SELECTED PROTON THERAPY BIBLIOGRAPHY
2008–2016

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FOREWORD

Since IBA first started to develop proton therapy solutions, we have focused on collaboration and sharing information. This culture of cooperation allows us to work collectively with clinical partners to extend the body of knowledge in Proton Therapy.

Our purpose is simply to offer more cancer patients 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 exercise with care; nevertheless, the reader needs be aware that the selection only represents a small percentage of the amount of publications available on proton therapy. We encourage you to interpret this information carefully and exercise your own critical and scientific judgment.

The IBA team believes in the benefits of proton therapy for patients and society. These information exemplify 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

- 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.

GENERAL ARTICLES

- 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.

- 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.

- 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-and-neck cancer. The results showed the risk was either significantly lower with PT or, at least, did not exceed the risk induced by conventional IMRT.

- Chung C.S. et al., “Comparative analysis of second malignancy risk in patients treated with Proton Therapy versus conventional Photon Therapy”, Red Journal S0360-3016(08)01001-8, International Journal of Radiation Oncology, Biology, 2008 September 1. 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

  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.

  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.

  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.

  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.

  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.

  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.

  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.

  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.

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.


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.


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.


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.


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.


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.


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

  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.

  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.

  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.

  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.

  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.

  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.

  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.

  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.

  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

  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.

  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 MALIGNANCIES

  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.

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

  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.

  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.

  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.

  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.

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.


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.


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


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.


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


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.


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.

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.


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.


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.


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.


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.


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.


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.


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.


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.


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 MALIGNANCIES**


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.

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 improves provided 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.


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 MALIGNANCIES

  The authors report a trend toward improved local control and improved progression-free survival with proton therapy compared to transcatheater arterial chemoembolization (TACE), the “standard treatment” for unresectable hepatoma.

  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.

  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.

  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.

  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.

  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.

  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.

  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.

  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.

  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.
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.

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.

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.

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.

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.

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 MALIGNANCIES

  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.

  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.

  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.

  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.

  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.

  This study shows the safety and feasibility of 1 week of chemoradiation with PT and capecitabine followed by early surgery.

GASTROINTESTINAL MALIGNANCIES

  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.

  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.
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.

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.

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.

CERVICAL MALIGNANCIES

In patients who are not eligible for brachytherapy, IMPT as a boost technique additionally to external beam radiation therapy provides good target coverage and conformity and superior dose-volume parameters, compared with recommendations to MRI-guided brachytherapy. For selected patients, IMPT might be a valid alternative to brachytherapy and also superior to reference VMAT plans.

PROSTATE MALIGNANCIES

Five-year clinical outcomes with image-guided PT for prostate cancer included extremely high efficacy, minimal physician-assessed toxicity, and excellent patient-reported outcomes.

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.

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.

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.
Selected Proton Therapy Bibliography | September 2016


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.


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


A study was undertaken to assess clinical outcomes and the role of PT for local control of osteosarcoma. It was shown that PT to deliver high radiotherapy doses allows locally curative treatment for some patients with unresectable or incompletely resected osteosarcoma.

PEDIATRIC MALIGNANCIES


Compared to photon RT, proton therapy reduces the radiation dose to OAR, which is expected to translate into less long-term morbidity. Proton therapy for pediatric Hodgkin lymphoma shows no short-term severe toxicity and yields similar short-term control to recently published large multi-institutional clinical trials.


Data indicate the safety and effectiveness of proton therapy in this study assessing the clinical outcomes and late side effects of pencil beam scanning proton therapy delivered to children with intracranial ependymoma.


This paper assesses the clinical outcomes in children with rhabdomyosarcoma (RMS) treated with pencil beam scanning PT. PBS proton therapy led to excellent outcomes, with minimal late non-ocular toxicity and good QoL.


This paper compares long term IQ change in pediatric patients with brain tumors treated with proton therapy or RT. It remains unclear if proton therapy results in clinically meaningful cognitive sparing that significantly exceeds that of modern radiation therapy protocols. Additional long-term data are needed.


Brain tumors are the most frequent radiation therapy indications in pediatrics, with frequent late toxic effects on cognitive, osseous, visual, auditory and hormonal systems. Both proton therapy and carbon ion therapy show promising results, with the benefit of decreasing late effects without altering global survival.
This paper reports disease control, survival and treatment-associated toxicity with the use of proton therapy for re-irradiation of intracranial ependymoma. Proton therapy appears safe and efficacious for this specific indication of treatment.

