

Proton Therapy Efficacy: Clinical Summaries

Proton therapy (PT), an advanced form of radiotherapy, is capable of efficiently treating cancerous tumors while reducing radiation doses to surrounding healthy tissues and organs. With its unique characteristics, PT can, therefore, deliver curative radiation doses to tumors while also resulting in fewer complications and side effects than standard radiation therapy.

Large numbers of trials continue to examine the clinical advantages of this treatment modality. This document summarizes recent key publications and their clinical findings, as well as important ongoing studies. It is not intended to be an exhaustive list of PT literature.

Proton Therapy for Liver Cancer: Hepatocellular Carcinoma (HCC)

Sanford NN, Pursley J, Noe B, et al. *Int J Radiat Oncol Biol Phys*. 2019; in press.

Protons versus photons for unresectable hepatocellular carcinoma: liver decompensation and overall survival.

- Patients with unresectable HCC received proton therapy (PT, n = 49) versus photon ablative radiation therapy.
- Results showed median overall survival of:
 - 31 months with PT
 - 14 months with photon therapy
- PT also showed a decreased risk of non–classic radiation-induced liver disease (odds ratio, 0.26; p = 0.03).
- PT was associated with improved survival, which may be due to decreased posttreatment liver decompensation.

Chadha AS, Gunther JR, Hsieh CE, et al. *Radiother Oncol*. 2019;133:54-61.

Proton beam therapy (PT) outcomes for localized unresectable hepatocellular carcinoma.

- In this population (n = 46), high-dose PT is associated with high rates of local control (LC) and overall survival (OS) for unresectable HCC, and dose escalation may further improve outcomes.
- With multivariate analysis, higher biologically effective dose significantly predicted improved OS (p = 0.023; HR = 0.308).
- Among patients with inherently compromised liver function—who would not otherwise be candidates for standard radiation therapy—PT is a potential definitive treatment option for unresectable HCC patients.

Kim TH, Park JW, Kim BH, et al. *Cancers*. 2019;11(2):230.

Does risk-adapted proton beam therapy (PT) have a role as a complementary or alternative therapeutic option for HCC?

- In this study (n = 243) the 5-year local recurrence-free survival and overall survival rates were 87.5% and 48.1%, respectively; grade ≥ 3 toxicity was 0.4%.
- PT could achieve promising long-term tumor control and be used as an alternative or complementary therapy in all stages of HCC.

Yu JI, Yoo GS, Cho S, et al. *Radiat Oncol J*. 2018;36(1):25-34.

Initial clinical outcomes of proton beam radiotherapy (PT) for HCC.

- PT treatment (n = 101) showed a favorable infield complete response rate of 69.2% and partial response rate of 17.9%.
- There was a grade III duodenal ulcer (n = 1), yet the overall 5.0% rate of other gastroduodenal toxicities were mild and acceptable compared to other recent studies (which reported 9.8%).

Fuduka K, Okumura T, Abei M, et al. *Cancer Sci*. 2017;108:497-503.

Long-term outcomes of proton beam therapy (PT) in patients with previously untreated HCC.

- PT showed favorable 5-year efficacies, with local tumor control, progression-free survival, and overall survival, respectively, as follows:
 - 94%, 28%, and 69% for stage 0/A
 - 87%, 23%, and 66% for stage B
 - 75%, 9%, and 25% for stage C
- There were no grade ≥ 3 adverse effects in this population (n = 129).
- In conclusion, PT achieved long-term tumor control with minimal toxicity.

Kim TH, Park JW, Kim BH, et al. *Oncotarget*. 2017;9(3):4034-4043.

Optimal time of tumor response evaluation and effectiveness of hypofractionated proton beam therapy (PT) for inoperable or recurrent HCC.

- Though the optimal time of response for HCC radiotherapy has not been well-defined, the authors found that complete response was achieved in 94% of patients (total population n = 71) within 1 year after PT, with a median time to CR of about 6 months.
- There were no grade ≥3 toxicities.
- PT could be good alternative for HCC patients unsuitable for surgical resection or local ablative therapy.

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

Hong TS, Wo JY, Yeap BY, et al. *J Clin Oncol*. 2016;34(5):460-468.

Multi-institutional phase II study of high-dose hypofractionated proton beam therapy (PT) in patients with localized, unresectable HCC and intrahepatic cholangiocarcinoma (ICC).

- The 2-year data (n = 92) showed:
 - Local control of 94.8% for HCC and 94.1% for ICC
 - Overall survival of 63.2% for HCC and 46.5% for ICC
- High-dose hypofractionated PT revealed high local control rates for HCC and ICC, safely supporting ongoing phase III trials.

Bush DA, Smith JC, Slater JD, et al. *Int J Radiat Oncol Biol Phys*. 2016;95(1):477-482.

Randomized clinical trial comparing proton beam radiation therapy (PT) with transarterial chemoembolization (TACE) for HCC: results of an interim analysis.

- Among these patients (n = 69) there was similar overall survival for PT and TACE, yet with PT there was a trend toward improved local tumor control (88% vs 45%, p = 0.06) and progression-free survival (48% vs 31%, p = 0.06).
- Significantly reduced hospitalization after PT vs TACE (24 vs 166 days, p < 0.001) may indicate reduced toxicity with PT.

Dionisi F, Widesott L, Lorentini S, et al. *Radiother Oncol*. 2014;111(1):1-10.

Is there a role for proton therapy (PT) in the treatment of HCC? A systematic review.

- Data from 16 studies reporting on more than 900 patients revealed that, at the time of publication, passive scattering was the most frequently used PT delivery technique.
- Local control was approximately 80% at 3-5 years; average 5-year overall survival was 32%. There was low toxicity (mainly GI).
- There is a strong rationale to enroll patients in prospective studies.

Fukumitsu N, Sugahara S, Nakayama H, et al. *Int J Radiat Oncol Biol Phys*. 2009;74(3):831-836.

A prospective study of hypofractionated proton beam therapy (PT) for patients with HCC.

- This study examined patients (n = 51) with HCC more than 2 cm away from the porta hepatis or gastrointestinal tract, all of whom were treated with PT.
- Results at 3 and 5 years post treatment, respectively, showed:
 - Local control rates of 94.5% and 87.8%
 - Overall survival rates of 49.2% and 38.7%
- Post-treatment serum alpha-fetoprotein values were significantly reduced when compared with pretreatment values (p < 0.0001).
- There were 3 patients who experienced late sequelae of grade 2+; all remaining patients experienced only minor acute reactions of grade 1 or less.

Key Ongoing Studies

Hong T, et al.

A Phase III randomized trial of protons vs photons for HCC.

- This randomized Phase III trial (estimated n = 186) is examining proton therapy (PT) vs photon therapy in hepatocellular carcinoma patients.
 - Primary outcome measures: overall survival
 - Secondary outcome measures: progression-free survival, local progression, and toxicity
- Estimated completion: 2027

Lin SM, Huang BS, et al.

Proton beam radiotherapy (PT) vs switching control radiofrequency ablation for patients with medium or large treatment-naïve HCC.

- Patients (estimated n = 166) in this prospective, randomized trial will be treated with either PT or multiple-electrode radiofrequency ablation with switching controller (ME-SWC RFA).
 - Primary outcome measures: local control rate
 - Secondary outcome measures: overall survival, distant metastasis-free survival
- The investigators will also use next generation sequencing (NGS) to examine the gene expression profile of tumor samples.
- Estimated completion: 2021

Devera M, et al.

Randomized controlled trial of transarterial chemoembolization (TACE) vs proton beam radiotherapy (PT) for the treatment of HCC.

- This is the first randomized trial to compare, head-to-head, the efficacy of TACE vs PT in HCC patients (estimated n = 220).
 - Primary outcome measures: overall survival
 - Secondary outcome measures: time to progression, downstaging

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Proton Therapy for Non-Small Cell Lung Cancer (NSCLC)

Kim H, Pyo H, Noh JM, et al. *Radiat Oncol*. 2019;14(1):19.

Preliminary result of definitive radiotherapy (RT) in patients with NSCLC who have underlying idiopathic pulmonary fibrosis: comparison between x-ray and proton therapy (PT).

