Washington State Health Care Authority

Proton beam therapy – re-review

Clinical Expert

Smith Apisarnthanarax, MD

Associate Professor of Radiation Oncology

Director of Clinical Research

Associate Residency Program Director, Proton Therapy Fellowship Director,

Department of Radiation Oncology

University of Washington, Seattle Cancer Care Alliance

Applicant name Smith Apisarnthanarax			
Street address 1959 NE Pacific St., Box 356043	City Seattle	State WA	ZIP Code 98195

1. Business activities

(a) If you or a member of your household was ***an officer or director of a business*** during the immediately preceding calendar year and the current year to date, provide the following:

Title	Business name and address	Business type

(b) If you or a member of your household did business under an assumed business name during the immediately preceding calendar year or the current year to date, provide the following information:

Business name	Business address	Business type

2. Honorarium

If you ***received an honorarium of more than $100*** during the immediately preceding calendar year and the current year to date, list all such honoraria.

Received from	Organization address	Service performed
Medtronic	3555 Koger Blvd. Ste 200, Duluth, GA, 3	Consultant for fiducial markers

3. Sources of income

(a) Identify ***income source(s) that contributed 10 percent or more of the combined total gross household income*** received by you or a member of your household during the immediately preceding calendar year and the current year to date.

Source name and address	Received by	Source type
University of Washington	Myself	Salary

(b) Does any income source listed on the previous page relate to, or could it reasonably be expected to relate to, business that has, or may, come before the Committee?

☐ Yes ☒ No	**If "yes," describe:**

(c) Does an income source listed on the previous page have a legislative or administrative interest in the business of the Committee?

☐ Yes ☒ No	**If "yes," describe:**

4. Business shared with a lobbyist

If you or a member of your household ***shared a partnership, joint venture, or similar substantial economic relationship with a paid lobbyist***, were employed by, or employed, a paid lobbyist during [----missing text----], please list the following:

(Owning stock in a publicly traded company in which the lobbyist also owns stock is not a relationship that requires disclosure.)

Lobbyist name	Business name	Type business shared

Provide the information requested in items 5, 6, and 7 below only if:

(a) Your response involves an individual or business that you or a member of your household did business with, or reasonably could be expected to relate to do business that has or may come before the Health Technology Clinical Committee.

(b) The information requested involves an individual or business with a legislative or administrative interest in the Committee.

5. Income of more than $1,000

If you or a member of your household ***shared a partnership, joint venture, or similar substantial economic relationship with a paid lobbyist***, were employed by, or employed, a paid lobbyist during [----missing text----], please list the following:

(Owning stock in a publicly traded company in which the lobbyist also owns stock is not a relationship that requires disclosure.)

Income source	Address	Description of income source

6. Business investments of more than $1,000

(Do not list the amount of the investment or include individual items held in a mutual fund or blind trust, a time or demand deposit in a financial institution, shares in a credit union, or the cash surrender value of life insurance.)

If you or a member of your household had a personal, beneficial interest or investment in a business during the immediate preceding calendar year of more than $1,000, list the following:

Business name	Business address	Description of business

7. Service fee of more than $1,000

(Do not list fees if you are prohibited from doing so by law or professional ethics.)

List each ***person for whom you performed a service for a fee of more than $1,000*** in the immediate preceding calendar year or the current year to date.

Name	Description of service

I certify that I have read and understand this Conflict of Interest form and the information I have provided is true and correct as of this date.

Print name: Smith Apisarnthanarax

Check one: ☒ Committee member ☐ Subgroup member ☐ Contractor

[redacted]	02/26/2019
Signature	Date

SMITH APISARNTHANARAX, MD

1959 NE Pacific St, Seattle, WA 98195 | apisarn@uw.edu | 425-505-7722

EDUCATION AND TRAINING

University of North Carolina, Chapel Hill, NC
Chief Resident, Department of Radiation Oncology
07/2007-06/2008
Resident, Department of Radiation Oncology
07/2005 – 06/2009

University of Texas M.D. Anderson Cancer Center, Houston, TX
Postdoctoral Research Fellow, Department of Experimental Radiation Oncology
K.S. Clifford Chao, M.D. laboratory
07/2003 – 06/2005

Evanston Hospital (NorthShore University Health System), Evanston, IL
Intern, Department of Medicine
06/2002 – 06/2003

Warren Alpert Medical School of Brown University, Providence, RI
M.D., Program in Liberal Medical Education
08/1998 – 05/2002

Brown University, Providence, RI
B.A., Psychology, Program in Liberal Medical Education
08/1994 – 07/1998

CURRENT POSITION

Associate Professor of Radiation Oncology

Clinical Research Director

Associate Residency Program Director

Proton Therapy Fellowship Director
University of Washington School of Medicine, Seattle, WA

ACADEMIC APPOINTMENTS

Associate Professor of Radiation Oncology
University of Washington School of Medicine, Seattle, WA
05/2013 – Present

Assistant Professor of Radiation Oncology
University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
09/2009 – 04/2013

CERTIFICATION AND LICENSURE

American Board of Radiology, Radiation Oncology
2010 – Present

Washington State Medical License, 2013 – Active
Pennsylvania State Medical License, 2009 – Inactive
New Jersey State Medical License, 2009 – Inactive
North Carolina State Medical License, 2006 – Inactive

HONORS AND AWARDS

2nd place, "Proton Therapy: Advanced Applications for the Most Challenging Cases" Cureus publishing competition, 2017

University of Washington Radiation Oncology Residency Teacher Award, 2016

Association of Residents in Radiation Oncology (ARRO) Educator of the Year, 2011

Travel Grant Award, American Society of Therapeutic Radiology and Oncology (ASTRO) Translational Symposium, 2008

Roentgen Resident/Fellow Research Award, Radiological Society of North America (RSNA), 2008

Scholars in Training (SIT) Travel Award, Radiation Research Society (RRS), 2008

1st Place Clinical/Translational Poster, University of North Carolina Lineberger Comprehensive Cancer Center Annual Scientific Retreat, 2008

Methods in Clinical Cancer Research Workshop Selected Attendee, AACR/ASCO, 2008

Travel Award, Best of American Society of Clinical Oncology (ASCO), 2007

Travel Award, International Society of Gastrointestinal Oncology (ISGIO), 2005

PROFESSIONAL MEMBERSHIPS/ ACTIVITIES

American Society of Therapeutic Radiology and Oncology (ASTRO)
Abstract Reviewer, Gastrointestinal Track
2018 – Present
Full Member
2009 – Present

Journal Peer Reviewer
Hepatology, 2018 – Present
Journal of the National Comprehensive Cancer Network, 2018 – Present
Journal of Clinical Oncology, 2018 – Present
Physica Medica: European Journal of Medical Physics, 2017 – Present
Liver Transplantation, 2017 – Present
BMC Cancer, 2015 – Present
International Journal of Particle Therapy, 2015 – Present
American Journal of Clinical Oncology, 2015 – Present
Cancer, 2013 – Present
International Journal Radiation Oncology Biology Physics, 2009 – Present
Practical Radiation Oncology, 2009 – Present

EDITORIAL BOARDS

International Journal Radiation Oncology Biology Physics
Associate Editor, Gastrointestinal Section
2015 – Present

COMMITTEES

NATIONAL
ABR Radiation Oncology Online Assessment GI committee
2018 – Present

RSS Liver SRS/SBRT Accreditation Committee
2018 – Present

ACR/ASTRO Practice Parameter for the Performance of Proton Beam Radiation Therapy Committee
2017 – Present

College of American Pathologists (CAP) Committee
2013 – Present

INSTITUTIONAL
Clinical Research Oversight Committee
Fred Hutchinson/University of Washington Cancer Consortium
2014 – Present

Scientific Review Committee
Fred Hutchinson/University of Washington Cancer Consortium
2014 – 2017

Member, Data Safety Monitoring Committee

University of Pennsylvania/Abramson Cancer Center
2010 – 2013

Patient Education Committee, Chairperson
University of Pennsylvania Radiation Oncology
2011 – 2012

Residency Education Committee
University of North Carolina Radiation Oncology
2007 – 2008

DEPARTMENTAL
Residency Clinical Competency Committee
University of Washington Radiation Oncology
2014-Present

Residency Education Committee
University of Pennsylvania Radiation Oncology
2011 – 2013

CLINICAL TRIALS / ACTIVITES

Functional Liver Imaging with Sulfur Colloid SPECT/CT in Primary and Metastatic Liver Cancer Patients Receiving Liver-Directed Treatment: A Pilot Study, PI

RTOG 1112: Randomized Phase III Study of Sorafenib Versus Stereotactic Body Radiation Therapy Followed by Sorafenib in Hepatocellular Carcinoma, Institutional Site PI

NRG-GI001: Randomized Phase III Study of Focal Radiation Therapy for Unresectable, Localized Intrahepatic Cholangiocarcinoma, Institutional Site PI

EDUCATIONAL ACTIVITIES

Preceptor, Cultural Competency and Awareness in the Doctor-Patient Relationship: Communication and Culture Course
University of Pennsylvania Perelman School of Medicine
2010

Preceptor, Doctoring Course
University of Pennsylvania Perelman School of Medicine
2011 – 2013

LECTURES
"Notes, Notes, Notes: Tips of Making a Great Radiation Oncology Note," University of Washington, Radiation Oncology, resident didactic lecture, 07/2017.

GRANTS

McCabe Pilot Award: Pilot Study of Imaging Proliferation with ^{18}F-FLT to Assess Early Treatment Response to Chemoradiotherapy in Locally Advanced Rectal Cancer, McCabe Advisory Committee, (Smith Apisarnthanarax, PI: Daniel Pryma, Co-Investigator), $34,548/annual direct costs, 1% effort (Role in grant: PI)
10/2010 – 10/2011

PUBLICATIONS

PEER REVIEWED

1. **Apisarnthanarax S**, Chougule P. Intravascular brachytherapy: a review of the current vascular biology. *American Journal of Clinical Oncology* 26(3): e13-21, Jun 2003. PMID: 12796611.
2. **Apisarnthanarax S**, Chao KS. Current imaging paradigms in radiation oncology. *Radiation Research* 163(1): 1-25, Jan 2005. PMID: 15606303.
3. Frank SJ, Chao KS, Schwartz DL, Weber RS, **Apisarnthanarax S**, Macapinlac HA. Technology insight: PET and PET/CT in head and neck tumor staging and radiation therapy planning. *Nature Clinical Practice: Oncology* 2(10): 526-33, Oct 2005. PMID: 16205772.
4. **Apisarnthanarax S**, Elliott DD, El-Naggar AK, Asper JA, Blanco A, Ang KK, Garden AS, Morrison WH, Rosenthal D, Weber RS, Chao KS. Determining optimal clinical target volume margins in head-and-neck cancer based on microscopic extracapsular extension of metastatic neck nodes. *International Journal of Radiation Oncology, Biology, Physics* 64(3): 678-83, Mar 2006. PMID: 16243444.
5. **Apisarnthanarax S**, Alauddin MM, Mourtada F, Ariga H, Raju U, Mawlawi O, Han D, Bornmann WG, Ajani JA, Milas L, Gelovani JG, Chao KS. Early detection of chemoradioresponse in esophageal carcinoma by 3'-deoxy-3'-3H-fluorothymidine using preclinical tumor models. *Clinical Cancer Research* 12(15): 4590-7, Aug 2006. PMID: 16899606.
6. Sims-Mourtada J, Izzo JG, **Apisarnthanarax S**, Wu TT, Malhotra U, Luthra R, Liao Z, Komaki R, van der Kogel A, Ajani JA, Chao KS. Hedgehog: an attribute to tumor regrowth after chemoradiotherapy and a target to improve radiation response. *Clinical Cancer Research* 12(21): 6565-72, Nov 2006. PMID: 17085672.
7. **Apisarnthanarax S**, Tepper JE. Crossroads in the combined-modality management of gastroesophageal junction carcinomas. *Gastrointestinal Cancer Research* 2(5): 235-43, Sep 2008. PMID: 19259307.
8. **Apisarnthanarax S**, Dhruva N, Ardeshirpour F, Tepper JE, Shores CG, Rosenman JG, Shockley WW, Hayward MC, Hayes DN. Concomitant radiotherapy and chemotherapy for high-risk nonmelanoma skin carcinomas of the head and neck. *International Journal of Surgical Oncology* 2011(464829), 2011. PMID: 22312508.
9. Eblan MJ, Corradetti MN, Lukens JN, Xanthopoulos E, Mitra N, Christodouleas JP, Grover S, Fernandes AT, Langer CJ, Evans TL, Stevenson J, Rengan R, **Apisarnthanarax S**. Brachial plexopathy in apical non-small cell lung cancer treated with definitive radiation: dosimetric analysis and clinical implications. *International*

Journal of Radiation Oncology, Biology, Physics 85(1): 175-81, Jan 2013. PMID: 22658442.

10. Wojcieszynski AP, Berman MA, Wan F, Plastaras JP, Metz JM, Mitra N, **Apisarnthanarax S**. The impact of radiation therapy sequencing on survival and cardiopulmonary mortality in the combined modality treatment of esophageal cancer. *Cancer* 119(11): 1976-1984, Jun 2013. PMID 23400669.
11. Xanthopoulos E, Corradetti MN, Mitra N, Fernandes AT, Kim M, Grover S, Christodouleas JP, Evans TL, Stevenson J, Langer CJ, Lee TT, Lin L, Simon CB, **Apisarnthanarax S**, Rengan R. Impact of PET-staging in limited-stage small cell lung cancer. *Journal of Thoracic Oncology* 8(7): 899-905, Jul 2013. PMID 23608814.
12. **Apisarnthanarax S**, Swisher-McClure S, Chiu WK, Kimple RJ, Harris SL, Morris DE, Tepper JE. Applicability of randomized trials in radiation oncology to standard clinical practice. *Cancer* 119(16): 3092-3099, Aug 2013. PMID 23674290.
13. Corradetti MN, Mitra N, Bonner Millar LP, Byun J, Wan F, **Apisarnthanarax S**, Christodouleas J, Anderson N, Simone CB, Teo BK, Rengan R. A moving target: image guidance for stereotactic body radiation therapy for early-stage non-small cell lung cancer. *Practical Radiation Oncology* 3(4): 307-315, Oct-Dec 2013. PMID: 24674403.
14. Whaley TW, Fernandes AT, Sackmann R, Plastaras JP, Teo BK, Grover S, Perini RF, Metz JM, Pryma DA, **Apisarnthanarax S**. Clinical utility of integrated PET/CT imaging in the clinical management and radiation treatment planning of locally advanced rectal cancer. *Practical Radiation Oncology* 4(4): 226-232, July 2014. PMID 25012830.
15. Berman AT, Both S, Sharkoski T, Goldrath K, Tochner Z, **Apisarnthanarax S**, Metz JM, Plastaras JP. Proton reirradiation of recurrent rectal cancer: dosimetric comparison, toxicities, and preliminary outcomes. *International Journal of Particle Therapy* 2014, 10.1029/theijpt-d-13-00002.1.
16. Thompson RF, Myeker S, Zhai, H, Both, S, **Apisarnthanarax S**, Metz JM, Plastaras JP, Ben-Josef E. A dosimetric comparison of IMRT, PBS, and DS in unresectable cancers of the head of pancreas. *Medical Physics* 41(8): 081711, Aug 2014. PMID 25086521.
17. Grover S, Jones J, Teitelbaum U, **Apisarnthanarax S**. Radiation recall myositis: two sites, one patient. *Practical Radiation Oncology* 5(1): 39-42, Jan-Feb 2015. PMID 25413426.
18. Xanthopoulos EP, Handorf E, Simone CB, Grover S, Fernandes AT, Sharma S, Corradetti MN, Evans TL, Langer CJ, Mitra N, Shah A, **Apisarnthanarax S**, Lin LL, Rengan R. Definitive dose thoracic radiotherapy in oligometastatic non-small-cell lung cancer (NSCLC): a hypothesis-generating study. *Practical Radiation Oncology* Jan 2015, 10.1016/j.prro.2014.11.006. PMID:25649540.
19. Gandhi SJ, Liang X, Ding X, Zhu TC, Ben-Josef E, Plastaras JP, Metz JM, Both S, **Apisarnthanarax S**. Clinical decision tool for optimal delivery of liver stereotactic

body radiation therapy: Photons versus protons. *Practical Radiation Oncology* Feb 2015, 10.1016/j.prro.2015.01.004. PMID:25703530.

20. Fernandes AT, **Apisarnthanarax S**, Yin L, Zou W, Rosen M, Plastaras JP, Ben-Josef E, Metz JM, Teo BK. Comparative assessment of liver tumor motion using cine-magnetic resonance imaging versus 4-dimensional computed tomography. *International Journal of Radiation Oncology, Biology, Physics* 91(5): 1034-1040, Apr 2015. PMID: 25832694.
21. Bowen SR, Saini J, Chapman TR, Miyaoka RS, Kinahan PE, Sandison GA, Wong T, Vesselle HJ, Nyflot MJ, **Apisarnthanarax S**. Differential hepatic avoidance radiation therapy: proof of concept in hepatocellular carcinoma patients. *Radiotherapy Oncology* 115(2): 203-210, May 2015. PMID: 25934165.
22. Chapman TR, Kumarapeli AR, Nyflot MJ, Bowen S, Yeung R, Vesselle H, Yeh MM, **Apisarnthanarax S**. Functional imaging of radiation liver injury in a liver metastasis patient: imaging and pathologic correlation**.** *Journal of Gastrointestinal Oncology* 6(3): E44-47, June 2015. PMID 26029465.
23. Yeh MM, Yeung RS, **Apisarnthanarax S**, Bhattacharya R, Cuevas C, Harris WP, Hon TLK, Padia SA, Park JO, Riggle KM, Daoud SS. Multidisciplinary perspective of hepatocellular carcinoma: a pacific northwest experience. *World Journal of Hepatology* 7(11): 1460-1483, June 2015. PMID: 26085907.
24. Coveler AL, Richard P, **Apisarnthanarax S**, Chiorean EG. Is there a best radiosensitizing agent in the treatment of locally advanced rectal cancer? *Current Colorectal Cancer Reports* 12(4): 189-200, Aug 2016.
25. Bowen SR, Chapman TR, Borgman J, Miyaoka RS, Kinahan PE, Liou IW, Sandison GA, Vesselle HJ, Nyflot MJ, **Apisarnthanarax S**. Measuring total liver function on sulfur colloid SPECT/CT for improved risk stratification and outcome prediction of hepatocellular carcinoma patients. *European Journal of Nuclear Medicine and Molecular Imaging Research* 6(1): 57, Dec 2016. PMID: 27349530.
26. Zeng YC, Vyas S, Dang Q, Shultz L, Bowen SR, Shankaran V, Farjah F, Oelschlager BK**, Apisarnthanarax S**, Zeng J. Proton therapy posterior beam approach with pencil beam scanning for esophageal cancer: clinical outcome, dosimetry, and feasibility. *Strahlentherapie Onkologie* 192(12): 913-921, Dec 2016. PMID: 27596221.
27. Tseng YD, **Apisarnthanarax S**, Liao JL, Bhatia S, Nghiem PT, Parvathaneni U. Factors influencing radiation treatment recommendations in early-stage Merkel cell carcinoma: a survey of US-based radiation oncologists. *Expert Rev Anticancer Ther*. 2017 Mar;17(3):281-287. PMID: 28103445.
28. Mullen TD, Kim EY, **Apisarnthanarax S**. Short-course radiation therapy versus long-course chemoradiation in the neoadjuvant treatment of locally advanced rectal cancer: new insights from randomized trials. *Current Colorectal Cancer Reports* 2017;13:165. https://doi.org/10.1007/s11888-017-0359-4
29. Matesan MM, Bowen SR, Chapman TR, Miyaoka RS, Velez JW, Wanner MF, Nyflot MJ, **Apisarnthanarax S**, Vesselle HJ. Assessment of functional liver reserve: old and new

in [^{99m}Tc]sulfur colloid scintigraphy. *Nucl Med Commun*. 2017 Jul;38(7):577-586. PMID: 28591006. doi: 10.1097/MNM.0000000000000695.

30. Yeung RH, Chapman TR, Bowen SR, **Apisarnthanarax S**. Proton beam therapy for hepatocellular carcinoma. *Expert Review of Anticancer Therapy* 21: 1-14, Aug 2017. PMID: 28825506. doi: 10.1080/14737140.2017.1368392.
31. Boimel PJ, Berman AT, Li J, **Apisarnthanarax S**, Both S, Lelionis K, Larson GL, Teitelbaum U, Lukens JN, Ben-Josef E, Metz JM, Plastaras JP. Proton beam reirradiation for locally recurrent pancreatic adenocarcinoma. *J Gastrointest Oncol*. 2017 Aug;8(4):665-674. PMID: 28890817. doi: 10.21037/jgo.2017.03.04.
32. Sharma S, Whaley JT, Zou W, Shepherd AF, Xanthopoulos EP, Christodouleas, Both S, Rengan R, Simone II CB, **Apisarnthanarax S**. Incidental nodal irradiation in locally advanced non-small cell lung cancer treated with involved-field IMRT. *Applied Radiation Oncology*, 2017;6(4): 21-27.
33. **Apisarnthanarax S**, Saini J, O'Ryan-Blair A, Castro J, Bowen SR. Intensity modulated proton therapy with advanced planning techniques in a challenging hepatocellular carcinoma patient. *Cureus* 9(9): e1674. PMID:29152431. doi:10.7759/cureus.1674.
34. Kesarwala AH, Lu DJ, Xanthopoulos E, **Apisarnthanarax S**, Cengel KA, Evans T, Aggarwal C, Cohen RB, Langer CJ, Rengan R, Simone CB II. The role of advanced imaging in assessing response to definitive chemoradiation prior to prophylactic cranial irradiation in limited-stage small cell lung cancer. *Clin Lung Cancer*. 2018 Mar;19(2):e205-e209. PMID: 29153967. doi: 10.1016/j.cllc.2017.10.001.
35. Tseng Y, Wootton L, Nyflot M, **Apisarnthanarax S**, Rengan R, Bloch C, Sandison G, St James S. Four-dimensional computer tomography scans for conformal thoracic treatment planning: Is a single scan sufficient to capture thoracic tumor motion? *Phys Med Biol*. 2018 Jan 18;63(2):02NT03. PMID: 29346116. doi: 10.1088/1361-6560/aaa44e.
36. Shabason JE, Chen J, **Apisarnthanarax S**, Damjanov N, Giantonio B, Loaiza-Bonilla A, O'Dwyer PJ, O'Hara M, Reiss KA, Teitelbaum U, Wissel P, Drebin JA, Vollmer C, Kochman M, Mick R, Vergara N, Jhala N, Doucette A, Lukens JN, Plastaras JP, Metz JM, Ben-Josef E. A phase I dose escalation trial of nab-paclitaxel and fixed dose radiation in patients with unresectable or borderline resectable pancreatic cancer. *Cancer Chemother Pharmacol*. 2018 Mar;81(3):609-614. PMID: 29362902. doi: 10.1007/s00280-018-3519-6.
37. Chapman T, Bowen SR, Schaub SK, Yeung RH, Kwan SW, Park JO, Yu L, Harris WP, Johnson GE, Liou IW, Nyflot MJ, **Apisarnthanarax S**. Towards consensus reporting of radiation-induced liver toxicity in the treatment of primary liver malignancies: defining clinically relevant endpoints. *Practical Radiation Oncology* 8: 157-166, May-June 2018. PMID 29426691.
38. Yeung RH, Bowen SR, Chapman TR, MacLennan GT, **Apisarnthanarax S**. Chest wall toxicity after hypofractionated proton beam therapy for liver malignancies. *Pract Radiat Oncol*. 2017 Dec 24. pii: S1879-8500(17)30383-1. PMID:29452863. doi: 10.1016/j.prro.2017.12.00.7

39. 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. PMID: 29805947. doi: 10.7759/cureus.2378.
40. Smith WP, Richard PJ, Zeng J, **Apisarnthanarax S**, Rengan R, Phillips MH, Decision analytic modeling for the economic analysis of proton radiotherapy for non-small cell lung cancer. *Transl Lung Cancer Res*. 2018 Apr;7(2):122-133. PMID: 29876311. doi: 10.21037/tlcr.2018.03.27.
41. 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. PMID: 29805947.
42. Smith WP, Richard PJ, Zeng J, **Apisarnthanarax S**, Rengan R, Phillips MH, Decision analytic modeling for the economic analysis of proton radiotherapy for non-small cell lung cancer. *Transl Lung Cancer Res.* 2018 Apr;7(2):122-133. PMID: 29876311.
43. Price RG, Apisarnthanarax S, Schaub SK, Nyflot MJ, Chapman TR, Matesan M, Vesselle HJ, Bowen SR. Regional radiation dose-response modeling of functional liver in hepatocellular carcinoma patients with longitudinal sulfur colloid SPECT/CT: a proof of concept. *Int J Radiat Oncol Biol Phys*. 2018 Jun 19 pii: S0360-3016(18)31008-3. PMID: 29932945.
44. Macomber MW, Schaub SK, **Apisarnthanarax S**. Case reports: liver abscess after hepatic stereotactic body radiation therapy. *Pract Radiat Oncol*. 2018 Feb 21. pii: S1879-8500(18)30068-7. PMID: 29935956. doi: 10.1016/j.prro.2018.02.008. PMID: 2980594.
45. Schaub SK, Hartvigson PE, Lock MI, Høyer M, Brunner TB, Cardenes HR, Dawson LA, Kim EY, Mayr NA, Lo SS, **Apisarnthanarax S**. Stereotactic body radiation therapy for hepatocellular carcinoma: current trends and controversies. *Technol Cancer Res Treat*. 2018 Jan 17: 1-19. PMID: 30068240.
46. Schaub SK, **Apisarnthanarax S**, Price RG, Nyflot MJ, Chapman TR, Matesan M, Vesselle HJ, Bowen SR. Functional liver imaging and dosimetry to predict hepatotoxicity risk in cirrhotic patients with primary liver cancer. *Int J Radiat Oncol Biol Phys.* 2018 Aug 28. pii: S0360-3016(18)33615-0. doi: 10.1016/j.ijrobp.2018.08.029. PMID:30170100
47. Tseng YD, Nguyen MH, Baker K, Cook M, Redman M, Lachance K, Bhatia S, Liao JJ, **Apisarnthanarax S**, Nghiem PT, Parvathaneni U. Effect of host immune status on the efficacy of radiotherapy and recurrence-free survival among 805 Merkel cell carcinoma patients. *Int J Radiat Oncol Biol Phys*. 2018 Oct 1;102(2):330-339. PMID: 30191867.
48. Lee HJ Jr, Macomber MW, Spraker MB, Bowen SR, Hippe DS, Fung A, Russell KJ, Laramore GE, Rengan R, Liao J, **Apisarnthanarax S**, Zeng J. Early toxicity and patient reported qualityof-life in patients receiving proton therapy for localized prostate cancer: a single institutional review of prospectively recorded outcomes. *Radiat Oncol*. 2018 Sep 17;13(1):179. PMID: 30223877.

49. Chuong MD, Badiyan S, Hall M, **Apisarnthanarax S**. Improving the therapeutic index for nonoperable esophageal cancer patients with modern radiation technologies. Appl Radiat Oncol. 2018: 7(3)8-14.
50. **Apisarnthanarax S**, Bowen S, Combs SE. Proton Beam Therapy and Carbon Ion Radiotherapy for Hepatocellular Carcinoma. *Seminars in Radiation Oncology*. 2018 Oct;28(4):309-320. doi.org/10.1016/j.semradonc.2018.06.008
51. Schaub SK, MD, Ermoian RP, Wang CL, O'Malley RB, Kim EY, Shuman WP, Hendrickson K, **Apisarnthanarax S**. Bridging the radiation oncology and diagnostic radiology communication gap: a survey to determine usefulness and optimal presentation of radiotherapy treatment plans for radiologists. *Curr Probl Diagn Radiol*. In press https://doi.org/10.1067/j.cpradiol.2019.02.009

NON-PEER REVEWED

1. **Apisarnthanarax S**, Chia-Hsien Cheng J, Jabbour SK, Liauw SL, Murphy JD, Chang DT. Gastrointestinal cancers-changing the standard for rectal cancer and establishing a new standard for liver tumors. *International Journal of Radiation Oncology, Biology, Physics* 95(3): 930-6, Jul 2016. PMID: 27302509.
2. **Apisarnthanarax S**, Jabbour SK, Liauw SL, Murphy JD, Olsen JR, Chang DT. Gastrointestinal cancers: timing is everything. *Int J Radiat Oncol Biol Phys*. 2017 Dec 1;99(5):1051-1058. PMID: 29165271. doi: 10.1016/j.ijrobp.2017.05.040.
3. Chapman TR, Bowen SR, **Apisarnthanarax S**. Call for standardization of RILD toxicity reporting and multi-institutional collaboration (Letter to the editor). *Pract Radiat Oncol*. 2017 Dec 30. pii: S1879-8500(17)30388-0. PMID: 29477714. doi: 10.1016/j.prro.2017.12.012.
4. Olsen JR, Murphy JD, Hallemeier CL, **Apisarnthanarax S**, Huguet F, Jabbour SK. Cross-modality comparisons between radiofrequency ablation and stereotactic body radiotherapy for treatment of hepatocellular carcinoma: limitations of the national cancer database (Letter to the editor). J Clin Oncol. 2018 Aug 20;36(24):2564-2565. PMID: 29945521.
5. Jabbour SK, **Apisarnthanarax S**, Hallemeier CL, Huguet F, Murphy JD, Olsen JR. GI cancers-modulating the modern management of gastrointestinal malignancies: a look at liver metastases, rectal cancer, esophagogatric cancer, and anal cancer. Int J Radiat Oncol Biol Phys. 2018 Jul 15;101(4):749-758. PMID: 29976479.
6. Olsen JR, Murphy JD, Huguet F, Hallemeier CL, **Apisarnthanarax S**, Jabbour SK. GI cancers-carving out the optimal local therapies in the gastrointestinal tract. Int J Radiat Oncol Biol Phys. 2018 Oct 1;102(2):233-242. PMID: 30191854.

BOOKS

1. *Practical Essentials of Intensity Modulated Radiation Therapy*, 2nd ed. KS Chao, **S Apisarnthanarax**, G Ozyigit (eds.). Philadelphia: Lippincott Williams & Wilkins, 2005.

BOOK CHAPTERS

1. Chao KS, Ang KK, **Apisarnthanarax S**, Ozyigit G: Nodal target volumes for head and neck cancer. *Practical Essentials of Intensity Modulated Radiation Therapy*, 2nd ed. KS Chao, S Apisarnthanarax, G Ozyigit (eds.). Philadelphia: Lippincott Williams & Wilkins, 2005.
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5. **Smith Apisarnthanarax**, Rosanna Yeung, Stephen Bowen, and Tobias R. Chapman, *Proton Beam Therapy for Hepatic Malignancies*, Gastrointestinal Malignancies, Ed. Suzanne Russo, Sarah Hoffe, Edward Kim, Springer, 2018, pg. 171-193

ABSTRACTS/ POSTER PRESETNATIONS

1. Stern JI, **Apisarnthanarax S**, Paleologos NA, Vick NA: Temozolomide as long-term maintenance treatment for gliomas. *Annals of Neurology*, Abstracts 54: S31, 2003, poster presentation.
2. **Apisarnthanarax S**, Ardeshirpour F, Hayes DN, Morris DE, Tepper JE, Varia M, Shores C, Rosenman J: Chemoradiation for high risk nonmelanoma skin carcinomas of the head and neck. *RSNA Annual Meeting* 2007, poster presentation.
3. **Apisarnthanarax S**, Kimple R, Harris SL, Morris DE, Tepper JE: Applicability of randomized trials in radiation oncology to standard clinical practice at a single institution. *ASTRO 50th Annual Meeting* 2008, poster presentation.
4. **Apisarnthanarax S**, Harris SL, Tang X, Chang S, Tepper JE: Variable dosimetric advantages of IMRT compared to 3D-CRT techniques in anal cancer. *American Radium Society 92nd Annual Meeting* 2010, poster presentation.
5. Berman AM, Both S, Sharkoski T, Metz JM, **Apisarnthanarax S**, Tochner Z, Plastaras JP: Prospective trial of proton re-irradiation of recurrent pelvic tumors: dosimetric analysis. *ASTRO 53rd Annual Meeting* 2011, poster presentation.
6. Rengan R, Xanthopoulos E, Fernandes AT, Orisamolu A, **Apisarnthanarax S**, Christodouleas JP, Mitra N, Lin L, Sterman D, Langer CJ: Predictors for radiation pneumonitis in 293 consecutively treated non-small cell lung cancer (NSCLC)

patients receiving definitive radiation therapy. *2011 ASCO Annual Meeting and ASTRO 53rd Annual Meeting* 2011, poster presentation.

7. Whaley JT, Shillington K, Watson K, Metz JM, Plastaras JP, **Apisarnthanarax S**: A feasibility study of volumetric modulated arc therapy for locally advanced rectal cancer and dosimetric comparison with conventional IMRT. *American Radium Society 93rd Annual Meeting* 2011, poster presentation.
8. Berman AM, Wojcieszynski A, **Apisarnthanarax S**, Metz JM, Plastaras JP: Long-term cardiopulmonary mortality after radiation for locally advanced esophageal cancer. *ASCO GI Symposium* 2012, poster presentation.
9. Wojcieszynski A, Berman AM, Plastaras JP, Metz JM, **Apisarnthanarax S**: Survival differences between preoperative and postoperative radiation in esophageal cancer treated with combined modality therapy: A SEER analysis. *ASCO GI Symposium* 2012, poster presentation.
10. Xanthopoulos E, Grover S, Corradetti MN, Fernandes AT, Kim Miranda, Simone CB, Christodouleas JP, Evans TL, Stevenson J, Langer CJ, **Apisarnthanarax S**, Rengan R: Impact of PET staging in limited-stage SCLC. *ASCO Annual Meeting* 2012, poster presentation.
11. Kesarwala AH, Lu DJ, Xanthopoulos E, **Apisarnthanarax S**, Evan TL, Aggarwal C, Cohen RB, Langer CJ, Rengan R, Simone CB: The role of advanced imaging in assessing response to definitive chemoradiation prior to prophylactic cranial irradiation in limited-stage small cell lung cancer. *ASTRO 54th Annual Meeting* 2012, poster presentation.
12. Sharma S, Whaley JT, Zou JW, Fernandes AT, Xanthopoulos E, Simone CB, Christodouleas JP, Both S, Rengan R, **Apisarnthanarax S**: Incidental nodal irradiation in stage III lung cancer treated with involved field radiation: comparison between 3DCRT and IMRT. *Chicago Multidisciplinary Symposium in Thoracic Oncology* 2012, poster presentation.
13. Hertan L, Grover S, Plastaras JP, Metz JM, **Apisarnthanarax S**: Adjuvant radiation therapy in resected ampullary carcinoma: impact on survival outcomes. *ASTRO 54th Annual Meeting* 2012, poster presentation.
14. Whaley JT, Sackmann RK, Plastaras JP, Teo BK, Grover S, Perini RF, Pryma DA, Metz JM, **Apisarnthanarax S**: Clinical utility of integrated FDG PET-CT imaging in the clinical management and radiation treatment planning of locally advanced rectal cancer. *ASTRO 54th Annual Meeting* 2012, poster presentation.
15. Plastaras JP, Berman AM, **Apisarnthanarax S**, Both S, Varillo K, Larson GL, Ben-Josef E, Metz JM: Proton reirradiation of locally recurrent pancreatic and ampullary adenocarcinomas. *ASCO GI Symposium* 2013, poster presentation.
16. Fernandes AT, Whaley JT, Teo BK, Plastaras JP, Metz JM, Perini RF, Pryma DA, **Apisarnthanarax S**: Predicting outcomes in patients with locally-advanced rectal cancer using pretreatment FDG-PET imaging. *ASCO GI Symposium* 2013, poster presentation.

17. Lukens JN, Mick R, Demas KL, **Apisarnthanarax S**, Metz JM, McCall D, O'Dwyer PJ, Teitelbaum U, Both S, Plastaras JPP. Acute toxicity of proton versus photon chemoradiation therapy for pancreatic adenocarcinoma: a cohort study; *ASTRO 55th Annual Meeting* 2013, poster presentation.
18. Gandhi SJ, Liang X, Ding, X, Zhu TC, Ben-Josef E, Plastaras JP, Metz JM, Both S, **Apisarnthanarax S**. Development of a decision tree analysis tool for optimal delivery of liver stereotactic body radiation therapy: photons versus protons. *ASTRO 55th Annual Meeting* 2013, poster presentation.
19. Byun J, Hertan LM, Grover S, Plastaras JP, Metz JM, **Apisarnthanarax S**. Role of adjuvant radiation therapy in ampullary carcinoma: Propensity-score matched SEER analysis. *ASCO GI Symposium* 2014, poster presentation.
20. Yerramilli D, Sohal D, Teitelbaum U, Wissel P, Damjanov N, Giantonio B, O'Dwyer P, Plastaras JP, Ben-Josef E, Metz JM, Kucharczuk J, Williams N, **Apisarnthanarax S**. Adjuvant chemotherapy after trimodality therapy in locally advanced esophageal cancer. *ASCO GI Symposium* 2014, poster presentation.
21. Gandhi SJ, Liang X, Ding, X, Zhu TC, Ben-Josef E, Plastaras JP, Metz JM, Both S, **Apisarnthanarax S**. Development and validation of a treatment decision model for optimal delivery of liver stereotactic body radiation therapy (SBRT): photons versus protons. *ASCO GI Symposium* 2014, poster presentation.
22. Richard P, Phillips M, Zeng J, Halasz L, MD, Fang LC, **Apisarnthanarax S**, Rengan R. Development of a multi-parametric cost effectiveness model for comparison of therapeutic modalities in definitive radiotherapy for stage III non-small cell lung cancer (NSCLC). *ASTRO 56th Annual Meeting* 2014, poster presentation.
23. Kusano AS, Voss JC, Bremjit PJ, Fichera A, Koh WJ, Kim EY, **Apisarnthanarax S**. Preoperative short course radiation for locally advanced rectal cancer: a national opinion survey. *ASTRO 56th Annual Meeting* 2014, poster presentation.
24. **Apisarnthanarax S**, Chapman TR, Vesselle HJ, Miyaoka RS, Kinahan PE, Sandison GA, Nyflot MJ, Bowen SR. Quantitative imaging of global variability and regional heterogeneity in liver function with 99mtc-sulfur colloid spect/ct in hepatocellular carcinoma patients. *ASTRO 56th Annual Meeting* 2014, poster presentation.
25. Biomel PJ, Berman AT, Li J, Apisarnthanarax S, Both S, Lelionis K, Larson GL, Lukens JN, Ben-Josef E, Metz JM, Plastaras JPP. Proton reirradiation for locally recurrent pancreatic adenocarcinoma. *ASTRO 57th Annual Meeting* 2015, poster presentation.
26. Cao N, Saini J, Bowen S, **Apisarnthanarax S**, Rengan R, Wong T. CTV-based robustness optimization versus PTV-based conventional optimization for intensity modulated proton therapy planning. *ASTRO 57th Annual Meeting* 2015, poster presentation.
27. Chapman TR, Bowen SR, Nyflot MJ, **Apisarnthanarax S**. Defining radiation induced liver toxicity in the treatment of hepatocellular carcinoma: which metric is most predictive for survival? *ASCO GI Symposium 2016*, poster presentation.
28. Shabason JE, Chen J, **Apisarnthanarax S**, Damjanov N, Giantonio B, Loaiza-**Bonilla A,** O'Dwyer P, O'Hara M, Reiss-Binder K, Teitelbaum U, Wissel P, Drebin J, Vollmer

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29. Yeung R, Macomber M, Zeng J, **Apisarnthanarax S**. Pencil Beam Scanning Proton Treatment of Mobile Distal Esophageal Carcinomas Produce Similar Pathologic Complete Response Rates as Photon Treatment. *American Radium Society 99th Annual Meeting 2017*, poster presentation.
30. Yeung R, Rodriguez A, Macomber M, Oelschlager BK, Farjah F, Shankaran V, Zeng K, **Apisarnthanarax S**. Single posterior field pencil-beam scanning protons for esophageal cancer: preliminary toxicity and outcome analysis and comparison with intensity-modulated radiation therapy. *PTCOG 56th Annual Meeting 2017*, poster presentation.

