Molina Clinical Policy
Neutron and Proton Beam Radiation Therapy
Policy Number: 417

Last Approval: 8/9/2023
Next Review Due By: August 2024

POLICY SECTIONS

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

POLICY DESCRIPTION

The purpose of this policy is to provide general information applicable to the review and appropriateness of Radiation Therapy services. Although a service, supply or procedure may be medically necessary, it may be subject to limitations and/or exclusions under a member's benefit plan. If a service, supply, or procedure is not covered and the member proceeds to obtain the service, supply or procedure, the member may be responsible for the cost. Decisions regarding treatment and treatment plans are the responsibility of the physician. This policy is not intended to direct the course of clinical care a physician provides to a member, and it does not replace a physician's independent professional clinical judgment or duty to exercise special knowledge and skill in the treatment of members. NCH is not responsible for, does not provide, and does not hold itself out as a provider of medical care. The physician remains responsible for the quality and type of health care services provided to a member.

RELATED POLICIES

Policy No.	Policy Title
N/A	

BACKGROUND

Neutron Beam Radiation Therapy (NBRT) differs from other forms of radiation particle treatment such as protons or electrons as they have no electrical charge. The treatment effects are the results of the neutron mass producing dense radiation energy distributions. This effect is high energy linear transfer (LET) and may offset the negative effects of low oxygen tension in tumors leading to increased rate of control in hypoxic tumors. Proton Beam Radiation Therapy (PBRT) is a type of external radiation treatment. Using a stereotactic planning and delivery system, positively charged subatomic particles (protons) are targeted to a specific cancer. Protons behave differently than x-rays or photons in that they have a low energy deposition rate as they enter the body, followed by a steep increased energy deposition when they reach their target (the Bragg peak).

Radiation Therapy Treatment Process:

A. Consultation

B. Simulation

C. Treatment Planning

D. Treatment Delivery

INDICATIONS and/or LIMITATIONS OF COVERAGE

NEUTRON BEAM RADIATION THERAPY (NBRT)

Indications for Use/Inclusion Criteria[1-10]

All requests for NBRT require Clinical Review.

A. Neutron Beam Radiation Therapy is medically necessary only in the treatment of:

1. Salivary gland cancers – when recurrent OR in the case of a second primary cancer OR following resection with gross residual disease or positive margins OR for re-treatment of a previously irradiated area.

Exclusion Criteria

A. All other cancers are not considered medically necessary for Neutron Beam Radiation Therapy.

PROTON BEAM RADIATION THERAPY (PBRT)

Indications for Use/Inclusion Criteria[11-87]

A. Proton Beam Radiation Therapy is medically necessary only in the treatment of:

1. Chordomas and Chondrosarcomas of the base of the skull or spine when disease is localized (non-metastatic).
2. Primary or metastatic CNS malignancies.
3. Hepatocellular cancer or intrahepatic cholangiocarcinoma – when unresectable and non-metastatic.
4. Melanoma of the uveal tract – with no evidence of metastasis or extra scleral extension.
5. Pediatric cancers – in all cases of pediatric cancers (in patients 18 yrs. old or younger) except in cases of bone metastases (see exclusion criteria below).
6. Cancer of the nasal cavity and paranasal sinuses – when tumor involves the base of skull and proton therapy is needed to spare the orbit, optic nerve, optic chiasm, or brainstem.
7. Re-irradiation – for re-treatment of a previously irradiated area.

Exclusion Criteria

A. All other cancers are not considered medically necessary for Proton Beam Radiation Therapy.

B. Pediatric cancers in cases where the treatment is for previously untreated bone metastases.

EXCLUSION CRITERIA

Neutron Beam Radiation Therapy

A. All other cancers (not listed above in the 'Indications' section) are not considered medically necessary for Neutron Beam Radiation Therapy.

Proton Beam Radiation Therapy

A. All other cancers (not listed above in the 'Indications' section) are not considered medically necessary for Proton Beam Radiation Therapy

B. Pediatric cancers in cases where the treatment is for previously untreated bone metastases.

ATTACHMENTS

None

APPLICABLE CPT / HCPCS PROCEDURE CODES

CPT (Current Procedural Terminology) Codes

CPT	Description
77423	High energy neutron radiation treatment delivery, 1 or more isocenter(s) with coplanar or non-coplanar geometry with blocking and/or wedge, and/or compensator(s)
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

HCPCS (Healthcare Common Procedure Coding System) Code

HCPCS	Description
S8030	Scleral application of tantalum ring(s) for localization of lesions for proton beam therapy

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

08/09/2023	Updated references.
06/14/2023	Removed indication that all proton beam require clinical review by physician and also need for IMRT vs PBRT comparison study requirement. Added code 77423.
08/10/2022	Adopted NCH policy and retired MCP.

