Washington State Health Care Authority

Proton Beam Therapy: Re-review

Final data abstraction appendices

April 15, 2019

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Proton Beam Therapy: Re-Review

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FINAL DATA ABSTRACTION APPENDICES

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APPENDIX A. Bladder Cancer

Appendix Table A1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in bladder cancers

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Takaoka 2017 *High RoB* Retrospective Case Series Japan Funding: This work was supported in part by a JSPS Grant-in-Aid for Scientific Research (C) (26462397) and a JSPS Grant-in-Aid for Scientific Research (B) (26293349) COI: None declared	**Diagnosis**: muscle-invasive bladder cancer (cT2-3N0M0) **Indication**: Curative Intent	N=70 Male, %: 74% Median Age (range): 65 (36 to 85) years **History of non-muscle-invasive bladder cancer:** • yes: 13% • no: 87% **Multiple Tumors:** • Single: 71% • multiple: 29% **Size of Tumor:** • -<5cm : 87% • ≥5 cm: 13% **T Status:** • T2: 73% • T3: 27% **Tumor Location:** • Bladder Neck: 10% • Others: 90% **Hydronephrosis:**	Trimodal therapy (transurethral tumor resection, small pelvis photon RT, intra-arterial chemotherapy as induction) followed by proton beam therapy boost **Total PBT Dose: 36.3 GyE (3.3Gy equivalent fractional dose in 11 fractions over 2 weeks)** **Total Dose (including small pelvic photon RT): 77.7 Gy (in 34 fraction)**	**Median F/U:** 40.8 (7.2 to 234) months	**OS (95% CI)** • 3-year: 90% (NR) • 5-year: 82% (NR) • 10-year: 78% (NR) **PFS (95% CI)** • 3-year: 80% (NR) • 5-year: 77% (NR) • 10-year: 73% (NR) **Time to Progression** • 3-year: 82% • 5-year: 82% • 10-year: 82% **Progression/Recurrence, % (n/N):** • overall: 17% (12/70) • muscle invasive bladder cancer: 5.7% (4/70) • visceral metastases: 5.7% (4/70) • pelvis lymph node metastases: 5.7% (4/70) **Mortality:** • due to disease progression: 10% (7/70)	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 *Acute Toxicities*: timeframe NR *Late Toxicities*: timeframe NR **Acute hematological Toxicities (timeframe NR), % (n/N)** • Grade 2: -leukopenia: 13% (19/70) -anemia: 4% (3/70) -urinary frequency: 7% (5/70) -urinary tract pain: 4% (3/70) • Grade ≥3: 26% (18/70) -white blood cell decrease: 21% (15/70) -febrile neutropenia: 1.4% (1/70) -anemia: 1.4% (1/70) -platelet count decrease: 1.4% (1/70) • discontinued treatment due to acute toxicity: 0% (0/70) **Acute non-hematological toxicities(timeframe NR), % (n/N):** • Grade ≥3: 1.4% (1/70) -grade 4 thromboembolic event: 1.4% (1/70) **Late Toxicities (timeframe NR), % (n/N)** • Grade 2: -urinary tract hemorrhage: 4% (3/70) -rectal hemorrhage: 1% (1/70) • Grade 3: 3% (2/70) **-urinary tract obstruction: 3% (2/70)**

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
		• negative: 90% • positive: 10% **Concomitant Carcinoma In Situ:** • negative: 66% • positive: 13% • unknown: 21%				

CI = confidence interval; cm = centimeter; COI = conflict of interest; CTCAE = Common Terminology Criteria for Adverse Events; F/U = follow-up; Gy = Gray (unit); GyE = Gray Equivalent; NR = not reported; OS = overall survival; PBT = proton beam therapy; PFS = progression free survival; RoB = risk of bias; RT = radiation therapy;

APPENDIX B. Bone

Appendix Table B1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in bone cancers

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Aibe 2018 Retrospective Case Series *High RoB* Japan Funding: Practical Research for Innovative Cancer Control grant (grant 15ck0106034h0102) from the Japan Agency for Medical Research and Development for English language editing and the submission fees COI: None declared --- Includes volumetric data.	**Diagnosis**: Bone (primary Sacral Chordoma) **Indication:** Curative Intent	N=33 Male: 55% Median Age (range): 71 (41 to 87) years **ECOG Performance Status:** • 0: 6% • 1: 85% • 2: 9%	Definitive PBT **PBT Dose: 70.4Gy(RBE) in 32 fractions**	**Median F/U:** 37 (14 to 90) months	**OS (95% CI)** • 3-year: 92.7% (88.6% to 96.7%) **PFS (95% CI)** • 3-year: 89.6% (78.2% to 100.0%) **DFS (95% CI)** • 3-year: 81.9% (67.3% to 96.4%) **Distant Metastasis-Free Survival (95% CI)** • 3-year: 88.2% (75.5% to 100.0%) **Cause-Specific Survival (95% CI)** • 3-year: 95.7% (87.3% to 100.0%) **Recurrence/Progression, % (n/N)** • overall: 18.2% (6/33) • isolated local progression: 9% (3/33) • local progression after distant metastasis: 3% (1/33)	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 *Acute Toxicities*: Timeframe NR *Late Toxicities*: Timeframe NR **Acute Toxicities, % (n/N)** • Grade 2: -dermatitis: 39% (13/33) -Ulceration of skin: 3% (1/33) -pain: 64% (21/33) -Urinary retention: 6% (2/33) -Leg edema or numbness: 6% (2/33) • Grade 3: 3% (1/33) -dermatitis: 3% (1/33) **Late Toxicities, % (n/N)** • Grade 2: -pain: 58% (19/33) -sacral insufficiency fracture: 12% (4/33) -Ileus: 3% (1/33) -Rectal Bleeding: 3% (1/33) -Urinary retention: 6% (2/33) -Numbness of the leg: 6% (2/33) • Grade 3: -pain: 6% (2/33) -sacral insufficiency fracture: 6% (2/33) - Ileus: 3% (1/33)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
					• local progression and distant metastasis: 3% (1/33) • distant metastasis: 3% (1/33) • Median Time to Local Progression (range): 28 (7 to 46) months **Mortality, % (n/N)**: • all-cause: 12% (4/33) • attributable to chordoma: 6% (2/33) • pneumonitis: 3% (1/33) • natural causes (unspecified): 3% (1/33)	
Chowdhry 2016 Retrospective Case Series *High RoB* USA Funding: NR COI: none declared	**Diagnosis**: Bone (thoracolumbar spinal malignancies) **Indication:** Curative Intent	N=68 Male: NR Median Age (range): 54.15 years **Histology:** • chordoma: 42.7% • chondrosarcoma: 36.7% • osteosarcoma: 2.9% • other sarcoma: 14.7% • other (not specified): 2.9% **Smoking History:**	High Dose (≥5200 cGy) RT, Photon followed by Proton Median Total Dose Range: 7020 cGy (5940 to 7820 cGy) Photon Dose Range: 1980-3060 cGy Proton: remainder of total dose after photon dose was completed by protons	**Median F/U All Patients (range):** 12.9 (NR) months.	**OS (95% CI)** • 5-year: 88.7% (74.7% to 95.2%)	**Harms** *Toxicity Grading Criteria:* RTOG/EORTC *Acute Toxicities*: ≤3 months *Late Toxicities:* >3 months **Freedom from Grade ≥2 Neurological Injury (95% CI)** • 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%) **Late RTOG Toxicities (>3 months), % (n/N):** • Grade 2: 0% (0/68) • Grade 3: 11.7% (8/68) • permanent Grade 4: 0% (0/68) **Spinal Injury, % (n/N):** • Potentially radiation-related Spinal injury: 1.5% (1/68)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
		39.7%				-spinal cord compression with later diagnosis of myelodysplastic syndrome and transient paralysis: 1.5% (1/68) • Surgery-Related: 11.7% (8/68) • Disease Progression-related: 10.3% (7/68)
Indelicato 2016 Prospective Case Series *High RoB* USA Funding: NR COI: None declared	**Diagnosis**: Bone (Spinal Chordomas/Chondrosarcomas) **Indication:** Mixed • Curative Intent: 76.5% • Salvage: 23.5%	N=51 Male, %: 72.5% Median Age (range): 58 (22 to 83) years **Histology:** • chordoma: 67% • chondrosarcoma: 33% **Location:** • sacrum: 41% • cervical spine: 39% • thoracolumbar spine: 20% **Primary Disease**: • primary: 76.5% • recurrent: 23.5% **Disease burden:** • Gross: 52.9% • Microscopic: 47.1%	PBT (23 patients also treated with photon RT) Median Total Dose (range): 70.2 (64.2 to 75.6) Gy(RBE)	**Median F/U:** 44.4 (3.6 to 92.4) months	**OS (95% CI)** • 4-year: 72% (NR) **Cause-Specific Survival** • 4-year: 72% (NR) **DFS (95% CI)** • 4-year: 57% (NR) **Local Control (95% CI)** • 4-year: 58% (NR) **Freedom from Distant Metastases (95% CI)** • 4-year: 86% (NR) **Recurrence/ Progression, % (n/N)** • overall: 49% (25/51) • local: 35.3% (18/51) • local and distant: 11.8% (6/51) • distant: 2% (1/51) • Median Time to Local Progression (range): 20.4 (2.4 to 72) months	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 *Late Toxicities:* Timeframe NR **Late Toxicities, % (n/N)** • Grade 2: 2% (1/51) -bilateral radiation nephritis: 2% (1/51) • Grade NR: -sacral soft tissue necrosis: 4% (2/51) -T1 vertebral fracture requiring fusion surgery: 2% (1/51) -chronic urinary tract infections: 2% (1/51) -surgery for necrotic bone cyst: 2% (1/51) **Secondary Malignancies (possibly treatment related), % (n/N):** • overall: 4% (2/51) -bladder cancer within 2 years: 2% (1/51) -B-cell lymphoma within 5.5 years: 2% (1/51)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Kabolizadeh 2017 retrospective Case Series *High RoB* USA Funding: NR COI: None declared --- Also includes volumetric data.	**Diagnosis**: Bone (spinal and sacral chordoma) **Indication:** Curative Intent	N=40 Males, %: 52.5% Median Age (range): 67 (36 to 94) years **Median Maximal Tumor Diameter (range):** 7.7cm (1.4 to 25.5 cm) **Tumor Location**: • cervical: 22.5% • thoracic: 2.5% • lumbar: 7.5% • sacral: 67.5% • gluteus muscles: 15% • pyriformis: 10% • paraspinal: 5%	Photon-Proton RT Median Photon Dose (range): 30.6 Gy (0 to 68 Gy) Median Proton Dose (range): 46.8 GyRBE (0 to 79.2 GyRBE)	**Median F/U:** 50.3 (2 to 216.4) months.	**OS (95% CI)** • 3-year: 89.1% (73.5% to 95.8%) • 5-year: 81.9% (63.7% to 91.6%) **Disease Specific Survival (95% CI)** • 3-year: 97.2% (81.9% to 99.6%) • 5-year: 89.4% (70% to 96.5%) **Local Control (95% CI)** • 3-year: 96.9% (79.8% to 99.6%) • 5-year: 85.4% (65.4% to 94.3%) **Distant Failure (95% CI)** • 3-year: 11.7% (4.5% to 28.3%) • 5-year: 20.2% (9.3% to 40.5%) **Mortality, % (n/N)**: • due to secondary malignancies: 2.5% (1/40)	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 *Acute Toxicities:* Timeframe NR *Late Toxicities:* Timeframe NR **Acute RT-related Toxicities, % (n/N):** • Grade ≤2: -Pain/Dermatitis: reported as most common (data NR) - Nausea/Vomiting: 10% (4/40) - mucositis: 12.5% (5/40) - diarrhea: 12.5% (5/40) **Late RT-related toxicities, % (n/N):** • Grade 2: -rectal bleeding: 10% (4/40) • Grade NR: -sacral insufficiency fractures: (10/40) -foot drop: 5% (2/40) -erectile dysfunction: 2.5% (1/40) -perineal numbness: 2.5% (1/40) -worsening urinary/fecal incontinence: 5% (2/40) -bowel perforation/fistula formation: 2.5% (1/40) -spinal cord injuries: 0% (0/40) -soft tissue necrosis: 0% (0/40) **Secondary Malignancies, % (n/N):** • overall: 5% (2/40) -undifferentiated pleomorphic sarcoma/malignant histiocytoma (succumbed to lung cancer): 2.5% (1/40) -small cell lung cancer after subsequent C2 chordoma: 2.5% (1/40)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Rotondo 2015 Retrospective Case Series *High RoB* USA Funding: support for this study was received in part by the Federal Share of program income earned by Massachusetts General Hospital on National Cancer Institute grant no. C06 CA059267, Proton Therapy Research and Treatment Center. Dr. Rotondo, Ms. Kobayashi, Dr. Chen, Ms. Szymonifka, Mr. Ferreira, and Dr. DeLaney received direct or indirect	**Diagnosis**: Bone (Spine Chordomas: sacrococcygeal, lumbar, thoracic) **Indication** Mixed • Curative intent: 74.8% • salvage: 25.2%	N=126 Male, %: 62.2% Mean Age (range): 53.2 (5 to 88) years **Histology** • chondroid chordoma: 22% • nonchondroid chordoma 78% **Tumor Location** • thoracic: 12.6% • lumbar: 31.5% • sacrococcygeal: 55.9% **Operation**: • en bloc: 48.8% • intralesional: 48.8% • unknown: 2.4% **Resection** • gross total resection: 76.4% • subtotal resection: 23.6% **Margin Status**	3D-conformal passive scatter PBT & photon Median Total RT Dose (range): 72.4 (46.3 to 83.6) Gy(RBE) Median Photon Dose (range): 32.5 (0 to 58.0) Gy Median PBT Dose (range): 39.9 (18.0 to 77.4) Gy(RBE)	**Median F/U (range):** 41 months (NR)	**OS (95% CI) [n=126]** • 5-year: 81% (69% to 88%) • 10-year: 53% (35% to 68%) **Local Control (95% CI) [n=127 lesions]** • 5-year: 62% (50% to 72%) • 10-year: 49% (33% to 64%) **Regional Control (95% CI) [n=127 lesions]** • 5-year: 92% (83% to 96%), • 10-year: 84% (67% to 93%) **Locoregional Control (95% CI) [n=127 lesions]** • 5-year: 60% (48% to 70%) **Distant Control (95% CI) [n=127 lesions]** • 5-year: 77% (66% to 84%) • 10-year: 63% (46% to 75%) **Disease Status** • Alive (at time of analysis), % (n/N) -no evidence of disease; 62.2% (69/111) -progression-free: 7.2% (8/111) -with disease: 30.6% (34/111)	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 **RT-related Toxicities, % (n/N)** • Grade ≥3 -Wound infection among patients getting preoperative RT: 16.6% (10/60) -Wound dehiscence among patients getting preoperative RT: 5% (3/60) -Wound infection among patients getting post-op RT: 12.1% (7/58) -insufficiency fractures: 4.8% (6/126) -motor neuropathies: 3.2% (4/126) -Spine nonunion &/or hardware failure: 2.4% (3/126) -High-grade, radiation-associated soft tissue sarcoma: <1%(1/126) -Postop CSF leak after preop RT: <1%(1/126) -Osteonecrosis: <1%(1/126) -rectal bleeding: <1%(1/126) -Late proctitis, rectal pain, tenesmus: <1%(1/126) -Amenorrhea: <1%(1/126) -erectile dysfunction: <1%(1/126) **Neurological Status at last F/U Compared with Baseline** • improved status: 5.6% (7/126) • stable status: 48.4% (61/126) • deteriorated status: 42.9% (54/126) • unknown status: 3.2% (4/126) • Causes for deterioration in status: -surgery: 42.6% (23/54) -radiotherapy: 16.6% (9/54) -progressive local disease: 40.8% (22/54)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
support from the Federal Share COI: None declared		• R0: 26.8% • R1: 44.9% • R2: 23.6% • unknown: 4.7%			**Recurrence/Progression, % (n/N):** • local: 30.2% (38/126) • regional: 6.3% (8/126) • distant: 20.6% (26/126) **Mortality, % (n/N)** • all-cause (at time of analysis): 11.9% (15/126) • all-cause (at last follow-up): 22.2% (28/126) • disease progression: 8.7% (11/126) • other cause (not specified): <1% (1/126) • other cancer: 1.6% (2/126) • unknown: <1% (1/126)	**Secondary Malignancies, % (n/N):** • overall: <1% (1/126) -High-grade, radiation-associated soft tissue sarcoma: <1%(1/126)
Snider 2018 Retrospective case series *High RoB* Switzerland Funding: NR COI: None declared --- Includes multivariate analyses for local control, disease control	**Diagnosis**: Bone (spinal chordoma) **Indication:** Mixed • Curative intent: 70% • salvage: 30%	N=100 Male, %: 57% Median Age (range): 55.5 (25 to 81) years **Tumor Location** • cervical: 46% • thoracic: 4% • lumbar: 12% • sacral: 38%	Either Pencil Beam Scanning PBT (n=88), or photon-proton (n=12) Median RT Dose 74 (range, 59.4-77) Gy (RBE)	**Median F/U (range):** 65.5 (13 to 175) months	**OS (95% CI)** • 5-year: 81% (76.8 to 85.6%) • Median OS: 157 months **Disease Failure, % (n/N):** • local failure: 37% (37/100) • any failure: 42% (42/100) **Local Control (95% CI)** • 5-year: 63% (57.7% to 68.7%); median, 103 months **Disease Control (95% CI)** • 5-year: 57% (50.9% to 62.1%); • Median Disease Control: 82 months	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 *Acute Toxicities:* ≤3 months *Late Toxicities:* >3 months **Freedom from Grade ≥3 Acute Toxicity (95%CI):** • 5-year: 89% (85.5% to 91.9%) **Freedom from long term or persistent Grade ≥3 toxicity (95%CI)** • 5-year): 94% (88.6% to 98.6%) **Acute or Late toxicities, % (n/N):** • Grade ≥3: 11% (11/100) • Grade 4 toxicities: 0% (0/100) **Acute toxicities, % (n/N):**

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
and overall survival					**Mortality:** • all-cause: 26% (26/100)	• Grade ≥3: 8% (8/100) -moist desquamation in non-skin folds: 6% (6/100) -mucositis: 1% (1/100) - mucositis and dysphagia: 1% (1/100) • **Late Toxicities, % (n/N):** Grade ≥3: 5% (5/100) - vertebral/sacral insufficiency fracture: 3% (3/100) -aspiration pneumonia: 1% (1/100) -esophageal stenosis requiring dilation: 1% (1/100) **Secondary Malignancies, % (n/N):** 1% (1/100) (rhabdomyosarcoma of the bladder)

CI = Confidence Interval; cm = centimeter; COI = Conflict of Interest; CTCAE = Common Terminology Criteria for Adverse Events; DFS = Disease Free Survival; EORTC = European Organization for the Research and Treatment of Cancer; F/U = Follow-up; NR = Not Reported; OS = Overall Survival; PBT = Proton Beam Therapy; PFS = Progression Free Survival; RoB = Risk of Bias; RTOG = Radiation Therapy Oncology Group

APPENDIX C. Brain, Spinal, Paraspinal

Appendix Table C1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in Brain, Spinal and Paraspinal cancers

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Barney 2014 Retrospective Case Series *High RoB* USA Funding: none reported. COI: none declared	**Diagnosis** Brain (various craniospinal malignancies) **Indication:** Curative Intent	N=50 Male, %: 66% Median Age (range): 26.7 (16 to 63) years **Histology:** • medulloblastoma: 38% (19/50) • Germ Cell Tumors: 18 (9/50) • Nongerminomatous Germ Cell Ttumors: 12% (6/50) • pineoblastoma: 14% (7/50) • ependymoma: 4% (2/50) • atypical teratoid rhabdoid tumor: 2% (1/50) • glioma: 2% (1/50) • papillary tumor: 2% (1/50)	PBT (80% received chemotherapy in addition) with 94% receiving additional conformal proton boost **Median Cranio-Spinal PBT Dose: 30.6 (15 to 39.6) Gy** **Median Total Boost Dose (range): 54 (24 to 58.6) Gy**	**Median F/U (range):** 20.1 (0.3 to 59) mos.	**OS (95% CI)** • 2-year: 96% (NR) • 5-year: 84% (NR) **PFS (95% CI)** • 2-year: 82% (NR) • 5-year: 68% (NR) **Recurrence/Progression, % (n/N)** • overall: 14% (7/50) • in-field local recurrence: 10% (5/50) • extracranial metastases: 4% (2/50) **Mortality, % (n/N)** • disease progression: 4% (2/50)	**Harms** *Toxicity Grading Criteria:* RTOG *Acute Toxicities:* ≤3 mos *Late Toxicities:* >3 mos **Acute Toxicities, % (n/N)** • Grade ≤2: -nausea/vomiting: 100% (50/50) -dermatitis: 100% (50/50) -ototoxicity: 100% (26/26) -Anemia: 100% (46/46) -leukopenia: 91.3% (42/46) -thrombocytopenia: 95.7% (44/46) • Grade ≥3: -leukopenia: 9% (4/46) -thrombocytopenia (grade 3): 2% (1/46) -thrombocytopenia (grade 4): 2% (1/46) -ototoxicity: 4% (1/26) [only 26 patients assessed for this outcome] **Patients requiring packed red blood cell transfusions, % (n/N):** • overall: 10% (5/50) • also received granulocyte colony stimulating factor: 80% (4/5) • also received platelet transfusion: 20% (1/5) **Weight Loss** • patients with ≤2% weight loss: 60% (30/50)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
		• choroid plexus papilloma: 2% (1/50) • rhabdoid meningioma: 2% (1/50) • acute lymphoblast/tic leukemia: 4% (2/50) **Modified Chang M Stage:** • M0: 60% • M1: 2% • M2: 16% • M3: 18% • M4: 0% **Chemotherapy:** • any: 80% • neoadjuvant: 40% • concurrent: 30% • adjuvant: 65%				• patients with >2-5% weight loss: 30% (15/50) • patients with >5%-10%: 8% (4/50) • patients with >10% weight loss: 2% (1/50)
Dutz 2018 Retrospective Case Series *High RoB* Germany Funding: NR	**Diagnosis:** Brain (various) **Indication:** Curative Intent	N=113 Male: 60% Median Age (range): 49.3 (21.2 to 79.9) years **Histology**: • pituitary adenoma: 9%	Double-scattering PBT Median Total Dose (Range): 60.0 (30.0–74.0) Gy	**Median F/U (range):** NR <u>Loss to F/U</u> 6% (7/113)	NR	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 *Acute Toxicities:* timeframe NR **<u>Exploratory Cohort (n=113)</u>** **Acute Toxicities, % (n/N)** • <u>Grade 0:</u> -alopecia: 14% (15/111) -erythema: 13% (15/113) -fatigue: 31% (35/112)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
COI: None declared --- Also includes data on two 'validation cohorts'		• meningioma: 13% • craniopharyngeoma: 1% • astrocytoma: 1% • (Oligo)astrocytoma and • Oligodendroglioma (II): 9% • (Oligo)astrocytoma and • Oligodendroglioma (III): 27% • glioblastoma • other: 19% **Location:** • brain: 68% • skull-base: 31% • -other: 1%				-nausea: 84% (82/98) -pain: 51% (57/113) • <u>Grade 1:</u> -alopecia: 23% (26/111) -erythema: 51% (57/113) -fatigue: 47% (53/112) -nausea: 13% (13/98) -pain: 29% (33/113) • <u>Grade 2:</u> -alopecia: 63% (70/111) -erythema: 35% (40/113) -fatigue: 19% (21/112) -nausea: 3% (3/98) -pain: 16% (18/113) • <u>Grade 3</u> -alopecia: 0% (0/111) -erythema: 1% (1/113) -fatigue: 3% (3/112) -nausea: 0% (0/98) -pain: 4% (5/113) **<u>All Cohorts (n=280)</u>** **Acute Toxicities, % (n/N)** • <u>Grade 3</u> -alopecia: 0% (0/280) -erythema: >1% (1/280) -fatigue: 1.8% (5/280) -nausea: 0% (0/280) -pain: 2.1% (6/280)
Kang 2018 retrospective Case Series	**Diagnosis**: Central Neurocytomas **Indication:** Mixed	N=24 eligible, 16 treated Male: 42% Median Age (range): 21 years (14 to 60 years)	Adjuvant PBT (n=6) after non Gross Tumor Resection surgery with or without chemotherapy; or	**Median F/U (range):** 56 (3 to 185) mos	**PFS (adjuvant PBT) (95%CI)** • <u>5-year:</u> 100% (NR) **Recurrence/Progression, % (n/N)** • overall: 45.8% (11/24)	Harms *Toxicity Grading Criteria:* CTCAE version 4.0 Transient (Acute/Subacute) Toxicities: <6 mos PBT-related Transient Toxicities • <u>Grade NR:</u>

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
High RoB USA Funding: COI: One or more authors have received research funding or in-kind donations from PBT related organizations. ---	-curative intent: 37.5% -salvage: 62.5%	Median Tumor Size (range): 4.5 (1.4 to 6.8) cm **Initial Therapy** • gross total resection only: 21% • non-gross total resection: 54% • non-gross total resection + adjuvant PBT: 17% • non-gross total resection + adjuvant PBT + chemotherapy: 8%	salvage PBT (n=10) after disease recurrence **Adjuvant PBT Dose (range): 52.2 (50.4 to 54) Gy (RBE) , 1.8 Gy (RBE) per fraction** **Salvage PBT Total dose: 54 Gy(RBE)**		• Median Time to Recurrence/Progression (range): 22 (13 to 141) mos **Post-Salvage PBT Disease Control (95% CI)** • 100% (NR) • Median Disease Control: 67 mos	-fatigue: 8 events -alopecia: 6 events -radiation dermatitis: 5 events -permanent mild-to-moderate concentration impairment: 4 events • Grade II: 24% (10/42 events) -nausea causing decreased oral intake: 2 events -fatigue affecting daily responsibilities: 3 events -unexplained weigh gain: 1 event -presyncope: 1 event -concentration impairment affecting work performance: 2 events -nocturnal seizures: 1 event • Grade III or higher: 0% (0/24) PBT-related neurotoxicity • Grade I to II: 44% (7/16)
Maquilan 2014 Prospective Case Series *High RoB* USA Funding: Supported by the Department of Radiation Oncology at the University of	**Diagnosis**: Brain (low grade gliomas or meningiomas) **Indication:** Curative Intent	N=23 Male: 39.1% Median Age (range): 44 (18 to 75 years) **Histology**: • astrocytoma: 39.1% • oligodendroglioma: 8.7% • oligoastrocytoma:17.4%	**PBT (type NR)** **Median PBT Dose (range): 54 (NR) Gy(RBE) , 1.8 Gy(RBE) per fraction**	**Median F/U (range):** NR (0 to 9) mos	NR	Harms *Toxicity Grading Criteria:* CTCAE version 4.0 Acute Toxicities: ≤3 mos [overall] Acute toxicities, % (n/N) • Grade 3: - Fatigue: 4.3% (1/23) -Anorexia: 0% (0/23) -Nausea: 0% (0/23) -Headache: 4.3% (1/23) -Insomnia: 0% (0/23) Acute (week 1) toxicities, % (n/N) • Grade 1:

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Pennsylvania. COI: None declared		• meningioma: 26.1% • low-grade glioma: 8.7% **Tumor Location:** • left: 34.8% • right: 43.5% • central: 13% • mixed: 8.7% **Extent of Resection:** • subtotal: 39.1% • gross total: 47.8% • biopsy: 13%				- Fatigue: 38.1% (8/21) -Anorexia: 19% (4/21) -Nausea: 0% (0/21) -Headache: 27.3% (6/22) -Insomnia: 5.3% (1/19) • Grade 2: -Fatigue: 4.8% (1/21) -Anorexia: 0% (0/21) -Nausea: 0% (0/21) -Headache: 9.1% (2/22) -Insomnia: 0% (0/19) • Grade 3: -Fatigue: 4.8% (1/21) -Anorexia: 0% (0/21) -Nausea: 0% (0/21) -Headache: 0% (0/22) -Insomnia: 0% (0/19) Acute (week 3) toxicities, % (n/N) • Grade 1: -Fatigue: 60.9% (14/23) -Anorexia: 0% (0/23) -Nausea: 21.7% (5/23) -Headache: 43.5% (10/23) -Insomnia: 17.4% (4/23) • Grade 2: -Fatigue: 8.7% (2/23) -Anorexia: 0% (0/23) -Nausea: 0% (0/23) -Headache: 4.3% (1/23) -Insomnia: 0% (0/23) • Grade 3: -Fatigue: 4.8% (1/21) -Anorexia: 0% (0/23) -Nausea: 0% (0/23) -Headache: 4.3% (1/23) -Insomnia: 0% (0/23)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
						Acute (1 month) toxicities, % (n/N) • Grade 1: -Fatigue: 50% (3/6) -Anorexia: 28.6% (2/7) -Nausea: 0% (0/12) -Headache: 10% (1/10) -Insomnia: 20% (2/10) • Grade 2: -Fatigue: 16.7% (1/6) -Anorexia: 14.3% (1/7) -Nausea: 0% (0/12) -Headache: 10% (1/10) -Insomnia: 0% (0/10) • Grade 3: -Fatigue: 16.7% (1/6) -Anorexia: 0% (0/7) -Nausea: 0% (0/12) -Headache: 0% (0/10) -Insomnia: 0% (0/10) Acute (1.5 mos) toxicities, % (n/N) • Grade 1: -Fatigue: 61.9% (13/21) -Anorexia: 4.8% (1/21) -Nausea: 14.3% (3/21) -Headache: 19% (4/21) -Insomnia: 33.3% (7/21) • Grade 2: -Fatigue: 28.6% (6/21) -Anorexia: 4.8% (1/21) -Nausea: 0% (0/21) -Headache: 9.5% (2/21) -Insomnia: 4.8% (1/21) • Grade 3: -Fatigue: 4.8% (1/21) -Anorexia: 0% (0/21)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
						-Nausea: 0% (0/21) -Headache: 0% (0/21) -Insomnia: 0% (0/21)
Mizumoto 2016 Retrospective Case Series *High RoB* Japan Funding: This work was partially supported by grants-in-aid for Scientific Research (B) (15H04901) and Young Scientists (B) (25861064) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. COI: NR Subset of larger study (46/165) who received PBT+Photon	**Diagnosis**: Brain Tumor (glioblastoma multiforme) **Indication:** Curative Intent	N=46 Male: 52% Median Age (range): 58 (24 to 76) years **Tumor Location:** • frontal lobe: 50% • temporal lobe: 34.8% • parietal lobe: 6.5% • occipital lobe: 8.7% **Pre-RT Surgery:** • biopsy: 2.2% • partial resection: 30.4% • subtotal resection/gross total resection:67.4%	**Postoperative High Dose RT (Photon with PBT boost) with concurrent ChT (ACNU, n=23; TMZ, n=23)** **Total Dose Range: 50.4 to 96.6 GyE** **Photon Dose: 50.4 Gy in 28 fractions** **PBT Boost: 23.1-46.2 GyE in 14-28 fractions**	**Median F/U (range):** 42.1 (20.0 to 116.3) mos	**OS (95% CI)** • 1-year: 82.6% (NR) 2-year:47.6% (NR) • Median OS: 21.1 (range, 2.8 to 116.3; 95% CI 6.3 to 10.3) mos **PFS (95% CI)** • 1-year: 37% (NR) • 2-year: 11.6% (NR) **Disease Status, % (n/N)** • progressive or enhanced lesion at last follow-up: 91.3% (42/46) • recurrence: 67.4% (31/46) **Mortality, % (n/N)** • all-cause: 71.7% (33/46) • cancer-related: 60.9% (28/46) • unrelated to tumor occurrence: 10.9% (5/46)	Harms *Toxicity Grading Criteria:* CTCAE version 3.0 and RTOG/EORTC Late Radiation Morbidity Scheme Acute Toxicities: ≤3 mos Late Toxicities: >3 mos Non-hematologic acute toxicity • Grade 3: 4.4% (2/46) Acute Toxicities, % (n/N) • Grade 2: -Anemia: 13% (6/46) -Leukopenia: 30.4% (14/46) - neutropenia: 13% (6/46) - Lymphopenia: 17.4% (8/46) - Thrombcytopenia: 15.2% (7/46) -Nausea and vomiting: 4.4% (2/46) -Dermatitis: 15.2% (7/46) -Otitis: 2.8% (1/46) -Seizure: 4.4% (2/46) • Grade 3 or 4: -Anemia: 8.7% (4/46) -Leukopenia: 26.1% (12/46) (likely Chemotherapy-related) - neutropenia: 32.6% (15/46) (likely Chemotherapy-related) - Lymphopenia: 50% (23/46) (likely Chemotherapy-related) - Thrombocytopenia: 10.9% (5/46) (likely Chemotherapy-related) -Nausea and vomiting: 2.8% (1/46) -Otitis: 2.8% (1/46)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
while the rest received photon only						**Late Radiation necrosis, % (n/N):** 23.9% (11/46)

Murray 2017
 	
Retrospective Case Series
 	
High RoB
 	
Switzerland
 	
Funding: NR
COI: None disclosed
 	
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Also Contains volumetric. data. Also provides subpopulation data on young vs old, etc…
	Diagnosis:
	Intracranial meningiomas
	
	Indication:
	Mixed
	• Curative intent: 76%
	• Salvage: 24%
		N=96
		
		Male: 30.2%
		Median Age (range): 52.8 (3 to 77) years
		
		Histology:
		• Benign, WHO Grade I: 63.5%
		• atypical, WHO grade II: 34.1%
		• anaplastic, WHO grade III: 2.1%
		
		Tumor Location
		• non-skull base: 33.3%
		• skull base: 66.7%
		
		Indication for Treatment:
		• initial: 55.2%
		• recurrence: 17.7%
		• progression: 27.1%
		
		Gross Total Resection:
			PBT
			3-field beam technique with IMPT
			
			WHO Grade I tumors:
			-Median Dose (range): 54.0 (50.4 to 64.0) Gy(RBE)
			
			WHO Grade II or III:
			-median dose (range): 62 (54 to 68) Gy(RBE)
				Median F/U (range):
				56.9 (12.1 to 207.2) mos
					OS (95% CI)
					• 5-year: 88.2% (80.8% to 95.6%)
					  • WHO grade 1: 92.1%
					  • WHO grade 2/3: 80.7%
					
					Local Control (95% CI)
					• 5-year [all patients]: 86.4% (78.4% to 94.4%)
					• 5-year[WHO grade I]: 95.7% (NR)
					• 5-year Local Control [WHO grade II/III]: 68% (NR)
					
					Local Failures (95% CI)
					• 14% (13/96)
					• median time to failure: 32.4 mos
					
					Mortality, % (n/N):
					• all-cause: 14.6% (14/96)
					  • WHO grade 1: 8.3% (8/96)
					  • WHO grade 2: 6.3% (6/96)
					• tumor related: 9.3% (9/96)
					  • WHO grade 1: 4.2% (4/96)
					  • WHO grade 2: 5.2% (5/96)
						Harms
						Toxicity Grading Criteria: CTCAE version 4.0
						Acute Toxicities: ≤3 mos
						Late Toxicities: >3 mos
						
						Grade ≥3 Toxicity-Free Survival (95% CI):
						• 5-year: 89.1% (82.2% to 96%).
						
						Acute Toxicities, % (N/N):
						• Any grade: 90.6% (87/96)
						• Grade ≤2:
						-alopecia (grade 1/2): 65.6% (63/96)
						-radiation dermatitis (grade 1/2): 47.9% (46/96)
						• Grade 3: 1% (1/96)
						-symptomatic brain edema: 1% (1/96)
						
						Late Toxicities, % (N/N):
						• Grade NR: 45% (43/96)
						-optic tract: 33% (14/96)
						-pituitary: 23% (10/96)
						-fatigue/impaired healing: 14% (6/96)
						
						High Grade Toxicities, % (N/N):
						• Any Grade: 10% (10/96)
						• Grade ≥3:
						-optic toxicities: 7.3% (7/96)
						-late, transient brain edema: 1.4% (1/96)
						-brain necrosis: 2.1% (2/96)
						• Grade 5: 1% (1/96)
						-brain necrosis leading to death: 1% (1/96)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
		• yes: 11.8% • no: 88.2%				

ACNU = nimustine; CI = confidence interval; cm = centimeter; COI = conflict of interest; CR = complete response; CTCAE = Common Terminology ; Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; F/U = follow-up; Gy = Gray (unit); Gy(RBE) = Gray (Relative Biological Equivalent); IMPT = Intensity Modulated Proton Therapy; mos = months; NR = not reported; OS = overall survival; PBT = proton beam therapy; PFS = progression free survival; RoB = risk of bias; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; TMZ = Temozolomide; WHO = World Health Organization

* Among the 81 patients who had significant dose of irradiation 'through' the pituitary.

† Among the 112 patients who experienced full or partial inclusion of optic apparatus in radiation fields.

Appendix Table C2. Study characteristics and patient demographics: nonrandomized comparative studies of proton beam therapy in brain, spinal and paraspinal cancers

Study Intervention/ comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Comparative Cohort Studies							
Adeberg 2017 Retrospective matched-pairs comparative cohort *Moderately high* Germany	122	**Photon+PBT Boost (n = 66):** Photon Dose (range): 50.0 (50.0 to 50.4) Gy in 2.0 Gy (1.8 to 2.0) fractions PBT Boost Dose: 10 Gy(RBE) in 2.0 Gy(RBE) fractions **Photon (n = 66):**	**Inclusion:** Patients w/ histologically confirmed supratentorial primary high-grade glioma (HGG) and subtotal surgical resection or biopsy; Karnofsky's performance status (KPS) score ≥70; proton boost started ≤4 days after completion of photon therapy	PBT vs. Photon Median age (range): 57.9 (20.0 to 77.0) vs 57.9 (21.6 to 77.9) Male, %: 63.6% vs 57.6% Median KPS in % (range): 90% (70 to 100) vs 90% (70 to 100) Temozolomide Therapy, % (n/N): 93.9% (62/66) vs 87.9% (58/66)	PBT vs. Photon **F/U (median [range]):** 15 mos vs 15 mos **% F/U:** 95.4% (63/66) vs. 100% (66/66)	Median OS and PFS Pseudoprogression Harms (acute toxicity, Pseudoprogression)	Funding: acknowledge financial support of the Dietmar-Hopp-Stiftung. COI: NR Notes:

Study Intervention/ comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		Total Photon Dose (range): 60.0 Gy (59.4 to 60.0 Gy) in 2.0 Gy fractions (1.8–2.0 Gy) • Patients in Photon+Proton boost cohort were pair matched with a cohort who underwent conventional RT and were matched by age, KPS, resection status, temozolomide therapy, and photon planning target volume dimension.	**Exclusion:** patients were excluded if dosing was not 50.0 Gy (range: 50.0–50.4 Gy) and target volumes were not delineated	Biopsy only, % (n/N): 19.7% (13/66) vs 6.6% (10/66) Gross residual tumor at RT <1.5 cm^2: 74% vs. 81% ≥1.5 cm^2: 26% vs. 19% Any chemotherapy: 84% vs. 81% Histology -Glioblastoma: 95.4% (63/66) vs 95.4% (63/66) -anaplastic astrocytoma: 3% (2/66) vs 3% (2/66) -anaplastic oligodendroglioma: 1.6% (1/66) vs 1.6% (1/66)			
Bronk 2018 Retrospective comparative cohort *Moderately High*	99	**PBT (n = 34):** Passive scatter (n=29) or scanning beam (n=5) Oligodendroglioma (n=25): PBT Dose (range): 54 (40 to 57) Gy(RBE)	**Inclusion:** Patients ≥18 years; histologically confirmed grade II or III oligodendroglioma or astrocytoma per 2007 WHO criteria; treated between 2004 and 2015 **Exclusion:** NR	PBT vs Photon **Overall (n=34 vs. 65):** Median age (range): all patients, 48 (24 to 94) years Male: 64.7% vs 64.6% Tumor Location: frontal lobe: 52.9% vs 61.5%; other: 47.1% vs 38.5%	PBT vs Photon Overall **Radiographic F/U (median [range]):** 34 mos. vs 46 mos. **% F/U:** 100%	Pseudoprogression	Funding: NR COI: NR Notes: Data provided for all patients, and for the two main histologies.

Study Intervention/ comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
USA		Astrocytoma (n=9): PBT Dose (range): 50.4 (50.4 to 57) Gy(RBE) **IMRT (n = 65):** Oligodendroglioma (n=42): Photon Dose (range): 57 (50 to 57) Gy(RBE) Astrocytoma (n=23): Photon Dose (range): 57 (50 to 60) Gy(RBE)		Grade 2: 52.9% vs 27.7% 3: 47.1% vs 72.3% Surgery: subtotal resection: 64.7% vs 66.2%; gross total resection: 35.3% vs 33.8% Concurrent ChT (Yes): 3% vs. 20% Adjuvant ChT (Yes): 52.9% vs 55.4% **Oligodendroglioma (n=25 vs. 42)** Median age (range): 47 (24 to 71) vs. 51.5 (34 to 94) years Male: 64% vs. 64.3% Tumor Location frontal lobe: 64% vs. 66.6% -ther: 36% vs. 33.3% Grade: 2: 44% vs. 28.6% 3: 56% vs. 71.4% Surgery: subtotal resection: 64% vs. 69% -gross total resection: 36% vs. 31% Concurrent ChT (Yes): 0% vs. 7%	**Oligodendroglioma Radiographic F/U (median [range]):** 38 mos. vs 46 mos. **Astrocytoma Radiographic F/U (median [range]):** 24 mos. vs 46 mos. **Median F/U patients with pseudoprogression (median [range]):** 22 vs 45 mos, p=0.040		

Study Intervention/ comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
				Adjuvant ChT (Yes): 64% vs. 50% **Astrocytoma (n=9 vs. 23)** Median age (range): 46 (26 to 53) vs. 47 (24 to 67) years Male: 66% vs. 65.2% Tumor Location frontal lobe: 22% vs. 52.2% other: 78% vs. 47.8% Grade: 2: 78% vs. 26.1% 3: 22% vs. 73.9% Surgery: subtotal resection: 66% vs. 61% gross total resection: 34% vs. 39% Concurrent ChT (Yes): 11.1% vs. 43.5% Adjuvant ChT (Yes): 22.2% vs .65.2%			
Gunther 2017 Retrospective comparative cohort *Moderately High* Germany	37	**PBT (n = 14):** Passive scatter Median PBT dose (IQR): 21.8 Gy (21.3 to 23.6) **Photon (n = 23):**	**Inclusion:** Patients ≥18 years; pathologically confirmed disease (either acute or chronic leukemia, lymphoma or myeloma) and confirmed CNS involvement; received craniospinal irradiation prior to stem cell transplant	PBT vs. Photon Median age (range): 37 (26 to 51) vs 39 (28 to 45) years Male, %: 57% vs 65% Histology -Acute Lymphoblastic leukemia: 43% vs 52%	**F/U, all patients (median [IQR]):** 8 (6 to 17.5) mos **F/U, all surviving patients (median [IQR]):**	Disease response Survival (cause-specific survival and overall survival) Harms (acute and late toxicity, neurotoxicity)	Funding: NR COI: None declared Notes:

Study Intervention/ comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		Median radiation dose (IQR): 24 Gy (23.4 to 24.0) All patients: • received craniospinal radiation for CNS involvement (8 as part of initial therapy and 29 at time of CNS relapse) • Two patients (unspecified cohort) received either prior CNS RT at skull base, or radiosurgery for meningioma, treatment plans adjusted accordingly to avoid 3>6 Gy cumulative dose to whole brain. • typically received multiple salvage chemotherapy regimens prior to CSI.	**Exclusion:** NR	-acute myeloblastic leukemia: 29% vs 17% -chronic lymphocytic leukemia: 0% vs 4% -chronic myelocytic leukemia: 21% vs 9% -lymphoma (not otherwise specified): 7% vs 13% -myeloma: 0% vs 4% Treatment Indication -consolidation: 93% vs 74% -gross disease treatment: 7% vs 26%	16 (9 to 32) mos **% F/U:** 100%		

Study Intervention/ comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		• went on to received hematopoietic stem cell transplantation					
Mozes 2017 Retrospective matched-pairs comparative cohort *Moderately High* Germany	66 (see note)	**PBT (n = 27):** Median PBT dose (range): 56 GyE 54 to 58) GyE in 1.8 or 2 GyE daily fractions **IMRT (n = 16):** Median radiation dose (range): 56 Gy (39.6 to 60) in 1.8 or 2 Gy daily fractions **FSRT (n = 23):** Median radiation dose (IQR): 56 Gy (39.6 to 60) in 1.8 or 2 Gy daily fractions • Patients from Group B (IMRT and FSRT) were	**Inclusion:** Patients with inoperable (even biopsy not feasible), residual or recurrent intracranial meningioma **Exclusion:** NR	PBT vs IMRT vs FSRT N=27 vs 16 vs 23 Median age (range): NR vs NR vs NR Male, %: 14.8% vs 31.3% vs 26.1% WHO Grade -unknown: 37% vs 25% vs 34.8% -I: 63% vs 44% vs 39.1% -II: 0% vs 19% vs 17.4% -III: 0% vs 12% vs 8.7% Tumor Location: -skull base: 85.2% vs 81.3% vs 52.2% -olfactory: 11.1% vs 0% vs 0% -falx celebri: 0% vs 0% vs 8.7% -convexity: 0% vs 12.5% vs 13% -cavernous sinus: 0% vs 0% vs 17.4% -*N. opticus*: 0% vs 0% vs 8.7% -craniocervical junction: 0% vs 6.3% vs 0%	**F/U, radiographic (median [IQR]):** 24 vs 24 vs 24 mos **% F/U:** IC (cannot be determined)	1-year and 2-year absolute TV shrinkage, relative TV	Funding: NR COI: None declared Notes: An additional group of 11 patients who received IMRT with carbon boost was excluded from our analysis based on our inclusion criteria.

Study Intervention/ comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		matched by similar age, gender and tumor volume to patients from Group A (proton) for the purposes of comparison		Indication: -inoperable tumor: 37% vs 25% vs 34.8% -residual disease: 11.1% vs 18.8% vs 30.4% -recurrent disease: 51.9% vs 56.3% vs 34.8% Mean initial Tumor Volume 26.1 ± 22.2 cm^3 vs 37.3 ± 29.5 cm^3 vs 26.7 ± 23.1 cm^3			
Jhaveri 2018 Retrospective Database Comparative Cohort & Retrospective Propensity Score Matched Comparative Database Cohort Moderately High	49,575	**<u>Entire Cohort</u>** **PBT (n=170)** **Photon RT (n=49,405)** 3DCRT (n=5,196) IMRT (n=20,215) Photon RT NOS (n=23,994) **<u>Propensity Matched Cohort</u>** **PBT (n=161)** **Photon RT (n=161)**	**Inclusion:** The database was queried for patients diagnosed with CNS malignancy from 2004 to 2013. Adult patients (age >18) with invasive, histologically confirmed, WHO Grade IIV gliomas were included. **Exclusion**: Patients with non-glial histology (metastases, sarcoma, meningioma, hemangioma, embryonal tumors, ventricular tumors, and primitive neuroendocrine	**<u>Entire Cohort</u>** [All data reported for all patients only] Male: 58.6% Mean (SD) Age: 57.3 (13.96) years Race White: 91.1% Black: 5.4% Other/Unknown: 3.6% Grade of Glioma Low grade: 8.8% High grade: 91.2% Surgery: 79.8%	**<u>Entire Cohort</u>** **PBT vs. Photon RT** **Median F/U**: 50.3 vs. 62.3 months (62.1 for entire group) **% F/U:** NR	Overall survival	Funding: COI: None Notes: The 2014 Brain/Central Nervous System National Cancer Database Participant User File was used to select patients for this study.

Study Intervention/ comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
USA			tumors); patients who did not specifically receive RT to the brain; Patients with Karnofsky Performance Status of <60%; Patients who received inadequate RT dose (<45Gy), unconventional RT techniques (Cobalt, Electrons, Linac radiosurgery, Gamma Knife, Brachytherapy, Radium, and radioisotope), prolonged RT course (> 70 days), and cases with missing outcomes	Gross total resection: 12.2% Subtotal resection: 11.9% Biopsy: 9.8% Other: 55% Unknown: 11.1% Chemotherapy (yes): 83.6% Charlson-Deyo Score 0: 77.8% 1 to 2+: 22.2% <u>Propensity Score Matched Cohort</u> Male: 59.57% vs. 59.57% Mean (SD) Age: 49.4 (0.88) 49.4 (14.51) years Grade of Glioma Low grade: 26.69% vs. 26.69% High grade: 73.31% vs. 73.31% Surgery: 87.08% vs. 87.08%			

Study Intervention/ comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
				Chemotherapy (yes): 78.7% vs. 78.7% Charlson-Deyo Score 0: 86.45% vs. 86.45% 1 to 2+: 13.55% vs. 13.55%			

cm = centimeter; CNS = Central Nervous System; COI = Conflict of Interest; CSI = Cranial Spinal Irradiation; F/U = follow-up; FSRT = Fractionated stereotactic radiation therapy; Gy = Gray; IMRT = intensity modulated radiation therapy; IQR = Interquartile Range; KPS = Kranofsky's Performance Status; NR = Not reported; OS = Overall Survival; PBT = Proton Beam Therapy; PFS = Progression Free Survival; RBE = Relative Biological Effectiveness; RT -= radiation therapy; TV = tumor volume; WHO = World Health Organization

Appendix Table C3. Detailed data abstraction: nonrandomized comparative studies of proton beam therapy in brain, spinal and paraspinal cancers

Study Intervention/ comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Cohort studies			
Adeberg 2017 Photon+PBT (n=66) vs. Photon (n=66) Retrospective matched-pair cohort *Moderately high*	PBT vs. Photon **1 year-OS** 75% vs 85% (estimated from graph) **2 year-OS** 40% vs 43% (estimated from graph) **3 year-OS** 12% vs 28% (estimated from graph)	NR	PBT vs. Photon For toxicity: CTCAE classification (v.4.03) **Acute Toxicity (≤3 mos.), % (n/N):** • ≥ Grade 2 : 9% (6/66) vs. 14% (9/66) • Grade 3: 0% (0/66) vs. 7.5% (5/66), p<0.1 **intracranial pressure** • Grade 2: 6% (4/66) vs. 0% (0/66)

Study Intervention/ comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Germany	**Median OS (range):** 19.1 (4 to 41) mos vs 20.9 (3 to 53) mos, p=0.125 **1 year-PFS** 31% vs 21% (estimated from graph) **2 year-PFS** 8% vs 2% (estimated from graph) **Median PFS (range):** 8.8 (2 to 32) mos vs 7.2 (2 to 39) mos, p=0.430 **Mortality, % (n/n):** -1 year: 23% (15/66) vs 15% (10/66) -'at time of evaluation': 59.1% (39/66) vs 69.7% (46/66)		• Grade 3: 0% (0/66) vs. 5% (3/66) **intracranial pressure with decrease in fine motor skills:** • Grade 2: 2% (1/66) (same patient included above for intracranial pressure) vs. 0% (0/66) **generalized seizures** • Grade 2: 2% (1/66) (same patient included above for intracranial pressure) vs. 0% (0/66) • Grade 3: 0% (0/66) vs. 3% (2/66) **persistent visual deficits** • Grade 2: 0% (0/66) vs 5% (3/66) **transient hemiparesis** • Grade 2: 0% (0/66) vs 2% (1/66) **worsening of pre-existing symptoms:** 6% (4/66) (3 grade 2) vs. 17% (11/66) (4 grade 2, 3 grade 3) **Neurocognitive Deficits, % (n/N):** • pre-RT: 30.3% (20/66) vs 42.4% (28/66) • stable: 15.2% (10/66) vs 27.3% (18/66) • worsened: 3% (2/66) vs 6.1% (4/66) • improved: 12.1% (8/66) vs 9.1% (6/66) • new: 9.1% (6/66) vs 3% (2/66) **Sensorimotor Deficits, % (n/N):** • pre-RT: 39.4% (26/66) vs 30.3% (20/66) • stable: 28.8% (19/66) vs 19.7% (13/66) • worsened: 3% (2/66) vs 4.5% (3/66) • improved: 7.6% (5/66) vs 6.1% (4/66)

Study Intervention/ comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			• new: 10.6% (7/66) vs 13.6% (9/66) **Seizures, % (n/N):** • pre-RT: 6.1% (4/66) vs 3% (2/66) • stable: 1.5% (1/66) vs 0% (0/66) • worsened: 0% (0/66) vs 0% (0/66) • improved: 4.5% (3/66) vs 3% (2/66) • new: 1.5% (1/66) vs 6.1% (4/66) **Pseudoprogression, % (n/N):** 8% (4/66) vs 8% (4/66) (all located in the treatment field and adjacent to initial tumor); none required additional corticosteroid therapy) **Radiation Necrosis outside of treatment field, % (n/N):** 0% (0/66) vs 0% (0/66)
Bronk 2018 PBT (n=34) vs IMRT (n=65) Retrospective comparative cohort *Moderately High* USA	NR	NR	**Pseudoprogression, % (n/N):** • Overall: 14.7% (5/34) vs 13.8% (9/65), p=1.0 ○ 21% (3/14) were symptomatic; headaches (n=2) and increase in seizure frequency (n=2) • Oligodendroglioma: 16% (4/25) vs 14.3% (6/42), p=1.0 ○ time to progression: 48 vs. 131 days, p<0.01 • Astrocytoma: (46 p=1.0 ○ time to progression: p>0.05 between groups
Gunther 2017 PBT (n=14) vs. Photon (n=23)	*PBT vs Photon* **1 year-OS** 70% vs 38% (estimated from graph); stable out to 45 months.	NR	*PBT vs Photon* Mucositis during CSI: Radiation Therapy Oncology Group scale Mucositis during SCT: WHO grades

Study Intervention/ comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Retrospective comparative cohort *Moderately High* Germany	**Actuarial 6-month survival after CSI:** 78.6% vs 69.6%, p=0.15 **Disease Status** • **CNS Relapse** (CSF+ for lymphoma cells): 7.1% (1/14) vs 0% (0/23), p=1.0 ○ this patient also had concurrent systemic relapse and died from disease **Mortality**: 46% (17/36) (not reported by group) • graft rejection or failure: 2.8% (1/36) • infection: 11.1% (4/36) • acute respiratory distress syndrome: 2.8% (1/36) • acute graft-versus-host disease: 2.8% (1/36) • recurrent disease: 2.8% (1/36) • liver failure: 2.8% (1/36) • cause not specified: 25% (9/36)		**Toxicity during CSI, % (n/N):** • Any Mucositis: 7% (1/14) vs. 44% (10/23), p=0.03 ○ Grade 0 or unknown: 93% (13/14) vs. 57% (13/23) ○ Grade I: 0% (0/14) vs. 22% (5/23) ○ Grade II: 0% (0/14) vs. 13% (3/23) ○ Grade III: 7% (1/14) vs. 9% (2/23) p=0.10 for comparison of grades • Any Mucositis (patients without total body irradiation): 8% (1/13) vs. 47% (7/15), p=0.04 • Infection: 57% (8/14) vs. 35% (8/23), p=0.31 • Gastrointestinal toxicity: 29% (4/14) vs. 30% (7/23), p=1.0 • Any CNS toxicity: 21% (3/14) vs. 13% (3/23), p=0.65 **Toxicity during and after SCT, % (n/N):** • Any Mucositis: 50% (7/14) vs. 48% (11/23), p=0.90 • Infection: 86% (12/14) vs. 87% (20/23), p=1.0 • Neutropenic fever: 29% (4/14) vs. 57% (13/23), p=0.17 • Gastrointestinal toxicity: 79% (11/14) vs. 70% (16/23), p=0.71 • CNS toxicity: 29% (4/14) vs. 35% (8/23), p=1.0 • Cardiovascular toxicity: 29% (4/14) vs. 30% (7/23), p=1.0 • Pulmonary toxicity: 21% (3/14) vs. 17% (4/23), p=1.0 • Graft-versus-host disease: 43% (6/14) vs. 26% (6/23), p=0.29 **Other complications during and after SCT, % (n/N):**

Study Intervention/ comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			• ICU admission: 26% (9/37) [for hypotension (n=2), diabetic ketoacidosis (n=1), acute respiratory failure (n=5), hyponatremia (n=1)]; p>0.05 for PBT vs. photon (data NR) **Long-term Toxicity, % (n/N):** • Severe neurotoxicity (characterized by diffuse demyelination and necrosis, neurocognitive impairment, lower extremity weakness, incontinence, difficulty swallowing): 7.1% (1/14) vs 0% (0/23), p=0.38
Mozes 2017 Proton (n=27) vs. IMRT (n=16) vs. FRST (n=23) Retrospective comparative cohort *Moderately High* Germany	*Proton vs. IMRT vs. FSRT* **<u>Tumor Volume (TV) (cm^3) outcomes</u>** *Baseline:* • **Mean TV (±SD):** 26.1 ± 22.2 vs. 37.3 ± 29.5 vs. 26.7 ± 23.1 *1-year:* • **Mean TV (±SD):** 23.5 ± 19.8 vs. 34.6 ± 28.0 vs. 20.5 ± 14.3 • **Absolute TV shrinkage (mean change versus baseline ±SD):** -3.7 ± 4.6 vs. -4.3 ± 4.1 vs. -7.0 ± 14.7, p=NS for all comparisons (p=0.001 for change from baseline for proton, p=0.003 for IMRT, p=0.042 for FSRT) • **Relative TV (%, ±SD):** 86.4% ± 15.6 vs. 89.2% ± 24.9 vs. 84.0% ± 22.9 *2-years:* • **Mean TV (±SD):** 24.3 ± 20.7 vs. 23.5 ± 17.5 vs. 13.9 ± 10.0	NR	**NR**

Study Intervention/ comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	• **Absolute TV shrinkage (mean change from initial value ±SD):** NR vs. - 9.0 ± 5.2 vs. -4.7 ± 3.9, p=NS for all comparisons (p=NR for change from baseline for proton, p=0.017 for IMRT, p=0.001 for FSRT) • **Relative TV (%, ±SD):** 86.2% ± 9.2 vs. 69.4% ± 17.7 vs. 77.0% ± 14.6 Only the IMRT and FSRT groups showed significant absolute TV shrinkage after 2 years compared with the 1 year value: -3.4 ± 1.5 (p=0.02) vs. -1.3 ± 1.8 (p=0.04) No significant differences in TV changes between the IMRT and FSRT groups Radiation modality (photon vs. particle) was not a significant independent predictive factor for volumetric response at the two-year follow- up.		

cm = centimeter; CNS = Central Nervous System; COI = Conflict of Interest; CSI = Cranial Spinal Irradiation; CTCAE = Common Terminology Criteria for Adverse Events; F/U = follow-up; FSRT = Fractionated stereotactic radiation therapy; Gy = Gray; IMRT = intensity modulated radiation therapy; IQR = Interquartile Range; KPS = Kranofsky's Performance Status; NR = Not reported; NS = Not statistically significant; OS = Overall Survival; PBT = Proton Beam Therapy; PFS = Progression Free Survival; RBE = Relative Biological Effectiveness; RT -= radiation therapy; SCT = stem cell transplant; SD = Standard Deviation; TV = tumor volume; WHO = World Health Organization

APPENDIX D. Breast

Appendix Table D1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in Breast Cancers

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Bush 2014 Retrospective Case Series *High RoB* USA Funding: NR COI: None declared	**Diagnosis**: Breast Cancer (invasive nonlobular carcinoma) **Indication:** Curative Intent	N=100 Female: 100% Median Age (range): 63 (41 to 83) years **Histology** • ductal: 90% • mucinous: 5% • tubular: 4% • medullary: 1% **Involved breast:** • Right: 48% • Left: 52% **T Status** • T1a: 8% • T1b: 44% • T1c: 34% • T2: 14% **Estrogen Receptor Status** • ER+: 88% • PR+: 70%	PBT followed by chemotherapy (13%) or hormone therapy (78%). **PBT Dose: NR**	**Median F/U (range):** 60 mos (NR)	**OS (95% CI)** • 5-year: 95% (NR) **DFS (95% CI)** • 5-year: 94% (NR) **Tumor Recurrence-Free Survival (95% CI):** 97% (93% to 100%) **Recurrence/Progression, % (n/N)** • Local: 0% (0/100)	**Harms** *Toxicity Grading Criteria:* NR *Acute toxicities:* ≤3 mos *Late toxicities:*>3 mos **Acute Toxicities, % (n/N)** • Grade ≤2: -radiation dermatitis: 62% (62/100) • Grade ≥3: -skin reactions: 0% (0/100) **Late skin reactions, events** • Grade 1: -telangiectasia: 7 events
Cuaron 2015	**Diagnosis** Breast Cancer	N=30	**Uniform scanning PBT**	**Median F/U**	**Recurrence/Progression, % (n/N)**	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Retrospective Case Series *High RoB* USA Funding: NR COI: None declared	**Indication:** Curative Intent	Female: 100% Median Age (range): 49 (29 to 86) years **Histology:** • invasive ductal carcinoma: 90% • invasive lobular carcinoma: 10% **Involved Breast:** • Right: 10% • Left: 90% **Chemotherapy** • neoadjuvant: 43.3% • adjuvant: 46.7% • anthracyclineba sed: 70% • concurrent Herceptin: 13.3% • none: 10% **Surgery**: • lumpectomy: 13.3% • chest wall wide local excision (recurrence): 6.7%	**Median Total Dose: 50.4 Gy(RBE)**	**(range):** 9.3 (2.3 to 18.6) mos **Loss to F/U after 3 mos:** 6.6% (2/30)	• distant (liver) metastases within 12 mos: 3.3% (1/30)	*Acute Toxicities:* Timeframe NR **Acute Toxicities, % (n/N)** • Grade 1: -dermatitis: 25% (7/28) -skin pain: 10.7% (3/28) - fatigue: 46.4% (13/28) -esophagitis: 39.3% (11/28) -lymphedema: 28.6% (8/28) -Reconstructive complications: 3.6% (1/28) -chest wall pain: 3.6% (1/28) • Grade 2 -dermatitis: 71.4% (20/28) -moist desquamation: 28.6% (8/28) -skin pain: 25% (7/28) -fatigue: 3.6% (1/28) -esophagitis: 28.6% (8/28) -chest wall pain: 3.6% (1/28) • Grade 3 -reconstructive complications: 3.6% (1/28)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
		• Mastectomy + implant reconstruction: 46.7% • Mastectomy + autologous reconstruction: 3.3% • Mastectomy no reconstruction: 30%				
Ovalle 2018 Retrospective Case Series *High RoB* USA Funding: Supported in part by Cancer Center Support (Core) Grant CA016672 from the National Institute of Cancer, National Institutes of Health, to The University of Texas MD	**Diagnosis**: Breast Cancer **Indication**: Curative Intent	N=43 Female: 100% Median Age (range): **Histology:** • ductal: 79.1% (others NR) **Stage**: • I: 74.4% (others NR)	Passive scatter PBT PBT Dose: 34 Gy in 10 fractions over 1 week	**Median F/U (range):** ≥6 (NR) mos	NR	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 **Acute Skin Toxicities (grades NR), % (n/N)** • Grades NR: -Faint erythema: 28% -patchy erythema in an area ≤50% of the treated skin: 8% -visible skin reaction within 1 week post-treatment: 74% -visible skin reaction within two to six weeks post-treatment: 93% -dry desquamation: 16% -moist desquamation: 2.3% (1/43) **Late Skin Toxicities (6 mos post-treatment), % (n/N)** • Grades NR: -mild hyperpigmentation in treated skin 6 mos post-treatment: 33% (14/43) -skin thickening at 6 mos post-treatment: 40% (17/43)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Anderson Cancer Center COI: None declared						-seroma/hematoma: 14% (6/43) -fat necrosis: 2.3% (1/43) -retraction/asymmetry of skin: 26% (11/43)
Verma 2017 Retrospective Case Series *High RoB* USA Funding: Authors report no funding received for work. COI: Two authors have minority ownership in a PBT center.	**Diagnosis:** Breast Cancer **Indication**: Curative Intent	N=91 Female: 98% Median Age (range): 54 (25 to 78) years **Histology** • invasive ductal carcinoma: 82% • Invasive lobular carcinoma: 11% • mixed: 6% • other: 1% **Involved Breast** • right: 36% • left: 62% • bilateral: 2% **Chemotherapy Timing:** • adjuvant: 46% • neoadjuvant: 51% • none: 3% **T Status:** • T1: 21% • T2: 38% • T3: 29% • T4: 12%	Uniform scanning PBT or pencil beam scanning; in context of either breast conservation (29%, 27/91) or post-mastectomy (71%, 66/91); patients receiving post-mastectomy PBT also received scar boost (between 9.0 and 19.8 Gy(RBE) Median PBT Dose (range): 50.4 (44.8 to 50.4) Gy(RBE)	**Median F/U (range):** 15.5 (NR) mos	**Recurrence/Progression, % (n/N)** • overall: 13.2% (12/91) • distant: 8.8% (8/91) • local: 2% (2/91) • local and distant: 2% (2/91) • Median Time to Failure (range): 8 mos (NR) **Mortality, % (n/N)** • all-cause: 6.7% (6/91) • due to recurrence: 5.5% (5/91)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: ≤ 3 mos **Acute Toxicities, % (n/N)** • <u>Grade 1:</u> -dermatitis: 23% (21/93) -esophagitis: 31% (28/91) -fatigue: 46% (42/91) -breast/chest wall pain: 50% (47/93) • <u>Grade 2:</u> -dermatitis: 72% (67/93) -esophagitis: 33% (30/91) -fatigue: 15% (5/91) -breast/chest wall pain: 29% (27/93) • <u>Grade 3:</u> -dermatitis: 5% (5/93) -esophagitis: 0% (0/91) -fatigue: 0% (0/91) -breast/chest wall pain: 1% (1/93) • <u>Grades NR</u> -uncomplicated rib fracture: 2.2% (2/91) -clinically evident lymphedema: 3.3% (3/91)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
		N Status • N0: 10% • N1: 54% • N2: 16% • N3: 19% • NX: 1%				

CI = confidence interval; COI = conflict of interest; CTCAE = Common Terminology Criteria for Adverse Events; DFS = disease free survival; F/U = follow-up; Gy = Gray (unit); Gy(RBE) = Gray (Relative Biological Equivalent); mos = months; NR = not reported; OS = overall survival; PBT = proton beam therapy; RoB = risk of bias;

Appendix Table D2. Study characteristics, patient demographics and detailed data abstraction: Nonrandomized Comparative Studies of Proton Beam Therapy in Breast Cancers

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Chowdhary 2019 Retrospective comparative database (NCDB) study The NCDB 2015 Participant User File for breast cancer was obtained for this analysis, which	724,492	All patients underwent surgery followed by radiation **PBT (n=871)** Median dose: 60 Gy **Photon RT or Photon RT + electron boost (n=723,621)** Median dose: 60.4 Gy	**Inclusion**: stage 0–III breast patients undergoing surgery and post-operative radiotherapy; Patients receiving EBRT to the breast and regional lymph nodes were. **Exclusion**: Patients with metastatic disease at diagnosis; patients without survival outcomes; patients not undergoing surgery or RT; patients receiving RT to a site other than breast, any RT prior to	*PBT vs. Photon RT* Median age: 59 vs. 60 years % Male: 0.6% Race - White: 84.6% vs. 83.8% - Black: 6.4% vs. 11.1% - Other: 5.1% vs. 9% Stage - 0: 13.5% vs. 10.1% - I: 44.8% vs. 46.2% vs - II: 23% vs. 27.3% - III: 15.2% vs. 12.8% - Unknown: 3.6% vs. 3.6%	**Median F/U (range):** 74.6 (NR) vs. 62.2 (NR) months, p<0.001 **% F/U:** NR	Overall Survival	Funding: None COI: None

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
included patients diagnosed between 2004 and 2014. *Moderately High* USA		Treatment Intent: Curative	surgery, an RT dose <39 or >70G y, or non-EBRT modalities.	Charlson-Deyo comorbidity score - 0: 90.7% vs. 86.4% - 1: 7% vs. 11.5% - ≥2: 2.3% vs. 2.2% Laterality - Right: 45.9% vs. 49.5% - Left: 54.1% vs. 50.5% Chemotherapy (yes): 42.9% vs. 45.7% Endocrine therapy (yes): 63.9% vs. 68.9% Surgery (all patients had some form of surgery) - Breast-conserving surgery: 76.6% vs. 79.9% - Mastectomy: 23.3% vs. 20% - Not specified: 0.1% vs. 0.1% Lymph node irradiation (yes): 23.7% vs. 22.2%			
Teichman 2018 [PBT patients are primarily drawn from Bush 2014 (case series)]	129	**Partial Breast Proton Therapy (PBPT) (n=72)** Dose: 40 CGE in 10 daily fractions **Whole Breast Irradiation (WBI) with x-rays (n=57)**	**Inclusions:** Patients with a first diagnosis of early stage (stage 0 to 2) breast cancer treated at Loma Linda University Medical Center from 2003 to 2012 and received breast-conservation therapy (usually lumpectomy)	PBPT vs. WBI Median Age (range) (at time of survey, not diagnosis): 72.5 (53 to 94) vs. 70 (46 to 86) Race/Ethnicity Caucasian: 83.3% vs. 61.4%	**Median F/U (range):** 84 vs. 72 months **Mean F/U**: 89.28 vs. 74.76 months, p=0.006	Cosmesis (Harvard scale) score(scale 0-4, higher scores=better outcomes) Breast Cancer Treatment	Funding: This work was supported by the James M Slater Endowment for Proton Therapy Research.

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Retrospective Comparative Cohort Moderately High USA		Dose: 50 Gy to entire breast + 10 Gy boost to the tumor bed	followed by partial breast proton therapy or whole breast irradiation; disease-free survivors >5 years postdiagnosis; >age 40 at diagnosis; no chemotherapy (hormonal therapy permitted); tumor size ≤3 cm. **Exclusion**: NR	African American: 4.2% vs. 3.5% Hispanic: 8.3% vs. 17.5% Asian: 4.2% vs. 15.8% Native American: 0% vs. 1.8% [The ratio of Caucasian to non-Caucasian patients was higher in the PBPT group (p=0.015)] Involved Breast Left: 56.9% vs. 50.9% Right: 43.1% vs. 49.1% Stage 0: 20.8% vs. 21.1% I: 66.7% vs. 66.7% II: 12.5% vs. 12.3% Median Tumor Size (range): 1.37 (<0.01 to 3.0) vs. 1.24 (0.02 to 2.8) cm Surgery Lymph node surgery: 97.2% vs. 96.5% Re-excision: 25% vs. 24.5% Wider margins, initial treatment: 4.2% vs. 5.3% Oncoplasty/Mammoplasty: 4.2% vs. 0% Endocrine therapy	**F/U %:** 6.5% (9/138)	Outcome Scale score (scale 0-4, higher scores=better outcomes) Brief fatigue inventory score Severity of fatigue score Medical Outcomes Study Short Form 20 item Health Survey score Body Image scale score	COI: This work was supported by the James M Slater Endowment for Proton Therapy Research.

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
				Currently taking: 4.2% vs. 10.5% Past: 51.3 % vs. 59.6%			

COI: conflict of interest; EBRT = External Beam Radiation Therapy; F/U = Follow-up; NR = Not reported; PBT = Proton Beam Therapy; QOL = Quality of Life; ROB = Risk of Bias; RT = Radiation Therapy

Appendix Table D3. Detailed data abstraction: nonrandomized comparative studies of proton beam therapy in breast cancers

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Chowdhary 2019 N=724,492 Retrospective database comparative study (National Cancer Data Base) Moderately High USA	*PBT vs. Photon RT* 5-year Overall Survival (95% CI) 91.9% (NR) vs. 88.9% (NR), p<0.001 (unadjusted); adj. HR* 0.85 (0.68 to 1.07), p=0.168 In a second multivariate analysis, PBT, relative to proton/electron boost therapy, was not significant for OS within any of the stratified subsets: **Laterality** • Left-sided: adj. HR 0.78 (95% CI 0.57–1.08), p=0.14 • Right-sided: adj. HR 0.93 (95% CI 0.68–1.28), p=0.67	NR	NR

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	Quadrant • Inner: adj. HR 0.60 (95% CI 0.28–1.25), p=0.17 • Outer: adj. HR 0.48 (95% CI 0.15–1.48), p=0.20 **Type of surgery** • Mastectomy: adj. HR 0.79 (95% CI 0.60–1.04), p=0.10 • Breast conservation: adj. HR 1.03 (95% CI 0.69–1.54), p=0.89 **Nodal status** • Positive: adj. HR 1.07 (95% CI 0.77–1.50), p=0.68 • Negative: adj. HR 0.75 (95% CI 0.55–1.02), p=0.07 **N2-N3 status** • Positive: adj. HR 1.04 (95% CI 0.65–1.65), p=0.88 • Negative: adj. HR 0.81 (95% CI 0.63–1.05), p=0.12 **Type of radiation** • Breast and lymph nodes: adj. HR 0.94 (95% CI 0.61–1.44), p=0.77 • Breast only: adj. HR 0.82 (95% CI 0.63–1.07), p=0.14		
Teichman 2018 Partial Breast Proton Therapy (PBPT) (n=72) vs. Whole Breast Irradiation (WBI) with x-rays (n=57)	NR	**Mean (SD) Cosmesis (Harvard scale) score** 3.4 (0.75) vs. 2.44 (0.96), p<0.001 **Mean Breast Cancer Treatment Outcome Scale scores** - Cosmetic: 1.45 vs. 1.88, p<0.001	NR

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
[Includes patients from Bush 2014 Case Series] Retrospective Comparative Cohort Moderately High USA		- Breast Specific Pain: 1.42 vs. 1.25, p=0.005 - Edema: 1.07 vs. 1.12, p=0.526 - Functionality: 1.11 vs. 1.17, p=0.311 **Mean Brief fatigue inventory score** 15.3 (17.11) vs. 27.25 (22.26), p<0.002 **Proportion of patients feeling unusually tired or fatigued in the last week (question 1 on the Brief Fatigue Inventory questionnaire which is not calculated into the overall score)** 25.4% (18/71) vs. 62.7% (32/51), p<0.001 **Medical Outcomes Study Short Form 20 item Health Survey score** Of the 20 questions, significant differences were seen in six. **Mean Body Image scale score** 12.04 (3.75) vs. 13.91 (5.25), p<0.03 **Upper arm/mobility issues**: 1.19 vs. 1.30, p=0.348	

Adj. = adjusted; CI = Confidence interval; COI: conflict of interest; HR = Hazard ratio; NR = Not reported; PBT = Proton Beam Therapy; ROB = Risk of Bias; RT = Radiation Therapy
*Race, Charlson-Deyo comorbidity score, facility (academic vs. nonacademic), household income, regional location, residence (urban vs. rural), laterality, pT-stage, pN-stage, receptor status, receipt of chemotherapy, receipt of endocrine therapy, type of surgery, and year of diagnosis.