ORAL PRESENTATIONS

INTERNATIONAL MEETINGS

1. **Apisarnthanarax S**, Petermann KB, Cox AD, Sharpless NE: Unexpected in vivo antagonism between two active agents, ionizing radiation and the farnesyltransferease inhibitor lonafarnib, in a genetically engineered murine model of RAS-induced melanoma. *Radiation Research Society 45th Annual Meeting* 2008, oral presentation.
2. **Apisarnthanarax S** , Eblan MJ, Corradetti MN, Lukens NJ, Christodouleas JP, Rengan R, Langer CJ, Evans TL, Stevenson J, Xanthopoulos E, Fernandes AT: Brachial plexopathy in apical non-small cell lung cancer treated with definitive radiation: dosimetric analysis and clinical implications. *14th World Conference on Lung Cancer and ASTRO 53rd Annual Meeting* 2011, oral presentation.
3. Xanthopoulos E, Fernandes AT, **Apisarnthanarax S**, Christodouleas JP, Eaby-Sandy B, Langer CJ, Evans TL, Lin L, Hahn SM, Rengan R: Definitive dose thoracic radiotherapy in oligometastatic stage IV non-small cell lung cancer (NSCLC). *14th World Conference on Lung Cancer and ASTRO 53rd Annual Meeting* 2011, oral presentation.
4. Fernandes AT, Teo BK, Yin L, Rosen M, Plastaras JP, Ben-Josef E, Metz JM, **Apisarnthanarax S**. Comparative assessment of liver tumor motion using cineMRI versus 4DCT. *ASTRO 55th Annual Meeting* 2013, oral presentation.
5. **Apisarnthanarax S**, Vyas S, Tseng YD, St. James S. Geometric variations in gastrointestinal organs-at-risk: implications for liver hypofractionated proton treatment planning. *ASTRO 58th Annual Meeting 2016*, ePoster discussion.

NATIONAL MEETINGS

1. **Apisarnthanarax S**, Saini J, Miyaoka RS, Kinahan PE, Sandison GA, Wong T, Vesselle HJ, Nyflot MJ, Bowen SR. Proton therapy functional liver avoidance planning using ^{99m}Tc-sulfur colloid SPECT/CT: a feasibility study. *PTCOG-NA 1st Annual Meeting* 2014, oral presentation.
2. Lee H, Zeng J, Macomber MR, Sparker M, Blakaj A, Liao J, Russell K, Laramore G, Rengan R, **Apisarnthanarax S**. Hip Toxicity in Patients Receiving Proton Beam Therapy for Prostate Cancer, *PTCOG-NA 4st Annual Meeting* 2014, oral presentation, 10/2017.

INVITED PRESENTATIONS

INTERNATIONAL

1. "PET/CT Imaging in Radiation Oncology: Improving Oncologic Care," Ramathibodhi Hospital, Bangkok, Thailand, 03/2012.
2. "Advanced Radiation Therapy in GI Cancers: From Photons to Protons," Thai Society of Therapeutic Radiology and Oncology (THASTRO), Pattaya, Thailand, 03/2012.
3. "Protons for GI Cancers," Thai Society of Therapeutic Radiology and Oncology (THASTRO), Pattaya, Thailand, 03/2014.

NATIONAL

1. "Radiation Therapy for Painful Bone Metastases," 2010 World Conference on Interventional Oncology, Philadelphia, PA, 06/2010.
2. "Emergencies in Radiation Oncology," Thai Physicians Association of America (TPAA), Dallas/Fort Worth, TX, 09/2012.
3. “Primary Liver Cancers: Optimizing Proton Therapy,” Proton Therapy Co-Operative Group-North America (PTCOG-NA) Annual Meeting, Houston, TX, 10/2014.
4. “Proton Beam Therapy for Primary Liver Cancers,” Proton Therapy Co-Operative Group - North America (PTCOG-NA) 4th Annual Meeting, Chicago, IL, 10/2017.
5. “Hepatocellular Carcinoma: Proton Beam Therapy,” Radiosurgery Society (RSS) Annual Scientific Meeting, Las Vegas, NV, 11/2017.
6. “Clinical Decision: Photons or Protons?” Clinical Liver Focus Group, Miami Cancer Institute, Miami, FL, 01/2018.
7. “Fine Needle Pre-Loaded Fiducial Markers for Image-Guided Radiotherapy of Upper GI Malignancies: Rationale, Patient Selection, and Collaboration with Gastroenterology,” Houston, TX, 02/2018.
8. “SABR versus Percutaneous RFA for Liver Tumors,” World Conference on Interventional Oncology, Boston, MA, 06/2018.
9. “Functional Liver Imaging and Advanced Radiation for Hepatic Cancers: Escaping Plato’s Cave,” Grand Rounds, Visiting Professor, Department of Radiation Oncology, Oregon Health Science University, Portland, OR, 09/2018.

REGIONAL

1. "Radiation Therapy for Pancreatic Cancer: Respice Adspice Prospice," Seattle Cancer Care Alliance Network CME, Columbia Basin Hematology and Oncology, Kennewick, WA, 10/2013.
2. "Advanced Radiation Therapy for Liver Cancers," Regional Liver Cancer Conference: Challenges in Primary and Secondary Liver Cancer Management, Spokane, WA, 09/2018.

LOCAL

1. "Radiation Therapy for Liver Cancers," American Association of Radiologic Technologists CME, University of Washington, Seattle, WA, 01/2014.
2. "Emerging Therapies in Colorectal Cancer: Why Radiation Therapy for Rectal Cancer," Seattle
3. Cancer Care Alliance Network CME, Multicare, Tacoma, WA, 09/2015.
4. "Precision Radiation Therapy in GI Cancers: What it Mean for the Radiologist," University of Washington, Seattle, WA, 02/2016.
5. "Radiation Therapy of the Liver: Current and Future Direction," Seattle Cancer Care Alliance Advances and Current Management of GI Cancers: A Multidisciplinary Approach Symposium, Seattle, WA, 03/2016.
6. "Updates in Gastrointestinal Cancer," Washington State Radiological Society, Seattle, WA, 11/2016.
7. "Fiducial Markers for Image-Guided Radiotherapy of Upper GI Malignancies," University of Washington, Seattle, WA, 09/2017.

OTHER SCHOLARLY ACTIVITIES

1. "Proton Beam Therapy for Hepatocellular Carcinoma," Radiosurgery Society, webinar, 02/2017.
2. "Proton Therapy for Hepatobiliary Carcinoma," American Association for Medical Dosimetrists, webinar, 07/2017.
3. "ACR-ASTRO Practice Parameter for the Performance of Proton Beam Radiation Therapy,"2018, https://www.astro.org/ASTRO/media/ASTRO/Patient%20Care%20and%20Research/PDFs/Proton-Therapy-RO.pdf

PROFESSIONAL COMMUNITY ACTIVITIES

1. "Radiation Therapy for Advanced Non-Small Cell Lung Cancer," Focus on Lung Cancer Conference, lecture, 2009 – 2010.
2. "Proton Radiation Therapy for Neuroendocrine Tumors," Focus on Neuroendocrine Tumors Conference, lecture, lecture, 2011.
3. "New Developments in Radiation Therapy for Colorectal Cancer," Update in Colorectal Cancer Conference, lecture, 2011.

4. Moderator, Residency/Fellowship Match Session, Thai American Physicians Foundation (TAPF) 2011 Annual Meeting, San Diego, CA, 07/2011.
5. "Cancer Prevention and Sceening: What You Can Do," Thai Professional Day, Thai Association of Washington State, Seattle, WA, lecture, 05/2018.

Washington State Health Care Authority

Agency medical director comments

Proton Beam Therapy – Re-Review

Judy Zerzan MD, MPH
Chief Medical Officer
Washington State Health Care Authority

May 17, 2019

Washington State Health Care Authority

Proton Beam Therapy

Adoption: July 11, 2014

Number and Coverage Topic:

20140516A – Proton Beam Therapy

HTCC Coverage Determination:

Proton Beam Therapy is a **covered benefit with conditions** consistent with the criteria identified in the reimbursement determination.

HTCC Reimbursement Determination:

Limitations of Coverage

Proton Beam Therapy is a **covered benefit with conditions** for:

- Ocular cancers
- Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma)
- Central nervous system tumors
- Other non-metastatic cancers with the following conditions:
  - Patient has had prior radiation in the expected treatment field with contraindication to all other forms of therapy, and
  - At agency discretion.

Non-Covered Indicators

Proton Beam Therapy is **not covered** for all other conditions.

Re-review

Proton Beam Therapy

- Original Proton Beam Therapy (PBT) determination: **July 2014**
- Basis for re-review: Newly available published evidence.
  - Adults and pediatrics
  - 189 new studies (137 adult/53 pediatric) met inclusion criteria
  - Quality of comparable studies marginally better
  - Table A provides the best summary

3

Ionizing Radiation Treatment

- 3D-conformal RT (3DRT)
  Delivers radiation to a 3d volume using imaging studies and software to precisely target RT delivery
- Intensity Modulated RT (IMRT)
  Delivers a non-uniform beam to the target by changing the intensity of the beam
- Proton beam therapy (PBT)
  Uses a beam of protons to irradiate diseased tissue

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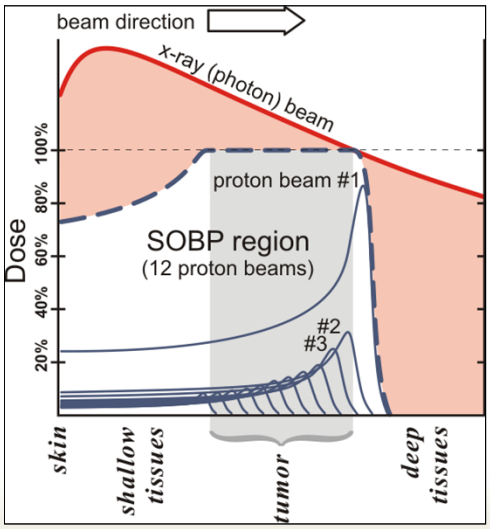
What is Proton Beam Therapy?



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Key Questions #1 and #2

1. What is the comparative impact of PBT with curative intent on:

a) Survival;
b) Disease progression;
c) Health-related quality of life; and
d) Other patient outcomes?

2. What is the comparative impact of salvage treatment on:

a) Survival;
b) Disease progression;
c) Health-related quality of life; and
d) Other patient outcomes?

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Key Questions #3

3. What are the comparative harms associated with the use of PBT:
   a) Relative to its major alternatives, including acute (*i.e., within the first 90 days after treatment*) and late *(>90 days*) toxicities;
   b) Systemic effects such as fatigue and erythema;
   c) Toxicities specific to each cancer type; and
   d) Risks of secondary malignancy, and radiation dose?

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Key Questions #4 and #5

4. What is the differential effectiveness and safety of PBT according to factors such as:

Age	Disability	Treatment protocols	Race/ethnicity
Sex	Comorbidities	Tumor characteristics	

5. What is the comparative cost-effectiveness of PBT in the short- and long-term?

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Proton Beam Therapy Concerns

Agency Medical Directors

SAFETY	=	Medium
EFFICACY	=	High
COST	=	High

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Proton Beam Therapy

Diagnosis Codes

Range of diagnosis codes utilized for claims analysis*

ICD-10	ICD-10 Description/ICD-9 Description	ICD-9
C00-C14	Malignant Neoplasm of Lip, Oral cavity, and Pharynx	140-149
C15-C26	Malignant Neoplasm of Digestive Organs	150-159
C30-C39	Malignant Neoplasm of Respiratory and Intrathoracic	160-165
C40-C41	Malignant Neoplasm of Bone and Articular Cartilage	170-176
C43-C44	Malignant Neoplasm of Skin	170-176
C45-C49	Malignant Neoplasm of Mesothelial and Soft Tissue	170-176
C50	Malignant Neoplasm of Breast	170-176
C51-C63	Malignant Neoplasm of Genital organs	179-189
C64-C68	Malignant Neoplasm of Urinary Tract	190
C69-C72	Malignant Neoplasm of Eye, Brain, CNS	191-192
C73-C75	Malignant Neoplasm of Endocrine	194
C76-C80	Malignant Neoplasm Ill Defined, Secondary (and Other)	195
C81-C96	Malignant Neoplasm of Lymphoid	196, 200-208
D37-D48, D49	Neoplasm uncertain or unspecific behavior	235-239
D10-D36, D3A	Benign tumors	210-229

*1) Not all diagnosis codes were represented in the data.
2) Utilization and cost analyses contain V and/or Z codes when substituted for a primary diagnosis.

Proton Beam Therapy

Procedure Codes

CPT	Procedure Code Description
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

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2013 – 2017
Proton Beam Therapy
Sessions and Total Treatment Paid Dollars (Pd$)
N = 63; 70% Medicare/UMP

PEBB/UMP	2013-2014	2015	2016	2017
Avg Number of Sessions	31	23	18	20
Avg Pd$/Session	$4,648	$4,683	$2,365	$2,474
Avg Pd$ Total Treatment	$144,095	$107,717	$44,997	$53,520

Medicare/UMP	2013-2014	2015	2016	2017
Avg Number of Sessions	30	30	27	39
Avg Pd$/Session as Secondary Payer	$235	$227	$225	$220
Avg Pd$ Total Treatment as Secondary Payer	$9,112	$6,131	$6,553	$6,409

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2013 – 2017
Proton Beam Therapy
Sessions and Total Treatment Paid Dollars (Pd$)[1]
Total Treatment includes all services incurred on day of Proton Beam Treatment Session
N = 183

MEDICAID MCO/FFS	2013	2014	2015	2016	2017
Avg Number of Sessions	27	23	23	19	22
Avg Pd$[1]/Session	$1,698	$598	$655	$667	$654
Avg Pd$[1] Total Treatment	$56,087	$18,697	$18,281	$18,543	$21,019

1 Average Pd$ calculated using Line_Paid_Amt field. If Line_Paid_Amt was $0, and Allow_Amt was >$0, MCO_Reported_Paid_Amount was used.

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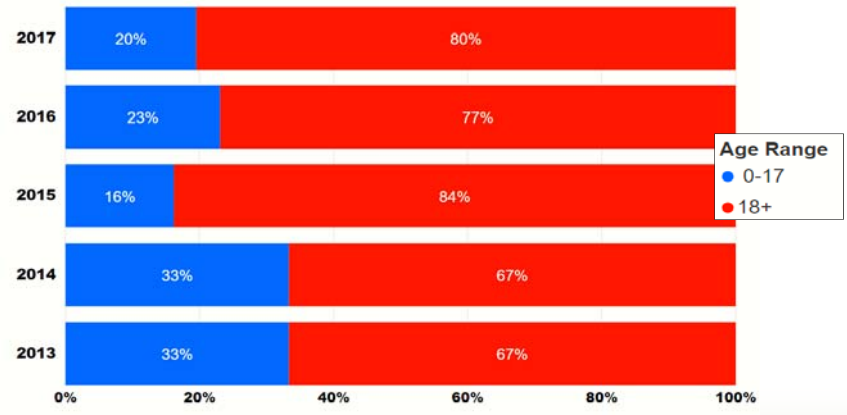
2013 – 2017
PEBB/UMP, Medicare/UM, and Medicaid MMC/FFS
Distribution of Patients receiving Proton Beam Therapy by Age Range
N= 246



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Proton Beam Therapy

Current State Agency Policies

Covered with Conditions
per HTCC Determination

- PEBB/UMP
- Medicaid Managed Care and Fee-for-Service
- Labor and Industries

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Proton Beam Therapy Other Payers

Aetna: (last reviewed 05.09.2018)

1. Chordomas or chondrosarcomas
2. Malignancies in children (21 years of age and younger)
3. Uveal melanomas confined to the globe

United Healthcare: (last reviewed 01.01.2019)

1. Intracranial arteriovenous malformations (AVMs)
2. Ocular tumors, including intraocular/uveal melanoma
3. Skull-based tumors
4. Localized, unresectable hepatocellular carcinoma with conditions
5. PBT may be covered for a diagnosis that is not listed above as proven, including recurrences or metastases in selected cases with conditions

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Proton Beam Therapy Other Payers

Cigna: (last reviewed 01-17-2019)

1. Chordomas and chondrosarcomas of the base of the skull, localized and in the postoperative setting
2. Uveal melanoma, when PBT is considered preferential compared to brachytherapy
3. Select cases of localized unresectable hepatocellular carcinoma
4. Stage IIA seminoma
5. Malignancies in children (age less than 18 years)

Medicare: (last reviewed 9-2017)

1. Had NCD in 2015, later retired
   - Target volume close to critical structure, avoid a "hotspot", previous irradiation to avoid exceeding cumulative dose
2. Included ocular tumor, skull base, CNS, primary HCC, pediatric CNS and head and neck
3. Coverage considered investigational in other areas

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Guidelines

National Comprehensive Cancer Network

- May be appropriate for bone, CNS, head and neck, liver, lung, lymphoma, ocular, sarcoma, thymoma
- Not Recommended for prostate

AIM Specialty Network

- Recommend for CNS, ocular, pediatric
- Not Recommended for breast, esophageal, GI, pancreatic, gyn, head and neck, liver, lung, lymphoma, prostate

American College of Radiology

- Recommend for head and neck, may be appropriate for lymphoma and prostate
- Not Recommended for bone, gyn, lung

National Institute for Health and Care Excellence (NICE)

- Recommend brain, spinal, paraspinal and pediatric

Proton Beam Therapy

Adult Summary

Similar conclusions or no new data:

- Bladder
- Bone
- Breast
- GI
- GYN
- Head and neck
- Lung
- Lymphoma
- Mixed/various/other
- Prostate
- Sarcoma
- Seminoma
- Thymoma
- Arteriovenous malformations
- Hemangiomas
- Pituitary adenomas
- Prostate

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Proton Beam Therapy

Adult Summary

CHANGES FROM THE LAST REPORT

Brain/spinal

- Larger studies, benefits and harms are similar

Esophageal

- Increased OS after one year and PFS better
- More GI events but rest of adverse effects lower esp. pulmonary

Liver

- OS, PFS and local control similar compared to TACE
- Fewer hospitalizations for complications
- *ongoing RCT this is early data

Ocular

- 5 year OS lower with PBT but fewer local recurrence over 10 years
- One study visual acuity worse and one better with PBT

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Proton Beam Therapy

Adult Recommendation

Cover with conditions if:

- Esophageal
- Liver
- Brain
- Ocular

- **Non-coverage all other**

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Proton Beam Therapy

Pediatric Summary

Similar conclusions with very few new studies:

- Bone
- Head/neck
- Ocular
- Lymphoma
- Rhabdomyosarcoma
- Mixed/various

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Proton Beam Therapy

Pediatric Summary

Brain

- Incremental benefit in terms of decreased harms (hypothyroidism)
- Overall survival and tumor recurrence similar maybe slight trend towards favoring PBT

Salvage in ocular tumors and salivary tumors

- Small comparative study of each, insufficient
- Less grade 2 or 3 mucositis trend

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Proton Beam Therapy

Pediatric Recommendation

- **Cover with conditions if:**
  - Central nervous system
  - Non-coverage all other

  OR

- **Cover all pediatric cancers**

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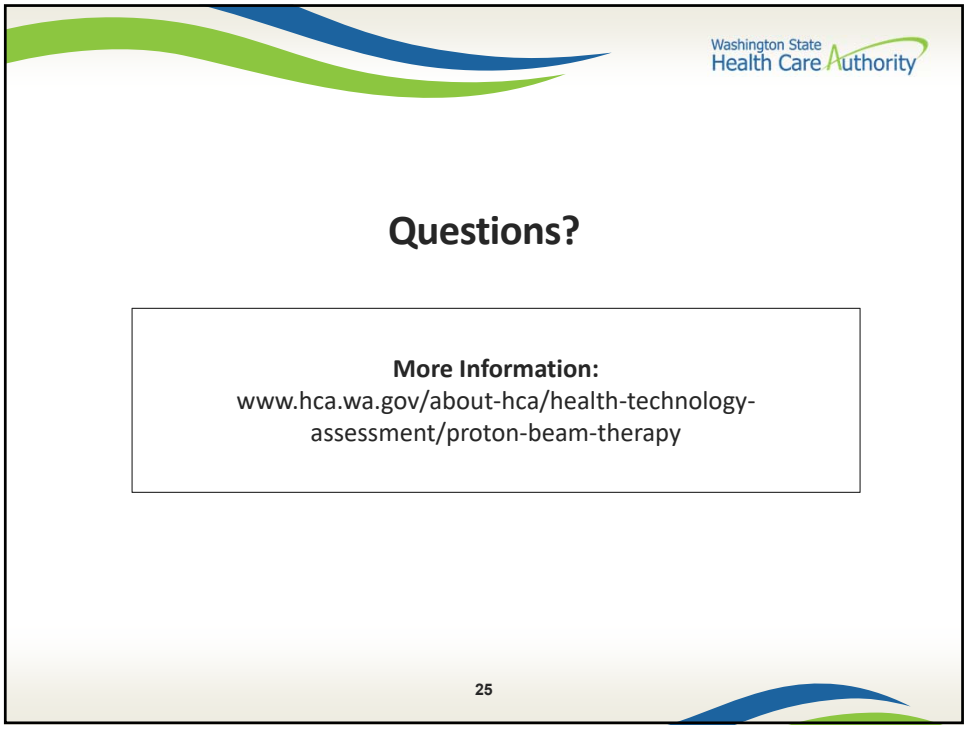
Washington State Health Care Authority
Questions?
More Information:
www.hca.wa.gov/about-hca/health-technology-assessment/proton-beam-therapy
25

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Scheduled presentations:

Proton Beam Therapy – re-review

	Name	
1	Andrew l. Chang, MD	National Association for Proton Therapy
2	William F. Hartsell, MD	National Association for Proton Therapy
3	Sameer Keole, MD	National Association for Proton Therapy
4	Steven Frank, MD	National Association for Proton Therapy
5	Ramesh Renan, MD	Seattle Cancer Care Alliance
6	Ralph Emoian, MD	Seattle Cancer Care Alliance
7	Charles Bloch, MD	Seattle Cancer Care Alliance
8	Jing Zeng, MD	Seattle Cancer Care Alliance
9	Annika Andrews	Seattle Cancer Care Alliance

(Order subject to change.)

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	☐	☑
2.	Equity interests such as stocks, stock options or other ownership interests.	☑	☐
3.	Status or position as an officer, board member, trustee, owner.	☑	☐
4.	Loan or intellectual property rights.	☐	☑
5.	Research funding.	☐	☑
6.	Any other relationship, including travel arrangements.	☑	☐

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I am the owner and President of Proton Doctors Professional Corporation, which employees physicians who treat patients with Proton Therapy.

Travel is being paid for by the Seattle Cancer Care Alliance, who are the operators of the proton center in Seattle.

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	☐	☑

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

[redacted] 2019 Apr 26 Andrew Chang

Date *Print Name*

So we may contact you regarding your presentation, please provide the following:

[redacted]

[redacted]

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.	X	
3.	Status or position as an officer, board member, trustee, owner.	X	
4.	Loan or intellectual property rights.		X
5.	Research funding.	X	
6.	Any other relationship, including travel arrangements.	X	

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Varian, Elekta, Eli Lily, C4 Imaging, Augmenix, Hitachi; Grants - Honoraria, Board Membership, Advisory, Consultant, ownership; No relationship with NCCN.

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources:

Travel funding [redacted] Seattle Cancer Care Alliance (SCCA).

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 4/26/19
Date

Steven Frank
Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address:

Phone Number:

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	☐	☑
2.	Equity interests such as stocks, stock options or other ownership interests.	☐	☑
3.	Status or position as an officer, board member, trustee, owner.	☑	☐
4.	Loan or intellectual property rights.	☐	☑
5.	Research funding.	☐	☑
6.	Any other relationship, including travel arrangements.	☑	☐

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Board Member - American Society for Radiation Oncology; Board Member and Chair

Proton Collaborative Group (co-operative research group); Travel Funding - SCCA

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	☐	☑

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X William F Hartsell, MD — Digitally signed by William F Hartsell, MD DN: cn=William F Hartsell, MD, o, ou, email=whartsell@chicagocancer.org, c=US Date: 2019.04.29 13:51:06 -05'00'

Signature

4/25/19

Date

William F. Hartsell, MD

Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: _____

Phone Number: _____

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	☐	☑
2.	Equity interests such as stocks, stock options or other ownership interests.	☐	☑
3.	Status or position as an officer, board member, trustee, owner.	☐	☑
4.	Loan or intellectual property rights.	☐	☑
5.	Research funding.	☐	☑
6.	Any other relationship, including travel arrangements.	☑	☐

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

SCCA is paying travel expenses for this meeting

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	☐	☑

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 9/26/14
Date

Sameer Keole
Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: keole.sameer@mayo.edu

Phone Number: [redacted]

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	☐	☒
2.	Equity interests such as stocks, stock options or other ownership interests.	☐	☒
3.	Status or position as an officer, board member, trustee, owner.	☐	☒
4.	Loan or intellectual property rights.	☐	☒
5.	Research funding.	☐	☒
6.	Any other relationship, including travel arrangements.	☒	☐

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I serve as Medical Director of the SCCA proton Center. I do not derive any salary directly from the center, but receive an administrative Stipend from The University of Washington.

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	☐	☒

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 4/23/19 [redacted]

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: _____

Phone Number: _____

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	☐	☒
2.	Equity interests such as stocks, stock options or other ownership interests.	☐	☒
3.	Status or position as an officer, board member, trustee, owner.	☐	☒
4.	Loan or intellectual property rights.	☐	☒
5.	Research funding.	☐	☒
6.	Any other relationship, including travel arrangements.	☐	☒

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	☐	☒

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

[redacted] 4/25/19 Ralph Ermeling, MD

Signature Date Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: ralphpe@uw.edu

Phone Number: [redacted]

Washington Health Technology Assessment

Explanation of relationship with SCCA Proton Therapy:

There could be a perception that because part of my practice is at SCCA Proton Therapy I would have a conflict of interest. I do not believe this is the case for the following reasons:

1. I am employed by the University of Washington which is a separate entity from SCCA Proton Therapy.
2. My employer is contracted to provide physician services to SCCA Proton Therapy, but SCCA Proton Therapy does not underwrite my salary.
3. The vast majority of my renumeration is from salary.
4. The small portion of my renumeration related to the patients I treat is largely independent of whether I treat them at SCCA Proton Therapy or other sites of practice. (If there are subtle differences, I am not aware of them.)
5. My employer (University of Washington) does not set goals for how many patients I treat at SCCA Proton Therapy.
6. I do not receive grants or other financial assistance from SCCA Proton Therapy.

Ralph Ermoian, MD

Associate Professor of Radiation Oncology

University of Washington

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	✓	
2.	Equity interests such as stocks, stock options or other ownership interests.		✓
3.	Status or position as an officer, board member, trustee, owner.		✓
4.	Loan or intellectual property rights.		✓
5.	Research funding.		✓
6.	Any other relationship, including travel arrangements.		✓

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I am an employee of the University of Washington School of Medicine and providing clinical services at the SCCA Proton Therapy Facility

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		✓

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X Charles Bloch Digitally signed by Charles Bloch Date: 2019.04.23 12:41:15 -07'00' 4/23/19 Charles Bloch

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: cdbloch@uw.edu

Phone Number: 206-306-2834

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	☐	☑
2.	Equity interests such as stocks, stock options or other ownership interests.	☐	☑
3.	Status or position as an officer, board member, trustee, owner.	☐	☑
4.	Loan or intellectual property rights.	☐	☑
5.	Research funding.	☐	☑
6.	Any other relationship, including travel arrangements.	☐	☑

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	☐	☑

If yes to #7, provide name and funding Sources:

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

x Jing Zeng Digitally signed by Jing Zeng Date: 2019.04.21 00:01:53 -07'00' 4/21/2019 Jing Zeng

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: jzeng13@uw.edu

Phone Number: 206-598-4110

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.	X	
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.	X	

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I am the President & CEO of the SCCA Proton Therapy Center. I am a board member of same. The company reimburses work related travel expenses.

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	X	

If yes to #7, provide name and funding Sources:

see above - paid executive of SCCA Proton Therapy Center.

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 4-26-19 Annakarin Andrews "Annika"

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: annika.andrews@seattleprotons.org

Phone Number: [redacted]

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		✓
2.	Equity interests such as stocks, stock options or other ownership interests.		✓
3.	Status or position as an officer, board member, trustee, owner.		✓
4.	Loan or intellectual property rights.		✓
5.	Research funding.		✓
6.	Any other relationship, including travel arrangements.		✓

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		✓

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

[redacted] 4/25/2019 BAO-NGOC NGUYEN

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: bao-ngoc.nguyen@seattleprotons.org

Phone Number: [redacted]

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Employed at Seattle Cancer Care Alliance Proton Therapy Center

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

[redacted] 25 April 2019
Date

Jason Dixon
Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: Jason.Dixon@seattleprotons.org

Phone Number: [redacted]

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		✓
2.	Equity interests such as stocks, stock options or other ownership interests.		✓
3.	Status or position as an officer, board member, trustee, owner.		✓
4.	Loan or intellectual property rights.		✓
5.	Research funding.		✓
6.	Any other relationship, including travel arrangements.		✓

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

N/A

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	✓	

If yes to #7, provide name and funding Sources: employee of Seattle Proton Center LLC (dba SCCA Proton Therapy Center)

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

[redacted] 4/25/2019 Kimberly M. Dansie

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: kimberly.dansie@seattleprotons.org

Phone Number: [redacted]

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	Yes	
2.	Equity interests such as stocks, stock options or other ownership interests.		
3.	Status or position as an officer, board member, trustee, owner.		
4.	Loan or intellectual property rights.		
5.	Research funding.		
6.	Any other relationship, including travel arrangements.		

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Seattle Cancer Care Alliance Proton Therapy Center

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 4/25/2019 Christopher Bodewell

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: [redacted]

Phone Number: [redacted]

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Seattle Cancer Care Alliance Proton Therapy Center

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 4/25/19 [redacted]

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: Meredith.cassels@seattleprotons.org

Phone Number: [redacted]

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	✓	
2.	Equity interests such as stocks, stock options or other ownership interests.		✓
3.	Status or position as an officer, board member, trustee, owner.		✓
4.	Loan or intellectual property rights.		✓
5.	Research funding.		✓
6.	Any other relationship, including travel arrangements.		✓

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		✓

If yes to #7, provide name and funding Sources:

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 4/26/19 Date Lindsay Knapp Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: Lindsay.Knapp@seattleprotons.org

Phone Number: [redacted]

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 4/25/19 Amy Walgamott

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: amy.walgamott@seattleprotons.org

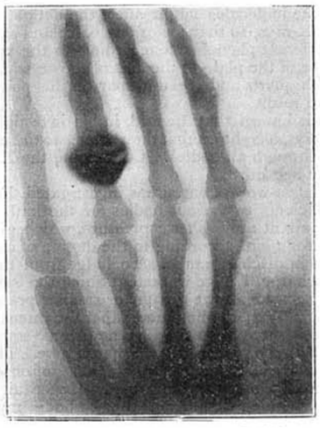
Phone Number: [redacted]

History of Proton Radiation Therapy

Andrew L. Chang, MD
President, PDPC
AndrewLChangMD@gmail.com

History of Radiation

- First x-ray image by Wilhelm Roentgen
  - Submitted for publication Dec 28, 1895
  - Published Jan 5, 1896 “On A New Kind Of Rays”
    - *Nature* 53 pg 274-276
  - Winning first Nobel Prize for Physics 1901



“I have seen my death” –Bertha Roentgen

History of Radiation Oncology

- 1896: Radioactivity discovered by Becquerel in uranium compounds;
- 1898: Discovery of radioactivity in radium and polonium by Marie and Pierre Curie.
  - Becqurel, Curie, and Curie win 1903 Nobel Prize in physics
- 1906: From Paris, first publication of the use of radium implants in the treatment of cervical cancer
- 1952: Discovery of DNA structure

History of Proton Therapy

- 1904: William Bragg describes the Bragg peak (wins Nobel Prize in Physics 1915)
- 1930: Ernest Lawrence's "proton merry-go-round" – the first cyclotron (800 KeV) (for which he wins the Nobel Prize in 1939)
- 1946: Radiological Use of Fast Protons by Robert Wilson (*Radiology.* ***47*** *(5): 487–491. November 1946)*
- 1954: First medical use – UC Berkeley
- 1961: Routine practice at Harvard, LBL
- 1989: FDA approved device for proton therapy

Proton Therapy is NOT Experimental

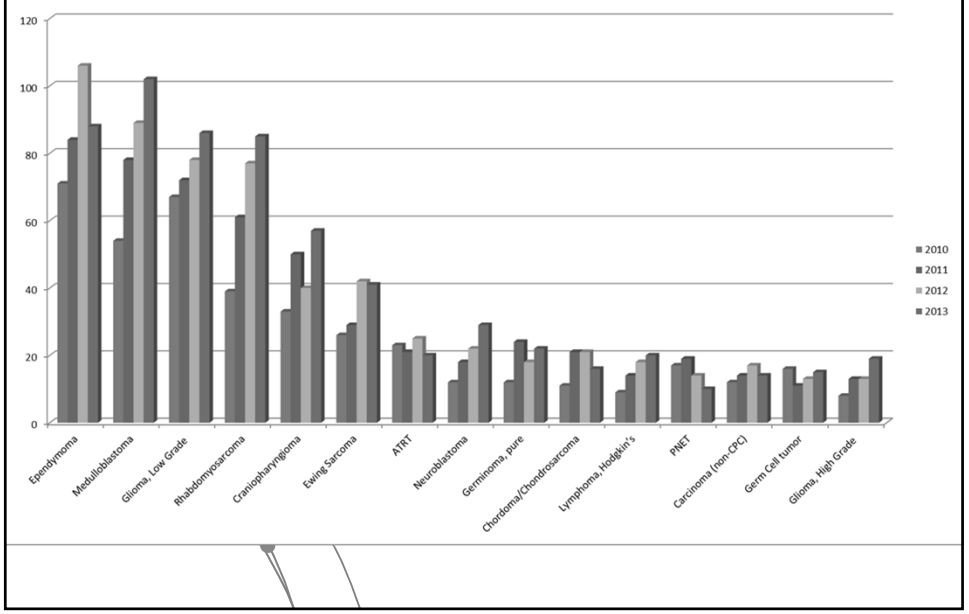
- Over 150,000 patients worldwide have been treated with proton therapy
- First patient treatments with proton therapy occurred in 1954
- Neither of the two largest medical regulatory bodies in the United States consider proton therapy experimental for the treatment of cancer
  - FDA approved first device in 1989
  - Medicare pays for proton therapy in the treatment of cancer
- **No oncologists consider proton therapy experimental for the treatment of cancer**

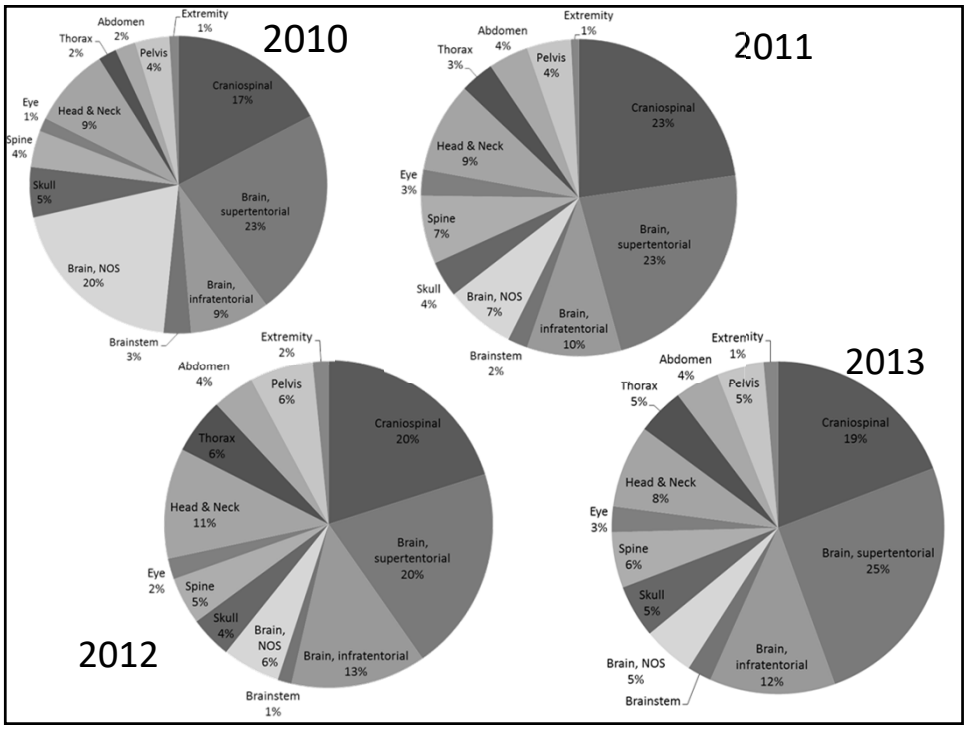
Pediatric Proton Therapy: Patterns of Care across the United States

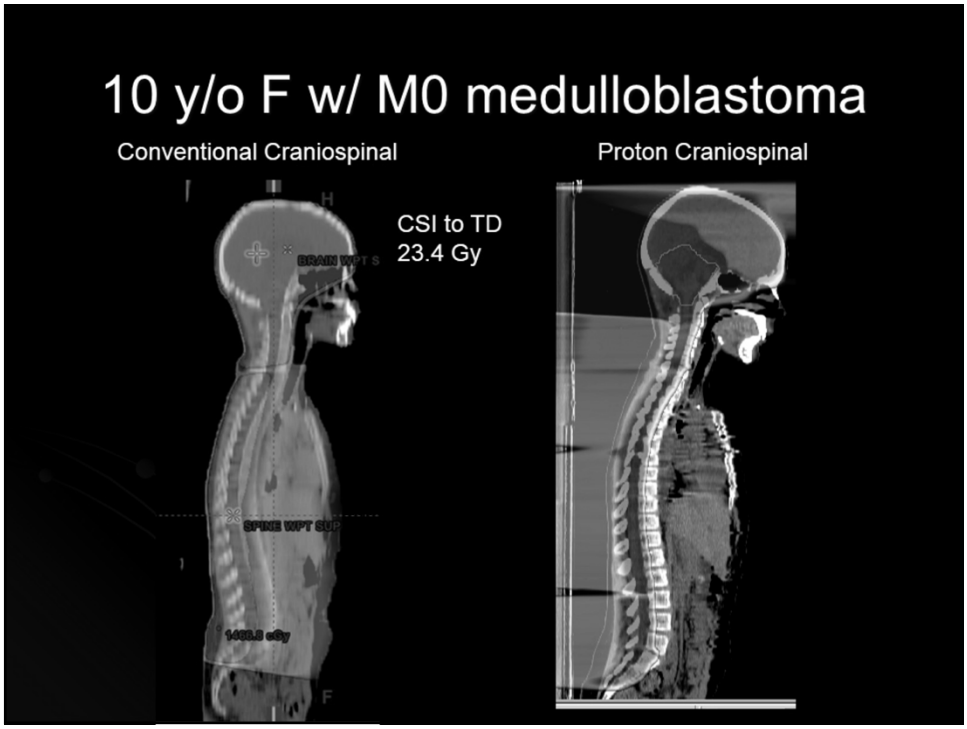
Andrew L. Chang, MD[1]; Toruun I. Yock, MD[2]; Anita Mahajan, MD[3]; Christine Hill-Kaiser, MD[4]; Sameer Keole, MD[5]; Lilia Loredo, MD[6]; Oren Cahlon, MD[7]; Kevin P. McMullen, MD[8]; William Hartsell, MD[9]; and Daniel J. Indelicato, MD[10]