REFERENCES

1. Aihara T, Morita N, Kamitani N, Kumada H, Ono K, Hiratsuka J, Harada T. Boron neutron capture therapy for advanced salivary gland carcinoma in head and neck. Int J Clin Oncol. 2014;19(3):437-44. doi: 10.1007/s10147-013-0580-3. Epub 2013 Jun 25. PMID: 23797210.
2. Allen AM, Pawlicki T, Dong L, Fourkal E, Buyyounouski M, Cengel K, Plastaras J, Bucci MK, Yock TI, Bonilla L, Price R, Harris EE, Konski AA. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. Radiother Oncol. 2012 Apr;103(1):8-11. doi: 10.1016/j.radonc.2012.02.001. Epub 2012 Mar 9. PMID: 22405807.
3. American Society for Radiation Oncology (ASTRO). ASTRO model policies: proton beam therapy (PBT). Approved June 2017. https://www.astro.org/Daily- Practice/Reimbursement/Model-Policies.

4. Badiyan SN, Rutenberg MS, Hoppe BS, Mohindra P, Larson G, Hartsell WF, Tsai H, Zeng J, Rengan R, Glass E, Katz S, Vargas C, Feigenberg SJ, Simone CB 2nd. 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. Pract Radiat Oncol. 2019 Jul-Aug;9(4):280-288. doi: 10.1016/j.prro.2019.02.008. Epub 2019 Feb 23. PMID: 30802618.
5. Blue Cross and Blue Shield Association, Evidence-based Practice Center. Radiotherapy treatments for head and neck cancer update. Comparative effectiveness review. Number 144. Published February 4, 2014. Effective Health Care Program, Agency for Healthcare Research and Quality (AHRQ). https://effectivehealthcare.ahrq.gov/.
6. Böker A, Pilger D, Cordini D, Seibel I, Riechardt AI, Joussen AM, Bechrakis NE. Neoadjuvant proton beam irradiation vs. adjuvant ruthenium brachytherapy in transscleral resection of uveal melanoma. Graefes Arch Clin Exp Ophthalmol. 2018 Sep;256(9):1767-1775. doi: 10.1007/s00417-018-4032-7. Epub 2018 Jun 16. PMID: 29907945.
7. Brada M, Pijls-Johannesma M, De Ruysscher D. Current clinical evidence for proton therapy. Cancer J. 2009 Jul-Aug;15(4):319-24. doi: 10.1097/PPO.0b013e3181b6127c. PMID: 19672149.
8. Burmeister J, Spink R, Liang L, Bossenberger T, Halford R, Brandon J, Delauter J, Snyder M. Commissioning of intensity modulated neutron radiotherapy (IMNRT). Med Phys. 2013 Feb;40(2):021718. doi: 10.1118/1.4766878. PMID: 23387741.
9. Bush DA, Smith JC, Slater JD, Volk ML, Reeves ME, Cheng J, Grove R, de Vera ME. Randomized Clinical Trial Comparing Proton Beam Radiation Therapy with Transarterial Chemoembolization for Hepatocellular Carcinoma: Results of an Interim Analysis. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):477-482. doi: 10.1016/j.ijrobp.2016.02.027. Epub 2016 Feb 13. PMID: 27084661.
10. Chang JY, Verma V, Li M, Zhang W, Komaki R, Lu C, Allen PK, Liao Z, Welsh J, Lin SH, Gomez D, Jeter M, O'Reilly M, Zhu RX, Zhang X, Li H, Mohan R, Heymach JV, Vaporciyan AA, Hahn S, Cox JD. Proton Beam Radiotherapy and Concurrent Chemotherapy for Unresectable Stage III Non-Small Cell Lung Cancer: Final Results of a Phase 2 Study. JAMA Oncol. 2017 Aug 10;3(8):e172032. doi: 10.1001/jamaoncol.2017.2032. Epub 2017 Aug 10. Erratum in: JAMA Oncol. 2017 Sep 1;3(9):1286. Erratum in: JAMA Oncol. 2017 Dec 1;3(12):1742. PMID: 28727865; PMCID: PMC5824219.
11. Chen YL, Liebsch N, Kobayashi W, Goldberg S, Kirsch D, Calkins G, Childs S, Schwab J, Hornicek F, DeLaney T. Definitive high-dose photon/proton radiotherapy for unresected mobile spine and sacral chordomas. Spine (Phila Pa 1976). 2013 Jul 1;38(15):E930-6. doi: 10.1097/BRS.0b013e318296e7d7. PMID: 23609202.
12. Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiat Oncol Biol Phys. 2013 Sep 1;87(1):46-52. doi: 10.1016/j.ijrobp.2013.04.030. Epub 2013 Jun 15. PMID: 23778197.
13. Combs SE. Does Proton Therapy Have a Future in CNS Tumors? Curr Treat Options Neurol. 2017 Mar;19(3):12. doi: 10.1007/s11940-017-0447-4. PMID: 28365895.