APPENDIX E. Esophageal

Appendix Table E1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in esophageal cancers

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Ishikawa 2015 Retrospective Case Series *High RoB* Japan Funding: supported by Grants-in-Aid for scientific research from the Ministry of Education, Culture, Sports, Science, and Technology (24591832) of Japan COI: none declared	**Diagnosis**: Esophageal Cancer **Indication:** curative intent	N=40 Male: 95% Median Age (range): 69 (52 to 79) years **Tumor Location** • cervical esophagus 5% • upper thoracic esophagus: 25% • middle • Thoracic esophagus: 52.5% • lower thoracic esophagus: 17.5% **T Status** • T1: 40% • T2: 22% • T3: 18% • T4: 10% **N Status** • N0: 47% • N1: 28% • N2: 18% • N3: 7%	PBT with concurrent chemotherapy; boost dose when residual tumors suspected PBT Total Dose: 60 GyE in 30 fractions PBT Boost Dose: 4 to 10 GyE	**Median F/U (range):** 24 (7 to 66) mos	**OS (95% CI)** • 2-year: 75.1% (59.6% to 90.6%) • 3-year: 70.4% (53.4% to 87.4%) **Disease Specific Survival (95% CI):** • 2-year: 77% (62.1% to 92.7%) **Disease-Specific Survival (Stage I to II patients) (n=25)** • 2-year: 100% **Disease-Specific Survival (Stage III patients) (n=15)** • 2-year: 30.1%, **p<0.001 (compared to Stage I to II disease)** **Locoregional Control (95% CI)** • 2-year: 66.4% (50.4 to 82.4%) **Tumor Response:** • CR: 75% (30/40) • PR: 20% (8/40) **Recurrence/Progression, % (n/N):**	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities:* ≤3 mos *Late Toxicities*: <3 mos **Acute Hematological toxicities, % (n/N):** • Grade 3: -any: 20% (8/40) • Grade 4: -any: 5% (2/40) **Acute Non-hematological Toxicities, % (n/N):** • Grade 1: -Bone Marrow: 17% (1/40) -Esophagus: 25% (10/40) -Treatment-related Skin Toxicities: 67% (27/40) • Grade 2: -Bone Marrow: 58% (23/40) -Esophagus: 53% (21/40) -Treatment-related Skin Toxicities: 28% (11/40) • Grade 3: -Bone Marrow: 20% (8/40) -Esophagitis: 22% (9/40) -Dermatitis: 5% (2/40) -Encephalopathy : 2.5% (1/40) • Grade 4: -Bone Marrow: 5% (2/40) -Esophagus: 0% (0/40) -Treatment-related Skin Toxicities: 0% (0/40)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
		Stage • I: 40% • II: 22% • III: 38%			• overall: 40% (16/40) • local: 20% (8/40) • lymph nodes: 10% (4/40) • local and lymph nodes: 2.5% (1/40) • distant: 7.5% (3/40) **Mortality, % (n/N)** • all-cause: 22.5% (9/40) • due to progression: 20% (8/40) • intercurrent disease without recurrence: 2.5% (1/40)	**Late Toxicities, % (n/N)** • Grade 1 -Heart: 92% (37/40) -Lung: 98% (39/40) -Esophagus: 85% (34/40) • Grade 2 -Heart: 8% (3/40) -Lung: 2% (1/40) - Esophagus: 10% (4/40) • Grade 3: -Heart: 0% (0/40) - Lung: 0% (0/40) - Esophagus: 5% (2/40) • Grade 4: -Heart: 0% (0/40) -Lung: 0% (0/40) -Esophagus: 0% (0/40) • Grade NR: -asymptomatic pleural effusion: 2.5% (1/40) -asymptomatic pericardial effusion: 7.5% (3/40) -esophageal stricture: 2.5% (1/40) -esophageal ulcer: 2.5% (1/40)
Takada 2016 Retrospective Case Series *High RoB* Japan Funding: authors report no specific funding	**Diagnosis:** Esophageal Cancer **Indication:** curative intent	N=47 Male: 78.7% Median Age (range): 63 (47 to 77) years **Histology:** • squamous cell carcinoma: 97.9%	PBT with Chemotherapy, X-Ray Therapy Median Total Dose (Range): 73.4 (64.6 to 80.0) Gy Median X-Ray Dose (range): 36 (12.6 to 40) Gy	**Median F/U (range):** 29 (5 to 63) mos	**OS (95% CI)** • 3-year: 59.2% (45.7% to 76.8%) **PFS (95% CI)** • 3-year: 56.3% (43.0% to 73.7%) **Local Control (95% CI)** • 3-year: 67.7% (54.9% to 83.6%)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities:* NR *Late Toxicities*: NR **Acute Hematological Toxicities, % (n/N):** • Grade ≥3: -leukopenia: 55.3% (26/47) -Neutropenia: 44.7% (21/47) -Anemia: 4.3% (2/47) -Thrombocytopenia: 27.7% (13/47)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
received for this work. COI: none declared		• adenocarcinoma: 2.1% **Tumor Location** • upper thoracic: 21.3% • middle thoracic: 40.4% • lower thoracic: 36.2% • abdominal esophagus: 2.1% **ECOG Status** • 0: 12.8% • 1: 83% • 2: 4.3% **Stage:** • IA: 21.3% • IB: 0% • IIA: 6.4% • IIB: 19.1% • IIIA: 31.9% • IIIB: 2.1% • IIIC: 19.1%	Medan PBT Dose (range): 37.4 (28.6 to 63.8) GyE		**Mortality, % (n/N):** • all-cause: 36.2% (17/47) • treatment-related: 4.3% (2/47)	**Acute Non-Hematological Toxicities, % (n/N):** • Grade ≥3: -Nausea and vomiting: 2.1% (1/47) -esophagitis: 10.6% (5/47) -pneumonitis: 0% (0/47) **Late Toxicities, % (n/N):** • Grade 2: -Pericarditis: 0% (0/47) -Pericardial Effusion: 19.1% (9/47) -Pleural Effusion: 2.1% (1/47) -pneumonitis: 2.1% (1/47) -Esophageal Stenosis: 2.1% (1/47) -Esophageal Fistula: 0% (0/47) • Grade 3: -Pericarditis: 0% (0/47) -Pericardial Effusion: 0% (0/47) -Pleural effusion: 0% (0/47) -pneumonitis: 2.1% (1/47) -Esophageal Stenosis: 4.3% (2/47) -Esophageal Fistula: 2.1% (1/47) • Grade 4: -Pericarditis: 0% (0/47) -Pleural effusion: 0% (0/47) -Pericardial Effusion: 0% (0/47 -Pericardial effusion: 0% (0/47) -pneumonitis: 0% (0/47) -Esophageal Stenosis: 0% (0/47) -Esophageal Fistula: 0% (0/47)

CI = confidence interval; COI = conflict of interest; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; F/U = follow-up; Gy = Gray (unit); GyE = Gray Equivalent; mos = months; NR = not reported; OS = overall survival; PBT = proton beam therapy; PFS = progression free survival; PR = partial response; RoB = risk of bias

Appendix Table E2. Study characteristics and patient demographics: nonrandomized comparative studies of proton beam therapy in esophageal cancers

Study Intervention/ Comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Cohort studies							
Fang 2018 Retrospective matched-pair cohort *Moderately High* USA Same cacner center as Shiriashi but different indications	448, 220 (propensity matched)	Chemotherapy and radiation **(PBT** or **IMRT)** with (29%) or without (71%) induction chemotherapy, without surgical treatment: **PBT (n = 110):** 50.4 Gy (or cobalt gray equivalent) in 28 fractions (92%). A smaller group was treated to 45 Gy in 25 fractions (6.5%). **IMRT (n = 110):** 50.4 Gy (or cobalt gray equivalent) in 28 fractions (92%). A smaller group was treated to 45 Gy in 25 fractions (6.5%).	**Inclusion:** esophageal cancer treated **nonsurgically** with chemotherapy and radiation; treated between March 2004 and June 2016. **Exclusion:** early, distant metastatic disease within 1 month of completing radiation; patients with cervical tumor location or tumor histology other than squamous cell or adenocarcinoma	PBT vs. IMRT Median age (range): 70 (41 to 86) vs. 69 (44 to 84) years Male %: 94% vs. 77% Stage: • I: 3.6% vs. 5.5% • IIA: 31.8% vs. 30.9% • IIB: 3.6% vs. 3.6% • III: 58.2% vs. 56.4% • IVA: 2.7% vs. 3.6% KPS score • 70: 9% vs. 10% • 80-100: 91% vs. 90% Tumor location in esophagus • upper and middle: 23.6% vs. 23.6% • lower: 76.4% vs. 76.4% Histology • adenocarcinoma: 71.8% vs. 76.4% • squamous cell: 28.2% vs. 23.6% Induction Chemotherapy: 27.3% vs. 28.2%	**Median F/U from end of RT:** 55 months (95% CI, 48 to 64); for all 448 patients (NR for matched group) **% F/U:** 49.1% (220/448)	Overall survival (OS) Disease-free survival (DFS) Locoregional relapse-free survival (LRRFS) Lymphopenia	Funding: statistical analysis was supported in part by a Cancer Center Support Grant (National Cancer Institute Grant P30 CA016672) COI: None relevant to this article. Several report consultantship, grants, and/or honorarium from various companies, outside the scope of the work. Notes:

Study Intervention/ Comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		• Patients were paired by propensity score matching into 110 pairs (out of 448 total eligible), variables included: age, PTV, clinical stage, KPS, tumor location, and treatment with induction chemotherapy					
Lin 2017 Retrospective comparative cohort *Moderately High* USA	1224 eligible, 580 propensity matched	Neoadjuvant concurrent chemo-radiotherapy and surgical resection (84% esophagectomy) with either: **PBT (n = 111):** Mean Lung Dose (SD): 6.1 (2.6) Gy Mean Heart Dose (SD): 13.2 (5.2) Gy **3D-CRT (n = 214):**	**Inclusion:** non-metastatic esophageal cancer, treated with neoadjuvant concurrent CRT and surgical resection **Exclusion:** patients treated with upfront surgery (without nCRT) or who underwent salvage esophagectomy	PBT vs. 3D-CRT vs. IMRT Age • >65 years: 32% vs. 36% vs. 26% • ≤65 years: 68% vs. 64% vs. 74% Male %: 89% vs. 82% vs. 87% ECOG Performance Status: • Score 0: 99% vs. 98% vs. 95% • Score 1: 1% vs. 2% vs. 5% Baseline FDG PET (Yes): 99% vs. 99% vs. 99% Mean tumor length (SD): 5.3 (2.4) vs. 5.2 (2.5) vs. 5.2 (2.5) Tumor Location	**Median F/U, radiographic (range):** NR vs. NR vs. NR **% F/U:** 47.4% (580/1224)	Mortality Postoperative Complications	Funding: provided in part by The University of Texas MD Anderson Cancer Center and by the National Cancer Institute Cancer Center Support Grant CA016672. COI: Two authors have had consulting and/or

Study Intervention/ Comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		Mean Lung Dose (SD): 10.5 (3.9) Gy Mean Heart Dose (SD): 28.4 (7.4) Gy **IMRT (n = 255):** Mean Lung Dose (SD): 9.5 (3.2) Gy Mean Heart Dose (SD): 22.4 (6.7) Gy • Radiation doses for lung and heart were statistically significantly different between modalities and as a whole (p<0.0001)		• Upper/middle: 1.8% vs. 11.7% vs. 5.5%; PBT vs. 3D-CRT, **p<0.004** • Lower/GEJ/cardia: 98.2% vs. 88.3% vs. 94.5% Histology • AC: 96% vs. 90% vs. 94% • SCC: 5% vs. 10% vs. 6% Clinical Stage: • 1 or 2: 36% vs. 37% vs. 36.% • 3 or 4: 64% vs. 63% vs. 64% Induction Chemotherapy (Yes): 39% vs. 4% vs. 35%; PBT vs. 3D-CRT, **p<0.001** History of HTN (Yes): 61% vs. 49% vs. 49%; PBT vs. 3D-CRT **(p=0.049)** and vs. IMRT **(p=0.041)** History of CAD (Yes): 9% vs. 15% vs. 13% Smoking at diagnosis (Yes): 18% vs. 29% vs. 24%; PBT vs. 3D-CRT, **p=0.035**			leadership roles, and/or received research and/or honorarium from various industry organizations.
Makishima 2015 Retrospective comparative cohort	44	**PBT (n = 25):** Passive scatter PBT; Median Radiation Dose: 60 (range, 60–70) GyE **XRT (n = 19):**	**Inclusion:** patients undergoing definitive concurrent chemoradiotherapy **Exclusion:** NR	PBT vs. XRT Age: NR Male %: NR Tumor Location • Cervical: 12% vs. 37% • Thoracic: 88% vs. 63% • Abdominal: 0% vs. 0%	PBT vs. XRT **Median F/U:** 24 (± 4.7) vs. 20 (± 5.1) months	Mortality Harms	Funding: supported by the Ministry of Education, Science, Sports and Culture of Japan [Scientific

Study Intervention/ Comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Moderately High Japan		Median Radiation Dose: 60 Gy • All patients received concurrent chemotherapy		Stage (UICC 7th) • 0: 4% vs. 0% • IA: 28% vs. 21% • IB: 12% vs. 0% • IIA: 4% vs. 0% • IIB: 16% vs. 5% • IIIA: 12% vs. 21% • IIIB: 4% vs. 21% • IIIC: 20% vs. 32%			Research (B) (24390286), Challenging Exploratory Research (24659556), Young Scientists (B) (25861064) and Scientific Research (C) (24591832)]. Funding to pay the Open Access publication charges for this article was provided by Grants-in-Aids for scientific research from the Ministry of Education, Culture, Sports, Science, and Technology (24390286, 24591832). COI: NR

Study Intervention/ Comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
							Notes:
Shiraishi 2018 Retrospective matched pair cohort *Moderately High* USA	480 eligible, 272 propensity matched	Chemotherapy and RT **(PBT** or **IMRT)** with (36%) or without (64%) induction chemotherapy, followed by surgical resection: **PBT (n=136)** Median Radiation Dose (range): 50.4 Gy at 1.8 Gy per fraction **IMRT (n=136)** Median Radiation Dose (range): 50.4 Gy at 1.8 Gy per fraction • Patients were propensity matched in 136 pairs according to similar characteristics (from 480 total eligible)	**Inclusion:** patients with no distant metastases at presentation, treated with preoperative concurrent CRT using PBT or IMRT with or without induction chemotherapy followed by surgery; treated between March 2005 and March 2016 **Exclusion: NR**	*PBT vs. IMRT* Median Age (range): 63 (26 to 76) years vs. 60 (26 to 82) years Male %: 90% vs. 87% Stage: • I: 2% vs. 1% • IIA: 28% vs. 36% • IIB: 5% vs. 3% • III: 60% vs. 58% • IVA: 4% vs. 2% Tumor Location: • upper-middle: 4% vs. 3% • lower: 96% vs. 97% Induction Chemotherapy: • Yes: 35% vs. 37% Histology: • AC: 96% vs. 98% • SCC: 4% vs. 2%	NR **% F/U:** 56.6% (272/480)	Acute Lymphopenia	Funding: supported in part by the Cancer Center Support Grant (NCI Grant P30 CA016672). COI: NR

Study Intervention/ Comparator, Design, RoB, Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Xi 2017 Retrospective comparative cohort *Moderately High* USA	343 eligible and included	**PBT (n = 132):** Median Radiation Dose (range): 50.4 (45.0 to 66.0) Gy **IMRT (n = 211):** Median Radiation Dose: 50.4 (41.4 to 66.0) Gy • patients generally received concurrent chemotherapy	**Inclusion:** patients w/ biopsy-confirmed thoracic esophageal adenocarcinoma or squamous cell carcinoma; treated between January 2007 and June 2014 **Exclusion:** M1 disease, did not have baseline positron emission tomography/computed tomography (PET/CT), had prior or concomitant malignancy, received adjuvant chemotherapy, received surgery within 6 months after CRT, or had incomplete clinical records	PBT vs. IMRT Age • >67 years: 30% vs. 62% • ≤67 years: 71% vs. 38% **p<0.001** Male %: 82% vs. 79% Smoking History (Yes): 74% vs. 72% Alcohol History (Yes): 61% vs. 59% ECOG Performance Status • 0: 25% vs. 27% • 1-2: 75% vs. 73% Weight Loss • <10%: 80% vs. 73% • ≥10%: 20% vs. 27% Histology: • AC: 68% vs. 74% • SCC: 32% vs. 27% Tumor Location • upper/middle: 29% vs. 27% • distal/GEJ: 71% vs. 73% Clinical TNM stage: • I/II: 36% vs.33% • III: 64% vs. 67% Induction Chemotherapy (Yes): 29% vs. 28% Salvage surgery (Yes): 8% vs. 13%	PBT vs. IMRT **Median F/U for survivors, (95%CI):** 44.8 (11.9 to 110.3) mos vs. 65.1 (19.4 to 115.3) mos **% F/U:** 100%	Survival Recurrence Harms	Funding: funded in part by The Mabuchi Research Fund and The University of Texas MD Anderson Cancer Center and by National Cancer Institute Cancer Center Support Grant CA016672. COI: One author has received research funding/honoraria from and served as a consultant for various industry organizations.

AC: adenocarcinoma; ECOG: Eastern Cooperative Oncology Group; GEJ: gastro-esophageal junction; PBT: proton beam therapy; PET: positron emission tomography; SCC: squamous cell carcinoma; SD: standard deviation.

Appendix Table E3. Detailed data abstraction: nonrandomized comparative studies of proton beam therapy in esophageal cancers

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Cohort studies			
Fang 2018 PBT (n=110) vs. IMRT (n=110) Retrospective matched-pair cohort *Moderately High* USA ---	PBT vs. IMRT **OS (95% CI)** *All patients in matched cohort* • Univariate analysis: HR 0.82 (0.56 to 1.20) p=0.3 [IMRT as referent] • Multivariate analysis: NR for all patients *Patients with stage III to IVA Disease* [all estimated from figure] • 1-year: 80% vs. 78% • 2-year: 66% vs. 49% • 3-year: 48% vs. 38% • 4-year: 42% vs. 30% • 5-year: 42% vs. 19% • Univariate analysis: HR 1.52 (0.96 to 2.41) p=0.08 [IMRT as referent] • Multivariate Analysis: adj. HR 1.48 (0.93 to 2.35) p=0.10 [IMRT as referent; adjusted for log (PTV)] **Disease Free Survival** *Patients with stage III to IVA Disease* [all estimated from figure]	**NR**	*PBT vs. IMRT* Criteria: CTCEA v. 4.0 **Acute Lymphopenia during radiation therapy, % (n/N)** • Grades 0 to 3: 69% (76/110) vs. 52.7% (58/110) • Grade 4: 31% (34/110) vs. 47% (52/110) • Univariate analysis: OR 2.13 (1.19 to 3.82); p=0.01 [PBT as the referent] • Univariate analysis: OR 0.5 (0.29 to 0.87) p=0.01 [IMRT as the referent] • Multivariate analysis: adj. OR 0.47 (0.26 to 0.84) p =0.01 [IMRT as the referent; adjustments are not defined]

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms

	• 1-year: 55% vs. 45%
	• 2-year: 45% vs. 26%
	• 3-year: 41% vs. 23%
	• 4-year: 41% vs. 23%
	• 5-year: 41% vs. 18%
	  • Univariate analysis: HR 1.50 (0.98 to 2.31) p=0.06 [IMRT as the referent]
	  • Multivariate analysis: adj. HR 1.42 (0.92 to 2.19) p=0.11 [IMRT as the referent; adjusting for log (PTV) and lymphocyte count reduction]
	
	Local-Regional Recurrence Free Survival
	Treatment modality (IMRT or PBT) was not significantly associated with LRRFS		

Lin 2017
 	
PBT (n=111) vs. 3D-CRT (n=214) vs. IMRT (n=255)
 	
Retrospective comparative cohort
 	
Moderately High
 	
USA
--- 	
	PBT vs. 3D-CRT vs. IMRT
	
	Mortality
	• 30 days postop: 0% (0/111) vs. 1.9% (4/214) vs. 1.2% (3/255); Chi Squared p-value: p=0.425
	• 60 days postop: 0.9% (1/111) vs. 2.3% (5/214) vs. 2.7% (7/255); Chi Squared p-value: p=0.590
	• 90 days postop: 0.9% (1/111) vs. 4.2% (9/214) vs. 4.3% (11/255); Chi Squared p-value: p=0.264 (clinically meaningful difference between PBT vs. other groups according to authors)
		NR	*PBT vs. 3D-CRT vs. IMRT*
			
			<u>Postoperative Complications, % (n/N)</u>
			• **Pulmonary:** 16.2% (18/111) vs. 39.5% (85/214) vs. 24.2% (62/255); Chi Squared p-value: <0.001
			  ○ *PBT vs. 3D-CRT*: adj. OR 0.34 (95% CI 0.19 to 0.61), p<0.001
			  ○ *PBT vs. IMRT*: adj. OR 0.58 (95% CI 0.32 to 1.05), p=0.08
			• **Cardiac:** 11.7% (13/111) vs. 27.4% (59/214) vs. 11.7% (30/255); Chi Squared p-value: p<0.001
			  ○ *PBT vs. 3D-CRT*: adj. OR 0.34 (95% CI 0.17 to 0.66), p=0.002
			  ○ *PBT vs. IMRT*: adj. OR 0.87 (95% CI 0.42 to 1.77), p=0.70

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			• **Wound:** 4.5% (5/111) vs. 15.3% (33/214) vs. 14.1% (36/255); Chi Squared p-value: p=0.014 ○ *PBT vs. 3D-CRT*: adj. OR 0.26 (95% CI 0.10 to 0.68), p=0.006 ○ *PBT vs. IMRT*: adj. OR 0.28 (95% CI 0.11 to 0.73), p=0.009 • **Gastrointestinal:** 18.9% (21/111) vs. 20.9% (45/214) vs. 23.0% (59/255); Chi Squared p-value: 0.656 <u>Readmission within 60 days or death during same hospitalization, % (n/N)</u>: 17.1% (19/111) vs. 23.7% (51/214) vs. 15.6% (40/255); Chi Squared p-value: p=0.070 <u>Mean Length of Hospital Stay, Days (95% CI)</u> 9.3 (8.2 to 10.3) vs. 13.2 (11.7 to 14.7) vs. 11.8 (10.9 to 12.7); Chi Squared p-value: p<0.001
Makishima 2015 PBT (n = 25) vs. XRT (n = 19) Retrospective comparative cohort *Moderately High* Japan	*PBT vs. XRT* **Mortality (mean 24 vs. 20 month f/u):** 20% (5/25) vs. 31.6% (6/19)	NR	*PBT vs. XRT* **Cardiopulmonary "Late" (not defined) adverse effects (CTCAE criteria)** **All pulmonary events grade ≥2**: 0% (0/25) vs. 42.1% (8/19) <u>Pharmacological pneumonitis, % (n/N)</u> • Grade 0-1: 100% (25/25) vs. 94.7% (18/19) • Grade 2: 0% (0/25) vs. 0% (0/19) • Grade 3: 0% (0/25) vs. 0% (0/19) • Grade 4: 0% (0/25) vs. 0% (0/19) • Grade 5: 0% (0/25) vs. 5.3% (1/19)

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			Lung infection, % (n/N): • Grade 0-1: 100% (25/25) vs. 94.7% (18/19) • Grade 2: 0% (0/25) vs. 0% (0/19) • Grade 3: 0% (0/25) vs. 0% (0/19) • Grade 4: 0% (0/25) vs. 0% (0/19) • Grade 5: 0% (0/25) vs. 5.3% (1/19) Radiation pneumonitis, % (n/N) • Grade 0-1: 100% (25/25) vs. 78.9% (15/19) • Grade 2: 0% (0/25) vs. 15.8% (3/19) • Grade 3: 0% (0/25) vs. 5.3% (1/19) • Grade 4: 0% (0/25) vs. 0% (0/19) • Grade 5: 0% (0/25) vs. 0% (0/19) Pulmonary effusion, % (n/N) • Grade 0-1: 100% (25/25) vs. 89.5% (17/19) • Grade 2: 0% (0/25) vs. 5.3% (1/19) • Grade 3: 0% (0/25) vs. 5.3% (1/19) • Grade 4: 0% (0/25) vs. 0% (0/19) • Grade 5: 0% (0/25) vs. 0% (0/19) **All cardiac events (i.e., pericardial effusion) grade ≥2:** 4% (1/25) vs. 52.6% (10/19) Pericardial effusion, % (n/N) • Grade 0-1: 96% (24/25) vs. 47.4% (9/19) • Grade 2: 4% (1/25) vs. 52.6% (10/19) • Grade 3: 0% (0/25) vs. 0% (0/19) • Grade 4: 0% (0/25) vs. 0% (0/19) • Grade 5: 0% (0/25) vs. 0% (0/19)

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Shiraishi 2018 PBT (n=136) vs. IMRT (n=136) Retrospective matched pair cohort *Moderately High* USA --- Authors also report HRs for each group related to overall survival, and ORs for each group related to rate of grade IV lymphopenia	NR	NR	*PBT vs. IMRT* Criteria: NR **Acute Lymphopenia during neoadjuvant chemoradiation therapy % (n/N)** • Grades 0 to 3: 82.4% (112/136) vs. 59.6% (81/136) • Grade 4: 17.6% (24/136) vs. 40.4% (55/136); OR 0.32 (95% CI 0.18 to 0.55), p=0.0001; adj OR 0.29 (95% CI 0.16 to 0.52), p<0.0001
Xi 2017 PBT (n = 132) vs. IMRT (n = 211) Retrospective comparative cohort *Moderately High* USA --- Also has separate OS, PFS, LRFFS, and DMFS for early	*PBT vs. IMRT* **1-4 year OS (estimated from graph):** 1 year: 88% vs. 85% 2 year: 70% vs. 50% 3 year: 55% vs. 39% 4 year: 44% vs. 35% **5 Year-OS:** 41.6% vs. 31.6%, p=0.011; adj. HR 1.45 (95% CI 1.09-1.94), p=0.010 -In patients without early distant recurrences (n=266): p=0.019 (favors PBT)	*PBT vs. IMRT* Patients with Locoregional Recurrence only who went on to receive salvage surgery, % (n/N): 33% (9/27) vs. 34% (17/50), p=0.953	*PBT vs. IMRT* **Treatment-Related Toxicities (criteria: CTCEA v.3.0)** **Grade 3 or 4 (overall):** 37.9% (50/132) vs. 45.0% (95/211); p=0.19 **Grade 5 (overall):** 0.8% (1/132) vs. 1.9% (4/211), p=0.65 Fatigue, % (n/N) • Grade 1: 27.3% (36/132) vs. 21.8% (46/211) • Grade 2: 28.8 (38/132) vs. 31.8% (67/211) • Grade 3: 3.8% (5/132) vs. 4.3% (9/211)

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
distant recurrences by modality.	-In patients without induction chemotherapy (n=246): p=0.041 (favors PBT) **1-4 year PFS (estimated from graph):** 1 year: 62% vs. 50% 2 year: 50% vs. 33% 3 year: 42% vs. 28% 4 year: 39% vs. 24% **5 Year-PFS:** 34.9% vs. 20.4%, p=0.001; adj. HR 1.56 (95% CI 1.19-2.05), p=0.001 -In patients without early distant recurrences (n=266): p=0.002 (favors PBT) -In patients without induction chemotherapy (n=246): p=0.012 (favors PBT) **1-4 year Distant metastasis free survival (estimated from graph):** 1 year: 78% vs. 69% 2 year: 69% vs. 57% 3 year: 69% vs. 55% 4 year: 65% vs. 51% **5 Year-Distant Metastasis Free Survival:** 64.9% vs. 49.6%, p=0.031 -In patients without early distant recurrences (n=266): p=0.023 (favors PBT) -In patients without induction chemotherapy (n=246): p=0.025 (favors PBT)		• Grade 4: 0% (0/132) vs. 0% (0/211) • Grade 5: 0% (0/132) vs. 0% (0/211) <u>Weight loss, % (n/N)</u> • Grade 1: 47.7% (63/132) vs. 45.5% (96/211) • Grade 2: 10.6 (14/132) vs. 10.4 (22/211) • Grade 3: 0.8% (1/132) vs. 1.4% (3/211) • Grade 4: 0% (0/132) vs. 0% (0/211) • Grade 5: 0% (0/132) vs. 0% (0/211) <u>Nausea, % (n/N)</u> • Grade 1: 18.2% (24/132) vs. 14.2% (30/211) • Grade 2: 15.9% (21/132) vs. 27.5% (58/211) • Grade 3: 6.8% (9/132) vs. 7.1% (15/211) • Grade 4: 0% (0/132) vs. 0% (0/211) • Grade 5: 0% (0/132) vs. 0% (0/211) <u>Anorexia, % (n/N)</u> • Grade 1: 16.7% (22/132) vs. 12.8% (27/211) • Grade 2: 18.2% (24/132) vs. 17.1% (36/211) • Grade 3: 1.5% (2/132) vs. 1.9% (4/211) • Grade 4: 0% (0/132) vs. 0% (0/211) • Grade 5: 0% (0/132) vs. 0% (0/211) <u>Esophagitis, % (n/N)</u> • Grade 1: 9.1% (12/132) vs. 11.8% (25/211) • Grade 2: 34.1% (45/132) vs. 31.3% (66/211) • Grade 3: 11.4% (15/132) vs. 14.2% (30/211) • Grade 4: 0% (0/132) vs. 0% (0/211) • Grade 5: 0% (0/132) vs. 0.5 (1/211) <u>Pneumonitis, % (n/N)</u>

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	1-4 year Locoregional failure free survival (estimated from graph): 1 year: 80% vs. 70% 2 year: 70% vs. 60% 3 year: 65% vs. 58% 4 year: 63% vs. 52% **5 Year-Locoregional Failure Free Survival** 59.9% vs. 49.9%, p=0.075; adj. HR 1.46 (95% CI 1.02-2.10), p=0.041 -In patients without early distant recurrences (n=266): p=0.025 (favors PBT) -In patients without induction chemotherapy (n=246): ?? **Recurrence/Progression** • Locoregional Recurrence: 33.3% vs. 41.7%, p=0.121 • Distant Recurrence: 33.3% vs. 45%, p=0.032 • Early Distant Recurrence prior to surgery: 18.2% vs. 25.1% **Subgroup analysis by clinical TNM stage:** • Stage I/II (n=117): no statistically significant differences were identified in 5-year OS (p=0.199), PFS (p=0.133), LRFFS (p=0.822), or DMFS (p=0.08) • Stage III (n=226): ○ 5-year OS: 34.6% vs 25.0%, p=0.038 ○ 5-year PFS: 33.5% vs. 13.2%, p=0.005		• Grade 1: 7.6% (10/132) vs. 8.1% (17/211) • Grade 2: 2.3% (3/132) vs. 3.8% (8/211) • Grade 3: 0.8% (1/132) vs. 1.9% (4/211) • Grade 4: 0% (0/132) vs. 0.50% (1/211) • Grade 5: 0.8% (1/132) vs. 0.50% (1/211) <u>Skin reaction, % (n/N)</u> • Grade 1: 23.5% (31/132) vs. 29.9% (63/211) • Grade 2: 8.3% (11/132) vs. 5.7 (12/211) • Grade 3: 1.5 (2/132) vs. 0.9% (2/211) • Grade 4: 0% (0/132) vs. 0% (0/211) • Grade 5: 0% (0/132) vs. 0% (0/211) <u>Pulmonary fibrosis, % (n/N)</u> • Grade 1: 5.3% (7/132) vs. 6.2% (13/211) • Grade 2: 0.8% (1/132) vs. 1.4% (3/211) • Grade 3: 0% (0/132) vs. 0% (0/211) • Grade 4: 0% (0/132) vs. 0% (0/211) • Grade 5: 0% (0/132) vs. 0% (0/211) <u>Pleural effusion, % (n/N)</u> • Grade 1: 14.4% (19/132) vs. 23.7% (50/211) • Grade 2: 4.5% (6/132) vs. 4.7% (10/211) • Grade 3: 0.8% (1/132) vs. 1.9% (4/211) • Grade 4: 0% (0/132) vs. 0% (0/211) • Grade 5: 0% (0/132) vs. 0% (0/211) <u>Pericardial effusion, % (n/N)</u> • Grade 1: 10.6% (14/132) vs. 10.9% (23/211) • Grade 2: 0% (0/132) vs. 0% (0/211) • Grade 3: 0.8% (1/132) vs. 2.4% (5/211) • Grade 4: 0% (0/132) vs. 0% (0/211)

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	○ 5-year LRFFS: 62.6% vs 43.4%, p=0.051 ○ 5-year DMFS: 60% vs. 42%, p=0.191		• Grade 5: 0% (0/132) vs. 0% (0/211) <u>Esophageal fistula, % (n/N)</u> • Grade 1: 0% (0/132) vs. 0% (0/211) • Grade 2: 0% (0/132) vs. 0% (0/211) • Grade 3: 0% (0/132) 0.9% (2/211) • Grade 4: 0% (0/132) vs. 0% (0/211) • Grade 5: 0% (0/132) vs. 0.50% (1/211) <u>Esophageal stricture, % (n/N)</u> • Grade 1: 1.5% (2/132) vs. 0.9% (2/211) • Grade 2: 3% (4/132) vs. 2.8% (6/211) • Grade 3: 9.8% (14/132) vs. 7.6% (6/211) • Grade 4: 0% (0/132) vs. 0% (0/211) • Grade 5: 0% (0/132) vs. 0.50% (1/211)

AC = adenocarcinoma; adj. OR = adjusted odds ratio. ECOG = Eastern Cooperative Oncology Group; GEJ = gastroesophageal junction; IMRT = intensity modulated radiation therapy; PBT = proton beam therapy; SCC = squamous cell carcinoma

APPENDIX F. Gastrointestinal

Appendix Table F1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in gastrointestinal cancers

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Hong 2014 Prospective Case Series *High RoB* USA Funding: supported by National Institutes of Health (NIH) grant P01-CA021239; Proton Beam National Cancer Institute/Federal Share Program grants C06-CA059267 (to TFD) and C06-CA059267 (to TSH); a Spiro Award (to DGD); NIH grants P01-CA80124 (to RKJ, YB, and DGD) and R01-CA159258 (to DGD); and	**Diagnosis**: Gastrointestinal (resectable pancreatic ductal adenocarcinoma) **Indication**: Curative Intent	N=48 male: 54% Median Age (range): 65 (49 to 92) years **Median Tumor Size:** 2.9 (1.1 to 4.3) cm **Surgery Status:** • underwent surgical resection: 77% • did not undergo surgery: 22.9% **Reasons for Surgical Ineligibility** • due preoperative diagnosis of distal cholangiocarcinoma: 9.1% • due to metastatic progression: 18.2%	3D passive scatter PBT (Neoadjuvant short-course PBT with chemotherapy, followed by surgery and further chemotherapy) PBT Total Dose: 25 GyE (5 fractions of 5 GyE over 1 week)	**Median F/U (range):** 38 (NR) mos	**OS (95% CI) (n=48)** • 1-year: 65% (NR) [estimated from graph] • 2-year: 42% (NR) (95% CI 28 to 55) • 3-year: 23% (NR) [estimated from graph] • 4-year: 23% (NR) [estimated from graph] • Median OS: 17.3 (95% CI 11.2 to 29.5) mos **PFS (95% CI) (n=48)** • 1-year: 44%(NR) [estimated from graph] • 2-year: 24% (NR) [estimated from graph] • 3-year: 17.5% (NR) [estimated from graph] • 4-year: 10% (NR) [estimated from graph] • Median PFS: 10.4 (95% CI 7.5 to 17.1) mos **Recurrence/Progression, % (n/N)** • Locoregional: 16.2% (6/37) [Among surgically resected patients only] • distant metastases: 73% (35/48)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 3.0 *Acute Toxicities:* ≤3 mos **Acute Preoperative treatment-related toxicities, % (n/N)** • Grade 2: -Colitis: 0% (0/35) -Nausea and vomiting: 8.6% (3/35) -Constipation: 2.9% (1/35) -Dehydration: 2.9% (1/35) -Diarrhea, no prior colostomy: 2.9% (1/35) -Flatulence: 2.9% (1/35) -Chest wall pain: 0% (0/35) -Abdominal pain: 2.9% (1/35) -Limb pain: 2.9% (1/35) -Weight loss: 5.7% (2/35) • Grade 3 -Colitis: 2.9% (1/35) -Nausea and vomiting: 0% (0/35) -Constipation: 0% (0/35) -Dehydration: 0% (0/35) -Diarrhea, no prior colostomy: 0% (0/35) -Flatulence: 0% (0/35) -Chest wall pain: 2.9% (1/35) -Abdominal pain: 0% (0/35) -Limb pain: 0% (0/35) -Weight loss: 0% (0/35) • Grade 4: 0% (0/35) • Grade 5: 0% (0/35)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
American Cancer Society research grant RSG-11-073-01-TBG (to DGD COI: NR --- Two patients were excluded due to final diagnosis of cholangiocarcinoma and autoimmune pancreatitis. Harms are related to ChT AND PBT and they do not specify further. Certain PFS and OS values (when noted) are estimated from graphs.		• due to unresectable disease at exploration: 72.7%			**Mortality** • all-cause: 75% (36/48)	
Kim 2018 Retrospective Case Series *High RoB* South Korea	**Diagnosis**: Gastrointestinal **Indication:** Curative Intent	N=37 Male: 54.1% Median Age (range): 72 (52 to 92) years **Histology**:	Simultaneous Integrated Boost-PBT (SIB-PBT) with induction and/or concurrent chemotherapy (n=8 prior to PBT, n=31 concurrently) and potential for	**Median F/U all patients (range):** 16.7 (2.3 to 32.1) mos	**OS (95% CI)** • 1-year: 75.7% (61.8% to 89.6%) • Median OS: 19.3 (16.5 to 22) mos **PFS (95% CI)** • 1-year: 64.8% (47.7% to 81.9)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 3.0 *Acute Toxicities:* ≤3 mos **Acute Hematological Toxicity during PBT treatment, % (n/N)** • <u>Grade 0:</u> -Leukopenia, Grade 0: 75.7% (28/37) -Anemia, Grade 0: 59.4% (22/37)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Funding: supported by the National Cancer Center Grant (NCC 1710060 and 1710030). The funding source had no role in study design, data collection, analysis or interpretation of data. COI: none declared		• adenocarcinoma: 100% **Tumor Location** • head: 62.2% • body/tail: 37.8% **Median Tumor Size (range):** 3.6 (2.0 to 7.3) cm **T Status** • T3: 13.5% • T4: 86.5% **N Status** • N0: 91.9% • N1: 8.1% **Induction Chemotherapy:** 21.6% **Concurrent Chemotherapy**: 83.8%	surgical resection (n=35) PBT Dose Planning Target Volume 1: 45 GyE PBT Dose Planning Target Volume 2: 30 GyE	**Median F/U living patients (range):** 19.8 (14.5 to 32.1) mos	• Median Local PFS: 15.3 (11.6 to 19.0) mos **RFS (95% CI)** • 1-year: 33.2% (17.5% to 48.9%) • Median Recurrence Free Survival: 9.8 (95% CI, 7.1 to 12.4) mos **Progression/Recurrence, % (n/N)** • local: 48.6% (18/37) • regional: 18.9% (7/37) • distant: 70.3% (26/37) **Overall Treatment Response, % (n/N):** • PR: 21.6% (8/37) • SD: 45.9% (17/37) • PD: 32.4% (12/37) **Primary Tumor Response, % (n/N)** • PR: 37.8% (14/37) • SD: 62.2% (23/37) • PD: 0% (0/37) **Mortality**: • All-cause: 67.6% (25/37)	-Thrombocytopenia: 97.3% (36/37) • Grade 1: -Leukopenia, Grade I: 21.6% (8/37) -Anemia, Grade I: 32.4 (12/37) -Thrombocytopenia: 2.7% (1/37) • Grade 2: -Leukopenia, Grade II: 2.7% (1/37) -Anemia, Grade II: 8.1% (3/37) -Thrombocytopenia: 0% (0/37) • Grade ≥3: 0% (0/37) **Acute Non-Hematological Toxicity during PBT treatment, % (n/N)** • Grade 0: -Hand-foot syndrome: 100% (37/37) -Anorexia: 81.1% (30/37) -Vomiting: 86.5% (32/37) -Diarrhea: 100% (37/37) -Abdominal pain: 83.8% (31/37) -Stomatitis: 94.6% (35/37) • Grade 1: -Hand-foot syndrome: 0% (0/37) -Anorexia: 10.8% (4/37) -Vomiting: 8.1% (3/37) -Diarrhea: 0% (0/37) -Abdominal pain: 16.2% (6/37) -Stomatitis: 2.7% (1/37) • Grade 2: -Hand-foot syndrome: 0% (0/37) -Anorexia: 8.1% (3/37) -Vomiting: 5.4% (2/37) -Diarrhea: 0% (0/37) -Abdominal pain: 0% (0/37) -Stomatitis: 2.7% (1/37) • Grade ≥3: 0% (0/37)

CI = confidence interval; ChT = Chemotherapy; COI = conflict of interest; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; F/U = follow-up; Gy = Gray (unit); GyE = Gray Equivalent; mos = months; NR = not reported; OS = overall survival; PBT = proton beam therapy; PD = progressive disease; PFS = progression free survival; PR = partial response; RFS = recurrence free survival; RoB = risk of bias; SD = stable disease;

Appendix Table F2. Study characteristics and patient demographics: nonrandomized comparative studies of proton beam therapy in gastrointestinal cancers

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Cohort studies							
Maemura 2017 Retrospective comparative cohort *Moderately high* Japan	25	**PBT (n = 10):** Spot-scanning PBT PBT Dose Range: 50 GyE (via standard 3-D conformal irradiation) to 67.5 GyE (escalated dose via a field-in-field technique) **Photon (n = 15):** Hyper-fractionated accelerated radiotherapy (HART) Photon Dose: 56 GyE • All patients received induction	**Inclusion:** Patients w/ locally advanced and unresectable histologically or cytologically confirmed pancreatic cancer (adenocarcinoma); >20 years old; KPS >70, lack of prior radiotherapy or chemotherapy for another malignancy within past 5 years **Exclusion: NR**	PBT vs Photon Mean age (range): 64.5 (46 to 73) vs. 64.2 (43 to 83) years Male %: 50% vs. 47% Mean KPS (SD): 88 (4.2) vs 85 (6.3) Tumor Site • Head: 80% vs 87% • Body and Tail: 20% vs 13% Unresectable factor • SMA or CA: 80% vs 67% • SMV/PV: 10% vs 27% • Other: 10% vs 7% Tumor marker • CEA (mg/mL, mean SD): 5.2 ± 3.8 vs. 4.8 ± 4.9 • CA19-9 (U/mL, mean SD): 279 ± 511 vs. 215 ± 291	PBT vs Photon **Median F/U (range):** NR vs NR **% F/U:** 100% vs 100%	Overall Survival Disease Control Harms (toxicities)	Funding: NR COI: NR Notes:

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		chemotherapy, combination of gemcitabine and S-1; >2 cycles prior to radiation					

CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; KPS: Karnofsky performance status; SD: standard deviation; SMA: superior mesenteric artery; CA: celiac axis; SMV: superior mesenteric vein; PV: portal vein.

Appendix Table F3. Detailed data abstraction: nonrandomized comparative studies of proton beam therapy in gastrointestinal cancers

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Cohort studies			
Maemura 2017 PBT (n=10) vs Photon (n=15) Retrospective comparative cohort *Moderately high* Japan	*PBT vs. Photon* **Overall-survival (OS)** • 1-year OS: 80% vs. 86.7% • 2-year OS: 45% vs. 33.3% • 3-year OS: 22.5% vs. 26.6% p=NS **Median OS:** 22.3 vs. 23.4 months, p=NS	*PBT vs. Photon* **CEA response** • >50% decrease: 40% (4/10) vs. 53.3% (8/15) • <50% decrease: 20% (2/10) vs. 13.3% (2/15) • Increase: 20% (2/10) vs. 33.3% (5/15) p=NS **CA19-9 response**	**Harms** RT-related Hematological Toxicities, % (n/N) Leukopenia • Grade 2: 10% (1/10) vs 13% (2/15) • Grade 3: 0% (0/10) vs 20% (3/15) • Grade 4: 0% (0/10) vs 0% (0/15) Neutropenia: • Grade 2: 0% (0/10) vs 0% (0/15) • Grade 3: 0% (0/10) vs 0% (0/15) • Grade 4: 0% (0/10) vs 0% (0/15) Anemia:

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
--- Time to Progression – see graph?	**Mortality (at time of analysis):** 60% (6/10) vs. 73% (11/15), p=NS **Overall Treatment Response, % (n/N)** • Disease control rate: 80% (8/10) vs. 93% (14/15) ○ Partial response (PR): 20% (2/10) vs 53.3% (8/15) ○ Stable disease (SD): 60% (6/10) vs 40% (6/15) • Progressive disease (PD): 20% (2/10) vs 6.7% (1/15) p=NS **Mean Tumor Reduction Rate (SD):** 1.6 (35.7) vs 29.9 (22.1), p<0.05 **Disease Failure, % (n/N)** • Local progression: 40% (4/10) vs 60% (9/15) • Metastasis: 30% (3/10) vs. 20% (3/15) ○ Lung: 10% (1/10) vs 0% (0/15) ○ Liver: 30% (3/10) vs 6.7% (1/15) ○ Peritoneum: 10% (1/10) vs 13.3% (2/15) 2 patients in the PBT group exhibited simultaneous progression of local and metastatic lesions **Median time to progression (TTP):** 15.4 vs. 15.4 months	• >50% decrease: 50% (5/10) vs. 26.7% (4/15) • <50% decrease: 40% (4/10) vs. 60% (9/15) • Increase: 10% (1/10) vs. 13.3% (2/15) p=NS	• Grade 2: 0% (0/10) vs 0% (0/15) • Grade 3: 0% (0/10) vs 0% (0/15) • Grade 4: 0% (0/10) vs 0% (0/15) Thrombocytopenia: • Grade 2: 10% (1/10) vs 20% (3/15) • Grade 3: 0% (0/10) vs 6.7% (1/15) • Grade 4: 0% (0/10) vs 0% (0/15) *No grade 4 toxicities occurred in either group* <u>RT-related Non-hematological Toxicities, % (n/N)</u> Malaise • Grade 2: 0% (0/10) vs 0% (0/15) • Grade 3: 0% (0/10) vs 0% (0/15) • Grade 4: 0% (0/10) vs 0% (0/15) Nausea • Grade 2: 0% (0/10) vs 7% (1/15) • Grade 3: 0% (0/10) vs 0% (0/15) • Grade 4: 0% (0/10) vs 0% (0/15) Anorexia • Grade 2: 0% (0/10) vs 20% (3/15) • Grade 3: 0% (0/10) vs 0% (0/15) • Grade 4: 0% (0/10) vs 0% (0/15) Ulcer • Grade 2: 10% (1/10) vs 0% (0/15) • Grade 3: 10% (1/10) vs 0% (0/15) • Grade 4: 0% (0/10) vs 0% (0/15) *No grade 4 toxicities occurred in either group*

CA19-9: cancer antigen 19-9; CEA: carcinoembryonic antigen; NS: not statistically significant; SD: standard deviation

APPENDIX G. Head and Neck (including Skull-Base)

Appendix Table G1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in head & neck (including skull-base) cancers

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
Dagan 2016 Retrospective Case Series *High RoB* USA Funding: NR COI: None declared --- Authors report single worst toxicity per patient; as a result summary numbers for overall grade proportions were calculated by AAI.	**Diagnosis**: Head & Neck (Sinonasal excluding melanoma, sarcoma and lymphoma) **Indication**: Curative Intent • primary: 92% • recurrent: 8%	N=84 Male: 58% Median Age (range): 59 (28 to 81) years **Primary Tumor Location:** • nasal cavity or ethmoid: 80% • maxillary: 18% • frontal or spheroid: 2% **Histology:** • Olfactory neuroblastoma: 27% • Squamous cell carcinoma: 26% • Adenoid cystic carcinoma: 17% • Adenocarcinoma 10% • Sinonasal undifferentiated carcinoma: 8% • Neuroendocrine carcinoma: 5%	PBT (n=80) or PBT+Photon (n=4) **Median PBT Dose: 73.8 Gy (RBE),**	**Median F/U all patients (range):** 28.8 (NR) mos **Median F/U survivors (range):** 32.4 mos	**OS (95% CI)** • 1-year: 95.1% (NR) • 2-year: 80.2% (NR) • 3-year: 68.4% (NR) **Disease-free survival (95% CI)** • 1-year: 80.7% (NR) • 2-year: 71.1% (NR) • 3-year: 62.7% (NR) **Cause-specific survival (95% CI)** • 1-year: 95.1% (NR) • 2-year: 81.5% (NR) • 3-year: 69.6% (NR) **Local control (95% CI)** • 1-year: 92.4% (NR) • 2-year: 85.1% (NR) • 3-year: 82.7% (NR) **Regional (Neck) control (95% CI)** • 1-year: 95.2% (NR) • 2-year: 93.6% (NR) • 3-year: 93.6% (NR) **Freedom from distant metastasis (95% CI)** • 1-year: 88% (NR)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Late Toxicities:* timeframe NR **Late Toxicities, % (n/N)** • Grade 2: 11% (10/84) -CNS necrosis (grade II): 11% (10/84) • Grade 3: 11.9% (10/84) -unilateral vision loss: 1.2% (1/84) -bone or soft-tissue necrosis: 6% (5/84) • Grade 4: 2.4% (2/84) -unilateral vision loss: 1.2% (1/84) -bone or soft-tissue necrosis: 1.2% (1/84) • Grade 5: 1.2% (1/84) -CNS necrosis leading to death: 1.2% (1/84) **Secondary Malignancies, % (n/N)** -Out-of-field unknown primary adenocarcinoma of the liver (<5 years after treatment): 1.2% (1/84)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		• Mucoepidermoid carcinoma: 3.5% • Other: 3.5% **Tumor Grade** • I: 14% • II: 18% • III: 51% • Not available: 17% **Surgery Status** • Gross Total Resection or Subtotal Resection: 87% (GTR 88%, STR 12%) • biopsy only: 13% **Chemotherapy:** • yes: 75% **T Status:** • T1: 2.5% • T2: 3.5% • T3: 25% • T4: 69% **N Status:** • N0: 90.5% • N1: 3.5% • N2: 6%			• 2-year: 82% (NR) • 3-year: 73.2% (NR) **Recurrence/Progression, % (n/N)** • Local: 14.3% (12/84) • Regional and Distant: 4.8% (4/84) • Distant Metastases: 20.2% (17/84) **Mortality** • all-cause (at last follow-up): 36% (30/84) • due to disease progression: 30.9% (26/84) • due to secondary malignancy: 1.2% (1/84) • possibly RT-related: 3.6% (3/84)	
Demizu 2017 Retrospective Case Series	**Diagnosis**: Head & Neck (skull base	N=96 Male: 53.1%	PBT (n=93) or PBT+photon (n=3)	**Median F/FU (range):** 52.6	**OS (95% CI)** • 5-year: 75.3% (65.7% to 84.9%)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities:* timeframe NR *Late Toxicities:* timeframe NR

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
High RoB Japan Funding: Japan Agency for Medical Research and Development, Practical Research for Innovative Cancer Control (15ck0106034h0102), Translational Research Network Program (C33) COI: None declared	chordomas: 70%) And Bone (<30%) **Indication**: Curative Intent • primary: 76% • recurrent: 24%	Median Age (range): 56 (20 to 80) years **Histology** • Chordoma: 75.0% • chondrosarcoma: 20.8% • osteosarcoma: • 4.2% **Tumor location** • Skull-base: 70.8% • Cervical: 8.3% • Lumbar: 5.2% • Lumbosacral: 2.1% • Sacral: 13.6% **Surgery** • yes: 72.9% **Chemotherapy:** • yes: 4.2%	Median Dose (range): 70 (50 to 84) Gy(RBE)	(6.3 to 131.9) mos	**PFS (95% CI)** • 5-year: 49.6% (38.6% to 60.6%) **Local Control (95% CI)** • 5-year: 71.1% (60.1% to 82.1%) **Recurrence/Progression, % (n/N)** • Local: 28.1% (27/96) • Regional/Distant Recurrence: 19.8% (19/96) **Mortality, % (n/N):** • Treatment-related deaths: 0% (0/96)	**Acute Toxicities, % (n/N)** • Grade 3: 9.4% (9/96) -dermatitis: 4.2% (4/96) • Grade ≥4: 0% (9/96) **Late Toxicities, % (n/N)** • Grade ≥3: 9.4% (9/96) -musculoskeletal and connective tissue disorders (grade 3): 3.1% (3/96) -blurred vision and pain (grade 3): 1% (1/96) -middle ear inflammation (grade 3): 1% (1/96) -pain (grade 3): 1% (1/96) -tissue necrosis (grade 4): 2.1% (2/96) -brainstem infarction: 1% (1/96)
Deraniyagala 2014 Retrospective Case Series *High RoB* USA Funding: NR	**Diagnosis**: Head & Neck (skull base chordomas) **Indication**: Curative Intent	N=33 Male: 53.1% Median Age (range): 56 (20 to 80)years **Brainstem Involvement** • yes: 33.3%	PBT Median Planning Target Volume dose (range): 74 (70 to 79) CGE	**Median F/U (range):** 21 (3 to 58) mos	**OS (95% CI)** • 2-year: 92% (NR) **Local Control (95% CI)** • 2-year: 86% (NR) **Recurrence/Progression, % (n/N)** • Overall: 12.1% (4/33) • Local: 12.1% (4/33)	**Harms** *Toxicity Grading Criteria:* NR **General Toxicities, % (n/N)** -unilateral hearing loss (grade 2, partially corrected by hearing aid): 18% (6/33) -higher brainstem or visual toxicities (grade 2 or higher): 0% (0/33)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
COI: NR		**Optic Pathway Involvement** • yes: 9% **Surgery**: • Gross Total Resection: 27% • Subtotal Resection: 67% • Biopsy only: 6%			-progression during treatment: 3% (1/33) -in-field recurrence post-treatment: 9% (3/33) • Regional metastases: 0% (0/33) • Distant metastases: 0% (0/33)	
Feuvret 2016 Retrospective Case Series *High RoB* France Funding: NR COI: None declared	**Diagnosis**: Head & Neck (skull base chondrosarcomas) **Indication** Curative Intent • primary: 85.5% • recurrent: 14.5%	N=159 Male: 45.3% Median Age (range): 40 (12 to 83) **Surgery Status** • complete resection: 8.2% • debulking: 83.6% • biopsy only: 8.2% **Grade** • I:48.5% • II: 51.5% **Tumor Locations** • Petrous bone only: 37.7% • petrous + clivus:13.8% • petrous + Cavernous sinus: 4.4%	PBT (n=28) or PBT+photon (n=131) Median Total Dose (range): 70.2 (67 to 71) Gy(RBE) Median PBT Dose (range): 36.6 (16.2 to 70.2) Gy(RBE)	**Median clinical F/U (range):** 77 (2 to 214) mos **Median Radiological F/U (range):** 65 (2 to 197) mos	**OS (95% CI)** • 5-year: 94.9% (91.3 to 98.7) • 10-year: 87% (79.7 to 95.0) **PFS (95% CI)** • 5-year: 93.2% (89.0 to 97.6) • 10-year: 84.2% (76.5 to 92.7) **Local Control (95% CI)** • 5-year: 96.4% (93.0 to 100.0) • 10-year: 93.5% (88.3 to 98.9) **Recurrence** • Overall: 3.8% (6/159) • in-field local recurrence: 2.5% (4/159) • local and distant recurrence: <1% (1/159) • regional recurrence: <1% (1/159)	**Harms** *Toxicity Grading Criteria:* NR *Acute Toxicities*: ≤3 mos *Late Toxicities:* >3 mos **Acute toxicities, % (n/N)** • Grade ≤2: 100% (159/159) **Rate of Grade 1 to 2 Late toxicities (95% CI)** • 5-year: 42.9% (32.3 to 50.4) • 10-year: 57.2% (42.8 to 68.4) **Rate of Grade 3 Late toxicities (95% CI)** • 5-year: 10% (NR) • 10-year:10% (NR) **Late toxicities, % (n/N)** • Grade 1: <1% (1/159) -visual field defects: <1% (1/159) • Grade 2: 23.9% (38/159) -hormone replacement: 13.2% (21/159) -hyperprolactinemia: 1.3% (2/159) -memory loss: 2.5% (4/159) -unilateral hearing injury: 1.9% (3/159) -unilateral serous otitis: 1.3% (2/159)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		• petrous + Occipital bone: 1.3% • petrous + clivus + cavernous bone: 1.3% • Cavernous sinus: 23.3% • Clivus: 8.2% • Sphenoid bone: 5% • Sphenoid and ethmoid bones: 3.8% • C0: 1.3%			• Median Time to local recurrence (range): 39.1 (5.3 to 77) mos **Mortality** • All-cause: 10.1% (16/159) • intercurrent disease: 8.2% (13/159) • disease progression: 1.9% (3/159)	-temporal lobe necrosis: 2.5% (4/159 -trigeminal nerve injury: <1% (1/159) -hemorrhage around the tumor with no neurologic deficit: <1% (1/159) • Grade ≥3: 6.9% (11/159) -severe unilateral hearing loss (required a hearing aid): 5% (8/159) -surgery for drug-resistant epilepsy due to temporal lobe necrosis: <1% (1/159) -radionecrosis after stereotactic hypofractionated RT for recurrence 5 years after PBT (lead to death): <1% (1/159) -suspected brainstem glioma found on magnetic resonance spectroscopy 7 years after proton therapy (lead to death): <1% (1/159)
Fung 2018 Retrospective Case Series *High RoB* France Funding: None reported COI: None declared	**Diagnosis**: Head & Neck (skull base chondrosarcomas) **Indication** Mixed Curative • Curative Intent: 77.4%; • salvage: 22.6%)	N=106 Male: 56.6% Median Age (range): 40 (12 to 83) years **Surgery** • Complete Resection: 4.7% • Incomplete Resection: 94.3% • Biopsy only: <1% **Brainstem abutment/compression** • Yes: 71.7%	PBT+photon (n=91) or PBT only (n=15) Prescribed Dose Levels 73.8 Gy(RBE) (n = 36) 72 Gy(RBE) (n = 21), 70.2 Gy(RBE) (n = 23) 68.4 Gy (RBE) (n = 26)	**Median F/U (range):** 61 (11 to 119) mos	**OS (95% CI)** • 2-year: 99% (98 to 100) • 4-year: 90.2% (87 to 93.4) • 5-year: 88.3% (84.2 to 92.4) **Local Control (95% CI)** • 2-year: 88.6% (84.4 to 92.8) • 4-year: 78.3% (71.2 to 85.4) • 5-year: 75.1% (66.6 to 83.6) **Recurrence/Progression, % (n/N):** • overall: 29.2% (31/106) • local: 21.7% (23/106) • regional: 2.8% (3/106) • distant: 4.7% (5/106) **Mortality**	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: ≤3 mos *Late Toxicities:* >3 mos **Freedom from Grade III-V Late Toxicities (95% CI)** • 5-year: 93% (NR) **Late toxicities, % (n/N)** • Grade 2: 23.6% (25/106) -hyperprolactinemia: 2.8% (3/106) -hormone replacement therapy: 13.2% (14/106) -memory loss: 1.8% (2/106) -temporal lobe necrosis: 1.8% (2/106) -hearing loss: 3.8% (4/106)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		Optic pathways abutment/compression • Yes: 52.8% **Extension to cervical spine** • Yes: 16%			• all-cause: 11.3% (12/106) -from local failure: 9.4% (10/106) -acute pneumonia with severe heart failure (unrelated to chordoma): <1% (1/106) -radiation-related encephalopathy necrosis: <1% (1/106)	• Grade ≥3: 6.6% (7/106) -unilateral optic neuropathy (grade 3) and temporal lobe necrosis (grade 5) leading to death: <1% (1/106) -temporal lobe necrosis (grade 3): <1% (1/106) -hearing loss (grade 3): 4.7% (5/106)
Gray 2014 Retrospective Case Series *High RoB* USA Funding: NR COI: NR	**Diagnosis**: Head & Neck (anterior skull-based malignancies) **Indication** Curative Intent	N=48 eligible, 31 analyzed Male: 67.7% Median Age (range): 51 (12 to 82) years **Histology** • Squamous cell carcinoma: 9.7% • Olfactory neuroblastoma: 54.9% • Melanoma: 6.5% • Sarcoma: 6.5% • Adenoid cystic carcinoma: 3.2% • Sinonasal undifferentiated carcinoma: 9.7% • Adenocarcinoma: 6.5% • Basal cell carcinoma: 3.2%	Postoperative PBT (n=28), and/or adjuvant chemotherapy (n=11) Median PBT Dose (range): 63.7 (16.2 to 72) Gy	**Median F/U (range):** minimum of 18 mos	**Mortality** • perioperative mortality: 2.3% (1/48)	**Harms** *Toxicity Grading Criteria:* NR *Acute/Intermediate Toxicities*: ≤6 mos *Late Toxicities:* >6 mos **Acute/Intermediate complications, % (n/N)** • overall: 35.5% (11/31) -intracranial infection: 9.7% (3/31) -diplopia: 6.5% (2/31) -periorbital cellulitis: 6.5% (2/31) -facial cellulitis: 6.5% (2/31) -nasocutaneous fistula: 6.5% (2/31) **Late Complications, % (n/N)** • overall: 54.8% (17/31) -orbital complications: 41.9% (13/31) -epiphora: 22.6% (7/31) -diplopia: 9.7% (3/31) -radiation retinopathy: 6.5% (2/31) -ectropion: 3.2% (1/31) -intraorbital hemorrhage: 6.5% (2/31)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						-radiation keratopathy leading to -blindness: 3.2% (1/31) -wound complications: 19.4% (6/31) -delayed facial cellulitis: 3.2% (1/31) -nasocutaneous fistula: (5/31) -intracranial: 12.9% (4/31) -breakdown of the pericranial flap reconstruction leaiding to encephalocele and CSF leak: 3.2% (1/31) -encephalocele: 3.2% (1/31)
Gunn 2016 Retrospective Case Series *High RoB* USA Funding: Supported in part by the National Institutes of Health (NIH)/National Cancer Institute (NCI) Cancer Center Support (Core) Grant CA016672 and a U19 CA021239 to The University	**Diagnosis**: Head & Neck (oropharyngeal squamous carcinoma) **Indication** Curative Intent	N=50 Male: 84% Median Age (range): NR **Tumor Location** • Tonsil: • 54% • Base of tongue: • 42% • Glossopharyngeal sulcus: • 4% **Stage** • I: 2% • II: 0% • III: 18% • IVA: 74% • IVB: 6% **Smoking Status**	Intensity Modulated PBT (multifield n=46, single-field n=4) with or without induction and/or concurrent chemotherapy Median Dose (Range): 70 Gy (60 to 70)	**Median F/U (range):** 29 (8 to 49) mos	**OS (95% CI)** • 2-year: 94.5% (81.4 to 98.5) **PFS (95% CI)** • 2-year: 88.6% (75.8 to 95.1) • 4-year (estimated from graph): 66% **Mortality, % (n/N)** • overall: 4% (2/50) -unknown cause: 2% (1/50) -locoregional progression: 2% (1/50)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: ≤3 mos *Late Toxicities:* >3 mos **Acute toxicities, % (n/N):** • Grade 0 -Dermatitis radiation: 2% (1/50) -Oral mucositis: 4% (2/50) -Dysphagia: 22% (11/50) -Weight Loss: 50% (25/50) -Dry Mouth: 76% (38/50) -Dysgeusia: 26% (13/50) • Grade 1 -Dermatitis radiation: 10% (5/50) -Oral mucositis: 2% (1/50) -Dysphagia: 18% (9/50) -Weight Loss: 40% (20/50) -Dry Mouth: 14% (7/50) -Dysgeusia: 26% (13/50) • Grade 2 -Dermatitis radiation: 42% (21/50)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
of Texas MD Anderson Cancer Center COI: One or more authors receive various support from a variety of industry organizations; authors reportfunders/supporters played no role in the study design, collection, analysis, and interpretation of data, manuscript writing, or decision to submit the report for publication		• never: 50% • current: 46% • former: 4% **P16 status** • positive: 88% • unknown: 10% • negative: 2% **T Status:** • T1: 30% • T2: 50% • T3: 12% • T4: 8% **N Status:** • N0: 2% • N1: 18% • N2a: 12% • N2b: 48% • N2c: 16% • N3: 4%				-Oral Mucositis 36% (18/50) -Dysphagia: 36% (18/50) -Weight Loss: 8% (4/50) -Dry Mouth: 8% (4/50) -Dysgeusia: 48% (24/50) • Grade 3 -Dermatitis radiation: 46% (23/50) -Oral mucositis: 58% (29/50) -Dysphagia: 24% (12/50) -Weight Loss: 2% (1/50) -Dry Mouth: 2% (1/50) -Dysgeusia: 0% (0/50) • Grade ≥4: - Dermatitis radiation: 0% (0/50) - Oral mucositis: 0% (0/50) - Dysphagia: 0% (0/50) - Weight Loss: 0% (0/50) - Dry Mouth: 0% (0/50) - Dysgeusia: 0% (0/50) **Late Toxicities, % (n/N):** • Grade 0-4 -bone necrosis: 0% (0/50) • Grade 0 -Dysphagia: 40% (20/50) -Dry Mouth: 2% (1/50) -Dysgeusia: 24% (12/50) -Oral mucositis: 80% (40/50) • Grade 1 -Dysphagia: 22% (11/50) -Dry Mouth: 46% (23/50) -Dysgeusia: 48% (24/50) -Oral mucositis: 14% (7/50) • Grade 2

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						-Dysphagia: 26% (13/50) -Dry Mouth: 50% (25/50) -Dysgeusia: 28% (14/50) -Oral mucositis: 6% (3/50) • Grade 3 -Dysphagia: 12% (6/50) -Dry Mouth: 2% (1/50) -Dysgeusia: 0% (0/50) -Oral mucositis: 2% (1/50) • Grade ≥4: 0% (0/50) - Dysphagia: 0% (0/50) - Dry Mouth: 0% (0/50) - Dysgeusia: 0% (0/50) - Oral mucositis: 0% (0/50)
Hayashi 2016 Retrospective Case Series *High RoB* Japan Funding: NR COI: NR	**Diagnosis**: Head & Neck (recurrent oral cavity squamous cell carcinoma) **Indication:** Salvage	N=46 Male: 60.8% Median Age (range): 66 (28 to 94) years **Prior Surgery:** 46% **Prior Irradiation:** 54% **Primary tumor site** • Tongue: 58.7% • Upper gingiva: 15.2% • Lower gingiva: 10.9% • Hard palate: 4.3% • Floor of mouth: 6.5% • Buccal mucosa: 4.3%	PBT with concurrent chemotherapy Median PBT Dose (range): 55(28.6 to 74.8) GyE	**Median F/U (range):** 24 (3 to 72) mos	**OS (95% CI)** • 1-year: 65% (NR) • 2-year: 46% (NR) **Local Control (95% CI)** • 1-year: 81% (NR) • 2-year 70% (NR) **Treatment Response, % (n/N):** • CR: 87% (40/46) • PR: 13% (6/46) **Lymph Metastases Treatment Response, % (n/N):** • CR: 91.7% (22/24) • PR: 8.3% (2/24) **Recurrence/Progression, % (n/N):**	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: Timeframe NR *Late Toxicities*: Timeframe NR **Hematological toxicities, % (n/N)** • Grade 1 -Anemia: 22% (10/46) -Leukopenia: 11% (5/46) -Neutropenia: 4% (2/46) -Thrombocytopenia: 7% (3/46) • Grade 2 -Anemia: 22% (10/46) -Leukopenia: 22% (10/46) -Neutropenia: 24% (11/46) -Thrombocytopenia: 24% (11/46) • Grade 3 -Anemia: 15% (7/46) -Leukopenia: 20% (9/46) -Neutropenia: 20% (9/46) -Thrombocytopenia: 17% (8/46)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		Lymph Node Metastases Prior to Treatment: 52% (24/46) **T Status** • T2: 13% • T3: 26.1% • T4a: 50% • T4b: 10.8% **N Status** • N0: 47.8% • N1: 21.7% • N2b: 13% • N2c: 17.4% **Stage**: • II: 4.3% • III: 34.8% • IVA/IVB: 60.9%			• overall: 19.6% (9/46) • local: 13% (6/46) • in-field lymph node: 4% 2/46) • regional lymph node: 2% (1/46) **Mortality, % (n/N):** • distant metastases (lung): 30% (14/46) • local progression: 13% (6/46) • RT-related: sepsis infection after surgery for osteoradionecrosis: 2.2% (1/46) • peritoneal metastases: NR • pleural dissemination: NR • pneumonia: 2% (1/46)	• Grade 4 -Anemia: 0% (0/46) -Leukopenia: 0% (0/46) -Neutropenia: 0% (0/46) -Thrombocytopenia: 2% (1/46) • Grade 5: 0% (0/46) **Non-hematological toxicities, % (n/N)** • Grade 1 -Dermatitis: 0 (0/46) -Mucositis: 0% (0/46) -Dysphagia: 2% (1/46) -Fever: 50 (23/46) -Alopecia: 11 (7/46) -Nausea/vomiting: 2% (1/46) -Osteoradionecrosis: 2% (1/46) -Xerostomia: 0% (0/46) -Dysgeusia: 7 (3/46) -Dysarthria: 0% (0/46) • Grade 2 -Dermatitis: 43% (20/46) -Dysphagia: 24 (11/46) -Mucositis: 28 (13/46) -Fever: 11 (5/46) -Alopecia: 7 (3/46) -Nausea/vomiting: 0% (0/46) -Osteoradionecrosis: 24% (11/46) -Xerostomia: 54 (25/46) -Dysarthria: 0% (0/46) -Dysgeusia: 57 (26/46) • Grade 3 -Dermatitis: 57% (26/46) -Dysphagia: 65% (30/46) -Mucositis: 72 (33/46)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						-Fever: 0% (0/46) -Alopecia: 0% (0/46) -Nausea/vomiting: 0% (0/46) -Osteoradionecrosis: 13% (6/46) -Xerostomia: 0% -Dysarthria: 0% (0/46) -Dysgeusia: 0% (0/46) • Grade 4 -Dermatitis: 0% (0/46) -Mucositis: 0% (0/46) -Dysphagia: 0% (0/46) -Fever: 0% (0/46) -Alopecia: 0% (0/46) -Nausea/vomiting: 0% (0/46) -Osteoradionecrosis: 2.2% (1/46) -Xerostomia: 0% -Dysgeusia: 0% (0/46) -Dysarthria: 0% (0/46) • Grade 3-4 -osteoradionecrosis: 15.2% (7/46)
Hayashi 2017 Retrospective Case Series *High RoB* Japan Funding: NR COI: None declared ---	**Diagnosis**: Head & Neck (recurrent oral cancer) **Indication:** Salvage	N=34 Male: 55.9% Median Age (range): 68 (38 to 94) years **Prior Treatment** • EBRT: 79.4% • braychotherapy: 14.7% • PBT: 5.9% **Histology** • Squamous cell carcinoma: 88.2%	PBT with concurrent chemotherapy Median PBT Dose(range): 50 (28.6 to 55) GyE in 13–25 fractions over 3–5 weeks	**Median F/U (range):** 25 (3 to 77) mos	**OS (95% CI)** • 1-year: 62% (NR) • 2-year: 42% (NR) **Local Control (95% CI)** • 1-year: 77% • 2-year: 60% **Recurrence/Progression, % (n/N):** • local: 14.7% (5/34) • regional: 2.9% (1/34) • distant: 41.2% (14/34)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: ≤2 mos *Late Toxicities:* >2 mos **Acute Toxicities, % (n/N)** • Grade 2: -leukopenia: 47.1% (16/34) -thrombocytopenia: 11.8% (4/34) -anemia: 23.5% (8/34) -oral mucositis: 67.6% (23/34) -radiation dermatitis: 64.7% (22/34) -dysphagia: 20.6% (7/34) • Grade 3

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
Authors report that 14 died of distant metastases but did not report whether there were more who had distant metastases but did not die.		• Adenoid cystic carcinoma: 5.9% • Mucoepidermoid carcinoma: 2.9% • Ameloblastic carcinoma: 2.9% **Tumor Location** • Tongue: 38.2% • Upper gingiva: 26.5% • Lower gingiva: 14.7% • Buccal mucosa: 8.8% • Floor of mouth: 5.9% • Hard palate: 5.9% **Performance status (ECOG)** • 0: 64.7% • 1: 35.3% **Stage** • I: 0% • II: 2.9% • III: 26.5% • IVA: 55.9% • IVB: 14.7% **T Status** • T1: 0% • T2: 5.9% • T3: 20.6%			**Treatment Response, % (n/N):** • CR: 64.7% (22/34) • PR: 35.3% (12/34) **Mortality, % (n/N):** • overall: 61.8% (21/34) -distant metastases (lung): 41.2% (14/34) -local progression: 11.8% (4/34) -other causes (not specified): 8.8% (3/34)	-leukopenia: 17.6% (6/34) -thrombocytopenia: 23.5% (8/34) -anemia: 2.9% (1/34) -oral mucositis: 32.4% (11/34) -radiation dermatitis: 29.4% (10/34) -dysphagia: 35.2% (12/34) -dysphagia (requiring percutaneous endoscopic gastrostomy): 17.6% (6/34) -severe dysphagia (requiring nasogastric tubes for feeding): 11.8% (4/34) • Grade 4: 2.9% (1/34) -thrombocytopenia: 2.9% (1/34) • Grade 5: 0% (0/34) **Late Toxicities, % (n/N)** • Grade 2: -Dry mouth: 58.8% (20/34) -Osteonecrosis: 32.4% (11/34) • Grade 3: 2.9% (1/34) -Osteonecrosis: 2.9% (1/34) • Grade ≥4: 0% (0/34)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		• T4a: 52.9% • T4b: 20.6% **N Status** • N0: 52.9% • N1: 20.6% • N2a: 0% • N2b: 17.6% • N2c: 8.8% • N3: 0%				
McDonald 2015 Retrospective Case Series *High RoB* USA Funding: Supported in part by the Jesse N. Jones, III, Memorial Fund for Head and Neck Cancer Research at the Indiana University Melvin and Bren Simon Cancer Center. COI: None declared	**Diagnosis**: Head & Neck (skull base chordoma, chondrosarcoma, adenoid cystic carcinoma, or sinonasal malignancies) **Indication:** Curative Intent	N=66 Male: 50% Median Age (range): NR (15 to 78) years **Clival Based Tumor** • yes: 36.3% **Smokers**: 13.6%	PBT with (n=54) or without concurrent chemotherapy (n=12) Median PBT Dose (range): 75.6 (62 to79.2) Gy(RBE)	**Median F/U (range):** 31 (6 to 96) mos	**OS (95% CI)** • 3-year: 84.9% (74.9% to 94.9%)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 **Rate of any grade temporal lobe radiation necrosis:** 3-year: 12.4% (95% CI 6.1% to 18.7%) **Rate of Radiation Necrosis (95% CI)** 3-year: grade ≥2: 5.7% (1.2% to 10.2%) **Radiation Necrosis, % (n/N)** • total number of involved temporal lobes: 16 lobes • any grade Radiation Necrosis in temporal lobe(s):18.2% (12/66) • grade 1 -asympomatic radiographic changes: 10.6% (7/66) • grade 2 -symptomatic , unilateral, requiring transient steroid use: 1.5% (1/66) • Grade 3 -symptomatic, requiring hyperbaric oxygen therapy, seizure medication, or bevacizumab: 4.5% (3/66)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						• Grade 4 -symptomatic, bitemporal, requiring transient hospitalization and protracted medical management: 1.5% (1/66) • Median time to development of radiation necrosis(range): 21 (8 to 51) mos
McDonald 2016 Retrospective Case Series *High RoB* USA Funding: supported in part by the biostatistics and bioinformatics of Winship Cancer Institute of Emory University and NIH/ NCI under award number P30CA138292CO I: None declared --- Includes multivariate analysis (HR, p-values) for OS, Local Failure and Distant	**Diagnosis**: Head & Neck (recurrent and second primary) **Indication:** Salvage	N=61 Male: 60.7% Median Age (range): 68 (15 to 78) years **Histology** • squamous cell: 52.5% • adenoid cystic carcinoma: 16.4% • Undifferentiated carcinoma: 8.2% • Salivary duct carcinoma: 4.9% • Mucoepidermoid carcinoma: 4.9% • Esthesioneuroblastoma: 3.3% • Sinonasal undifferentiated • carcinoma: 3.3% • Adenocarcinoma: 3.3% • Carcinoma ex pleomorphic • Adenoma: • 1.6% • Basal cell carcinoma: 1.6%	PBT with concurrent (n=18), induction (n=2) or no (n=41) chemotherapy Median Total PBT Dose (residual disease): 66 Gy (RBE) Median Total PBT Dose (gross disease): 70.2 Gy (RBE)	**Median F/U (range):** 15.2 mos **Median Survivor F/U(range):** 28.7 mos	**OS (95% CI)** • 1-year: 56% [estimated from graph] • 2-year: 32.7% (20.8% to 45.1%) • Median OS: 16.5 (10.2 to 21.9) mos **cumulative incidence of local failure with death as a competing risk (95% CI)** • 2-year: 19.7% (95% CI 10.8% to 30.5%) **cumulative incidence of Regional nodal failure (95% CI)** • 2-year: 3.3% (0.6% to 10.2%) **cumulative incidence of Distant metastases (95% CI)** • 2-year: 38.3% (26.0% to 50.5%) **Recurrence/Progression, % (n/N)** • Overall: 59% (36/61) • Local only: 16.4% (10/61)	**Harms** *Toxicity Grading Criteria:* NR *Acute Toxicities*: ≤3 mos *Late Toxicities:* >3 mos **Acute toxicities. % (n/N)** • overall Grades 0 to 2: 47.5% • overall grade 3: 13.1% • overall grade 4: 0% • overall grade 5: 1.6% • Grade 0 -Dermatitis: 21.3% (13/61) -Xerostomia: 95.1% (58/61) -Dysphagia: 95.1% (58/61) -Mucositis: 85.2% (52/61) -Ocular: 93.4% (57/61) -Soft tissue/bone: 93.4% (57/61) -CNS: 98.4% (60/61) • Grade 1 -Dermatitis: 32.8% (20/61) -Xerostomia: 1.6% (1/61) -Dysphagia: 1.6% (1/61) -Mucositis: 0% (0/61) -Ocular: 4.9% (3/61) -Soft tissue/bone: 0% (0/61) -CNS: 0% (0/61) • Grade 2 -Dermatitis: 41% (25/61)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
Metastasis as related to a number of factors (location, GTV, residual disease, KPS) Late toxicities reported for n=53 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.		**Disease Status** • Recurrent: 90.2% • Second primary: 9.8% **Prior Treatment** • Salvage Surgery before Reirradiation: 47.5% • previous chemotherapy: 59% **Tumor Location:** • skull-base: 90.2% • cervical: 8.2% • oropharyngeal: 1.7% • **Smoking** never: 63.9% • <10 packyears: 4.9% • >10 packyears: 24.6% • unknown: 6.6% **T and N Status** • T0N2: 6.6% • T0N3: 1.6% • T2N0: 8.2% • T3N0: 3.3% • T4N0: 72%			• Local plus distant metastases: 3.3% (2/61) • Regional nodal only: 3.3% (2/61) • Distant metastasis: 36.1% (22/61) • Median time to failure (IQR; range): 4.9 (1.5 to 7.8; 0 to 8.7) mos **Mortality, % (n/N)** • all-cause (3 months): 13.1% (8/61)* • treatment toxicity-related: 4.9% (3/61) • disease progression (metastatic): 3.3% (2/61) • other (not specified): 4.9% (3/61) **Weight Loss, % (n/N):** • lost >10% of pretreatment weight: 0% (0/61) • Median percentage of weight loss, % (IQR; range): 2% (IQR 0% to 4%; range -10% to 10%)	-Xerostomia: 1.6% (1/61) -Dysphagia: 3.3% (2/61) -Mucositis: 11.5% (7/61) -Ocular: 1.6% (1/61) -Soft tissue/bone: 1.6% (1/61) -CNS: 0% (0/61) • <u>Grade 3:</u> -Dermatitis: 4.9% (3/61) -Xerostomia: 0% (0/61) -Dysphagia: 0% (0/61) -Mucositis: 3.3% (2/61) -Ocular: 0% (0/61) -CNS: 0% (0/61) -Soft tissue/bone: 4.9% (3/61) • <u>Grade 4</u> -Dermatitis: 0% (0/61) -Xerostomia: 0% (0/61) -Dysphagia: 0% (0/61) -Mucositis: 0% (0/61) -Soft tissue/bone: 0% (0/61) -Ocular: 0% (0/61) -CNS: 0% (0/61) • <u>Grade 5</u> -Dermatitis: 0% (0/61) -Xerostomia: 0% (0/61) -Dysphagia: 0% (0/61) -Mucositis: 0% (0/61) -Ocular: 0% (0/61) -Soft tissue/bone: 0% (0/61) -CNS: 1.6% (1/61) • <u>Grade ≥3</u> -soft-tissue/Bone Necrosis: 15.1% (8/53) [survivors] **Late toxicities, % (n/N)**

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		• T4N1: 4.9% • T4N2: 3.3%				• overall grade 0 to 2: 22.6% • overall grade 3: 15.1% • overall grade 4: 5.7% • overall grade 5: 3.8% • Grade 0 -brain radiation necrosis: (45/53) -Soft tissue/bone: 69.8% (37/53) -Xerostomia: 94.3% (50/53) -Orbital: 98.1% (52/53) -CNS: (47/53) • Grade 1 -brain radiation necrosis: 5.7% (3/53) -Soft tissue/bone: 5.7% (3/53) -Xerostomia: 1.9% (1/53) -Orbital: 0% (0/53) -CNS: 0% (0/53) • Grade 2 -brain radiation necrosis: 9.4% (5/53) -Soft tissue/bone: 5.7% (3/53) -Xerostomia: 3.8% (2/53) -Orbital: 1.9% (1/53) -CNS: 3.8% (2/53) • Grade 3 -Grade III brain radiation necrosis: 0% (0/53) -Grade III Soft tissue/bone: 15.1% (8/53) -Grade III Xerostomia: 0% (0/53) -Grade III Orbital: 0% (0/53) -Grade III CNS: 1.9% (1/53) • Grade 4 -brain radiation necrosis: 0% (0/53) -Soft tissue/bone: 1.9% (1/53) -Xerostomia: 0% (0/53) -Orbital: 0% (0/53) -CNS: 3.8% (2/53)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						• Grade 5 -brain radiation necrosis: 0% (0/53) -Soft tissue/bone: 1.9% (1/53) -Xerostomia: 0% (0/53) -Orbital: 0% (0/53) -CNS: 1.9% (1/53)
Morimoto 2014 Retrospective Case Series *High RoB* Japan Funding: COI: None declared --- A group of patients who received carbon ion (n=10) were excluded because data was reported separately. OS and Local PFS also provided by pathological cancer type and according to primary site, , extent of tumor,	**Diagnosis**: Head & Neck (unresectable locally advanced Head & Neck cancers with skull base invasion) **Indication:** Curative Intent	N=179 eligible, 47 analyzed Male: 53.2% Age Groups: • <60: 55.3% • ≥60: 44.7% **Histology:** • adenoid cystic carcinomas: 46.8% • squamous cell carcinomas: 27.7% • olfactory • neuroblastomas: • 8.5% • adenocarcinomas: 6.4% • malignant melanomas: 4.3% • undifferentiated carcinomas: 6.4% **Primary Tumor Location** • paranasal sinus: 70.2% • nasal cavity: 8.5%	PBT Median PBT Dose (Range): NR (65-70.2) GyE	**Median F/U (range):** 32 (6.4 to 80.4) mos	**OS (95% CI), (n=57)** • 3-year: 60% (NR) **Local PFS (95% CI), (n=57)** • 3-year: 56% (NR) **Treatment Response, % (n/N)** • CR: 4.3% (2/47) • PR: 44.7% (21/47) • SD: 51.1% (24/47) **Distant Metastasis** **Recurrence/Progression, % (n/N):** • Local: 46.8% (22/47) • Regional lymph node metastasis: 10.6% (5/47) • Distant: 42.6% (20/47)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: timeframe NR *Late Toxicities:* timeframe NR **Acute toxicity, % (n/N)** • Grade ≥4: 0% (0/47) **Late toxicity, % (n/N)** • Grade 2: -optic nerve disorder: 4.3% (2/47) - extraocular muscle paralysis: 2.1% (1/47) • Grade 3: -optic nerve disorder: 6.4% (3/47) -cataract: 2.1% (1/47) -meningismus: 2.1% (1/47) -pharyngeal mucositis: 2.1% (1/47) -hearing impaired: 2.1% (1/47) • Grade 4: - optic nerve disorder: 4.3% (2/47) - edema cerebral: 2.1% (1/47)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
and initial treatment response. OS and LPFS are given for the whole cohort of PBT (n=47) and carbon ion (n=10)		• nasopharynx: 10.6% • parapharnygeal space: 2.1% • parotid gland: 4.3% • external and middle ear: 4.2% **Extent of Tumor** • anterior skull base: 40.4% • middle skull base: 23.4% • cavernous sinus: 21.3% • middle skull base & cavernous sinus: 14.9%				
Nakamura 2017 Retrospective Case Series *High RoB* Japan Funding: supported in part by Grants-in-Aid for Scientific Research (16K10412) from the Ministry of	**Diagnosis**: Head & Neck (olfactory neuroblastoma) **Indication:** Curative Intent	N=42 Male: 40% Median Age (range): 51 (20 to 87) years **Histopathology** • Kadish A: 12% • Kadish B: 21% • Kadish C: 67%	PBT alone (n=18) or with induction and/or concurrent chemotherapy (n=24) Total Dose: 65 (65 to 70) Gy(RBE)	**Median F/U (range):** 69 (7 to 186) mos	**OS (95% CI),** • 5-year Kadish A: 100% • 5-year Kadish B: 86% • 5-year Kadish C: 76% **PFS (95% CI)** • 5-year Kadish A: 80% • 5-year Kadish B: 65% • 5-year Kadish C: 39% **Recurrence/Progression, % (n/N)** • overall: 47.6% (20/42) • local: 14.3% (6/42) • local and regional: 4.8% (2/42)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 3.0 *Acute Toxicities*: ≤3 mos *Late Toxicities:* >3 mos **Acute Toxicities, % (n/N)** • Grade 3: -mucositis: 9.5% (4/42) -dermatitis: 2.4% (1/42) • Grade ≥4: 0% (0/42) **Late Toxicities, % (n/N)** • Grade 3: -ipsilateral visual impairment: 2.4% (1/42) • Grade 4: -bilateral visual impairment: 2.4% (1/42) - ipsilateral visual impairment: 4.8% (2/42)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
Education, Science and Culture of Japan, by Health Science Research Grants from the Ministry of Health and Welfare, and by the National Cancer Center Research and Development Fund (25-A-10 & 28-A-14 COI: One author reports receiving grants and personal fees from multiple industry organizations. --- OS and PFS only provided by histology and not overall population. Authors found a significant difference in OS between <50					• local and distant: 4.8% (2/42) • regional: 19% (8/42) • distant: 4.8% (2/42)	- liquorrhea: 2.4% (1/42) • <u>Grade ≥3:</u> -brain necrosis: 0% (0/42)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
and 50 and older patients.						
Phan 2016 Retrospective Case Series *High RoB* USA Funding: NR COI: NR	**Diagnosis**: Head & Neck (reirradiation , various histologies) **Indication:** Salvage • recurrent disease: 91.7% • second primary: 8.3%	N=60 Male: 71.6% Median Age (range): NR (26-81) years **Histology** • squamous cell carcinoma: 66.7% • adenoid cystic carcinoma: 11.7% • adenocarcinoma: 10% • neuroendocrine (not specified): 5% • other salivary (not specified): 3.3% • sarcoma: 1.7% • benign (not specified): 1.7% **Salvage Surgery:** • Yes: 58.3% **Retreatment Chemotherapy** • yes: 76.7% **Tumor Locations:** • oropharynx: 25% • oral cavity: 5%	Passive scatter PBT (n=15) or IMPT (n=45) Median Squamous Cell Carcinoma PBT Dose (range): 66 (59.4 to 70) Gy Median Non-Squamous Cell Carcinoma PBT Dose (range): 62 (50-70)	**Median F/U (range):** 13.6 (0 to 50) mos	**OS (95% CI)** • 1-year: 81.3% (NR) • 2-year: 69% (NR) **PFS (95% CI)** • 1-year: 60.1% (NR) • 2-year: 48.2% (NR) **Locoregional Failure-Free Survival (95% CI)** • 1-year:68.4% (NR) • 2-year: 55.9% (NR) **Distant Metastasis-Free Survival (95% CI)** • 1-year: 74.9% (NR) • 2-year: 63.7% (NR) **Locoregional Control (95% CI)** • 1-year: 80.8% (NR) • 2-year: 72.8% (NR) **Recurrence/Progression, % (n/N)** • Local: 15% (9/60) • Regional: 5% (3/60) • Locoregional: 20% (12/60) • Distant: 13.3% (8/60)† • median time to recurrence: 8.8 (3 to 43.6) mos **Mortality**	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: ≤1 mos *Late Toxicities:* ≥2 mos **Rate of grade 3 late toxicities** • 1-year: 16.7% (10/60) **Actuarial Rate of grade 3 late toxicities** • 1-year: 11.9% (NR) • 2-year: 26% (NR) **Rate of feeding tube independence** • 1-year: 82% (NR) • 2-year: 82% (NR) **Acute Toxicities, % (n/N)** • Grade 1 to 2: -mucositis: 5% (3/60) -odynophagia: 5% (3/60) -dysphagia: 5% (3/60) -xerostomia: 3.3% (2/60) -pain: : 3.3% (2/60) -dermatitis: 10% (6/60) • Grade 3: 30% (18/60) -dermatitis: 13.3% (8/60) -mucositis: 10% (6/60) -odynophagia: 10% (6/60) -dysphagia: 5% (3/60) -xerostomia: 3.3% (2/60) -weight loss: 3.3% (2/60) • Grade 4