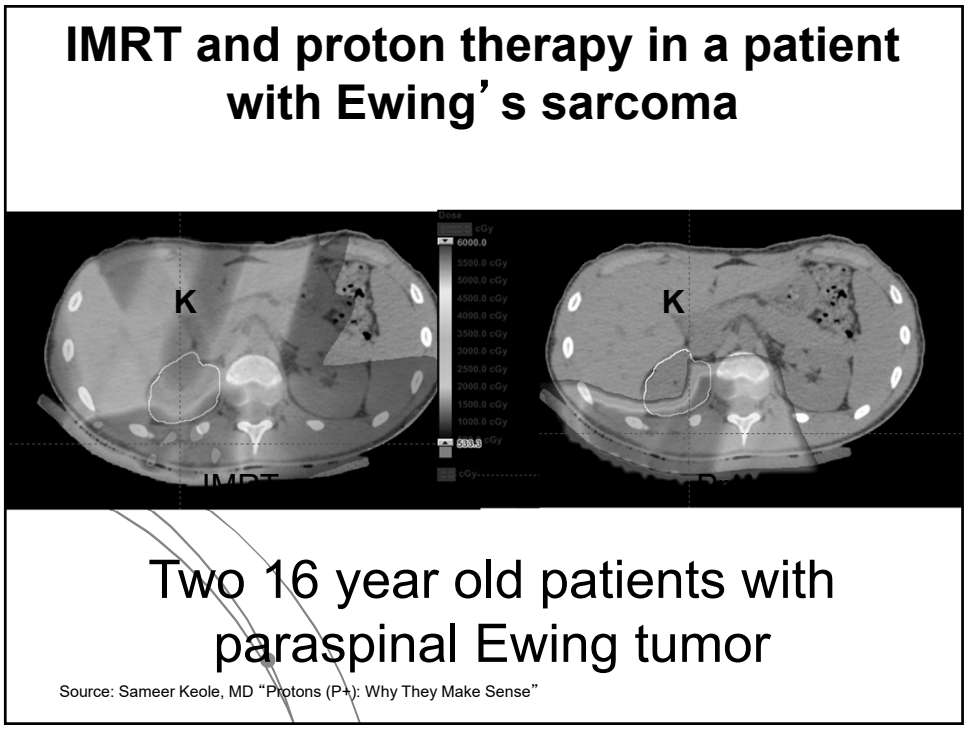
- All operating US proton facilities in 2010, 2011, 2012, & 2013 were sequentially surveyed.
- In 2013, 722 children and adolescents (14 – 157) treated with proton therapy in 11 US centers
  - In 2012, 694 pediatric patients (6 – 140)
  - In 2011, 613 pediatric patients (4 – 124)
  - In 2010, 465 pediatric patients (1 – 111)
- In PTCOG Survey of 2014, 989 pediatric patients treated
- In 2013, 22% of pediatric patients treated at US proton therapy centers were from outside the United States (range 4.0% – 51.1%), and in 2012: 19% (0% - 60.8%)

Top 15 histologic diagnoses

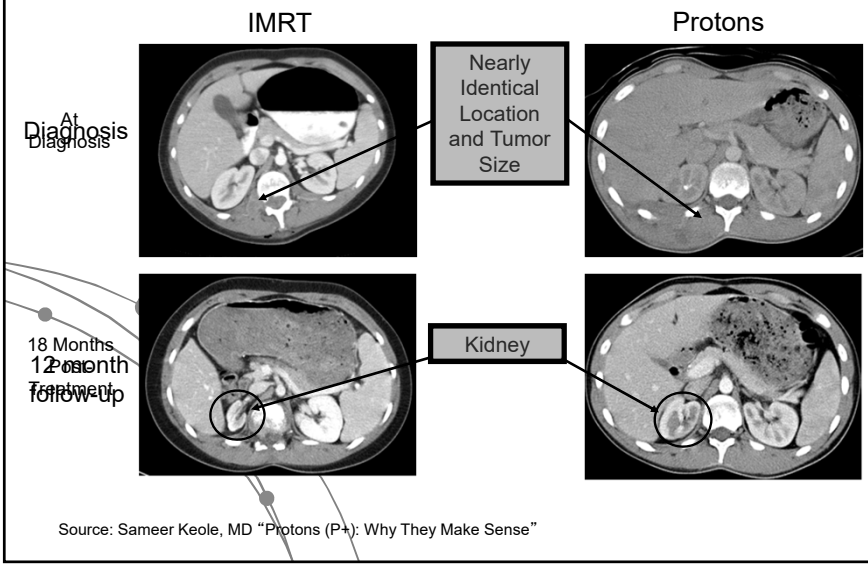




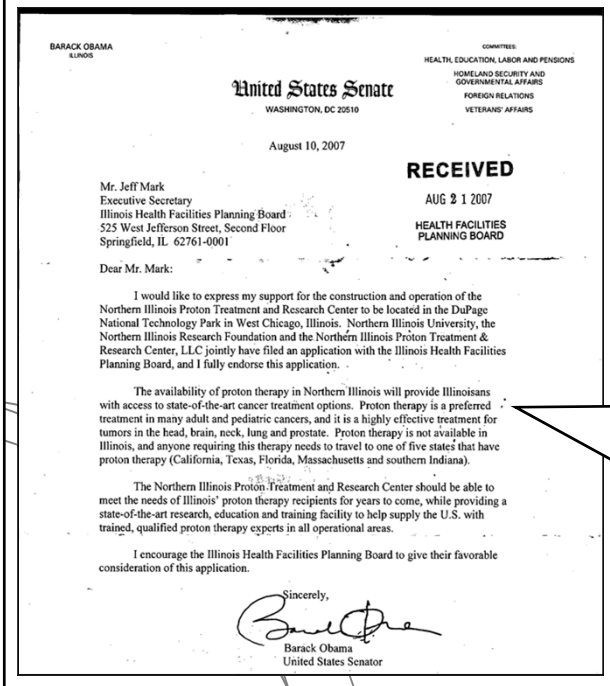

10 y/o F w/ M0 medulloblastoma
Conventional Craniospinal
Proton Craniospinal
CSI to TD
23.4 Gy


IMRT and proton therapy in a patient with Ewing's sarcoma
K
K
Two 16 year old patients with paraspinal Ewing tumor
Source: Sameer Keole, MD "Protons (P+): Why They Make Sense"

Ewing's sarcoma follow-up



Source: Sameer Keole, MD "Protons (P+): Why They Make Sense"



BARACK OBAMA
ILLINOIS

COMMITTEES:
HEALTH, EDUCATION, LABOR AND PENSIONS
HOMELAND SECURITY AND GOVERNMENTAL AFFAIRS
FOREIGN RELATIONS
VETERANS' AFFAIRS

United States Senate
WASHINGTON, DC 20510

August 10, 2007

RECEIVED
AUG 2 1 2007
HEALTH FACILITIES PLANNING BOARD

Mr. Jeff Mark
Executive Secretary
Illinois Health Facilities Planning Board
525 West Jefferson Street, Second Floor
Springfield, IL 62761-0001

Dear Mr. Mark:

I would like to express my support for the construction and operation of the Northern Illinois Proton Treatment and Research Center to be located in the DuPage National Technology Park in West Chicago, Illinois. Northern Illinois University, the Northern Illinois Research Foundation and the Northern Illinois Proton Treatment & Research Center, LLC jointly have filed an application with the Illinois Health Facilities Planning Board, and I fully endorse this application.

The availability of proton therapy in Northern Illinois will provide Illinoisans with access to state-of-the-art cancer treatment options. Proton therapy is a preferred treatment in many adult and pediatric cancers, and it is a highly effective treatment for tumors in the head, brain, neck, lung and prostate. Proton therapy is not available in Illinois, and anyone requiring this therapy needs to travel to one of five states that have proton therapy (California, Texas, Florida, Massachusetts and southern Indiana).

The Northern Illinois Proton Treatment and Research Center should be able to meet the needs of Illinois' proton therapy recipients for years to come, while providing a state-of-the-art research, education and training facility to help supply the U.S. with trained, qualified proton therapy experts in all operational areas.

I encourage the Illinois Health Facilities Planning Board to give their favorable consideration of this application.

Sincerely,

Barack Obama
United States Senator

"Proton therapy is a preferred treatment in many adult and pediatric cancers, and is a highly effective treatment for tumors in the head, brain, neck, lung and prostate"

'The Cause of My Life'

Inside the fight for universal health care.
Published July 18, 2009 by Edward M. Kennedy

In 1964, I was flying with several companions to the Massachusetts Democratic Convention when our small plane crashed and burned short of the runway. My friend and colleague in the Senate, Birch Bayh, risked his life to pull me from the wreckage. Our pilot, Edwin Zimny, and my administrative assistant, Ed Moss, didn't survive. With crushed vertebrae, broken ribs, and a collapsed lung, I spent months in New England Baptist Hospital in Boston. To prevent paralysis, I was strapped into a special bed that immobilizes a patient between two canvas slings. Nurses would regularly turn me over so my lungs didn't fill with fluid. I knew the care was expensive, but I didn't have to worry about that. I needed the care and I got it.

Now I face another medical challenge. Last year, I was diagnosed with a malignant brain tumor. Surgeons at Duke University Medical Center removed part of the tumor, and I had proton-beam radiation at Massachusetts General Hospital. I've undergone many rounds of chemotherapy and continue to receive treatment. Again, I have enjoyed the best medical care money (and a good insurance policy) can buy.

But quality care shouldn't depend on your financial resources, or the type of job you have, or the medical condition you face. Every American should be able to get the same treatment that U.S. senators are entitled to.

This is the cause of my life.

"…I had proton beam radiation at Massachusetts General Hospital…I have enjoyed the best medical care money (and a good insurance policy) can buy…Every American should be able to get the same treatment that U.S. Senators are entitled to"

United States District Court
Southern District of Florida

Case 1:19-cv-21258-UU Document 6 Entered on FLSD Docket 04/29/2019 Page 1 of 1

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

CASE NO: 19-21258-CIV-SCOLA

Richard Cole, on behalf of himself and all others similarly situated,
Plaintiff,
vs.
United Healthcare Insurance Company,
Defendant.
_____/

Order of Recusal

The undersigned judge, to whom this cause was assigned, recuses himself and refers this cause to the Clerk of Court for reassignment pursuant to 28 U.S.C. § 455 and Local Rule 3.6 for the following reasons:

In early 2017, the Court was diagnosed with prostate cancer. In determining the best course of treatment, the Court consulted with top medical experts throughout the country. All the experts opined that if I opted for radiation treatment, proton radiation was by far the wiser course of action. Although the Court opted for surgery, rather than radiation, those opinions still resonant.

Further, a very close friend of the Court was diagnosed with cancer in 2015. He opted to have proton radiation treatment at M.D. Anderson in Houston. His health care provider, United Healthcare, refused to pay for the treatment. Fortunately, he had the resources to pay $150,000 for the treatment and only upon threat of litigation did United Healthcare agree to reimburse him.

It is undisputed among legitimate medical experts that proton radiation therapy is not experimental and causes much less collateral damage than traditional radiation. To deny a patient this treatment, if it is available, is immoral and barbaric.

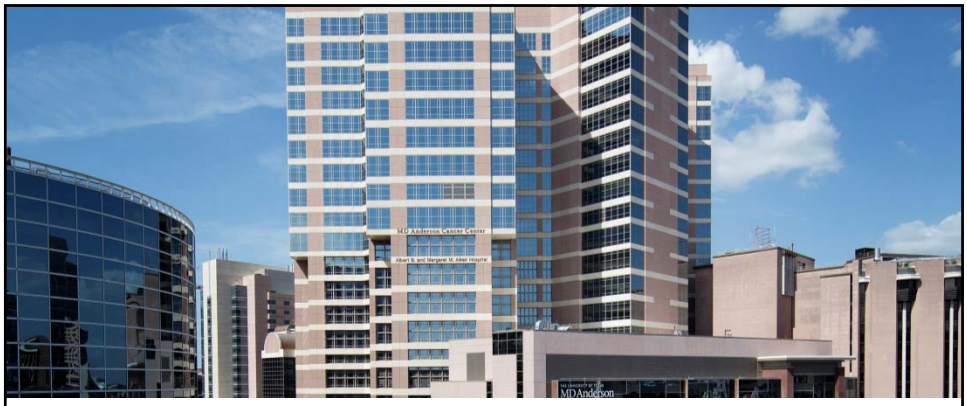
The Court's opinions in this matter prevent it from deciding this case fairly and impartially.

DONE AND ORDERED in Miami, Florida, this 29th day of April, 2019.

Robert N. Scola, Jr.
United States District Judge

"It is undisputed among legitimate medical experts that proton radiation therapy is not experimental… To deny a patient this treatment, if it is available, is immoral and barbaric."

Thank you



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Proton Beam Radiation for Oropharyngeal Cancer

Steven J. Frank, MD
Professor and Deputy Head, Radiation Oncology
Executive Director, UT Particle Therapy Institute

MD Anderson |

DISCLOSURES

- NCI U19 IMPT vs IMRT Oropharynx
- Honoria or Grants from ELEKTA, NIH/NCI, Varian, Hitachi, Eli Lilly
- Varian Advisory Board/Consultant
- Founder and Director C4 Imaging

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Define the Value of Proton Therapy

$$\text{Value} \uparrow = \frac{\Sigma\ (\text{Outcomes})}{\Sigma\ (\text{Costs})}$$

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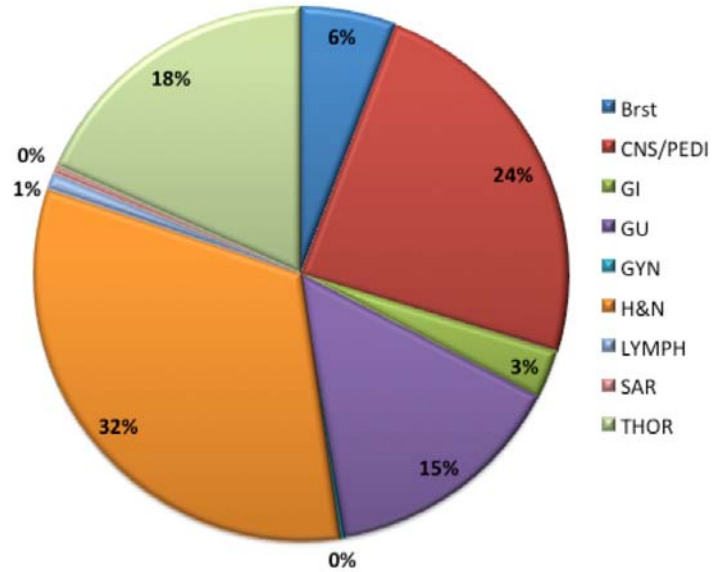
All Disease Sites Treated with Protons – FY'18



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D., Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D., William H. Westra, M.D., Christine H. Chung, M.D., Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D., Rita Axelrod, M.D., C. Craig Silverman, M.D., Kevin P. Redmond, M.D., and Maura L. Gillison, M.D., Ph.D.

- 72 Gy in 42 fx in 6 wks
- 70 Gy in 35 fx in 7 wks
- CDDP 100 mg/m2 q3w

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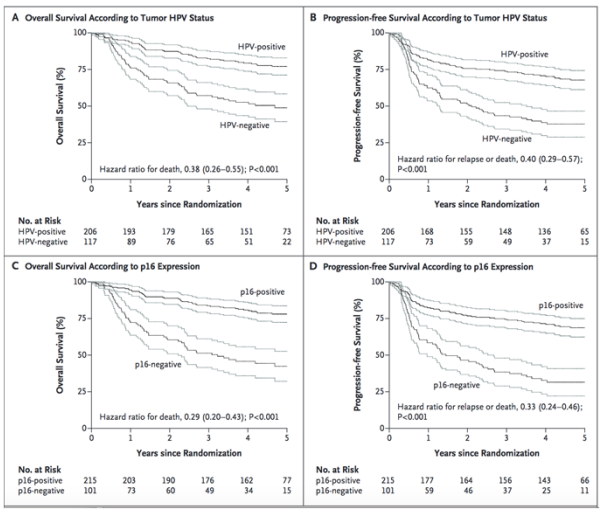
Conclusion: HPV status is an independent prognostic factor for Overall survival and Progression-free Survival for patients with OPSCC



Ang KK et al. NEJM 2010

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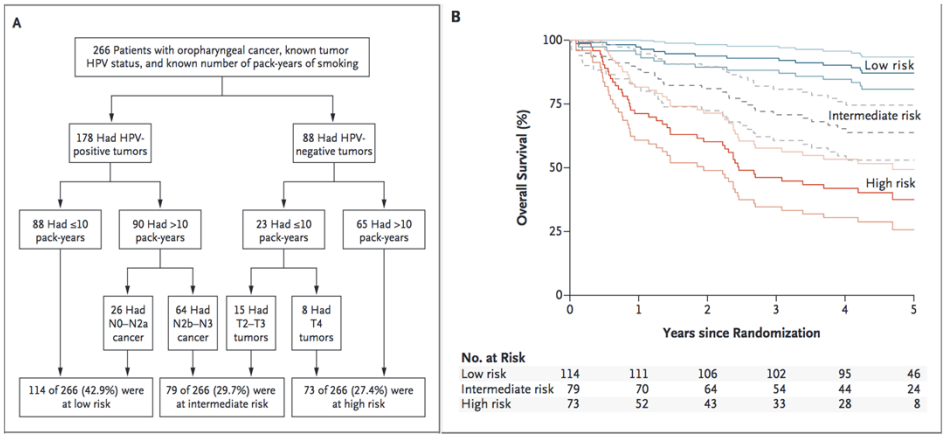
Conclusion: Classification of patients into risk of death categories; low risk, intermediate risk, high risk



Ang KK et al. NEJM 2010

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The Peak of Intensification for Oropharyngeal Tumors

VOLUME 32 · NUMBER 27 · SEPTEMBER 20 2014
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

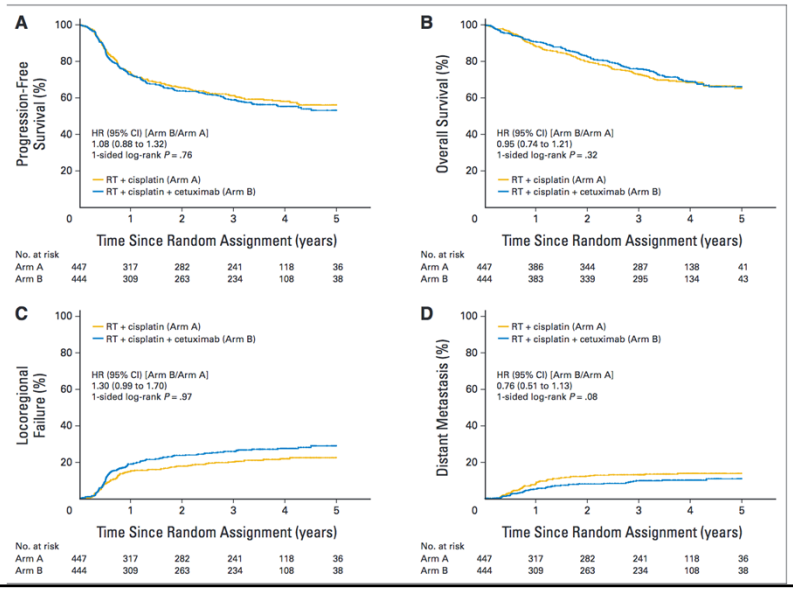
Randomized Phase III Trial of Concurrent Accelerated Radiation Plus Cisplatin With or Without Cetuximab for Stage III to IV Head and Neck Carcinoma: RTOG 0522

K. Kian Ang,† Qiang Zhang, David I. Rosenthal, Phuc Felix Nguyen-Tan, Eric J. Sherman, Randal S. Weber, James M. Galvin, James A. Bonner, Jonathan Harris, Adel K. El-Naggar, Maura L. Gillison, Richard C. Jordan, Andre A. Konski, Wade L. Thorstad, Andy Trotti, Jonathan J. Beitler, Adam S. Garden, William J. Spanos,† Sue S. Yom, and Rita S. Axelrod

- OPC (70%), Larynx (22.6%), Hypopharynx (7.4%)
- Radiation Therapy: 72/42 fx (3DRT or 70/35 in 6 wks (IMRT)
- CDDP: 100 mg/m2 q3w
- Cetuximab: 400mg/m2 and 250 mg/m2 weekly

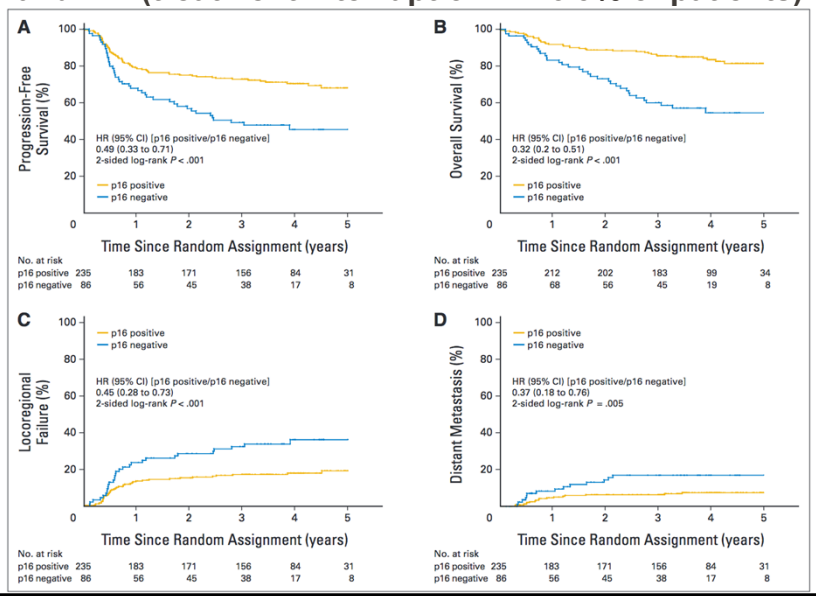
MD Anderson | RTOG 0522 9

Conclusion: Adding Cetuximab to Radiation-Cisplatin did not improve outcomes



MD Anderson | RTOG 0522 10

Conclusion: p16+ patients had better OS, PFS and less LF and DM (treatment interruption in 26.9% of patients)



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RTOG-0522 (n=425)
Phase III IMRT/CDDP +/- Cetuximab

- PEG use at 6 months 34.6%
  - Patients with recurrence at 1 year excluded
  - PEG use at 6 months 41% (not excluded)
- Overall Survival by PEG use at 6 months
  - **HR (Y/N) 2.62 [1.33- 5.16] (p < 0.004)**
- FACT-HN Functional Well Being
  - **Mean 1.5 vs. -0.5 (p < 0.012)**

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RTOG 0522 – Toxicity Arm A:
IMRT + Cisplatin

Feeding tube dependency:

1 yr: 21.2%

2 yr: 13.5%

3 yr: 12.1%

Ang et al. *JCO* 2014; 32(27)

RTOG 0522 – p16+ OPC

Disease outcomes at 3 yrs:

Progression-free survival (PFS): 72.8%

Overall survival (OS): 85.6%

Local regional failure (LRF): 17.3%

Distant Metastasis (DM): 6.5%

Ang et al. *JCO* 2014; 32(27)

Feeding tube, PRO and survival in RTOG studies

Feeding tube rates in RT-cisplatin treated patients

RTOG 0522 (n=568):

6 months following RT start (4 months post RT): 40.7%

RTOG 1016 (n=384):

End of treatment: 51.6%; 4 months post RT: 27.7%

Feeding tube, survival and quality of life in RTOG 0522

- unpublished NRG analysis in patients without a recurrence/progressive disease in their first year on study.
- patients with a feeding tube at 6 months vs. those without are associated with an increased hazard of death (univariate analysis; multivariate pending)
- patients without feeding tubes experienced an improvement in functional well-being while those with a feeding tube did not (p=0.012).
- Formal NRG request for full ancillary study ongoing

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SEER/MEDICARE
PEG Tubes and Survival

SEER/Medicare analysis on the relationship between feeding tube and survival

N=3183 pts aged 65-80, any HN site with complete information, excluding stage I-II larynx

Multivariate analysis (cox model, or competing risk) adjusted on age, race, comorbidity, tumor stage, tumor site, type of RT, performance of surgery, use of chemotherapy and placement of feeding tube during treatment

Feeding tube 6 months post RT predicts dependency in the long term

Source: Blanchard and Frank Unpublished

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PEG Tube Dependency
Correlates with Worse Survival

SEER/MEDICARE Database – PEG Dependency 6m

- 47% increase risk of death
- 56% increase risk of death related to cancer

(note: statistical association is unchanged when patients die within 12 and within 24 months post-treatment)

	Cox model			Competing risks survival					
	Overall			Cancer Death			Other Death		
	HR	95% CI		HR	95% CI		HR	95% CI	
On tube 8 months since RT start									
Yes vs. No	**1.47**	**1.28**	**1.68**	**1.56**	**1.30**	**1.86**	1.09	0.89	1.34

Source: Blanchard and Frank Unpublished

De-Intensification Strategies with Radiation Therapy

Primary Intention:

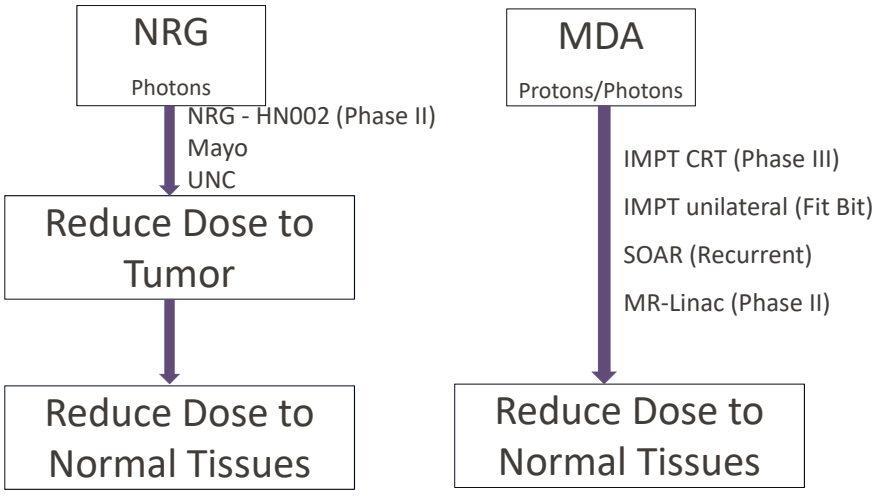
- Reduce radiation dose to normal tissues

Secondary Intention:

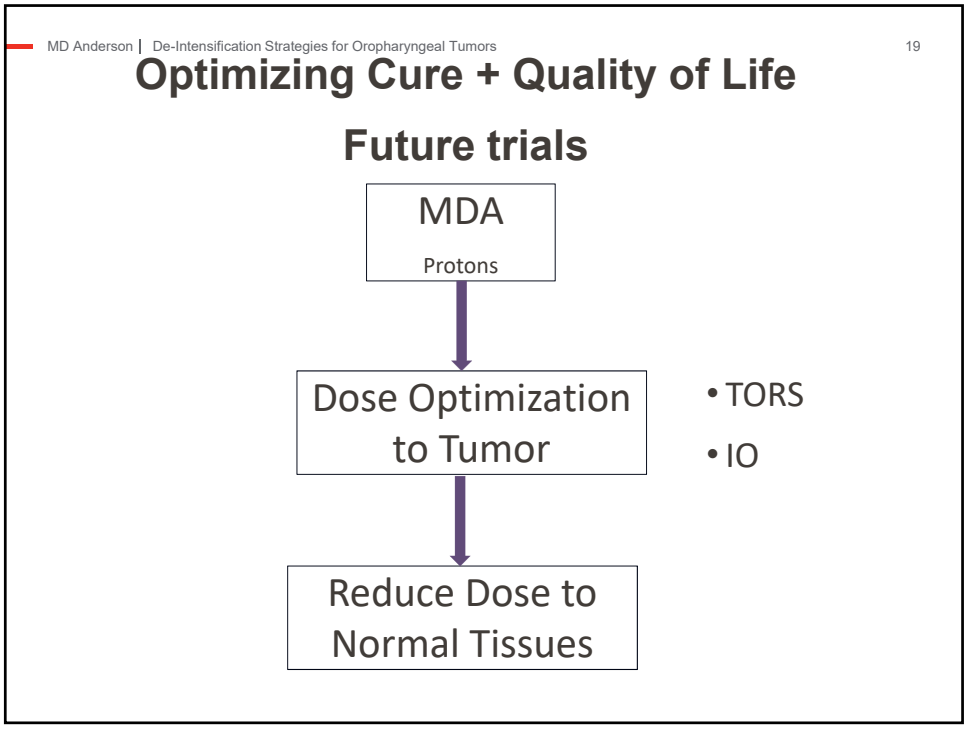
- Reduce radiation dose to tumor thereby reducing dose to normal tissues

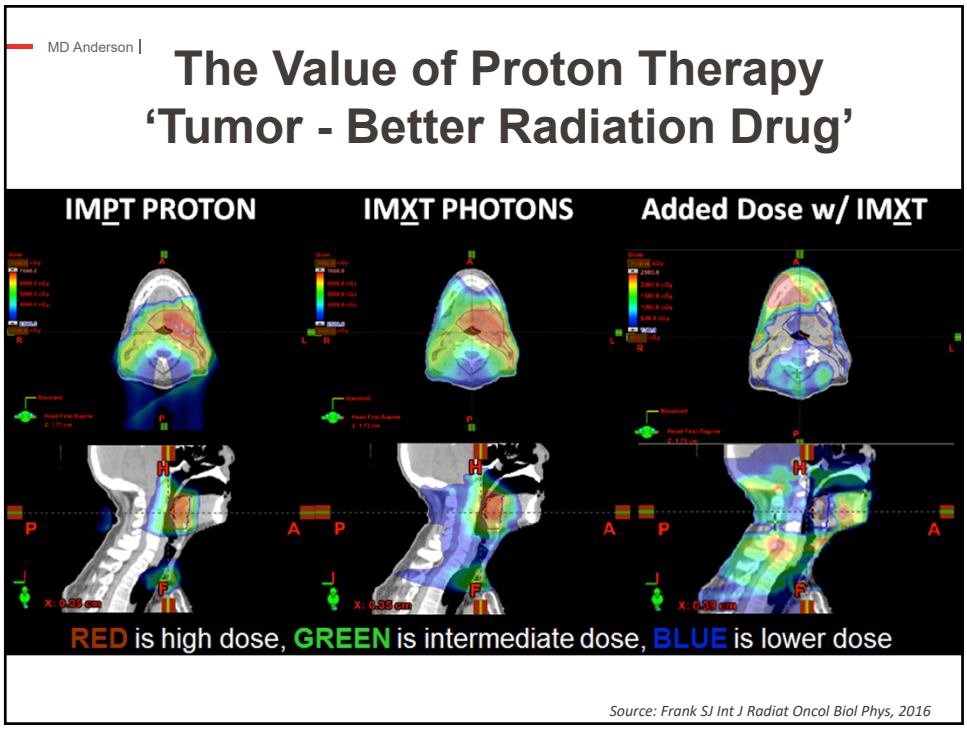
Optimizing Cure + Quality of Life

Reduce Radiation Dose to Normal Tissue Structures



MDA RO PI's: Frank, Gunn, Phan, Fuller


MD Anderson | De-Intensification Strategies for Oropharyngeal Tumors
19
Optimizing Cure + Quality of Life
Future trials
MDA
Protons
Dose Optimization to Tumor
Reduce Dose to Normal Tissues
• TORS
• IO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The Value of Proton Therapy
'Tumor - Better Radiation Drug'
IMPT PROTON
IMXT PHOTONS
Added Dose w/ IMXT
RED is high dose, GREEN is intermediate dose, BLUE is lower dose
Source: Frank SJ Int J Radiat Oncol Biol Phys, 2016

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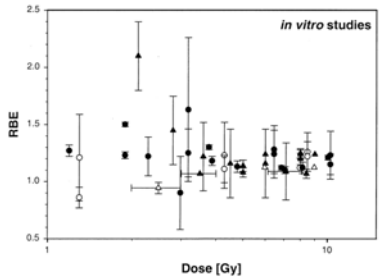
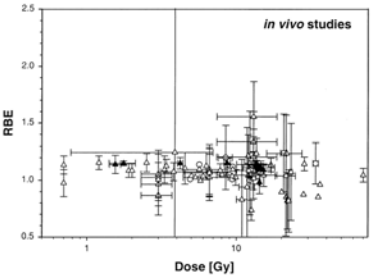
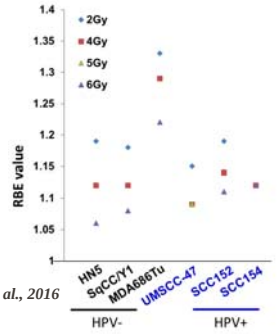
Relative Biological Effectiveness (RBEs) variations of protons in HN cancer cell lines [HPV +/-]

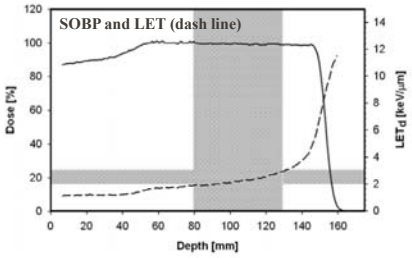




Paganetti H, et al., 2002



Frank, et al., 2016



Paganetti H, et al., 2014

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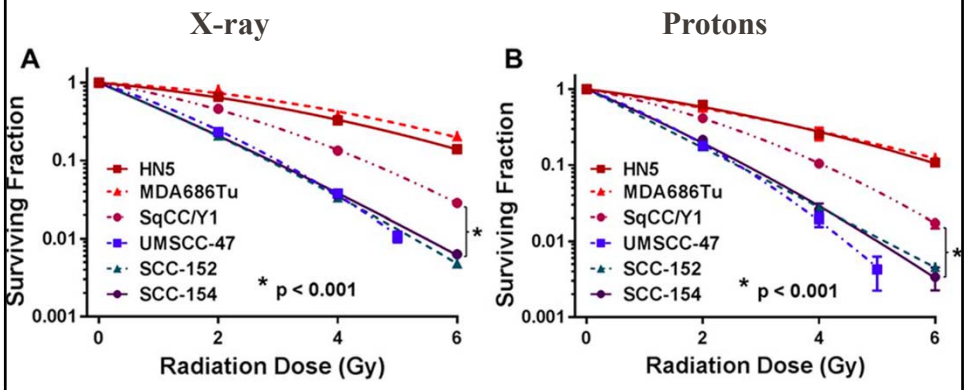
Effect of HPV status on the response of HNSCC cell lines by photons or protons



Wang L and Frank SJ, et al., *Head and Neck* 2016

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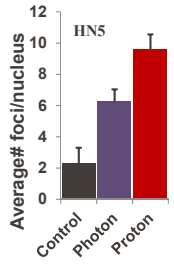
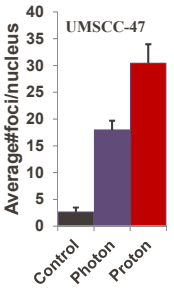
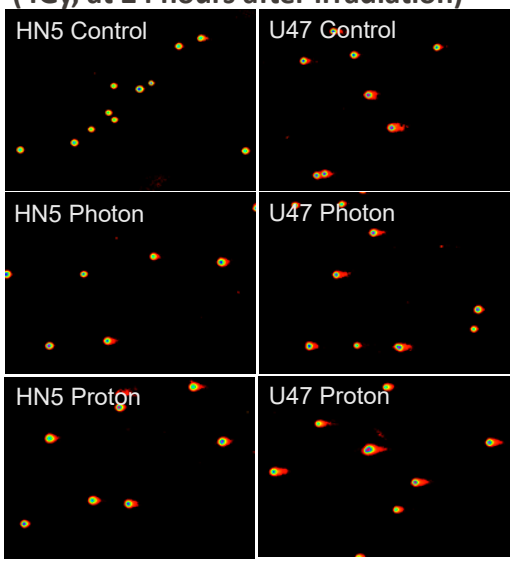
More unrepaired DNA double strand breaks caused by proton beams versus X-ray (4Gy, at 24 hours after irradiation)





53BP1 foci



Tail Moment

Wang L et al, Head and Neck 2016

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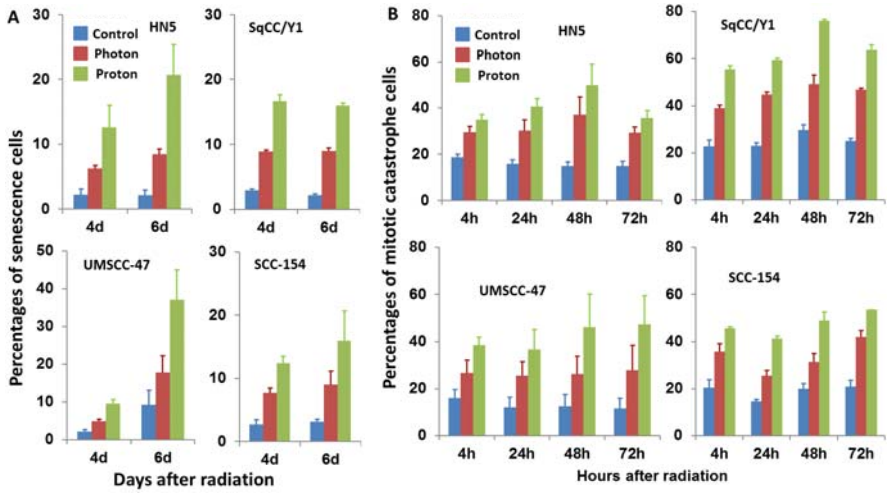
More cell senescence and mitotic catastrophe caused by proton beams versus X-ray (4 Gy irradiation)



Wang L & Frank SJ (AACR-AHNS 2017)

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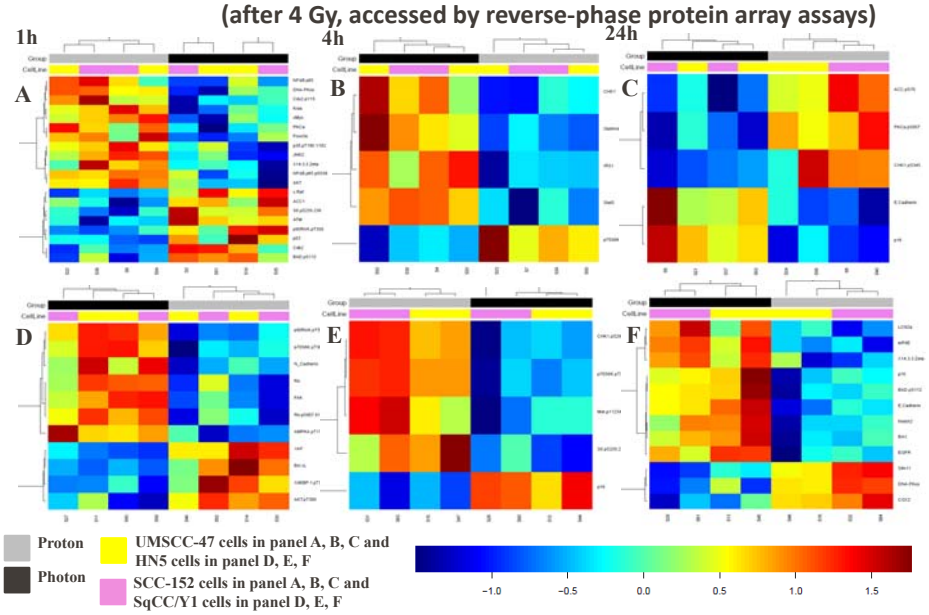
Different protein expression profile caused by proton beams versus X-ray

(after 4 Gy, accessed by reverse-phase protein array assays)



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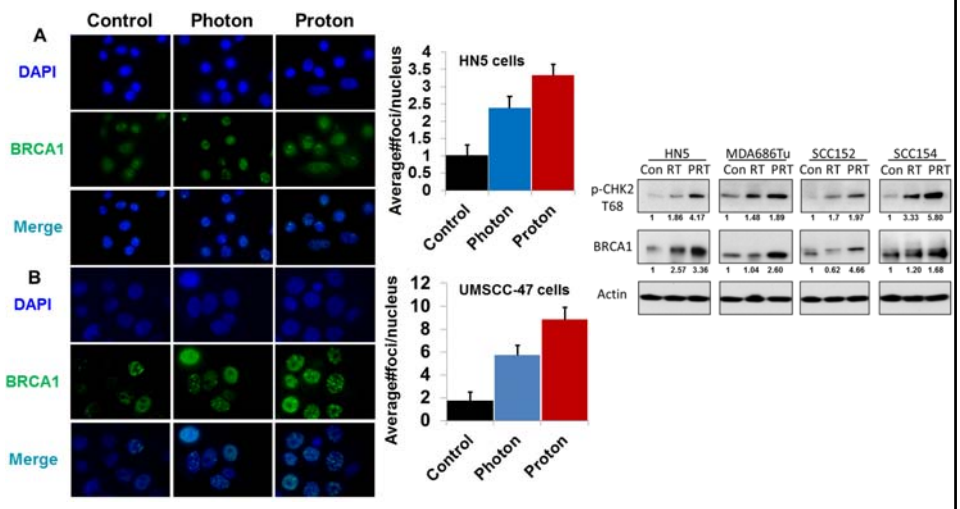
Difference of DNA damage repair related proteins caused by proton beams versus X-ray

(at 4 hours after 4 Gy irradiation)



Wang L & Frank SJ (AACR-AHNS 2017)

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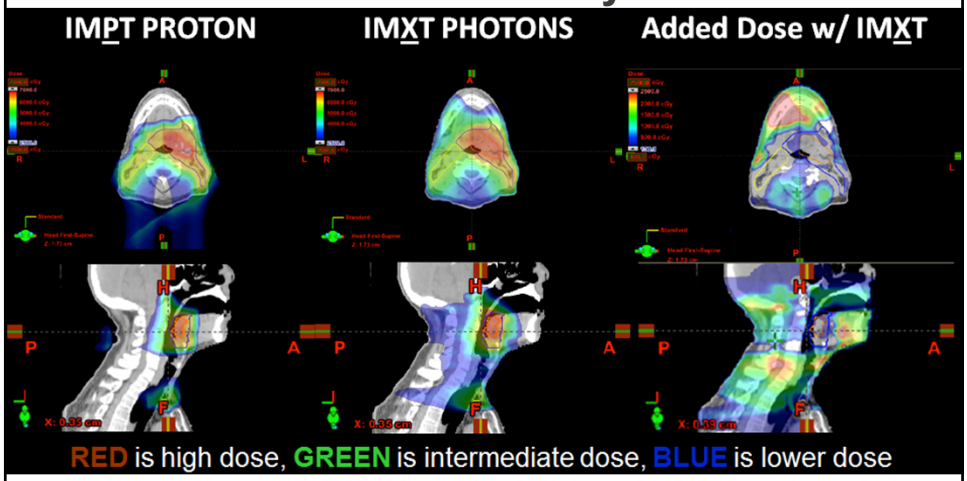
The Value of Proton Therapy
'Normal Tissue: Eliminates unnecessary radiation'



Source: Frank SJ Int J Radiat Oncol Biol Phys, 2016

VOLUME 26 · NUMBER 2 · JANUARY 10 2008
JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Should Randomized Clinical Trials Be Required for Proton Radiotherapy?

