Evidence Brief: Proton Beam Therapy for Treatment of Localized Prostate Cancer

Supplemental Materials

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APPENDIX A: SEARCH STRATEGY

SYSTEMATIC REVIEWS

Search for current systematic reviews (limited to last 7 years) **Date Searched: 02-07-22**			
A. Bibliographic Databases:	**#**	**Search Statement**	**Results**
MEDLINE: Systematic Reviews Ovid MEDLINE(R) ALL 1946 to February 04, 2022	1	exp Prostatic Neoplasms/ OR (prostate neoplasm$1 OR prostate cancer$1 OR prostatic cancer$1 OR prostatic neoplasm$1).ti,ab.	173582
	2	Protons/ OR Proton Therapy/ OR (proton* OR (proton adj2 therap*)).ti,ab.	159620
	3	1 AND 2	1074
	4	(systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt.	499549
	5	3 and 4	37
	6	limit 5 to english language and yr=”2015-current”	21
CDSR: Protocols and Reviews EBM Reviews - Cochrane Database of Systematic	1	Prostatic Neoplasms.kw. OR (prostate neoplasm$1 OR prostate cancer$1 OR prostatic cancer$1 OR prostatic neoplasm$1).ti,ab.	52
	2	(Protons OR Proton Therapy).kw. OR (proton* OR (proton adj2 therap*)).ti,ab.	29
	3	1 AND 2	0

Reviews 2005 to December 02, 2021			

Search for current systematic reviews (limited to last 7 years) **Date Searched: 02-07-22**		
B. Non-bibliographic databases	**Evidence**	**Results**
AHRQ: evidence reports, technology assessments, U.S Preventative Services Task Force Evidence Synthesis	http://www.ahrq.gov/research/findings/evidence-based-reports/search.html Search: prostate cancer AND proton therapy	0
CADTH	https://www.cadth.ca Search: prostate cancer AND proton therapy	0
ECRI Institute	https://guidelines.ecri.org/ Search: prostate cancer AND proton therapy Sanda MG, Chen RC, Crispino T, Freedland S, Greene K, Klotz LH, Makarov DV, Nelson JB, Reston J, Rodrigues G, Sandler HM, Taplin ME, Cadeddu JA. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Linthicum (MD): American Urological Association Education and Research, Inc.; 2017 Apr. 56 p. [283 references]	1
HTA: Health Technology Assessments (UP TO 2016)	http://www.ohsu.edu/xd/education/library/ See CDSR search above	0
NHS Evidence	http://www.evidence.nhs.uk/default.aspx Search: prostate cancer AND proton therapy Hayes, Inc. Proton beam therapy for prostate cancer. 2016. World Health Organization. WHO list of priority medical devices for cancer management. 2017.	2
EPPI-Centre	http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=62 Use browser search function [CNTL + F] for keyword search Search: prostate cancer; proton therapy	0

NLM	http://www.ncbi.nlm.nih.gov/books Search: prostate cancer AND proton therapy AHRQ. Therapies for Clinically Localized Prostate Cancer. 2020.	1
VA Products - VATAP, PBM and HSR&D publications	A. http://www.hsrd.research.va.gov/research/default.cfm B. http://www.research.va.gov/research_topics/ C. https://va.dimensions.ai/discover/publication Search: prostate cancer AND proton therapy	0

Search for systematic reviews currently under development (includes forthcoming reviews & protocols) **Date Searched: 02-07-22**		
D. Under development	**Evidence**	**Results**
PROSPERO (SR registry)	http://www.crd.york.ac.uk/PROSPERO/ Search: prostate cancer AND proton therapy Miloslav Klugar, Jitka Klugarová, Radim Líčeník, Zuzana Kelnarová, Andrea Pokorná, Ondřej Májek, Martin Doležel, Marek Babjuk, Vlastimil Válek, Karel Odrážka, Ladislav Dušek. Effectiveness of proton therapy in comparison with other types of radiation therapy in prostate cancer: a rapid review. PROSPERO 2019 CRD42019125204 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019125204 Miloslav Klugar, Jitka Klugarová, Radim Líčeník, Zuzana Kelnarová, Andrea Pokorná, Ondřej Májek, Martin Doležel, Marek Babjuk, Vlastimil Válek, Karel Odrážka, Ladislav Dušek. Effectiveness of proton therapy in comparison with standard and other types of radiation therapy in prostate cancer: umbrella review. PROSPERO 2019 CRD42019125202 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019125202 Lina Wang, Xiaohu Wang, Juntao Ran, Qiuning Zhang, Xiaoming Hou, Guangwen Zhang, Yichao Geng, Shuangwu Feng, Xueshan Zhao, Chengcheng Li. Efficacy and toxicity of carbon ion therapy or proton therapy for prostate cancer: a systematic review and meta-analysis. PROSPERO 2020 CRD42020148933 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020148933	3

PRIMARY STUDIES

Search for primary literature **Date searched: 02-09-22**		
MEDLINE [Ovid MEDLINE(R) ALL 1946 to February 08, 2022]		
#	**Search Statement**	**Results**
1	exp Prostatic Neoplasms/ OR (prostate neoplasm$1 OR prostate cancer$1 OR prostatic cancer$1 OR prostatic neoplasm$1).ti,ab.	173681
2	Protons/ OR Proton Therapy/ OR (proton* OR (proton adj2 therap*)).ti,ab.	159712
3	1 AND 2	1077
4	limit 3 to English language and yr=”2015-current”	444
CINAHL		
#	**Search Statement**	**Results**
1	(MH "Prostatic Neoplasms+")	33515
2	TI (prostate neoplasm$1 OR prostate cancer$1 OR prostatic cancer$1 OR prostatic neoplasm$1) OR AB (prostate neoplasm$1 OR prostate cancer$1 OR prostatic cancer$1 OR prostatic neoplasm$1)	58
3	1 OR 2	33528
4	(MH "Proton Therapy") OR (MH "Protons")	2347
5	TI (proton N2 therap*)) OR AB (proton N2 therap*))	2417
6	4 OR 5	3662
7	3 AND 6	258
8	limit 7 to English language and yr=”2015-Current”	108

APPENDIX B: SCIENTIFIC INFORMATION PACKET (SIP) REQUESTS

REQUESTED INFORMATION FROM MANUFACTURERS AND VENDORS

Data collection: Please describe your Center's standard data collection mechanisms.

Published studies: Please provide a list of all published studies that meet our review inclusion criteria for population, intervention, comparison, outcome, and study design. In the list, indicate whether the protocol and results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number.

Unpublished studies: Please also provide a list of all unpublished studies that meet our review inclusion criteria for population, intervention, comparison, outcome, and study design. For these, we ask that you submit a summary that includes the following elements: internal study number, ClinicalTrials.gov trial number where applicable, study dates, location, design, indication and diagnosis, inclusion and exclusion criteria, primary and secondary outcomes, patient population description, baseline characteristics (demographics and important prognostic characteristics), number of patients screened/eligible/enrolled/lost to follow-up/withdrawn/analyzed, effectiveness/efficacy, and safety results. In order for us to include data from unpublished studies, however, you also must submit a sufficient amount of detail on their methods to allow for adequate assessment of study quality using the criteria listed below. Data that does not meet these requirements may not be included in the report.

Quality assessment criteria for controlled trials:

- Was the assignment to the treatment groups really random?
- Was the treatment allocation concealed?
- Were the groups similar at baseline in terms of prognostic factors?
- Were the eligibility criteria specified?
- Were outcome assessors blinded to the treatment allocation?
- Was the care provider blinded?
- Was the patient kept unaware of the treatment received?
- Was an intention-to-treat (ITT) analysis conducted, or was data provided from which ITT results could be calculated (ie, number assigned to each group, number of subjects who finished in each group, and their results)?
- Did the study maintain comparable groups? Were there post-randomization exclusions of patients with specific characteristics?
- Was attrition, crossovers, adherence, and/or contamination reported?
- Was there differential loss to follow-up or overall high loss to follow-up?
- Quality assessment criteria for non-randomized studies (observational studies)
- Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)? For cohort studies, was an inception cohort identified?
- Was there important differential loss to follow-up or overall high loss to follow-up?
- Were the patient outcomes specified and defined prior to the start of data collection?
- Was there a clear description of the techniques used to identify the outcomes?

- Was there non-biased and accurate ascertainment of outcomes (independent ascertainers; validation of ascertainment technique)?
- Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
- Did the duration of follow-up correlate to reasonable timing for investigated events?

Unpublished, supplemental data for published studies. Examples of this include additional detail about study methods, additional outcomes, and results of additional subgroup analyses that did not appear in the publication.

A list of ongoing studies your company has sponsored for this indication. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including a study number, the study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.

Description of whether the above studies constitute ALL Phase II and above clinical trials sponsored by your company for this indication and an index outlining the relevant information in each submitted file.

MANUFACTURERS AND VENDORS CONTACTED

Company	Contact Info	Response
Hitachi	Phone: +1 408 986-6300 Research & Development US Headquarters Phone: (650) 244-7400 2535 Augustine Dr, 3rd Floor, Santa Clara, CA 95054, USA	n/a
IBA Strategic Marketing (Ion Beam Applications)	info-worldwide@iba-group.com	n/a
Mevion Medical Systems	Email: research@mevion.com Americas & Headquarters 300 Foster St Littleton, MA 01460, USA Phone: +1 978 540-1500 Fax: +1 978 540-1501	n/a
Sumitomo Heavy Industries	Industrial Equipment Division Phone: +81-(0)3-6737-2565 or +81-(0)6-7635-3629 USA Office 1833 Vultee St Allentown, PA 18103, USA Phone: +1 610 791-6700 Fax: +1 610 791-0440	n/a

Company	Contact Info	Response
Varian Medical Systems	Michael Davis, MS, JD, *Director, Research, & Educational Grants* Email: michael.davis@varian.com Camille Noel, MSCI, PhD, *Medical Science Liaison* Email: camille.noel@varian.com Raymond Schulz, MSc, *Clinical & Publications Manager* Email: raymond.schulz@varian.com	n/a
ProNova Solutions (Provision Healthcare)	Phone: +1 865 862-4112 Pronova Solutions 330 Pellissippi Place Maryville, TN 37804, USA Phone: +1 865 862-4100	Referred to Provision Cares Proton Therapy Center.
Optivus Proton Therapy	Corporate Office Optivus Proton Therapy, Inc. Phone: +1 909 799-8300 1475 South Victoria Court San Bernardino, CA 92408, USA	n/a
ProTom International	Sales & Development 610 Parker Square Flower Mound, TX 75028, USA Email: info@protominternational.com Cheryl Smith, *VP, Administration* csmith@protominternational.com	n/a

APPENDIX C: EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type, 8=Outdated or ineligible systematic review.