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		• nasopharynx: 13.3% • larynx: 1.6% • parotid: 11.&% • orbit: 5% • sinonasal: 20% • neck/unknown primary: 5% • other: 13.3% • **Smoking** Never: 41.7% • <10 packyears: 16.7% • >10 packyears: 41.7%			• All-Cause: 1.7% (1/60) • potentially treatment-related: 1.7% (1/60)	-osteoradionecrosis (potentially treatment-related): 3.3% (2/60) • Grade 5 -multisite organ failure and acute cerebral infarction: 1.7% (1/60) **Late Toxicities, % (n/N)** • Grade 1 to 2: -dysphagia: 1.7% (1/60) -ototoxicity: 3.3% (2/60) -osteoradionecrosis: 1.7% (1/60) -neurotoxicity: 1.7% (1/60) • Grade 3: 20% (12/60) -dysphagia: 1.7% (1/60) - xerostomia: 1.7% (1/60) -feeding tube placed during RT or <1 month after RT: 46% (6/13) -neurotoxicity: 3.3% (2/60) -tracheostomy: 3.3% (2/60)
Romesser 2016 Retrospective Case Series *High RoB* USA Funding: Authors report no specific funding for study. COI: One author has minority	**Diagnosis**: Head & Neck (reirradiation , various histologies) **Indication for treatment** Salvage	N=91 Males: 70.7% Median Age: 63 (IQR 51.5 to 70) years **Initial Tumor Site** • oropharynx: 85.5% • nasal cavity and paranasal sinuses: 13% • oral cavity: 13% • larynx/hypopharynx: 10.9% • salivary glands: 12%	Uniform-scanning PBT Median PBT Dose (range): 60.6 Gy (RBE).	**Median Survivor F/U (range):** 13.3 mos (IQR 8.2 to 19.2) mos **Median F/U all patients (range):** 10.4 (IQR, 5.3 to 17.5) mos	**OS (95% CI)** • 1-year: 65.2% (NR) **Incidence of Locoregional Failure with death as competing risk (95% CI)** • 1-year: 25.1% **Freedom from Distant Metastases (95% CI)** • 1-year: 84% (NR) **Progression/Recurrence, % (n/N)** • locoregional: 33.7% (31/92)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: ≤3 mos *Late Toxicities:* >3 mos **Acute toxicities, % (n/N)** • Grade 0 - dysphagia: 37.9% (25/66) - mucositis: 40.7% (37/91) - nausea: 69.2% (63/91) - dysgeusia: 54.9% (50/91) - esophagitis: 62.1% (41/66) - dermatitis: 11% (10/91) • Grade 1 -dysphagia: 28.8% (19/66) -mucositis: 31.9% (29/91)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
investment in a proton therapy center (ProCure)		• nasopharynx: 9.8% • various skin malignancies: 5.4% • skull-base: 8.7% • others: 8.7% **Recurrent Histological Subtype** • Squamous Cell Carcinoma: 56.5% • adenocarcinoma: 9.8% • nasopharyngeal carcinoma: 4.3% • sarcoma: 5.4% • adenoid cystic carcinoma: 2.2% • Sinonasal undifferentiated carcinoma: 3.3% • acinic cell carcinoma: 2.2% • olfactory neuroblastoma: 2.2% • myoepithelial carcinoma: 2.2% • merkel cell carcinoma: 1.1% • basal cell carcinoma: 1.1% • esthesioneuroblastoma: 2.2% • other: 7.6%			• distant metastases: 16.3% (15/92) • median time to locoregional failure: 7.0 (IQR, 4.2 to 13.3) mos • median time to distant metastases: 8.6 (IQR, 4.6 to 12.8) mos **Mortality**: • all-cause: 44% (40/91) • treatment related toxicity: 5% (3/60) • median time to death (IQR): 7.3 (4.7 to 12.9) mos	-nausea: 23.1% (21/91) -dysgeusia: 25.3% (23/91) -esophagitis: 18.2% (12/66) -dermatitis: 41.8% (38/91) • Grade 2 -dysphagia: 24.2% (16/66) -mucositis: 17.6% (16/91) -nausea: 7.7% (7/91) -dysgeusia: 19.8% (18/91) -esophagitis: 10.6%(7/66) -dermatitis: 44% (40/91) • Grade 3 -dysphagia: 9.1% (6/66) -mucositis: 9.9% (9/91) -nausea: 0% (0/91) -dysgeusia: 0% (0/91) -esophagitis: 9.1% (6/66) -dermatitis: 3.3% (3/91) • Grade 4 -dysphagia: 0% (0/66) -mucositis: 0% (0/91) -nausea: 0% (0/91) -dysgeusia: 0% (0/91) -esophagitis: 0% (0/66) -dermatitis: 0% (0/91) **Late toxicities, % (n/N)‡** • Grade 0 - Skin: 63.8% (44/69) - Induration/fibrosis§: 67.2% (45/67) - Xerostomia: 58.0% (40/69) - Trismus §: 69.2% (45/65) - Dysphagia**: 73.2% (41/56) - Bleeding: 97.1% (67/69) • Grade 1

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		Chemotherapy: • yes: 52.2% **Salvage Surgery** • yes: 39.1% **Smoking:** • never: 46.7% • unknown: 6.5% • <10 pack-years: 8.7% • ≥ 19 pack-years: 38%				-Skin: 23.2% (16/69) -Induration/fibrosis: 32.8% (22/67) -Xerostomia: 37.7% (26/69) -Dysphagia: 17.9% (10/56) -Bleeding: 0% (0/69) • <u>Grade 2</u> -Skin: 4.3% (3/69) -Induration/fibrosis: 0% (0/67) -Xerostomia: 4.3% (3/69) -Trismus: 6.2%(4/65) -Dysphagia: 1.8% (1/56) -Bleeding: 0% (0/69) • <u>Grade 3</u> -Skin: 1.4% (1/69) -Induration/fibrosis: 0% (0/67) -Xerostomia: 0% (0/69) -Trismus: 0% (0/65) -Dysphagia: 7.1% (4/56) -Bleeding: 0% (0/69) • <u>Grade 4</u> -Skin: 7.2% (5/69) -Induration/fibrosis: 0% (0/67) -Xerostomia: 0% (0/69) -Trismus: 0% (0/65) -Dysphagia: 0% (0/56) -Bleeding: 0% (0/69) • <u>Grade 5</u> -Skin: 0% (0/69) -Induration/fibrosis: 0% (0/67) -Xerostomia: 0% (0/69) -Trismus: 0% (0/65) -Dysphagia: 0% (0/56) -Bleeding: 2.9% (2/69)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
Stieb 2018 Retrospective Case Series *High RoB* USA Funding: NR COI: None declared	**Diagnosis**: Head & Neck (extracranial chordomas & chondrosarcomas) **Indication:** Mixed • Curative Intent: 62% • Salvage: 38%	N=76 Male: 53% Median Age (range): 53 (23 to 79) years **Histology:** • chordoma: 72.4% • chondrosarcoma: 27.6% **Tumor Location** • cervical spine: 68% • thoracic spine: 22% • lumbar: 9%	Pencil Beam Scanning PBT alone Median PBT Dose (range): 73.9 (59.4 to 75.2) Gy(RBE)	**Median F/U all patients (range):** 65.5 (13 to 173) months	**OS (95% CI)** • 5-year: 75% (64% to 86%) • Median OS: 65 (62 to 79) months **Local Control (95% CI)** • 5-year: 61% (49% to 73%) **Recurrence/Progression, % (n/N)** • none: 57.9% (44/76) • overall: 42.1% (32/76) • local: 26.3% (20/76) • distant: 6.6% (5/76) • local and distant: 9.2% (7/76) **Mortality, % (n/N)** all-cause: 30.3% (23/76)	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.03 *Acute Toxicities:* ≤3 months *Late Toxicities:* >3 months **Late neurotoxicity-free survival (95% CI)** • 5-year: 86% (77% to 95%) **Acute Neurological Toxicities, % (n/N)** • grade ≤2: 5.3% (4/76) -neuropathic pain (grade I): 1.3% (1/76) -neuropathic pain (grade II): 2.6% (2/76) -hyposensibility: (grade II) 2.6% (2/76) [occurred twice in same patient] • grade ≥3: 0% (0/76) **Late Neurological Toxicities** • any Grade: 15.8% (12/76) • Grade 1: -Lhermitte's Syndrome : 5.3% (4/76) -Hypersensibility : 2.6% (2/76) -Hyposensibility : 1.3% (1/76) -Neuropathic pain : 1.3% (1/76) -Changes in MRI : 1.3% (1/76) • Grade 2: -Neuropathic pain: 2.6% (2/76) -parasthesia: 2.6% (2/76) -Hypersensibility : 2.6% (2/76) -Hyposensibility: 1.3% (1/76) -trigeminal nerve inflammation: 1.3% (1/76) • Grade 4: -myelopathy: 1.3% (1/76)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
Takayama 2016 Prospective Case Series *High RoB* Japan Funding: NR COI: None declared.	**Diagnosis:** Head & Neck (Stage III-IVB tongue cancer) **Indication:** Curative Intent	N=33 Male: 67% Median age (range): 53 (25 to 69) years **ECOG Performance Status** • 1: 73% • 2: 27% **Reasons for not performing surgery** • refusal: 97% • inoperable: 3% **T Status:** • T2: 18% • T3: 30% • T4a: 52% **N Status** • N0: 15% • N1: 36% • N2b: 18% • N2c: 27% • N3: 3% **Stage** • III: 24% • IVA: 73% • IVB: 3%	Alternating chemoradiotherapy followed by concurrent chemotherapy with PBT Median Total RT Dose Primary Tumor (range): 69.0 (55.8 to 73.0) Gy Median Total RT Dose to Metastatic Cervical Lymph Nodes (range) 69.0 (64.6 to 84) Gy Median Total PBT Dose 28.6–39.6 Gy(RBE)	**Median F/U (range):** 43 (7 to 68) mos	**OS (95% CI)** • 3-year: 87.0% (75.7 to 99.9%) **PFS (95% CI)** • 3-year: 74.1% (60.0 to 91.6%) **Local Control (95%CI)** • 3-year: 86.6% (75.0 to 100%) **Regional Control (95%CI)** • 3-year: 83.9% (71.7 to 98.0%) **Treatment Response, % (n/N)** • CR: 84.8% (28/33) • PR: 15.2% (5/33) **Recurrence/Progression, % (n/N):** • overall: 24.2% (8/33) • local: 6.1% (2/33) • cervical lymph node (regional): 9.1% (3/33) • local and regional: 3% (1/33) • local and distant: 3% (1/33) • regional and distant: 3% (1/33) • Median Time to recurrence (range) 6 (5 to 31) mos	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: timeframe NR *Late Toxicities:* >24 mos **Acute toxicities, % (n/N)** • Grade 1 -Mucositis: 0% (0/33) -Dermatitis: 0% (0/33) -Neutropenia: 3% (1/33) -Anemia: 36.4% (12/33) -Thrombocytopenia: 15.2% (5/33) -Nausea: 45.5% (15/33) -Dry mouth: 36.4% (12/33) -Weight loss: 63.6% (21/33) -Hepatobiliary disorders: 3% (1/33) -Fever: 9.1% (3/33) -Depression: 3% (1/33) -Catheter-related infection: NR -Grade I Edema (face, neck): 72.7% (24/33) • Grade 2 -Edema (face, neck): 0% (0/33) -Mucositis: 21.2% (7/33) -Dermatitis: 66.6% (22/33) -Neutropenia: 36.4% (12/33) -Anemia: 39.4% (13/33) -Thrombocytopenia: 9.1% (3/33) -Dry mouth: 54.5% (18/33) -Nausea: 30.3% (10/33) -Grade I Hiccups: 12.1% (4/33) -Hiccups: 12.1% (4/33) -Depression: 6.1% (2/33) -Catheter-related infection: 0% (0/33) -Hepatobiliary disorders: 0% (0/33) -Fever: 12.1% (4/33)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
					Mortality, % (n/N) • all-cause: NR • due to disease progression: 9.1% (3/33) • due to secondary cancers (not reported whether RT-related): 3% (1/33) • due to treatment-related toxicity: 0% (0/33)	-Weight loss: 30.3% (10/33) • Grade 3 -Mucositis: 78.8% (26/33) -Dermatitis: 33.3 (11/33) -Neutropenia: 48.4% (16/33) -Anemia: 0% (0/33) -Thrombocytopenia: 0% (0/33) -Nausea: 18.2% (6/33) -Dry mouth: 9.1% (3/33) -Weight loss: 6.1% (2/33) -Hiccups: 3% (1/33) -Hepatobiliary disorders: 0% (0/33) -Fever: 0% (0/33) -Depression: 0% (0/33) -Catheter-related infection: 12.1% (4/33) -Edema (face, neck): 0% (0/33) • Grade 4 -Mucositis: 0% (0/33) -Dermatitis: 0% (0/33) -Neutropenia: 3% (1/33) -Anemia: 0% (0/33) -Thrombocytopenia: 0% (0/33) -Nausea: NR -Dry mouth: NR -Weight loss: NR -Hiccups: 0% (0/33) -Hepatobiliary disorders: 0% (0/33) -Fever: 0% (0/33) -Depression: 0% (0/33) -Catheter-related infection: NR **Late toxicities, % (n/N)** • Grade 1 - Osteonecrosis of jaw: 0% (0/30) - Dysgeusia: 36.7% (11/30)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						- Xerostomia: 56.7% (17/30) - Dental caries: 0% (0/30) • Grade 2 - Osteonecrosis of jaw: 3.3% (1/30) - Dysgeusia: 16.7% (5/30) - Xerostomia: 3.3% (1/30) - Dental caries: 33.3% (10/30) • Grade 3 - Osteonecrosis of jaw: 0% (0/30) - Dysgeusia: NR - Xerostomia: 0% (0/30) - Dental caries: 13.3% (4/30) • Grade 4 -Osteonecrosis of jaw: 0% (0/30) -Dysgeusia: NR -Xerostomia: NR -Dental caries: NR
Toyomasu 2018 Retrospective Case Series *High RoB* Japan Funding: NR COI: None declared. --- An additional group (n=21) of patients received carbon ion instead of	**Diagnosis:** Head & Neck (Sinonasal Squamous Cell Carcinoma) **Indication:** Curative Intent	N=38 Male: 71% Median Age (range): 60 (35 to 89) years **Performance Status** • 0: 16% • 1: 76% • 2: 8% **Tumor Location** • Maxillary sinus: 58% • Ethmoid sinus: 29% • Nasal cavity: 5% • Frontal sinus: 5% • Sphenoid sinus: 3%	PBT PBT Dose Protocols received by patients -65 Gy (RBE): 44% -70.2 Gy (RBE): 44% -70 Gy (RBE): 12%	**Median F/U (range):** 30 months (8 to 127) mos **Median Survivor F/U (range):** 65 (9 to 127) mos	**OS (95% CI), (n=59)** • 3-year: 56.2% (NR) • 5-year: 41.6% (NR) **PFS (95% CI), (n=59)** • 3-year: 42.9% (NR) • 5-year: 34.7% (NR) **Local Control (95% CI), (n=59)** • 3-year: 54% (NR) • 5-year: 50.4% (NR) **Mortality** **Mortality, % (n/N)** • due to treatment-related toxicity (grade 5): 2.6% (1/38)	**Harms (n=38)** *Toxicity Grading Criteria:* CTCAE version 4.0 *Acute Toxicities*: timeframe NR *Late Toxicities:* timeframe NR **Acute toxicities, % (n/N)** • Grade 3: 10.5% (4/38) -dermatitis: 10.5% (4/38) **Late toxicities, % (n/N)** • Grade ≥3: 18.4% (7/38) • Grade 3: -Oral cavity fistula: 2.6% (1/38) -Oral hemorrhage: 2.6% (1/38) -Sinus pain: 2.6% (1/38) - Glaucoma: 2.6% (1/38) - Olfactory nerve disorder: 2.6% (1/38)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
PBT; OS, PFS and Local Control are reported only for overall cohort.		**Stage** • I: 3% • II: 3% • III: 13% • IVA: 47% • IVB: 26% • unclassified: 8%				• Grade 4: -Sinus disorder: 2.6% (1/38) -skin ulceration: 2.6% (1/38) -Retinopathy: 2.6% (1/38) -Glaucoma: 5.3% (2/38) -Optic nerve disorder: 5.3% (2/38) -Brain necrosis: 5.3% (2/38) -Cerebrospinal fluid leakage: 2.6% (1/38) • Grade 5: -Brain necrosis: 2.6% (1/38)
Vogin 2015 Retrospective Case Series *High RoB* France Funding: NR COI: NR	**Diagnosis:** Head & Neck (ectopic reccurence of skull-base and cervical chordomas) **Indication:** Salvage	N=13 Male: 46% Median Age (range): 49 (12 to 67) years	Surgery and postop Proton-Photon RT Median cumulative RT Dose (range): 70.2 (67 to 74) Gy(isoE)	**Median F/U (range):** 83 (26 to 176) mos	**Recurrence/Progression, % (n/N):** • single-site relapse along surgical or biopsy pathway: 38.4% (5/13) • remote prevertebral relapse: 46% (6/13) • subcutaneous distant metastasis: 23.1% (3/13) • lung distant metastasis: 15.4% (2/13) • regional nodal: 15.4% (2/13) • Median time to relapse: 19.5 (14 to 27) mos **Mortality, % (n/N)** • all-cause: 46% (6/13)	**NR**
Weber 2018 Retrospective Case Series	**Diagnosis:** Head & Neck (skull-base	N=251 Male: 43.4%	PBT with (n=135) or without photons (n=116)	**Median F/U (range):** 87.3 mos	**OS (95% CI)** • 7-year: 93.6% (89.6 to 96.7) **Failure Free Survival (95% CI)**	**Harms** *Toxicity Grading Criteria:* CTCAE (version NR) **Toxicity-Free Survival (95% CI)**

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
High RoB Switzerland Funding: NR COI: None declared	chondrosarcomas) **Indication:** Curative Intent	**Received Pre-RT Surgery:** 100% **Brainstem compression prior to RT**: 53.4% **Optic Apparatus compression prior to RT**: 45.8%	Mean administered dose ±SD: -institution 1: 69.67 ± 1.49 -institution 2: 69.86 ± 1.63	**Median Survivor F/U (range):** 88 mos	• 7-year:93.1% (89.6 to 96.7) **Progression/Recurrence, % (n/N):** • overall: 6% (15/251) • local: 4.4% (11/251) • distant: 1.2% (3/251) • local and distant: <1% (1/251) **Mortality, % (n/N):** • all-cause: 10% (25/251) • tumor progression: 4% (10/251) • other tumors: 2% (5/251) • secondary radiation induced cancers (probably): >1% (2/251) • other (not specified): 4% (10/251)	• 7-year: 84.2% (79.3 to 89.5) **Acute Toxicities, % (n/N):** • Grade ≥2: 0% (0/251) **Late Toxicities, % (n/N):** • Grade ≥3: 15.1% (38/251) • Grade 5: <1% (1/251) -brain necrosis: <1% (1/251)
Weber 2016 Retrospective Case Series *High RoB* Switzerland Funding: NR COI: None declared	**Diagnosis:** Head & Neck (low grade skull-base chondrosarcoma and chordoma) **Indication:** Curative Intent • Curative intent: 77%	N=222 Male: 52.7% Mean Age ± SD: 40.8 ± 18.4 years **Histology** • chordoma: 68% • chondrosarcoma: 32% **Indication** **Surgery** • Subtotal Resection: 96.8%	Pencil Beam PBT Mean PBT Dose(SD): 72.5(2.2) Gy(RBE)	**Median F/U (range):** 50 (4 to 176) mos	**OS (95% CI)** • 5-year: 86.4% (81.0% to 92.2%) • 7-year: 80.0% (72.4% to 88.4%) **Local Control (95% CI)** • 5-year: 81.4% (75.5% to 87.7%) • 7-year: 78.3% (71.4% to 85.9%)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Late Toxicities:* >3 mos **Toxicity Free Survival, Grade ≥3 (95% CI)** • 5-year: 87.2 (82.4 to 92.3) • 7-year: 87.2 (82.4 to 92.3) **Late Toxicities, % (n/N):** • Grade ≥3: 8.1% (18/222) -grade 3 unilateral optic neuropathy: 2.3% (5/222) -grade 3temporal lobe necrosis: 5.9% (13/222)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
	• recurrent: 23%	• Gross Total Resection: 3.2% **Brainstem Compression:** • yes: 11.3% • abutment: 20.7% **Optic Apparatus Compression** • yes: 10.8% • abutment: 19.8% **Postoperative Complications:** 30.6%			**Distant Metastasis-Free Survival (95% CI)** • 5-year: 91.6% (91.6% to 98.6%) • 7-year: 91.6% (91.6% to 98.6%) **Progression/Recurrence, % (n/N):** • local: 15.8% (35/222) • distant: 3.6% (8/222) **Mortality, % (n/N):** • All-cause: 13.1% (29/222) • local progression: 9% (20/222) • other (not specified): 4% (9/222)	-grade 3cerebellum brain parenchymal necrosis: <1% (1/222) -grade 4 bilateral optic neuropathy: <1% (2/222)
Zenda 2015 Retrospective Case Series *High RoB* Japan Funding: NR COI: None declared	**Diagnosis:** Head & Neck (malignancies of the nasal cavity, para-nasal sinuses, or skull base) **Indication:** Curative Intent	N=112 eligible, 112 analyzed (survival/mortality), 90 analyzed (safety) Male: 57.8% Median Age: 57 (17 to 84) years **Tumor Location** • maxillary sinus: 13.3% • ethmoid sinus: 8.9% • sphenoid sinus: 5.6% • nasal cavity: 68.9%	PBT alone (n=43) or with prior surgery (n=16), or with prior chemotherapy (n=20) or concurrent chemotherapy (n=11) Median Total PBT Dose: 65 GyE, or 60 GyE (mucosal melanoma patients only)	**Median F/U (range):** 57.5 (12.4 to 162.7) mos	**OS (95% CI), (n=112)** • 5-year:64.2% **PFS (95% CI), (n=112)** • 5-year: 44.5% **Recurrence/Progression, % (n/N):** • Overall: 49.1% (55/11) • local: 23.2% (26/112) • regional: 112.5% (14/112) • distant: 13.4% (15/112) **Mortality, % (n/N):** • All-cause: 10.7% (12/112)	**Harms (n=90)** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: timeframe NR *Late Toxicities:* timeframe NR **Late toxicities, % (n/N)** <u>Median Time to onset of grade ≥2 late toxicity (excluding cataract):</u> 39.2 (2.7 to 99.8) mos • <u>Grade 1:</u> - Hearing Loss: 1.1% (1/90) - Nerve Disorder: 0% (0/90) - Encephalomyelitis Infection: 0% (0/90) - Cataract: 1.1% (1/90)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		• other: 3.3% **Tumor Type** • Squamous Cell Carcinoma: 24.4% • adenoid cystic carcinoma: 16.6% • olfactory neuroblastoma: 30% • melanoma: 15.6% • others: 13.3% **T Status** • T1: 4.4% • T2: 17.8% • T3: 10% • T4: 60% • Tx: 7.8% **N Status** • N0: 96.7% N1a: 3.3% • N2: 0%				- Optic Nerve Disorder: 0% (0/90) - Brain Necrosis: 5.5% (5/90) - Soft Tissue Necrosis: 0% (0/90) - Bone Necrosis: 0% (0/90) • <u>Grade 2:</u> - Hearing Loss: 1.1% (1/90) - Nerve Disorder: 1.1% (1/90) - Encephalomyelitis Infection: 0% (0/90) - Cataract: 1.1% (1/90) - Optic Nerve Disorder: 4.4% (4/90) - Brain Necrosis: 1.1% (1/90) - Soft Tissue Necrosis: 0% (0/90) - Bone Necrosis: 4.4% (4/90) • <u>Grade 3:</u> 18.9% (17/90) - Hearing Loss: 2.2% (2/90) - Nerve Disorder: 1% (1/90) - Encephalomyelitis Infection: 0% (0/90) - Cataract: 5.6% (5/90) - Optic Nerve Disorder: 1.1% (1/90) - Brain Necrosis: 1.1% (1/90) - Soft Tissue Necrosis: 1.1% (1/90) - Bone Necrosis: 2.2% (2/90) • <u>Grade 4:</u> 6.7% (6/90) - Hearing Loss 0% (0/90) - Nerve Disorder: 0% (0/90) - Encephalomyelitis Infection:2.2% (2/90) - Cataract: 0% (0/90)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						- Optic Nerve Disorder: 4.4% (4/90) - Brain Necrosis: 0% (0/90) - Soft Tissue Necrosis: 0% (0/90) -: Bone Necrosis 0% (0/90)
Zenda 2016 Prospective Case Series *High RoB* Japan Funding: supported by a Ministry of Health, Labour and Welfare grant-in-aid for cancer research COI: none declared	**Diagnosis:** Head & Neck (mucosal melanoma of nasal cavity and para-nasal sinuses) **Indication:** Curative Intent	N=32 Male: 37.5% Median Age (range): 73 (36 to 89) years **Tumor Site** • nasal cavity: 87.5% • paranasal sinus: 12.5% **Performance Status** • 0 to 1: 100% **T, N, M status** • T3N0M0: 34.4% • T4N0M0: 65.6%	PBT Median Total PBT Dose: 60 GyE	**Median F/U (range):** 36.4 mos	**OS (95% CI),** • 2-year: 55.9% • 3-year: 46.1% **PFS (95% CI),** • 3-year: 36.4% **Local Control (95% CI)** • 1-year: 75.8% (63.8% to 92.4%) **Recurrence/Progression, % (n/N):** • Overall: 68.8% (22/32) • local: 12.5% (4/32) • local and distant: 6.3% (2/32) • regional: 12.5% (4/32) • regional and distant: 12.5% (4/32) • distant: 28.1% (9/32) **Mortality** • due to distant metastases: 93.3% (n=NR)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: timeframe NR *Late Toxicities:* timeframe NR **Acute Toxicities, % (n/N)** • Grade 1 - Neutropenia: 0% (0/32) - Anemia: 3.1% (1/32) - Thrombocytopenia: 0% (0/32) - Nausea/Headache: 0% (0/32) - Conjuctivitis: 34.4% (11/32) - Mucositis: 15.6 % (5/32) - Dermatitis: 28.1 % (9/32) • Grade 2 - Neutropenia: 0% (0/32) - Anemia: 0% (0/32) - Thrombocytopenia: 0% (0/32) - Nausea/Headache: 3.1% (1/32) - Conjuctivitis: 12.5% (4/32) - Mucositis: 28.1% (9/32) - Dermatitis: 59.3% (19/32) • Grade 3 - Neutropenia: 0% (0/32) - Anemia: 0% (0/32)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						- Thrombocytopenia: 0% (0/32) - Nausea/Headache: 0% (0/32) - Conjuctivitis: 0% (0/32) - Mucositis: 3.1% (1/32) - Dermatitis: 12.5% (4/32) • Grade 4 - Neutropenia: 0% (0/32) - Anemia: 0% (0/32) - Thrombocytopenia: 0% (0/32) - Nausea/Headache: 0% (0/32) - Conjuctivitis: 0% (0/32) - Mucositis: 0% (0/32) - Dermatitis: 0% (0/32)

CGE = Cobalt Gray Equivalent; CI = confidence interval; cm = centimeter; CNS = central nervous system; COI = conflict of interest; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; EBRT = external beam radiation therapy; ECOG = Eastern Cooperative Oncology Group; F/U = follow-up; Gy = Gray (unit); GyE = Gray Equivalent; Gy(RBE) = Gray (Relative Biological Equivalent); IMPT = Intensity Modulated Proton Therapy; IQR = Interquartile Range; mos = months; NR = not reported; OS = overall survival; PBT = proton beam therapy; PFS = progression free survival; PR = partial response; RoB = risk of bias; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; SD = standard deviation; WHO = World Health Organization;
* In McDonald 2016 n=53 patients were reported to have survived past 3 months post-reirradiation; however some of the treatment related deaths were said to occur after this period. No clear total of end-of-study mortality was reported.
†In Phan 2016, 8 sites of distant metastasis were reported as "most common sites"; whether or not there were more patients with distant recurrence not clearly described.
‡ Romesser 2016: Late AEs limited to patients (n=69) with follow-up >90 days unless otherwise noted.
§ Romesser 2016: Trismus data limited to patients without symptoms prior to treatment
** Romesser 2016: Dysgeusia limited to patients without G-tube (feeding tube) in place

Appendix Table G2. Study characteristics and patient demographics: nonrandomized comparative studies of proton beam therapy in head & neck (including skull-base) cancers

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Cohort studies							
Blanchard 2016 [Crossover with Gunn 2016 (case series)] Retrospective Matched-Pair Cohort *Moderately High* USA	512 and 50 eligible IMRT and PBT patients, 150 propensity matched	**Intensity modulated PBT (n = 50):** IMPT Gross Tumor plus margins: 66 Gy (small volume disease), 70 Gy (advanced disease), 54 to 63 (elective regions) **Intensity modulated photon RT (n = 100):** IMRT Gross Tumor plus margins: 66 Gy (small volume disease), 70 Gy (advanced disease), 54 to 63 (elective regions) • Patients matched on unilateral/bilateral treatment, disease site, human papillomavirus status, T and N	**Inclusion:** Adults with oropharynx cancer **Exclusion:** NR	*PBT vs. Photons* Median Age (range): 61 years (37 to 84) vs. 55.5 years (34 to 78) • ≤60: 46% vs. 67%, **p<0.01** • >60: 54% vs. 33% Male %: 54% vs. 33% Stage • -I: 2% • -II: 0% • -III: 18% • -IVA: 74% • -IVB: 6% Smoking History: • 0 pack years: 50% vs. 45% • 0 to 10 pack years: 8% vs. 17% • >10 pack years: 42% vs. 38% T Status • T1 to T2: 80% vs. 80% • T3 to T4: 20% vs. 20% N-Status • N0 to N1: 20% vs. 20% • N2 to N3: 80% vs. 80% Tumor Location • Tonsil: 54% vs. 54% • Base of tongue: 46% vs. 46% Induction Chemotherapy (yes): 40% vs. 44%	*PBT vs. Photons* **Median F/U (range):** 29 (8 to 49) months vs. 33 (2 to 55) months **% F/U:** 26.6% (150/562)	Survival Disease Control Disease Failure Mortality Harms	Funding: Supported in part by the National Institutes of Health (NIH)/ National Cancer Institute (NCI) Cancer Center Support (Core) Grant CA016672 and U19 CA021239 to The University of Texas MD Anderson Cancer Center. Dr. Blanchard received funding from The Foundation Nuovo Soldati for Medical Research, the Philippe Foundation and the FRM grant SPE20150331822 COI: None declared

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		status, smoking, and for receiving concomitant chemotherapy **Indication:** Curative Intent		Concurrent Chemotherapy (yes): 64% vs. 64% Neck Dissection: • pre-RT: 6% vs. 11% • post-RT: 12% vs. 15%			Notes:
Romesser 2016 Retrospective Comparative Cohort *Moderately High* USA	41	**PBT (n=18)** Uniform scanning beams Median PBT dose to primary site (IQR): 66.0 (IQR 61.2 to 66.0) Gy(RBE) **Intensity modulated RT (n=23)** 4-6 static IMRT beams (ipsilateral preferred) Median RT dose to primary site (IQR): 66.0 (IQR 66.0 to 66.0) Gy • Patients with resectable disease underwent surgical resection prior to	**Inclusion:** Unilateral head and neck irradiation for major salivary gland cancer or cutaneous squamous cell carcinoma metastasis to major salivary gland **Exclusion:** NR	PBT vs. IMRT Median age: 60.4 vs. 60.9 years Male %: NR Median tumor size: 2.2 vs. 2.7 cc Tumor location • parotid gland: 78% vs. 91% • submandibular gland: 22% vs. 10% Unresectable disease (yes): 11% vs. 9% Perineural Involvement (yes) (surgery patients only): 44% vs. 57% Lymphovascular Invasion (yes) (surgery patients only): 6% vs. 29% Neck Nodal Irradiation (yes): 50% vs. 26% Concurrent chemotherapy: 22% vs. 30%	IMPT vs. IMRT **Median F/U (range):** 16.1 (IQR, 8.7 to 24.4) vs. 4.7 (1.6 to 7.9) months, **p < 0.001** **% F/U:** 100%	Overall Survival Disease Status Toxicities	Funding: NR COI: One author has a minority investment in ProCure (Proton Therapy center) Notes:

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		irradiation (90%; 37/41); those with unresectable (7%; 3/41) or medically inoperable (2%; 1/41) disease were treated with definitive RT with or without concurrent chemotherapy					
Sio 2016 Retrospective Comparative Cohort *Moderately High*	86	**Intensity modulated PBT (n=35)** Mean PBT dose (SD): 67.0 (4.1) Median PBT dose (range): 70.0 (59.0 to 70.0) **Intensity modulated photon RT (n=46)** Mean RT dose (SD): 69.3 (2.4) Median RT dose (range): 70.00 (58.0 to 70.0)	**Inclusion:** Age >18 years; tissue diagnosis of squamous cell carcinoma originating in the oropharynx (base of tongue, tonsil, or other subsites); concurrent chemotherapy as part of definitive therapy (i.e., no surgical resection of either primary tumors or nodal stations at initial management; induction chemotherapy was allowed); no prior radiotherapy; no evidence of distant	IMPT vs. IMRT Mean Age (SD): 59.1 (10.2) vs. 58.2 (9.9) Male %: 86% vs. 91% Primary tumor location • Base of tongue: 57% vs. 50% • Tonsil: 31% vs. 50% • Other: 11% vs. 0% T Status • T1 to T2: 89% vs. 61% • T3 to T4: 11% vs. 37% N Status: • N0 to N2a: 43% vs. 26% • N2b to N3: 57% vs. 74% TNM Stage • I: 3% vs. 2% • II: 3% vs. 4%	IMPT vs. IMRT **Median F/U (IQR):** 7.7 (3.97 to 22.77) months vs. 2.7 (0.3 to 10.27) months **% F/U:** 51% (18/35) vs 61% (28/46)	MDASI-HN	Funding: Funded in part by NCI R21 CA132109 to Xin Shelley Wang; NCI R01 CA026582 to Charles S. Cleeland; and Cancer Center Support (Core) Grant CA016672 to The University of Texas MD Anderson Cancer Center from the US National Cancer Institute, National Institutes of Health. The

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
			metastases; scanning-beam IMPT or photon-based IMRT treatment at a single institution; and completed the MDASI once before beginning radiotherapy (baseline) and at least 3 of the 6 weekly MDASI surveys scheduled during RT (acute phase) or 1 survey within the first 3 months after radiotherapy (subacute phase); chronic phase data (i.e., surveys collected more than 3 months after radiotherapy) were optional. **Exclusion:** surgical resection of either primary tumors or nodal stations at initial management; prior radiotherapy; evidence of distant metastases	• III: 26% vs. 15% • IVA-B: 69% vs.78% Induction Chemotherapy (yes): 74.3% vs. 23.9% HPV_P16 status • Negative: 6% vs. 4% • Positive: 74% vs. 13% • Unknown: 20% vs. 83% P<0.0001			project described was also supported in part by Award Number U19 CA021239 from the National Cancer Institute. COI: The survey instrument used in the study is patented and licensed to the sponsoring research center and one of the authors.
Zhang 2017 Retrospective Comparative Cohort	584 eligble and analyzed	**IMPT (n=50)** Mean Mandibular Dose:	**Inclusion:** Patients w/ oropharyngeal cancer **Exclusion:** NR	IMPT vs. IMRT Age - ≤60: 56.4% vs. 44% - >60: 43.6% vs. 56%	IMPT vs. IMRT **Median F/U (IQR):**	Harms	Funding: Various funds received from NIH/NIDCR, NIH National Cancer

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Moderately High		25.6, **p<0.001 vs. IMRT** **IMRT (n=534)** Mean Mandibular Dose: 41.2 Gy		Male, %: 86.5% vs. 84% Tumor Location - base of tongue: 48.7% vs. 42% - tonsil/other: 51.3% vs. 58% T-Status: -T1 to T2: 80% vs. 65% -T3 to T4: 20% vs. 35% N-Status: -N0 to N1: 20% vs. 17.2% -N2 to N3: 80% vs. 82.8% Tumor Side: -left: 44.6% vs. 52% -right: 53.9% vs. 44% -midline: 0.4% vs. 2% -bilateral: 1.1% vs. 2% Induction Chemotherapy -yes: 40.6% vs. 40% Concurrent Chemotherapy -yes: 67.4% vs. 64%	34.6 vs. 33.8 months, p=0.854 **% F/U:** 100% vs 100%		Institute Head and Neck Specialized Programs of Research Excellence Developmental Research Program and others COI: None declared. Notes:
Simon 2018 Retrospective Comparative Cohort Moderately High	47	**Surgery + PBT (n=23)** 1.8 Gy daily, five days a week for eight weeks, to deliver a total dose of 70 Gy	**Inclusion**: Skull base Chondrosarcoma, surgical resection in our department and immunohistochemical confirmation of the diagnosis. Markers used were anti-	Surgery + PBT vs. PBT alone Male: 57% vs. 41% Mean age (range): 42 (12 to 69) vs. 52 (10 to 85) Tumor Grade	Median F/U (range): 91 months (7 to 182) % F/U: 95.7% (45/47)	Disease specific survival Disease progression Progression free survival	Funding: None COI: None

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
France		[n=4 received combined photon/proton treatment] **Surgery alone (n=24)**	brachyurea, anti-D240 and anti-PS100 antibodies (if not initially available, frozen samples were retrieved for immunohistology). Grade I and II CSA were included, as the treatment and prognosis are identical. All patients were operated on by a team of ENT, neurosurgeons or both, trained in skull base surgery, either by endoscopic surgery or open surgery. **Excludsion**: NR	Grade II: 97.9% (46/47) [all patients] Tumor Location - Anterior skull-base: 4% vs. 50% - Petroclival: 96% vs. 50% p=0.02 Mean Tumor Size (range): 33 (16 to 67) vs. 39 (15 to 70) Symptom presentation - Diplopia: 57% vs. 29% - Headache: 35% vs. 17% - Nasal Obstruction: 4% vs. 29% Surgical approach - Pterional: 22% vs. 21% - Transcochlear: 0% vs. 8% - Infratemporal fossa: 13% vs. 0% - Retrosigmoid: 4% vs. 21% - Lateral rhinotomy: 4% vs. 25%, p=0.05 - Endonasal: 52% vs. 50% Extent of resection - Gross total resection: 13% vs. 54% - Partial resection: 87% vs. 46% p=0.003		Mortality Harms	

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
McDonald 2016 Retrospective Comparative Cohort Moderately High USA	40	**3D conformal PBT (n=14)** Median Primary Tumor dose (range): 71.4 (63 to 75.6) Gy(RBE) Median Neck Dose node negative (range): 50.2 (45.0 to 58.0) Gy(RBE) Median Neck Dose node positive (range): 72.9 (70.0 to 75.6) Gy (RBE) **IMRT (n=26)** With (n=14) or without (n=12) concurrent PBT Median Primary Tumor dose (range): 71.8 (66 to 76.4) Gy(RBE) Median Neck Dose node negative (range): 52.3 (40.0 to 59.4) Gy(RBE)	**Inclusion:** Patients w/ nasopharynx, nasal cavity or paranasal sinus cancers; any T stage, N0-2 receiving radiation either definitively or following surgery; given with or without chemotherapy, who received radiation to the primary tumor site and bilateral cervical lymph node regions. **Exclusion:** Patients with a prior history of head and neck radiation or with a second concomitant active malignancy were excluded.	PBT vs. IMRT Median Age (range): 46.7 (16 to 71) vs. 54.1 (22 to 77) Male, %: 78.6% vs. 53.8% Tumor Location -Nasopharynx: 14.3% vs. 57.7%, **p=0.02** -nasal/paranasal: 85.7% vs. 42.3% Histology -squamous cell carcinoma: 21.4 % vs. 50.0 % -Poorly differentiated carcinoma: 0% vs. 19.2% -Sinonasal undifferentiated: 35.7 % vs. 15.4 % -Esthesioneuroblastoma: 35.7% vs. 3.8% -Neuroendocrine carcinoma: 0% vs. 3.8% -Lymphoepithelioma: 7.1 % vs. 3.8% -High grade mucoepidermoid carcinoma: 0% vs. 3.8% Neck Dissection -upfront: 7.1% vs. 0% -none: 85.7% vs. 96.2% -adjuvant/salvage: 7.1% vs. 3.8%		Harms	Funding: supported in part by the biostatistics and bioinformatics of Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. COI: None declared

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		Median Neck Dose node positive (range): 68.3 (59.4 to 70.29) Gy (RBE)		Chemotherapy -none: 14.3% vs. 11.5% -induction: 21.4% vs. 0% -concurrent: 50% vs. 88.5% -concurrent and adjuvant: 14.2% vs. 0% Gastrostomy tube placement: 14.3 % vs. 84.6%			
Holliday 2015 Retrospective Matched Paris Comparative Cohort Moderately High USA	30	**IMPT (n=10)** 70 Gy to be given in 33 to 35 fractions of 2 to 2.12 Gy per fraction **IMRT (n=20)** 70 Gy to be given in 33 to 35 fractions of 2 to 2.12 Gy per fraction	**Inclusion:** NR **Exclusion:** NR	IMPT vs. IMRT Diagnosis: nasopharyngeal cancer Median Age (IQR): 45 (18 to 55) vs. 51 (39 to 59) Male: 70% vs. 70% WHO grade I: 0% vs. 10% II/III: 90% vs. 75% Unknown: 10% vs. 15% Chemotherapy Induction: 80% vs. 75% Concurrent: 100% vs. 90% Adjuvant: 10% vs. 0%	IMPT vs. IMRT Median follow-up (IQR): 21.6 (13.6 to 28.6) months) vs. 25.8 (17.2 to 36.7) months % F/U: NR	Disease Progression Mortality Harms	Funding: NR COI: None
Sharma 2018 Prospective Comparative Cohort Moderately High	64	**PBT PBS (n=31)** Median Dose: 61.7 Gy **IMRT via volumetric modulated arc therapy (n=33)**	**Inclusion:** Patients with Oropharyngeal squamous cell carcinoma, treated at the University of Pennsylvania between 2013 and 2015 initially with transoral robotic	PBT vs. IMRT Male: 87% vs. 82% Mean Age: 60 vs. 58 years Primary site Tonsil: 65% vs. 61%	PBT vs. IMRT Median F/U: NR % F/U: NR	EORTC QOL Scores	Funding: NR COI: None

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
USA		Median Dose: 62.6 Gy	surgery and selective neck dissection, followed by adjuvant radiation, with or without chemotherapy (according to standard indications) **Exclusion**: NR	Base of tongue: 35% vs. 39% Stage I-III: 13% vs. 15% IVA: 87% vs. 85% Nodal Status N0: 6% vs.3% N1-N2b: 94% vs.88% N2c-N3: 0% vs. 9% T Stage Tis, T1, T2: 90% vs. 97% T3: 10% vs. 3% Chemotherapy: 59% vs. 62%			

IMPT = Intensity modulated proton therapy; PBT = Proton Beam Therapy; Gy = Gray; RoB = Risk of Bias; NR = Not reported; F/U = Follow-up; COI = Conflict of interest; IMRT = Intensity Modulated Radiation Therapy; RT = Radiation therapy; IQR = Interquartile range; RBE = Relative Biological Effectiveness; HPV = Human papilloma virus; OS = Overall Survival; MDASI-HN = MD Anderson Symptom Index – Head and Neck

Appendix Table G3. Detailed data abstraction: nonrandomized comparative studies of proton beam therapy in head & neck (including skull-base) cancers

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Cohort studies			
Blanchard 2016 [Crossover with Gunn 2016 (case series)] IMPT (n=50) vs. IMRT (n=100) Retrospective Matched-Pair Cohort *Moderately High* USA	*PBT vs. Photon* **3 year-OS** 94.3% vs. 89.3% HR 0.42 (95% CI 0.09 to 1.91), p=0.26 adj. HR (multivariate analysis) 0.55 (95% CI 0.12 to 2.5), p=0.44 **Mortality** 4% (2/50) vs. 10% (10/100) **3 year-PFS** 86.4% vs. 85.8% (total of 22 events, 7 PBT and 15 photon) HR 1.02 (95% CI 0.41 to 2.54), p=0.96 adj. HR 1.00 (95% CI 0.39 to 2.6), p=0.99 **3 year-Locoregional Control rates** 91.0% vs. 89.7% HR 1.03 (95% CI 0.35 to 3.02), p=0.96 **Locoregional relapse (disease failure):** 10% (5/50) vs. 10% (10/100) **3 year-Distant Control rates** 97.8% vs. 93.5% HR 0.33 (95% CI 0.04 to 2.74), p=0.30	NR	*PBT vs. Photon* **Harms** [adjusted for age; dichotomized at 60 years] **Acute grade ≥3 dermatitis:** p=0.15 between groups **Acute grade ≥3 mucositis:** p=0.90 between groups Toxicities During RT • **G-tube presence:** 24% (12/50) vs. 38% (38/100); adj. OR 0.53 (95% CI 0.24 to 1.15), p=0.110 • **Patient rated fatigue grade 2 or 3:** 78% (39/50) vs. 86.6% (84/NR); adj. OR 0.49 (95% CI 0.20 to 1.23), p=0.130 • **ER visit:** 32% (16/50) vs. 32% (32/100); adj. OR 0.95 (95% CI 0.45 to 2.0), p=0.890 • **Unscheduled hospitalization:** 20% (10/50) vs. 21% (21/100); adj. OR 0.92 (95% CI 0.39 to 2.2); p=0.840 Toxicities Post RT (3 months) • **G-tube presence:** 12% (6/50) vs. 23% (23/100); adj. OR 0.43 (95%CI 0.16 to 1.17), p=0.100 • **Weight Loss >20% (grade 3) compared to baseline:** 8.3% (4/NR) vs. 13.5% (13/NR); adj. OR 0.64 (95%CI 0.19 to 2.11), p=0.460

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	Distant relapse (disease failure): 2% (1/50) vs. 7% (7/100)		• **G-tube OR weight loss >20% (grade 3):** 18% (9/50) vs. 34% (34/100); adj. OR 0.44 (95%CI 0.19 to 1.0), **p=0.050** • **Patient rated xerostomia grade 2 or 3:** 42% (21/50) vs. 61.2% (60/NR); adj. OR 0.38 (95%CI 0.18 to 0.79), **p=0.009** • **Patient rated fatigue grade 2 or 3:** 40.8% (20/NR) vs. 36.2% (34/NR); adj. OR 1.1 (95%CI 0.53 to 2.27), p=0.800 <u>Toxicities Post-RT (12 months)</u> • **G-tube presence:** 2% (1/50) vs. 7.8% (7/NR) adj. OR 0.16 (95%CI 0.02 to 1.37); p=0.09 • **Weight Loss >20% (grade 3) compared to baseline:** 6.7% (3/NR) vs. 19.3% (7/NR); adj. OR 0.28 (95%CI 0.08 to 1.05), p=0.06 • **G-tube OR weight loss >20% (grade 3):** 8% (4/50) vs. 24.7% (22/NR); adj. OR 0.23 (95%CI 0.07 to 0.73), **p=0.01** • **Patient rated xerostomia grade 2 or 3:** 42% (21/50) vs. 47.2% (42/NR); adj. OR 0.63 (95%CI 0.30 to 1.33), p=0.23 • **Patient rated fatigue grade 2 or 3:** 14.6% (7/NR) vs. 22.1% (17/NR); adj. OR 0.5 (95%CI 0.18 to 1.36), p= 0.17

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Romesser 2016 PBT (n=18) vs. IMRT (n=23) Retrospective Comparative Cohort *Moderately High* USA	PBT vs. IMRT **1 year-OS** 83.3% vs. 93.3%, p=0.08 **1 year-locoregional control** 80% vs. 95.5%, p=0.47 **1 year-freedom from distant metastases (n=38;** excludes 1 and 2 patients, respectively, who had distant metastases prior to RT): 83.3% vs. 93.3%; p=0.66 **Progression/Recurrence** • local: 5.6% (1/18) vs. 8.7% (2/23) • distant: 5.9% (1/17) vs. 19% (4/21) (excludes 1 and 2 patients, respectively, who had distant metastases prior to RT)	NR	*PBT vs. IMRT* CTCAE v 4.0 <u>Acute Dermatitis, % (n/N):</u> Acute dermatitis grade ≥2: 100.0% (18/18) vs. 73.9% (17/23), **p=0.019** • Grade 0: 0.0% (0/18) vs. 0.0% (0/23) • Grade 1: 0.0% (0/18) vs. 26.1% (6/23) • Grade 2: 72.2% (13/18) vs. 39.1% (9/23) • Grade 3: 27.8% (5/18) vs. 34.8% (8/23) • Grade 4: 0.0% (0/18) vs. 0.0% (0/23) <u>Acute Mucositis, % (n/N):</u> Acute mucositis grade ≥2: 16.7% (3/18) vs. 52.2% (12/23), **p=0.02** • Grade 0: 66.7% (12/18) vs. 13.0% (3/23) • Grade 1: 16.7% (3/18) vs. 34.8% (8/23) • Grade 2: 16.7% (3/18) vs. 43.5% (10/23) • Grade 3: 0.0% (0/18) vs. 8.7% (2/23) • Grade 4: 0.0% (0/18) vs. 0.0% (0/23) <u>Acute Nausea, % (n/N):</u> Acute nausea grade ≥2: 11.1% (2/18) vs. 56.5% (13/23), **p=0.003** • Grade 0: 83.3% (15/18) vs. 30.4% (7/23) • Grade 1: 5.6% (1/18) vs. 13.0% (3/23) • Grade 2: 11.1% (2/18) vs. 56.5% (13/23) • Grade 3: 0 (0.0%) vs. 0 (0.0%) • Grade 4: NR

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			Acute Dysgeusia, % (n/N): Acute dysgeusia grade ≥2: 5.6% (1/18) vs. 65.2% (15/23), **p<0.001** • Grade 0: 77.8% (14/18) vs. 17.4% (4/23) • Grade 1: 16.7% (3/18) vs. 17.4% (4/23) • Grade 2: 5.6% (1/18) vs. 65.2% (15/23) • Grade 3, 4: NR Acute Dysphagia, % (n/N): • Grade 0: 83.3% (15/18) vs. 52.2% (12/23) • Grade 1: 11.1% (2/18) vs. 39.1% (9/23) • Grade 2: 5.6% (1/18) vs. 8.7% (2/23) • Grade 3: 0.0% (0/18) vs. 0.0% (0/23) • Grade 4: 0.0% (0/18) vs. 0.0% (0/23) Acute Fatigue, % (n/N): • Grade 0: 61.1% (11/18) vs. 8.7% (2/23) • Grade 1: 33.3% (6/18) vs. 82.6% (19/23) • Grade 2: 5.6% (1/18) vs. 8.7% (2/23) • Grade 3: 0.0% (0/18) vs. 0.0% (0/23) • Grade 4: NR **Requiring a treatment break**, % (n/N): 16.7% vs. 21.7%, p=0.684 **Requiring a prophylactic**, % (n/N): 0% vs. 0% **Requiring reactive gastrostomy tube or tracheostomy**, % (n/N): 0% vs. 0%

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Sio 2016 IMPT (n=35) vs. IMRT (n=46) Retrospective Comparative Cohort *Moderately High*	NR	IMPT vs. IMRT **Average (mean ± SD) symptom burden score in the top 11 (most severe) items on the MDASI-HN** **Top 5 scores*** • Baseline: 1.0 vs. 1.4, p=NS • Acute Phase: 6.0 vs. 6.5, p=NS • Subacute Phase: 5.15 (2.66) vs. 6.58 (1.98), **p=0.013** • Chronic Phase: 3.8 vs. 4.1, p=NS [Baseline, acute and chronic estimated from graph] **Top 11 scores*** • Baseline: 1.2 vs. 1.5, p=NS • Acute Phase: 5.4 vs. 5.7, p=NS • Subacute Phase: 4.8 vs. 5.5, p=NS • Chronic Phase: 2.7 vs. 3.0, p=NS [all estimated from graph] **MDASI-HN Food Taste** • Baseline: 1.09 (1.93) vs. 1.07 (2.34) • Acute Phase: 6.88 (2.75) vs.7.65 (2.54) • Subacute Phase: 5.76 (3.60) vs. 7.70 (2.44), **p=0.010** • Chronic Phase: 4.50 (3.43) vs. 4.43 (2.99)	NR

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		MDASI-HN Dry Mouth • Baseline: 1.14 (1.96) vs. 0.91 (2.21) • Acute Phase: 5.55 (3.13) vs. 6.24 (2.57) • Subacute Phase: 5.27 (3.28) vs.6.65 (2.51) • Chronic Phase: 5.47 (3.06) vs. 5.79 (2.44) **MDASI-HN Swallowing/Chewing** • Baseline: 0.83 (1.22) vs. 1.87 (2.76), **p=0.041** • Acute Phase: 6.24 (3.03) vs. 6.17 (2.81) • Subacute Phase: 5.19 (3.07) vs. 6.40 (2.62) • Chronic Phase: 3.76 (3.05) vs. 3.18 (2.64) **MDASI-HN Fatigue** • Baseline: 1.68 (2.00) vs. 1.80 (2.60) • Acute Phase: 5.33 (3.01) vs. 6.00 (2.49) • Subacute Phase: 4.69 (3.00) vs. 5.77 (2.47) • Chronic Phase: 2.53 (2.18) vs. 3.14 (2.26) **MDASI-HN Pain** • Baseline: 1.77 (2.76) vs. 1.83 (2.92) • Acute Phase: 5.97 (2.72) vs. 5.09 (2.41) • Subacute Phase: 4.19 (3.18) vs. 4.05 (2.81) • Chronic Phase: 1.59 (2.21) vs. 1.21 (1.66) **MDASI-HN Appetite** • Baseline: 0.89 (1.79) vs. 1.39 (2.53)	

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		• Acute Phase: 5.85 (3.27) vs. 6.13 (3.04) • Subacute Phase: 4.68 (3.53) vs. 6.37 (3.21); **p=0.048** • Chronic Phase: 2.12 (3.08) vs. 4.14 (3.01), **p=0.036** **MDASI-HN Mucus** • Baseline: 0.57 (1.17) vs. 1.35 (2.68) • Acute Phase: 5.73 (2.91) vs. 6.09 (2.78) • Subacute Phase: 4.88 (3.66) vs. 6.14 (2.92) **p=0.038** • Chronic Phase: 2.24 (2.84) vs. 2.89 (2.64) **MDASI-HN Sleep** • Baseline: 2.03 (2.58) vs. 2.11 (2.82) • Acute Phase: 4.36 (3.54) vs. 4.72 (2.92) • Subacute Phase: 4.04 (3.69) vs. 4.00 (2.68) • Chronic Phase: 2.47 (2.98) vs. 2.57 (2.41) **MDASI-HN Mouth Sores** • Baseline: 0.43 (0.95) vs. 0.93 (2.38) • Acute Phase: 5.48 (2.84) vs. 5.76 (3.05) • Subacute Phase: 5.35 (3.51) vs. 5.00 (3.23) • Chronic Phase: 1.28 (3.20) vs. 1.39 (1.89) **MDASI-HN Drowsiness** • Baseline: 1.46 (2.08) vs. 1.78 (2.80) • Acute Phase: 4.55 (3.34) vs. 4.93 (2.83)	

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		• Subacute Phase: 4.35 (3.16) vs. 4.63 (2.73) • Chronic Phase: 2.18 (2.56) vs. 2.11 (2.38) **MDASI-HN Distress** • Baseline: 1.83 (2.70) vs. 2.17 (2.46) • Acute Phase: 3.21 (2.90) vs. 3.24 (2.87) • Subacute Phase: 3.42 (3.35) vs. 3.40 (2.63) • Chronic Phase: 2.00 (3.02) vs. 2.21 (2.57) **Proportion of patients (%, n/N) with moderate to severe symptoms (scores of 4-10) in the top 11 (most severe) items on the MDASI-HN** **MDASI-HN Food Taste** • Baseline: 14.3% (5/35) vs. 8.7% (4/46) • Acute Phase: 91% (30/33) vs. 93.5% (43/46) • Subacute Phase: 65.4% (17/26) vs. 93% (40/43); **p<0.003** • Chronic Phase: 60.7% (17/28) vs. 50% (9/18) **MDASI-HN Dry Mouth** • Baseline: 8.6% (3/35) vs. 10.9% (5/46) • Acute Phase: 69.7% (23/33) vs. 87% (40/46)	

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		• Subacute Phase: 65.4% (17/26) vs. 83.7% (36/43) • Chronic Phase: 77.8% (14/18) vs. 82.1% (23/28) **MDASI-HN Swallowing/Chewing** • Baseline: 2.9% (1/35) vs. 21.7% (10/46), **p=0.014** • Acute Phase: 81.8% (27/33) vs. 78.3% (36/46) • Subacute Phase: 65.4% (17/26) vs. 81.4% (35/43) • Chronic Phase: 38.9% (7/18) vs. 35.7% (10/28) **MDASI-HN Fatigue** • Baseline: 22.9% (8/35) vs. 19.6% (9/46) • Acute Phase: 69.7% (23/33) vs. 80.4% (37/46) • Subacute Phase: 73.1% (19/26) vs. 81.4% (35/43) • Chronic Phase: 27.8% (5/18) vs. 50% (14/28) **MDASI-HN Pain** • Baseline: 17.1% (6/35) vs. 21.7% (10/46) • Acute Phase: 78.8% (26/33) vs. 73.9% (34/46) • Subacute Phase: 50% (13/26) vs. 53.5% (23/43)	

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		• Chronic Phase: 16.7% (3/18) vs. 14.3% (4/28) **MDASI-HN Appetite** • Baseline: 2.9% (1/35) vs. 15.2% (7/46) • Acute Phase: 75.8% (25/33) vs. 73.9% (34/46) • Subacute Phase: 57.7 (15/26) vs. 74.4% (32/43) • Chronic Phase: 22.2% (4/18) vs. 50% (14/28) **MDASI-HN Mucus** • Baseline: 5.7% (2/35) vs. 15.2% (7/46) • Acute Phase: 72.75 (24/33) vs. 73.9% (34/46) • Subacute Phase: 61.5% (16/26) vs. 83.7% (36/43), **p=0.038** • Chronic Phase: 27.8% (5/18) vs. 35.7% (10/28) **MDASI-HN Sleep** • Baseline: 25.7% (9/35) vs. 23.9% (11/46) • Acute Phase: 51.5% (17/33) vs. 60.9% (28/46) • Subacute Phase: 53.9% (14/26) vs. 58.1% (25/43) • Chronic Phase: 33.3% (6/18) vs. 35.7% (10/28) **MDASI-HN Mouth Sores**	

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		• Baseline: 2.9% (1/35) vs. 8.7% (4/46) • Acute Phase: 78.8% (26/33) vs. 76.1% (35/46) • Subacute Phase: 69.2% (18/26) vs. 69.8% (30/43) • Chronic Phase: 11.1% (2/18) vs. 14.3% (4/28) **MDASI-HN Drowsiness** • Baseline: 14.3% (5/35) vs. 19.6% (9/46) • Acute Phase: 57.6% (19/33) vs. 60.9% (28/46) • Subacute Phase: 65.4% (17/26) vs. 67.4% (29/43) • Chronic Phase: 22.2% (4/18) vs. 21.4% (6/28) **MDASI-HN Distress** • Baseline: 28.6% (10/35) vs. 26.1% (12/46) • Acute Phase: 45.5% (15/33) vs. 39.1% (18/46) • Subacute Phase: 42.3% (11/26) vs. 48.8% (21/43) • Chronic Phase: 22% (4/18) vs. 25% (7/28)	
Zhang 2017 IMPT (n=50) vs. IMRT (n=534)	NR	NR	CTCAE v 4.0 Median Time to Osteoradionecrosis 11.4 (6.74 to 16.1) months

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Retrospective Comparative Cohort *Moderately High*			<u>Patients with any grade Osteoradionecrosis</u> 2% (1/50) vs. 7.7% (41/534) <u>Patients with Osteoradionecrosis</u> -Grade 1: 2% (1/50) vs. 4.3% (23/534) -Grade 2: 0% (0/50) vs. <1% (1/534) -Grade 3: 0% (0/50)vs. <1% (5/534) -Grade 4: 0% (0/50) vs. 2.2% (12/534)
Simon 2018 Surgery + PBT (n=23) vs. Surgery alone (n=24) Moderately High France	Surgery + PBT (n=23) vs. Surgery alone (n=24) [All patients] Surgery + PBT (n=22) vs. Surgery alone (n=12) [Petroclival patients only] <u>Disease Specific OS (95% CI)</u> • All patients - 5-year: 100% vs. 89.8% (76.2% to 100%) - 10-year: 100% vs. 89.8% (76.2% to 100%) p=0.138 • Petroclival patients only (n=34) - 5-year: 100% vs. 76.4% (46.1% to 100%) - 10-year: 100% vs. 76.4% (46.1% to 100%) p=0.028 <u>PFS (95% CI)</u> • All patients - 5-year: 100% vs. 67.8% (47.7% to 88.0%) - 10-year: 87.5% (64.6% to 100%) vs. 58.2% (33.5% to 82.8%)	NR	**PBT induced complications (n=28)† vs. Surgery induced complications (n=47), % (n/N)** • All complications: 68% (19/28) vs. 26% (12/47), p<0.001 • All Grade ≥3: 25% vs. 11%, p=0.10 • Death due to complication: 0% (0/47) vs. 2% (1/47), p=0.44 • Cerebro-spinal fluid leak: 0% (0/28) vs. 13% (6/47), p=NR • Meningitis: 0% (0/28) vs. 9% (4/47), p=NR • Cranial nerve palsy: 11% (3/28) vs. 19% (9/47), p=0.34 • Any Hearing Loss: 71.4% (20/28) vs. 14.9% (7/47) - Sensorineural: 39% vs. 6%, p<0.001 - Conductive, p=0.28 - Severe, p=0.02 • Dizziness: 14% (4/28) vs. 0% (0/47), p=0.008 • Pulmonary Embolism: 0% (0/28) vs. 2% (1/47), p=NR • Vision loss: 11% (3/28) vs. 0% (0/47), p=NR • Hypopituarism: 18% (5/28) vs. 0% (0/47), p=NR

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	p=0.006 • Petroclival patients only (n=34) - 5-year: 100% vs. 50% (15.4% to 84.6%) - 10-year: 85.7% (59.8% to 100%) vs. 50.0% (15.4% to 84.6%) p=0.001 <u>Proportion of patients experiencing local relapse, % (n/N)</u> • All patients 4.3% (1/23) vs. 33% (8/24) [5 of the 9 patients above experiencing local relapse went on to receive secondary proton therapy.] <u>Proportion of patients experiencing regional relapse, % (n/N)</u> • All patients: 0% <u>Proportion of patients experiencing distance metastasis, % (n/N)</u> • All patients: 0% <u>Mortality, % (n/N)</u> [only reported for all patients grouped together] - All-cause: 8.5% (4/47) - Disease-related: 4.3% (2/47) [1 patient died to complications related to surgery]		• Temporal lobe radionecrosis: 18% (5/28) vs. 0% (0/47), p=NR
McDonald 2016	NR	NR	PBT vs. IMRT

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
3D conformal PBT (n=14) vs. IMRT (n=26) Retrospective Comparative Cohort Moderately High USA			**G-tube dependent** [Multivariate analysis] • At completion of RT: OR 0.03 (95 % CI <0.01 to 0.15), p<0.001 • 1-month post RT: OR 0.11 (95% CI <0.01 to 0.61), p=0.028 **Equivalent Morphine Dose greater at baseline than at completion of RT**: OR 0.09 (95% CI 0.01 to 0.57), p=0.006 [Multivariate analysis]
Holliday 2015 IMPT (n=10) vs. IMRT (n=20) Retrospective Matched Pairs Comparative Cohort Moderately High USA	IMPT v. IMRT **Proportion of patients experiencing disease failure, % (n/N)** • Local failure: 0% (0/10) vs. 5% (1/20) • Distant metastatic disease: 10% (1/10) vs. 5% (1/20) **Mortality, % (n/N)** • All-cause: 10% (1/10) vs. 5% (1/20) [The IMPT patient died of unknown causes with diffuse metastatic disease and the IMRT patient died of aspiration pneumonia and respiratory insufficiency]	NR	IMPT vs. IMRT **Acute Toxicities, % (n/N)** • Any Grade 3 event: 50% (5/10) [9 events] vs. 90% (18/20) [30 events], p=0.015 • Grade 3 Dermatitis: 40% (4/10) vs. 25% (5/20) **[**All 30 patients experienced some degree of acute radiation dermatitis. There was no significant difference in the severity of skin toxicity by treatment type (p=0.412)**]** • Grade 4/5: 0% vs. 0% **Late Toxicity, % (n/N)** • Any Grade 3 event: 30% (3/10) [5 events] vs. 15% (3/20) [3 events], p=0.542 **Proportion of patients requiring Gastrostomy tube placement during or after RT, % (n/N)** 20% (2/10) vs. 65% (13/20), p=0.02; OR 9.33 (95% CI 1.74 to 75.96), p=0.008

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			Median time required for Gastrostomy tube placement (among those whom required it (IQR): 5.3 (4 to 9) months vs. 3.2 (2.5 to 7.3) months, p=0.23 **Proportion of patients with a swallowing dysfunction after treatment, % (n/N)** 0% (0/10) vs. 15% (3/20), p=0.175 **Median percentage body weight lost from the beginning to the end of radiation (IQR)** 5.7% (4.5% to 11.2%) vs. 7.6% (6.1% to 12.1%), p=0.333
Sharma 2018 **PBT PBS (n=31) vs. IMRT via volumetric modulated arc therapy (n=33)** Prospective Comparative Cohort Moderately High USA	NR	PBT vs. IMRT **QOL Scores from 3 questionnaires: EORTC QLQ-30 v.3, EORTC OLO-H&N35 and the GRIX** *(0-100 scale; 10 point difference is clinically significant)* *For xerostomia, lower score = better QoL* *For global health, higher score = better outcomes* <u>3 months</u> Fatigue: 26.5 vs. 26.5, p=0.63 Head & Neck pain: 25 vs. 28.85, p=0.34 Painkiller use (%): 30.77 vs. 35.71, p=1 Xerostomia: 50 vs. 47.62, p=0.96	Both VMAT and PBS patients had a 0% rate of percutaneous endoscopic **gastrostomy tube dependence** at 6 months.

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		Moderate-severe dry mouth: 50 vs. 57.14, p=1 Xerostomia day: 41.2 vs. 43.06, p=0.81 Xerostomia night: 33.33 vs.47.01, p=0.11 Sticky saliva day: 29.37 vs. 38.46, p=0.38 Sticky saliva: 48.72 vs. 45.24, p=0.81 Dental problems: 0 vs. 19.05, p=0.016 Physical function: 88.1 vs. 87.62, p=0.83 Role function: 80.77 vs. 70.24, p=0.43 Global health: 69.05 vs. 66.03, p=0.41 <u>6 months</u> Fatigue: 8.5 vs. 20.47, p=0.07 Head & Neck pain: 8.33 vs. 18.86, p=0.08 Painkiller use (%): 16.67 vs. 21.05, p=1 Xerostomia: 39.58 vs. 52.63 p=0.14 Moderate-severe dry mouth: 22.22 vs. 63.16 p=0.02 Xerostomia day: 25.8 vs. 39.2 p=0.038 Xerostomia night: 22.8 vs. 35.1 p=0.042 Sticky saliva day: 15.43 vs. 20.47 p=0.6 Sticky saliva: 27.08 vs. 26.32 p=0.9 Dental problems: 1.96 vs. 17.54 p=0.048	

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		Physical function: 97.04 vs. 89.47 p=0.006 Role function: 96.3 vs. 76.32, p=0.0008 Global health: 83.33 vs. 73.15, p=0.09 <u>12 months</u> Fatigue: 4.86 vs. 22.22, p=0.17 Head & Neck pain: 8.33 vs. 21.97, p=0.011 Painkiller use (%): 17.65 vs. 36.36, p=0.38 Xerostomia: 23.53 vs. 54.55, p=0.003 Moderate-severe dry mouth: 11.76 vs. 50.00, p=0.038 Xerostomia day: 19.61 vs. 33.33, p=0.06 Xerostomia night: 17.65 vs. 30.56, p=0.10 Sticky saliva day: 17.65 vs. 22.22, p=0.31 Sticky saliva: 27.45 vs. 39.39, p=0.38 Dental problems: 5.88 vs. 21.21, p=0.13 Physical function: 98.96 vs. 87.88, p=0.24 Role function: 97.92 vs. 78.79, p=0.041 Global health: 81.86 vs. 72.73, p=0.13	

CI = Confidence interval; COI = Conflict of interest; F/U = Follow-up; Gy = Gray; HPV = Human papilloma virus; IMPT = Intensity modulated proton therapy; IMRT = Intensity Modulated Radiation Therapy; IQR = Interquartile range; MDASI-HN = MD Anderson Symptom Index – Head and Neck; NR = Not reported; NS = Not statistically significant; OR = Odds ratio; OS = Overall Survival; PBT = Proton Beam Therapy; RBE = Relative Biological Effectiveness; RoB = Risk of Bias; RT = Radiation therapy; SD = Standard Deviation
*Before treatment (baseline), during treatment (acute), within the first 3 months after treatment (subacute), and afterward (chronic phases).

APPENDIX H. Liver

Appendix Table H1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in liver cancers

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Fukuda 2017 *RoB*: High Prospective Case Series Japan Funding: Japan Society for the Promotion of Science, (Grant/Award Number: '24390286', '24659556') COI: None --- Provides subpopulation analysis for young vs. old, male vs. female, etc.	**Diagnosis**: Previously untreated HCC **Indication**: Curative Intent	N=129 Median Age: 72 years (range, 39-86) Male: 66.7% **Primary Tumor Sites**: Liver **Tumor Characteristics:** • Number of tumors 1: 74.4% 2: 17.8% ≥3: 7.8% • Tumor Size ≤3cm: 38.8% >3cm: 61.2% **Stage**: • 0/A stage: (30/129) • B stage: (34/129) • C stage: (65/129) **Comorbidities**: • Serious non-liver related disease: 20.2% • Thrombocytopenia (prior to PBT) - grade 2: 20% - grade 3: 5.5%	**PBT**: NR **PBT Dose (range)**: • GI protocol: 77 GyE in 35 fractions (n=54) • Hilar protocol: 72.6 GyE in 22 fractions (n=45) • Standard protocol: 66 GyE in 10 fractions (n=30) **Additional Treatments in conjunction with PBT:** None	**Median F/U (95% CI):** 55 (43 to 67) months	**Primary Outcomes** **5-year OS (95% CI)** • *0/A Stage:* 69% (49% to 89%) • *B stage:* 66% (48% to 84%) • *C stage:* 25% (11% to 40%) p<0.001 **5-year PFS (95% CI)** • *0/A Stage:* 28% (9% to 46%) • *B stage:* 23% (8% to 38%) • *C stage:* 9% (0% to 18%) p=0.057 **5-year LC (95% CI)** • *0/A Stage:* 94% (82% to 100%) • *B stage:* 87% (75% to 99%) • *C stage:* 75% (58% to 92%) p=0.228 **Proportion of patients experiencing local**	*Toxicity Grading Criteria:* CTCAE v.2 **Toxicity** *Radiation dermatitis was common, but no patients had severe complications due to PBT*

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		Risk Classification: NR			**progression**: 9.3% (12/129) **Proportion of patients experiencing disease progression at any site**: 54.3% (70/129) **Mortality** • Disease-related: 19.4% (25/129) • All-cause: 45% (58/129) [Due to HCC (n=25), liver failure (n=9), non-liver-related disease (n=16), or unknown reasons (n=8)] **<u>Secondary Outcomes</u>** **Subsequent Therapy to treat progression** • TACE: 12.4% (16/129) • PBT: 10.1% (13/129) • RFA: 6.2% (8/129) • PEIT: 1.6% (2/129) • RT: 0.8% (1/129) • Hepatic arterial infusion chemotherapy: 0.8% (1/129)	

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					• Unknown: 7.8% (10/129) • Best supportive care alone: 12.4% (16/129)	
Oshiro 2017 *RoB*: High Retrospective Case Series Japan Funding: This research was supported in part by a Grant-in-Aid for Scientific Research (B) (15H04901). COI: None ---	**Diagnosis:** HCC **Indication:** Curative Intent	N=83 patients, 92 tumors Median Age: 69 years (range, 46 to 86) Male: 79.5% **Primary Tumor Sites**: Liver Caudate: 3% (3/92 tumors) Lateral: 8% (7/92 tumors) Medial: 14% (13/92 tumors) Anterior: 42% (39/92 tumors) Posterior: 33% (30/92 tumors) **Tumor Characteristics:** Child-Pugh Classification (based on first course of treatment) A: 88% (73/83) B: 12% (10/83) **Risk Classification**: NR	**PBT:** Respiratory gated double-scatter PBT All patients received at least 2 courses of PBT 2 courses: n=83 3 courses: n=15 4 courses: n=3 **Median PBT Dose (range):** 1st treatment: 71 GyE 2nd treatment: 70 GyE 3rd treatment: 70 GyE 4th treatment: 69.3 GyE **Additional Treatments in conjunction with PBT:** 63.9% (53/83) received treatment prior to PBT	**Median F/U (range):** 45 (5 to 153) months	**Primary Outcomes** **OS (95% CI)** • *2-year:* 87.5% (80.2% to 94.8%) • *5-year*: 49.4% (37.6% to 61.2%) **Mortality** • Disease-related: 9.6% (8/83) [100% due to hepatic failure] **Secondary Outcomes** NR	*Toxicity Grading Criteria:* CTCAE v.4 **Acute Toxicity, % (n/N)** *Severe (≥grade 3) acute toxicity was not observed* • Intestinal Bleeding: 1.2% (1/83)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Mizumoto 2014 *RoB*: High Retrospective Case Series Japan Funding: Supported in part by Grants-in-Aid for Scientific Research (B) (24390286); Young Scientists (B) (25861064); and Scientific Research (C) (24591832) from the Ministry of Education, Science, Sports and Culture of Japan. COI: None --- Provides sub population analysis by Child-Pugh classification, young vs. old. Male vs. female, etc…	**Diagnosis:** HCC **Indication:** Curative Intent	N=250 Median Age: 71 years (range, 43 to 88) Male: 71% **Primary Tumor Sites**: Liver **Tumor Characteristics**:Child-Pugh Classification: A: 79% (197/250) B/C: 21% (53/250) Median tumor size: 35 mm (6 to 130) Portal Vein Tumor Thrombosis: 14% (36/250) **Risk Classification**: NR	**PBT:** Respiratory gated double-scatter PBT **PBT Dose:** - Tumors within 2 cm of the gastrointestinal tract: 77.0 GyE in 35 fractions or 74 GyE in 37 fractions - Tumors within 2 cm of the porta hepatis 72.6 GyE in 22 fractions - All other tumors: 66 GyE in 10 fractions **Additional Treatments in conjunction with PBT:** Prior to PBT RFA, TAE, or surgery: 48% (120/250)	**Median F/U (range):** NR Patients were followed through December 2013, and were treated between January 2002 and November 2009	**Primary Outcomes** **OS (95% CI)** • *1-year:* 83% (78% to 88%) • *3-year:* 63% (56% to 70%) • *5-year*: 51% (42% to 60%) **LC (95% CI)** • *1-year:* 98% (96% to 100%) • *3-year:* 85% (78% to 91%) • *5-year*: 51% (78% to 91%) **Mortality** • Disease-related: 28.8% (72/250) • All-cause: 34% (85/250) **Secondary Outcomes** NR	NR
Mizuhata 2018	**Diagnosis:** HCC within 2 cm of the digestive tract	N=40	**PBT:** Respiratory-gated 3D conformal	**Median F/U (range):** 19.9	**Primary Outcomes** **OS (95% CI)**	*Toxicity Grading Criteria:* CTCAE v.4

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
RoB: High Retrospective Case Series Japan Funding: Supported by JSPS KAKENHI (Grants-in-Aid for Scientific Research) Grant Number 16K10273. COI: None ---	**Indication:** Curative Intent	Median Age: 72 years (range, 38 to 87) Male: 70% **Primary Tumor Sites**: Liver **Tumor Characteristics:** Median tumor size: 37 mm (range, 11-124) Child Pugh Score: A: 70% (28/40) B: 30% (12/40) Tumor Thrombosis: 60% (24/40) **Comorbidities**: Anticoagulation: 5% (2/40) Esophageal varices: 22.5% (9/40) History of GI bleeding or ulcers: 7.5% (3/40) **Risk Classification**: NR	PBT administered without the use of fiducial markers **PBT Dose Range:** 60 to 80 cobalt gray equivalents in 20 to 38 fractions **Additional Treatments in conjunction with PBT:** Prior to PBT TACE: 40% (16/40) RFA: 27.5% (11/40) PEIT: 2.5% (1/40) Surgery: 20% (8/40)	(1.2 to 72.3) months	• *1-year:* 86% (75% to 98%) • *2-year:* 76% (62% to 91%) **PFS (95% CI)** • *1-year:* 70% (55% to 86%) • *2-year:* 60% (42% to 79%) **2-year LC (95% CI)** 94% (83% to 100%) **Secondary Outcomes** NR	**Acute Toxicity, % (n/N)** • Bleeding gastric ulcer *-Grade 3:* 2.5% (1/40) • Uncontrollable ascites *-Grade 3:* 2.5% (1/40) [Both patients completed PBT earlier than planned protocol due to their acute toxicities] Other toxicities experienced included Grade 1 and 2 skin toxicities; actual numbers are NR **Late Toxicity, % (n/N)** *No patient experienced grade 3+ toxicity* • Gastrointestinal Bleeding *-Grade 2:* 2.5% (1/40) • Rib fracture with pain *-Grade 2:* 2.5% (1/40)
Grassberger 2018 *RoB*: High Prospective Case Series USA	**Diagnosis:** HCC (n=22) or ICC (n=21) **Indication:** Curative Intent	N=43 Median Age: HCC: 69.5 years (range, 54-88) ICC: 66.4 years (range, 36-82) Male: 67.4%	**PBT:** NR **Median PBT Dose (range):** 58 Gy (45-67.7) **Additional Treatments in**	**Median F/U (range):** 42 (NR) months	**Primary Outcomes** **OS (95% CI)** [Estimated from Figure 1] • **1-year** - *ICC:* 60% (NR) - *HCC*: 79% (NR) • **2-year** - *ICC*: 34% (NR)	NR