Michael Goitein, *Department of Radiation Oncology, Harvard Medical School, Boston, MA*
James D. Cox, *Division of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX*

Would we agree to receive 25 Gy to a large fraction of our brain or abdomen in exchange for some thousand of dollars, with no known credibly hypothesized medical benefit?

Once protons is clinically available, is the burden of proof on conventional x-ray therapy?

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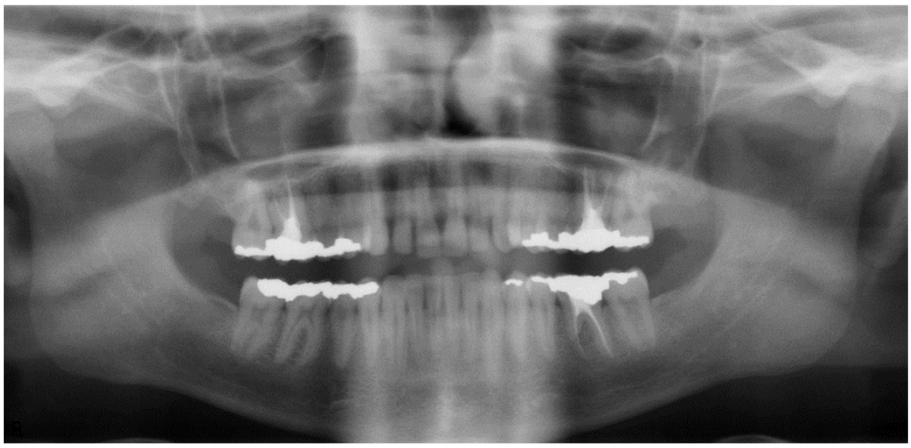
How many extra intra-oral x-ray equivalents is IMRT over IMPT?



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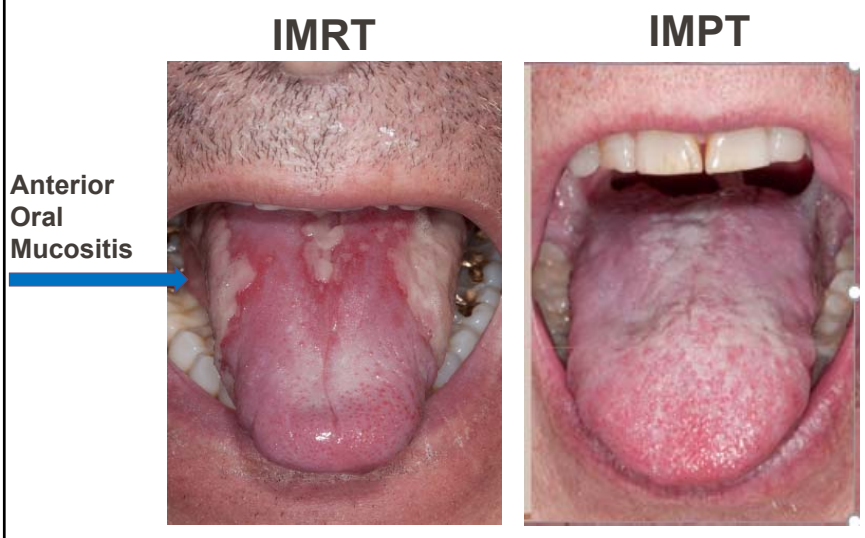
Side effect of 25 Gy



50% reduction in feeding tubes

Frank SJ et al. *IJROBP* 2014

MD Anderson

How many intra-oral x-rays is 25 Gy?

5

50

500

5000

5,000,000

MD Anderson

How many intra-oral x-rays is 25 Gy?

5,000,000

1 Gy – 1 Sv

Each Intral oral x-ray is 0.002 mSv

200,000 intra-oral x-ray per 1 Gy

http://www.radiologyinfo.org/en/safety/?pg=sfty_xray

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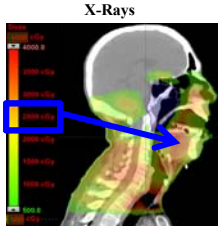
Why Proton Therapy?

*25 Gy (25 Sv) of Unnecessary Radiation =

Added Radiation w/ X-Rays



12,500
H&N CTs (2 mSv)

5,000,000
Intraoral X-Rays (0.002 mSv)

25,000x
General Public Annual Limit (1.0 mSv)

+83%
Additional Cancer Risk* (2,500 CTs, 65 yo)

*http://www.xrayrisk.com/calculator/calculator-normal-studies.php

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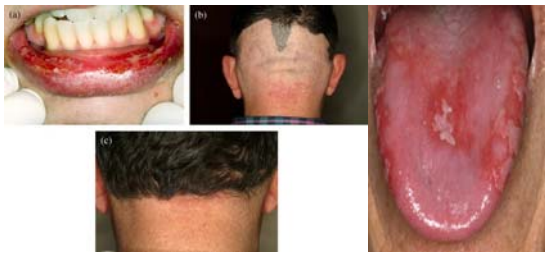
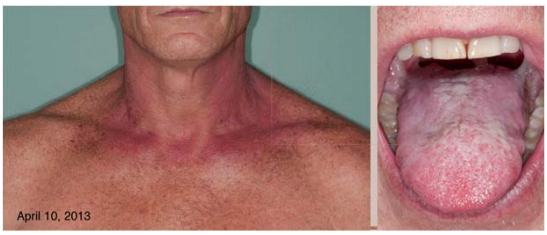
IMRT for Oropharyngeal Carcinoma-Beam Path Toxicities



Source: Rosenthal et al. *Int J Radiat Oncol Biol Phys* 2008

Beam path toxicities seen with **IMRT** including AOC mucositis.



Patient with HPV+ BOT SCC after 66 of 66 Gy(RBE) IMPT

Less out-of-field mucositis seen with **IMPT**.

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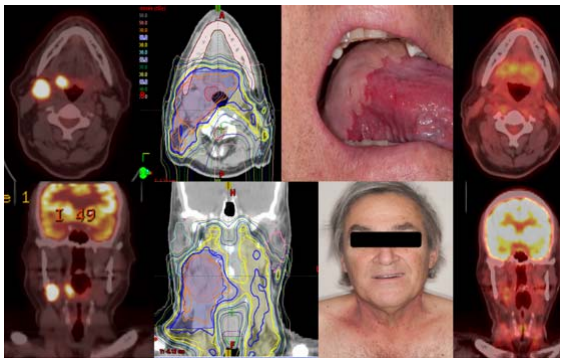
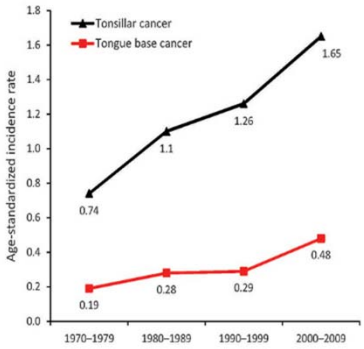
Proton Therapy for Oropharyngeal Tumors
50% reduction in feeding tubes





Frank SJ et al. IJROBP 2014
Frank SJ et al. ASTRO 2013

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IMPT - Oropharyngeal Tumors

3/2011 – 7/2014, MD Anderson Cancer Center

50 consecutive oropharynx patients

IMPT (46 – MFO, 4 – SFO)

84% male, 16% female

50% never smokers

98% Stage III-IV

64% concurrent CRT

98% evaluable p16+

Source: Gunn and Frank, *et al. Int J Radiat Oncol Biol Phy*

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IMPT
Oropharyngeal Tumors

Median follow-up – 29 months

No CTC-AE Grade 4/5 toxicities

11 pts had gastrostomy tube during treatment

0 patient had gastrostomy tube at last follow-up

5 pts had disease recurrence

1 local, 1 LR, 2 regional, 1 distant

2-yr actuarial OS (94.5%) and PFS (88.6%)

Source: Gunn and Frank *et al. Int J Radiat Oncol Biol Phys, 2016*

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Potential Benefit for OPC-Dosimetric Advantages

1st 25 patients treated w/ IMPT for OPC

Matched with 25 patients treated w/ IMRT

Structures	IMPT Mean± SD(cGy)	IMRT Mean± SD(cGy)	P value
AOC-mean	829±590	3047±789	**<0.0001**
POC-mean	4054±1530	5060±804	**0.0001**
BOT-mean	3896±1692	5145±1012	**0.0169**
IPC-mean	3276±1071	2879±1584	0.0667
SPC-mean	5525±1300	5795±1127	0.5434
MPC-mean	4818±1782	5463±936	0.5364

Source: Holliday and Frank et al., *Medical Dosimetry* 2016

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Potential Benefit for OPC-Dosimetric Advantages

Structures	IMPT Mean± SD(cGy)	IMRT Mean± SD(cGy)	P value
Brainstem-mean	770±373	1860±879	<0.0001
Cerebellum-mean	1255±427	1891±760	0.0006
WB-mean	230±105	438±381	0.0026
AP-mean	1457±899	3072±650	<0.0001
DVC-mean	1751±869	3148±630	<0.0001
NA-mean	1912±986	3327±628	<0.0001
SN-mean	1545±850	3116±872	<0.0001
MO-mean	1963±980	3235±685	<0.0001
PONS-mean	584±364	1268±653	0.0002
LV-mean	755±652	1638±1038	0.0035
FV-mean	683±845	1762±±860	<0.0001
RV-mean	738±407	1179±682	0.0134

Source: Medical Dosimetry 2016

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Potential Benefit for OPC-Dosimetric Advantages

Structures	IMPT Mean± SD(cGy)	IMRT Mean± SD(cGy)	P value
Hard Palate-mean	1197±908	2632±1036	**<0.0001**
Larynx-mean	2952±910	2645±1517	**0.036**
Lt_Ant_Digastric_M-mean	2965±1901	4817±1540	**0.0017**
Mandible-mean	2658±932	3811±913	**<0.0004**
Mylohyoid_M-mean	3202±1769	4570±1702	**0.0156**
Rt_Buccinator_M-mean	1405±916	3395±1206	**<0.0001**
Lt_Buccinator_M-mean	1197±1000	4264±1108	**<0.0001**
Lt_Lateral_Pterygoid_M-mean	3383±1729	5460±1547	**0.01**
Lt_Masseter_M-mean	2189±1400	3381±1079	**0.004**
Lt_Medial_Pterygoid_M-mean	3991±2352	5460±1547	**0.004**

Source: Medical Dosimetry 2016

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IMPT Benefit for OPC-Toxicity Reduction

- The 25 pts treated with IMPT for OPC matched with 25 pts treated with IMRT

	IMPT (N = 25) No. (%)	Matched IMRT (N = 25) No. (%)	Entire IMRT Cohort (N = 998) No. (%)	p-value (IMPT v. Matched IMRT)
Feeding Tube Incidence	5 (20%)	12 (48%)	475 (48%)	0.037

- Feeding tube duration was similar: 4.2 (2.6-11.6) mo IMPT and 4.7 (1.4-20) mo IMRT

Source: Frank et al ASTRO 2013

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IMPT Benefit for OPC-Toxicity Reduction

25 IMPT patients evaluated by a speech pathologist prior to (77%) and after (100%) treatment

	Number of Patients	%
Dysphagia per SLP	2	8%
Abnormal MBS	1	4%
Aspiration (per MBS)	0	0%
Stricture (per MBS/EGD)	0	0%

Figure 1. Distribution of acute toxicities (n=25)

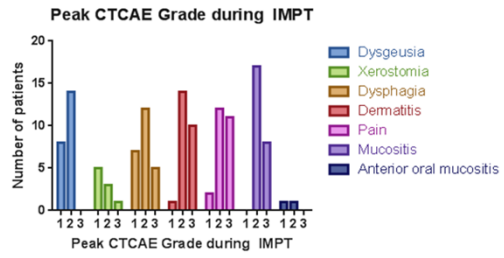
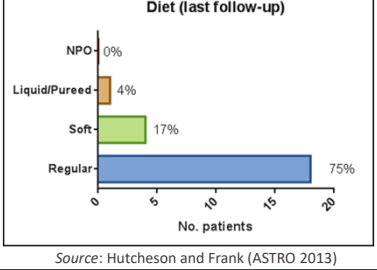


Figure 2. Dietary outcomes (n=25)



Source: Hutcheson and Frank (ASTRO 2013)

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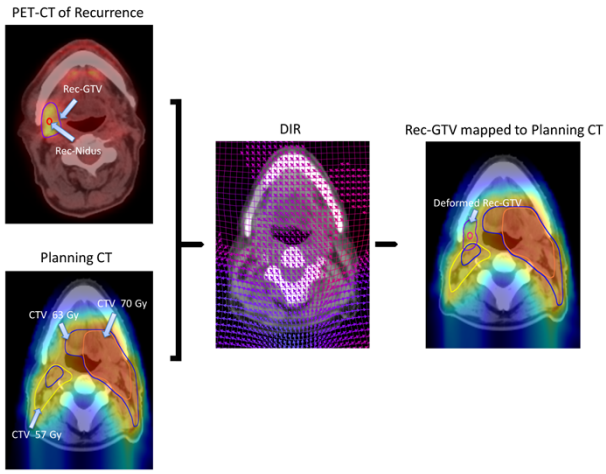
OPC recurrence analysis



Source: Gunn and Frank et al. Int J Radiat Oncol Biol Phys, 2016

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IMPT vs IMRT for OPC
First comparative results of PROs

OPC 2006-2015 at MDACC

Prospective registries

IMPT or IMRT with chemotherapy

- 35 CRT with IMPT
- 46 CRT with IMRT

PRO- MDASI-HN

Source: Sio and Frank *et al. Int J Radiat Oncol Biol P*

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IMPT vs IMRT for OPC
First comparative results of PROs

Baseline similar between groups

Top 5 symptoms

- Taste problems
- Dry mouth
- Swallowing-chewing difficulties
- Lack of appetite
- Fatigue

Source: Sio and Frank *et al. Int J Radiat Oncol Biol Ph*

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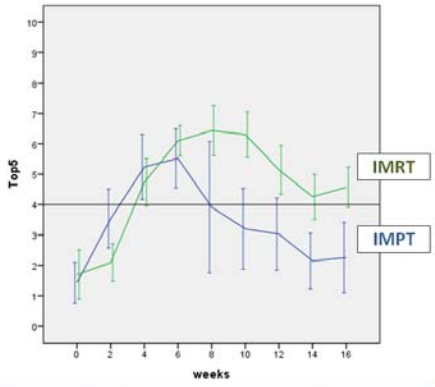
IMPT vs IMRT for OPC
First comparative results of PROs



Symptom Burden by MDASI	IMPT	IMRT	P-value
AUC	63.9	110.4	0.0006
AUC (4-10)	8.7	36.4	0.004

Source: Sio and Frank *et al. Int J Radiat Oncol Biol Ph*

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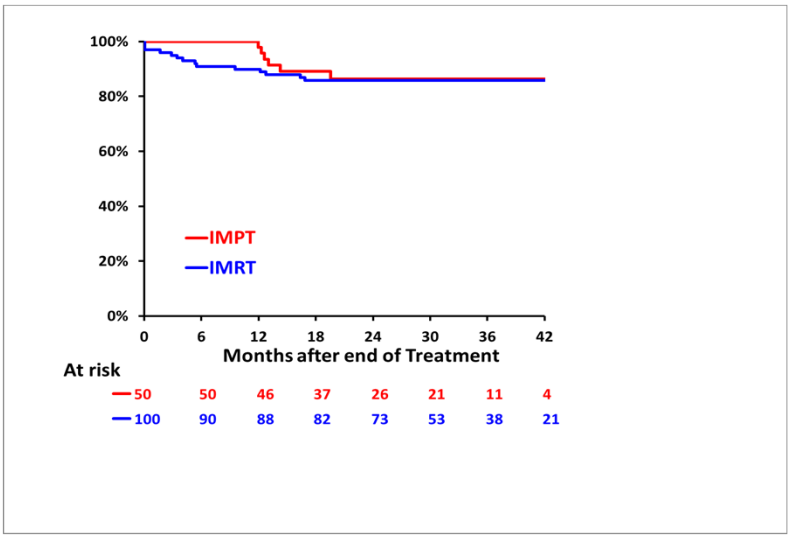
Oropharyngeal Cancer SCC IMPT vs IMRT – PFS



Blanchard P et al. *Radiotherapy and Oncology* 2017

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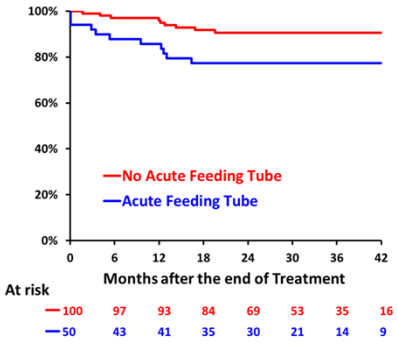
MDACC case-Matched analysis IMPT vs IMRT

Deleterious effect of feeding tube placement on survival:

- **HR: 3.09 (1.19-8.00), p=0.02**
- **Adjusted on age, T and N stage and comorbidity index**

Progression Free Survival according to feeding tube insertion during treatment



Source: Blanchard and Frank et al. Radiotherapy and Oncology 2017

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Which Head and Neck Disease Sites are Randomized Trials Permissible?

Salivary Gland Tumors

- Unresectable Adenoid Cystic Carcinoma

Periorbital Tumors

Nasopharyngeal Cancer

Oropharyngeal Cancer

Paranasal Sinus Tumors

- Postoperative Radiation in Areas of Tissue Heterogeneity

Reirradiation

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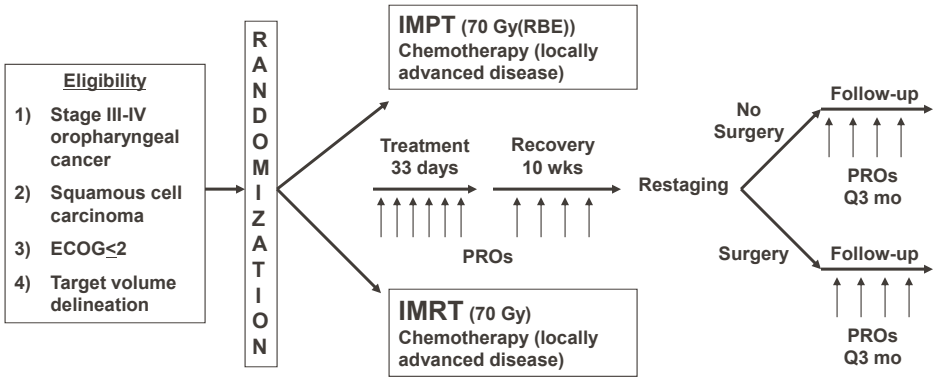
H-N Phase III Randomized Trial Oropharyngeal Cancer - IMPT vs IMRT



Frank – PI, Busse, Foote Co-PIs

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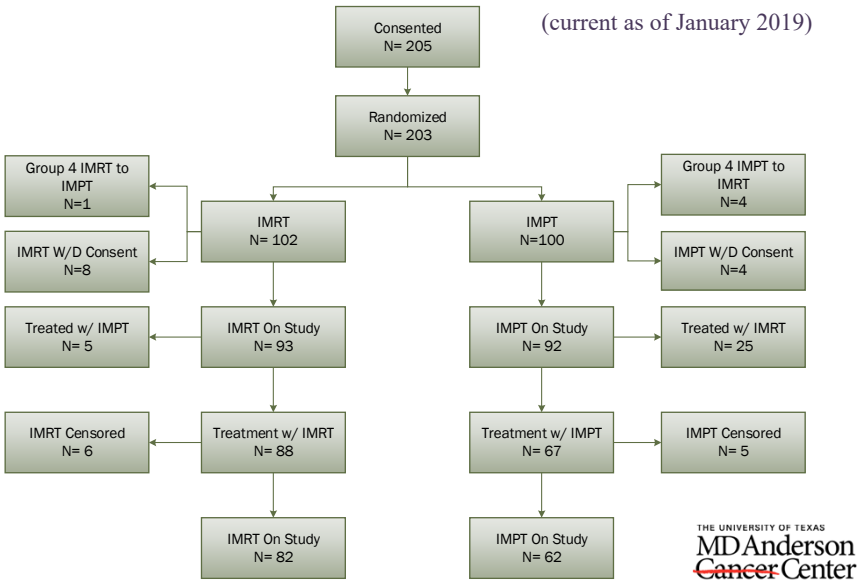
Study CONSORT Diagram

(current as of January 2019)



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The value proposition for HN proton therapy

$$\text{Value} \uparrow = \frac{\Sigma\,(\text{Outcomes}) \uparrow}{\Sigma\,(\text{Costs}) \downarrow}$$

Phase II-III Randomized Trial of Advanced Stage Oropharynx Tumors

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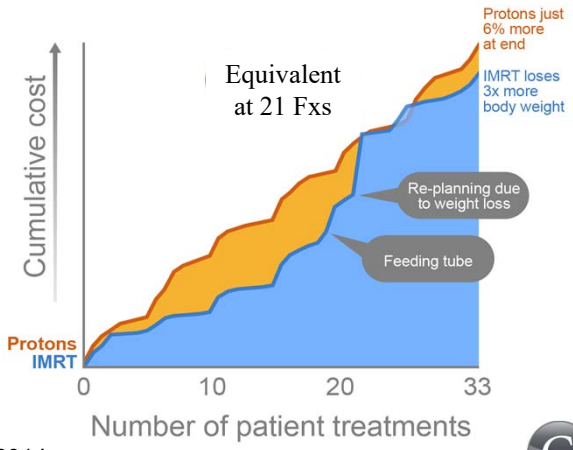
Value Proposition- H&N

Cumulative Cost of Care During Radiation Therapy

$$\text{Value} \uparrow = \frac{\Sigma \text{ (Outcomes)}}{\Sigma \text{ (Costs)} \downarrow}$$



Thaker N et al. *Oncology Payers* 2014

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National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Head and Neck Cancers

Version 1.2017 — February 6, 2017

NCCN.org

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NCCN Updates

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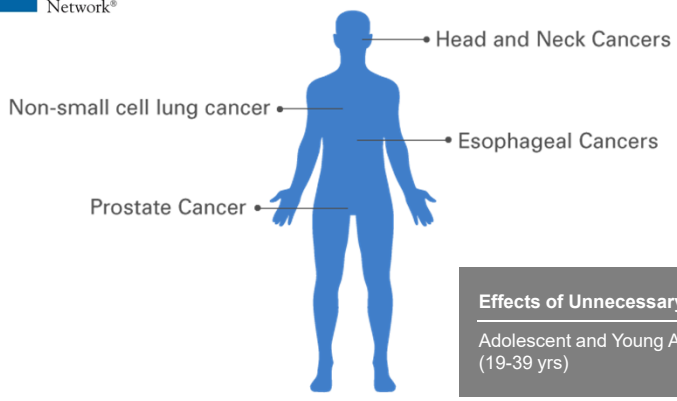
National Comprehensive Cancer Network®



Effects of Unnecessary Radiation

Adolescent and Young Adult Guidelines (19-39 yrs)

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Conclusion

Head and Neck proton therapy is safe and effective

IMPT is the future of head and neck radiation therapy

Randomized trials are needed to define the value

- N. America – Oropharynx HPV+

The biology will inform for ***dose*** de-escalation (?MATH?)

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Better Outcomes with Lower Costs: The High Value of PBT Coverage

A State-Wide Self-Funded Employer Success

Steven J. Frank, MD
Professor and Deputy Head, Radiation Oncology
Executive Medical Director, Particle Therapy Institute

May 1st, 2019

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Disclosures

- NCI U19 IMPT vs IMRT Oropharynx
- Honoria and/or Grants from ELEKTA, Eli Lilly, NIH/NCI, Varian, Hitachi, Augmenix and IBA
- Varian Advisory Board/Consultant
- Founder and Director, C4 Imaging

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Value-based Pilot with Texas System

Third party administrators (TPA) often cite overutilization and cost as justifications for restrictive proton beam therapy (PBT) coverage policies.

We collaborated with a state-wide self-funded employer, The University of Texas System (UTS), to implement a PBT coverage pilot ensuring appropriate access to care without increasing cost.

This pilot conducts a value-based assessment of PBT through evaluation of utilization trends and comprehensive charge analysis of medical claims.

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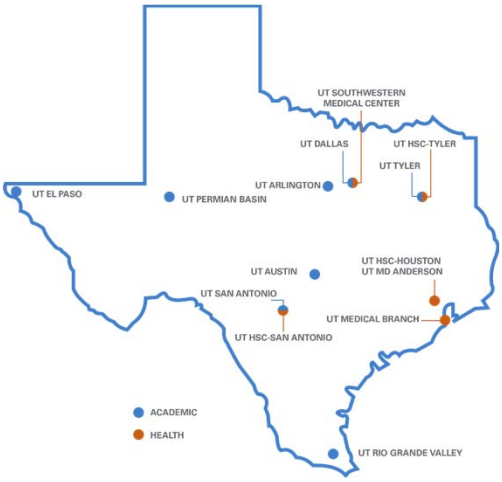
UT System Facts



The University of Texas System
Fourteen institutions. Unlimited possibilities.

14 INSTITUTIONS

$19.5B OPERATING BUDGET

1.6M INPATIENT VISITS

8.2M OUTPATIENT VISITS

105K EMPLOYEES IN TX

186K COVERED LIVES

59K DEGREES AWARDED

$2.9B IN RESEARCH

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Background Summary - 2015

Topic: UT SELECT Coverage for Proton Therapy
Date: May 19, 2015 (Austin, TX)
Attendees: UT System, BCBS-TX, and MDACC
2015 Discussion Points:

- Proton Beam Therapy (PBT) has high measurable value
- PBT is safe, effective, and medically necessary when prescribed
- UT System employees and dependents have limited access for PBT
- BCBS-TX policy does not incorporate current peer reviewed literature
- BCBS-TX definition of medical necessity is not consistent with Medicare (TX)
- Proposed PBT coverage for UT SELECT agrees with MD Anderson Proton Therapy Policy (MDAPTP), AMA, Medicare, and Retired Novitas LCD.
- MD Anderson self-funded cancer management program uses MDAPTP
- UT System wanted to minimize impact on policy holders
- Estimated additional cost to UT System < 0.5% of total medical claims

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Background Summary – 2015

Action Item:

Determine pilot structure and complete cost analysis with UT System & BCBS-TX

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Pilot Structure & Endpoint

The pilot obtained Institutional IRB approval.

All patients enrolled on a IRB approved prospective clinical trial.

Coverage for head and neck, esophageal, breast, lung, prostate, and randomized clinical trials.

Value based analysis

- Patient satisfaction (PROs)
- Clinical outcomes and toxicities
- Total net charges (cost of care)

A primary endpoint was cost of care

- Claims = 1 month pre-treatment, treatment, and ≥ 6 months post-treatment.

UT System provides administrative override to BCBS-TX and payment at contracted in-network rate.

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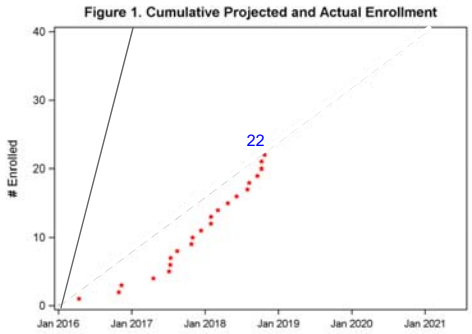
Proton Therapy Coverage Pilot Status

Enrollment

1st patient – April, 2016

Permitted enrollment – 40/year

Actual treated in 3 yrs – 22 pts (only 7/year)



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Pilot Data and Analysis

Average prior authorization time was reduced to <1 business day (BD) vs. 17 BDs (prior to pilot)

9 HN, 8 GU, 3 BRST, & 2 THOR (22 PBT total)

22 additional patients who met pilot eligibility were treated w/ X-Rays during same timeframe

Out of these, 17 were case-matched to 17 photon patients with ≥6 month follow-up

PBT claims were compared with case-matched photon patients (enrollment period, employer, site, indication, & stage)

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Case-Match: Patient Demographics

Variable	Protons (n=17) No. Patients (%)	Photons (n=17) No. Patients (%)	P Value*
Service			
HN	7 (41)	7 (41)	0.99
GU	6 (35)	6 (41)	
Breast	3 (18)	3 (18)	
Thoracic	1 (6)	1 (6)	
Sex			
Male	11 (65)	11 (65)	0.99
Female	6 (35)	6 (35)	
Age			
Mean, (range)	64 (39-85)	59 (47-77)	0.12
ECOG			
1-2	3 (18)	4 (24)	0.99
0	14 (72)	13 (76)	
Follow-Up			
Mean, (range)	16.2 (6.5-33.2)	21.0 (7.7-32.5)	0.07

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Case-Match: Treatment Factors

Variable	Protons (n=17) No. Patients (%)	Photons (n=17) No. Patients (%)	P Value*
Stage (AJCC VII)			
3-4	5 (29)	7 (41)	0.85
0-2	11 (65)	9 (53)	
Recurrence	1 (6)	1 (6)	
Histology			
Squamous	4 (24)	5 (29)	0.99
Non-Squamous	13 (76)	12 (71)	
Indication			
Definitive	10 (59)	8 (47)	0.49
Adjuvant	7 (41)	9 (53)	
No. of Fractions			
Mean, (range)	28 (10-39)	28 (5-39)	0.84
Chemotherapy			
Yes	6 (35)	4 (24)	0.45
No	11 (65)	13 (76)	

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Proton Therapy Coverage Pilot Status

QoL Data Reliability

Highly Reliable QoL (Quality of Life) data

- 81.4% (PBT Pilot) vs. 69% (Related Protocols)

	# expected by protocol	# of Collected	*Complete Rate (%)	*Average Compliance Rate of all Related Protocols
Baseline	18	17	94.4%	94.4%
During Treatment	37	32	86.5%	69.0%
Follow-up	42	30	71.4%	43.7%
Overall	**97**	**79**	★ **81.4%**	**69.0%**

*Statistical comparison was not made at this point, due to the limited sample size

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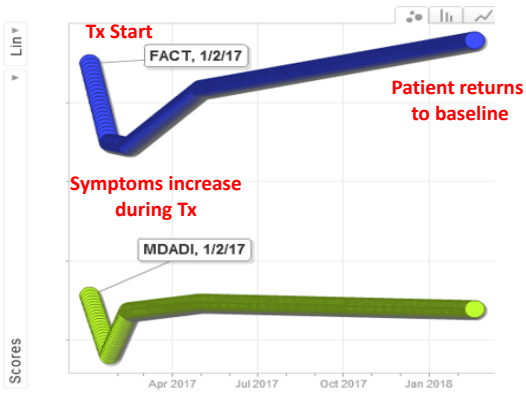
Outcomes - Clinical

Quality of Life (QOL)

NO Grade 4 or 5 Toxicities
(Hospitalization, ICU, Death)

Patients Quality of Life returning to baseline faster

Figure 4. MDADI and FACT Score Change over Time
(The lower scores indicate the more severe symptom burden)



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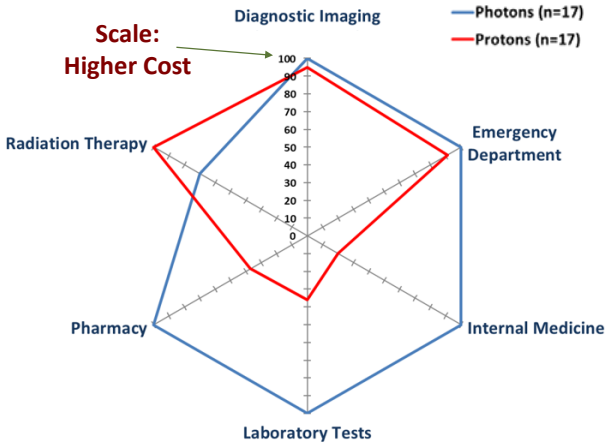
Outcomes – Cost Comparison

(Normalized Relative Average Cost Ratios)



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PBT Pilot Total Cost of Care Analysis *Summary*

Cost	Cost per Covered Life	% of Claims
$748,819 Projected	$2.38 Projected	0.10% Projected
-$426,522 Actual	-$2.29 Actual	-0.06% Actual
-$1,175,341 Total Difference	-$4.68 Total Difference	-0.16% Total Difference

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PBT Pilot Cost Analysis Summary

NET employer cost savings with PBT

The average net billed charges were -21.0% lower for PBT

Percentage of RT-to-Total charges was 77% vs. 65% for PBT & Photons (p=.09)

Photon (X-Ray) patients had more ancillary costs [IM, Pharm, Lab, ER, DI]

Hypofractionated PBT regimens add value [5/17 patients]

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Proton Therapy Coverage Pilot Summary

Outcomes have been excellent

The cost to the UT System is less than expected

Patient selection is rigorous and accrual was less than predicted

Patient, Physician, and Administrative satisfaction is very high

Administrative burden has been significantly reduced

Protocol data is very reliable

Patient Reported Outcomes are favorable

Proton Therapy is safe and effective

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Conclusions

The UT System and MD Anderson have demonstrated that a successful proton therapy coverage pilot is feasible

Collaboration with employers can improve access & reduce cost

The UT System has committed to the expansion of proton therapy

Comprehensive PBT coverage for all UT System policy holders

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Conclusion

Objective evidence-based treatment guidelines and policies can ensure appropriate patient selection while reducing administrative burden.

Patient, physician, & administrative satisfaction is very high.

Protocol data is very reliable, patient reported outcomes are favorable, PBT is safe and effective.

This state-wide insurance coverage pilot demonstrates that appropriate access to PBT does not result in overutilization or increased employer cost.

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Proton Therapy's Next Generation

The MD Anderson Proton Therapy Center [2]

A Pioneer in
Proton Therapy

MD Anderson Proton Therapy Center

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Acknowledgements

Matthew Ning, MD
Aashish Shah, MD,JD
Laura Chambers (UT System Executive Director of Office Employee Benefits)
Laura Garlock (UT System, Sr Benefits Analyst)
Ben Melson (MDACC Sr VP & CFO)
Jim Incalcaterra (Exec. Director, Financial Planning & Analysis)
Michelle Ruben (Director, Clinical Rev./ Reimbursement)
Robin Simmons (Assoc. Dir, Rev Cycle Analytics)
Annette Johnson (Revenue Cycle Analytics)
Kathleen Garrett (Revenue Cycle Analytics)
Rong Ye (Statistical Analyst)
Menna Teferra (Research Admin)
Kristen Cover (VP Marketing and Communications)
Maru Navarro (Graphic Designer)

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Thank you! Questions?

