Washington State Health Care Authority

Proton Beam Therapy: Re-review

Final main appendices

April 15, 2019

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Proton Beam Therapy: Re-Review

Aggregate Analytics, Inc.

FINAL MAIN APPENDICES

April 15, 2019

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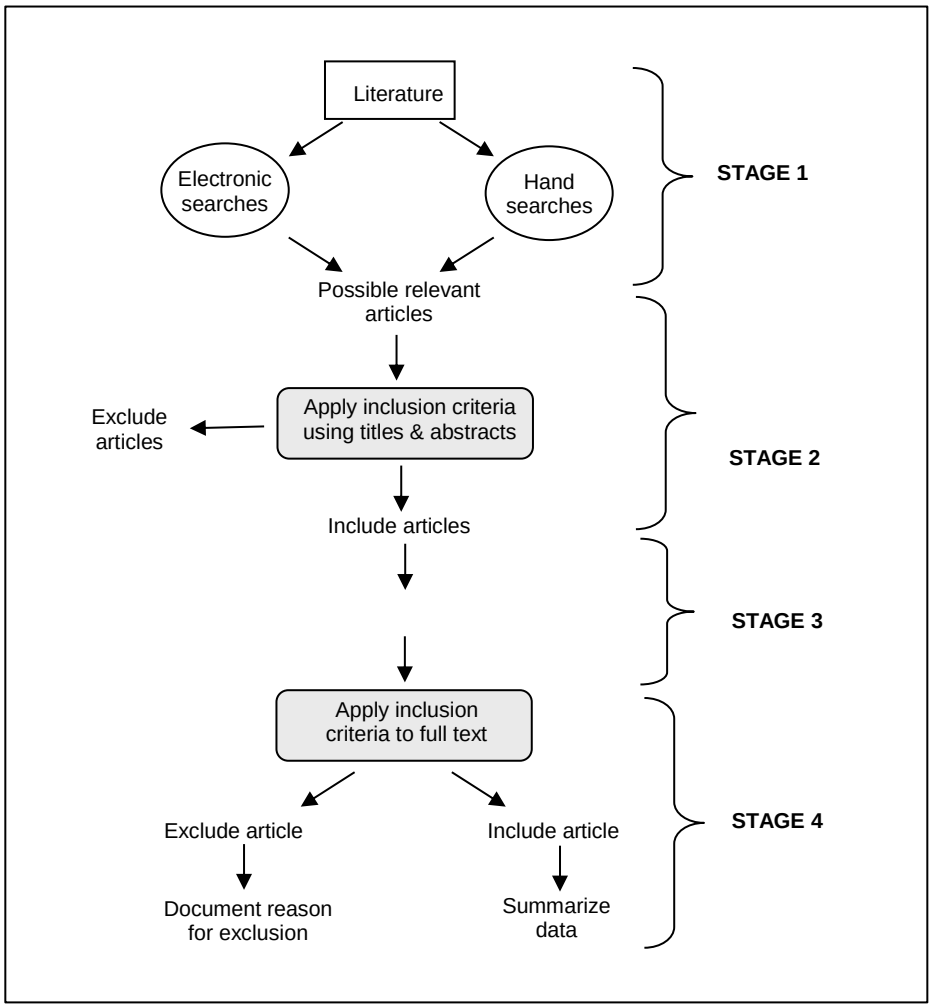
APPENDIX A. Algorithm for Article Selection



APPENDIX B. Search Strategies

Below is the search strategy for PubMed. Parallel strategies were used to search other electronic databases listed below. Keyword searches were conducted in the other listed resources. In addition, hand-searching of included studies was performed.

Search strategy (PubMed)
Search date: November 2013 through 12/31/2018
Filters: Abstract available, English

1	“proton therapy”[MeSH] OR "proton therapy"[TIAB] OR "proton beam"[TIAB] OR "particle therapy"[TIAB] OR "PBT"[TIAB] OR "proton radiation therapy"[TIAB] OR “PBRT”[TIAB] OR “hadron therapy”[TIAB] OR “proton radiotherapy”[TIAB]	2792
2	“neoplasms”[MeSH] OR cancer*[TIAB] OR tumor*[TIAB] OR tumour*[TIAB] OR carcinoma*[TIAB] OR malignan*[TIAB]	735,008
3	“proton pump inhibitor”[MeSH] OR "proton pump"[TIAB]	4113
4	#1 AND #2 NOT #3	1778

Search strategy (EMBASE)
Search date: November 2013 through 12/31/2018
Filters: conference abstract, conference paper, conference review, editorial, erratum, letter, review, short survey

Electronic Database Searches
The following databases have been searched for relevant information:

Agency for Healthcare Research and Quality (AHRQ)
Cochrane Database of Systematic Reviews
Cochrane Registry of Clinical Trials (CENTRAL)
Cochrane Review Methodology Database
Database of Reviews of Effectiveness (Cochrane Library)
EMBASE
PubMed
ClinicalTrials.gov
Informational Network of Agencies for Health Technology Assessment (INAHTA)
NHS Economic Evaluation Database

Additional Economics, Clinical Guideline and Gray Literature Databases

AHRQ - Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google

APPENDIX C. Excluded Articles

Articles excluded as primary studies after full text review, with reason for exclusion.

Appendix Table C1. List of Excluded Articles

	Citation	Reason for exclusion after full-text review
1.	Farnia B, Philip N, Georges RH, et al. Reirradiation of recurrent pediatric brain tumors after initial proton therapy. International Journal of Particle Therapy 2016;3:1-12.	Excluded pediatric; Only 5/12 pts got PBT as 2nd radiation tx; No info on 1st PBT provided) [wrong intervention]
2.	Uhl M, Edler L, Jensen AD, Habl G, Oelmann J, Röder F, Jäckel O, Debus J, Herfarth K. Randomized phase II trial of hypofractionated proton versus carbon ion radiation therapy in patients with sacrococcygeal chordoma-the ISAC trial protocol. Radiation Oncology. 2014 Dec;9(1):100.	Excluded bone; Trial Protocol
3.	Jahangiri A, Chin AT, Wagner JR, Kunwar S, Ames C, Chou D, Barani I, Parsa AT, McDermott MW, Benet A, El-Sayed IH. Factors predicting recurrence after resection of clival chordoma using variable surgical approaches and radiation modalities. Neurosurgery. 2014 Dec 29;76(2):179-86.	Excluded brain/spinal; too few proton patients
4.	Melone AG, D'Elia A, Santoro F, Salvati M, Delfini R, Cantore G, Santoro A. Intracranial hemangiopericytoma—our experience in 30 years: a series of 43 cases and review of the literature. World neurosurgery. 2014 Mar 1;81(3-4):556-62.	Excluded brain/spinal; too few proton patients
5.	Alvarado MD, Conolly J, Park C, Sakata T, Mohan AJ, Harrison BL, Hayes M, Esserman LJ, Ozanne EM. Patient preferences regarding intraoperative versus external beam radiotherapy following breast-conserving surgery. Breast cancer research and treatment. 2014 Jan 1;143(1):135-40.	Excluded breast; non proton-related
6.	Galland-Girodet S, Pashtan I, MacDonald SM, Ancukiewicz M, Hirsch AE, Kachnic LA, Specht M, Gadd M, Smith BL, Powell SN, Recht A. Long-term cosmetic outcomes and toxicities of proton beam therapy compared with photon-based 3-dimensional conformal accelerated partial-breast irradiation: a phase 1 trial. International Journal of Radiation Oncology* Biology* Physics. 2014 Nov 1;90(3):493-500.	Excluded breast, too few proton patients
7.	Stick LB, Yu J, Maraldo MV, Aznar MC, Pedersen AN, Bentzen SM, Vogelius IR. Joint estimation of cardiac toxicity and recurrence risks after comprehensive nodal photon versus proton therapy for breast cancer. International Journal of Radiation Oncology* Biology* Physics. 2017 Mar 15;97(4):754-61.	Excluded breast; lack of clinical data
8.	Macomber MW, Kollar LE, Bowen SR, Gopan O, Rengan R, Zeng J, Patel SA. Heart Dose and Outcomes in Radiation Treatment for Esophageal Cancer. International Journal of Radiation Oncology• Biology• Physics. 2015 Nov 1;93(3):E167-8.	Excluded esophageal; Not a true comparison, lack of outcomes of interest
9.	Davuluri R, Jiang W, Fang P, Xu C, Komaki R, Gomez DR, Welsh J, Cox JD, Crane CH, Hsu CC, Lin SH. Lymphocyte nadir and esophageal cancer survival outcomes after chemoradiation therapy. International Journal of Radiation Oncology* Biology* Physics. 2017 Sep 1;99(1):128-35.	Excluded esophageal; Not a true comparison, lack of outcomes of interest

	Citation	Reason for exclusion after full-text review
10.	Demizu Y, Fujii O, Terashima K, Mima M, Hashimoto N, Niwa Y, Akagi T, Daimon T, Murakami M, Fuwa N. Particle therapy for mucosal melanoma of the head and neck. Strahlentherapie und Onkologie. 2014 Feb 1;190(2):186-91.	Excluded head & neck; not a comparison of interest (proton vs carbon)
11.	Takagi M, Demizu Y, Hashimoto N, Mima M, Terashima K, Fujii O, Jin D, Niwa Y, Morimoto K, Akagi T, Daimon T. Treatment outcomes of particle radiotherapy using protons or carbon ions as a single-modality therapy for adenoid cystic carcinoma of the head and neck. Radiotherapy and Oncology. 2014 Dec 1;113(3):364-70.	Excluded head & neck; proton half proton, half carbon, noncomparative
12.	Nantavithya C, Gomez DR, Wei X, Komaki R, Liao Z, Lin SH, Jeter M, Nguyen QN, Li H, Zhang X, Poenisch F. Phase 2 Study of Stereotactic Body Radiation Therapy and Stereotactic Body Proton Therapy for High-Risk, Medically Inoperable, Early-Stage Non-Small Cell Lung Cancer. International Journal of Radiation Oncology• Biology• Physics. 2018 Jul 1;101(3):558-63.	Excluded lung; too few patients per treatment arm
13.	Weber DC, Badiyan S, Malyapa R, Albertini F, Bolsi A, Lomax AJ, Schneider R. Long-term outcomes and prognostic factors of skull-base chondrosarcoma patients treated with pencil-beam scanning proton therapy at the Paul Scherrer Institute. Neuro-oncology. 2015 Aug 30;18(2):236-43.	Excluded head & neck; overlapping populations with two included case series (Weber 2018, Weber 2016a)
14.	Sethi RV, Shih HA, Yeap BY, Mouw KW, Petersen R, Kim DY, Munzenrider JE, Grabowski E, Rodriguez-Galindo C, Yock TI, Tarbell NJ. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. Cancer. 2014 Jan 1;120(1):126-33.	Excluded pediatric; duplicate publication/already addressed in prior (2014) report
15.	Wilkinson B, Morgan H, Gondi V, Larson GL, Hartsell WF, Laramore GE, Halasz LM, Vargas C, Keole SR, Grosshans DR, Shih HA. Low Levels of Acute Toxicity Associated With Proton Therapy for Low-Grade Glioma: A Proton Collaborative Group Study. International journal of radiation oncology, biology, physics. 2016 Oct 1;96(2S):E135.	Excluded brain/spinal; only abstract available
16.	Lester SC, Lin SH, Chuong M, Bhooshan N, Liao Z, Arnett AL, James SE, Evans JD, Spears GM, Komaki R, Haddock MG. A multi-institutional analysis of trimodality therapy for esophageal cancer in elderly patients. International Journal of Radiation Oncology* Biology* Physics. 2017 Jul 15;98(4):820-8.	Excluded esophageal; too few proton beam therapy patients
17.	Ning MS, Tang L, Gomez DR, Xu T, Luo Y, Huo J, Mouhayar E, Liao Z. Incidence and predictors of pericardial effusion after chemoradiation therapy for locally advanced non-small cell lung cancer. International Journal of Radiation Oncology* Biology* Physics. 2017 Sep 1;99(1):70-9.	Excluded Lung; proton comparison data not available, not a true comparison of proton vs IMRT
18.	Bütof R, Simon M, Löck S, Troost EG, Appold S, Krause M, Baumann M. PORTAF–postoperative radiotherapy of non-small cell lung cancer: accelerated versus conventional fractionation–study protocol for a randomized controlled trial. Trials. 2017 Dec;18(1):608.	Excluded lung; study protocol only, no published results found
19.	Chang JY, Li H, Zhu XR, Liao Z, Zhao L, Liu A, Li Y, Sahoo N, Poenisch F, Gomez DR, Wu R. Clinical implementation of intensity modulated proton therapy for thoracic malignancies. International Journal of Radiation Oncology* Biology* Physics. 2014 Nov 15;90(4):809-18.	Excluded lung; modeling study, no outcomes of interest

	Citation	Reason for exclusion after full-text review
20.	Fujii O, Demizu Y, Hashimoto N, Takagi M, Terashima K, Mima M, Jin D, Nagano F, Katsui K, Okimoto T, Iwata H. Particle therapy for clinically diagnosed stage I lung cancer: comparison with pathologically proven non-small cell lung cancer. Acta Oncologica. 2015 Mar 16;54(3):315-21.	Excluded lung; Only 58% of population treated with protons, does not include individual analysis
21.	McAvoy S, Ciura K, Wei C, Rineer J, Liao Z, Chang JY, Palmer MB, Cox JD, Komaki R, Gomez DR. Definitive reirradiation for locoregionally recurrent non-small cell lung cancer with proton beam therapy or intensity modulated radiation therapy: predictors of high-grade toxicity and survival outcomes. International Journal of Radiation Oncology* Biology* Physics. 2014 Nov 15;90(4):819-27.	Excluded lung; Only 19% of population treated with protons, does not include individual analysis
22.	Ning MS, Tang L, Gomez DR, Xu T, Luo Y, Huo J, Mouhayar E, Liao Z. Incidence and predictors of pericardial effusion after chemoradiation therapy for locally advanced non-small cell lung cancer. International Journal of Radiation Oncology* Biology* Physics. 2017 Sep 1;99(1):70-9.	Excluded lung; only 40% of population treated with protons, does not include individual analysis
23.	Shusharina N, Liao Z, Mohan R, Liu A, Niemierko A, Choi N, Bortfeld T. Differences in lung injury after IMRT or proton therapy assessed by 18FDG PET imaging. Radiotherapy and Oncology. 2018 Jul 1;128(1):147-53.	Excluded lung; Does not analyze outcomes of interest based on proton or IMRT; cannot use cumulative data provided because only 38% were treated with PBT
24.	Zschaeck S, Simon M, Löck S, Troost EG, Stützer K, Wohlfahrt P, Appold S, Makocki S, Bütof R, Richter C, Baumann M. PRONTOX–proton therapy to reduce acute normal tissue toxicity in locally advanced non-small-cell lung carcinomas (NSCLC): study protocol for a randomised controlled trial. Trials. 2016 Dec;17(1):543.	Excluded lung; study protocol only, no published results found
25.	Bhakta N, Liu Q, Yeo F, Baassiri M, Ehrhardt MJ, Srivastava DK, Metzger ML, Krasin MJ, Ness KK, Hudson MM, Yasui Y. Cumulative burden of cardiovascular morbidity in paediatric, adolescent, and young adult survivors of Hodgkin's lymphoma: an analysis from the St Jude Lifetime Cohort Study. The lancet oncology. 2016 Sep 1;17(9):1325-34.	Excluded lymphoma; no mention of PBT, no outcomes of interest
26.	Winkfield KM, Gallotto S, Niemierko A, Adams JA, Tarbell NJ, Chen YL. Proton therapy for mediastinal lymphomas: An 8-year single-institution report. International Journal of Radiation Oncology• Biology• Physics. 2015 Nov 1;93(3):E461.	Excluded lymphoma; abstract only
27.	Hoppe BS, Flampouri S, Zaiden R, Slayton W, Sandler E, Ozdemir S, Dang NH, Lynch JW, Li Z, Morris CG, Mendenhall NP. Involved-node proton therapy in combined modality therapy for Hodgkin lymphoma: results of a phase 2 study. International Journal of Radiation Oncology* Biology* Physics. 2014 Aug 1;89(5):1053-9.	Excluded lymphoma; Case series with <30 patients, and does not provide subpopulation analysis for the 5 pediatric patients included in the study
28.	Mosci C, Lanza FB, Mosci S, Barla A. Quantitative echography in primary uveal melanoma treated by proton beam therapy. Canadian Journal of Ophthalmology/Journal Canadien d'Ophtalmologie. 2014 Feb 1;49(1):60-5.	Excluded ocular; no outcomes of interest
29.	Syed ZA, Pineda II R. Cataract surgery after proton-beam irradiation for uveal tumors. Journal of Cataract & Refractive Surgery. 2017 Oct 1;43(10):1328-34.	Excluded ocular; too few patients (<30) and not a rare condition

	Citation	Reason for exclusion after full-text review
30.	Angi M, Kalirai H, Taktak A, Hussain R, Groenewald C, Damato BE, Heimann H, Coupland SE. Prognostic biopsy of choroidal melanoma: an optimised surgical and laboratory approach. British Journal of Ophthalmology. 2017 Aug 1;101(8):1143-6.	Excluded ocular; Only 35% of population treated with protons, does not include individual analysis, no outcomes of interest.
31.	DeParis SW, Taktak A, Eleuteri A, Enanoria W, Heimann H, Coupland SE, Damato B. External validation of the Liverpool uveal melanoma prognosticator online. Investigative ophthalmology & visual science. 2016 Nov 1;57(14):6116-22.	Excluded ocular; only 42% of population treated with protons
32.	Seibel I, Riechardt AI, Erb-Eigner K, Böker A, Cordini D, Heufelder J, Joussen AM. Proton Beam Irradiation: A Safe Procedure in Postequatorial Extraocular Extension From Uveal Melanoma. American journal of ophthalmology. 2018 Jul 1;191:49-53.	Excluded ocular; too few patients (<30) and not a rare condition
33.	Sellam A, Coscas F, Lumbroso-Le Rouic L, Dendale R, Lupidi M, Coscas G, Desjardins L, Cassoux N. Optical Coherence Tomography Angiography of Macular Features After Proton Beam Radiotherapy for Small Choroidal Melanoma. American journal of ophthalmology. 2017 Sep 1;181:12-9.	Excluded ocular; too few patients (<30) and not a rare condition
34.	Seibel I, Cordini D, Rehak M, Hager A, Riechardt AI, Böker A, Heufelder J, Weber A, Gollrad J, Besserer A, Joussen AM. Local recurrence after primary proton beam therapy in uveal melanoma: risk factors, retreatment approaches, and outcome. American journal of ophthalmology. 2015 Oct 1;160(4):628-36.	Excluded ocular; Patients included in a larger study that reports the same outcomes with longer follow-up
35.	Seibel I, Cordini D, Hager A, Riechardt AI, Rehak M, Böker A, Böhmer D, Heufelder J, Joussen AM. Cataract development in patients treated with proton beam therapy for uveal melanoma. Graefe's Archive for Clinical and Experimental Ophthalmology. 2016 Aug 1;254(8):1625-30.	Excluded ocular; Patients included in a larger study that reports the same outcomes with longer follow-up
36.	Holliday EB, Esmaeli B, Pinckard J, Garden AS, Rosenthal DI, Morrison WH, Kies MS, Gunn GB, Fuller CD, Phan J, Beadle BM. A multidisciplinary orbit-sparing treatment approach that includes proton therapy for epithelial tumors of the orbit and ocular adnexa. International Journal of Radiation Oncology* Biology* Physics. 2016 May 1;95(1):344-52.	Excluded ocular; too few patients (<30) and not a rare condition
37.	Habl G, Hatiboglu G, Edler L, Uhl M, Krause S, Roethke M, Schlemmer HP, Hadaschik B, Debus J, Herfarth K. Ion Prostate Irradiation (IPI)–a pilot study to establish the safety and feasibility of primary hypofractionated irradiation of the prostate with protons and carbon ions in a raster scan technique. BMC cancer. 2014 Dec;14(1):202.	Excluded prostate; study protocol only, no published results found
38.	Slater IV JM, Bush DA, Grove R, Slater JD. The prognostic value of percentage of positive biopsy cores, percentage of cancer volume, and maximum involvement of biopsy cores in prostate cancer patients receiving proton and photon beam therapy. Technology in cancer research & treatment. 2014 Jun;13(3):227-31.	Excluded prostate; no outcomes of interest
39.	Pompe RS, Davis-Bondarenko H, Zaffuto E, Tian Z, Shariat SF, Leyh-Bannurah SR, Schiffmann J, Saad F, Huland H, Graefen M, Tilki D. Population-Based Validation of the 2014 ISUP Gleason Grade Groups in Patients Treated With Radical Prostatectomy, Brachytherapy, External Beam Radiation, or no Local Treatment. The Prostate. 2017 May;77(6):686-93.	Excluded prostate; Does not describe type of external beam radiation therapy

	Citation	Reason for exclusion after full-text review
40.	Pettersson A, Nygren P, Persson C, Berglund A, Turesson I, Johansson B. Effects of a dietary intervention on gastrointestinal symptoms after prostate cancer radiotherapy: long-term results from a randomized controlled trial. Radiotherapy and Oncology. 2014 Nov 1;113(2):240-7.	Excluded prostate; follow-up study to an RCT that was published in 2012, does not provide new data
41.	Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, Iravani A, Kong G, Kumar AR, Murphy DG, Eu P. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. The Lancet Oncology. 2018 Jun 1;19(6):825-33.	Excluded prostate; does not include PBT-related information
42.	Arimura T, Ogino T, Yoshiura T, Toi Y, Kawabata M, Chuman I, Wada K, Kondo N, Nagayama S, Hishikawa Y. Effect of Film Dressing on Acute Radiation Dermatitis Secondary to Proton Beam Therapy. International Journal of Radiation Oncology* Biology* Physics. 2016 May 1;95(1):472-6.	Excluded prostate; lack of data related to intervention of interest
43.	Walsh S, Roelofs E, Kuess P, Lambin P, Jones B, Georg D, Verhaegen F. A validated tumor control probability model based on a meta-analysis of low, intermediate, and high-risk prostate cancer patients treated by photon, proton, or carbon-ion radiotherapy. Medical physics. 2016 Feb 1;43(2):734-47.	Excluded prostate; Modeling study; no outcomes of interest
44.	Moteabbed M, Trofimov A, Sharp GC, Wang Y, Zietman AL, Efstathiou JA, Lu HM. A prospective comparison of the effects of interfractional variations on proton therapy and intensity modulated radiation therapy for prostate cancer. International Journal of Radiation Oncology* Biology* Physics. 2016 May 1;95(1):444-53.	Excluded prostate; Modeling study; no outcomes of interest
45.	Habl G, Uhl M, Katayama S, Kessel KA, Hatiboglu G, Hadaschik B, Edler L, Tichy D, Ellerbrock M, Haberer T, Wolf MB. Acute toxicity and quality of life in patients with prostate cancer treated with protons or carbon ions in a prospective randomized phase II study—the IPI Trial. International Journal of Radiation Oncology* Biology* Physics. 2016 May 1;95(1):435-43.	Excluded prostate; not a comparison of interest (proton vs carbon)
46.	Kelly KJ, Yoon SS, Kuk D, Qin LX, Dukleska K, Chang KK, Chen YL, Delaney TF, Brennan MF, Singer S. Comparison of perioperative radiation therapy and surgery versus surgery alone in 204 patients with primary retroperitoneal sarcoma: a retrospective two-institution study. Annals of surgery. 2015 Jul;262(1):156.	Excluded soft tissue sarcoma; Unclear as to how many patients received PBT; patients could have received either proton or photon RT and numbers are not provided as to who got what treatment
47.	Vogel J, Lin L, Simone CB, Berman AT. Risk of major cardiac events following adjuvant proton versus photon radiation therapy for patients with thymic malignancies. Acta Oncologica. 2017 Aug 3;56(8):1060-4.	Excluded Thymoma; Modeling study; no outcomes of interest
48.	Vogel J, Lin L, Litzky LA, Berman AT, Simone II CB. Predicted rate of secondary malignancies following adjuvant proton versus photon radiation therapy for thymoma. International Journal of Radiation Oncology* Biology* Physics. 2017 Oct 1;99(2):427-33.	Excluded Thymoma; Modeling study; no outcomes of interest
49.	De B, Khakoo Y, Souweidane MM, Dunkel IJ, Patel SH, Gilheeney SW, De Braganca KC, Karajannis MA, Wolden SL. Patterns of relapse for children	Excluded pediatric; Only 22% of population treated with protons,

	Citation	Reason for exclusion after full-text review
	with localized intracranial ependymoma. Journal of neuro-oncology. 2018 Jun 1;138(2):435-45.	does not include individual analysis
50.	Ducassou A, Padovani L, Chaltiel L, Bolle S, Habrand JL, Claude L, Carrie C, Muracciole X, Coche-Dequeant B, Alapetite C, Supiot S. Pediatric Localized Intracranial Ependymomas: A Multicenter Analysis of the Société Française de lutte contre les Cancers de l'Enfant (SFCE) from 2000 to 2013. International Journal of Radiation Oncology* Biology* Physics. 2018 Sep 1;102(1):166-73.	Excluded pediatric; Only 8% of population treated with protons, does not include individual analysis
51.	Mahajan A, Strother D, Pollack I, Merchant T, Williams-Hughes C, Buxton A, Zhou T, Krailo M, Reddy A. Atrt-10. Early Post Radiation Changes And Efficacy In Children With Atrt Treated On Cog Acns 0333: A Comparison Of Proton Vs Photon Therapy. Neuro-oncology. 2017 Jun;19(Suppl 4):iv3.	Excluded pediatric; abstract only
52.	Green DM, Merchant TE, Billups CA, Stokes DC, Broniscer A, Bartels U, Chintagumpala M, Hassall TE, Gururangan S, McCowage GB, Heath JA. Pulmonary function after treatment for embryonal brain tumors on SJMB03 that included craniospinal irradiation. International Journal of Radiation Oncology* Biology* Physics. 2015 Sep 1;93(1):47-53.	Excluded pediatric; Only 6.7% of population treated with protons, does not include individual analysis
53.	Yock TI, Bhat S, Szymonifka J, Yeap BY, Delahaye J, Donaldson SS, MacDonald SM, Pulsifer MB, Hill KS, DeLaney TF, Ebb D. Quality of life outcomes in proton and photon treated pediatric brain tumor survivors. Radiotherapy and Oncology. 2014 Oct 1;113(1):89-94.	Excluded pediatric; Includes PBT data that was previously published as a case series in 2012, and thus would have been captured in the prior report
54.	MacEwan I, Chou B, Moretz J, Loredo L, Bush D, Slater JD. Effects of vertebral-body-sparing proton craniospinal irradiation on the spine of young pediatric patients with medulloblastoma. Advances in radiation oncology. 2017 Apr 1;2(2):220-7.	Excluded pediatric; Case series of only 7 patients with Medulloblastoma. Other studies with a greater number of patients with this diagnosis have been included
55.	Mizumoto M, Oshiro Y, Takizawa D, Fukushima T, Fukushima H, Yamamoto T, Muroi A, Okumura T, Tsuboi K, Sakurai H. Proton beam therapy for pediatric ependymoma. Pediatrics International. 2015 Aug;57(4):567-71.	Excluded pediatric; Case series of only 6 patients with Medulloblastoma. Other studies with a greater number of patients with this diagnosis have been included
56.	Affinita, M., Ferrari, A., Milano, G., Scarzello, G., Leonardis, F., Coccoli, L., . . . Bisogno, G. (2018). Long-term results in children with head and neck rhabdomyosarcoma: A report from the Italian Soft Tissue Sarcoma Committee. Pediatric Blood & Cancer, 65(3), N/a.	Excluded pediatric; Patients do not receive PBT
57.	Brodin NP, Munck af Rosenschöld P, Blomstrand M, Kiil-Berthlesen A, Hollensen C, Vogelius IR, Lannering B, Bentzen SM, Björk-Eriksson T. Hippocampal sparing radiotherapy for pediatric medulloblastoma: impact of treatment margins and treatment technique. Neuro-oncology. 2013 Dec 9;16(4):594-602.	Excluded pediatric; Modeling study, no outcomes of interest
58.	Brodin NP, Vogelius IR, Björk-Eriksson T, Munck af Rosenschöld P, Maraldo MV, Aznar MC, Specht L, Bentzen SM. Optimizing the radiation therapy dose prescription for pediatric medulloblastoma: Minimizing	Excluded pediatric; Modeling study, no outcomes of interest

	Citation	Reason for exclusion after full-text review
	the life years lost attributable to failure to control the disease and late complication risk. Acta Oncologica. 2014 Apr 1;53(4):462-70.	
59.	Moteabbed M, Yock TI, Paganetti H. The risk of radiation-induced second cancers in the high to medium dose region: a comparison between passive and scanned proton therapy, IMRT and VMAT for pediatric patients with brain tumors. Physics in Medicine & Biology. 2014 May 14;59(12):2883.	Excluded pediatric; Modeling study, no outcomes of interest
60.	Munck af Rosenschold P, Engelholm SA, Brodin PN, Jørgensen M, Grosshans DR, Zhu RX, Palmer M, Crawford CN, Mahajan A. A retrospective evaluation of the benefit of referring pediatric cancer patients to an external proton therapy center. Pediatric blood & cancer. 2016 Feb;63(2):262-9.	Excluded pediatric; Modeling study, no outcomes of interest
61.	Jouglar E, Wagner A, Delpon G, Campion L, Meingan P, Bernier V, Demoor-Goldschmidt C, Mahé MA, Lacornerie T, Supiot S. Can We Spare the Pancreas and Other Abdominal Organs at Risk? A Comparison of Conformal Radiotherapy, Helical Tomotherapy and Proton Beam Therapy in Pediatric Irradiation. PloS one. 2016 Oct 20;11(10):e0164643.	Excluded pediatric; Planning study – patients only treated with conformal radiotherapy and helical tomography
62.	Glaser SM, Dohopolski MJ, Balasubramani GK, Flickinger JC, Beriwal S. Glioblastoma multiforme (GBM) in the elderly: initial treatment strategy and overall survival. Journal of neuro-oncology. 2017 Aug 1;134(1):107-18.	Excluded brain/spinal; abstract only
63.	McDonald MW, Linton OR, Moore MG, Ting JY, Cohen-Gadol AA, Shah MV. Influence of residual tumor volume and radiation dose coverage in outcomes for clival chordoma. International Journal of Radiation Oncology* Biology* Physics. 2016 May 1;95(1):304-11.	Excluded brain/spinal; abstract only
64.	Russo AL, Adams JA, Weyman EA, Busse PM, Goldberg SI, Varvares M, Deschler DD, Lin DT, Delaney TF, Chan AW. Long-term outcomes after proton beam therapy for sinonasal squamous cell carcinoma. International Journal of Radiation Oncology* Biology* Physics. 2016 May 1;95(1):368-76.	Excluded head & neck; abstract only
65.	Komatsu S, Kido M, Asari S, Toyama H, Ajiki T, Demizu Y, Terashima K, Okimoto T, Sasaki R, Fukumoto T. Particle radiotherapy, a novel external radiation therapy, versus liver resection for hepatocellular carcinoma accompanied with inferior vena cava tumor thrombus: A matched-pair analysis. Surgery. 2017 Dec 1;162(6):1241-9.	Excluded liver; One of the treatment arms is particle therapy in which only 73.7% of the patients were treated with PBT
66.	Sorin Y, Ikeda K, Kawamura Y, Fujiyama S, Kobayashi M, Hosaka T, Sezaki H, Akuta N, Saitoh S, Suzuki F, Suzuki Y. Effectiveness of particle radiotherapy in various stages of hepatocellular carcinoma: a Pilot study. Liver cancer. 2018 Oct.	Excluded liver; not a comparison of interest (proton vs carbon)
67.	Takamatsu S, Yamamoto K, Maeda Y, Kawamura M, Shibata S, Sato Y, Terashima K, Shimizu Y, Tameshige Y, Sasaki M, Asahi S. Evaluation of focal liver reaction after proton beam therapy for hepatocellular carcinoma examined using Gd-EOB-DTPA enhanced hepatic magnetic resonance imaging. PloS one. 2016 Dec 1;11(12):e0167155.	Excluded liver; No outcomes of interest
68.	Moschos MM, Moustafa GA, Lavaris A, Damaskos C, Laios K, KARATHANOU E, Ladas DS, Asproudis I, Garmpis N, Kalogeropoulos C.	Excluded Ocular; no outcomes of interest

	Citation	Reason for exclusion after full-text review
	Depression in Choroidal Melanoma Patients Treated with Proton Beam Radiotherapy. Anticancer research. 2018 May 1;38(5):3055-61.	