- Because idiopathic pulmonary fibrosis (IPF) can lead to fatal complications post RT, patients who developed IPF were evaluated (n = 30) to determine therapeutic differences in conventional x-ray RT vs PT.
- Outcomes associated with PT vs x-ray RT, respectively, were as follows:
 - Treatment-related death: 0% vs 18.2%
 - The 1-year overall survival: 66.7% vs 46.4%
- PT may be helpful to reduce acute and fatal complications related to IPF.

Badiyan SN, Rutenberg MS, Hoppe BS, et al. *Pract Radiat Oncol*. 2019. pii: S1879-8500(19)30056-6.

Clinical outcomes of patients with recurrent lung cancer reirradiated with proton therapy on the Proton Collaborative Group and University of Florida Proton Therapy Institute Prospective Registry Studies.

- This is the largest such cohort of patients treated with PT published to date (2019): 479 patients with NSCLC and 158 patients with small cell lung cancer (SCLC).
- Pencil beam scanning (PBS) may be ideally suited for reirradiation in the setting of recurrent disease.
- Overall the findings showed that reirradiation with PT is well tolerated and with acceptable toxicity and encouraging efficacy.

Stage I NSCLC

Nantavithya C, Gomez DR, Wei X, et al. *Int J Radiat Oncol Biol Phys*. 2018;101(3):558-563.

Phase 2 study of stereotactic body radiation therapy (SBRT) and stereotactic body proton therapy (SBPT) for high-risk, medically inoperable, early-stage NSCLC.

- Data at 3 years (n = 19) revealed the following from the SBPT group vs the SBRT group, respectively:
 - The 3-year overall survival differed significantly: 90% vs 27.8%
 - Local control: 90% vs 87.5%
 - Regional control: 90% vs 47.6%
- Poor accrual led to early closure of the trial, thus limiting accurate assessment of efficacy.

Chi A, Chen H, Wen S, et al. *Radiother Oncol*. 2017;123(3):346-354.

Comparison of particle beam therapy and stereotactic body radiotherapy (SBRT) for early stage non-small cell lung cancer: a systematic review and hypothesis-generating meta-analysis.

- This systematic review examined 72 SBRT studies and 9 hypo-fractionated particle beam therapy studies.
- Particle beam therapy (proton or carbon ions) was associated with improved overall survival (OS; p = 0.005) and progression-free survival (p = 0.01) in a univariate meta-analysis.
- Yet OS did not reach statistical significance in the final multivariate meta-analysis.

Makita C, Nakamura T, Takada A, et al. *Acta Oncol*. 2015;54(3):307-314.

High-dose proton beam therapy (PT) for stage I NSCLC: clinical outcomes and prognostic factors.

- Among all patients (n = 56), those with peripherally located tumors were given 66 Gy relative biological dose effectiveness (RBE) over 10 fractions (Protocol A) while those with centrally located tumors were given 80 Gy (RBE) over 25 fractions (Protocol B).
- The 3-year results showed:
 - Overall survival of 81.3%
 - Progression-free survival of 73.4%
 - Local control of 96.0%
 - No significant differences in outcomes between the two protocols

Kanemoto A, Okumura T, Ishikawa H, et al. *Clin Lung Cancer*. 2014;15(2):e7-12.

Outcomes and prognostic factors for recurrence after high-dose proton beam therapy (PT) for centrally and peripherally located stage I NSCLC.

- Patients (n = 74) with centrally or peripherally located stage I NSCLCs (n = 80 sites) were treated with PT. A protocol using 72.6 Gy (relative biological effectiveness, RBE) in 22 fractions was used for centrally located tumors, and 66 Gy (RBE) in 10 or 12 fractions was used for peripherally located tumors.
- Results at 3 years revealed:
 - Overall survival of 76.7%
 - Disease-specific survival of 83.0%
 - Progression-free survival of 58.6%
 - Local control rate of 86.2% for stage IA tumors and 67.0% for stage IB tumors
 - Local control rate of 63.9% for centrally located tumors using 72.6 Gy (RBE) and 88.4% for peripherally located tumors using 66 Gy (RBE)
- Radiation dose was shown to be the most significant prognostic factor for tumor control (vs other factors: tumor diameter or patient age).

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

Bush DA, Cheek G, Zaheer S, et al. *Int J Radiat Oncol Biol Phys*. 2013;86(5):964-968.

High-dose hypofractionated proton beam radiation therapy (PT) is safe and effective for central and peripheral early-stage NSCLC: results of a 12-year experience at Loma Linda University Medical Center.

- Eligible subjects (n = 111), who were medically inoperable or refused surgery, received hypofractionated PT to the primary tumor only.
- The initial dose was 51 Gy in 10 fractions, followed by 60 Gy in 10 fractions. An interim analysis showed that local control was insufficient with 60 Gy and the protocol was amended to increase the dose to 70 Gy in 10 fractions for the final phase of the trial.
- Results revealed:
 - All patients showed improved overall survival (OS) with increasing dose level.
 - A significant improvement in OS was noted with increasing PT dose of up to 70 Gy. The 4-year OS was 18% at 51 Gy, 32% at 60 Gy, and 51% at 70 Gy (p = 0.006).
 - The 4-year data for peripheral T1 tumors revealed: local control of 96%, disease-specific survival of 88%, and OS of 60%.
- High-dose hypofractionated PT achieves excellent outcomes for lung carcinomas that are peripherally or centrally located. The 70-Gy regimen has been adopted as standard therapy for T1 tumors at our institution.

Locally Advanced NSCLC

Liao Z, et al. *J Clin Oncol*. 2018;36(18):1813-1822.

Bayesian adaptive randomization trial of passive scattering proton therapy (PSPT) and intensity modulated photon radiotherapy (IMRT) for locally advanced NSCLC.

- This randomized trial compared outcomes with PSPT (n = 57) vs IMRT (photon) (n = 92), both with concurrent chemotherapy.
- PSPT significantly reduced heart exposure, both radiation dose and heart volume.
- PSPT did not improve dose-volume indices for lung, and there was no benefit in radiation pneumonitis and local failure—presumably reflecting the use of relatively large safety margins for the 3-D scattering proton beams.

Chang JY, Verma V, Li M, et al. *JAMA Oncol*. 2017;3(8):e172032.

Proton beam radiotherapy and concurrent chemotherapy for unresectable stage III NSCLC: final results of a phase 2 study.

- Of the 64 patients enrolled, 17 were available at last follow-up: the 5-year data show that concurrent chemotherapy and passively scattered proton beam therapy (PT) to treat unresectable NSCLC offer promising clinical outcomes and comparable toxicity rates (compared with historical photon data):
 - Survival was 27% at last follow-up.
 - Median overall survival was 26.5 months.

Higgins KA, O'Connell K, Liu Y, et al. *Int J Radiat Oncol Biol Phys*. 2017;97(1):128-137.

National cancer database analysis of proton versus photon radiation therapy in NSCLC.

- Study data 2004-2012 identified 243,822 patients—243,474 treated with photon radiation and 348 treated with proton therapy (PT). Data revealed:
 - Patients in an area with < \$46,000 annual median income were less likely to receive PT.
 - The 5-year overall survival, via propensity matched analysis, was better with PT (22%) vs non-PT (16%; p = 0.025).
 - For stage II and III patients, non-PT was associated with worse survival compared with PT (p < 0.01).

Oshiro Y, Mizumoto M, Okumura T, et al. *J Thorac Oncol*. 2012;7(2):370-375.

Results of proton beam therapy (PT) without concurrent chemotherapy for patients with unresectable stage III NSCLC.

- Planned total doses in this retrospective study (n = 57) ranged from 50 to 84.5 GyE (median, 74 GyE).
- Results revealed:
 - Median overall survival (OS) of 21.3 months
 - 1- and 2-year OS of 65.5% and 39.4%, respectively
 - 1- and 2-year local control rates of 79.1% and 64.1%, respectively
 - Toxicity: grade ≥ 3 lung toxicity in 6 patients; grade ≤ 2 esophageal toxicity; no cardiac toxicity
- While the prognosis of patients with unresectable stage III NSCLC is poor without chemotherapy, these data suggest that high-dose PT is beneficial and tolerable for these patients.

Sejpal S, Komaki R, Tsao A, et al. *Cancer*. 2011;117(13):3004-3013.