Citation	Exclude Reason
Bai X, Lim G, Grosshans D, Mohan R, Cao W. Robust optimization to reduce the impact of biological effect variation from physical uncertainties in intensity-modulated proton therapy. *Physics in Medicine & Biology*. 2019;64(2):025004.	E6
Beckmann K, Garmo H, Nilsson P, Franck Lissbrant I, Widmark A, Stattin P. Radical radiotherapy for prostate cancer: patterns of care in Sweden 1998-2016. *Acta Oncologica*. 2020;59(5):549-557.	E4
Borowicz DM, Shipulin KN, Mytsin GV, et al. Ultra-Hypofractionated Proton Therapy in Localized Prostate Cancer: Passive Scattering versus Intensity-Modulated Proton Therapy. *Journal of Personalized Medicine*. 2021;11(12):06.	E4
Bryant CM, Henderson RH, Nichols RC, et al. Consensus Statement on Proton Therapy for Prostate Cancer. *International Journal of Particle Therapy*. 2021;8(2):1-16.	E7
Bryant CM, Hoppe BS. Promising long-term results with proton therapy for localized prostate cancer. *Nature Reviews Urology*. 2021;18(3):137-138.	E7
Choo R, Hillman DW, Daniels T, et al. Proton Therapy of Prostate and Pelvic Lymph Nodes for High Risk Prostate Cancer: Acute Toxicity. *International Journal of Particle Therapy.* 2021;8(2):41-50.	E6
Chung C, Yock T, Nelson K, Xu Y, Keating N, Tarbell N. Incidence of Second Malignancies Among Patients Treated with Proton versus Photon Radiation. *International Journal of Radiation Oncology, Biology, Physics.* 2013;87(1).	E3
Chuong MD, Hartsell W, Larson G, et al. Minimal toxicity after proton beam therapy for prostate and pelvic nodal irradiation: results from the proton collaborative group REG001-09 trial. *Acta Oncologica.* 2018;57(3):368-374.	E6
Coen JJ, Paly JJ, Niemierko A, et al. Long-Term Quality of Life Outcome After Proton Beam Monotherapy for Localized Prostate Cancer. *International Journal of Radiation Oncology*Biology*Physics.* 2012a;82(2):e201-e209.	E6
Cuaron JJ, Harris AA, Chon B, et al. Anterior-oriented proton beams for prostate cancer: A multi-institutional experience. *Acta Oncologica.* 2015;54(6):868-874.	E6
Deville Jr C, Jain A, Wei-Ting H, et al. Initial report of the genitourinary and gastrointestinal toxicity of postprostatectomy proton therapy for prostate cancer patients undergoing adjuvant or salvage radiotherapy. *Acta Oncologica.* 2018;57(11):1506-1514.	E6
Duttenhaver JA, Shipley WU, Perrone T, et al. Protons or megavoltage X-rays as boost therapy for patients irradiated for localized prostatic carcinoma an early phase I/II comparison. *Cancer.* 1983;51(9):1599-1604	E4
Efstathiou JA, Kamran SC, Spratt DE. Protons Versus Photons for Prostate Cancer: An Answer That Is Long Overdue and Coming. *International Journal of Radiation Oncology, Biology, Physics*. 2021;110(4):1098-1100.	E7
Galbraith ME, Ramirez JM, Pedro LW. Quality of life, health outcomes, and identity for patients with prostate cancer in five different treatment groups. *Oncology nursing forum.* 2001;28(3):551-560.	E3
Habl G, Uhl M, Katayama S, et al. Acute Toxicity and Quality of Life in Patients With Prostate Cancer Treated With Protons or Carbon Ions in a Prospective	E3

Citation	Exclude Reason
Randomized Phase II Study--The IPI Trial. *International Journal of Radiation Oncology, Biology, Physics*. 2016;95(1):435-443.	
Haque W, Butler EB, Teh BS. Stereotactic body radiation therapy for prostate cancer-a review. *Chinese Clinical Oncology*. 2017;6(Suppl 2):S10.	E2
Holtzman AL, Hoppe BS, Letter HP, et al. Proton Therapy as Salvage Treatment for Local Relapse of Prostate Cancer Following Cryosurgery or High-Intensity Focused Ultrasound. *International Journal of Radiation Oncology, Biology, Physics.* 2016;95(1):465-471.	E6
Hoppe BS, Bryant C, Sandler HM. Radiation for Prostate Cancer: Intensity Modulated Radiation Therapy versus Proton Beam. *The Journal of urology*. 2015;193(4):1089-1091.	E7
Jagt TZ, Breedveld S, van Haveren R, Heijmen BJM, Hoogeman MS. Online-adaptive versus robust IMPT for prostate cancer: How much can we gain? *Radiotherapy & Oncology*. 2020;151:228-233.	E4
Kaiser A, Eley JG, Onyeuku NE, et al. Proton Therapy Delivery and Its Clinical Application in Select Solid Tumor Malignancies. *Journal of Visualized Experiments*. 2019;144(02):06.	E7
Kamran SC, McClatchy DM, 3rd, Pursley J, et al. Characterization of an Iodinated Rectal Spacer for Prostate Photon and Proton Radiation Therapy. *Practical Radiation Oncology*. 2021;05:05.	E7
Khmelevsky EV, Kancheli IN, Khoroshkov VS, Kaprin AD. Morbidity dynamics in proton-photon or photon radiation therapy for locally advanced prostate cancer. *Reports of Practical Oncology & Radiotherapy.* 2018;23(1):21-27.	E4
Kim E, Jang WI, Kim MS, et al. Clinical utilization of radiation therapy in Korea, 2016. *Journal of Radiation Research*. 2020;61(2):249-256.	E4
Kirk ML, Tang S, Zhai H, et al. Comparison of prostate proton treatment planning technique, interfraction robustness, and analysis of single-field treatment feasibility. *Practical Radiation Oncology*. 2015;5(2):99-105.	E4
Koerber SA, Katayama S, Sander A, et al. Prostate bed irradiation with alternative radio-oncological approaches (PAROS) - a prospective, multicenter and randomized phase III trial. *Radiation Oncology*. 2019;14(1):122.	E7
Kole TP, Nichols RC, Lei S, et al. A dosimetric comparison of ultra-hypofractionated passively scattered proton radiotherapy and stereotactic body radiotherapy (SBRT) in the definitive treatment of localized prostate cancer. *Acta Oncologica*. 2015;54(6):825-31.	E4
Konski A, Speier W, Hanlon A, Beck JR, Pollack A. Is Proton Beam Therapy Cost Effective in the Treatment of Adenocarcinoma of the Prostate? *Journal of Clinical Oncology*. 2007;25(24):3603-3608.	E6
Kowalchuk RO, Hillman D, Daniels TB, et al. Assessing concordance between patient-reported and investigator-reported CTCAE after proton beam therapy for prostate cancer. *Clinical and Translational Radiation Oncology*. 2021;31:34-41.	E4
Lee HJ, Macomber MW, Spraker MB, et al. Early toxicity and patient reported quality-of-life in patients receiving proton therapy for localized prostate cancer: a single institutional review of prospectively recorded outcomes. *Radiation Oncology.* 2018;13(1):.	E6
Lee WR. Proton-beam therapy after radical prostatectomy: Continued DVH idolatry? *Cancer*. 2019;125(23):4136-4138.	E7

Citation	Exclude Reason
Li M, Li X, Yao L, et al. Clinical Efficacy and Safety of Proton and Carbon Ion Radiotherapy for Prostate Cancer: A Systematic Review and Meta-Analysis. In. *Frontiers in Oncology.* Vol 112021:709530.	E8
Lockney NA, Henderson RH, Swarts SG, et al. Measuring Radiation Toxicity Using Circulating Cell-Free DNA in Prostate Cancer Patients. *International Journal of Particle Therapy*. 2022;8(3):28-35.	E4
Lockney NA, Zhang M, Morris CG, et al. Radiation-induced tumor immunity in patients with non-small cell lung cancer. *Thoracic Cancer*. 2019;10(7):1605-1611.	E1
Ma D, Bronk L, Kerr M, et al. Exploring the advantages of intensity-modulated proton therapy: experimental validation of biological effects using two different beam intensity-modulation patterns. *Scientific Reports*. 2020;10(1):3199.	E6
Maeda Y, Sato Y, Shibata S, et al. Effects of organ motion on proton prostate treatments, as determined from analysis of daily CT imaging for patient positioning. *Medical Physics*. 2018;45(5):1844-1856.	E4
Maeda Y, Sato Y, Yamamoto K, et al. Stability of daily rectal movement and effectiveness of replanning protocols for sparing rectal doses based on the daily CT images during proton treatment for prostate cancer. *Journal of Applied Clinical Medical Physics*. 2020;21(10):109-121.	E4
Manganaro L, Attili A, Bortfeld T, Paganetti H. Spatiotemporal optimisation of prostate intensity modulated proton therapy (IMPT) treatments. *Physics in Medicine & Biology*. 2022;27:27.	E4
Marteinsdottir M, Paganetti H. Applying a variable relative biological effectiveness (RBE) might affect the analysis of clinical trials comparing photon and proton therapy for prostate cancer. *Physics in Medicine & Biology*. 2019;64(11):115027.	E4
Matsukawa K, Arimura T, Orita M, et al. Health-related quality of life in Japanese patients with prostate cancer following proton beam therapy: an institutional cohort study. *Japanese Journal of Clinical Oncology*. 2020;50(5):519-527.	E6
Mayer EN, Tward JD, Bassett M, et al. Management of Radiation Therapy Oncology Group grade 4 urinary adverse events after radiotherapy for prostate cancer. *BJU International*. 2017;119(5):700-708.	E2
Mendenhall WM, Glassman G, Morris CG, et al. Bacterial Urinary Tract Infection after Transrectal Placement of Fiducial Markers prior to Proton Radiotherapy for Prostate Cancer. *International Journal of Particle Therapy.* 2016;3(1):21-26.	E6
Moteabbed M, Harisinghani M, Paganetti H, Trofimov A, Lu HM, Efstathiou JA. Proton vs. photon radiotherapy for MR-guided dose escalation of intraprostatic lesions. *Acta Oncologica*. 2021;60(10):1283-1290.	E4
Moteabbed M, Trofimov A, Khan FH, et al. Impact of interfractional motion on hypofractionated pencil beam scanning proton therapy and VMAT delivery for prostate cancer. *Medical Physics*. 2018;14:14.	E4
Moteabbed M, Trofimov A, Sharp GC, et al. A Prospective Comparison of the Effects of Interfractional Variations on Proton Therapy and Intensity Modulated Radiation Therapy for Prostate Cancer. *International Journal of Radiation Oncology, Biology, Physics*. 2016;95(1):444-453.	E4
Narter F. Re: A Literature Review of Proton Beam Therapy for Prostate Cancer in Japan. *Journal of Urological Surgery*. 2019;6(1):81-81.	E7
Nichols RC, Morris CG, Bryant C, et al. Serum Testosterone 60 Months after Passive-Scatter Proton Therapy for Localized Prostate Cancer. *Cancer Investigation.* 2019;37(2):85-89.	E6