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Acknowledgments

Proton Physics Team

- Michael Gillin
- Ron Zhu
- Rhade Mohan
- Narayan Sahoo
- Richard Wu
- Falk Poenisch
- Xiaodong Zhang

Proton Dosimetry Team

Proton Therapy Team

Head and Neck Team

- K. Kian Ang
- David Rosenthal
- William Morrison
- Adam Garden
- Brandon Gunn
- Beth Beadle
- Jack Phan
- Dave Fuller

Matthew Palmer

Hitachi

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A Pioneer in
Proton Therapy

MD Anderson Proton Therapy Center

HTCC Public Comments

Re-Review of Proton Therapy

May 17, 2019

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine
Proton Therapy Center

Speakers

- **Ramesh Rengan, MD, PhD**
  - Ceding their time to Dr. Rengan: Lindsay Knapp, Meredith Fane, Meredith Cassels
- **Ralph Ermoian, MD**
  - Ceding their time to Dr. Ermoian: Amy Walgamott
- **Charles Bloch, PhD, DABMP, DABR, FAAPM**
- **Jing Zeng, MD**

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine
Proton Therapy Center

Ramesh Rengan, MD, PhD

Professor and Interim Chair, Department of Radiation Oncology, University of Washington School of Medicine

Medical Director, SCCA Proton Therapy Center
Associate Member, Clinical Research Division, Fred Hutchinson Cancer Research Center

Conflict of Interest Disclosure

- Medical Director of the SCCA Proton Center
  - No direct salary

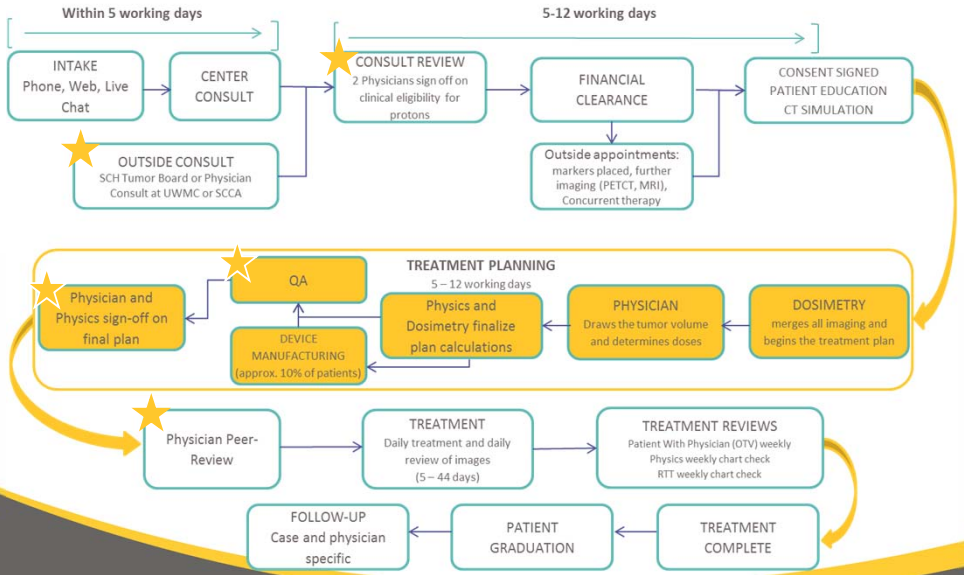
General Radiation Principles

1. There is no benefit to radiation to normal tissues
2. Proton therapy reduces radiation to normal tissues compared to x-ray radiation by 10-90% in most situations
3. Reduction of harm from this reduction in radiation exposure is not something that can be captured in prospective randomized trials

General Radiation Principles

- Reduction of radiation exposure (ALARA) has been accepted as basic standard clinical practice without prospective clinical trial evidence to support it
  - Worldwide acceptance of proton therapy for children
  - Low-dose CT scanners: no randomized trials required for deployment
- HOWEVER, healthcare resources are finite
  - We must be good stewards of expensive and labor-intensive technology
  - Our center has a rigorous process for patient selection for suitability for proton therapy

Selection Process & Peer Review



Prior to patient treatment, each case is reviewed *at least*

5

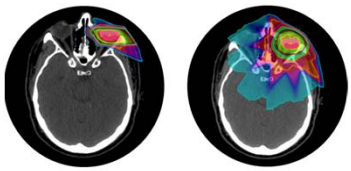
times to ensure protons are the superior treatment option

Who Benefits from Proton Therapy?

- Pediatric Patients
- Re-irradiation
- Ocular
- Tumors near Organs at Risk (OARs)

Ocular Tumors

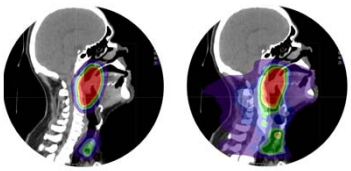
Protons Photons



Decrease in radiation exposure to underlying brain tissue, when using protons

Head & Neck Cancers

Protons Photons



Images represent a reduction in radiation to the head and brain, when using protons

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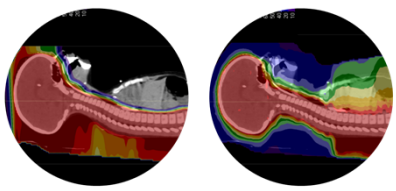
Medulloblastoma: Craniospinal Irradiation

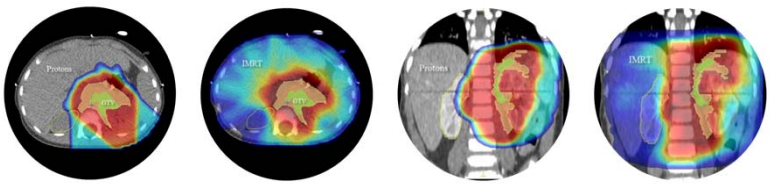
Protons Photons



Images represent a reduction in radiation to the entire chest and abdomen cavities, when using protons

Pediatric Neuroblastoma

Protons Photons Protons Photons



Images represent a reduction in radiation to the abdomen, when using protons

Commitment to Evidence Generation

- 2 registries & more than 25 open clinical trials
  - Disease sites include breast, brain, prostate, thoracic, pediatric, and other cancers
- 70% of the Center's patients have enrolled in the Proton Collaborative Group registry
- Over 100 patients have enrolled in proton clinical trials since the Center's opening in 2013

Coverage Variance Across the U.S.

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	Ped CNS/Brain	Other Peds	Adult Brain/CNS	Adult MSK	Adult H&N	Adult Lung/Thoracic	Adult Breast	Adult GI/GU	Adult Re-irradiation	Adult Prostate	Adult Lymphoma	Adult Ocular
Aetna	✓	✓	x	✓	x	x	x	✓	✓	x	x	✓
United Healthcare	✓	✓	x	✓		x	x	✓	✓	✓	x	✓
Medicare Plans	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Florida Blue	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
CareFirst BCBS of Maryland, D.C., & Virginia	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
National and State Specific Guidelines for Coverage												
Existing WA HTA Guidelines (2014)	✓	✓	✓	✓	x	x	x	x	✓	x	x	✓
Estimated WA HTA policy based on re-review	✓	x	x	✓	x	x	x	✓		x	x	x
ASTRO Group 1	✓	✓	✓	✓	✓	x	x	✓	✓	x	x	✓
ASTRO Group 2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Third Party External Reviewers												
AIM	✓	✓	✓	✓	x	x	x	x	✓	x	x	✓
Evicore	✓	✓	✓	✓	x	x	x	✓	✓	x	x	✓

✓ Covered ✓ Covered with Conditions x Not Covered

- The evidence report would suggest a proton beam therapy coverage policy in Washington State that would be among the most restrictive in the country.
- Overly restrictive coverage policies can come with severe consequences to patients' health and to the financial well-being of insurers.
- Aetna Settlement=$25 Million

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Proton Therapy Center

Ralph Ermoian, MD

Pediatric Radiation Oncologist, UW Medical Center, Seattle Children's, SCCA Proton Therapy Center

Associate Professor, Department of Radiation Oncology, University of Washington School of Medicine

Adjunct Associate Professor, Pediatrics, University of Washington School of Medicine

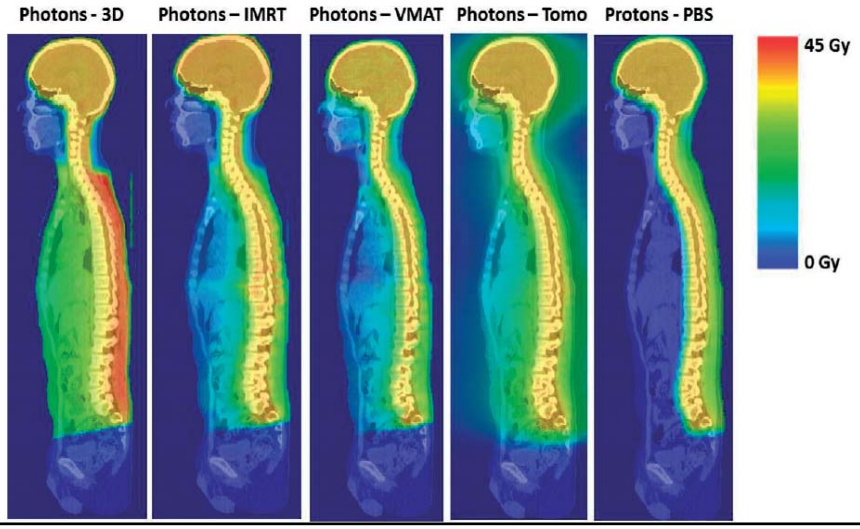
Conflict of Interest Disclosure

- None

Pediatric Patients

- We consider photons or protons for each patient, about 2/3 receive protons and 1/3 receive photons
  - Common to decline referrals when we feel photons at least as good
- Distribution of proton patients
  - 2/3 have brain/central nervous system tumors;
  - 1/3 have rhabdomyosarcoma, neuroblastoma, bone tumors, and lymphoma, and other non-brain tumor
- Matches the increasing use of protons in treating children in the world's 54 proton centers (Radiother Oncol. 2019 Mar;132:155-161)
  - We are only proton center in the Northwest

Craniospinal Irradiation: If a patient lives another 60 years, which plans serves her/him best?



Acta Oncologica, 57:9, 1240-1249

Our basis for treating many patients with protons

- Many studies at least equivalent disease control
- Side effects impact patients for decades to come
- Studies show proton therapy associated with:
  - Excellent neurocognitive outcomes (J Neurooncol. 2018 Mar;137(1):119-126, Int J Radiat Oncol Biol Phys. 2018 Oct 1;102(2):391-398)
  - Reduced endocrine problems (Neuro Oncol. 2013 Nov;15(11):1552-9)
  - Decreased risk of secondary malignancies (Int J Radiat Oncol Biol Phys. 2019 Mar 1;103(3):680-685.)
  - High quality of life (J Neurooncol. 2018 Mar;137(1):119-126)
  - Cost effective (Cancer. 2015 May 15;121(10):1694-702, Cancer. 2013 Dec 15;119(24):4299-307)

Challenges of Data Generation

- RCT would require parents consenting to their children being randomized to receive photons with much higher doses to developing normal tissue with known increased risks and side effects
- Benefits of treating with protons in pediatric tumors, including neurocognitive and secondary malignancies, will take decades to manifest
- Children's Oncology Group (COG)—the largest pediatric oncology cooperative research organization– allows for physician discretion rather than randomization of radiation modality on most protocols.
  - Likely will have later subset analysis
- We participate in most COG trials and offer our patients enrollment on two registry studies (including a national proton registry trial)

Proton Coverage for Pediatric Patients is the Standard in the Northwest

- Most insurers—private and public--cover protons.
  - Only a handful of insurance denials among hundreds of referred pediatric patients; all but one overturned
  - Oregon public insurance provides coverage for pediatric patients
  - Kaiser California and British Columbia Cancer Agency
  - Other states referring to our center include Alaska, Hawaii, Idaho, Montana, and Utah
  - Evicore has recently updated is coverage to include all patients receiving craniospinal irradiation and all pediatric malignancies
  - *It would be remarkable if Washington were the exception.*

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Charles Bloch, PhD, DABMP, DABR, FAAPM

Associate Professor, Department of Radiation Oncology, University of Washington School of Medicine

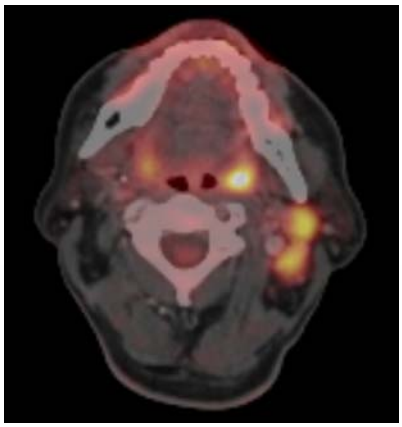
Associate Director of Medical Physics, Seattle Proton Therapy Center

Conflict of Interest Disclosure

- University of Washington Employee
- Physicist at the SCCA Proton Therapy Center

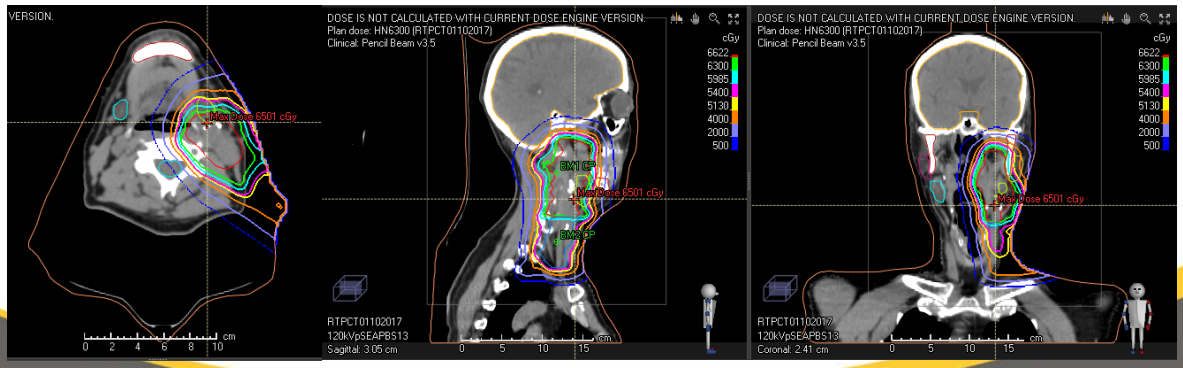
About Me

- Medical Physicist with 25+ years of experience with proton therapy
- UW Employee providing clinical support at the SCCA Proton Therapy Center
- Head & Neck Cancer Patient
  - Surgery in Dec. 2016
  - Proton radiation therapy January – March 2017
  - Cancer free for 2+ years



Why Proton Therapy was the Superior Modality for Me

- Unilateral disease – left tonsil primary, positive lymph nodes in left neck
- Salivary Gland preservation – important for dental health (poor dental health associated with heart disease), speech, eating.



Coverage Denied

- HCA decided not to cover protons for my type of cancer
  - UW to everyone: We provide the best treatment options anywhere
  - UW to employees: Except for you

- Recommendations in the final report continue to discount the benefits of proton therapy, including improved **quality of life**, and reductions in costs from potential side effects.

My Outcome after Proton Therapy

- Reduced risk of secondary cancers
- Reduced risk of side effects and associated health costs
  - No PEG feeding tube required
  - Preservation of salivary function
  - Reduced risk of swallowing dysfunction
  - Reduced risk of aspiration pneumonia
- Continued working during first 3 weeks of RT
- Returned to work full time 2 weeks after completion of RT

My Outcome after Proton Therapy

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Fred Hutch · Seattle Children's · UW Medicine
Proton Therapy Center

Jing Zeng, MD

Associate Professor, Department of Radiation Oncology, University of Washington School of Medicine

Associate Medical Director, Seattle Proton Therapy Center

Conflict of Interest Disclosure

- Associate Medical Director of the SCCA Proton Center
  - No direct salary

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United Healthcare	✓	✓	✗	✓		✗	✗	✓	✓	✓	✗	✓
Medicare Plans	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
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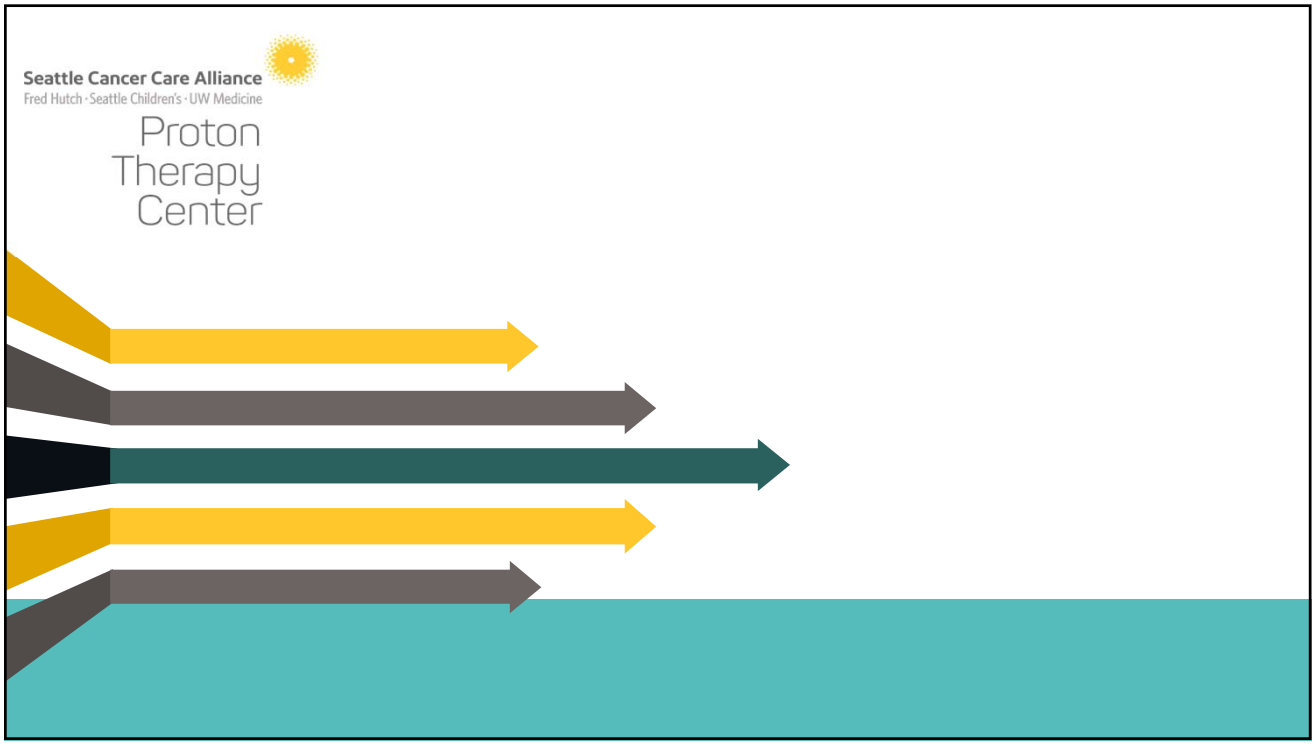
Evicore	✓	✓	✓	✓	✗	✗	✗	✓	✓	✗	✗	✓

✓ Covered ✓ Covered with Conditions ✗ Not Covered

- The evidence report would suggest a proton beam therapy coverage policy in Washington State that would be among the most restrictive in the country.
- Everywhere else in the country has been increasing coverage for proton therapy, Washington State is taking steps backwards from 2014 to now

Our Recommendations

- Proton therapy coverage should include:
  - All patients enrolled in a trial or registry
    - Consistent with HCA policy for IMRT Coverage
  - Ocular melanoma
  - Brain/spinal
  - All pediatric patients
  - Reirradiation
  - Tumors in close proximity to organs at risk such as head and neck cancers, left sided breast cancer and some lymphomas



Proton Beam Therapy: Re-Review

Presentation to

Washington State Health Care Authority

Health Technology Clinical Committee

Andrea C. Skelly, PhD, MPH
May 17, 2019

Report prepared by:
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Shelby Kantner, BA
Naomi Schwartz, BA, MPH
Aaron Ferguson, BA

1

Update of 2014 Report

- **2014 Report**: Systematic review and budget impact analysis
- **Rationale:** Newly available published evidence
- **Objective**: Update the 2014 HTA on proton beam therapy (PBT) by systematically reviewing, critically appraising and analyzing new research evidence on the safety and efficacy of PBT, both as a primary or as a salvage therapy (i.e., for recurrent disease or failure of initial therapy), for the treatment of multiple types of cancer as well as selected noncancerous conditions in adults and children.
- **Consistent with the 2014 report, comparative studies are the focus of the update.**

2

Background: Cancer

- It's estimated that 1.7 million new cases of cancer are diagnosed yearly and cancerous conditions are responsible for over half a million deaths per year. There are > 100 cancer types.
- The National Cancer Institute projects the total cost of cancer care in the United States in 2020 to be $174 billion.
- Tumors that respond well to radiation therapy are referred to radiosensitive tumors; radiation therapy may be curative for the following (but not limited to these):
  - prostate cancers
  - head and neck cancers
  - non-small cell lung cancer

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Background: Radiation Therapy (RT)

~50% of all cancer patients benefit from RT in the management of their disease; it may be the sole therapy used

RT may be used for a variety of reasons

- cure a radiosensitive tumor
- shrink a tumor pre-operatively
- prevent recurrence or spread postoperatively (adjuvant treatment)
- treat a recurrent tumor or as a palliative treatment

Most common forms of RT are external beam radiation therapy (EBRT) and brachytherapy (internal radiation therapy)

- **EBRT:** Radiation is delivered externally using a machine to aim high-energy beams directly at the tumor from outside the body
- **Brachytherapy:** Radiation is delivered internally; small seeds of radioactive material are directly placed into or very close to the tumor

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Background: Radiation Therapy (RT) Planning

- **Goal:** damage cancer cells while minimizing damage to surrounding healthy cells including sensitive structures and organs at risk (OARs)
- Two-dimensional Radiation Therapy (**2DRT**)/Conventional Radiation Therapy (**CRT**)
  - Utilizes X-ray technology used to take two-dimensional scans of the tumor location
- Three-dimensional Conformal Radiation Therapy (**3DCRT**)
  - Utilizes computer-based three-dimensional imaging (CT, MRI) to more accurately map the location and size of the tumor in three dimensions, as well as identify any critical organs at risk (OAR; RT beams are matched very precisely to the shape of the tumor and delivered from all directions.

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Background: Radiation Therapy (RT) Delivery

- **Classification** of EBRT may be by the type of beam or particle used (i.e. electron, photon or proton) with photon RT being the most widely available and commonly used.
- **Intensity Modulated Radiation Therapy** (**IMRT**): beam intensity can be altered to lessen intensity near OARS, deliver high dose to tumor volume; may be done with photons or protons
- **Stereotactic Radiosurgery (SRS)/Stereotactic Body Radiation Therapy (SBRT)**: may deliver photons, protons, gamma rays in fewer fractions at a much higher dose vs. IMRT; brain/spine most common use; rigid immobilization required due to smaller planning target volumes
- **Delivery techniques specific to PBT**
  - passive scattering
  - uniform scanning
  - pencil beam scanning (PBS)

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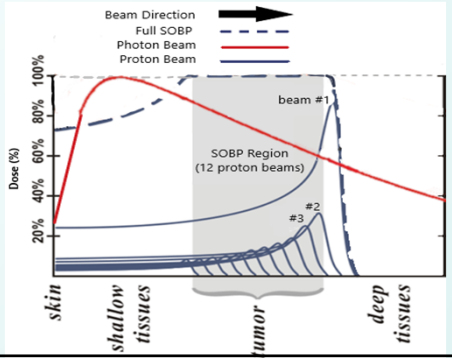
Background: Physical Properties of Radiation Particles

- **Photons:** neutrally charged, light; characterized by a high deposit of energy near to the body surface with an exponential decrease of energy release as a function of depth ("**exit dose**"). Healthy tissue downstream from the tumor could be at an increased risk of exposure to unnecessary radiation.
- **Protons:** heavy positively charged particles; PBT deposits peak radiation energy more precisely at or around the target followed by sharp decline in energy output to deeper tissues via a phenomenon known as the **Bragg peak**. A greater dose of radiation may be delivered to the target neoplasm(s) while mitigating unwanted radiation delivered to surrounding tissue.

Figure adapted from Levin, et. al. Br J Cancer. 2005;93(8):849-854 and 2014 report



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Background: Radiation Therapy (RT) Delivery

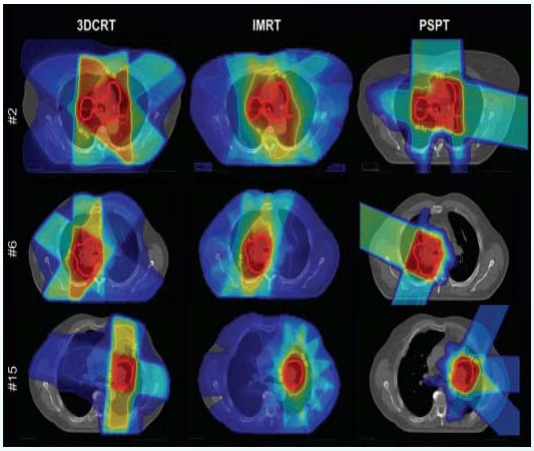

Image from Roelofs, Erik, et al. *Journal of Thoracic Oncology* 7.1 (2012): 165-176.

Comparison of dose distributions of three-dimensional conformal photon radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and passive scattered conformal proton therapy (PSPT) treatment plans

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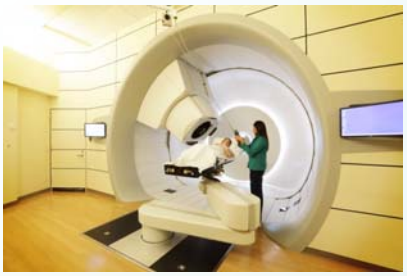
Background: Radiation Therapy (RT) Delivery



- **Proton Beam Therapy** treatment room (gantry) at the Seattle Cancer Care Alliance Proton Therapy Center
- Protons are delivered using a cyclotron

- **Photon RT treatment** room (gantry) at Beacon Hospital for delivering CRT, IMRT, and 3DCRT (photons)
- Photons are delivered using a Linear Accelerator (LINAC)

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Background: Harms of Radiation Therapy (RT)

- Side effects of RT occur when healthy tissues in the path of the radiation beam are damaged
- Effects vary from person to person depending on a variety of factors:
  - location of the tumor/field of radiation
  - type of RT/method of delivery
  - timing of treatment
  - dose per fraction and total dose
  - a person's overall health
  - patient age, developmental stage

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10

Background: Additional Considerations

- Assumption that the biological effects of protons are equivalent to that of photons, challenged by recent studies that suggest there is less certainty
- There is more uncertainty around the end of the dose range when deep-seated tumors are considered
- The effects of neutrons, which are produced by passively-scattered proton beams, result in additional radiation dose to the patient and their effects on the patient are less known

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Key Questions

1. What is the **comparative impact of PBT treatment with curative intent** on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options?
2. What is the **comparative impact of salvage treatment** (including treatment for recurrent disease) with PBT versus major alternatives on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options?
3. What are the **comparative harms associated with the use of PBT relative to its major alternatives,** including acute (i.e., within the first 90 days after treatment) and late (>90 days) toxicities, systemic effects such as fatigue and erythema, toxicities specific to each cancer type (e.g., bladder/bowel incontinence in prostate cancer, pneumonitis in lung or breast cancer), risks of secondary malignancy, and radiation dose?
4. What is the **differential effectiveness** and safety of PBT according to factors such as age, sex, race/ethnicity, disability, presence of comorbidities, tumor characteristics (e.g., tumor volume and location, proliferative status, genetic variation) and treatment protocol (e.g., dose, duration, timing of intervention, use of concomitant therapy)?
5. What is the **comparative cost-effectiveness of PBT** in the short- and long-term relative to other types of radiation therapy, radiation therapy alternatives or other cancer-specific treatment options (e.g., surgery, chemotherapy)?

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PICO Scope: Inclusion Criteria

- **Population**: Persons undergoing cancer treatment for primary or recurrent disease, to include:
  - bone cancer, brain, spinal, and paraspinal tumors, breast cancer, esophageal cancer, gastrointestinal cancer, gynecologic cancer, head and neck cancer, liver cancer, lung cancer, lymphomas, ocular tumors, pediatric cancers, prostate cancer, sarcomas, seminoma, thymoma, other cancers, and noncancerous conditions (arteriovenous malformations, hemangiomas, other benign tumors)
- **Interventions:** Proton Beam Therapy
- **Comparators**: Other radiation alternatives (e.g., intensity-modulated radiation therapy (IMRT), stereotactic radiation techniques and other external beam therapies, and brachytherapy). Other treatment alternatives specific to each condition type treated, and may include chemotherapy, immunotherapy, surgical procedures, and other devices (e.g., laser therapy for ocular tumors)
- **Primary Outcomes (SOE):** Improvement in OS, PFS, or LC; adverse events directly attributable to PBT; cost-effectiveness outcomes (QALY, ICER)

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PICO Scope: Inclusion Criteria

Study Design:

- KQ1-4: **focus on high quality (low risk of bias) comparative studies (e.g., RCT, comparative observational studies**); case series were considered but were not the primary focus of evaluation
- KQ3: studies reporting direct PBT harms
- KQ5: full formal economic analyses

Publication: Full-length studies published in English in peer-reviewed journals; studies published subsequent to the 2014 report. (EXLUDED – meeting abstracts, white papers, editorials, letters; model policies were not within report scope)

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Threats to internal validity: Bias and Confounding

Selection bias	• Control selection • Loss to follow-up • Confounding by indication (treatment allocation) • Self-selection, differential referral
Attrition bias	• Loss to f/u, differential f/u, exclusions • Handling of missing data
Performance bias	• Concurrent interventions equal • Measurement of potential confounders • Protocol adherence
Detection bias	• Comparable length of f/u in each group • Blinded assessment • Validated, reliable measurement • Consistent measurement of groups
Reporting bias	• Reporting of specified outcomes
Confounding	• Baseline characteristics (measured and unmeasured)

➢ ***All may impact observation of an effect or lack of effect. Many are difficult to control in retrospective comparative cohort studies.***

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Individual Studies: Risk of Bias

Criteria

- Random sequence generation (RCT)
- Statement of allocation concealment (RCT)
- Intent-to-treat analysis (RCT)

RCTs and observational studies *

- Blind, independent assessment of outcomes/analysis
- **Complete follow-up of >80%**
- **<10% difference in follow-up between groups**
- **Controlling for possible confounding**
  - Multivariate analysis, matching (including propensity)

*case series are considered at high risk of bias

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Strength of Evidence (SOE) Criteria – Appendices D, E

Overall *body of evidence* for primary outcomes:

- **Risk of bias (one criterion)**: the extent to which majority of included studies protect against bias
- **Consistency:** degree to which estimates are similar in terms of range and variability.
- **Directness:** evidence directly related to patient health outcomes.
- **Precision**: level of certainty surrounding the effect estimates.
- **Publication/reporting bias:** selective reporting or publishing.

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SOE –Application of criteria (see report methods)

- RCT evidence initially considered "High"; Observational evidence is initially considered "Low".
- Where RCTs are unavailable, unethical or not feasible, ***high quality*** nonrandomized observational studies (NROS) may provide "best evidence";
  - **The quality of nonrandomized studies is not elevated** (bias may still be present). Decision makers need to accept and consider the greater uncertainty of such evidence; one should not have greater confidence in the effect estimates from such studies;
  - NROS with **few** methods limitations, **which control for bias** may be initially considered "Moderate" vs. "Low" when such studies may be at lower risk of bias due to confounding;
  - Ideally, studies which controlled for confounding with ≥ 80% follow-up and ≤10% difference in follow-up between treatments.

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Systematic Review Process

Studies meeting eligibility criteria
Efficacy: RCTs; Effectiveness: Observational studies
Harms: RCTs, Observational studies
Full Economic studies

Risk of Bias Appraisal (Study)
Low, Moderately Low,
Moderately High, High
Synthesis/Analysis

Overall Strength of Evidence Determination (GRADE/AHRQ)
Across **comparative studies** reporting primary outcomes

Strength of Evidence Ratings	
High	Very confident that effect is true.
Moderate	Moderately confident.
Low	Limited confidence.
Insufficient	No evidence or no confidence in effect.

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Reconciliation with 2014 report, net health benefit

General considerations: Evidence quality, comparators, whether new evidence was a major change in the evidence base or substantial changes in effect size or statistical significance beyond "borderline", evidence of substantial harm

Net health benefit-considers clinical benefit and potential harms vs. comparators (based on ICER 2014 report methods);

- **Superior**: moderate-to-large net health benefit vs. comparator(s)
  E.g. ↑effectiveness (mod to large), ↓ in harms
- **Incremental:** a small net health benefit vs. comparators(s)
  E.g. small ↑ effectiveness, no difference in harms; or no difference in effectiveness, small ↓ in harms
- **Comparable:** while there may be tradeoffs in effectiveness or harms, overall net health benefit is comparable vs. comparator(s)
- **Inferior:** a negative net health benefit vs. comparator(s)
- **Insufficient:** Evidence is insufficient to determine the presence and magnitude of a potential net health benefit vs. comparators(s)

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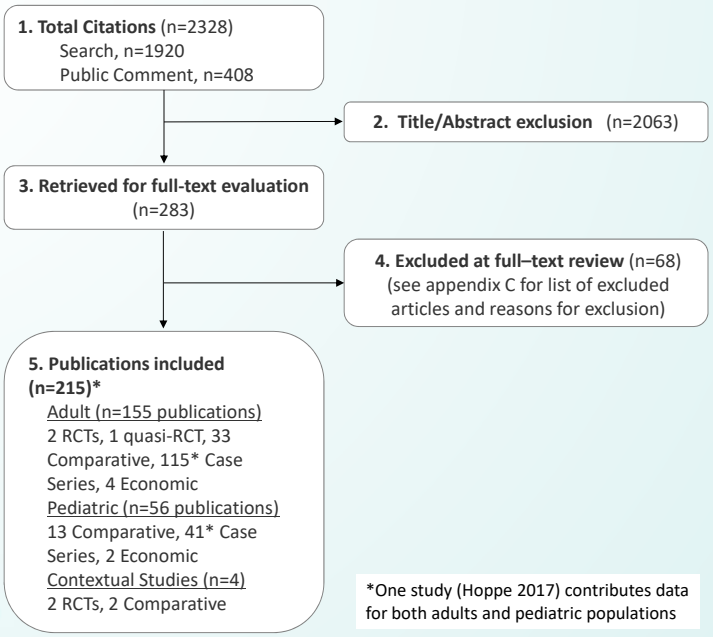
Literature Search Results



*One study (Hoppe 2017) contributes data for both adults and pediatric populations

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Overview of Evidence Base

2014 Report: 2 RCTs; 38 comparative (most retrospective; indirect non-contemporaneous case series); 245 case series; 13 economic; 4 contextual

2019 Report: 2 RCTs, 1-quasi RCT; 49 comparative (47 retrospective); 156 case series; 6 cost-effectiveness; 4 contextual

Retrospective comparative study limitations which may impact results:

- treatment groups based on historical changes in RT methods; differential length of follow-up
- Potential for treatment selection bias/confounding by indication
- Completeness of F/U and loss to F/U poorly reported or could not be determined
- Differences in baseline characteristics in most studies; potential for residual confounding

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Organization of Results

Results for comparative studies reported by tumor category/location

KQ 1. Comparative impact, PBT with curative intent

KQ 2. Comparative impact, PBT for salvage, recurrent disease

KQ 3. Comparative harms and safety

KQ 4. Differential effectiveness or safety (no studies identified)

KQ 5. Comparative cost-effectiveness (where available)

Pediatric Tumors

- Comparative studies KQ1-5*
- Overview comparing 2014 and 2018 report

Adult Tumors

- Comparative studies KQ1-5*
- Overview comparing 2014 and 2019 report

*Summaries of cases series data are found Appendix F, page 26

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Evidence Base: Pediatric Tumors

2014 report: Did not report by tumor location; included 1 poor quality comparative cohort and 41 case series

2019 update: New studies (since 2014 report) by tumor type

Tumor	Comparative, # studies (# publications)	Case series* # publications
Bone	0	1
Brain	8 studies (6 retrospective, 2 prospective); (11 publications) 2 Economic	25
Head and neck	1 retrospective (Safety)	3
Lymphoma	0	2
Ocular	1 retrospective (Salvage)	2
Soft-tissue (sarcoma)	0	6
Various/mixed	0	2

Studies: Bulk of the new evidence is in pediatric brain tumors; all comparative studies at moderately high ROB, 2 were prospective; case series considered to be high ROB

Analytics

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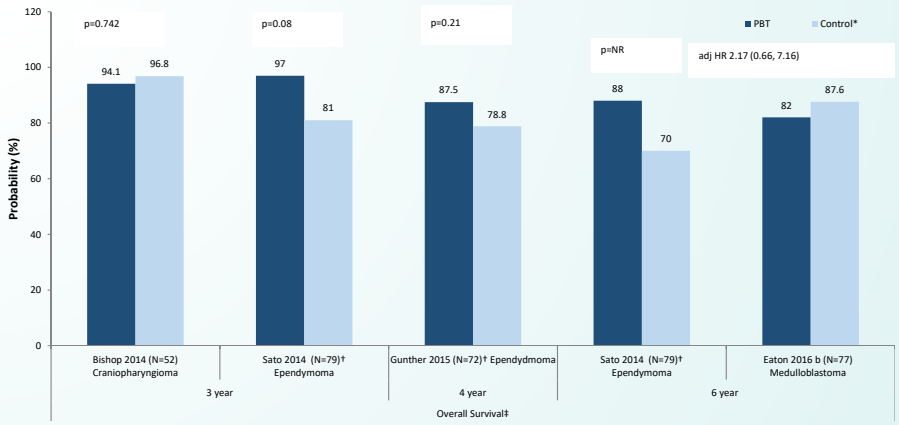
KQ 1 (Curative Intent): Pediatric Brain Tumors, Overall Survival



OS: Compared with IMRT or 3DRT, no statistical differences at any time across 3 retrospective and 1 prospective study; some differences may be clinically important. (SOE Low)

Additional retrospective study: HR 0.99 (95% CI 0 .41 to 2.4) for PBT vs. CRT (SOE Low)

Case series: Appendix F

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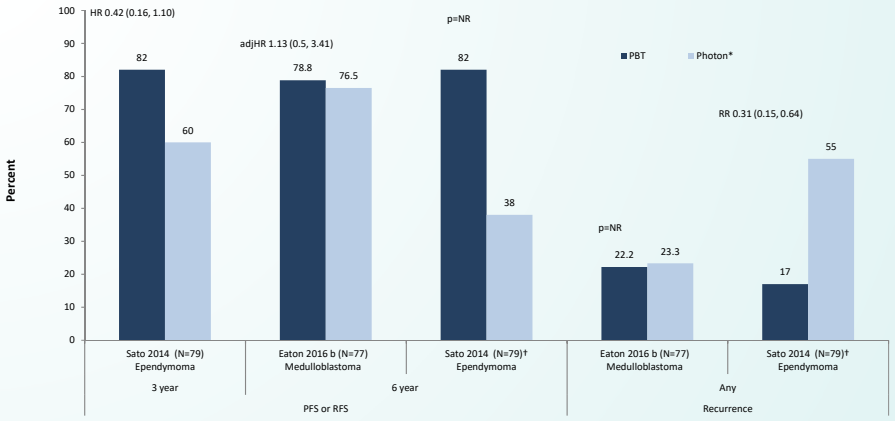
KQ 1 (curative intent): Pediatric Brain Tumors; PFS, Recurrence



PFS: Versus IMRT or 3DRT, PBT tended to have better PFS; NS for ependymoma at 3 years, NR at 6 year; NS for medulloblastoma. (SOE Low)

Sato: Lower recurrence with PBT; Disease-related mortality PBT (4.9%) versus IMRT (31.6%) (SOE Low)

Case series: Summaries in Appendix F Tables

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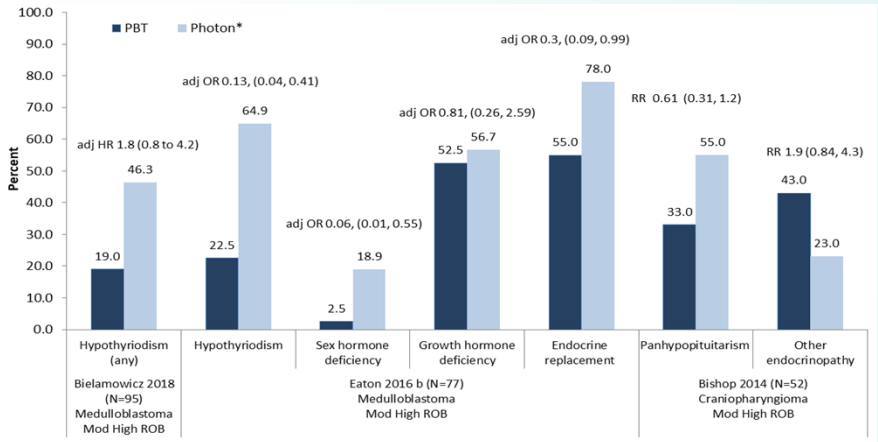
KQ 3: Pediatric Brain Tumors; Safety – Endocrine-related



Endocrine-related toxicities: Tended to be less common with PBT vs. 3DRT or IMRT; statistical significance not uniformly reached; all patients in Eaton and Bielamowicz had chemotherapy; (SOE Low)

Roles of sample size, selection bias and potential for residual confounding are not clear. Eaton prospectively enrolled PBT group; others are retrospective studies.