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Funding: Supported by grants from the National Cancer Institute Proton Beam Federal Share Program (to T.S.H. and D.G.D.). The work of R.K.J. and D.G.D. was supported by NIH grant P01CA080124. COI: None ---		**Primary Tumor Sites**: Liver **Comorbidities** Presence of cirrhosis: 90.7% (39/43) **Risk Classification:** NR	**conjunction with PBT:** None		- *HCC*: 56% (NR) **<u>Secondary Outcomes</u>** NR	
Hong 2016 *RoB*: High Prospective Case Series USA Funding: Supported by National Institutes of Health Grant No. 2P01CA021239-29A1 Revised and in part by the Cancer Clinical	**Diagnosis:** Biopsy proven, unresectable or locally recurrent HCC (n=44) or ICC (n=39) **Indication:** Curative Intent for newly diagnosed (94%) or locally recurrent (6%) disease	N=83 Median Age: 67.6 years (range, 29.9-89.7) Male: 61.4% **Primary Tumor Sites**: Liver **Comorbidities**: Underlying liver disease: 56.6% Cirrhosis: 85.2% **Risk Classification**: NR	**PBT:** 3D passively scattered **Median PBT Dose (range):** 58 Gy **Additional Treatments in conjunction with PBT:** Surgical Resection: 4.8% (4/83) TACE: 6% (5/83) RFA: 2.4% (2/83) Chemotherapy: 32.5% (27/44) Other: 15.7% (15/44)	**Median F/U (range):** 19.5 (0.6 to 55.9) months	**<u>Primary Outcomes</u>** **OS (95% CI)** • 1-year - *HCC:* 76.5% - *ICC:* 69.7% • 2-year - *HCC:* 63.2% - *ICC:* 46.5% **PFS (95% CI)** • 1-year - *HCC:* 56.1% - *ICC:* 41.4% • 2-year - *HCC:* 39.9% - *ICC:* 25.7%	*Toxicity Grading Criteria:* CTCAE v.3 **<u>Toxicity, % (n/N)</u>** *At least one radiation-related toxicity:* 85.5% (71/83); 4 patients with at least one grade 3 • Liver Failure -*Grade ≤2:* 0% (0/83) -*Grade 3*: 1% (1/83) (Same patient with ascites below) • Nonmalignant ascites -Any grade: 1% (1/83) -*Grade 3*: 1% (1/83)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Investigator Team Leadership Award, awarded by the National Cancer Institute through a supplement to Grant No. P30CA006516. COI: TH received research funding from Novartis, BY was stock/ownership in SISCAPA Assay Technologies, DR holds pataent/royalties.intelectual property for UpToDate and McGraw Hill, Several authors have received honoraria or have held consulting or advisory roles. All other authors report no conflicts of interest. ---					**2-year LC (95% CI)** • *All patients:* 94.4% (87.2% to 98.2%) • *HCC:* 94.8% (NR) • *ICC:* 94.1% (NR) **Proportion of Patients Experiencing Progression** • HCC - Any progression: 43.2% (19/44) - Hematogeneous progression: 36.4% (16/44) - Local failure with other progression: 4.5% (2/44) - Nodal progression: 2.3% (1/44) • ICC - Any progression: 69.2% (27/39) - Hematogeneous progression: 53.9% (21/39) - Isolated local failure: 12.8% (5/39) - Nodal progression: 2.3% (1/39) **<u>Secondary Outcomes</u>** NR	(Same patient with liver failure) • Platelets (Thrombocytopenia) -Any grade: 1% (1/83) -Grade 3: 1% (1/83) • Fatigue -Any grade: 1% (1/83) • Hyperpigmentation -Any grade: 12% (10/83) • Rash -Any grade: 61% (51/83) • Anorexia -Any grade: 25% (17/83) • Nausea -Any grade: 30% (25/83) • Ulcer (GI/Stomach) -Any grade: 1% (1/83) -*Grade 3*: 1% (1/83) • Vomiting -Any grade: 10% (8/83) • Hemorrhage/bleeding -Any grade: 1% (1/83) • Hyperbilirubinemia -Any grade: 1% (1/83) -*Grade 3*: 1% (1/83) • Musculoskeletal/soft tissue toxicity -Any grade: 4% (3/83) • Neurology Toxicity -Any grade: 2% (2/83) • Abdominal Pain -Any grade: 22% (19/83)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						• Pulmonary/upper respiratory toxicity -Any grade: 5% (4/83) • Other Blood/bone morrow toxicity -Any grade: 5% (4/83) • Other dermatology/skin toxicity -Any grade: 4% (3/83) • Other GI toxicity -Any grade: 20% (18/83) • Other metabolic/laboratory toxicity -Any grade: 10% (8/83) • Other pain -Any grade: 13% (11/83)
Yeung 2018 *RoB*: High Retrospective Case Series USA Funding: NR COI: None ---	**Diagnosis:** Liver malignancies (n=30 HCC, n=6 ICC, n=1 metastasis) **Indication:** Curative Intent	N=37 patients, 39 tumors Median Age: 66 years (range, 46-82) Male: % **Primary Tumor Sites**: Liver **Comorbidities**: • Diabetes: 27% (10/37) • Hypertension: 56.8% (21/37) • Coronary artery disease: 8.1% (3/37)	**PBT:** Hypofractionated PBT Uniform scanning 79.5% (31/39 lesions) Pencil beam scanning: 21.6% (8/39 lesions) **Median PBT Dose (range):** 60 GyE (range, 35-67.5) in 15 fractions **Additional Treatments in**	**Median F/U (range):** 11 (2 to 44) months	NR	*Toxicity Grading Criteria:* CTCAE v.4 **<u>Toxicity, % (n/N)</u>** • Chest wall pain (requiring narcotic analgesics) - *Grade 1:* 2.7% (1/37) - *Grade 2:* 19% (3/37) - *Grade 3:* 11% (4/37)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		• Connective tissue disorder: 8.1% (3/37) **Tumor Characteristics**: • Child-Pugh Classification: A: 56.8% (21/37) B: 27% (10/37) C: 13.5% (5/37) • Median Tumor Size: 102 cm (range, 1-860) **Risk Classification**: NR	**conjunction with PBT:** NR			
Fukumitsu 2015 Retrospective Case Series *RoB*: High Japan Funding: NR COI: None --- Provides subpopulation analysis by treatment strategy and tumor site, tumor localization,	**Diagnosis:** Metastatic Liver Tumors **Indication among patients with lesions confined to the liver**: Curative Intent (73%; 62/85) or Palliative (27%; 23/85)	N=140, 133 completed treatment* Median Age: NR Male: 83% **Primary Tumor Sites**: Colorectum, 42.9% (60/140); Pancreas, 13.6% (19/140); Breast, 8.6% (12/140); Stomach, 8.6% (12/140); Other; 26.4% (37/140) Confined to the liver: 60.7% (85/140) Solitary tumor: (49/85)	**PBT:** Double-Scatter **Median PBT Dose (range)**: 72.6 Gy (RBE) (9-77) **Additional Treatments in conjunction with PBT:** Neoadjuvant (before PBT) Chemotherapy: (4/140) TACE: (3/140) RFA: (2/140) PEIT: (2/140) Hormone Therapy: (1/140)	**Median F/U (range):** NR	**<u>Primary Outcomes</u>** **OS (95% CI):** *2-year:* 46% (NR) *5-year:* 24% (NR) • Lesions confined to liver (n=85): 28% ○ Curative tx (n=62): 30% ○ Palliative tx (n=23): 23% p=0.012 (curative vs. palliative0 • Lesions both in and outside liver (n=55): 16% p=0.007 (confined vs. in and outside)	*Toxicity Grading Criteria:* CTCAE v.4 **<u>Late Toxicity Grade >3, % (n/N)</u>** • Rib fracture: 0.8% (1/133) • Cholangitis: 0.8% (1/133) **<u>Proportion of patients showing an elevation of more than 2 on the Child-Pugh score†</u>**: 6% (8/133)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
and concurrent therapy		Multiple tumors (36/85) Inside and outside the liver: 39.9% (55/140) **Risk Classification:** NR	Combined Therapy: (5/140) Concurrent (during PBT) Chemotherapy: (26/140) Hormone Therapy: (2/140) Hyperthermia: (1/140) Chemotherapy + hyperthermia: (1/140) Immunotherapy: (1/140) Adjuvant (After PBT, but not for new lesions or recurrent tumors) Chemotherapy: (42/140) Immunotheraoy: (5/140) Hormone therapy: (4/140) Other: (2/140)		**LC (95% CI) (n=124)** [16 patients had no follow-up CT]: *2-year:* 66% (NR) *5-year:* 53% (NR) **Secondary Outcomes** **Subsequent Therapy to treat new lesions or recurrent tumors** • PBT: 7.9% (11/140) • Chemotherapy: 6.4% (9/140) • Chemotherapy + PBT: 3.6% (5/140) • PBT + RT: 2.1% (3/140) • Surgery + chemotherapy: 1.4% (2/140) • Other: 2.1% (3/140)	
Kim 2017 *RoB*: High Retrospective Case Series South Korea	**Diagnosis:** HCC with tumor vascular thrombosis **Indication:** Curative Intent: 24.4% (10/41) For Recurrent/Residual Disease: 75.6% (31/41)	N=41 Median Age (range): 55 years (24–81) Male: 85.4% **Primary Tumor Sites**: Liver **Risk Classification**: NR	**PBT:** Simultaneous integrated boost-proton beam therapy **PBT Dose:** NR **Additional Treatments in**	**Median F/U (range):** 15.2 (NR) months	**Primary Outcomes** **Local Progression Free Survival (95% CI)** All patients • *2-year:* 88.1% (NR) **Relapse-free Survival (95% CI)** All patients	*Toxicity Grading Criteria:* CTCAE v.3 **Acute Toxicity, % (n/N) [All patients]** *No patient experienced grade ≥3 acute toxicity.* • Elevated Alanine Aminotransferase

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Funding: Supported by National Cancer Center Grant (NCC 1410160 and 1610590). COI: None ---			**conjunction with PBT:** 75.6% (31/41) of patients had some sort of treatment prior to PBT		• *2-year:* 25% (NR) **OS (95% CI)**: All patients • *2-year:* 51.1% (NR) **Mortality, % (n/N)** All patients • Disease-related: 48.8% (20/41) **Proportion of patients experiencing disease recurrence:** 75.6% (31/41) • Local recurrence: 12.2% (5/41) • Intrahepatic recurrence: 61% (25/41) • Distant Metastasis: 41.5% (17/41) **Primary Tumor's Response to PBT** • All patients (n=41) - CR: 34.1% (14/41) - PR: 48.7% (20/41) - SD: 14.6% (6/41) - PD: 2.4% (1/41) • Treatment for Recurrent/Residual Disease (n=31) - CR: 41.9% (13/31)	- *Grade 1*: 4.9% (2/41) • Leukopenia - *Grade 1*: 4.9% (2/41) (Same patients experiencing thrombocytopenia below) • Thrombocytopenia - *Grade 1*: 4.9% (2/41) (Same patients experiencing Leukopenia above) **<u>Late Toxicity, % (n/N) [All patients]</u>** • Gastric/Duodenal Ulcers -*Grade 1:* 4.9% (2/41) -*Grade 2:* 4.9% (2/41)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					- PR: 41.9% (13/31) - SD: 12.9% (4/31) - PD: 3.2% (1/31) • Treatment with Curative Intent - CR: 10% (1/10) - PR: 70% (7/10) - SD: 20% (2/10) - PD: 0% (0/10) p-value for the difference between treatment indications: 0.218 **Tumor Vascular Thrombosis Response to PBT** • Treatment for Recurrent/Residual Disease - *CR:* 41.9% (13/31) - *PR:* 25.8% (8/31) - *SD:* 29.1% (9/31) - *PD:* 3.2% (1/31) • Treatment with curative Intent - *CR:* 10% (1/10) - *PR:* 60% (6/10) - *SD:* 30% (3/10) - *PD:* 0% (0/10) p-value for the difference between treatment indications: 0.146	

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					<u>Secondary Outcomes</u> **Requirements for additional treatments due to residual or recurrent disease** • Sorafenib ± TACE ± RFA ± chemotherapy: 46.3% (19/41) • TACE ± chemotherapy: 14.6% (6/41) • Chemotherapy: 2.4% (1/41) • Surgical Resection: 2.4% (1/41) • RFA: 2.4% (1/41)	
Kim 2018 *RoB*: High Retrospective Case Series South Korea Funding: This study was supported by National Cancer Center Grant (NCC 1710060 and 1710030).	**Diagnosis:** Inoperable or recurrent HCC **Indication:** Treatment for recurrent/residual disease: 77.6% Curative Intent: 24.4%	N=71 Median Age: 63 years (range, 40-92) Male: 84.5% **Primary Tumor Sites**: Liver (unclear as to where other sites may have been) **Tumor Characteristics:** Tumor Size <3: 90.1% (64/71) ≥3: 9.9% (7/71) Child-Pugh Classification†	**PBT:** Hypofractionated PBT **PBT Dose:** 66 GyE in 10 fractions **Additional Treatments in conjunction with PBT:** To PBT site: TACE: 89.1% (49/71) TACE + RFA and/or PEIT: 10.9% (6/71) To other site:	**Median F/U (range):** 31.3 (4.2 to 47) months	**<u>Primary Outcomes</u>** **3-year Local Progression Free Survival (95% CI)** 89.9% (81.8% to 98%) **3-year Relapse Free Survival (95% CI)** 26.8% (14.9% to 38.7%) **3-year OS (95% CI)** 74.4% (63.1% to 85.7%)	*Toxicity Grading Criteria:* CTCAE v.3 **<u>Acute Toxicity, % (n/N)</u>** *No patient experienced grade 3+ toxicity* • Leukopenia/thrombocytopenia *-Grade 1:* 8.5% (6/71) **<u>Late Toxicity, % (n/N)</u>** • 0% (0/71)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
COI: None --- Provides subpopulation analysis based on several patient characteristics for survival outcomes		A: 95.8% (68/71) B: 4.2% (3/71) **Risk Classification**: NR	TACE ± RFA ± PEIT: 73.3% (44/71) Surgical resection ± TACE ± RFA ± PEIT ± Sorafenib: 23.3% (14/71) RFA: 3.4% (2/71)		**Proportion of patients experiencing disease recurrence**: 69% (49/71) • Local progression: 8.5% (6/71) [n=2 who achieved CR; n=4 who did not achieve CR] • Intrahepatic recurrence: 69% (49/71) • Distant Metastasis: 15.5% (11/71) **Tumor Response, % (n/N)** • All patients - CR: 93% (66/71) - PR: 0% (0/71) - SD: 1.4% (1/71) - PD: 5.6% (4/71) **Mortality‡** • Disease-related: 21.1% (15/71) • All-cause: 22.5% (16/71) **Actuarial CR Rates (95% CI)** • *3-months:* 21.3% (11.7% to 30.9%)	

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					• *6-months:* 60% (48.5% to 71.6%) • *9-months:* 81.8% (72.6% to 91%) • *1-year:* 89.4% (81.9% to 96.8%) **Secondary Outcomes** NR	
Yu 2018 *RoB*: High Prospective Case Series South Korea Funding: Supported by a Samsung Medical Center grant (No. GF01130081), a Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (No. NRF-	**Diagnosis:** HCC **Indication:** Salvage: 49% Consolidative: 31% Palliative: 18% Definitive: 3%	N=101 Median Age: 63 years (range, 35-91) Male: 86.1% **Primary Tumor Sites**: Liver **Tumor Characteristics:** Child-Pugh Classification: A: 80% (80/101) B: 8% (8/101) C: 1% (1/101) Portal Vein Tumor Thrombosis: 28.7% (29/101) **Risk Classification**: NR	**PBT:** Multi-beam PBT, Wobbling beam PBT, or Line scanning PBT *Two patients were treated with PBT twice, one because of a synchronous multiple intrahepatic tumor, and another because of a metachronous outfield intrahepatic recurrence.* **Median PBT Dose (range):** NR **Additional Treatments in conjunction with PBT:** • Surgical resection: 17.8% (18/101)	**Median F/U (range):** 4.9 (1.3 to 14.6) months	**Primary Outcomes** **Tumor Response at 1-month follow-up** • CR: 37.6% (38/101) • PR: 18.8% (19/101) • SD: 24.8% (25/101) • PD: 18.8% (19/101) **Tumor Response at 3-months follow-up** • CR: 53.8% (42/78) • PR: 10.3% (8/78) • SD: 5.1% (4/78) • PD: 30.8% (24/78) **Proportion of patients having locally progressive disease, % (n/N)**: 5.9% (6/101) **Secondary Outcomes** NR	*Toxicity Grading Criteria:* CTCAE v.4 **Proportion of patients experiencing radiation-induced liver disease, % (n/N)** • *Classic type*: 0% (0/101) • *Non*-classic type: 4% (4/101) [Measured by a worsening of Child-Pugh score by 2] **Proportion of patients experiencing gastroduodenal toxicity**: 5% (5/101) **Acute toxicity, % (n/N)** • Anemia - *Grade 1:* 56.4% (57/101) - *Grade 2:* 3% (3/101) - *Grade 3:* 2% (2/101) • Leukopenia

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
2015R1D1A1A01060945), and a grant from the Marine Biotechnology Program (No. 20150220) funded by the Ministry of Oceans and Fisheries, Korea. COI: None			• Transplantation: 1% (1/101) • RFA: 38.6% (39/101) • TACE: 96% (97/101) • RT: 15.8% (16/101) • Sorafenib: 3% (3/101)			- *Grade 1:* 24.8% (25/101) - *Grade 2:* 19.8% (20/101) - *Grade 3:* 3% (3/101) • Thrombocytopenia - *Grade 1:* 47.5% (48/101) - *Grade 2:* 24.8% (25/101) - *Grade 3:* 9.9% (10/101) • Aspartate Aminotranferase: - *Grade 1:* 39.6% (40/101) - *Grade 2:* 2% (2/101) - *Grade 3:* 1% (1/101) • Alanine Aminotransferase - *Grade 1:* 24.8% (25/101) - *Grade 2:* 4% (4/101) - *Grade 3:* 1% (1/101) • Alkaline phosphatase - *Grade 1:* 34.7% (35/101) • Hypoalbuminemia - *Grade 1:* 15.8% (16/101) - *Grade 2:* 8.9% (9/101) • Hyperalbuminemia - *Grade 1:* 10.9% (11/101)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						- *Grade 2:* 11.9% (12/101) - *Grade 3:* 4% (4/101) - *Grade 4:* 1% (1/101) • Anorexia - *Grade 1:* 11.9% (12/101) - *Grade 2:* 1% (1/101) • Nausea - *Grade 1:* 3% (3/101) - *Grade 2:* 2% (2/101) • Vomiting - *Grade 1:* 5% (5/101) • Abdominal pain - *Grade 1:* 9.9% (10/101) - *Grade 2:* 3% (3/101) • Dermatitis - *Grade 1:* 18.8% (19/101) - *Grade 2:* 5% (5/101)
Hong 2017 Prospective Case Series *RoB*: High USA Funding: Supported by Federal Share of program income earned by	**Diagnosis:** Liver metastasis from a solid tumor (including multifocal HCC) **Indication:** Curative Intent	N=89 Median Age: 67.6 years (34.2 to 88.9) Male: 62.9% **Primary Tumor Site**: Adenocarcinoma Colorectal: 38.2% (34/89) Pancreas: 14.6% (13/89) Esophagogastric: 13.5% (12/89) Breast: 3.4% (3/89)	**PBT:** Passively scattered proton based stereotactic body radiation therapy **Median PBT Dose (range): 40 GyE (range, 30–50 GyE)** **Additional Treatments in conjunction with PBT:**	**Median F/U (range):** 30.1 (14.7 to 53.8) months	**Primary Outcomes** **OS (95% CI)** • *1-year:* 66.3% (55.5% to 75.1%) • *2-year:* 35.9% (25.8% to 46.2%) • *3-year:* 20.8% (12.4% to 30.8%) **PFS (95% CI)** • *1-year:* 24.7% (16.3% to 30.4%)	*Toxicity Grading Criteria:* CTCAE v.3 **Toxicity, % (n/N)** *87.6% (78/89) experienced at least one radiation-related toxicity* Gastrointestinal disorders • Abdominal pain *-Grade 1:* 20.2% (18/89) *-Grade 2:* 3.4% (3/89) • Nausea *-Grade 1:* 13.5% (12/89)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Massachusetts General Hospital, Proton Therapy Research and Treatment Center (C06 CA059267), a Cancer Clinical Investigator Team Leadership Award awarded by the National Cancer Institute through a supplement to P30CA006516 (TSH), the American Cancer Society 123420RSG-12-224-01-DMC (HW), and National Cancer Institute 2P50CA127003-06A1 (JWC). COI: NR ---		Gallbladder: 3.4% (3/89) Non-Small Cell Lung: 3.4% (3/89) Prostate 1.1% (1/89) Small Bowel/Duodenal: 1.1% (1/89) <u>HCC</u> Liver: 9.0% (8/89) <u>Neuroendocrine Tumor</u> Small Bowel/Duodenal: 2.2% (2/89) Colorectal: 1.1% (1/89) Pancreas: 1.1% (1/89) <u>Squamous Cell Carcinoma</u> Anal: 1.1% (1/89) Colorectal: 1.1% (1/89) Non-Small Cell Lung: 1.1% (1/89) <u>Adenoid Cystic Carcinoma</u> Head and Neck: 1.1% (1/89) <u>Merkel Cell Carcinoma</u> Head and Neck: 1.1% (1/89) <u>Hemangiopericytoma</u>	Patients may have had prior therapy including chemotherapy, biological therapy, or liver-directed therapy including TACE, RFA, or microwave ablation three or more weeks prior to first radiation treatment. Hormonal therapies were permitted to be continued through treatment**.**		• *2-year:* 9.2% (4.0% to 16.9%) **LC (95% CI)** • *1-year:* 71.9% (62.3% to 80.9%) • *2-year:* 61.2% (50.8% to 71.8%) **<u>Secondary Outcomes</u>** NR	• Diarrhea -*Grade 1:* 4.5% (4/89) • Vomiting -*Grade 1:* 3.4% (3/89) • Bloating -*Grade 1:* 1.1% (1/89) • Constipation -*Grade 1:* 1.1% (1/89) • Diverticulitis -*Grade 2:* 1.1% (1/89) • Flatulence -*Grade 1:* 1.1% (1/89) • Nonspecific gastrointestinal symptoms -*Grade 1:* 1.1% (1/89) • Stomach pain -*Grade 1:* 1.1% (1/89) <u>General disorders and administration site conditions</u> • Fatigue -*Grade 1:* 53.9% (48/89) -*Grade 2:* 14.6% (13/89) • Pain -*Grade 1:* 3.4% (3/89) • Malaise -*Grade 1:* 1.1% (1/89) (1/89) <u>Injury, poisoning, and procedural complications</u> • Dermatitis

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		Pancreas: 1.1% (1/89) <u>Acinar Cell Carcinoma</u> Pancreas: 1.1% (1/89) **Comorbidities**: Liver Cirrhosis: 6.7% (6/89) **Risk Classification**: NR **Disease status at enrollment:** • Progressing: 84% • Stable: 9% • Responding 3% • Metastatic, newly diagnosed: 3%				-*Grade 1:* 43.8% (39/89) -*Grade 2:* 3.4% (3/89) • Fracture -*Grade 1:* 2.2% (2/89) <u>Investigations</u> • Platelet count decreased -*Grade 1:* 2.2% (2/89) -*Grade 2:* 2.2% (2/89) • Weight loss -*Grade 1:* 1.1% (1/89) -*Grade 2:* 1.1% (1/89) <u>Metabolism and nutrition disorders</u> • Anorexia -*Grade 1:* 13.5% (12/89) -*Grade 2:* 2.2%(2/89) • Hyperglycemia -*Grade 1:* 1.1% (1/89) • Hyponatremia -*Grade 1:* 1.1% (1/89) <u>Musculoskeletal and connective tissue disorders</u> • Flank pain -*Grade 1:* 3.4% (3/89) • Chest wall pain -*Grade 1:* 1.1% (1/89) • Pain in extremity -*Grade 1:* 1.1% (1/89)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						<u>Reproductive system and breast disorders</u> • Pelvic pain -*Grade 1:* 1.1% (1/89) <u>Respiratory, thoracic, and mediastinal disorders</u> • Cough -*Grade 1:* 1.1% (1/89) • Dyspnea -*Grade 1:* 1.1% (1/89) • Pneumonitis -*Grade 1:* 1.1% (1/89) <u>Skin</u> • Skin hyperpigmentation -*Grade 1:* 6.7% (6/89) • Dry skin -*Grade 1:* 1.1% (1/89) • Hyperhidrosis -*Grade 1:* 1.1% (1/89) • Pruritus -*Grade 1:* 1.1% (1/89) • Telangiectasia -*Grade 1:* 1.1% (1/89)

CI = Confidence Interval; COI = Conflict of Interest; CR = Complete Response; F/U = Follow-up; HCC = Hepatocellular Carcinoma; ICC = Intrahepatic cholangiocarcinoma; LC = Local Control; OS = Overall Survival; PBT = Proton Beam Therapy; PEIT: Percutaneous ethanol injection therapy; PD = Progressive Disease; PFS = Progression Free Survival; PR = Partial Response; RFA = radiofrequency ablation; RT = Radiation therapy; SD = Stable Disease; TACE = transcatheter arterial chemoembolization

*Reasons for not completing treatment: tumor progression (n=2), liver dysfunction (n=1), massive ascites (n=1), poor physical condition (n=1), dullness (n=1), jaundice (n=1)

†The Child–Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. The scoring system incorporates five parameters: serum bilirubin, serum albumin, prothrombin time, severity of ascites, and grade of encephalopathy. Based on the sum of the points from these five parameters, the patient is categorized into one of three classes: A, B, or C, with class C being the most severe.

‡Due to intrahepatic disease progression (*n* = 10), liver failure by progression of LC (*n* = 2), bone metastasis (*n* = 2), brain metastasis (*n* = 1), and pneumonia (*n* = 1), not related with treatment

Appendix Table H2. Study characteristics and patient demographics: comparative studies of proton beam therapy in liver cancers

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
RCTs							
Bush 2016 RCT *Moderately High* USA	69	**PBT (n=33)**: Passive scattering; RBE of 1.1; Median total dose: 70.2 Cobalt-gray equivalents in 15 fractions 82% received a single treatment; all others received up to 3 courses; total treatment courses: 38 **TACE (n=36)**: Performed by interventional radiologist Single treatment: 58% received a single treatment; all others received up to 4 (for persistent disease) Initial treatment: ethiodol chemotherapy (16 treatments); in 2009, switch to	**Inclusion**: Patients with untreated, newly diagnosed HCC either by tissue biopsy or clinically with history of cirrhosis, characteristic imaging findings, and/or elevated a-fetoprotein; who were deemed to be candidates for TACE by an interventional radiologist according to standard guidelines and deemed to be eligible for PBT by the participating radiation oncologist and evaluated proximity of tumors to adjacent normal tissue structures, such as bowel. **Exclusion**: Patients with Child C cirrhosis, model for end-stage liver disease >25 mg/dL, bilirubin >3 mg/dL, and large-volume, unstable ascites.	PBT vs. TACE Mean Age (years): 61.4 vs. 58.9 % Male: 76% vs. 67% Biopsy: 27% vs. 33% Presence of Cirrhosis: 97% vs. 94.4% Patients with multiple tumors: 54.5% vs. 55.6% Mean maximal tumor size, cm (range): 3.2 (1.8 to 6.5) vs. 3.2 (2.0 to 6.5) Mean bilirubin, mg/dL (range): 1.59 (0.4 to 3.4) vs. 1.73 (0.3 to 4.7) Mean albumin, mg/dL (range): 3.42 (2.3 to 4.2) vs. 3.23 (2.1 to 4.7) α-fetoprotein, ng/mL (range): 23.2 (2 to 150) vs. 22.8 (2 to 100)	All patients **F/U (median [range])**: 28 months (NR) **% F/U** - *All patients*: CD* - PBT vs. TACE: CD*	2-year OS, LC, PFS Harms	Funding: Ken Venturi endowment for proton therapy research COI: None

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		chemotherapy-eluting microspheres (47 treatments)					
Nonrandomized Comparative Cohorts							
Sanford 2019 [32 patients in this study were dually enrolled in Hong 2016 (Case Series)] Retrospective Comparative Cohort ROB USA	133	**PBT (n=49)** 3D passively scattered Median dose (IQR): 67 Gy (60 to 70) **IMRT (n=84)** Median dose (IQR): 67 Gy (67 to 82)	**Inclusion**: Patients treated between June 2008 and December 2017, 18 years or older, unresectable HCC **Exclusion**: Patients who had received prior liver-directed external beam radiation therapy or had extrahepatic disease at diagnosis or who received another course of liver radiation therapy less than 12 months after completion of the index treatment	PBT vs. IMRT Median age (IQR): 65 (60 to 74) vs. 69 (61 to 79) % Male: 80% vs. 73% Disease status - Curative intent: 84% vs. 83% - For a recurrence: 16% vs. 17% Comorbidities - Underlying cirrhosis: 96% vs. 77%, p=0.006 - Hepatitis B: 12% vs. 5% - Hepatitis C: 49% vs. 29% Tumor thrombus: 27% vs. 35% Previous therapy - Ablation: 10% vs. 10% -Chemoembolization: 6% vs. 14% - Selective internal radiation therapy: 0% vs. 2% - Chemotherapy: 0% vs. 8% - Resection: 2% vs. 1% - Multiple: 6% vs. 10%	**Median F/U:** 14 months **% F/U:** NR	Overall Survival Local Failure Locoregional Failure Child-Pugh Score	Funding: NR COI: NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
				Median Gross Tumor Volume (IQR): 106 (36 to 209) mL vs. 118 (45 to 269) mL ECOG Performance Status - 0: 47% vs. 38% - 1: 49% vs. 46% - 2/3: 4% vs. 15% Median Child-Pugh score (IQR): 5 (5 to 6) vs. 6 (5 to 7), p=0.008 Median ALBI score (IQR): -2.34 (-2.73 to -1.78) vs. -2.68 (-2.9 to -2.06), p=0.03 Median rV10Gy (IQR): 50.5 (43.8-59.9) vs. 60.0 (51.5-71.0), p=0.0003			

CD = Cannot be Determined; COI = conflict of interest; F/U = follow-up; HCC = Hepatocellular carcinoma; LC = Local control; NR = not reported; OS = Overall survival; PFS = Progression free survival; RoB = Risk of Bias; TACE = Transarterial chemoembolization

*Follow-up and differential loss to follow-up cannot be determined (number of eligible patients and number of patients lost per treatment group not provided, of 70 patients enrolled, 1 was lost to follow-up of those 70)

Appendix Table H3. Detailed data abstraction: comparative studies of proton beam therapy in liver cancers

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate Outcomes	Harms
RCTs			
Bush 2016 PBT (n=33) vs. TACE (n=36) RCT *Moderately High* USA	PBT vs. TACE **2-year OS (95% CI)** • *All patients*: 59% (NR) • *Patients who received liver transplant after assigned HCC therapy*: 82% (NR) [For both outcomes above authors state that there was no significant difference between treatment arms, but fail to provide any statistics regarding this claim] **2-year LC (95% CI)** 88% (NR) vs. 45% (NR); p=0.06 **2-year PFS (95% CI)** 48% (NR) vs. 31% (NR); p=0.06 **Proportion of patients receiving liver transplants after treatment (n=12 vs. 10) who achieved pathologic complete response, % (n/N)** 25% (3/12) vs. 10% (1/10); p=0.38	NR	PBT vs. TACE **Acute treatment-related** toxicities were "generally limited to fatigue and radiation skin reaction for PBT patients and abdominal pain and nausea for TACE patients, which were experienced by most patients." "Serious complications from PBT were uncommon events" (no data provided). **Proportion of patients hospitalized for a complication within 30 days of treatment (i.e. not for a routine observation), % (n/N)** 6.1% (2/33) vs. 41.7% (15/36) **Total days hospitalized within 30 days of treatment**: 24 (0.73 days per patient) vs. 166 (4.6 days per patient); p<0.001 • **Days hospitalized for routine observation within 30 days of treatment:** 0 vs. 53 • **Days hospitalized with complications within 30 days of treatment:** 24 vs. 113; p=NR **Proportion on patients with acute complications leading to hospitalization, % (n/N)** • Liver failure: 6.1% (2/33) vs. 2.8% (1/36) • Abdominal pain: 0% (0/33) vs. 13.9% (5/36) • Spontaneous bacterial peritonitis: 0% (0/33) vs. 2.8% (1/36) • Hepatorenal syndrome: 0% (0/33) vs. 5.6% (2/36) • Nausea: 0% (0/33) vs. 5.6% (2/36)

			• GI bleed: 0% (0/33) vs. 11.1% (4/36) • Cellulitis: 0% (0/33) vs. 2.8% (1/36) • Vomiting: 0% (0/33) vs. 2.8% (1/36) • Acute renal failure: 0% (0/33) vs. 2.8% (1/36) • Perihaptic bleed: 0% (0/33) vs. 2.8% (1/36) • Peritoneal hematoma: 0% (0/33) vs. 2.8% (1/36) • Angina requiring coronary bypass: 0% (0/33) vs. 2.8% (1/36)
Nonrandomized Comparative Cohort			
Sanford 2019 PBT (n=49) vs. IMRT (n=84) [32 patients receiving protons in this study were dually enrolled in Hong 2016 (case series)] Retrospective Comparative Cohort USA	PBT vs. IMRT **OS (95% CI)** • 2-year: 59.1% vs. 28.6%, adj. HR 0.47 (95% CI 0.27 to 0.82), p=0.008 **Cumulative Incidence of Local Failure** HR 0.74 (95% CI 0.18 to 3.01), p=0.67 **Local Control (95% CI)** • 2-year: 93% (NR) vs. 90% (NR), p=NR **Cumulative Incidence of Locoregional (local and locoregional combined) Recurrences, % (n/N)** 53% (26/49) vs. 42% (36/84), adj. HR 0.98 (95% CI 0.54 to 1.75), p=0.93 **Mortality, % (n/N)** • All-cause: 31% (15/49) vs. 25% (21/84) [All died without evidence of disease progression]	NR	PBT vs. IMRT **Radiation-induced Liver Disease (RILD)** *(n=100 patients whose nonclassic RILD status could be calculated or inferred – nonclassic RILD defined as worsening in baseline Child-Pugh score by 2+ points at 3 months post-treatment)* • Number who developed RILD: n=4 vs. n=17 (proportion could not be calculated because denominators were not provided) • PBT associated with a decreased risk of non-classic radiation induced liver disease: OR 0.26 (95% CI 0.08 to 0.86), p=0.03 [modality difference persisted in multivariable models controlling for prognostic variables] • Development of non-classic radiation induced liver disease at 3 months was associated with worse OS (HR 3.83 (95% CI 2.12 to 6.92), p<0.001) • Incidence of death from liver failure among patients who died without disease progression (n=36): 53.3% (8/15) vs. 90.5% (19/21); RR 0.59, (95% CI 0.36 to 0.97) [calculated by AAI]

CI = Confidence Interval; COI = Conflict of Interest; GI = Gastrointestinal; HCC = Hepatocellular carcinoma; LC = Local control; NR = not reported; NS = Not significant; OS = Overall survival; PBT = Proton beam therapy; PFS = Progression free survival; RoB = Risk of Bias; TACE = transarterial chemoembolization

*At the time of transplantation, the explanted liver was evaluated for residual tumor and was categorized as complete pathologic response, microscopic residual disease, or gross residual disease. A pathologic complete response was defined as no evidence of disease in the explanted liver at time of transplantation.

APPENDIX I. Lung

Appendix Table I1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in lung cancers

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
Chang 2017a Prospective Case Series *High RoB* USA Funding: This research was supported in part by National Cancer Institute grant P01 CA021239, NCI Cancer Center Core Support Grant CA016672, and NCI Clinical and Translational Science Award UL1 RR024148 to MD Anderson. COI: None declared. ---	**Diagnosis**: Lung (early stage T1 or T2 NSCLC) **Indication:** curative intent	N=35 Male: 45.7% Mean Age (range): 73 (66 to 83) years **T Status** • T1: 34.3% • T2: 57.2% • T3: 8.6% **Tumor histological type:** • Squamous cell carcinoma: 48.5% • Adenocarcinoma: 31.4% • Squamous cell carcinoma & adenocarcinoma: 2.9% • Neuroendocrine carcinoma: 2.9% • Non-small cell carcinoma: 14.3% **Tumor Location** • central or superior: 71.4% • peripheral: 28.6%	**Passive Scatter PBT** **Median Total PBT Dose: 87.5 Gy (RBE) in 35 2.5-Gy fractions over 7 weeks**	**Mean F/U (95% CI):** 83.1 months (69.2 to 97.1 months)	**Survival** **OS (95% CI)** • 1-year: 85.7% (NR) 2-year: 60% (NR) • 3-year: 42.9% (NR) • 5-year: 28.1% (NR) • Median Duration (range): 33.2 mos (NR) **PFS (95% CI)** • 1-year: 80% • 2-year: 64.4% • 3-year: 53.6% • 5-year: 53.6% **Local Recurrence-Free Survival** • 1-year: 97.1% • 3-year: 85% • 5-year: 85% **Regional Recurrence-Free Survival** • 1-year: 96.9% • 3-year: 89.2% • 5-year: 89.2% **Distant Metastasis-Free Survival**	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 **General Toxicities, % (n/N)** • Grade 2 - Dermatitis: 51.4% (18/35) - Radiation Pneumonitis: 11.4% (4/35) - Esophagitis: 2.9% (1/35) - Rib Fracture: 2.9% (1/35) - Heart Toxicities: 5.7% (2/35) - Chest Wall Pain: 2.9% (1/35) • Grade 3: - Radiation Pneumonitis: 2.9% (1/35) - Dermatitis: 2.9% (1/35) • Grade 4: 0% (0/35) • Grade 5: 0% (0/35)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		Median Gross Tumor: 42.9 (4.2 to 435) cm^3			• 1-year: 85.7% • 3-year: 62.2% • 5-year: 54.4% **Recurrence/Progression, % (n/N)** • overall: 42.9% (15/35) -local and distant: 11.4% (4/35) -local only: 0% (0/35) -regional and distant: 2.9% (1/35) -regional only: 5.7% (2/35) -distant only: 22.9% 8/35) • <u>Sites of Metastases:</u> -liver: 14.3% (5/35) -brain: 8.6% (3/35) -lung: 8.6% (3/35) -adrenal gland: 5.7% (2/35) -bone: 5.7% (2/35) -pleura: 2.9 (1/35)	
Chang 2017b Prospective Case Series *High RoB* USA Funding: This study was supported in part by National Cancer Institute grants P01	**Diagnosis**: Lung (locally advanced unresectable NSCLC) **Indication:** Curative intent	N=64 Male, %: 66% Median Age (range): 70 (37 to 78) years **Histology:** • squamous cell carcinoma: 44% • adenocarcinoma: 39% • NSCLC (not otherwise specified): 17%	**Passive Scatter PBT with concurrent chemotherapy** **Total PBT Dose: 74 Gy(RBE)**	**Median F/U (range):** 27.3 mos (NR) **Median Survivor F/U (range):** 79.6 mos (NR)	**Survival** **OS (95% CI)** • 5-year: 29% (18% to 41%) • Median OS (range): 26.5 mos (NR) **PFS (95% CI)** • 5-year: 22% (12% to 32%) **Locoregional Recurrence (95% CI)** • 5-year: 28% (18% to 43%) **Distant Metastasis (95% CI)**	**Harms** *Toxicity Grading Criteria:* CTCAE version 3.0 *Acute Toxicities*: ≤3 mos *Late Toxicities:* >3 mos **Acute toxicities, % (n/N)** <u>Pulmonary</u> • Grade 1: -cough: 42% (27/64) -dyspnea: 25% (16/64) -pleural effusion: 2% (1/64) -pneumonitis: 6.2% (4/64) -wheezing: 3.1% (2/64) • Grade 2: -Lobary atelectasis: 3.1% (2/64)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
CA021239 and CA16672; funder had no role in design and conduct of study COI: One author reports receipt of research funds and honoraria from Varian and is a shareholder in Global Oncology One ---		**Stage** • IIIA: 47% • IIIB: 53% **T Status** • T0 to T2: 58% • T3 to T4: 42% • N0 to N1: 9% • N2 to N3: 91% **Median KPS (range):** 90 (70 to 100)			• 5-year: 54% (40% to 68%) **Recurrence/Progression, % (n/N):** • local: 16% (10/64) • regional: 14% (9/64) • distant: 48% (31/64) **Mortality** • all-cause: 73.4% (47/64)	-cough: 3.1% (2/64) -dyspnea : 16% (10/64) -hemoptysis: 2% (1/64) -hoarseness: 2% (1/64) -pleural effusion: 3.1% (2/64) -pneumonitis: 2% (1/64) • Grade 3: -cough: 3.1% (2/64) -dyspnea : 6.2% (4/64) • Grade 4: 0% (0/64) • Grade 5: 0% (0/64) <u>Gastrointestinal</u> • Grade 1: -Constipation : 3.1% (2/64) -dyspepsia : 2% (1/64) -dysphagia : 39% (25/64) -esophagitis : 2% (1/64) -nausea : 2% (1/64) • Grade 2: -Constipation : 6.2% (4/64) -diarrhea : 5% (3/64) -dyspepsia : 2% (1/64) -dysphagia : 11% (7/64) -esophagitis : 28% (18/64) -gastritis : 2% (1/64) -nausea : 10% (7/64) -odynophagia : 6.2% (4/64) -vomiting : 3.1% (2/64) • Grade 3: -esophagitis : 8% (5/64) -esophageal stricture : 2% (1/64) -nausea : 2% (1/64) • Grade 4: 0% (0/64)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						• Grade 5: 0% (0/64) <u>Cardiac</u> • Grade 1: -Arrhythmia (grade 1): 2% (1/64) -Tachycardia (grade 1): 2% (1/64) • Grade 2: -Tachycardia (grade 2): 3.1% (2/64) -Arrhythmia (grade 2): 2% (1/64) -Palpitations (grade 2): 2% (1/64) • Grade 3: 0% (0/64) • Grade 4: 0% (0/64) • Grade 5: 0% (0/64) <u>Hematologic toxicities</u> • Grade 1: -Anemia : 25% (16/64) -leukopenia : 17% (11/64) -thrombocytopenia : 28% (18/64) -thrombocytopenia : 8% (5/64) • Grade 2: -leukopenia : 47% (30/64) -neutropenia : 8% (5/64) -Blood urea nitrogen increase : 3.1% (2/64) -Elevated creatinine : 2% (1/64) -Anemia : 16% (10/64) -Hypocalcemia : 2% (1/64) -Hypomagnesemia : 2% (1/6) • Grade 3: -Anemia : 5% (3/64) -Hyponatremia : 5% (3/64) -hypotension : 2% (1/64) -leukopenia : 22% (14/64) -neutropenia : 5% (4/64)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						• Grade 4: -leukopenia: 1.6% (1/64) • Grade 5: 0% (0/64) <u>Acute General toxicities</u> • Grade 1: -Anorexia : 3.1% (2/64) -Dermatitis : 38% (24/64) -Dizziness : 2% (1/64) -Fatigue : 5% (3/64) -Pain : 5% (3/64) -Pruritus : 2% (1/64) -Rash: 2% (1/64) -Sourness : 2% (1/64) -Weight loss : 19% (12/64) • Grade 2: -Anorexia : 8% (5/64) -Dehydration : 6% (4/64) -Dermatitis : 34% (22/64) -Dizziness : 2% (1/64) -Fatigue : 19% (12/64) -Fever : 5% (3/64) -Pain : 14% (9/64) -Weight loss :3.1% (2/64) • Grade 3: -Dehydration : 6% (4/64) -Dermatitis : 8% (5/64) -Fatigue : 9% (6/64) -Fever : 3.1% (2/64) -Hyperpigmentation : 5% (3/64) -Pain : 3.1% (2/64) -Weight loss : 5% (3/64) • Grade 4: 0% (0/64) • Grade 5: 0% (0/64)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						Acute other toxicities • Grade 1: -Alopecia : 2% (1/64 • Grade 2: -Anxiety : 2% (1/64) -Candidiasis : 3.1% (2/64) -Infection : 2% (2/64) -Insomnia : 2% (1/64) -Muscle weakness : 2% (1/64) -Peripheral motor neuropathy : 3.1% (2/64) -Peripheral sensory neuropathy : 3.1% (2/64) • Grade 3: -Candidiasis : 2% (1/64) -Infection : 2% (1/64) • Grade 4: 0% (0/64) • Grade 5: 0% (0/64) **Late Toxicities, % (n/N)** Late Pulmonary • Grade 1: -cough : 3.1% (2/64) -dysphagia : 2% (1/64) -dyspnea : 9% (6/64) -pleural effusion : 23% (15/64) -pneumonitis : 3.1% (2/64) -pulmonary hemoptysis : 2% (1/64) • Grade 2: -Lobary atelectasis : 5%% (3/64) -lung atelectasis : 2$ (1/64) -cough : 9% (6/64) -dyspnea : 9% (6/64) -bronchial stricture : 3.1% (2/64) -pleural effusion : 9% (6/64) -pneumonitis : 16% (10/64) -wheezing : 2% (1/64)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						• Grade 3: -dyspnea : 3.1% (2/64) -pleural effusion : 3.1% (2/64) -pneumonitis : 12% (8/64) • Grade 4: -dyspnea : 2% (1/64) -bronchial fistula : 2% (1/64) • Grade 5: 0% (0/64) <u>Late Gastrointestinal toxicities,</u> • Grade 1: -nausea : 2% (1/64) • Grade 2: -esophagitis : 5% (3/64) -esophageal stricture : 2% (1/64) -nausea : 2% (1/64) • Grade 3: -esophagitis : 2% (1/64) • Grade 4: -esophagitis : 2% (1/64) • Grade 5: 0% (0/64) <u>Late cardiac toxicities, % (n/N)</u> • Grade 2: -arrhythmia : 6% (4/64) -pericardial effusion : 3.1% (2/64) • Grade 3: -pericardial effusion : 3.1% (2/64) -tachycardia: 2% (1/64) • Grade 4: 0% (0/64) • Grade 5: 0% (0/64)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						Late hematologic/electrolyte toxicities • Grade 1: -anemia : 3.1% (2/64) -leukopenia : 2% (1/64) • Grade 2: -anemia : 5% (3/64) • Grade 3: -anemia : 2% (1/64) -leukopenia : 2% (1/64) • Grade 4: 0% (0/64) • Grade 5: 0% (0/64) Late General toxicities • Grade 1: -dermatitis : 2% (1/64) -dizziness : 2% (1/64) -weight loss : 5% (3/64) • Grade 2: -dehydration : 2% (1/64) -weight loss : 8% (8/64) • Grade 3: -dermatitis : 2% (1/64) -fatigue : 2% (1/64) -weight loss : 2% (1/64) • Grade 4: 0% (0/64) • Grade 5: 0% (0/64) Late other toxicities, % (n/N) • Grade 1: -alopecia : 2% (1/64) -peripheral motor neuropathy : 2% (1/64) • Grade 2: 0% (0/64) • Grade 3: 0% (0/64) • Grade 4: 0% (0/64)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						• Grade 5: 0% (0/64)
Chao 2017 Prospective Case Series *High RoB* USA Funding: NR COI: One or more authors report grants, personal fees, and/or stock ownership, in various biotechnology corporations.	**Diagnosis**: Lung (recurrentNSCLC) **Indication**: Salvage Treatment	N=57 Male: 44% Median Age (range): 65 (41 to 86) years **Histology:** • Adenocarcinoma: 54% • Squamous cell carcinoma: 44% • NSCLC: 2% **Stage** • IA: 14% • IB: 7% • IIA: 2% • IIB: 5% • IIIA: 51% • IIIB: 11% • IV: 11% **T Status** • T1: 25% • T2: 39% • T3: 16% • T4: 19% • Unknown: 2% **N Status** • N0: 35% • N1: 7% • N2: 47% • N3: 4%	**Double scatter or pencil beam scanning PBT** **Median PBT Dose (range): 66.6 (30 to 74) Gy**	**Median F/U (range):** 7.8 (1 to 40) mos **Median Survivor F/U (range):** 9.8 (1 to 40) mos	**Survival** **OS (95% CI)** • 1-year: 59% (NR) • 2-year: 43% (NR) • Median OS: 14.9% (NR) **PFS (95% CI)** • 1-year: 58% (NR) • 2-year: 38% (NR) **Recurrence/Progression, % (n/N)** • local: 16% (9/57) • regional: 9% (5/57) • distant: 11% (6/57) **Mortality** • all-cause: 42% (24/57) • due to toxicities: 10.5% (6/57)	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 *Acute Toxicities*: ≤3 mos *Late Toxicities:* >3 mos **Rate of any grade ≥2 toxicity** • 1Y: 55% **Acute Toxicity, % (n/N)** Grade ≥3: 39% (22/57) **Late Toxicity, % (n/N)** • Grade ≥3: 12% (7/57) • Grade 4: -neutropenia: 5.3% (3/57) -pericardial effusion: 1.8% (1/57) • Grade 5: 10.5% (6/57) - Bronchopulmonary Hemorrhage: 1.8% (1/57) - Neutropenic sepsis: 1.8% (1/57) - Anorexia(probably RT-related): 1.8% (1/57) - Pneumonitis(probably RT-related): 1.8% (1/57) - Hypoxic respiratory failure/pleural effusion: 1.8% (1/57) - Tracheoesophageal Fistula (probably RT-related): 1.8% (1/57)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		• Unknown: 7% **M Status** • M0: 89% • M1: 11% **Concurrent Chemotherapy:** • yes: 68%				
Hatayama 2016 Retrospective case series *High RoB* Japan Funding: NR COI: None declared --- Two of the 50 patients had an extra tumor each.	**Diagnosis**: Lung (peripheral stage I NSCLC) **Indication:** Curative intent	N=50 Male: 70% Median Age (range): 72.5 (54 to 87) years **Stage** • IA: 85% • IB: 15% **Histology** • Adenocarcinoma: 44% • Squamous cell carcinoma: 12% • Large cell carcinoma: 2% • Clinical malignancy: 42%	**PBT** **Total PBT Dose: 66 GyE**	**Median F/U (range):** 22.8 (5.6 to 60.1) mos	**OS (95% CI)** • 3-year: 87.9% (73.2% to 94.8%) **PFS (95% CI)** • 3-year: 76.3% (86.9% to 59.3%) **Local Control (95% CI)** • 3-year: 95.7% (95% CI, 98.9%-83.8%) **Treatment Response, % (n/N):** • CR: 23% (12/52 tumors) **Recurrence/Progression, % (n/N):** • local: 4% (2/50) • distant: 18% (9/50) **Mortality, % (n/N)** • All-cause: 10% (5/50) -disease progression: 2% (1/50) -other (not specified): 8% (4/50)	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 *Acute Toxicities*: ≤6 mos *Late Toxicities:* >6 mos **Acute Toxicities, % (n/N)** • Grade 1: -Pneumonitis: 84% (42/50) -dermatitis: 66% (33/50) • Grade 2: -Pneumonitis: 2% (1/50) -dermatitis: 6% (3/50) • Grade 3-5: -pneumonitis: 0% (0/50) -dermatitis: 0% (0/50) **Late Toxicities, % (n/N)** • Grade ≤2: -rib fractures (in-field): 29% (15/50) • Grade 3-5: -rib fracture: 0% (0/50)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
Ishikawa 2016 Retrospective case series *High RoB* Japan Funding: NR COI: None declared	**Diagnosis**: Lung (stage I NSCLC) **Indication**: Curative Intent	N=52 Male: 63.5% Median Age (range): 78 (61 to 89) years **Tumor Size (range):** 24.55 (10 to 48) mm **Stage** • 1A: 75% • 1B: 25% **Histology** • Adenocarcinoma: 50% • Squamous cell carcinoma: 19.2% • bronchioloalveolar carcinoma: 5.8% • ground glass opacity: 25%	**PBT** **Total Dose PBT (peripheral tumors, n=27): 66 Gy** **Total Dose PBT (tumors adjacent to proximal bronchial tree, esophagus or heart, n=25): 80 Gy**	**Median F/U (range):** 33 (11 to 50) mos	**NR**	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 *Acute Toxicities*: ≤6 mos *Late Toxicities:* >6 mos <u>Incidence of Grade 2 Rib Fracture</u> • 3-year (95% CI): 30.2% (95% CI 14.9 to 52.1%) • Median Time to Rib Fracture (range):17 (9 to 29) mos <u>Rib Fracture, % (n/N)</u> • Grade 2: 23.1% (12/52) • Grade 3: 0% (0/52) • Grade 4: 0% (0/52)
Kanemoto 2014 Retrospective case series *High RoB* Japan Funding: partly supported by the "Funding Program for	**Diagnosis**: Lung (stage I NSCLC) **Indication**: Curative Intent	N=74 Male: NR Median Age (range): 75 (51 to 86) years **Comorbidities** • cardiovascular disease: 21.6% • respiratory disease: 44.6% • other cancers: 43.2%	**PBT** **Total Dose PBT (peripheral tumors, n=): 66 Gy(RBE)** **Total Dose PBT (centrally located tumors, n=): 72.6 Gy(RBE)**	**Median F/U (range):** 31 (7.3 to 104.3) mos	**Survival** **OS (95% CI)** • 3-year: 76.7% (NR) • 5-year: 65.8% (NR) **PFS (95%CI)** • 3-year: 58.6% (NR) • 5-year: 52.5% (NR)	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 and RTOG/EORTC late radiation scheme *Acute Toxicities*: ≤3 mos *Late Toxicities:* >3 mos **Acute Toxicities, % (n/N)** • <u>Grade 2:</u> -skin reaction: 2.7% (2/74) -esophagitis: 1.4% (1/74) • <u>Grade 3:</u>

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
World-Leading Innovative R&D on Science and Technology (FIRST Program)," initiated by the Council for Science and Technology Policy (CSTP), and by a Grand-in Aid for Scientific Research from the Japanese Society for the Promotion of Science, Tokyo, Japan (B) 24390286 COI: None declared		**Disease Status** • Single Tumor: 82% • 2 tumor masses: 8% **Median Tumor Diameter (range):** 22 (10 to 48) mm **Histology** • Adenocarcinoma: 40% • Squamous cell carcinoma: 33% • Non-small-cell carcinoma: 8% • Unproven: 20% **Tumor Location** • Centrally located tumor: 26% • Peripherally located tumor: 74%			**Disease Specific Survival (95% CI)** • 3-year: 83.0% (NR) • 5-year: 73.8%(NR) **Local Control (95% CI)** • 3-year: 81.8% (NR) • 5-year: 81.8% (NR) **Local Control [Central Tumors] (95% CI)** • 3-Year: 63.9% **Local Control [peripheral tumors] (95% CI)** • 3-Year: 88.4% **Recurrence/Progression, % (n/N)** • overall: 40.5% (30/74) • Sites of Recurrence: -local: 11 -regional lymph nodes: 16 -lungs: 6 -other: 15 **Mortality, % (n/N)** • All-cause: 25.7% (19/74)	-pneumonitis: 1.4% (1/74) **Late Toxicities, % (n/N)** • Grade 3: -pneumonitis: 1.4% (1/74) -skin ulcer: 1.4% (1/74) • Grade 4: -rib fracture: 14.9% (11/74)
Lee 2016 Retrospective case series *High RoB*	**Diagnosis**: Lung (stage I and recurrent NSCLC) **Indication**:	N=55 Male: 78% Median Age (range): 75 (47 to 89) years **Histology**	**PBT** **Total Dose PBT (range):** **NR (50 to 72) CGE**	**Median F/U (range):** 29 (4 to 95) mos	**OS (95% CI)** • 3-year: 54.9% • Median OS: 48.6 (4 to 95) mos **Lymph Node Metastasis Free Survival (95% CI)**	**Harms** *Toxicity Grading Criteria:* CTCAE version 3.0 **General toxicities, % (n/N)** • Grade 1: -Pulmonary: 45.5% (25/55) -atelectasis: 3.6% (2/55)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
South Korea Funding: This study was supported by a National Cancer Center Grant (NCCCTS10494) COI: None declared	Mixed (Curative Intent, 77%; and Salvage, 23%)	• adenocarcinoma: 44% • squamous cell carcinoma:40% • Non-small cell lung cancer not specified: 9% • not confirmed: 7% **ECOG** • 0:25% • 1: 67% • 2: 7% **Tumor Location:** • central: 24% • peripheral: 76%			• 3-year: 78.4% (NR) **Distant Metastasis Free Survival (95% CI)** • 3-year: 76.5% **Local Control (95% CI)** • 3-year: 85.4% (NR) • Median Time to Local Progression (range): 9.3 (5 to 14) mos **Recurrence/Progression, % (n/N)** • local: 12.7% (7/55) **Mortality, % (n/N)** • all-cause: 43.6% (24/55) -disease progression: 20% (11/55) -other causes (unknown): 23.6% (13/55)	-Chest pain: 16.4% (9/55) -skin (dermatitis): 3.6% (2/55) -gastrointestinal bleeding: 0% (0/55) -rib fracture: 0% (0/55) • Grade 2: -Pulmonary: 12.7% (7/55) -soft tissue fibrosis: 7.2% (4/55) -atelectasis: 9.1% (5/55) -Chest pain: 14.5% (8/55) -skin (dermatitis): 1.8% (1/55) -gastrointestinal bleeding: 3.6% (2/55) -rib fracture: 5.5% (3/55) • Grade 3: 0% (0/55) • Grade 4: 0% (0/55) • Grade 5: 1.8% (1/55) -symptomatic idiopathic pulmonary fibrosis: 1.8% (1/55)
Makita 2015 Retrospective case series *High RoB* Japan Funding: NR COI: None declared ---	**Diagnosis**: Lung (stage I NSCLC) **Indication**: Curative Intent	N=56 Male: 64.3% Median Age (range): 77 (61 to 89) years **Histology** • adenocarcinoma: 64.3% • squamous cell carcinoma: 17.9% • unknown: 17.9% **ECOG**	**PBT** **Total Dose (range) peripheral tumors: 66 Gy(RBE) in 10 fractions over 2 weeks** **Total Dose (range) central tumors: 80 Gy(RBE) in 25**	**Median F/U (range):** 33.7 (4.6 to 57.5) mos	**Survival** **OS (95% CI)** • 3-year: 81.3% (75.9 to 86.7%) **PFS (95% CI)** • 3-year: 73.4% (67.2 to 79.6%) **Local Control (95% CI)** • 3-year: 96.0% (93.2 to 98.8%)	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 *Acute Toxicities*: timeframe NR *Late Toxicities:* timeframe NR **Acute toxicities, % (n/N)** • Grade 1: -dermatitis: 46.4% (26/56) -esophagitis: 1.8% (1/56) • Grade 2: -dermatitis: 17.9% (10/56) -esophagitis: 0% (0/56) • Grade 3:

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
Study composed of two cohorts receiving different doses of PBT (for peripheral or centrally located tumors), data reflects combined results of all patients.		• 0: 69.6% • 1: 23.2% • 2: 7.1% **Indication** • inoperable: 76.8% • refused surgery: 23.2% **Tumor Location** • upper right: 17.9% • middle right: 1.8% • lower right: 19.6% • upper left: 35.1% • lower: 24.6%	**fractions in 5 weeks**		**Recurrence/Progression, % (n/N)** • local: 3.6% (2/56) • regional: 5.4% (3/56) • distant: 8.9% (5/56) • carcinomatous pleuritis: 3.6% (2/56)	-dermatitis: 1.8% (1/56) -esophagitis: 0% (0/56) • Grade 4: 0% (0/56) • Grade 5: 0% (0/56) **Late toxicities, % (n/N)** • Grade 1: -soft tissue damage: 14.3% (8/56) -rib fracture: 17.9% (10/56) -radiation pneumonitis: 53.6% (30/56) -pericardial effusion: 0% (0/56) • Grade 2: -soft tissue damage: 3.6% (2/56) -rib fracture: 17.9% (10/56) -radiation pneumonitis: 16.1% (9/56) -pericardial effusion: 1.8% (1/56) • Grade 3: -soft tissue damage: 0% (0/56) -rib fracture: 0% (0/56) -radiation pneumonitis: 1.8% (1/56) -pericardial effusion: 0% (0/56)
Nguyen 2015 prospective case series *High RoB* Funding: NR COI: None declared	**Diagnosis**: Lung (stage II and III NSCLC) **Indication**: Curative Intent	N=134 Male: 54.5% Median Age (range): 69 (NR) years **Histology** • Squamous: 44% • non squamous: 56%	**Passive scatter PBT** **Maximum Dose (range): 74 (60 to 74.1) Gy(RBE)**	**Median F/U (range):** 56.4 (NR) mos	**OS (95% CI)** • Median OS (Stage II): 40.4 mos • Median OS (Stage III): 30.4 mos **DFS (95% CI)** • 5-year (Stage II): 17.3% (NR) • 5-year (Stage III): 18% (NR)	**Harms** *Toxicity Grading Criteria:* CTCAE version 3.0 **General toxicities, % (n/N)** • Grade 0: -radiation pneumonitis: 51% (68/134) -esophagitis: 51% (69/134) -dermatitis: 55% (74/134) • Grade 1: -radiation pneumonitis: 26% (35/134) -esophagitis: 19% (25/134) -dermatitis: 25% (33/134) • Grade 2:

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
--- OS only provided via graph by stage.					**Regional Failure Free Survival (95% CI)** • 3-year: 55.8% (NR) • 5-year: 54.4% (NR) **Distant Metastasis Free Survival (95% CI)** • 3-year: 50.3%(NR) • 5-year: 45.8%(NR)	-radiation pneumonitis: 22% (29/134) -esophagitis: 25% (33/134) -dermatitis: 19% (14/134) • Grade 3: 12% (16/134) -radiation pneumonitis: 1.5% (2/134) -esophagitis: 4.5% (6/134) -dermatitis: 6% (8/134) • Grade 4: <1% (1/134) -esophageal stricture: <1% (1/134)
Ono 2018 retrospective case series *High RoB* Japan Funding: None reported. COI: None declared --- Cohort composed of elderly patients.	**Diagnosis**: Lung (elderly with NSCLC) **Indication**: Curative Intent	N=78 eligible, **35 analyzed** Male: 26% Median Age (range): 82 (80 to 87) years **ECOG** • 0: 40% • 1: 43% • 2: 17% **Stage** • I: 60% • II: 37% • III: 3% **Tumor Location** • right upper: 11% • right middle: 6% • right lower: 23% • left upper: 40% • left lower: 20% **Histology**:	**PBT** **Median Total PBT Dose (range): 80 (60 to 80) Gy(RBE)**	**Median F/U (range):** 34 (10 to 72) mos	**OS (95% CI)** • 1-year: 97.1% (91.6 to 100%) • 2-year: 74.3% (59.8 to 88.8%) • 3-year: 67.2% (50.3 to 83.3%) • Median Overall Survival Time: 56 (33.1 to 78.9) mos **Cancer Specific Survival (95% CI)** • 3-year: 76.3% (60.4 to 92.2%) **Local Control (95% CI)** • 3-year: 86.5% (74.0 to 99.0%) **Recurrence/Progression, % (n/N):** • local: 11.4% (4/35) • regional lymph node: 5.7% (2/35)	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 *Acute Toxicities*: ≤6 mos *Late Toxicities:* >6 mos **General Toxicities, % (n/N)** • Grade 0: -pneumonitis: 5.7% (2/35) -rib fracture: 74.3% (26/35) -dermatitis radiation: 14.3% (5/35) • Grade 1: -pneumonitis: 88.6% (31/35) -rib fracture: 14.3% (5/35) -dermatitis radiation: 62.9% (22/35) • Grade 2: -pneumonitis: 5.7% (2/35) -rib fracture: 11.4% (4/35) -dermatitis radiation: 20% (7/35) • Grade 3: -pneumonitis: 0% (0/35) -rib fracture: 0% (0/35) -dermatitis radiation: 2.9% (1/35) • Grade 4: -pneumonitis: 0% (0/35) -rib fracture: 0% (0/35) -dermatitis radiation: 0% (0/35)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
		• squamous cell carcinoma: 48.5% • adenocarcinoma: 48.5% • NSCLC: 3% **Median Diameter of lung Tumor (range):** 32 (10 to 67) mm			• lung metastasis outside treatment field: 17.1% (6/35) **Mortality, % (n/N):** • all-cause: 48.6% (17/35) -disease progression: 25.7% (9/35) -newly diagnosed cancer: 11.4% (4/35) -other diseases: 11.4% (4/35)	• grade 5: -pneumonitis: 0% (0/35) -rib fracture: 0% (0/35) -dermatitis radiation: 0% (0/35)
Rwigema 2017 prospective case series *High RoB* USA Funding: None reported. COI: None declared. --- Initial treatment response only available for n=27 patients.	**Diagnosis**: Lung (limited state small cell lung cancer, LS-SCLC) **Indication**: Curative Intent	N=30 Male: 30% Median Age (range): 68 (57 to 81) **ECOG** • 0: 40% • 1: 50% • 2: 6.7% • 3: 3.3% **Prior Malignancy** • NSCLC: 16.7% • breast cancer: 10% • bladder cancer: 10% • cervical cancer: 3.3% • colon cancer: 3.3%	**Double scattering (86.7%), uniform scanning (10%), or pencil beam scanning (3.3%) PBT with concurrent chemotherapy** **Median PBT Dose (range): 63.9 (45 to 66.6) CGE in 33 to 37 fractions daily or twice daily**	**Median F/U (range):** 14 (2 to 42) mos	**OS (95% CI)** • 1-year: 71.5% (NR) • 2-year: 57.6% (NR) • Median OS: 28.2 mos (NR) **Recurrence Free Survival (95% CI)** • 1-year: 63% (NR) • 2-year: 42% (NR) • Median Recurrence Free Survival: 14.3 mos (NR) **Local Control (95% CI)** • 1-year: 85% (NR) • 2-year: 68.6% (NR) **Treatment Response , % (n/N)** • CR: 40.7% (11/27) • PR: 55.6% (15/27) • SD: 3.7% (1/27)	**Harms** *Toxicity Grading Criteria:* CTCAE version 4.0 **Hematological Toxicities, % (n/N)** • Grade 1: -thrombocytopenia: 3.3% (1/30) • Grade 2 : -low hemoglobin levels: 33.3% (10/30) -thrombocytopenia: 3.3% (1/30) -lymphopenia: 6.7% (2/30) • Grade 3: -low hemoglobin levels: 23.3% (7/30) -neutropenia: 20% (6/30) -thrombocytopenia: 10% (3/30) -lymphopenia: 10% (3/30) • Grade 4: -neutropenia: 20% (6/30) -febrile neutropenia: 3.3% (1/30) -lymphopenia: 33.3% (10/30) **non-hematological toxicities, % (n/N)** • grade 1: -cough: 46.7% (14/30) -dyspnea:43.3 % (13/30)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
					Recurrence/Progression, % (n/N) • local: 6.7% (2/30) • in-field: 16.7% (5/30) • locoregional (outside field): 20% (6/30) • -distant: 23.3% (7/30)	-pneumonitis: 26.7% (8/30) -pleural effusion: 10% (3/30) -pericardial effusion: 0% (0/30) -dermatitis: 56.7% (17/30) -esophagitis: 33.3% (10/30) -fatigue: 40% (12/30) -anorexia: 30% (9/30) • grade 2: -cough: 3.3% (1/30) -dyspnea: 20% (6/30) -pneumonitis: 10% (3/30) -pleural effusion: 6.7% (2/30) -pericardial effusion: 0% (0/30) -dermatitis: 10% (3/30) -esophagitis: 43.3% (13/30) -fatigue: 43.3% (13/30) -anorexia:13.3 % (4/30) • grade 3: 3.3% (1/30) -cough: 0% (0/30) -dyspnea: 0% (0/30) -pneumonitis: 3.3% (1/30) -pleural effusion: 0% (0/30) -pericardial effusion: 3.3% (1/30) -dermatitis: 0% (0/30) -esophagitis: 0% (0/30) -fatigue: 0% (0/30) -anorexia: 3.3% (1/30) • grade 4: 3.3% (1/30) -cough: 0% (0/30) -dyspnea: 0% (0/30) -pneumonitis: 0% (0/30) -pleural effusion: 0% (0/30) -pericardial effusion: 0% (0/30) -dermatitis: 0% (0/30) -esophagitis: 3.3% (1/30) -fatigue: 0% (0/30)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
						-anorexia: 0% (0/30) • grade 5: 0% (0/30) -cough: 0% (0/30) -dyspnea: 0% (0/30) -pneumonitis: 0% (0/30) -pleural effusion: 0% (0/30) -pericardial effusion: 0% (0/30) -dermatitis: 0% (0/30) -esophagitis: 0% (0/30) -fatigue: 0% (0/30) -anorexia: 0% (0/30)
Moreno 2018 Retrospective case series *High RoB* USA Funding: NR COI: teven H. Lin, MD, PhD, has received research funding from Elekta, STCube Pharmaceuticals, Peregrine, Hitachi Chemical Inc,	**Diagnosis**: NSCLC **Indication**: Curative Intent	N=506 Median Age (range): 70 (42 to 89) years Male: 53% Race White: 88% Black: 6% Other: 6% Comorbidity Score 0: 66% 1: 22% ≥2: 12% Tumor Stage I: 25% II: 13% III: 47%	**PBT Modality**: NR **Median PBT Dose** - Cancer Community Program: 60 Gy **Academic/Research Facilities: 66.6 Gy**	**Median F/U**: - Cancer Community Program: 23.5 months Academic/Research Facilities: 15.2 months	**5-year OS (95% CI)** • Stage I: 36% (95% CI NR) • Stage II: 34% (95% CI NR) • Stage II: 23% (95% CI NR) • Stage IV: 5% (95% CI NR) **Effect of Radiation dose on OS, HR (95% CI) [<60 Gy as referent]** • 60 to 64 Gy: 1.18 (0.77 to 1.8), p=0.459 • 65 to 69 Gy: 1.45 (0.87 to 2.42), p=0.159 ≥70 Gy: 0.63 (0.41 to 0.95), p=0.027	**NR**

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Primary/Secondary Outcomes	Safety
and Roche/Genentech; has served as consultant for AstraZeneca; and has received honoraria from US Oncology and ProCure. All other authors have no conflicts of interest to disclose.		IV: 16% Primary Tumor Location Left Upper Lobe: 27% Left Lower Lobe: 12% Right Upper Lobe: 29% Right Middle Lobe: 3% Right Lower Lobe: 14% Other/Unknown: 14% Chemotherapy: 67% Surgery: 13% Lobectomy: 8% Pneumonectomy: 1% Other/unknown: 5%				

CGE = Cobalt Gray Equivalent; CI = confidence interval; cm = centimeter; COI = conflict of interest; CTCAE = Common Terminology Criteria for Adverse Events; DFS = Disease Free Survival; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organszation for Research and Treatment of Cancer; F/U = follow-up; Gy = Gray (unit); GyE = Gray Equivalent; Gy(RBE) = Gray (Relative Biological Equivalent); KPS = Karnofsky Performance Score; LS-SCLC = Limited State Small-Cell Lung Cancer mos = months; NR = not reported; NSCLC = non-small-cell lung cancer; OS = overall survival; PBT = proton beam therapy; PFS = progression free survival; RoB = risk of bias; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group

Appendix Table I2. Study characteristics and patient demographics: comparative studies of proton beam therapy in lung cancers

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
RCTs							
Liao 2018 Randomized Controlled Trial *Moderately High* USA Bayesian Adaptive RCT: initial 20 patients randomly assigned (20 per arm); subsequent patients underwent adaptive random assignment, with the randomization probability proportional to the 1-year failure rate in each arm	272 enrolled, 181 eligible, 149 analyzed and treated, 173 ITT; 149 per-protocl/as randomized/analyzed; 39 not randomly assigned	**As randomized population**: **PBT (n=57)** Passive scatter with concurrent chemotherapy Mean Lung Dose (range): 16.1 (6.9-22.1) Gy(RBE) Mean Esophagus Dose (range): 23.6 (0.04-49.9) Gy(RBE) Mean Heart Dose (range): 5.9 (0.4-21.1) Gy(RBE) **IMRT (n=92)** with concurrent chemotherapy Mean Lung Dose (range):	**Inclusion:** Patients ≥18 years old; stage II to IIIB NSCLC, or stage IV NSCLC with a single brain metastasis or isolated tumor recurrence after surgical resection that could be treated definitely with concurrent chemoradiation; KPS≥ 70; baseline pulmonary function of forced expiratory volume in 1 second ≥ 1 L; patients who had received systemic chemotherapy (regardless of response before enrollment) were also eligible **Exclusion: NR** **Indication:** Curative Intent	**PBT vs. IMRT (randomized group, n=149)** N=57 vs. 92 Male: 22% vs. 32% Median Age (range): 67 (39 to 78) vs. 66 (33 to 85) years KPS • ≤80: 25% vs. 41% • ≥90: 13% vs. 21% Smoking History • Never: 2% vs. 6% • Ever: 36% vs. 56% Induction Chemotherapy: 28.2% vs. 40.9% Histology • Adenocarcinoma: 20% vs. 33% • Squamous Cell Carcinoma: 11% vs. 21% • NSCLC (unspecified): 6% vs. 4.7% • -Large Cell: 0.7% vs. 1% • -Other: 0% vs. 2% Stage • IIA/B: 5% vs. 4% • IIIA: 14% vs. 30% • IIIB: 16% vs. 19% • IV: 2% vs. 3% Recurrent Disease:	PBT vs. IMRT **Median F/U, all patients (range):** 25.7 (NR) vs. 24.1 months **Median F/U, survivors (range):** 48.8 (NR) months vs. 36.4 **% F/U [overall]:** 54.8% (149/272) **% F/U [randomized]:** 87.6% (92/105) vs 75% (57/76)	Local Failure Harms	Funding: Supported by National Cancer Institute Grants No. P01 CA021230, U19 CA021239, and P30 CA016672. COI: One or more authors declare relationships (honoraria, travel and accommodations, speakerships, consulting or advisory roles, research funding, and/or stock or other ownerships) with various industry corporations (see full details in study) Notes: 272 patients signed informed consent and were

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		16.6 (0.4-22.7) Gy(RBE) Mean Esophagus Dose (range): 26.9 (3.36-47.62) Gy(RBE) Mean Heart Dose (range): 10.1 (0.6-34.6) Gy(RBE) **ITT population**: **PBT (n=72)** with concurrent chemotherapy Mean Lung Dose (range): 17.2 (6.9-22.24) Gy(RBE) Mean Esophagus Dose (range): 23.8 (0.04-49.9) Gy(RBE) Mean Heart Dose (range): 6.9 (0.4-23.4) Gy(RBE)		0.1% vs. 6% **PBT vs. IMRT (ITT population, n=173)** N=72 vs. 101 Male: 25% vs. 31% Median Age (range): 66 (37 to 78) vs. 66 (33 to 85) years KPS • ≤80: 27.2% vs. 39.3% • ≥90: 14.4% vs. 19.1% Smoking History • never: 2.3% vs. 5.2% • ever: 39.3% vs. 53.2% Induction Chemotherapy: 27.7% vs. 39.9% Histology • Adenocarcinoma: 21% vs. 31% • Squamous Cell Carcinoma: 15% vs. 20% • NSCLC (unspecified): 5% vs. 4% • Large Cell: 0.6% vs. 1% • Other: 0% vs. 1.7% Stage • IIA/B: 5% vs. 4% • IIIA: 16% vs. 28% • IIIB: 17% vs. 18% • IV: 3% vs. 3% Recurrence: 1% vs. 6% **PBT vs. IMRT (non-randomized, n=39)**			then excluded for a variety of reasons. 225 had plans generated and a further 44 were excluded; 181 with plans that allowed randomization were then randomly allocated and 173 were available for ITT analysis whereas 149 were randomized and treated and used in main analysis.

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		IMRT (n=101) with concurrent chemotherapy Mean Lung Dose (range): 16.7 (0.4-22.7) Gy(RBE) Mean Esophagus Dose (range): 27.4 (3.4-47.6) Gy(RBE) Mean Heart Dose (range): 10.2 (0.6-35.8) Gy(RBE) **Non-randomized population**: **PBT (n=13)** with concurrent chemotherapy Mean Lung Dose (range): 20.5 (4.2 to 22.8) Gy(RBE) Mean Esophagus Dose (range): 34.7 (16.3 to 59.8) Gy(RBE)		N=13 vs 26 Male: 46.2% vs 50% Median Age (range): 66 (42 to 76) vs. 65 (39 to 79) years KPS • ≤80: 92.3% vs. 76.9% • ≥90: 7.7% vs. 23.1% Smoking History • never: 7.7% vs. 11.5% • ever: 92.3% vs. 88.5% Induction Chemotherapy: 46.2% vs. 46.2% Histology • Adenocarcinoma: 30.8% vs 73.1% • Squamous Cell Carcinoma: 53.8% vs. 15.4% • NSCLC (unspecified): 15.4% vs. 3.8% • Large Cell: 0% vs. 0% • Other: 0% vs. 7.7% Stage • IIA/B: 0% vs. 0% • IIIA: 30.8% vs. 26.9% • IIIB: 61.5% vs. 46.2% • IV: 0% vs. 15.4% Recurrence: 7.7% vs. 11.5%			

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		Mean Heart Dose (range): 13.9 (0.4 to 29.4) Gy(RBE) **IMRT (n=26)** with concurrent chemotherapy Mean Lung Dose (range): 20.4 (3.8 to 26.7) Gy(RBE) Mean Esophagus Dose (range): 35.0 (2.3 to 49.8) Gy(RBE) Mean Heart Dose (range): 14.6 (1.2 to 36.7) Gy(RBE) =					
Cohort studies							
Higgins 2017 Retrospective Comparative Cohort (database)	243,822	**PBT (n = 348):** Median Dose (Range): 60 Gy (NR) **Non-proton (n = 243,474):**	**Inclusion:** Patients w/ stage I to IV NSCLC receiving radiation to lungs or chest **Exclusion:** Patients with missing outcomes	All Male: 56.8% Median Age (range): 68 years Tumor Location: • C340, main bronchus: 6.2%	Proton vs. non-proton **Median F/U (range):** 39.6 vs. 59.5	OS	Funding: supported in part by the Biostatistics and Bioinformatics Shared Resource of Winship Cancer

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Moderately High USA		Median Radiation Dose (range): 59.4 (NR) Gy Modalities: -External Beam-not otherwise specified (n=44,687) -3D-Conformal (n=36,406) -Photons (n=140,035) -IMRT (n=22,346) • Certain data is reported PBT vs. non-PBT, others are PBT vs. each modality • Propensity score matching was used in two separate multivariate analyses		• C341, upper lobe, lung: 57.2% • C342, middle lobe, lung: 3.7% • C343, lower lobe, lung: 22.7% • C348, overlapping lesion of lung: 1.5% • C349, lung, NOS: 8.8% Surgery • yes: 12.6% Stage • 0 to I: 14.9% • II to III: 59.8% • IV: 25.3% Histology • adenocarcinoma: 30.6% • squamous cell carcinoma: 37.6% • other: 31.8% Laterality: • left: 54.5% • right: 37.2% • other: 8.3% Chemotherapy • yes: 68.4% Mean Tumor Size (SD): 4.9 (4.51) cm^3	**% F/U:** unable to be determined*		Institute of Emory University and the National Institutes of Health/National Cancer Institute under award number P30CA138292. COI: None declared Notes:
Niedzielski 2017 Retrospective Comparative Cohort	134	**PBT (n=49)** Passive scatter Treatment Dose -74 Gy: 71.4% (35/49)	**Inclusion:** Patients w/ NSCLC **Exclusion:** Patients who missed multiple weekly 4-dimensional computed tomography scans or	PBT vs. IMRT N = 49 vs. 85 Male: 61.2% vs. 52.9% Median Age (range): 67 (38 to 76) years vs. 65 (43 to 85) years Histology	**NR** **% F/U:** cannot be determined*	Harms	Funding: NR COI: None declared. Notes: Mainly contains data on

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Moderately High USA		-66 Gy: 20.4% (10/49) -60 Gy: 8.2% (4/49) **IMRT (n=85)** Treatment Dose -74 Gy: 62.4% (53/85) -66 Gy: 32.9% (28/85) -60 Gy: 4.7% (4/85)	treatment planning data were excluded	• Squamous cell carcinoma: 36.7% vs. 34.1% • Adenocarcinoma: 51% vs. 58.8% • Large cell carcinoma: 4.1% vs. 3.5% • other: 8.2% vs. 3.5% Smoking History • current smoker: 53.1% vs. 21.2% • former smoker: 42.9% vs. 68.2% • never: 4% vs. 10.6% Stage • IIA: 4.1% vs. 3.5% • IIB: 12.2% vs. 3.5% • IIIA: 40.8% vs. 45.9% • IIIB: 40.8% vs. 42.4% • IV: 2.1% vs. 4.7%			biomarkers and dosimetry.
Remick 2017 Retrospective Comparative Cohort *Moderately High* USA	61	**PBT (n=27)** Double scatter (n=22) or pencil beam scanning (n=5) Median PBT Dose (range): 50.4 (50.4 to 66.6) Gy **IMRT (n=34)** Median RT Dose (range): 54 (50 to 72) Gy	**Inclusion:** Patients undergoing post-op RT for NSCLC with positive microscopic margins and/or positive N2 lymph nodes. **Exclusion:** Patients who received neoadjuvant concurrent proton/chemotherapy as part of an institutional protocol (n=20) and those who had palliative surgery (n=2) to alleviate	PBT vs. IMRT N=27 vs. 34 Male, %: 52% vs. 41% Median Age (range): 65 (38 to 77) years vs. 63 (38 to 80) years Smoking History • yes: 74% vs. 76% Histology (**p<.001**): • Squamous cell carcinoma: 7% vs. 20% • Adenocarcinoma: 67% vs. 79% • Large cell: 4% vs. 0% • Other: 22% vs. 0%	Proton vs. IMRT **Median F/U (range):** 23.1 (2.3 to 42.0) months vs. 27.9 (0.5 to 87.4) months **% F/U**: 100%	OS, LRFS, Disease Failure, Mortality, Harms	Funding: NR COI: None declared. Notes:

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
			symptomatic airway compression before radiation treatment were excluded from this analysis.	Chemotherapy • neoadjuvant: 7% vs. 12% • sequential: 70% vs. 59% • concurrent: 22% vs.32%			
Tucker 2016 Retrospective Comparative Cohort *Moderately High* USA	468	**PBT (n=45)** Passive Scatter Median PBT dose (range): 63 (60 to 76) Gy(RBE) **3DCRT (n=193)** Median PBT dose (range): 63 (60 to 76) Gy(RBE) **IMRT (n=230)** Median PBT dose (range): 63 (60 to 76) Gy(RBE)	**Inclusion:** Patients w/ pathologically confirmed primary NSCLC with clinical stage IIIA or IIIB disease, good performance status (Eastern Cooperative Oncology Group [ECOG] score 0–1), radiation dose of P60 Gy, no treatment interruptions lasting more than 7 days, and complete clinical and follow-up information on age, sex, smoking history, tumor histology, and gross tumor volume (GTV). **Exclusion:** NR	All N= 45 vs. 230 Male, %: 56.4% Median (range: 64 (34 to 87) years Histology • Adenocarcinoma: 34.8% • non-small cell not otherwise specified: 28.4% • Squamous cell carcinoma: 36.8% Stage • IIIA: 44.4% • IIIB: 55.6%	**F/U (range):** 24 months (NR) **% F/U:** cannot be determined*	OS	Funding: Supported in part by Cancer Center Support (Core) Grant CA016672 from the National Cancer Institute to The University of Texas MD Anderson Cancer Center COI: None declared
Wang 2016 Prospective Comparative Cohort *Moderately High* USA	82	**PBT (n=26)** Median Radiation dose (range): 74.0 (54.0 to 74.0) Gy(RBE) **3DCRT (n=22)** Median Radiation dose (range):	**Inclusion:** Patients ≥18 years old w/ pathologic diagnosis of locally advanced, unresectable primary or recurrent NSCLC **Exclusion:** NR **Indication**:	PBT vs. 3DCRT vs. IMRT N=26 vs. 22 vs. 34 Male: 53.9% vs. 45.4% vs. 50% Median Age (range): 65.5 (43.0 to 79.0) vs. 63.7 (42.5 to 77.9) vs. 65.6 (48.1 to 77.8) years BMI (kg/m^2): 27.3 (20.5 to 38.9) vs. 25.1 (19.6 to 45.2) vs. 27.0 (19.7 to 42.2) Stage	NR **% F/U:** Cannot be determined*	MDASI Symptom Burden	Funding: supported by grants from the National Cancer Institute of the National Institutes of Health: NCI R21 CA132109 to Dr. Wang; NCI R01 CA026582 to

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		63.0 (50.4 to 70.0) Gy(RBE) **IMRT (n=34)** Median Radiation dose (range): 63.0 (41.4 to 70.0) Gy(RBE) • All patients received concurrent chemotherapy. • PBT received significantly higher radiation dose than 3DCRT (**p<0.001**) or IMRT (**p=0.002**)	• PBT = recurrent tumor after surgery and/or chemotherapy • photon RT (3DCRT or IMRT) = nonoperable NSCLC	• I/II: 34.8% vs. 9.1% vs. 29.4% • III: 65.2% vs. 90.9% vs. 70.6% ECOG, **p=0.023** • 0 to 1: 100% vs. 81.8% vs. 93.9% • 2 to 3: 0% vs. 18.2% vs. 6.1% Prior Chemotherapy: 50% vs. 59.1% vs. 26.5%, **p=0.036** Prior Surgery: 57.7% vs. 90.9% vs. 97.1%, **p<0.001**			Dr. Cleeland; NCI P01 CA021239 to Drs. Delaney and Mohan (co-principal investigators); and MD Anderson Cancer Center Support Grant NCI P30 CA016672. The funding agency played no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication COI: None declared

3DCRT = Three-dimensional Conformal Radiotherapy; COI = Conflict of Interest; ECOG = Eastern Cooperative Oncology Group; F/U = Follow-up; Gy = Gray; IMRT = Intensity modulated radiation therapy; ITT = Intention to treat; KPS = Karnofsky performance score; LRFS = local recurrence free survival; MDASI = MD Anderson Symptom Index; NR = Not reported; NSCLC = non-small cell lung cancer; OS = Overall Survival; PBT = Proton Beam Therapy; RBE = Relative Biological Effectiveness; RoB = Risk of Bias; RT = Radiation therapy

*Follow-up data from the following studies could not be determined:

Higgins 2017: excluded patients with missing outcome data.

Niedzielski 2017: excluded patients with missing CT or treatment planning data.

Tucker 2016: did not describe number of patients excluded due to incomplete clinical/follow-up data.

Wang 2016: information on eligible population not adequately provided.