Citation	Exclude Reason
Nihei K, Ogino T, Onozawa M, et al. Multi-institutional Phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities. *Int J Radiat Oncol Biol Phys.* 2011;81(2):390-396.	E6
Ontario H. Proton Beam Therapy for Cancer in Children and Adults: A Health Technology Assessment. In. *Ontario Health Technology Assessment Series.* Vol 212021:1-142.	E8
Paganetti H. Relating the proton relative biological effectiveness to tumor control and normal tissue complication probabilities assuming interpatient variability in alpha/beta. *Acta Oncologica*. 2017;56(11):1379-1386.	E6
Paganetti H, Giantsoudi D. Relative Biological Effectiveness Uncertainties and Implications for Beam Arrangements and Dose Constraints in Proton Therapy. *Seminars in Radiation Oncology*. 2018;28(3):256-263.	E7
Pan HY, Jiang J, Shih YT, Smith BD. Adoption of Radiation Technology Among Privately Insured Nonelderly Patients With Cancer in the United States, 2008 to 2014: A Claims-Based Analysis. *Journal of the American College of Radiology*. 2017;14(8):1027-1033.e2.	E4
Pang EPP, Knight K, Park SY, et al. Duration-dependent margins for prostate radiotherapy-a practical motion mitigation strategy. *Strahlentherapie und Onkologie*. 2020;196(7):657-663.	E4
Parthan A, Pruttivarasin N, Davies D, et al. Comparative Cost-Effectiveness of Stereotactic Body Radiation Therapy Versus Intensity-Modulated and Proton Radiation Therapy for Localized Prostate Cancer. *Frontiers in Oncology*. 2012;2.	E6
Pedersen J, Liang X, Bryant C, Mendenhall N, Li Z, Muren LP. Normal tissue complication probability models for prospectively scored late rectal and urinary morbidity after proton therapy of prostate cancer. *Physics & Imaging in Radiation Oncology*. 2021;20:62-68.	E4
Pedersen J, Liang X, Casares-Magaz O, et al. Multivariate normal tissue complication probability models for rectal and bladder morbidity in prostate cancer patients treated with proton therapy. *Radiotherapy & Oncology*. 2020;153:279-288.	E4
Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys*. 2002;53(5):1097-105.	E2
Pugh TJ, Choi S, Nogueras-Gonzalaez GM, et al. Proton Beam Therapy for Localized Prostate Cancer: Results from a Prospective Quality-of-Life Trial. *International Journal of Particle Therapy.* 2016;3(1):27-36.	E6
Quinn TJ, Hamstra D. Hypofractionation in Prostate Cancer Using Proton Beam. *International Journal of Radiation Oncology, Biology, Physics*. 2019;105(4):723-726.	E7
Ricco A, Hanlon A, Lanciano R. Propensity Score Matched Comparison of Intensity Modulated Radiation Therapy vs Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Survival Analysis from the National Cancer Database. *Frontiers in Oncology*. 2017;7:185.	E2
Sandler H. Reply by Author. *Journal of Urology*. 2015;194(5):1508-9.	E7
Schulz-Ertner D, Tsujii H. Particle Radiation Therapy Using Proton and Heavier Ion Beams. *Journal of Clinical Oncology*. 2007;25(8):953-964.	E7
Schwarz M, Molinelli S. What can particle therapy add to the treatment of prostate cancer? *Physica Medica*. 2016;32(3):485-91.	E7
Shipley WU, Verhey LJ, Munzenrider JE, et al. Advanced prostate cancer: The results of a randomized comparative trial of high dose irradiation boosting with	E3

Citation	Exclude Reason
conformal protons compared with conventional dose irradiation using photons alone. *International journal of radiation oncology, biology, physics.* 1995;32(1):3-12.	
Sidaway P. Prostate cancer: Proton therapy delays progression. *Nature Reviews Urology*. 2016;13(4):181.	E7
Slater JM, Slater JD, Kang JI, et al. Hypofractionated Proton Therapy in Early Prostate Cancer: Results of a Phase I/II Trial at Loma Linda University. *International Journal of Particle Therapy.* 2019;6(1):1-9.	E6
Taneja SS. Re: Five-Year Biochemical Results, Toxicity, and Patient-Reported Quality of Life after Delivery of Dose-Escalated Image Guided Proton Therapy for Prostate Cancer. *Journal of Urology*. 2017;197(1):149-152.	E7
Tang C, Lei X, Smith GL, et al. Influence of Geography on Prostate Cancer Treatment. *International Journal of Radiation Oncology, Biology, Physics*. 2021;109(5):1286-1295.	E4
Thompson AB, Hamstra DA. Rectal Spacer Usage with Proton Radiation Therapy for Prostate Cancer. *International Journal of Radiation Oncology, Biology, Physics*. 2020;108(3):644-648.	E7
Tung CJ. Proton therapy. *Biomedical Journal*. 2015;38(5):389-90.	E7
Vapiwala N. Re: Radiation for Prostate Cancer: Intensity Modulated Radiation Therapy versus Proton Beam: B. S. Hoppe, C. Bryant and H. M. Sandler. *J Urol* 2015;193:1089-1091. *Journal of Urology*. 2015;194(5):1507-8.	E7
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Verma V, Simone CB, 2nd, Mishra MV. Quality of Life and Patient-Reported Outcomes Following Proton Radiation Therapy: A Systematic Review. *Journal of the National Cancer Institute*. 2018;110(4):01.	E8
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APPENDIX D: EVIDENCE TABLES

CHARACTERISTICS OF INCLUDED COMPARATIVE STUDIES

Note: Studies in bold are prioritized in synthesis as having a sufficiently similar comparison group.

Author Year *N*	Study Design *Country*	Participants Mean/Median Age *Follow-up*	Prostate Cancer Details	Proton Beam Dose (Gy) *PBT Details*	Comparator
Bai 2020[1] *N=262*	Retrospective cohort *USA*	71.1 *3 months*	Localized early prostate cancer	60–78 *60 Gy in 20 fractions, 70.2 Gy in 26 fractions, or 78 Gy in 39 fractions*	IMRT
Barsky 2021[2] ***N=260***	**Retrospective cohort** ***USA***	**Age NR** ***5 years***	**Post-radical prostatectomy prostate cancer**	**70.2 (median)**	**IMRT**
Coen 2012[3] ***N=282***	**Retrospective cohort** ***USA***	**66** ***8 years***	**Localized prostate cancer**	**79.2** ***Proton boost of 28.8 Gy before 3DCRT photon therapy (79.2 Gy total)***	**Brachytherapy**
Dutz 2019[4] ***N=58***	**Retrospective cohort** ***Germany***	**72.7** ***3 months – 1 year***	**Localized prostate cancer**	**74–76** ***74–76 Gy in 37-38 fractions***	**IMRT**
Fang 2014[5] ***N=188***	**Retrospective cohort** ***USA***	**Age NR** ***3 months – 2 years***	**Localized prostate cancer**	**79.2** ***79.2 Gy in 44 fractions***	**IMRT**
Gray 2013[6] *N=371*	Retrospective cohort *USA*	68.1 *3 – 24 months*	Localized prostate cancer	74–82 *PBT Details NR*	IMRT

Author Year *N*	Study Design *Country* *Follow-up*	Participants Mean/Median Age	Prostate Cancer Details	Proton Beam Dose (Gy) *PBT Details*	Comparator
Halpern 2016[7] *N=17,889*	Retrospective Cohort *USA* *1 year*	Age NR	Localized prostate cancer	PBT dosage and details NR	SBRT
Hoppe 2014[8] *N=1,447*	Prospective cohort *USA* *2 years*	66.4	Localized prostate cancer	76–82 *2 Gy per fraction*	IMRT
Kim 2011[9] *N=41,737*	Retrospective cohort *USA* *Follow-up NR*	Age NR	Localized prostate cancer	PBT dosage and details NR	EBRT
Liu 2021[10] ***N=276,880***	**Retrospective cohort** ***USA*** ***10 years***	**68**	**Localized prostate cancer**	**≥60 Gy** ***PBT Details NR***	**Brachytherapy**
Pan 2018[11] ***N=3,434***	**Retrospective cohort** ***USA*** ***2 years***	**<65**	**Localized prostate cancer**	**PBT dose NR** ***Median 39 fractions***	**IMRT**
Santos 2019[12] ***N=307***	**Retrospective cohort** ***USA*** ***3 months – 5 years***	**Age NR**	**Post-radical or salvage prostatectomy**	**66.0–70.2** ***66 to 70.2 Gy in 1.8 to 2.0 Gy fractions***	**IMRT**
Sheets 2012[13] ***N=1,368***	**Retrospective cohort** ***USA*** ***1 year***	**Age NR**	**Localized prostate cancer**	**PBT dosage and details NR**	**IMRT**
Vapiwala 2021[14] ***N=1,850***	**Retrospective cohort** ***USA*** ***3 months***	**67**	**Localized early prostate cancer**	**60–72.5** ***2.5–3 Gy per fraction***	**IMRT**

Author Year *N*	Study Design *Country* *Follow-up*	Participants Mean/Median Age	Prostate Cancer Details	Proton Beam Dose (Gy) *PBT Details*	Comparator
Xiang 2020[15] *N=10,700*	Retrospective cohort *USA* *5.21 years*	59.4	Localized prostate cancer	56.4–81.0 *2.5–5 Gy per fraction*	IMRT
Yu 2013[16] *N=942*	Retrospective cohort *USA* *6 – 12 months*	Age NR	Localized early prostate cancer	PBT dosage and details NR	IMRT

Abbreviations. 3DCRT=Three-dimensional conformal radiation therapy; EBRT=external beam radiation therapy; Gy=the gray (symbol: Gy) is a derived unit of ionizing radiation dose in the International System of Units (SI); IMRT=intensity modulated radiation therapy; NR=not reported; PBT=proton beam therapy; RCT=randomized controlled trial; SBRT=stereotactic body radiation therapy; USA=United States of America; XRT=x-ray beam irradiation.