Early findings on toxicity of proton beam therapy (PT) with concurrent chemotherapy for NSCLC.

- In this population (n = 62) authors examined PT vs photon radiotherapy (RT) delivered either as 3-D conformal RT (3D-CRT) or intensity-modulated RT (IMRT).
- Median total radiation was greater at 74 Gy (RBE) for PT versus 63 Gy for the photon groups.
- Severe (grade ≥ 3) pneumonitis and esophagitis rates were, respectively (p < 0.001 for all):
 - PT group: 2% and 5%, despite the higher radiation dose
 - IMRT group: 9% and 44%
 - 3D-CRT group: 30% and 18%

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

Chang JY, Komaki R, Lu C, et al. *Cancer*. 2011;117(20):4707-4713.

Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III NSCLC.

- In this population (n = 44), passively scattered proton-beam therapy (PT) was used concurrently with chemotherapy.
- At 1 year overall survival was 86%, and progression-free survival was 63%.
- 20.5% (n = 9) of patients experienced local disease recurrence; only 9.1% (n = 4) had isolated local failure. No patients experienced grade 4 or 5 proton-related adverse events.
- The median survival time of 29.4 months is encouraging for unresectable stage III NSCLC.

Postoperative Radiation Therapy (PORT) for NSCLC

Remick JS, Schonewolf C, Gabriel P, et al. *Clin Lung Cancer*. 2017;18(4):364-371.

First clinical report of proton beam therapy (PT) for postoperative radiotherapy for NSCLC.

- Patients with locally advanced NSCLC received PORT—either PT (n = 27) or intensity-modulated radiation therapy (IMRT, n = 34)—and data on the two treatments, respectively, were:
 - Grade 3 radiation esophagitis in 1 of 27 (3.7%) vs 4 of 34 (11.8%) patients
 - 1-year median overall survival of 85.2% vs 82.4%

Key Ongoing Studies

Simone CB, Liao Z, et al.

A Phase III randomized trial comparing overall survival after photon vs proton chemoradiotherapy for inoperable stage II-III NSCLC.

- This randomized study (estimated n = 330) is examining efficacy of proton chemoradiotherapy (PT) vs photon chemoradiotherapy.
 - Primary outcome measure: overall survival
 - Secondary outcome measures: progression-free survival, adverse events
- Estimated completion: 2025

Hoppe B, et al.

A Phase I/II study of hypofractionated proton therapy (PT) for stage II-III NSCLC.

- This study (estimated n = 61) is assessing the safety and efficacy of hypofractionated PT with concurrent chemotherapy.
 - Primary outcome measure: maximum tolerated dose of radiotherapy, 12-month survival
 - Secondary outcome measures: adverse events, disease control, overall survival
- Estimated completion: 2038

Schild SE, et al.

Phase II trial of standard chemotherapy plus proton beam therapy (PT) to determine optimal dose of PT for unresectable Stage 2/3 NSCLC.

- This randomized study (estimated n = 120) is examining efficacy of proton therapy (PT) dosage.
 - Primary outcome measure: progression-free survival
- Estimated completion: 2023

Proton Therapy for Central Nervous System (CNS) Cancers

Petr J, Platzek I, Hofheinz F, et al. *Radiother Oncol*. 2018;128(1):121-127.

Photon vs proton radiochemotherapy: effects on brain tissue volume and perfusion.

- Post-resection, glioblastoma patients underwent adjuvant photon (n = 47) or proton radiochemotherapy (n = 19). Results showed that the tissue volume decrease in gray matter (GM) and white matter (WM) depends on radiation dose to the healthy hemisphere and also differs between treatment modalities:
 - Photon: decreased GM of -2.2% (p < 0.001) and WM of -1.2% (p < 0.001) vs pre-radiotherapy baseline
 - Proton: no significant differences in GM (0.3%, p = 0.64) or WM (-0.4%, p = 0.58) vs baseline
- The decrease in perfusion was comparable for both treatment modalities.
- Proton therapy may reduce brain-volume loss when compared to photon therapy.

Weber DC, Schneider R, Goitein G, et al. *Int J Radiat Oncol Biol Phys*. 2012;83(3):865-871.

Spot scanning-based proton therapy (PT) for intracranial meningioma: long-term results from the Paul Scherrer Institute.

- The 5-year actuarial local control and overall survival rates were 84.8% and 81.8%, respectively, for the entire cohort (n = 39) and 100% for benign histology.
- PT is a safe and effective treatment for patients with untreated, recurrent, or incompletely resected intracranial meningiomas.

Silander H, Pellettieri L, Enblad P, et al. *Acta Neurol Scand.* 2004;109(2):85-90.

Fractionated, stereotactic proton beam treatment of cerebral arteriovenous malformations (AVMs).

- Proton therapy (PT) is successful in a relatively high proportion of intermediate- and large-sized cerebral AVMs (n = 26).
- The advantage of PT (compared with gamma knife and LINAC stereotactic irradiation) is that protons can irradiate even large volumes with a very sharp dose profile against normal surroundings.
- Thus, PT is a valuable option for treating AVMs larger than 10 ml.

Weber DC, Chan AW, Bussiere MR, et al. *Neurosurgery.* 2003;53(3):577-586.

Proton beam radiosurgery for vestibular schwannoma: tumor control and cranial nerve toxicity.

- The 2- and 5-year tumor control rates were 95.3% and 93.6% (n = 88).
- Proton beam stereotactic radiosurgery has been shown to be an effective means of tumor control, exhibiting a high radiological response rate.
- Results showed excellent facial and trigeminal nerve function preservation rates.

Noël G, Habrand JL, Mammar H, et al. *Strahlenther Onkol.* 2002;178(9):480-485.

Highly conformal therapy using proton component in the management of meningiomas. Preliminary experience of the Centre de Protonthérapie d'Orsay.

- Patients with intracranial meningiomas were treated with an escalated dose of external conformal fractionated radiation therapy combining photons and protons (n = 17).
- The 4-year local control rate was 87.5% and overall survival rate was 88.9%.
- In both benign and more aggressive meningiomas, the combination of conformal photons and protons with a dose escalated by 10-15% offers clinical improvements in most patients as well as radiological long-term stabilization.

Key Ongoing Studies

Witt Nystrom P, et al.

Proton radiotherapy (PT) for primary CNS tumours in adults: a prospective Swedish multicentre study.

- This study (estimated n = 500) consists of 2 sequential cohorts evaluated for the feasibility, safety, and toxicity of PT.
 - Primary outcome measures: acute and long-term adverse events
 - Secondary outcome measure: local and regional tumor control, quality of life, normal tissue sparing
- Estimated completion: 2030

Shih HA, et al.

A Phase I/II trial of increased dose intensity modulated proton therapy (IMPT) for high-grade meningiomas.

- This study (estimated n = 60) is evaluating the ability of the IMPT dose to target the desired tumor and provide less dose to the surrounding tissues.
 - Primary outcome measures: assessing safety and utility of post-operative IMPT
 - Secondary outcome measures: duration of local tumor control and overall survival
- Estimated completion: 2024

Mehta M, et al.

Dose-escalated photon IMRT or proton beam radiation therapy versus standard-dose radiation therapy and temozolomide in treating patients with newly diagnosed glioblastoma.

- This randomized phase II trial (estimated n = 606) is studying outcomes of dose-escalated photon intensity-modulated radiation therapy (IMRT) or PT compared with standard-dose radiation therapy when given with temozolomide.
 - Primary outcome measures: overall survival
 - Among secondary outcome measures: progression-free survival, treatment-related toxicity, and changes in neurocognitive function
- Estimated completion: 2026

Grosshans D, et al.

Proton beam therapy (PT) or intensity-modulated radiation therapy (IMRT) in preserving brain function in patients with IDH mutant grade II or III glioma.

- This randomized phase II trial (estimated n = 120) is studying PT vs IMRT in terms of side effects and preservation of brain function.
 - Primary outcome measures: changes in cognition as measured by the CTB COMP score
 - Among secondary outcome measures: changes in quality of life and symptoms
- Estimated completion: 2030

Proton Therapy for Cancer at Base of Skull and Chordomas

Zhou J, Yang B, Wang X, et al. *World Neurosurg.* 2018;117:46-53.