Appendix Table I3. Detailed data abstraction: comparative studies of proton beam therapy in lung cancers

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
RCTs			
Liao 2018 PBT (n=57) vs. IMRT (n=92) Randomized Controlled Trial *Xxxx RoB* USA --- Contains data on ITT population and a non-randomized group group. The data from these other analysis sets is only in KM survival graphs however. Survival rates estimated from graph (also includes 2, 3, 4, 5 year time frames on graph; only 1 year estimated at the moment).	PBT vs. IMRT **Randomized group, n=57 vs. 92** (results from analyses of ITT and those not randomly assigned were consistent with data from this group, see below) **Median OS Time** 26.1 months vs. 29.5 months; p=0.297 **OS** (all data estimated from figure S4) • 1-year: 72% vs. 84% • 2-year: 57% vs. 62% • 3-year: 36% vs.38% • 4-year: 32% vs. 37% • 5-year: 19% vs. 37% Log-rank p=0.30 **Local Failure:** (all data estimated from figure 3c) • 1-year: 10.5% vs. 10.9% • 2-year: 36% vs. 31% • 3-year: 37% vs. 32% • 4-year: 37% vs. 32% • 5-year: 37% vs. 38% p=0.86	NR	**PBT vs. IMRT (randomized)** **Randomized group, n=57 vs. 92** Radiation pneumonitis at 1 year: • grade ≥3: 10.5% (6/57) vs. 6.5% (6/92), p=0.537 -grade 3: 10.5% (6/57) vs. NR -grade 4: 0% (0/57) vs. NR -grade 5: 0% (0/57) vs. 2.2% (2/92) (after 1 year no cases of radiation pneumonitis reported per figure 3b) **ITT population, n=72 vs. 101** Rate of Grade ≥3 Radiation pneumonitis • 1-year: 8% vs. 7% • 2-year: 8% vs. 7% • 3-year: 8% vs. 7% • 4-year: 8% vs. 7% • 5-year: 8% vs. 7% Log-rank p=0.58 **Nonrandomized, n=13 vs. 26** • 1-year: 19% vs. 19% • 2-year: 19% vs. 19% • 3-year: 19% vs. 19% • 4-year: 19% vs. 19% • 5-year: 19% vs. 19%

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	Combined rate of radiation pneumonitis and local failure: (all data estimated from figure 3a): • 1-year: 21.1% vs. 17.4%, p=0.175; • 2-year: 38% vs. 36% • 3-year: 43% vs. 37% • 4-year: 43% vs. 37% • 5-year: 43% vs. 37% Log-rank p=0.55 Adj HR (multivariate analysis, IMRT as referent) 1.35 (95% CI 0.73 to 2.48), p=0.34 **ITT population, n=72 vs. 101** (all data estimated from graphs with the exception of HRs from multivariable analysis) **OS** (all data estimated from figure S4) • 1-year: 75% vs. 82% • 2-year: 56% vs. 60% • 3-year: 26% vs. 37% • 4-year: 38% vs. 32% • 5-year: 24% vs. 32% Log-rank p=0.30 **Local Failure:** (all data estimated from figure S3) • 1-year: 9% vs. 10% • 2-year: 27% vs. 26% • 3-year: 37% vs. 32% • 4-year: 37% vs. 32%		Log-rank p=0.94

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	• 5-year: 37% vs. 39% Log-rank p=0.99 **Combined rate of radiation pneumonitis and local failure:** (all data estimated from figure S3): • 1-year: 19% vs. 19% • 2-year: 36% vs. 35% • 3-year: 38% vs. 36% • 4-year: 38% vs. 36% • 5-year: 38% vs. 36% Log-rank p=0.78 Adj HR (multivariate analysis, IMRT as referent) 1.02 (95% CI 0.53 to 1.98), p=0.94 **Nonrandomized, n=13 vs. 26** **OS** (all data estimated from figure S4) • 1-year: 69% vs. 57% • 2-year: 43% vs. 43% • 3-year: 25% vs. 32.5% • 4-year: NC • 5-year: NC Log rank p=0.97 **Local Failure:** (all data estimated from figure S3) • 1-year: 6% vs. 3% • 2-year: 6% vs. 3% • 3-year: 26% vs. 26% • 4-year: NC • 5-year: NC		

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	Log-rank p=0.93 **Combined rate of radiation pneumonitis and local failure:** (all data estimated from figure S3): • 1-year: 25% vs. 24% • 2-year: 39% vs. 24% • 3-year: 39% vs. 36% • 4-year: NC • 5-year: NC Log-rank p=0.79 Adj HR (multivariate analysis; IMRT as referent): 0.83 (95% CI 0.33 to 2.11), p=0.7		
Cohort studies			
Higgins 2017 Proton (n=348) vs. Photons (n=243,474) (i.e., IMRT, photons, 3D conformal, external beam) Retrospective Comparative Cohort (National Cancer Database) XXXX RoB USA --- Also contains multivariate analyses (two propensity	<u>Proton vs. Photons (all stages)</u> **1 year-OS** 63.3% (95% CI 57.9% to 68.2%) vs. 49.4% (95% CI 49.2% to 49.6%) **5 year-OS** • All non-proton: 23.1% (95%CI 17.4% to 29.3%) vs. 13.5% (95%CI 13.4% to 13.7%), Log-rank **p<0.0001;** Adjusted HR for **survival**, proton vs. photon: 1.21 (95% CI 1.06 to 1.39), p=0.005 Adjusted HR for **risk of death**, photon vs. proton: 1.46, p <0.001	NR	NR

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
matched analyses). Also contains data on stage II and III patients (by modality). Also contains univariate and multivariate HRs (proton vs. each modality and overall).	• Proton vs. 3D-Conformal: 23.1% vs. 14.7%, p<0.01, adj. HR 1.16 (95% CI 1.01 to 1.33), p=0.035 • Proton vs. External-Beam NOS: 23.1% vs. 13.5%, p<0.01, adj. HR 1.26 (95% CI • 1.10 to 1.44), p<0.001 • Proton vs. IMRT: 23.1% vs. 17.2%, p=0.286, adj. HR 1.05 (95% CI 0.91 to 1.20), p=0.524 • Proton vs. Photons: 23.1% vs. 12.6%, p<0.01, adj. HR 1.25 (95% CI 1.09 to 1.43), p=0.001 *No significant difference in 5-year OS for stage IV patients by treatment modality.* **Median OS** 18.6 (95% CI 15.1 to 21.2) vs. 11.7 (95% CI 11.7, 11.8) months. *Propensity-matched analysis, 1:1: proton (n=308) vs. photon (n=308), all stages (a priori analysis)* OS probabilities NR HR 1.16 (95% CI 0.97 to 1.39), p=0.12 *Propensity-matched analysis, 5:1: proton (n=309) vs. photon (n=1541), all stages (not the a priori design)* **1 year-OS**		

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	62.0% (95%CI 56.2% to 67.2%) vs. 54.2% (95%CI 51.6% to 56.7%) **5 year-OS** 22.3% (95%CI 16.3% to 28.9%) vs. 15.7% (95%CI 13.5% to 18.1%), Log-rank p=0.025; adj. HR 1.18 (95% CI 1.02 to 1.37), p=0.026 **Median Survival** 18.4 (95%CI 14.8 to 21.2) months vs. 14 (95% CI 12.8 to 15.6) months. <u>Proton vs. Photons</u> **<u>(stages II and III)</u>** *Proton vs. 3D-Conformal vs. External-Beam NOS vs. IMRT vs. Photons* **1 year-OS** 61.8% (95% CI 54.4% to 68.4%) vs. 57.2% (95% CI 56.6% to 57.9%); vs. 53.8% (95% CI 53.1% to 54.4%); vs. 61.1% (95% CI 60.3% to 61.9%); vs. 53.3% (95% CI 53.0% to 53.7%) **5 year-OS** 22.3% (95% CI 14.6% to 31.0%) vs. 16.9% (95% CI 16.3% to 17.5%); vs. 15.8% (95% CI 15.3% to 16.4%); vs. 18.0% (95% CI 17.2% to 19.0%); vs. 15.0% (95% CI 14.7% to 15.3%) **Adjusted HR (95% CI) for Survival** <u>Proton vs. Photon:</u>		

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	• *Excluding pts. with a missing radiation dose:* HR 1.35 (95% CI 1.10 to 1.64), p<0.01 • *Including pts. with a missing radiation dose:* HR 1.19 (95% CI 0.99 to 1.42), p=0.057 <u>Proton vs.:</u> • *External Beam NOS:* HR 1.23 (95% CI 1.01 to 1.43), p=0.04) • *Photons:* HR 1.23 (95% CI 1.03 to 1.47, p=0.02) • *3D Conformal:* HR 1.12 (95% CI 0.94 to 1.34), p=0.19 • *IMRT:* HR 1.02 (95% CI 0.85 to 1.22, p=0.83). **Median Survival** 17.4 (95% CI 13.4 to 21.5) months. vs. 15.2 (95% CI 14.9 to 15.5) months. vs. 13.6 (95% CI 13.3 to 13.9) months. vs. 17.2 (95% CI 16.7 to 17.6) months. vs. 13.4 (95% CI 13.2 to 13.6) months. On propensity-matched Kaplan Meier analysis (5:1, 880 photon, 176 proton), there were no statistically significant differences between proton and photon therapy (22% vs. 17%, p=0.408).		
Niedzielski 2017 PBT (n=49) vs. IMRT (n=85)	NR	<u>Biomarkers of esophageal toxicity</u> No statistically significant difference between groups in the esophageal expansion imaging biomarkers:	PBT vs. IMRT <u>Patients with esophagitis, % (n/N)</u> -Grade 0: 18.4% (9/49) vs. 28.2% (24/85) -Grade II: 59.2% (29/49) vs. 54.1% (46/85)

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Retrospective Comparative Cohort XXXX RoB USA		• the maximum axial expansion of a single slice (MaxExp1) • the axial length of the esophagus with at least 30% expansion (LenExp30%)	-Grade III: 22.4% (11/49) vs. 17.6% (15/85); OR 1.40 (95% CI 0.69 to 2.87); p=0.37 Chi-squared p-value for the difference in grades between groups = 0.42
Remick 2017 PBT (n=27) vs. IMRT (n=34) Retrospective Comparative Cohort XXXX RoB USA	PBT vs. IMRT **Overall Survival (OS)** • **1-year**: 85.2% (95% CI 72.8% to 99.7%) vs. 82.4% (95% CI 70.5% to 96.2%) • **2-year**: 77.8% (95% CI 63.6% to 95.2%) vs. 73.2% (95% CI 59.6% to 89.9%) p=0.65 for OS between groups (timing NR) **Local Recurrence-Free Survival** • **1-year:** 92.3% (95% CI 82.5% to 100%) vs. 93.3% (95% CI 84.8% to 100%) • **2-year:** 93.1% vs. 85.7% p=0.82 for local recurrence-free survival between groups (timing NR) **Disease Failure:** • Local (isolated) recurrence: 11.1% (3/27) vs. 5.9% (2/34) (outside radiation field in 1 patient each) • Regional (isolated) recurrence: 3.7% (1/27) vs. 2.9% (1/34) • Local + Regional recurrence: 0% (0/27) vs. 2.9% (1/34) • Distant failure: 40.7% (11/27) vs. 50% (17/34)	NR	PBT vs. IMRT ***No grade 4 or 5 treatment-related toxicities were observed.*** Criteria: CTCAE v 4.0 <u>Patients with Grade II acute (not defined) toxicities, % (n/N)</u> **Lung** • Hoarseness: 0% (0/27) vs. 2.9% (1/34) • Cough: 11.1% (3/27) vs. 17.6% (6/34) • Dyspnea: 18.5% (5/27) vs. 14.7% (5/34) • Radiation pneumonitis: 3.7% (1/27) vs. 8.8% (3/34) **Gastrointestinal** • Esophagitis dysphagia and/or odynophagia: 18.5% (5/27) vs. 29.4% (10/34) • Dypepsia: 11.1% (3/27) vs. 23.5% (8/34) • Nausea: 0% (0/27) vs. 8.8% (3/34) • Vomiting: 0% (0/27)vs. 2.9% (1/34) • Diarrhea: 0% (0/27)vs. 5.9% (2/34) • Constipation: 3.7% (1/27) vs. 14.7% (5/34) **Other** • Fatigue: 22.2% (6/27) vs. 26.5% (9/34) • Anorexia: 22.2% (6/27) vs. 17.6% (6/34)

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	Mortality Overall: 33.3% (9/27) vs. 52.9% (18/34) • respiratory failure related: 18.5% (5/27) (4 sepsis or pneumonia, 1 due to lymphangitic carcinoma) vs. 11.8% (4/34) (3 with documented lung progression and/or pleural effusion) • urosepsis: 0% (0/27) vs. 2.9% (1/34) • metastatic breast cancer: 0% (0/27) vs. 2.9% (1/34) • unknown (not well documented): 14.8% (4/27) vs. 35.3% (12/34)		• Dehydration: 0% (0/27) vs. 2.9% (1/34) • Dermatitis: 37% (10/27) vs. 11.8% (4/34) <u>Patients with Grade III acute (not defined) toxicities, % (n/N)</u> **Lung** • Hoarseness: 0% (0/27)vs. 2.9% (1/34) • Cough: 0% (0/27)vs. 0% (0/34) • Dyspnea: 0% (0/27) vs. 0% (0/34) • Radiation pneumonitis: 3.7% (1/27) vs. 2.9% (1/34) **Gastrointestinal** • Esophagitis dysphagia and/or odynophagia: 3.7% (1/27) vs. 11.8% (4/34) • Dypepsia: 0% (0/27) vs. 0% (0/34) • Nausea: 0% (0/27) vs. 2.9% (1/34) • Vomiting: 0% (0/27)vs. 0% (0/34) • Diarrhea: 0% (0/27)vs. 0% (0/34) • Constipation: 0% (0/27) vs. 0% (0/34) **Other** • Fatigue: 0% (0/27)vs. 8.8% (3/34) • Anorexia: 0% (0/27)vs. 2.9% (1/34) • Dehydration: 0% (0/27) vs. 2.9% (1/34) • Dermatitis: 0% (0/27) vs. 0% (0/34)
Tucker 2016 PBT (n=45) vs. 3DCRT (n=193) vs. IMRT (n=230) Retrospective Comparative Cohort	PBT vs. 3DCRT vs. IMRT **2 year-OS** 56% (95% CI 40% to 69%) vs. 39% (95% CI 32% to 46%) vs. 52% (95% CI 45% to 58%); **p=0.015**	NR	NR

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
XXXX RoB USA			
Wang 2016 PBT (n=26) vs. 3DCRT (n=22) vs. IMRT (n=34) Prospective Comparative Cohort XXXX RoB USA --- Symptom burden represents mixed modeling of weekly change	NR	PBT vs. 3DCRT vs. IMRT <u>MDASI Symptom Burden During Treatment (Weeks 1-7), estimate (SE):</u> Pain: 0.20 (0.08), p=0.024 vs. 0.43 (0.09), p<0.001 vs. 0.44 (0.08), p<0.001 Sore Throat: 0.10 (0.06), p=0.097 vs. 0.65 (0.10), p<0.001 vs. 0.50 (0.08), p<0.001 Fatigue: 0.16 (0.10), p=0.132 vs. 0.22 (0.08) p=0.019 vs. 0.41 (0.07), p<0.001 Drowsiness: 0.22 (0.10) p=0.050 vs. 0.30 (0.11) p=0.016 vs. 0.32 (0.06) p<0.001 Lack of Appetite: 0.16 (0.11), p=0.151 vs. 0.48 (0.12), p<0.001 vs. 0.36 (0.08), p<0.001 Disturbed Sleep: 0.02 (0.11), p=0.826 vs. 0.15 (0.12), p=0.249 vs. 0.06 (0.08), p=0.409 <u>MDASI Symptom Burden Post Treatment (Weeks 7-12)</u> Pain: -0.10 (0.10), p=0.341 vs. -0.14 (0.14), p=0.308 vs. -0.40 (0.13), p=0.005 Sore Throat: 0.06 (0.07), p=0.409 vs. -0.54 (0.15), p=0.001= vs. -0.37 (0.12), p=0.004 Fatigue: 0.19 (0.12), p=0.117 vs. -0.14 (0.08), p=0.093 vs. -0.44 (0.11), p<0.001 Drowsiness: -0.06 (0.11), p=0.599 vs. -0.11 (0.11), p=0.352; -0.31 (0.10), p=0.003	NR

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		Lack of Appetite: -0.13 (0.13) p=0.317 vs. -0.48 (0.14), p=0.002 vs. -0.28 (0.13), p=0.037 Disturbed Sleep: -0.03 (0.12), p=0.796 vs. -0.30 (0.13), p=0.030 vs. -0.04 (0.12), p=0.728	

3DCRT = Three-dimensional Conformal Radiotherapy; CI = Confidence Interval; COI = Conflict of Interest; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; F/U = Follow-up; Gy = Gray; HR = Hazard Ratio; IMRT = Intensity modulated radiation therapy; ITT = Intention to treat; KPS = Karnofsky performance score; LRFS = locoregional failure free survival; MDASI = MD Anderson Symptom Index; NC = Not Calculable; NOS = Not otherwise specified; NR = Not reported; NSCLC = non-small cell lung cancer; OS = Overall Survival; PBT = Proton Beam Therapy; RBE = Relative iological Effectiveness; RoB = Risk of Bias; RT = Radiation therapy; SE = Standard Error

APPENDIX J. Lymphomas

Appendix Table J1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in lymphomas

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Hoppe 2017 *RoB*: High Prospective Case Series USA Funding: None COI: None --- Provides subpopulation analysis by risk group	**Diagnosis**: Hodgkin's Lymphoma **Indication**: Curative Intent	N=138 Median Age: 20 years (range, 6-57) [42% (59/138) <19 years] Male: 53% **Primary Tumor Sites**: NR **Tumor Characteristics:** Bulky Disease: 57.4% (78/138) **Risk Classification**: Favorable (I/II A, non-bulky), 29.7% (41/138); Unfavorable (I/II with B or bulky), 28.2% (39/138); High (I/II B bulky, III, or IV), 42% (58/138)	**PBT**: Passive-scatter, 46.4% (64/138); Uniform-scanning, 41.3% (57/138); PBS, 12.3% (17/138) **Median PBT Dose (range)**: Pediatric patients: 21 Gy (RBE) (15–36 Gy) Adult patients: 30.6 Gy (RBE) (20–45 Gy) **Additional Treatments in conjunction with PBT:** Chemotherapy, 100%	**Median F/U (range):** 32 (5 to 92) months	**Primary Outcomes** **3-year Relapse Free Survival, % (95% CI)** • *Adults*: 96% (NR) • *Pediatric*: 87% (NR) **Proportion of patients experiencing recurrence, % (n/N)** • *All patients:* 7.2% (10/138) • *Adults*: 5% (4/79) • *Pediatric*: 10.2% (6/59) **Secondary Outcomes** NR	*Toxicity Grading Criteria:* NR **Toxicity, % (n/N)** • Anorexia -*Grade 1*: 11.6% (16/138) -*Grade 2*: 2.9% (4/138) • Anxiety/depression/agitation -*Grade 1: 13.8% (19/138)* -*Grade 2: 0.7% (1/138)* • Constipation -*Grade 1: 8.9% (12/138)* • Cough -*Grade 1*: 38.4% (53/138) -*Grade 2*: 1.4% (2/138) • Diarrhea -*Grade 1*: 2.2% (3/138) • Dry Mouth -*Grade 1*: 19.6% (27/138) -*Grade 2*: 0.7% (1/138) • Dyspepsia -*Grade 1*: 79.7% (11/138) -*Grade 2*: 1.4% (2/138) • Dyspnea -*Grade 1*: 21.7% (30/138) • Esophagitis -*Grade 1*: 34.8% (48/138) -*Grade 2*: 18.2% (25/138) • Fatigue -*Grade 1*: 49.3% (68/138)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						-*Grade 2*: 5.1% (7/138) • Hoarseness -*Grade 1*: 11.6% (16/138) • Hypothyroidism -*Grade 2*: 2.2% (3/138) • Mucositis -*Grade 1*: 1.4% (2/138) • Nausea -*Grade 1*: 21% (29/138) -*Grade 2*: 2.9% (4/138) • Pain -*Grade 1*: 15.9% (22/138) -*Grade 2*: 0.7% (1/138) • Performance Status -*Grade 1*: 5.1% (7/138) -*Grade 2*: 0.7% (1/138) • Pulmonary (fibrosis/pneumonitis/effusion) -*Grade 1*: 4.3% (6/138) • Vomiting -*Grade 1*: 5.8% (8/138) -*Grade 2*: 1.4% (2/138) • Radiation Dermatitis -*Grade 1*: 68.8% (95/138) -*Grade 2*: 5.8% (8/138)
Hoppe 2016 RoB: High Prospective Case Series USA	**Diagnosis:** Hodgkin's Lymphoma **Indication**: Curative Intent	N=40 Age <12 years: 8% 12–18 year: 28% 19–29 years: 45% 30–40 years: 10% >40 years: 10% Male: 53%	**PBT Modality:** passive scatter or uniform scanning techniques; no patients were treated with pencil beam scanning	**Median F/U (range): 21 (4 to 47) months**	**2-year Relapse Free Survival (95% CI):** 85% (NR) **Proportion of patients experiencing relapse**: 7.5% (3/40)	*No grade 3 acute toxicities occurred among the patients.* *Grade 1 to 2 Toxicities, % (n/N)* *Anorexia: 7.5% (3/40)* *Constipation: 2.5% (1/40)*

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Funding: NR COI: NR		Tumor Stage I: 10% II: 58% II: 20% IV: 13% Tumor Location Mediastinum: 93% Non-mediastinum: 8% B Symptoms (yes): 48% Bulky disease (yes): 65% Risk Level Favorable: 23% Unfavorable: 45% High: 33%	**Median PBT Dose: 30 Gy** 21 to 25.5 Gy: 40% 25.6 to 31 Gy: 43% 31.1 to 36 Gy: 18% **Additional Treatments** Chemotherapy: 85% (11 pediatric patients and 23 adult patients)			*Cough: 30% (12/40)* *Dermatitis: 87.5% (35/40)* *Diarrhea: 2.5% (1/40)* *Dry mouth: 2.5% (1/40)* *Dyspepsia: 2.5% (1/40)* *Dysphagia: 2.5% (1/40)* *Dyspnea: 0% (0/40)* *Esophagitis: 42.5% (17/40)* *Fatigue: 35% (14/40)* *Hoarseness: 25% (10/40)* *Nausea: 10% (4/40)* *Pain: 12.5% (5/40)* *Peripheral neuropathy: 12.5% (5/40)* *Pharyngitis: 7.5% (3/40)* *Vomiting: 0% (0/40)*
Nanda 2017 RoB: High Prospective Case Series USA Funding: NR COI: None	**Diagnosis: Hodgkin's Lymphoma (84.7%) or Non-Hodgkin's Lymphoma (15.3%) involving the Thorax** **Indication: Refractory/Relapsed Disease: 18.6%** **Curative Intent: 81.4%**	N=59 Median Age (range): 30.6 (15 to 45) years History of smoking: 6.8% Mediastinal Involvement: 93.2% Bulky Disease: 66.1%	**PBT Modality**: NR **Median Dose (range)** Adults (>18 years): 30.6 Gy (RBE) Children (≥18 years): 25.5 Gy (RBE) **Additional Treatments** Chemotherapy ABVD: 49.2% ABVE-PC 24: 40.7%	**Median F/U (range):** 24.1 (6 to 82) months	**NR**	**<u>Acute Toxicity, % (n/N)</u>** Pulmonary Toxicities Grade 1: 35.6% (21/59) Grade 2: 5.1% (3/59) Grade 3: 0% (0/59) **<u>Late Toxicity, % (n/N)</u>** Pulmonary Toxicities Grade 1: 45.8% (27/59) Grade 2: 0% (0/59) Grade 3: 0% (0/59)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
			R-CHOP: 6.8% Other: 3.4% Second or third line: 18.6% Stem cell transplant: 11.9%			

CI = Conflict of interest; COI = Conflict of interest; Gy = Gray; NR = not reported; PBT = Proton beam therapy; RBE = relative biological effectiveness

APPENDIX K. Mixed Populations

Appendix Table K1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in mixed populations

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Moskvin 2014 Retrospective Case Series *High RoB* USA Funding: NR COI: None declared --- Population is broadly mixed pediatric and adult. Also provides grade of skin reaction stratified by age (pediatric and adults); also includes mean irradiated skin area data	**Diagnosis**: Various Brain and Spine Malignancies **Indication:** Curative Intent	N=389 eligible, 90 analyzed Male: 67.8% Median Age (range): 11.2 (1.6 to 76.7) years **Diagnosis** • Astroblastoma: 4.4% (4/90) • Astrocytoma: 1.1% (1/90) • Atypical teratoid rhabdoid tumor 5.5% (5/90) • Chondrosarcoma: 10% (9/90) • Chordoma: 14.4% (13/90) • Ependymoma 31.1% (28/90) • Ewing's sarcoma: 2.2% (2/90) • Grade I ant cell tumor: 1.1% (1/90) • Medulloblastoma: 23.3% (21/90)	PBT **Grade I Median PBT Skin Dose: 4655 cGy** **Grade II Median PBT Skin Dose: 5220 cGy** **Grade III Median PBT Skin Dose: 5500 cGy**	**Median F/U:** NR	NR	*Toxicity Grading Criteria:* CTCAE ver. 3.0 *Acute Toxicities:* timeframe NR ***Harms [all patients]*** **Acute Toxicities, % (n/N)** • Skin Toxicities -Grade 1: 56.6% (51/90) -Grade 2: 17.7% (16/90) -Grade 3: 8.8% (8/90) -Grade 4: 2.2% (2/90) ***Harms [pediatric <5, n=20]*** **Acute Toxicities, % (n/N)** • Skin Toxicities -Grade 1: 85% (17/20) -Grade 2: 15% (3/20) -Grade 3: 0% (0/20) ***Harms [pediatric age 5 to 12, n=19]*** **Acute Toxicities, % (n/N)** • Skin Toxicities -Grade 1: 73.68% (14/19) -Grade 2: 10.53% (2/19) -Grade 3: 15.79% (3/19) ***Harms [pediatric age 12 to 21, n=15]*** **Acute Toxicities, % (n/N)** • Skin Toxicities -Grade 1: 66.67% (10/15) -Grade 2: 20% (3/15) -Grade 3: 13.3% (2/15)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
		• Neuroblastoma : 1.1% (1/90) • Non-small cell lung metastatic: 1.1% (1/90) • Osteosarcoma: 1.1% (1/90) • Primitive neuroectodermal tumor: 2.2% (2/90) • Sarcoma: 1.1% (1/90)				***Harms [adult age >21, n=23]*** **Acute Toxicities, % (n/N)** • Skin Toxicities -Grade 1: 43.48% (10/23) -Grade 2: 34.78% (8/23) -Grade 3: 21.74% (5/23)
Nishioka 2014 Prospective Case Series *High RoB* Japan Funding: supported by the Clinical Trials Core Hospitals project of the Japanese Ministry of Health, Labour and Welfare and the Japan Society for the Promotion of	**Diagnosis**: Mixed, Various **Indication:** Curative Intent	N=97 eligible, 56 analyzed Male: 73.2% Median Age (range): 66 (1 to 87) years **Chemotherapy:** • concurrent: 1.8% • adjuvant: 17.9% **Lesion Locations:** • prostate: 30.4% (17/56) • bone/soft tissue: 17.9% (10/56) • liver: 12.5% (7/56)	Spot-scanning PBT **Median PBT Dose: 65 (20 to 76) GyE**	**Median F/U (range):** 12 mos (NR) **% F/U:** 87.5%	**Mortality, % (n/N)** • all-cause (within 12 mos): 7.1% (4/56) • due to disease progression: 3.6% (2/56)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities:* ≤3 mos *Late Toxicities:* >3 mos **Incidence of acute PBT-related Grade 4 adverse events (95% CI):** 0% (0% to 6.38%) **Acute Toxicities, % (n/N)** • Grade 1 to 2: -radiation dermatitis: 55.4% (31/56) -elevated alanine aminotransferase : 23.2% (13/56) -thrombocytopenia: 17.9% (10/56) • Grade 3 or 4 (PBT-related): -hematological: 0% (0/56) • Grade ≥3 (unlikely to be PBT-related toxicities) -anemia: 1.8% (1/56) -hypokalemia: 1.8% (1/56)

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
Science (JSPS) KAKENHI Grant Number 15H04899. COI: None declared ---		• lung: 10.7% (6/56) • CNS: 8.9% (5/56) • colon: 3.6% (2/56) • pancreas: 3.6% (2/56) • kidney: 3.6% (2/56) • others: 8.9% (5/56)				-thrombocytopenia: 1.8% (1/56) -esophageal varix hemorrhage: 1.8% (1/56) -elevated alanine aminotransferase: 1.8% (1/56) **Late PBT-related non-hematological toxicities, % (n/N)** • Grade ≥3: -osteoradionecrosis (fracture of left femoral neck): 1.8% (1/56)
Zhang 2018 Retrospective Case Series *High RoB* China Funding: supported by Pudong Science and Technology Development Fund, PKJ2016-Y44. COI: None declared. --- Also includes univariable and multivariable models for predictive	**Diagnosis:** Various/Mixed **Indication:** Curative Intent	N=375 Male: 72% Mean Age (SD): 54.3(16.1) years **Diagnoses:** • head & neck: 45% • lung or thymic: 20% • liver, gallbladder, pancreatic or rectal: 13% • ovarian, endometrial, prostate: 21% • other: 1% **Tumor** • head and neck: 45.1%	Particle therapy alone (n=328) or particle+photon (n=47). Total Radiation Dose: • ≥70 Gy: 21.9% • <70 Gy: 78.1% Median Total Radiation Dose by Site (range): • Head & Neck: 62.1 (50.0 to 72.5) • Lung: 64.5 (45.0 to 90.0) • Pancreas: 63.3 (37.8 to 69.0) • Liver: 58.7 (50.0 to 65.0)	**Median F/U (range):** NR		**Weight Loss** • Average Weight Loss: 0.55 kg (0.08%) • Mean Body weight decrease (SD): -2.2 (2.3) kg • Average weight loss among patients with critical weight loss: 8.7% (3.0%) of body weight • Average weight loss among patients without critical weight loss: 0.2 (2.6%) of body weight

Author (year), Study Site	Condition	Population	Total PBT Dose	F/U	Survival Outcomes	Safety
influences on weight loss.		• others: 54.9% **Stage** • I to II: 34% • III to IV: 66% **Indication:** • Concurrent Chemotherapy: 13.9% • Post-Surgery: 45.3% • Post-RT: 17.9% • Post-Chemotherapy: 44.3% **Pre-Therapy BMI** • <18.5: 8.8% • 18.5 to 23.9: 50.7% • ≥ 24: 40.5%	• Prostate: 63.6 (45.0 to 75.0) • Ovarian: 63.0 (58.0 to 69.0) • Colorectum: 59.8 (48.0 to 74.0)			

BMI = Body Mass Index; CI = confidence interval; cGy = centigray (unit) COI = conflict of interest; CTCAE = Common Terminology Criteria for Adverse Events; F/U = follow-up; GyE = Gray Equivalent; Kg = kilogram; NR = not reported; PBT = proton beam therapy; RoB = risk of bias; SD = standard deviation;

APPENDIX L. Non-Cancerous Tumors

Appendix Table L1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in non-cancerous tumors

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Zeisberg 2014 Retrospective Case Series High RoB USA Funding: NR COI: None declared --- Includes some data visual acuity of patients treated with prior RT. Also includes data on tumor thickness/size, and dose size and their relationship with visual outcome.	**Diagnosis:** Choroidal Hemangiomas **Intent**: Curative Intent (82% first-line treatment)	N=50 Male: 64% Mean Age (range): 49.1 (21 to 80) years Patients Symptomatic at Diagnosis: 92% Exudative retinal detachment: 44% • involving fovea: 14% Macular Edema: 78% Retinal Ischemia: 0% Rubeosis: 0% Indication • first line treatment: 82% • at least one prior therapy: 18% Tumor Location • adjacent to foveal region: 36% • adjacent to optic disc: 30% • adjacent to foveal and optic disc: 18%	**PBT** **Mean Total PBT Dose: 20 CGE**	**Mean F/U (range): 55.4 (13 to 132) mos**	**Measures of Tumor Regression** **Tumor Thickness Decrease** • Baseline: 3.5 mm • Last F/U: 1.8 mm • p-value: <0.001 **Visual Acuity** **Patients with two line improvement in visual acuity, % (n/N)** • 2 years: 36.8% (NR) • 3 years: 44.4% (NR) • 4 years: 58.8% (NR) **Minimal Visual Improvement** • baseline: 6/15 • last F/U: 6/12	*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 or median not specified] *-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

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		• neither adjacent to fovea or optic disc: 16%				• 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 Retrospective Case Series *RoB*: High France Funding: NR COI: NR ---	**Diagnosis**: Circumscribed choroidal hemangioma **Indication**: • Curative Intent, 77% (33/43) • Recurrent Treatment, 23% (10/43)	N=43 Median Age (range): 52 years (NR) Male: 74.4% **Primary Tumor Sites**: Retroequatorial: 95.3% (41/43) Macular or perimacular: 60.4% (26/43) Equatorial: 4.7% (2/43) **Tumor Characteristics:**	**PBT**: NR **Total PBT Dose**: 20 Gy (RBE) **Additional Treatments prior to PBT** PDT only: 16.3% (7/43) PDT + Anti-VEGF: 4.7% (2/43) PDT + argon laser Photocoagulation: 2.3% (1/43)	**Median F/U (range):** 25.7 (7 to 62) months	**<u>Primary Outcomes</u>** **Median Visual Acuity** Pretreatment vs. posttreatment: 20/63 vs. 20/25 *Visual acuity had stabilized or improved by more than 2 lines in 37 patients (86%).* **Proportion of patients with hemangioma scar on ultrasound that was less than 1.5-mm thick and was considered to**	*No patient presented radiation maculopathy or papillopathy.* **Complete attachment of the exudative retinal detachment**: 97.6% (42/43)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		Median tumor diameter: 10.10 mm (range, 6 to 22.80)			**be flat, with an atrophic scar on angiography**: 53.5% (23/43) **<u>Secondary Outcomes</u>** NR	
El Shafie 2018 Retrospective Case Series *High RoB* USA Funding: NR COI: NR	**Diagnosis**: Benign skull base meningiomas **Indication**: Mixed Curative: • adjuvant/additive: 15.5% • curative intent: 38.2% • salvage: 46.4%	N=110 Male: 20% Median Age (range): 52 (45 to 59) years **Histology** • WHO Grade I (benign): 54.5% • WHO Grade II (benign): 6.4% WHO Grade III: 0.9% • unknown (not surgically investigated): 38.2% **Tumor Locations:** • sphenoid wing: 38.2% • petroclival region: 20.9% • cavernous sinus 3.6% • sella: 9% • olfactory nerve: 3.6% **Treatment Setting:**	Raster-scanning PBT (n=104) or photon+carbon ion boost (n=6) Median PBT Dose (Range): 54 (50 to 60 Gy) Gy (RBE)	**Median F/U (95% CI):** 46.8 mos (95% CI 39.9 to 53.7)	**OS (95% CI)** • 5-year (from start of therapy): 96.2% (NR) • 6-year (from start of therapy): 92% (NR) • 10-year (from diagnosis): 98.1% (NR) • 15-year (from diagnosis): 90.7% (NR) • Median OS: 57.97 (95% CI 50.6 to 62.5) mos **PFS (95% CI)** • 3-year: 100% (NR) • 5-year: 96.6% (NR) • Median PFS: 46.8 (39.9 to 53.7) mos **Median Time to Progression (range):** 55.6 (40 to 67.3) mos **Recurrence/Progression,% (n/N):** • Overall: 3.6% (4/110) • local: 3.6% (4/110)	**Harms** *Toxicity Grading Criteria:* CTCAE ver. 4.0 *Acute Toxicities*: ≤6 mos *Late Toxicities:* >6 mos **Acute toxicities, % (n/N)** • <u>Grade 1 to 2:</u> -focal alopecia: 63.6% (70/110) -moderate fatigue: 47.3% (52/110) -focal skin irritation: 40% (44/110) -headaches: 22.7% (25/110) -nausea: 20.9% (23/110) -facial pain: 10.9% (12/110) -dysgeusia: 7.3% (8/110) -lymphedema: 6.4% (7/110) -xerostoma: 4.5% (5/110) -mucositis: <1% (1/110) • <u>Grade ≥3:</u>

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		• adjuvant/additive: 15.5% • definite: 38.2% • due to tumor progression: 46.4%			**Mortality** • all-cause: 5.5% (6/110) • due to disease progression 0% (0/110) • secondary malignancies (not reported to be RT-related): 1.8% (2/110) • non-cancer comorbidities: 2.7% (3/110) • other (unknown/not specified: <1% (1/110)	-focal alopecia: 0% (0/110) -fatigue: 0% (0/110)) -skin irritation: 0% (0/110) -headaches: 0% (0/110) -prolonged nausea due to intracranial pressure: <1% (1/110) -facial pain: 0% (0/110) -dygeusia: 0% (0/110) -lymphedema: 0% (0/110) -xerostemia: 0% (0/110) -severe ulcerating mucositis (grade III) <1% (1/110) -radionecrosis: 0% (0/110) **Late toxicities, % (n/N)** • <u>Grade 1 to 2:</u> -focal alopecia: <1% (1/110) -fatigue: 9.1% (10/110) -skin irritation: 0% (0/110) -headaches: 9.1% (10/110) -nausea: 0% (0/110) -facial pain: 1.8% (2/110) -dygeusia: 2.7% (3/110)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						-lymphedema: 2.7% (3/110) -xerostemia: 3.6% (4/110) -mucositis: 0.9% (1/110) -radionecrosis: 0% (0/110) • Grade ≥3: -focal alopecia: 0% (0/110) -fatigue: <1% (1/110) -skin irritation: -headaches: 0% (0/110) -nausea: -facial pain: 0% (0/110) -dygeusia: 0% (0/110) -lymphedema: 0% (0/110) -xerostemia: 0% (0/110) -mucositis: 0% (0/110) -radiogenic hypopituitarism: <1% (1/110) -radionecrosis: 2.7% (3/110)
Vlachogiannis 2017 Retrospective Case Series *High RoB* Sweden	**Diagnosis:** Brain (Benign Meningiomas) **Indication:** Curative Intent	**N=170** **Male: 20.6%** **Mean Age (range): 54.2 (22 to 85) years** **Surgery:**	Hypofractionated passive scattering PBT Mean PBT Dose (range): 21.9 (14 to 46) Gy	**Median F/U (range):** 84 mos Loss to follow-up:	**PFS (95% CI)** • 5-year: 93% (NR) • 10-year: 85% (NR) **Progression/Recurrence, % (n/N)** • overall: 11.8% (20/170)	**Harms** *Toxicity Grading Criteria:* NR **Radiation-Related complications**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Funding: No funding was received for this research. COI: None declared		• underwent surgery: 74% • refused surgery or had unacceptably high perioperative risk: 26% **Tumor Location:** • Skull base: 91% • convexity: 6% • centrally: 3% **Radiation Therapy Timing:** • post subtotal resection: 49.4% • at tumor relapse: 24.7% • primary: 25.9%		0.6% (1/170)	• within 5 years: 65% (13/20) **Mortality, % (n/N)** • all-cause: 13.5% (23/170) • disease-specific mortality (meningioma): 1.7% (3/170) • unidentified cause: 3.5% (6/170)	**(timeframe NR), % (n/N):** -overall: 9.4% (16/170) -pituitary insufficiency: 7.4% (6/81)* -radiation necrosis: 2.9% (5/170) -clinically significant radiation necrosis: 20% (1/5) -visual impairment: 4.4% (5/112)† -visual impairment leading to blindness: 20% (1/5) -expansive tumor cyst (unknown nature): 0.6% (1/170)
Wattson 2014 *RoB*: High Retrospective Case Series USA Funding: NR COI: B.M.K.B. has served as the principal investigator of research grants to	**Diagnosis**: Pituitary Adenoma **Indication**: Treatment for salvage therapy or residual/recurrent tumor	**N=165** **Median Age (range): 43 years (12 to 84))** **Male: 34%** **Primary Tumor Sites: Pituitary** **Risk Classification**: NR **Tumor Characteristics:** • *Cushing* Disease: 48% • *Nelson* Syndrome: 6%	**PBT**: 3D conformal passive scattered proton therapy using 2 to 5 beams • *Proton* stereotactic radiosurgery: 92% • *Fractionated* stereotactic proton therapy: 8% **PBT Dose**: 20 Gy (RBE)	**Median F/U (range)**: 51.6 (6 to 247.2 months	**<u>Primary Outcomes</u>** NR **<u>Secondary Outcomes</u>** **Biochemical Complete Response Rate, % (95% CI)** • *3-year*: 42% (34% to *51%*) • *5-year*: 59% (50% to 69%) **Local Control, % (n/N):** 98% (137/140)	*Toxicity Grading Criteria:* NR **Toxicity/Adverse Events, % (n/N)** • *Temporal lobe seizures*: 2.4% (4/165) • *Cranial nerve palsy*: 1.2% (2/165) • *Necrosis of the ethmoid sinus*: 0.6% (1/165) **Actuarial Rate of New Pituitary Hormone**

the Massachusetts General Hospital from Novartis and as a consultant for HRA Pharma, Novartis, and Pfizer. H.A.S. is an editor for this journal and is a writer for UpToDate. The authors report no other conflict of interest. --- Provides subpopulation analysis by type of pituitary adenoma		• *Growth* Hormone – secreting adenoma: 37% • *Prolactin*-secreting adenoma: 7% • Thyroid stimulating: 2% **Prior irradiation: yes: 8%**	**Additional Treatments in conjunction with PBT:** • *Prior* resection, 98.2% (162/165); • *Prior* photon irradiation, 8.5% (14/165)			**Deficiencies (n=127), % (95%, CI)** • *3-year*: 45% (NR) • *5-year*: 62% (NR) **Secondary Malignancy**: 0%

3D = three-dimensional; CGE = Cobalt Gray Equivalent; CI = confidence interval; COI = conflict of interest; F/U = follow-up; mm = millimeter; mos = months; NR = not reported; PBT = proton beam therapy; PDT = photodynamic therapy; RBE = relative biological effectiveness; RoB = risk of bias; RT = radiation therapy; VEGF = vascular endothelial growth factor

APPENDIX M. Ocular

Appendix Table M1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in ocular cancers

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Kamran 2014 *RoB*: High Retrospective Case Series USA Funding: NR COI: H.A.S. is an editor of this journal. The authors report no other conflict of interest. ---	**Diagnosis**: Uveal Metastasis from any primary tumor **Indication**: Curative Intent	N=77 patients, 99 eyes Median Age at diagnosis of primary tumor (range): 52 years (NR) Median Age at diagnosis of uveal metastasis (range): 58 years (NR) Male: 32% **Primary Tumors** Breast: 49% (38/77) Lung: 17% (17/77) Renal cell: 5% (4/90) Thyroid: 3% (3/77) Colon: 2% (2/77) Esophageal: 2% (2/77) Other: 14% (11/77) **Eyes involved:** Unilateral: 71% (55/77) Bilateral: 29% (22/77) **Retinal detachment at presentation**: 42% (32/99 eyes)	**PBT**: NR **Median PBT Dose**: 20 Gy (RBE) **Treatment received for primary disease** Chemotherapy alone: 8% (6/77) Radiation alone: 5% (4/77) Surgery alone: 12% (9/77) Chemotherapy + surgery: 17% (13/77) Chemotherapy + radiation: 12% (9/77) Radiation + surgery: 5% (4/77) All 3 modalities: 32% (25/77) Unknown or no treatment: 9% (7/77) **Prior whole brain irradiation**: 10% (8/77)	**Median F/U (range):** 77 (NR) months	**Primary Outcomes** **Proportion experiencing local failure, % (n/N)**: 6% (6/99) eyes; 6.7% (5/77) patients **Proportion developing new uveal metastases, % (n/N)**: 2% (2/99) eyes; 2.6% (2/77) patients **Actuarial cumulative incidence of local failure (95% CI)**: • *12-months:* 8% (3% to 22%) **Visual acuity after treatment – per eye, % (n/N)** Improved or stable: 38% (38/99) Decreased 30% (30/99) Unknown 31% (31/99) **Cumulative incidence of either vasculopathy or decreased visual acuity- per eye (95% CI)** • *6-weeks*: 27% (18% to 39%)	**Toxicity, % (n/N)** *Any grade:* 31% (24/77) [All adverse effects were scored minor and included dry eye, pain, flashes, floaters, tearing, and blurry vision] **Retinal detachment resolution (n=13 eyes), % (n/N)**: 46% (6/13) **Radiation Vasculopathy – per eye, % (n/N)**: 7% (7/99) **Enucleation, % (n/N)** 1.3% (1/77)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					• *6-months*: 46% (34% to 60%) • *10-months*: 59% (45% to 74%) • *1*-year: 73% (56% to 87%) **Secondary Outcomes** NR	
Konstantinidis 2014 Retrospective Case Series *RoB*: High UK Funding: None COI: None ---	**Diagnosis**: Choroidal Melanoma **Indication**: Curative Intent	N=63 Median Age (range): 60 years (19 to 83) Male: 62%	**PBT**: NR **Median PBT Dose (range)**: NR **Additional Treatments in conjunction with PBT:** NR	**Median F/U (range):** 30 (24 to 204) months	**Primary Outcomes** **Mortality, % (n/N)** • All-cause: 23.8% (15/63) • Disease-related: 10% (6/63) **10-year actuarial all-cause mortality ± SE**: 20% ± 0.05% **10-year actuarial metastatic mortality ± SE:** 12% ± 0.04% **Proportion of patients experiencing local recurrence**: 3.2% (2/63) **10-year Actuarial rate of eye retention**: 95% (SE, 0.02) **Visual acuity, % (n/N)**	**Complications, % (n/N)** • *Neovascular glaucoma*: 1.6% (1/63) • *Radiation-related maculopathy and/or neuropathy:* 23.8%, (15/63) • *Cataract*: 17.5% (11/63) • *Exudative retinal detachment*: 9.5% (6/63) **Proportion of patients requiring enucleation, % (n/N)**: 6.3% (4/63) **Other safety outcomes** 46.7% (7/15) of patients with irradiation the eyelid rim developed some degree of madarosis

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					• 6/12 or better: 50.8% (32/63) • 6/36 or better: 58.7% (37/63) **<u>Secondary Outcomes</u>** NR	53.3% (8/15) of the 15 patients whose treatment involved the eyelid rim reported subjective symptoms *Grittiness*: 46.7% (7/15) *Itching*: 20% (3/15) *Epiphora*: 13.3% (2/15) *Foreign body sensation*: 13.3% (2/15) *Pain*: 40% (6/15) 12.5% (6/48) of patients treated without eyelid rim involvement reported subjective symptoms *Grittiness*: 6.3% (3/48) *Mild foreign body sensation*: 4.2% (2/48) *Tenderness*: 4.2% (2/48) *Mild epiphora*: 4.2% (2/48) *Redness*: 6.3% (3/48)
Lane 2015 Retrospective Case Series	**Diagnosis**: Uveal melanoma- Choroidal and ciliary body tumors	N=3088 Median Age (range): 61.3 years (10.3 to 94.2)	**PBT**: NR **Median PBT Dose (range)**: NR	**Median F/U (range):** 147.6 (12 to	**<u>Primary Outcomes</u>** **Mortality, % (n/N)** • All-cause: 48.3% (1490/3088)	NR

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
RoB: High USA Funding: The MEEI Melanoma Research Fund provided financial support only COI: Dr. Gragoudas reports having been an advisor to Aura Biosciences and MPM Capital; having received royalties from QLT Phototherapeutics Inc; and having been a consultant for Ocata Therapeutics (formerly known as Advanced Cell Technology Inc). All other authors report none ---	**Indication**: Curative Intent	Male: 49.9% **Tumor Size**: Small: 31.2% (964/3088) Medium: 41.7% (1287/3088) Large: 27% (835/3088) **Ciliary body involvement**: 26.7% (823/3088)	**Additional Treatments in conjunction with PBT:** NR	402) months	• Disease-related: 20.1% (620/3088) **Cumulative all-cause mortality rate (95% CI)** • *15-year:* 49.0% (47% to 51.1%). • *20-year:* 58.6% (56.4% to 60.8%) • *25 year:* 66.8% (64.2% to 69.4%) **Cumulative – unadjusted melanoma-related mortality rates** • *15-year:* 24.6% (22.8% to 26.4%) • *25 year:* 66.8% 24.5% to 28.5%) **Proportion of patients developing metastasis**: 53.1% (639/3088) **<u>Secondary Outcomes</u>** NR	
Papakostas 2017 Retrospective Case Series	**Diagnosis**: Large uveal melanomas **Indication**: Curative Intent	N=336 Median Age (range): 61 years (24 to 90) Male: 55.4%	**PBT**: NR **Total PBT Dose**: 70 Gy (RBE)	**Median F/U (range):** 84 (2.8 to	**<u>Primary Outcomes</u>** **Visual acuity 20/200 or better (95% CI)**	**Proportion of Patients Developing Neovascular Glaucoma**: 25.3% (85/336)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
USA Funding: Dr Papakostas is supported by the Ronald G. Michels Fellowship Foundation COI: Dr Gragoudas reported receiving grant support from the Grimshaw Gudewitz Foundation and serving as a paid consultant for Astellas Pharma, Aura Pharmaceuticals, Iconic Therapeutics, and QLT. Dr Kim reported receiving grant support from Genentech and serving as a paid advisory board member for Castle Biosciences and Iconic Therapeutics. No other disclosures were reported. ---		**Tumor Characteristics** • Median Tumor Height: 8.7 mm (range, 2 to 17.1) • Retinal Detachment: 76.2% (256/336) **Baseline Visual Acuity** • 20/40 or better: 39% (131/336) • 20/50 to 20/100: 22.0% (74/336) • 20/125 to 20/800: 23.5% (79/336)	**Additional Treatments:** NR	286.8) months	• *1-year:* 48.6% (41.8 to 55.0) • *3-years:* 22.6% (16.9 to 28.9) • *5-years:* 15.9% (10.6 to 22.1) • *10-years:* 8.7% (4.1 to 15.6) **Eye Retention (95% CI)** • *1-year:* 95.1% (92.1% to 97.0%) • *3-years:* 85.8% (80.9% to 89.5%) • *5-years:* 77.4% (71.1% to 82.5%) • *10-years:* 70.4% (61.5% to 77.6%) **Rates of Local Recurrence (95% CI)** • *1-year:* 2.3% (1.1% to 4.8%) • *3-years:* 5.0% (2.9% to 8.5%) • *5-years:* 7.8% (4.8%-12.6%) • *10-years:* 12.5% (6.5%-23.2%) **Melanoma-related Mortality Rates (95% CI)**	**Kaplan-Meier Estimates of Neovascular Glaucoma** • *1-year:* 6.5% (4.2 to 9.9) • *3-years:* 28.4% (23.2 to 34.5) • *5-years:* 34.9% (28.9 to 41.7) • *10-years:* 36.1% (29.8 to 43.2)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					• *1-year:* 2.4% (1.22% to 4.80%) • *10-years:* 48.5% (43.0% to 54.4%) **<u>Secondary Outcomes</u>** NR	
Patel 2016 Retrospective Case Series USA Funding: NR COI: NR --- Provides subgroup analysis by tumor size, presence of comorbidities, age, etc…	**Diagnosis**: Choroidal melanoma located 1 disc diameter or less from the fovea and more than 1 DD away from the optic nerve **Indication**: Curative Intent	N=351 Mean Age (range): 58 years (14.62 to 91.47) Male: 55.3% **Median Tumor Size**: 12 mm x 4 mm **Tumor Characteristics** • Tumors within 1 disc diameter of the fovea: 97.4% (343/351) • Tumors involving the fovea: 25.6% (90/351) • Tumors >2 DD away from the nerve: 49.6% (174/251) **Comorbidities** • Diabetes: 8.3% (29/351) • Hypertension: 29.4% (72/351)	**PBT**: NR **Total PBT Dose**: 50 Gy (RBE) **Additional Treatments**: None	**Median F/U (range):** 68.7 (0.8 to 264.7) months	**<u>Primary Outcomes</u>** **Proportion of Patients Developing a Secondary Metastasis**: 19.9% (70/351) **Mortality, % (n/N)** • Disease-related: 19.9% (70/351) [all of secondary metastasis] **Visual Acuity, % (n/N)** • 20/40 or better: 18.8% (66/351) • 20/50 to 20/100: 25.6% (90/351) • 20/125 to 20/800: 25.6% (90/351) • Counting Fingers or worse: 39.3% (138/351) **Cumulative Rates of Vision Retention after Irradiation in patients**	**<u>Proportion of patients undergoing enucleation, % (n/N)</u>**: 6% (22/351)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					with baseline vision of 20/200 or better • *1-year:* 77.7% • *3-years*: 53.5% • *5-years*: 35.5% *For those patients with a baseline visual acuity of 20/40 or better, 61.7% and 16.2% of patients retained this level of vision 1 year and 5 years after proton beam irradiation* <u>Secondary Outcomes</u> NR	
Polishchuk 2017 Prospective Case Series *RoB*: High USA Funding: NR COI: None --- Provides Multivariate analysis in the favorable BCVA	**Diagnosis**: Uveal Melanoma **Indication**: Curative Intent	N=645 Median Age (range): 60.3 years (17 to 94) Male: 51% **Tumor Characteristics** Favorable vs. Unfavorable: 66% (425/645) vs. 34% (220/645) Mean Tumor Diameter ± SD: 10.7 mm ± 3.4 mm Mean Distance to fovea ± SD: 4 mm ± 4.3	**PBT**: NR **Total PBT Dose**: 56 Gy (RBE) **Additional Treatments**: NR	**Median F/U (range):** 52.9 (2.6 to 212.8) months	<u>**Primary Outcomes**</u> **Best Corrected Visual Acuity, % (n/N)** • Favorable BCVA group - *24-months* - BCVA ≥ 20/100: 70% - *60-months* - Maintained BCVA ≥ 20/40: 45% - Declined BCVA to between 20/50 and 20/100: 10% - Declined to BCVA of counting fingers or worse: 27% • Unfavorable BCVA group	NR

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Group to identify significant independent predictors of BCVA loss		Involving ciliary body, % (n/N): 10% (66/645) Involving macula, % (n/N): 30% (191/351)			- *24-months* - BCVA ≥ 20/100: 36% - *60-months* - Improved BCVA ≥ 20/40: 12% - BCVA between 20/50 and 20/100: 9% - BCVA between 20/200 and 20/400: 11% - BCVA of counting fingers or worse: 68% **Secondary Outcomes** NR	
Rahmi 2014 Retrospective Case Series *RoB*: High France Funding: NR COI: None ---	**Diagnosis**: Iris Melanomas **Indication**: Curative Intent	N=36 Median Age (range): 54.4 years (22–82) Male: 66.7% **Tumor Characteristics** Unilateral: 100% Mean Visual Acuity: 20/25 Pseudophakic: 5.6% (2/36) Ciliary Body involvement: 17% (6/36)	**PBT**: proton fixed horizontal beam line **Total PBT Dose**: 60 Cobalt Gray Equivalent **Additional Treatments**: NR	**Median F/U (range):** 50 (15 to 136) months	**Primary Outcomes** **Proportion of patients achieving local control**: 100% **Mortality, % (n/N)** • All-cause: 5.6% (2/36) • Disease-specific: 0% (0/36) **Mean BCVA at last follow-up**: 20/32 **Secondary Outcomes** NR	**Post-irradiation complications, % (n/N)** • Post-irradiation cataract: 62% (25/36) • Glaucoma (new case): 6% (2/36) • Hyphema: 3% (1/36) • Recurrent corneal ulcer: 6% (2/36) • Dystrophic corneal edema: 3% (1/36) • Uveitis: 3% (1/36) • Blephartitis: 3% (1/36)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		Mean tumor diameter: 3.8 mm (range, 2.5 to 8) **Primary Tumor Location** Inferior Iris: 72% (26/36) Infero-nasal quadrant: 33% (12/36) Inferiorly: 25% (9/36) Inferotemporally: 14% (5/36) Superioir Iris: 25% (9/36) Superotemporally: 14% (5/36) Superiorly: 6% (2/36); Superonasally: 6% (2/36) **Comorbidities** Cataract: 11% (4/36) Hyphema: 3% (1/36)				• Temporary dry eye syndrome with conjunctival hyperemia and delayed conjunctival telangiectasia: 61% (22/36) • Sectorial iris atrophy: 3% (1/36) **Proportion of patients requiring enucleation**, % (n/N): 0% (0/36)
Riechardt 2014 Retrospective Case Series *RoB*: High Germany	**Diagnosis**: Recurrent uveal melanoma **Indication**: Salvage therapy	N=48 Mean Age (range): 61 years (32 to 84) Male: NR **Median tumor height** ± SD : 3.8 mm ± 1.7 **Primary Tumor Sites**	**PBT**: NR **Total PBT Dose**: 54.5 Gy (RBE) **Additional Treatments**: NR	**Median F/U (range):** 81 (13 to 228) months	**Primary Outcomes** **Overall Survival, 95 % CI** • *5-year:* 89.1% (NR) • *10-year*: 77.4% (NR) **Metastasis-free survival, 95% CI** • *5-year:* 80.7% (NR) • *10-year*: 70.1% (NR)	**Proportion of patients receiving enucleation**: 2.1% (1/48)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Funding: NR COI: Dr Riechardt has received travel, accommodation, and meeting expenses support from the EORTC/Melanoma group. Dr Rehak has received speaker honoraria from Novartis, Bayer, and Allergan and has received travel, accommodation, meeting expenses support from Novartis and Bayer. Dr Hager has received travel, accommodation, and meeting expenses support from the American Academy of Ophthalmology. Dr Joussen has received payment for development of educational presentations from Novartis and travel, accommodation, and meeting		Subfoveally: 29.2% (14/48) Juxtafoveally: 12.5% (6/48) Parafoveally: 52.1% (25/48) Circumpapilary: 8.3% (4/48) Juxtapapilary: 33.3% (16/48) Parapapulary: 52.1% (25/48)			**Proportion of patients achieving local control 10-years after PBT**: 92.1% **Proportion of patients experiencing re-recurrence**: 6.3% (3/48) **10-year preservation of the globe**: 97.7% **Median Visual Acuity (range)** • Baseline: 20/63 (20/16 to hand movements) • 5-year: 20/400 (20/50 to hand movements) **5-year Kaplan-Meier estimator for a VA worse than 20/200, 95% CI**: 24% **Proportion of patients found to have no light perception**: 4.2% (2/48) **<u>Secondary Outcomes</u>** **Requirement for subsequent therapy**	

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
expenses support from Novartis, Alcon, and Allergan. Dr Gundlach was supported by Grant ''Ernst und Berta Grimmke Stiftung'', Ratingen, Germany Involved in Prof. M. H. Foerster established the therapy unit at Helmholtz Zentrum Berlin and was responsible for the indications for treatment and the therapy of the patients till the end of 2009. ---					• Cataract Surgery: 25% (10/40 pre-PBT phakic patients) • Vitrectomy: 12.5% (6/48)	
Riechardt 2017 Retrospective Case Series *RoB*: High Germany Funding: None COI: None	**Diagnosis**: Choroidal Melanoma **Indication**: Curative Intent	N=629 Mean Age (range): 59.3 (16 to 88) years Male: 52.2% **Tumor Characteristics** • TNM Classification T1: 38.3% T2: 47.7% T3: 12.7% T4: 1.3%	**PBT**: NR **Total PBT Dose**: 60 Cobalt Gray Equivalents	**Median F/U (range):** 62.4 months (3.6 to 170.4)	**Primary Outcomes** **5-year OS (95% CI)**: 94% (92% to 96%) **5-year Metastasis Free Survival (95% CI):** 90% (87% to 92%) **5-year Kaplan-Meier analysis of tumor-associated death (95% CI)**: 3% (1.8% to 4.9%)	**5-year Kaplan-Meier estimator for the absence of radiation-induced retinopathy (95% CI)**: - *All patients:* 14.2% (NR) - *Patients with Neovascular Glaucoma*: 3% (NR)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
---					**<u>Secondary Outcomes</u>** NR	- *Patients without Neovascular Glaucoma*: 15.5% (NR) **5-year Kaplan-Meier estimator for the absence of optic neuropathy (95% CI)**: • 5-year - *All Patients:*36.6% (NR) • 3-year - *Patients with Neovascular Glaucoma*: 6.1% - *Patients without Neovascular Glaucoma:* 32.1% Log-rank p-value<0.001 **5-year Kaplan-Meier estimation for Neovascular Glaucoma (95% CI):** 10.5% (8% to 13.5%) **Proportion of patients developing neovascularization of the iris**: 20.8% (131/629) - Neovascular glaucoma: 47.3% (62/131) [68.3% of

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						which received laser coagulation] **Proportion of patients requiring Enucleation**: 4% (25/629) [FN: Due to local recurrence (n=10), phthisis bulbi (n=2) and multiple vitreoretinal surgeries, amaurosis, and decompensation of intraocular pressure without Neovascular glaucoma (n=1)]
Sandinha 2014 Retrospective Case Series *RoB*: High UK Funding: None COI: None ---	**Diagnosis**: Iris Melanoma **Indication**: Curative Intent	N=150 patients, 150 eyes Median Age (range): Male: NR **Tumor Characteristics** Median Tumor Thickness: 2.4 mm (range, 1.1 to 4.9) Ciliary body involvement: 2% (3/150)	**PBT**: NR **Total PBT Dose**: 53.1 Gy (RBE)	**Median F/U (range):** 66 (24 to 108) months	**Primary Outcomes** **Proportion of patients experiencing local recurrence**: 5.3% (8/0150) [focal (n=2), diffuse (n=6)] **Secondary Outcomes** NR	**Proportion of eyes requiring enucleation**: 4% (6/150 eyes) *1 eye underwent iridocyclectomy and 1 received a second course of PBT*
Schönfeld 2014 Retrospective Case Series	**Diagnosis**: Choroidal melanoma of the intermediate zone of the fundus	N=62 Mean Age (SD): 57.7 years (13.6) Male: 46.8%	**PBT**:	**Median F/U (range):** 70.3 (NR) months	**Primary Outcomes** **5-year rate of local tumor relapse**: 3.9%	**Proportion of patients receiving Enucleation, % (n/N):** 3.2% (2/62)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
RoB: High Germany Funding: NR COI: G.W.: payment for lectures including service on speakers bureaus; N.E.B.: payment for lectures including on speakers bureaus (Alcon, Hoya) and board membership (Novartis); A.M.J.: payment for development of educational presentations (Novartis) and travel/accommodations/meeting expenses (Novartis, Alcon, and Allergan). The authors indicate no funding support ---	**Indication**: Curative Intent	**Tumor Characteristics** Mean tumor size: 7.6 mm (1.7 to 12.6) Tumor-to-fovea distance: 2 mm to 10.1 mm Tumor-to-disc distance: 2.0 to 11.3 mm **Comorbidities** Diabetes mellitus: 3.2% (2/62) Glaucoma: 3.2% (2/62) Exudative retinal detachment: 48 eyes	**Total PBT Dose**: 60 Cobalt Gray Equivalents **Additional Treatments** PBT alone, n=18 (29%) PBT plus subsequent endoresection, n=44 (71%)		**Cumulative Local Tumor Control (95% CI)**: -5-year: 96.1% (NR) -10-year: 96.1% (NR) **5-year rate of distant metastasis**: 13.4% **Metastasis-free survival (95% CI)** • *5-year:* 86.6% (NR) • *10-year:* 81.8% (NR) **Cumulative metastasis-related mortality** • *5-year: 10.6%* • *10-year: 16.9%* **Mortality, % (n/N)** • *Disease-related: 12.9% (8/62)* • *All-cause: 16.1%* (10/62) **Visual acuity, % (n/N)** • High (20/16 to 20/50 Snellen or -0.1 to 0.4 logMAR) - *baseline*: 66.1% (41/62)	**5-year rate of enucleation**: 3.7% **Proportion of patients requiring enucleation**: 3.2% (2/62)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					- *final follow-up*: 27.4% (17/62) • Medium (20/63 to 20/160 Snellen or 0.5 to 0.9 logMAR): - *baseline:* 25.8% (16/62) - *final follow-up:* 19.4% (12/62) • Low (20/200 Snellen or 1.0 logMAR and worse) - *baseline:* 8.1% (5/62) - *final follow-up:* 53.2% (33/62) **<u>Secondary Outcomes</u>** **Subsequent Treatments**: • Phacoemulsification with intraocular lens implant to the posterior chamber: 69.4% (43/62) • Cataract surgery: NR, but indicated to be common • Virectomy: 71% (44/62) • Secondary irradiation owing to recurrent tumor growth: 1.6% (1/62)	

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					• Surgical intervention for proliferative vitreoretinopathy or Nonresorbing exudative detachment: 6.5% (4/62)	
Mathis 2018 Prospective Case Series *RoB*: High France Funding: NR COI: Thibaud Mathis: Bayer, Novartis, Allergan; Laurent Kodjikian: Consultancy for Bayer, Novartis, Allergan, Thea, Alcon. ---	**Diagnosis**: Ocular Tumors [Choroidal/Ciliary Body Melanoma (75.3%), Conjunctival Melanomas or Carcinomas (8%), Iris Melanoma (4.4%), Choroidal hemangiomas (2.3%), Eyelid Tumors (1.7%), Other (7.8%) **Indication**: Curative Intent	N=474 Mean Age (SD): 63.1 years (13.9) Male: 50%	**PBT**: Beam delivery technique used a single thin tantalum scattering foil associated with Plexiglas range shifter and modulating wheel providing spread-out Bragg peak **Total PBT Dose**: 60 Gy (RBE)	**Median F/U (range):** 16.8 (NR) months	**Primary Outcomes** NR **Secondary Outcomes** NR	**Proportion of patients experiencing phosphenes following PBT**: 62.93% (298/474)
Seibel 2017 [This study contains heavy cross over with patients	**Diagnosis**: Choroidal (94.9%) or ciliary body (5.1%)melanoma **Indication**: Curative Intent	N=2499 Median Age (range): 61 years (15 to 94) Male: % **Tumor Characteristics**	**PBT**: NR **Total PBT Dose**: 60 cobalt gray equivalent	**Median F/U (range):** 51.2 (12 to 170) months	**Primary Outcomes** NR **Secondary Outcomes** NR	**Adverse Events (all patients), % (n/N)** Radiation retinopathy: 53.4% (1334/2499) Neovascular glaucoma: 12.6%(315/2499)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
included in Seibel 2016b] Retrospective Case Series *RoB*: High Germany Funding: None COI: Antonia Joussen: Payment for development of educational presentations (Novartis Pharma GmbH, Nurnberg, Germany) and travel/accommodations/meeting expenses (Novartis Pharma GmbH, Nurnberg, Germany; Alcon Pharma GmbH, Freiburg im Breisgau, Germany; and Pharm-Allergan GmbH, Frankfurt am Main, Germany). All other report no COI. ---		T Category T1: 27.9% T2: 37.9% T3: 24.7% T4: 9.5% Stage I: 25.4% IIA: 33.4% IIB: 20.0% IIIA: 11.8% IIIB: 3.9% IIIC: 0.5% Median Tumor Thickness: 5.8 mm (range, 1 to 16.4) Median largest basal diameter: 12.2 mm (range, 1 to 26.1) Median distance to fovea: 1.9 mm (range, 0 to 21.5) Median distance to optic disc: 2.7 mm (range, 0 to 22.2.0)	**Additional Treatments** Endoresection: 17.8% (445/2499) Endodrainage-Virectomy: 9.7% (242/2499) Transscleral resection: 5% (125/2499)			Radiation optic neuropathy: 54.8% (1370 /2499) **5-year rates of globe preservation (95% CI):** 94.8% (NR) **5-year rates of neovascular glaucoma**: • Endoresection Group (n=445): 11.6% • Endodrainage group (n=242): 21.3% p=0.03 **5-year rates of optic neuropathy** • Endoresection Group (n=445): 58.4% • Endodrainage group (n=242): 43.7% **Enucleation Free Survival:** • Endoresection Group (n=445) - *5-year:* 94.8% (95% CI, NR) - *10-year:* 92.2% (95% CI, NR) • Endodrainage group (n=242)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						- *5-year:* 94.3% (95% CI, NR) - *10-year:* Not Calculable • No adjuvant surgery group (n=1812): - 5-year: 93.5% -10-year: 52.1% **Proportion of patients requiring enucleation**: 4.4% (110/2499) Owing to neovascular glaucoma: 3.1% (78/2499) Owing to local recurrence: 1.1% (27/2499) Owing to scleral necrosis: 0.2% (4/2499) Owing to choroidal hemorrhage: 0.04% (1/2499)
Seibel 2016b [This study contains heavy cross over with patients included in Seibel 2017] Retrospective Case Series	**Diagnosis**: Choroidal or ciliary body melanoma **Indication**: Curative Intent	N=1127 Median Age (range): 61 years (16 to 89) Male: 4.5% **Tumor Characteristics** Median Tumor Thickness (range): 3.6 mm (0.1 to 14.1 mm)	**PBT**: NR **Total PBT Dose**: 60 Cobalt Gray Equivalent **Additional Treatments**: None	**Median F/U (range):** 46.2 months (12 to 170.4)	**<u>Primary Outcomes</u>** **Median Visual Acuity (range)** • Baseline: 0.3 logMAR (hand motions to 0.0 logMAR) • Final follow-up: 1.3 logMAR (no light perception to 0.0 logMAR)	**Incidence of radiation-induced complications, % (n/N)** Retinopathy: 68.1% (768/1127) Neuropathy: 41% (463/1127) **Retinopathy-free survival**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
RoB: High Germany Funding: None COI: Prof. A. Joussen and Dr. M. Rehak report personal fees from Bayer, personal fees from Novartis, and personal fees from Allergan, outside the submitted work. All other authors report no COI ---		Largest basal diameter (range): 10.9 mm (3.0 to 22.4 mm) Median distance to fovea (range): 0.6 mm (0 to 18.5 mm) Median distance to optic disc (range): 1.6 mm (0 to 18.7 mm) Median distance to equator (range): 5.4 mm (0 to 18.0 mm)			**Secondary Outcomes** NR	• 1-year: 87% • 2-year: 53% • 3-year: 33% • 4-year: 21% • 5-year: 15% • 10-year: 7% **Optic neuropathy-free survival** • 1-year: 92% • 2-year: 73% • 3-year: 61% • 4-year: 52% • 5-year: 48% • 10-year: 26% **Proportion of patients that developed radiation retinopathy-related macular edema (n=490 patients with information available)**: 30% (163/490)
Thariat 2016 [Overlap of patients in Thariat 2016/2017a/2017b/ 2017c] Retrospective Case Series	**Diagnosis**: Parapapillary Uveal Melanoma [Tumors that are close to the optic disk, as opposed to those that are touching the optic disk] **Indication**: Curative Intent	N=865 Mean Age: 61.7 years (range, 13 to 93) Male: 52.2% **Tumor Characteristics** • Median maximal diameter: 14.40 mm • (range, 4.1-24.0 mm)	**PBT**: NR **Total PBT Dose**: 52 Gy (RBE)	**Median F/U (range):** 69 months (6 to 240)	**Primary Outcomes** **Overall Survival (95% CI)** • *2-year*: 94.5% (NR) • *5-year:* 82.4% (NR) • *10-year:* 69.7% (NR) • *15-year:* 57.7% (NR) **Metastasis-Free Survival (95% CI)**	**Proportion of patients requiring enucleation**: 12% (104/865) **Adverse Outcomes, % (n/N)** • Intravitreous hemorrhage or hyphema: 11.5%

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
RoB: High France Funding: NR COI: None --- Provides subpopulation analysis based on age, comorbidities, tumor characteristics, etc.		• Median maximal thickness: 4.90 mm (range, 1.0-14.70 mm) • Median distances to the papilla: 0.90 mm • (range: 0.00-3.00) • Median distance to the macula: 0.90 mm (range: 0.00-8.00) • Tumor abutted the papilla: 35.1% of tumors • Tumor-to-fovea distance ≤3 mm: 74.2% of patients • Peritumoral retinal detachment: 35% • Inferior retinal detachment: 15.7% **Comorbidities** • Extensive retinal Detachment: 2.1% • Intravitreous hemorrhage: 7.4% • Cataracts: 22.6% • Pseudophakic: 9.8%			• *2-year*: 98.5% (NR) • *5-year:* 95.6% (NR) • *10-year:* 70% (NR) • *15-year:* 55.4% (NR) **Mean Relapse-free Survival (95% CI)** • *2-year*: 96.6% (NR) • *5-year:* 92.7% (NR) • *10-year:* 88.8% (NR) **Proportion of patients experiencing local recurrence**: 10.5% (91/865) **Mortality, % (n/N)**: • All-cause: 20.9% (181/865) **Visual Acuity, % (n/N),** Baseline vs. last follow-up • Ability to experience light perception: 80.5% vs. 80.8% • ≤1.0 logMAR (≥20/200): 61.6% vs. 47.2% • Mean change in visual acuity: 0.89 logMAR	• Peritumoral retinal detachment: 12.5% • Inferior retinal detachment: 1.1% • Extensive retinal detachment: 1.6% • Development of new cataracts: 6.1% • Inflamation: 10.5% • Dry eye syndrome: 9.4% (0.4% with focal corneal ulceration) • Neovascular Glaucoma: 17.9% • Radiation-induced optic neuropathy: 47.5% • Maculopathy: 33.6%

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					• Median change in visual acuity: 0.70 logMAR • Proportion of patients that lost >0.3 logMAR: 38.3% • Proportion of patients with steady or better logMAR: 38.3% **<u>Secondary Outcomes</u>** NR	
Thariat 2017a [Overlap of patients in Thariat 2016/2017a/2017b/ 2017c] Retrospective Case Series *RoB*: High France Funding: None COI: NR --- Provides univariate and multivariate analyses of	**Diagnosis**: Uveal Melanoma [with specific focus on which quadrant the tumor is located in] **Indication**: Curative Intent	N=853 Median Age ± SD: 64 years ± 13.8 Male: 48.2% **Tumor Characteristics** Maximal tumor diameter ± SD: 15.7mm ± 4.7 Tumor Height ± SD: 5.6mm ± 2.8 Distance to optic disk ± SD: 5mm ± 4.9 **Tumor Location (quadrant)** Temporal: 30.5% (260/853) Superotemporal: 11.4% (97/853) Other: 58.2% (496/853)	**PBT**: NR **Total PBT Dose**: 52 Gy (RBE)	**Median F/U (IQR):** 44 (18 to 60) months	**<u>Primary Outcomes</u>** **Overall Survival, 95% CI** • *Temporal*: 85.6% (78.1% to 90.7%) • *Superotemporal:* 95.5% (86% to 98.6%) • *Other*: 89.5% (85.5% to 92.5%) p=0.471 **Incidence of locoregional relapses, 95% CI** • *Temporal*: 6.2% (2.9% to 12.6%) • *Superotemporal:* 6.4% (2.2% to 17.8%) • *Other*: 5.4% (3.3% to 8.8%) p=0.689	**Incidence of Dry Eye Syndrome – all grades (95% CI)** • *1-year:* 6% (4.5% to 7.9%) • *2-year:* 11.2% (9.1% to 13.8%) • *5-year:* 23% (19% to 27.7%) **Incidence of Severe Dry Eye Syndrome (95% CI)** • *1-year:* 2.1% (1.3% to 3.4%) • *2-year:* 4.8% (3.5% to 6.8%) • *5-year:* 10.9% (8.2% to 14.4%)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
prognostic factors for severe dry eye syndrome and differential visual acuity		**Comorbidities** Diabetes: 12.2% (69/853) [Data presented as reported in study] High blood pressure 28.4% (184/853) [Data presented as reported in study] Menopausal status (for females) 81.5% (360/853)			**Incidence of metastasis, 95% CI** • *Temporal*: 16.9% (11.8% to 24%) • *Superotemporal:* 14.5% (7.2% to 28%) • *Other*: 14.5% (10.9% to 19.2%) p=0.903 **<u>Secondary Outcomes</u>** NR	**Proportion of patients requiring enucleations**: 3.4% (29/853)
Thariat 2017b [Overlap of patients in Thariat 2016/2017a/2017b/ 2017c] Prospective Case Series *RoB*: High France Funding: NR COI: NR --- Provides univariate analysis for	**Diagnosis**: Uveal Melanoma [without preexisting cataracts or implants] **Indication**: Curative Intent	N=1696 Median Age (SD): 59.9 years (13.8) Male: 50.1% **Tumor Characteristics** Mean Tumor Diameter ± SD: 14.7 ± 4.3 Median distance to optic disk (IQR): 3.9 (1.4 to 7.3) **Comorbidities** Diabetes: 5% (85/1696) Hypertension: 11.7% (198/1696) **Stage** T1-T2: 57.1% (967/1696) T3-T4: 42.9% (726/1696)	**PBT**: NR **Total PBT Dose**: 60 Gy (RBE)	**Median F/U (IQR):** 49 months (23 to 90)	**<u>Primary Outcomes</u>** **5-year Overall Survival, 95% CI** 87.4% (85.4% to 89.2%) **Proportion of patients experiencing relapse**: 5.7% (97/1696) **<u>Secondary Outcomes</u>** NR	**Cumulative incidences of cataracts, 95% (CI)** • *1-year:* 4.9% (4.0% to 6.1%) • *3-year:* 12.0% (10.4% to 13.8%) • *5-year:* 18.7% (16.5% to 21.1%) **Cumulative incidences of vision impairing cataracts, 95% (CI)** • *1-year:* 1.2% (0.8% to 1.9%) • *3-year:* 6.7% (5.5% to 8.1%) • *5-year:* 12.8% (10.9% to 14.9%)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
predictors of vision impairing cataracts						**Proportion of patients having enucleation**: 8.6% (146/1696)
Thariat 2017c [Overlap of patients in Thariat 2016/2017a/2017b/ 2017c] Retrospective Case Series *RoB*: High France Funding: NR COI: NR --- Provides prognostic factors for vision loss	**Diagnosis**: Iris Melanoma **Indication**: Curative Intent [8.4% (9/107) had previous proton therapy for incomplete resection]	N=107 Median Age (range): 57 years (22.8 to 86.7) Male: 44.4% **Tumor Characteristics** Unilateral: 100% Median tumor diameter (IQR): 4.49 (2.7 to 6.4) Ciliary body involvement: 22.4% (24/107) **Comorbidities** Pupillary deformation: 68.6% (72/107) Cataracts: 31.7% (34/107) **Tumor Stage** T1: 72.9% (78/107) T2: 21.5% (23/107) T3: 5.6% (6/107)	**PBT**: NR **Total PBT Dose**: 60 Gy (RBE) **Additional Treatments** Fine-needle aspiration biopsy: 12.4% (13/107) Primary sectorial iridectomy: 9.3% (10/107) Iridectomy for benign lesion 20 years before diagnosis: 0.9% (1/107) Fine-needle aspiration biopsy and iridectomy: 1.8% (2/107)	**Median F/U (range):** 49.5 months (1.1 to 151.6)	**Primary Outcomes** **Proportion of Patients Experiencing Local Relapse:** 4.7% (5/107) **5-year cumulative incidence of relapse, 95% CI**: 7.5% (3.1% to 17.5%) **Mortality, % (n/N)** • All-cause: 6.5% (7/107) [FN: n=3 of other cancers, n=2 of cardiovascular comorbidities] • Disease related: 0% (0/107) **Visual Acuity, % (n/N)** • Improved or remained stable: 59.4% (60/101) • Median BCVA, baseline vs. last-follow-up: 1.0 logMAR vs. 0.9 logMAR (range, 0.0 to 1.0); p<0.001 **Secondary Outcomes** NR	**Proportion of pre-PBT cataract free patients experiencing cataracts post PBT (n=54)**: 51.1% (31/54) **Adverse Outcomes, % (n/N)** • Atrophic neuropathy: 4.7% (5/107) • Hyphema: 4.7% (5/107) • Uveitis: 3.7% (4/107) • Scleral necrosis: 0.9% (1/107) • Transient dry corneal syndrome: 53.8% (35/65) • Mild and transient conjunctival complications: 50.8% (33/65) • Transient blepharitis: 0.9% (1/107) • Sectorial Madrosis: 1.8% (2/107) • Chronic Corneal complications 5.6% (6/107)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						Proportion of Patients Developing Secondary Glaucoma: 7.6% (8/107)
Weber 2015 Retrospective Case Series *RoB*: High Canada Funding: NR COI: None --- Also provides outcomes based on stage	**Diagnosis**: Non-Peripapillary Choroidal and Ciliary Body Melanoma **Indication**: Curative intent	N=77 Median Age (range): 60 years (28 to 88) Male: 60% **Tumor Characteristics** Tumor Type Chorodial Melanoma: 88% (68/77) Ciliary Body Melanoma: 12% (9/77) Unilateral: 100% (77/77) Ciliary Body involvement: 35% (27/77) Angle involvement: 85% (65/77) **Stage** T Stage: T1: 12% (9/77) T2: 27% (21/77) T3: 56% (43/77) T4: 5% (4/77) Stage: I: 4% (3/77) IIa: 29% (22/77) IIb: 45% (35/77)	**PBT**: NR **Total PBT Dose**: 60 Gy (RBE)	**Median F/U (range):** 47 months (0 to 221)	**Primary Outcomes** **Overall Survival, 95% CI** • *2-year:* 91.1% (NR) • *5-year:* 76.8% (NR) • *10-year: 62.7% (NR)* **Ocular (Local) Control, 95% CI** • *2-year:* 98.5% (NR) • *5-year:* 85.1% (NR) • *10-year: 85.1% (NR)* **Metastasis-free Survival, 95% CI** • *2-year:* 89.6% (NR) • *5-year:* 71.6% (NR) • *10-year*: 57.2% (NR) **Proportion of patients maintaining visual acuity of counting fingers or better (n=75)** • *2-year:* 73.2% • *5-year*: 61.4% • *10-year*: 61.4% **Proportion of patients maintaining visual acuity**	**Ocular Complications, % (n/N)** • Radiation retinopathy: 25% • Catarct: 54% • Rubeosis: 45% • Neovascular Glaucoma: 23% **Proportion of patients requiring enucleation**: 15.6% (12/77) [n=2 due to ocular recurrence; n=10 due to toxicity] **Rates of Enucleation**: • *2-year:* 4.2% • *5-year:* 22% • *10-year*: 22%