This retrospective study evaluates acute toxicity profiles and dosimetric data for children with salivary gland tumors treated with adjuvant photon/electron-based radiation therapy or proton therapy. Proton therapy was associated with a more favorable acute toxicity and dosimetric profile. Continued follow-up is needed to identify long-term toxicity and survival data.

Proton therapy may prove to be cost effective if chronic medical complications can be avoided. This paper is the first evidence-based guide for identifying children with brain tumors who may benefit the most from proton therapy with respect to endocrine dysfunction: Proton therapy proves to be more cost effective when the hypothalamus can be spared.

This study provides the first evidence-based guide for identifying children with brain tumors who may benefit the most from PT with respect to endocrine dysfunction. Indeed, PT may be more cost effective when the radiation dose to the hypothalamus can be spared, but not when tumors are involving or directly adjacent to the hypothalamus.

Esthesioneuroblastoma of the paranasal sinus comprises less than 3% of tumors in pediatric and adolescent patients. The collective adult literature indicates a critical role for radiotherapy in attaining cure, yet pediatric outcome data is limited. This study shows that PT provides excellent locoregional disease control even in patients with locally advanced disease and intracranial extension.

The aim of this study is to evaluate the efficacy of PT for pediatric patients with ependymoma. Proton beam therapy for pediatric ependymoma is safe, does not have specific toxicities, and can reduce irradiation of normal brain tissue.

The aim of this analysis is to assess the early clinical results of PBS PT in the treatment of young children with non-metastatic atypical teratoid/rhabdoid tumor of the central nervous system. PBS PT is proven to be an effective treatment for those patients, with manageable acute toxicity.

Atypical teratoid/rhabdoid tumor (AT/RT) of the CNS is a rare cancer primarily affecting children younger than 5 years old. This paper is the largest report of children with AT/RT treated with PT, and preliminary survival outcomes in this young pediatric population are encouraging compared to historic results.

PT offers superior low and intermediate radiation dose distribution compared with photon RT for brain and skull base tumors. This article investigates the tolerance of the pediatric brainstem to PT and shows that the utilization of current national brainstem dose guidelines is associated with a low risk of brainstem toxicity in pediatric patients. For posterior fossa tumors, particularly after aggressive surgery, the study suggests more conservative dosimetric guidelines should be considered.

This paper compares PT with IMRT for pediatric craniopharyngioma in terms of disease control, cyst dynamics and toxicity.


This paper compares the acute toxicity of PT craniospinal irradiation (CSI) to that of conventional RT CSI in children with brain tumors: the incidence rates of thrombocytopenia and diarrhoea were lower with PT than with RT, and one month after treatment, the recovery from leukopenia and thrombocytopenia was better in patients treated with PT.


PT has been used safely and effectively for medulloblastoma, primitive neuro-ectodermal tumors, craniopharyngioma, ependymoma, germ cell intracranial tumors, low-grade glioma, retinoblastoma, rhabdomyosarcoma and other soft tissue sarcomas, Ewing’s sarcoma and other bone sarcomas. Other possible applications are emerging. The main advantage of PT is the sparing of intermediate-to-low-dose to healthy tissue.


Primary low-grade gliomas are common brain tumors of childhood, and many of them require radiation therapy as definitive treatment. Increased conformality could decrease the incidence and severity of late effects. PT appears to be associated with good clinical outcomes, especially when the tumor location allows for increased sparing of the left temporal lobe, hippocampus, and hypothalamic-pituitary axis.


This study describes the early clinical outcomes of a prospective phase 2 study of consolidative involved-node PT as a component of combined-mode therapy in patients with stages I to III Hodgkin lymphoma with mediastinal involvement.


The incidence of second malignant tumors is a clinically observed adverse late effect of radiation therapy. This study aims to evaluate the risk of second cancer incidence for pediatric patients with brain/head and neck tumors and compare passive scattering and pencil beam scanning PT, IMRT and VMAT.


This study examines the metastatic and survival rates, eye retention probability and visual outcomes of juvenile patients after PT for uveal melanoma. It is shown that metastatic and survival rates are significantly better for juvenile than for adult patients.


Radiotherapy plays an integral role in the local control of pediatric sarcomas, which often arise adjacent to critical structures and growing organs. PT shows either equivalent or improved outcomes, and lower toxicity for soft tissue sarcoma compared to RT. For bone and cartilaginous sarcomas, a clearer advantage exists for PT due to its ability to increase total dose while respecting adjacent structures.