Comparison of the effectiveness of radiotherapy with photons and particles for chordoma after surgery: a meta-analysis.

- In this meta-analysis of 25 studies, particle therapy was more effective after surgery for chordoma than conventional radiotherapy (CRT).
- The 10-year overall survival was higher with particle therapy than with stereotactic radiotherapy (SRT).
- Proton therapy is a significant and effective therapy for chordoma patients after surgery.

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

Amichetti M, Amelio D, Cianchetti M, et al. *Clin Oncol*. 2017;2:1195.

The treatment of chordoma and chondrosarcoma of the skull base with particular attention to radiotherapy.

- We are seeing the evolution of radiation techniques able to adequately treat the target and to reduce treatment risk.
- Particle therapy—protons and carbon ions—are being used more widely and are considered a standard of irradiation.
- Proton-beam therapy with wide en bloc excision is the treatment standard in managing chordomas at many quaternary-care cancer centers.

Kabolizadeh P, Chen YL, Liebsch N, et al. *Int J Radiat Oncol Biol Phys*. 2017;97(2):254-262.

Updated outcome and analysis of tumor response in mobile spine and sacral chordoma treated with definitive high-dose photon/proton radiation therapy.

- This retrospective analysis examined patients (n = 40) with unresected chordoma treated with photon/proton radiation therapy.
- The 5-year data revealed: local control 85.4%, overall survival 81.9%, disease-specific survival 89.4%, and distant failure 20.2%.
- The median maximum volumetric regressions were as follows: total target volume, 43.2%; soft tissue target volume, 70.4%.
- These results continue to support the use of high-dose definitive radiation therapy for selected patients.

Weber DC, Malyapa R, Albertini F, et al. *Radiother Oncol*. 2016;120(1):169-174.

Long-term outcomes of patients with skull-base low-grade chondrosarcoma and chordoma patients treated with pencil beam scanning (PBS) proton therapy.

- At a mean follow-up of 50 months (n = 222), the rate of local failures was 15.8%.
- The 7-year high-grade toxicity-free survival was 87.2%.
- Proton therapy using PBS is an effective treatment for skull base tumors, with acceptable late toxicity.

Amichetti M, Amelio D, Cianchetti M, et al. *Neurosurg Rev*. 2010;33(2):155-165.

A systematic review of proton therapy (PT) in the treatment of chondrosarcoma (CSA) of the skull base.

- Per this review's inclusion criteria, four articles, reporting the most recent updated results, were included in the analysis of clinical outcomes (n = 254).
- PT following maximal surgical resection shows a very high probability of medium- and long-term cure with a relatively low risk of significant complications.

Amichetti M, Cianchetti M, Amelio D, et al. *Neurosurg Rev*. 2009;32(4):403-416.

Proton therapy (PT) in chordoma of the base of the skull: a systematic review.

- Radiation therapy has shown to be a valuable modality for local control postoperatively, particularly when using charged particle radiotherapy.
- A review of limited studies (7 uncontrolled single-arm studies, n = 416) revealed that PT has shown better results compared to conventional photon irradiation, resulting in the best long-term (10-year) outcomes for this type of tumor.
- There were relatively few significant complications considering the high doses delivered.

Ares C, Hug EB, Lomax AJ, et al. *Int J Radiat Oncol Biol Phys*. 2009;75(4):1111-1118.

Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report.

- Among patients (n = 64) treated with spot-scanning proton therapy (PT), 5-year rates of disease-specific survival (DSS) and overall survival (OS) were:
 - Chordomas: 81% DSS and 62% OS
 - Chondrosarcomas: 100% DSS and 91% OS
- Actuarial 5-year freedom from high-grade toxicity was 94%.
- These data support safety and efficacy of spot-scanning PT.

Noël G, Habrand JL, Mammar H, et al. *Int J Radiat Oncol Biol Phys*. 2001;51(2):392-398.

Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protonthérapie d'Orsay experience.

- In treating these patients (n = 45) photons represented two-thirds of the total dose and protons one-third. The median total dose delivered within the gross tumor volume was 67 cobalt gray equivalent.
- The 3-year data revealed:
 - Chordomas: local control 83.1% and overall survival (OS) 91%
 - Chondrosarcomas: local control 90% and OS 90%
- Photons combined with a proton boost of one-third the total dose offers an excellent chance of cure and acceptable toxicity. These results should be confirmed.

Munzenrider JE, Liebsch NJ. *Strahlenther Onkol*. 1999;175 Suppl 2:57-63.

Proton therapy for tumors of the skull base.

- The 10-year data for local control rates revealed:
 - For skull base tumors, with combined proton-photon therapy, rates are highest for chondrosarcomas at 94%, intermediate for male chordomas at 65%, and lowest for female chordomas at 42%.

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- For cervical spine tumors, local control rates are not significantly different for chordomas (54%) and chondrosarcomas (48%), nor is there any difference in local control between males and females.
- Observed treatment-related morbidity has been judged acceptable, in view of the major morbidity and mortality which accompany uncontrolled tumor growth.

Key Ongoing Study

Debus J, et al.

Randomized trial of proton vs carbon ion radiation therapy in patients with chordoma of the skull base: clinical Phase III study.

- Proton therapy (PT) is the gold standard for treating skull base chordomas.
- This prospective, randomized clinical phase III trial (estimated n = 319) is examining whether carbon ion irradiation is superior to standard PT in chordomas.
 - Primary outcome measure: local-progression-free survival
 - Secondary outcome measure: overall survival, metastasis-free survival, toxicity
- Estimated completion: 2023

Proton Therapy for Head & Neck Cancer

Romesser PB, Cahlon O, Scher E, et al. *Radiother Oncol.* 2016;118(2):286–292.

Proton beam radiation therapy (PBRT) results in significantly reduced toxicity compared with intensity-modulated radiation therapy (IMRT) for head and neck tumors that require ipsilateral radiation.

- For ipsilateral head and neck treatments, patients received either PBRT (n = 18, 43.9%) or IMRT (n = 23, 56.1%).
- Findings:
 - Compared to PBRT, IMRT plans delivered a higher median maximum dose to structures (brainstem, spinal cord, oral cavity, contralateral parotid, contralateral submandibular areas).
 - PBRT, compared to IMRT, had significantly lower rates of grade ≥ 2 acute dysgeusia (5.6% vs. 65.2%, $p < 0.001$), mucositis (16.7% vs. 52.2%, $p = 0.019$), and nausea (11.1% vs. 56.5%, $p = 0.003$).
- The unique properties of PBRT spare more normal tissue, an advantage that seemingly translates into lower rates of acute treatment-related toxicity.

McDonald MW, Liu Y, Moore MG, et al. *Rad Oncol.* 2016;11:32.

Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy (IMRT).

- In this retrospective trial proton therapy (n = 14), vs IMRT (n = 26), was associated with:
 - Significantly reduced radiation dose to non-target normal tissues
 - Lower rate of gastrostomy tube dependence
 - Reduced rate of required opioid pain medication

Phan J, Sio TT, Nguyen TP, et al. *Int J Radiat Oncol Biol Phys.* 2016;96(1):30–41.

Reirradiation of head and neck cancers with proton therapy: outcomes and analysis.

- Patients (n = 60) in this retrospective study received reirradiation using either passive scatter proton therapy (PSPT) (25%) or intensity modulated proton therapy (IMPT) (75%).
- Data showed rates of:
 - Locoregional failure-free survival: 68.4% at 1 year
 - Overall survival: 83.8% at 1 year
 - Acute grade 3 toxicity: 30%
- Proton therapy can be a safe and effective curative reirradiation strategy.

Blanchard P, Garden AS, Gunn GB, et al. *Radiother Oncol.* 2016;120:48–55.

Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer: a case matched analysis.

- Patients received either IMPT (n = 50) or IMRT (n = 100) at a median follow-up of 32 months.
- There were no statistically significant differences in:
 - Overall survival ($p = 0.44$)
 - Progression-free survival ($p = 0.96$)
- IMPT is associated with reduced rates of feeding tube dependency and severe weight loss—without jeopardizing outcome.

Sio TT, Lin HK, Shi Q, et al. *Int J Radiat Oncol Biol Phys.* 2016;95(4):1107–1114.