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KQ 3: Pediatric Brain Tumors; Safety – Endocrine-related CASE SERIES

Author/Year	Toxicity	% (n/N) or % (95% CI)
Indelicato 2018	Late Grade ≥2 Hormone Deficiency	7.3% (13/179)*
MacDonald 2013	Hypothyroidism (Grade NR)	3.2% (1/32)
	Growth Hormone Deficiency	8% (2/25)
Yock 2016	Cumulative Incidence, Any Hormone Deficiency†	
	3-year	27% (16% to 39%)
	5-year	55% (41% to 67%)
	7-year	63% (48% to 75%)
Greenberger 2014	K-M 10 year Rate, Any Endocrine Deficiency	50% (95% CI NR) ‡

*33% of patients had pre-radiation chemotherapy. Growth Hormone Deficiency most common 11/13.

†52/59 patients had concurrent chemotherapy; 6 patients had photon RT for part of treatment. growth hormone deficiency was most common followed by thyroid deficiency.

‡Assessed in all patients with intracranial tumors (n=29). Data estimated from figure; driven by high % of growth hormone deficiency and hypothyroidism.

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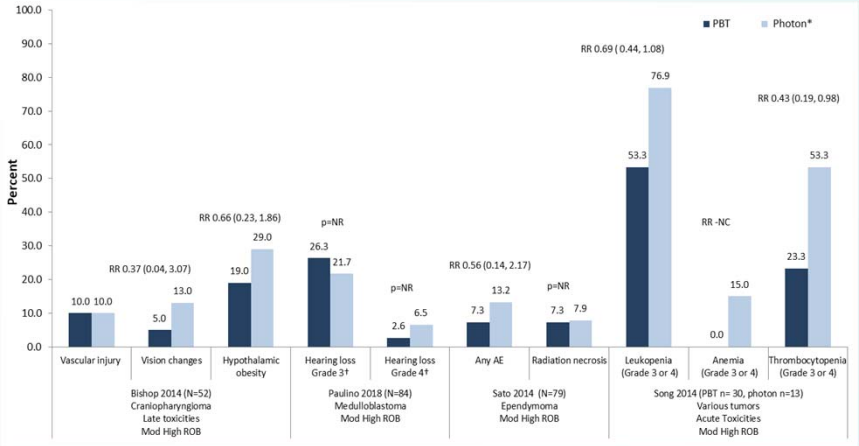
KQ 3: Pediatric Brain Tumors; Safety – Other Toxicities



Other toxicities (acute and late): Tended to be similar or less common with PBT vs. 3DRT or IMRT; statistical significance not uniformly reached; all studies were retrospective (SOE Low); Note: Song 2014 PBT n = 30, photon n =13

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KQ 3: Pediatric Brain Tumors; Specific toxicities CASE SERIES with >100 patients

Toxicity	Studies	%n/N or Range
White matter lesion	Bojaxhiu 2018	Any grade: 11% (11/171) Grade 3: 0.6% (1/171)
Radiation Necrosis (early or late)	Bojaxhiu 2018	Any grade: 17% (29/171) Grade 4: 0.6% (1/171) Grade 5: 1.2% (2/171)
Radiation injury to CNS or brainstem	Gentile 2018, Indelicato 2014,2018 Giantsoudi 2016	Grade 3: 0.6% (3/516) to 1.8% (2/111) Grade 4: 0.2% (1/516) to 0.9% (1/111) Grade 5 (Death): 0.3 (1/131)to 0.6% (1/313)
Vasculopathy	Indelicato 2017 Indelicato 2018 Hall 2018	Grade NR: 1.8% (3/166) Grade 2+: 3.4% (6/179) 3 yr cumulative, serious: 2.6% (CI NR)
Vascular Injury	Hall 2018	Stroke w/permanent deficit: 1.2% (7/644)
Hearing loss	Indelicato 2018	Grade ≥2 (hearing aid): 6.1% (11/179)*

Tables in Appendix F, Tables 60-68

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KQ 3: Pediatric Brain Tumors; Safety – Neurocognitive

Change per year in IQ scores	Kahalley 2016 (N=150) Various brain tumors; Retro cohort 32.4 vs. 64.8 months	Consistency Unknown Serious Imprecision Yes[3] (-1)	**PBT vs. Photon RT** FSIQ (adjusted β coefficient, 95%CI) **All patients** -0.7 (-1.6 to 0.2) vs. -1.1 (-1.8 to -0.4); p=0.51 **CSI:** - 0.8 vs. -0.9 (CIs NR); p=0.89 **Focal RT:** 0.6 (-2.0 to 0.8) vs. -1.6 (-3.0 to -0.2); p=0.34	**NS difference PBT and photon RT** ⊕⊕ **LOW**
	Kahalley 2019 (N=93) Various brain tumors Prospective, ongoing cohort 33.6 to 37.2 months	Consistency Unknown Serious Imprecision Yes[3] (-1)	**Focal PBT vs. surgery** NS differences FSIQ , any subscale; scores remained stable for both groups over time. **CSI PBT vs. surgery** (adjusted β coefficient, 95%CI) FSIQ: -2.1 (-3.8 to -0.3), p = 0.020 PSI; -2.6 (-4.7 to -0.3), p = 0.019. NS differences for all other subscales (all p-values >0.05)	**NS for focal PBT vs. surgery;** **CSI PBT associated decline in FSIQ and PSI vs. surgery; clinical significance is not described.** ⊕⊕◯◯ **LOW**

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KQ 5: Pediatric Brain Tumors; Cost-effectiveness

	Hirano 2014 (Japan); QHES: 50 (poor quality)
Population; Interventions	6 year olds with medulloblastoma PBT (following chemotherapy) vs. CRT
ICER	Depends on utility: EQ-5D: $21,716/QALY, HU13: $11,773/QALY SF-6D: $20,150/QALY
Author's Conclusion	**At threshold of $46,729/QALY (JPY 5 million/QALY), PBT is more cost-effective than conventional X-ray therapy**
Limitations	• **Inadequate description of PBT costs; incomplete delineation of operational costs** • **Clinical outcomes data are from case series** • **Radiation doses derived from small series (8 patients)** • **Limited outcomes considered: no long-term outcomes related to motor/physical or intellectual challenges or long-term health challenges or costs** • **Utilities based on hearing aid use, not specific to post-radiation population of children** • **Utilities derived from western countries and adult populations; may not be applicable to this study population; ICER varies by utility used** • **May not be applicable to US**

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KQ 5: Pediatric Brain Tumors; Cost-effectiveness

	Mailhot Vega 2015 (USA), QHES: 48/100 (poor quality)
Population	Pediatric patients with CNS tumors; hypothetical cohorts exposed at age 4 or 12 PBT (timing, use as sole therapy unclear) vs. CRT
ICER	ICERs ranged based on proton-photon dose combinations; many, particularly at lower doses of PBT, were cost-effective or cost-saving at a WTP of $50K/QALY. PBT was not cost-effective at the highest PBT dose (30 Gray [Gy]) vs. photon RT
Author's Conclusion	**PBT may be more cost effective when radiation dose to the hypothalamus can be spared, but PBT may not be cost effective when tumors involve or are directly adjacent to the hypothalamus and radiation dose is high**
Limitations	• **Limited parameters in model; no long-term toxic effects (e.g. auditory, cognitive) other than GHD; parameters, assumptions not transparently described;** • **Data from case-series; no long term comparative data to validate assumption of no difference in treatments or lifetime horizon** • **Basis of PBT including operational costs not detailed; no detailed costing** • **Sensitivity analyses were limited** • **Utilities from adult study; assumes costs of therapy for adults and children are similar**

Pediatric Tumors: Head/neck

KQ 1, 2, 4, 5: No comparative evidence identified

KQ3. Safety, toxicities

Outcome	Studies, Year, N, Tumor	Reason for Downgrade	PBT vs. other RT* Effect estimate (95% CI)	Conclusion Quality (SoE)
Acute Toxicity	Grant (N=24) 1 Retro cohort (N=24) salivary gland tumors (rare)	Serious ROB Yes[1] (-1) Consistency Unknown Imprecision Yes[3] (-1)	**<u>adjuvant PBT vs. adjuvant photon RT</u>** Grade 2/3 toxicities: Dysphagia (0 vs. 3/11); Otitis externa (1/13 vs. 2/11); Mucositis (6/13 vs. 10/11, RR 0.51 (0.27, 0.94)	Mucositis less common following adjuvant PBT; other toxicities were similar between groups. ⊕◯◯◯ **INSUFFICIENT**

* PBT (passive scatter n=8, intensity modulated n=5) vs. other RT (electron beam n=8, IMRT n=3)

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Pediatric Tumors: Ocular, KQ 2 (Salvage), 3 (Safety)

KQ 1, 4, 5: No comparative evidence identified

Outcome	Studies, Year, N, Tumor	Reason for Downgrade	PBT vs. other RT * Effect estimate (95% CI)	Conclusion Quality (SoE)
Enucleation	Agarwal 2016 (N=39 patients, 47 eyes) Retinoblastoma Retrospective cohort	Serious ROB Yes[1] (-1) Consistency Unknown Imprecision Yes[3] (-2)	OS: 97.4% across groups Enucleation-free survival: 38.5% vs. 54.5% Enucleation performed: 37.5% (6/16 eyes) vs. 29.6% (8/27 eyes)	Enucleation-free survival was lower with PBT (small sample size) ⊕◯◯◯ **INSUFFICIENT**
Toxicity			**PBT vs. ERT** **Acute Toxicity:** PBT 93.8% vs. ERT 74.1%; p =0.22 (mostly skin erythema) **Late/long-term** (# eyes): ≥1 event: 62.5% (10/16 eyes) vs. 55.6% (15/27 eyes); p=0.275 **PBT vs. Other Tx*** Cataract: 5 vs. 10 Vitreous hemorrhage: 3 vs. 4 Radiation retinopathy: 2 vs. 3 Visual acuity Δ: 0 vs. 4 Strabismus: 1 vs. 2	Although acute toxicities were more common with PBT vs. ERT, differences were not statistically significant. Evidence is limited. ⊕◯◯◯ **INSUFFICIENT**

* PBT (passive scatter, n=16 eyes) vs. photon or electron RT (n=27 eyes) or brachytherapy (n=4 eyes).

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Pediatric Tumors- Summary

Condition	Incidence per 100,000	Numbers of Studies (2019 are NEW)		Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE		Impact of new comparative studies
		2014	2019	2014	2019	2014 vs. 2019
All Cancer Types	18.3	CC=1; CS=41; Econ=3	**CC=10**; CS=41	**Incremental B: = H: ↓ Low****	**See below**	**See below**
Brain	3.1	---	**CC=8**; CS=25 Econ = 2	**N/A**	**Incremental B: = H: ↓ Low**	**New: 6 retrospective, 2 prospective suggest incremental net benefit of PBT; low quality economic**
Bone	0.9	---	CS=1	N/A	Insufficient	N/A
Head/Neck	NR‡	---	**CC= 1;** CS=3	N/A	**Insufficient**	N/A
Ocular (salvage)	0.4	---	**CC=1;** CS=2	N/A	**Insufficient**	N/A
Lymphoma	2.4	---	CS=2	N/A	Insufficient	N/A
Rhabdomyosarcoma	NR	---	CS=6	N/A	Insufficient	N/A
Mixed/Various	NR	---	CS=1	N/A	Insufficient	N/A

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SUMMARY of 2019 findings: Pediatric

Incremental Net Health Benefit of PBT vs. other tx (mostly photon): brain tumors based on 6 retrospective, 2 prospective cohorts

No comparative evidence identified: (Summary in Appendix F)
- Bone, Lymphoma, soft tissue (rhabdomyosarcoma)
- Various/mixed

No evidence met inclusion criteria for other pediatric conditions

Insufficient evidence to determine comparative net health benefit
- head/neck (salivary gland tumors),
- Salvage treatment for ocular tumors (retinoblastoma)

Economic: 2 poor quality CUA; Conclusions regarding CE are challenging given data sources used (case series, utilities from other populations), model limitations (parameters, time horizon) and limited sensitivity analyses

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SUMMARY: Pediatric

- **2014 vs. 2019**: 10 new comparative studies, (8 retrospective); 8 in patients w/ brain tumors vs. 1 poor quality comparative study was included in 2014; 2014 report did not separate out pediatric tumor types
- **Pediatric brain tumors**:
  - Low SOE suggests incremental comparative net health benefit of PBT (benefits comparable, harms lower)
- **Other pediatric tumors**: comparative evidence for head/neck and ocular tumors and case series for other tumor categories was considered insufficient
- **KQ4:** no evidence identified

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Adult tumors

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Evidence Base Overview –New Studies, Adult Tumors

Tumor	Comparative*			Case series*		
	Total	Curative	Salvage	Total	Curative	Salvage
Bladder	0	0	0	1	1	0
Bone	0	0	0	8	8	0
Brain	5	3	2	6*	5*	1
Breast	2, 1 Econ	2	0	4	4	0
Esophageal	5	5	0	2	2	0
GI (Pancreas)	1	1	0	2	2	0
Head and neck	8, 1 Econ	8	0	23	18	5
Liver	2 (1 RCT), 1 Econ	2 (1 RCT)	0	12	8	4
Lung	7 (1 RCT)†	6 (1 RCT)†	1	12	11	1
Lymphoma	0	0	0	3	3	0
Ocular	3, 1 Econ	3	0	22	21	1
Prostate	4 (1 quasi-RCT)	4 (1 quasi-RCT)	0	11 (12 pub)	11 (12 pub)	0
Hemangiomas (benign)	0	0	0	2	2	0
Other benign tumors†	0	0	0	4*	3*	1
Various/mixed	0	0	0	3	3	0
TOTAL	37†, 4 Econ	34†	3	114 (115 pub)*	101 (102 pub)*	13

Adult tumors results

- Focus on new comparative studies reporting primary outcomes (OS, PFS)
  - 34 curative intent, 3 salvage
  - All but 3 studies (2 RCTs, 1 quasi- RCT) were retrospective cohorts which were at moderately high risk of bias
  - Not all studies reported on primary outcomes
- Results presented alphabetically by tumor type/location for comparative studies

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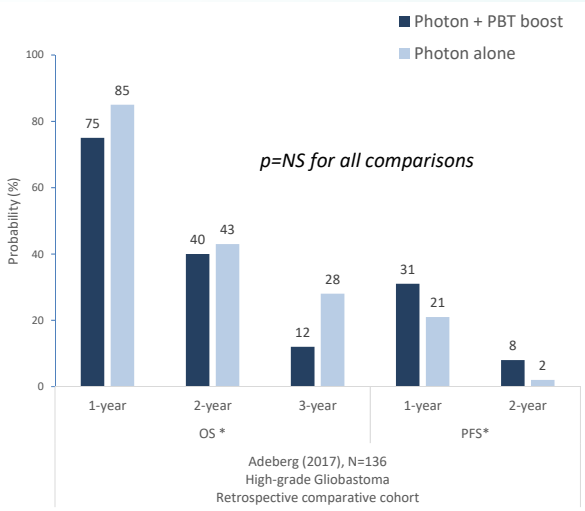
KQ 1 (Curative Intent): Adult brain tumors

Overall (OS) and Progression-Free Survival (PFS)

Glioblastoma



Glioma

Probability of 5-year OS PBT vs. any photon Jhaveri 2018 (Retrospective, NCDB study)	
Entire cohort (N=49,575)	Propensity score-matched (n=322)
adj. HR 0.66, 95% CI (0.53 to 0.83); favors PBT	46.1% vs. 35.5%, p=0.009

SOE Low for all

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KQ 2 (Salvage Therapy): Adult brain tumors

Outcome	Studies, Year, N, Tumor	Reason for Downgrade	PBT (passive scatter) vs. Photon Effect estimate (95% CI)	Conclusion Quality (SoE)
Probability, overall survival	Gunther 2017 (N=37) Retro cohort CNS involvement in lymphoma or leukemia (pre-SCT)	Serious ROB Yes[1] (-1) Consistency Unknown Serious Imprecision Yes[3] (-1)	**OS** 6 mos.: 78.6% vs. 69.6%, p=0.15 1 year: 70% vs. 38%, p=NR	No statistical difference between groups in OS at 6 months, statistical testing not reported at 1 year; no statistical difference in CNS relapse risk. Sample size may have played a role in these findings. ⊕◯◯◯ INSUFFICIENT
CNS relapse			7% (1/14) vs. 0% (0/23); p=1.0	

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KQ 3 (Safety): Adult brain tumors

Outcome	Studies, Year, N, Tumor	Reason for Downgrading	PBT boost + photon vs. Photon alone Effect estimate (95% CI)	Conclusion Quality (SoE)
Acute Toxicity (≤3 mos.)	Adeberg 2017 (N=132) Retro case-matched cohort Primary Glioblastoma (high-grade) *Curative Intent*	Consistency Unknown Serious Imprecision Yes[3] (-1)	**Grade ≥2**: 9% (6/66) vs. 14% (9/66), p=NR **Grade 3**: 0% (0/66) vs. 7.5% (5/66), p<0.1	NS differences between groups; unclear if some may be clinically important. Sample size may have played a role in these findings. ⊕⊕◯◯ LOW
Radiation necrosis			0% (0/66) vs 0% (0/66)	
Change in symptomology, % (n/N)			Neurocognitive deficits‡‡ **Worse**: 3% (2/66) vs. 6% (4/66) **New:** 9% (6/66) vs. 2% (2/66) Sensorimotor deficits‡‡ **Worse**: 3% (2/66) vs. 5% (3/66) **New:** 11% (7/66) vs. 14% (9/66) Seizures‡‡ **Worse**: 0% (0/66) vs. 0% (0/66) **New:** 2% (1/66) vs. 6% (4/66) p=NS for all	

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KQ 3 (Safety): Adult brain tumors

Outcome	Studies, Year, N, Tumor	Reason for Downgrade	PBT vs. Photon Effect estimate (95% CI)	Conclusion Quality (SoE)
Acute Toxicity (during CSI)	Gunther 2017 (N=37) Retro cohort CNS involvement in lymphoma or leukemia (pre-SCT) *Salvage Therapy*	Serious ROB Yes[1] (-1) Consistency Unknown Serious Imprecision Yes[3] (-1)	• Mucositis, any Grade: 7% (1/14) vs. 44% (10/23); RR 0.16 (0.02 to 1.15)** • Mucositis, **Grade 3**: 7% (1/14) vs. 9% (2/23), p=0.1 • Gastrointestinal (Grade NR): 29% (4/14) vs. 30% (7/23), p=1.0 • CNS (Grade NR): 21% (3/14) vs. 13% (3/23), p=0.65	PBT resulted in a lower frequency of mucositis (any grade); no other differences were seen over acute or late term. Sample size may have played a role in these findings. ⊕◯◯◯ INSUFFICIENT
"Late" Toxicity			Severe CNS neurotoxicity††: 7% (1/14) vs. 0% (0/23), p=NS	

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KQ 3: Adult Brain Tumors; Specific toxicities CASE SERIES

Outcome	# Studies	# With outcome	Total N (range of N's)	Median F/U (months)	% or Range (95%CI)
Acute Grade ≥3	6	29	515 (23-280)	20.1 to 56.9	0% to 17.4%*
Late Grade ≥3	2	14	142 (46 to 96)	42.1 to 56.9	3.1% to 23.9%*
5-yr, Toxicity-free survival (Grade ≥3)	1	N/A	96	56.9	89.1% (82-96%)
% of weight lost	1	≤2%: 30 >2-5%: 15 >5-10%: 4 >10%: 1	50	20.1	≤2%: 60% >2-5%: 30% >5%-10%: 8% >10%: 2%
Radiation Necrosis (Late, grade NR)	1	11	46	42.1	23.9%
Brain Necrosis (Late Grade ≥3)	1	3	96	56.9	3.1%
PBT-related neurotoxicity, Grade ≤2§	1	7	16	56	44%
RT-related Mortality	1	1	96	56.9	1%

Appendix Table F9

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Summary: Adult brain tumors

Condition	Incidence (per 100,000)	Numbers of Studies		Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE		Impact of new studies (retrospective comparative)
		2014	2019	2014	2019	2014 vs.2019
Brain/Spinal	6.5	CC=2; CS=6	CC=5; CS=6	Incremental B: = H: ↓ Low	**PBT vs. photon** Unclear B: ↑ H: NR Low (curative); **PBT boost + photon vs. photon** Comparable B: = H: = Low (curative); Insufficient (salvage)	3 new retrospective cohort studies (2 curative, 1 salvage) of different interventions and tumor types vs. 2014 report. The net health benefit for PBT vs. photon is unclear from 1 large data base study which did not report harms. For PBT boost + photon 1, comparative study lead to different conclusions regarding harms

2014 vs. 2019: Different tumors for curative intent (medulloblastoma, intramedullary glioma vs. high grade glioblastoma, high grade glioma) and **different PBT protocols and comparators** (PBT vs photon, IMRT in 2014, PBT boost vs. photon, PBT vs. photon in 2019) across reports contribute to different conclusions regarding NHB. Studies in the 2019 report were larger (including one large database study which did not report harms). Evidence for PBT vs. photon for CNS metastasis (salvage) was insufficient.

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KQ 1 (Curative Intent): Adult breast cancer, OS

Outcome	Studies, Year, N, Tumor	Reason for Downgrading	PBT vs. Photon/Electron Boost Effect estimate (95% CI)	Conclusion Quality (SoE)
Probability overall survival (OS) **5 Years**	Chowdhary 2019 (N=724,492) Retro comparative database study (NCDB)	Consistency Unknown	91.9% vs. 88.9% (unadjusted probabilities) Adjusted HR† 0.85 (95% CI, 0.68 to 1.07), p=0.12 NS differences is OS were identified during additional stratified analyses	No statistical difference between PBT versus photon/electron boost therapy for the probability of OS at 5 years. ⊕⊕◯◯ LOW

- Study did not report on safety/harms;
- No comparative studies were identified for KQ2 (salvage), 3 (safety), or 4 (differential efficacy/safety)

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KQ 3: Breast Cancer; Toxicities
CASE SERIES

Outcome	Studies	# With outcome	Total N (range of N's)	Median F/U (months)	Range (95%CI)
Acute Grade ≥2	1	62	100	60	62%
Acute Grade ≥3	2	1	128	9.3 to 60	0 - 3.6%
Late Grade ≥2	1	NR	100	60	7 [events]

Limited information available from case series;

Appendix Table F12

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KQ 5, Cost-effectiveness: Adult breast cancer

	Mailhot Vega 2016 (USA), QHES 73/100;
Population	Women with breast cancer aged 40, 50, or 60; with or without CRFs (Hypothetical cohorts)
Interventions	PBT (timing, intent unclear) vs. Photon
ICER	• Varied by dose, ± cardiac risk factors, age; Range for 50 year old women, no CRF $890,000/QALY (lowest doses) to $90,000/QALY (highest doses); with ≥1 CRF, $90,000/QALY to $49,000/QALY • Doses cost-effective at $50,000/QALY in women with o no CRFs: none; ≥1 CRF: beginning at mean heart dose (MHD) 9 Gy and 10 Gy for 50 and 60 years • Doses cost-effective at $100,000/QALY in women with o no CRFs: MHD 10 Gy for 40 year-old women, 9 Gy for 50 year-old women o ≥1 CRF: MHD ≥6 Gy for 40, 60 year-old women; MHD ≥5 Gy for 50 year-olds
SA	• No CRFs: PBT not cost-effective at $50,000;/QALY cost-effective at $100,000 /QALY in all ages (7 Gy for 50 year-old, 9 Gy for 40 & 60 year-old) • ≥1 CRF, ICERs range: $49,757/QALY to $161,285/QALY based on age, dose
Author's Conclusion	**• For women w/o CRFs, PBT not cost-effective at a WTP of $50,000/QALY. PBT more likely to be cost-effective for women with ↑ risk of CHD and for younger patients.**
Limitations	**• Unclear Markov model methods; sensitivity analyses show substantial variation in CE** **• Outcomes other than CHD, death not modeled; utilities not detailed;** **• Lifetime horizon, but no *comparative* long-term data** **• PBT: not clear that costs captured all aspects of operation** **• Components of CHD treatment costs not reported; modeled PCI but not CABG** **• Data from case series on PBT, case-control study of radiation-related risk for IHD in women receiving RT between 1958 and 2001 (impact of newer RT methods is unclear)**

Summary: Adult breast cancer

Condition	Incidence (per 100,000)	Numbers of Studies		Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE		Impact of new retrospective comparative studies
		2014	2019	2014	2019	2014 vs.2019
Breast	124.7	CS=4; Econ=3	CC=1 CS=4; Econ=1	Insufficient none	Unclear B: = H: NR Low	1 new retrospective data base study reports on OS; no comparative studies addressing harms were identified

2019 Economic, 1 CUA: Hypothetical cohort models suggest PBT is not cost effective in women w/o CRFs vs. photon RT but may be for younger women and those with ↑ CAD risk, depending on dose. Modeling is based on case-series and case-control data (which may not reflect more recent RT methods), model parameters are not well documented; sensitivity analyses show substantial variation in CE.

2014 vs. 2019: In the absence of studies directly comparing the safety/adverse events PBT with other radiation therapy, the net health benefit is unclear.

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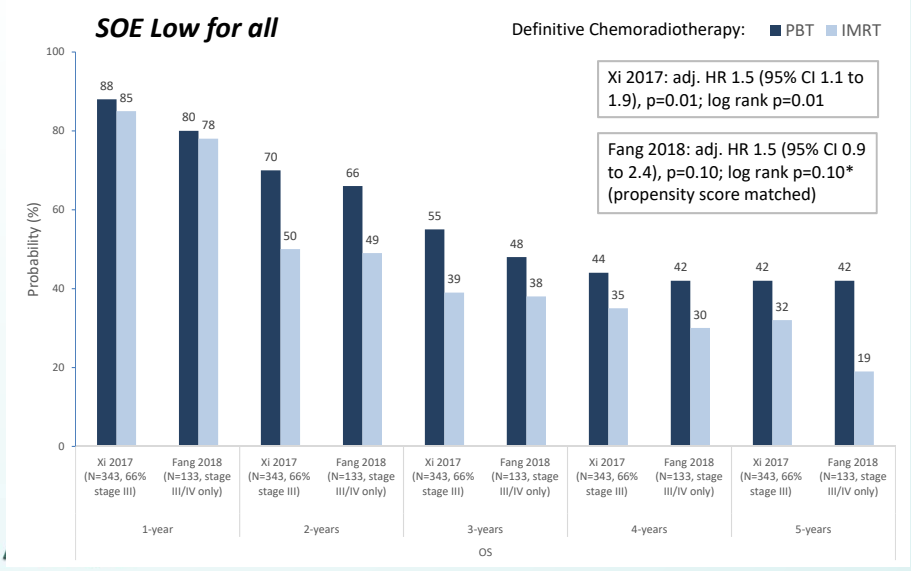
KQ 1 (Curative Intent): Adult esophageal tumors

Overall Survival (retrospective cohort studies)



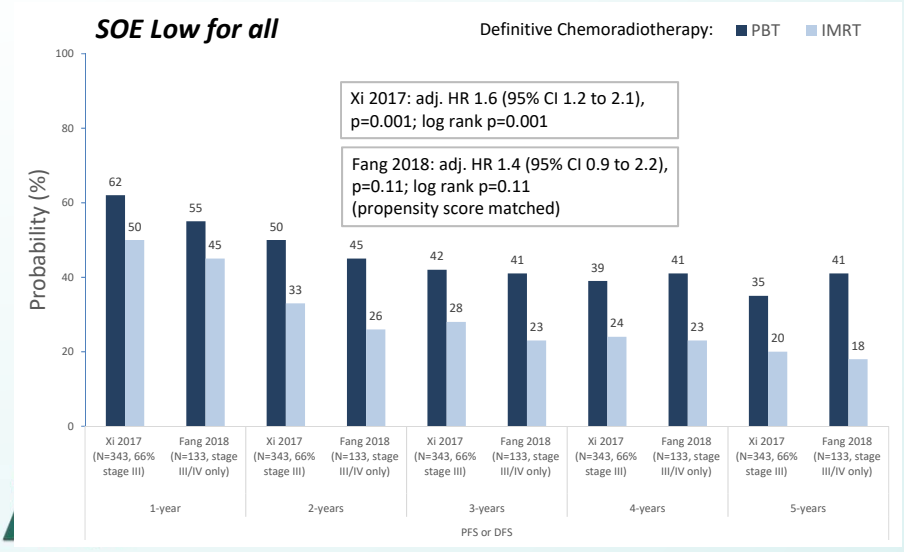
KQ 1 (Curative Intent): Adult esophageal tumors

Mortality (retrospective cohort studies)

Author, Year, N,	Tumor type	Timing	PBT % (n/N)	Photon (various) % (n/N)	Effect size (95% CI) P-value*
Makishima (2015) N=44 Definitive Chemoradiotherapy ***SOE Insufficient***	SCC (100%)	NR (median f/u 22.3 mos.)	20% (5/25)	XRT: 31.6% (6/19)	RR 0.63 (0.23 to 1.77)†
Lin (2017), N=580 Trimodal Therapy (Chemotherapy, Radiation and Surgery) ***SOE Low***	AC (92%) or SCC (8%)	1 mo. post-op	0% (0/111)	Any photon: 1.5% (7/469) • 3DCRT: 1.9% (4/214) • IMRT: 1.2% (3/255)	p=0.425
		2 mos. post-op	0.9% (1/111)	Any photon: 2.6% (12/469) • 3DCRT: 2.3% (5/214) • IMRT: 2.7% (7/255)	P=0.590
		3 mos. post-op‡	0.9% (1/111)	Any photon: 4.3% (20/469) • 3DCRT: 4.2% (9/214) • IMRT: 4.3% (11/255)	p=0.264‡

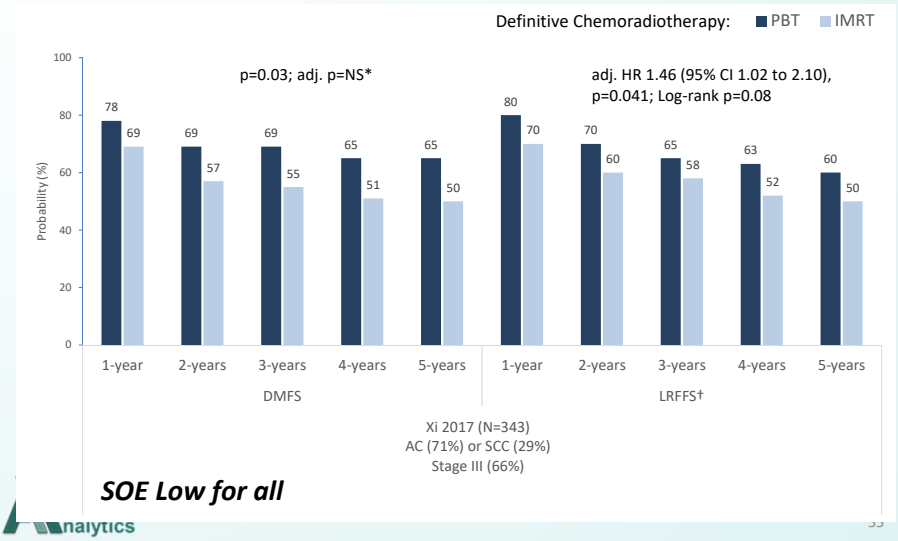
KQ 1 (Curative Intent): Adult esophageal tumors

Progression- or Disease-Free Survival



KQ 1 (Curative Intent): Adult esophageal tumors

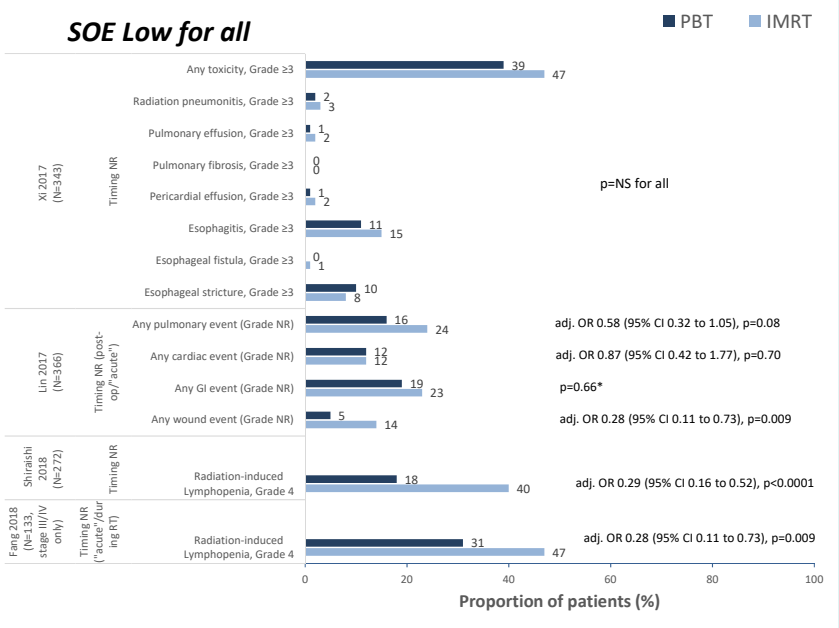
Distant Metastasis- and Locoregional Failure-Free Survival



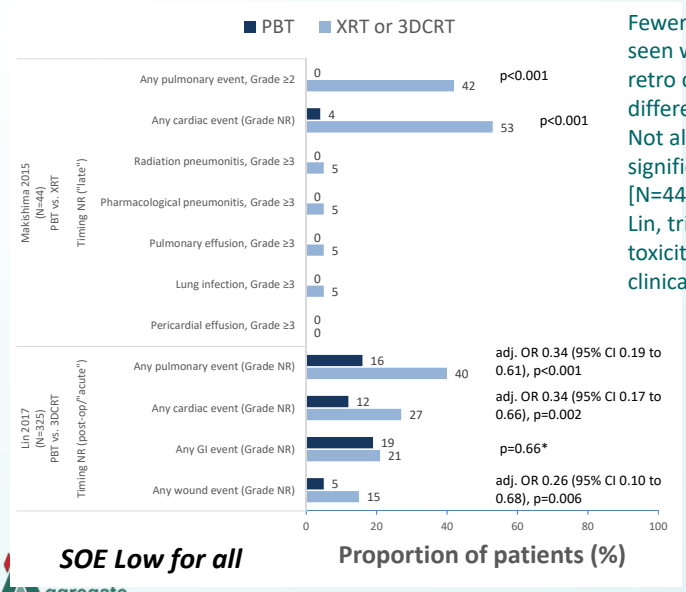
SOE Low for all

KQ 3 (Safety): Adult esophageal tumors

SOE Low for all



KQ 3 (Safety): Adult esophageal tumors



Fewer AEs/toxicities were seen with PBT across two retro cohort studies with different treatment protocols; Not all were statistically significant. (Makishima [N=44], chemoradioatherapy, Lin, trimodal therapy); toxicity grade NR for Lin; clinical significance is unclear

SOE Low for all

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KQ 3: Esophageal tumors; Toxicities CASE SERIES

Outcome	Studies	# With outcome	Total N	F/U (mos)	Range (95%CI)
Acute Hematological Grade 3, 4 (NOS)	1	10	40	24	25%
Acute Grade 3 or 4					
Leukopenia	1	26	47	29	55.3%
Neutropenia		21			44.7%
Thrombocytopenia		13			27.7%
Nausea and vomiting		1			2.1%
Esophagitis		5			10.6%
Pneumonitis		0			0%
Late Grade 3					
Any	1	2	40	24	5%
Pericarditis, pericardial effusion	1	0	47	29	0%
Lung (pneumonitis)		1			2.1%
Esophageal		3			6.4% (4.3% stenosis, 2.1% fistula)

Small sample sizes noted; Appendix Table F15

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Summary: Adult esophageal tumors

Condition	Incidence (per 100,000)	Numbers of Studies		Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE		Impact of new retrospective comparative studies
		2014	2019	2014	2019	2014 vs.2019
Esophageal	4.6	CC=2; CS=7	CC=5; CS=2	Insufficient none	Incremental B: ↑ H: = Low	New retrospective comparative evidence lead to different conclusions

2014 vs. 2019: The 2014 report included 2 (1 large) fair-quality comparative studies and concluded that the evidence was limited and inadequate to compare the potential benefits and harms of PBT relative to other radiation modalities.

Evidence from 5 new retrospective comparative observational studies suggest that PBT may of incremental benefit compared to IMRT and other forms of radiation (3DCRT, XRT) with better survival outcomes and similar, or slightly better safety profile (SOE Low). Results for safety were mixed; for some outcomes differences may be clinically important.