APPENDIX D. Risk of Bias, Class of Evidence, Strength of Evidence, and QHES Determination

Each included comparative study is rated against pre-set criteria that resulted in a Risk of Bias (RoB) assessment and presented in a table. Criteria for RoB assessment are listed in the Tables below. Risk of bias assessments were not conducted for case series; all were considered High risk of bias.

Definition of the risk of bias categories

Risk of Bias	Definition
Low risk of bias	Study adheres to commonly held tenets of high quality design, execution and avoidance of bias
Moderately low risk of bias	Study has potential for some bias; does not meet all criteria for low risk of bias but deficiencies not likely to invalidate results or introduce significant bias
Moderately high risk of bias	Study has flaws in design and/or execution that increase potential for bias that may invalidate study results
High risk of bias	Study has significant potential for bias; does not include design features geared toward minimizing bias and/or does not have a comparison group

Appendix Table D1. Definition of the risk of bias for studies on therapy

Risk of Bias	Studies of Therapy*	
	Study design	**Criteria***
Low risk: Study adheres to commonly held tenets of high quality design, execution and avoidance of bias	Good quality RCT	• Random sequence generation • Statement of allocation concealment • Intent-to-treat analysis • Blind or independent assessment of PET/CT (interpreter blinded to clinical assessment/status) • Blind or independent assessment for subjective outcome(s) • Pre-specified threshold for definition of a positive test. • Attrition (≤ 20% overall) • Comparable f/u time or accounting for time at risk • Controlling for possible confounding‡ • Full reporting of specified outcomes
Moderately low risk:	Moderate quality RCT	• Violation of one or two of the criteria for good quality RCT

Risk of Bias	Studies of Therapy*	
	Study design	**Criteria***
Study has potential for some bias; study does not meet all criteria for class I, but deficiencies not likely to invalidate results or introduce significant bias	Good quality cohort	• Blind or independent assessment of PET/CT (interpreter blinded to clinical assessment/status) • Blind or independent assessment for subjective outcome(s) • Pre-specified threshold for definition of a positive test. • Attrition (≤ 20% overall) • Comparable f/u time or accounting for time at risk • Controlling for possible confounding‡ • Full reporting of specified outcomes
Moderately High risk: Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results	Poor quality RCT	• Violation of three or more of the criteria for good quality RCT
	Moderate quality cohort	• Violation of any of the criteria for good quality cohort
	Case-control	• Any case-control design
High risk: Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes	Poor quality cohort Case series	• Violation of two or more criteria for a good quality cohort • Any case series design

* Additional domains evaluated in studies performing a formal test of interaction for subgroup modification (i.e., HTE) based on recommendations from Oxman and Guyatt:
  - Is the subgroup variable a characteristic specified at baseline or after randomization? (subgroup hypotheses should be developed a priori)
  - Did the hypothesis precede rather than follow the analysis and include a hypothesized direction that was subsequently confirmed?
  - Was the subgroup hypothesis one of a smaller number tested?

† Outcome assessment is independent of healthcare personnel judgment. Reliable data are data such as mortality or re-operation.

‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods) at time of randomization or allocation to treatment based on PET results. Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Determination of Overall Strength (Quality) of Evidence

The strength of evidence for the overall body of evidence for all critical health outcomes was assessed by one researcher following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ).[6] The strength of evidence was based on the highest quality evidence available for a given outcome. In

determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- Risk of bias: the extent to which the included studies have protection against bias
- Consistency: the degree to which the included studies report results are similar in terms of range and variability.
- Directness: describes whether the evidence is directly related to patient health outcomes.
- Precision: describes the level of certainty surrounding the effect estimates.
- Publication bias: is considered when there is concern of selective publishing.

Bodies of evidence consisting of RCTs were initially considered as High strength of evidence (SoE), while those that comprised nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There could also be situations where the nonrandomized studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association). Publication and reporting bias are difficult to assess. Publication bias is particularly difficult to assess with fewer than 10 RCTs (AHRQ methods guide). When publication bias was unknown in all studies and this domain is often eliminated from the strength of evidence tables for our reports. The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are probably stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; important or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed.

All AHRQ “required” and “additional” domains (risk of bias, consistency, directness, precision, and if possible, publication bias) are assessed. Bodies of evidence consisting of RCTs were initially considered as High strength of evidence, while those comprised of nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There are also situations where the *nonrandomized* studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association).

Appendix Table D2. Example methodology outline for determining overall strength of evidence (SoE):

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table below.

Baseline strength: HIGH = RCTs. LOW = observational, cohort studies, administrative data studies.

DOWNGRADE: Risk of bias for the individual article evaluations (1 or 2); Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *a priori* and no test for interaction (2)

UPGRADE (non-randomized studies): Large magnitude of effect (1 or 2); Dose response gradient (1) done for observational studies ***if no downgrade for domains above***

Outcome	Strength of Evidence	Conclusions & Comments	Baseline SOE	DOWNGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** RCTs	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**MODERATE**	Summary of findings	**LOW** Cohort studies	**NO** consistent, direct, and precise estimates; high quality (moderately low ROB)	**YES** Large effect
Outcome	**LOW**	Summary of findings	**HIGH** RCTs	**YES (2)** Inconsistent Indirect	**NO**

*Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation. Additional domains: dose-response, strength of association, publication bias.

**Single study = "consistency unknown", may or may not be downgraded

ROB for Contextual Questions: Formal, detailed risk of bias assessment was not done for systematic reviews or studies included for the contextual question, however notes on key critical appraisal elements for systematic reviews adapted from the AMSTAR tool and QUADAS tool for diagnostic accuracy studies and pertinent epidemiologic principles were made to provide *a general* context for evidence quality.

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al.[82] QHES embodies the primary components relevant for critical appraisal of economic studies. It also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (e.g., with respect to age, gender, medical conditions, etc.)? To what extent are the populations for each intervention comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (e.g., complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc.)?
- How were the data and/or patients selected or sampled (e.g., a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?

Appendix Table D3. Definitions of the different levels of evidence for registry studies

Risk of Bias	Study design	Criteria
Moderately low risk: Study has potential for some bias; does not meet all criteria for class I but deficiencies not likely to invalidate results or introduce significant bias	Good quality registry	• Designed specifically for conditions evaluated • Includes prospective data only • Validation of completeness and quality of data • Patients followed long enough for outcomes to occur • Independent outcome assessment* • Complete follow-up of ≥ 85% • Controlling for possible confounding† • Accounting for time at risk‡
Moderately high risk: Study has flaws in design and/or execution that increase potential for bias that may invalidate study results	Moderate quality cohort	• Prospective data from registry designed specifically for conditions evaluated with violation of 2 of the rest of the criteria in level II
High risk: Study has significant potential for bias; does not include design features geared toward minimizing bias and/or does not have a comparison group	Poor quality cohort	• Prospective data from registry designed specifically for conditions evaluated with violation of 3 or more of the rest of the criteria in level II • Retrospective data or data from a registry not designed specifically for conditions evaluated

* Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, and reoperation.

† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

‡ Equal follow-up times or for unequal follow-up times, accounting for time at risk.

APPENDIX E. Study Quality: Risk of Bias evaluation

Appendix Table E1. Risk of Bias assessment: proton beam therapy for brain, spinal, and paraspinal cancers

Methodological Principle	Adeberg 2017 Case-matched	Bronk 2018	Gunther 2017	Mozes 2017 Case-matched	Jhaveri 2018 NCDB study
Study design					
Randomized controlled trial					
Prospective Cohort Study					
Retrospective Cohort Study	▪	▪	▪	▪	▪
Prospective Case Series					
Retrospective Case Series					
Random sequence generation*	N/A	N/A	N/A	N/A	N/A
Concealed allocation*	N/A	N/A	N/A	N/A	N/A
Intention-to-treat*	N/A	N/A	N/A	N/A	N/A
Independent/blind assessment	No	Yes – radiologist blinded (focus on pseudo-progression)	No	No	No
Complete follow-up of ≥80%	Unclear	Unclear	No (54%)‡	Unclear	Unclear
<10% difference in follow-up between groups	Unclear	Unclear	Yes	Unclear	Unclear
Controlling for possible confounding†	Yes	Yes	No	No	Yes
Risk of Bias	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**

*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding present.
‡Authors state that consecutive patients were enrolled. Seventeen (46%) patients died.

Appendix Table E2. Risk of Bias assessment: proton beam therapy for breast cancer

Methodological Principle	Chowdhary 2019 NCDB study	Teichman 2018
Study design		
Randomized controlled trial		
Prospective Cohort Study		
Retrospective Cohort Study	■	■
Prospective Case Series		
Retrospective Case Series		
Random sequence generation*	N/A	N/A
Concealed allocation*	N/A	N/A
Intention-to-treat*	N/A	N/A
Independent/blind assessment	No	No
Complete follow-up of ≥80%	Unclear	Unclear
<10% difference in follow-up between groups	Unclear	Unclear
Controlling for possible confounding†	Yes	No
Risk of Bias	**Moderately High**	**Moderately High**

NCDB = National Cancer Data Base.
*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding present.
‡Authors state that consecutive patients were enrolled. Seventeen (46%) patients died.

Appendix Table E3. Risk of Bias assessment: proton beam therapy for esophageal cancers

Methodological Principle	Fang 2018 Propensity-matched	Lin 2017	Makishima 2015	Shiraishi 2018 Propensity-matched	Xi 2017
Study design					
Randomized controlled trial					
Prospective Cohort Study					
Retrospective Cohort Study	■	■	■	■	■
Prospective Case Series					
Retrospective Case Series					
Random sequence generation*	N/A	N/A	N/A	N/A	N/A
Concealed allocation*	N/A	N/A	N/A	N/A	N/A
Intention-to-treat*	N/A	N/A	N/A	N/A	N/A
Independent/blind assessment	No	No	No	No	No
Complete follow-up of ≥80%	Unclear	Unclear	No (75%)	Unclear	Unclear
<10% difference in follow-up between groups	Unclear	Unclear	Yes (75% vs. 68%)	Unclear	Unclear
Controlling for possible confounding†	Yes	Yes	No	Yes	Yes

Risk of Bias	Moderately High	Moderately High	Moderately High	Moderately High	Moderately High

*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding present.

Appendix Table E4. Risk of Bias assessment: proton beam therapy for gastrointestinal cancers

Methodological Principle	Maemura 2017
Study design	
Randomized controlled trial	
Prospective Cohort Study	
Retrospective Cohort Study	■
Prospective Case Series	
Retrospective Case Series	
Random sequence generation*	N/A
Concealed allocation*	N/A
Intention-to-treat*	N/A
Independent/blind assessment	No
Complete follow-up of ≥80%	No
<10% difference in follow-up between groups	Yes
Controlling for possible confounding†	No
Risk of Bias	**Moderately High**

*Applies only to randomized controlled trials

†Groups must be comparable on baseline characteristics or evidence of control for confounding present

Appendix Table E5. Risk of Bias assessment: proton beam therapy for head & neck cancers

Methodological Principle	Simon 2018	Blanchard 2016 Case-matched	Romesser 2016	Sio 2016	Holliday 2015 Matched-pairs	McDonald 2016	Sharma 2018	Zhang 2017
Study design								
Randomized controlled trial								
Prospective Cohort Study							▪	
Retrospective Cohort Study	▪	▪	▪	▪	▪	▪		▪
Prospective Case Series								
Retrospective Case Series								
Random sequence generation*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Concealed allocation*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Intention-to-treat*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Independent/ blind assessment	No	No	No	No	No	No	No	No
Complete follow-up of ≥80%	Yes†	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
<10% difference in follow-up between groups	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Controlling for possible confounding†	No§	Yes	No	No	Yes	Yes	Yes	No
Risk of Bias	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately Low**

*Applies only to randomized controlled trials

†Groups must be comparable on baseline characteristics or evidence of control for confounding present

Appendix Table E6. Risk of Bias assessment: proton beam therapy for chondrosarcomas

Methodological Principle	Simon 2018
Study design	
Randomized controlled trial	
Prospective Cohort Study	
Retrospective Cohort Study	■
Prospective Case Series	
Retrospective Case Series	
Random sequence generation*	N/A
Concealed allocation*	N/A
Intention-to-treat*	N/A
Independent/blind assessment	No
Complete follow-up of ≥80%	Yes†
<10% difference in follow-up between groups	Unclear
Controlling for possible confounding†	No§
Risk of Bias	**Moderately High**

*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding present

Appendix Table E7. Risk of Bias assessment: proton beam therapy for liver cancers

Methodological Principle	Sanford 2019	Bush 2016
Study design		
Randomized controlled trial		■
Prospective Cohort Study		
Retrospective Cohort Study	■	
Prospective Case Series		
Retrospective Case Series		
Random sequence generation*	N/A	Yes
Concealed allocation*	N/A	Unclear*
Intention-to-treat*	N/A	Yes
Independent/blind assessment	No	No
Complete follow-up of ≥80%	No‡	Yes
<10% difference in follow-up between groups	Unclear	Yes
Controlling for possible confounding†	Yes	Yes
Risk of Bias	**Moderately High**	**Moderately Low**

*Randomization was done by the study statistician, but it is unclear as to whether patients and/or investigators were made aware of their random assignment.
†Groups must be comparable on baseline characteristics or evidence of control for confounding present

Appendix Table E8. Risk of Bias assessment: proton beam therapy for lung cancers

Methodological Principle	Liao 2018*	Higgins 2017†	Niedzielski 2017	Remick 2017	Tucker 2016	Wang 2016
Study design						
Randomized controlled trial	■					
Prospective Cohort Study						■
Retrospective Cohort Study		■	■	■	■	
Prospective Case Series						
Retrospective Case Series						
Random sequence generation†	Yes	N/A	N/A	N/A	N/A	N/A
Concealed allocation†	Unclear	N/A	N/A	N/A	N/A	N/A
Intention-to-treat†	Yes	N/A	N/A	N/A	N/A	N/A
Independent/blind assessment	Unclear/Yes**	No	No	No	No	No§
Complete follow-up of ≥80%	Yes††	Unclear	Unclear	Yes	Unclear	Unclear
<10% difference in follow-up between groups	Yes (ITT)†† No (PP)††	Unclear	Unclear	Yes	Unclear	Unclear
Controlling for possible confounding‡	Yes	Yes	No	No	Yes	Yes
Risk of Bias	**Moderately Low**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**

*Bayesian Adaptive Randomization: the initial 20 patients were randomly assigned equally to each arm; subsequent patients underwent adaptive random assignment, with the randomization probability proportional to the 1-year failure rate in each arm.

†Propensity-matched analysis using data from the National Cancer Database: 243,822 non-small-cell lung cancer patients diagnosed between the years 2004 and 2012.

Applies only to randomized controlled trials

‡Groups must be comparable on baseline characteristics or evidence of control for confounding present.

§ MDASI is a patient-reported outcome instrument and their only primary outcome.

** Unclear (local failure), and Yes (Overall Survival and Radiation Pneumonitis).

†† Follow up for Intention to Treat (92%; 167/181) and Per-Protocol (82%; 149/181). Differential follow-up Yes for Intention to Treat [95%; 72/76 vs. 95%; 101/105] and No for Per-Protocol [75%;57/76 vs. 88%; 92/105]

Appendix Table E9. Risk of Bias assessment: proton beam therapy for ocular cancers

Methodological Principle	Böker 2018 Matched case	Lin 2017 Propensity score matched (NCD)	Sikuade 2015
Study design			
Randomized controlled trial			
Prospective Cohort Study			
Retrospective Cohort Study	■	■	■
Prospective Case Series			
Retrospective Case Series			
Random sequence generation*	N/A	N/A	N/A
Concealed allocation*	N/A	N/A	N/A
Intention-to-treat*	N/A	N/A	N/A
Independent/blind assessment	Unclear	Unclear	Unclear
Complete follow-up of ≥80%	No	No	Unclear
<10% difference in follow-up between groups	Unclear (or Yes?)	Unclear (or Yes?)	Unclear
Controlling for possible confounding†	Yes	Yes	No
Risk of Bias	**Moderately High**	**Moderately High**	**Moderately High**

NCD = National Cancer Database

*Randomization was done by the study statistician, but it is unclear as to whether patients and/or investigators were made aware of their random assignment.

†Groups must be comparable on baseline characteristics or evidence of control for confounding present

Appendix Table E10. Risk of Bias assessment: proton beam therapy for prostate cancers

Methodological Principle	Khmelevsky 2018 (quasi-RCT)	Fang 2015 (case-matched)	Dutz 2019	Pan 2018 Propensity score matched
Study design				
Randomized controlled trial				
Prospective Cohort Study	■			
Retrospective Cohort Study		■	■	■
Prospective Case Series				
Retrospective Case Series				
Random sequence generation*	No	N/A	N/A	N/A
Concealed allocation*	No	N/A	N/A	N/A
Intention-to-treat*	Yes	N/A	N/A	N/A
Independent/blind assessment	No	No	No	No
Complete follow-up of ≥80%	Unclear	No	Unclear	No
<10% difference in follow-up between groups	Unclear	No	Unclear	No
Controlling for possible confounding†	Yes	Yes	Yes	Yes
Risk of Bias	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**

NCD = National Cancer Database
*Randomization was done by the study statistician, but it is unclear as to whether patients and/or investigators were made aware of their random assignment.
†Groups must be comparable on baseline characteristics or evidence of control for confounding present

Appendix Table E11. Risk of Bias assessment: proton beam therapy for pediatric cancers

		Brain, spinal, paraspinal									Head and neck	Ocular
Methodological principle	**Bishop 2014**	**Eaton 2016a/2016b**	**Gunther 2015†**	**Kahalley 2016**	**Kahalley 2019**	**Kopecky 2017**	**Paulino 2018‡**	**Sato 2017†**	**Song 2014**	**Bielamowicz 2018‡**	**Grant 2015**	**Agarwal 2016**
Study design												
Randomized Control Trial												
Prospective cohort study		■ §			■							
Retrospective cohort study	■		■	■		■	■	■	■	■	■	■
Case-control study												
Cross-sectional study												
Case-series												
Random sequence generation*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Concealed allocation*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Intention-to-treat*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Independent or blind assessment*	No	No	No	No	No	No	No	No	No	No	No	No
Complete follow-up of ≥80%	No	No	No	No	No	No	Yes	No	No	No	Yes	Yes
<10% difference in follow-up between groups	No	No	No	Unclear	Unclear	No	No	Unclear	Unclear	No	Yes	Unclear

Controlling for possible confounding	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No
Risk of Bias	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**

Mod. = moderately; NA = Not applicable

*Blinded assessment or analysis of outcomes was not explicitly reported in any study and likely not done given the retrospective nature of the studies.

†Gunther and Sato appear to use the same underlying populations and report on different outcomes

‡Paulino and Bielamowicz appear to use the same underlying populations and report on different outcomes

§Only data for the PBT group were prospectively collected; retrospective data from another institution were used for the comparison group

Appendix Table E12. Risk of Bias assessment: studies included for contextual questions

Methodological Principle	Vargas 2018	Nakajima 2018	Pugh 2013
Study design			
Randomized controlled trial	■		
Prospective Cohort Study			
Retrospective Cohort Study		■	■
Prospective Case Series			
Retrospective Case Series			
Random sequence generation*	Yes	N/A	N/A
Concealed allocation*	Yes	N/A	N/A
Intention-to-treat*	Yes	N/A	N/A
Independent/blind assessment	Yes (safety) No (Quality of Life)	Yes (safety) No (quality of life)	No
Co-interventions applied equally	Yes	Yes	Yes
Complete follow-up of ≥80%	Yes	Unclear‡	Unclear §
<10% difference in follow-up between groups	Yes	Unclear‡	Unclear §
Controlling for possible confounding†	Yes	Yes	Yes
Risk of Bias	**Low**	**Moderately High**	**Moderately High**

*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding present
‡ Study excluded patients with less than 6 months follow-up, don't report overall follow-up length; cannot be determined based on given information
§ Study excluded patients with less than 2 years follow-up; cannot be determined based on given information

Appendix Table E13. Quality of Health Economic Studies (QHES) scores: economic studies

QHES Question (points possible)		Hirano 2014	Leung 2017	Mailhot Vega 2015	Mailhot Vega 2016	Moriarty 2015	Sher 2018
1.	Was the study **objective** presented in a clear, specific, and measurable manner? (7 pts)	7	7	7	7	7	7
2.	Were the **perspective** of the analysis (societal, third-party payer, etc.) and reasons for its selection stated? (4 pts)	4	4	4	0	4	4
3.	Were **variable estimates** used in the analysis from the best available source (i.e. randomized controlled trial = best, expert opinion = worst)? (8 pts)	0	0	0	8	8	8
4.	If estimates came from a **subgroup analysis**, were the groups prespecified at the beginning of the study? (1 pt)	1	1	1	1	1	1
5.	Was **uncertainty** handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions? (9 pts)	9	9	0	9	9	9
6.	Was **incremental analysis** performed between alternatives for resources and costs? (6 pts)	6	6	6	6	6	6
7.	Was the methodology for **data abstraction** (including the value of health states and other benefits) stated? (5 pts)	5	0	5	0	5	5
8.	Did the **analytic horizon allow time** for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate? (7 pts)	7	5	7	7	7	7
9.	Was the **measurement of costs** appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8 pts)	0	0	0	8	8	8
10.	Were the primary **outcome measure(s)** for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included? (6 pts)	0	0	0	6	6	6

QHES Question (points possible)	Hirano 2014	Leung 2017	Mailhot Vega 2015	Mailhot Vega 2016	Moriarty 2015	Sher 2018
11. Were the health outcomes **measures/scales valid** and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used? (7 pts)	0	0	0	0	0	7
12. Were the **economic model** (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner? (8 pts)	0	8	0	0	8	8
13. Were the choice of economic model, **main assumptions, and limitations** of the study stated and justified? (7 pts)	0	0	7	7	7	0
14. Did the author(s) explicitly discuss direction and magnitude of potential **biases**? (6 pts)	0	0	0	6	6	6
15. Were the **conclusions/recommendations** of the study justified and based on the study results? (8 pts)	8	8	8	8	8	8
16. Was there a statement disclosing the **source of funding** for the study? (3 pts)	3	3	3	0	3	0
Total score:	**50**	**51**	**48**	**73**	**93**	**90**

APPENDIX F. Summary Tables of Case Series

Appendix Table F1. Summary Tables of Case Series of Proton Beam Therapy in Bone Cancers – Primary Outcomes for KQ1 [Curative]

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
Probability of Overall Survival			
3-year			
All studies	2[1,46]	73 (33 to 40)	89.1% to 92.7%
Sacral chordoma	1[1]	33	92.7% (88.6% to 96.7%)
Spinal/sacral chordomas	1[46]	40	89.1% (73.5% to 95.8%)
5-year			
All studies	2[11,46]	108 (40 to 50)	81.9% to 88.7%
Thoracolumbar spinal malignancies	1[11]	50	88.7% (74.7% to 95.2%)
Spinal/sacral chordomas	1[46]	40	81.9% (63.7% to 91.6%)
Probability of Progression Free Survival			
3-year			
Sacral chordoma	1[1]	33	89.6% (78.2% to 100.0%)
Probability of Disease Free Survival			
3-year			
Sacral chordoma	1[1]	33	81.9% (67.3% to 96.4%)
Probability of Distant Metastasis Free Survival			
3-year			
Sacral chordoma	1[1]	33	88.2% (75.5% to 100.0%)
Probability of Cause (Disease) -Specific Survival			
3-year			
All studies	2[1,46]	73 (33 to 40)	95.7% to 97.2%
Sacral chordoma	1[1]	33	95.7% (87.3% to 100.0%)
Spinal/sacral chordomas	1[46]	40	97.2% (81.9% to 99.6%)
5-year			
Spinal/sacral chordomas	1[46]	40	89.4% (70% to 96.5%)
Probability of Local Control			
3-year			
Spinal/sacral chordomas	1[46]	40	96.9% (79.8% to 99.6%)
5-year			
Spinal/sacral chordomas	1[46]	40	85.4% (65.4% to 94.3%)
Probability of Distant Failure			
3-year			
Spinal/sacral chordomas	1[46]	40	11.7% (4.5% to 28.3%)
5-year			
Spinal/sacral chordomas	1[46]	40	20.2% (9.3% to 40.5%)

CI = confidence interval

Appendix Table F2. Summary Tables of Case Series of Proton Beam Therapy in Bone Cancers – Additional Primary Outcomes for KQ1 [Curative]

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Mortality					
Disease-related Mortality					
Sacral chordoma	1[1]	37	2	33	6%
All-cause Mortality					
All studies	2[1,46]	37 to 50.3	7	73 (33 to 40)	7.5% to 12%
Sacral chordoma	1[1]	37	4	33	12%
Spinal/sacral chordomas	1[46]	50.3	3	40	7.5%
Secondary Malignancy-Related Mortality					
Spinal/sacral chordomas	1[46]	50.3	3	40	7.5%
Treatment-Related Mortality					
Sacral chordoma	1[1]	37	1	33	3%
Progression/Relapse/Treatment Failure					
Overall					
Sacral chordoma	1[1]	37	6	33	18.2%
Local					
Sacral chordoma	1[1]	37	3	33	3%
Local after Distant					
Sacral chordoma	1[1]	37	1	33	3%
Local & Distant					
Sacral chordoma	1[1]	37	1	33	3%
Distant					
Sacral chordoma	1[1]	37	1	33	3%

F/U = follow-up;

Appendix Table F3. Summary Tables of Bone Case Series – Primary Outcomes for KQ1 [Mixed Curative and Salvage]