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		IIIa: 18% (14/77) IIIb: 3% (2/77) IIIc: 1% (1/77)			**of 20/200 or better (n=67)** • *2-year:* 56.8% • *5-year*: 37% • *10-year*: 37% **Proportion of patients maintaining visual acuity of 20/50 or better in tumor-effected eye (n=50)** • 2-*year*: 60.4% • *5-year:* 39.5% • *10-year*: 39.5% **Secondary Outcomes** NR	
Wildering 2015 Retrospective Case Series *RoB*: High Germany Funding: NR COI: none --- Provides analysis for vision loss based on presence or absence of glaucoma	**Diagnosis**: Iris melanoma **Indication**: Curative Intent	N=54 Median Age (range): 60 years (10 to 89) Male: 51.9% **Tumor Characteristics** Contact with the anterior chamber angle: 92.6% (50/54) Signs of diffuse tumor seeding to the anterior chamber angle or iris surface: 90.7% (49/54) Ciliary body extension: 9.3% (5/54) **Stage** T1: 88.9% (48/54)	**PBT**: 68-megaelectron volt proton beam **Total PBT Dose**: 50 Cobalt Grey Equivalent **Additional Treatments** Biopsy: 44.4% (24/54)	**Median F/U (range):** 54.8 months (5.5 to 159.6)	**Primary Outcomes** **5-year Probability of Local Tumor Control**: 94.7% (95% CI NR) **5-year Probability of Eye Retention (95% CI)**: 95.1% (NR) **Proportion of patients developing metastasis**: (1/54) **Median Visual Acuity** • Baseline: 20/25 • 1-year: 20/32	**Proportion of patients receiving enucleation**: 5.6% (3/54) **Proportion of patients having developed glaucoma following PBT**: 29.6% (16/54) **Proportion of patients developing radiation induced cataract**: 42.6% (23/54) **Proportion of patients developing radiation induced cataract or had a cataract worsen due**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		T2: 7.4% (4/54) T3: 3.7% (2/54)			• 2-year: 20/35 • 3-year: 20/40 • 5-year: 20/45 • 7-year: 20/35 **Kaplan-Meier estimates for vision loss (95% CI)** • 3-year: 9.2% (NR) • 5-year: 18.4% (NR) **Mean intraocular pressure (range)** • Baseline: 21 mm Hg (10 to 65) • Final follow-up: 21 mm Hg (8 to 60) **Secondary Outcomes** NR	**to radiation**: 81.5% (44/54) **Proportion of patients with recurrent, but finally healed, corneal erosion**: 3.7% (2/54) **Transient Hyphaema**: 3.7% (2/54) **Iris Rubeosis**: 1.9% (1/54) *Engorgement of perilimbal conjunctival vessels developed frequently. During tumour regression, visibility and engorgement of tumour vessels arose in some patients.*
Wildering 2016 Retrospective Case Series *RoB*: High Germany Funding: NR COI: None	**Diagnosis**: choroidal or ciliochoroidal, nonmetastasised melanoma with a minimum tumor thickness of 7 mm and a largest basal diameter of <23 mm **Indication**: Curative Intent	N=106 Mean Age (range): 57.7 years (25 to 81) Male: 51.9% **Tumor Characteristics** • Tumor type: - Choroidal melanoma: 18.9% (20/106)	**PBT**: Neoadjuvant PBT **Total PBT Dose**: 54.5 Gy **Additional Treatments** All patients underwent transscleral resection following PBT	**Median F/U (range):** 38.4 months (1.3 to 96.6)	**Primary Outcomes** **Proportion of patients experiencing local recurrence**: 4.7% (5/106) **Kaplan-Meier estimates for local-recurrence** (95% CI) • 3-year: 4.2% (NR) • 5-year: 10.4% (NR)	**Proportion of patients developing rubeotic glaucoma**: 16% (17/106) **Proportion of patients requiring enucleation**: 9.4% (10/106) [n=1 due to local recurrence]

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
--- Predictors of local recurrence and metastasis were investigated with log-rank testing		- Ciliochoroidal melanoma: (86/106) 81.1% • Median tumor thickness: 10.5 mm • Median largest basal diameter: 16.5 mm • Median tumor distance to fovea: 9.1 mm • Median tumor distance to optic disk: 8.5 mm • Anterior involvement: 23.6% (25/106) • Retinal detachment: (88/106) 83% • Extraocular extension: 12.3% (13/106) **Stage**: T1: (1/106) T2: (2/106) T3: (62/106) T4: (41/106)			**Proportion of eyes that maintained visual acuity of 20/200 or better**: (44/94 eyes) 46.8% **Proportion of patients with a visual acuity of less than counting fingers, % (n/N)** • 1-year: 16% (17/106) • 3-year: 11.3% (12/106) • 5-year: 6.6% (7/106) **Secondary Outcomes** **Additional vitreoretinal surgery after transscleral resection**: 69.8% (74/106) [Indications were intraocular hemorrhage (n=20), retinal detachment (n=13), both of the former (n=40)] **Additional surgery for retinal detachment**: 50% (53/106) **Additional surgery for cataracts**: 94% (94/100) initially phakic patients)	
Bellocq 2018 Retrospective Case Series	**Diagnosis**: Uveal Melanoma **Indication**: Curative Intent	N=508 Age 40 –49: 24.6%	NR	**Mean F/U (for living patients)**:	Overall Survival (Standard Error) • All patients - 5-year: 74.1% (2%)	NR

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
RoB: High France Funding: NR COI: Laurent Kodjikian was the Principal Investigator for trials sponsored by Novartis, Bausch and Lomb, Théa, Alcon; has sat on advisory boards for Alcon, Alimera, Allergan, Bayer, Bausch and Lomb, Novartis, Théa; and received lecture fees from Alcon, Alimera, Allergan, Bayer, Bausch and Lomb, Novartis, Théa. For the remaining authors there are no conflicts of interest. --- Provides prognostic data/analysis		50–59: 20.3% 59–69: 29.1% >70: 26.0% Male: 48% Tumor laterality Right side: 50.8% Left side: 49.2% Location Pre-equatorial: 18.9% On the equator: 41.1% Retro-equatorial: 40% Cilary body involvement: 24.8% Distance to optic disk (mm) ≤3 mm: 46.9% >3 mm: 53.1% Juxtapapillary location: 16.3% Distance to macula ≤3 mm: 51.6% >3 mm: 48.4% Tumor stage T1: 35.1% T2: 40.7% T3: 23.2% T4: 1.0%		239.4 months	- 10-year: 57.2% (2.4%) - 15-year: 46.5% (2.6%) • Patients that developed metastasis (n=169) - 1-year: 62.1% (3.8%) - 2-years: 26.0% (3.5%) - 5-years: 6.0% (2.1%) <u>Specific Survival (i.e. death by metastasis) (Standard Error)</u> - 5-year: 79.1% (1.9%) - 10-year: 67.6% (2.4%) - 15-year: 62.7% (2.6%) <u>Local Recurrence Free Survival (Standard Error)</u> - 5-year: 92.8% (1.2%) - 10-year: 91.3% (1.4%) - 15-year: 89.9% (1.7%) <u>Metastasis Free Survival (Standard Error)</u> - 5-year: 74.3% (2.0%) - 10-year 65.7% (2.3%) - 15-year: 58.4% (2.7%) <u>Proportion of Patients Developing Metastasis, % (n/N)</u> 31.7% (169/508) [151 of these patients died]	

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		Tumor diameter ≤11 mm: 68.1% >11 mm: 31.9% Initial exudative retinal detachment: 71.7% Bruch's membrane rupture: 38.8% Iris root involvement: 4.1%			Mean Survival Time for Patients that Developed Metastasis (Standard Error) 1.78 (0.15) years	

BCVA = best corrected visual acuity; CI = Confidence interval; COI = Conflict of interest; F/U – Follow-up; Gy = Gray; IQR = interquartile range; NR = not reported; PBT = Proton beam therapy; PDT = photodynamic therapy; RBE = relative biological effectiveness; SD = Standard deviation; SE = standard error

Appendix Table M2. Study characteristics and patient demographics: comparative studies of proton beam therapy in ocular cancers

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Cohort studies							
Boker 2018 Retrospective matched-pairs cohort study *Moderately High* Germany	140 (matched-pairs from a total of 242)	**PBT (+ TSR) (n = 70 matched-pairs** [out of 106]**):** Neoadjuvant PBT and subsequent transscleral resection (TSR); total dose 54.5 Gray (divided into 4 sessions of 15 CGE each); treated after 2004 **Brachytherapy (+TSR) (n = 70 matched-pairs** [out of 136]**):** **T**ransscleral resection (TSR) and adjuvant ruthenium brachytherapy; mean dose 470 Gray (range 400-500); treated from 1993 to 2004	**Inclusion:** patients with large uveal melanomas that had been treated with transscleral resection with a predefined protocol, either with adjuvant ruthenium brachytherapy (Ru-106 group, n 136,), or with neoadjuvant proton beam therapy. **Exclusion:** NR	*PBT vs. Brachytherapy* Mean age (± SD) : 57 ± 12 vs. 50 ± 12 years Male: 47% vs. 40% Histological type: Spindle cell: 47% vs. 47% Epitheloid: 53% vs. 53% Retinal detachment (No): 80% vs. 70% Tumor thickness (mean ± SD): 10.4 ± 1.7 vs. 10.3 ± 1.8 Ciliary body infiltration (Yes): 81% vs. 81%	**F/U (median [range]):** *Tumor recurrence***:** 34.4 months (0.8 to 120 mos.) *Tumor-specific survival and metastasis*: 39.8 months (0.8 to 120 mos.) **% F/U** - All patients: CD* - PBT vs. Brachytherapy: CD*	Tumor recurrence rate (local tumor control) Tumor-specific survival and metastasis (systemic tumor control) Visual acuity Secondary complications	Funding NR Authors declare no COIs
Lin 2017 Retrospective cohort study	N=1224 overall	**PBT (n=228 overall, 226 matched cohort)**	**Inclusion:** choroid melanoma, presented between 2004 and 2013	PBT vs. Brachytherapy **Overall population**	**PBT:** 29 mos. **Brachytherapy:** 37 mos.	OS	Funding NR Authors declare no COIs

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
(National Cancer Database) *Moderately High*	N=452 propensity matched cohort	median dose 56 Gy (range, 50 to 70.4) **Brachytherapy (n=996 overall, 226 matched cohort)**	**Exclusion:** nodal or metastatic disease, incomplete staging information including basal diameter and tumor thickness, or received surgery or chemotherapy	Mean age (±SD): 60.6 ± 13.0 vs. 61.0 ± 13.3 Male: 54% vs. 52% Caucasian: 86% vs. 96% Academic center: 99% vs. 76% Treatment center experience: >20 pts.: 90% vs. 77% >50 pts.: 90% vs. 56% Charlson-Deyo score: 0: 82% vs. 83% 1: 17% vs. 14% ≥2: 1% vs. 3% Tumor size: T1: 40% vs. 36% T2: 36% vs. 36% T3: 18% vs. 20% T4: 6% vs. 8% Ciliary or extraocular extension: 8% (18/224) vs. 11% (100/880) Basal diameter (mean ± SD): 10.5 ± 4.3 vs. 11.0 ± 7.9 Thickness (mean ± SD): 5.5 ± 6.1 vs. 5.8 ± 7.9 **Propensity score-matched cohort** Mean age (±SD): 60.6 ± 13.0 vs. 61.0 ± 13.5 Male: 54% vs. 54% Caucasian: 86% vs. 93%, p=0.046 Academic center: 99% vs. 98% Treatment center experience:	**% F/U** - All patients: CD† - PBT vs. Brachytherapy: CD†		

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
				>20 pts.: 89% vs. 81%, p=0.02 >50 pts.: 89% vs. 67%, p<0.001 Charlson-Deyo score: 0: 82% vs. 82% 1: 17% vs. 15% ≥2: 1% vs. 3% Tumor size: T1: 39% vs. 42% T2: 37% vs. 34% T3: 18% vs. 18% T4: 6% vs. 6% Ciliary or extraocular extension: 8% vs. 9% Basal diameter (mean ± SD): 10.6 ± 4.3 vs. 9.9 ± 4.5 Thickness (mean ± SD): 5.5 ± 6.1 vs. 6.1 ± 10			
Sikuade 2015 Retrospective cohort study *Moderately High* United Kingdom	191	**PBT (n=106)** insertion of tantalum markers performed under general anaesthesia; total dose of 58.4 Gy (53.1 Cobalt Gray equivalent) in four daily fractions **Stereotactic radiosurgery (n=85):** retrobulbar	**Inclusion:** uveal melanoma, treated between 2001 and 2011 **Exclusion:** nodal or metastatic disease, incomplete staging information including basal diameter and tumor thickness, or received surgery or chemotherapy	PBT vs. Stereotactic radiotherapy Mean age: 57 years (median 59, range 24 to 82) vs. 63 years (median 64, range 17 to 87), p=0.002 Male: 59% vs. 67% Left eye: 53% vs. 56% Right eye: 47% vs. 44% Mean basal diameter: 11.2 mm (median 11, range 3.6 to 20.8) vs. 9.6 mm (median 9.8, range 3.6 to 17.6), p=0.09	**PBT:** mean 34 mos. (median 29, range 7 to 95) **Stereotactic radiotherapy:** mean 39 mos. (median 27, range 6 to 124) **% F/U:** CD‡	Visual acuity Complications	Funding NR Authors declare no COIs

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		anesthesia with or without placement of stay-sutures in the horizontal rectus muscles; MRI or CT guidance; dose of 35 Gy delivered via Gamma Knife in a single session		Mean thickness: 4.3 mm (median 4, range 1 to 11.6) vs. 3.9 mm (median 3.4, range 0.7 to 8.7) Mean distance of tumor to the optic disc: 2.9 mm (median 2, range 0 to 15) vs. 2.2 mm (median 0, range 0 to 18)			

CD = cannot be determined; CI = Confidence Interval; COI = Conflict of Interest; F/U = follow-up; Gy = Gray; mm = millimeter; NR = Not Reported; OS = Overall Survival; PBT = Proton Beam Therapy; RoB = Risk of Bias; SD = Standard Deviation; TSR = Trans scleral resection

*Follow-up and differential loss to follow-up cannot be determined (number of eligible patients and number of patients lost not provided; of the 242 patients with large uveal melanomas and treated with transscleral resection, 57.8% (140/242) were matched and followed)

†Follow-up and differential loss to follow-up cannot be determined. Out of 7821 patients with non-metastatic choroid melanoma 64% (4981/7821) had incomplete or missing data. After study eligibility exclusions for surgery, RT to non-involved eye, coding not related to brachytherapy or PBT, use of boost RT and systemic therapy (n=1616), 996 brachytherapy patients and 228 PBT patients (n= 1224) were included in the analysis. Of the 1224 patients deemed includable by the authors, patients were matched 1:1 by propensity score resulting in 226 patients per treatment arm

‡Follow-up and differential loss to follow-up cannot be determined (number of eligible patients and number of patients lost not provided)

Appendix Table M3. Detailed data abstraction: comparative studies of proton beam therapy in ocular cancers

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Cohort studies			
Böker 2018 N=140 matched-pairs **PBT (+TSR) (n=70; treated after 2004)) vs. Brachytherapy (+TSR) (n=70; treated from 1993 to 2004)** Retrospective cohort study *Moderately High* Germany	PBT vs. Brachytherapy **Recurrence rate (95% CI):** • *3-year*: 4% (1.2% to 17.8%) vs. 24.6% (15.8% to 37.1%), p<0.001 • *5-year*: 9.1% (2.9% to 27.3%) vs. 27.5% (17.8% to 41.1%), p<0.001 • *10*-year: 9.1% (2.8% to 27.3%) (3/70) vs. 36.5% (20.7% to 59.1%) (18/70); HR ~4 (95% CI NR), aHR 7.69 (95% CI 2.22 to 26.06) for brachytherapy, p<0.001 *Overall recurrence rate*: 24.3% (14.0% to 40.1%) (total of 21 tumor recurrences) • *3-year overall*: 14.8% (9.5% to 22.6%) • *5-year overall*: 18.6% (12.0% to 28.9%) **Metastasis rate (95% CI):** • *3-year*: 23.2% (5.6% to 37.1%) vs. 13.2% (6.8% to 24.9%), p=NS • *5-year*: 31.8% (20.7% to 46.8%) vs. 30.3% (18.3% to 47.5%), p=NS • *10*-year: 40.1% (26.6% to 58.6%) (19/70) vs. 56.9% (34.9% to 80.8%) (18/70); aHR 0.951 (95% CI 0.48 to 1.86) for PBT, p=0.884 *Overall metastasis rate*: 54.4% (35.7% to 75.4%) (total of 37 metastasis) • *3-year overall*: 18.5% (12.6% to 26.9%) • *5-year overall*: 30.1% (22.3% to 41.7%)	PBT vs. Brachytherapy **Visual acuity (logMAR), median (IQR)** • *Baseline*: 0.4 (0.2 to 0.7) vs. 0.3 (0.1 to 0.7), p=0.031 • *1 year*: 0.8 (0.5 to 1.3) vs. 1.5 (IQR 1–2), p<0.001 • *2 years:* 1.2 (IQR 0.8–1.5) vs. 0.8 (IQR 0.4–1.2), p<0.001 • *3-5 years*: PBT significantly worse than brachytherapy (p= 0.007, 0.036, 0.011) • *6-7 years*: PBT worse than brachytherapy but difference not statistically significant (p=0.074 and 0.412) **Enucleation** 8.5% (6 eyes) vs. 15.7% (11 eyes), p=0.196	PBT vs. Brachytherapy Complications • Rubeosis of the iris: 1.4% (1/70) vs. 0% (0/70), p=0.316 • Neovascular glaucoma: 1.4% (1/70) vs. 1.4% (1/70)

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Lin 2017 N=1224 overall; 452 propensity score-matched cohort **PBT (n=228 overall, 226 matched cohort) vs. Brachytherapy (n=996 overall, 226 matched cohort)** Retrospective cohort study (National Cancer Database) *Moderately High* USA	PBT vs. Brachytherapy **OS (95% CI)** <u>*Overall population*</u>: 2-year OS: 92% (NR) vs. 96% (NR) 5-year OS: 54% (NR) vs. 81% (NR), p<0.001 On multivariate analysis, the following were associated with increased risk of mortality: • older age (HR 1.05, 95% CI 1.04 to 1.07, p<0.001) • larger tumor diameter (12-18 mm, HR 2.25, 95% CI 1.54 to 3.27, p<0.001; >18 mm, HR 3.56, 95% CI 1.25 to 10.1, p=0.017) • treatment at academic facility (HR 2.07) • protons (HR 1.91, 95% CI 1.24 to 2.95), p=0.003 <u>*Propensity score-matched cohort*</u>: 2-year OS: 93% (NR) vs. 97% (NR) 5-year OS: 51% (NR) vs. 77% (NR), p=0.008 On multivariate analysis, the following were associated with increased risk of mortality: • older age (HR 1.06, 95% CI, 1.03 to 1.09), p<0.001 • larger tumor diameter (12-18 mm, HR 2.48, 95% CI 1.40 to 4.42, p=0.002; >18 mm, HR 6.41, 95% CI 1.45 to 28.35, p=0.014) protons (HR 1.89, 95% CI 1.06 to 3.37) p=0.031	NR	NR
Sikuade 2015 N=191 **PBT (n=106) vs.**	PBT vs. Stereotactic radiosurgery **Proportion Surviving:** 87% (92/106) vs. 84% (71/85)	PBT vs. Stereotactic radiosurgery **Enucleation**: 1.9% (2/106) vs. 2.4% (2/85)	PBT vs. Stereotactic radiosurgery **Radiation retinopathy:** 30% (31/106) vs. 24% (20/85)

Study Intervention/ Comparator, Design, RoB, Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Stereotactic radiosurgery (n=85) Retrospective cohort study *Moderately High* United Kingdom The following were significantly associated with an increased likelihood of severe visual loss when treated with stereotactic radiosurgery compared with PBT: • tumor touching the optic nerve, p=0.008 • tumor located >3mm from the fovea, p=0.04 (no difference for the following: tumors located >0.5mm from optic disc; tumors situated beneath or touching the fovea)	**Mortality:** 13% (14/106) vs. 16% (14/85) *due to metastatic disease*: 6.7% (7/106) vs. 8.2% (7/85) [50% of all deaths in both groups; 7/14) **Visual acuity ≥6/60:** 55% (58/106) vs. 33% (28/85) **Significant visual loss** (i.e., loss of ≥3 Snellen lines): 45% (48/106) vs. 65% (55/85) **Eye retention rate**: 95.3% (101/106) vs. 97.6% (83/85) **Local tumor recurrence**: 2.8% (3/106) vs. 0% (0/85); all underwent secondary enucleation		**Optic neuropathy:** 13% (14/106) vs. 28% (23/85) **Rubeotic glaucoma:** 4.7% (5/106) vs. 11% (9/85) *Requiring enucleation:* 1.9% (2/106) [40% (2/5) with rubeotic glaucoma] vs. 2.4% (2/85) [22% (2/9) with rubeotic glaucoma]

CI = Confidence Interval; HR = Hazard Ratio; IQR = Interquartile range; mm = millimeter; NR = Not reported; NS = Not significant; OS = Overall Survival; PBT = Proton Beam Therapy; RoB = Risk of Bias; TSR = Transscleral resection

APPENDIX N. Pediatric

Appendix Table N1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in pediatric bone cancers

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Weber 2017 RoB: High Retrospective Case Series Switzerland Funding: NR COI: None --- Also provides subpopulation data on male vs female, etc…	**Diagnosis**: Pediatric Bone and soft tissue sarcoma (Ewing sarcoma) **Indication**: Curative Intent	N=38 Median Age (range): 9.9 years (0.4-38.9) Male: 63.2% **Primary Tumor Sites**: - spine, 44.7%; - pelvis-sacrum, 18.4%; - skull, 13.2%; - paranasal sinus/nasal cavity, 10.5%; - lower limb, 5.3%; - skull-base, 5.3%; - abdomen, 2.6% **Tumor Characteristics**: Soft tissue extension, 44.7% Skeletal, 81.6%; Extraskeletal, 18.4% Presenting with metastases at diagnosis, 11% (4/38)	**PBT** Delivered using PBS paradigm **Median PBT Dose (Range)**: 54.9 Gy (RBE) (45.0–69.6) delivered in daily fractions of 1.8-2.0 Gy (RBE) **Additional Treatments in conjunction with PBT**: Surgery, chemotherapy, and PBT, 47.4%; Biopsy, chemotherapy, and PBT, 52.6%; Anesthesia, 34%	**Median F/U (range)**: 49.6 (9.2 to 131.7) months	**Primary Outcomes** **OS (95% CI)** • 5-year: 83.0% (69.1% to 96.9%) **LC (95% CI)** • 5-year: 81.5% (68.0% to 95.0%) **Metastasis-free Survival (95% CI)** 5-year: 76.4% (60.1% to 92.7%)	*Toxicity Grading Criteria*: CTCAE v.4.0 **Acute Toxicity, % (n/N)** • Most common acute side effect was grade 1 and 2 skin erythema and mucositis (Actual data NR) • No acute toxicity > grade 2 was observed **Late Toxicity, % (n/N)** • All late toxicity: 29 events in 20 patients [52.6% of patients had at least 1 late toxicity event] - Grade 1: 16 events - Grade 2: 11 events - Grade 3: 2 events • Residual alopecia - Grade 1: 13.8% (4/29) - Grade 2: 10.3% (3/29) • Hyperpigmentation - Grade 1: 10.3% (3/29) • Kyphoscoliosis - Grade 1: 10.3% (3/29) - Grade 3: 3.4% (1/29) • Kidney function impairment - Grade 1: 10.3% (3/29) • Chronic nasal repletion - Grade 1: 3.4% (1/29) • Lung fibrosis

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						- Grade 1: 3.4% (1/29) • Dry eye syndrome - Grade 1: 3.4% (1/29) • Endocrine dysfunction - Grade 2: 10.3% (3/29) - Grade 3: 3.4% (1/29) • Bone growth impairment: - Grade 2 10.3% (3/29) • Esophageal stricture - Grade 2: 3.4% (1/29) • Lymphedema - Grade 2: 3.4% (1/29) **Secondary Malignancies, % (n/N)**: 0% (0/38) **5-year TFS (95% CI)** • *All patients:* 90.9% (78.9–100.0)

CI = Confidence Interval; F/U = Follow-up; LC = Local Control; NR = Not reported; OS = Overall Survival; PBT = Proton Beam Therapy; TFS = Toxicity Free Survival

Appendix Table N2. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in pediatric brain, spinal, and paraspinal cancers

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Giantsoudi 2016 RoB: High Retrospective Case Series USA Funding: This study was supported by National Institutes of Health/National Cancer Institute award P01CA021239 and Federal Share of program income earned by Massachusetts General Hospital on C06 CA059267, Proton Therapy Research and Treatment Center. RVS was supported by the Doris Duke Charitable Foundation. COI: NT's spouse is a member of the medical advisory	**Diagnosis**: Pediatric Brain (medulloblastoma) **Indication:** Curative Intent	N=111 Median age (range): 7 years (2.7 to 22) Male: 59% Caucasian: 86% **Primary Tumor Sites:** Brain, 100% **Tumor Characteristics:** Classic, 73%; Anaplastic, 16%; Desmoplastic, 9%; Anaplastic and desmoplastic, 1%; Nodular, 1% **Risk classification: High, 32%; Standard, 68%**	**PBT** Craniospinal passively scattered PBT followed by involved field boost (n=69) or whole posterior fossa boost (n=42) **PBT Dose range: 18-36 Gy(RBE)** **Boost field PBT dose range: 50.4-59.4 Gy(RBE)**	**Median F/U (range)**: 50.4 (NR) months	NR	*Toxicity Grading Criteria*: NR **Patients with CNS Radiation Injury, % (n/N):** 3.6% (4/111) • who required a shunt: 0% (0/4) • progressed to chemotherapy: 100% (4/4) • developed acute renal failure during chemotherapy: 25% (1/4) **Radiation Injuries in CNS injury patients, % (n/N):** • Grade 3 (recovered later): 50% (2/4) • Grade 4 (remained paraplegic and dependent on tracheostomy and feeding tube): 25% (1/4) • Developed grade 2 cervical injury (later fully recovered): 25% (1/4)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
board of ProCure. All other authors report no conflicts of interest. --- Also provides data related to LET (linear energy transfer) and RBE weighted dose calculations per patient (tables and in text) for CNS radiation injury and 5-year cumulative incidence of CNS radiation injury						**Post-treatment Adverse Events in CNS injury patients:** • Osteonecrosis of the right temporal bone at 16 mos followed by brainstem necrosis at 6 years and 8 months: 25% (1/4) • Additional brainstem injury at 27.4 months: 25% (1/4) **Patients who showed radiographic treatment change but developed no symptoms (n=111): 5.6% (6/107)** **5-year Cumulative Incidence of CNS radiation injury:** • grade 2 to 4: 3.6% • grade 3+ : 2.7% **5-year Cumulative Incidence of brainstem radiation injury or necrosis: 2.7%**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Kamran 2018 RoB: High Prospective Case Series USA Funding: Supported in part by award P01CA021239 from the National Cancer Institute; the Federal share of program income earned by Massachusetts General Hospital on C06 CA059267, Proton Therapy Research and Treatment Center; a grant from the Children's Cancer Recovery Foundation; and a grant from the Susan McDaniel Brain Tumor Fund. COI: Torunn I. Yock has received grants for the Pediatric Proton Consortium Registry from IBA, Protom, and Elekta for work performed	**Diagnosis**: Pediatric Brain (Medulloblastoma, 93.1%; PNET, 6.9%) **Indication**: Curative intent	**N=116** **Median Age: 7.6 years (range, 2.1 to 18.1)** **Male: 55%** **Primary Tumor Sites:** **Posterior fossa syndrome: 30% (30/116)** **Risk Classification:** **Standard: 66% (77/116);** **High:34% (39/116)**	**PBT**: NR **Median PBT Dose (Range)**: NR	**Median F/U (range)**: 60 (12 to 127.2) months	**Primary Outcomes** NR **Secondary Outcomes** **PedsQoL Total Core Score**: • *Child Report:* average 1.8 (95% CI, 1.2-2.4) point increase per year from average baseline of 65.9 • *Parent*-Proxy Report: average 2.0 (95% CI, 1.4-2.7) point increase per year from average baseline of 59.1 **PedsQoL Physical Score**: • *Child report:* average 3.3 (95% CI, 2.6-4.1) point increase per year from average baseline of 58.2 • *Parent-proxy report*: average 4.0 point (95% CI, 3.1-4.8) increase per year from average baseline of 49.9	NR

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
outside of the current study					**Psychosocial Score** • *Child report:* average 0.9 (95% CI, 0.5-1.5) point increase per year from average baseline of 70.8 • *Parent-proxy report*: average 0.8 point (95% CI, 0.2-1.4) increase per year from average baseline of 65.8	
Yock 2016 RoB: High Retrospective Case Series USA Funding: US National Cancer Institute and Massachusetts General Hospital COI: NJT's spouse owns stock options in ProCure. The other authors declare no competing interests. --- This study does subpopulation analysis	**Diagnosis**: Pediatric Brain, Spinal, Paraspinal (Medulloblastoma, 100% (59/59)) **Indication**: Curative Intent	**N=59** **Median Age: 6.6 years (IQR, 5.1-9.9)** **Male: 56%** **Tumor Characteristics:** - **Classic, (76% (45/59);** - **Desmoplastic or nodular variant, 10% (6/59);** - **Anaplastic or large cell variant, 14% (8/59);** - **Metastatic Disease, 5.1% (3/59)** **Primary Tumor Sites: NR** **Risk Classification: Standard, 66% (39/59);**	**PBT**: NR Use of photons for <20% radiation dose: 10% (6/59) **Median total PBT Dose (Range)**: NR **Additional Treatments in conjunction with PBT**: Shunt, 20% (12/59); Introductory Chemotherapy, 100% (59/59); Tumor Resection, 98% (58/59); Concurrent chemotherapy, 88.1%	**Median F/U (range)**: 84 (NR) months	**<u>Primary Outcomes</u>** **OS (95% CI)** • *5-year*: 83% (70% to 90%) • *7-year*: 81% (67% to 89%) **PFS (95% CI)** • *5-year:* 80% (67% to 88%) • *7-year:* 75% (61% to 84%) **Mortality, % (n/N)** • Disease-related: 20.3% (12/59) • All-cause: 22% (13/59) **<u>Secondary Outcomes:</u>** NR	*Toxicity Grading Criteria*: CTCAE v.3.0 [acute and late effects]; Pediatric Oncology Group ototoxicity scale (0–4) [ototoxicity] **<u>Cumulative Incidence of Ototoxicity (95% CI) (n=45 patients)</u>** • *3-year:* 12% (4%-25%) • *5-year:* 16% (6%-29%) **<u>Proportion of Patients Experiencing Grade 3-4 Hearing Loss (n=45)</u>***:* • *All patients:* 15.6% (7/45)

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on high vs. low risk, male vs. female, etc…		**Intermediate, 10% (6/39);** **High, 24% (14/24)**				- *Both ears:* 9% (4/45) - *One ear:* 6.7% (3/45) **<u>Cumulative incidence of any hormone deficiency (95% CI):</u>** • *3-year*: 27% (16%–39%) • *5-year*: 55% (41%–67%) • *7-year*: 63% (48%–75%) **<u>Cumulative incidence of growth hormone deficiency (95% CI):</u>** • *3-year*: 22% (12%–33%) • *5-year*: 46% (33%–59%) • *7-year*: 55% (40%–68%) **<u>Cumulative incidence of thyroid deficiency (95% CI):</u>** • *3-year*: 12% (5%–22%) • *5-year*: 21% (11%–32%) • *7-year*: 26% (15%–38%)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						Cumulative incidence of adrenal or cortisol deficit (95% CI): • *3-year*: 5% (1%–13%) • *5-year*: 9% (3%–17%) • *7-year*: 9% (3%–17%) **Cumulative incidence of sex hormone deficit (95% CI):** • *3-year*: 3% (1%–11%) • *5-year*: 3% (1%–11%) • *7-year*: 3% (1%–11%) **Acute Toxic Effects (n=59)** • All acute toxic effects -*Grade 1*: NR -*Grade 2:* 190 events in 59 patients -*Grade 3:* 55 events in 39 patients -*Grade 4:* 12 events in 12 patients

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						• Alopecia -*Grade 2*: 100% (59/59) • Fatigue -*Grade 1*: 37% (22/59) -*Grade 2*: 31% (18/59) -*Grade 3*: 8% (5/39) • Anorexia -*Grade 1*: 24% (14/59) -*Grade 2*: 24% (14/59) -*Grade 3*: 12% (7/59) • Nausea -*Grade 1*: 25% (42/59) -*Grade 2*: 7% (7/59) -*Grade 3*: 3% (2/59) • Vomiting -*Grade 1*: 27% (16/59) -*Grade 2*: 24% (14/59) -*Grade 3*: 3% (2/59) • Radiation dermatitis (scalp or back) -*Grade 1*: 44% (75/59)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						-*Grade 2*: 20% (12/59) -*Grade 3*: 3% (2/59) • Oesophagitis, pharyngitis, or dysphagia -*Grade 1*: 15% (9/59) -*Grade 2*: 15% (9/59) -*Grade 3*: 5% (3/59) • Headache -*Grade 1*: 22% (13/59) -*Grade 2*: 7% (4/59) • Weight loss -*Grade 1*: 10% (6/59) -*Grade 2*: 7% (4/59) • Neutropenia -*Grade 1*: 2% (1/59) -*Grade 2*: 37% (23/59) -*Grade 3*: 32% (19/59) -*Grade 4*: 8% (5/59) • Anaemia (haemoglobin) -*Grade 1*: 17% (10/59)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						-*Grade 2*: 47% (28/59) -*Grade 3*: 5% (3/59) • Lymphopenia -*Grade 2*: 10% (6/59) -*Grade 3*: 17% (10/59) -*Grade 4*: 12% (7/59) • Thrombocytopenia -*Grade 1*: 17% (10/59) -*Grade 2*: 2% (1/59) -*Grade 3*: 3% (2/59) **<u>Late Toxic Effects (n=58)</u>** • All patients -*Grade 1*: NR -*Grade 2*: 26 events in 19 patients -*Grade 3*: 8 events in 7 patients -*Grade 4*: 1 event in 1 patients • Stroke -*Grade 4*: 2% (1/58) • Cataracts

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						- *Grade 1*: 19% (11/58) - *Grade 2*: 2% (1/58) - *Grade 3*: 8% (4/58) • Obesity - *Grade 2*: 10% (5/58) - *Grade 3*: 4% (2/58) • Alopecia - *Grade 1*: 27% (16/58) - *Grade 2*: 7% (4/58) • CNS brainstem injury - *Grade 3*: 2% (1/58) • Ataxia - *Grade 1*: 41% (24/58) - *Grade 2*: 8% (4/58) • Headaches - *Grade 1*: 12% (7/58) - *Grade 2*: 7% (4/58) • Dysphasia - *Grade 1*: 5% (3/58) - *Grade 2*: 4% (2/58) • Chronic fatigue

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						- *Grade 1*: 9% (5/58) - *Grade 2*: 4% (2/58) • Depression - *Grade 1*: 3% (2/58) - *Grade 2*: 3% (2/58) • Scoliosis - *Grade 1*: 7% (4/58) - *Grade 2*: 2% (1/58) • Truncal muscle weakness - *Grade 2*: 2% (1/58) • Nystagmus - *Grade 1*: 17% (10/58) **Mean Change per year in Full-scale IQ score (95% CI)**: -1.5 (-2.1 to -0.9); p<0.0001 **Mean Change per year in Verbal Comprehension Index score (95% CI)**: -1.3 (-2.0 to -0.7); p<0.0001 **Mean Change per year in Perceptual**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						reasoning index score (95% CI): -0.4 (-1.0 to 0.3); p=0.249 **Mean change per year in working memory score (95% CI):** -0.8 (-1.8 to 0.3); p=0.169 **Mean change per year in processing speed score (95% CI):** -2.4 (-3.2 to -1.6); p<0.0001
Sethi 2014 RoB: High Retrospective Case Series USA Funding: Supported by the Doris Duke Charitable Foundation (R.V.S.). Research was supported by the National Cancer Institute of the National Institutes of Health under Award Number P01CA021239	**Diagnosis**: Pediatric Brain, Spinal, Paraspinal (Medulloblastoma) **Indication**: Curative Intent	**N=109** **Median Age: 7.4 years (2.2 to 22.7)** **Male: 58.7%** **Primary Tumor Sites: NR** **Tumor Characteristics:** **Tumor Type:** - **Classic, 74.3% (81/109);** - **Anaplastic, 15.6% (17/109);** - **Desmoplastic, 9.2%(10/109);**	**PBT**: Boost - Involved-field only, 64.2% (70/109) - Whole posterior fossa, 35.8% (39/109) **Median total PBT Dose (Range)**: 23.4 Gy (RBE) (18 to 36) **Additional Treatments in conjunction with PBT**: **Gross total Resection, 73.4% (80/109);** **Subtotal Resection, 25% (27/109);**	**Median F/U (range)**: 38.8 (1.4 to 119.2) months	**Primary Outcomes** **Relapse/Progression (Treatment failure)**: 14.7% (16/109) **Mortality, % (n/N)** • Disease-related: 11% (12/109) **Secondary Outcomes** NR	NR

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
and the Federal Share of program income earned by Massachusetts General Hospital on C06 CA059267, Proton Therapy Research and Treatment Center. COI: N.J.T.'s spouse is on the medical advisory board of ProCure. All other authors deny any real or potential conflicts of interest.		- **Anaplastic plus desmoplastic, 0.9%(1/109)** **Metastases at diagnosis: 18.3% (20/109)** **Risk Classification: Standard: 67.9% (74/109)** **High: 32.1% (35/109)**	**Biopsy only, 1.8% (2/109)**			
Ares 2016 RoB: High Prospective Case Series Switzerland Funding: NR COI: NR	**Diagnosis**: Pediatric Brain (Ependymoma) **Indication**: Curative Intent	**N=50** **Median Age (range): 2.6 years (1.1-15.2)** **Male: 72%** **Primary Tumor Sites: Infratentorial, 72% (36/50); Supratentorial, 28% (14/50)** **Presence of residual disease following tumor resection (prior to PBT): 34% (17/50) [Residual tumor ≥1.5 cc 18% 9/50)]**	**PBT** PBS by using energy-degraded beams from the 590-MeV cyclotron until 2005 and subsequently the dedicated 250-MeV cyclotron **Median PBT Dose (Range)**: 59.4 Gy (RBE) (54–60) delivered in 1.8–2 Gy (RBE) per fraction	**Mean F/U (range)**: 43.4 (8.5 to 113.7) months	**<u>Primary Outcomes</u>** **Actuarial OS (mean ± SD)** • 5-year: 84% ± 6.8% **Mortality, % (n/N)** • Disease related: 10% (5/50) **Actuarial LC (mean ± SD)** • 5-year: 78.8% ± 7.5% **Proportion of patients experiencing in-field**	*Toxicity Grading Criteria*: CTCAE v.4.0 **<u>Late Toxicity, % (n/N)</u>** • All events: 48% (24/50) of patients had ≥1 event [33 events] - *Grade 1*: 8% (19/50) [24 events] - *Grade 2 AE*: 12% (6/50) [6 events] - *Grade ≥3 AE*: 6% (3/50) [3 events] • Unilateral reduced hearing

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		Risk Classification: Grade 3, 92% (46/50)	**Additional Treatments in conjunction with PBT**: Surgical tumor resection prior to PBT, 100% (50/50); Second look surgery prior to PBT, 11% (22/50); Postoperative chemotherapy before PBT, 86% (43/50); Patients younger than 5 received general anesthesia, 86% (44/50);		**local failure, % (n/N):** 14% (7/50)* • *Infratentorial Ependymoma*: 16.7% (6/36) • *Supratentorial Ependymoma*: 7.1% (1/14) [This 1 patient developed supratentorial metastasis] **Proportion of patients presenting with macroscopic residual disease prior to PBT that experienced disease progression following PBT (n=17)** • *Complete Response*: 76% (13/17) • *Stabilization or partial response within a mean of 19 months*: 17.6% (3/17) • *Developed progressive disease immediately* after PBT: 5.8% (1/17) **<u>Secondary Outcomes</u>** NR	- Grade 1: 2% (1/50) • Concentration problems - *Grade 1*: 2% (1/50) • Asymptomatic transient MRI changes of leukoencephalopathy - *Grade 1*: 18% (9/50) • Permanent growth hormone deficiency requiring replacement - *Grade 2*: 6% (3/50) • Permanent central hypothyroidism requiring replacement - *Grade 2*: 6% (3/50) • Definitive deafness - *Grade ≥3*: 4% (2/50) • Fatal brainstem necrosis - *Grade ≥3*: 2% (1/50) **<u>Secondary Malignancies, % (n/N)</u>**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						• *All patients:* 0% (0/50)
De 2018 RoB: High Retrospective Case Series USA Funding: Supported by the National Institutes of Health/National Cancer Institute Cancer Center Support Grant (P30 CA008748). This work is also supported by a gift from Jack and Susan Rudin and the Louis and Rachel Rudin Foundation. COI: None	**Diagnosis**: Pediatric Brain (medulloblastoma 59% (34/58); Pineoblastoma, 10% (6/58); Neuroblastoma, 9%(5/58); Other, 22% (13/58)) **Indication**: Curative Intent	**N=58** **Median Age (range): 8 years (2-18)** **Male: 69%** **Primary Tumor Sites: NR** **Risk Classification: NR**	**PBT** Proton CSI Multiple beam approaches were used to treat the whole brain, including opposed laterals, posterior obliques, and a single posteroanterior portal. Although utilizing PBS, a gradient structure allowing for a gradual match line was used in lieu of feathered match lines. Whole vertebral body spinal target volume, 67%; Partial vertebral body spinal target volume, 33% **PBT Dose**: Most common doses were 23.4, 36, and 18 Gy(RBE) used for 40%, 36%, and 16% of patients, respectively, delivered in 1.8 Gy(RBE) fractions	**Median F/U (range)**: 19 (2 to 58) months		**<u>Among patients with radiographic evaluation</u>**: 64% (37/58) • *Straightening of cervical lordosis*: 4% • *Mild midthoracic scoliotic curvature*: 2%) • *Clinical or radiographic evidence of lordosis or scoliosis*: 0% **<u>Among patients with Cobb angle evaluation</u>**: 28% (16/58) • Cobb angle before PBT vs. after PBT: 2.7 degrees (range, 0.7 to 5.9) vs. 3.8 degrees (range, 1.2 to 9.4); p<0.01 No patient met the scoliosis diagnostic criterion of a Cobb angle of ≥10 degrees at any time **<u>Among patients with growth curve</u>**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
			Additional Treatments in conjunction with PBT: Boost RT to ≥ 1 sites was additionally given to all patients with cumulative median dose 54 Gy(RBE) (range, 18 to 59.4 Gy[RBE])			**evaluations**: 64%(37/58) • Median height percentile and z-score before PBT vs. median height percentile and z-score after PBT: 43.2% (range, 0.3% to 91.5%) and −0.3 (range, −2.8 to +1.2) vs. 24.4% (range, 0.3% to 85.8%) and −0.8 (range, −2.9 to +1.1); p<0.001 (adjusted for age)
Gentile 2018 RoB: High Retrospective Case Series USA Funding: NR COI: None	**Diagnosis**: Pediatric Brain **(Medulloblastoma, 62.5% (135/216); Anaplastic Medulloblastoma, 8.8% (19/216); Ependymoma, 13.9% (30/216); Anaplastic Ependymoma, 12.0% (26/216); ATRT, 2.8% (6/216))** **Indication**: Curative Intent	**N=216** **Median Age (range): 6.6 years (0.5-23.1)** **Male: 58.3%** **Primary Tumor Sites: Posterior Fossa, 100% (216/216)** **Risk Classification: NR**	**PBT** Conformal PBT **Median PBT Dose Range**: 54 Gy RBE (range, 46.8-59.4) in fractions of 1.8 Gy(RBE) **Additional Treatments in conjunction with PBT**: Surgery: GTR, 70.4% NTR, 16.2% STR, 12.0% Biopsy only, 1.4%; Shunt placement: 25.5%;	**Median F/U (range)**: 50.4 (1.2 to 183.6) months	**Primary Outcomes** **OS (95% CI)**: • 3-year: 95.0% (NR) • 5-year: 87.3% (NR) **PFS (95% CI)**: • 3-year: 87.2% (NR) • 5-year: 82.6% (NR) **Mortality, % (n/N)** • All-cause: 8.3% (18/216) **Secondary Outcomes** NR	**Brain Stem Injury (Late Toxicity)** • *All patients:* 2.3% (5/216) - Grade 2: 20% (1/5) - Grade 3: 60% (3/5) - Grade 4: 20% (1/5) • *Medulloblastoma*: 1.9% (3/159) • *Ependymoma*: 3.6% (2/56) • *ATRT*: 0% (0/6) **5-year cumulative incidence of brain stem injury** • *All patients:* 2.0% (95% CI, 0.7%-4.8%)†

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
			Posterior fossa boost: 22.2%; Involved-field boost: 77.8%; Treatment with chemotherapy: 83.3% Methotrexate, 8.3%; Intrathecal chemotherapy, 2.8%; Concurrent chemotherapy, 57.9%; High-dose chemotherapy with stem cell rescue, 13.4%; Adjuvant chemotherapy, 74.1%			
Greenberger 2014 RoB: High Retrospective Case Series USA Funding: NR COI: N. J. Tarbell has a spouse on the Medical Advisory	**Diagnosis**: Pediatric Brain (primary low-grade glioma) **Indication**: Curative Intent	**N=32** **Median Age: 7.4 years (range, 0.8-20.4)** **Male: 53.1%** **Primary Tumor Sites: Infratentorial: 34.4% (11/32); Supratentorial 56.3% (18/52); Spinal: 9.4% (3/32)** **Tumor Characteristics: Neurofibromatosis type 1: 6.3%**	**PBT** Protons only: 71.9% (23/32); Protons and photons: 28.1% (9/32) **Median PBT Dose**: 52.2 Gy (RBE) (range, 48.6-54 Gy (RBE)) at a median fraction dose of 1.8 Gy (RBE) **Additional Treatments in conjunction with PBT:**	**Median F/U (range)**: 88.8 (NR) months	**Primary Outcomes** **OS (95% CI)**: • 8-year: 100% (NR) **PFS (95% CI)**: • 8-year: 82.8% (NR) • 6-year: 89.7% (NR) **Secondary Outcomes:** NR	**Development of moya-moya disease requiring pial synangiosis surgery**: • *All patients: 6.3%* (2/32) [Both patients presented with type 1 neurofibromatosis prior to treatment] **Visual Function for patients with intracranial tumors**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Board of Procure and has stock options (value $0). The authors report no other conflict of interest. --- Also does subpopulation analysis on neurocognitive outcomes based on age, high/low risk, etc…		**Risk Classification:** **High risk (n=15);** **Intermediate-risk (n=4);** **Low-risk (n=10)** **WHO grade I (pilocytic astrocytoma): 59.4% (19/32);** **WHO grade 2: 18.8% (6/32);** **Low grade (not otherwise specified): 6.3% (2/32)**	Surgery - None: 15.6% - Biopsy only: 18.8% - 1 resection: 53.1% - ≥2 resections: 12.5% - Shunt(s): 18.8% Chemotherapy: 84.4% (27/32)			**Decreased Acuity (n=18 patients)** • *Improvement*: 27.8% (5/18) • *Stable*: 55.6% (10/18) • *Deterioration*: 16.7% (3/18) **Optic Nerve pallor/atrophy (n=18)** • *Improvement:* 5.6% (1/18) • *Stable*: 88.9% (16/18) • *Deterioration*: 5.6% (1/18) **Visual Field Deficit (n=29)** • *Improvement:* 3.4% (1/29) • *Stable*: 93.1% (27/29) • *Deterioration*: 3.4% (1/29) **Nystagmus (n=29)** • *Improvement:* 0% (0/29) • *Stable:* 93.1% (27/29) • *Deterioration:* 6.9% (2/27) **Ptosis (n=29)** • *Improvement:* 0% (0/29)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						• *Stable:* 96.6% (28/29) • *Deterioration:* 3.4% (1/29) **Afferent pupillary defect (n=29)** • *Improvement: 0% (0/29)* • *Stable: 93.1% (27/29)* • *Deterioration:* 6.9%(2/29) **Impaired upgaze** • *Improvement: 0% (0/29)* • *Stable: 96.6% (28/29)* • *Deterioration:* 3.4%(1/29) **Diplopia** • *Improvement: 0% (0/29)* • *Stable: 96.6% (28/29)* • *Deterioration:* 3.4%(1/29) **Esophoria/exophoria** • *Improvement: 0% (0/29)* • *Stable: 96.6% (28/29)* • *Deterioration:* 3.4%(1/29)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						<u>Endocrine Function for patients with intracranial tumors, %</u> [Data are estimated from Figures 3B and 3C] • *Any Endocrine Deficiency*: 50% • *Growth Hormone Deficiency:* 60% • *Hypothyroidism:* 45% • *Cortisol Insufficiency:* 23% • *Testosterone Deficency:*18% • *Elevated Prolactin:* 12% • *Diabetes Insipidus:* 10% • *Precocious Puberty:* 5% **<u>Mean change ± SD in IQ from baseline to follow-up (n=11):</u>** -0.7 ± 9.2; p=0.80 **<u>Mean change ± in verbal comprehension Index from baseline to follow-up (n=12)</u>**: -0.5 ± 11.7; p=0.95

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						Mean change ± in Perceptual Reasoning Index from baseline to follow-up (n=12) -0.17 ± 9.8; p=0.95
Hall 2018 RoB: High Retrospective Case Series USA Funding: NR COI: J.A.B. received travel reimbursement and honorarium from IBA for an educational program. D.J.I. received travel reimbursement from IBA for an educational program.	**Diagnosis**: Pediatric Brain (Craniopharyngioma, 21% (135/644); Ependymoma, 21% (135/644); Low-grade glioma, 20% (131/644); Medulloblastoma/PNET, 13% (80/644); Ewing/RMS/NRSTS, 11% (73/644); Other, 14% (90/644)) **Indication**: Curative Intent	**N=644** **Median Age: 7.6 years (0.7-21.8)** **Male: 55%** **Primary Tumor Sites: Sellar/suprasellar: 42%; Thalamic/basal ganglia: 11%; Hemispheric/lateral ventricles: 20%; Posterior fossa: 27%** **Risk Classification: NR**	**PBT**: NR **PBT Dose**: 54 CGE (range, 25.2-75.6) **Additional Treatments in conjunction with PBT:** Chemotherapy: 50.5% (325/644); Gross/Near Total Resection: 39% (251/644); Subtotal resection/biopsy: 56% (363/644)	**Median F/U (range)**: 36 (1.2 to 115.2) months	NR	**3-year cumulative rate of any vasculopathy‡**: 6.4% (95% CI, NR) **Proportion of patients experiencing vasculopathy by tumor type**: • *Craniopharyngioma*: 19.3% (26/135) • *Medulloblastoma/ pancreatic neuroendocrine tumor*: 8.8% • *Ependymoma*: 5.9% (8/135) • *Skull base sarcomas*: 5.5% (4/73); • *Low-grade gliomas*: 3.1% (4/131) **3-year cumulative rate of serious vasculopathy**: 2.6% **Development of asymptomatic vessel narrowing**: 4.7% (30/644)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						<u>3-year rates of cerebrovascular accidents</u>: 0.5% **<u>Proportion of patients that developed a cerebrovascular accidents</u>**: 2% (7/344) **<u>3-year rate of transient ischemic attacks</u>**: 1.2% **<u>Proportion of patients requiring revascularization surgery</u>:** 1.2% (4/344) **<u>Proportion of patients developing an asymptomatic aneurysm</u>**: 2% (7/344)
Indelicato (2014) RoB: High Prospective Case Series USA Funding: NR	**Diagnosis**: Pediatric Brain and Skull-base Tumors (Ependymoma, 23.3% (73/313); Craniopharyngioma, 21.7% (68/313); Low-grade glioma, 21.2% (66/313); Medulloblastoma/primitive	**N=313** **Median Age: 5.9 years (range, 0.5-17.9)** **Male: 53.7%** **Primary Tumor Sites: Supratentorial, 52.4% (164/313); Posterior fossa, 36.4% (114/313); Skull base, 11.2% (35/313)**	**PBT** Passive Scatter Beam, 100% (313/313); Combined photon therapy: 9.9% (31/313) **PBT Dose Range**: NR **Additional Treatments in conjunction with PBT:**	**Median F/U (range)**: 24 (NR) months	**<u>Primary Outcomes</u>** **OS (95% CI)**: 2-year: 90.5% (NR) **<u>Secondary Outcomes</u>** NR	*Toxicity Grading Criteria*: CTCAE v. 4.0 **<u>Proportion of patients experiencing brainstem toxicity</u>**: • *All patients, any grade:* 3.5% (11/313) - *Grade 2:* 2.2% (7/313)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
COI: None --- Does minimal subpopulation analysis for old vs. young, tumor location etc…	neuroectodermal tumor, 12.1% (38/313); Parameningeal rhabdomyosarcoma 4.2%, (13/313); Other, 17.6% (55/313)) **Indication**: Curative Intent	**Risk Classification: NR**	Gross total or near total resection: 34.8% (109/313); Extended or permanent shunting: 23.3% (73/313); Chemotherapy: 49.5% (155/313); Intrathecal or high-dose intravenous Methotrexate: 15.3% (48/313);			- *Grade 3:* 0.3% (1/313) - *Grade 4:* 0.6% (2/313) - *Grade 5:* 0.3% (1/313) **2-year cumulative incidence brainstem injury**: • *Any*: 3.8% ± 1.1% • *Grade 3+*: 2.1% ± 0.9%
Indelicato (2017) [Crossover with patients in Indelicato 2018] RoB: High Retrospective Case Series USA Funding: NR COI: None	**Diagnosis**: Pediatric Brain and Spinal Tumors (Ependymoma, 34% (57/166) Low-grade glioma, 33% (54/166); Craniopharyngioma, 27% (45/166); Germ cell tumor, 2% (3/166); Meningioma, 2% (3/166); Medulloblastoma/ PNET, 1% (2/166) Pituitary adenoma, 1% (2/166) **Indication**: NR	**N=166** **Median Age: 7 years (range, 1-9)** **Male: 54%** **Primary Tumor Sites:** • **Ependymoma subgroup (n=57)** - **Supratentorial: 32% (18/57)** - **Posterior fossa: 63% (36/57)** - **Spinal: 5% (3/57)** • **Low grade glioma (n=54)** - **Supratentorial: 65% (35/54)** - **Brainstem: 17% (9/54)** - **Cerebellum: 9% (5/54)** - **Spinal: 9% (5/54)**	**PBT** NR **Median PBT Dose (Range)**: 54 Gy (RBE) (52.2–54) [Craniopharyngioma subgroup only] **Additional Treatments in conjunction with PBT:** Chemotherapy: 13.3% (22/166); Anesthesia: 30%	**Median F/U (range)**: 31.2 (2.4 to 91.2) months **Loss to follow-up**: 0%	**Primary Outcomes** **3-year OS (95% C))** • *All patients:* 96% (NR) • *Ependymoma subgroup:* 92% (NR) • *Low*-grade glioma subgroup: 95% (NR) • *Craniopharyngioma subgroup:* 100% (NR) **3-year PFS (95% CI)** • *All patients:* 87% (NR) • *Ependymoma subgroup:* 77% (NR) • *Low*-grade glioma subgroup: 87% (NR)	**Serious Late Toxicity, % (n/N)** • *New-onset seizures*: 1.8% (3/166) • *Symptomatic (Consisting of stroke or transient ischemic event) vasculopathy* : 1.8% (3/166) • *Symptomatic brainstem necrosis*: 0.6% (1/166) • *Symptomatic peritumoral edema*: 0.6% (1/166) • *Hearing loss*: 1.8% (3/166) **Proportion of patients requiring new endocrine replacement, % (n/N)**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		Tumor Characteristics: **Neurofibromatosis: 1.2% (2/166)** **Risk Classification:** • **Ependymoma subgroup (n=57)** - **Grade 1: 5% (3/57)** - **Grade 2: 32% (18/57)** - **Grade 3: 63% (36/57)** • **Low grade glioma subgroup (n=54)** - **Grade 1: 61% (33/54)** - **Grade 2: 22% (12/54)** - **Unknown: 17% (9/54)**			• *Craniopharyngioma subgroup:* 100% (NR) **3-year LC (95% CI)** • *All patients:* 91% (NR) • *Ependymoma subgroup:* 85% (NR) • *Low-grade glioma subgroup:* 88% (NR) • *Craniopharyngioma subgroup:* 100% (NR) **Mortality, % (n/N)** • All-cause: 4.2% (7/166) • Disease-related: 3.6% (6/166) **Secondary Outcomes** **Requirement for subsequent therapy**: • *Unplanned shunt revisions:* 2.4% (4/166) • *surgical cyst drainage during PBT:* 1.8% (3/166) • *Gram-negative sepsis, hyponatremia, and*	9% (15/166) **Proportion of Craniopharyngioma patients experiencing cyst expansion within 18 months of completing PBT, % (n/N)** 7.8% (13/166) **Other Adverse Events, % (n/N)** • *Unplanned Shunt Revision*: 2.4% (4/166) • *Surgical cyst drainage:* 2.4% (4/166) • *Gram-negative sepsis, hyponatremia, and cryptosporidium infection requiring ICU admission*: 0.6% (1/166)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					cryptosporidium infection requiring ICU admission: 0.6% (1/166) • *Steroids:* 0.6% (1/166)	
Indelicato (2018) [Crossover with patients in Indelicato 2017] RoB: High Prospective Case Series USA Funding: Dr. Indelicato and Dr. Bradley have received prior funding from an unrestricted educational grant from IBA COI: All other authors report no conflicts of interest --- Also does subpopulation analysis on OS, PFS, and LC	**Diagnosis**: Pediatric Brain (Intracranial ependymoma) **Indication**: Curative intent	**N=179** **Median Age: 3.5 years (range, 0.7-21.3)** **Male: 57.5%** **Primary Tumor Sites:** **Posterior fossa, 66.5% (119/179)** **Risk Classification:** **Tumor grade 2, 32.9% (59/179);** **Tumor grade 3, 67% (120/179)**	**PBT** Double scatter PBT, 100% (179/179); PBT+photon RT, 6.1% (11/179) **Median PBT Dose (Range)**: 59.4 Gy (52.2 to 59.4) **Additional Treatments in conjunction with PBT:** Surgical operation, 100%; Chemotherapy, 53% (95/179); Anesthesia, 67.6% (121/179)	**Median F/U (range)**: 38.4 (1.2 to 115.2) months **Loss to follow-up**: 1.1% (2/179)	**<u>Primary Outcomes</u>** **OS (95% CI)**: 3-year: 90.4% (NR) **PFS (95% CI)**: 3-year: 75.9% (NR) **LC (95% CI)**: 3-year: 85.4% (78.3% to 90.4%) **Freedom from Isolated Distant Recurrence, % (n/N)**: 3-year: 84.6% (77.8% to 89.6%) **<u>Secondary Outcomes</u>** NR	*Toxicity Grading Criteria*: CTCAE v.4.0 **<u>Acute Toxicity (Grade ≥2), % (n/N)</u>** • *Nausea/Vomiting:* 10% (18/179) [requiring ondansetron] • *Headache:* 0.6% (1/179) [requiring opioid analgesia] **<u>Late Toxicity (Grade ≥2), % (n/N)</u>** • *Growth Hormone Deficiency:* 6.1% (11/179) • *Other Hormone Deficiency:* 1.1% (2/179) • *Hearing loss:* 6.1% (11/179) [all requiring hearing aids: seven with bilateral and four with unilateral] • *Vasculopathy:* 3.4% (6/179)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
based on age, sex, race, etc…						• *Symptomatic brainstem toxicity:* 5.6% (10/179) - Grade 2: 4.5% (8/179) - Grade 3: 0.5% (1/179) - Grade 5: 0.5% (1/179) **<u>Development of Secondary Malignancy, % (n/N)</u>** 0% (0/179)
Jacola (2016) RoB: High Prospective Case Series USA Funding: This work was supported by the National Cancer Institute (St. Jude Cancer Center Support, CORE, grant number P30 CA21765), the American Lebanese Syrian Associated	**Diagnosis**: Pediatric Brain (craniopharyngioma) **Indication**: Curative Intent	**N=62** **Age Range: 0-21 years** **Male: 51.6%** **Primary Tumor Sites:** **Left, 12.9%** **Right, 51.6%** **Midline, 17.7%** **Bifrontal, 4.8%** **Tumor Characteristics** • Hypothalamic Involvement§ **- Grade 1: 30.6%;** **- Grade 2: 56.5%** **Risk Classification: NR**	**PBT**: NR **Median PBT Dose (Range)**: NR **Additional Treatments in conjunction with PBT**: Catheter only – craniotomy, 4.8%; Catheter only – burr hole, 12.9%; Resection – craniotomy, 51.6%; Resection – transphenoidal, 17.7%	**Median F/U (range)**: NR	**<u>Primary Outcomes</u>** NR **<u>Secondary Outcomes</u>** **Visual Acuity (right)** • *Reduced, no functional impairment*: 16.1% (10/62) • *Reduced, functional impairment*: 11.3% (7/62) • *Blind*: 4.8% (3/62) **Visual Acuity (left)** • *Reduced, no functional impairment*: 9.7% (6/62)	NR

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Charities (ALSAC), and the National Cancer Institute (Pediatric Oncology Education Program, grant number R25CA23944). COI: None					• *Reduced, functional impairment*: 14.5% (9/62) • *Blind*: 6.5% (4/62) **Proportion of patients experiencing excessive day time sleepiness**: 75.8% (47/62) **Epworth Sleepiness Scale** (n=52)** • *Impaired (total score >10)*: 40.4% (21/52) • *Unimpaired (total score ≤9)*: 59.6% (31/52)	
Kralik (2018) [Crossover with Kralik 2017/2015] RoB: High Retrospective Case Series USA Funding: None	**Diagnosis**: Pediatric Primary Brain Tumors (Medulloblastoma/ PNET, 28% (28/100); Ependymoma, 19% (19/100); Craniopharyngioma , 17% (17/100); Pilocytic/Pilomyxoi d astrocytoma, 9% (9/100); Germinoma, 7% (7/100);	**N=100** **Age: 8.1 years (range 0.75-18)** **Male: 63%** **Primary Tumor Sites: Supratentorial, 50%; Infratentorial, 27% Multifocal, 2%** **Risk Classification: NR**	**PBT**: NR **Median PBT Dose (Range)**: 57 months (range, 7-116) **Additional Treatments in conjunction with PBT:** NR	**Median F/U (range)**: 57 months	NR	**<u>Proportion of patients experiencing cerebral microbleeds following completion of PBT, % (n/N)</u>** • *1-year:* 43% (16/37) • *2*-years: 66% (27/41) • *3*-years: 80% (20/25) • *4*-years: 81% (26/32) • *5-years*: 83% (35/42)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
COI: None	GBM/Anaplastic Astrocytoma, 4% (4/100); ATRT, 3% (3/100); Brainstem glioma, 5% (5/100); Other, 8% (8/100) **Indication**: Curative Intent					• *>5-years*: 81% (29/36) **Patients presenting with imaging appearance consistent with a cavernous malformation. % (n/N)**: 4% (4/100)
Kralik (2017) [Crossover with Kralik 2018/2015] RoB: High Retrospective Case Series USA Funding: NR COI: None	**Diagnosis**: Primary Brain Tumor (Medulloblastoma/ PNET, 33.3%; Craniopharyngioma, 18.7%; Pilocytic/pilomyxoid astrocytoma, 13.3%; Other, 34.7%) **Indication**: Curative Intent	**N=75** **Mean Age: 7.9 years (range, 1.5-18)** **Male: 60%** **Primary Tumor Sites: Supratentorial, 50.6%; Infratentorial, 36% Multifocal, 2.7%** **Risk Classification: NR**	**PBT**: NR **Mean Cranial PBT Dose (Range)**: 53.7 Gy (30-59.4) **Additional Treatments in conjunction with PBT**: Chemotherapy (% NR)	**Median F/U (range)**: 51.6 months	NR	*Toxicity Grading Criteria*: NR **Proportion of patients experiencing radiation-induced large vessel cerebral vasculopathy**: 6.7% (5/75) **Freedom from radiation-induced large vessel cerebral vasculopathy (95% CI)**: • *3-year*: 96% (88%-99%) • *4-year*: 95% (86%-98%) • *5-year*: 95% (85%-98%)
Kralik (2015) [Crossover with Kralik 2017/2018]	**Diagnosis**: Pediatric Primary Brain Tumor	**N=60** **Average Age: 7.2 years (range, 0.8-18)** **Male/Female ratio: 2.5:1**	**PBT**: NR **Median Cranial PBT Dose (Range)**: 54.0 Gy (21–59.4)	**Median F/U (range)**: 18 (6 to 34) months	NR	*Toxicity Grading Criteria*: NR **Proportion of patients developing**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
RoB: High Retrospective Case Series USA Funding: NR COI: NR	(Medulloblastoma and PNET, 31.7% (19/60); Ependymoma, 20% (12/60); Germinoma, 6.7% (4/60); Other, 30% (18/60) **Indication**: Curative Intent	**Primary Tumor Sites: NR** **Risk Classification: NR**	**Additional Treatments in conjunction with PBT**: Chemotherapy (% NR)			**radiation necrosis, % (n/N)** • *All patients*: 31% (16/52) *-Grade 1 asymptomatic:* 75% (12/16) *-Grade 3 symptomatic:* 25% (4/16)
MacDonald (2014) RoB: High Retrospective Case Series USA Funding: R.V.S. was supported as a clinical research fellow by a grant from the Doris Duke Charitable Foundation to Harvard Medical School. B.Y.Y. and a portion of this research was supported by the Federal Share of program income earned by Massachusetts General Hospital on	**Diagnosis**: Pediatric Brain (Ependymoma) **Indication**: Curative Intent	**N=70** **Median Age: 38 months (range, 3 months to 20 years)** **Male: 47%** **Primary Tumor Sites: Infratentorial, 73% (51/70); Supratentorial, 27%(19/70)** **Tumor Characteristics: Tumor grade** - **Differentiated (classic): 53% (37/70)** - **Anaplastic: 47% (33/70)** **Risk Classification: NR**	**PBT**: conformal proton plan using at least 3 fields **Mean PBT Dose (Range)**: **Additional Treatments in conjunction with PBT**: Chemotherapy, 30% (21/70); Gross total resection, 66% (46/70); Subtotal resection, 33% (23/70); Near-total resection, 1% (1/70); Shunt, 76% (29/38) of patients with hydrocephalus;	**Median F/U (range)**: 46 (12 to 140.4) months	**Primary Outcomes** **OS (95% CI)** • 3-year: 95% (NR) **PFS (95%CI)** • 3-year: 76% (NR) **LC (95% CI)** • *3-year*: 83% (NR) • *5-year*: 77% (NR) **Distant Control (95% CI)** • *3-year*: 86% (NR) • *5-year*: 83% (NR) **Mortality, % (n/N)** • Disease-related: 10% (7/70) **Proportion of patients experiencing progression**: 25.7% (18/70)	**Complications, % (n/N)** • *Hypothyroidism*: 3.1% (1/32) [only assessed for in 32 patients] • *Growth Hormone Deficiency*: 8% (2/25) • *Cervical subluxation*: 2.9% (2/70) • *Tumor Necrosis (with symptoms of brainstem compression)*: 1.4% (1/70) • *Brainstem Necrosis*: 0% (0/70) • *Hearing loss*: 8.7% (2/23) **Secondary Malignancy** 0% (0/70)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
C06 A059267, Proton Therapy Research and Treatment Center. COI: N.T. was on the medical advisory board of ProCure until 2008 and has stock options in ProCure that are currently without value. N.T.'s spouse continues to serve on the medical advisory board of ProCure. Actual or potential conflicts of interest do not exist for any other author. --- Does subpopulation analysis for PFS and OS based one age, sex, tumor type, etc.					**Secondary Outcomes** **Mean SIB-R (n=28)** • Baseline: Baseline: 100.1 • Final follow-up: 100.8 p=0.809	**Average Change in Height (n=57 patients)** Median loss of 2.6 percentiles per patient **Mean MDI/Full-scale IQ score (n=14)** • Baseline*:* 108.5 • Final follow-up: 111.3 p=0.475
Mokhtech (2018) RoB: High Retrospective Case Series USA Funding: NR	**Diagnosis**: Pediatric Brain (non-metastatic intracranial nongerminomatous germ cell tumors) **Indication**: NR	**N=14** **Median Age: 11 years** **Male: 64%** **Primary Tumor Sites: Pineal, 50% (7/14); Suprasellar, 43% (6/14)** **Bifocal, 7% (1/14)** **Tumor Characteristics:**	**PBT**: double-scattered proton therapy **PBT Dose (all patients)**: 54 Gy (RBE) at 1.8 Gy (RBE) per fraction **Additional Treatments in conjunction with PBT**:	**Median F/U (range)**: 33.6 (8.04 to 120) months	**Primary Outcomes** **PFS (95% CI)** • 3-year: 86% (NR) **Mortality, % (n/N)** • Disease-related: 0% (0/14) **Proportion of patients experiencing disease**	*Toxicity Grading Criteria*: CTCAE v.4.0 **Late or Acute Toxicity (Grade ≥2)** • Cataracts - *Grade 2*: 14.3% (2/14) [no surgery required]

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
COI: None		**Mixed, 50% (7/14); Choriocarcinoma, 14% (2/14); Immature teratoma, 14% (2/14); Yolk sac, 7% (1/14); Unknown, 14% (2/14)** **Risk Classification: NR**	Induction chemotherapy, 100% (14/14); Gross total resection/Near total resection, 36% (5/14); Subtotal resection/biopsy, 50% (7/14); Ventriculoperitoneal shunts, 28.9% (4/14)		**progression**: 50% (7/14)	- *Grade 3*: 7% (1/14) [surgery required] -Grade 4 and 5: 0% • Hormone Deficiency - *Grade 2*: 7% (1/14)
Park (2017) Prospective Case Series South Korea Funding: This study was supported by National Cancer Center Research Grant No. 1610590 and 1611460. COI: None --- This study only provides subpopulation analysis based primarily on tumor location and amount of radiation dose	**Diagnosis**: Pediatric Brain (intracranial germ cell tumor) **Indication**: Curative Intent	**N=34 baseline data, 20 with follow-up data** **Median Age: 12 years (range, 7 to 18.1)** **Male: 67.6%** **Primary Tumor Sites: Suprasellar, 23.5 (8/34); Pineal gland, 29.4% (10/34); Basal ganglia, 17.6% (6/34); Bifocal, 29.4% (10/34)** **Tumor Characteristics: Germinoma, 52.9% (18/34); non-germinomatous germ cell tumor or mized intracranial germ cell tumor, 47.1% (16/34)** **Risk Classification: NR**	**PBT**: passive double-scattered proton therapy **PBT Dose (Range)**: 39.6 Gy (30.0-55.8) **Additional Treatments in conjunction with PBT**: Chemotherapy, 100% (34/34); Shunt, 58.8% (20/34); Gross total resection, 8.8% (3/34); Near total resection/subtotal resection, 11.8% (4/34); Biopsy, 70.6% (24/34)	**Median F/U (range)**: 15 (6 to 28.8) months	**Primary Outcomes** NR **Secondary Outcomes** **Proportion of Patients with Psychological Impairments, % (n/N)** Total behavior problems†† • Suprasellar: 16.7% (NR) • Pineal: 22.2% (NR) • Basal Ganglia: 50% (NR) • Bifocal: 12.5% (NR)	**Proportion of Patients with Neurocognitive Impairments, % (n/N)** K-WAIS/K-WISC FSIQ • Suprasellar: 14.3% (NR) • Pineal: 30% (NR) • Basal Ganglia: 83.3% NR) • Bifocal: 20% (NR) **KWISC/KWAIS IQ Score, Mean ± SD: Baseline:** 96.74 ± 21.36 **Mean Change Score ± SD** *Baseline to 1 to 2 years after PBT* Radiation Field • Cranial spinal irradiation: -0.80 ± 17.79 (n=10)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						• Whole ventricle irradiation: 5.30 ± 6.04 (n=10) p=0.327 Radiation Dose • ≤39.6: 4.41 ± 9.14 (n=12) • >39.6: -1.00 ± 18.14 (n=8) p=0.387
Pulsifer (2018) RoB: High Prospective Case Series USA Funding: This project was supported by Award Number P01CA021239 from the National Cancer Institute and by the Federal Share of program income earned by the Massachusetts General Hospital on C06 CA059267 Proton Therapy Research and Treatment Center	**Diagnosis**: Pediatric Brain (Medulloblastoma, 34.8 (54/155); Craniopharyngioma, 18.1% (28/155); Ependymoma, 16.1% (25/155); Glial (astrocytoma; glioma), 14.2% (22/155); Germ cell, 7.7% (12/155) Other, 9% (14/155)) **Indication**: Curative Intent	**N=155** **Age: 8.9 years (range, 1-22.5)** **Male: 48.4%** **Primary Tumor Sites:** **Infratentorial, 51.6% (80/155)** **Supratentorial, 48.4% (75/155)** **Risk Classification: NR**	**PBT**: CSI, 38.7 (60/155); Focal, 61.3% (95/155) **Median total PBT Dose (Range)**: CSI: 54.0 Gy (RBE) (range, 30.6-54.0 Gy (RBE)) Focal: 52.2 Gy (RBE) (range, 30.6-57.6 Gy (RBE)) **Additional Treatments in conjunction with PBT**: **Shunt, 32.5% (25/155);** **Chemotherapy, 63.2% (95/155);** **Biopsy, 11.6% (18/155);** **Near/subtotal resection, 34.8% (54/155);** **Gross total resection, 51% (79/155);**	**Median F/U (range)**: 43.2 (13.2 to 136.8) months	NR	Mental Development Index/Full-scale IQ score ± SD (n=114) • Baseline: 105.4 ± 14.3 • Final follow-up: 102.5 ± 14.8 p=0.005 Mean Scales of Independent Behavior - Revised Broad Independence ± SD (n=147) • Baseline: 102.4 ± 18.0 • Final follow-up: 100.4 ± 16.3 p=0.261

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
COI: NR --- Does subpopulation analysis for both of the outcomes listed based on age, sensory deficit, sex, etc.			Daily anesthesia during radiation, 45.2% (70/155)			
Ventura (2018) RoB: High Prospective Case Series USA Funding: NR COI: N.J.T. was on the medical advisory board of ProCure until 2008 and has stock options in ProCure that are currently without value. N.J.T.'s spouse continues to serve on the medical advisory board of ProCure. K.A.K. has stock or other ownership in Merk, Johnson and J	**Diagnosis**: Pediatric Brain, Spinal, Paraspinal (Medulloblastoma, 43.9 (29/65); Glial (astrocytoma; glioma), 15.2% (10/65); Craniopharyngioma , 16.7% (11/65); Ependymoma, 15.2% (10/65) Other, (9.1% (6/65)) **Indication**: Curative Intent	**N=65** **Mean Age ± SD: 12.4 ± 3.7 years** **Male: 43.9%** **Primary Tumor Sites: Infratentorial, 55.4% (36/65); Supratentorial, 44.6% (29/65)** **Risk Classification: NR**	**PBT**: -Medulloblastoma: CSI + a boost to the tumor site in the posterior Fossa -Craniopharyngioma, low-grade glioma, and Ependymoma: radiation to the tumor site alone (partial brain radiation) -Germ cell tumor patients: either CSI or partial brain radiation including a whole ventricle volume followed by a boost to the tumor site **Median total PBT Dose (Range)**: NR **Additional Treatments in conjunction with PBT**: Surgical resection, 86.4% (57/65);	**Mean F/U (range)**: 38.4 (12 to 106.8) months	**<u>Primary Outcomes</u>** NR **<u>Secondary Outcomes</u>** <u>Executive Functioning (at final follow-up)</u> **Mean Continuous performance test score ± SD (range)** ‡‡: 41.7 ± 18.3 (4.2 to 99.9) **Mean Behavior Rating Inventory of Executive Function Global executive composite score ± SD (range)** §§: 49.4 ± 10.3 (31 to 78) **Mean behavior assessment system for children**	**<u>Proportion of patients that developed posterior fossa syndrome</u>:** 9.2% (6/65) *All outcomes below are reported at last follow-up* <u>Intellectual Abilities</u> **Mean Wechsler Full-scale IQ score ± SD (range)**: 103.7 ± 15.0 (78 to 138) - *Mean Working Memory Index* ± SD (range): 101.6 ± 13.2 (70 to 150) - *Mean Processing Speed Index* ± SD (range): 89.5 ± 15.7 (65 to 121) <u>Academic Skills</u> **Mean Wechsler individual achievement test**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
ohnson, CVS, Pfiser, Eli Lily, and Novo Nordisk. K.A.K. has a consulting or advisory role in Roche. Actual or potential conflicts of interest do not exist for any other author. --- Does subpopulation analysis across several different demographic variables			Chemotherapy, 66.7% (44/65)		**(attention subscale) score ± SD (range)*****: 47.8 ± 10.8 (33 to 76) Quality of Life **Mean Pediatric Quality of Life Inventory Child-report for School functioning ± SD (range)**: 73.1 ± 18.2 (10 to 100) [Scores of less than 69.7 are considered to be at risk for impairment]	**score for Word reading ± SD (range)**: 104.0 ± 14.1 (64 to 137) **Mean Wechsler individual achievement test score for numerical operations ± SD (range):** 102.4 ± 16.4 (61 to 148) **Mean Wechsler individual achievement test score for spelling ± SD (range):** 103.7 ± 13.8 (72 to 133)
McGovern (2014) RoB: High Retrospective Case Series USA COI: NR Funding: This work was supported by the	**Diagnosis:** Pediatric Brain, Spinal, Paraspinal (ATRT) **Indication**: Curative Intent	**N=31** **Median Age: 19 months (range, 4 – 55)** **Male: 42%** **Primary Tumor Sites: Disease confined to the primary site in the brain: 52% (16/32)** **Tumor Characteristics: Degree of Metastasis** **Stage M0, 50% (16/32);**	**PBT:** Passive scatter PBT **Median total PBT Dose (Range)**: Local radiation (n=17) with median dose of 50.4 Gy RBE (range, 9 – 54) CSI (n=14) with median tumor dose was 54 Gy RBE (range, 43.2 – 55.8)	**Median F/U (range)**: 24 (3 to 53) months	**Primary Outcomes** **2-year OS (95% CI)** • *From diagnosis*: 68.3% (52.9% - 88.1%) • *From end of radiation*: 52.9% (36.0% - 77.8%) **2-year PFS (95% CI)** • *From diagnosis*: 47.6% (32.2% - 70.5%)	*Toxicity Grading Criteria*: Radiation Therapy Oncology Group Criteria **Acute Toxicity, % (n/N)** Authors state most patients developed grade 1 or 2 skin toxicities of erythema and alopecia but no data is provided • Sepsis

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Cancer Center Support Grant (NCI Grant P30 CA016672).		**Stage M1, 9.7% (3/31);** **Stage M2, 16.1% (5/31);** **Stage M3, 19.4% (6/31);** **Stage M4, 3% (1/32)** ***One patient had synchronous disease in the kidney.***	**Additional Treatments in conjunction with PBT**: Chemotherapy prior to radiation, 84% (26/31); Chemotherapy during radiation, 35% (11/31); Gross total resection, 48% (15/31); Subtotal resection, 42% (13/31); Biopsy alone, 10% (3/31); Second look surgery, 6% (2/31)		• *From end of radiation* 45.9% (29.4% - 71.4%) **Mortality, % (n/N)** • All-cause: 42% (13/31) **<u>Secondary Outcomes</u>** NR	- *Grade 4*: 3.2% (1/31) - *Grade 5*: 3.2% (1/31) • Neutropenia - *Grade 3*: 6.5% (2/31) • Emesis - *Grade 3*: 3.2% (1/31) • Pancytopenia - *Grade 3*: 3.2% (1/31) - *Grade 4*: 6.5% (2/31) • Thrombocytopenia - *Grade 4*: 3.2% (1/31) • Hypertension - *Grade 4*: 3.2% (1/31) • Anemia - *Grade 3*: 3.2% (1/31) **<u>Proportion of patients not completing planned radiotherapy due to toxicity</u>**: 6.5% (2/31) ††††

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Ray 2013 RoB: High Retrospective Case Series Switzerland COI: NR Funding: NR ---	**Diagnosis**: Pediatric Lepatomeningeal Spinal Metastases: 100% Medulloblastoma, 40.9% (9/22); Ependymoma, 13.6% (3/22); ATRT, 18.2% (4/22); PNET, 13.6% (3/22); Other, 13.6% (3/22) **Indication**: Curative Intent	**N=22** **Median Age: 5 years (range, 1-17)** **Male: 73%** **Risk Classification: NR**	**PBT:** standard PBT techniques for CSI **Median PBT dose:** 37.8 Gy (range, 21.6 to 54)	**Median F/U (range):** 14 (4 to 33) months	**Primary Outcomes** *There was no statistical difference (p=0.39) in OS between the different diagnoses (ATRT, Ep, Med, PNET, and other)* **Local Control (95% CI)** • *3-month:* 77.3% (NR) • *6-month:* 72.1% (NR) • *12-month:* 68% (NR) **Mortality, % (n/N)** • All-cause: 32% (7/22) **Secondary Outcomes** NR	*The most frequently encountered toxicity of therapy was grade 1 skin erythema*
Weber (2015) RoB: High Retrospective Case Series Switzerland	**Diagnosis:** Pediatric Non-metastatic ATRT **Indication**: Curative Intent	**N=15** **Mean Age ± SD: 17.4 ± 7.0 months** **Male: 53%** **Tumor Characteristics: NR** **Primary Tumor Sites:**	**PBT:** PBS **PBT Dose (Range)**: 54 Gy (RBE) **Additional Treatments in conjunction with PBT**:	**Median F/U (range)**: 33.4 (9.7 to 69.2) months	**Primary Outcomes** **OS (95% CI)** • 2-year: 64.6% (39.9% to 89.9%) **PFS (95% CI)** • 2-year: 66% (41.7% to 90.3%)	*Toxicity Grading Criteria*: CTCAE v.4.0 **Proportion of patients experiencing a decreased performance status of WHO 2 after PT, % (n/N):** 13 % (2/15)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
COI: None Funding: NR --- Provides subpopulation analysis by clinical and therapeutic factors		**Posterior fossa, 63.6% (9/15)** **Risk Classification: NR**	Subtotal resection, 46.7% (7/15); Gross total resection, 46.7% (7/15); Biopsy only, 6.7% (1/15); Chemotherapy, 46.7% (7/15)		**Local Failure Free Survival (95% CI)** • 2-year: 78% (55.7% to 100%) **Distant Brain Failure Free Survival (95% CI)** • 2-year: 76.6% (43.9% to 100%) **Proportion of patients experiencing tumor recurrence or progression**: 40% (6/15) **Proportion of Patients presenting with local failure**: 20% (3/15) **Proportion of Patients presenting with distant brain failure**: 26.7% (4/15) **Mortality, % (n/N)** • Disease-related: 40% (6/15) **Secondary Outcomes**	**Acute Toxicity, % (n/N)** • Bone Marrow Toxicity - *Grade 1*: (11/15) - *Grade 2*: (2/15) • Alopecia - *Grade NR*: 100% (15/15) • Erythema - *Grade 1-2*: 93.3% (14/15) **Late Toxicity, % (n/N)** • Motor Dysfunction - *Grade 1*: 6.7% (1/15) - *Grade 4*: 6.7% (1/15) **Toxicity Free Survival (95% CI)** • 2-year: 90% (71.4% to 100%)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					Mean ± SD Pediatric QoL – Parent Proxy Scores • *Total Score* *-Baseline (n=8):* 44.20 ± 18.53 *-2-months (n=7*): 42.01 ± 17.84 • *Physical* -Baseline (n=8): 39.59 ± 22.31 *-2*-months (n=8): 43.59 ± 21.03 • *Emotion* *-Baseline (n=9)*: 41.53 ± 18.98 -2-months (n=8): 44.19 ± 21.04 • *Social (n=7 vs. 7)*: -Baseline (n=7) 47.07 ± 28.44 *-2*-months: 35.86 ± 26.79 • *Kindergarten/School* *-Baseline (n=7):* 56.25 ± 4.17 -2-months (n=7): 62.50 ± 8.33 • *Psycho-social (n=7 vs. 7)*:	

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					-Baseline (n=7): 45.35 ± 16.91 *-2-months (n=7):* 43.71 ± 15.43	
Bojaxhiu, 2018 RoB: High Retrospective Case Series Switzerland Funding: Financial support was provided by Prof. Dr D. M. Aebersold (Bern University Hospital) COI: None --- Also provides subpopulation data on grade 1 vs grade 2, etc…	**Diagnosis**: Pediatric Brain (Endymoma, 34% (64/171); Low-grade glimoma, 12% (20/171); Chordoma, 9% (16/171); Craniopharyngioma, 9% (16/171); Medulloblastoma; 5% (9/171); Atypical teratoid rhabdoid tumor, 7% (12/171); Germ cell tumor, 5% (8/171); Choroid plexus carcinoma, 5% (9/171); Chondrosarcoma, 4% (6/171); Menginioma, 2% (4/171); Primitive neuroectodermal tumor, 2% (4/171); Other, 5% (9/171))	N=171 Median Age (Range): 3.3 years (0.3 to 17.0) Male: 50% **Primary Tumor Sites**: Skull base, 15%, (25/171); Optic pathway 5% (9/171); Infratentorial, 41% (70/171); Supratentorial, 39% (67/171) **Tumor Size:** <5 cm, 56% (96/171); >5 cm, 43% (74/171); Multiple lesions, 1% (1/171) **Risk Classification**: WHO grade 1-2, 26% (44/171); WHO grade 3-4; 54% (92/171); None, 20% (35/171)	**PBT** PBS with energy-degraded beams from the 590-MeV cyclotron until 2005 and with the dedicated 250-MeV cyclotron thereafter **Median PBT Dose (Range)**: 54 Gy (RBE) (40.0-74.1) delivered in a median dose per fraction of 1.8 Gy (RBE) (1.5-2.0) **Additional Treatments in conjunction with PBT:** Chemotherapy prior to PBT, 61% (105/171); Concomitant chemotherapy, 18% (30/171); Adjuvant chemotherapy 19% (32/171); Total tumor resection, 37% (63/171);	**Median F/U (range)**: 49.8 (5.9 to 194.7) months	**Primary Outcomes** **Mortality, % (n/N)** • All-cause: 1.2% (2/171) **Secondary Outcomes** NR	**Patients developing Radiation Necrosis, % (n/N)** • *All patients:* 17% (29/171) - *Grade 1:* 9.9% (17/171) - *Grade 2:* 4.7% (8/171) - *Grade 4:* 1.2% (2/171) - *Grade 5:* 1.2% (2/171) - *Symptomatic:* 7% (12/171) - *Asymptomatic:* 9.9% (17/171) **Symptoms of patients with symptomatic Radiation Necrosis (n=12), % (n/N)** • *Mental status alternation:* 66.4% (3/12) • *Motor function impairment:* 66.7% (8/12) • *Unclear:* 8.3% (1/12)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
	Indication: Curative intent: 64% (110/171) Salvage therapy (for recurrent disease): 36% (61/171)		Subtotal tumor resection, 51% (87/171); Patients receiving general anesthesia during PBT, 64% (110/171)			**Proportion of patients developing White Matter Lesion, % (n/N)** • *All patients:* 11% (18/171) - *Grade 1:* 7.6% (13/171) - *Grade 2:* 2.3% (4/171) - *Grade 3:* 0.6% (1/171) - *Symptomatic:* 2.9% (5/171) - *Asymptomatic:* 7.6% (13/171) **Symptoms of patients with symptomatic White Matter Lesion (n=5), % (n/N)**: • *Mental status alternation:* 20% (1/5) • *Motor function impairment:* 60% (3/5) • *Seizures:* 20% (1/5) **5-year Radiation Necrosis free survival:** 83% (95% CI, NR)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						5-year White Matter Lesion free survival: 87% (95% CI, NR) **5-year Radiation Necrosis/White Matter Lesion free survival**: 70% (95% CI, NR) **Proportion of patients presenting with MRI parenchymal brain alterations (by tumor type), % (n/N)** • *Ependymoma*: 39% (25/64) • *Low-grade glioma*: 30% (6/20) • *Chordoma and chondrosarcoma*: 23% (5/22) • *Medulloblastoma*: 22% (2/9) • *Atypical teratoid rhabdoid tumor*: 17% (2/12) • *Choroid plexus carcinoma:* 25% (1/4)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						• *Germ cell tumor*: 13% (1/8) • *Craniopharyngioma*: 7% (1/15) **Risk of developing Radiation Necrosis by treatment aim, HR (95% CI)** Curative intent vs. salvage therapy: 0.96 (0.43 to 2.03); p =0.927 **Risk of developing a White Matter Lesion by treatment aim, HR (95% CI)** Curative intent vs. salvage therapy: 0.37 (0.35 to 1.27); p =0.239

AE = Adverse Events; ATRT = Atypical teratoid rhabdoid tumor; CI = Confidence Interval; CI = Cranial Spinal Irradiation; CNS = Central nervous system; COI = Conflict of Interest; CTCAE = Common Terminology Criteria for Adverse Events; F/U = Follow-up; GBM = Glioblastoma multiform; Gy = Gray; HR = Hazard Ratio; ICU – Intensive Care Unit; IQ = Intelligence Quotient; IQR = Interquartile Range; KWAIS – Korean Wechsler Intelligence Scale for Adults; KWISC – Korean Wechsler Intelligence Scale for Children; MDI = Mental Development Index; NR = Not Reported; NRSTS = Non-Rahabdomyosarcoma; OS = Overall Survival; PBT = Proton Beam Therapy; PFS = Progression Free Survival; PNET = Primitive neuroectodermal tumor; QoL = Quality of Life; RBE = Relative Biological Effectiveness; RMS = Rahabdomyosarcoma; RoB = Risk of Bias; RT = Radiation therapy; SD = Standard Deviation; SIB-R = Scales of Independent Behavior; WHO = World Health Organization
*All patients presenting with local or distant failure in this study were patients having received postoperative chemotherapy prior to irradiation. 28.6% (2/7) of all those that experienced local failure presented with synchronous microscopic cerebral spinal fluid dissemination
†1 medulloblastoma patient who had a grade 2 injury in the spinal cord at the C1 level was excluded because it was technically outside of the brainstem.
‡Vasculopathy was defined as any asymptomatic vessel narrowing identified on imaging or found after symptomatic presentations from transient ischemic attacks or cerebrovascular
§Grade 1: involvement of the anterior hypothalamus; and Grade 2: involvement of the anterior and posterior hypothalamic area (i.e., involving the mammillary bodies and the area beyond the mammillary bodies).