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KQ 1, 3: Results and summary, Adult GI tumor (Pancreas)

Outcome	Studies, Year, N, Tumor	Reason for Downgrading	PBT (spot scanning) vs. HART Effect estimate (95% CI)	Conclusion Quality (SoE)
Probability, overall survival (OS)	Maemura 2017 (N=25) Retro cohort Adenocarcinoma (locally advanced, unresectable)	Serious ROB Yes[1] (-1) Consistency Unknown Serious Imprecision Yes[3] (-1)	**OS** 1-year: 80% vs. 86.7% 2-year: 45% vs. 33.3% 3-year: 22.5% vs. 26.6%	NS difference between PBT and HART for OS, disease control, local progression, metastasis or acute toxicities. Sample size is small. ⊕◯◯◯ INSUFFICIENT
Disease control, local progression, metastasis			**Disease Control:** 80% (8/10) vs 93% (14/15), **Progression**: 40% (4/10) vs 60% (9/15) **Metastasis**: Any: 30% (3/10) vs. 20% (3/15)	
Acute Toxicity (≤3 mos.)			No grade 4 toxicities occurred in either group; Grade 3 toxicities **Leukopenia** 0% (0/10) vs. 20% (3/15) **Thrombocytopenia:** 0% (0/10) vs. 6.7% (1/15) **Ulcer:** 10% (1/10) vs 0% (0/15)	

2014 report: 7 case series only; Insufficient evidence (different tumors)

2019 report: Similar conclusions; evidence from 1 small poor quality cohort study is insufficient to draw firm conclusions

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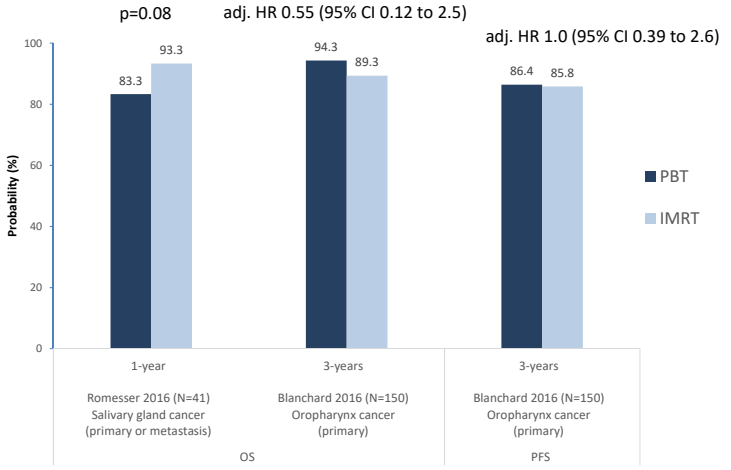
KQ 1 (Curative Intent): Adult head and neck (non-skull base)

Overall, Progression-Free Survival, Mortality



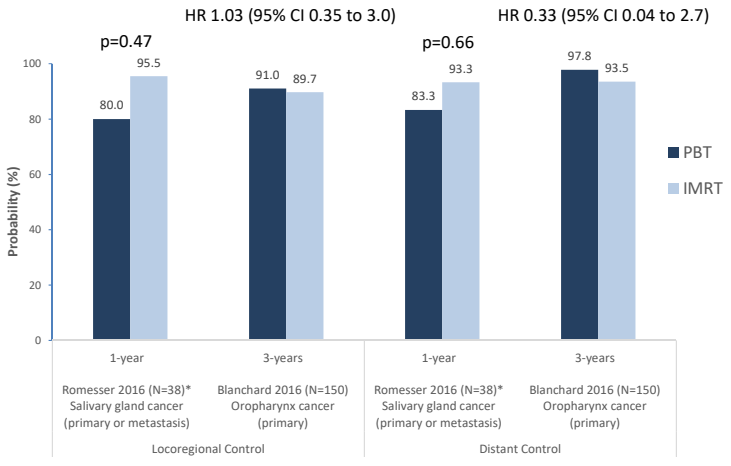
All-cause-mortality:
1 small matched-pairs cohort (N=30, primary nasopharyngeal cancer) [Holliday 2015]:
PBT 10% (1/10);
IMRT 5% (1/20);
p=NS

*SOE **Low** for primary oropharyngeal and nasopharyngeal cancer;*
***Insufficient** for salivary cancer (primary or metastatic)*

61

KQ 1 (Curative Intent): Adult head and neck (non-skull base)

Locoregional and Distant Control (No SOE)



1 small matched-pairs retro cohort (N=30, primary nasopharyngeal cancer) [Holliday 2015]:

Local Failure
PBT 0%; IMRT 5% (1/20)

Distant Metastases
PBT 10% (1/10);
IMRT 5% (1/20)

p=NS for both

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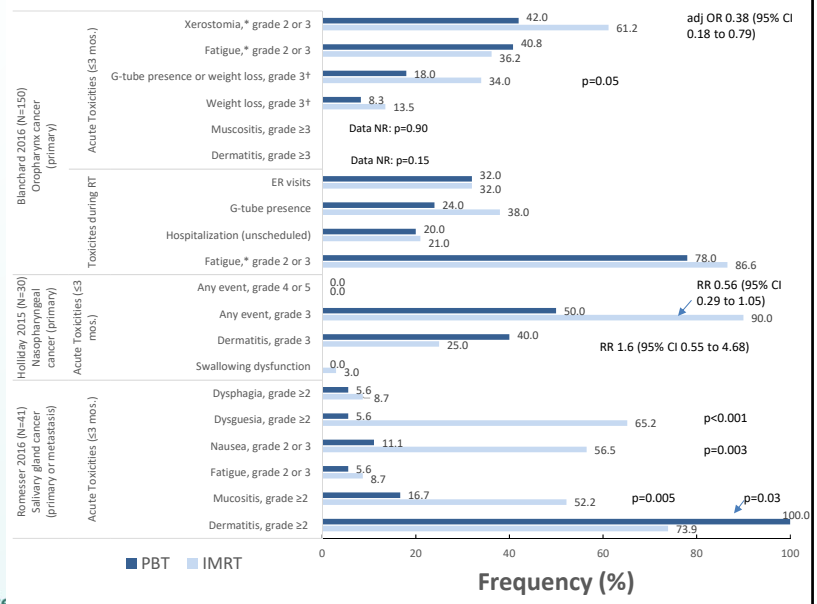
KQ 3 (Safety): Adult head and neck (non-skull base)

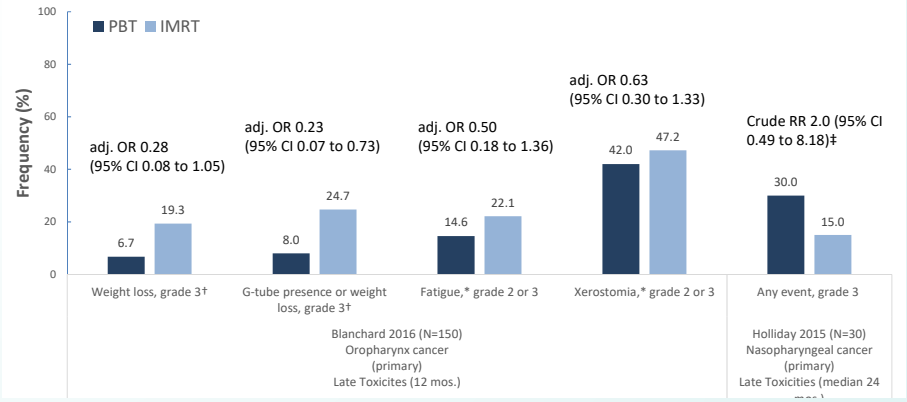
ACUTE toxicity, adverse events; NS differences in grade ≥ 3 for PBT vs. IMRT (3 studies)

SOE Low



KQ 3 (Safety): Adult head and neck (non-skull base)

LATE toxicity, adverse events



NS difference between PBT and IMRT with the exception of the composite outcome of g-tube + weight loss (neither outcome alone was significant) across two retrospective cohort studies; some differences may be of clinical importance. **SOE Low**

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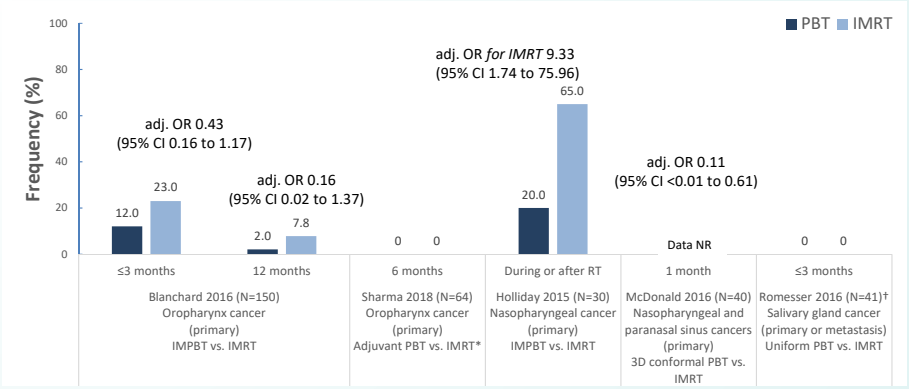
KQ 3 (Safety): Adult head and neck (non-skull base)

Gastrostomy Tube Dependence



Retrospective studies, NS difference for PBT vs. IMRT in largest study, 2 smaller studies; two small studies (different tumors) report significantly lower g-tube dependence w/PBT; the large CIs suggest effect estimate instability, data are NR for the other; differences may be clinically important;

SOE LOW

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KQ 3 (Safety): Adult head and neck (non-skull base)

Osteoradionecrosis

		Grade	IMPBT (n=50) % (n)	IMRT (n=534) % (n)	RR (95% CI)†
Zhang 2017 (N=584) Primary Oropharyngeal Cancer Retro cohort	Late toxicities (>6 months)*	Any	2.0% (n=1)	7.7% (n=41)	RR 0.26 (0.04 to 1.85)
		Grade 1	2.0% (n=1)	4.3% (n=23)	RR 0.46 (0.06 to 3.37)
		Grade 2	0%	0.2% (n=1)	NC; p=0.76
		Grade 3	0%	0.9% (n=5)	NC; p=0.49
		Grade 4	0%	2.2% (n=12)	NC; p=0.29

SOE Insufficient

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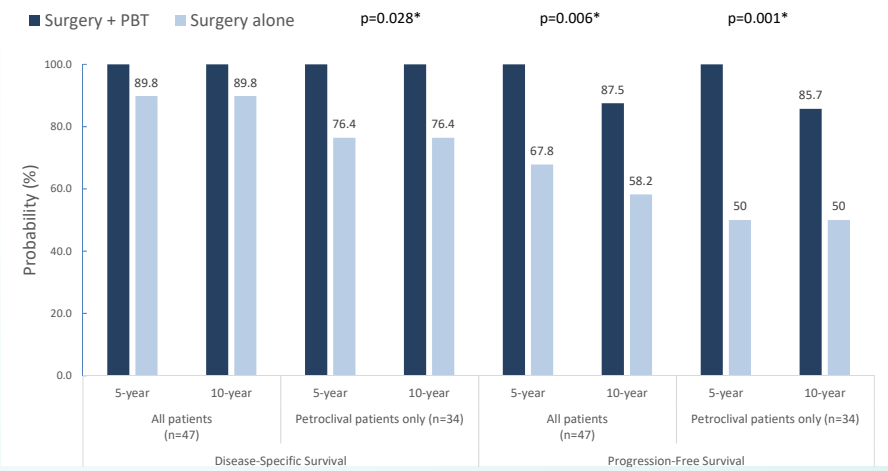
KQ 1 (Curative Intent): Adult head/neck (Skull base Chondrosarcoma) Disease-Specific and Progression-Free Survival



NS difference for PBT + surgery vs surgery in DSS at 5 or 10 years across patients in one small retro cohort; PFS was better with PBT; DSS and PFS were better with PBT in subanalysis of those with petroclival lesions

SOE Insufficient

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KQ 3 (Safety): Adult head and neck (Skull base Chondrosarcoma) (small retrospective cohort)

	PBT (N=28)*		Surgery (N=47)†		RR (95% CI)‡
	%	n	%	n	
Any complication	68%	19	26%	12	2.7 (1.5 to 4.6)
Sensorineural hearing loss	39%	11	6%	3	6.2 (1.9 to 20.2)
Severe hearing loss	21%	6	4%	2	5.0 (1.1 to 23.3)
Dizziness	14%	4	0%	0	NC, p=0.008
Conductive hearing loss	11%	3	4%	2	p=0.28
Any grade ≥3 toxicity	25%	7	11%	5	p=0.10
Cranial nerve palsy	11%	3	19%	9	p=0.34
Treatment-related death	0%	0	2%	1	p=0.44
Vision loss	11%	3	-----	-----	-----
Hypopituitarism	18%	5	-----	-----	-----
Temporal lobe necrosis	18%	5	-----	-----	-----
Cerebrospinal fluid leak	-----	-----	13%	6	-----
Meningitis	-----	-----	9%	4	-----
Pulmonary embolism	-----	-----	2%	1	-----

SOE Insufficient : Most complications were more common with PBT (+ surgery) vs. surgery alone; "any" complication, hearing loss outcomes and dizziness were significantly higher with PBT; sample size is small, confidence intervals from crude RRs are large.

KQ 3: Head and Neck Tumors; Selected acute toxicities reported across multiple CASE SERIES

Outcome	# Studies	# With outcome	Total N (range of N's)	Median F/U (months)	Range (95%CI)
Acute Grade ≥3 (any)	2	0	235 (76-159)	65.5 to 77	0%
Acute Grade ≥3 (specific)	1*	NR	33	43	(below)
Dermatitis		11			33%
Mucositis		23			79%
Neutropenia		17			51%
Nausea		6			18%
Acute Grade 3 only (no Grade 4)	1†	NR	50	29	(below)
Dermatitis		23			46%
Mucositis		29			58%
Dysphagia		12			24 %
Any Acute Grade 3	2	23	102 (42-60)	13.6-69	12% - 30%
Acute treatment related- death	3	2	154 (33-61)	13.6 -43	0% -1.7%

* Tongue † oropharyngeal

Sample sizes for most are small precluding detection of rare events;

Appendix Table F 25 has complete listing

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KQ 3: Head and Neck Tumors; Selected late toxicities reported across multiple CASE SERIES

Outcome	# Studies	# With outcome	Total N (range of N's)	Median F/U (months)	Range (95%CI)
Late Grade ≥3 (any) (>3 months)	7	55	699 (34 -222)	13.6- 77	1.3% to 20%
Late Grade ≥3 (any) (time NR)	4	77	512 (38-251)	15.2-87.3	9.4% -24%
2, 5 year rates, any late Grade 3 (skull-based chrondrosarcoma)	1	N/A	159	77	42.9% (32.3, 50.4) 57.2% (42.8 ,68.4)
CNS necrosis (time NR)	2	2	306 (84-222)	28.8 -50	0.5% to 1.2%
Brain necrosis (Grade ≥3)	5	6	643 (38-251)	30 -87.3	0% to 7.9%
Temporal Lobe Rad Necrosis (Grade 3)	1	13	222	50	5.9%
Bone, soft tissue necrosis (Time NR)	5	19	349 (33-96)	24-57.5	0% to 15.2%
Late treatment related- death	6	9	332 (34-84)	13.3-30	0% to 3.7%
Toxicity-free survival (any grade)	1	N/A	251	88	84.2% (79.3- 89.5)

Appendix Table F 25 has complete listing

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KQ 5, Cost-effectiveness: Oropharyngeal squamous cell carcinoma

	Sher 2018 (USA); QHES 90/100
Population	65 year old patients with stage III-IVB oropharyngeal squamous cell carcinoma
Interventions	PBT (timing unclear, accompanied by chemotherapy) vs. IMRT
ICER	**Societal perspective:** HPV positive: $390,000/QALY; HPV negative: $695,000/QALY **Payer perspective:** HPV positive: $288,000/QALY; HPV negative: $516,000/QALY
One-way SA	Even under assumptions favoring PBT to reduce PEG dependence, improve long-term xerostemia, ICERs above $100,000/QALY (range $101,000/QALY to $1 million/QALY)
Other SA	Probability PBT cost-effective 0% (both perspectives) at WTP of $100,000/QALY and 0.4% (payer) and 0% (societal) at WTP $150,000/QALY PBT cost effective for 55 year-old patients at WTP $100,000/QALY in 0.4% for payer and 2% for societal; at WTP $150,000/QALY 25% (payer), 2% (societal) were cost-effective
Author's Conclusion	**PBT is not cost-effective using either societal or payer perspective; at extremes of PBT superiority it becomes cost-effective for younger HPV-positive patients**
Limitations	• **Oncologic outcomes assumed to be same for IMRT, PBT despite limited evidence** • **Lifetime time horizon, however no long-term comparative data available** • **Improved side effect profile of PBT assumed from minimal 1 case series** • **Societal costs assumed to be same for both treatment modalities** • **Disutilities for toxicities assumed to be additive, potentially under-estimating QALYs from IMRT**

Summary: Adult head and neck tumors

Condition	Incidence (per 100,000)	Numbers of Studies		Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE		Impact of new Retrospective comparative studies
		2014	2019	2014	2019	2014 vs.2019
Oropharyngeal, Nasopharyngeal, paranasal sinus, and oral cancers	17.2‡§	CC=1; CS=15; Econ=2	CC=7; CS=14; Econ=1	Insufficient low	Comparable B: = H: = Low	7 additional, larger comparative studies lead to different conclusions
Chondrosarcoma of the skull base		CC=1 CS=15	CC=1 CS=9	Insufficient low	Insufficient	Similar conclusions

2014 vs. 2019: The 2014 report had 2 poor quality retrospective studies and concluded that the evidence was inadequate to compared potential benefit and harms of PBT vs. other radiation modalities.

7 new larger retrospective observational studies suggests net health benefits of PBT are comparable vs. IMRT for non-skull base tumors (SOE Low); statistical significance for harms was in consistent. Evidence is still insufficient for skull-base chondrosarcoma (1 small study).

PBT was not cost-effective in 1 CUA in patients w/oropharyngeal squamous cell carcinoma

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KQ 1 (Curative Intent): Adult liver (HCC)

Overall and Progression-Free Survival

Outcome	Studies, Year, N, Tumor	Reason for Down-grade	Effect estimate (95% CI)	Conclusion Quality (SoE)
Randomized Controlled Trial			**PBT vs. TACE**	
Probability, overall survival (OS), Progression-free survival (PFS) **2 Years**	Bush 2016 (N=69) RCT	Consistency Unknown Precision (-1)	**OS**: 59% (NR) (all patients) • liver transplant post-treatment (n=22): 82% (NR) p=NS for both, data not provided by group **PFS**: 48% (NR) vs. 31% (NR); p=0.06	No significant difference in OS; PBT tended to result in improved PFS compared with TACE patients (not statistically significant). Results are from interim analysis of an ongoing trial. ⊕⊕⊕◯ MODERATE
Retrospective Cohort			**PBT vs. IMRT**	
Probability, overall survival (OS) **2 years**	Sanford 2019 (N=133) Retrospective cohort study	Consistency Unknown Precision (-1)	**OS**: 59.1% vs. 28.6%; adj. HR 0.47 (95% CI 0.27 to 0.82)	OS was significantly higher following PBT vs. IMRT ⊕⊕◯◯ LOW

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KQ 3 (Safety): Adult liver (HCC)

Randomized Controlled Trial

Outcome	Studies, Year, N, Tumor	Reason for Down-grading	Effect estimate (95% CI)	Conclusion Quality (SoE)
Acute Toxicity (≤3 mos.)	Bush 2016 (N=69) RCT	Consistency Unknown Precision (-1)	Acute toxicity, generally limited to the following, which were experience by most patients (no data provided)*: • PBT: fatigue and radiation skin reaction • TACE: abdominal pain and nausea	Limited information provided on acute toxicity. Significantly fewer patients who received PBT required hospitalization in the month following treatment compared with TACE patients; total days hospitalized were significantly fewer in the PBT vs. the TACE group. Results are from interim analysis of an ongoing trial. ⊕⊕⊕◯ MODERATE
Hospital-ization % (n/N) **≤1 month**			**For an acute event**: 6.1% (2/33) vs. 41.7% (15/36); p<0.001 **Total days hospitalized:** **Overall**: 24 (0.73 days per patient) vs. 166 (4.6 days per patient); p<0.001; for • *routine observation*: 0 vs. 53 • *complications:* 24 vs. 113	

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KQ 3 (Safety): Adult liver (HCC)

Observational Comparative Study

Outcome	Studies, Year, N, Tumor	Reason for Down-grading	Effect estimate (95% CI)	Conclusion Quality (SoE)
Incidence of nonclassic radiation-induced liver disease (RILD)* 3 months	Sandford 2019 (N=100)† Retrospective cohort study	Consistency Unknown Precision (-1)	adj. OR 0.26 (95% CI 0.08 to 0.86) (PBT, n=4 patients; IMRT, n=17 patients) Authors also report that the development of RILD at 3 months was associated with significantly worse OS (HR 3.83; 95% CI 2.12 to 6.92).	Lower risk of RILD in the acute period with PBT versus IMRT ⊕⊕◯◯ LOW
Death due to liver failure Median 14 months	Sandford 2019 (N=36)‡ Retrospective cohort study	Consistency Unknown Precision (-1)	53% (8/15) vs. 91% (19/21); RR 0.59 (95% CI 0.36 to 0.97)§	Lower risk of death due to liver failure with PBT versus IMRT; however data was from a small subset of patients. ⊕◯◯◯ INSUFFICIENT

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KQ 3: Liver cancer, PBT toxicities

CASE SERIES

Outcome	# Studies	# with outcome	Total N (range of N's)	Range of Median F/U (mos)	Range
Curative Intent (HCC)					
Acute Toxicity ≥ Grade 3	2	2	123 (40 to 83)	19.9 to 45	0% to 5%
Late Toxicity ≥ Grade 3	1	0	40	19.9	0%
Toxicity NOS (HCC or ICC) ≥ Grade 3	3	8‡	249 (37 to 129)	11 to 55	5% to 11%
Treatment-related liver failure, death	2	4	250	(within 4-6 mos.)	0% to 2%
Mixed Curative					
Acute Toxicity ≥ Grade 3	3	1	213 (41 to 101)	4.9 to 31.3	0% to 1%
Late Toxicity ≥ Grade 3	2	0	112 (41 to 71)	15.2 to 31.9	0% to 0%
Radiation-Liver Disease	1	4	101	4.9	4%
Gastroduodenal Toxicity		5			5%
Salvage					
Acute Toxicity ≥ Grade 3	1	0	89	30.1	0%
Metastatic Liver Tumors (Mixed curative)					
Late Toxicity ≥ Grade 3	1	2	133	NR	1.6%
↑ of >2 Child-Pugh Score		8			6%

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Appendix Table F31-34

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KQ 5, Cost-effectiveness: Inoperable HCC

	Leung 2017 (Taiwan), QHES 51/100
Population	Inoperable advanced, large hepatocellular carcinoma **PBT study**: Age 70, 67% male; Child-Pugh Class A 67%; tumor size 45mm; Hepatitis C 87% **SBRT study:** Age 69.4, 78.4% male; Child-Pugh Class A 100%; tumor size 72mm; Hepatitis C 28%
Intervention(s)	PBT (timing unclear, possibly primary treatment) vs. Stereotactic body radiation therapy (SBRT)
ICER	NT$557,907/2.61 QALY = NT$213,354/QALY (New Taiwan Dollars)
One-way SA	Very sensitive to utilities and direct costs in stable and progressive disease states (range NR)
Other SA	Monte Carlo simulations: At NT$2,157,024 /QALY, PBT has 97% chance of being cost-effective and SBRT has 4% chance
Author's Conclusion	**PBT is cost-effective for inoperable advanced HCC at a WTP threshold for Taiwan**
Limitations	• **Data from separate case series of PBT and SBRT; study selection not transparent ; basis of utilities not described** • **Intervention and comparator populations not comparable: differences in patient populations including tumor size, Child-Pugh class, other factors; impact on analysis unclear** • **Components and basis for some medical costs not detailed** • **Did not include non-cancer deaths** • **One-way sensitivity analysis not clearly presented; limited evaluation of assumptions, robustness of model is not clear** • **May not be applicable to US**

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Summary: Adult liver (HCC)

Condition	Incidence (per 100,000)	Numbers of Studies		Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE		Impact of new comparative studies
		2014	2019	2014	2019	2014 vs.2019
Liver	8.1	CC=3; CS=26	RCT=1; CC=1 CS=12; Econ=1	Comparable B: = H: = Low	PBT vs. TACE Incremental B: = H: ↓ Moderate PBT vs. IMRT Incremental B: = H: ↓ Low	RCT interim results with different comparator (TACE). Hospitalization was a surrogate for toxicity (see report). PBT vs. Photon; larger cohort study. Net health benefit vs. comparators across both reports is unclear.

2014 vs. 2019: The 2014 report included 3 comparative cohort studies (2 prospective, 1 retrospective) and concluded that PBT net health benefits were comparable vs. other treatments (photon, chemotherapy only, carbon ion; SOE low). 1 new RCT and 1 new larger comparative study suggest that PBT has incremental benefit vs. TACE and IMRT with similar efficacy/effectiveness but with a reduction in harms (SOE Moderate for TACE, Low for IMRT).

2019 Economic: 1 poor quality CUA (Taiwan) likely not applicable to US; Conclusions regarding CE are challenging given methodological concerns

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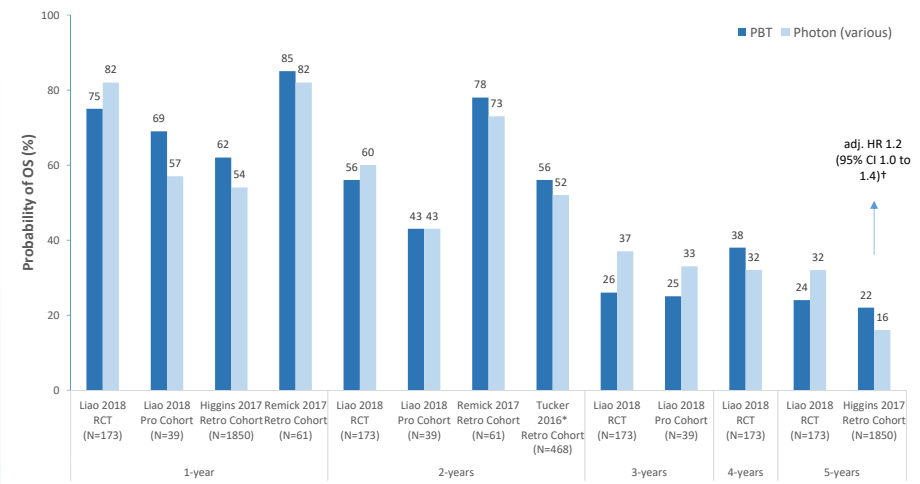
KQ 1 (Curative): non-small cell lung cancer (NSCLC), OS



Overall Survival: NS differences between groups at 1-5 years in 1 RCT (SOE Moderate) or across 4 retrospective cohort studies (SOE Low); some differences may be clinically important

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KQ 1 (Curative): NSCLC, other effectiveness outcomes

Outcome	Time	Studies, Year, N, Tumor	Reason for Downgrade	PBT vs. Photon * Effect estimate (95% CI)†	Conclusion Quality (SoE)
Cumulative incidence of local failure (%)‡	1-5 years	Liao 2018 N=173 (ITT) RCT NSCLC	Consistency Unclear Serious Imprecision Yes[3] (-1)	• 1-year: 9% vs. 10% • 2-year: 27% vs. 26% • 3-year: 37% vs. 37% • 4-year: 37% vs. 32% • 5-year: 37% vs. 39% p=0.99	NS difference at any timepoint ⊕⊕⊕◯ MODERATE
Observational studies					
Probability, Local Recurrence-Free Survival (LRFS)	1-2 year	Remick 2017 N=61 Retro cohort NSCLC	Serious ROB Yes[1] (-1) Consistency Unclear Serious Imprecision Yes[3] (-1)	• 1-year: 92.3% (82.5%–100%) vs. 93.3% (84.8%–100%) • 2-year: 93.1% vs. 85.7% p=0.82	NS difference at any timepoint ⊕◯◯◯ INSUFFICIENT
Local Failure	1-2 years	Liao 2018§ N=39 Pro cohort NSCLC		• Cumulative incidence‡: • 1-year: 6% vs. 3% • 2-year: 6% vs. 3% • 3-year: 26% vs. 26% p=0.93	
	2-years	Remick 2017 N=61 Retro cohort NSCLC		11.1% (3/27) vs. 5.9% (2/34), p=NS	

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KQ 3 (Safety): non-small cell lung cancer (NSCLC)

Outcome	Time	Studies, Year, N,	Reason for Downgrade	PBT vs. Photon (various)* Effect estimate (95% CI)	Conclusion Quality (SoE)
Randomized controlled trials					
Rate of radiation pneumonitis, Grade ≥3‡	1-5 years	Liao 2018 N=173 (ITT) RCT	Consistency Unclear Serious Imprecision (-1)	8% vs. 7% at 1, 2, 3, 4 and 5 years; p=0.58	NS differences ⊕⊕⊕◯ MODERATE
Retrospective cohort studies					
Radiation esophagitis	NR (median 26 mos)	Remick 2017 N=61 Retro cohort	Serious ROB (-1) Serious Imprecision (-1)	Grade 3: 3.7% (1/27) vs. 11.8% (4/34), p=NR	NS differences for any grade 3 outcome; some differences may be clinically important; sample sizes are small. ⊕◯◯◯ INSUFFICIENT
	NR	Niedzielski 2017 N=134 Retro cohort	Serious ROB (-1) Serious Imprecision (-1)	Grade 3: 22.4% (11/49) vs. 17.6% (15/85); OR 1.4 (0.7 to 2.9), p=0.37	
Radiation pneumonitis	NR (median 26 months)	Remick 2017 N=61 Retro cohort	Serious ROB (-1) Serious Imprecision (-1)	Grade 3: 3.7% (1/27) vs. 2.9% (1/34), p=NR	
Radiation dermatitis				Grade 3: 0% (0/27) vs. 0% (0/34), p=NR	

NS differences PBT vs. IMRT for other acute toxicities reported in Remick; (Table 32)

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KQ 3: NSC Lung cancer; Acute PBT toxicities CASE SERIES

Outcome	# Studies	# With outcome	Total N (range of N's)	Median F/U (months)	Range (95%CI)
Acute Grade ≥3 (any) NSCLC	4	24	237 (50-74)	7.8-33.7	0%- 39%
Acute Grade ≥3					
Pulmonary	1	14	64	27.3	9.4%
Cardiac		0			0%
GI		7			10.9%
Hematologic		NR			2%-22%
General		NR			3%-9%
Acute treatment related- death	1	0	64	27.3	0%

Small sample sizes preclude identification of rare events
Appendix Table F35

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KQ 3: NSC Lung cancer; Late PBT toxicities CASE SERIES

Outcome	# Studies	# With outcome	Total N (range of N's)	Median F/U (months)	Range (95%CI)
Late Grade ≥3 (any) NSCLC	4	14†	237 (50-74)	7.8 -33.7	0% -17.6%*
Grade ≥3 Pulmonary	1	14	64	27.3	21.9%
Grade ≥3 Cardiac		3			4.7%
Grade ≥3 GI		2			3.1%
Grade ≥3 Hematologic		2			3.1%
Late tx related- death (≥3 mos)	3	7‡	162 (50-57)	7.8-29	0% -10.5%
Late tx related- death (time NR)	2	0	70 (35 + 35)	80- 83.1	0%
Grade 2 rib fracture (3-year)	1	N/A	52	33	30% (14.9 -52.1%)
Radiation necrosis	1	0	56	33.7	0%
Grade ≥3 Toxicities (any, Time NR) NSCLC	4	21	125 (35-55)	29 -83.1	1.8% to 12.7%
Toxicities (any, Time NR) LS-SCLC					
Hematologic Grade 3	1	NR	30	14	10%-23%
Hematologic Grade 4		NR			3%-33%
Non-hematologic		5			16.7%
Treatment-related death		0			0%

Small sample sizes preclude identification of rare events; Appendix Table F35

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Summary: Adult Lung Cancer

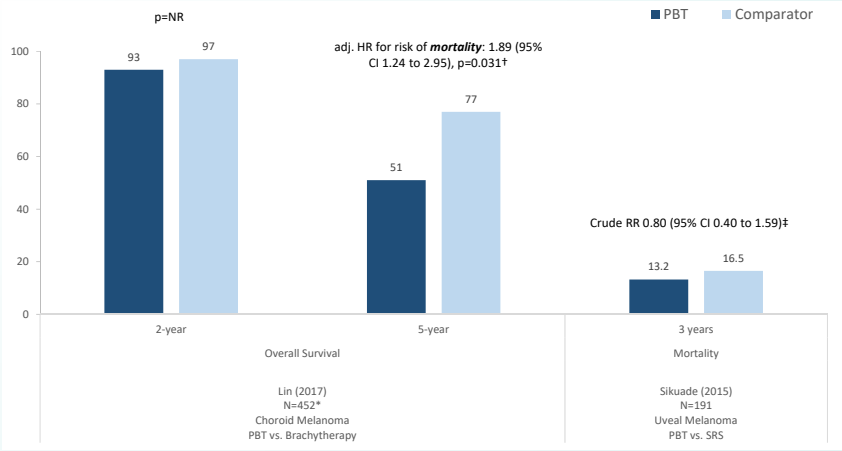
Condition	Incidence (per 100,000)	Numbers of Studies		Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE		Impact of new comparative studies
		2014	2019	2014	2019	2014 vs. 2019
Lung	60.5	CC=4; CS=19; Econ=2	RCT=1; CC=6§; CS=11	**Comparable B: = H: = Low****	**Comparable B: = H: = Low**	**Similar conclusions; addition of a RCT**

**2014-discrepancies in SOE between Table ES2 and Table 3; Low was listed in the ES table and text

- Data on primary outcomes were available for KQ 1 and 3 in studies of PBT for curative intent for treatment of NSCLC with PBT vs. IMRT, 3DXRT or various RT types
- **KQ2**: The comparative study identified did not report on survival or safety (see report)
- **KQ 4 and 5:** no comparative studies identified
- **2014 vs. 2019:** The 2014 report included 3 large comparative studies and concluded that net health benefits for PBT were comparable to other RT (IMRT, 3DCRT, carbon ion, SOE low). Evidence from 1 RCT and 5 comparative observational studies published subsequent to the prior report also suggest that PBT is comparable to IMRT and other forms of radiation for benefits and harms. (SOE Low)

84

KQ 1 (Curative): Adult ocular tumors



OS, Mortality: NS difference in OS at 2 years (PBT vs. BT) or mortality (PBT vs. SRS) in 2 retrospective cohort studies; however a significantly **higher** risk of mortality at 5 years was reported for PBT vs. BT in choroid melanoma patients **(SOE Low).**

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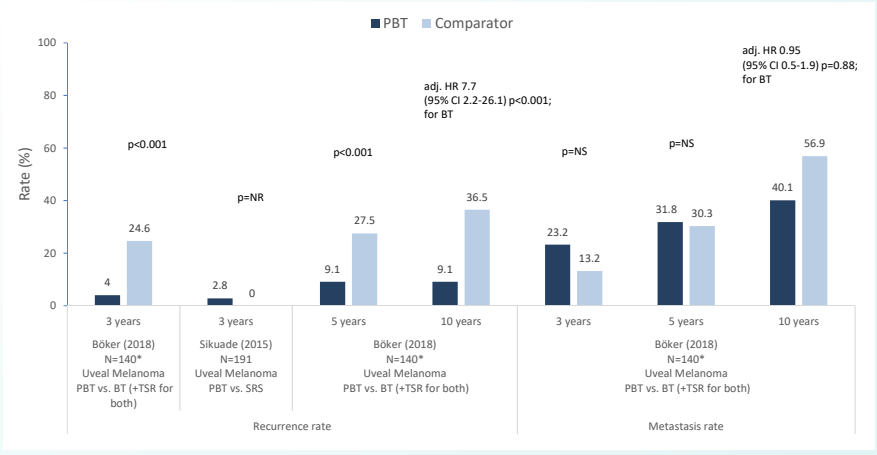
KQ 1 (Curative, effectiveness): Adult ocular tumors



Recurrence: Significantly less common for PBT vs BT (+ TSR for all) at 3 years (SOE Low); NS difference in local recurrence for PBT vs. SRS (SOE Insufficient).

Metastasis: NS difference at anytime point in one study.

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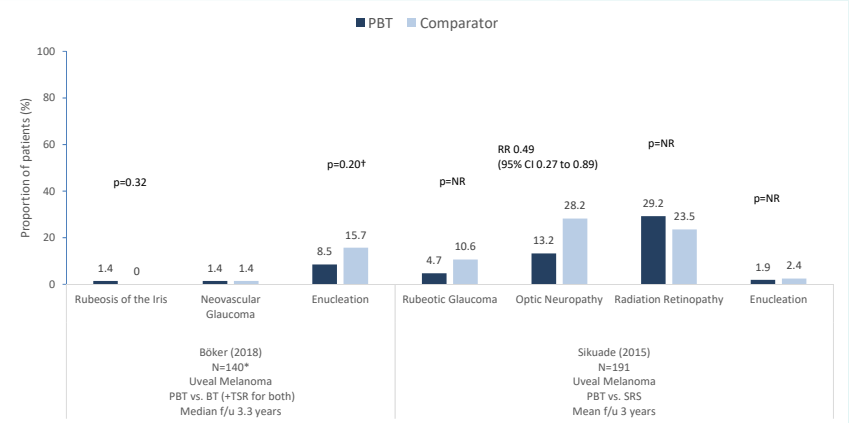
KQ 3 (adverse events): Adult ocular tumors



Adverse events: Optic neuropathy was significantly less common with PBT vs. SRS; no other significant differences noted for either retrospective study (SOE Low).

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KQ 3: Ocular tumors; Adverse events, CASE SERIES

Outcome (all cancers)	# Studies	# With outcome	Total N (range of N's)	Median F/U (months)	Range (95%CI)
Enucleation	14	428	7298 (36- 2499)	30 -77	0% -15.6%
Neovascular Glaucoma	8	513	4611 (36 -2499)	30- 84	0% - 25%
Secondary Glaucoma	3	22	203 (36 -107)	49.5-70.3	6% -20%
Cataracts	8	444	2907 (36-1696)	30 - 70.3	6.1% -62%†
Retinopathy	7	2521	5596 (36-2499)	46.2 -54.8	0% - 68.1%
Maculopathy	4	600	2975 (63- 1696)	30 -69	7.2% - 49%
Neuropathy	6	2391	635 (63-2499)	30-69	4.7% -54.8%
Rubeosis	4	77	518 (36 -351)	47 - 68.7	0% -45%
Scleral necrosis	4	5	5696 (36-2499)	49.5-54.8	0% -0.9%
Papillopathy	3	25	441 (36 to 351)	50 to 68.7	0% to 7.1%
Retinal detachment	4	152	1341 (62 to 865)	30 to 70.3	3.1% to 15.2%

Appendix Table F51

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KQ 3: Ocular tumors; Event probabilities, CASE SERIES

Outcome (KM probabilities)	# Studies	Total N (range)	Range
5-year Enucleation-free survival	3	2889 (54 -2499)	77.4% to 95.1%
5-year Neovascular Glaucoma	3	3464	10.5% to 34.9%
5-year Globe Preservation	1	2499	94.8%
1, 2, 3, 4, 5, 10 year Retinopathy-free Survival	1	1127	87%, 53%, 33%, 21%, 15%, 7%
1, 2, 3, 4, 5, 10 year Optic Neuropathy-free Survival			92%, 73%, 61%, 52%, 48%, 26%
1, 3, 5 year Incidence of Cataracts	1	1696	4.9%, 12%, 18.7%
1, 3, 5 year Vision-Impairing Cataracts			1.2%, 6.7%, 12.8%
1, 2, 5 year Incidence of Dry Eye	1	853	6%, 11.2%, 23%
1, 2, 5 year Incidence of Severe Dry Eye			2.1%, 4.8%, 10.9%
5 yr Absence, Radiation-induced Retinopathy	1	629	14.2%
5 year Absence of Optic Neuropathy			36.6%

Appendix Table F52

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KQ 5, Cost-effectiveness: Adults, intraocular melanoma

	Moriarty 2015 (USA), QHES 88/100
Population	59 years of age with intraocular melanoma; 5 year time horizon
Intervention(s)	PBT (timing unclear) vs. enucleation
ICER	$106,100/QALY
One-way SA	• Model sensitive to 13 parameters for all therapies: probability of local recurrence, end-of-life costs for disease, treatment costs , post-treatment utility • ICER range for low parameter values: $9,543/QALY to $234,683/QALY • ICER range for high parameter values: $9,522/QALY to $441,750/QALY
Author's Conclusion	**PBT was not cost-effective compared to enucleation at WTP of $50,000/QALY; Results were not robust to sensitivity analyses and showed that decreased payment rates for PBT could be result in PBT being dominant over enucleation**
Limitations	• **RR for progression from local recurrence to distant metastasis derived from study using plaque brachytherapy; may not apply to other treatment strategies** • **No costs of treatment complications** • **QOL data from study of general melanoma (not specific to this population)** • **Strong assumptions about costs (costs for recurrence; cost of radiotherapy substituted with cost of enucleation; no cost specific to distant metastasis)** • **Frequency of enucleation as treatment option is unclear**

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Summary: Adult Ocular Tumors

Incidence (per 100,000)	Numbers of Studies		Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE		Impact of new comparative studies
	2014	2019	2014	2019	2014 vs.2019
0.9	RCT=1; CC=8; CS=45	CC=3; CS=21; Econ=1	**Superior (Incremental)* B: ↑ H: ↓ Moderate**	**PBT vs. BT alone** Inferior B: ↓ H: = Low **PBT + TSR vs. BT + TSR** Incremental B: ↑ H: = Low **PBT vs. SRS** Insufficient	3 additional comparative studies with very different comparators. Prior report included primarily enucleation (4/7 studies) as comparator, also TTT (1 study); remaining 2 studies were indirect comparisons of case series. The net health benefit across all comparators (across both reports) is unclear.