Outcome, Timing, Cancer Type	Studies	Total N (range)	Range (95% CI)
Probability of Overall Survival			
4-year			
Spinal chordomas/chondrosarcomas	1 [42]	51	72% (NR)
5-year			
All Studies	3 [16,95,102]	276 (50 to 126)	81% to 84%
Thoracic, Lumbar, Sacral Spine Malignancies	2 [16,95]	176 (50 to 126)	81% to 84%
Cervical, Thoracic, Lumbar, Sacral Spine Malignancies	1[102]	100	81%
8-year			
Thoracic, Lumbar, Sacral Spine Malignancies	1 [16]	50	65% (NR)
10-year			
Thoracic, Lumbar, Sacral Spine Malignancies	1[95]	126	65% (NR)
Probability of Disease Free Survival			
4-year			
Spinal chordomas/chondrosarcomas	[42]	51	57% (NR)
Probability of Recurrence Free Survival			
5-year			
Thoracic, Lumbar, Sacral Spine Malignancies	1 [16]	50	64% (NR)
8-year			
Thoracic, Lumbar, Sacral Spine Malignancies	1 [16]	50	52% (NR)
Probability of Freedom from Distant Metastasis			
4-year			
Spinal chordomas/chondrosarcomas	1 [42]	51	86% (NR)
Probability of Cause-Specific (Disease-Specific) Survival			
4-year			
Spinal chordomas/chondrosarcomas	1 [42]	51	72% (NR)
Probability of Local Control			
4-year			
Spinal chordomas/chondrosarcomas	1 [42]	51	58% (NR)
5-year			
All Studies	3 [16,95,102]	276 (50 to 126)	62% to 81%
Thoracic, Lumbar, Sacral Spine Malignancies	2 [16,95]	176 (50 to 126)	62% to 81%
Cervical, Thoracic, Lumbar, Sacral Spine Malignancies	1[102]	100	63%
8-year			
Thoracic, Lumbar, Sacral Spine Malignancies	1 [16]	50	74% (NR)
10-year			
Thoracic, Lumbar, Sacral Spine Malignancies	1[95]	126	49% (33% to 64%)
Probability of Regional Control			
5-year			
Thoracic, Lumbar, Sacral Spine Malignancies	1[95]	126	92% (83% to 96%)
10-year			
Thoracic, Lumbar, Sacral Spine Malignancies	1[95]	126	84% (67% to 93%)

Outcome, Timing, Cancer Type	Studies	Total N (range)	Range (95% CI)
Probability of Distant Control			
5-year			
Thoracic, Lumbar, Sacral Spine Malignancies	1[95]	126	77% (66% to 84%)
10-year			
Thoracic, Lumbar, Sacral Spine Malignancies	1[95]	126	63% (46% to 75%)

CI = confidence interval; NR = not reported

Appendix Table F4. Summary Tables of Case Series of Proton Beam Therapy in Bone Cancers – Additional Primary Outcomes for KQ1 [Mixed Curative and Salvage]

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Mortality					
Disease-related Mortality					
Thoracic, Lumbar, Sacral Spine Malignancies	2 [16,95]	41 to 87.6	21	176 (50 to 126)	8.7% to 20%
All-cause Mortality					
All studies	3 [16,95,102]	41 to 87.6	95	276	22.2% to 36%
Thoracic, Lumbar, Sacral Spine Malignancies	2 [16,95]	41 to 87.6	46	176 (50 to 126)	22.2% to 36%
Cervical, Thoracic, Lumbar, Sacral Spine Malignancies	1 [102]	65.5	26	100	26%
Secondary Malignancy-Related Mortality					
Thoracic, Lumbar, Sacral Spine Malignancies	2 [16,95]	41 to 87.6	5	176 (50 to 126)	1.6% to 6%
Other (not specified)					
Thoracic, Lumbar, Sacral Spine Malignancies	2 [16,95]	41 to 87.6	6	176 (50 to 126)	<1% to 10%
Progression/Relapse/Treatment Failure					
Overall					
All Studies	2 [16,42]	44.4 to 87.6	42	101 (50 to 51)	34% to 49%
Thoracic, lumbar, sacral spine malignancies	1 [16]	87.6	17	50	34%
Spinal chordomas/chondrosarcomas	1 [42]	44.4	25	51	49%
Local					
All Studies	4 [16,42,95,102]	41 to 87.6	87	303 (50 to 126)	22% to 35.3%
Thoracic, Lumbar, Sacral Spine Malignancies	2 [16,95]	41 to 87.6	49	176 (50 to 126)	22% to 30.2%
Spinal Chordomas	2 [42,102]	44.4 to 65.5	38	127 (51 to 76)	26.3% to 35.3%
Local & Distant					
Sacral chordoma	2 [42,102]	44.4 to 65.5	13	127 (51 to 76)	9.2% to 11.8%
Regional					
Thoracic, Lumbar, Sacral Spine Malignancies	2 [16,95]	41 to 87.6	9	176 (50 to 126)	2% to 6.3%

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Regional & Distant					
Thoracic, Lumbar, Sacral Spine Malignancies	1 [16]	87.6	1	50	
Distant					
All Studies	4 [16,42,95,102]	41 to 87.6	36	176 (50 to 126)	
Thoracic, Lumbar, Sacral Spine Malignancies	2 [16,95]	41 to 87.6	30	176 (50 to 126)	8% to 20.6%
Spinal Chordomas	2 [42,102]	44.4 to 65.5	6	127 (51 to 76)	2% to 6.6%

F/U = follow-up;

Appendix Table F5. Summary Tables of Case Series of Proton Beam Therapy in Bone Cancers – Safety Outcomes

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
Acute Toxicities (≤3 months)					
Grade ≤2					
Thoracic, Sacral, Lumbar Spinal Malignancies	1[16]	0	50	87.6	0%
Grade ≥3					
All Studies	2[16,102]	9	150	65.5 to 87.6	2% to 8%
Thoracic, Sacral, Lumbar Spinal Malignancies	1[16]	1	50	87.6	2%
Cervical, Thoracic, Lumbar, Sacral Spine Chordomas	1[102]	8	100	65.5	8%
Acute Toxicities (timeframe NR)					
Grade ≥3					
Sacral chordoma	1[1]	1	33	37	3%
Late Toxicities					
Any Grade					
Spinal/sacral chordomas	1[46]	Grade 2: 4* Grade NR: 17†	40	50.3	Grade 2: 10%* Grade NR: 42.5%†
Grade ≥3					
All Studies	3[11,16,102]	19	218 (50 to 100)	12.9 to 87.6	5% to 12%
Cervical, Thoracic, Lumbar, Sacral Spine Chordomas	1[102]	5	100	65.5	5%
thoracolumbar spinal malignancies	1[11]	8	68	12.9	11.7%
Thoracic, Sacral, Lumbar Spinal Malignancies	1[16]	6†	50	87.6	12%†
Late Toxicities (timeframe NR)					
Grade 2					
spinal chordomas/chondrosarcomas	1[42]	1	51	44.4	2%
Grade ≥3					
Sacral chordoma	1[1]	5†	33	37	15%†
Secondary Malignancies					
All Studies	4[42,46,95,102,124]	4	317 (40 to 126)	44.4 to 65.5	0% to 2%

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
Sacral/Vertebral Fracture (Grade ≥3)					
All Studies	6 [1,16,42,46,95,102]	23	385 (33 to 126)	37 to 87.6	2% to 25%
Thoracic, Sacral, Lumbar Spinal Malignancies	1[16]	1	50	87.6	2%
spinal chordomas/chondrosarcomas	1[42]	1‡	51	44.4	2%‡
Spinal/sacral chordomas	4[1,46,95,102]	21‡	284 (33 to 126)	37 to 65.5	3% to 25%‡
Bone or Soft Tissue Necrosis					
Grade NR					
All Studies	3 [42,46,95]	4	217 (40 to 126)	41 to 50.3	0% to 5.9%
spinal chordomas/chondrosarcomas	1[42]	3§	51	44.4	5.9%
Spinal/sacral chordomas	1[46]	0	40	50.3	0%
Spine Chordomas	1 [95]	1	126	41	<1%
Spinal Cord Injury					
RT-related					
All Studies	3[11,16,46]	1	158 (40 to 68)	12.9 to 50.3	0% to 1.5%
thoracolumbar spinal malignancies	2[11,16]	1	118 (50 to 68)	12.9 to 87.6	0% to 1.5%
Spinal/sacral chordomas	1[46]	0	40	50.3	0%
Radiation-Related Deterioration in Neurological Status					
Spine Chordomas	1 [95]	9	126	41	7.1%
Probability of Freedom from Grade ≥2 Neurological Injury					
thoracolumbar spinal malignancies	1[11]	5-year: N/A 6-year: N/A 8-year: N/A	68	12.9	5-year: 92.9% (74.6% to 98.2%) 6-year: 80.9% (55.3% to 92.7%) 8-year: 80.9% (55.3% to 92.7%)
Probability of Freedom from Late Toxicities					
Grade ≥3					
thoracolumbar spinal malignancies	1[102]	N/A	100	65.5	94% (88.6% to 98.6%)

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
Actuarial Risk of Toxicities					
any grade					
thoracolumbar spinal malignancies	1[16]	5-year: N/A 8-year: N/A	50	87.6	5-year: 16% (NR) 8-year: 19% (NR)
Grade ≥3					
thoracolumbar spinal malignancies	1[16]	5-year: N/A 8-year: N/A	50	87.6	5-year: 10% (NR) 8-year: 13% (NR)

CI = confidence interval; F/U = follow-up; N/A = not applicable; NR = not reported

* Kabolizadeh 2017: Other late toxicities were reported but no grades were given.

† Patients may or have had more than one toxicity, and patient totals were not clearly reported across toxicities/grades. Totals of patients with toxicities are estimated based on given data for the following studies: Kabolizadeh et al., 2017, Delaney et al., 2014, and Aibe et al., 2018

‡ Grade not reported for vertebral fracture in the following studies: Indelicato 2016 and Kabolizadeh 2017

§ Indelicato 2016: Includes two patients with sacral soft tissue necrosis and one with necrotic bone cyst requiring surgery.

Appendix Table F6. Summary Tables of Case Series of Proton Beam Therapy in Brain, Spinal, and Paraspinal Cancers – Primary Outcomes for KQ1 [Curative]

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
Probability of Overall Survival			
1-year			
Glioblastoma multiforme	1[73]	46	82.6% (NR)
2-year			
All studies	2 [4,73]	96 (46 to 50)	47.6% to 96%
Mixed Diagnoses [primarily medulloblastoma 38% and germ cell tumors (germinomatous 18% and non-germinomatous 12%)]	1[4]	50	96% (NR)
Glioblastoma multiforme	1[73]	46	47.6% (NR)
5-year			
Mixed Diagnoses [primarily medulloblastoma 38% and germ cell tumors (germinomatous 18% and non-germinomatous 12%)]	1[4]	50	84% (NR)
Meningiomas (WHO grade 2/3)	1[78]	35	80.7% (65.0% to 96.4%)
Glioblastoma multiforme	1[73]	46	30% (estimate from graph)
8-year			
Low-grade Glioma	1[64]	23	100% (NR)
Median Overall Survival			
Glioblastoma multiforme	1[73]	46	21.1 (6.3 to 10.3) months
Probability of Progression Free Survival			
1-year			
Glioblastoma multiforme	1[73]	46	37% (NR)
2-year			
All studies	2 [4,73]	96 (46 to 50)	11.6% to 82%
Mixed Diagnoses [primarily medulloblastoma 38% and germ cell tumors (germinomatous 18% and non-germinomatous 12%)]	1[4]	50	82% (NR)
Glioblastoma multiforme	1[73]	46	11.6% (NR)
5-year			
Mixed Diagnoses [primarily medulloblastoma 38% and germ cell tumors (germinomatous 18% and non-germinomatous 12%)]	1[4]	50	68% (NR)
Probability of Local Control			
5-year			
Meningiomas (WHO grade 2/3)	1[78]	35	68.0% (48.6% to 87.4%)

CI = confidence interval; NR = not reported

Appendix Table F7. Summary Tables of Case Series of Proton Beam Therapy in Brain, Spinal, and Paraspinal Cancers – Additional Primary Outcomes for KQ1 [Curative]

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Mortality					
Disease-related Mortality					
All studies	2 [4,73]	20.1 to 42.1	35	96	4% to 71.7%
Glioblastoma	1 [4]	42.1	33	46	71.7%
Mixed Diagnoses	1 [73]	20.1	2	50	4%
All-cause Mortality					
All studies	2 [4,73]	20.1 to 42.1	58	96 (46 to 50)	4% to 71.7%
Glioblastoma	1 [4]	42.1	33	46	71.7%
Mixed Diagnoses	1 [73]	20.1	2	50	4%
Progression/Relapse/Treatment Failure					
All studies	2 [4,73]	20.1 to 42.1	101	96 (46 to 50)	14% to 67.4%
Glioblastoma	1 [73]	42.1	31*	46	67.4%
Mixed Diagnoses	1 [4]	20.1	7	50	14%
Mixed Curative					
Mortality					
Disease-related Mortality					
Meningiomas	1 [78]	56.9	9	96	9.3%
All-Cause					
Meningiomas	1 [78]	56.9	14	96	14.6%
Local Failures					
Disease-related Mortality					
Meningiomas	1 [78]	56.9	13	96	14%

F/U = follow-up;
* Mizumoto 2016: Relapse data here is the proportion of patients judged to have recurrence on MRI (excluding those with radiation necrosis).

Appendix Table F8. Summary Tables of Case Series of Proton Beam Therapy in Brain, Spinal, and Paraspinal Cancers – Primary Outcomes for KQ2 [mixed salvage/curative]

Outcomes, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
Probability of Progression Free Survival			
5-year			
Central Neurocytomas	1[49]	16*	100% (NR)
Probability of Disease Control			
5-year			
Central Neurocytomas	1[49]	16*	100% (NR)

CI = confidence interval; NR = not reported
* Among 16 patients who received surgery plus adjuvant or salvage PBT

Appendix Table F9. Summary Tables of Case Series of Proton Beam Therapy in Brain, Spinal, and Paraspinal Cancers – Safety Outcomes

Outcome, Grade/Timing, Cancer Type	Studies	Number Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95%CI)
Acute Toxicity					
Grade ≥3					
All studies	6[4,19,49,64,73,78]	29	515 (23 to 280)	20.1 to 56.9	0% to 17.4%
Glioblastoma	1 [73]	8*	46	42.1	17.4%
Mixed Diagnoses	2[4,19]	18†	326 (46 to 280)	NR to 20.1	4.3% to 13%
Low Grade Gliomas	1 [64]	2	23	NR	8.7%
Central Neurocytomas	1 [49]	0	24	56	0%
Meningioma	1[78]	1‡	96	56.9	1%
Late Toxicity					
Grade ≥3					
All Studies	1[73,78]	14	142 (46 to 96)	42.1 to 56.9	3.1% to 23.9%
Meningioma	1[78]	3	96	56.9	3.1%
Glioblastoma	1 [73]	11	46	42.1	23.9%
Toxicity Free Survival (Grade ≥3)					
5-year					
Meningioma	1[78]	N/A	96	56.9	89.1% (82.2% to 96%)
Weight Loss					
% of weight lost					
Mixed Brain, Spinal Diagnoses	1[4]	≤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 (grade NR)					
Late - >3 months					
Glioblastoma	1 [73]	11	46	42.1	23.9%
Brain Necrosis (included in Late Toxicities)					
Grade ≥3					
Meningioma	1[78]	3	96	56.9	3.1%
Neurotoxicity [PBT-related]§					
Grade ≤2 – timing NR					
Central Neurocytomas	1 [49]	7	16	56	44%
RT-related Mortality					
Meningioma	1[78]	1	96	56.9	1%

CI = confidence interval; F/U = follow-up; N/A = not applicable; NR = not reported
* Patients with grade 3 or 4 toxicities considered likely to be related to chemotherapy by the authors are not included in this total.
† Dutz 2018: Totals of patients with toxicities are estimated based on given data. Patients may have had more than one toxicity, and patient totals were not clearly reported across toxicities.
‡ Out of whole population rather than just malignant (WHO grade 2/3; n=35; 36%); Toxicity not stratified by malignant and benign.
§ Neurotoxicities include "cognitive disturbance, concentration/memory impairment, headache, seizure, presyncope".

Appendix Table F10. Summary Tables of Case Series of Proton Beam Therapy in Breast Cancer – Primary Outcomes for KQ1 [Curative]

Outcome, Timing, Cancer Type	No. of Studies	Total N (range of N's)	Range (95% CI)
Probability of Overall Survival			
5-year			
Breast Cancer	1[7]	100	95% (NR)
Probability of Disease Free Survival			
5-year			
Breast Cancer	1[7]	100	94% (NR)
Probability of Tumor Recurrence Free Survival			
5-year			
Breast Cancer	1[7]	100	97% (93% to 100%)

CI = confidence interval; NR = not reported

Appendix Table F11. Summary Tables of Case Series of Proton Beam Therapy in Breast Cancer – Additional Primary Outcomes for KQ1 [Curative]

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Mortality					
Disease-related Mortality					
Breast Cancer	1[114]	15.5	5	91	5.5%
All-cause Mortality					
Breast Cancer	1[114]	15.5	6	91	6.7%
Progression/Relapse/Treatment Failure					
Overall					
Breast Cancer	1[114]	15.5	12	91	13.2%
Local					
Breast Cancer	1[114]	15.5	2	91	2%
Local and Distant					
Breast Cancer	2[7,114]	15.5 to 60	2	191 (91 to 100)	0% to 2%
Distant					
Breast Cancer	2 [14,114]	9.3 to 15.5	9	121 (30 to 91)	3.3% to 8.8%

F/U = follow-up;

Appendix Table F12. Summary Tables of Case Series of Proton Beam Therapy in Breast Cancer – Safety Outcomes

Outcome, Grade, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range
Acute Toxicities*					
Grade ≤2					
Breast Cancer	1[7]	62	100	60	62%
Grade ≥3					
Breast Cancer	2[7,14]	1	128	9.3 to 60	0% to 3.6%
Late Toxicities					
Grade ≤2					
Breast Cancer	1[7]	NR	100	60	7 [events]

F/U = follow-up;
*Cuaron 2015 did not define timeframe for acute toxicites

Appendix Table F13. Summary Tables of Case Series of Proton Beam Therapy in Esophageal Cancer – Primary Outcomes for KQ1 [Curative]

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
Probability of Overall Survival			
2-year			
Esophageal	1 [43]	40	75.1% (59.6% to 90.6%)
3-year			
Esophageal	2 [43,104]	87 (40 to 47)	59.2% to 70.4%
Probability of Progression Free Survival			
3-year			
Esophageal	1[104]	47	56.3% (43.0% to 73.7%)
Probability of Cause-Specific Survival			
2-year			
Esophageal	1 [43]	40	77% (62.1% to 92.7%)
Probability of Locoregional Control			
2-year			
Esophageal	1 [43]	40	66.4% (50.4% to 82.4%)
Probability of Local Control			
3-year			
Esophageal	1[104]	47	67.7% (54.9% to 83.6%)

CI = confidence interval;

Appendix Table F14. Summary Tables of Case Series of Proton Beam Therapy in Esophageal Cancer – Additional Primary Outcomes for KQ1 [Curative]

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Progression/Relapse/Treatment Failure					
Overall					
Esophageal	1 [43]	24	16	40	40%
Local					
Esophageal	1 [43]	24	8	40	20%
Locoregional					
Esophageal	1 [43]	24	1	40	2.5%
Regional					
Esophageal	1 [43]	24	4	40	10%
Distant					
Esophageal	1 [43]	24	3	40	7.5%
Tumor Response					
Complete Response					
Esophageal	1 [43]	24	30	40	75%
Partial Response					
Esophageal	1 [43]	24	8	40	20%

F/U = follow-up; N/A = not applicable; NR = not reported

Appendix Table F15. Summary Tables of Case Series of Proton Beam Therapy in Esophageal Cancer – Safety Outcomes

Outcome, Grade, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range
Acute Hematological Toxicities					
Grade 3 or 4					
Any (NOS)*	1[43]	10	40	24	25%
Grade 4					
Any (NOS)	1[43]	2	40	24	5%
Grade 3 or 4					
Leukopenia	1[104]	26	47	29	55.3%
Neutropenia	1[104]	21	47	29	44.7%
Thrombocytopenia	1[104]	13	47	29	27.7%
Acute Non-Hematological Toxicities					
Grade 3					
Esophagitis	1[43]	9	40	24	22%
Dermatitis	1[43]	2	40	24	5%
Grade 4					
Esophagitis	1[43]	0	40	24	0%
Dermatitis	1[43]	0	40	24	0%
Grade 3 or 4					
Nausea and vomiting	1[104]	1	47	29	2.1%
Esophagitis	1[104]	5	47	29	10.6%
Pneumonitis	1[104]	0	47	29	0%
Late Toxicity					
Grade 3					
Any*	1[43]	2	40	24	5%
Heart (Pericarditis, pericardial effusion)	1[104]	0	47	29	0%
Lung (pleural effusion, pneumonitis)	1[104]	1	47	29	2.1% (pneumonitis)
Esophageal	1[104]	3	47	29	6.4% (4.3% stenosis, 2.1% fistula)
Grade 4					
Any†	2[43,104]	0	87 (40 to 47)	24-29	0%

F/U = follow-up; NOS = not otherwise specified.
Includes
*Includes toxicity of the heart, lung and esophagus; the two cases of grade 3 late toxicity were esophagitis.
†Includes toxicity of the heart, lung and esophagus.

Appendix Table F16. Summary Tables of Case Series of Proton Beam Therapy in Gastrointestinal Cancers – Primary Outcomes for KQ1 [Curative]

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
Probability of Overall Survival			
1-year			
Adenocarcinoma	2 [34,51]	85 (37 to 48)	65%* to 75.7%
2-year			
Adenocarcinoma	1[34]	48	42% (28% to 55%)
3-year			
Adenocarcinoma	1[34]	48	23%* (NR)
4-year			
Adenocarcinoma	1[34]	48	23%* (NR)
Median Overall Survival			
Adenocarcinoma	2 [34,51]	85 (37 to 48)	17.3 to 19.3 months
Probability of Progression Free Survival			
1-year			
Adenocarcinoma	2 [34,51]	85 (37 to 48)	44%* to 64.8%
2-year			
Adenocarcinoma	1[34]	48	24%* (NR)
3-year			
Adenocarcinoma	1[34]	48	17.5%* (NR)
4-year			
Adenocarcinoma	1[34]	48	10%* (NR)
Median Progression Free Survival			
Adenocarcinoma	2 [34,51]	85 (37 to 48)	10.4 to 15.3 months
Probability of Recurrence Free Survival			
1-year			
Adenocarcinoma	1[51]	37	33.2% (17.5% to 48.9%)
Median Recurrence Free Survival			
Adenocarcinoma	1[51]	37	9.8 (7.1 to 12.4) months

CI = confidence interval; NR = not reported
*Estimated from graph

Appendix Table F17. Summary Tables of Case Series of Proton Beam Therapy in Gastrointestinal Cancers – Additional Primary Outcomes for KQ1 [Curative]

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Mortality					
All-cause Mortality					
Adenocarcinoma	2 [34,51]	16.7 to 38	61	85 (37 to 48)	67.6% to 75%
Progression/Relapse/Treatment Failure					
Local					
Adenocarcinoma	1[51]	16.7	18	37	48.6%
Locoregional					
Adenocarcinoma	[34]	38	6	37*	16.2%
Regional					
Adenocarcinoma	1[51]	16.7	7	37	18.9%
Distant					
Adenocarcinoma	2 [34,51]	16.7 to 38	61	85 (37 to 48)	70.3% to 73%
Overall Treatment Response					
Partial Response					
Adenocarcinoma	1[51]	16.7	8	37	21.6%
Stable Disease					
Adenocarcinoma	1[51]	16.7	17	37	45.9%
Progressive Disease					
Adenocarcinoma	1[51]	16.7	12	37	32.4%
Primary Tumor Response					
Partial Response					
Adenocarcinoma	1[51]	16.7	14	37	37.8%
Stable Disease					
Adenocarcinoma	1[51]	16.7	23	37	62.2%
Progressive Disease					
Adenocarcinoma	1[51]	16.7	0	37	0%

F/U = follow-up;
*Only reported among surgically resected patients

Appendix Table F18. Summary Tables of Case Series of Proton Beam Therapy in Gastrointestinal Cancers – Safety Outcomes

Outcome, Grade, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range
Acute Toxicities*					
Grade ≥3					
Pancreatic adenocarcinoma	1[51]	0	37	16.7	0%
Late Toxicities†					
Grade ≥3					
Pancreatic adenocarcinoma	1[51]	0	37	16.7	0%
Timing NR					
Grade 3‡					
Pancreatic adenocarcinoma	1[34]	2	35	38	5.7%
Grade ≥4					
Pancreatic adenocarcinoma	1[34]	0	35	38	0%

F/U = follow-up;
*Hematological toxicities included leukopenia, anemia, thrombocytopenia and Non-hematological toxicities included hand-foot syndrome, anorexia, vomiting, diarrhea, abdrominal pain, and stomatitis.
†Such as gastrointestinal bleeding or duodenal ulcer.
‡One case of colitis (2.9%) and one case of chest wall pain (2.9%).

Appendix Table F19. Summary Tables of Case Series of Proton Beam Therapy in Head & Neck (including Skull-Base) Cancers – Primary Outcomes for KQ1 [Curative]

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
Probability of Overall Survival			
1-year			
Sinonasal, nasal, paranasal (to include on mucosal melanoma)	3[15,131,132]	228 (32 to 112)	88% to 95.1% (NR)
2-year			
All studies	5[15,18,29,131,132]	227 (32 to 112)	60% to 94.5%
Oropharyngeal	1[29]	50	94.5% (81.4% to 98.5%)
Sinonasal, nasal, paranasal	2[15,132]	196 (84 to 112)	80% to 80.2%
Mucosal melanoma of the nasal cavity and para-nasal sinuses [rare]	1[131]	32	60%
Skull-base Chordomas	1[18]	33	92% (NR)

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
3-year			
All studies	6 [15,29,65,76,107,131]	312 (32 to 84)	46.1% to 94.5%
Oropharyngeal	1[29]	50	94.5% (81.4% to 98.5%)
Sinonasal, nasal, paranasal cancers	1 [15]	84	68.4%
Mucosal melanoma of the nasal cavity and para-nasal sinuses [rare]	1[131]	32	46.1%
Mixed Diagnoses	2 [65,76]	113 (47 to 66)	61% to 84.9%
Tongue Cancer	1 [107]	33	87.0% (75.7% to 99.9%)
4-year			
Oropharyngeal	1[29]	50	94.5% (81.4% to 98.5%)
5-year			
All studies	3[21,79,132]	313 (42 to 159)	64.2% to 94.9%
Skull-base Chondrosarcomas and Chordomas	1[21]	159	94.9%
Sinonasal, nasal, paranasal Zenda 2015: squamous cell, 24%; adenoid cycstic, 17%; olfactory neuroblastoma, 30%	1[132]	112	64.2%
Olfactory Neuroblastoma	1 [79]	42	76% to 100%* (average 81%) Kadish A (n=5): 100% Kadish B (n=9): 86% Kadish C (n=28): 76%
7-year			
Skull-base Chondrosarcomas and Chordomas	1[124]	251	93.6% (89.6% to 96.7%)
10-year			
Skull-base Chondrosarcomas	1 [21]	159	87% (79.7% to 95.0%)
Probability of Progression Free Survival			
2-year			
Oropharyngeal	1[29]	50	88.6% (75.8% to 95.1%)
Mucosal melanoma of the nasal cavity and para-nasal sinuses [rare]	1[131]	32	36.4%
3-year			
All studies	4[29,76,107,131,132]	274 (32 to 112)	36.4% to 88.6%
Oropharyngeal	1[29]	50	88.6% (75.8% to 95.1%)
Sinonasal, nasal, paranasal	2 [131,132]	144 (32 to 112)	36.4% to 48.2% [36% in mucosal melanoma]

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
Mixed Head & Neck Diagnoses (primarily paranasal, 70%)	1[76]	47	56% (NR)
Tongue Cancers	1 [107]	33	74.1% (NR)
4-year			
Oropharyngeal	1[29]	50	68%
5-year			
All studies	3[21,79,132]	313 (42 to 159)	[36.5] 39% to 93.2%
Skull-base Chondrosarcomas and Chordomas	1[21]	159	93.2 (89.0% to 97.6%)
Sinonasal, nasal, paranasal	1 [132]	112	44.5%
Olfactory Neuroblastoma	1 [79]	42	39% to 80%* Kadish A (n=5): 80% Kadish B (n=9): 65% Kadish C (n=28): 39%
10-year			
Skull-base Chondrosarcomas	1[21]	159	84.2% (76.5% to 92.7%)
Probability of Disease Free Survival			
1-year			
Sinonasal	1[15]	84	80.7% (NR)
2-year			
Sinonasal	1[15]	84	71.1% (NR)
3-year			
Sinonasal	1[15]	84	62.7% (NR)
Probability of Cause-Specific Survival			
1-year			
Sinonasal	1[15]	84	95.1 % (NR)
2-year			
Sinonasal	1[15]	84	81.5% (NR)
3-year			
Sinonasal	1[15]	84	69.6% (NR)
Probability of Failure Free Survival			
7-year			
Skull-based chondrosarcomas	1[124]	251	93.1% (89.6 to 96.7)
Probability of Freedom from Distant Metastases			
1-year			
Sinonasal	1[15]	84	88% (NR)
2-year			
Sinonasal	1[15]	84	82% (NR)
3-year			

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
Sinonasal	1[15]	84	73.2% (NR)
Probability of Local Control			
1-year			
Sinonasal	1[15]	84	92.4%
Mucosal melanoma of the nasal cavity and para-nasal sinuses [rare]	1[131]	32	75.8% (63.8% to 92.4%)
2-year			
Sinonasal	1[15]	84	85.1%
3-year			
All Studies	2[15,107]	117 (33 to 84)	82.7% to 86.6%
Sinonasal	1[15]	122 (38 to 84)	82.7%
Tongue Cancer	1 [107]	33	86.6% (75.0% to 100%)
5-year			
Skull-base chondrosarcomas and chordomas	1[21]	159	96.4%
8-year			
Skull-base chondrosarcomas and chordomas	1[15]	77	89.7% (NR)
10-year			
Skull-base Chondrosarcomas and Chordomas	1[21]	159	93.5% (88.3% to 98.9%)
Probability of Regional Control			
1-year			
Sinonasal	1[15]	84	95.2% (NR)
2-year			
Sinonasal	1[15]	84	93.6% (NR)
3-year			
All Studies	2[15,107]	117 (33 to 84)	83.9% to 93.6%
Sinonasal	1[15]	84	93.6% (NR)
Tongue Cancer	1 [107]	33	83.9% (71.7% to 98.0%)

CI = confidence interval; NR = not reported
*This range represents the three OS values reported by histopathology within this study (no overall value was reported).