14. Cuaron JJ, Chang C, Lovelock M, Higginson DS, Mah D, Cahlon O, Powell S. Exponential Increase in Relative Biological Effectiveness Along Distal Edge of a Proton Bragg Peak as Measured by Deoxyribonucleic Acid Double-Strand Breaks. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):62-69. doi: 10.1016/j.ijrobp.2016.02.018. Epub 2016 Feb 13. PMID: 27084629; PMCID: PMC5005074.
15. Dagan R, Bryant C, Li Z, Yeung D, Justice J, Dzieglewiski P, Werning J, Fernandes R, Pirgousis P, Lanza DC, Morris CG, Mendenhall WM. Outcomes of Sinonasal Cancer Treated With Proton Therapy. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):377-385. doi: 10.1016/j.ijrobp.2016.02.019. Epub 2016 Feb 12. PMID: 27084655.
16. Davis C, Sikes J, Namaranian P, Laramore G, Dillon JK. Neutron Beam Radiation Therapy: An Overview of Treatment and Oral Complications When Treating Salivary Gland Malignancies. J Oral Maxillofac Surg. 2016 Apr;74(4):830-5. doi: 10.1016/j.joms.2015.10.014. Epub 2015 Oct 28. PMID: 26611376.
17. DeLaney TF, Liebsch NJ, Pedlow FX, Adams J, Weyman EA, Yeap BY, Depauw N, Nielsen GP, Harmon DC, Yoon SS, Chen YL, Schwab JH, Hornicek FJ. Long-term results of Phase II study of high dose photon/proton radiotherapy in the management of spine chordomas, chondrosarcomas, and other sarcomas. J Surg Oncol. 2014 Aug;110(2):115-22. doi: 10.1002/jso.23617. Epub 2014 Apr 19. PMID: 24752878.
18. Douglas JG, Laramore GE, Austin-Seymour M, Koh W, Stelzer K, Griffin TW. Treatment of locally advanced adenoid cystic carcinoma of the head and neck with neutron radiotherapy. Int J Radiat Oncol Biol Phys. 2000 Feb 1;46(3):551-7. doi: 10.1016/s0360-3016(99)00445-9. PMID: 10701733.
19. ECRI Institute–Penn Medicine Evidence-based Practice Center. Therapies for clinically localized prostate cancer: update of a 2008 systematic review. Comparative effectiveness review. Number 146. 2014. Agency for Healthcare Research and Quality (AHRQ). https://effectivehealthcare.ahrq.gov/.
20. Efstathiou JA, Trofimov AV, Zietman AL. Life, liberty, and the pursuit of protons: an evidence-based review of the role of particle therapy in the treatment of prostate cancer. Cancer J. 2009 Jul-Aug;15(4):312-8. doi: 10.1097/PPO.0b013e3181b14ec0. PMID: 19672148.
21. Fitzek MM, Thornton AF, Harsh G 4th, Rabinov JD, Munzenrider JE, Lev M, Ancukiewicz M, Bussiere M, Hedley-Whyte ET, Hochberg FH, Pardo FS. Dose-escalation with proton/photon irradiation for Daumas-Duport lower-grade glioma: results of an institutional phase I/II trial. Int J Radiat Oncol Biol Phys. 2001 Sep 1;51(1):131-7. doi: 10.1016/s0360-3016(01)01589-9. PMID: 11516862.
22. Fitzek MM, Thornton AF, Rabinov JD, Lev MH, Pardo FS, Munzenrider JE, Okunieff P, Bussière M, Braun I, Hochberg FH, Hedley-Whyte ET, Liebsch NJ, Harsh GR 4th. Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial. J Neurosurg. 1999 Aug;91(2):251-60. doi: 10.3171/jns.1999.91.2.0251. PMID: 10433313.
23. Frank SJ, Blanchard P, Lee JJ, Sturgis EM, Kies MS, Machtay M, Vikram B, Garden AS, Rosenthal DI, Gunn GB, Fuller CD, Hutcheson K, Lai S, Busse PM, Lee NY, Lin A, Foote RL. Comparing Intensity-Modulated Proton Therapy With Intensity-Modulated Photon Therapy for Oropharyngeal Cancer: The Journey From Clinical Trial Concept to Activation. Semin Radiat Oncol. 2018 Apr;28(2):108-113. doi: 10.1016/j.semradonc.2017.12.002. PMID: 29735186; PMCID: PMC5942581.
24. Gray PJ, Paly JJ, Yeap BY, Sanda MG, Sandler HM, Michalski JM, Talcott JA, Coen JJ, Hamstra DA, Shipley WU, Hahn SM, Zietman AL, Bekelman JE, Efstathiou JA. Patient-reported outcomes after 3-dimensional conformal, intensity-modulated, or proton beam radiotherapy for localized prostate cancer. Cancer. 2013 May 1;119(9):1729-35. doi: 10.1002/cncr.27956. Epub 2013 Feb 22. PMID: 23436283; PMCID: PMC3759976.
25. Grutters JP, Kessels AG, Pijls-Johannesma M, De Ruysscher D, Joore MA, Lambin P. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. Radiother Oncol. 2010 Apr;95(1):32-40. doi: 10.1016/j.radonc.2009.08.003. Epub 2009 Sep 3. PMID: 19733410.