Intensity modulated proton therapy (IMPT) vs intensity modulated photon radiation therapy (IMRT) for oropharyngeal cancer: first comparative results of patient-reported outcomes.

- Patients received either IMPT (n = 35) or IMRT (n = 46) with concurrent chemotherapy.
- Among the top 11 symptoms—e.g., taste issues, dry mouth, swallowing/chewing difficulties, suppressed appetite, and fatigue—changes in taste and appetite during the subacute and chronic phases favored IMPT (all $p < 0.048$).
- Symptom burden was lower among IMPT patients.

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

Zenda S, Akimoto T, Mizumoto M, et al. *Radiother Oncol*. 2016;118(2):267-271.

Phase II study of proton beam therapy (PT) as a nonsurgical approach for mucosal melanoma of the nasal cavity or para-nasal cavity or para-nasal sinuses.

- In this study, an indirect comparison with surgical outcomes, data on patients (n = 32) treated with PT revealed:
 - Local control: 75.8% at 1 year
 - Overall survival: 46.1% at 3 years
 - Primary cause of death: cancer due to distant metastases in 93.3%
- PT showed sufficient local control benefits for mucosal melanoma as an alternative treatment of surgery.

Russo AL, Adams JA, Weyman EA, et al. *Int J Radiat Oncol Biol Phys*. 2016;95(1):368-376.

Long-term outcomes after proton beam therapy (PT) for sinonasal squamous cell carcinoma (SCC).

- Patients (n = 54) with Stage III and IV SCC of the nasal cavity and paranasal sinus received PT.
- After most had undergone prior surgical resection (69%), long-term data showed:
 - Actuarial local control rate: 80% at 2 and 5 years
 - Overall survival: 67% and 47%, respectively, at 2 and 5 years
- These long-term results reveal that PT is well tolerated and yields good locoregional control for sinonasal SCC.

Holliday EB, Garden AS, Rosenthal DI, et al. *Int J Particle Ther*. 2015;2:19-28.

Proton therapy reduces treatment-related toxicities for patients with nasopharyngeal cancer: a case-match control study of intensity-modulated proton therapy (IMPT) and intensity-modulated photon therapy (IMRT).

- Patients received either IMPT (n = 10) or IMRT (n = 20), and most patients received induction chemotherapy.
- Investigators reported a significantly decreased mean dose to the oral cavity and brainstem in patients treated with IMPT.
- Patients treated with IMPT had significantly reduced acute toxicity as evidenced by decreased rates of gastrostomy tube placement.

Patel SH, Wang Z, Wong WW, et al. *Lancet Oncol*. 2014;15(9):1027-1038.

Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis.

- Investigators evaluated 43 cohorts from 41 non-comparative observational studies.
- There was a statistically significant improvement with charged particle therapy when evaluating:
 - Pooled overall survival—at 5 years and at longest follow-up
 - Locoregional control—at longest follow-up, though there was no difference at 5 years

Key Ongoing Studies

Frank S, et al., for MD Anderson investigators.

Intensity-modulated proton therapy (IMPT) for oropharyngeal cancer.

- In this ongoing randomized, controlled trial, patients (estimated n = 520) receive either IMPT or intensity modulated radiation therapy (IMRT).
- The trial is examining whether there are fewer side effects with proton therapy—due to its reduced dose to healthy tissues such as those in the oral cavity, brain stem, salivary glands, and larynx.
- Compared to IMRT, IMPT for oropharyngeal cancer typically delivers a 25-Gy-lower radiation dose to healthy tissue (≈ 5 million dental x-rays).
- Investigators hope the **ongoing trial** can help define the value of proton therapy for oropharyngeal cancer patients who often experience adverse effects from radiation therapy.

Lee N, et al.

Study of proton therapy (PT) versus photon beam radiotherapy in the treatment of head and neck cancer.

- This randomized study (estimated n = 132) is comparing the effects of PT with intensity-modulated radiation therapy (IMRT).
 - Primary outcome measure: incidence of grade 2+ acute mucositis at 1 year
- Estimated completion: 2021

Proton Therapy for Esophageal Cancer

Lester SC, Lin SH, Chuong M, et al. *Int J Radiat Oncol Biol Phys*. 2017;98(4):820-828.

A multi-institutional analysis of trimodality therapy for esophageal cancer in elderly patients.

- The study evaluated 571 patients treated with trimodality therapy (neoadjuvant chemoradiation therapy [nCRT] followed by esophagectomy); 35% (n = 202) were age 65 or older.
- The data showed:
 - Elderly patients had a two-fold increased risk for both cardiac and pulmonary toxicities.
 - Infrequent grade 3+ acute toxicities from nCRT were clinically similar regardless of age.
 - Freedom from esophageal cancer and disease-free survival were similar, though overall survival was significantly shorter in the elderly cohort.

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

- It is not known whether the increases in radiation dose conformality have a more significant benefit in elderly patients.
- Because toxicities and mortality were within published standards for trimodality therapy, such therapy is a reasonable treatment option for appropriately selected elderly patients.

Xi M, Xu C, Liao Z, et al. *Int J Radiat Oncol Biol Phys*. 2017;99(3):667-676.

Comparative outcomes after definitive chemoradiotherapy using proton beam therapy (PT) versus intensity modulated radiation therapy (IMRT) for esophageal cancer: a retrospective, single-institutional analysis.

- Patients who had received definitive chemoradiotherapy (CRT) using either PT (n = 132) or IMRT (n = 211) were retrospectively analyzed.
- Compared with IMRT, PT was associated with:
 - Significant improvement in overall survival (p = 0.011), progression-free survival (p = 0.001), and distant metastasis-free survival (p = 0.031)
 - Marginal improvement in locoregional failure-free survival (p = 0.075)
 - No significant intergroup survival differences for stage I/II patients
- Compared with IMRT, PT may be associated with improved survival, especially in locally advanced disease cases.

Lin SH, Merrell KW, Shen J, et al. *Radiother Oncol*. 2017;123(3):376-381.

Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer (EC).

- Data were reviewed from EC patients treated with neoadjuvant chemoradiation (nCRT): 3D conformal radiation therapy (RT) (3D) in 214 (37%) patients, intensity modulated RT (IMRT) in 255 (44%), and proton beam therapy (PT) in 111 (19%).
- Results revealed:
 - Mean hospital length of stay was significantly associated with treatment modality: PT at 9.3 days, IMRT at 11.6 days, and 3D at 13.2 days (p < 0.0001).
 - Pulmonary complications were lowest for PT (16.2%), intermediate for IMRT (24.2%), and highest for 3D (39.5%).
 - Wound complications were lowest for PT (4.5%) and similar between IMRT (14.1%) and 3D (15.3%).
 - The 90-day postoperative mortality rates varied: PT at 0.9%, IMRT at 4.3%, and 3D at 4.2% (p = 0.264).
- Advanced technologies (IMRT and PT) were associated with significantly reduced rate of postoperative complications, with PT displaying the greatest benefit in a number of endpoints.

Chuong MD, Hallemeier CL, Jabbour SK, et al. *Int J Radiat Oncol Biol Phys*. 2016;95(1):488-497.

Improving outcomes for esophageal cancer using proton beam therapy (PT).

- This review article focuses on issues such as motion management, reirradiation, dose escalation, and potential cost effectiveness.
- There is a growing body of evidence to suggest that the dosimetric benefits of PT may result in clinically significant reduction in acute and long-term treatment-related toxicities compared with photon radiotherapy.
- Strong consideration should be given to enrolling eligible patients to available esophageal PT clinical trials.

Wang J, Wei C, Tucker SL, et al. *Int J Radiat Oncol Biol Phys*. 2013;86(5):885-891.

Predictors of postoperative complications after trimodality therapy for esophageal cancer.

- The study assessed complications after trimodality therapy (n = 444) using different types of radiation.
- Pulmonary and gastrointestinal complications were higher in patients treated with 3-D conformal radiation therapy (3D-CRT) versus either:
 - Intensity modulated radiation therapy (IMRT): odds ratio 2.018 with 3D-CRT vs 1.704 with IMRT
 - Proton beam therapy (PT): odds ratio 3.154 with 3D-CRT vs 1.55 with PT
- Complication rate data revealed:
 - IMRT: pulmonary complication rate of 24% (compared to 33%–46% in previously published studies)
 - PT: with an even lower incidence of pulmonary complications at 14% and a GI complication at 18%
- The modality of radiation can be a strong mitigating factor in postoperative complications.