Appendix Table F20. Summary Tables of Case Series of Proton Beam Therapy in Head & Neck (including Skull-Base) Cancers – Additional Primary Outcomes for KQ1 [Curative]

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Mortality					
Disease-related Mortality					
All studies	6[15,21,27,107,123,124]	18 to 87.3	48	654 (31 to 251)	1.9% to 30.9%
Skull-based Malignancies	4[21,27,123,124]	18 to 87.3	19	537 (31 to 251)	1.9% to 6.5%
Sinonasal	1[15]	28.8	26	84	30.9%
Tongue Cancer	1 [107]	43	3	33	9.1%
All-cause Mortality					
All studies	6[15,21,27,123,124,131]	18 to 87.3	90	733 (31 to 251)	4% to 36%
Sinonasal, Nasal, Paranasal and Skull-Base Malignancies	2[15,131]	28.8 to 57.5	42	196 (84 to 90)	10.7%to 36%
Skull-Base Malignancies	4[21,27,123,124]	18 to 87.3	48	537 (31 to 251	4% to 10.1%
Treatment Related Mortality – Late (>3 months)					
All studies	3 [15,107,112]	28.8 to 43	4	155 (33 to 84)	0% to 3.6%
Tongue Cancer	1 [107]	43	0	33	0%
Sinonasal, Nasal, Paranasal	2 [15,112]	28.8 to 30	4	122 (38 to 84)	2.6% to 3.6%*
Secondary Malignancy-related Mortality					
All studies	2[15,124]	28.8 to 87.3	3	335 (84 to 251)	<1% to 1.2%
Sinonasal, Nasal, Paranasal	1[15]	28.8	1	84	1.2%
Skull-base chondrosarcomas	1[124]	87.3	2	251	<1%
Progression/Relapse/Treatment Failure					
Overall					
All studies	8[18,21,79,107,123,124,131,132]	21 to 87.3	84	739 (32 to 251)	2.5% to 47.6%
Skull-base Chordomas and Chondrosarcomas	4[18,21,123,124]	21 to 87.3	56	542 (33 to 251)	2.5% to 28.1%
Sinonasal, Nasal, Paranasal	2[131,132]	36.4 to 57.5	77	122 (32 to 90)	49.1% to 68.8%
Olfactory Neuroblastoma	1 [79]	69	20	42	47.6%
Tongue Cancer	1 [107]	43	8	33	24.2%

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Local					
All studies	8 [21,76,79,107,123,124,131,132]	32 to 87.3	81	870 (32 to 251)	2.5% to 46.8%
Skull-base Chordomas and Chondrosarcomas	3 [21,123,124]	69.2 to 87.3	21	487 (77 to 251)	2.5% to 7.8%
Sinonasal, Nasal, Paranasal	2 [131,132]	36.4 to 57.5	30	144 (32 to 122)	12.5% to 23.2%
Mixed Head & Neck Diagnoses	1 [76]	32	22	47	46.8%
Olfactory Neuroblastoma	1 [79]	69	6	42	14.3%
Tongue Cancer	1 [107]	43	2	33	6.1%
Loco-regional					
All studies	2 [79,107]	43 to 69	3	75 (33 to 42)	3% to 4.8%
Olfactory Neuroblastoma	1 [79]	69	2	42	4.8%
Tongue Cancer	1 [107]	43	1	33	3%
Regional					
All studies	7 [21,76,79,107,123,131,132]	30 to 77	52	502 (32 to 159)	0% to 19%
Sinonasal, Nasal, Paranasal	2 [131,132]	36.4 to 57.5	18	144 (32 to 122)	12.5% to 12.5%
skull base chondrosacromas	2 [21,123]	69.2 to 77	1	236 (77 to 159)	0% to <1%
Mixed Head & Neck Diagnoses	1 [76]	32	22	47	10.6%
Olfactory Neuroblastoma	1 [79]	69	8	42	19%
Tongue Cancer	1 [107]	43	3	33	9.1%
Distant					
All studies	9 [15,18,21,76,79,123,124,131,132]	21 to 87.3	66	837 (32 to 251)	0% to 42.6%
Sinonasal, Nasal, Paranasal	3 [15,131,132]	28.8 to 57.5	41	228 (32 to 112)	13.4% to 28.1%
Skull base Chordomas and Chondrosacromas	4 [18,21,123,124]	21 to 87.3	3	520 (33 to 251)	0% to 1.2%
Mixed Head & Neck Diagnoses	1 [76]	32	20	47	42.6%
Olfactory Neuroblastoma	1 [79]	69	2	42	4.8%
Locoregional					
All studies	2 [79,107]	43 to 69	3	75 (33 to 42)	3% to 4.8%
Olfactory Neuroblastoma	1 [79]	69	2	42	4.8%
Tongue Cancer	1 [107]	43	1	33	3%

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Local and Distant					
All studies	5[21,79,107,124,131]	36.4 to 87.3	7	517 (32 to 251)	<1% to 6.3%
Olfactory Neuroblastoma	1 [79]	69	2	42	4.8%
Tongue Cancer	1 [107]	43	1	33	3%
Skull base Chondrosacromas	2[21,124]	77 to 87.3	2	410 (159 to 251)	<1% to <1%
Sinonasal, Nasal, Paranasal	1[131]	36.4	2	32	6.3%
Regional and Distant					
All studies	3[15,107,131]	28.8 to 43	9	149 (32 to 84)	3% to 12.5%
Tongue Cancer	1 [107]	43	1	33	3%
Sinonasal, Nasal, Paranasal	2[15,131]	28.8 to 36.4	8	116 (32 to 84)	4.8% to 12.5%

F/U = follow-up; N/A = not applicable; NR = not reported
*Considered "possibly related to RT"

Appendix Table F21. Summary Tables of Case Series of Proton Beam Therapy in Head & Neck (including Skull-Base) Cancers – Primary Outcomes for KQ1 [Mixed Curative]

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
Probability of Overall Survival			
2-year			
Skull-base chondrosarcomas	1[24]	106	99% (98% to 10%)
4-year			
Skull-base chondrosarcomas	1[24]	106	90.2% (87% to 93.4%)
5-year			
Skull-base chondrosarcomas, chordomas and Sarcomas;	4[17,24,103,123]	500 (76 to 222)	75% to 88.3% Stieb 75% Demizu 75.3% PFS 49.6 Fung 88.3% Weber 86.4%
7-year			
Skull-base chondrosarcomas	1[123]	222	80.0% (72.4% to 88.4%)
Probability of Progression Free Survival			
5-year			
Skull-base chordomas/chondrosarcomas	1[17]	96	49.6%

Probability of Distant Metastasis Free Survival			
5-year			
Skull-base chordomas and chondrosarcomas	1[123]	222	91.6% (91.6% to 98.6%)
7-year			
Skull-base chordomas and chondrosarcomas	1[123]	222	91.6% (91.6% to 98.6%)
Probability of Local Control			
2-year			
skull-base chorodoma	1[24]	106	88.6% (84.4% to 92.8%)
4-year			
skull-base chorodoma	1[24]	106	78.3% (71.2% to 85.4%)
5-year			
skull-base chordomas and chondrosarcomas	4[17,24,103,123]	500 (76 to 222)	71.1% to 81.4%
7-year			
skull-base chordomas and chondrosarcomas	1[123]	222	78.3% (71.2% to 85.4%)

CI = confidence interval; NR = not reported

Appendix Table F22. Summary Tables of Case Series of Proton Beam Therapy in Head & Neck (including Skull-Base) Cancers – Additional Primary Outcomes for KQ1 [mixed curative]

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Mortality					
Disease-related Mortality					
Skull-based Malignancies	2[24,123]	50 to 61	30	328 (106 to 222)	9% to 9.4%
All-cause Mortality					
Skull-based and Cervical Malignancies	3[24,103,123]	50 to 65.5	64	404 (76 to 222)	11.3% to 30.3%
Treatment Related Mortality					
Skull-based Malignancies	2[17,24]	52.6 to 61	1	202 (96 to 106)	0% to <1%
Intercurrent Disease					
Skull-based Malignancies	1[24]	61	1	106	<1%
Other Causes (not specified)					
Skull-based Malignancies	1[123]	50	9	222	4%
Progression/Relapse/Treatment Failure					
Overall					
Skull-based Malignancies	2[24,103]	61 to 65.5	63	182	29.2% to 42.1%
Local					
Skull-based and Cervical Malignancies	4[17,24,103,123]	50 to 65.5	105	500 (76 to 222)	15.8% to 28.1%

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Regional					
Skull-based Malignancies	1[24]	61	3	106	2.8%
Distant					
Skull-based and Cervical Malignancies	2[24,103,123]	50 to 65.5	18	404 (76 to 222)	3.6% to 6.6%
Local and Distant					
Skull-based Malignancies	1[103]	65.5	7	76	9.2%
Regional and Distant					
Skull-based Malignancies	1[17]	52.6	19	96	19.8%

F/U = follow-up;

Appendix Table F23. Summary Tables of Case Series of Proton Beam Therapy in Head & Neck (including Skull-Base) Cancers – Primary Outcomes for KQ2 [Salvage]

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range
Probability of Overall Survival			
1-year			
All Studies	5[31,32,67,87,94]	292 (34 to 91)	56% to 81.3% Hayashi 2017, 62% (oral cancer, primarily SCC, primarily tongue and upper/lower gingiva) Hayashi 2016, 65% (oral cancer, SCC), primarily tongue and upper/lower gingiva McDonald 2016 56% (various head and neck, primarily SCC, followed by ACC) Phan 2016 81.3% (various head and neck, primarily SCC, followed by ACC) Romesser 65.2% (various head and neck, primarily SCC, ACC, adenocarcinoma)
Oral Cancers	2[31,32]	80 (34 to 46)	62% to 65%
Mixed Head & Neck Diagnoses	3[67,87,94]	212 (60 to 91)	56% to 81.3%
2-year			
All Studies	4[31,32,67,87]	201 (34 to 61)	32.7% to 69% Hayashi 2017, 42% (oral cancer, primarily SCC, primarily tongue and upper/lower gingiva) Hayashi 2016, 46% (oral cancer, SCC), primarily tongue and upper/lower gingiva McDonald 2016 32.7% (primarily SCC, followed by ACC) 32.7% Phan 2016 69% (various head and neck, primarily SCC, followed by ACC)

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range
Oral Cancers	2[31,32]	80 (34 to 46)	42% to 46%
Mixed Head & Neck Diagnoses	3[67,87,94]	213 (60 to 92) 60 61 92	32.7% to 69%
Median Overall Survival			
Mixed Head & Neck Diagnoses	1[67]	61	16.5 (95% CI 10.2 to 21.9) months
Probability of Progression Free Survival			
1- and 2-year			
Mixed Head & Neck Diagnoses	1[87]	60	1 year: 60.1% (NR) 2 year: 48.2%
Probability of Locoregional Failure Free Survival			
1- and 2-year			
Mixed Head & Neck Diagnoses	1[87]	60	1 year: 68.4% (NR) 2 year: 55.9% (NR)
Incidence of Locoregional Failure			
1-year			
Mixed Head & Neck Diagnoses	1[94]	91	25.1%
Incidence of Local Failure			
1-year			
Mixed Head & Neck Diagnoses	1[67]	61	19.7% (10.8% to 30.5%)
Incidence of Regional Failure			
1-year			
Mixed Head & Neck Diagnoses	1[67]	61	3.3% (0.6% to 10.2%)
Probability of Distant Metastasis Free Survival			
1-year			
Mixed Head & Neck Diagnoses	2[87,94]	151 (60 to 91)	74.9% to 84%
2-year			
Mixed Head & Neck Diagnoses	2[87,94]	151 (60 to 91)	63.7% to 66%
Probability of Local Control			
1-year			
Oral Cancer	2[31,32]	80 (34 to 46)	77% to 81%

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range
2-year			
Oral Cancer	2[31,32]	80 (34 to 46)	60% to 70%
Probability of Locoregional Control			
1- and 2-year			
Mixed Head & Neck Diagnoses	1[87]	60	1 year: 80.8% (NR) 2 year: 72.8% (NR)

CI = confidence interval; NR = not reported

Appendix Table F24. Summary Tables of Case Series of Proton Beam Therapy in Head & Neck (including Skull-Base) Cancers – Additional Primary Outcomes for KQ2 [Salvage]

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Mortality					
All-Cause Mortality					
All Studies	6[31,32,67,87,94,118]	13.3 to 83	78	335 (13 to 91)	5% to 61.8%
Oral Cancer	2[31,32]	24 to 25	21*	80	47.8% to 61.8%
Mixed Head & Neck Diagnoses	3[67,87,94]	13.3 to 15.2	51	212	5% to 46%
Ectopic Recurrence of Skull based Chordoma	1[118]	83	6	13	46%
Disease-related Mortality					
All Studies	2[31,67]	15.2 to 25	20	95 (34 to 61)	3.3% to 52.9%
Mixed Head & Neck Diagnoses	1[67]	15.2	2	61	3.3%
Oral Cancers	1[31]	25	18	34	52.9%
Radiation Related Mortality					
Oral Cancers	1[32]	24	1†	46	2.2%
Treatment Related Mortality					
Mixed Head & Neck Diagnoses	3[67,87,94]	13.3 to 15.2	8	190 (60 to 69)	2.9% to 4.9%
Other Causes (not specified)					
All Studies	2[31,67]	15.2 to 25	6	95 (34 to 61)	4.9% to 8.8%
Mixed Head & Neck Diagnoses	1[67]	15.2	3	61	4.9%
Oral Cancers	1[31]	25	3	34	8.8%
Progression/Relapse/Treatment Failure					
Overall					
All studies	3[31,67,118]	15.2 to 83	51	120 (13 to 61)	19.6% to 59%
Oral Cancer	1[31]	24	9	46	19.6%

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	Total N (range of N's)	Range
Mixed Head & Neck Diagnoses	1[67]	15.2	36	61	59%
Ectopic Recurrence of Skull based Chordoma	1[118]	83	6	13	46%
Local					
All studies	4[31,32,67,87]	13.6 to 25	30	120 (13 to 61)	19.6% to 59%
Oral Cancer	2[31,32]	24 to 25	11	80 (34 to 46)	13% to 14.7%
Mixed Head & Neck Diagnoses	2[67,87]	13.6 to 15.2	19	121 (60 to 61)	15% to 16.4%
Regional					
All studies	4[31,32,67,87]	13.6 to 25	9	120 (13 to 61)	19.6% to 59%
Oral Cancer	2[31,32]	24 to 25	4	80 (34 to 46)	2.9% to 6.5%
Mixed Head & Neck Diagnoses	2[67,87]	13.6 to 15.2	5	121 (60 to 61)	3.3% to 5%
Locoregional					
Mixed Head & Neck Diagnoses	2[87,94]	13.3 to 13.6	43	151 (60 to 91)	20% to 33.7%
Local and Distant					
Mixed Head & Neck Diagnoses	1[67]	15.2	2	61	3.3%
Distant					
All studies	4[31,67,87,94]	13.3 to 25	59	247 (34 to 92)	19.6% to 59%
Oral Cancer	1[31]	25	14‡	34	41.2%
Mixed Head & Neck Diagnoses	3[67,87,94]	13.3 to 15.2	45	213 (60 to 92)	13.3% to 36.1%
Overall Treatment Response					
Complete Response					
Oral Cancer	2[31,32]	24 to 25	62	80 (34 to 46)	64.7% to 87%
Partial Response					
Oral Cancer	2[31,32]	24 to 25	18	80 (34 to 46)	13% to 35.3%

F/U = follow-up;
*Mortality not clearly reported in Hayashi 2016; 47.8% is the minimum clearly stated proportion for all-cause mortality but the study indicates an uncertain number of others in addition.
†Sepsis from surgery to treat osteoradionecrosis
‡Hayashi 2017 reports that 14 died of distant metastasis but does not state whether there were more who had distant metastasis but did not die

Appendix Table F25. Summary Tables of Case Series of Proton Beam Therapy in Head & Neck (including Skull-Base) Cancers – Safety Outcomes

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
Acute Toxicities (≤3 months)					
Grade ≥3					
Skull-based or Cervical chordomas, chondrosarcomas	2[21,103]	0	235 (76 to 159)	65.5 to 77	0% [neurological] to 0%
Grade 3					
Mixed head and neck (recurrent disease)	1[67]	8	61	15.2	13.1%
Mixed head and neck (recurrent disease)	1[94]	0 to 9	66, 91*	10.4	0% to 9.9*%
Oropharyngeal cancer	1[29]	NR (patients could experience more than 1 event)	50	29	All grade 3 (no grade 4 or 5 events occurred) Derm radiation: 46% (23) Oral mucositis: 58% (29) Dysphagia: 24% (12) Weight loss: 2% (1) Dry mouth: 2% (1)
Olfactory Neuroblastoma	1[79]	5	42	69	12% All grade 3 (no grade 4 or 5 events occurred)
Mixed Diagnoses (recurrent)	1[87]	18	60	13.6	30%
Grade ≥4					
Oral cancer (recurrent)	1 [31]	Grade 4: 1 Grade 5: 0	34	25	Grade 4: 2.9% Grade 5: 0%
Mixed head and neck (recurrent disease)	1[67]	Grade 4: 0 Grade 5: 1	61	15.2	Grade 4: 0% Grade 5: 1.6%
Mixed head and neck (recurrent disease)	1[94]	0	66, 91*	10.4	0%
Acute Toxicities (timeframe NR)					
Grade ≥2					
Skull-base chondrosacromas	1[124]	0	251	87.3	0%
Grade ≥3					
Skull-based chordomas, chondrosarcomas	1[17]	9	96	52.6	9.4%
Tongue cancer (stage III-IV)	1[107]	NR (patients could have	33	43	Mucositis: 79% (26)

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
		more than one event)			Neutropenia: 51 % (17), dermatitis: 33% (11) Neutropenia grade 3: 48.4% (16) catheter-related infection: 18% (4) Nausea: 18.2% (6) Dry mouth: 9.1% (3) Weight Loss: 6.1% (2) Hiccups: 3% (1) Neutropenia (Grade 4): 3% (1)
Sinonasal	1[112]	4	38	30	11%
Grade ≥4					
Mixed Head & Neck Diagnoses	1[76]	0	47	32	0%
Acute Toxicities (≤6 months)					
Any grade					
anterior skull based malignancies	1[27]	11	31	>18†	35.5%
Late Toxicities (>3 months)					
Grade ≤2					
All studies	2[24,67]	37	159 (53 to 106)	15.2 to 61	22.6% to 23.6%
Skull-base chondrosacromas	1[24]	25	106	61	23.6%
Mixed head and neck (recurrent disease)	1[67]	12	53	15.2	22.6%
Grade ≥3					
All studies	7 [21,24,31,79,87,103,123]	55	699 (34 to 222)	13.6 to 77	1.3% to 20%
skull-base chondrosarcoma and chordoma Fung 2018 (recurrent)	4[21,24,103,123]	37	563 (76 to 222)	50 to 77	1.3% to 8.1%
Oral Cancer (recurrent)	1[31]	1	34	25	2.9%
Olfactory Neuroblastoma	1[79]	5	42	69	11.9%
Mixed Diagnoses (recurrent)	1[87]	12	60	13.6	20%
Grade 3, 4, and 5					
Mixed head and neck (recurrent disease)	1[67]	Grade 3: 9 Grade 4: 3 Grade 5: 2	53	15.2	Grade 3: 15.1% Grade 4: 5.7% Grade 5: 3.8%

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
Mixed head and neck (recurrent disease)	1[94]	Grade 3: 1 to 4 Grade 4: 5 Grade 5: 2	56 to 69*	10.4	Grade 3: 0% to 7.1% Grade 4: 7.2% Grade 5: 2.9%
Late Toxicities (>6 months)					
Any grade					
anterior skull based malignancies	1[27]	17	31	>18	54.8%
Late Toxicities (>24 months)					
Grade ≥3					
Tongue cancer (stage III-IV)	1[107]	4	30	43	13%
Late Toxicities (timeframe NR)					
Grade ≥3					
All diagnoses	4[15,17,76,112,124]	77	512 (38 to 251)	15.2 to 87.3	9.4% to 24%
Sinonasal	2[15,112]	20	118 (38 to 84)	28.8 to 30	18% to 24%
Mixed Head & Neck Diagnoses	1[76]	10	47	32	21.2%
Skull-base chordomas and chondrosacromas	2[17,124]	47	347 (96 to 251)	52.6 to 87.3	9.4% to 15.1%
Grades 3, 4, 5					
Sinonasal	1[132]	Grade 3: 17§ Grade 4: 6 Grade 5: 0	90	57.5	Grade 3: 18.9%§ Grade 4: 6.7% Grade 5: 0%
Sinonasal	1[131]	Grade 3: 5§ Grade 4: 0 Grade 5: 0	32	57.5	Grade 3: 15.6%§ Grade 4: 0% Grade 5: 0%
General Toxicities (timeframe NR)					
Grade ≤2					
skull-base chordomas	1[18]	6	33	21	18.2%
Grade 3 Hematological					
Oral Cancer (recurrent)	1 [32]	7 to 9§	46	24	15% to 20%§
Grade 3 Non-Hematological					
Oral Cancer (recurrent)	1 [32]	Dermatitis: 26 Dysphagia: 30 Mucositis: 33 Fever: 0 Alopecia: 0 Nausea/vomiting: 0 Osteoradionecrosis: 6	46	24	Dermatitis: 57% Dysphagia: 65% Mucositis: 72 Fever: 0% Alopecia: 0% Nausea/vomiting: 0% Osteoradionecrosis: 13% Xerostomia: 0% Dysarthria: 0%

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
		Xerostomia: 0% Dysarthria: 0 -Dysgeusia: 0			Dysgeusia: 0%
Grade ≥3					
skull-base chordomas	1[18]	0	33	21	0%
Grade ≥4 Hematological					
Oral Cancer (recurrent)	1 [32]	1	46	24	2.2%
Grade ≥4 Non-Hematological					
Oral Cancer (recurrent)	1 [32]	1	46	24	2.2%
Secondary Malignancies					
All Studies	2 [15,18]	1	117	21 to 28.8	0% to 1.2%
skull-base chordomas	1[18]	0	33	21	0%
Sinonasal	1[15]	1	84	28.8	1.2%
Actuarial Rate of Late Grade 3 Toxicities					
1-year					
Mixed Diagnoses (recurrent)	1[87]	N/A	60	13.6	11.9% (NR)
2-year					
Mixed Diagnoses (recurrent)	1[87]	N/A	60	13.6	26% (NR)
Rate of Late Grade 3 Toxicities					
2-year					
skull-base chondrosarcomas	1[21]	N/A	159	77	42.9% (32.3 to 50.4)
5-year					
skull-base chondrosarcomas	1[21]	N/A	159	77	57.2% (42.8 to 68.4)
Freedom from Grade ≤3 Late Visual Toxicities					
Grade ≤3					
skull-base chondrosarcomas	1[24]	N/A	106	61	93% (NR)
Toxicity Free Survival Grade ≥3					
5-year					
skull-base chondrosarcoma and chordoma	1[123]	N/A	106	50	87.2 (82.4 to 92.3)
7-year					
skull-base chondrosarcoma and chordoma	1[123]	N/A	106	50	87.2 (82.4 to 92.3)
8-year					
skull-base chondrosarcoma and chordoma	[123]	N/A	77	69.2	90.8%

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
Toxicity Free Survival [any grade]					
5-year					
skull-base chondrosarcoma and chordoma	1[124]	N/A	251	87.3 to 88	84.2% (79.3 to 89.5)
Late Neurotoxicity Free Survival					
5-year					
Cervical chondrosarcomas	1[103]	N/A	76	65.5	86% (77% to 95%)
Radiation Necrosis					
Grade ≥3					
Mixed Diagnoses	1[65]	4	66	31	6.1%
Any grade					
Mixed Diagnoses (recurrent)	1[87]	3	60	13.6	5% [of these 2 were grade 4-5: 3%]
Estimate of the incidence of Temporal Lobe Radiation Necrosis [any grade]					
3-year					
Mixed Diagnoses	1 [65]	N/A	66	31	12.4% (6.1% to 18.7%)
Temporal Lobe Radiation Necrosis (grade 3, "Late")					
Skull base chordoma and chondrosarcoma	1[123]	13	222	50	5.9%
Estimate of the incidence of symptomatic Radiation Necrosis [grade ≥2]					
3-year					
Mixed Diagnoses	1[65]	N/A	66	31	5.7% (1.2% to 10.2%)
Radiation-related encephalopathy necrosis					
"Late" - Timing NR					
skull-base chondrosarcomas	1[24]	1 [died 27 mos. post-PBT]	106	61	1.0%
Bone or soft tissue necrosis (included under grade >=3 events)					
"Late" – (>3 months)					
All Studies	3 [29,31,66]	9	137 (34 to 53)	15.2 to 25	0% to 15.1%
Mixed Diagnoses (recurrent)	1 [67]	8	53‡	15.2	15.1%

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
Oral Cancer Hayashi (recurrent)	2 [29,31]	1	84 (34 to 50)	25 to 29	0% to 2.9%
"Late" - Timing NR**					
All Studies	5 [15,17,32,107,132]	19	349 (33 to 96)	24 to 57.5	0% to 15.2%
Sinonasal	2 [15,132]	10	174 (84 to 90	28.8 to 57.5	3.3% to 8.3%
Skull Base Chordomas	1 [17]	2	96	52.6	2.1%
Oral Cancer Hayashi (recurrent)	2 [32,107]	7	79 (33 to 46)	24 to 43	0% to 15.2%
CNS necrosis					
"Late" - Timing NR					
All Studies	2 [15,123]	2	306 (84 to 222)	28.8 to 50	0.5% to 1.2%
Sinonasal	1 [15]	1	84	28.8	1.2
Skull base chordoma and chondrosarcoma	1 [123]	1	222	50	0.5%
Brain necrosis (grade >=3)					
Late (>3 months)					
All Studies	5 [79,112,123,124,132]	6	643 (38 to 251)	30 to 87.3	0% to 7.9%
Olfactory Neuroblastoma	1 [79]	0	42	69	0%
Sinonasal	2 [112,132]	4	128 (38 to 90)	30 to 57.5	1.1% to 7.9%
Skull-base chondrosarcoma	1 [124]	1	251	87.3	0.3%
Skull base chordoma and chondrosarcoma	1 [123]	1	222	50	0.5%
Weight Loss					
lost >10% of pretreatment weight					
Mixed head and neck (recurrent disease)	1 [67]	0	61	15.2	0% (0/61)
Median % of weight loss/gain					
Mixed head and neck (recurrent disease)	1 [67]	N/A	61	15.2	2% (range, -10% to 10%)
Treatment-related deaths					
Acute (≤3 months)					
All Studies	3 [67,87,107]	2	154 (33 to 61)	13.6 to 43	0% to 1.7%
Mixed head and neck (recurrent disease)	2 [67,87]	2††	121 (60 to 61)	13.6 to 15.2	1.6% to 1.7%
Tongue cancer (stage III-IV)	1 [107]	0	33	43	0%

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
Late (>3 months)					
All Studies	6 [15,31,32,67,94,112]	9	332 (34 to 84)	13.3 to 30	0% to 3.7%
Mixed Head & Neck Diagnoses (recurrent)	2 [67,94]	4	130 (53 to 69)	13.3 to 15.2	2.9% to 3.7%
Oral Cancers Hayashi 2017 (recurrent)	2 [31,32]	1‡‡	80 (34 to 46)	24	0% to 2.2%
Sinonasal, Nasal, Paranasal	2 [15,112]	4	122 (38 to 84)	28.8 to 30	2.6% to 3.6%§§

CI = confidence interval; F/U = follow-up; IQR = interquartile range; N/A = not applicable; NR = not reported
*In Romesser et al, certain toxicities were reported with an N=66 (patients who reported outcomes during acute phase) as well as an N=56, 67 or 69 (patients who reported outcomes during late phase). A range is reported for certain acute toxicities as some patients may have had more than one toxicity, and patient totals could not be determined.
†Gray et al., 2014 reported a 'minimum' follow-up of 18 months; no other information was given
‡An N of 53 is used (instead of total N=61) due to "nine patients" who "survived <3 months" who were not counted for risk of late toxicities. Despite saying nine, the difference is 8 patients; not sure if typo.
§Patients may have had more than one toxicity, patient totals not clearly reported.
** Takayama et al. reported a definition of late toxicity as >24 months, others did not report definitions.
†† Radiation-induced brainstem edema, which might have precipitated a fall that led to a subdural hematoma
‡‡Death from sepsis from surgery to treat osteoradionecrosis
§§ Considered "possibly related to RT".