26. Gunn GB, Blanchard P, Garden AS, Zhu XR, Fuller CD, Mohamed AS, Morrison WH, Phan J, Beadle BM, Skinner HD, Sturgis EM, Kies MS, Hutcheson KA, Rosenthal DI, Mohan R, Gillin MT, Frank SJ. Clinical Outcomes and Patterns of Disease Recurrence After Intensity Modulated Proton Therapy for Oropharyngeal Squamous Carcinoma. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):360-367. doi: 10.1016/j.ijrobp.2016.02.021. Epub 2016 Feb 12. PMID: 27084653; PMCID: PMC5474303.
27. Hattangadi-Gluth JA, Chapman PH, Kim D, Niemierko A, Bussière MR, Stringham A, Daartz J, Ogilvy C, Loeffler JS, Shih HA. Single-fraction proton beam stereotactic radiosurgery for cerebral arteriovenous malformations. Int J Radiat Oncol Biol Phys. 2014 Jun 1;89(2):338-46. doi: 10.1016/j.ijrobp.2014.02.030. Epub 2014 Apr 11. PMID: 24726288.
28. Hoppe BS, Hill-Kayser CE, Tseng YD, Flampouri S, Elmongy HM, Cahlon O, Mendenhall NP, Maity A, McGee LA, Plastaras JP. Consolidative proton therapy after chemotherapy for patients with Hodgkin lymphoma. Ann Oncol. 2017 Sep 1;28(9):2179-2184. doi: 10.1093/annonc/mdx287. PMID: 28911093; PMCID: PMC5834068.
29. Huber PE, Debus J, Latz D, Zierhut D, Bischof M, Wannenmacher M, Engenhart-Cabillic R. Radiotherapy for advanced adenoid cystic carcinoma: neutrons, photons or mixed beam? Radiother Oncol. 2001 May;59(2):161-7. doi: 10.1016/s0167-8140(00)00273-5. PMID: 11325445.
30. Indelicato DJ, Bradley JA, Rotondo RL, Nanda RH, Logie N, Sandler ES, Aldana PR, Ranalli NJ, Beier AD, Morris CG, Mendenhall NP. Outcomes following proton therapy for pediatric ependymoma. Acta Oncol. 2018 May;57(5):644-648. doi: 10.1080/0284186X.2017.1413248. Epub 2017 Dec 14. PMID: 29239262.
31. Indelicato DJ, Rotondo RL, Uezono H, Sandler ES, Aldana PR, Ranalli NJ, Beier AD, Morris CG, Bradley JA. Outcomes Following Proton Therapy for Pediatric Low-Grade Glioma. Int J Radiat Oncol Biol Phys. 2019 May 1;104(1):149-156. doi: 10.1016/j.ijrobp.2019.01.078. Epub 2019 Jan 23. PMID: 30684665.
32. Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e400S-e419S. doi: 10.1378/chest.12-2363. PMID: 23649448.
33. Kahalley LS, Douglas Ris M, Mahajan A, Fatih Okcu M, Chintagumpala M, Paulino AC, Whitehead WE, Minard CG, Stancel HH, Orobio J, Xue JJ, Warren EA, Grosshans DR. Prospective, longitudinal comparison of neurocognitive change in pediatric brain tumor patients treated with proton radiotherapy versus surgery only. Neuro Oncol. 2019 Jun 10;21(6):809-818. doi: 10.1093/neuonc/noz041. PMID: 30753584; PMCID: PMC6558072.
34. Kong FS. What Happens When Proton Meets Randomization: Is There a Future for Proton Therapy? J Clin Oncol. 2018 Jun 20;36(18):1777-1779. doi: 10.1200/JCO.2017.76.5479. Epub 2018 Jan 12. PMID: 29328862.
35. Leeman JE, Romesser PB, Zhou Y, McBride S, Riaz N, Sherman E, Cohen MA, Cahlon O, Lee N. Proton therapy for head and neck cancer: expanding the therapeutic window. Lancet Oncol. 2017 May;18(5):e254-e265. doi: 10.1016/S1470-2045(17)30179-1. Epub 2017 Apr 26. PMID: 28456587.
36. Lewis GD, Holliday EB, Kocak-Uzel E, Hernandez M, Garden AS, Rosenthal DI, Frank SJ. Intensity-modulated proton therapy for nasopharyngeal carcinoma: Decreased radiation dose to normal structures and encouraging clinical outcomes. Head Neck. 2016 Apr;38 Suppl 1:E1886-95. doi: 10.1002/hed.24341. Epub 2015 Dec 26. PMID: 26705956.