Lin SH, Komaki R, Liao Z, et al. *Int J Radiat Oncol Biol Phys*. 2012;83(3):e345-e351.

Proton beam therapy (PBT) and concurrent chemotherapy for esophageal cancer.

- This was the first reported clinical experience using concurrent chemotherapy (CChT) and passive scattering PBT (MD Anderson). Nearly half (n = 29) of the 62 patients were treated with preoperative therapy.
- These early findings suggest that while this modality is associated with a few severe toxicities, the clinical outcomes are encouraging.

Mizumoto M, Sugahara S, Okumura T, et al. *Int J Radiat Oncol Biol Phys*. 2011;81(4):e601-e606.

Hyperfractionated concomitant boost proton beam therapy (PT) for esophageal carcinoma.

- In this small analysis (n = 19), patients were treated with hyperfractionated photon therapy and PT.
- The 1- and 5-year findings:
 - Survival rates: 79.0% and 42.8%, respectively
 - Local control rates: 93.8% and 84.4 %, respectively
- Hyperfractionated PT is safe and effective for patients with esophageal cancer.
- Further studies may establish the appropriate role and treatment schedule for PT.

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

Mizumoto M, Suahara S, Nakayama H, et al. *Strahlenther Onkol.* 2010;186:482.

Clinical results of proton-beam therapy (PT) for locoregionally advanced esophageal cancer.

- In this study 64.7% (n = 33) of patients received photon and PT as a boost; the remaining 35.3% (n = 18) received PT only.
- The findings revealed:
 - Overall 5-year actuarial survival rate of 21.1%
 - Overall response rate of 92%: 78% with a complete response at 4 months and 14% with partial response
 - Late toxicity seemed to be reduced in our study compared to those performed with standard chemoradiotherapy, in which heart and lung late toxicity is common
 - There was no lung and heart late toxicity of grade ≥ 3 , which is due to the excellent dose localization of a proton beam that avoids damage to healthy tissues
- While PT appears to be an effective treatment for patients with locally advanced esophageal cancer, further studies are needed to determine other factors such as the best combination of PT with chemotherapy.

Key Ongoing Studies

Lin S, et al.

Phase III randomized trial of proton beam therapy (PT) vs intensity modulated photon radiotherapy (IMRT) for the treatment of esophageal cancer.

- This randomized study (estimated n = 300) is comparing PT vs IMRT in patients with stage I-IVA esophageal cancer.
 - Primary outcome measures: overall survival, treatment-related grade 3+ cardiopulmonary adverse events
 - Secondary outcome measures: pathologic response rate, Grade 4 lymphopenia during chemoradiation, locoregional failure, distant metastatic-free survival, progression-free survival
- Estimated completion: 2032

Plastaras J, et al.

Phase I dose escalation of neoadjuvant proton beam radiotherapy (PT) with concurrent chemotherapy in locally advanced esophageal cancer.

- This trial (estimated n = 30) is evaluating the efficacy of preoperative PT in combination with carboplatin and paclitaxel.
 - Primary outcome measure: incidence of adverse events
- Estimated completion: 2019

Proton Therapy for Left-Sided Breast Cancer

Verma V, Iftekaruddin Z, Badar N, et al. *Radiother Oncol.* 2017;123(2):294-298.

Proton beam radiotherapy (PT) as part of comprehensive regional nodal irradiation for locally advanced breast cancer.

- Adjuvant PT targeted the intact breast/chest wall and comprehensive regional nodes including the axilla, supraclavicular fossa, and internal mammary lymph nodes (n = 91).
 - Grades 1, 2, and 3 dermatitis occurred in 23%, 72%, and 5%, respectively.
 - Grades 1, 2, and 3 esophagitis developed in 31%, 33%, and 0%, respectively.
- PT displays acceptable toxicity in the setting of comprehensive regional nodal irradiation.

Bradley JA, Dagan R, Ho MW, et al. *Int J Radiat Oncol Biol Phys.* 2016;95(1):411-421.

Initial report of a prospective dosimetric and clinical feasibility trial demonstrates the potential of protons to increase the therapeutic ratio in breast cancer compared with photons.

- This study (n = 18) compared proton therapy (PT) and conventional radiation, with median follow-up of 20 months.
- PT for regional node irradiation after mastectomy or breast-conserving therapy (BCT) significantly improves cardiac dose, especially for left-sided patients, and lung V5 and V20 in all patients without excessive acute toxicity.
- PT also improves target coverage for the internal mammary nodes and level 2 axilla, which may positively impact long-term survival in breast cancer patients.

Bush DA, Do S, Lum S, et al. *Int J Radiat Oncol Biol Phys.* 2014;90(3):501-505.

Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes.

- In this study (n = 100) proton therapy (PT) partial breast irradiation (PBI) was delivered post-operatively to patients with early stage breast cancer.
 - Disease-free survival was 94% and overall survival was 95%
 - There were no cases of grade 3+ toxicity
- PT for PBI produced excellent ipsilateral breast recurrence-free survival with minimal toxicity.
- Cosmetic results may be improved over those reported with photon-based techniques due to reduced breast tissue exposure with PT, skin-sparing techniques, and the dose fractionation schedule used in this trial.

Key Ongoing Studies

Bekelman J, Cahlon O, McDonald S, et al.

Pragmatic randomized trial of proton vs photon therapy for patients with non-metastatic breast cancer: a RADiotherapy COMParative effectiveness (RADCOMP) consortium trial.

- This randomized study (estimated n = 1,720) is comparing proton therapy (PT) vs photon therapy in patients with locally advanced breast cancer.

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

- Primary outcome measures: major cardiovascular events, defined as atherosclerotic coronary heart disease or other heart disease death, myocardial infarction, coronary revascularization, or hospitalization for major cardiovascular event (heart failure, valvular disease, arrhythmia, or unstable angina)
- Secondary outcome measures: breast cancer recurrence, quality of life, toxicity, long-term survival
- Estimated completion: 2030

Chang A, et al.

Phase II protocol of proton therapy (PT) for partial breast irradiation in early stage breast cancer.

- This study (estimated n = 132) is assessing the efficacy of PT in patients with early stage breast cancer.
 - Primary outcome measure: freedom from ipsilateral breast recurrence
 - Secondary outcome measures: toxicity, quality of life, overall survival
- Estimated completion: 2033

Proton Therapy for Pancreatic Cancer

Maemura K, Mataka Y, Kurahara H, et al. *Pancreatology*. 2017;17(5):833-838.

Comparison of proton beam radiotherapy (PT) and hyper-fractionated accelerated chemoradiotherapy (HART) for locally advanced pancreatic cancer.

- Patients with locally advanced pancreatic cancer received either PT (n = 10) or HART (n = 15).
- Results in the HART group and PT group, respectively:
 - Disease control rates of 93% and 80%
 - Local progression in 60% and 40%
- PT was feasible and was associated with lower rates of local recurrence. Survival benefit was similar in both groups.

Verma V, Lin SH, Simone CB, et al. *J Gastrointest Oncol*. 2016;7(4):644-664.

Clinical outcomes and toxicities of proton radiotherapy (PT) for gastrointestinal neoplasms: a systematic review.

- Authors analyzed 38 original investigations of PT in comparison to photon radiotherapy.
- The limited quality (and quantity) of data hamper direct comparisons and conclusions.
- Nonetheless data suggest that PT offers the potential for significant reduction in treatment-related toxicities without compromising survival or local control for multiple gastrointestinal malignancies.

Hong TS, Ryan DP, Borger DR, et al. *Int J Radiat Oncol Biol Phys*. 2014;89(4):830-838.

A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy (PT) and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma.

- Patients (n = 35 in phase 2) with pancreatic ductal adenocarcinoma (PDAC) received short-course (2-week) PT and capecitabine, followed by pancreaticoduodenectomy.
- There were significant associations between worse survival and the KRAS point mutation change from glycine to aspartic acid at position 12, stromal CXCR7 expression, and circulating biomarkers CEA, CA19-9, and HGF (all p < 0.05).
- The study met the primary endpoint: revealing a rate of 4.1% grade 3 toxicity for neoadjuvant short-course proton-based chemoradiation.
- Treatment was associated with favorable local control.