Appendix Table F26. Summary Tables of Case Series of Proton Beam Therapy in Liver Cancers – Primary Outcomes for KQ1 [Curative]

Outcome, Timing, Cancer Type	Studies	Total N (Range of N's)	Range of Probabilities
Probability of Overall Survival			
1-year			
All studies	4[26,36,70,72]*	416 (21 to 250)	60% to 86%
HCC	4[26,36,70,72]	356 (22 to 250)	76.5% to 86%
ICC	2[26,36]	60 (21 to 39)	60% to 69.7%
2-year			
All studies	4[26,36,70,84]*	249 (21 to 83)	34% to 87.5%
HCC	4[26,36,70,84]	189 (22 to 83)	56% to 87.5%
ICC	2[26,36]	60 (21 to 39)	34% to 46.5%
3-year			
HCC	1[72]	250	63%
5-year			
All studies	3[22,72,84]	462 (83 to 250)	46% to 51%
HCC	2[72,84]	333 (83 to 250)	49.4% to 51%
	1[22]†	129	46% overall 0/A stage: 69% (n=30) B stage: 66% (n=34) C stage: 25% (n=65)
Probability of Progression Free Survival			
1-year			
All studies	2[36,70]‡	123 (39 to 44)	41.4% to 70%
HCC	2[36,70]	84 (40 to 44)	56.1% to 70%
ICC	1[36]	39	41.4%
2-year			
All studies	2[36,70]‡	123 (39 to 44)	25.7% to 60%
HCC	2[36,70]	84 (40 to 44)	39.9% to 60%
ICC	1[36]	39	25.7%
5-year			
HCC	1[22]§	129	0/A stage: 28% (n=30) B stage: 23% (n=34) C stage: 9% (n=65)
Probability of Local Control			
1-year			
HCC	1[72]	250	98% (96% to 100%)
2-year			
All studies	2[36,70]‡	123 (40 to 44)	94% to 94.8%
HCC	2[36,70]	84 (40 to 44)	94% to 94.8%
ICC	1[36]	39	94.1%

Outcome, Timing, Cancer Type	Studies	Total N (Range of N's)	Range of Probabilities
3-year			
HCC	1[72]	250	85% (78% to 91%)
5-year			
All studies	2[22,72]	379 (129 to 250)	83% to 85%
HCC	1[72]	250	85% (78% to 91%)
	1[22]§	129	0/A stage: 94% (n=30) B stage: 87% (n=34) C stage: 75% (n=65)

F/U = Follow-up; HCC = Hepatocellular Carcinoma; ICC = Intrahepatic cholangiocarcinoma
*Two studies (Hong 2016 and Grassberger 2018) report outcomes for two populations, HCC and ICC patients, separately.
†Study only provides OS stratified by stage.
‡One study (Hong 2016) reports outcomes for two populations, HCC and ICC patients, separately.
§ Study only provides PFS and LC stratified by stage.

Appendix Table F27. Summary Tables of Case Series of Proton Beam Therapy in Liver Cancers – Additional Primary Outcomes for KQ1 [Curative/Mixed Curative]

Outcome, Timing, Cancer Type	Studies	Range of Median F/U Times (months)	Number of Patients Experiencing outcome	Total N (Range of N's)	Range of Proportions
Mortality					
All-cause					
HCC	3[22,72,84]	45 to 55	105	462 (83 to 250)	22.5% to 45%
Disease-related					
HCC	2[22,72]	55 to NR	143	379 (129 to 250)	35% to 45%
Disease Progression/Recurrence					
All studies	2[22,36]*	19.5 to 55	58 (12 to 46)	(83 to 129)	9.3% to 55%
HCC	2[22,36]	19.5 to 55	31 (12 to 19)	212 (83 to 129)	9.3% to 43.2%
ICC	1[36]	19.5	27	39	69.2%
Secondary Outcomes					
Additional Treatment for Progression or Recurrence					
HCC	1[22]	55			
TACE	---	---	16	129	12.4%
PBT	---	---	13	129	10.1%
RFA	---	---	8	129	6.2%
PEIT	---	---	2	129	1.6%
RT	---	---	1	129	0.8%
Hepatic Arterial Infusion	---	---	1	129	0.8%
Unknown treatment	---	---	10	129	7.8%
Best supportive care	---	---	16	129	12.4%
Mixed Curative					
Secondary Outcomes					
Additional Treatment for Progression or Recurrence					
Metastases	1[23]	NR			
PBT	---	---	11	140	7.9%
Chemotherapy	---	---	9	140	6.4%
Chemotherapy + PBT	---	---	5	140	3.6%
PBT + RT	---	---	3	140	2.1%
Surgery + Chemotherapy	---	---	2	140	1.4%
Unknown	---	---	3	140	2.1%

F/U = Follow-up; HCC = Hepatocellular Carcinoma; ICC = Intrahepatic cholangiocarcinoma; PBT = Proton beam therapy; PEIT: Percutaneous ethanol injection therapy; RFA = radiofrequency ablation; RT = Radiation therapy; TACE = transcatheter arterial chemoembolization

*One study (Hong 2016) reports outcomes separately by HCC and ICC patients.

Appendix Table F28. Summary Tables of Case Series of Proton Beam Therapy in Liver Cancers –Primary Outcomes for Salvage Therapy in Metastatic Liver Cancer

Outcome, Timing, Cancer Type	Studies	Range of N's	Range of Probabilities
Probability of Overall Survival			
1-year	1[35]	89	66.3%
2-year	2[23,35]	89, 140	35.9% to 46%
3-year	1[35]	89	20.8%
5-year	1[23]	140	25%
Probability of Progression Free Survival			
1-year	1[35]	89	24.7%
3-year	1[35]	89	9.2%
Probability of Local Control			
1-year	1[35]	89	71.9%
2-year	1[23]	124*	66%
3-year	1[35]	89,	61.2%
5-year	1[23]	124*	53%

*Local control only in those who had abdominal imaging (out of 140)

Appendix Table F29. Summary Tables of Case Series of Proton Beam Therapy in Liver Cancers – Primary Outcomes for KQ2 [Mixed Salvage]

Outcome, Timing	Studies	Total N (Range of N's)	Range of Probabilities
Probability of Overall Survival			
2-year*	1[50]	41	51.1%
3-year	1[52]	71	74.4%
Probability of Local Progression Free Survival			
2-year*	1[50]	41	88.1%
3-year	1[52]	71	89.9%
Probability of Relapse Free Survival			
2-year*	1[50]	41	25%
3-year	1[52]	71	26.8%

*This study was in patients who had HCC with tumor vascular thrombosis

Appendix Table F30. Summary Tables of Case Series of Proton Beam Therapy in Liver Cancers – Additional Primary Outcomes for KQ2 [Mixed Salvage]

Outcome, Timing/Cancer Type	Studies	Range of Median F/U Times (months)	Number of Patients Experiencing outcome	Total N (Range of N's)	Range of Proportions
Disease Progression					
Local/Intrahepatic Recurrence/Progression	3[50,52,129]	4.9 to 31.3	58 (6 to 38)	213 (41 to 101)	5.9% to 53.5%
Metastasis	2[50,52]	15.2 to 31.3	28 (11 to 17)	112 (71 to 41)	15.5% to 41.5%
Mortality					
All-cause	1 [52]	31.3	16	71	22.2%
Disease-related	2[50,52]	15.2 to 31.3	36 (16 to 20)	112 (71 to 41)	21.1% to 48.8%
Tumor Response					
CR	3[50,52,129]	4.9 to 31.3	122 (14 to 66)	190 (41 to 78)	34.1% to 93%
PR	3[50,52,129]	4.9 to 31.3	28 (8 to 20)	190 (41 to 78)	0% to 48.7%
SD	3[50,52,129]	4.9 to 31.3	11 (1 to 6)	190 (41 to 78)	1.4% to 14.6%
PD	3[50,52,129]	4.9 to 31.3	29 (1 to 24)	190 (41 to 78)	2.4% to 30.8%
Secondary Outcomes					
Additional Treatment for Progression or Recurrence					
Metastases	1 [52]	15.2			
Sorafenib ± TACE ± RFA ± chemotherapy	---	---	19	41	46.3%
TACE ± chemotherapy	---	---	6	41	14.6%
Chemotherapy	---	---	1	41	2.4%
Surgical Resection	---	---	1	41	2.4%
RFA	---	---	1	41	2.4%

CR = Complete Response; F/U = Follow-up; SD = Stable Disease; PD = Progressive Disease; PEIT: Percutaneous ethanol injection therapy; PR = Partial Response; RFA = radiofrequency ablation; RT = Radiation therapy; TACE = transcatheter arterial chemoembolization

Appendix Table F31. Summary Tables of Case Series of Proton Beam Therapy in Liver Cancers – Safety Outcomes [Curative]

Outcome/Cancer Type/Grade	Studies	Number of Patients with outcome	Total N (range of N's)	Range of Median F/U (months)	Range
Curative Intent					
Acute Toxicity					
HCC					
≤ Grade 2	1[70]	NR*	40	19.9	NA*
≥ Grade 3	2[70,84]	2 Mizuhata 2 Oshiro 0	123 (40 to 83)	19.9 to 45	0% to 5%
Late Toxicity					
HCC					
≤ Grade 2	1[70]	2	40	19.9	5%
≥ Grade 3	1[70]	0	40	19.9	0%
Toxicity NOS					
All Diagnoses					
≤ Grade 2	3[22,36,127]	75† Yeung 4 (11%) Hong	249 (37 to 129)	11 to 55	11% to 85.5%
≥ Grade 3	3[22,36,127]	8‡ Hong 4 (4.8%) Yeung 4 (11%)	249 (37 to 129)	11 to 55	5% to 11%
HCC					
≤ Grade 2	1[22]	NR*	129	55	Data NR*
≥ Grade 3	1[22]	0	129	55	0%
HCC/ICC					
≤ Grade 2	2[36,127]	75 Yeung 4 (11%)	120 (37 to 83)	11 to 19.5	11% to 85.5%
≥ Grade 3	2[36,127]	8 Hong 4 (4.8%) Yeung 4 (11%)	120 (37 to 83)	11 to 19.5	4.8% to 11%
Treatment-related toxicity resulting in liver failure and death (within 4-6 mos.)	Mizumoto 2014 Oshiro 2017 0	4 0	250 83%		0% to 2%

F/U = Follow-up; HCC = Hepatocellular Carcinoma; ICC = Intrahepatic cholangiocarcinoma; NOS = Not otherwise specified; NR = Not reported

* Mizuhata reported only that skin reactions of grade 1 or 2 were confirmed but the number of patients was not reported.

†Fukuda reported that radiation dermatitis was common but no patients had grade 3 or higher.

‡Fukuda reported that hematologic abnormalities were the only toxicities grade >2; hematologic toxicities were difficult to assess the relation to PBT, because cirrhotic patients usually have baseline abnormalities.

Appendix Table F32. Summary Tables of Case Series of Proton Beam Therapy in Liver Cancers – Safety Outcomes [Mixed Curative – Fukumitsu 2015]

Outcome/Cancer Type/Grade	Number of Patients with outcome	Total N (range of N's)	Range of Median F/U (months)	Range
Metastatic Liver Tumors				
Late Toxicity				
≥ Grade 3	2	133	NR	1.6% (2/133)
Other Safety Outcomes				
Patients with elevation of >2 on Child-Pugh Score	8	133	NR	6% (8/133)

F/U = Follow-up; NR = Not reported
*A score of greater than 2 on the Child-Pugh score is indicative of radiation-induced liver disease.

Appendix Table F33. Summary Tables of Case Series of Proton Beam Therapy in Liver Cancers – Safety Outcomes [Salvage – Hong 2017]

	Number of Patients with outcome	Total N (range of N's)	Range of Median F/U (months)	Range
Toxicity – Timing NOS				
Acute Toxicity				
≤ Grade 2	78	89	30.1	87.6%
≥ Grade 3	0	89	30.1	0%

F/U = Follow-up; NOS = Not otherwise specified

Appendix Table F34. Summary Tables of Case Series of Proton Beam Therapy in Liver Cancers – Safety Outcomes [Mixed Curative]

	Studies	Number of Patients with outcome	Total N (range of N's)	Range of Median F/U (months)	Range
Acute Toxicity					
HCC					
≤ Grade 2	3[50,52,129]	10*	213 (41 to 101)	4.9 to 31.3	8.5% to 9.8%
≥ Grade 3	3[50,52,129]	1	213 (41 to 101)	4.9 to 31.3	0% to 1%
Late Toxicity					
HCC					
≤ Grade 2	2[50,52]	4	112 (41 to 71)	15.2 to 31.9	0% to 9.8%
≥ Grade 3	2[50,52]	0	112 (41 to 71)	15.2 to 31.9	0% to 0%
Other Safety					
HCC					
Radiation-induced Liver Disease	1[129]	4	101	4.9	4%
Gastroduodenal Specific Toxicity	1[129]	5	101	4.9	5%

F/U = Follow-up; HCC = Hepatocellular Carcinoma

Appendix Table F35. Summary Tables of Case Series of Proton Beam Therapy in Lung Cancers –Primary Outcomes [Curative]

Outcomes, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
Probability of Overall Survival			
1-year			
All Studies	3[9,83,96]	100 (30 to 35)	71.5% to 97.1%
NSCLC	2[9,83]	70 (35 to 35)	85.7% to 97.1%
LS-SCLC	1[96]	30	71.5%
2-year			
All Studies	3[9,83,96]	100 (30 to 35)	57.6% to 74.3%
NSCLC	2[9,83]	70 (35 to 35)	60% to 74.3%
LS-SCLC	1[96]	30	57.6%
3-year			
NSCLC	6[9,30,48,63,80,83]	384 (35 to 134)	42.9% to 87.9%
5-year			
NSCLC	4[8,9,48,80]	307 (35 to 134)	28.1% to 65.8%

Outcomes, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
NSCLC	1[75]	506	• Stage I: 36% • Stage II: 34% • Stage III: 23% • Stage IV: 5%
Median Overall Survival			
All Studies	5[8,9,80,83,96]	298 (30 to 134)	26.5 to 56 months
NSCLC	4[8,9,80,83]	268 (35 to 134)	26.5 to 56 months
LS-SCLC	1[96]	30	28.2 months
Probability of Progression Free Survival			
1-year			
All Studies	2 [9,96]	65 (30 to 35)	63% to 80%
NSCLC	1 [9]	35	80%
LS-SCLC	1 [96]	30	63%
2-year			
All Studies	2 [9,96]	65 (30 to 35)	42% to 64.4%
NSCLC	1 [9]	35	64.4%
LS-SCLC	1 [96]	30	42%
3-year			
NSCLC	4[9,30,48,63]	215 (35 to 74)	53.6% to 76.3%
5-year			
NSCLC	3[8,9,48]	173 (35 to 74)	22.0% to 53.6%
Probability of Local Recurrence Free Survival			
1-year			
NSCLC	1 [9]	35	97.1% (NR)
3-year			
NSCLC	1 [9]	35	85% (NR)
5-year			
NSCLC	1 [9]	35	85% (NR)
Probability of Regional Recurrence Free Survival			
1-year			
NSCLC	1 [9]	35	96.9% (NR)
3-year			
NSCLC	2[9,80]	169 (35 to 134)	55.8% to 89.2%
5-year			
NSCLC	2[9,80]	169 (35 to 134)	54.4% to 89.2%
Probability of Distant Metastasis Free Survival			
1-year			
NSCLC	1 [9]	35	85.7% (NR)
3-year			

Outcomes, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
NSCLC	2[9,80]	169 (35 to 134)	50.3% to 62.2%
5-year			
NSCLC	2[9,80]	169 (35 to 134)	54.4% to 45.8%
Rate of Locoregional Recurrence			
5-year			
NSCLC	1[8]	64	28% (18% to 43%)
Rate of Distant Metastasis			
5-year			
NSCLC	1[8]	64	54% (40% to 68%)
Probability of Disease Specific Survival			
3-year			
NSCLC	2[48,83]	109 (35 to 74)	76.3% to 83%
5-year			
NSCLC	1[48]	74	73.8%
Probability of Local Control			
1-year			
LS-SCLC	1 [96]	30	85% (NR)
2-year			
LS-SCLC	1 [96]	30	68.6% (NR)
3-year			
NSCLC	4 [30,48,63,83]	215 (35 to 74)	81.8% to 96%
5-year			
NSCLC	1[48]	74	81.8% (NR)

LS-SCLC = limited stage small-cell lung cancer; NR = not reported; NSCLC = non-small cell lung cancer;

Appendix Table F36. Summary Tables of Case Series of Proton Beam Therapy in Lung Cancers – Additional Primary Outcomes [Curative]

Outcome/Cancer Type	No. of Studies	Range of Median F/U times (months)	No. of Patients Experiencing Outcome	Total N (range)	Range, % (n/N)
Mortality					
All-cause Mortality					
NSCLC	4[8,30,48,83]	22.8 to 34	88	223 (35 to 74)	10% to 73.4%
Due to Disease Progression					
NSCLC	2[30,83]	22.8 to 34	10	85 (35 to 50)	2% to 25.7%
Due to Secondary Malignancies					
NSCLC	1[83]	34	4	35	11.4%
Due to Other Diseases					
NSCLC	1[83]	34	4	35	11.4%
Due to Other Causes (not specified)					
NSCLC	1[30]	22.8	4	35	11.4%
Treatment Response					
Complete Response					
All Studies	2[30,96]	14 to 22.8	23	77	23% to 40.7%
NSCLC	1[30]	22.8	12	50	23%
LS-SCLC	1[96]	14	11	27	40.7%
Partial Response					
LS-SCLC	1[96]	14	15	27	55.6%
Stable Disease					
LS-SCLC	1[96]	14	1	27	3.7%
Recurrence/Progression					
Overall					
NSCLC	2	31 to 83.1	45	109 (35 to 74)	40.5% to 42.9%
Local					
All Studies	6[8,9,30,63,83,96]	14 to 83.1	20	270 (30 to 64)	0% to 16%
NSCLC	5[8,9,30,63,83]	22.8 to 83.1	18	240 (35 to 64)	0% to 16%
LS-SCLC	1[96]	14	2	30	6.7%
Locoregional					
LS-SCLC	1[96]	14	11	30	18.3%
Regional					
NSCLC	4[8,9,63,83]	27.3 to 83.1	16	190 (35 to 64)	5.4% to 14%
Regional & Distant					
NSCLC	1[9]	83.1	1	35	2.9%
Local & Distant					
NSCLC	1[9]	83.1	4	35	11.4%

Outcome/Cancer Type	No. of Studies	Range of Median F/U times (months)	No. of Patients Experiencing Outcome	Total N (range)	Range, % (n/N)
Distant					
All Studies	6[8,9,30,63,83,96]	14 to 83.1	66	270 (30 to 64)	8.9% to 48%
NSCLC	5[8,9,30,63,83]	22.8 to 83.1	59	240 (35 to 64)	8.9% to 48%
LS-SCLC	1[96]	14	7	30	23.3%

LS-SCLC = Limited Stage Small Cell Lung Cancer; NSCLC = Non-Small Cell Lung Cancer;

Appendix Table F37. Summary Tables of Case Series of Proton Beam Therapy in Lung Cancers –Primary Outcomes [Mixed Curative]

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range (95% CI)
Probability of Overall Survival			
3-year			
NSCLC	1 [57]	55	54.9% (NR)
Probability of Regional Recurrence Free Survival			
3-year			
NSCLC	1 [57]	55	78.4% (NR)
Probability of Distant Metastasis Free Survival			
3-year			
NSCLC	1 [57]	55	76.5% (NR)
Probability of Local Control			
3-year			
NSCLC	1 [57]	55	85.4% (NR)

CI = confidence interval; F/U = follow-up; LS-SCLC = limited stage small-cell lung cancer; NSCLC = non-small cell lung cancer; N/A = not applicable; NR = not reported

Appendix Table F38. Summary Tables of Case Series of Proton Beam Therapy in Lung Cancers – Additional Primary Outcomes [Mixed Curative]

Outcome/Cancer Type	No. of Studies	Range of Median F/U times (months)	No. of Patients Experiencing Outcome	Total N (range)	Range, % (n/N)
Mortality					
All-cause Mortality					
NSCLC	1[57]	29	24	55	43.6%
Due to Disease Progression					
NSCLC	1[57]	29	11	55	20%
Other Causes (unknown)					
NSCLC	1[57]	29	13	55	23.6%
Recurrence/Progression					
Local	1[57]	29	7	55	12.7%

Appendix Table F39. Summary Tables of Case Series of Proton Beam Therapy in Lung Cancers –Safety Outcomes

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
Acute Toxicity					
Grade ≥3					
NSCLC Chao (recurrent)	4[10,30,36,48,63]	24	237 (50 to 74)	7.8 to 33.7	0% to 39%
NSCLC	1 [8]†	Pulmonary: 6 Gastrointestinal: 7 Cardiac: 0 Hematological: N/A General: N/A Other: 2	64	27.3	Pulmonary: 9.4% Gastrointestinal: 10.9% Cardiac: 0% Hematological: 2% to 22% General: 3.1% to 9% Other: 3.1%
Late Toxicities					
Grade ≥3					
NSCLC Chao (recurrent)	4[10,30,36,48,63]	14†	237 (50 to 74)	7.8 to 33.7	0% to 17.6%*
NSCLC	1[8]†	Pulmonary: 14	64	27.3	Pulmonary: 21.9%

Outcome, Grade/Timing, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
		Gastrointestinal: 2 Cardiac: 3 Hematological: 2 General: 3 Other: 2			Gastrointestinal: 3.1% Cardiac: 4.7% Hematological: General: 4.7% Other: 3.1%
General Toxicities (timeframe NR)					
Grade ≥3					
NSCLC	4[9,57,80,83]	21	125 (35 to 55)	29 to 83.1	1.8% to 12.7%
LS-SCLC	1 [96]	Hematological grade 3 or 4: N/A Non-Hematological: 5	30	14	Hematological (grade 3): 10% to 23.3% Hematological (grade 4): 3.3% to 33.3% Non-Hematological: 16.7%
Incidence of Grade 2 Rib Fracture					
3-year					
NSCLC	1[44]	N/A	52	33	30.2% (14.9 to 52.1%)
Rate of Any Grade ≥2 Toxicity					
1-year					
NSCLC (recurrent)	1[10]	N/A	57	7.8	55%
Radiation Necrosis (Grade ≥3)					
NSCLC	1 [63]	0	56	33.7	0%
Treatment-related Mortality					
Acute (<3 months)					
NSCLC	1[8]	0	64	27.3	0%
Timeframe NR					
NSCLC	2 [9,80,83]	0	70 (35 to 35)	80 to 83.1	0% to 0%
LS-SCLC	1 [96]	0	30	14	0%
Late (≥3 months)					
NSCLC Chao (recurrent)	3 [10,30,57]§	7‡	162 (50 to 57)	7.8 to 29	0% to 10.5%

CI = confidence interval; F/U = follow-up; LS-SCLC = limited stage small-cell lung cancer N/A = not applicable; NSCLC = non-small-cell lung cancer; NR = not reported

*One study in this range defined acute toxicities as those occurring within 6 months of treatment, whereas others cut off at 3 months

† Values are estimates of total patients with a category of toxicity based on values of specific toxicities in each category. Ranges are given where data was too heterogeneous to estimate. Patients may have had more than one toxicity, and patient totals were not clearly reported across toxicities.
‡ Three of the six grade 5 toxicities in Chao et al., 2017 were deemed probably related to RT.
§ Lee did not describe acute/late toxicity timing definitions, however they reported that the sole grade 5 toxicity occurred 3 months after PBT.

Appendix Table F40. Summary Tables of Case Series of Proton Beam Therapy in Mixed Cancers and Single Studies of Various Cancers – Primary Outcomes for KQ1 [Curative]

Study Characteristics	Outcome, Timing, Cancer Type	Timing	Range (95% CI)
Bladder			
Takaoka 2017[106] N=70 Median F/U: 40.8 months Diagnosis: Muscle-invasive bladder cancer Treatment Intent: Curative	Primary Outcomes		
	Probability of Overall Survival	3-year	90% (NR)
		5-year	82% (NR)
		10-year	78% (NR)
	Probability of Progression Free Survival	3-year	80% (NR)
		5-year	77% (NR)
		10-year	73% (NR)
	Time to Progression	3-year	82% (NR)
		5-year	82% (NR)
		10-year	82% (NR)
Lymphoma			
Primary Outcomes			
Hoppe 2017[37] N=138 Median F/U: 32 months Diagnosis: Hodgkin's Lymphoma Treatment Intent: Curative	Probability of Relapse Free Survival	3-year	• *Adults*: 96% (NR) • *Pediatrics*: 87% (NR)
Hoppe 2016[38] N=40 Median F/U: 21 months Diagnosis: Hodgkin's Lymphoma Treatment Intent: Curative	Probability of Relapse Free Survival	2-year	• *Mixed Adults (65%) and Pediatrics (35%)*: 85% (NR)

CI = confidence interval; F/U = Follow-up; N/A = not applicable; NR = not reported

Appendix Table F41. Summary Tables of Case Series of Proton Beam Therapy in Mixed Cancers and Single Studies of Various Cancers – Additional Primary Outcomes for KQ1 [Curative]

Study Characteristics	Cancer Type, Outcome, Subcategory of Outcome	% (n/N)
Mixed Diagnoses		
Nishioka 2014[81] N=56 Median F/U: 12 months Diagnosis: Mixed* Treatment Intent: Purely Curative	Primary Outcomes	
	Mortality	
	All-cause Mortality	7.1% (4/56)
	Disease-related Mortality	3.6% (2/56)
Bladder Cancer		
Takaoka 2017[106] N=70 Median F/U: 40.8 months Diagnosis: Muscle-invasive bladder cancer Treatment Intent: Curative	Primary Outcomes	
	Mortality	
	Disease-related Mortality	10% (7/70)
	Disease Progression	
	Any progression	17% (12/70)
	Local	5.7% (4/70)
	Regional	5.7% (4/70)
	Distant	5.7% (4/70)
Lymphoma		
Primary Outcomes		
Hoppe 2017[37] N=138 Median F/U: 32 months Diagnosis: Hodgkin's Lymphoma Treatment Intent: Purely Curative	Any Disease Progression	• *All patients:* 7.2% (10/138) • *Adults*: 5% (4/79) • *Pediatric*: 10.2% (6/59)
Hoppe 2016[38] N=40 Median F/U: 21 months Diagnosis: Hodgkin's Lymphoma Treatment Intent: Curative	Any Disease Progression	Mixed adults and pediatrics: 7.5% (3/40)

F/U = follow-up

Appendix Table F42. Summary Tables of Case Series of Proton Beam Therapy in Mixed Cancers and Single Studies of Various Cancers – Additional Primary Outcomes for KQ2 [Salvage]

Study Characteristics	Outcome, Timing, Cancer Type	Timing	Range (95% CI)
Lung Cancer			
Chao 2017[10] N=57 Diagnosis: Non-small Cell Lung Cancer Median F/U: 7.8 months Treatment Intent: Mixed Curative/Salvage	Primary Outcomes		
	Probability of Overall Survival	1-year	59% (NR)
		2-year	43% (NR)
	Probability of Progression Free Survival	1-year	58% (NR)
		2-year	38% (NR)
Brain/Spinal Tumors			
Kang 2018[49] N=24 overall, 16 (67%) treated with adjuvant or salvage PBT Diagnosis: Central Neurocytomas Median F/U: 56 months Treatment Intent: Mixed Curative/Salvage	Primary Outcomes		
	Probability of Progression Free Survival	5-year	100% (NR)*
	Probability of Disease Control	5-year	100% (NR)*
Ocular Tumors			
Riechardt 2014[92] N=48 Diagnosis: Recurrent Uveal Melanoma Median F/U: 81 months Treatment Intent: Salvage	Primary Outcomes		
	Probability of Overall Survival	5-year	89.1%
		10-year	77.4%
	Probability of Metastasis Free Survival	5-year	80.7%
		10-year	70.1%
	Probability of Globe Preservation	10-year	97.7%
	Probability of VA worse than 20/200	5-year	24%
Non-cancerous (benign) Tumors			
Wattson 2014[119] N=165 Diagnosis: Pituitary Adenoma Median F/U: 51.6 months Treatment Intent: Salvage	Secondary Outcomes		
	Biochemical Complete Response Rate	3-year	42% (34% to 51%)
		5-year	59% (50% to 69%)

CI = confidence interval; F/U = follow-up; NR = not reported; PBT = Proton Beam Therapy
*Among 16 PBT treated patients

Appendix Table F43. Summary Tables of Case Series of Proton Beam Therapy in Mixed and Various Cancers – Additional Primary and Secondary Outcomes for KQ2 [Salvage]