37. Liao Z, Lee JJ, Komaki R, Gomez DR, O'Reilly MS, Fossella FV, Blumenschein GR Jr, Heymach JV, Vaporciyan AA, Swisher SG, Allen PK, Choi NC, DeLaney TF, Hahn SM, Cox JD, Lu CS, Mohan R. Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2018 Jun 20;36(18):1813-1822. doi: 10.1200/JCO.2017.74.0720. Epub 2018 Jan 2. Erratum in: J Clin Oncol. 2018 Aug 20;36(24):2570. PMID: 29293386; PMCID: PMC6008104.
38. Macomber MW, Bowen SR, Gopan O, Yeung R, Apisarnthanarax S, Zeng J, Patel S. Heart Dose and Outcomes in Radiation Treatment for Esophageal Cancer. Cureus. 2018 Mar 27;10(3):e2378. doi: 10.7759/cureus.2378. PMID: 29805947; PMCID: PMC5969818.
39. Marshall TI, Chaudhary P, Michaelidesová A, Vachelová J, Davídková M, Vondráček V, Schettino G, Prise KM. Investigating the Implications of a Variable RBE on Proton Dose Fractionation Across a Clinical Pencil Beam Scanned Spread-Out Bragg Peak. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):70-77. doi: 10.1016/j.ijrobp.2016.02.029. Epub 2016 Feb 13. PMID: 27084630; PMCID: PMC4838672.
40. McDonald MW, Liu Y, Moore MG, Johnstone PA. 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. Radiat Oncol. 2016 Feb 27;11:32. doi: 10.1186/s13014-016-0600-3. PMID: 26922239; PMCID: PMC4769827.
41. McDonald MW, Zolali-Meybodi O, Lehnert SJ, Estabrook NC, Liu Y, Cohen-Gadol AA, Moore MG. Reirradiation of Recurrent and Second Primary Head and Neck Cancer With Proton Therapy. Int J Radiat Oncol Biol Phys. 2016 Nov 15;96(4):808-819. doi: 10.1016/j.ijrobp.2016.07.037. Epub 2016 Aug 3. PMID: 27788954.
42. Mishra MV, Aggarwal S, Bentzen SM, Knight N, Mehta MP, Regine WF. Establishing Evidence-Based Indications for Proton Therapy: An Overview of Current Clinical Trials. Int J Radiat Oncol Biol Phys. 2017 Feb 1;97(2):228-235. doi: 10.1016/j.ijrobp.2016.10.045. Epub 2016 Nov 8. PMID: 28068231.
43. Mizumoto M, Tsuboi K, Igaki H, Yamamoto T, Takano S, Oshiro Y, Hayashi Y, Hashii H, Kanemoto A, Nakayama H, Sugahara S, Sakurai H, Matsumura A, Tokuuye K. Phase I/II trial of hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2010 May 1;77(1):98-105. doi: 10.1016/j.ijrobp.2009.04.054. Epub 2009 Aug 19. PMID: 19695794.
44. Mizumoto M, Yamamoto T, Takano S, Ishikawa E, Matsumura A, Ishikawa H, Okumura T, Sakurai H, Miyatake S, Tsuboi K. Long-term survival after treatment of glioblastoma multiforme with hyperfractionated concomitant boost proton beam therapy. Pract Radiat Oncol. 2015 Jan-Feb;5(1):e9-16. doi: 10.1016/j.prro.2014.03.012. Epub 2014 May 19. PMID: 25413424.
45. Moreno AC, Frank SJ, Garden AS, Rosenthal DI, Fuller CD, Gunn GB, Reddy JP, Morrison WH, Williamson TD, Holliday EB, Phan J, Blanchard P. Intensity modulated proton therapy (IMPT) - The future of IMRT for head and neck cancer. Oral Oncol. 2019 Jan;88:66-74. doi: 10.1016/j.oraloncology.2018.11.015. Epub 2018 Nov 21. PMID: 30616799; PMCID: PMC6615027.
46. Nakajima K, Iwata H, Ogino H, Hattori Y, Hashimoto S, Toshito T, Hayashi K, Akita K, Baba F, Nakamae K, Mizoe JE, Shibamoto Y. Clinical outcomes of image-guided proton therapy for histologically confirmed stage I non-small cell lung cancer. Radiat Oncol. 2018 Oct 11;13(1):199. doi: 10.1186/s13014-018-1144-5. PMID: 30305125; PMCID: PMC6180633.
47. National Cancer Institute (NCI). NCI dictionary of cancer terms. https://www.cancer.gov/publications/dictionaries/cancer-terms.
48. National Comprehensive Cancer Network (NCCN). Guidelines Version 2.2023 Head and Neck Cancers, Salivary Gland Tumors. https://www.nccn.org/guidelines/category_1.