CHARACTERISTICS OF INCLUDED NONCOMPARATIVE STUDIES WITH SUBGROUPS

Author **Year** ***N***	**Study Design** ***Country***	**Participants** **Mean/Median Age** ***Follow-up***	**Prostate Cancer Details**	**Proton Beam Dose (Gy)**	**Subgroups Compared**
Arimura 2018[17] *N=218*	Case series *Japan*	65 *5 years*	Localized prostate cancer	70–78	Prostate Cancer Risk Groups
Bryant 2016[18] *N=1327*	Case series *USA*	66 *5 years*	Localized prostate cancer	74–82	Prostate Cancer Risk Groups
Bryant 2016[19] *N=184*	Case series *USA*	65 *2 years*	Localized prostate cancer	70–82	Race
Bryant 2017[20] *N=1066*	Case series *USA*	66 *5 years*	Localized prostate cancer	78	Race
Bulman 2021[21] *N=243*	RCT *USA*	71 *36 months*	Localized prostate cancer	2–≥6	Fractionation
Colaco 2015[22] *N=1285*	Case series *USA*	66 *3 years*	NR	72–82.3	Dosage
Deville 2020[23] *N=100*	Case series *USA*	64 *5 years*	Post radical prostatectomy	66.6–75.6	Prostate Cancer Risk Groups
Goenka 2017[24] *N=81*	Case series *USA*	Age NR *6 months*	NR	79.2	Prostate Size
Grewal 2019[25] *N=184*	Case series *USA*	67 *4 years*	Localized prostate cancer	70	Prostate Cancer Risk Groups

Author **Year** ***N***	**Study Design** ***Country***	**Participants** **Mean/Median Age** ***Follow-up***	**Prostate Cancer Details**	**Proton Beam Dose (Gy)**	**Subgroups Compared**
Ha 2019[26] *N=82*	RCT *Korea*	68 *7 years*	Localized prostate cancer	47–60	Fractionation
Hattori 2021[27] *N=127*	Case series *Japan*	69 *60 months*	Localized prostate cancer	74–78	Prostate Cancer Risk Groups
Henderson 2013[28] *N=171*	*Prospective cohort* USA	Age NR *5 years*	Low-intermediate risk prostate cancer	78–82	IPSS Scores
Henderson 2017[29] *N=215*	Case series *USA*	65 *5 years*	Localized prostate cancer	70–72.5	Prostate Cancer Risk Groups
Henderson 2021[30] *N=582*	Case series *USA*	65.1 *5 years – 7 years*	Localized prostate cancer	70–72.5	Prostate Cancer Risk Groups
Ho 2018[31] *N=254*	Case series *USA*	56 *7 years*	Prostate cancer	76–82 or 70–72.5	Prostate Cancer Risk Groups
Holtzman 2019[32] *N=1005*	Case series *USA*	67 *5 years*	Localized prostate cancer	78 RBE	Potency
Iizumi 2021[33] *N=289*	Case series *Japan*	68 *Follow-up NR*	Localized prostate cancer	74–78 or 63–70	Dosage
Iwata 2018[34] *N=1291*	Case series *Japan*	68 *5 years*	Localized prostate cancer	70–80 or 63–66	Prostate Cancer Risk Groups
Johansson 2019[35] *N=504*	Case series *Sweden*	66 *5 years – 10 years*	Localized prostate cancer	87	Prostate Cancer Risk Groups

Author **Year** ***N***	**Study Design** ***Country***	**Participants** **Mean/Median Age** ***Follow-up***	**Prostate Cancer Details**	**Proton Beam Dose (Gy)**	**Subgroups Compared**
Kharod 2021[36] *N=102*	Case series *USA*	67.8 *5 years*	Post prostatectomy prostate cancer	66.0–78.2	Adjuvant vs Salvage PBT
Kim 2013[37] *N=82*	RCT *Korea*	68 *42 months*	Localized prostate cancer	35–60	Dosage
Kubes 2019[38] N=200	Case series *Czech Republic*	64.3 *36 months*	Early-stage prostate cancer	36.25	Prostate Cancer Risk Groups
Kubes 2021[39] *N=284*	Case series *Czech Republic*	64.5 *5 years*	Localized prostate cancer	36.23	Prostate Cancer Risk Groups
Lee 2016[40] *N=1289*	Case series *USA*	66 *3 years*	NR	78–82	TURP vs No TURP
Lee 2019[41] *N=192*	Case series *USA*	68 *2 years*	Localized prostate cancer	79.2	Prostate Cancer Risk Groups
Makishima 2017[42] *N=93*	Retrospective cohort *Japan*	68 *55 months – 5 years*	NR	78	Prostate Cancer Risk Groups
Mendenhall 2014[43] *N=211*	Case series *USA*	68 *45 years*	Localized prostate cancer	78–82	Prostate Cancer Risk Groups
Mishra 2019[44] *N=1343*	Case series *USA*	65.4 *3 years*	Localized prostate cancer	>75	Pencil Beam vs Passive Scattering

Author **Year** ***N***	**Study Design** ***Country***	**Participants** **Mean/Median Age** ***Follow-up***	**Prostate Cancer Details**	**Proton Beam Dose (Gy)**	**Subgroups Compared**
Mishra 2020[45]	Case series	65.1	Localized prostate cancer	>75	Pencil Beam vs Passive Scattering
N=304	*USA*	*1 year*			
Murakami 2020[46]	Case series	68	Localized prostate cancer	63–80	Prostate Cancer Risk Groups
N=1075	*Japan*	*Follow-up NR*			
Nakajima 2018[47]	Case series	69.5	Localized prostate cancer	60–78	Fractionation
N=526	*Japan*	*Follow-up NR*			
Negoro 2020[48]	Case series	68	Localized prostate cancer	70–78	Time of Day
N=168	*Japan*	*Follow-up NR*			
Takagi 2017[49]	Case series	69	Localized prostate cancer	74–78	Prostate Cancer Risk Groups
N=1375	*Japan*	*5 years – 8 years*			
Takagi 2020[50]	Case series	68	Localized prostate cancer	74	Prostate Cancer Risk Groups
N=2021	*Japan*	*5 years – 10 years*			
Vargas 2018[51]	RCT	65	Low risk prostate cancer	38 & 79.2	Fractionation
N=82	*USA*	*5 years*			

Abbreviations. Gy=the gray (symbol: Gy) is a derived unit of ionizing radiation dose in the International System of Units (SI); PBT=proton beam therapy; RBE=relative biological effectiveness; RCT=randomized controlled trial; TURP=transurethral resection of the prostate; USA=United States of America.

OUTCOME DATA OF INCLUDED COMPARATIVE STUDIES

Note: Studies in bold are prioritized in synthesis as having a sufficiently similar comparison group.

Author Year ***N***	Comparator	Outcome ***Details*** ***Timing***	Results	Description of Tests Conducted	Other Outcomes Reported
Bai 2020[1] *N=262*	IMRT	Quality of Life *Bowel Function (EPIC-26)* *3 months*	Mean change: -1.2 vs -9.3, *p* = 0.02	P-value for difference in change scores between treatment groups (Wilcoxon rank-sum test)	NR
		Quality of Life *Urinary Irritative/ Obstructive Symptoms (EPIC-26)* *3 months*	Mean change: 1.7 vs -2.4, *p* = 0.03	P-value for difference in change scores between treatment groups (Wilcoxon rank-sum test)	
		Quality of Life *Urinary Incontinence (EPIC-26)* *3 months*	Mean change: -0.4 vs -2.5, *p* = 0.21	P-value for difference in change scores between treatment groups (Wilcoxon rank-sum test)	
Barsky 2021[2] ***N=260***	**IMRT**	**Biochemical Failure** ***Biochemical failure by institutional metrics*** ***5 years***	**29 (45%) vs 80 (41%)** **HR = 1.15, 95% CI [0.74, 1.82], *p* = 0.52**	**Utilized data from matched cohort and multivariable analyses**	**Follow-up outcomes from Santos 2019. Local, regional, and distant failure and 2 other measures of biochemical failure.**
		Overall Survival	**1 (2%) vs 9 (5%)**	**Utilized data from matched cohort**	

		All-cause mortality ***5 years***	**HR = 0.64, 95% CI [0.07, 5.91], *p* = 0.69**	**and multivariable analyses**	
		Prostate-cancer-specific Survival ***Prostate-cancer-specific mortality*** ***5 years***	**0 (0%) vs 2 (1%)**	**NR**	
Coen 2012[3] ***N=282***	**Brachytherapy**	**Overall Survival** ***Details NR*** ***8 years***	**93% vs 96%, *p* = 0.45**	***P*-value for difference in overall survival proportion**	**Also presents BF data by risk group**
		Biochemical Failure ***Biochemical failure by Phoenix definition*** ***8 years***	**7.7% vs 16.1%** **HR = 1.3, 95% CI (0.7, 2.5), *p* = 0.42**	***P*-value for difference in biochemical failure proportion**	
		Disease Recurrence ***Freedom from distant metastasis*** ***8 years***	**99% vs 96%, *p* = 0.21**	***P*-value for difference in recurrence proportion**	
Dutz 2019[4] ***N=58***	**IMRT**	**Early GU Toxicity** ***Early (up to 3 months) GU toxicity*** ***3 months***	**27 (93.1%) vs 26 (89.7%), *p* = 0.45**	***P*-value for proportion of early GU toxicity between groups** **Used matched cohort of 58 pts**	**NR**