Study Characteristics	Cancer Type, Outcome, Subcategory of Outcome	% (n/N)
Lung Cancer		
Chao 2017[10] N=57 Diagnosis: Non-small Cell Lung Cancer Median F/U: 7.8 months Treatment Intent: Mixed Curative/Salvage	Primary Outcomes	
	Mortality	
	All-cause Mortality	42% (24/57)
	Disease-related Mortality	10.5% (6/57)
	Disease Progression	
	Local	16% (9/57)
	Regional	9% (5/57)
	Distant	11% (6/57)
Brain/Spinal Tumors		
Kang 2018[49] N=24 overall, 16 (67%) treated with adjuvant or salvage PBT Diagnosis: Central Neurocytomas Median F/U: 56 months Treatment Intent: Mixed Curative/Salvage	Primary Outcomes	
	Any Disease Progression	71.7% (11/24)
Ocular Tumors		
Riechardt 2014[92] N=48 Diagnosis: Recurrent Uveal Melanoma Median F/U: 81 months Treatment Intent: Salvage	Primary Outcomes	
	Proportion Achieving Local Tumor Control at 10-years	92.1% (NR)
	Enucleation	2.1% (1/48)
	Proportion with Re-recurrence	6.3% (3/48)
	Proportion with no light perception post-PBT	4.2% (2/48)
	Median Visual Acuity (Range)	- Baseline: 20/63 (20/16 to HM) - 5-year: 20/400 (20/50 to HM)
	Secondary Outcomes	
	Requirement for Secondary Treatment	
	Cataract Surgery	25% (10/24)*
	Vitrectomy	12.5% (6/48)

F/U = follow-up; HM = hand movements; NR = Not reported; PBT = Proton Beam Therapy
*Outcome calculated for only pre-PBT phakic patients

Appendix Table F44. Summary Tables of Case Series of Proton Beam Therapy in Mixed Cancers and Various Cancers –Safety Outcomes

Outcome, Grade, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
Acute Toxicities (timeframe NR)					
Grade 1					
Mixed Diagnoses	1[77]	51	90	NR	56.6%
Grade 2					
Mixed Diagnoses	1[77]	51	90	NR	17.7%
Grade ≥3					
Mixed Diagnoses	2[77,81]	11	146 (56 to 90)	NR	1.8% to 10%
Grade ≥3 Hematological Toxicities					
Mixed Diagnoses	1[81]	1	56	12	1.8%
Grade ≥3 Non-Hematological Toxicities					
Mixed Diagnoses	1[81]	0	56	12	0%
Late Toxicities (timeframe NR)					
Grade ≥3					
Mixed Diagnoses	1[81]	1	56	12	1.8%
Incidence of Grade 4 Acute Toxicities (timeframe NR)					
Grade 4					
Mixed Diagnoses	1[81]	N/A	56	12	0% (0% to 6.38%)
Osteoradionecrosis (included in grade ≥3 Late Toxicities)					
Mixed Diagnoses	1[81]	1	56	12	1.8%
Weight Loss					
Average Weight Loss					
Mixed Diagnoses	1[133]	N/A	375		0.55 kg
Mean Body weight Decrease					
Mixed Diagnoses	1[133]	N/A	375		-2.2 (2.3) kg
Average % body weight lost among patients with critical weight loss					
Mixed Diagnoses	1[133]	N/A	NR		8.7% (3.0%)
Average % body weight lost among patients without critical weight loss					
Mixed Diagnoses	1[133]	N/A	NR		0.2 (2.6%)
BLADDER CANCER					
Acute Toxicity (timeframe NR)					
Hematological Grade ≥3					
muscle-invasive bladder cancer	1[106]	18	70	15	26%

Outcome, Grade, Cancer Type	Studies	Number of Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95% CI)
Non-Hematological Grade ≥3					
muscle-invasive bladder cancer	1[106]	1	70	15	1.4%
Late Toxicity (timeframe NR)					
Grade ≥3					
muscle-invasive bladder cancer	1[106]	2	70	15	3%

F/U = Follow-up; N/A = not applicable; NR = not reported; SD = standard deviation;

Appendix Table F45. Summary Tables of Case Series of Proton Beam Therapy in Non-Cancerous Tumors – Primary and Secondary Outcomes for KQ1 [Curative]

Study Characteristics	Cancer Type, Outcome, Subcategory of Outcome	% (n/N)
Zeisberg 2014[130] N=50 Mean F/U: 55.4 months Diagnosis: Choroidal Hemangiomas Treatment Intent: Curative	Primary Outcomes	
	Tumor Thickness	Baseline: 3.5mm Final F/U: 1.8 mm **p<0.001**
	Proportion of patients with two line improvement in visual acuity	2-years: 36.8% 3-years: 44.4% 4-years: 58.8%
	Proportion of patients with Retinal detachment	Baseline: 44% (22/50) Post-PBT: 0% (0/50)
	Median Visual Acuity	Baseline: 6/15 Final F/U: 6/12
Mahdjoubi 2017[61] N=43 Mean F/U: 25.7 months Diagnosis: Circumscribed Choroidal Hemangioma Treatment intent: Mixed Curative/Salvage	Primary Outcomes	
	Median Visual Acuity	Baseline: 20/63 Post-PBT: 20/25
	Proportion of patients with Visual Acuity <20/200	Baseline: 23.2% (10/43) Post-PBT: 7% (7/43)
	Proportion of patients with Visual Acuity >20/40	Baseline: 27.9% (12/43) Post-PBT: 65% (28/43)
	Proportion of patients with Visual Acuity =20/20	Baseline: 2.3% (1/43) Post-PBT: 34.9% (15/43)
	Proportion of patients with stabilized or two line improvement in visual acuity	Post-PBT: 86% (37/43)
	Proportion of patients with Retinal detachment	Baseline: 90.7% (39/43) Post-PBT: 2.3% (1/43)
	Proportion of patients with hemangioma scar on ultrasound that was less than 1.5-mm thick and was considered to be flat, with an atrophic scar on angiography	53.5% (23/43)

Study Characteristics	Cancer Type, Outcome, Subcategory of Outcome	% (n/N)
El Shafie 2018[20] N=110 Median F/U: 46.8 months Diagnosis: Benign Skull-base Meningiomas	Primary Outcomes	
	Probability of Overall Survival	5-year: 96.2% (NR) 6-year: 92% (NR) 10-year(from diagnosis): 98.1% (NR) 15-year(from diagnosis): 90.7% (NR)
	Probability of Progression Free Survival	3-year: 100% (NR) 5-year: 96.6%
	Mortality	Disease-related : 0% (0/110) All-cause: 5.5% (6/110) Intercurrent Disease: 2.7% (3/110) Other Causes (not specified): <1% (1/110)
	Proportion of patients with disease Progression	Overall: 3.6% (4/110) Local: 3.6% (4/110)
Vlachogiannis 2017[116] N=170 Median F/U: 84 months Diagnosis: Benign Meningiomas Treatment intent: Curative	Primary Outcomes	
	Probability of Progression Free Survival	5-year: 93% (NR) 10-year: 85% (NR)
	All-cause Mortality	13.5% (23/170)
	Proportion of patients with disease Progression	Overall: 11.8% (20/170)
Wattson 2014 [119] N=165, 144, 140 Median F/U: 52 months Diagnosis: Functional Pituitary Adenoma Treatment intent: Recurrent	Primary Outcomes	
	Proportion of Patients with Local Control	98% (137/140)
	Probability of Complete Response (n=144)	3-year: 42% (34% to 51%) 5-year: 59% (50% to 69%) Median Time to Complete Response: 47 (36 to 59) months

Appendix Table F46. Summary Tables of Case Series of Proton Beam Therapy in Non-Cancerous Tumors –Safety Outcomes for Hemangiomas

Author (year), Study Site	Safety
Zeisberg 2014 [130] Diagnosis: Hemangiomas (Choroidal) N=50 Mean F/U (range): 55.4 (13 to 132) mos Indication • first line treatment: 82% • at least one prior therapy: 18%	*Toxicity Grading Criteria: Finger Classification or NR* **General Adverse Effects, % (n/N)** • Radiation retinopathy (Finger classification) Any stage: 46% (23/50) -Stage I: 32% (16/50) -Stage II: 10% (5/50) -Stage IV: 4% (2/50) *Time to Radiation Retinopathy* (range): 10.3 (1.2 to 106.5) months* *Mean Duration of Radiation Retinopathy (range): 14.5 (5.5 to 71.1) months* • Radiation Optic Neuropathy: 8% (4/50) *Time to radiation optic neuropathy (range*): 35.6 (5 to 105.6) month • Vitreous hemorrhage (secondary to retinopathy): 4% (2/50) *Time to vitreous hemorrhage (range):* 45 (11.1 to 78.9) months • Retinal vein occlusion: 4% (2/50) • Intraocular pressure: 6% (3/50) *Time to intraocular pressure (range*): 65.3 (37 to 80) months • Dry eye syndrome: 18% (9/50) *Time to dry eye syndrome (range):* 46.6 (3.5 to 124) months • Cataract formation: 20% (10/50) *Time to cataract formation (range)*: 46.6 (3.5 to 124) months • Retinal re-detachment: 0% (0/50) • Rubeosis: 0% (0/50)
Mahdjoubi 2017 [61] Diagnosis: Choroidal hemangioma N=43 Median F/U (range): 25.7 (7 to 62) months	*No patient presented radiation maculopathy or papillopathy.* **Complete attachment of the exudative retinal detachment**: 97.6% (42/43)

*Median or mean not specified

Appendix Table F47. Summary Tables of Case Series of Proton Beam Therapy in Non-Cancerous Tumors –Safety Outcomes for Other Benign Tumors

Outcome, Grade/Timing, Cancer Type	Studies	Number Patients Experiencing Outcome	Total N (range of N's)	Range of Median F/U times (months)	Range (95%CI)
Acute Toxicities (≤6 months)					
Grade ≥3					
skull base meningiomas (benign)	1[20 136]	2*	110	46.8	1.8%
General Toxicities					
Grade NR					
Meningioma	1[116]	16	70	84	9.4%
Late Toxicities (>24 months)					
Any Grade					
skull base meningiomas (benign)	1[20 136]	5*	110	46.8	4.5%
Secondary Malignancies					
Functional Pituitary Adenomas (salvage)	1[119]	0	143	52	0%
Radiation Necrosis					
Grade ≥3					
Skull Based Meningiomas (benign)	1 [20]	3	110	46.8	2.7%
Meningioma (recurrent)	1[119]	1	165	52	<1%
Rate of Hormone Deficiency requiring replacement therapy					
3-year					
Meningioma (recurrent)	1[119]	N/A	143	52	45% (NR)
5-year					
Meningioma (recurrent)	1[119]	N/A	143	52	62% (NR)

CI = confidence interval; F/U = follow-up; N/A = not applicable; NR = not reported
*Patients may have had more than one toxicity, patient totals not clearly reported.

Appendix Table F48. Summary Tables of Case Series of Proton Beam Therapy in Ocular Cancers – Primary Outcomes for KQ1 [curative]

Outcome, Timing, Cancer Type	Number of Studies	Total N (range of N's)	Range of Probabilities
Probability of Overall Survival			
2-year			
All studies	2[108,120]	942 (77 to 865)	91.1% to 94.5%
Choroidal Melanoma	1[120]	77	91.1%
Uveal Melanoma	1[108]	865	94.5%
5-year			
All studies	5[5,93,108,109,120]	3775 (77 to 1696)	74.1% to 94%
Choroidal Melanoma	2[93,120]	706 (77 to 629)	76.8% to 94%
Uveal Melanoma	3[5,108,109]	3069 (508 to 1696)	74.1% to 87.4%
10-year			
All studies	3[5,108,120]	1450 (77 to 865)	57.2% to 69.7%
Choroidal Melanoma	1[120]	77	62.7%
Uveal Melanoma	2[5,108]	1373	57.2% to 69.7%
15-year			
Uveal Melanoma	2[5,108]	1373	46.5% to 57.7%
Timing NOS			
Uveal Melanoma	1[108]*	853	Temporal: 85.6% (n=260) Superotemporal: 95.5% (n=97) Other: 89.5% (n=496)
Probability of Local Control			
2-year			
Choroidal/Ciliary Body Melanoma	1[120]	77	98.5%
5-year			
All studies	4[5,98,120,125]	702 (54 to 508)	85.1% to 96.1%
Choroidal/Ciliary Body Melanoma	1[120]	77	85.1%
Iris Melanoma	1[125]	54	94.7%
Choroidal Melanoma	1[98]	62	96.1%
Uveal Melanoma	1[5]	508	92.8%

Outcome, Timing, Cancer Type	Number of Studies	Total N (range of N's)	Range of Probabilities
10-year			
All studies	3[98,120]	647 (62 to 508)	85.1% to 96.1%
Choroidal/Ciliary Body Melanoma	1[120]	77	85.1%
Choroidal Melanoma	1[98]	62	96.1%
Uveal Melanoma	1[5]	508	91.3%
15-year			
Uveal Mealanoma	1[5]	508	89.9%
Probability of Metastasis Free Survival			
2-year			
All studies	2[108,120]	942 (77 to 865)	89.6% to 98.5%
Choroidal Melanoma	1[120]	77	89.6%
Uveal Melanoma	1[108]	865	98.5%
5-year			
All studies	5[5,93,98,108,120]	2141 (62 to 865)	71.6% to 95.6%
Choroidal Melanoma	3[93,98,120]	768 (62 to 629)	71.6% to 90%
Uveal Melanoma	2[5,108]	1373	74.3% to 95.6%
10-year			
All studies	4[5,98,108,120]	1512 (62 to 865)	57.2% to 81.8%
Choroidal Melanoma	2[98,120]	139 (62 to77)	57.2% to 81.8%
Uveal Melanoma	2[5,108]	1373	65.7% to 70%
15-year			
Uveal Melanoma	2[5,108]	1373	55.4% to 58.4%
Kaplan Meier Rate of Secondary Metastasis			
Timing NOS			
Uveal Melanoma	1	853	Temporal: 16.9% (n=260) Superotemporal: 14.5% (n=97) Other: 14.5% (n=496)
Kaplan Meier Rate of Local Recurrence/Relapse			
1-year			
All studies	2[47,85]	413 (77 to 336)	2.3% to 8%
Uveal Melanoma	1[85]	336	2.3%
Uveal Metastasis	1[47]	77	8%
3-year, 5-year, 10-year			
Uveal Melanoma	1[85]	336	5%, 7.8%, 12.5%

Outcome, Timing, Cancer Type	Number of Studies	Total N (range of N's)	Range of Probabilities
Timing NOS			
Uveal Melanoma	1[110]	853	Mean 4 year follow-up: Temporal: 6.2% (n=260) Superotemporal: 6.4% (n=97) Other: 5.4% (n=496)
Kaplan Meier Analysis of Tumor Related Death			
5-year			
Choroidal Melanoma	1[93]	629	3%

F/U = follow-up; NC = Not calculable; NOS = Not otherwise specified
*One study (Thariat 2017a) reported OS, Kaplan Meier Rate of Metastasis, and Kaplan Meier Rate of Local Recurrence/Relapse by tumor location and did not provide timing of the measure. Median follow-up for this study was 44 months (range, 18 to 60).

Appendix Table F49. Summary Tables of Case Series of Proton Beam Therapy in Ocular Cancers – Additional Primary Outcomes for KQ1 [curative]

Outcome, Cancer Type	Studies	Range of Median F/U Times (months)	Number of Patients Experiencing Outcome	N (Range of N's)	Range
Mortality					
Disease-related Mortality					
All studies	6[53,56,86,90,98,111]	30 to 147.6	704	3707 (36 to 3088)	0% to 20.1%
Choroidal Melanoma	3[53,86,98]	30 to 68.7	84	476 (62 to 351)	9.5% to 19.9%
Choroidal/Ciliary Body Melanoma	1[56]	147.6	620	3088	20.1%
Iris Melanoma	2[90,111]	49.5 to 50	0	143 (107 to 36)	0% to 0%
All-cause Mortality					
All studies	6[53,56,90,98,108,111]	30 to 147.6	1705	4221	5.6% to 48.3%
Choroidal Melanoma	2[53,98]	30 to 70.3	25	125 (62 to 63)	16.1% to 23.8%
Choroidal/Ciliary Body Melanoma	1[56]	147.6	1490	3088	48.3%
Iris Melanoma	2[90,111]	49.5 to 50	9	143 (36 to 107)	5.6% to 6.5%
Uveal Melanoma	1[108]	69	181	865	20.9%
Local/Regional Recurrence					
All studies	6[47,53,97,109,111,126]	30 to 77	122	2199 (63 to 1696)	3.2% to 6.5%
Choroidal Melanoma	2[53,126]	30 to 38.4	7	169 (63 to 106)	3.2% to 4.7%
Iris Melanoma	2[97,111]	49.5 to 66	13	203 (107 to150)	4.7% to 5.3%
Uveal Melanoma	1[109]	49	97	1696	5.7%
Uveal Metastasis	1[47]	77	5	77	6.5%
Secondary Metastasis					
All studies	2[47,86]	68.7 to 77	72	428	2.6% to 19.9%
Choroidal Melanoma	1[86]	68.7	70	351	19.9%
Uveal Metastasis	1[47]	77	2	77	2.6%

Appendix Table F50. Summary Tables of Case Series of Proton Beam Therapy in Ocular Cancers – Secondary Outcomes for KQ1 [curative]

Outcome, Cancer Type	Studies	Range of Median F/U Times (months)	Number of Patients Experiencing Outcome	N (Range of N's)	Range
Requirements for Additional Treatment					
Cataract Surgery	1[126]*	38.4	94	100	94%
Vitrectomy	2[98,126]	38.4 to 70.3	118	168 (62 to 106)	69.8% to 71%
Phacoemulsification + intraocular lens implant	1[98]	70.3	43	62	69.4%
Re-irradiation for Recurrence	1[98]	70.3	1	62	1.6%
Surgical intervention for proliferative vitreoretinopathy or nonresorbing exudative retinal detachment	2[98,126]	38.4 to 70.3	57	168 (62 to 106)	6.5% to 50%

F/U = follow-up;
*One other study (Schönfeld 2014) reported that surgery for cataracts was common, but no data is provided.

Appendix Table F51. Summary Tables of Case Series of Proton Beam Therapy in Ocular Cancers – Safety Outcomes

Outcome/Cancer Type	Studies	Number of patients with outcome	N (Range of N's)	Range of Median F/U (months)	Range
Enucleation					
All Diagnoses	14[47,53,86,88,90,93,97,98,100,109,110,120,125,126]	428	7298 (36 to 2499)	30 to 77	0% to 15.6%
Choroidal Melanoma	6[53,86,93,98,120,126]	75	1288 (62 to 629)	30 to 70.3	3.2% to 15.6%
Choroidal/Ciliary Body Melanoma	1[100]	110	2499	51.2	4.4%
Iris Melanoma	3[90,97,125]	9	240 (36 to 150)	50 to 55	0% to 5.6%
Uveal Melanoma	3[88,109,110]	233	3194 (645 to 1696)	44 to 53	3.4% to 9.0%
Uveal Metastasis	1[47]	1	77	7.7	1.3%
Glaucoma					
Neovascular Glaucoma					
All Diagnoses	8[53,85,90,93,100,108,120,126]	513	4611 (36 to 2499)	30 to 84	0% to 25%
Choroidal Melanoma	4[53,93,120,126]	98	875 (63 to 629)	30 to 62.4	2% to 23%
Choroidal/Ciliary Body Melanoma	1[100]	315	2499	51.2	12.6%

Outcome/Cancer Type	Studies	Number of patients with outcome	N (Range of N's)	Range of Median F/U (months)	Range
Iris Melanoma	1[90]	0	36	36	0%
Uveal Melanoma	2[85,108]	240	1201 (336 to 865)	69 to 84	18% to 25%
Secondary Glaucoma					
All Diagnoses	3[90,98,111]	22	203 (36 to 107)	49.5 to 70.3	6% to 20%
Choroidal Melanoma	1[98]	12	60	62	20%
Iris Melanoma	2[90,111]	10	143 (36 to 107)	49.5 to 50	6% to 7.6%
Glaucoma Type NOS					
All Diagnoses	2[109,125]	182	1750 (54 to 1696)	49 to 54.8	9.8% to 29.6%
Iris Melanoma	1[125]	16	54	54.8	29.6%
Uveal Melanoma	1[109]	166	1696	49	9.8%
Cataracts					
All Diagnoses	8*[53,90,98,108,109,111,120,125]	444	2907 (36 to 1696)	30 to 70.3	6.1% to 62%†
Choroidal Melanoma	3[53,98,120]	79	202 (62 to 77)	62 to 77	17.5% to 54%
Iris Melanoma	3[90,111,125]	79	144 (36 to 54)	49.5 to 54.8	42.6% to 62%†
Uveal Melanoma	2‡[108,109]	286	2561 (865 to 1696)	49 to 69	6.1% to 13.7%
Retinopathy					
All Diagnoses	7[90,99,100,109,111,120,125]	2521	5596 (36 to 2499)	46.2 to 54.8	0% to 68.1%
Choroidal Melanoma	2[99,120]	787	1204 (77 to 1127)	46.2 to 47	25% to 68.1%
Choroidal/Ciliary Body Melanoma	1[100]	1334	2499	51.2	53.4%
Iris Melanoma	3[90,111,125]	0	197 (36 to 107)	49.5 to 54.8	0% to 0%
Uveal Melanoma	1[109]	400	1696	49	23.6%
Maculopathy					
All Diagnoses	4[53,86,108,109]	600	2975 (63 to 1696)	30 to 69	7.2% to 49%
Choroidal Melanoma	2[53,86]	187	414 (63 to 351)	30 to 68.7	23.8% to 49%
Uveal Melanoma	2[108,109]	413	2561 (865 to 1696)	49 to 69	7.2% to 33.6%‡
Neuropathy					
All Diagnoses	6[53,99,100,108,109,111]	2391	635 (63 to 2499)	30 to 69	4.7% to 54.8%
Choroidal Melanoma	2[53,99]	478	1190 (63 to 1127)	30 to 46.2	23.8% to 41%

Outcome/Cancer Type	Studies	Number of patients with outcome	N (Range of N's)	Range of Median F/U (months)	Range
Choroidal/Ciliary Body Melanoma	1[100]	1370	2499	51.2	54.8%
Iris Melanoma	1[111]	5	107	49.5	4.7%
Uveal Melanoma	2‡[108,109]	538	2561 (865 to 1696)	49 to 69	7.5% to 47.5%
Rubeosis					
All Diagnoses	4[86,90,120,125]	77	518 (36 to 351)	47 to 68.7	0% to 45%
Choroidal Melanoma	2[86,120]	76	428 (77 to 351)	47 to 68.7	11.7% to 45%
Iris Melanoma	2[90,125]	1	90 (36 to 54)	50 to 54.8	0% to 1.9%
Scleral Necrosis					
All Diagnoses	4[90,100,111,125]	5	5696 (36 to 2499)	49.5 to 54.8	0% to 0.9%
Choroidal/Ciliary Body Melanoma	1[100]	4	2499	51.2	0.2%
Iris Melanoma	3[90,111,125]	1	197 (36 to 107)	46.5 to 54.8	0% to 0.9%
Papillopathy					
All Diagnoses	3[86,90,125]	25	441 (36 to 351)	50 to 68.7	0% to 7.1%
Choroidal Melanoma	1[86]	25	351	68.7	7.1%
Iris Melanoma	2[90,125]	0	90 (36 to 54)	50 to 54.8	0% to 0%
Papillopathy					
All Diagnoses	4[53,86,98,108]	152	1341 (62 to 865)	30 to 70.3	3.1% to 15.2%
Choroidal Melanoma	3[53,86,98]	21	476 (62 to 351)	30 to 70.3	3.1% to 9.5%
Uveal Melanoma	1[108]	131	865	69	15.2%

F/U = follow-up; NC = Not Calculable; NOS = Not otherwise Specified
*One series[126] in patients who received Tran scleral resection and neoadjuvant PBT had 94% (94/100 initially phakic patients) undergo cataract surgery. Cataract was determined to be a post-operative complication and therefore not the result of radiation.
†Rahmi 2014 reports that 62% (25/36) of patients had post-irradiation cataracts. If this was calculated as 25 of 36 the percentage would be calculated to be 69.4%. The percentage of 62% will be used here as it is reported in the author's text.
‡Likely that ~67.6% of pts in Thariat 2016 are also included in Thariat 2017b. 2017b only included pts without pre-exisiting cataracts or implants

Appendix Table F52. Summary Tables of Case Series of Proton Beam Therapy in Ocular Cancers – Additional Safety Outcomes

Outcome/Timing/Cancer Type	Studies	N (Range of N's)	Range of Probabilities
Probability of Enucleation Free Survival			
1-year			
Uveal Melanoma	1[85]	336	95.1%
3-year			
Uveal Melanoma	1[85]	336	85.8%
5-year			
All studies	3[85,100,125]	2889 (54 to 2499)	77.4% to 95.1%
Choroidal/Ciliary Body Melanoma	1[100]	2499	Patients with Endoresection: 94.8% (n=445) Patients with Endodrainage: 94.3% (n=242) Patients without adjuvant surgery: 93.5% (n=1812)
Iris Melanoma	1[125]	54	95.1%
Uveal Melanoma	1[85]	336	77.4%
10-year			
All studies	2[85,100]	2835	NC
Uveal Melanoma	1[85]	336	70.4%
Choroidal/Ciliary Body Melanoma	1[100]	2499	Patients with Endoresection: 92.2% (n=445) Patients with Endodrainage: NC (n=242) Patients without adjuvant surgery: 52.1% (n=1812)
KM Rate of Neovascular Glaucoma			
1-year			
Uveal Melanoma	1[85]	336	6.5%
3-year			
Uveal Melanoma	1[85]	336	28.4%
5-year			
All studies	3[85,93,100]	3464	10.5% to 34.9%
Choroidal/Ciliary Body Melanoma	1[100]	687	Endoresection group (n=445): 11.6% Endodrainage group (n=242): 21.3%
Choroidal Melanoma	1[93]	629	10.5%
Uveal Melanoma	1[85]	336	34.9%
10-year			
Uveal Melanoma	1[85]	336	36.1%
KM Rate of Globe Preservation			
5-year			
Choroidal/Ciliary Body Melanoma	1[100]	2499	94.8%
Probability of Retinopathy Free Survival			
1-year, 2-year, 3-year, 4-year, 5-year, 10-year			

Outcome/Timing/Cancer Type	Studies	N (Range of N's)	Range of Probabilities
Choroidal/Ciliary Body Melanoma	1[99]	1127	87%, 53%, 33%, 21%, 15%, 7%
Probability of Optic Neuropathy Free Survival			
1-year, 2-year, 3-year, 4-year, 5-year, 10-year			
Choroidal/Ciliary Body Melanoma	1[99]	1127	92%, 73%, 61%, 52%, 48%, 26%
KM Incidence of Dry Eye			
1-year, 2-year, 5-year			
Uveal Melanoma	1[110]	853	6%, 11.2%, 23%
KM Incidence of Severe Dry Eye			
1-year, 2-year, 5-year			
Uveal Melanoma	1[110]	853	2.1%, 4.8%, 10.9%
KM Incidence of Cataracts			
1-year, 3-year, 5-year			
Uveal Melanoma	1[109]	1696	4.9%, 12%, 18.7%
KM Incidence of Vision Impairing Cataracts			
1-year, 3-year, 5-year			
Uveal Melanoma	1[109]	1696	1.2%, 6.7%, 12.8%
KM Estimator for Absence of Radiation-Induced Retinopathy			
5-year			
Choroidal Melanoma	1[93]	629	14.2%
KM Estimator for Absence of Optic Neuropathy			
5-year			
Choroidal Melanoma	1[93]	629	36.6%

KM = Kaplan-Meier; NC = Not calculable

Appendix Table F53. Summary Tables of Case Series of Proton Beam Therapy in Prostate Cancer – Primary Outcomes for KQ1 [curative]

Outcome, Timing, Risk Level	Studies	Total N (Range of N's)	Probability, Range
Probability of Overall Survival			
5-year			
Low	4[6,13,45,69,105]	4202 (211 to 1375)	93% to 98.4%
Intermediate	5[3,6,13,45,69,105]	4408 (204 to 1375)	88% to 97%
High	5[3,6,13,45,69,105]	4408 (204 to 1375)	86% to 98%
Very High	1[105]	1375	90%
7-year			
Low/Intermediate Risk	1[33]	254	98.7%
8-year			
Low	1[105]	1375	94%
Intermediate	1[105]	1375	90%
High	1[105]	1375	89%
Very High	1[105]	1375	86%
Probability of Clinical Relapse Free Survival			
5-year			
Low	1[45]	1291	100%
Intermediate	1[45]	1291	98.2%
High	1[45]	1291	95.9%
Probability of Progression Free Survival			
5-year			
Intermediate	1[3]	204	97%
High	1[3]	204	83%
Probability of Freedom From Distant Metastasis			
5-year			
Low	1[6,13]	1327	99%
Intermediate	1[6,13]	1327	99%
High	1[6,13]	1327	98%
Probability of Freedom From Nodal Metastasis			
5-year			
Low	1[6,13]	1327	99%
Intermediate	1[6,13]	1327	99%
High	1[6,13]	1327	96%

Appendix Table F54. Summary Tables of Case Series of Proton Beam Therapy in Prostate Cancer – Additional Primary and Secondary Outcomes for KQ1 [curative]

	Studies	Range of Median F/U Times (months)	Number of patients experiencing outcome	Total N (range of N's)	Range
Mortality					
Disease-related	8[3,6,13,33,45,62,89,105,113]	18 to 423	59	5016 (49 to 1375)	0% to 3.1%
All-cause	8[3,6,13,33,45,62,89,105,113]	18 to 423	227	5016 (49 to 1375)	0% to 6.6%
Disease Progression					
Biochemical Failure [secondary outcome]	5[6,13,45,62,89,105]	55 to 423	292	4509 (93 to 1375)	1.1% to 10.6%
Local/Regional Recurrence/Relapse	3[3,89,105]	52 to 70	42	2002 (204 to 1375)	0.8% to 8%
Metastasis	4[3,45,89,105]	52 to 70	20+	3293 (204 to 1375	0.5% to 2.9%