49. National Comprehensive Cancer Network (NCCN). Radiation Compendium 2.2023, Head and Neck Cancers, Salivary Gland Tumors. https://www.nccn.org/guidelines/category_1.
50. National Institutes of Health (NIH). U.S. National Library of Medicine (NLM). Course: finding and using health statistics: glossary. February 24, 2020. https://www.nlm.nih.gov/nichsr/usestats/glossary.html.
51. NCQA UM 2023 Standards and Elements.
52. Olsen DR, Bruland OS, Frykholm G, Norderhaug IN. Proton therapy - a systematic review of clinical effectiveness. Radiother Oncol. 2007 May;83(2):123-32. doi: 10.1016/j.radonc.2007.03.001. Epub 2007 May 11. PMID: 17499374.
53. Pan HY, Jiang J, Hoffman KE, Tang C, Choi SL, Nguyen QN, Frank SJ, Anscher MS, Shih YT, Smith BD. Comparative Toxicities and Cost of Intensity-Modulated Radiotherapy, Proton Radiation, and Stereotactic Body Radiotherapy Among Younger Men With Prostate Cancer. J Clin Oncol. 2018 Jun 20;36(18):1823-1830. doi: 10.1200/JCO.2017.75.5371. Epub 2018 Mar 21. PMID: 29561693; PMCID: PMC6008105.
54. Patel SH, Wang Z, Wong WW, Murad MH, Buckey CR, Mohammed K, Alahdab F, Altayar O, Nabhan M, Schild SE, Foote RL. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. Lancet Oncol. 2014 Aug;15(9):1027-38. doi: 10.1016/S1470-2045(14)70268-2. Epub 2014 Jun 26. PMID: 24980873.
55. Paulino AC, Mahajan A, Ye R, Grosshans DR, Fatih Okcu M, Su J, McAleer MF, McGovern S, Mangona VA, Chintagumpala M. Ototoxicity and cochlear sparing in children with medulloblastoma: Proton vs. photon radiotherapy. Radiother Oncol. 2018 Jul;128(1):128-132. doi: 10.1016/j.radonc.2018.01.002. Epub 2018 Jan 17. PMID: 29373195.
56. Phan J, Sio TT, Nguyen TP, Takiar V, Gunn GB, Garden AS, Rosenthal DI, Fuller CD, Morrison WH, Beadle B, Ma D, Zafereo ME, Hutcheson KA, Kupferman ME, William WN Jr, Frank SJ. Reirradiation of Head and Neck Cancers With Proton Therapy: Outcomes and Analyses. Int J Radiat Oncol Biol Phys. 2016 Sep 1;96(1):30-41. doi: 10.1016/j.ijrobp.2016.03.053. Epub 2016 Apr 13. PMID: 27325480.
57. Pompos A, Durante M, Choy H. Heavy Ions in Cancer Therapy. JAMA Oncol. 2016 Dec 1;2(12):1539-1540. doi: 10.1001/jamaoncol.2016.2646. PMID: 27541302; PMCID: PMC5894097.
58. Pötter R, Prott FJ, Micke O, Haverkamp U, Wagner W, Willich N. Results of fast neutron therapy of adenoid cystic carcinoma of the salivary glands. Strahlenther Onkol. 1999 Jun;175 Suppl 2:65-8. doi: 10.1007/BF03038892. PMID: 10394401.
59. Qi WX, Fu S, Zhang Q, Guo XM. Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Radiother Oncol. 2015 Mar;114(3):289-95. doi: 10.1016/j.radonc.2014.11.033. Epub 2014 Dec 9. PMID: 25497556.
60. Rockhill JK, Laramore GE. Chapter 20: Neutron Beam Radiotherapy. In: Gunderson L, Tepper J. editors. Clinical Radiation Oncology, 4th eds. Philadelphia, PA: Churchill Livingstone; 2016; (20):373-375.
61. Romesser PB, Cahlon O, Scher E, Zhou Y, Berry SL, Rybkin A, Sine KM, Tang S, Sherman EJ, Wong R, Lee NY. Proton beam radiation therapy results in significantly reduced toxicity compared with intensity-modulated radiation therapy for head and neck tumors that require ipsilateral radiation. Radiother Oncol. 2016 Feb;118(2):286-92. doi: 10.1016/j.radonc.2015.12.008. Epub 2016 Feb 8. PMID: 26867969; PMCID: PMC4980117.