		Late GU Toxicity ***Late (1 year) GU toxicity*** ***1 year***	**10 (45.5%) vs 14 (63.3%), *p* = 0.53**	***P*-value for proportion of late GU toxicity between groups**	
		Early GI Toxicity ***Early (up to 3 months) GI toxicity*** ***3 months***	**19 (65.5%) vs 16 (55.2%), *p* = 0.6**	***P*-value for proportion of early GI toxicity between groups**	
		Late GI Toxicity ***Late (1 year) GI toxicity*** ***1 year***	**5 (22.7%) vs 8 (36.4%), *p* = 0.35**	***P*-value for proportion of late GI toxicity between groups**	
		Quality of Life ***EORTC QLC*** ***1 year***	**NR**	**No significant differences in any QoL scores (19 subscales) between groups at 3 months or 1 year**	
Fang 2014[5] ***N=188***	**IMRT**	**Early GI Toxicity** ***Early (up to 3 months) GI toxicity*** ***3 months***	**OR = 0.27, 95% CI [0.06, 1.24], *p* = 0.09**	**Data from multivariable analysis**	**NR**
		Late GI Toxicity ***Late (beyond 3 months) GI toxicity***	**HR = 1.24, 95% CI [0.53-2.94], *p* = 0.62**	**Data from multivariable analysis**	

		2 years			
		Early GU Toxicity ***Early (up to 3 months) GU toxicity*** ***3 months***	**OR = 0.69, 95% CI [0.32, 1.51], *p* = 0.36**	**Data from multivariable analysis**	
		Late GU Toxicity ***Late (beyond 3 months) GU toxicity*** ***2 years***	**HR = 0.56, 95% CI [0.22, 1.41], *p* = 0.22**	**Data from multivariable analysis**	
Gray 2013[6] *N=371*	IMRT	Quality of Life *Bowel/Rectal Domain (PCSI/EPIC)* *3 months*	Mean Change (SD): -1.7 (8.3) vs -16 (21.4) PBT: *p* = 0.62 IMRT: *p < 0.001*	NSD from baseline in PBT group (*p* = 0.62) but significant worsening from baseline in IMRT group (*p* < 0.001)	QoL at 12 months
		Quality of Life *Urinary Irritation/ Obstruction (PCSI/EPIC)* *3 months*	Mean Change (SD): -4.8 (13.8) vs -16.5 (19.9) PBT: *p* = 0.002 IMRT: *p* < 0.001	Significant worsening from baseline in PBT (*p* = 0.002) and IMRT (*p* < 0.001) groups	
		Quality of Life *Urinary Incontinence (PCSI/EPIC)* *3 months*	Mean Change (SD): -0.9 (12.6) vs -7.9 (18) PBT: *p* = 0.516 IMRT: *p* < 0.001	NSD from baseline in PBT group (*p* = 0.516) but significant worsening in IMRT group (*p* < 0.001)	
		Quality of Life	Mean Change (SD): -3.7 (6.4) vs -7.4 (16.6)	Significant worsening from baseline in PBT	

	Bowel/Rectal Domain (PCSI/EPIC) *24 months*	PBT: $p = 0.004$ IMRT: $p < 0.001$	($p = 0.004$) and IMRT ($p < 0.001$) groups
	Quality of Life *Urinary Irritation/ Obstruction (PCSI/EPIC)* *24 months*	Mean Change (SD): -2.3 (10.5) vs 1.7 (14.2) PBT: $p = 0.241$ IMRT: $p = 0.164$	NSD from baseline in PBT or IMRT groups
	Quality of Life *Urinary Incontinence (PCSI/EPIC)* *24 months*	Mean Change (SD): -4.1 (12) vs -5.1 (16) PBT: $p = 0.08$ IMRT: $p = 0.001$	NSD from baseline in PBT group but significant worsening in IMRT group
3DCRT	Quality of Life *Bowel/Rectal Domain (PCSI/EPIC)* *3 months*	Mean Change (SD): -1.7 (8.3) vs -7.2 (13.4) PBT: $p = 0.062$ 3DCRT: $p < 0.001$	NSD from baseline in PBT group but significant worsening in CRT group
	Quality of Life *Urinary Irritation/ Obstruction (PCSI/EPIC)* *3 months*	Mean Change (SD): -4.8 (13.8) vs -4.7 (12.3) PBT: $p = 0.002$ 3DCRT: $p < 0.001$	Significant worsening from baseline in PBT and CRT groups
	Quality of Life *Urinary Incontinence (PCSI/EPIC)*	Mean Change (SD): -0.9 (12.6) vs -2.6 (16.7) PBT: $p = 0.516$ 3DCRT: $p < 0.097$	NSD from baseline in PBT group but significant worsening in CRT group

		3 months			
		Quality of Life *Bowel/Rectal Domain (PCSI/EPIC)* *24 months*	Mean Change (SD): -3.7 (6.4) vs -4.3 (7.8) PBT: p = 0.004 3DCRT: p < 0.001	Significant worsening from baseline in PBT and CRT groups	
		Quality of Life *Urinary Irritation/ Obstruction (PCSI/EPIC)* *24 months*	Mean Change (SD): -2.3 (10.5) vs -2 (12.4) PBT: p = 0.241 3DCRT: p = 0.08	NSD from baseline in PBT or CRT groups	
		Quality of Life *Urinary Incontinence (PCSI/EPIC)* *24 months*	Mean Change (SD): -4.1 (12) vs -1.9 (14.1) PBT: p = 0.08 3DCRT: p = 0.161	NSD from baseline in PBT or CRT groups	
Halpern 2016[7] *N=17889*	SBRT	Late GI Toxicity *Gastrointestinal complications* *1 year*	59 (16.3%) vs 48 (20.3%)	NR	NR
		Late GU Toxicity *Urinary non-incontinence complications* *1 year*	19 (5.2%) vs 23 (9.7%)	NR	
		Any GU Toxicity	25 (6.9%) vs 37 (15.6%)	NR	

	Urinary incontinence *1 year*		
	Other Adverse Events	17 (4.7%) vs 38 (16%)	NR
	Erectile dysfunction *1 year*		
Brachytherapy	Late GI Toxicity	59 (16.3%) vs 814 (19.7%)	NR
	Gastrointestinal complications *1 year*		
	Late GU Toxicity	19 (5.2%) vs 1038 (25.1%)	NR
	Urinary non-incontinence complications *1 year*		
	Any GU Toxicity	25 (6.9%) vs 1330 (32.2%)	NR
	Urinary incontinence *1 year*		
	Other Adverse Events	17 (4.7%) vs 471 (11.4%)	NR
	Erectile dysfunction *1 year*		
IMRT	Late GI Toxicity	59 (16.3%) vs 2018 (18.8%)	NR

	Gastrointestinal complications *1 year*		
	Late GU Toxicity	19 (5.2%) vs 1053 (9.8%)	NR
	Urinary non-incontinence complications *1 year*		
	Any GU Toxicity	25 (6.9%) vs 1399 (13.1%)	NR
	Urinary incontinence *1 year*		
	Other Adverse Events	17 (4.7%) vs 777 (7.3%)	NR
	Erectile dysfunction *1 year*		
Mixed	Late GI Toxicity	59 (16.3%) vs 476 (19.5%)	NR
	Gastrointestinal complications *1 year*		
	Late GU Toxicity	19 (5.2%) vs 623 (25.6%)	NR
	Urinary non-incontinence complications *1 year*		

		Any GU Toxicity *Urinary incontinence* *1 year*	25 (6.9%) vs 802 (32.9%)	NR	
		Other Adverse Events *Erectile dysfunction* *1 year*	17 (4.7%) vs 239 (9.8%)	NR	
Hoppe 2014[8] *N=1447*	IMRT	Quality of Life *Bowel summary, (minimally detectable diff. from baseline, EPIC)* *2 years*	37% vs 38%, *p* = 0.99	*P*-value for comparison of proportions	NR
		Quality of Life *Urinary incontinence, (minimally detectable diff. from baseline, EPIC)* *2 years*	32% vs 34%, *p* = 0.99	*P*-value for comparison of proportions	
		Quality of Life *Urinary/irritative obstructive, (minimally detectable diff. from baseline, EPIC)* *2 years*	17% vs 18%, *p* = 0.99	*P*-value for comparison of proportions	

		Quality of Life *Sexual summary, (minimally detectable diff. from baseline, EPIC)* *2 years*	40% vs 41%	*P*-value for comparison of proportions	
Kim 2011[9] *N=41737*	EBRT	Any GI Toxicity *Any GI toxicity, events per person-year per 1000* *Timing NR*	20.1% vs 8.8%, $p < 0.001$	Comparison across radiation therapy modalities	Also reports GI bleeding, GI fistula, GI stricture, GI colostomy. Table 2 reports percentages, Table 4 reports HR
	3DCRT	Any GI Toxicity *Any GI toxicity, events per person-year per 1000* *Timing NR*	20.1% vs 9.3% HR = 2.13, 95% CI [1.45, 3.13]	PBT vs 3DCRT	
	IMRT	Any GI Toxicity *Any GI toxicity, events per person-year per 1000* *Timing NR*	20.1% vs 8.9% HR = 3.32, 95% CI [2.12, 5.20]	PBT vs IMRT	
	Brachytherapy	Any GI Toxicity *Any GI toxicity, events per person-year per 1000* *Timing NR*	20.1% vs 5.3%	NR	

	Waiting	Any GI Toxicity *Any GI toxicity, events per person-year per 1000* *Timing NR*	20.1% vs 2.1% HR = 13.7, 95% CI [9.09, 20.8]	PBT vs conservative management	
Liu 2021[10] ***N=276880***	**EBRT**	**Overall Survival** ***Details NR*** ***10 years***	**85.6% vs 60.1%** **HR = 1.72, 95% CI [1.51, 1.96], *p* < 0.001**	**EBRT vs PBT, multivariate analysis**	**NR**
	Brachytherapy	**Overall Survival** ***Details NR*** ***10 years***	**85.6% vs 74%** **HR = 1.38, 95% CI [1.21, 1.58], *p* < 0.001**	**Brachytherapy vs PBT, multivariate analysis**	
Pan 2018[11] ***N=3434***	**IMRT**	**Late GU Toxicity** ***ICD-9 Composite urinary toxicity*** ***1 year***	**23.1% vs 31.6%** **HR = 0.72, 95% CI [0.63, 0.83], *p* < 0.001**	**PBT vs IMRT**	**NR**
		Late GI Toxicity ***ICD-9 Bowel toxicity*** ***1 year***	**7.4% vs 7.7%** **HR = 1.27, 95% CI [1.05, 1.55], *p* = 0.02**	**PBT vs IMRT**	
		Other Adverse Events ***ICD-9 Erectile dysfunction***	**10.6% vs 18.1%** **HR = 0.71, 95% CI [0.59, 0.84], *p* < 0.001**	**PBT vs IMRT**	