Terashima K, Demizu Y, Hashimoto N, et al. *Radiother Oncol*. 2012;103(1):25-31.

A phase I/II study of gemcitabine-concurrent proton radiotherapy (GPT) for locally advanced pancreatic cancer without distant metastasis.

- Patients (n = 50) with locally advanced pancreatic cancer (LAPC) were assigned to treatment group:
 - P-1: gastrointestinal (GI)-adjacent LAPC (50 Gy equivalent [GyE] in 25 fractions)
 - P-2: non-GI-adjacent LAPC (70.2 GyE in 26 fractions)
 - P-3: patients regardless of GI-adjacency (67.5 GyE in 25 fractions using the field-within-a-field technique)
- Results revealed:
 - Grade 3 or greater late gastric ulcer and hemorrhage: 10% in P-2 and P-3.
 - The one-year freedom from local-progression, progression-free survival, and overall survival rates were 81.7%, 64.3%, and 76.8%, respectively.
- Study limitations included study size and follow-up periods; however, GPT showed high efficacy

Hong TS, Ryan DP, Blaszkowsky LS, et al. *Int J Radiat Oncol Biol Phys*. 2011;79(1):151-157.

Phase I study of preoperative short-course chemoradiation with proton beam therapy (PT) and capecitabine for resectable pancreatic ductal adenocarcinoma of the head.

- The patients, who had localized resectable, adenocarcinoma of the head of the pancreas, received varying dose levels of PT.
- The study is limited due to its small size (n = 15).
- Preoperative chemoradiation with 1 week of PT and capecitabine followed by early surgery is feasible. A Phase II study was initiated.

Key Ongoing Studies

Kaiser A, et al.

Phase I study of concurrent nab-paclitaxel + gemcitabine with hypofractionated, ablative proton therapy (PT) for locally advanced pancreatic cancer (LAPC).

- This trial (estimated n = 24) aims to determine the maximum tolerated dose of the chemotherapy drugs nab-paclitaxel and gemcitabine when combined with hypofractionated PT.
 - Primary outcome measures: maximum tolerated dose of gemcitabine and nab-paclitaxel in patients receiving PT
 - Secondary outcome measures: primary tumor response, disease-free survival, overall survival, toxicity
- Estimated completion: 2022

Nichols RC, et al.

A Phase II trial of escalated dose proton radiotherapy (PT) with elective nodal irradiation and concomitant chemotherapy for patients with unresectable, borderline resectable, or medically inoperable pancreatic adenocarcinoma.

- This trial (estimated n = 60) will determine if an increase in the number of surgical resection pancreatic adenocarcinoma is higher than historical data by using a combined treatment of PT with oral chemotherapy.
 - Primary outcome measure: overall 12-month survival
 - Secondary outcome measure: surgical resection rate
- Estimated completion: 2040

Proton Therapy for Pediatrics

Hill-Kayser CE, Tochner Z, Li Y, et al. *Int J Radiat Oncol Biol Phys.* 2019;104;2:401-408.

Outcomes after proton therapy (PT) for treatment of pediatric high-risk neuroblastoma.

- PT may promote organ sparing, but long-term outcomes were not studied until now.
- In this study (n = 45) most primary tumors (89%) were adrenal; 10 metastatic sites in 8 patients were radiated.
- Type of PT:
 - 42% received double scattered proton beams
 - 58% received pencil beam scanning, which required less planning time and resources than double scattered plans
- The 3-, 4-, and 5-year data showed, respectively:
 - Overall survival rates of 89%, 80%, and 80%
 - Disease-free survival rates of 77%, 70%, and 70%
 - 97% freedom from primary site recurrence—at all time points
- Acute toxicities during treatment were mainly grade 1; no patients demonstrated grade 3 or 4 long-term renal or hepatic toxicity.
- Findings revealed excellent outcomes and support the expanded use of PT in neuroblastoma and other high-risk childhood cancers. This treatment maximizes normal tissue preservation and is appropriate for this patient population.

Huynh M, Marcu LG, Giles E, et al. *Cancer Treat Rev.* 2018;70:272-288.

Current status of proton therapy (PT) outcome for paediatric cancers of the central nervous system—analysis of the published literature.

- PT for treating pediatric cancers was found to provide survival and tumor control outcomes comparable to photon therapy.
- Yet PT, with its high dose conformality, exhibited reduced incidence of severe acute and late toxicities—including endocrine, neurological, IQ, and quality-of-life deficits.

Ares C, Albertini F, Frei-Welte M, et al. *J Neurooncol.* 2016;128:1;137-145.

Pencil beam scanning proton therapy (PT) for pediatric intracranial ependymoma.

- Between July 2004 and March 2013, 50 patients with intracranial ependymoma (n = 46, grade 3) received involved-field PT at Paul Scherrer Institute.
- At 5 years local control rate was 78% and overall survival rate was 84%.
- Local control and survival rates are encouraging considering the high grade histology in 92% of the patients and the number of patients with residual tumor ≥ 1.5 cc. The rates of late effects compare favorably with published photon-treated cohorts.

Macdonald SM, Sethi R, Lavally B, et al. *Neuro Oncol.* 2013;15(11):1552-1559.

Proton radiotherapy (PT) for pediatric central nervous system ependymoma: clinical outcomes for 70 patients.

- Patients (n = 70) with localized ependymoma received treatment with involved-field PT at Massachusetts General Hospital.
- At 46-month medial follow-up, data showed:
 - Local control of 83%
 - Progression-free survival of 76%
 - Overall survival of 95%
- Outcomes for children treated with PT compare favorably with the literature.

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

Hattangadi JA, Rombi B, Yock TI, et al. *Int J Radiat Oncol Biol Phys*. 2012;83(3):1015–1022.

Proton radiotherapy (PT) for high-risk pediatric neuroblastoma: early outcomes and dose comparison.

- Patients with stage III-IV disease were treated and followed for a median of 38 months.
- PT achieved substantial normal tissue sparing compared with intensity modulated radiation therapy (IMRT). IMPT allowed additional sparing of the kidneys, lungs, and heart.
- Preliminary outcomes reveal excellent local control with PT for high-risk neuroblastoma, although distant failures occurred.

Key Ongoing Studies

Lucas JT, et al. St. Jude Children's Research Hospital.

Evaluation of proton therapy (PT) in pediatric cancer patients.

- This Phase IV clinical trial is observing and evaluating the safety of PT in children (estimated n = 1,000).
 - Primary objective: to estimate the incidence of radiation-associated grade 3 and grade 4 non-hematologic toxicities at 1, 3, 5, and 10 years in a radiated region specific manner after treatment with PT
 - Secondary objective: to estimate the incidence of necrosis, vasculopathy, and symptomatic and permanent neurologic deficits during the same timeframe
- Estimated completion: 2037

Lim DH, et al.

Registry for analysis of quality of life, normal organ toxicity and survival of pediatric patients treated with proton therapy (PT).

- This study will evaluate the effect of PT on quality of life (QOL) and long-term normal tissue toxicities (estimated n = 400).
 - Primary outcome measure: QOL after PT
 - Secondary outcome measures: QOL and adverse events at 3-6 months and at 1, 3, 5, and 10 years
- Estimated completion: 2025

Hess CB, Indelicato DJ, Paulino AC, et al. *Front Oncol*. May 24, 2018.

An update from the Pediatric Proton Consortium Registry.

- A large prospective population of children (n = 1,854 in this registry alone) irradiated with proton therapy (PT) has reached a critical milestone to facilitate long-awaited clinical outcomes.
- This is an important resource for investigators both in the consortium and for those who wish to access the data for academic research.

Proton Therapy for Lymphoma

Hoppe BS, Hill-Kayser CE, Tseng YD, et al. *Ann Oncol*. 2017;28(9):2179-2184.

Consolidative proton therapy (PT) after chemotherapy for patients with Hodgkin lymphoma.