62. Romesser PB, Cahlon O, Scher ED, Hug EB, Sine K, DeSelm C, Fox JL, Mah D, Garg MK, Han-Chih Chang J, Lee NY. Proton Beam Reirradiation for Recurrent Head and Neck Cancer: Multi-institutional Report on Feasibility and Early Outcomes. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):386-395. doi: 10.1016/j.ijrobp.2016.02.036. Epub 2016 Feb 17. PMID: 27084656; PMCID: PMC4997784.
63. Ronson BB, Schulte RW, Han KP, Loredo LN, Slater JM, Slater JD. Fractionated proton beam irradiation of pituitary adenomas. Int J Radiat Oncol Biol Phys. 2006 Feb 1;64(2):425-34. doi: 10.1016/j.ijrobp.2005.07.978. Epub 2005 Oct 27. PMID: 16257131.
64. Sachsman S, Flampouri S, Li Z, Lynch J, Mendenhall NP, Hoppe BS. Proton therapy in the management of non-Hodgkin lymphoma. Leuk Lymphoma. 2015;56(9):2608-12. doi: 10.3109/10428194.2015.1014364. Epub 2015 May 18. PMID: 25669925; PMCID: PMC4732409.
65. Saltzman AF, Cost NG. Current Treatment of Pediatric Bladder and Prostate Rhabdomyosarcoma. Curr Urol Rep. 2018 Feb 22;19(1):11. doi: 10.1007/s11934-018-0761-8. PMID: 29468476.
66. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, Freedland SJ, Greene K, Klotz LH, Makarov DV, Nelson JB, Rodrigues G, Sandler HM, Taplin ME, Treadwell JR. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. J Urol. 2018 Mar;199(3):683-690. doi: 10.1016/j.juro.2017.11.095. Epub 2017 Dec 15. PMID: 29203269.
67. Sanford NN, Pursley J, Noe B, Yeap BY, Goyal L, Clark JW, Allen JN, Blaszkowsky LS, Ryan DP, Ferrone CR, Tanabe KK, Qadan M, Crane CH, Koay EJ, Eyler C, DeLaney TF, Zhu AX, Wo JY, Grassberger C, Hong TS. Protons versus Photons for Unresectable Hepatocellular Carcinoma: Liver Decompensation and Overall Survival. Int J Radiat Oncol Biol Phys. 2019 Sep 1;105(1):64-72. doi: 10.1016/j.ijrobp.2019.01.076. Epub 2019 Jan 23. PMID: 30684667.
68. Seifert V, Stolke D, Mehdorn HM, Hoffmann B. Clinical and radiological evaluation of long-term results of stereotactic proton beam radiosurgery in patients with cerebral arteriovenous malformations. J Neurosurg. 1994 Nov;81(5):683-9. doi: 10.3171/jns.1994.81.5.0683. PMID: 7931614.
69. Sheets NC, Goldin GH, Meyer AM, Wu Y, Chang Y, Stürmer T, Holmes JA, Reeve BB, Godley PA, Carpenter WR, Chen RC. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA. 2012 Apr 18;307(15):1611-20. doi: 10.1001/jama.2012.460. PMID: 22511689; PMCID: PMC3702170.
70. Simone CB 2nd, Bogart JA, Cabrera AR, Daly ME, DeNunzio NJ, Detterbeck F, Faivre-Finn C, Gatschet N, Gore E, Jabbour SK, Kruser TJ, Schneider BJ, Slotman B, Turrisi A, Wu AJ, Zeng J, Rosenzweig KE. Radiation Therapy for Small Cell Lung Cancer: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2020 May-Jun;10(3):158-173. doi: 10.1016/j.prro.2020.02.009. Epub 2020 Mar 23. PMID: 32222430.
71. Sio TT, Lin HK, Shi Q, Gunn GB, Cleeland CS, Lee JJ, Hernandez M, Blanchard P, Thaker NG, Phan J, Rosenthal DI, Garden AS, Morrison WH, Fuller CD, Mendoza TR, Mohan R, Wang XS, Frank SJ. Intensity Modulated Proton Therapy Versus Intensity Modulated Photon Radiation Therapy for Oropharyngeal Cancer: First Comparative Results of Patient-Reported Outcomes. Int J Radiat Oncol Biol Phys. 2016 Jul 15;95(4):1107-14. doi: 10.1016/j.ijrobp.2016.02.044. Epub 2016 Feb 18. PMID: 27354125; PMCID: PMC5409532.
72. Stannard C, Vernimmen F, Carrara H, Jones D, Fredericks S, Hille J, de Kock E. Malignant salivary gland tumours: can fast neutron therapy results point the way to carbon ion therapy? Radiother Oncol. 2013 Nov;109(2):262-8. doi: 10.1016/j.radonc.2013.08.013. Epub 2013 Sep 14. PMID: 24044797.