		1 year			
Santos 2019[12]	**IMRT**	**Early GU Toxicity**	**12 (21.8%) vs 43 (78.2%)**	**IMRT vs PBT, multivariate analysis**	**Only age at diagnosis reported**
N=307		***Acute grade ≥ 2 GU toxicity***	**OR = 1.19, 95% CI [0.45, 3.12], *p* = 0.724**		
		3 months			
		Late GU Toxicity	**8 (17.8%) vs 37 (82.2%)**	**IMRT vs PBT, multivariate analysis**	
		Late grade ≥ 2 GU toxicity	**OR = 0.96, 95% CI [0.30, 2.15], *p* = 0.951**		
		5 years			
		Early GI Toxicity	**19 (27.1%) vs 78 (39.6%)**	**IMRT vs PBT, multivariate analysis**	
		Acute grade ≥ 1 GI toxicity	**OR = 0.9, 95% CI [0.31, 2.61], *p* = 0.845**		
		3 months			
		Late GI Toxicity	**19 (27.1%) vs 67 (34%)**	**IMRT vs PBT, multivariate analysis**	
		Late grade ≥ 1 GI toxicity	**OR = 0.72, 95% CI [0.4, 1.32], *p* = 0.292**		
		5 years			
Sheets 2012[13]	**IMRT**	**Late GI Toxicity**	**17.8% vs 12.2%**	**IMRT vs PBT**	**NR**
N=1296		***ICD9 Gastrointestinal events***	**RR = 0.66, 95% CI [0.55, 0.79]**		
		4 years			
		Late GU Toxicity	**6.3% vs 7.5%**	**IMRT vs PBT**	
			RR = 1.25, 95% CI [0.99, 1.58]		

ICD9 Urinary non-incontinence events		
4 years		
Late GU Toxicity	**3.3% vs 3.1%**	**IMRT vs PBT**
ICD9 Urinary incontinence events	**RR = 0.96, 95% CI [0.7, 1.32]**	
4 years		
Other Adverse Events	**7.4% vs 6.6%**	**IMRT vs PBT**
Erectile dysfunction events	**RR = 0.89, 95% CI [0.7, 1.12]**	
4 years		
Any GU Toxicity	**1 (1%) vs 1 (1%)**	**Proportions based on those completing treatment (Table 2)**
Urinary incontinence		
8 years		
Other Adverse Events	24 (60%) vs 24 (63%)	Proportions based on those completing treatment (Table 2)
Loss of full potency		
8 years		
Other Adverse Events	1% vs 0%	NR
Any grade 4 complication		

		8 years			
		Overall Survival *Details NR* *8 years*	55% vs 51%	NR	
		Prostate-cancer-specific Survival *Disease-specific survival* *8 years*	67% vs 62%	NR	
		Disease Progression *Local control* *8 years*	73% vs 59%	NR	
		Progression-free Survival *Tumor-free survival* *8 years*	20% vs 16%	NR	
Vapiwala 2021[14] ***N=1850***	**IMRT**	**Late GU Toxicity** ***CTCAE grade 3+*** ***>3 months***	**1.6% vs 3.7%** **OR = 0.55, 95% CI [0.15, 1.99], *p* = 0.55**	**PBT vs IMRT, multivariate analysis**	**NR**
		Late GI Toxicity ***CTCAE grade 2+***	**11.1% vs 4.8%** **OR = 2.68, 95% CI [0.8, 8.98], *p* = 0.11**	**PBT vs IMRT, multivariate analysis**	**NR**

		>3 months			
		Early GU Toxicity ***CTCAE grade 3+*** ***3 months***	**0% vs 2.7%, *p* = 0.002**	***P*-value for comparison of proportions**	**Early toxicity analysis on a subgroup of patients with available data**
		Early GI Toxicity ***CTCAE grade 2+*** ***3 months***	**3.8% vs 4.4%, *p* = 0.67**	***P*-value for comparison of proportions**	
Xiang 2020[15] ***N=10,700***	**IMRT**	**Disease Recurrence** **Risk of second cancer** **≥ 5 years**	**AOR = 0.18, 95% CI [0.14, 0.24], *p* < 0.0001**	**PBRT vs IMRT multivariable logistic regression**	**NR**
		Disease Recurrence **Risk of second cancer** **≥ 5 years**	**AOR = 0.46, 95% CI [0.44, 0.49), *p* < 0.0001**	**PBRT vs IMRT pooled multivariate analysis**	
Yu 2013[16] ***N=942***	**IMRT**	**Late GI Toxicity** ***12-month GI toxicity*** ***12 months***	**31 (9.9%) vs 64 (10.2%)** **OR = 0.97, 95% CI [0.61, 1.53], *p* = 0.89**	**NR**	**NR**
		Late GU Toxicity ***12-month GI toxicity***	**59 (18.8%) vs 110 (17.5%)** **OR = 1.08, 95% CI [0.76, 1.54], *p* = 0.66**	**NR**	

12 months		
Other Toxicity	**14 (4.5%) vs 35 (5.6%)**	**NR**
Other late toxicity	**OR = 0.78, 95% CI [0.41, 1.50], *p* = 0.46**	
12 months		

Abbreviations. 3DCRT=three-dimensional conformal radiation therapy; BF=biochemical failure; BRFS=biochemical relapse free survival; CI=confidence interval; CRT=conformal radiation therapy; CTCAE=Common Terminology Criteria for Adverse Events; EBRT=external beam radiation therapy; EORTC=European Organization for Research and Treatment of Cancer; EPIC=Expanded Prostate Cancer Index Composite; GU=genitourinary; GI=gastrointestinal; HR=hazards ratio; Gy=the gray (symbol: Gy) is a derived unit of ionizing radiation dose in the International System of Units (SI); ICD-9=International Classification of Diseases; IMRT=intensity modulated radiation therapy; NSD=no significant difference; OR=odds ratio; PBT=proton beam therapy; PCSI=Prostate Cancer Symptom Indices; pts=patients; QoL=quality of life; RCT=randomized controlled trial; SBRT=stereotactic body radiation therapy; SD=standard deviation; TFS=tumor free survival; USA=United States of America; XRT=x-ray radiation therapy.

OUTCOME DATA OF INCLUDED NONCOMPARATIVE STUDIES WITH SUBGROUPS

Author Year *N*	**Subgroups**	**Outcome *Details Timing***	**Results**	**Description of Tests Conducted**	**Other Outcomes Reported**
Arimura 2018[17] *N=218*	Intermediate Risk High Risk	Overall Survival *Details NR* *5 years*	96% vs 98%, *p* = 0.673	Overall survival between risk groups (Kaplan-Meier)	GI/GU toxicity, sexual QoL
		Progression-free Survival *Details NR* *5 years*	97% vs 83%, *p < 0.01*	Freedom from biochemical failure between risk groups (Kaplan-Meier)	
Bryant 2016[18] *N=1327*	Low Risk Intermediate Risk High Risk	Progression-free Survival *Freedom from biochemical failure by Phoenix definition* *5 years*	99% vs 94% vs 75%, *p < 0.01*	Freedom from biochemical failure between risk groups (Kaplan-Meier)	GI toxicity, QoL Multivariable analysis of predictors of GU toxicity and freedom from biochemical failure
		Prostate-cancer-specific Survival *Cause-specific survival* *5 years*	98% vs 97% vs 95%	NR	
		Late GU Toxicity *GR3+ GU toxicity*	(Low vs High) HR = 0.9, 95% CI [0.4, 1.9] (Intermediate vs High) HR = 0.8, 95% CI [0.4, 1.8]		

		5 years			
Bryant 2016[19] *N=184*	African American Patients White Patients	Late GI Toxicity *GR2+ GI toxicity* *2 years*	23% vs 29%, *p* = 0.45	Univariate regression and repeated-measures ANOVA	NR
		Late GU Toxicity *GR3 GU toxicity* *2 years*	4.4% vs 0%, *p* = 0.12	Univariate regression and repeated-measures ANOVA	
		Quality of Life *EPIC-26: urinary irritative/obstructive, bowel, urinary incontinence, sexual* *2 years*	NR	No significant differences between African American and white subgroups in QoL domains at 2 years	
Bryant 2017[20] *N=1066*	African American Patients White Patients	Biochemical Failure *Phoenix definition* *2.8 years (AA)* *3.4 years (W)*	6 (8.8%) vs 81 (8.1%)	NR	Freedom from biochemical progression by risk group and race Median EPIC scores for bowel, urinary irritative/obstructive, and urinary incontinence domains were not significantly different for African American or white patients (data NR)
		Progression-free Survival Freedom from biochemical progression 5 years	92.1% vs 92.4%, *p* = 0.65 HR = 0.8, *p* = 0.55	Kaplan-Meier method (African American vs white patients) In multivariate analyses, race was not a predictor of 5-year FFBP	