Ependymoma is treated with maximal surgical resection and localized radiotherapy. Minimizing unnecessary exposure to radiation is of paramount importance for young children. PT spares healthy tissue outside the target region, and outcomes for children treated with PT compare favorably with the literature.

Upfront chemotherapy followed by 3D PT presents good disease early outcomes for very young children with medulloblastoma or supratentorial primitive neuroectodermal tumor.


PT appears to be well tolerated in pediatric patients with CNS malignancies. Acute toxicity can be managed with supportive care.


Early screening for breast cancer may be unnecessary after craniospinal irradiation with PT, whereas it should be considered with X-ray therapy, given doses to the breast that approach the Children’s Oncology Group-recommended threshold.


Spot-scanning PT shows excellent clinical outcomes with acceptable rates of late toxicity in pediatric patients with chordoma or chondrosarcoma of the skull base or axial skeleton.


This study presents preliminary clinical outcomes including late effects on pediatric Ewing’s sarcoma patients treated with PT. This treatment modality was well tolerated with few adverse events.


Pediatric patients who received radiation therapy are at risk of developing side effects such as radiogenic second cancer. PT confers lower predicted risk of second cancer than RT for pediatric medulloblastoma patients receiving craniospinal irradiation.


PT offers a powerful treatment option in the pediatric population, where adverse events related to radiation exposure are of concern. This study reports acute toxicities and preliminary outcomes for pediatric patients with ependymomas of the spine treated with PT at the MD Anderson Cancer Center.


Children treated for CNS tumors with conventional RT or cranial radiation therapy (CRT) are at high risk of neurocognitive impairment or dysfunction. Delaying CRT or reducing dose of CRT in adjuvant chemotherapy was associated with better long-term cognitive function. Proton therapy represents an alternative to photon radiotherapy, which may now offer the next step with respect to both survival and long-term neurocognitive functioning.


The increasing efficacy of pediatric cancer therapy has produced many long-term survivors who now struggle with serious morbidities mostly related to radiation therapy. PT holds great promise to drastically reduce these treatment-related late effects in long term survivors by reducing dose to normal tissue.

This paper reports the clinical outcomes of 7 children with bladder/prostate rhabdomyosarcoma treated with PT and compares PT plans with matched IMRT plans, with an emphasis on dose savings to reproductive and skeletal structures. PT provides significant dose savings to normal structures compared to IMRT and is well tolerated in this patient population.


This paper reports early clinical outcomes for children with CNS germ cell tumors treated with PT and compares dose distributions for IMRT, 3D-CPT and IMPT with PBS for whole-ventricular irradiation with and without an involved-field boost. Preliminary disease control with PT compares favorably to the literature and dosimetric comparisons demonstrate the advantage of PT over IMRT for whole-ventricle radiation, with superior dose distributions and fewer beam angles.


This paper evaluates outcomes and tolerance of high-dose RT and PT in the management of skull base and cervical canal primary bony malignancies in children. High-dose combined fractionated photon-proton therapy is well tolerated in children and allows excellent local control with minimal long-term toxicity.


This study reports on clinical outcomes for pediatric patients treated with PT for intracranial ependymoma and compares the dose distributions of IMRT, 3D conformal PT and IMPT.

WEB REFERENCES

- National Association for Proton Therapy: www.proton-therapy.org
- OncoLink: www.oncolink.org
- Pediatric Proton Foundation: www.pediatricprotonfoundation.org
- Proton Therapy Today: www.protontherapytoday.com
- Particle Therapy Co-Operative Group: www.ptcog.ch
The amount of research on Proton Therapy is growing day by day. We have summarized some of this key research in a series of white papers and we are preparing new ones on a regular basis.

These publications are available to download at [http://www.iba-worldwide.com/media-room/whitepapers](http://www.iba-worldwide.com/media-room/whitepapers)

- “Proton Therapy In Oncology”, A General Overview Of Current Practice, Opportunities And Challenges, Fall 2015
- “Treating Pediatric Tumors With Proton Therapy”, Current Practice, Opportunities And Challenges, Fall 2015
- “Treating Central Nervous System Tumors with Proton Therapy”, Current Practices, Opportunities and Challenges, To be defined
- “Treating Sarcoma (large / retroperitoneal / extremities) with Proton Therapy”, Current Practices, Opportunities and Challenges, To be defined
- “Re-irradiation with Proton Therapy”, Current Practices, Opportunities and Challenges, To be defined

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