*There is a discrepancy in the 2014 report between the summary table and report text

2019 Economic: 1 good quality CUA of PBT vs. enucleation for intraocular melanoma found PBT not cost effective at WTP of $50K/QALY; results were not robust to sensitivity analysis.

KQ 2, 4: No comparative studies identified

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Summary: Adult Ocular Tumors

Tumor	2014 Report		2019 Report	
	# studies	Comparator* (vs. PBT)	# studies	Comparator* (vs. PBT)
Ocular	8 (2 NCCS)	Enucleation (4) PBT + TTT (2) (1 RCT) PBT + endoresection (1) PBT + chemotherapy (1) PBT + laser (1)	3	Brachytherapy + TSR (1) **Brachytherapy alone (1)** Stereotactic radiosurgery (1)

2014 vs. 2019 report: The net health benefit across reports (and comparators) is unclear

- **There are substantial differences in comparators (above); tumor types differed**
- **2014 report:** ES table listed superior net health benefit for PBT; improved benefits appears to be based on statistically significant increases in OS across two cohort studies at 2-5 years, 50% higher probability of metastasis -free survival and lower cancer and metastasis-related mortality with PBT compared with enucleation. Determination of less harm is less clear. In the report, authors state "Limited, low-quality evidence suggests comparable rates of harm for PBT relative to treatment alternatives in patients with ocular tumors" consistent with incremental net benefit
- **2019 report:** Comparisons generally less invasive for 3 new cohort studies; Net health benefit varied by comparator. Most studies were of uveal melanoma

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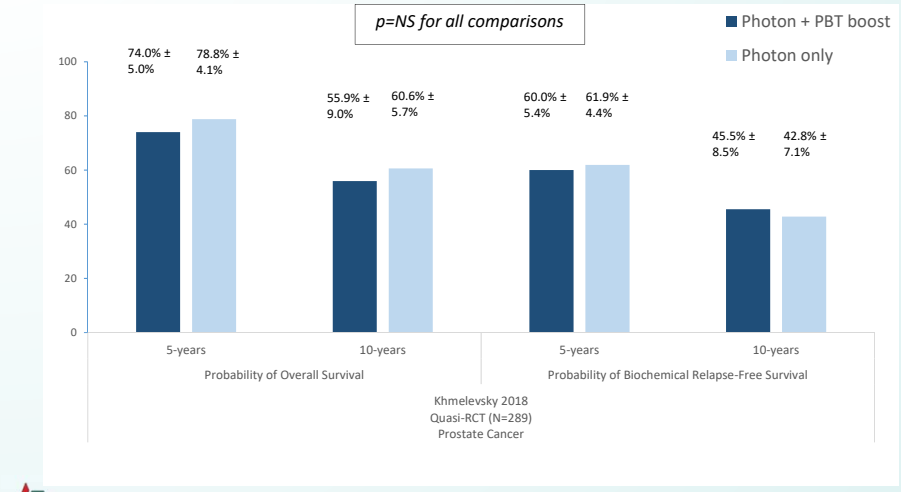
KQ 1 (Curative Intent): Prostate

Overall and Biochemical Relapse-Free Survival, Quasi RCT



SOE Low

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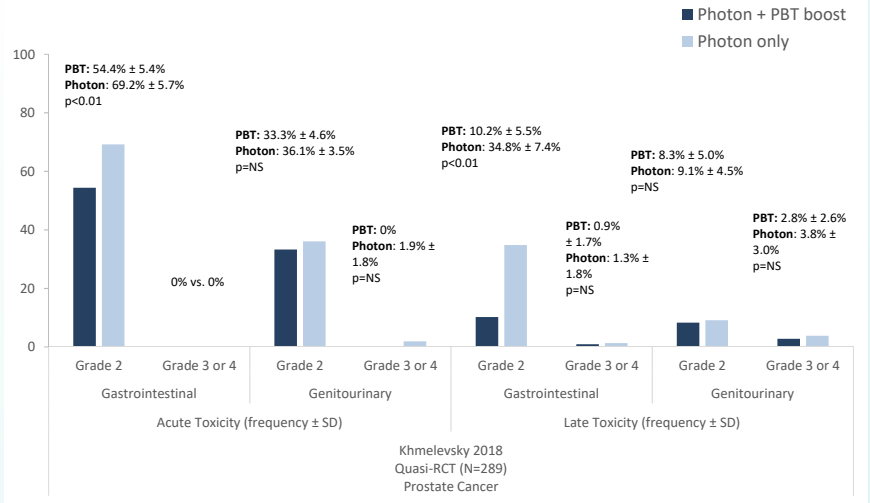
KQ 3 (Safety): Prostate

Toxicity – quasi-RCT



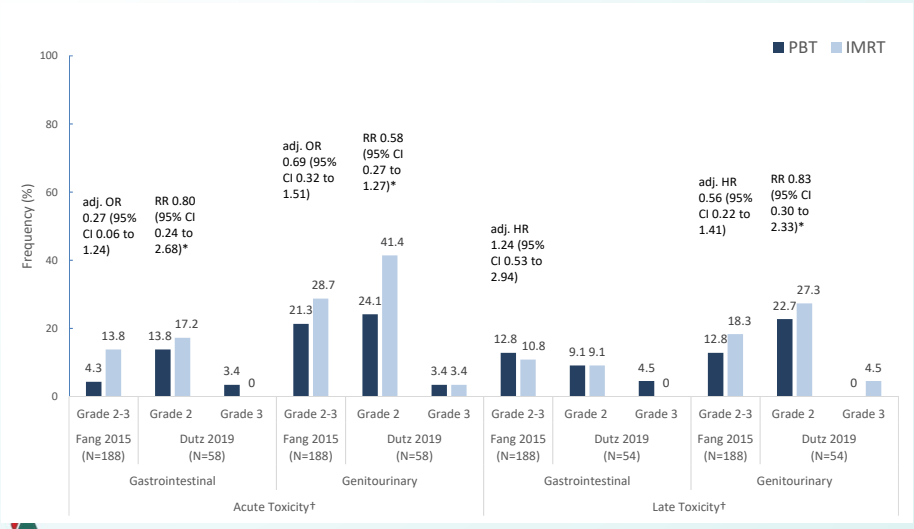
Actuarial frequency of GI and GU toxicities Grade ≥3: 1.7% vs. 8.7%, p=NR

SOE Low

94

KQ 3 (Safety): Prostate

Toxicity – Retrospective cohortstudies



SOE Low

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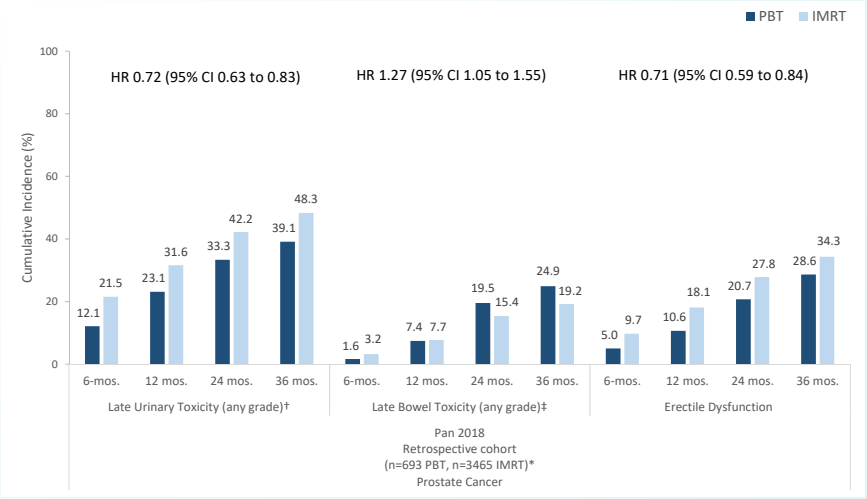
KQ 3 (Safety): Prostate

Toxicity – Retrospective cohort studies (database) (cont.)



SOE Low

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KQ 3: Prostate Cancer; Toxicities
CASE SERIES

Outcome	# Studies	# With outcome	Total N (range of N's)	Median F/U (months)	Range (95%CI)
Acute Grade ≥3 Toxicity					
Gastrointestinal	4	0	761 (49 to 423)	18 to 62.4	0%
Genitourinary	5	12	1423 (49 to 1289)	14.5 to 66	0% to 0.9%
Late Grade ≥3 Toxicity					
Gastrointestinal	8	18	4809 (49 to 1375)	14.5 to 70	0% to 1.2%
Genitorurinary	8	67	4809 (49 to 1375)	14.5 to 70	0% to 4.7%

Outcome, timing, grade	Studies	N	Rate, %
5-year Incidence of Late Grade 3 GI Toxicity	1	1327	0.6%
5-year Rate, Late Gastrointestinal Toxicities; Grades 1, 2, 3			10%, 3.8%, 0.1%
5-year Rate, Late Genitourinary Toxicities; Grades 1, 2, 3			8.9%, 1.9%, 0.1%
Cumulative Incidence, Argon plasma coagulation application for rectal bleeding	1	423	5.6%

Appendix Tables F56, 57

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KQ 4 (Contextual Studies): Prostate
Comparison of PBT Dose, Fractionation, Delivery Method

Hypo- vs. standard fractionation (1 RCT, 1 retrospective cohort)
- NS differences between groups in QoL (various measures) and GI or GU toxicities grade ≥3; no treatment related deaths

"Moderate" (MHF) vs. "extreme" (EHF) hypofractionation (1 RCT)
- 7-year OS: 97.5% for the entire population (3 deaths total; 7-year BCFFS statistically lower in the EHF group (46.2% vs. 76.2%; adjusted HR 3.2, 95% CI 1.5 to 6.9, p=0.003)
- NS differences between groups in acute or late GI or GU toxicities grade ≥3

Passive scatter vs. spot scanning technique (1 retrospective cohort)
- NS differences between groups in QoL (EPIC questionnaire) or cumulative frequencies of grade ≥2 GU and GI toxicities or of argon plasma coagulation application for rectal bleeding

SOE not done for contextual studies

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Summary: Adult Prostate Cancer

Condition	Incidence (per 100,000)	Numbers of Studies		Net Health Benefit vs. Comparators Type of Net Benefit (B, H) SOE		Impact of new comparative studies
		2014	2019	2014	2019	2014 vs. 2019
Prostate	109.2	RCT=1 CC=9; CS=19; Econ=3	Quasi-RCT=1; CC=3; CS=11	Comparable B: = H: = Low**	Comparable B: = H: = Low	Similar conclusions (addition of a quasi-RCT and 3 retrospective cohorts)

2014 vs. 2019: The 2014 report included 1 RCT and 5 comparative studies (4 were NCCS) that reported clinical outcomes and concluded that net health benefits for PBT were comparable to other treatments (photons alone, IMRT, 3DCRT, brachytherapy, watchful waiting; SOE low). Evidence from 1 new quasi-RCT and 3 new retrospective cohort studies also suggest that PBT is comparable to photons alone and IMRT for benefits and harms. **(SOE Low)**

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SUMMARY: Adult conditions/tumors

- 2014 vs. 2019: 37 new comparative studies were identified.
- New studies identified for some tumors/conditions for which only case series (insufficient evidence) were available in the 2014 report; 4 new CUA were identified
- SOE was Low for all conditions/outcomes with the exception of one study of HCC
- Comparative net health benefit based on new evidence changed for some conditions; differences in comparators, tumor types, PBT treatment approaches and study quality likely explain differences in NHB considerations between the 2014 and 2019 reports.
- No studies permitted evaluation of differential effectiveness or safety

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SUMMARY - Adult tumors

- **No *comparative* evidence for**:
  - Bladder cancer
  - Bone cancer
  - Lymphoma
  - Benign tumors (hemangioma, meningioma, pituitary)
  - Various/mixed tumor types
- **No evidence meeting inclusion criteria was identified for**:
  - Sarcoma
  - Seminoma
  - Thymoma
  - AVMs

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SUMMARY - Adult tumors (cont.)

The net health benefit of PBT was *incremental* to other treatments:

- Esophageal tumors
- Liver tumors
- Ocular tumors (PBT + TSR vs. brachytherapy + TSR)

The net health benefit of PBT was *comparable* to other treatments

- Brain/spinal tumors (curative) (PBT boost vs. photons alone)
- Head and neck tumors (non-skull-base)
- Lung cancer
- Prostate cancer

The net health benefit of PBT was *inferior* to other treatments for:

- Ocular tumors (PBT vs. brachytherapy alone)

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SUMMARY - Adult tumors (cont.)

There was *insufficient or unclear* evidence of a net health benefit from comparative studies for:

- Brain/spinal tumors (salvage)
- Breast cancer
- GI tumors (Pancreas)
- Head and neck *skull-base* tumors (Chondrosarcoma)
- Ocular tumors (PBT vs. stereotactic radiotherapy)

Economic Studies: Conclusions are limited from hypothetical models; clinical data were from case series, many models did not fully specify factors that may impact CE or describe model inputs; for some sensitivity analyses suggest substantial variation in cost-effectiveness.

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General SUMMARY

- Focus of 2014 and 2019 reports was on comparative studies
- Comparative evidence base: Retrospective cohort studies at moderately high risk of bias;
  - –Selection bias
  - –Attrition bias
  - –Confounding/residual confounding
- RCTs may not be ethical or feasible in some populations.
- SOE took into account lack of RCT evidence and challenges of doing RCTs; however,
  - –the quality of NROS is **not** elevated;
  - –the greater uncertainty regarding effects needs to be considered

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General SUMMARY

- Comparators 2014 vs. 2019 reports differed; for some conditions, comparators may not reflect current practices; 2014 report included non-FDA approved treatments (e.g., carbon ion)
- Heterogeneity across studies and the reports with regard to conditions/tumor types, stages, use of chemotherapy and adjunctive treatments and PBT treatment approaches
- >150 case series on many different tumor types do not answer questions of comparative effectiveness or safety.

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Questions?

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Washington State Health Care Authority

Key Questions and Background

Proton beam therapy – re-review

Background:

Clinical need and target population

Overall, it's estimated that 1.7 million new cases of cancer are diagnosed yearly and cancerous conditions are responsible for over half a million deaths per year. Treatment options for cancerous and noncancerous conditions vary depending on the type and stage of cancer and can include radiation therapy, chemotherapy, targeted therapy (e.g. inhibitor drugs), immunotherapy (including monoclonal antibodies) and surgery. In recent years the use of proton beam therapy (PBT) has expanded to include a variety of conditions including a number of cancer types, noncancerous brain tumors and cancerous conditions afflicting the central nervous system as well as eyes, lungs, liver, prostate, spine, and pelvis.

Technology of interest

The use of protons for radiotherapy has a history of over 60 years of clinical use. In conventional radiotherapy, photons deliver radiation across tissue depths on the way toward the target tumor and beyond. In contrast, PBT, which is a form of external beam radiotherapy, deposits peak radiation energy more precisely at or around the target followed by sharp decline in energy output to deeper tissues via a phenomenon known as the Bragg peak (Larsson, 1958). Because the proton beam is focused on a specific area, a greater dose of radiation may be delivered to the target neoplasm(s) while mitigating unwanted radiation delivered to surrounding tissue (Levin, 2005). PBT use was initially directed towards conditions where sparing sensitive adjacent normal tissues was considered to be of utmost importance (such as cancerous or noncancerous malformations of the brain stem, eye, or spinal cord) or for many pediatric tumors because of the particular risk of pronounced acute and long-term toxicity in pediatric patients (Thorp, 2010). PBT may be most promising for tumors in close proximity to organs at risk (OAR).

In the past two decades the number of centers offering PBT has increased to over 20, with more planned or under construction, even given the high cost of facility construction and operation. Despite increasing availability of PBT and its potential for precise delivery of radiation therapy, evidence of its effectiveness compared with other forms of therapy and with the emerging techniques, such as intensity modulated radiation therapy (IMRT) is evolving and currently not unclear for some conditions.

Policy context/reason for selection:

This topic was originally reviewed in 2014. It is being re-reviewed in 2018 due to newly available published evidence.

Objectives

The aim of this report is to update the 2014 HTA on proton beam therapy (PBT) by systematically reviewing, critically appraising and analyzing new research evidence on the safety and efficacy of PBT, as a primary or as a salvage therapy (i.e., for recurrent disease or failure of initial therapy), for the treatment of multiple cancer types as well as selected noncancerous conditions in adults and children.

Key questions (from previous report):

1. What is the comparative impact of proton beam therapy (PBT) treatment with curative intent on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy) for the following conditions:
    a. Cancers
        i. Bone tumors
        ii. Brain, spinal, and paraspinal tumors
        iii. Breast cancer
        iv. Esophageal cancer
        v. Gastrointestinal cancers
        vi. Gynecologic cancers
        vii. Head and neck cancers (including skull base tumors)
        viii. Liver cancer
        ix. Lung cancer
        x. Lymphomas
        xi. Ocular tumors
        xii. Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma)
        xiii. Prostate cancer
        xiv. Soft tissue sarcomas
        xv. Seminoma
        xvi. Thymoma
        xvii. Other cancers
    b. Noncancerous Conditions
        i. Arteriovenous malformations
        ii. Hemangiomas
        iii. Other benign tumors (e.g., acoustic neuromas, pituitary adenomas)
2. What is the comparative impact of salvage treatment (including treatment for recurrent disease) with proton beam therapy versus major alternatives on survival, disease progression, health-related quality of life, and other patient outcomes versus radiation therapy alternatives and other cancer-specific treatment options (e.g., surgery, chemotherapy) for the condition types listed in key question 1?
3. What are the comparative harms associated with the use of proton beam therapy relative to its major alternatives, including acute (i.e., within the first 90 days after treatment) and late (>90 days) toxicities, systemic effects such as fatigue and erythema, toxicities specific to each cancer type (e.g., bladder/bowel incontinence in prostate cancer, pneumonitis in lung or breast cancer), risks of secondary malignancy, and radiation dose?

4. What is the differential effectiveness and safety of proton beam therapy according to factors such as age, sex, race/ethnicity, disability, presence of comorbidities, tumor characteristics (e.g., tumor volume and location, proliferative status, genetic variation) and treatment protocol (e.g., dose, duration, timing of intervention, use of concomitant therapy)?
5. What is the comparative cost-effectiveness of proton beam therapy in the short- and long-term relative to other types of radiation therapy, radiation therapy alternatives or other cancer-specific treatment options (e.g., surgery, chemotherapy)?

Final scope: (based on previous report and consideration of public comment)

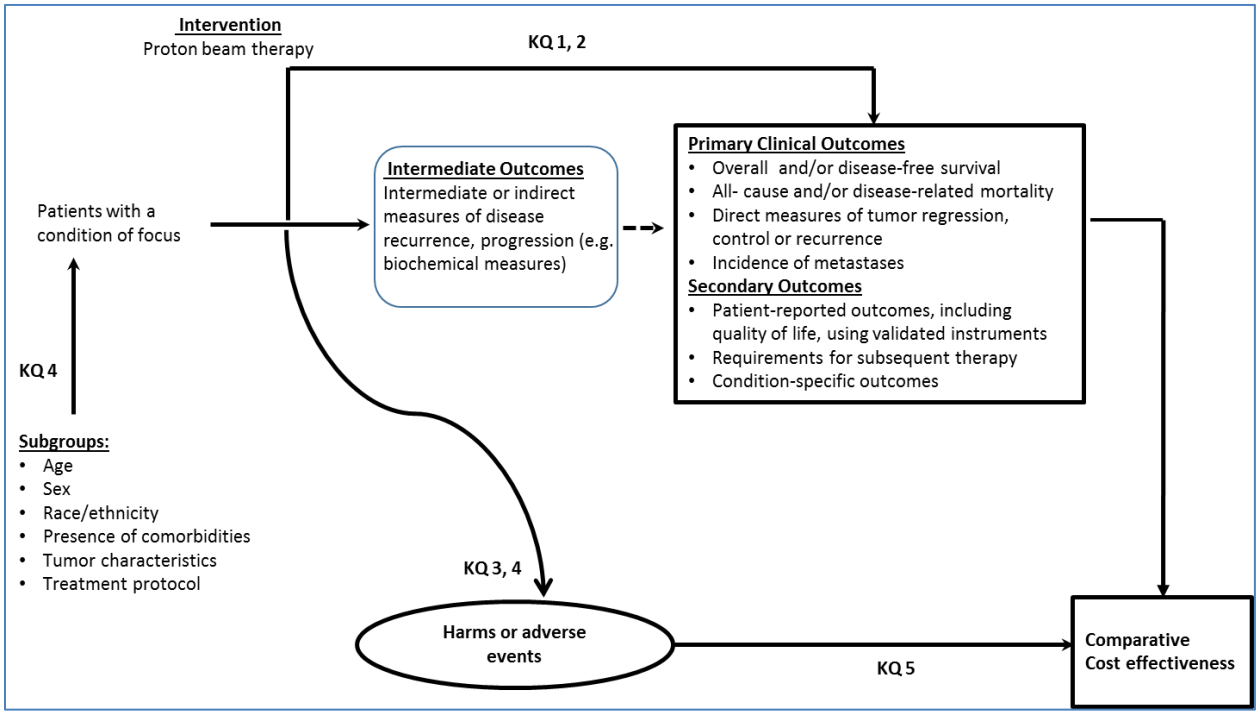
Inclusion and exclusion

Study Component	Inclusion	Exclusion
Population	Adults and children undergoing treatment of primary or recurrent disease to include: • Cancers (bone, brain/spinal/paraspinal, breast, esophageal, gastrointestinal, gynecologic, head and neck, liver, lung, ocular, pediatric, and prostate cancers; lymphomas, sarcomas, seminomas, thymomas, other cancers) • Noncancerous conditions (arteriovenous malformations, hemangiomas, other benign tumors).	• Conditions not amenable to proton-beam therapy or for which proton beam therapy would be contra-indicated.
Interventions	• Proton beam therapy (PBT) use as a • Curative therapy • Primary or monotherapy • "Salvage" treatment (e.g. following failure of initial therapy or disease recurrence) • "Boost" mechanism to conventional radiation • Combination therapy with other treatments (e.g., chemotherapy, surgery).	• Devices or therapies that are not FDA approved or cleared
Comparator	• Other radiation therapy alternatives (e.g., intensity-modulated radiation therapy (IMRT), stereotactic radiation techniques, other external beam therapies, and brachytherapy) • Other treatment alternatives specific to each condition type treated; may include chemotherapy, immunotherapy, surgical procedures, and other devices (e.g., laser therapy for ocular tumors). • Dose/fractionation comparison (will be included for completeness as was done in prior report) but not formally evaluated as evidence	• Technologies or treatments that are not widely available or are no longer routinely used • Devices or therapies that are not FDA approved or cleared

Study Component	Inclusion	Exclusion
Outcomes	**Clinical outcomes**: <u>Primary</u> • Overall survival/disease-free survival • All-cause and/or disease-related mortality • Direct measures of tumor regression, control or recurrence • Incidence of metastases <u>Secondary or indirect (intermediate) measures</u> • Patient reported outcomes, including health-related quality of life (HrQoL), based on validated instruments • Requirements for subsequent therapy • Other outcomes specific to particular conditions (e.g., visual acuity for ocular tumors, shunt requirements for arteriovenous malformations) • Intermediate measures of tumor recurrence such as biochemical measures **Safety outcomes**: • Treatment-related harms, with a focus on adverse effects requiring medical attention, to include: ♦ Generalized effects (e.g., fatigue, erythema) ♦ Localized toxicities specific to each condition (e.g., urinary incontinence in prostate cancer, pulmonary toxicity in lung or breast cancer) to include consideration of: ▪ Early (≤90 days post-treatment) ▪ Late (>90 days post-treatment) • Secondary malignancy risk due to radiation exposure **Economic outcomes**: • Long term and short term comparative cost-effectiveness measures (e.g. ICER)	• Non-clinical outcomes
Study Design	• Focus will be on highest quality (lowest risk of bias) comparative studies (e.g., randomized controlled trials, comparative cohort studies with concurrent controls) for questions 1-4. • Case series will be considered but will not be the primary focus of evaluation for each key question. • Case series in children with <10 patients will be considered if no comparative studies are available. • Case series designed specifically to evaluate safety may be included • Dosimetry and planning studies may be included for context. To the extent that they specifically answer the key questions, information will be included as part of the evidence base.	• Simulation studies • Studies of low quality (high risk of bias) • Comparative studies with fewer than 10 per treatment arm • Case reports • Case series in adults with <30 patients; Case series of ≥ 10 patients may be considered for very rare conditions. • Studies comparing modes of therapy; dose comparisons may be included for completeness/context per previous report

Study Component	Inclusion	Exclusion
	• Formal, full economic studies will be sought for question 5. Studies using modeling may be used to determine cost-effectiveness.	
Publication	• Studies published in English in peer reviewed journals, technology assessments or publically available FDA reports • Studies published subsequent to the 2014 report (previous report search date through February 2014) • For question 5, comparative, full formal economic analyses (e.g., cost-effectiveness, cost-utility studies) published in English in a peer reviewed journal	• Abstracts, editorials, letters • Duplicate publications of the same study that do not report different outcomes or follow-up times • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when full results are published in later versions • Incomplete economic evaluations such as costing studies

Figure 1. Analytic framework



HTCC Coverage and Reimbursement Determination
Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

3. Factors for Consideration - Importance

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical committee findings and decisions

Efficacy considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next step: Cover or no cover

If not covered, or covered unconditionally, the chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next step: Cover with conditions

If covered with conditions, the committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.
2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical committee evidence votes

First voting question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Discussion document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety outcomes	Importance of outcome	Safety evidence/ confidence in evidence
Endocrine-related toxicities (e.g. thyroid, hormone, etc.)		
Other Toxicities (e.g. vascular, vision, hearing etc)		
White Matter Lesion		
Radiation Necrosis		
Injury to CNS or Brainstem		
Vascular		
Hearing Loss		
Neurocognitive		
Enucleation		
Osteoradionecrosis		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence
Overall Survival (OS)		
Progression Free Survival (PFS)		
Mortality		
Distant Metastasis		
Locoregional Failure-Free Survival		

Cost outcomes	Importance of outcome	Cost evidence
Cost		
Cost effectiveness		

Special population / Considerations outcomes	Importance of outcome	Special populations/ Considerations evidence
Age		
Race		
Gender		
Ethnicity		

For safety:

Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For efficacy/ effectiveness:

Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For cost outcomes/ cost-effectiveness:

Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____Not covered _____ Covered unconditionally _____ Covered under certain conditions

Discussion item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next step: proposed findings and decision and public comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?
2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next step: final determination

Following review of the proposed findings and decision document and public comments:

Final vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome chair will lead discussion to determine next steps.

Medicare Coverage and Guidelines
[From page 51 of Final Evidence Report]
Table 1. Overview of Medicare and Payer Policies

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
Centers for Medicare and Medicaid Services [7,9,10]	71 references, evidence not characterized	At present, there is no NCD for proton beam therapy; additionally, the only published LCD (L34634) on PBT that covered all states (including Washington) and was used in the prior report was retired as of Sept. 1st 2017 (https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34634&ver=15&Date=&DocID=L34634), however, two LCDs (L35075 and L36658) applying to twelve states (not including Washington) are active with similar coverage conditions as the retired LCD. Conditions of the active and retired LCDs are provided below with additions from the active LCDs highlighted in bold: Conditions for Medical Necessity CMS considers PBT reasonable when sparing the surrounding normal tissue cannot be adequately achieved with photon-based radiotherapy and is of added clinical benefit to the patient. Examples of treatment advantage may include: 1. The target VOLUME is in close proximity to one or more critical structures and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s) 2. A decrease in the amount of dose inhomogeneity in a large treatment VOLUME is required to avoid an excessive dose "hotspot" within the treated VOLUME to lessen the risk of excessive early or late normal tissue toxicity. 3. A photon-based technique would increase the probability of clinically meaningful normal tissue toxicity by exceeding an integral dose-based metric associated with toxicity. 4. The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue. Conditions considered frequently supported by the above requirements (Group 1) include: • Ocular Tumors, including intraocular melanomas • Skull-base tumors including but not limited to: ○ Chordomas ○ Chondrosarcomas ○ Primary or metastatic tumors of the spine where spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated • Unresectable benign or malignant tumors of the CNS, including but not limited to: ○ Astrocytoma, glioblastoma, medulloblastoma, acoustic neuroma, craniopharyngioma, benign and atypical meningioma, pineal gland tumors, and arteriovenous malformations • Primary hepatocellular cancer treated in a hypofractionated regimen • Pediatric Primary or benign solid tumors in children treated with curative intent and occasional palliative	Rationale: NR

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
		treatment of childhood tumors when at least one of the four criteria noted above apply • Pituitary neoplasm • Advanced staged and/or unresectable malignant lesions of the head and neck • Malignant tumors of the paranasal and other accessory sinuses • Unresectable retroperitoneal sarcoma • **Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients** Coverage is considered investigational and limited to providers who have demonstrated experience in data collection and analysis with a history of publication in the peer-reviewed medical literature for the following conditions (group 2): • Unresectable lung cancers, upper abdominal cancers, and left breast tumors • Advanced, unresectable pelvic tumors, pancreatic and adrenal tumors • Skin cancer with nerve innervation of the skull base • Unresectable lesions of the liver, biliary tract, anal canal and rectum • Non-metastatic prostate cancer, with documented clinical staging and demonstration of clinical necessity of PBT • **Hodgkin or Non-Hodgkin Lymphoma involving the mediastinum or in non-mediastinal sites where PBT has the potential to reduce the risk of pneumonitis or late effects of radiation therapy**	
Bellwether Policies			
Aetna (2018) [14]	Literature Review (166 references) including: 1 CER (VHA 2015), 2 CADTH assessments, 1 assessment of economic evaluation (VATAP, Flynn 2010), 1 AHRQ assessment (Trikalinos 2009),4 HTAs (Wild 2013,RIHTA 2011, ICER 2008, Washington HTA 2014), guidelines from ASTRO NCCN, ACR, and Alberta Health Services; 7 SRs	Aetna considers proton beam radiotherapy (PBRT) **medically necessary** in any of the following radiosensitive tumors: a. Chordomas or chondrosarcomas arising at the base of the skull or cervical spine without distant metastases; or b. Malignancies in children (21 years of age and younger); or c. Uveal melanomas confined to the globe (i.e., not distant metastases) (the uvea is comprised of the iris, ciliary body, and choroid [the vascular middle coat of the eye]). Aetna considers proton beam radiotherapy for treatment of prostate cancer **not medically necessary** for individuals with localized prostate cancer because it has not been proven to be more effective than other radiotherapy modalities for this indication. Proton beam therapy for metastatic prostate cancer is considered experimental and investigational. Aetna considers proton beam radiotherapy **experimental and investigational** for all other indications, including the following indications in adults (over age 21) (not an all-inclusive list) because its effectiveness for these indications has not been established: • Adenoid cystic carcinoma • Age-related macular degeneration (AMD) • Angiosarcoma	Rationale: NR

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
	(Lodge 2007; Lance, 2010; Brada et al, 2009; Efstathiou et al, 2009; ICER, 2008; Wilt et al, 2008; Brada et al, 2007; Olsen et al, 2007), various studies	• Atypical meningioma • Bladder cancer • Brain tumors • Breast cancer • Cardiac intimal sarcoma • Carotid body tumor • Cavernous hemangioma • Cervical cancer • Cholangiocarcinoma • Choroidal hemangioma • Dermatofibrosarcoma protuberans • Desmoid fibromatosis • Desmoid tumor (aggressive fibromatosis) • Ependymoma • Esophageal cancer • Ewing's sarcoma • Fibrosarcoma of the extremities • Gangliomas • Glioma • Head and neck cancer (including nasopharyngeal carcinoma) • Hemangioblastoma • Hemangioendothelioma • Hepatocellular carcinoma • Lymphomas (Large cell lymphoma, Hodgkin's lymphoma, Non-Hodgkin lymphoma) • Intracranial arterio-venous malformations • Leiomyosarcoma of the extremities • Liposarcoma • Liver metastases • Lung cancer (including non-small-cell lung carcinoma) • Maxillary sinus tumor • Mesothelioma • Multiple myeloma • Nasopharyngeal tumor • Non-uveal melanoma • Oligodendroglioma • Optic nerve schwannoma • Optic nerve sheath meningioma • Pancreatic cancer • Parotid gland tumor • Pineal tumor • Pituitary neoplasms • Rectal cancer • Retroperitoneal/pelvic sarcoma • Rhabdomyoma • Sacral chordoma • Salivary gland tumors (e.g., sublingual gland tumor, submandibular gland tumor) • Seminoma • Sino-nasal carcinoma • Small bowel adenocarcinoma • Soft tissue sarcoma • Squamous cell carcinoma of the eyelid, tongue/glottis • Thymic tumor	

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
		• Thymoma • Tonsillar cancer • Uterine cancer • Vestibular schwannoma • Yolk cell tumor	
Anthem (2018) [18]	Literature review (149 references) including: Guidelines from ASTRO, ACR, AAO, NCCN; 1 BCBS technology assessment, 2 ongoing trials; 4 AHRQ reviews	Updated 02/2018 Anthem considers proton beam radiation therapy, with or without stereotactic techniques, as **medically necessary** for any of the following conditions: a. As primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) involving tumors of up to 24 mm in largest diameter and 14 mm in height, and with no evidence of metastasis or extrascleral extension; or b. As postoperative therapy for individuals who have undergone biopsy or partial resection of a chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (for example, skull-base chordoma or chondrosarcoma) or cervical spine and have residual, localized tumor without evidence of metastasis; or c. Pituitary adenoma when conventional stereotactic radiation is not an available option; or d. Intracranial arteriovenous malformation (AVM) not amenable to surgical excision or other conventional forms of treatment; or e. Central nervous system (CNS) lesions including but not limited to, primary or metastatic CNS malignancies or AVM, adjacent to critical structures such as the optic nerve, brain stem or spinal cord; or f. Primary or benign solid tumors in children treated with curative intent. Proton beam radiation therapy is considered **not medically necessary** for the following condition: Choroidal neovascularization secondary to age-related macular degeneration (AMD). Proton beam radiation therapy is considered **investigational and not medically necessary** when criteria are not met and for all other indications, including, but not limited to, the treatment of: Localized prostate cancer.	Rationale: NR

[From page 26 of Final Evidence Report]

Table 2. Summary of proton beam therapy recommendations by cancer type across guidelines, appropriateness criteria, CMS coverage, and payer policies

Guideline & Appropriateness Criteria				CMS and Payer Policies
Condition	**Recommendation**	**Strength of Recommendation**	**Evidence Quality**	**Coverage**
Bone Cancer [202,229]	NCCN: M ACR*: N	NCCN: Moderate ACR*: NR	NCCN: 2A ACR*: NR	Investigational or NR
Brain, Spinal, Paraspinal Cancer[74,105,202]	NCCN: M (CNS cancers) NICE: Y AIM: Y (CNS tumors, chordomas, chondrosarcoma)	NCCN: Moderate NICE: NR AIM: NR	NCCN: 2A NICE: NR AIM: NR	LCDs† CMS[7,9,10]: Y (unresectable, pituitary, chordomas, chondrosarcomas) Payer Policies Aetna: Y (chordomas/chondrosarcomas of skull, cervical spine; pituitary, Intracranial arteriovenous malformation ; CNS)
Breast Cancer[105]	AIM: N	AIM: NR	AIM: NR	Investigational or NR
Esophageal Cancer[105]	AIM: N	AIM: NR	AIM: NR	Investigational or NR
Gastrointestinal Cancer[105]	AIM: N AIM: N (pancreatic)	AIM: NR	AIM: NR	Investigational or NR
Gynecologic Cancer [105,229]	AIM: N ACR*: N	AIM: NR ACR*: NR	AIM: NR ACR*: NR	Investigational or NR
Head & Neck Cancer [105,202,229]	NCCN: M AIM: N ACR*: Y	NCCN: Moderate AIM: NR ACR*: NR	NCCN: 2A AIM: NR ACR*: NR	LCDs† CMS[7,9,10]: Y (advanced/unresectable; paranasal/sinus)
Liver Cancer [105,202]	NCCN: M AIM: N	NCCN: Moderate AIM: NR	NCCN: 2A AIM: NR	Investigational or NR
Lung Cancer [74,105,144,202]	ASCO: Y (pleural mesothelioma) NCCN: M (pleural mesothelioma & NSCLC) AIM: N ACR*: N	ASCO: Strong NCCN: Moderate AIM: NR ACR*: NR	ASCO: Intermediate NCCN: 2A AIM: NR ACR*: NR	Investigational or NR
Lymphomas [105,202,229]	NCCN: M AIM: N ACR: M	NCCN: Moderate AIM: NR	NCCN: 2A AIM: NR	Investigational or NR
Ocular Cancers [105,202]	NCCN: M (uveal melanoma) AIM: Y	NCCN: Moderate AIM: NR	NCCN: 2A AIM: NR	LCDs† CMS[7,9,10]: Y Payer Policies Aetna: Y (uveal) Anthem: Y (uveal) Anthem: N (choroidal neovascularization secondary to age-related macular degeneration)

Guideline & Appropriateness Criteria				CMS and Payer Policies
Condition	**Recommendation**	**Strength of Recommendation**	**Evidence Quality**	**Coverage**
Pediatric Cancers [74,229]	NICE: Y AIM: Y	NICE: NR AIM: NR	NICE: Not sufficient	LCDs† CMS[7,9,10]: Y Payer Policies Aetna: Y Anthem: Y
Prostate Cancer [74,105,202,211,229]	ASTRO: N NCCN: N NICE: N AIM: N ACR*: M	ASTRO: Moderate NCCN: Moderate AIM: NR ACR: NR	ASTRO: Grade C NCCN: 2A AIM: NR ACR*: NR	Aetna: N
Sarcomas [202]	NCCN: M	NCCN: Moderate	NCCN: 2A	LCDs† CMS: Y (unresectable retroperitoneal sarcoma)
Seminomas	NR	NR	NR	Investigational or NR
Thymomas [202]	NCCN: M	NCCN: Moderate	NCCN: 2A	Investigational or NR

ACR = American College of Radiology; AIM = American Imaging Management; ASTRO = American Society for Radiation Oncology; CMS = Centers for Medicare and Medicaid Services; CNS = central nervous system; LCD = local coverage determination; NCCN = National Cancer Care Network; NICE = The National Institute for Health and Care Excellence; NR = not reported; Y = Yes.
*ACR ratings are associated with N, M, and Y ratings based on their 1-9 rating system; in this table N = 1, 2, 3 (usually not appropriate); M = 4, 5, 6 (may be appropriate); and Y = 7, 8, 9 (usually appropriate). For more information on their rating system see Appendix Table L2.
†At the time of this report the only CMS policy related to proton beam therapy and applied to Washington State had been retired as of Sept. 2017; two LCDs active in twelve states (not including Washington State) are active however, with only minor differences in coverage determinations. Information on the coverage decisions are reported here for reference, more detail is available in section 2.7, Table 1.