73. Steinmeier T, Schulze Schleithoff S, Timmermann B. Evolving Radiotherapy Techniques in Paediatric Oncology. Clin Oncol (R Coll Radiol). 2019 Mar;31(3):142-150. doi: 10.1016/j.clon.2018.12.005. Epub 2019 Jan 11. PMID: 30639254.
74. Verma V, Rwigema JM, Malyapa RS, Regine WF, Simone CB 2nd. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. Radiother Oncol. 2017 Oct;125(1):21-30. doi: 10.1016/j.radonc.2017.08.005. Epub 2017 Sep 20. PMID: 28941560.
75. Verma V, Shah C, Mehta MP. Clinical Outcomes and Toxicity of Proton Radiotherapy for Breast Cancer. Clin Breast Cancer. 2016 Jun;16(3):145-54. doi: 10.1016/j.clbc.2016.02.006. Epub 2016 Feb 12. PMID: 26995159.
76. Verma V, Simone CB 2nd, Mishra MV. Quality of Life and Patient-Reported Outcomes Following Proton Radiation Therapy: A Systematic Review. J Natl Cancer Inst. 2018 Apr 1;110(4). doi: 10.1093/jnci/djx208. PMID: 29028221.
77. Wang J, Wei C, Tucker SL, Myles B, Palmer M, Hofstetter WL, Swisher SG, Ajani JA, Cox JD, Komaki R, Liao Z, Lin SH. Predictors of postoperative complications after trimodality therapy for esophageal cancer. Int J Radiat Oncol Biol Phys. 2013 Aug 1;86(5):885-91. doi: 10.1016/j.ijrobp.2013.04.006. PMID: 23845841; PMCID: PMC3786201.
78. Wang Z, Nabhan M, Schild SE, Stafford SL, Petersen IA, Foote RL, Murad MH. Charged particle radiation therapy for uveal melanoma: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys. 2013 May 1;86(1):18-26. doi: 10.1016/j.ijrobp.2012.08.026. Epub 2012 Oct 3. PMID: 23040219.
79. Widesott L, Amichetti M, Schwarz M. Proton therapy in lung cancer: clinical outcomes and technical issues. A systematic review. Radiother Oncol. 2008 Feb;86(2):154-64. doi: 10.1016/j.radonc.2008.01.003. Epub 2008 Jan 31. PMID: 18241945.
80. Wiltink LM, Nout RA, Fiocco M, Meershoek-Klein Kranenbarg E, Jürgenliemk-Schulz IM, Jobsen JJ, Nagtegaal ID, Rutten HJ, van de Velde CJ, Creutzberg CL, Marijnen CA. No Increased Risk of Second Cancer After Radiotherapy in Patients Treated for Rectal or Endometrial Cancer in the Randomized TME, PORTEC-1, and PORTEC-2 Trials. J Clin Oncol. 2015 May 20;33(15):1640-6. doi: 10.1200/JCO.2014.58.6693. Epub 2014 Dec 22. PMID: 25534376.
81. Yang P, Xu T, Gomez DR, Deng W, Wei X, Elhalawani H, Jin H, Guan F, Mirkovic D, Xu Y, Mohan R, Liao Z. Patterns of Local-Regional Failure After Intensity Modulated Radiation Therapy or Passive Scattering Proton Therapy With Concurrent Chemotherapy for Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2019 Jan 1;103(1):123-131. doi: 10.1016/j.ijrobp.2018.08.031. Epub 2018 Aug 28. PMID: 30165127.
82. Yu JB, Soulos PR, Herrin J, Cramer LD, Potosky AL, Roberts KB, Gross CP. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. J Natl Cancer Inst. 2013 Jan 2;105(1):25-32. doi: 10.1093/jnci/djs463. Epub 2012 Dec 14. PMID: 23243199; PMCID: PMC3536640.
83. Zelefsky MJ, Pei X, Teslova T, Kuk D, Magsanoc JM, Kollmeier M, Cox B, Zhang Z. Secondary cancers after intensity-modulated radiotherapy, brachytherapy and radical prostatectomy for the treatment of prostate cancer: incidence and cause-specific survival outcomes according to the initial treatment intervention. BJU Int. 2012 Dec;110(11):1696-701. doi: 10.1111/j.1464-410X.2012.11385.x. Epub 2012 Aug 13. PMID: 22889401.
84. Zhou J, Yang B, Wang X, Jing Z. Comparison of the Effectiveness of Radiotherapy with Photons and Particles for Chordoma After Surgery: A Meta-Analysis. World Neurosurg. 2018 Sep;117:46-53. doi: 10.1016/j.wneu.2018.05.209. Epub 2018 Jun 5. PMID: 29879512.
85. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, Bush DA, Lunt M, Spiegel DY, Skowronski R, Jabola BR, Rossi CJ. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol. 2010 Mar 1;28(7):1106-11. doi: 10.1200/JCO.2009.25.8475. Epub 2010 Feb 1. PMID: 20124169; PMCID: PMC2834463.