- The study examined early outcomes for patients receiving chemotherapy followed by consolidative PT.
- Results revealed:
 - The 3-year relapse-free survival rate was 92% for all patients (96% for adults and 87% for pediatric patients [p=0.18]).
 - When evaluated post-chemo by positron emission tomography/computed tomography, patients with only a partial chemo response had worse 3-year progression-free survival compared with other patients (78% vs 94%; p=0.0034).
 - There were no grade 3 radiation-related toxicities.

Proton Therapy for Reirradiation

Badiyan SN, Rutenberg MS, Hoppe BS, et al. *Pract Radiat Oncol*. 2019. pii: S1879-8500(19)30056-6.

Clinical outcomes of patients with recurrent lung cancer reirradiated with proton therapy on the Proton Collaborative Group and University of Florida Proton Therapy Institute Prospective Registry Studies.

- This is the largest such cohort of patients treated with PT published to date (2019): 479 patients with NSCLC and 158 patients with small cell lung cancer (SCLC).
- Pencil beam scanning (PBS) may be ideally suited for reirradiation in the setting of recurrent disease.
- Overall the findings showed that reirradiation with PT is well tolerated and with acceptable toxicity and encouraging efficacy

Verma V, Rwigema JM, Malyapa RS, et al. *Radiother Oncol*. 2017;125(1):21-30.

Systematic assessment of clinical outcomes and toxicities of proton radiotherapy (PT) for reirradiation (ReRT).

- Authors analyzed 14 original investigations, with malignancies in the: central nervous system (CNS n = 6), head/neck (H&N n = 4), lung (n = 2), and gastrointestinal system (n = 2).
- Findings included:
 - Among the CNS studies evaluated: for chordomas, reRT afforded a 2-year local control and overall survival of 85% and 80%, respectively. In addition, multiple PT reRT studies for adult gliomas illustrate no grade ≥3 toxicities.
 - PT for H&N shows appropriate local/locoregional control and favorable toxicity profiles vs photon therapy.
 - PT for recurrent lung cancer can achieve favorable survival with expected toxicities or complications.
 - PT for GI induced very few high-grade complications.

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

Chao HH, Berman AT, Simone CB, et al. *J Thorac Oncol*. 2017;12(2):281-292.

Multi-institutional prospective study of reirradiation with proton beam radiotherapy (PT) for locoregionally recurrent non-small cell lung cancer (NSCLC).

- In this prospective study, 57 patients with recurrent NSCLC in or near their prior radiation field were treated at one of three proton centers.
- Findings showed that:
 - The 1-year rates of overall and progression-free survival were 59% and 58%, respectively.
 - Acute and/or late toxicity \geq grade 3 occurred in 42%.
 - Decreased overall survival was seen with increased mean esophagus dose ($p = 0.007$).
- PT for recurrent NSCLC is feasible but can be associated with significant toxicity.

Guttmann DM, Frick MA, Carmona R, et al. *Radiother Oncol*. 2017;124(2):271-276.

A prospective study of proton reirradiation for recurrent and secondary soft tissue sarcoma.

- In this prospective trial 23 patients underwent proton therapy (PT) reirradiation.
- Results revealed:
 - Median overall survival was 44 months.
 - Progression-free survival was 29 months.
 - In extremity patients, amputation was spared in 7/10 (70%).
 - There were no grade 4-5 toxicities.
 - One patient (4%) experienced acute grade 3 dysphagia.
 - Common grade 2 acute toxicities were fatigue (26%), anorexia (17%), and urinary incontinence (13%).
- PT reirradiation of recurrent/secondary soft tissue sarcomas is well tolerated.

Boimel PJ, Berman AT, Li J, et al. *J Gastrointest Oncol*. 2017;8(4):665-674.

Proton beam reirradiation for locally recurrent pancreatic adenocarcinoma.

- Proton therapy (PT) can potentially limit dose and toxicity to previously irradiated normal tissues. This study examined 15 patients who received PT for reirradiation, 14 of whom received double scattered PT.
- Most patients ($n = 10$) received concurrent chemotherapy.
- Results revealed that:
 - Median overall survival (OS) was 16.7 months.
 - OS at 1 year was 67%.
 - The "in-field" failure free survival at 1 year was 87%.
 - Concurrent chemotherapy was associated with a higher median survival.
- PT was well tolerated, resulted in prolonged clinical outcomes vs historical controls, and it should be considered a treatment option (with concurrent chemotherapy) in selected patients with locally recurrent pancreatic adenocarcinoma.

Romesser PB, Cahlon O, Scher ED, et al. *Int J Radiat Oncol Biol Phys*. 2016;95(1):386-395.

Proton beam reirradiation for recurrent head and neck cancer: multi-institutional report on feasibility and early outcomes.

- There has been increased interest in proton therapy (PT) for curative-intent reirradiation therapy (re-RT) among patients with locally recurrent head and neck cancer (HNC).
- This retrospective analysis, which included consecutive patients ($n = 92$) who received uniform scanning beams, revealed:
 - 84.0% actuarial 12-month freedom from distant metastasis
 - 65.2% overall survival
 - Acute toxicities of grade 3+ included mucositis (9.9%), dysphagia (9.1%), esophagitis (9.1%), and dermatitis (3.3%)
 - Late toxicities of grade 3+ included skin toxicity (8.7%) and dysphagia (7.1%)
- PT re-RT of HNC can provide effective tumor control with acceptable acute and late toxicity profiles.

McAvoy S, Ciura K, Wei C, et al. *Int J Radiat Oncol Biol Phys*. 2014;90(4):819-827.

Definitive reirradiation for locoregionally recurrent non-small cell lung cancer (NSCLC) with proton beam therapy (PT) or intensity modulated radiation therapy (IMRT): predictors of high-grade toxicity and survival outcomes.

- There were 102 patients who underwent reirradiation at a single center.
- Outcomes:
 - Median local failure-free survival of 11.4 months
 - Distant metastasis-free survival of 11.4 months
 - Overall survival of 14.7 months
 - Acceptable toxicity: 7% with esophageal grade ≥ 3 and 10% with pulmonary grade ≥ 3
- PT and IMRT are options for reirradiation of NSCLC, but patient selection is important to maximize benefits and minimize side effects.

Proton Therapy Reduced Side Effects and Improved Quality of Life for Several Types of Cancer

Baumann BC, Mitra N, Harton J, et al. ASCO. June 2019. Abstract.

Comparative effectiveness of proton therapy versus photon therapy as part of concurrent chemoradiotherapy for locally advanced cancer.

- Researchers at University of Pennsylvania conducted a comparative effectiveness study of adult non-metastatic cancer patients treated with curative intent with proton chemo-radiotherapy vs. photon chemo-radiotherapy from 2011-2016 ($n = 1,483$).

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

- Included were patients with non-metastatic lung, brain, head and neck, gastrointestinal, and gynecologic cancers.
- Results showed proton therapy with significantly lower relative risk of:
 - 90-day grade \geq 3 adverse events
 - 90-day grade \geq 2 adverse events
 - Decline in performance status during treatment
- For those with locally advanced cancer, proton chemo-radiotherapy was associated with significantly reduced acute adverse events—resulting in unplanned hospitalizations—with similar disease-free and overall survival.

Verma V, Simone CB, Mishra MV. *J Natl Cancer Inst.* 2018;110(4).

Quality of life and patient-reported outcomes following proton radiation therapy: a systematic review.

- There were 17 studies meeting eligibility criteria that reported on cancers of the skull base (n=1), brain (n=1), head/neck (n=1), lung (n=1), breast (n=2), prostate (n=8), and pediatric (n=3)—all studies delivering proton therapy (PT).
- PT provides favorable quality of life (QOL) and patient-reported outcome profiles for select brain, head/neck, lung, and pediatric cancers; measures for prostate and breast cancers were more modest.
- These results have implications for cost-effective cancer care.
- These results can furthermore benefit from well-designed QOL evaluation in ongoing trials.

This bibliography is a representative selection, but not necessarily exhaustive list, of literature pertaining to proton therapy.

Important Safety Information

Radiation treatment is not appropriate for all cancers. For product-specific safety information and literature, please visit www.varian.com.

Medical Advice Disclaimer

Varian as a medical device manufacturer cannot and does not recommend specific treatment approaches. Individual treatment results may vary.



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