F/U = follow-up

Appendix Table F55. Summary Tables of Case Series of Proton Beam Therapy in Prostate Cancer – Secondary Outcomes for KQ1 [curative]

Outcome, Timing, Risk Level	Studies	Total N (Range of N's)	Probability, Range
Probability of Freedom From Biochemical Failure			
5-year			
Mixed Risk Levels	2[62,105]	1468 (93 to 1375)	89% to 99%
Low	3[6,13,45,105]	3991 (1291 to 1375)	97% to 99%
Intermediate	3[6,13,45,105]	3991 (1291 to 1375)	91% to 99%
High	3[6,13,45,105]	3991 (1291 to 1375)	76% to 98%
Very High	1[105]	1375	66%
7-year			
Low/Intermediate Risk	1[33]	254	97.8%
8-year			
Mixed Risk Levels	1[105]	1375	82%
Low	1[105]	1375	95%
Intermediate	1[105]	1375	87%
High	1[105]	1375	71%
Very High	1[105]	1375	55%

Appendix Table F56. Summary Tables of Case Series of Proton Beam Therapy in Prostate Cancer – Safety Outcomes

Outcome/Grade	Studies	Number of Patients with Outcome	N (Range of N's)	Range of Median F/U (months)	Range
Acute Toxicity					
Gastrointestinal Toxicity					
≤ Grade 2	4[3,6,12,13,89]	39	1997 (85 to 1285)	14.5 to 62.4	0% to 18.8%
≥ Grade 3	4[3,12,89,113]	0	761 (49 to 423)	18 to 62.4	0%
Genitourinary Toxicity					
≤ Grade 2	3[3,12,89]	324	712 (85 to 423)	14.5 to 62.4	23.5% to 94.1%
≥ Grade 3	5[3,6,12,13,89,113]	12	1423 (49 to 1289)	14.5 to 66	0% to 0.9%
Late Toxicity					
Gastrointestinal Toxicity					
≤ Grade 2	7[3,6,12,13,45,62,89,105]	645	4756 (85 to 1375)	14.5 to 70	3.4% to 31.4%
≥ Grade 3	8[3,6,12,13,45,62,89,105,113]	18	4809 (49 to 1375)	14.5 to 70	0% to 1.2%
Genitourinary Toxicity					
≤ Grade 2	6[3,12,45,62,89,105]	295	3471 (85 to 1375)	14.5 to 70	3.4% to 18.8%
≥ Grade 3	8[3,6,12,13,45,62,89,105,113]	67	4809 (49 to 1375)	14.5 to 70	0% to 4.7%
Toxicity NOS					
Gastrointestinal Toxicity					
≤ Grade 2	1[113]	6	49	18	13%
≥ Grade 3	1[113]	0	49	18	0%
Genitourinary Toxicity					
≤ Grade 2	1[113]	17	49	18	37%
≥ Grade 3	1[113]	0	49	18	0%

F/U = follow-up; NOS = not otherwise specified;

Appendix Table F57. Summary Tables of Case Series of Proton Beam Therapy in Prostate Cancer – Additional Safety Outcomes

Outcome Timing Risk Level	Studies	N (Range of N's)	Rate, %
5-year Actuarial Incidence of Late Grade 3 GI Toxicity	1[6,13]	1327	0.6%
Cumulative Incidence of Argon plasma coagulation application for rectal bleeding	1[89]	423	5.6%
5-year Rate of Late Gastrointestinal Toxicities			
Grade 1	1[105]	1375	10%
Grade 2	1[105]	1375	3.8%
Grade 3	1[105]	1375	0.1%
5-year Rate of Late Gastrointestinal Toxicities			
Grade 1	1[105]	1375	8.9%
Grade 2	1[105]	1375	1.9%
Grade 3	1[105]	1375	0.1%

Appendix Table F58. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Brain, Spinal and Paraspinal Tumors – Primary Outcomes for KQ1 [Curative]

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range
Probability of Overall Survival			
2-year			
All studies	3[40,68,121]	359 (15 to 313)	64.6% to 90.5%
ATRT	2[68,121]	46 (15 to 31)	64.6% to 68.3%
Mixed Diagnoses	1[40]	313	90.5%
3-year			
All studies	4†[25,39,40,60]	631 (70 to 206)	90.4% to 96%
Mixed Diagnoses*	2[25,40]	382 (166 to 216)	95% to 96%
Ependymoma	3‡[39,40,60]	306 (57 to 179)	90.4% to 95%
Craniopharyngioma	1[40]	45	100%
Low-grade Glioma	1[40]	54	95%
5-year			
All studies	3[2,25,128]	325 (50 to 216)	83% to 87.3%
Medulloblastoma	1[128]	59	83%
Ependymoma	1[2]	216	84%
Mixed Diagnoses*	1[25]	50	87.3%
7-year			
Medulloblastoma	1[128]	59	81%
8-year			
Low-grade Glioma	1[28]	32	100%
Probability of Progression Free Survival			
2-year			
ATRT	2[68,122]	46 (15 to 31)	47.6% to 66%
3-year			
All studies	4†[25,39,40,74]	575 (14 to 216)	75.9% to 87.2%
Mixed Diagnoses*	2[25,40]	382 (166 to 216)	87% to 87.2%

Outcome, Timing, Cancer Type	Studies	Total N (range of N's)	Range
Ependymoma	2‡[39,40]	236 (57 to 179)	75.9% to 77%
Intracranial Germ Cell Tumor	1[74]	14	86%
Craniopharyngioma	1[40]	45	100%
Low-grade Glioma	1[40]	54	87%
5-year			
All studies	2[25,128]	275 (59 to 216)	80% to 82.6%
Medulloblastoma	1[128]	59	80%
Mixed Diagnoses*	1[25]	216	82.6%
6-year			
Low-grade Glioma	1[28]	32	89.7%
7-year			
Medulloblastoma	1[128]	59	75%
8-year			
Low-grade Glioma	1[28]	32	82.8%
Probability of Local Control			
1-year			
Mixed Diagnoses*	1[91]	22	68%
2-year			
ATRT	1[122]	15	78%
3-year			
All studies	3§[39,40,60]	415 (70 to 179)	83% to 91%
Mixed Diagnoses§	1[40]	166	91%
Ependymoma	3‡[39,40,60]	306 (70 to 179)	83% to 85.4%
Craniopharyngioma	1[40]	45	100%
Low-grade Glioma	1[40]	54	91%
5-year			
Ependymoma	2[2,60]	120 (50 to 70)	77% to 78.8%
Probability of Distant Control			
3-year			
Ependymoma	2[39,60]	249 (70 to 179)	83% to 85.4%
5-year			
Ependymoma	1[60]	70	77%
Probability of Distant Brain Failure Free Survival			
2-year			
ATRT	1[122]	15	76.6%

ATRT = Atypical Teratoid Rhabdoid Tumors; F/U = Follow-up

*Mixed Diagnoses include Ependymoma, low-grade glioma, Craniopharyngioma, germ cell tumor, meningioma, Medulloblastoma, PNET, and pituitary adenoma. Some patients reported in this population be included in populations below.

†One study (Indelicato 2017) reports data for Mixed diagnoses (all patients) and specifically for Craniopharyngioma, Low-grade Glioma, and Ependymoma patients.

‡Two studies (Indelicato 2017 and Indelicato 2018) in patients with Ependymoma may contain some crossover in patients.

§One study (Indelicato 2017) reports LC for Ependymoma patients, Craniopharyngioma patients, Low-grade Glioma patients, and Mixed cancer types which includes the three mentioned prior in addition to others.

Appendix Table F59. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Brain, Spinal and Paraspinal Tumors – Additional Primary Outcomes for KQ1 [Curative]

Outcome, Cancer Type	Studies	Range of Median F/U times (months)	Number of Patients Experiencing Outcome	N	Range
Mortality					
Disease-related Mortality					
All studies	7[2,40,60,74,101,122,128]	31.2 to 84	49	483 (14 to 166)	0% to 40%
ATRT	1[122]	33.4	6	15	40%
Ependymoma	2[2,60]	43.4 to 46	12	120 (50 to 70)	10% to 10%
Intracranial Germ Cell Tumors	1[74]	33.6	0	14	0%
Medulloblastoma	2[101,128]	38.8 to 84	24	168 (59 to 109)	11% to 20.3%
Mixed Diagnoses	1[40]	31.2	7	166	4.2%
All-cause Mortality					
All studies	5[25,40,68,91,128]	14 to 84	59	494	0% to 40%
ATRT	1[68]	24	13	31	41.9%
Medulloblastoma	1[128]	84	13	59	22%
Mixed Diagnoses	3[25,40,91]	14 to 50	31	7 (22 to 216)	1.2% to 31.8%
Progression/Relapse/Treatment Failure					
All studies	4[2,60,74,101]	33.6 to 46	42	210 (14 to 109)	5.9% to 50%
Ependymoma	2[2,60]	43.4 to 46	19	87 (17 to 70)	5.9% to 25.7%
Intracranial Germ Cell	1[74]	33.6	7	14	50%
Medulloblastoma	1[101]	38.8	16	109	14.7%

ATRT = Atypical Teratoid Rhabdoid Tumors; F/U = Follow-up

Appendix Table F60. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Brain, Spinal and Paraspinal Tumors – Safety Outcomes (Endocrine Abnormalities)

Author/Year	Radiation-induced 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 of any Hormone Deficiency†	
	3-year	27% (16% to 39%)
	5-year	55% (41% to 67%)
	7-year	63% (48% to 75%)
Greenberger 2014	Kaplan Meier Rate of Any Endocrine Deficiency	
	10-year	50% (95% CI NR) ‡

CI = Confidence Interval; NR = Not Reported

*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.

Appendix Table F61. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Brain, Spinal and Paraspinal Tumors – Safety Outcomes (Hematological Toxicities)

McGovern 2014*	Acute Grade 3 Anemia	3.2% (1/31)
	Acute Grade 3 Emesis/Vomiting	3.2% (1/31)
	Acute Grade 3 Pancytopenia†	3.2% (1/31)
	Acute Grade 3 Neutropenia	6.5% (2/31)
	Acute Grade 4 Pancytopenia	6.5% (2/31)
	Acute Grade 4 Sepsis	3.2% (1/31)
	Acute Grade 4 Thrombocytopenia	3.2% (1/31)
	Acute Grade 5 Sepsis (death)‡	3.2% (1/31)
Yock 2016	Acute Grade 3 Anemia	5% (3/59)
	Acute Grade 3 Lymphopenia	17% (10/59)
	Acute Grade 3 Neutropenia	32% (19/59)
	Acute Grade 3 Thrombocytopenia	3% (2/59)
	Acute Grade 4 Lymphopenia	12% (7/59)
	Acute Grade 4 Neutropenia	8% (5/59)

*84% of patients had induction chemotherapy
†Patient did not receive any chemotherapy treatment
‡Sepsis from a Pseudomonas diaper rash

Appendix Table F62. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Brain, Spinal and Paraspinal Tumors – Safety Outcomes (Radiation-Induced Vascular Injury)

Author/Year	Radiation-induced Toxicity (Grade)	% (n/N) or % (95% CI)
Indelicato 2017†	Late Vasculopathy (Grade NR)	1.8% (3/166)
Indelicato 2018†	Late Vasculopathy (Grade 2+)	3.4% (6/179)
Kralik 2017	Late Vasculopathy (Grade NR)	6.7% (5/75)
Hall 2018	3-year Cumulative Rate of Serious Vasculopathy Events*	2.6% (95% CI NR)
	Stroke resulting in permanent neurological deficits	1.2% (7/644)
Yock 2016	Late Stroke (Grade 4)	2% (1/58)
Greenberger 2014	Development of Moya Moya Disease	6.3% (2/32)

*Serious vasculopathy events were defined as any vascular anomaly resulting in permanent neurologic deficits or that required revascularization surgery.
† Patient cross-over between Indelicato 2014 and 2018 is present.

Appendix Table F63. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Brain, Spinal and Paraspinal Tumors – Safety Outcomes (CNS/Brainstem Radiation Injury)

Author, Year	Timing	Location	% (n/N)
Grade 3			
Gentile 2018	Late	Brainstem	0.6% (3/516)
Indelicato 2018‡	NR*	Brainstem	0.6% (1/179)
Indelicato 2014‡	NR†	Brainstem	0.3% (1/313)
Yock 2016	Late	CNS/Brainstem	2% (1/58)
Giantsoudi 2016	Late	CNS/Brainstem	1.8% (2/111)
Grade 4			
Gentile 2018	Late	Brainstem	0.6% (1/516)
Giantsoudi 2016	Late	CNS	0.9% (1/111)
Indelicato 2014‡	NR†	Brainstem	0.6% (2/313)
Grade 5 (death)			
Indelicato 2018‡	NR*	Brainstem	0.6% (1/179)
Indelicato 2014‡	NR†	Brainstem	0.3% (1/313)

CNS = Central Nervous System; NR = Not Reported
*****The median duration to toxicity onset was 3 months for all Grade 2+ toxicities, and 9 of 10 toxicities occurred within 4 months (the outlier developed toxicity 66 months following radiation). The grade of the outlying patient is unknown.
†The median time to symptom onset was 3 months (range 2 – 12 months).
‡Patient cross-over between Indelicato 2014 and 2018 is present.

Appendix Table F64. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Brain, Spinal and Paraspinal Tumors – Safety Outcomes (Radiation Necrosis)

Author, Year	**Grade**	**Location**	**% (n/N)**
Acute			
Weber 2015	Grade ≥3	NR	0%
McGovern 2014	Grade ≥3	Multiple*	6.5% (2/31)
Bojaxhiu 2018	Grade 4	Brainstem	0.6% (1/171)
	Grade 5 (death)	Brainstem	1.2% (2/171)
Late			
McGovern 2014	Grade ≥2	NR	9.7% (3/31)
Kralik 2015	Grade 3	NR	7.7% (4/52)
Bojaxhiu 2018	Grade 4	Brainstem	0.6% (1/171)
Ares 2018	Grade 5 (death)	Brainstem	2% (1/50)
Timing NR			
MacDonald 2013	NR	Brainstem	0% (0/70)

* To include the pons, midbrain, and bilateral hemispheres

Appendix Table F65. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Brain, Spinal and Paraspinal Tumors – Safety Outcomes (Ototoxicity/Hearing Loss)

Author/Year	Radiation-induced Toxicity	% (n/N) or % (95% CI)
Ares 2018	Late Grade ≥3 Definitive Unilateral Deafness	4% (2/50)
Indelicato 2018	Late Grade ≥2 Hearing Loss Requiring Hearing Aids	6.1% (11/179)*
MacDonald 2013	Hearing Loss (Radiation-induced)	8.7% (2/23)†
Yock 2016	Grade ≥3 Hearing Loss	15.6% (7/45)
	Cumulative Incidence of Ototoxicity	
	3-year	12% (4% to 25%)
	5-year	16% (6% to 29%)

CI = Confidence Interval

*7 bilateral 4 unilateral - Of note, 8 of these 11 patients received cisplatin chemotherapy, including 6 of the 7 with bilateral hearing deficits

†Both of these patients received higher doses of radiation to their cochlea than the average median dose because of tumor extension into the foramen of Luschka.

Appendix Table F66. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Brain, Spinal and Paraspinal Tumors –Safety Outcomes (Neurological)

Author, year (enrollment years) Cancer type	Mean age at baseline testing (years)	Median F/U, months	Outcome	n with outcome data/total N	Mean Baseline Score ± SD	Mean Follow-up Score ± SD	Mean Change ± SD or Absolute Mean Difference‡	p-value
Studies conducted at Massachusetts General Hospital								
Pulsifer 2018 (2002 to 2017) Mixed Diagnoses	8.9 (36.8% under age 6)	43.2	FSIQ/ MDI	114/155	105.4 ± 14.3	102.5 ± 14.8	-2.9‡	**0.005**
			PSI	110/155	NR	89.8 ± 13.9	NR	NR
			WMI	105/155	NR	101.0 ± 13.8	NR	NR
			VCI	114/155	NR	107.3 ± 14.1	NR	NR
			PRI	113/155	NR	103.8 (14.9)	NR	NR
Ventura 2018† (NR) Mixed Diagnoses	Baseline: 9.3 Follow-up: 12.4	38.4	FSIQ	65/65	NR	103.7 (15.0)	NR	NR§
			PSI	65/65	NR	89.5 (15.7)	NR	NR§
			WMI	65/65	NR	101.6 (13.2)	NR	NR§
Yock 2016 (2003 to 2009) Medulloblastoma	Median at time of treatment : 6.6	84	FSIQ	54/59	104.5 (95% CI, 101.3 to 107.7)	NR	Change per year: -1.5 (95% CI, -2.1 to -0.9)	**<0.0001**
			VCI	53/59	109.2 (95% CI, 106 to 112.4)	NR	Change per year: -1.3 (95% CI, -2 to -0.7	**<0.0001**
			PRI	53/59	103.5 (95% CI, 100.2 to 106.8)	NR	Change per year: -0.4 (95% CI, -1.0 to 0.3)	0.249
			WMI	41/59	98.7 (95% CI, 94 to 103.3)	NR	Change per year: -0.8	0.169

Author, year (enrollment years) Cancer type	Mean age at baseline testing (years)	Median F/U, months	Outcome	n with outcome data/total N	Mean Baseline Score ± SD	Mean Follow-up Score ± SD	Mean Change ± SD or Absolute Mean Difference‡	p-value
							(95% CI, -1.8 to 0.3)	
			PSI	49/59	95.3 (95% CI, 91.5 to 99.2)	NR	Change per year: -2.4 (-3.2 to -1.6)	**<0.0001**
MacDonald 2014 (2000 to 2011) Ependymoma	Median at time of diagnosis: 3.2	24.6	FSIQ/ MDI	14/70	108.5 ± NR	111.3 ± NR	2.8‡	0.475
Greenberger 2018 (1995 to 2007) Low-grade Glioma	Median at time of diagnosis: 7.4	54	FSIQ	11/32	109.3 ± 9.3	108.5 ± 12.3	-0.7 ± 9.2	0.80
		58.8	VCI	12/32	113.2 ± 12.9	112.7 ± 13.9	-0.5 ± 11.7	0.88
		58.8	PRI	12/32	107.7 ± 10.5	107.5 ± 13.5	-0.17 ± 9.8	0.95
Studies conducted at other institutions								
Park 2017 (2008 to 2014) Germ Cell Tumors	At time of diagnosis: 12.3	15	FSIQ	20/34	All patients: 96.74 ± 21.36	NR	-0.80 ± 17.79** 5.30 ± 6.04††	NR

FSIQ = Full-scale Intelligence Quotient; MDI = Mental Development Index; NR = not reported; PRI = Perceptual Reasoning Index; PSI = Processing Speed Index; SD = standard deviation; Verbal Comprehension Index; WMI = Working Memory Index

*All but one study from Korea (Park 2017) were from the same institution, Massachusetts General Hospital and, based on patient enrollment dates, it is likely that there is overlap in study populations.

†Ventura 2018 appears to be a subset of the data reported in Pulsifer 2018 and included only children ≥6 years old

‡Absolute Mean Difference calculated by AAI

§Per authors, scores of less than 69.7 are considered to be at risk for impairment

**Data for patients with Cranial Spinal Irradiation (n=10)

††Data for patients with whole ventricle irradiation (n=10)

Appendix Table F67. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Brain, Spinal and Paraspinal Tumors –Safety Outcomes (Other)

Author, Year	Outcome (Grade)	% (n/N)
Bojaxhiu 2018	White Matter Lesion (Grade 3)	0.6% (1/171)
Mokhtech 2018	Cataract (Grade 3)	7.1% (1/14)
MacDonald 2013	Cavernomas (Grade NR)	2.9% (2/70)

NR = Not reported

Appendix Table F68. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Brain, Spinal and Paraspinal Tumors –Safety Outcomes (Toxicities)

Outcome/Cancer Type/Grade	Studies	Number of patients with outcome	Total N (range of N's)	Range of Median F/U (months)	Range
Acute Toxicity					
All Diagnoses					
≤ Grade 2	3[68,122,128]	74*	105 (15 to 59)	24 to 84	100% to 100%
≥ Grade 3	3[68,122,128]	58	105 (15 to 59)	24 to 84	0% to 83.1%
ATRT					
≤ Grade 2	2[68,122]	15*	46 (15 to 31)	24 to 33.4	100%*
≥ Grade 3	2[68,122]	9	46 (15 to 31)	24 to 33.4	0% to 29.1%
Medulloblastoma					
≤ Grade 2	1[128]	59	59	84	100%
≥ Grade 3	1[128]	49	59	84	83.1%
Late Toxicity					
All Diagnoses					
≤ Grade 2	4[2,25,122,128]	47	340 (15 to 216)	33.4 to 84	0.5% to 44.1%
≥ Grade 3	4[2,25,122,128]	16	340 (15 to 216)	33.4 to 84	1.9% to 13.6%
Mixed					
≤ Grade 2	1[25]	1	216	50.4	0.5%
≥ Grade 3	1[25]	4	216	50.4	1.9%
ATRT					
≤ Grade 2	1[122]	1	15	33.4	6.7%
≥ Grade 3	1[122]	1	15	33.4	6.7%
Ependymoma					
≤ Grade 2	1[2]	19	50	43.4	38%
≥ Grade 3	1[2]	3	50	43.4	6%
Medulloblastoma					
≤ Grade 2	1[128]	26	59	84	44.1%
≥ Grade 3	1[128]	8	59	84	13.6%
Toxicity Timing NOS					
All Diagnoses					
≤ Grade 2	3[41,74,91]	10*	349 (14 to 313)	14 to 33.6	2.2% to 21.4%*
≥ Grade 3	3[40,41,74]	16	493 (14 to 313)	24 to 33.6	1.3% to 7.1%%
Intracranial Germ Cell Tumor					
≤ Grade 2	1[74]	3	14	33.6	21.4%
≥ Grade 3	1[74]	1	14	33.6	7.1%
Mixed Diagnoses					
≤ Grade 2	2[41,91]	7*	335 (22 to 313)	14 to 31.2	2.2%*
≥ Grade 3	2[40,41]	15	479 (166 to 313)	24 to 31.2	1.3% to 6.6%

ATRT = Atypical Teratoid Rhabdoid Tumor; F/U = Follow-up; NOS = Not otherwise specified
*At least one study reported patients experiencing this outcome, but exact numbers are not reported by the authors and therefore not included in the total number of patients experiencing the outcome.

Appendix Table F69. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Head & Neck (including Skull-Base) Cancers – Primary Outcomes for KQ1

Outcomes, Timing	Studies	Total N (range of N's)	%
Probability of Overall Survival			
1-year	1[117]	69	93%
3-year	1[117]	69	90%
5-year	1[59]	8	87.5%
Probability of Local Control			
Timing NOS	1[59]	8	100%
1-year	1[117]	69	92%
3-year	1[117]	69	85%
Probability of Regional Control			
1-year	1[117]	69	94%
3-year	1[117]	69	86%
Probability of Distant Control			
1-year	1[117]	69	86%
3-year	1[117]	69	78%

Appendix Table F70. Summary Tables of Case Series (Lucas 2015) of Proton Beam Therapy in Pediatric Head & Neck (including Skull-Base) Cancers – Primary Outcomes for KQ1 [curative intent]

Outcomes, Timing	Median Follow-up	% (n/N)
Disease-related Mortality	55.2 months	12.5% (1/8)
Distant Failure	55.2 months	25% (2/8)

Appendix Table F71. Summary Tables of Case Series (Rassi 2018, N=18, Median F/U: 122 months) of Proton Beam Therapy in Pediatric Head & Neck (including Skull-Base) Cancers – Primary Outcomes for KQ1 [curative intent]

Outcome, Timing	%
Probability of Overall Survival	
5-year	64%
10-year	57%
20-year	57%
Probability of Progression Free Survival	
5-year	57%
10-year	57%
20-year	57%

Appendix Table F72. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Head & Neck (including Skull-Base) Cancers – Safety Outcomes

Author/Year	Radiation-induced Toxicity	% (n/N)
Lucas 2015	Acute Grade 3 Mucositis	25% (2/8)
	Acute Grade 3 Febrile Neutropenia	12.5% (1/8)
	Acute Grade 3 Nasea	12.5% (1/8)
	Acute Grade 3 Weightloss	12.5% (1/8)
	Late Grade 3 Retinopathy	12.5% (1/8)
	Late Grade 3 Optic Neuropathy	12.5% (1/8)
Vogel 2018	Acute Grade 3 Anorexia	22% (125/69)
	Acute Grade 3 Dehyration	1% (1/69)
	Acute Grade 3 Dry Mouth	3% (2/69)
	Acute Grade 3 Dysphgia	7% (5/69)
	Acute Grade 3 Mucosal Infection	1% (1/69)
	Acute Grade 3 Nausea	1% (1/69)
	Acute Grade 3 Oral Mucositis	4% (3/69)
	Acute Grade 3 Radiation Dermatitis	1% (1/69)
	New feeding tube placement	13% (9/69)
	Initiation or increasing opiate use during RT	29% (20/69)
	Hospitalized for dehydration and pain	1.5% (1/69)
	Any Grade 4 or 5 Toxicity	0% (0/69)

Appendix Table F73. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Soft Tissue Sarcomas – Primary Outcomes for KQ1 [curative]

Outcome, Timing	Studies	Total N (range of N's)	Probability, Range
Probability of Overall Survival			
1-year	1[71]	55	91.9%
2-year	2[71,115]	121 (55 to 66)	84.8% to 89%
3-year	1[54]	24	64%
5-year	3[54,58,121]	179 (39 to 83)	73% to 80.6%
Probability of Local Control			
1-year	1[71]	55	95.6%
2-year	2[71,115]	121 (55 to 66)	88% to 93.0%
3-year	1[54]	24	59%
5-year	2[55,58]	140 (57 to 83)	78.5% to 81%
Probability of Failure Free Survival			
3-year	1[54]	24	52%
Probability of Event Free Survival			
5-year	1[55]	57	69%
Probability of Progression Free Survival			
1-year	1[71]	55	81.6%
2-year	1[71]	55	72.4%
5-year	1[121]	39	72%

Appendix Table F74. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Soft Tissue Sarcomas – Additional Primary Outcomes for KQ1 [curative]

Outcome	Studies	Range of Median F/U Times (months)	Number of patients experiencing outcome	Total N (range of N's	Range
Mortality					
Disease-related	5[55,58,71,115,121]	18 to 47	49	300 (39 to 83)	9.1% to 23.1%
All-cause	1[71]	24.5	9	55	16.4%
Proportion of Patients Experiencing Recurrence or Progression					
	5[55,58,71,115,121]	18 to 47	60	300 (39 to 83)	16.7% to 25.6%

F/U = Follow-up

Appendix Table F75. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Soft Tissue Sarcomas – Safety Outcomes

Author/Year	Radiation-induced Toxicity	% (n/N) or % (95% CI)
Ladra 2014	Acute Grade 3 Radiation Dermatitis	9% (5/57)
	Acute Grade 3 Dry Eye	4.5% (2/44)*
	Acute Grade 3 Odynophagia	9.7% (3/31)†
	Acute Grade 3 Mucositis	3.3% (1/31)†
	Acute Grade 3 Otitis	3.3% (1/31)†
	Acute Grade 3 Elevated Liver Function Tests	12.5% (1/8)‡
	Late Grade 3 Cataract	8.3% (1/12)§
	Late Grade 3 Chronic Otitis	4.8% (1/21)†
	Late Grade 3 Retinopathy	4.8% (1/21)†
Leiser 2016	Acute Grade 3 Mucositis	12% (10/83)
	Acute Grade 3 Skin Toxicity	3.6% (3/83)
	Late Grade 3 Radiation-induced Cataracts	14.5% (12/83)
	Late Grade 3 Hypacusis (Hearing Impairment)	2.4% (2/83)
	Late Grade 3 Reduced Vision	1.2% (1/83)
Mizumoto 2018	Acute Grade 3+ Radiation-induced Toxicities	16% (9/55) [12 events]
	Late Grade 3+ Radiation-induced Toxicity	0% (0/55)
Vern-Gross 2016	Cataracts	13.6% (9/66)
	Hormonal Replacement Therapy	6.1% (4/66)
	Unilateral Hearing Support	1.5% (1/66)
Weber 2016	5-year Grade ≥3 Toxicity Free Survival	95% (94% to 96%)
	Late Grade 3 Radiation-induced Toxicity	8% (3/39)
	Late Grade 4 or 5 Radiation-induced Toxicity	0% (0/39)

*Outcome only assessed in patients receiving PBT to the orbital or head and neck region
†Outcome only assessed in patients receiving PBT to the Head and Neck region
‡Outcome only assessed in patients receiving PBT to the Gastrointestinal/Genitourinary region
§Outcome only assessed in patients receiving PBT to the Orbital region

Appendix Table F76. Summary Tables of Case Series of Proton Beam Therapy in Pediatric Mixed Cancer Populations –Primary Outcomes for KQ1 [curative]