Metastasis-free Survival *Distant metastasis-free survival* *5 years*	96.9% vs 92.6%, *p* = 0.96	Kaplan-Meier method (African American vs white patients)
Overall Survival *Details NR* *5 years*	93.9% vs 96.4%, *p* = 0.12	Kaplan-Meier method (African American vs white patients)
Late GU Toxicity *GR3+ GU toxicity* *Timing NR*	6.4% vs 2.1%, *p* = 0.06 HR = 2.5, *p* = 0.1	Kaplan-Meier method (African American vs white patients) Race was not a predictor of Gr 3+ GU toxicity
Late GI Toxicity *GR3 GI toxicity* *5 years*	0% vs 0.8%, *p* = 0.5	Kaplan-Meier method (African American vs White patients)
Quality of Life *EPIC sexual summary scores* *5+ years*	63 vs 53, *p* = 0.35	(Wilcoxon test) Median EPIC sexual summary score at 5+ years African American vs white Significant difference in median scores between AA patients and white

				patients at 2 years, but not 5 years	
Bulman 2021[21] *N=243*	Extreme hypofractionation Hypofractionation	Quality of Life *EPIC bowel (total)* *36 months*	Mean Change -4.58, $p < 0.01$ vs -1.42, $p = 0.07$	Extreme hypofractionation was associated with score decrease compared to conventional fractionation. Hypofractionation was not associated with score decrease compared to conventional fractionation.	NR
		Quality of Life *EPIC bowel function* *36 months*	-4.06, $p < 0.01$ vs -2.47, $p < 0.01$	Extreme hypofractionation was associated with score decrease compared to conventional fractionation. Hypofractionation was associated with score decrease compared to conventional fractionation.	
		Quality of Life *EPIC bowel bother* *36 months*	-5.12, $p < 0.01$ vs -0.4, $p = 0.66$	Extreme hypofractionation was associated with score decrease compared to conventional fractionation. Hypofractionation was not associated with score decrease compared to	

				conventional fractionation.	
Colaco 2015[22] *N=1285*	≤ 78 Gy > 78 Gy	Other Toxicity *GR2+ rectal bleeding* *3 years*	≤ 78 Gy: 15.1% HR = 0.9, 95% CI [0.4, 1.8], *p* = 0.9999	Multivariate proportional hazards regression ≤ 78 Gy vs > 78 Gy	Maximum GR3 toxicity, maximum GR2 toxicity
	Low Risk Intermediate Risk High Risk	Other Toxicity *GR2+ rectal bleeding* *3 years*	HR = 0.8, 95% CI [0.4, 1.8], *p* = 0.9999	Multivariate proportional hazards regression 3-way comparison between low, intermediate, and high risk	
Deville 2020[23] *N=100*	Gleason score < 7 Gleason score 7 Gleason score > 7	Progression-free Survival *Biochemical failure-free survival* *5 years*	< 7: 85%, 95% CI [51, 96] 7: 65%, 95% CI [50, 76] > 7: 18%, 95% CI [5, 41] < 7 vs 7: HR = 0.396, 95% CI [0.093, 1.695], *p* = 0.212 > 7 vs 7: HR = 3.530, 95% CI [1.824, 6.833], *p* < 0.001	Multivariate analyses	Distant metastasis free-survival, overall survival
Goenka 2017[24] *N=81*	Prostate size: <30 cm3 30-49 cm3 ≥50 cm3	Quality of Life *Urinary function (AUA score)* *6 months*	2.3 vs 3.2 vs 0.2, *p* = 0.06	ANOVA: Prostate size not associated with changes in AUA score	Urinary bother, GI bother
		Quality of Life *EPIC Urinary domain* *6 months*	-3.6 vs -3.1 vs 3.8, *p* = 0.76	ANOVA: Prostate size not associated with changes in EPIC urinary domain score	

		Quality of Life *EPIC GI domain* *6 months*	-3.7 vs -1.1 vs -0.55, *p* = 0.67	ANOVA: Prostate size not associated with changes in EPIC urinary domain score	
Grewal 2019[25] *N=184*	Low Risk Favorable Intermediate Risk Unfavorable Intermediate Risk	Progression-free Survival *Biochemical failure (Phoenix)-free survival* *4 years*	Low: 94.4%, 95% CI [89, 100] Favorable Intermediate: 92.5%, 95% CI [86, 100] Unfavorable Intermediate: 93.8%, 95% CI [88, 100] *p* > 0.4	Log rank difference between risk groups	Acute GI/GU toxicity, late GI/GU toxicity
		Overall Survival *Details NR* *4 years*	*p* > 0.7	Log rank difference between risk groups	
		Any GU Toxicity *GR2+ GU toxicity* *4 years*	2 (11%) vs 4 (5%) vs 8 (9%), *p* = 0.43	Fisher's exact test difference between risk groups	
		Any GI Toxicity *GR2+ GI toxicity* *4 years*	0 (0%) vs 11 (14%) vs 14 (16%), *p* = 0.21	Fisher's exact test difference between risk groups	
		Quality of Life *International Index of Erectile Function* *4 years*	*p* = 0.11	No difference between risk groups in GEE adjusted analysis	

		Quality of Life *EPIC urinary incontinence, urinary irritation, bowel, sexual, and hormonal scores* *4 years*	NR	No difference between risk groups in any EPIC domain in GEE adjusted analysis	
Ha 2019[26] *N=82*	Moderate Hypofractionation Extreme Hypofractionation	Biochemical Failure *Phoenix definition* *7 years*	15 vs 20	NR	Biochemical failure-free survival within risk groups
		Progression-free Survival *Biochemical failure-free survival* *7 years*	76.2% vs 46.2%, *p* = 0.005 HR = 3.24, 95% CI [1.51, 6.93], *p* = 0.003	NR	
		Early GI Toxicity *Acute GR1 GI toxicity* *Timing NR*	6 (11%) vs 6 (20%), *p* = 0.341	Fisher's exact test	
		Early GU Toxicity *Acute GR1+ GU toxicity* *Timing NR*	44 (85%) vs 17 (57%), *p* = 0.009	Fisher's exact test	
		Late GI Toxicity *Late GR1+ GI toxicity*	37 (71%) vs 20 (67%), *p* = 0.891	Fisher's exact test	

		Timing NR			
		Late GU Toxicity *Late GR1+ GU toxicity* *Timing NR*	20 (38%) vs 11 (37%), p = 0.835	Fisher's exact test	
Hattori 2021[27] *N=127*	Low Risk Intermediate Risk High/Very High Risk	Quality of Life *EPIC sexual domain summary scores* *60 months*	Mean Change Low: -10.4, p < 0.05 Intermediate: 4.6, p < 0.05 High/Very High: 2.1, p < 0.05	Wilcox signed-rank test Wilcox signed-rank test	NR
		Quality of Life *Erection Hardness Score* *60 months*	Mean Change Low: -0.7, p < 0.05 Intermediate: 0.1, NSD High/Very High: 0.1, NSD		
Henderson 2013[28] *N=171*	IPSS score 0-14 IPSS score 15-25	Early GU Toxicity *Acute GR2+ GU toxicity* *5 years*	13 (9.49%) vs 4 (11.76%), p = 0.7491	NR	NR
		Late GU Toxicity *GR2+ GU toxicity* *5 years*	26 (18.98%) vs 13 (39.39%), p = 0.014	NR	NR
Henderson 2017[29] *N=215*	Low Risk Intermediate Risk	Other Toxicity *Freedom from GR2+ rectal bleeding/proctitis*	91.7% vs 85.6%	NR	NR

		5 years			
		Other Toxicity *GR2+ toxicity* *5 years*	11 vs 13	NR	
		Other Adverse Events *Intercurrent disease or prostate cancer mortality* *5 years*	5 vs 3	NR	
		Overall Survival *Overall survival rates* *5 years*	96%, 95% CI [89.7, 98.5] vs 96.4%, 95% CI [89.3, 98.8]		
		Disease Progression Details NR 5 years	2 vs 6		
		Progression-free Survival *Freedom from biochemical progression*	98.3%, 95% CI [93.5, 99.6] vs 92.7%, 95% CI [84.2, 96.8], *p* = 0.0649	Log-rank test of differences between groups	
Henderson 2021[30] *N=582*	Low Risk Intermediate Risk	Overall Survival *Details NR*	97.7%, 95% CI [95, 99] vs 95.9%, 95% CI [92.5, 97.8]	NR	QoL, GU toxicity

5 years		
Overall Survival *Details NR*	96.1%, 95% CI [93.2, 97.8] vs 94.8%, 95% CI [91.6, 96.6], *p* = 0.6202	Kaplan-Meier test
7 years		
Disease Progression *Details NR*	3 vs 15	NR
5 years		
Disease Progression *Details NR*	3 vs 21	NR
7 years		
Progression-free Survival *Freedom from biochemical progression*	98.8%, 95% CI [96.4, 99.6] vs 95%, 95% CI [91.9, 97]	NR
5 years		
Progression-free Survival *Freedom from biochemical progression*	98.8%, 95% CI [96.4, 99.6] vs 91.9, 95% CI [87.8, 94.7]	NR
7 years		

		Metastasis-free Survival *Freedom from distant metastasis* *5 years*	100% vs 98.4%, *p* = 0.005	Log-rank test for difference between groups	
		Metastasis-free Survival *Freedom from distant metastasis* *7 years*	100% vs 97.9%	NR	
		Late GI Toxicity *Late GR3 GI toxicity* *5 years*	0.8% vs 2%	NR	
		Late GI Toxicity *Late GR3 GI toxicity* *7 years*	0.8% vs 2%	NR	
Ho 2018[31] *N=254*	Low Risk Intermediate Risk High Risk	Disease Progression *Biochemical progression* *7 years*	Low: 2 Intermediate: 5 High: 1	NR	QoL, overall survival
	Low Risk Intermediate Risk	Progression-free Survival	99.2% vs 97.7%	NR	

		Biochemical progression *7 years*			
Holtzman 2019[32] *N=1005*	Favorable Potency Intermediate Potency Poor Potency	Quality of Life *Potency Rate* *5 years*	Favorable: 80% Intermediate: 62% Poor: 37%	NR	NR
Iizumi 2021[33] *N=289*	2.0 Gy Dose 2.5 Gy Dose 3.0 Gy Dose	Early GU toxicity *GR1 GU toxicity* *Timing NR*	2.0 Gy: 35 (47.9%) 2.5 Gy: 52 (52%) 3.0 Gy: 45 (38.8%) *p* = 0.26	Kruskal-Wallis rank sum or Pearson's Chi Square for difference between dosage groups	NR
		Early GU toxicity *GR2 GU toxicity* *Timing NR*	2.0 Gy: 12 (16.4%) 2.5 Gy: 11 (11%) 3.0 Gy: 16 (13.8%)	NR	
		Early GU toxicity *GR3 GU toxicity* *Timing NR*	2.0 Gy: 1 (1.4%) 2.5 Gy: 0 (0%) 3.0 Gy: 0 (0%)	NR	
		Early GI Toxicity *GR1 GI toxicity* *Timing NR*	2.0 Gy: 2 (2.7%) 2.5 Gy: 1 (1%) 3.0 Gy: 1 (0.8%) *p = 0.21*	Kruskal-Wallis rank sum or Pearson's Chi Square for difference between dosage groups	
Iwata 2018[34] *N=1291*	Low Risk Intermediate Risk High Risk	Progression-free Survival *Biochemical relapse-free survival*	Low: 97%, 95% CI [93.4, 98.6] Intermediate: 91%, 95% CI [88.2, 93.2]	Significant differences were observed in treatment results	NR