**A modified version of the Epworth Sleepiness Scale was administered to subjectively measure daytime sleepiness. Caregivers were asked to rank the propensity for the child or adolescent to fall asleep in various everyday situations (0=no chance to 3=high chance of dozing) for each of the eight items, with a maximum score of 24. Higher scores indicate higher levels of excessive daytime sleepiness.
††Includes withdrawn, somatic complaints, depression/anxiety, social problems, thought problems, attention/hyperactivity, delinquent behavior, aggressive behavior, internalizing problems, externalizing problems
‡‡Assessed using the Continuous Performance Test, 2nd Edition, which provides an estimate of the probability that a given child's performance resembles that of a child with clinically significant attention problems.
§§Parent-report of Executive Functioning was obtained using the Behavior Rating Inventory of Executive Function (BRIEF). This measure provides a T-score with a mean of 50 and a SD of 10; higher scores indicate more problems with Executive Functioning
***BASC-2, (Attention Subscale) parent-report of attention difficulties were also collected using the Behavior Assessment System for Children, 2nd Edition. This measure provides a T-score; higher scores indicate more attention problems.
†††One patient was neutropenic during and after induction chemotherapy. She died after four fractions of radiation due to sepsis from a Pseudomonas diaper rash. Another patient 28 was thrombocytopenic throughout induction chemotherapy and developed severe hypertension with an acute intracranial bleed during radiation. She subsequently recovered and was alive with no evidence of recurrence at last follow-up.

Appendix Table N3. Study characteristics and patient demographics: comparative studies of proton beam therapy in pediatric brain, spinal, and paraspinal cancers

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Bishop 2014 Retrospective Cohort *Moderately High* USA	52	**PBT (n=21)**: Median total dose (Gy): 50.4 [passive scatter] **IMRT (n=31)**: Median total dose (Gy): 50.4 **Indication:** • Definitive: 13% • Post-op/adjuvant: 44% • Salvage: 42%	**Inclusion**: Patients w/ histologically confirmed craniopharyngioma; age ≤18 years at time of RT; treated with IMRT or PBT from 1996 through 2012 **Exclusion**: NR	PBT vs. IMRT Median age (years): 9.1 vs. 8.8 Male: 43% vs 45% Tumor size (cm): 4.5 vs. 3.6 Presenting symptoms • Headaches: 76% vs. 48%, p=0.038 • Visual defects: 52% vs. 81%, p=0.083 • Endocrinopathies: 19% vs. 39%	PBT vs. IMRT **F/U (median [range])**: 33.1 (10.5-65.6) vs. 106.1 (1.9-185.3) **p<0.001** **% F/U**: CD*	3-year OS, CFFS, and NFFS Cyst growth Harms	Funding: Cancer Center Support (Core) Grant CA016672 to The University of Texas M. D. Anderson Cancer Center. Subpopulation analysis for cyst growth, some toxic

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
				Extent of first surgery, p=0.032 • Cyst drainage, fenestration, shunting: 33% vs. 61% • Subtotal resection: 43% vs. 35% • Gross total resection: 24% vs. 3% Number of surgeries • 1: 71% vs. 55% • 2: 19% vs. 29% • 3: 10% vs. 13% • 3: 0% vs. 3% Radiation Intent • Postoperative: 38% vs. 48% • Definitive: 19% vs. 10% • Salvage: 43% vs. 42% Re-imaging during RT: 90% vs. 16%			effects available Also for OS, CFFS, NFFS by radiation intent
Eaton 2016a/2016b (2016 b – late endocrine abnormalities only) Prospective Cohort *Moderately High* US	2016a: 88 2016b: 77	**PBT (2016a, n=45; 2016b, n=40)**: Median (range) dose: 23.4 (18-27) Total dose range to primary (Gy): 54-55.8 [3D Conformal PBT] **Photon RT (2016a, n=43; 2016b, n=37)**: Median (range) dose: 23.4 (18-26.4)	**Inclusion**: Patients with standard risk medulloblastoma: age >3 years at diagnosis; <1.5 cm^2 residual disease after surgery; and M0 disease based on MRI of the spine and cerebrospinal fluid cytology examination **Exclusion**: NR	PBT vs. photon RT Median age (years): 6.2 (range 3.3 to 21.9) vs. 8.2 (range 3.4 to 19.5); p=0.011 Male: 56% vs. 67% Histology • Classic: 76% vs. 86% • Anaplastic: 13.% vs. 7% • Other: 11% vs. 3% Residual disease after surgery • <1.5 cm2: 11% vs 2% • None/GTR: 88.9% vs. 97.7% Chemotherapy: 100% vs. 100%	PBT vs. photon RT **F/U (median [range])**: • 2016a 74.4 months (6.1.2 to 79.2) vs. 84 months (69.6 to 106.8) • 2016b 69.9 (NR) vs. 84 (NR) months, p=0.01 (difference in	6-year OS and RFS Harms	Funding: NCI, award number P01CA021239, and the Federal Share of program income earned by Massachusetts General Hospital on C06 CA059267, Proton Therapy Research and

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		Total dose range to primary (Gy): 54-55.8 (n=1 had >55.8) [IMRT or 3DCRT] *All patients underwent maximal safe resection of the primary tumor followed by craniospinal irradiation and involved field or posterior fossa RT boost and chemotherapy (most often adjuvantly; some received pre-radiation chemotherapy)*		Location of RT boost • Tumor bed: 62% vs. 54% • Posterior fossa: 29% vs. 27% • PF > TB: 9% vs. 20%	f/u time between groups) **% F/U**: CD†		Treatment Center Subpopulation analysis for male vs. female etc. available
Gunther 2015 [Crossover of patients between Gunther 2015 and Sato 2017] Retrospective Cohort Study *Moderately High*	72	**PBT (n=37)**: Mean total dose (Gy): 57.2 (range, 53-59.4) **IMRT (n=35)**: Mean total dose (Gy): 55.9 (range, 50.4-59.4)	**Inclusion**: non-metastatic intracranial ependymoma (anaplastic and well-differentiated) who were treated between 2000 and 2013; Patients who had at least 1 MRI performed at least 6 months after RT **Exclusion**: any previous intracranial radiation	PBT vs. IMRT Median age (months): 31.4 vs. 73; p=0.06 Male: 59% vs. 54% Tumor location • Infratentorial: 70% vs. 60% • Supratentorial: 30% vs. 40% Diagnosis • Anaplastic ependymoma: 84% vs, 80% • Ependymoma: 16% vs. 20% Extent of resection	PBT vs. IMRT **F/U (median [range])**: All patients, 40.6 months (7.3-140.7) **% F/U**: CD‡	4-year OS Harms	Funding: Supported by National Institutes of Health/National Cancer Institute Clinical Trials Support Resource grant P30CA016672

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
USA				• Gross total resection: 97% vs. 80% • Subtotal resection: 3% vs. 20% Chemotherapy before RT: 14% vs. 20%; p=0.54 Chemotherapy after RT: 14% vs. 0%; p=0.054			
Sato 2017 [Crossover of patients between Gunther 2015 and Sato 2017] Retrospective Cohort Study *Moderately High* USA	79	**PBT (n=41)**: Median total dose (Gy): 55.8 (range, 50.40-59.40) **IMRT (n=38)**: Median total dose (Gy): 54.0 (range, 50.4-59.4) All patients underwent ≥1 surgical procedures at the time of the initial diagnosis to achieve a maximal safe resection	**Inclusion**: Patients with newly diagnosed localized intracranial ependymoma treated with PBT or photon RT between September 2000 and April 2013 at the Texas Children's cancer center or Texas MD Anderson Cancer Center; chemotherapy prior to RT was OK **Exclusion**: NR	PBT vs. IMRT Median age: 2.5 years (range, 0.5 to 18.7) vs. 5.7 years (range, 0.4 to 16.5); p=0.001 Male: 61% vs. 55% Histology • Grade II (differentiated): 20% vs. 18% • Grade III (anaplastic): 80% vs. 82% Tumor location (infratentorial): 76% vs. 61% Gross total resection: 93% vs. 76%; p=0.043 Chemotherapy before RT: 15% vs. 24%	PBT vs. IMRT **F/U (median [range])**: 31.2 months (7.2-86.4) vs. 58.8 (13.2-140.4); p<0.0001 **% F/U**: CD§	3-year OS and PFS 6-year Local recurrence-free survival Mortality Harms	Funding: None
Kahalley 2016 Retrospective Cohort Study RoB: Moderately high	150	**PBT (n=90)**: Mean total dose (Gy): 54.0 (30.0-60.0) [Passive scatter (90%), PBS (10%)] **Photon RT (n=60)**:	**Inclusion**: Patients with brain tumors treated with PBT from 2007 to 2012 or with photon RT from 2002 to 2007; age ≤18 years; only a single course of RT; English- or Spanish-speaking	PBT vs. IMRT Mean age (years): 9.2 (range, 1.7 to 18.2) vs. 8.1 (range, 1.2 to 18.0) Male: 60% vs. 55% Histology, p=0.002 • Glioma: 22% vs. 13%	PBT vs. Photon RT **F/U (median [±SD])**: 32.4 months (±22.8) vs. 64.8 months	Average change in IQ score per year	Funding: This work was supported, in part, by the Texas Children's Hospital Pediatric Pilot

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
USA		Mean total dose (Gy): 54.0 (30.6-59.4) [3D-CRT (8.3%), IMRT (45%), 3DCRT+IMRT boost (46.7%)]	**Exclusion**: High-grade gliomas, brainstem gliomas, and atypical teratoid/rhabdoid tumors	• Medulloblastoma/PNET: 38% vs. 47% • Ependymoma: 4% vs. 22% • Germ cell tumor: 19% vs. 5% • Other: 17% vs. 7% Tumor location • Infratentorial: 40% vs. 54% • Supratentorial: 60% vs. 46% Craniospinal irradiation: 57% vs. 52% Craniotomy: 87% vs. 97%, p=0.46 Ventriculoperitoneal shunt: 30% vs. 50%, p=0.01 Lansky/Karnofsky performance score ≤80: 39% vs. 58%; p=0.03	(±39.6); p<0.001 **% F/U** -all patients: 73% (150/205) -PBT vs. Photon RT: CD**		Research Fund and by the National Cancer Institute Grants K07CA157923 and R01CA187202
Kopecky 2017 Retrospective Cohort Study (NCDB database) *Moderately High* USA	1300 [n=783 included for survival analysis] (demographic data provided for 1277 patients only)	**PBT (n=117)** **IMRT (n=157)** **2D/3D CRT (n=1003)** Median total dose (Gy): All patients, 54	**Inclusion**: Age <19 years old; histologically-confirmed medulloblastoma; received both chemotherapy and RT **Exclusion**: diagnosed after 2009 (for survival analyses only; per NCDB data-use guidelines)	PBT vs. IMRT vs. 2D/3D CRT Mean age (all patients): 8.4 years (range, 0 to 18) Male: 55% vs. 67% vs. 66% Charlson-Deyo Comorbidity score • 0: 97% vs. 94% vs. 95% • 1: 2% vs. 5% vs 3% • 2: 1% vs. 1% vs. 2% Histology • Classic/Not otherwise specified: 86% vs. 84% vs. 85% • Desmoplastic: 9% vs. 10% vs. 9% • Large Cell: 6% vs. 6% vs. 6%	**F/U (median [range])**: All patients, 54 months **% F/U** - *All* patients: 60.2% (783/1300)	5-year OS	Funding: NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
				Chemotherpay: 100% vs. 100% vs. 100%			
Paulino 2018 Retrospective Cohort Study *Moderately High* USA	84	**PBT (n=38)**: Dose range (Gy): 54 Gy to 55.8 Gy [passively scattered PBT] **Photon RT (n=46)**: Dose range (Gy): 54 Gy to 55.8 Gy [3DCRT + IMRT boost] All patients underwent maximal safe resection followed by craniospinal irradiation, posterior fossa and/or tumor bed boost and cisplatin-based chemotherapy	**Inclusion**: Patients with medulloblastoma who were treated with RT and cisplantin-based chemotherapy **Exclusion**: NR	PBT (passively scattered) vs. Photon RT Median age (range): 7.6 years (2.9 to 14.5) vs. 9.0 years (3.0 to 18.0) Male: 74% vs. 70% Risk Category • Standard: 63% vs. 74% • High: 37% vs. 26% Shunt placement: 34% vs. 52% Posterior Fossa syndrome: 13% vs. 15% Radiotherapy boost • Posterior fossa boost: 0% vs. 13% • Posterior fossa followed by tumor bed boost: 0% vs. 63% • Tumor bed boost: 100% vs. 24% Chemotherapy: 100% vs. 100%	PBT (passively scattered) vs. Photon RT **F/U (median [range])**: 55.5 months (17–101) vs. 65.5 months (13–163) **% F/U** -All patients: 80% (86/107) -PBT vs. Photon RT: 86% (38/44) vs. 73% (46/63)	Harms (Hearing Loss)	Funding NR
Song 2014 Retrospective Cohort Study *Moderately High* Korea	43	**PBT CSI (n=30)**: Mean CSI dose (CGE or Gy): 29.4 (19.8-39.6) Mean total dose (Gy): 51.8 (range, 30.6 – 61.2) **Photon RT CSI (n=13)**:	**Inclusion**: Age <18 years; malignant brain tumor; underwent PBT at National Cancer Center, Korea, between April 2008 and December 2012 and photon RT between January 2003 and December 2012	PBT CSI vs. Photon RT CSI Median Age (years): 10 (range, 2 to 18) vs. 11 (range, 3 to 18) Male: 53% vs. 62% Histology • Medulloblastoma: 30% vs. 31% • Mixed germ cell tumors: 17% vs. 23%	All patients **F/U (median [range])**: 22 months (range, 2 to 118) **% F/U**: CD††	Harms	Funding: Supported by a grant from the National Cancer Center, Korea (no. 1010480)

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		Mean CSI dose (CGE or Gy): 32.1 (23.4-39.6) Mean total dose (CGE): 53.2 (range, 39.6 – 60.6)	**Exclusion**: Patients who received concurrent chemotherapy and patients who received both photon RT CSI and PBT CSI	• Germinoma: 20% vs. 8% • Non-germinomatous germ cell tumor: 10% vs. 8% • Other: 20% vs. 15% Treatment Aim • Curative Intent: 73% vs. 69% • Leptomeningeal seeding or recurrent tumor: 27% vs. 31% Chemotherapy prior: 87% vs. 77%			
Bielamowicz 2018 [Likely crossover of patients with Paulino 2018; studies report different outcomes] Retrospective Cohort Study *Moderately High* USA	95	**PBT (n=41)** Passive Scatter Mean dose (Gy): 55.3 (All patients received a tumor bed with margin boost) **Photon RT (n=54)** 3DCRT to the cranial spinal axis + IMRT boost Mean Dose (Gy): 55.4	**Inclusion**: All patients received upfront surgical resection followed by radiotherapy and adjuvant chemotherapy. Eligible patients for this study were those who had pre-radiation thyroid function labs and one or more set of thyroid function studies at least one-year post-radiotherapy. **Exclusion**: Patients without either baseline or subsequent thyroid function studies at least one year after the completion of radiation therapy	PBT vs. Photon Median age (range): 8.2 (2 to 18) years vs. 7 (2.3 to 14.4) years Male: 75.9% vs. 68.3% Diagnosis: Medulloblastoma, all Adjuvant Chemotherapy: 100% vs. 100% Maximal Safe Tumor Resection: 100% vs. 100% Risk Level: - Standard: 61% vs. 75.9% - High: 39% vs. 24.1%	All patients **F/U (median [range])**: 56.4 (26.4 to 115.2) vs. 121.2 (38.4 to 193.2); p<0.0001 **% F/U**: CD‡‡	Mortality Harms	
Kahalley 2019	93	**PBT (n=53)§§** - **PBT CSI (n=22)**	**Inclusion for PBT group**: (1) diagnosed with a primary brain tumor, (2) between the ages of 3-18 years	PBT CSI vs. PBT Focal vs. Surgery	**Median F/U:** NR	Neurological outcomes (FSIQ)	Funding: National Institutes of Health/Nationa

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Prospective Comparative Cohort Moderately High USA		Median dose (range): 54 Gy (45 to 54) - **PBT focal RT (n=31)** Median dose (range): 50.4 Gy (30 to 59.4) [p-value for the difference in dose: p=0.002] **Surgery (n=40)**	(inclusive) at enrollment, and (3) within 6 months of cranial PRT (focal or CSI) with no history of prior courses of RT **Inclusion for Surgery group**: (1) diagnosed with a primary brain tumor, (2) between the ages of 3-18 years (inclusive) at enrollment, and (3) within 6 months of surgical resection or biopsy, with no history of RT or plan for future RT at the time of enrollment. **Exclusion**: Patients diagnosed with brain stem glioma, high grade glioma, or atypical teratoid/rhabdoid tumor	Age (range): 10 (2.2 to 17.8) vs. 8.4 (1.0 to 16.5) vs. 9.3 (2.2 to 18.6) years Male: 59.1% vs. 45.2% vs. 52.5% Histology - Glioma: 4.5% vs. 51.6% vs. 80% - Medulloblastoma/PNET: 77.3% vs. 3.2% vs. 0% - Ependymoma: 0% vs. 19.4% vs. 0% - Germ Cell Tumor: 13.6% vs. 9.7% vs. 0% - Craniopharyngioma: 0% 12.9% vs. 10% - Other: 4.5% vs. 3.2% vs. 10% p<0.001 Tumor Location - Supratentorial: 27.3% vs. 67.7% vs. 75% - Infratentorial: 72.7% vs. 32.3% 25% p=0.001 Median Maximum Tumor Diameter (range): 4.3 (2.5 to 7.0) vs. 4.0 (1.5 to 7.4) vs. 4.6 (0.9 to 7.8) Ventriculoperitoneal shunt: 0% vs. 29% vs. 10%, p=0.007	**% F/U:** 74.5% (93/125)		l Cancer Institute (R01CA187202 to LSK); National Institutes of Health/National Cancer Institute (K07CA157923 to LSK) COI: None

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
				Posterior Fossa Syndrome: 40.9% vs. 3.2% vs. 7.5%, p=0.0004 Mean Baseline FSIQ (SD): 94.2 (16.3) vs. 95.9 (19.5) vs. 93.1 (17.3)			

CD = cannot be determined; COI = conflict of interest; CI = confidence interval; CFFS = Cystic Failure Free Survival; CRT = Conformal radiotherapy; CSI = Cranial spinal irradiation; HR = hazard ratio; IMRT = Intensity modulated radiation therapy; IMRT = Intensity Modulated Radiation therapy; MRI = Magnetic resonance imaging; NFFS = nodular failure-free survival; NR = Not Reported; OR = odds ratio; RoB = Risk of Bias; RT = Radiation Therapy

*Bishop 2014: Follow-up and differential loss to follow-up cannot be determined (number eligible not provided, number excluded and loss to follow-up not described; PBT only 2007 -2012)

†Eaton2016a/b: Follow-up and differential loss to follow-up cannot be determined (number of eligible patients and loss not described and in 2016 b, only patients with 3 years of follow-up with routine endocrine screening were included)

‡Follow-up and differential loss to follow-up cannot be determined (# eligible not provided, only Patients with least 1 MRI performed at least 6 months after RT included)

§Follow-up and differential loss to followup cannot be determined (# eligible not provided, of 93 newly diagnosed patients, 14 were lost to follow-up of those 93)

**Authors do not provide information on the number of patients lost from each treatment group so differential loss to follow-up cannot be determined.

††Follow-up and differential loss to follow-up cannot be determined (# eligible not provided, patient selection methods not clear)

‡‡Follow-up and differential loss to follow-up cannot be determined (# eligible not provided, patient selection methods not clear). Authors state that 27 patients were excluded for the following reasons. Twelve patients died within a year of diagnosis, six received subsequent follow up care at another institution, and nine were diagnosed within a year of our analysis and had insufficient follow-up time.

Appendix Table N4. Detailed data abstraction: comparative studies of proton beam therapy in pediatric brain, spinal, and paraspinal cancers

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Bishop 2014 PBT (n=21) vs. IMRT (n=31) Retrospective Cohort *Moderately High* USA	PBT vs. IMRT **3-year OS (95% CI)** 94.1% (NR) vs. 96.8% (NR); log-rank p=0.742 **Mortality (NR by group)**: 7.7% (4/52), due to: Cyst progression: 1.9% (1/52) Treatment-related morbidity: 5.8% (3/52) (uncontrolled diabetes insipidus and postoperative neurologic injury) **3-year CFFS (95% CI)** 67.0% (NR) vs. 76.8% (NR); log-rank p=0.994 **3-year NFFS (95% CI)** 91.7% (NR) vs. 96.4% (NR); log-rank p=0.546 **Nodular failure**: 4.8% (1/21) vs. 3.2% (1/31) (progression at 26 and 24 months, respectively) *No differences by RT intent (salvage vs. definitive or adjuvant) were observed in 3-year OS, CFFS, or NFFS rates (p=0.294 OS, p=0.412 CFFS, and p=0.951 NFFS)*	PBT vs. IMRT **Early Cyst Growth** (within 3 months of completing RT): 19% (4/21) vs. 42% (13/31); p=0.082 **Late Cyst Growth** (>3 months after RT): 19% (4/21) vs 32% (10/31); p=0.353 **Requiring additional intervention**: 14% (3/21) vs. 10% (3/31) (3 cyst drainage, 2 catheter placement, and 1 surgical fenestration)	PBT vs. IMRT Toxicity Grading Criteria: NR **Late Toxicity (newly acquired from start of radiation), % (n/N)** • Vascular: 10% (2/21) vs. 10% (3/31); p=1.00 • Vision: 5% (1/21) vs. 13% (4/31); p=0.637 • Hypothalamic obesity: 19% (4/21) vs. 29% (9/31); p=0.532 • Endocrinopathy: 76% (16/21) vs. 77% (24/31); p= 1.00 • Panhypopituitarism: 33% (7/21) vs. 55% (17/31); p=0.162 • Other: 43% (9/21) vs. 23% (7/31); p=0.139 [To include, Growth hormone deficits, hypothyroidism, adrenal insufficiency, sexual hormone deficiencies] **Vascular Injury (on imaging), % (n/N)** 9.5% (2/21) vs 9.7% (3/31); p=1.0 (3 had symptomatic strokes, 1 radiologic vascular malformation, 1 radiologic moyamoya) In the 22 patients receiving RT as salvage therapy, there was significantly more morbidity related to visual (p=0.017) and endocrine (p=0.024) dysfunction and a higher rate of panhypopituitarism (p=0.023) compared with patients who received RT as definitive or adjuvant therapy.

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Eaton 2016a/2016b **Eaton 2016a population** PBT (n=45) vs. photon RT (n=43) **Eaton 2016 b population** (Endocrine Abnormalities only*) PBT (n=40) vs. photon RT (n=37) photon RT) Prospective Cohort *Moderately High* USA	PBT vs. photon RT **6-year OS (95% CI)** 82.0% (65.4% to 91.1%) and 87.6% (72.7% to 94.7%); log-rank p=0.285; adj. HR† 2.17 (0.66-7.16); p=0.201 **6-year Recurrence-free survival (95% CI)** 78.8% (63% to 89%) and 76.5% (60.6% to 86.6%); log-rank p=0.948; adj. HR† 1.31 (0.5-3.41); p=0.584 **Total relapses/recurrences:** 22.2% (10/45) vs. 23.3% (10/43) • Diffuse or Leptomeningeal Disease: 50% (5/45) vs. 50% (5/43) • Isolated Focal Spine: 20% (2/45) vs. 30% (3/43) • Isolated Posterior Fossa: 10% (1/45) vs. 20% (2/43) • Isolated Brain, other: 10% (1/45) vs. 0% (0/43) • Posterior Fossa + Focal Spine: 10% (1/45) vs. 0% (0/43)	NR	PBT vs. photon RT **Proportion of patients developing a secondary malignancy, % (n/N):** 0% (0/45) vs. 7% (3/43) (anaplastic astrocytoma at 13 years, intracranial desmoid tumor at 4 years, thyroid cancer at 13 years) **Late Endocrine Abnormalities, % (n/N)** (Eaton 2016b) Univariate Analysis • *Hypothyroidism*: 22.5% (9/40) vs 64.9% (24/37); p<0.001 • *Growth hormone deficiency*: 52.5% (21/40) vs. 56.76% (21/37); p=0.708 *-Received growth hormone replacement*: 85.7% (18/21) vs. 76.2% (16/21), p=0.697 • *Adrenal insufficiency*: 5% (2/40) vs. 8.11% (3/37); p=0.667 • *Sex hormone deficiency*: 2.5% (1/40) vs. 18.92% (7/37); p=0.025 • *Precocious puberty*: 17.5% (7/40) vs. 16.22% (6/37); p=0.881 • *Endocrine replacement therapy*: 55% (22/40) vs. 78.38% (29/37); p=0.03 • *Mean height standard deviation score (±SD)* [n=36 vs. 23]: -1.19 (±1.22) vs. -2 (±1.35); p=0.02 • *BMI standard deviation score (±SD)* [n=36 vs. 24]: 0.6 (±1.08) vs. 0.38 (±1.17); p=0.453 **Multivariate Analysis – ORs or Parameter Estimates (95% CI), PBT vs. Photon:** • *Hypothyroidism*: OR 0.13 (0.04 to 0.41); p<0.001

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			• *Sex hormone deficiency*: OR 0.06 (0.01 to 0.55); p=0.013 • *Endocrine replacement therapy*: OR 0.30 (0.09 to 0.99); p=0.047 • *Height standard deviation score*: parameter estimate 0.89 (0.24 to 1.54); p=0.008 • *Growth hormone deficiency*: OR 0.81 (0.26 to 2.59); p=0.728 PRT remained a significant predictor of reduced risk of hypothyroidism, sex hormone deficiency, and need for endocrine replacement therapy and remained significantly associated with greater height SDS at last follow-up under the propensity adjusted models
Gunther 2015 [Crossover of patients between Gunther 2015 and Sato 2017] PBT (n=37) vs. IMRT (n=35) Retrospective Cohort Study *Moderately High* USA	PBT vs. IMRT **4-year OS (95% CI)** 87.5% (51.6% to 97.3%) vs. 78.8% (60.6% to 89.3%); log-rank p=0.21 **4-year disease-specific Survival (95% CI)** 90% vs. 78.8%; p=0.10 (only 1 death was no attributed to disease [toxicity])	NR	PBT vs. IMRT **Proportion of patients experiencing changes on MRI, % (n/N)** • *Overall*: 43.2% (16/37) vs. 17.1% (6/35) • *Grade 1*: 16.2% (6/37) vs. 2.9% (1/35) • *Grade 2*: 10.8% (4/37) vs. 14.3% (5/35) • *Grade 3*: 10.8% (4/37) vs. 0% (0/35) • *Grade 4*: 5.4% (2/37) vs. 0% (0/35) • *Symptomatic (consistent with treatment-related CNS injury)*‡: 10.8% (4/37) vs 8.6% (3/35) **Likelihood of experiencing imagining changes on MRI, PBT vs. IMRT**: Univariate analysis: OR 3.68 (95% CI, 1.23-10.99); p=0.019

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			Multivariate analysis: adj. OR 3.89 (95% CI, 1.20-12.61); p=0.024
Sato 2017 [Crossover of patients between Gunther 2015 and Sato 2017] PBT (n=41) vs. IMRT (n=38) Retrospective Cohort Study RoB: Moderately high USA	PBT vs. IMRT **OS (95% CI)** 3-years: 97% (83%-99%) vs. 81% (63%-90%); log-rank p=0.08 6-years: 88% (NR) vs. 70% (NR) [Estimated from figure 2C] **PFS (95% CI)** 3-year: 82% (64%-92%) vs. 60% (42%-74%); log-rank p=0.0307 HR (IMRT as reference), 0.422 (95% CI 0.16-1.10); p=0.077 6-year: 82% (NR) vs. 38% (NR) [Estimated from figure 2C] **Local recurrence-free survival (95% CI) [Estimated from Figure 2C]** 3-years: 88% (NR) vs. 65% (NR) 6-years: 88% (NR) vs. 40% (NR); log-rank p=0.01 **Proportion of patients experiencing recurrence, % (n/N)** 17% (7/41) vs. 55% (21/38), p=0.005 • Local recurrence: 86% (6/7) vs. 86% (18/21) **Disease-related mortality (disease progression)**	NR	PBT vs. IMRT Toxicity Grading Criteria: NR **Toxicity, % (n/N)** • *All events*: 7.3% (3/41) vs. 13.2% (5/38) • *Radiation Necrosis*: 7.3% (3/41) vs. 7.9% (3/38) (5 of the 6 required a steroid with or without bevacizumab) • *Stroke*: 0% (0/41) vs. 2.6% (1/38) • *Cavernoma*: 0% (0/41) vs. 2.6% (1/38)

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
	4.9% (2/41) vs. 31.6% (12/38)		
Kahalley 2016 PBT (n=90) vs. Photon RT§ (n=60) Retrospective Cohort Study *Moderately High* USA	NR	NR	PBT vs. Photon RT **Adjusted change in IQ score per year (beta coefficient, 95% CI)** • *All patients:* -0.7 (-1.6 to 0.2), p=0.13 vs. -1.1 (-1.8 to -0.4), p=0.004; p-value for the difference between PBT and photon RT = 0.51 ○ IQ scores were significantly higher in the PBT vs. the Photon group by 8.7 point on average, p=0.01 • *CSI patients (n=69):* -0.8 (NR), p=0.20 vs. -0.9 (NR), p=0.06; p-value for the difference between PBT and photon RT = 0.89 ○ IQ scores were significantly higher in the PBT vs. the Photon group by 12.5 point on average, p=0.004 *Focal RT patients (n=54):* -0.6 (-2.0 to 0.8), p=0.40 vs. -1.6 (-3.0 to -0.2), p=0.03; ; p-value for the difference between PBT and photon RT = 0.34
Kopecky 2017 PBT (n=117) vs. IMRT (n=157) vs. 2D/3D CRT (n=1003) Retrospective Cohort Study *Moderately High* USA	PBT vs. IMRT vs. 2D/3D CRT **5-year OS (all patient):** 79% (95% CI NR) *Univariate analysis for OS*: • 2D/3D CRT (referent): HR 1.00 • PBT: HR 0.99 (95% CI 0.41 to 2.4); p=0.98 • IMRT: HR 0.82 (95% CI 0.46 to 1.48); p=0.52	NR	NR
Paulino 2018	NR	NR	PBT (passively scattered) vs. Photon RT

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
PBT (passively scattered) (n=38) vs. Photon RT (n=46) Retrospective Cohort Study RoB: Moderately high USA			CTCAE criteria (v 3.0) **Hearing Loss (according to worse ear)** • *Grade 0:* 34.2% (13/38) vs. 21.7% (10/46) • *Grade 1:* 21.1% (8/38) vs. 39.1% (18/46) • *Grade 2:* 15.8% (6/38) vs. 10.9% (5/46) • *Grade 3:* 26.3% (10/38) vs. 21.7% (10/46) • *Grade 4:* 2.6% (1/38) vs. 6.5% (3/46) • *Grade 3 and 4:* 29.9% (11/38) vs. 28.3% (13/46), p=1.0 **Cumulative incidence of Grade 3 and 4 ototoxicity (hearing loss)** Left Ear: p=0.917 • *3-year:* 11.5% vs. 16.4% • *5-year:* 22.6% vs. 25.9% Right Ear: p=0.623 • *3-year:* 14.2% vs. 11.6% • *5-year:* 29.7% vs. 21.3%
Song 2014 PBT CSI (n=30) vs. Photon RT CSI (n=13) Retrospective Cohort Study *Moderately High* Korea	NR	NR	PBT CSI vs. Photon RT CSI Toxicity Grading Criteria: CTCAE v.4 **Acute Toxicity, % (n/N)** *Hematological toxicities* **Leukopenia**: p=0.069 • Grade 3: 57% (14/30) vs. 46% (6/13) • Grade 4: 7% (2/30) vs. 31% (4/13) **Granulocyte colony-stimulating factor administration**: 40% (12/30) vs. 31%(4/13); p=0.655 **Anemia**

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			• Grade 3: 0% (0/30) vs. 15% (2/13); p=0.493 • Grade 4: 0% (0/30) vs. 0% (0/13) **Red blood cell transfusion**: 50% (15/50) vs. 39% (5/13); p=0.486 **Thrombocytopenia**: p=0.012 • - Grade 3: 20% (6/30) vs. 31% (4/13) • - Grade 4: 3% (1/30) vs. 23% (3/13) **Platelet transfusion** • Grade *1 or 2*: 17% (5/30) vs. 46% (6/13); p=0.042 <u>*Nonhematological toxicities*</u> **Nausea** • Grade 1 or 2: 33% (10/30) vs. 46% (6/13); p=0.424 • Grade ≥3: 0% (0/30) vs. 0% (0/13) **Dysphagia** • Grade 1 or 2: 47% (14/30) vs. 15% (2/13); p=0.086 • Grade ≥3: 0% (0/30) vs. 0% (0/13) **Anorexia**: p=1.00 • Grade 1 or 2: 33% (10/30) vs. 31% (4/13) • Grade 3: 3% (1/30) vs. 0% (0/13) **Skin disorder** • Grade 1 or 2: 37% (11/30) vs. 31% (4/13); p=1.00 • Grade ≥3: 0% (0/30) vs. 0% (0/13) **Vomiting**: p=1.00 • Grade 1 or 2: 27% (8/30) vs. 31% (4/13) • Grade 3: 3% (1/30) vs. 0% (0/13) **Neurological disorders** • Grade 1 or 2: 13% (4/30) vs. 23% (3/13) • Grade ≥3: 0% (0/30) vs. 0% (0/13) **Diarrhea**: p=0.023 • Grade 1 or 2: 0% (0/30) vs. 15% (2/13) • Grade 3: 0% (0/30) vs. 8% (1/13)

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			Ophthalmic disorders • Grade 1 or 2: 7% (2/30) vs. 8% (1/13); p=1.00 • Grade ≥3: 0% (0/30) vs. 0% (0/13) **Cough** • Grade 1 or 2: 7% (2/30) vs. 8% (1/13); p=1.00 • Grade ≥3: 0% (0/30) vs. 0% (0/13) **Changes in haematological parameters from before starting CSI to 1 month after treatment, mean ± standard deviation** • White blood cell count: -0.57 ± 2.22 vs. -2.61 ± 2.27; p=0.009 • Haemoglobin (g/dl) corrected for transfusion: -0.57 ± 1.48 vs. -1.16 ±2.06; p=0.115 • Platelet count (x10^5cells/µl) corrected for transfusion: -0.68 ± 0.72 vs. -2.74 ±2.28; p=0.007
Bielamowicz 2018 {Patient crossover with Paulino 2018] PBT (n=41) vs. Photon RT (n=54) Retrospective Cohort Study *Moderately High* USA	PBT vs. Photon **Disease-related Mortality, % (n/N)** All: 11.6% (11/95) [n=1 due to a secondary glioblastoma]	NR	PBT vs. Photon **Proportion of patients developing hypothyroidism, % (n/N) [PBT as referent]** - *Any hypothyroidism*: 19.5% (8/41) vs. 46.3% (25/54); HR 1.85 (95% CI, 0.8 to 4.2), p=0.14 - *Primary Hypothyroidism*: 7.3% (3/41) vs. 20.4% (12/54); HR 2.1 (95% CI, 0.6 to 7.7), p=0.27 - *Central Hypothyroidism*: 9.8% (4/41) vs. 24% (13/54); HR 2.16 (95% CI 0.7 to 6.6), p=0.18 **5-year Hypothyroidism Free Rate (Kaplan Meier Analysis (95% CI)**** 76% (60% to 87%) vs. 59% (44% to 71%)
Kahalley 2019	NR	NR	PBT CSI vs. PBT Focal vs. Surgery

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
PBT CSI (n=22) vs. PBT Focal (n=31) vs. Surgery (n=40) Prospective Cohort Study Moderately High USA			**Adjusted change in FSIQ per year (beta coefficients, 95% CI) ††:** - PBT CSI vs. PBT Focal: -2.9 (-4.7 to -1.1), p=0.003 - PBT CSI vs. Surgery: -2.1 (-3.8 to -0.3), p=0.020 - PBT Focal vs. Surgery: 0.8 (-0.8 to 2.4), p=0.302 **Adjusted change in Verbal Comprehension Index per year (beta coefficients, 95% CI) ††:** - PBT CSI vs. PBT Focal: -1.0 (95% CI -2.9 to 0.9), p=0.316 - PBT CSI vs. Surgery: -1.0 (95% CI -2.8 to 0.8), p=0.274 - PBT Focal vs. Surgery: 0.0 (95% CI -1.7 to 1.6), p=0.963 **Adjusted change in Perceptual Reasoning Index per year (beta coefficients, 95% CI) ††:** - PBT CSI vs. PBT Focal: -1.1 (95% CI -3.6 to 1.5), p=0.399 - PBT CSI vs. Surgery: -0.7 (95% CI -3.1 to 1.8), p=0.591 - PBT Focal vs. Surgery: 0.4 (95% CI -1.8 to 2.6), p=0.699 **Adjusted change in Working Memory Index per year (beta coefficients, 95% CI) ††:** - PBT CSI vs. PBT Focal: -1.4 (95% CI -3.7 to 0.8), p=0.205 - PBT CSI vs. Surgery: -1.5 (95% CI -3.6 to 0.7), p=0.177 - PBT Focal vs. Surgery: 0.0 (95% CI -2.0 to 1.9), p=0.973 **Adjusted change in Perceptual Reasoning Index per year (beta coefficients, 95% CI) ††:** - PBT CSI vs. PBT Focal: -3.3 (95% CI -5.6 to

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			-1.1), p=0.005 - PBT CSI vs. Surgery: -2.6 (95% CI -4.7 to -0.5), p=0.019 - PBT Focal vs. Surgery: 0.7 (95% CI -1.2 to 2.7), p=0.450

CI = confidence interval; CFFS = Cystic Failure Free Survival; CRT = Conformal radiotherapy; CSI = Cranial spinal irradiation; HR = hazard ratio; IMRT = Intensity modulated radiation therapy; IMRT = Intensity Modulated Radiation therapy; MRI = Magnetic resonance imaging; NFFS = nodular failure-free survival; OR = odds ratio; RoB = Risk of Bias; RT = Radiation Therapy
*Eaton 2016a/2016b: Endocrine outcomes data from Eaton 2016b; Ten patients were ineligible due to early recurrent disease or death within 3 years of diagnosis and one patient was ineligible due to lack of available endocrine follow-up data, leaving 77 patients who met eligibility criteria for inclusion in the late endocrine effects analysis
†Eaton2016a/2016b: The following variables were removed from the model: Age at Diagnosis, Location of RT boost, Histology, Residual disease after surgery, days from surgery to RT, RT treatment length, Date of Diagnosis, and RT CSI dose (for RFS only).
‡Gunther 2015: Symptoms included ataxia, hemiplegia, cranial nerve palsy, right-side paralysis, respiratory compromise, facial weakness, and dystharia.
§Kahlley 2016: Photon RT included, three-dimensional conformal (8.3%), IMRT (45.0%), and three-dimensional conformal plus IMRT tumor bed (TB)/margin boost (46.7%).
**Meaningful statistical comparison was not possible due to the low number of patients in the proton group who had reached 5 years post XRT at the time of analysis.

Appendix Table N5. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in pediatric head & neck (including skull-base) cancers

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Lucas (2015) RoB: High Retrospective Case Series	**Diagnosis:** Pediatric Head and Neck (Esthesioneuroblastoma) **Indication:** Curative Intent	**N=8** **Median Age: 10 years (range 4–21)** **Male: 25%** **Primary Tumor Sites: Sinonasal cavity, 100% (8/8)**	**PBT**: Passively scattered PBT **Median total PBT Dose (Range)**: 59.4 Gy (RBE) (range, 54–70.2)	**Median F/U (range)**: 55.2 (9.6 to 112.8) months	**Primary Outcomes** **OS (95% CI)** • 5-year: 87.5% (NR) **LC (95% CI)**: 100% (NR) **Mortality, % (n/N)**	*Toxicity Grading Criteria*: CTCAE v.4.0 **Acute Toxicity, % (n/N)** • All Acute Toxic Effects - *Grade 1:* 5 events - *Grade 2:* 18 events

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
USA COI: None Funding: NR		**Risk Classification: Kadish** **B: 37.5% (3/8)** **C: 12.5% (1/8)** **D: 50% (4/8)** **Hymans grade** **1: 12.5% (1/8)** **2: 12.5% (1/8)** **3: 62.5% (5/8)** **3/4: 12.5% (1/8)**	**Additional Treatments in conjunction with PBT**: Surgery: 75% (6/8) Chemotherapy: 75% (6/8)		• Disease-related: 12.5% (1/8) **Proportion of patients experiencing distant failure:** 25% (2/8) **<u>Secondary Outcomes</u>** NR	- *Grade 3:* 5 events • Odynophagia - *Grade 2:* 37.5% (3/8) • Radiation Dermatitis - *Grade 1:* 37.5% (3/8) - *Grade 2*: 62.5% (5/8) • Mucositis - *Grade 2:* 25% (2/8) - *Grade 3:* 25% (2/8) • Dysguesia - *Grade 2:* 25% (2/8) • Soft-tissue necrosis - *Grade 2:* 12.5% (1/8) • Esophageal Infection - *Grade 2:* 12.5% (1/8) • Rhinitis/Sinusitis - *Grade 2: 25% (2/8)* - *Grade 3:* 12.5% (1/8) • Febrile Neutropenia - *Grade 3:* 12.5% (1/8) • Nausea - *Grade 1:* 12.5% (1/8) - *Grade 3: 12.5% (1/8)Grade 2:* 12.5% (1/8) • Emesis - *Grade 1:* 12.5% (1/8) • Weight Loss - *Grade 2:* 12.5% (1/8)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						- *Grade 3:* 12.5% (1/8) **<u>Late Toxicity, % (n/N)</u>** • All Late Toxic Effects - *Grade 1:* 3 events - *Grade 2: 5* events - *Grade 3:* 2 events • Epistaxis - *Grade 1:* 25% (2/8) • Retinopathy - *Grade 2:* 25% (2/8) - *Grade 3:* 12.5% (1/8) • Optic Neuropathy - *Grade 3:* 12.5% (1/8) • Endocrine abnormalities - *Grade 2:* 12.5% (1/8) • Hearing Loss (Bilateral) - *Grade 2:* 12.5% (1/8) • Xerostomia - *Grade 1:* 12.5% (1/8) - *Grade 2:* 12.5% (1/8) **<u>Proportion of patients acquiring a secondary malignancy</u>**: 0%
Rassi (2018) RoB: High Retrospective Case Series	**Diagnosis:** Pediatric Skull-base (Skull-base chordoma) **Indication:** Curative Intent (Initial Treatment): 72.2% (13/18)	**N=18** **Mean Age: 10.7 years (range, 0.8-22)** **Male: 38.9%** **Clival Tumor Sites: Upper, 22.6% (7/31);**	**PBT**: proton + photon RT, n=8 PBT, n=8; Unknown, n=2	**Median F/U (range)**: 122 (8 to 263) months	**<u>Primary Outcomes</u>** **OS ± SE (n=18)** • *5-year:* 64% ± 12% • *10-year:* 57% ± 12% • *20-year:* 57% ± 12% **PFS ± SE (n=18)**	NR

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
USA COI: None Funding: None --- Does subpopulation analysis for male vs. female, young vs. old, etc…	Treatment for a recurrence: 27.8% (5/18)	**Middle, 25.8% (8/31); Lower, 51.6% (16/31)** **Risk Classification: NR**	**PBT + photon Dose Range**: 75.6-79.8 Cobalt Grey Equivalent **PBT alone Dose Range**: NR **Additional Treatments in conjunction with PBT**: Tumor resection, 100% (18/18); Chemotherapy, 11.1% (2/18)		• *5-year:* 57% ± 12% • *10-year:* 57% ± 12% • *20-year:* 57% ± 12% **Secondary Outcomes** NR	
Vogel (2018) RoB: High Prospective Case Series USA COI: None Funding: NR ---	**Diagnosis:** Head and Neck (Rhabdomyosarcoma, 20.7% (35/69); Ewing sarcoma, 14.5% (10/69); Other, 34.8% (24/69) **Indication:** Curative Intent	**N=69** **Rhabdomyosarcoma (n=35)** **Median Age: 6 years (range, 1–22)** **Male: 63%** **Ewing sarcoma (n=10)** **Median age: 13 years (range, 2–23)** **Male: 60%:** **Other (n=24)** **Median Age: 14 years (range, 1–21)** **Male: 60%**	**PBT**: Rhabdomyosarcoma Double scatter PBT (51%); PBS PBT (37%); Mixed proton and IMRT (11%) Ewing sarcoma Double scatter PBT (20%); PBS PBT (60%); Mixed proton and IMRT (20%) Other Tumors Double scatter PBT (12%); PBS PBT (46%); Mixed proton and IMRT (42%)	**Median F/U (range)**: 13.9 (1.71 to 58.3) months	**Primary Outcomes** **OS (95% CI)** All patients • *1-year*: 93% (79% to 98%) • *3-year*: 90% (74% 96%) Rhabdomyosarcoma • *1-year*: 96% (73% to 99%) Ewing Sarcoma • *1-year*: 83% (27% to 98%) **Freedom from Local Recurrence (95% CI)** All patients • *1-year*: 92% (80% to 97%) • *3-year*: 85% (68% 93%)	*Toxicity Grading Criteria*: CTCAE v.4.0 **Acute Toxicity, % (n/N)** • Anorexia - Grade 1: 17% (12/69) - Grade 2: 12% (8/69) - Grade 3: 22% (15/69) • Dehydration - Grade 1: 1% (1/69) - Grade 2: 6% (4/69) - Grade 3: 1% (1/69) • Drymouth - Grade 1: 32% (22/69) - Grade 2: 3% (2/69) - Grade 3: 3% (2/69) • Dysgeusia - Grade 1: 20% (14/69)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
			PBT Dose Range: Rhabdomyosarcoma 36.0 to 59.4 Gy (RBE) in 1.8 Gy (RBE) fractions Ewing sarcoma 55.8 Gy to 65.6 Gy (RBE) in 1.8 Gy (RBE) fractions Other tumor histologies 36.0 Gy (RBE) to 81.0 (RBE) in 1.8–2.0 Gy (RBE) fractions **Additional Treatments in conjunction with PBT**: Rhabdomyosarcoma Biopsy, (32/35); Chemotherapy, 100% (35/35) Ewing sarcoma Biopsy, 80% (8/10); Chemotherapy, 100% (10/10) Other tumor histologies Biopsy, 29% (7/24)		Rhabdomyosarcoma • *1-year*: 84% (58% to 95%) Ewing Sarcoma • *1-year*: 86% (33% to 98%) **Freedom from Regional Recurrence (95% CI)** All patients • *1-year*: 94% (83% to 98%) • *3-year*: 86% (67% 94%) Rhabdomyosarcoma • *1-year*: 85% (61% to 95%) Ewing Sarcoma • *1-year*: 100% (100%) **Freedom from Distant Recurrence (95% CI)** All patients • *1-year*: 86% (70% to 93%) • *3-year*: 78% (54% 90%) Rhabdomyosarcoma • *1-year*: 95% (69% to 99%) Ewing Sarcoma • *1-year*: 86% (33% to 98%)	- Grade 2: 10% (7/69) • Dysphagia - Grade 1: 19% (13/69) - Grade 2: 13% (9/69) - Grade 3: 7% (5/69) • Fatigue - Grade 1: 41% (28/69) - Grade 2: 22% (15/69) • Headache - Grade 1: 6% (4/69) - Grade 2: 1% (1/69) • Mucosal infection - Grade 1: 3% (2/69) - Grade 2: 1% (1/69) - Grade 3: 1% (1/69) • Nausea - Grade 1: 13% (9/69) - Grade 2: 3% (2/69) - Grade 3: 1% (1/69) • Neck edema - Grade 1: 9% (6/69) - Grade 2: 1% (1/69) • Oral mucositis - Grade 1: 14% (10/69) - Grade 2: 20% (14/69) - Grade 3: 4% (3/69) • Radiation dermatitis - Grade 1: 61% (42/69)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
			Chemotherapy, 50% (12/24)		**<u>Secondary Outcomes</u>** NR	- Grade 2: 26% (18/69) - Grade 3: 1% (1/69) • Salivary inflammation - Grade 1: 20% (14/69) - Grade 2: 4% (3/69) • Taste change - Grade 1: 1% (1/69) - Grade 2: 4% (3/69) **Proportion of patients requiring new placement of a feeding tube**: 13% (9/69) **Proportion of patients initiating or increasing opiate use during radiation therapy**: 29% (20/69) **Proportion of patients hospitalized for dehydration and pain control**: 1.5% (1/69)

OS = Overall survival; LC = Local Control; RoB = Risk of Bias; COI = Conflict of Interest; NR = Not reported; F/U = Follow-up; RT = Radiation Therapy; SE =standard error; PFS = Progression Free Survival; Gy = Gray; RBE = Relative Biological Effectiveness; PBT = Proton Beam Therapy

Appendix Table N6. Study characteristics and patient demographics: comparative studies of proton beam therapy in pediatric head & neck (including skull-base) cancers

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Grant 2015 Retrospective Cohort Study *Moderately High* USA	24	**PBT (n=13)**: Median total dose (Gy): 60 *Passive scatter PBT, n=8; Intensity-modulated PBT, n=5* **Photon/electron-based RT (n=11)**: Median total dose (Gy): 60 *Electron beam therapy, n=8; IMRT, n=3* Surgeries included submandibular gland resection (n=4), superficial parotidectomy (n=7), and total parotidectomy (n=13); neck dissection (n=16), and 7of those patients were found to have nodal metastases	**Inclusion**: Age ≤18 years of age who had received adjuvant RT for primary salivary gland tumors between 1996 and 2014 **Exclusion**: NR	PBT vs. Photon/electron-based RT Median Age (range): 13 years (6-18) vs. 15 years (7-18) Male: 46% vs. 45% Tumor site • Parotid: 85% vs. 82% • Submandibular: 15% vs. 18% Histology • Mucoepidermoid carcinoma: 54% vs. 45% • Adenoid cystic carcinoma: 23% vs. 18% • Adenocarcinoma: 15% vs. 0% • Acinic cell carcinoma: 0% vs. 18% • Pleomorphic adenoma: 8% vs. 0% • Myoepithelioma: 0% vs. 9% • Undifferentiated carcinoma: 0% vs. 9% Tumor Grade • Low/intermediate: 54% vs. 45% • High: 15% vs. 27% • Unknown: 31% vs. 27% Chemotherapy: 7.9% vs. 9.1%	PBT vs. Photon/electron-based RT **F/U (median [range])**: 8 months (range, 2-48) vs. 92 months (range, 2-218); p<0.05 **% F/U**: 100%	Acute Toxicity	Funding: NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		The primary indications for RT were close (<1 mm) or positive surgical margins (n=21), extra-glandular extension (n=2), or tumor spillage (n=1)					

F/U = Follow-up; Gy = Gray; mm = millimeter; NR = Not reported; PBT = Proton Beam Therapy; RoB = Risk of Bias; RT = Radiation Therapy

Appendix Table N7. Detailed data abstraction: comparative studies of proton beam therapy in pediatric head & neck (including skull-base) cancers

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Grant 2015 PBT (n=13) vs. Photon/electron-based RT (n=11) Retrospective Cohort Study *Moderately High* USA	*At median follow-up no disease recurrence or deaths were observed in either group.*	NR	PBT vs. Photon/electron-based RT *Toxicity Grading Criteria: CTCAE v4* **Acute Toxicity (Grade 2 and 3), % (n/N)** • Dermatitis: 54% (7/13) vs. 55% (6/11); p=1.00 • Dysphagia: 0% (0/13) vs. 27% (3/11); p=0.08 • Otitis externa: 8% (1/13) vs. 18% (2/11); p=0.58 • Mucositis: 46% (6/13) vs. 91% (10/11);p<0.05

CTCAE = Common Terminology Criteria for Adverse Events; NR = Not reported; PBT = Proton Beam Therapy; RoB = Risk of Bias; RT = Radiation Therapy

Appendix Table N8. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in pediatric lymphomas

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Wray (2016) RoB: High Retrospective Case Series USA COI: None Funding: NR	**Diagnosis:** Pediatric Lymphoma (Hodgkin Lymphoma) **Indication:** Curative Intent	**N=22** **Age: 6–8 years, n=3; 12–15 years, n=5; 16–18 years, n=14** **Male: 50%** **Tumor Characteristics:** **Bulky disease: 76% (16/22)** **Relapsed disease: 18% (4/22)** **Primary Tumor Sites:** **Cervical/supraclavicular: 100 (22/22)** **Infraclavicular: 45% (10/22)** **Mediastinum: 91% (20/22)** **Lung hilum: 59% (13/22)** **Para-aortic: 41% (9/22)** **Mesenteric: 9% (2/22)** **Splenic: 41% (9/22)** **Pelvic/inguinal: 9% (2/22)** **Extranodal: 27% (6/22)** **Risk Classification:** **Intermediate risk: 29% (7/22)**	**PBT**: 77% (17/22) patients were treated with involved-site radiation therapy 41% (9/22) treated with a sequential proton boost **Median total PBT Dose (Range)**: 21 Gy (RBE) (15-36 Gy (RBE)) **Additional Treatments in conjunction with PBT**: Chemotherapy, 100% (22/22)	**Median F/U (range)**: 36 (10 to 79) months	**Primary Outcomes** **OS (95% CI)** • *2-year:* 94% (NR) • *3-year:* 94% (NR) **PFS (95% CI)** • *2-year:* 86% (NR) • *3*-year: 86% (NR) **Proportion of patients experiencing recurrence**: 13.6% (3/22) [All 3 patients that relapsed had high risk disease] **Secondary Outcomes** NR	*Toxicity Grading Criteria*: CTCAE v.4.0 *No PBT-related grade 3 or higher acute or late complications were observed.* **Acute Toxicity, % (n/N)** • All patients - *Grade 2:* 22.7% (5/22) • Esophagitis - *Grade 2:* 9.1% (2/22) • Nausea/vomiting - *Grade 2:* 4.5% (2/22) • Fatigue - *Grade 2:* 9.1% (1/22) **Late Toxicity, % (n/N)** • Chronic hypothyroidism - *Grade 2:* 9.1% (2/22) **Secondary Malignancy**: 0% **Cardiac Complications**: 0%

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		High risk: 50% (11/22)				
Hoppe 2018 [See Data Abstraction for Adult Lymphoma Studies]						

CI = Confidence Interval; COI = Conflict of Interest; CTCAE = Common Terminology Criteria for Adverse Events; NR = Not reported; OS = Overall Survival; PBT = Proton Beam Therapy; PFS = Progression Free Survival

Appendix Table N9. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in pediatric ocular cancers

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Mouw 2014 Retrospective Case Series RoB: High USA Funding: NR COI: H Shih is a senior editor of the IJROBP.	**Diagnosis**: Pediatric Retinoblastoma **Indication**: Curative Intent	N=49 patients, 60 eyes Median Age (range): 6 months (6 days to 30 months) Male: 47% **Eyes Involved:** Unilateral: 16% (8/49) Bilateral: 84% (41/49)	**PBT**: NR **Median PBT Dose (range)**: 44 Gy (RBE) (range, 40 to 46.8 **Additional Treatments in conjunction with PBT:** Chemotherapy: 51% (25/49) [n=22 prior to PBT] Laser photocoagulation	**Median F/U (range):** 96 (12 to 288) months	**Primary Outcomes** **Mortality, % (n/N)** • Disease Related: 0% **Proportion of patients developing metastases:** 0% **Proportion of patients with in field recurrence:** 0%	**Proportion of tumors requiring enucleation**: 18% (11/60) **Proportion of eyes and patients developing ocular complication requiring procedural correction**: 20% (12/60 eyes); 22% (11/49 patients) Cataracts: 4/12 eyes Radiation retinopathy: 3/12 yes Glaucoma: 1/12 eyes

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
---			and/or cryotherapy: 72% (43/60 eyes)		**<u>Secondary Outcomes</u>** **Visual Acuity, % (n/N) (n=30 eyes evaluated)** 20/40 or better (Good): 47% (14/30) 20/40 to 20/600 (Moderate): 23% (7/30) Worse than 20/600 (Poor): 30% (9/30)	Neovascularization: 1/12 eyes Other complications: 2/12 eyes Multiple complications: 1/12 eyes **Cosmetic complications likely associated with PBT, % (n/N)** Hypoplasia: 30.6% (15/49) Hyperpigmentation: 6.1% (3/49) Soft tissue fibrosis over the treatment portal: 2% (1/49)
Petrovic 2016 Retrospective Case Series RoB: High Switzerland Funding: NR COI: None --- Subpopulation analysis based on young vs. old	**Diagnosis:** Pediatric Uveal Melanoma **Indication:** Curative intent (1 patient had metastatic disease)	N=43 Median Age (range): 17.3 years (9 to 21) Male: 47% **Tumor Characteristics** Mean Largest Tumor Diameter (SD): 17 mm (4.3) Extrascleral extension: 12% (5/43) **Primary Tumor Location**: Iris: 21% (9/43) Ciliary Body: 16% (7/43) Anterior choroid: 21% (9/43)	**PBT**: NR **Median PBT Dose (range):** 60 Gy (RBE) **Additional Treatments in conjunction with PBT**: None	**Median F/U (range):** 155 (6 to 281) months	**<u>Primary Outcomes</u>** **Relative Survival Rate (95% CI)** • 5-year: 93% (84% to 100%) • 10-year: 93% (85% to 100%) • 15-years: 85% (72% to 99%) **Proportion of patients experiencing liver metastases**: 14% (6/43) **Rates of Metastasis (95% CI)** • 5-year: 8% (0% to 16%)	**Presence of Lens Opacities**: 39% (15/38) [excluding the 5 patients that received enucleation] **Proportion of Pseudophakic patients**: 16% (6/38) **Proportion of patients with retinal detachment**: 21% (8/38) **Vitreous or subretinal hemorrhage**: 2.6% (1/38) **Enucleation**: 12% (5/43)*

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		Posterior choroid: 42% (18/43) **Comorbidities**: Loss of vision: 67% (29/43) Metamorphopsia: 14% (6/43) Flashes of light: 9% (4/43) Floaters: 1/43 (2%)			• 10-year: 11% (0% to 20%) • 15-years: 19% (3% to 32%) **Proportion of patients achieving local tumor control**: 97.7% (42/43) **5-, 10-, and 15-year Kaplan-Meier eye retention rates**: 90% (80% to 100%) **<u>Secondary Outcomes</u>** **Mean BCVA (SD) [range]** • Baseline: 0.5 (±0.4) [0-1.25] • 6-months: 0.4 (±0.4) [0-1.5] • Last follow-up: 0.2 (±0.4) [0-1] (18% (7/38) had no light perception	

BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; COI = Conflict of Interest; F/U = Follow-up; PBT = Proton Beam Therapy; RoB = Risk of Bias; SD = Standard Deviation
*Due to presumed local recurrence (n=1), complications neovascular glaucoma (n=2), phthisis bulbi (n=1) and a painful pseudophakic bullous keratopathy in an otherwise non-functional eye (n=1)

Appendix Table N10. Study characteristics and patient demographics: comparative studies of proton beam therapy in pediatric ocular cancers

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Agarwal 2016 Retrospective cohort study *Moderately High* USA	39 (70 total effected eyes; 47 eyes treated with RT)	**PBT (n = 16 eyes):** passive scatter technique with either an appositional field or a combination of left and right anterior oblique beams and a vertex beam; Median total dose (Gy [RBE]): 36 (range, 36-45) **Photon or electron therapy (n= 27 eyes):** Median total dose (Gy [RBE]): 45 (range, 36-46) **Brachytherapy (n = 4 eyes):** Median total dose (Gy [RBE]): 45 (range, 36-46) **Treatment setting/ Indication:** First-line: 29.8% Second-line: 8.5%	**Inclusion:** patients with Retinoblastoma treated with radiation at a single institution between April 1990 and December 2012. **Exclusion:** NR	*Overall* Median age (range): 0.95 (0.02 to 8.9) years *PBT vs. photon vs. brachytherapy*: 1.9 (0.9 to 4.3) years vs. 1.4 (0.25 to 10.4) years vs. 1.8 (0.83 to 4.9) years Male: 49% Race Caucasian: 51%; Hispanic: 44% International Classification System stage B: 17% C: 8.5% D: 42.6% E: 14.9% Extraocular: 10.6% Unknown: 6.4% Type of disease Unilateral: 21% (n=8) Bilateral: 77% (n=30) Trilateral: 3% (n=1) Any chemotherapy: 72% (n=28) (46% [n=13] multiple regiments)	Overall **F/U (median [range]):** 96 (1 to 288) months *PBT vs. photon vs. brachytherapy*: 36 vs. 120 vs. 60 months **% F/U:** 97.4% (38/39)	OS and EFS Enucleation Locoregional failure Harms	Funding NR The authors have no COIs to disclose

Study Design RoB Country	N	Interventions Treatment Protocol	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		Postoperative: 8.5% Salvage: 53.2% • All patients underwent 2- or 3D CT planning • Radiation delivered with anesthesia					

COI = Conflict of Interest; CT = Computerized Tomography; EFS = Event Free Survival; EFS = Event Free Survival; F/U = Follow-up; Gy = Gray; NR = Not reported; OS = Overall Survival; PBT = Proton beam therapy; RBE = Relative Biological Effectiveness; RoB = Risk of Bias; RT = Radiation Therapy

Appendix Table N11. Detailed data abstraction: comparative studies of proton beam therapy in pediatric ocular cancers

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms

Agarwal 2016
 	
N=39 (70 total effected eyes; 47 of which were treated with RT)
PBT (n = 16 eyes) vs. Photon or electron therapy (n = 27 eyes) vs. Brachytherapy (n = 4 eyes)
 	
Retrospective cohort study
 	
Moderately High
 	
USA
	PBT vs. Photon vs. Brachytherapy
	
	OS (95% CI):
	Overall 97% (38/39) at final f/u
	(the 1 death from disease progression was in photon group; number of patients per group NR)
	
	EFS (95% CI):
	In patients with stage D and E disease: 38.5% (5/13) vs. 54.5% (6/11) vs. NR; p=0.621 (NOTE: f/u times significantly different, median 3 vs. 10 years)
	
	Locoregional failure:
	56.3% vs. 59.3% vs. NR, P=1.0
		NR	PBT vs. Photon (brachytherapy NR)
			
			Enucleation: 37.5% (6/16 eyes) vs. 29.6% (8/27 eyes) vs. 25% (1/4 eyes), p=NR
			
			Acute toxicities:
			Any (≥1 event): 93.8% vs. 74.1%; p=0.22
			• Erythema of skin: n=33
			• Hyperpigmentation: n=8
			• Erythema of the conjunctiva: n=5
			• Loss of eyelashes: n=4
			
			Late/Long-term toxicities:
			Any (≥1 event): 62.5% (10/16 eyes) vs. 55.6% (15/27 eyes); p=0.275
			• Cataracts: 31.9% (15/47 eyes)
			  ○ PBT only: 31.3% (5/16 eyes)
			• Vitreous hemorrhage: 14.9% (7/47 eyes)
			  ○ PBT only: 18.8% (3/16 eyes)
			• Radiation retinopathy: 10.6% (5/47 eyes)
			  ○ PBT only: 12.5% (2/16 eyes)
			• Isolated changes in visual acuity: 8.5% (4/47 eyes)
			  ○ PBT only: 0% (0/16 eyes)
			• Strabismus: 6.4% (3/47 eyes)
			  ○ PBT only: 6.3% (1/16 eyes)
			• Several less common toxicities (n=NR)

CI = Confidence Interval; COI = Conflict of Interest; EFS = Event Free Survival; EFS = Event Free Survival; F/U = Follow-up; NR = Not reported; OS = Overall Survival; PBT = Proton beam therapy; RoB = Risk of Bias; RT = Radiation Therapy

Appendix Table N12. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in pediatric soft tissue sarcomas

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Ladra (2014) RoB: High Prospective Case Series USA COI: **Consultant or Advisory Role:** Nancy J. Tarbell, ProCure (Uncompensated) **Stock Ownership:** Nancy J. Tarbell, ProCure Funding: Supported by Children's Oncology Group Chair Grant No. U10CA98543 and other philantrhopic sources (cog-foundation.org). The Children's	**Diagnosis:** Pediatric Rhabdomyosarcoma **Indication:** Curative Intent	**N=57** **Median Age: 3.5 years (range, 0.6-19.5)** **Male: 47%** **Tumor Characteristics: Embryonal/botryoid, 72% (41/57); Alveolar/undifferentiated, 28% (16/57)** **Primary Tumor Sites:** **Favorable: 33% (19/57)** **Orbital: n=13** **Head & Neck: n=4** **Perineal: n=1** **Biliary: n=1** **Unfavorable: 67% (38/57)** **Parameningeal: n=27** **Bladder/prostate: n=5** **Extremities: n=3** **Chest/abdomen: n=2** **Perianal: n=1** **Risk Classification:** **Stage 1: 32% (18/59)** **Stage 2: 25% (14/59)** **Stage 3: 40% (23/59)**	**PBT**: NR **Median total PBT Dose (Range)**: 50.4 Gy (RBE) (range, 36.0-50.4) **Additional Treatments in conjunction with PBT**: Chemotherapy, 100% (57/57); Surgical resection when clinically indicated; Anesthesia when necessary	**Median F/U (range)**: 47 (14 to 102) months	**Primary Outcomes** **OS (95% CI)** • 5-year: 78% (NR) **EFS (95% CI)** • 5-year: 69% (NR) **LC (95% CI)** • 5-year: 81% (NR) **Mortality, % (n/N)** • Disease-related: 19.3% (11/57) **Proportion of patients experiencing recurrence**: 27.1% (16/59) - isolated local treatment failures: 50% (8/16) - concurrent local and distant disease: 6.3% (1/16) - regional failures: 18.8% (3/16) - distant metastases only: 18.8% (3/16) - local, regional, and distant failure: 6.3% (1/16)	*Toxicity Grading Criteria*: CTCAE v.3.0 **Acute Toxicity, % (n/N)** **All patients (n=57)** • Fatigue - *Grade 2*: 5% (3/57) • Radiation Dermatitis - *Grade 2*: 31.6% (18/57) - *Grade 3*: 9% (5/57) **Orbital (n=13 patients receiving PBT in this location)** • Radiation dermatitis - *Grade 2*: 38.5% (5/13) - *Grade 3*: 7.7% (1/13) • Dry eye - *Grade 2*: 15.4% (2/13) - *Grade 3*: 7.7% (1/13) **Head and neck (n=31 patients receiving PBT in this location)** • Odynophagia - *Grade 2*: 12.9% (4/31) - *Grade 3*: 9.7% (3/31) • Radiation dermatitis - *Grade 2*: 32.3% (10/31) - *Grade 3*: 6.5% (2/31) • Mucositis - *Grade 2*: 62.3% (19/31) - *Grade 3*: 3.3% (1/31) • Dry eye

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Oncology Group is primarily funded by the National Cancer Institute and also receives additional funding from other granting agencies. --- Does sub-population analysis for EFS, OS, and LC by site location, low vs. high risk, etc…		**Stage 4: 3% (2/59)**			**<u>Secondary Outcomes</u>** NR	- *Grade 2*: 6.5% (2/31) - *Grade 3*: 3.3% (1/31) • Otitis - *Grade 2*: 3.3% (1/31) - *Grade 3*: 3.3% (1/31) **GI/genitourinary (n=8 patients receiving PBT in this location)** • Elevated liver function tests - *Grade 3*: 12.5% (1/8) • Radiation dermatitis - *Grade 2*: 25% (2/8) • Diarrhea - *Grade 2*: 25% (2/8) • Bladder spasm - *Grade 2*: 12.5% (1/8) • Painful bowel movement - *Grade 2*: 12.5% (1/8) **Trunk/extremity (n=5)** • Radiation dermatitis - *Grade 1*: 20% (1/5) - *Grade 2*: 40% (2/5) **<u>Late Toxic Effects, % (n/N)</u>** **Orbital (n=12)** • Cataract - *Grade 3*: 8.3% (1/12) • Dry eye - *Grade 2*: 16.7% (2/12) • Facial hypoplasia/asymmetry - *Grade 2*: 8.3% (1/12) • Epistaxis

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						- *Grade 2*: 8.3% (1/12) • Dry skin - *Grade 2*: 8.3% (1/12) **Head and Neck (n=21)** • Chronic otitis - *Grade 2*: 4.8% (1/21) - *Grade 3*: 4.8% (1/21) • Retinopathy - *Grade 3*: 4.8% (1/21) • Endocrine abnormalities - *Grade 2*: 14.3% (3/21) • Cerumen buildup - *Grade 2*: 14.3% (3/21) • Facial hypoplasia/asymmetry - *Grade 2*: 9.5% (2/21) • Hearing loss (unilateral) - *Grade 2*: 9.5% (2/21) • Cavernoma - *Grade 2*: 4.8% (1/21) • Cognitive disturbance - *Grade 2*: 4.8% (1/21) • Dry eye - *Grade 2*: 4.8% (1/21) **Trunk/Extremity** • Skeletal or muscle defect - *Grade 2*: 4.8% (1/21)
Ladra (2015) RoB: High	**Diagnosis:** Pediatric Soft tissue sarcoma (Parameningeal Rhabdomyosarcoma)	**N=24** **Median Age: 5.2 years (range, 2-18)** **Male: %**	**PBT**: Passively scattered PBT **Median total PBT Dose (Range)**:	**Median F/U (range)**: 49.2 (NR) months	**<u>Primary Outcomes</u>** **OS (95% CI)**: • 3-year: 64% (40% to 80%)	NR

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Retrospective Case Series USA COI: N. J. Tarbell holds stock options (zero value) in the ProCure corporation and has an immediate family member on the ProCure board of advisors. The authors report no other conflict of interest. Funding: Supported by the Federal Share of program income earned by Massachusetts General Hospital on C06 CA059267, Proton Therapy Research and Treatment Center. --- Provides subpopulation analysis for Local Failure and FFS based on age,	**Indication:** Curative Intent	**Tumor Characteristics:** **All patients presenting with gross residual disease after surgical resection** **Embryonal, 100% (24/24)** **Primary Tumor Sites:** **Parapharyngeal, 21% (5/24);** **Naspharynx, 21% (5/24);** **Masticator space, 21% (5/24);** **Paranasal/sinus, 17% (4/24);** **Infratemoral fossa, 12% (3/24);** **Auditory canal, 8% (2/24)** **Risk Classification:** **Intermediate, 92% (22/24);** **High, 8% (2/24)**	50.4 Gy RBE (50.4-55.8 Gy RBE) **Additional Treatments in conjunction with PBT**: Biopsy, 92% (22/24); Subtotal resection, 8% (2/24); Chemotherapy, 100% (24/24)		**FFS (95% CI)**: • 3-year: 52% (30% to 70%) **LC (95% CI)**: • 3-year: 59% (24% to 65%) **Secondary Outcomes** NR	

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
tumor volume, etc…						
Leiser (2016) RoB: High Retrospective Case Series Europe COI: None Funding: NR	**Diagnosis:** Pediatric Soft Tissue Sarcoma (Rhabdomyosarcoma) **Indication:** Curative Intent	**N=83** **Median Age: 4.5 years (range, 0.8–15.5)** **Male: 55%** **Tumor Characteristics:** **Embryonal, 89% (74/83);** **Alveolar, 11% (9/83)** **Primary Tumor Sites:** **Favorable** **Orbital, 20% (17/83);** **Head/neck non-parameningial, 4% (3/83);** **Urogenital non-bladder/prostate, 5% (4/83)** **Unfavorable** **Parameningial, 55% (46/83);** **Urogenital bladder/prostate, 7% (6/83);** **Other, 8% (7/83)** **Risk Classification:** **Low, 24% (20/83);** **Intermediate, 63% (52/83);** **High, 13% (11/83)**	**PBT:** PBS **Median total PBT Dose (Range)**: 54 Gy RBE (range, 41.4–64.8) **Additional Treatments in conjunction with PBT**: Chemotherapy, 100% (83/83); Anesthesia, 66% (55/83)	**Median F/U (months)**: 44 (0.9 to 126.3) months	**<u>Primary Outcomes</u>** **OS (95% CI)** • 5-year: 80.6% (71.8% to 90%) **LC (95% CI)** • 5-year: 78.5% (69.5% to 88.5%) **Mortality, % (n/N)** • Disease-related: 17% (14/83) **Proportion of patients experiencing tumor recurrence or progression**: 19% (16/83) - In-field local failure: 87.5% (14/16) - Marginal local failure: 12.5% (2/16) **<u>Secondary Outcomes</u>** **Median Pediatric QoL – parent proxy Scores (n=34)** • Self-esteem - Baseline: 67% (n=19) - 2-years: 73% (n=17) p<0.05	*Toxicity Grading Criteria*: Radiation Therapy Oncology Group toxicity scale [acute]; CTCAE v.4.0 [late] **<u>Acute Toxicity, % (n/N)</u>** *No grade 4–5 acute toxicities were observed* • Mucositis Membrane - *Grade 3*: 12% (10/83) • Skin toxicity - *Grade 3*: 2.4% (2/83) **<u>Late Toxicity, % (n/N)</u>** **Parameningial (n=46)** • Localized alopecia - *Any grade*: 17.4% (8/46) • Growth hormone deficiency - *Any grade*: 23.9% (11/46) • Other endocrinopathies - *Any grade*: 13% (6/46) • Facial hypoplasia - *Any grade*: 19.6% (9/46) • Visual complications - *Any grade*: 19.6% (9/46) - *Grade 3*: 6.5% (3/46)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					• Emotional functioning - Baseline: 64% (n=33) - 2-years: 73% (n=20) • Body image - Baseline: 64% (n=34) - 2-years: 80% (n=19) p<0.001 • Cognition - Baseline: 72% (n=34) -2-years: 72% (n=20) p=NS • Physical functioning - Baseline: 50% (n=32) - 2-years: 70% (n=20) p<0.001 • Social functioning peers - Baseline: 72% (n=32) - 2-years: 80% (n=20) p=NS • Social functioning family - Baseline: 67% (n=33) - 2-years: 90% (n=20)	• Hearing impairment - *Any grade*: 15.2% (7/46) - *Grade 3*: 4.3% (2/46) • Dental growth impairment - *Any grade*: 6.5% (3/46) • Chronic nasal and sinus congestion - *Any grade*: 4.3% (2/46) **Orbital (n=17)** • Localized alopecia - *Any grade*: 5.9% (1/17) • Growth hormone deficiency - *Any grade*: 17.6% (3/17) • Other endocrinopathies - *Any grade*: 11.8% (2/17) • Facial hypoplasia - *Any grade*: 29.4% (5/17) • Visual complications - *Any grade*: 29.4% (13/17) - *Grade 3*: 58.8% (10/17) **Urogenital (n=10)** • Hearing impairment - *Any grade*: 10% (1/10) • Urinary complications - *Any grade*: 30% (3/10) • Defecation problems - *Any grade:* 20% (2/10) **Other Location (n=10)**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					p<0.01 • Subjective well-being - Baseline: 51% (n=32) - 2-years: 85% (n=20) p<0.001	• Localized alopecia - *Any grade*: 10% (1/10) • Other endocrinopathies - *Any grade*: 10% (1/10) **<u>5-year incidence of grade 3 late toxicity (95% CI)</u>** • *Non*-ocular: 3.6% (1% to 12%) • *Ocular*: 18.4% (9% to 29%) **<u>Proportion of patients experiencing a secondary malignancy, % (n/N)</u>** 2.4% (2/83)*
Mizumoto (2018) [Patients in this study are also reported on in Mizumoto 2016/2017] Retrospective Case Series RoB: High Japan COI: NR	**Diagnosis:** Pediatric Rhabdomyosarcoma **Indication**: Curative intent	**N=55** **Median Age: 5 years, (range 0–19)** **Male: 63.6%** **Tumor Characteristics:** **Embryonal, 56.4% (31/55);** **Alveolar, 32.7% (18/55);** **Others, 10.9% (6/55)** **Primary Irradiation Sites:** **Head & neck, 67.3% (37/55);**	**PBT:** NR **Median total PBT Dose (Range)**: 50.4 Gy RBE (range, 36.0–60.0 Gy RBE) **Additional Treatments in conjunction with PBT**: Surgical resection, 75% (41/55); Chemotherapy, 96% (53/55)	**Median F/U (range)**: 24.5 (1.5 to 320.3) months	**<u>Primary Outcomes</u>** **OS (95% CI)** • *1*-year: 91.9% (84.3% to 99.5%) • *2-year*: 84.8% (75.2% to 94.3%) **PFS (95% CI)** • *1*-year: 81.6% (70.7%–92.5%) • *2-year*: 72.4% (59.6%–85.3%) **LC (95% CI)** • *1*-year: 95.6% (89.6%–100%)	**<u>Acute Toxicity, % (n/N)</u>** *12 events were radiation induced in 9 patients and 141 events were due to other treatment modalities (or cause of toxicity could not be determined) in 48 patients* • Appetite loss - *Grade 3*: 3.6% (2/55) • Dermatitis - *Grade 3*: 5.5% (3/55) • Mucositis - *Grade 3*: 9.1% (5/55) • Anemia

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Funding: Funding for the study was from institutional sources only. --- Provides subpopulation analysis for various risk levels		**Parameningeal, 5.5% (3/55)** **Prostate, 14.5% (8/55)** **Others, 12.7% (7/55)** **Risk Classification:** **Low, 16.4% (9/55)** **Intermediate, 70.9% (39/55)** **High, 12.7% (7/55)**			• *2-year*: 93.0% (85.3%–100%) **Proportion of patients experiencing recurrent disease:** 23.6% (13/55) - local recurrence: 38.5% (5/13) - distant metastases: 61.5% (8/13) **Mortality, % (n/N)** • All-cause: 16.4% (9/55) • Disease-related: 14.5% (8/55) **<u>Secondary Outcomes</u>** NR	- *Grade 3*: 32.7% (18/55) - *Grade 4*: 23.6% (13/55) • Decreased white blood cell count - *Grade 3*: 9.1% (5/55) - *Grade 4*: 70.9% (39/55) • Decreased neutrophil count - *Grade 3*: 9.1% (5/55) - *Grade 4*: 63.6% (35/55) • Decreased plate count - *Grade 3*: 16.4% (9/55) - *Grade 4*: 21.8% (12/55) • Electrolyte abnormality - *Grade 3*: 25.5% (2/55) - *Grade 4*: 1.8% (1/55) • GOT/GPT increased - *Grade 3*: 3.6% (2/55) • Blood bilirubin increased - *Grade 3 or 4*: 0% (0/55) • Infection - *Grade 3*: 3.6% (2/55) **<u>Late Toxicity, % (n/N)</u>**

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						9 grade 2 toxicities in 8 patients (14.5%) • Deformity - *Grade 2*: 1.8% (3/55) • Chronic Otis - *Grade 2*: 1.8% (1/55) • Growth hormone deficiency - *Grade 2*: 1.8% (1/55) • Hearing impairment - *Grade 2*: 1.8% (1/55)
Vern-Gross (2016) RoB: High Retrospective Case Series USA COI: D.J.I. has received a travel grant from Ion Beam Applications (IBA, Belgium, Netherlands). All other authors report no conflicts of interest. Funding: NR	**Diagnosis:** Pediatric Non-metastatic Rhabdomyosarcoma **Indication:** Curative Intent	**N=66** **Median Age: 4.1 years (range, 0.6 to 15.3)** **Male: NR**	**PBT**: Passive-scattered **Median total PBT Dose (Range)**: 50.4 Gy RBE (41.4-50.4) In 1.8 Gy RBE fractions per day **Additional Treatments in conjunction with PBT**: Chemotherapy: 100% Anesthesia in younger patients	**Median F/U (range)**: 18 (NR) months	**<u>Primary Outcomes</u>** **OS (95% CI)** 2-year: 89% (NR) **LC (95% CI)** 2-year: 88% (NR) **Proportion of Patients Developing Progressive Disease, % (n/N)**: 16.7% (11/66)† - embryonal: 64% (7/11) - alveolar: 36% (4/11) [all 11 patients underwent further treatment for chemotherapy alone or combined with surgical resection or reirradiation] **Mortality, % (n/N)**	**<u>Permanent Toxicity, % (n/N) [Timing NR]</u>** Cataracts: 13.6% (9/66) Hormonal Replacement Therapy: 6.1% (4/66) Unilateral Hearing Support: 1.5% (1/66)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					• Disease related: 9.1% (6/66) **Secondary Outcomes** NR	
Weber (2016) RoB: High Retrospective Case Series Switzerland COI: NR Funding: NR --- Provides subpopulation analysis for patients with specific tumor characteristics	**Diagnosis:** Pediatric Parameningeal rhabdomyosarcomas **Indication**: Curative Intent	**N=39** **Median Age: 5.8 years (range, 1.2-16.1)** **Male: 54%** **Tumor Characteristics: Embryonal, 97 (38/39); Alveolar, 0% (0/39); Undifferentiated, 3% (1/39)** **Presentation of distant metastasis at diagnosis, 13% (5/39)** **Primary Tumor Sites: Intracranial extension, 74% (29/39)** **Risk Classification: NR**	**PBT:** PBS **Median total PBT Dose**: 54 Gy (RBE) **Additional Treatments in conjunction with PBT**: Chemotherapy, 100% (39/39)	**Median F/U (range)**: 41 (9 to 106) months	**Primary Outcomes** **OS (95% CI)** • 5-year: 73% (69% to 95%) **PFS (95% CI)** • 5-year: 72% (67%-94%) **Proportion of patients experiencing failure**: 25.6% (10/39) - Infield local failure: 80% (8/10) - infield local failure and synchronous distant lung metastasis: 10% (1/10) - meningeal metastasis only: 10% (1/10) **Mortality, % (n/N)** • Disease-related: 23% (9/39) **Secondary Outcomes** NR	*Toxicity Grading Criteria*: CTCAE v.4.0 **5-year toxicity ≥ grade 3 free survival (95% CI)** 95% (94% to 96%) **Late Toxicity, % (n/N)** • Grade 1: 20.5% (8/39) • Grade 2: 25.6% (10/39) [40 grade 1 and 2 events in 18 patients]‡ • Grade 3: 7.7% (3/39) [4 events]§ **Other Adverse Events, % (n/N)** • Decreased Growth Velocity: 0% • Growth Hormone Replacement: 13% (5/39) • Other endocrinopathies: 5% (2/39) • Facial hypoplasia: 20% (8/39) • Visual complications: 8% (3/39) • Cataract: 13% (5/39)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						• Auditory Complications: 3% (1/39) • Dentition issues/cavities: 3% (1/39) • Chronic head and neck structure congestion: 13% (5/39) **Secondary Malignancy, % (n/N)**: 0% (0/39)

CI = Confidence Interval; COI = Conflict of Interest; CTCAE = Common Terminology Criteria for Adverse Events; F/U = Follow-up; FFS = Failure Free Survival; Gy = Gray; LC = Local Control; NR = Not Reported; OS = Overall Survival; PBS = Pencil Beam Scanning; PBT = Proton Beam Therapy; PFS = Progression Free Survival; QoL = Quality of Life; RBE = Relative Biological Effectiveness; RoB = Risk of Bias

*One patient experienced a radiation-induced osteosarcoma 51.6 months after PBT and another patient treated for an orbital RMS presented with an Ewing sarcoma on the contralateral side 64 months after PT. Of note, the region of the Ewing sarcoma did not receive any radiation dose.

