows that PT improves local control and significantly prolongs survival in these patients.*

## PANCREATIC CANCER

- **Hitchcock K E et al. Feasibility of pancreatectomy following high-dose proton therapy for unresectable pancreatic cancer. PubMed 28503258 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", PubMed 26883369, 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", PubMed 6380057, 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", PubMed 25086521, 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", PubMed 23477361, 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", PubMed 22245197, 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", PubMed 20421151, 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.*

## ESOPHAGEAL CANCER

- **Verma V et al. Advances in Radiotherapy Management of Esophageal Cancer. (PubMed 27775643) 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", (PubMed 27084662) 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", (PubMed 25755255) 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 histogram analysis. 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. (PubMed 28455153) 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.*

- **Chuong M.D. et al., "Improving Outcomes for Esophageal Cancer using Proton Beam Therapy", PubMed 27084662, International Journal of Radiation Oncology, Biology, Physics, 2016 May; 95(1):488-97.**
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  *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 histogram analysis. 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.*

## OTHER GASTROINTESTINAL MALIGNANCIES

- **Patel SA et al. Advancing Techniques of Radiation Therapy for Rectal Cancer. PubMed 27238474 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", PubMed 25734796, 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", PubMed 25415682, 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", PubMed 24490037, 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 CANCER

- **Lin LL et al. Initial Report of Pencil Beam Scanning Proton Therapy for Posthysterectomy Patients With Gynecologic Cancer. PubMed 26372435 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) 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? PubMed 27452411 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. PubMed 27380800 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. PubMed 26934821 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. PubMed 25981130 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 CANCER

- **Mendenhall N P et al. Comparison of clinical outcomes with IMRT and proton therapy for prostate cancer. J Clin Oncol 35, 2017 (suppl; abstr e16555)**
  *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.*

- **Henderson R H et al. Five-year outcomes from a prospective trial of image-guided accelerated hypofractionated proton therapy for prostate cancer. PubMed 28514929 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). PubMed 28366513 Eur Urol. 2017 Mar 30.**
  *49 literatures were identified and analyzed about cost and cost-effectiveness of RARP, IMRT and PBT. 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. PubMed 27558255 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. PubMed 27084659 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. PubMed 27084658 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", PubMed 24521677, 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", PubMed 25009446, 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", PubMed 22253020, 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", PubMed 21093164, 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", PubMed 20832180, 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", PubMed 20124169, Journal of Clinical Oncology (ASCO), 2010, 28 (7):1106-11.**

  *This randomized controlled trial aimed at testing 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

- **GUTTMANN DM ET AL. A PROSPECTIVE STUDY OF PROTON REIRRADIATION FOR RECURRENT AND SECONDARY SOFT TISSUE SARCOMA. PUBMED 28697854 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 29months, 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. PubMed 28463156 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 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. PubMed 28182320 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 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. PubMed 28506520 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. PubMed 27247057 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. PubMed 27084648 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. PubMed 26340380 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", PubMed 21448934, Cancer, 2011, 117(19):4522-30.**
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## PEDIATRIC MALIGNANCIES

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  *2004 (1.7%) and 2013 (17.5%). Patients with higher median household income with private/managed care were more likely received proton therapy than patients with Medicaid or no insurance. Improving access to proton therapy in underserved pediatric populations is essential.*

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- **Mailhot Vega R. et al., "Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children", PubMed 25641407, Cancer Cytopathology, 2015 May 15, 121(10):1694-702.**
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- **Alliance for Proton Therapy Access :** www.allianceforprotontherapy.org

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