Outcome, Timing, Cancer Type	N	% (95% CI)
Probability of Overall Survival		
1-year		
All Cancer Types*	343	82.7% (78.5% to 87%)
Brain Tumors	79	91.4% (NR)
Neuroblastoma	46	72% (NR)
Rhabdomyosarcoma	71	84.5% (NR)
Ewing Sarcoma	30	88.6% (NR)
3-year		
All Cancer Types*	343	67.4% (61.7%-73.2%)
Brain Tumors	79	81.7% (NR)
Neuroblastoma	46	57.6% (NR)
Rhabdomyosarcoma	71	74.3% (NR)
Ewing Sarcoma	30	73.1% (NR)
5-year		
All Cancer Types*	343	61.4% (54.8%-67.9%)
Brain Tumors	79	81.7% (NR)
Neuroblastoma	46	57.6% (NR)
Rhabdomyosarcoma	71	66.5% (NR)
Ewing Sarcoma	30	56.8% (NR)
10-year		
All Cancer Types*	343	58.7% (51.5%-65.9%)

*To include Brain tumor, 23%; Rhabdomyosarcoma, 9.1%; Neuroblastoma, 13.4%; Ewing sarcoma, 8.7%; Head and neck carcinoma, 7.9%; Chordoma, 4.1%; Brain stem tumor, 5%; Arteriovenous Malformations, 2.3%; Others, 14.9%

APPENDIX G. List of on-going studies

Appendix Table G1. List of on-going trials and studies of proton beam therapy for cancerous conditions reviewed in this report

	Studies	Status
1.	Trial ID: NCT02731001 Title: Proton Therapy to Reduce Acute Normal Tissue Toxicity in Locally Advanced Non-small-cell Lung Cancer (PRONTOX) Link: https://clinicaltrials.gov/ct2/show/NCT02731001	Recruiting; as of Sept. 2017 Estimated Completion: NR
2.	Trial ID: NCT01993810 Title: Phase III Randomized Trial Comparing Overall Survival After Photon vs Proton Chemoradiotherapy for Inoperable Stage II-IIIB Non-Small Cell Lung Cancer [open] Link: https://clinicaltrials.gov/ct2/show/NCT01993810	Recruiting; as of Sept 2018 Estimated Completion: NR
3.	Trial ID: NCT01963429 Title: Comparison between radiofrequency ablation and hypofractionated proton beam radiation for recurrent/residual hepatocellular carcinoma Link: https://clinicaltrials.gov/ct2/show/NCT01963429	Recruiting; as of Aug 2018 Estimated Completion: NR
4.	Trial ID: NCT01617161 Title: Prostate Advanced Radiation Technologies Investigating Quality of Life (PARTIQoL): A Phase III Randomized Clinical Trial of Proton Therapy vs IMRT for Low or Intermediate Link: https://clinicaltrials.gov/ct2/show/NCT01617161	Recruiting; as of July 2018 Estimated Completion: NR
5.	Trial ID: NCT01511081 Title: Randomized Phase II Study Comparing Stereotactic Body Radiotherapy (SBRT) With Stereotactic Body Proton Therapy (SBPT) for Centrally Located Stage I, Selected Stage II, and Recurrent Non-Small Cell Lung Cancer [closed] Link: https://clinicaltrials.gov/ct2/show/NCT01511081	Terminated; as of Dec 2017 Estimated Completion: NR
6.	Trial ID: NCT01854554 Title: Glioblastoma Multiforme (GBM) Proton vs. Intensity Modulated Radiotherapy (IMRT) Link: https://clinicaltrials.gov/ct2/show/NCT01854554	Recruiting; as of Jul 2018 Estimated Completion: NR
7.	Trial ID: NCT01512589 Title: Phase III Randomized Trial of Proton Beam Therapy vs Intensity-Modulated Radiation Therapy for the Treatment of Esophageal Cancer [open] Link: https://clinicaltrials.gov/ct2/show/NCT01512589	Active, Not Recruiting; as of Jul 2018 Estimated Completion: NR
8.	Trial ID: NCT01893307 Title: Phase II/III Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) vs Intensity- Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck Cancer [open] Link: https://clinicaltrials.gov/ct2/show/NCT01893307	Recruiting; as of Jul 2018 Estimated Completion: NR
9.	Trial ID: NCT02603341 Title: Pragmatic Randomized Trial of Proton vs Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial [open] Link: https://clinicaltrials.gov/ct2/show/NCT02603341	Recruiting; as of Aug 2018 Estimated Completion: NR
10.	Trial ID: NCT00915005 Title: Trial of Image-Guided Adaptive Conformal Photon vs Proton Therapy, With Concurrent Chemotherapy, for Locally Advanced Non-Small Cell Lung Carcinoma: Treatment Related Pneumonitis and Locoregional Recurrence Link: https://clinicaltrials.gov/ct2/show/NCT00915005	Active, Not recruiting; as of Feb 2018 Estimated Completion: NR
11.	Trial ID: NCT02179086	Recruiting; as of Aug 2018 Estimated Completion: NR

	Studies	Status
	Title: Dose-Escalated Photon IMRT or Proton Beam Radiation Therapy Versus Standard-Dose Radiation Therapy and Temozolomide in Treating Patients With Newly Diagnosed Glioblastoma Link: https://clinicaltrials.gov/ct2/show/NCT02179086	
12.	Trial ID: NCT02602756 Title: Study Assessing Two Models of Hypofractionated Proton therapy on Large Choroidal Melanomas Link: https://clinicaltrials.gov/ct2/show/NCT02602756	Active, not recruiting; as of Jul 2018 Estimated Completion: NR
13.	Trial ID: NCT02379000 Title: TTT Versus TTT and Triamcinolone to Decrease Exudation in Choroidal Melanoma After Proton Beam Therapy Link: https://clinicaltrials.gov/ct2/show/NCT02379000	Active, not recruiting; as of Feb 2017 Estimated Completion: NR
14.	Trial ID: NCT02942693 Title: Trail evaluating particle therapy with or without apatinib for H&N adenoid cystic carcinoma Link: https://clinicaltrials.gov/ct2/show/	Not yet recruiting; as of Oct 2016 Estimated Completion: NR
15.	Trial ID: NCT02783690 Title: A Trial of 15 Fraction vs 25 Fraction Pencil Beam Scanning Proton Radiotherapy After Mastectomy in Patients Requiring Regional Nodal Irradiation Link: https://clinicaltrials.gov/ct2/show/NCT02783690	Recruiting; as of Jun 2018 Estimated Completion: NR
16.	Trial ID: NCT03270072 Title: The Differential Impact of Proton Beam Irradiation Versus Conventional Radiation on Organs-at-risk in Stage II-III Breast Cancer Patients Link: https://clinicaltrials.gov/ct2/show/NCT03270072	Recruiting; as of Nov 2017 Estimated Completion: NR
17.	Trial ID: NCT03132532 Title: Phase II Trial of Standard Chemotherapy (Carboplatin & Paclitaxel) +Various Proton Beam Therapy (PBT) Doses Link: https://clinicaltrials.gov/ct2/show/NCT03132532	Recruiting; as of Estimated Completion: NR
18.	Trial ID: NCT03172299 Title: Prevention of Neovascular Glaucoma by Intravitreal Injections of Anti-VEGF in Patients Treated With Proton Therapy for a Large Choroidal Melanoma Link: https://clinicaltrials.gov/ct2/show/	Not Yet Recruiting; as of Jun 2017 Estimated Completion: NR
19.	Trial ID: NCT03285815 Title: Prostate Cancer - Localized Adenocarcinoma Proton Therapy Link: https://clinicaltrials.gov/ct2/show/NCT03285815	Recruiting; as of Sept 2017 Estimated Completion: NR
20.	Trial ID: NCT03180502 Title: Proton Beam or Intensity-Modulated Radiation Therapy in Preserving Brain Function in Patients With IDH Mutant Grade II or III Glioma Link: https://clinicaltrials.gov/ct2/show/NCT03180502	Recruiting; as of Aug 2018 Estimated Completion: NR
21.	Trial ID: NCT03186898 Title: Radiation Therapy With Protons or Photons in Treating Patients With Liver Cancer Link: https://clinicaltrials.gov/ct2/show/NCT03186898	Recruiting; as of Aug 2018 Estimated Completion: NR
22.	Trial ID: NCT01993810 Title: Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer Link: https://clinicaltrials.gov/ct2/show/NCT01993810	Recruiting; as of Sept 2018 Estimated Completion: NR
23.	Trial ID: NCT01758445 Title: Proton Radiation for Stage II/III Breast Cancer Link: https://clinicaltrials.gov/ct2/show/NCT01758445	Recruiting; as of Jan 2018 Estimated Completion: NR
24.	Trial ID: NCT01766297	Recruiting; as of Estimated Completion: NR

	Studies	Status
	Title: Phase II Protocol of Proton Therapy for Partial Breast Irradiation in Early Stage Breast Cancer Link: https://clinicaltrials.gov/ct2/show/NCT01766297	
25.	Trial ID: NCT01684904 Title: Proton Therapy for Esophageal Cancer Link: https://clinicaltrials.gov/ct2/show/NCT01684904	Recruiting; as of Estimated Completion: NR
26.	Trial ID: NCT02452021 Title: Pencil Beam Scanning Proton Radiotherapy for Esophageal Cancer Link: https://clinicaltrials.gov/ct2/show/NCT02452021	Active, not recruiting; as of Sept 2017 Estimated Completion: NR
27.	Trial ID: NCT02213497 Title: Dose Escalation of Neoadjuvant Proton Beam Radiotherapy With Concurrent Chemotherapy in Locally Advanced Esophageal Cancer Link: https://clinicaltrials.gov/ct2/show/NCT02213497	Recruiting; as of Jun 2018 Estimated Completion: NR

APPENDIX H. Guidelines & Appropriateness Criteria

PubMed was searched for guidelines related to the use of PET imaging for lymphoma. A key word search was conducted utilizing the following terms ((“proton therapy” [mesh] OR "proton therapy" [Tiab] OR "proton beam" [Tiab] OR "particle therapy" [Tiab]) AND (neoplasms [mesh] OR cancer* OR tumor* OR tumour* OR carcinoma* OR malignan*; Filters: Guideline; Practice Guideline; Abstract; English)) and yielded 979 citations going back to 2013. Hand-searching for documents from relevant organizations was also conducted with results detailed below

We focused on evidence-based guidelines that followed a formal process for quality guideline development.[1, 2] For multi-society guidelines, we did not include separate guidelines from individual organizations unless they represented a significant update, had a different focus or evidence base or included substantial new evidence. We did not include guidelines that did not contain recommendations specific to proton beam therapy. No pediatric-specific proton therapy guidelines were identified in our search, although NICE UK and AIM Specialty Health feature recommendations of medical necessity for cancerous conditions in pediatric populations. No ‘standard’ radiation dose information was reported. Consistent with the 2014 Proton Beam Therapy HTA, we focused on the following organizations and others deemed most applicable to North American practice:

- **National Institute for Health and Care Excellence (NICE UK)**
- **AIM Specialty Health Clinical Appropriateness Guidelines for Proton Beam Treatment**
- **American Society of Clinical Oncology (ASCO)**
- **American Society for Radiation Oncology (ASTRO) and collaborators [including AHRQ, American Urological Association (AUA) and Society of Urologic Oncology (SUO)]**
- **National Comprehensive Cancer Network (NCCN) Guidelines (various conditions)**
- **American College of Radiology (ACR) Appropriateness Criteria (summarized in a separate table below)**

Additionally, the following organizations were reviewed for relevant guidelines, including: Canadian Agency for Drugs and Technologies in Health, National Association for Proton Therapy, American Cancer Society, and Alberta Health Services, however no recent guidelines were found.

Appendix Table H1. Summary of guidelines of Proton Beam Therapy

Guideline (Year)	Evidence Base	Summary of Recommendations	Rating/Strength of Recommendation
NICE UK (2015, 2016)	Pediatric and Skull Base: Bibliography not provided; 5 guidelines and the UK National	NICE guidelines across all cancerous conditions were reviewed for recommendations relevant to PBT. No recommendations were found. To date NHS England has released three Clinical Commissioning Policies related to proton beam therapy (either as delivered in the UK or pursued overseas). The following conditions are commissioned for coverage:	Pediatric and Skull Base: NR Pediatric: evidence is **not sufficient;** based on review of evidence, grading system not described

Guideline (Year)	Evidence Base	Summary of Recommendations	Rating/Strength of Recommendation
	Cancer Strategy (2006) are cited as informing evidence as well as 1 uncited case series <u>Prostate:</u> 1 SR, 3 RCTs, 4 nonrandomized comparative studies, 1 SR of 2 cost-effectiveness analyses;	• Base of Skull & Spinal Chordoma • Base of Skull Chondrosarcoma <u>Pediatric:</u> • 'Adult type' Bone and Soft Tissue Sarcomas (excluding extremities) • Rhabdomyosarcoma (excluding extremities) • Ependymoma • Ewing's Sarcoma (excluding extremities) • Retinoblastoma • Pelvic Sarcoma • Optic Pathway and other selected Low Grade Glioma • Craniopharyngioma • Pineal Parenchymal Tumours (not Pineoblastoma) • Non-metastatic intracranial non-germinomatous germ cell tumours • Adenoma • Juvenile Angiofibroma • Meningioma (Excluding Grade 3) • Nasopharyngeal Carcinoma • Esthesioneuroblastoma • Salivary Gland Tumours • High naso-ethmoid, frontal and sphenoid tumours with base of skull involvement • Adenoid Cystic Carcinoma with perineural invasion The following conditions are not covered: • Prostate Cancer	
AIM Clinical Appropriateness Guidelines for Proton Beam Treatment (2018)	Evidence Review 48 references total including: 18 studies, 2 review of 7 studies, 3 SRs and meta-analyses,	**Overall** PBT may be appropriate in circumstances where intensity modulated radiation therapy (IMRT) or stereotactic would potentially damage critical structures, particularly in patients with a history of prior irradiation. PBT is also appropriate for pediatric patients because even low doses of scattered radiation in this population can affect growth and development and increase the risk of secondary malignancies later in life. In situations where there is a lack of high-quality evidence comparing proton outcomes with photon-based therapies, proton therapy will be considered not medically necessary. In situations where proton therapy is appropriate, PBT should be administered as monotherapy.	Decision based on review of evidence, no formal rating system described.

Guideline (Year)	Evidence Base	Summary of Recommendations	Rating/Strength of Recommendation
	3 RCTs, 2 AHRQ reviews, 1 meta-analysis, 2 SRs with 17 and 9 studies, 1 ASTRO review,	Proton beam therapy is considered **medically necessary** for the following conditions: CNS Tumors • For specific cases where adjacent critical structures cannot be adequately spared with IMRT or SRS. • For Arteriovenous Malformation when not amenable to excision of conventional treatment or adjactent to critical structures (optic nerve, brain stem or spinal cord) • In pediatric cases (age less than 21) Chordoma and Chondrosarcoma • As postoperative therapy for residual, localized tumors at base of skull and sacral chordomas and chondrosarcomas. Uveal Melanoma • As primary therapy involving tumors of up to 24 mm diameter and 14 mm height with no evidence of metastasis Pediatric Patients • Appropriate for under 21 years of age for all pediatric tumors Re-irradiation • Proton beam therapy is appropriate for the repeat irradiation of previously treated fields where the dose tolerance of surrounding normal structures would be exceeded with 3D conformal radiation or IMRT Proton beam therapy is considered **not medically necessary** or **investigational** in the following group of cancerous conditions: Breast cancer Esophageal cancer (investigational) Gastric cancer (investigational) Gynecologic cancer Head and neck cancer Hepatobiliary cancer Lung cancer Lymphoma (Hodgkin and non-Hodgkin) Pancreatic cancer (investigational) Prostate cancer	

Guideline (Year)	Evidence Base	Summary of Recommendations	Rating/Strength of Recommendation
ASCO (2018) Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline (2018)	Based on systematic review and expert consensus Evidence Base: 3 retrospective studies	Publicly available ASCO guidelines were reviewed for relevancy to proton beam therapy for cancerous and noncancerous conditions. Guidelines with PBT recommendations were found for the following condition: Malignant Pleural Mesothelioma Recommendation: For adjuvant or neoadjuvant hemithoracic radiation therapy, 3D or IMRT may be offered, respecting guidelines of organs at risk. Proton therapy may be considered in centers with significant experience, preferably in the context of a clinical trial (Evidence quality: **intermediate**; Strength of recommendation: **strong**).	Guidelines generated in part with Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software. Rating system not described further. In cases where evidence was lacking informal consensus of Expert Panel was used.
ASTRO (2017) Clinically Localized Prostate Cancer: AUA/ASTRO/ SUO Guideline	Based on systematic review Evidence Base: 1 retrospective population-based analysis	Publicly available guidelines and joint guidelines from ASTRO and ASTRO collaborators (AHRQ, American Urological Association (AUA), Society of Urologic Oncology (SUO)) were searched via (https://www.astro.org/Patient-Care-and-Research/Clinical-Practice-Statements) and were reviewed for relevancy to proton beam therapy for cancerous and noncancerous conditions. Guidelines with recommendations on proton beam therapy were obtained for the following condition: Clinically Localized Prostate Cancer Recommendation: Clinicians should inform localized prostate cancer patients who are considering proton beam therapy that it offers no clinical advantage over other forms of definitive treatment. Recommendation: **B (Moderate)**; Evidence Level: **Grade C**	Evidence rated based on American Urological Association (AUA) rating system: Evidence strength: **Grade A** (well-conducted and highly-generalizable randomized controlled trials [RCTs] or exceptionally strong observational studies with consistent findings), **Grade B** (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with

Guideline (Year)	Evidence Base	Summary of Recommendations	Rating/Strength of Recommendation
			consistent findings), or **Grade C** (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). Recommendation rating of **A (high), B (moderate)** or **C (low**) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.
NCCN (2018)	Evidence review and expert consensus 44 studies, 3	**All recommendations are category 2A.** According to NCCN Clinical Practice Guidelines, proton beam therapy may be appropriate, depending on clinical circumstances, for the following conditions: Lymphomas (B-Cell Lymphomas, T-Cell Lymphomas Hodgkin Lymphoma)	NCCN Categories of Evidence and Consensus **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the

Guideline (Year)	Evidence Base	Summary of Recommendations	Rating/Strength of Recommendation
	SRs, 2 meta-analysis, 1 guideline,	Bone Cancers CNS (brain) cancers] Head & Neck Cancers Hepatobiliary (Liver) Cancers Malignant Pleural Mesothelioma NSCLC Soft-Tissue Sarcoma Thymoma & Thymic Carcinomas Uveal Melanoma Proton beam therapy is considered appropriate only in the context of a clinical study for the following conditions: Prostate Cancer	intervention is appropriate **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate **Category 3**: Based upon any level evidence, there is major NCCN disagreement that the intervention is appropriate.

ASCO = American Society of Clinical Oncology; ASTRO = American Society for Radiation Oncology; CNS = central nervous system; NCCN = National Comprehensive Cancer Network; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; RCT = randomized controlled trial;

American College of Radiology Appropriateness Criteria

Appropriateness criteria from the American College of Radiology (ACR) were obtained from the ACR website. Each subcategory within every cancerous and non-cancerous condition was reviewed for updates to prior assessments reviewed in the prior report or newly published information relevant to proton beam therapy. Conclusions from assessments reviewed in the prior report are provided for each condition, followed by any new or updated assessments from 2014 to the present and a list of reviewed assessments. Details on the rating system used in ACR assessments are provided in the overview at the top of the table.

Appendix Table H2. Summary of Proton Beam Radiation Therapy recommendations in American College of Radiology Appropriateness Criteria

Assessments (year) [number of assessments]	Summary of Recommendations	Evidence Base for updated criteria
ACR Appropriateness Criteria (2014-2018)	ACR Appropriateness Criteria have been updated or newly released across the following conditions: Bone Tumors Gastrointestinal cancers Head and neck cancers (including skull base tumors) Lung Cancers Lymphomas Prostate Cancer <u>Ratings</u> ACR use a 9-point rating scale to describe the relative appropriateness of an intervention for the condition reviewed. In the scale **1, 2 and 3** indicate that an intervention is usually not appropriate, whereas **4, 5, 6** indicates it may be appropriate and **7, 8 and 9** indicate that it usually is appropriate. When provided, ratings are included below for each condition and assessment. Cancer-specific recommendations can be found below:	Literature Review and Expert Consensus Studies referenced in updated criteria listed can be found below:
Bone Tumors [3]	<u>Original Report (2011-2013)</u> PBT-based treatment plans are considered inappropriate (**rated 1-2**) in spinal and non-spinal bone metastases <u>Updates (2014-2018)</u> Criteria remain unchanged in criteria assessments released since the prior report. <u>Assessments reviewed:</u>	Proton specific studies not characterized.

Assessments (year) [number of assessments]	Summary of Recommendations	Evidence Base for updated criteria
	Metastatic Epidural Spinal Cord Compression and Recurrent Spinal Metastasis (2014), Non-Spine Bone Metastases (2014), Spinal Bone Metastases (2012)	
Gastrointestinal cancers [8]	Original Report (2011-2013) PBT not evaluated for these conditions Updates (2014-2018) There is early evidence that PBT is feasible for use in **borderline and unresectable pancreatic cancer**; however, the data are limited in number and maturity **(rating NR)**. Recommendation: No recommendations were made. In **Resectable pancreatic cancer**, neoadjuvant hypofractionated proton RT has been evaluated at a single institution and it appears to be safe with reasonable local control, although additional data are needed to determine long-term efficacy (**rating NR**). Recommendation: No recommendations were made. Two studies of PBT were addressed for **recurrent rectal cancer**. Particle therapy may be an option for recurrent rectal cancer as additional particle therapy facilities are opened, especially in patients who received previous RT (**rating NR**). Recommendation: particle therapy may be an option as additional particle therapy facilities are opened, especially in patients who received previous RT. PBT was not evaluated in other gastrointestinal cancers. Asssessments Reviewed Anal Cancer (2013), Borderline and Unresectable Pancreas Cancer (2016), Local Excision in Rectal Cancer (2014), Rectal Cancer—Metastatic Disease at Presentation (2014), Recurrent Rectal Cancer (2014), Resectable Pancreatic Cancer (2016), Resectable Rectal Cancer (2012), Resectable Stomach Cancer (2014)	6 studies
Gynecologic Cancers [11]	Original (2011-2013) The use of PBT as boost therapy in cervical cancer is not considered to be appropriate by the ACR.	Evidence for unchanged criteria not updated

Assessments (year) [number of assessments]	Summary of Recommendations	Evidence Base for updated criteria
	Updates (2014-2018) Criteria for cervical cancer remain unchanged. PBT remains unevaluated for other gynecologic cancers Assessments Reviewed: Adjuvant Management of Early Stage Endometrial Cancer (2016), Adjuvant Therapy in Vulvar Cancer (2015), Advanced Cervical Cancer (2012), Advanced Stage Endometrial Cancer (2014), Definitive Therapy for Early Stage Cervical Cancer (2012), Management of Locoregionally Advanced Squamous Cell Carcinoma of the Vulva (2012), Management of Recurrent Endometrial Cancer (2016), Management of Vaginal Cancer (2013), Pretreatment Evaluation and Follow-Up of Endometrial Cancer (2013), Pretreatment Planning of Invasive Cancer of the Cervix (2015), Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer (2014)	
Head and neck cancers (including skull base tumors) [9]	Original Report: (2011-2013) PBT not evaluated for this condition. Updates (2014-2018): ACR considers PBT usually appropriate (**rating 8-9**) for **Nasal and paranasal sinus cancers (updated 2016)**; they suggest proton therapy may be considered in cases where normal tissue constraints to critical structures (e.g., optic nerves, optic chiasm, spinal cord, brainstem, etc.) are not achievable using standard IMRT techniques. Recommendation: Intensity-modulated therapy, with photons or protons, reduces radiation-induced toxicity and should be preferentially considered over 3-D conformal RT. PBT is considered experimental for **nasopharyngeal carcinoma** (**updated 2015, rating NR**). Recommendation: no recommendations made. PBT is considered potentially appropriate (**rating 6**) retreatment of **recurrent head and neck cancer (2014)** after prior definitive radiation in select cases, though more	7 studies

Assessments (year) [number of assessments]	Summary of Recommendations	Evidence Base for updated criteria
	data is needed. Recommendation: Newer conformal radiation modalities, including stereotactic body radiation therapy and proton therapy, may be appropriate in select cases. Additional data are needed to determine which patient subsets will most likely benefit from these modalities. PBT was not evaluated in other head and neck cancers. Assessments Reviewed: Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck (2011), Aggressive Nonmelanomatous Skin Cancer of the Head and Neck (2014), Ipsilateral Radiation for Squamous Cell Carcinoma of the Tonsil (2014) , Locoregional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas (2015), Nasal Cavity and Paranasal Sinus Cancers (2016), Nasopharyngeal Carcinoma (2015), Retreatment of Recurrent Head and Neck Cancer after Prior Definitive Radiation (2014), Thyroid Carcinoma (2013), Treatment of Stage I T1 Glottic Cancer (2012	
Lung Cancers [6]	Original Report (2011-2013) PBT-based treatment plans are considered inappropriate (**rated 1-2**) for NSCLC patients with poor performance status or requirements for palliative treatment. Updates (2014-2018) Criteria not updated. PBT is considered potentially applicable in **nonsurgical treatment for locally advanced NSCLC: Good Performance Status/Definitive Intent**, but more prospective studies are needed (2014, **rating NR**). Recommendation: Proton therapy may have the potential to further spare critical normal tissues, although more prospective studies are needed. Assessments Reviewed: Early-Stage Non–Small-Cell Lung Cancer (2013), Induction and Adjuvant Therapy for N2 Non-Small-Cell Lung Cancer (2013), Non-Invasive Clinical Staging of Bronchogenic Carcinoma (2013), Nonsurgical Treatment for Locally Advanced Non-Small-Cell Lung Cancer: Good Performance Status/Definitive	2 studies, 1 ongoing RCT, 1 ongoing prospective study

Assessments (year) [number of assessments]	Summary of Recommendations	Evidence Base for updated criteria
	Intent (2014), Nonsurgical Treatment for Non-Small-Cell Lung Cancer: Poor Performance Status or Palliative Intent (2012), Radiation Therapy for Small-Cell Lung Cancer (2012)	
Lymphomas [8]	<u>Original Report (2011-2013)</u> PBT not evaluated for this condition. <u>Updates (2014-2018)</u> Updated criteria (2014) entail the use of ISRT and modern technology including IMRT, motion-control techniques, and proton therapy as radiation techniques for **diffuse large B-Cell Lymphoma (rating NR)**. For **favorable prognosis stage I and II Hodgkin Lymphoma (2016 update)**, ISRT is considered the standard treatment although PBT is considered a potential addition that may further reduce the radiation dose to normal structures (**rating NR**). In **unfavorable clinical stage I and II Hodgkin Lymphoma**, anterior-posterior fields are considered simple and efficacious, though proton RT may be useful to limit toxicities **(rating NR)**. For **localized nodal indolent Lymphoma (2013 update)** and **pediatric hodgkin lymphoma (2012 update)** proton therapy may be considered depending on the clinical scenario and whether an improvement in the therapeutic ratio is expected (**rating NR**). <u>Assessments Reviewed:</u> Diffuse Large B-Cell Lymphoma (2014), Follow-up of Hodgkin Lymphoma (2014), Hodgkin Lymphoma-Favorable Prognosis Stage I and II (2016), Hodgkin Lymphoma—Stage III and IV (2016), Hodgkin Lymphoma-Unfavorable Clinical Stage I and II (2015), Localized Nodal Indolent Lymphoma (2013), Pediatric Hodgkin Lymphoma (2012), Recurrent Hodgkin Lymphoma (2016)	2 studies

Assessments (year) [number of assessments]	Summary of Recommendations	Evidence Base for updated criteria
Prostate Cancer [7]	Original Report (2011-2013) The ACR Appropriateness Criteria® considers PBT for treatment planning in T1 and T2 prostate cancer as 'may be appropriate,' with lower ratings than for IMRT (**rating 6-7 versus 8-9**). Recommendation: There are only limited data comparing proton beam therapy to other methods of irradiation or to radical prostatectomy for treating stage T1 and T2 prostate cancer. Further studies are needed to clearly define its role for such treatment. Updates (2014-2018) PBT still considered possibly appropriate (**rating 5-6**) for **external beam radiation therapy treatment planning for clinically localized prostate cancer (2016)** Recommendations: Variant 1: If protons are used, treatment on a protocol is encouraged; variant 4: anterior-oriented beams or oblique beams are recommended; variant 5: treatment on a clinical trial is encouraged; variant 7: beam angles must be carefully considered due to limitations in proton beam path length Assessments Reviewed: Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer (2013), External Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer (2016), High-Dose-Rate Brachytherapy for Prostate Cancer (2013), Locally Advanced, High-Risk Prostate Cancer (2016), Permanent Source Brachytherapy for Prostate Cancer (2016), Postradical Prostatectomy Irradiation in Prostate Cancer (2014), Prostate Cancer–Pretreatment Detection, Surveillance, and Staging (2016)	6 studies, 1 clinical practice parameter
No assessment available.	Proton beam therapy not evaluated for the following conditions: Brain, spinal, and paraspinal tumors Breast Cancer Esophageal cancer Ocular Tumors Liver Cancers Pediatric cancers (e.g., medulloblastoma,	NA

Assessments (year) [number of assessments]	Summary of Recommendations	Evidence Base for updated criteria
	retinoblastoma, Ewing's sarcoma) Soft-tissue Sarcoma Seminoma Thymoma Other Noncancerous Conditions (Arteriovenous malformations; Hemangiomas) Other benign tumors e.g., acoustic neuromas, pituitary adenomas	

ACR = American College of Radiology; IMRT = intensity modulated radiation therapy; NR = not reported; PBT = proton beam therapy; RCT = randomized controlled trial

APPENDIX I. Clinical Expert Peer Review

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