†Disease progression was observed in 7 (64%) parameningeal, 2 (18%) head and neck (other), and 2 (18%) bladder/prostate subsites.

‡Toxicities included, Grade 1 or 2 soft tissue/bone asymmetry, Grade 1 dermatitis with patchy alopecia or hyperpigmentation, Grade 1 cataract, Grade 1 dental cavities, Grade 1 serous otitis, sinusitis or mastoiditis, Grade 1 dry eye, Grade 1 cognitive disturbance, Grade 2 failure of permanent tooth eruption, and Grade 2 endocrinopathies requiring hormonal replacement

§Grade 3 toxicities included 3 unilateral cataracts and 1 unilateral hearing impairment.

Appendix Table N13. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in mixed pediatric cancers

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Mizumoto (2016) Mizumoto (2017) RoB: High Retrospective Case Series Japan Funding: This work was partially supported by Grants-in-Aid for Scientific Research (B) (15H04901) and Young Scientists (B) (25861064) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. Japan Agency for Medical Research and Development, (Grant/Award Number:	**Diagnosis**: Pediatric Mixed, General, Various (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%; AVM, 2.3%; Others, 14.9%) **Indication**: Curative Intent (initial treatment), 75% (257/343); PBT for recurrent treatment (salvage), 25% (86/343)	**2016: (primary cohort) N=343,** **2017: (evaluation of late toxicities) n=62 with ≥5-years follow-up** **2016 (primary cohort) Median Age: 7 years (range, 0-19)** **Male: 55.4%** **Primary Tumor Sites:** **Central nervous system: 36.7%** **Head and neck: 30.6%** **Abdomen: 10%** **Chest: 13.1%** **Pelvis: 7%** **Extremities: 0.05%** **Others: 1.7%** **Risk Classification: NR**	**PBT**: Combination with photon radiotherapy, 7% (24/343) **Median total PBT Dose (Range)**: 50.4 Gy (10.8–100 Gy) **Additional Treatments in conjunction with PBT**: Surgery Preirradiation, 71.7% (216/343) Postirradiation, 2% (7/343) Chemotherapy Pre PBT, 36.2% (124/343); Pre + concurrent, 33.8% (116/343); Concurrent, 9% (31/343)	**Median F/U (range)**: 22.6 (0.4 to 374.3) months	**Primary Outcomes** **Overall Survival (95% CI)** • All Patients (n=343) - *1 year*: 82.7% (78.5%-87%) - *3-year*: 67.4% (61.7%-73.2%) - *5-year*: 61.4% (54.8%-67.9%) - *10-year*: 58.7% (51.5%-65.9%) • Brain Tumor (n=79) - *1-year*: 91.4% (NR) - *3-year*: 81.7% (NR) - *5-year*: 81.7% (NR) • Neuroblastoma (n=46) - *1-year*: 72% (NR) - *3-year*: 57.6% (NR) - *5-year*: 57.6% (NR) • Rhabdomyosarcoma (n=71) - *1-year*: 84.5% (NR) - *3-year*: 74.3% (NR) - *5-year*: 66.5% (NR) • Ewing Sarcoma (n=30) - *1-year*: 88.6% (NR) - *3-year*: 73.1% (NR) - *5-year*: 56.8% (NR)	*Toxicity Grading Criteria*: CTCAE v.3.0 **Toxic Effects (Acute/Late NR), % (n/N) [From 2016 report]** • Bone Deformity - *Grade 2:* 2.3% (8/343) - *Grade 3:* 0.6% (2/343) • Growth Hormone Deficiency - *Grade 2:* 2% (7/343) - *Grade 3:* 0.3% (1/343) • Thyroid Dysfunction - *Grade 2:* 2% (7/343) • Visual impairment - *Grade 4*: 0.6% (2/343) [both with loss of vision] • Hearing impairment - *Grade 2:* 0.9% (3/343) - *Grade 3:* 0.3% (1/343)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
'15ck0106186 h0001') COI: Dr. Hiroki Shirato received donations from Hitachi Ltd., Shimadzu Corp., and Jokoh. All other authors had no financial support or relationship to this manuscript. --- Provides subpopulation analysis for young vs. old, recurrent vs. new…etc.					• New Diagnosis (n=257) - *1-year*: 86.8% (82.4%-91.2%) - *3-year*: 73.7% (67.4%-80%) - *5-year*: 69.7% (62.8%-76.5%) • Recurrent Case (n=86) - *1-year*: 70.7% (60.6%-80.8%) - *3-year*: 50.1% (38.1%-62%) - *5-year*: 35.9% (20.5%-51.4%) **<u>Secondary Outcomes</u>** NR	• Brain necrosis/cerebral vascular disease - *Grade 2:* 0.6% (2/343) - *Grade 3:* 0.6% (2/343) - *Grade 4: 0.3%* (1/343) • Gastric/duodenum ulcer - *Grade 3:* 0.3% (1/343) • Pneumonitis - *Grade 3:* 0.3% (1/343) • Dysphagia - *Grade 3:* 0.3% (1/343) • Myelitis - *Grade 4:* 0.3% (1/343) • Tissue necrosis - *Grade 4:* 0.3% (1/343) **<u>Late Toxic Effects (n=62) [From 2017 report]</u>** • *All events ≥ Grade 2:* 35.5% (22/62) • Angiostenosis - *Grade 2:* 1.6% (1/62) - *Grade 4:* 1.6% (1/62)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						• Alopecia - *Grade 2:* 1.6% (1/62) • Brain injury - *Grade 3*: 3.2% (2/62) • Deformity - *Grade 2:* 8.1% (5/62) - *Grade 3:* 1.6% (1/62) • Dysphagia - *Grade 2:* 1.6% (1/62) - *Grade 3:* 1.6% (1/62) • Growth hormone deficiency - *Grade 2:* 3.2% (2/62) - *Grade 3:* 1.6% (1/62) • Hearing impairment - *Grade 2:* 4.8% (3/62) - *Grade 3:* 1.6% (1/62) • Headache - *Grade 2:* 1.6% (1/62) • Otitis media - *Grade 2:* 1.6% (1/62) • Pneumonitis - *Grade 3:* 1.6% (1/62) • Precocious puberty - *Grade 2:* 1.6% (1/62) • Seizure - *Grade 2:* 1.6% (1/62) • Thyroid dysfunction - *Grade 2:* 4.8% (3/62) • Visual impairment

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
						- *Grade 4:* 1.6% (1/62) • Xerostomia - *Grade 2:* 1.6% (1/62) **Rates of Late Toxic Effects ≥ Grade 2 (95% CI) (n=62)** • *5-year:* 18% (8%–27%) • *10-year:* 35% (22%–49%) • *20-year:* 45% (24%–65%) **Rates of Late Toxic Effects ≥ Grade 3 (95% CI) (n=62)** • *5-year:* 6% (0%–13%) • *10-year:* 17% (5%–28%) • *20-year:* 17% (5%–28%) **Proportion of patients developing a secondary malignancy, % (n/N)** 2% (7/343)* **Cumulative Incidences of Secondary Tumors (95% CI)**† • *10-year:* 8% (0%–18%) • *20-year: 16%* (0%–33%)

CI = Confidence Interval; COI = Conflict of Interest; CTCAE = Common Terminology Criteria for Adverse Events; F/U = follow-up; Gy = Gray; NR = Not Reported; PBT = Proton Beam Therapy; RoB = Risk of Bias

*Two patients with solid malignancies (osteosarcoma and thyroid cancer), four with blood malignancies, and one with benign pituitary adenoma. In-field tumor development only occurred in the patient with pituitary adenoma.

†The calculation of cumulative incidences of secondary tumors only includes 4 of the 7 patients mentioned under the proportion of patients developing a secondary tumor. It is unclear why there is discrepancy.

APPENDIX O. Prostate

Appendix Table O1. Study characteristics, patient demographics and detailed data abstraction: case series of proton beam therapy in mixed pediatric cancers

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Arimura 2018 *RoB:* High Retrospective Case Series Japan Funding: NR COI: None --- Provides subpopulation analysis for old vs. young, Gleason score, dosage, etc…	**Diagnosis**: Intermediate and High-risk Localized Prostate Cancer **Indication**: Curative Intent	N=204 Median Age (range): 65 years (39-86) Male: 100% **Primary Tumor Sites**: Prostate **Tumor Characteristics, % (n/N)**: Elevated glycated hemoglobin (HbA1c): 13% (27/204) **Risk Level:** Intermediate: 55% (112/204) High: 45% (92/204)	**PBT**: NR **PBT Doses**: 74 Gray (Gy) with 37 fractions, 30%; 78 Gray (Gy) with 39 fractions, 42%; 70 Gray (Gy) with 29 fractions, 28% **Additional Treatments in conjunction with PBT**: Coagulents, 15% (30/204)	**Median F/U (range)**: 52 (24 to 76) months	**Primary Outcomes** **5-year OS (95% CI)** • Intermediate-risk: 96% (NR) • High-risk: 98% (NR) p-value for the difference between the two groups = 0.673 **5-year PFS (95% CI)** • Intermediate-risk: 97% (NR) • High-risk: 83% (NR) p-value for the difference between the two groups = 0.002 **Mortality, % (n/N)** • Disease-related: 0.5% (1/204) • All-cause: 2.9% (6/204) **Proportion of patients relapsing**: 8% (17/204) **Proportion of patients diagnosed with metastasis**: 2.9% (6/204)	*Toxicity Grading Criteria*: NR **Acute Toxicities, % (n/N)** • Genitourinary retention problems - *Grade 2:* 15% (30/204) • Genitourinary Frequency problems - Grade 2: 10% (21/204) • Genitourinary Pain - Grade 2: 5% (10/204) **Late Toxicities, % (n/N)** • Rectal Hemorrhage - *Grade 2:* 3.9% (8/204) • Genitourinary retention problems - *Grade 2:* 1% (3/204) • Genitourinary Frequency problems - Grade 2: <1% (1/204)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					Secondary Outcomes **Median EPIC Sexual Summary Scores, all patients*** • *Baseline*: 49.15 • *1*-year: 43.36 • *2*-year: 40.45 • *3*-year: 39.59 • *4*-year: 39.90 • *5*-year: 40.53 • *6*-year: 40.63 p=NR	
Bryant 2016, Colaco 2015 [209 patients in this study are also reported on in Mendenhall 2014] *RoB:* High Prospective Case Series USA Funding: NR COI: None --- Provides subpopulation analysis	**Diagnosis**: Prostate Cancer **Indication**: Curative Intent	N=1327 Median Age (range): 66 years (41-88) Male: 100% **Primary Tumor Sites**: Prostate **Tumor Characteristics**: Perineural invasion, 19% (251/1327) Percentage of prostate zones positive on biopsy ≥50%, 33% (442/1327) **Risk Level:** Low, 41% (547/1327); Intermediate, 42% (551/1327);	**PBT**: Dose-escalated Image Guided **Median PBT Dose Range**: 78-80 Gy (RBE) **Additional Treatments in conjunction with PBT**: Concurrent chemotherapy, 4% (49/1327); Androgen deprivation therapy, 18% (244/1327)	**Median F/U (range)**: 66 (3.6 to 99.6) months	**Primary Outcomes** **5-year Freedom from distant metastasis**: - *low-risk*: 99% - *intermediate risk*: 99% - *high risk*: 98% **5-year Freedom from nodal metastasis**: - *low-risk*: 99% - *intermediate risk*: 99% - *high risk*: 96% **Mortality, % (n/N)** • Disease-related: 3.1% (41/1327) • All-cause: 4.1% (55/1327) **Secondary Outcomes** **Median (range) International Prostate Symptom**	*Toxicity Grading Criteria*: CTCAE v.4.0 Genitourinary toxicities occurring ≥6 months after PT were scored as late, and those occurring during treatment or <6 months after PBT were scored as acute. **Acute Toxicity, % (n/N)** **Genitourinary (n=1289)** From Bryant 2016 • Grade ≤2: NR • Grade ≥3: 0.9% (12/1289) - Urinary obstruction: 0.6% (8/1289) - Bladder irritation: 0.23% (3/1289)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
for risk group, young vs. old, several disease characteristics, etc…		High, 17% (229/1327) International Prostate Symptom score <15: 82% (1060/1327) **Comorbidities**: Diabetes, 13% (175/1327); Taking aspirin, 37% (437/1327); Prescription Anticoagulant, 9% (121/1327)			**Score:** *Baseline (n=1167):* 7 (0-34) *4-years (n=727):* 7 (0-30) *5-years (n=505)*: 7 (0-34) **Mean (SD) EPIC patient-reported QoL scores*:** *Baseline vs. 5-years* • Urinary/obstructive summary -Baseline: 87 ± 12 -4-years: 89 ± 12 -5-years: 88 ± 14 p=NR • Urinary incontinence summary -Baseline: 95 ± 16 -4-years: 89 ± 16 -5-years: 90 ± 16 p=NR • Bowel summary -Baseline: 87 ± 9 -4-years: 91 ± 13 -5-years: 92 ± 13 p=NR • Sexual Summary without ADT -Baseline: 67 ± 29	- Hematuria*:* 0.08% (1/1289) From Colaco 2015: **Gastrointestinal (n=1285)** • Grade ≤2: 0.2% (2/1285) - *Grade 2 Rectal Bleeding:* 0.2% (2/1285) • Any grade ≥3: NR **<u>Late Toxicity, % (n/N)</u>** **Genitourinary** From Bryant 2016: • Grade ≤2: NR • Grade ≥3: 4.7% (61/1289) - Urinary obstruction: 2.2% (29/1289) - Hematuria*:* 1.5% (19/1289) - Bladder Irritation: 0.4% (5/1289) - Combination of the above symptoms: 0.62% (8/1289) **Gastrointestinal** From Colaco 2015: • Grade ≤2: 31.4% (404/1285)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					-4-years: 51 ± 32 -5-years: 53 ± 33 p=NR; **MCID present** [defined as a mean difference of 10 to 12 points] • Sexual summary with ADT -Baseline: 34 ± 32 -4-years: 41 ± 33 -5-years: 37 ± 30 p=NR **5-year Freedom from biochemical progression**: - *low-risk*: 99% - *intermediate risk*: 94% - *high risk*: 74% **Proportion of patients experiencing biochemical failure**: 7.7% (94/1327)	- Rectal Bleeding: 31.4% (404/1285) From Bryant 2016: • Grade ≥3: 0.7% (9/1289) - Diarrhea: 0.08% (1/1289) - Rectal Bleeding: 0.5% (7/1289) - Rectal Ulceratioon: 0.08% (1/1289) **5-year actuarial incidence of late grade 3 Gastrointestinal toxicity**: 0.6%
Mendenhall 2014 [209 patients are also reported on in Bryant 2016/Colaco 2015] Prospective Case Series	**Diagnosis**: Prostate Cancer **Indication**: Curative Intent	N=211 Median Age (range): 68 years (40-88) Male: 100% **Primary Tumor Sites**: Prostate	**PBT:** Dose-escalated Image Guided **PBT Dose Protocols**: Low-risk disease: 78 (CGE) in 39 fractions [PR-01]; Intermediate-risk: 78 to 82 CGE [PR-02];	**Median F/U (range)**: 62.4 (NR) months	**Primary Outcomes** **5-year OS (95% CI)** • Low-risk: 93% (NR) • Intermediate-risk: 88% (NR) • High-risk: 86% (NR) **Secondary Outcomes**	Acute and Late Toxic Effects should have been captured in Bryant 2016 and Colaco 2015

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
RoB: High USA Funding: NR COI: Dr Bradford S. Hoppe received an honorarium from Procure for a lecture on proton therapy techniques for lung cancer. All other authors have no other conflicts of interest to disclose. ---		**Tumor Characteristics**: Medical comorbidity: 62% (131/211) **Risk Level:** Low-risk: 42.2% (89/211) Intermediate-risk: 38.9% (82/211): High-risk: 19% (40/211)	High-risk disease: 78 CGE with concomitant docetaxel followed by androgen deprivation [PR-03] **Additional Treatments in conjunction with PBT**: Anticoagulation: 55% (115/211)		**5-year Freedom from biochemical progression** • Low-risk: 99% (NR) • Intermediate-risk: 99% (NR) High-risk: 76% (NR) **Proportion of patients experiencing prostate-specific antigen (PSA) progression:** - PSA alone: 2.4% (5/211) - PSA with pelvic nodal failure: 1% (2/211) - PSA with pelvic nodal failure and/or distant metastases 1.4% (3/211)	
Ho 2018 Prospective Case Series *RoB:* High USA Funding: NR COI: None ---	**Diagnosis**: Prostate Cancer **Indication**: Curative intent	N=254 Median Age (range): 56 years (41-60) Male: 100% **Primary Tumor Sites**: Prostate **Risk Level, %(n/N):** Low: 56% (142/254) Intermediate: 42% (106/254) High: 2% (6/254)	**PBT**: Image guided double-scatter PBT **Median PBT Dose (Range)**: 76–82 Gy (RBE) or 70–72.5 Gy (RBE) depending on protocol **Additional Treatments in conjunction with PBT**:	**Median F/U (range)**: 85.2 (NR) months	**<u>Primary Outcomes</u>** **7-year OS (95% CI)**: 98.7% (NR) **Mortality, % (n/N)** • Disease-related: 0.4% (1/254) • All-cause: 1.6% (4/254) **<u>Secondary Outcomes</u>** **7-year biochemical-free survival (95% CI)**: 97.8% (NR)	NR

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					Mean EPIC patient-reported QoL scores*: • Mean sexual summary score: - Baseline: 83.9 - 1-year: 70.5 • Potency score: - Baseline: 89.7 - 1-year: 71.9 • Urinary incontinence: - Baseline: 95.9 - 1-year: 93 • Percentage of men pad-free on a daily basis: - Baseline: NR - 1-year: 99.6% • Urinary irritative and obstructive score: - Baseline: 89.7 - 1-year: 85.4 • Bowel summary score: - Baseline: 96.4 - 1-year: 88.4	
Iwata 2018 Retrospective Case Series *RoB:* High Japan	**Diagnosis**: Prostate Cancer **Indication**: Curative Intent	N=1291 Mean Age (SD): 68 (7) Male: 100% **Primary Tumor Sites**: prostate **Comorbidities**: -Diabetes mellitus: 10.5% (135/1291)	**PBT**: PBS **Median PBT Dose**: 74 Gy **Additional Treatments in conjunction with PBT**:	**Median F/U (range)**: 69 (7 to 107) months	**<u>Primary Outcomes</u>** **5-year OS (95% CI)** • Low-risk: 98.4% (95.2% to 99.5%) • Intermediate-risk: 96.8% (94.9% to 98.0%) • High-risk: 95.2% (93.0% to 96.7%)	*Toxicity Grading Criteria*: CTCAE v.4.0 **<u>Late Toxicity, % (n/N)</u>** • **Gastrointestinal Toxicity** **-** *Incidence rates of Grade 2+*: 4.1% (95% CI, 3.1% to 5.3%)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Funding: Supported by the National Cancer Center Research and Development Fund 28-A-14, JSPS KAKENHI Grant Number 15H05675, and Japan Agency for Medical Research and Development 17ck0106241h0002. COI: None --- Provides subpopulation analysis for age, dose, risk group, etc…		-Hypertension: 24.6% (318/1291) **Risk Level:** - Low: 16.7%(215/1291) - Intermediate: 40.3% (520/1291) - High: 43.1% (556/1291)	Androgen Deviation Therapy: 59.5% (768/1291)		**5-year Cause-specific Survival (95% CI)** • Low-risk: 100% • Intermediate-risk: 100% • High-risk: 99.6% (98.5% to 99.9%) **5-year Clinical Relapse Free Survival (95% CI)** • Low-risk: 100% (NR) • Intermediate-risk: 98.2% (96.6% to 99.1%) • High-risk: 95.9% (93.9% to 97.3%) **Mortality, % (n/N)** • All-cause: 4.4% (57/1291) • Disease-related: 0.3% (4/1291) **Proportion of patients developing metastases**: 2.2% (29/1291) **<u>Secondary Outcomes</u>** **Biochemical Relapse Free Survival** (95% CI) • Low-risk: 97% (93.4% to 98.6%) • Intermediate-risk: 91% (88.2% to 93.2%)	- *Grade 2:* 0.5% (6/1291) • **Genitourinary Toxicity** - *Incidence rates of Grade 2*+: 4.0% (95% CI, 3.1% to 5.3%) - *Grade 2:* 0.3% (4/1291)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					• High-risk: 83.1% (79.8% vs. 86.1%) **Proportion of patients with biochemical relapse** 10.6% (137/1291) [n=35 also presented with clinical relapse, as reported above]	
Makishima 2017 Retrospective Case Series *RoB:* High Japan Funding: NR COI: NR ---	**Diagnosis**: Prostate Cancer **Indication**: Curative Intent	N=93 Median Age (range): 68 (49 to 81) years Male: 100% **Primary Tumor Sites**: Prostate **Risk Level:** High: 49% (54/93) Intermediate: 35% (32/93) Low: 8% (7/93)	**PBT**: Passive scatter **PBT Dose**: Low-risk: 74 Gy in 37 fractions Intermediate- and High-risk: 78 Gy in 39 fractions **Additional Treatments in conjunction with PBT**: Complete androgen blockade was performed from 6 months prior to PBT for intermediate- or high-risk cases, and patients at high risk continued CAB for 3 years. No combination therapy was used for low-risk cases based on our criteria.	**Median F/U (range)**: 55 (32 to 97) months	**<u>Primary Outcomes</u>** **Mortality, % (n/N)** • All-cause: 1.1% (1/93) **<u>Secondary Outcomes</u>** **5-year cumulative biochemical relapse-free rate (95% CI):** 99.0% (93.2% to 99.9%) **Proportion of Patients Prostate Specific Antigen Free**: 98.9% (92/93)	*Toxicity Grading Criteria*: NR **<u>Late Toxicity, % (n/N)</u>** **Gastrointestinal Toxicity** • 5-year incidence rates of Grade 2+*:* 4.3% • Rectal Bleeding - *Grade 2:* 4.3% (4/93) **Genitourinary Toxicity** • 5-year incidence rates of Grade 2+: 4.3% • Non-infectious cystitis - *Grade 3:* 1.1% (1/93) • Urinary frequency - Grade 2: 4.3% (4/93) • Hematuria - *Grade 2*: 1.1% (1/93)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Pugh 2016 [Heavy crossover of patients with Pugh 2013] Prospective Case Series *RoB:* High USA Funding: Supported in part by the National Institutes of Health through M. D. Anderson's Cancer Center Support Grant (CA016672). COI: None ---	**Diagnosis**: Non-metastatic prostate cancer **Indication**: Curative Intent	N=423 Median Age (range): 65 years (5 to 82) Male: 100% **Primary Tumor Sites**: Prostate **Comorbidities:** Hemorrhoids: 37% (158/423) Diabetes: 11% (46/423) History of vascular disease: 12% (49/423) History of rectal surgery: 7% (30/423) **Risk Level:** Low: 43% (182/423) Intermediate: 56% (238/423) High: 1% (3/323)	**PBT** Passive Scatter: 81% (344/423) Intensity Modulated: 19% (79/423) **PBT Dose Range**: 75.6 to 78 Gy (RBE) in 1.8 to 2 Gy (RBE) fractions **Additional Treatments in conjunction with PBT**: Hormone Therapy: 37% (158/423); Anti-coagulant medications: 44% (186/423)	**Median F/U (range)**: 62.4 (NR) months	**Primary Outcomes** **Mortality, % (n/N)** • All-cause: 3.1% (13/423) **Proportion of patients with histologically confirmed failure, % (n/N)** Local recurrence: 0.5% (2/423) Regional nodal recurrence: 0.5% (2/423) **Secondary Outcomes** **Cumulative incidence of biochemical failure** 5.2% (95% CI, 3.0%-8.3 %) **Proportion of patients experiencing biochemical failure** 4% (17/423) **Proportion of patients receiving salvage therapy, % (n/N)**: 2.8% (12/423) **Mean EPIC patient QoL scores*** Bowel Domain • Summary score	*Toxicity Grading Criteria*: Modified Radiation Therapy Oncology Group **Acute Toxicity % (n/N)** **Genitourinary** - *Grade 2*: 46.3% (196/423) **Gastrointestinal** - *Grade 2*: 5% (21/423) **Cumulative incidence of grade 2 acute toxicity** • *Genitourinary***:** 46.3% (95% CI 42% to 51%) • *Gastrointestinal*: 5.0% (95% CI 3.1% to 7.3%) **Late Toxicity % (n/N)** **Genitourinary** - *Grade 2*: 16.1% (68/423) **Gastrointestinal** - *Grade 2*: 9.7% (41/423) - *Grade 3:* 0.2% (1/423) **Cumulative incidence of grade 2 late toxicity** • *Genitourinary***:** 15.9% (95% CI, 13%-20%). • *Gastrointestinal*: 9.7% (95% CI, 6.5%-12%)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					- Baseline: 95.2 - 4-years: 91.3 p=NR • Function score -Baseline: 94.2 -4-years: 91.3 p=NR • Bother score -Baseline: 96.1 -4-years: 91.3 p=NR <u>Sexual Domain</u> • Summary score: -Baseline: 57.8 -4-years: 47 p=NR • Function score -Baseline: 53.6 -4-years: 43.2 p=NR • Bother score -Baseline: 67 -4-year: 56.9 p=NR <u>Urinary Domain</u> • Summary score -Baseline: 90 -4-year: 89.7 p=NR	**<u>Cumulative incidence of argon plasma coagulation application for rectal bleeding</u>**: 5.6% (95% CI 3.7%-8.2%).

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					• Function score -Baseline: 95.9 -4-year: 93.7 p=NR • Bother score -Baseline: 85.7 -4-year: 86.8 p=NR <u>Hormonal Domain</u> • Summary score -Baseline: 90.2 -4-year: 92.2 p=NR • Function score -Baseline: 87.1 -4-years: 90.4 p=NR • *Bother* score -Baseline*:* 92.6 -4-*year*: 93.7 p=-NR	
Takagi 2017 Retrospective Case Series *RoB:* High Japan	**Diagnosis**: Localized Prostate Cancer **Indication**: Curative Intent	N=1375 Median Age (range): 69 years (44 to 92) Male: 100% **Primary Tumor Sites**: Prostate **Comorbidity**:	**PBT**: Passive Scatter **Median PBT Dose**: 74 Gy (RBE) **Additional Treatments in conjunction with PBT**:	**Median F/U (range)**: 70 (4 to 145) months	**<u>Primary Outcomes</u>** **OS (95% CI)** • 5-year - *Low-risk*: 98% (88% to 87%) - *Intermediate-risk*: 96% (94% to 98%)	*Toxicity Grading Criteria*: NR **<u>5-year Rate of Late GI Toxicities (95% CI)</u>** • *Grade* 1: 10% (8.5% to 12%) • *Grade* 2: 3.8% (2.8% to 4.8%)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Funding: NR COI: None ---		Diabetes: 11% (145/1375) **Risk Level:** Low: 18% (249/1375) Intermediate: 44% (602/1375) High: 33% (449/1375) Very High: 5% (75/1375)	Androgen Deprivation Therapy: 57% (785/1375) Anticoagulant drugs: 10% (142/1375)		- *High-risk*: 96% (93% to 97%) - *Very high-risk:* 90% (80% to 96%) • 8-year - *Low-risk*: 95% (88% to 98%) - *Intermediate-risk*: 90% (87% to 93%) - *High-risk*: 89% (84% to 99%) - *Very high-risk*: 86% (73% to 93%) [The OS rate for very high-risk patients was significantly worse than those of low-, intermediate-, and high-risk groups (P = 0.003, P = 0.010, and P = 0.047)] **Cancer-specific survival (95% CI)** • 5-year - *Low-risk*: 100% (100% to 100%) - *Intermediate-risk*: 100% (100% to 100%) - *High-risk*: 99% (97% to 100%) - *Very high-risk:* 95% (94% to 98%) • 8-year	• *Grade* 3: 0.1% (0% to 0.2%) **5-year Rate of Late GU Toxicities (95% CI)** • *Grade* 1: 8.9% (7.3% to 10%) • *Grade* 2: 1.9% (95% CI, 1.1–2.6%) • *Grade* 3: 0.1% (0.1% to 0.2%) **Late Toxicities, % (n/N)** **Gastrointestinal** • *Grade 1*: 59.6% (82/1375) • *Grade 2*: 3.9% (53/1375) • *Grade 3*: 0.7% (1/1375) **Genitourinary** • *Grade 1*: 8.7% (119/1375) • *Grade 2*: 2.4% (33/1375) • *Grade 3*: 0.7% (1/1375)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					- *Low-risk*: 100% (100% to 100%) - *Intermediate-risk*: 99% (97% to 100%) - *High-risk*: 98% (95% to 99%) - *Very high-risk*: 92% (81% to 97%) [The CSS rate for very high-risk patients was significantly worse than those of low-, intermediate- and high-risk groups (P < 0.001, P < 0.001, and P = 0.014)] **Proportion of patients experiencing clinical recurrence:** 3.1% (43/1375) [11 local recurrences, 15 (1.3%) pelvic lymph node metastases, 18 bone metastases, and 3 others] **Mortality, % (n/N)** • All-cause: 6.6% (91/1375) • Disease-related: 0.9% (12/1375) **<u>Secondary Outcomes</u>** **Proportion of patients experiencing**	

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					biochemical relapse: 13% (177/1375) **Freedom from biochemical relapse (95% CI)** • 5-year - *All patients*: 89% (87% to 91%) - *Low-risk*: 99% (96–100%) - *Intermediate-risk*: 91% (88–93%) - *High-risk*: 86% (82–89%) - *Very high-risk: 66% (53–76%)* • 8-year - *All patients*: 82% (79% to 84%) - *Low-risk*: 95% (88–98%) - *Intermediate-risk*: 87% (83–90%) - *High-risk*: 71% (64–77%) - *Very high-risk:* 55% (41–67%) [FN: The Freedom from biochemical relapse rate for very high-risk patients was significantly lower than those of low-,	

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					intermediate-, and high-risk groups ($P < 0.001$, $P < 0.001$, and $P < 0.001$)]	
Vargas 2016 Prospective Case Series *RoB:* High USA Funding: None COI: None ---	**Diagnosis**: Prostate Cancer (with a Gleason score of 6) **Indication**: Curative Intent	N=49 Median Age (range): 65 years (52 to 75) Male: 100% **Primary Tumor Sites**: Prostate **Risk Level:** Low: 100%	**PBT**: Hypo-fractionated PBT **PBT Dose**: 38 Gy (RBE) in 5 fractions	**Median F/U (range)**: 18 (NR) months	**<u>Primary Outcomes</u>** **Mortality, % (n/N)** • All-cause: 0% • Disease-related: 0% **<u>Secondary Outcomes</u>** **Mean ± change in EPIC patient QoL scores*** • Urinary Summary: -Baseline: 91.3 ± 8.2 -3-months: 87 ± 11.1; **p=0.04** -6 months: 88.7 ± 12.4; p=0.24 -1-year: 85.9 ± 12.6; **p=0.02** -1.5-years: 84 ± 12.6; **p=0.01** -2-years: 90 ± 7.3; p=0.88 • Bowel Summary -Baseline: 96.4 ± 4.3 -3-months: 91.9 ± 9.5**; p=0.003** -6 months: 87.5 ± 15.9; **p<0.001 [MID achieved]**	*Toxicity Grading Criteria*: CTCAE v.4.0 **<u>Acute and Late Toxicity, % (n/N)</u>** **Urinary** - *Grade 2*: 37% (17/49) **Bowel** - *Grade 2*: 13% (6/49)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					-1-year: 87.5 ± 14; **p<0.001 [MID achieved]** -1.5-years: 90.5 ± 11.1; **p=0.002** -2-years: 89.2 ± 11.2; **p=0.002** • Sexual Summary -Baseline: 60 ± 22.8 -3-months: 57.2 ± 24.6; p=0.57 -6 months: 55.9 ± 27.5; p=0.27 -1-year: 52.1 ± 25.3; p= 0.17 -1.5-years: 47.9 ± 25.9; p=0.06 -2-years: 46.6 ± 25.6; **p=0.053 [MID achieved]**	
Hoppe 2014 Prospective Case Series USA Funding: This work was supported by grants from the National Institute of	**Diagnosis:** Localized Prostate Cancer **Indication:** Curative Intent	N=1243 Mean Age: 66 years Male:100% **Primary Tumor Sites:** Prostate **Risk Level:** Low: 46% (567/1243) Intermediate: 43% (532/1243) High: 13% (27/1243)	**PBT:** NR **PBT Dose**: 99% (1226/1243) received between 78 Gy and 82 Gy (RBE)	**Median F/U (range)**: NR	**Primary Outcomes** NR **Secondary Outcomes** **Median EPIC QoL Scores at various time points*** [estimated from figure 4a-d] [a change from baseline >50% of the standard deviation at any point in	NR

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
Health (RO1 CA95662 and 1RC1CA14596) and the American College of Radiology-Radiation Therapy Oncology Group. COI: Dr. Hoppe reports receiving an honorarium from ProCure for lectures, and he serves on the board of the Proton Collaborative Group. Dr. Sandler is a board member of Eviti and he reports payment from Medivation, Millennium, Bayer Health, and Varian Health for consultant services. Dr. Sanda is a board member of Medicametrix, and he reports payment from Sanofi-Aventis for lectures. Dr. Hamstra reports payment from Myriad Health and Bayer Health for consultant services and payment from Varian Health for lectures.					time was considered an MCID] • Bowel Summary - *Baseline*: 100 - *6 months:* 96 (**p<0.05)** - *1 year:* 92 (**p<0.05; MCID**) *-2 years:* 96 (**p<0.05; MID)** • Urinary Incontinence - *Baseline:* 100 - *6 months:* 100 (**p<0.05)** - *1 year:* 100 (**p<0.05)** *-2 years:* 100 (**p<0.05)** • Urinary irritative/obstructive - *Baseline:* 87 - *6 months:* 94 - *1 year:* 87 (**p<0.05)** *-2 years:* 94 • Sexual Score - *Baseline:* 75 - *6 months:* 67 (**p<0.05)** - *1 year:* 62 (**p<0.05)** *-2 years:* 58 **Proportion of Men With Minimally Detectable Differences in EPIC Composite Scores*** • Bowel Summary:	

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
					*- 6 months:*25% *- 1 year:* 41% *-2 years:* 37% • Urinary Incontinence: *- 6 months:* 22% *- 1 year:* 31% *-2 years:* 32% • Urinary irritative/obstructive: *- 6 months:* 18% *- 1 year:* 23% *-2 years:* 17% • Sexual Score: *- 6 months:* 27% *- 1 year:* 36% *-2 years:*40%	
Chuang 2018 Prospective Case Series *RoB:* High USA COI: None Funding: NR	**Diagnosis:** Non-metastatic prostate cancer **Indication:** Curative Intent	N=85 Median Age (Range): 69 (53.9 to 79.9) years Male: 100% Median Pre-PBT PSA (Range) (): 8.21 (0.1 to 126.18) ng/mL Gleason score 6: 2.4% 7: 18.8% 8: 43.5% 9: 30.6% 10: 4.7%	**PBT modality** -Pencil Beam Scanning: 68.2% -Uniform scanning: 31.8% **Median Total Dose to Prostate and Seminal Vesicles (range)**: 79.4 (70 to 80.2) Gy	**Median F/U (range)**: 14.5 (2.8 to 49.2) months Patients with at least 12-months f/u (50.6%) and 24 months	NR	**Acute Toxicity, % (n/N)** <u>Gastrointestinal</u> Grade 1: 16.4% (14/85) Grade 2: 2.4% (2/85) Grade 3: 0% (0/85) <u>Genitourinary</u> Grade 1: 60% (51/85) Grade 2: 34.1% (29/85) Grade 3: 0% (0/85) **Late Toxicity, % (n/N)** <u>Gastrointestinal</u> Grade 1: 7.1% (6/85)

Author (year), Study Site	Diagnosis Indication	Population	PBT specifications	F/U	Primary Outcomes Secondary/Indirect Outcomes	Safety
		Clinical T stage T1: 34.1% T2: 48.2% T3: 16.5% Unknown: 1.2% Clinical N stage N0: 77.6% N1: 7.1% Unknown: 15.3% Clinical M stage M0: 83.5% M1a: 1.2% Unknown: 15.3% Androgen Deprivation Therapy Prior to PBT: 60% During PBT: 77.6%		f/u (21.2%)		Grade 2: 2.4% (2/85) Grade 3: 1.2% (1/85) <u>Genitourinary</u> Grade 1: 12.9% (11/85) Grade 2: 5.9% (5/85) Grade 3: 0% (0/85)

PBT = Proton Beam Therapy; NR = Not Reported; Gy = Grey; F/U = Follow-up; OS = Overall Survival; QoL = Quality of Life; COI = Conflict of Interest; SD = Standard Deviation; EPIC = expanded prostate cancer index composite; CGE = Cobalt Grey Equivalent; PSPT = Passive Scatter Proton Therapy; SSPT = Spot Scanning Proton Therapy; SS = Statistically Significant

*The Expanded Prostate Cancer Index Composite (EPIC) Quality of Life score measures health-related quality of life in men with prostate cancer. Scores were reported using a scale of 0 to 100, with higher scores indicating better outcomes.

Appendix Table O2. Study characteristics and patient demographics: comparative studies of proton beam therapy in prostate cancer

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
RCTs							
Khmelevsky 2018 RCT *Moderately High* Russia	272	**Photon RT + PBT Boost (n=116)**: Preliminary photon dose of 44 Gy in 22 fractions followed by 3 variants of proton boost fractionation: 3.0, 4.0, 5.5 Gy(RBE); Mean dose (prostate): 71.8 ± 0.1 Gy (RBE); Mean dose (small pelvis): 44.9 ± 0.4 Gy (RBE) **Photon RT alone (n=173)**: Standard conformal 8-field photon irradiation; Mean dose (prostate): 68.6 ± 0.4 Gy; Mean dose (small pelvis): 44.8 ± 0.3 Gy	**Inclusion**: Patients with locally advanced prostate cancer treated from 2000 to 2011 **Exclusion**: NR	*Photon RT + PBT boost vs. Photon RT alone* Mean age ± SD (years): 66.9 ± 6.4 vs. 69.0 ± 5.8 Male: 100% vs. 100% Stage: • T1N0M0: 11% ± 4% vs. 17% ± 5% • T2N0M0: 41% ± 4% vs. 39% ± 4% • T3-4N0M0: 48% ± 4% vs. 44% ± 3% • T2-3N1M0: 6% ± 2% vs. 5% ± 2% PSA (mean ng/ml): 28.7 ± 3.5 vs. 28.0 ± 2.7 Patients with PSA>50 mg/ml: 16% ± 4% vs. 11% ± 3% Progress Risk Group: • Low: 7.0% ± 3.1% vs. 3.8% ± 1.2% • Intermediate: 36.0% ± 4.0% vs. 46.5% ± 6.6% • High: 57.0% ± 5.2% vs. 49.7% ± 5.0% Neoadjuvant HT (ADT): 95% vs. 95% Previous surgeries at urinary tract:	*Photon RT + PBT boost vs. Photon RT alone* **F/U (median ± SD)**: 67.8 ± 3.1 months vs. 71.6 ± 2.9 **% F/U** - *All patients:* 94.1% (272/289) - Photon RT + *PBT boost vs. Photon RT alone*: CD*	5-year and 10-year Recurrence-free Survival and Biochemical relapse-free survival Harms	Funding: None COI: None Also provides data based on frequency of proton boost received Provides a cox regression model analysis in order to determine the independent risk factors for severe post irradiation complications of the lower urinary tract. (KQ2?)

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		p-value for the difference in mean irradiation dose to the prostate = <0.01		• Transurethral resection: 14% ± 4% vs. 17% ± 5% • Adenomectomy: 6% ± 3% vs. 9% ± 3% • Cystostomy: 3% ± 2% vs. 5% ± 2%			
Comparative Cohort Studies							
Fang 2015 Retrospective Cohort (Case match analysis) *Moderately High* USA	188	**PBT (n=94)**: Median total dose (Gy): 79.2 in 44 fractions [passive scatter] **Intensity-modulated RT (n=94)**: Median total dose (Gy): NR From a total of 394, 188 patients (94 pairs) matched for risk group, age at diagnosis, and prior gastrointestinal or genitourineal disorders.	**Inclusion**: Patients with histologically confirmed prostatic adenocarcinoma with no clinical or pathologic evidence of extraprostatic disease or pelvic lymph node involvement who were treated with PBT from January 2010 to December 2012 or with IMRT from July 2009 to December 2012 **Exclusion**: NR	PBT vs. IMRT Age 60-69 years: 50% vs. 46.8% Male: 100% vs. 100% Risk group: • Low: 55% vs. 55% • Intermediate: 31% vs. 37% • High: 7% vs. 7% Androgen-deprivation therapy: 16% vs. 29% Comorbidities: • Hypertension: 46% vs. 67% • Hemorrhoids: 14% vs. 10% • Diabetes mellitus: 14% vs. 23% • Prior GI disorders (yes): 12% vs. 15% • Prior GU disorders (yes): 16% vs. 22% ECOG PS • 0: 97% vs. 93%	PBT vs. IMRT **F/U (median [range])**: 29 months (5-65) vs. 47 months (5-10) **% F/U** - All patients: 100% (394/394)	Harms	Funding: supported by the University of Pennsylvania. Dr. Bekelman was supported by National Cancer Institute grant K07-CA163616: Effectiveness of Radiotherapy for Prostate Cancer. COI: Dr. Christodouleas is an employee of Elekta, AB.

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
				• 1: 3% vs. 7% • 2: 0% vs. 0% IPSS score, mean ± SD: 6.9 ± 5.8 (n=94) vs. 6.9 ± 6.0 (n=91) BSS score, mean ± SD: 92.7 ± 9.3 (n=76) vs. 96.6 ± 5.4 (n=54), p=0.003			
Pan 2018 Retrospective cohort (database) *Propensity score matched* *Moderately High* USA	4158	**PBT (n=693)**: Median number of treatment fractions: 39 **IMRT (n=3465)**: Median number of treatment fractions: 42 (From a total of 11,816 patients)	**Inclusion**: Patients age <65 years who received either IMRT, SBRT, or PBT radiation for localized prostate cancer between 2008 and 2015 (were part of the MarketScan Commercial Claims and Encounters database). **Exclusion**: Received brachytherapy or combined radiation modalities, or if pretreatment claims indicated metastatic disease, radical prostatectomy, or other malignancy.	PBT vs. IMRT Age (years): ≤55: 29% vs. 29% 56-60: 39% vs. 39% 61-64: 32% vs. 33% Male: 100% vs. 100% Comorbidity None: 87% vs. 89% 1: 10% vs. 9% ≥2: 3% vs. 2% Concurrent ADT: 19% vs. 19%	PBT vs. IMRT **F/U (median [range])**: 23 months (NR) vs. 23 months (NR) **% F/U**: CD	Harms	Funding/COI: HP- Research Funding: Varian Medical Systems CT- Stock or Other Ownership: Corvus Pharmaceuticals Research Funding: Varian Medical Systems Patents, Royalties, Other Intellectual Property: Patent #9,175,079 Travel, Accommodations, Expenses: Varian Medical Systems SF- Leadership: C4 Imaging

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
							Stock or Other Ownership: C4 Imaging Honoraria: Varian Medical Systems Consulting or Advisory Role: Varian Medical Systems Research Funding: Elekta, Hitachi Patents, Royalties, Other Intellectual Property: C4 Imaging Travel, Accommodations, Expenses: Varian Medical Systems MA- Stock or Other Ownership: CivaTech Oncology
Dutz 2019 Retrospective Propensity score Matched Comparative Cohort ROB Germany	58 (From a pool of 88)	**PBT (n=29)** - Conventionally fractionated - Treated between January 2015 and March 2017 - Median Dose: 74 Gy **IMRT (n=29)**	**Inclusion**: age over 18 years, histologically confirmed localized or locally advanced PCA without positive pelvic lymph nodes or distant metastases, and an Eastern Cooperative Oncology Group (ECOG) status ≤2	PBT vs. IMRT Median Age (range): 70.4 (49.3 to 83.6) vs. 74.9 (65.9 to 83.8) years, p=0.001 Median Prostate Specific Antigen level: 7 vs. 8.3 Risk Level (D'Amico) - Low: 6.9% vs. 0%	**Median F/U**: NR **% F/U:** NR	QoL Harms	Funding: NR COI: None

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		- Conventionally fractionated - Treated between May 2013 and December 2016 - Median Dose: 78 Gy **p-value for median dose <0.001**	**Exclusion**: NR	- Intermediate: 75.9% vs. 79.3% - High: 17.2% vs. 20.7% Receipt of Androgen Deprivation Therapy: 44.8% vs. 44.8% Receipt of Anticoagulants: 31% vs. 37.9% TURP: 6.9% vs. 3.4% Diabetes: 27.6% vs. 24.1% Pre-radiation Genitourinary Toxicity - 0: 55.2% vs. 69% - 1: 41.4% vs. 24.1% - 2: 3.4% vs. 3.4% - 3: 0% vs/ 3.4% Pre-radiation Gastrointestinal Toxicity - 0: 100% vs. 93.1% - 1: 0% vs. 3.4% - 2: 0% vs. 3.4%			

CD = cannot be determined; COI = conflict of interest; F/U = follow-up; Gy = Gray; IMRT = Intensity-modulated Radiation Therapy; PBT = Proton Beam Therapy; RBE = Relative Biological Effectiveness; RoB = Risk of Bias; SBRT – Stereotactic Body Radiotherapy; SD = standard deviation

*Differential loss to follow-up cannot be determined (number of patients lost per treatment group not provided, of 289 patients with T1-3N0-1M0 disease treated between 2010 and 2011, 17 were lost to follow-up of those 289)

†Differential loss to follow-up cannot be determined (number of eligible patients not provided, patients required to have had continuous coverage from 6 months before through 6 months after starting treatment).

Appendix Table O3. Detailed data abstraction: comparative studies of proton beam therapy in prostate cancer

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
RCTs			
Khmelevsky 2018 Photon RT + PBT boost (n=116) vs. Photon RT alone (n=173) RCT *Moderately High* Russia	Photon RT + PBT boost vs. Photon RT alone **OS** • *5-year*: 74% ± 5.0% vs. 78.8% ± 4.1%; p=NS • *10-year:* 55.9% ± 9.0% vs. 60.6% ± 5.7%; p=NS	Photon RT + PBT boost vs. Photon RT alone **Biochemical Relapse Free Survival** • *5-year:* 60% ± 5.4% vs. 61.9% ± 4.4%; p=NS • *10-year*: 45.5% ± 8.5% vs. 42.8% ± 7.1%; p=NS	Photon RT + PBT boost vs. Photon RT alone *Toxicity Grading Criteria*: Standard Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scale **Acute Toxicity** **Gastrointestinal** • *Grade ≤2*: 54.4% ± 5.4% vs. 69.2% ± 5.7%; p < 0.01 • *No grade 3–4 Gastrointestinal complications were observed in either group* **Genitourinary** • *Grade 2*: 33.3% ± 4.6% vs. 36.1% ± 3.5%; p=NS • *Grade 3-4*: 0% vs.1.9% ± 1.8%; p=NS **Late Toxicity** **Gastrointestinal** • *Grade 2*: 10.2% ± 5.5% vs. 34.8% ± 7.4%; p<0.01 • *Grade 3-4*: 0.9% ± 1.7% (n=1) vs. 1.3% ± 1.8% (n=2); p=NR **Genitourinary** • *Grade 2*: 8.3% ± 5.0% vs. 9.1% ± 4.5% p=NR • *Grade 3-4*: 2.8% ± 2.6% (n=3) vs. 3.8% ± 3.0% (n=5); p=NR

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			10-year cumulative actuarial frequency of Gastrointestinal and Genito-urineal Grade ≥3: 1.7% vs. 8.7% **<u>10-year Grade 3 or 4 Toxicity Free Survival (95% CI) [Estimated from Figure 2]</u>** **Gastrointestinal**: 99% vs. 98% (NR) **Genitourinary**: 90% vs. 92% (NR)
Cohort Studies			
Fang 2015 PBT (n=94) vs. IMRT (n=94) Retrospective Cohort (Case match analysis) *Moderately High* USA	NR	NR	PBT vs. IMRT *Toxicities were assessed according to CTCAE v.3* **<u>Acute Toxicity (≤90 days from start of radiation), % (n/N)</u>** [IMRT=referent] **Gastrointestinal** • *Grade 0*: 60.6% (57/94) vs. 41.5% (39/94) • *Grade 1*: 35.1% (33/94) vs. 44.7% (42/94) • *Grade 2*: 4.3% (4/94) vs. 13.8% (13/94) • *Grade 3*: 0% (0/94) vs. 0% (0/94) • Grade 0-1: 95.7% (90/94) vs. 86.2% (81/94) • Grade 2-3: 4.3% (4/94) vs. 13.8% (13/94) • *Any grade*: OR 0.25 (95% CI, 0.07 to 0.89); p=0.-03 adjusted OR* 0.27 (95% CI, 0.06 to 1.24); p= 0.09 **Genitourinary** • *Grade 0*: 4.3% (4/94) vs. 5.3% (5/94) • *Grade 1*: 74.5% (70/94) vs. 66% (62/94)

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			• *Grade 2*: 21.3% (20/94) vs. 28.7% (27/94) • *Grade 3*: 0% (0/94) vs. 0% (0/94) • Grade 0-1: 78.7% (74/94) vs. 71.3% (67/94) • Grade 2-3: 21.3% (20/94) vs. 28.7% (27/94) • *Any grade*: OR 0.63 (95% CI, 0.31-1.30); p=0.21 adjusted OR† 0.69 (95% CI, 0.32 to 1.51); p= 0.36 **Late Toxicity (>90 days from start of radiation), % (n/N)** [IMRT=referent] **Gastrointestinal** • *Grade 0*: 59.6% (56/94) vs. 47.3% (44/94) • *Grade 1*: 27.7% (26/94) vs. 41.9% (39/94) • *Grade 2*: 12.8% (12/94) vs. 8.6% (8/94) • *Grade 3*: 0% (0/94) vs. 2.2% (2/94) • Grade 2-3: 12.8% (12/94) vs. 10.8% (10/94) • *Any grade*: HR 1.28 (95% CI, 0.55-2.99); p=0.57 Adjusted HR‡ 1.24 (95% CI, 0.53 to 2.94); 0.62 **Genitourinary** • *Grade 0*: 17.0% (16/94) vs. 17.2% (16/94) • *Grade 1*: 70.2% (66/94) vs. 64.5% (60/94) • *Grade 2*: 10.6% (10/94) vs. 18.3% (17/94) • *Grade 3*: 2.1% (2/94) vs. 0% (0/94) • Grade 2-3: 12.8% (12/94) vs. 18.3% (17/94) • *Any grade*: HR 0.81 (95% CI, 0.38-1.74); p=0.59 Adjusted HR§ 0.56 (95% CI, 0.22 to 1.41); p=0.22 **Cumulative (from day 90) late toxicity rates** • **Gastrointestinal** (adjusted HR 1.24, p=0.62) ○ *1-year:* 9.7% vs. 3.4%

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			○ *2-year:* 13.7% vs. 9.9% • **Genitourinary** (adjusted HR 0.56, p=0.22) ○ *1-year:* 11.8% vs. 11.1% ○ *2-year:* 13.1% vs. 12.4%
Pan 2018 PBT (n=693) vs. IMRT (n=3465) Prospective Cohort *Moderately High* USA	NR	NR	PBT vs. IMRT **Cumulative Incidence of Toxicity:** ***6-months (proton n=693; IMRT n=3465)*** **Urinary (any grade)** • Any urinary Toxicity: 12.1% vs. 21.5% • Incontinence: 0% vs. 1.4% • Bleeding/irritation: 10.9% vs. 17.7% • Obstruction/retention: 2.7% vs. 5.8% • Stricture: 0.1% vs. 0.4% • Fistula: 0% vs. 0.1% **Bowel (any grade)** • Any Bowel Toxicity: 1.6% vs. 3.2% • Bleeding/proctitis: 1.4% vs. 3.1% • Ulcer/Stricture/Fistula: 0.1% vs. 0.1% • Incontinence: 0% vs. 0.1% • Proctectomy/hyperbaric oxygen: 0% vs. 0.1% **Other** • Erectile Dysfunction: 5.0% vs. 9.7% ***12-months (proton n=572; IMRT n=2862)*** **Urinary (any grade)** • Any urinary Toxicity: 23.1% vs. 31.6% • Incontinence: 0.5% vs. 3.0% • Bleeding/irritation: 21.2% vs. 26.4% • Obstruction/retention: 5.0% vs. 8.8% • Stricture: 0.5% vs. 1.1%

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			• Fistula: 0% vs. 0.1% **Bowel (any grade)** • Any Bowel Toxicity: 7.4% vs. 7.7% • Bleeding/proctitis: 7.0% vs. 7.3% • Ulcer/Stricture/Fistula: 0.6% vs. 0.4% • Incontinence: 0.2% vs. 0.2% • Proctectomy/hyperbaric oxygen: 0% vs. 0.3% **Other** • Erectile Dysfunction: 10.6% vs. 18.1% ***24-month (proton n=341; IMRT n=1718)*** **Urinary (any grade)** • Any urinary Toxicity: 33.3% vs. 42.2% • Incontinence: 2.1% vs. 5.9% • Bleeding/irritation: 31.1% vs. 36.0% • Obstruction/retention: 8.7% vs. 12.7% • Stricture: 0.7% vs. 2.6% • Fistula: 0% vs. 0.2% **Bowel (any grade)** • Any Bowel Toxicity: 19.5% vs. 15.4% • Bleeding/proctitis: 19.5% vs. 14.6% • Ulcer/Stricture/Fistula: 0.6% vs. 1.1% • Incontinence: 0.3% vs. 0.3% • Proctectomy/hyperbaric oxygen: 0.6% vs. 0.6% **Other** • Erectile Dysfunction: 20.7% vs. 27.8% ***36-months (proton n=205; IMRT n=1003)*** [IMRT as referent for HR (95% CI)] **Urinary (any grade)** • Any urinary Toxicity: 39.1% vs. 48.3%; HR 0.72 (0.63 to 0.83); p<0.001

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			• Incontinence: 3.5% vs. 7.5%; HR 0.36 (0.21 to 0.60); p<0.001 • Bleeding/irritation: 36.0% vs. 42.4%; HR 0.79 (0.68 to 0.91); p=0.002 • Obstruction/retention: 10.0% vs. 15.7%; HR 0.69 (0.53 to 0.90); p=0.006 • Stricture: 0.7% vs. 3.3%; HR 0.21 (0.08 to 0.58); p=0.002 • Fistula: 0% vs. 0.4%; HR NC **Bowel (any grade)** • Any Bowel Toxicity: 24.9% vs. 19.2%; HR 1.27 (1.05 to 1.55); p=0.02 • Bleeding/proctitis: 24.8% vs. 18.0%; HR 1.34 (1.10 to 1.63); p=0.004 • Ulcer/Stricture/Fistula: 1.0% vs. 1.4%; HR 0.94 (0.42 to 2.12); p=0.89 • Incontinence: 0.3% vs. 0.4%; HR 0.77 (0.17 to 3.40); p=0.73 • Proctectomy/hyperbaric oxygen: 0.6% vs. 0.9%; HR 0.72 (0.22 to 2.41); p=0.59 **Other** • Erectile Dysfunction: 28.6% vs. 34.3%; HR 0.71 (0.59 to 0.84); p=0.001
Dutz 2019 PBT (n=29) vs. IMRT (n=29) Retrospective Propensity score Matched Comparative Cohort	NR	PBT vs. IMRT **EORTC QLQ-C30 (general quality of life) questionnaire scores,** mean change (SD) from baseline:** • 3 months post radiation - Constipation subscale score: -6.7 (13.8) vs. 6.7 (22.5), p=0.034	PBT vs. IMRT RR (95% CI) calculated by AAI **<u>Acute (≤ 3months) Toxicities</u>** **Genitourinary** • Grade 1: 66% (19/29) vs. 45% (13/29) RR 1.46 (95% CI 0.90 to 2.37) • Grade 2: 24% (7/29) vs. 41% (12/29)

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
ROB Germany		[No statistically significant differences in the mean change from baseline were identified for any of the following subscales: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, diarrhea, financial difficulties] • 12 months post radiation - Global Health Status subscale score: -2.8 (26) vs. 8.3 (15), p=0.04 [No statistically significant differences in the mean change from baseline were identified for any of the following subscales: constipation, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, diarrhea, financial difficulties] **EORTC QLQ-PR25 (prostate-cancer specific) questionnaire scores,** mean change (SD) from baseline:** No statistically significant differences in mean change from baseline scores existed between the two groups for any of the subscale scores (uriniary symptoms, bowel symptoms, hormone treatment-related symptoms, incontinence aid)	RR 0.58 (95% CI 0.27 to 1.27) • Grade 3: 3% (1/29) vs. 3% (1/29) - Obstructive Symptoms: 3% (1/29) vs. 0% (0/29) - Pelvic Pain: 0% (0/29) vs. 3% (1/29) p=0.45 **Gastrointestinal** • Grade 1: 48% (14/29) vs. 38% (11/29) RR 1.27 (95% CI 0.70 to 2.32) • Grade 2: 14% (4/29) vs. 17% (5/29) RR 0.80 (95% CI 0.24 to 2.68) • Grade 3: 3% (1/29) vs. 0% (0/29), p=0.60 - Diarrhea: 3% (1/29) vs. 0% (0/29) p=0.60 **<u>Late (at 12 months after RT)</u>** **Genitourinary** • Grade 1: 23% (5/22) vs. 32% (7/22) RR 0.71 (95% CI 0.27 to 1.91) • Grade 2: 23% (5/22) vs. 27% (6/22) RR 0.83 (95% CI 0.30 to 2.33) • Grade 3: 0% (0/22) vs. 5% (1/22), p=0.32 - Obstructive Symptoms: 0% (0/22) vs. 5% (1/22) p=0.53 **Gastrointestinal** • Grade 1: 9% (2/22) vs. 27% (6/22) RR 0.33 (95% CI 0.08 to 1.47) • Grade 2: 9% (2/22) vs. 9% (2/22) • Grade 3: 5% (1/22) vs. 0% (0/22), p=0.32

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
			- Proctitis with rectal bleed: 5% (1/22) vs. 0% (0/22) p=0.35

EPIC = expanded prostate cancer index composite; Gy = Gray; HR = Hazard ratio; IMRT = Intensity-modulated Radiation Therapy; NC = Not calculable; NR = Not reported; NS = Not significant; OS = Overall survival; PBT = Proton Beam Therapy; RCT = Randomized Control Trial; RoB = Risk of Bias

*Fang 2015: OR adjusted for confounding by hypertension

† Fang 2015: OR adjusted for confounding by preradiation GU toxicity and by the independent predictors androgen-deprivation therapy and International Prostate Symptom Score

‡ Fang 2015: HR was adjusted for confounding by preradiation and acute GI toxicity

§ Fang 2015: HR was adjusted for confounding by preradiation and acute GU toxicity and by the independent predictor International Prostate Symptom Score

APPENDIX P. Contextual Studies

Appendix Table P1. Study characteristics and patient demographics: Contextual studies of proton beam therapy

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
Prostate Cancer							
RCTs							
Vargas 2018 RCT USA	79	**Hypofractionated PBT (n=46):** Dose (Gy): 38 Gy (RBE) in 5 treatments **Standard Fractionated PBT (n=33):** Median total dose (Gy): 79.2 Gy RBE in 44 treatments	**Inclusion**: low-risk prostate cancer; Gleason score of 6, cancer stage T1 to T2, American Urological Association (AUA) Symptom Index score ≤17, and prostate-specific antigen levels <10 ng/mL **Exclusion**: NR	Hypofractionated PBT vs. Standard Fractionated PBT Median age (years): 65 (range, 52-75) vs. 65 (range, 49-80) Male: 100% vs. 100% T stage: • T1c: 84% vs. 88% • T2a: 16% vs. 12% AUC Symptom Index: • Median (range): 4.69 (0-13) vs. 4.76 (0-17) • % with Score 0-10: 92% vs. 88% • % with Score 11-17: 8% vs. 12%	Hypofractionated PBT vs. Standard Fractionated PBT **F/U (median [range])**: 18 months vs. 18 months **% F/U**: all patients, 93.9% vs. 100%	Patient reported outcomes Harms	Funding: NR COI: None
Ha 2019 RCT Korea	82	**Moderate Hypofractionation (MHF) PBT (n=52)** - Group 1 Median total dose: 77.1 Gy Number of fractions: 20 Fractions/week: 4	**Inclusion**: Patients with biopsy-proven androgen-deprivation therapy (ADT)-naive prostate adenocarcinoma, stage T1-3N0M0 and an Eastern Cooperative Oncology Group performance status of 0–2	Median Age (range): 68 (44 to 85) vs. 68 (46 to 80) years ECOG Performance Status - 0: 19% vs. 33% - 1: 79% vs. 67% - 2: 2% vs. 0% Gleason score - ≤6: 67% vs. 57%	**Median F/U (range):** 90 months (15.6 to 115.2) **% F/U**: NR	Overall Survival Biochemical Failure Free Survival Harms	Funding: National Cancer Center Grant (NCC-1010480, NCC-1310080, NCC-1610590, and NCC-1710060). COI: None

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		- Group 2 Median total dose: 78.7 Gy Number of fractions: 15 Fractions/week: 3 - Group 3 Median total dose: 83.3 Gy Number of fractions: 10 Fractions/week: 2 **Extreme Hypofractionation (EHF) PBT (n=30)** - Group 4 Median total dose: 85 Gy Number of fractions: 5 Fractions/week: 2 - Group 5 Median total dose: 85 Gy Number of fractions: 5 Fractions/week: 1	**Exclusion**: NR	- 7: 27% vs. 33% - 8 to 10: 6% vs. 10% Initial PSA level - <10: 69% vs. 63% - 10 to 20: 23% vs. 37% - >20: 8% vs. 0% T stage T1: 38% vs. 30% T2: 48% vs. 63% T3: 13% vs. 7% Risk Level Low: 40% vs. 23% Intermediate: 37% vs. 60% High: 23% vs. 17%			
Retrospective Comparative							
Nakajima 2018	526	**Standard Fractionated PBT (n=272):**	**Inclusion**: histologically confirmed prostate cancer; T1–T3N0M0 disease according to the 7th	Hypofractionated PBT vs. Standard Fractionated PBT Type of PBT (All patients)	**Median F/U:** NR [minimum 6 months]	Patient reported outcomes Harms	Funding: COI COI: None

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
retrospective cohort Japan		Low-risk Dose: 74 Gy RBE in 37 franctions Intermediate and High-risk Dose: 78 Gy RBE in 39 fractions **Hypofractionated PBT (n=254):** Low-risk Dose: 60 Gy RBE in 20 fractions High-risk Dose: 63 Gy RBE in 21 fractions	edition of TNM staging of the Union for International Cancer Control; Eastern Cooperative Oncology Group Performance status of 0–2; age >20 years; no active concurrent malignancy, active infectious disease, or severe comorbidities; and written informed consent. **Exclusion**: Patients with prostate cancer other than adenocarcinoma and those with previous irradiation to the pelvis. Patients treated with standard PBT after starting the hypofractionated PBT trial in October 2014.	• Passive Scattering: 93.9% • Spot Scanning: 6.1% Median Age (range): 70 (52 to 88) years vs. 69 (47 to 86) years Male: 100% vs. 100% Clinical Tumor Classification • T1: 25% vs. 20% • T2: 60% vs. 62% • T3: 15% vs. 18% Risk Level • Low: 19% vs. 15% • Intermediate: 38% vs. 46% • High: 43% vs. 39% Comorbidities • Diabetes: 11% vs. 13% • Hypertension: 24% vs. 26% • Use of anticoagulants: 13% vs. 12% Performance Status • 0: 97% vs. 99% • 1: 3.1% vs. 1.5%			
Pugh 2013 Retrospective Comparative Cohort USA	291	**Passive Scatter PBT (n=226)** Dose: 76 Gy RBE in 38 fractions **Spot Scanning PBT (n=65)**	**Inclusion**: Men with previously untreated, nonmetastatic prostate cancer, minimum 2-years of follow-up, treated between 2006 and 2012	**Passive Scatter vs. Spot Scanning** Median Age (range): 63 (47 to 82) years vs. 69 (50 to 83) years; p=0.01 Male: 100% vs. 100%	**Median F/U (range)**: NR [24 months minimum] **% F/U**	QoL Harms	Funding: NR COI: NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding Notes
		Dose: 76 Gy RBE in 38 fractions	**Exclusion**: NR	Risk Level • Low: 39% vs. 49% • Intermediate: 61% vs. 49% • High: 0% vs. 2% p=0.05 Additional Treatments in conjunction with PBT • Hormone Therapy: 42% vs. 17%; p<0.001 • Anti-coagulant medications: 43% vs 51% Comorbidities • Hemorrhoids: 39% vs. 37%			

COI = Conflict of Interest; F/U = Follow-up; Gy = Gray; NR = Not reported; PBT = proton beam therapy; QoL = Quality of Life; RBE = Relative Biological Effectiveness; RoB = Risk of Bias

Appendix Table P2. Detailed data abstraction: contextual studies of proton beam therapy

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Prostate Cancer			
RCTs			
Vargas 2018 Hypofractionated PBT (n=46) vs. Standard Fractionated PBT (n=33) RCT RoB: Low USA	NR *Authors state the following*: "Long-term outcomes could not be extrapolated from the available follow-up data. However, as of manuscript preparation, no patients had treatment failure, and no deaths related or unrelated to treatment have occurred. Accrual is still ongoing."	Hypofractionated PBT vs. Standard Fractionated PBT **American Urological Association Symptom Index, Mean (SD)** • *Baseline*: 4.82 (3.92) vs. 4.55 (4.02); p=0.76 • *3 months*: 6.25 (4.06) vs. 4.54 (3.49); p=0.07 • *6 months*: 6.13 (5.63) vs. 5.04 (4.18); p=0.40 • *12 months*: 7.68 (5.39) vs. 4.59 (3.45); **p=0.04*** • *18 months*: 7.95 (7.97) vs. 4.81 (4.59); p=0.17 • *24 months*: 6.69 (4.71) vs. 4.47 (5.94); p=0.25 **EPIC Quality of Life Survey** **Urinary score** • *Baseline*: 91.27 (8.19) vs. 92.13 (8.03); p= 0.64 • *3 months*: 87.00 (11.12) vs. 91.70 (9.51); p= 0.08	Hypofractionated PBT vs. Standard Fractionated PBT *No grade ≥3 urinary or gastrointestinal tract AEs occurred in either study arm* **Any/Overall Toxicity Grade 2 through 36 months, % (n/N)** • *Gastrointestinal:* 13.0% (6/46) vs. 11.1% (3/27); p=0.99 • *Genitourinary*: 37.0% (17/46) vs. 40.7% (11/27); p=0.48 **Acute Toxicity Grade 2, % (n/N)** **During Treatment** • *Gastrointestinal:* 4.1% (2/49) vs. 0% (NR); p=0.77 • *Genitourinary*: 19.6% (9/46) vs. 25.9% (7/27); p=0.53 **3 months** • *Gastrointestinal:* 2.5% (1/40) vs. 0% (NR); p=0.99 • *Genitourinary*: 10% (4/40) vs. 0% (NR); p=0.29

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		• *6 months*: 88.69 (12.44) vs. 90.15 (11.02); p= 0.63 • *12 months*: 85.91 (12.55) vs. 91.51 (8.87); p= 0.11 • *18 months*: 84.01 (15.61) vs. 91.97 (11.89); p= 0.10 • *24 months*: 90.92 (7.30) vs. 91.31 (13.11); p= 0.92 **Bowel score** • *Baseline*: 96.39 (4.29) vs. 95.73 (5.19); p= 0.53 • *3 months*: 91.85 (9.50) vs. 94.10 (6.56); p= 0.28 • *6 months*: 87.60 (15.86) vs. 91.05 (11.65); p= 0.34 • *12 months*: 87.52 (14.00) vs. 92.44 (6.84); p= 0.18 • *18 months*: 90.48 (11.19) vs. 91.74 (9.26); p= 0.72 • *24 months*: 89.24 (13.67) vs. 93.28 (6.67); p= 0.29 **Erectile function score** • *Baseline*: 59.98 (22.75) vs. 61.33 (21.89); p= 0.79 • *3 months*: 57.16 (24.57) vs. 58.49 (20.18); p= 0.81 • *6 months*: 55.88 (27.47) vs. 56.54 (19.79); p= 0.92	**Late Toxicity Grade 2, % (n/N)** **6 months** • *Gastrointestinal:* 7.5% (3/40) vs. 3.8% (1/26); p=0.99 • *Genitourinary*: 17.5% (7/40) vs. 0% (NR); **p=0.04** **12 months** • *Gastrointestinal:* 3.2% (1/31) vs. 17.6% (3/17); p=0.12 • *Genitourinary*: 22.6% (7/31) vs. 11.8% (2/17); p=0.46 **24 months** • *Gastrointestinal:* 6.3% (1/16) vs. 5.9% (1/17); p=0.77 • *Genitourinary*: 12.5% (2/16) vs. 31.3% (5/16); p=0.39 **Need for mediation post-treatment, p=NS**: • For bowel symptoms: 6/46 vs. 3/27 • For urinary symptoms: 17/46 vs. 11/27 **Need for mediation at 6 months:** • For urinary symptoms: 7/46 vs. 0/27, p=0.04

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		• *12 months*: 52.12 (25.33) vs. 57.43 (20.46); p= 0.48 • *18 months*: 47.90 (25.87) vs. 55.44 (24.62); p= 0.38 • *24 months*: 46.55 (25.62) vs. 60.35 (22.04); p= 0.12	
Ha 2019 PBT MHF (n=52) vs. PBT EHF (n=30) RCT Korea	PBT MHF vs. PBT EHF 7-year OS was 97.5% for the entire study population. [The OS was not compared between the two groups because of the low frequency of events. 3 deaths occurred, 1 due to disease progression and 2 due to presence of other malignancies – it is unclear which group these patients belonged to.]	PBT MHF vs. PBT EHF **7-year Biochemical Failure Free Survival** • All Patients: 76.2% vs. 46.2%, p=0.005; adj. HR 3.24 (95% CI 1.51 to 6.93), p=0.003 - Low risk: 90.5% vs. 57.1%, p=0.154 - Intermediate risk: 83.5% vs. 42.9%, p=0.018 - High risk: 41.7% vs. 40%, p=0.786	PBT MHF vs. PBT EHF Overall, acute GU toxicities (grades 0-2) were more common in the MHF than the EHF group (85 vs. 57%, p=0.009), but late GI and GU toxicities did not differ between groups. **Acute Toxicity, % (n/N)** *Gastrointestinal* *Grade ≥3 toxicities were not observed in either group* *Genitourinary* *Grade ≥3 toxicities were not observed in either group* **Late Toxicity, % (n/N)** *Gastrointestinal* - *Grade 3*: 4% (2/52) vs. 0% (0/30) *Genitourinary* *Grade ≥3 toxicities were not observed in either group*

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
Retrospective Cohorts			
Nakajima 2018 Standard PBT (n=254) vs. Hypofractionated PBT (n=272) Retrospective cohort RoB: Moderately High Japan	Standard PBT vs. Hypofractionated PBT	Standard PBT vs. Hypofractionated PBT **Mean International Prostate Symptom Score** All-risk Levels • *Baseline*: 8.3 vs. 8.5 (n= 254 vs. 272) • *1-month*: 11 vs. 12.2 (p=0.036) (n=251 vs. 261) • *6-month*: 8.2 vs. 8.3 (n=249 vs. 240)	Standard PBT vs. Hypofractionated PBT **Acute Toxicity, % (n/N)** *Grade ≥3 acute toxicities were not observed in any group* All risk levels *Gastrointestinal* Grade 1: 0.8% (2/254) vs. 0.7% (2/272) *Genitourinary* Grade 2: 15% (38/254) vs. 5.9% (16/272); p<0.001 *Dermatitis* Grade 1: 18.1% (46/254) vs. 6.6% (18/272); p<0.001
Pugh 2013 Passive Scatter PBT (n=226) vs. Spot Scanning (n=65) Retrospective Comparative Cohort RoB: Moderately High USA	NR	Passive Scatter vs. Spot Scanning **Mean change in EPIC patient QoL scores at 12-months†** • *Bowel Function* PSPT: −5.5 (p<0.001) vs. SSPT: −4.6 (p<0.001) • *Bowel Bother* −7.7 (p<0.001) vs. SSPT: −9.4 (p<0.001) • *Sexual Function* −5.8 (p = 0.002) vs. −11.9 (p < 0.001) • *Sexual Bother* −8.5 (p = 0.001) vs. −7.4 (p = 0.084) • *Urinary Function*	All patients *Toxicity Grading Criteria*: Modified Radiation Therapy Oncology Group **2-year cumulative incidence of grade 2+ acute toxicity (95% CI)** • *Genitourinary*: 3.4% (95% CI 9.4% to 17.2 %) [no Grade 3+ events] • *Gastrointestinal*: 9.6% (95% CI 6.2% to 12.9%) [grade 3, n=1; no Grade 4+ events]

Study Intervention/ comparator Design RoB Country	Primary Outcomes	Secondary/Intermediate outcomes	Harms
		−7.8 (p<0.001) vs. −7.8 (p<0.001) • *Urinary Bother*‡ +2.2 (p = 0.016) vs. +0.2 (p = 0.898)	**Cumulative incidence of argon plasma coagulation application for rectal bleeding**: 3.8% (95% CI, 1.6%-5.9%).

AE = Adverse Event; CI = confidence interval; EPIC = Expanded Prostate Cancer Index; F/U = Follow-up; Gy = Gray; NR = Not reported; PBT = proton beam therapy; PSPT = passive scatter proton therapy; QoL = Quality of Life; RBE = Relative Biological Effectiveness; RoB = Risk of Bias; SSPT = Spot scanning proton therapy
*The absolute difference was 3 points, smaller than the 5-point difference needed to show clinical relevance (Table 4).
†p-values are for a significant mean difference, not for the comparison between the two groups
‡There was a statistically significant decline for both PSPT and SSPT in urinary bother between baseline and completion of treatment (−14 (p<0.001) vs. −12 (p<0.001)), but this resolved at the 2-year follow-up mark.