		5 years	High: 83.1%, 95% CI [79.8, 86.1]	among the three groups. P-value NR.	
		Overall Survival *Details NR* *5 years*	Low: 98.4%, 95% CI [95.2, 99.5] Intermediate: 96.8%, 95% CI [94.9, 98] High: 95.2%, 95% CI [93, 96.7]	NR	
		Prostate Cancer Specific Survival *Cause-specific survival* *5 years*	Low: 100% Intermediate: 100% High: 99.6%, 95% CI [98.5, 99.9]	NR	
		Disease Recurrence *Biochemical relapse-free rate* *5 years*	Low: 98.6%, 95% CI [95.6, 99.5] Intermediate: 93.9%, 95% CI [91.4, 95.7] High: 87.4%, 95% CI [84.3, 89.9]	NR	
		Disease Recurrence *Clinical relapse-free rate* *5 years*	Low: 100% Intermediate: 98.2%, 95% CI [96.6, 99.1] High: 95.9%, 95% CI [93.9, 97.3]		
Johansson 2019[35] *N=504*	Low Risk Intermediate Risk High Risk Very High Risk	Biochemical Failure *PSA relapse free rate* *5 years*	Low: 100% Intermediate: 93.7%, 95% CI [89.7, 97.8] High: 82.1%, 95% CI [75.6, 89.2] Very High: 71.5%, 95% CI [63.1, 81.1] $p < 0.001$	Kaplan-Meier test for difference between risk groups	Also reports data on locoregional relapse-free by risk group, GI/GU toxicity

Biochemical Failure *PSA relapse free rate* *10 years*	Low: 94.2%, 95% CI [88.1, 100] Intermediate: 86.7%, 95% CI [80.3, 93.6] High: 63.3%, 95% CI [53.5, 75] Very High: 54.5%, 95% CI [41, 72.3] $p < 0.001$	Kaplan-Meier test for difference between risk groups
Disease Recurrence *Distant metastasis-free rate* *5 years*	Low: 100% Intermediate: 98%, 95% CI [95.8, 100] High: 91%, 95% CI [86.1, 96.2] Very High: 80.9%, 95% CI [73.4, 89.2] $p < 0.001$	Kaplan-Meier test for difference between risk groups
Disease Recurrence *Distant metastasis-free rate* *10 years*	Low: 100% Intermediate: 92.7%, 95% CI [87.8, 97.8] High: 79%, 95% CI [71, 87.9] Very High: 69.4%, 95% CI [56.3, 85.6]	NR
Prostate Cancer Specific Survival *Details NR* *5 years*	Low: 100% Intermediate: 99.3%, 95% CI [98, 100] High: 99.2%, 95% CI [97.6, 100] Very High: 92.5%, 95% CI [87.3, 98.1] $p < 0.001$	Kaplan-Meier test for difference between risk groups
Prostate Cancer Specific Survival *Details NR*	Low: 100% Intermediate: 97.8%, 95% CI [94.7, 100] High: 87.2%, 95% CI [79.3, 95.8]	Kaplan-Meier test for difference between risk groups

10 years	Very High: 81.3%, 95% CI [71.8, 92] $p < 0.001$	
Metastasis-Free Survival *Details NR* *5 years*	Low: 94%, 95% CI [89.1, 99.3] Intermediate: 90.6%, 95% CI [86, 95.4] High: 86.4%, 95% CI [80.5, 92.6] Very High: 73.3%, 95% CI [65.2, 82.5] $p < 0.001$	Kaplan-Meier test for difference between risk groups
Metastasis-Free Survival *Details NR* *10 years*	Low: 85.5%, 95% CI [77.2, 94.6] Intermediate: 75.3%, 95% CI [67.6, 83.9] High: 61.7%, 95% CI [52.3, 72.9] Very High: 47.6%, 95% CI [34.8, 65.2] $p < 0.001$	Kaplan-Meier test for difference between risk groups
Overall Survival *Details NR* *5 years*	Low: 94.6%, 95% CI [90.2, 99.3] Intermediate: 92.4%, 95% CI [88.3, 96.6] High: 94.8%, 95% CI [91.1, 98.6] Very High: 85.7%, 95% CI [79.5, 92.5] $p = 0.001$	Kaplan-Meier test for difference between risk groups
Overall Survival *Details NR* *10 years*	Low: 88.3%, 95% CI [81.6, 95.5] Intermediate: 83%, 95% CI [76.8, 89.7] High: 77.1%, 95% CI [69.4, 85.7]	Kaplan-Meier test for difference between risk groups

			Very High: 67%, 95% CI [56.3, 79.8] *p* = 0.001		
		Late GI Toxicity *GR3+ GI toxicity* *10 years*	Intermediate vs Low: HR = 1.85, 95% CI [0.93, 3.66], *p* = 0.078 High vs Low: HR = 0.9, 95% CI [0.41, 1.97], *p* = 0.0798 Very High vs Low: HR = 0.59, 95% CI [0.23, 1.55], *p* = 0.286	Multivariate analyses	
		Late GI Toxicity *GR2+ GU toxicity* *10 years*	Intermediate vs Low: HR=1.13, 95% CI [0.60, 2.14], *p* = 0.708 High vs Low: HR = 1.00, 95% CI [0.51, 1.94], *p* = 0.996 Very High vs Low: HR = 0.87, 95% CI [0.41, 1.87], *p* = 0.726		
Kharod 2021[36] *N=102*	Adjuvant PBT Salvage PBT	Late GU Toxicity *GR3+ GU toxicity* *5 years*	12.5%, 95% CI [1.7, 53.7] vs 2.2%, 95% CI [0.6, 8.4], *p* = 0.42	Difference in rate of GU toxicity adjuvant vs salvage	NR
		Late GI Toxicity *GR2+ GI toxicity* *5 years*	0% vs 2.2%, 95% CI [0.6, 8.4], *p* = 0.62	Difference in rate of GI toxicity adjuvant vs salvage	
		Progression-free Survival	72%, 95% CI [40, 91] vs 57%, 95% CI [45, 68]	NR	

		Freedom from biochemical progression *5 years*			
		Metastasis-free Survival *Distant metastasis-free survival* *5 years*	91%, 95% CI [56, 99] vs 97%, 95% CI [90, 99]	NR	
		Overall Survival *Details NR* *5 years*	100% vs 93%, 95% CI [84, 97]	NR	
Kim 2013[37] *N=82*	60 CGE 54 CGE 47 CGE 35 CGE 35 CGE	Early GI Toxicity *GR1 GI toxicity* *42 months*	60 CGE: 1 (5%) 54 CGE: 3 (19%) 47 CGE: 2 (12%) 35 CGE: 3 (17%) 35 CGE: 3 (25%) *p* = 0.583	Difference between treatment arms	QoL
		Early GU toxicity *GR1+ GU toxicity* *42 months*	60 CGE: 17 (89%) 54 CGE: 14 (88%) 47 CGE: 13 (76%) 35 CGE: 10 (56%) 35 CGE: 7 (58%) *p* = 0.128	Difference between treatment arms	
		Late GI Toxicity *GR1 GI toxicity* *42 months*	60 CGE: 11 (58%) 54 CGE: 12 (75%) 47 CGE: 11 (65%) 35 CGE: 11 (61%) 35 CGE: 8 (67%)	Difference between treatment arms	

			p = 0.277		
		Late GU toxicity *GR1+ GU toxicity* *42 months*	60 CGE: 3 (16%) 54 CGE: 5 (31%) 47 CGE: 10 (59%) 35 CGE: 7 (39%) 35 CGE: 3 (25%) *p* = 0.122	Difference between treatment arms	
		Biochemical Failure *Biochemical failure (ASTRO)* *42 months*	60 CGE: 1 (5.3%) 54 CGE: 3 (18.8%) 47 CGE: 2 (11.8%) 35 CGE: 2 (11.1%) 35 CGE: 3 (25%)	NR	
Kubes 2019[38] *N=200*	Low Risk Intermediate Risk	Biochemical Failure *PSA relapse* *36 months*	1 (1.08%) vs 7 (6.5%)	NR	GI/GU toxicity
Kubes 2021[39] *N=284*	Low Risk Intermediate Favorable Risk Intermediate Unfavorable Risk	Disease-free survival *Progression-free Survival* *5 years*	Low: 96.9%, 95% CI (93.3, 100) Intermediate Favorable: 91.7%, 95% CI (86, 97.7) Intermediate Unfavorable: 83.5%, 95% CI (71.1, 98.1)	NR	GI/GU toxicity
		Biochemical Failure *Biochemical Relapse* *5 years*	Low: 4 Intermediate Favorable: 8 Intermediate Unfavorable: 5	NR	
		Overall Survival *Details NR* *5 years*	Low: 98.3%, 95% CI [96, 100] Intermediate Favorable: 94.9%, 95% CI [91, 99] Intermediate Unfavorable: 100%	NR	

Lee 2016[40] *N=1289*	TURP No TURP	Quality of Life *EPIC bowel* *3 years*	Mean Change: 0 vs -4.2, *p* = 0.4171	Adjusted difference between groups over time	NR
		Quality of Life *EPIC sexual* *3 years*	Mean Change: -17.5 vs -18.1, *p* = 0.01	Adjusted difference between groups over time	
		Quality of Life *EPIC urinary incontinence* *3 years*	Mean Change: -8.2 vs 0, *p* = 0.0363	Adjusted difference between groups over time	
		Quality of Life *EPIC urinary obstructive* *3 years*	Mean Change: -3.1 vs 6.3, *p* = 0.4293	Adjusted difference between groups over time	
	TURP	Any GU Toxicity *GR3 GU toxicity* *3 years*	17 (18%)	NR	
Lee 2019[41] *N=192*	Low Risk Intermediate Risk High Risk	Other Toxicity *GR2+ rectal bleeding* *2 years*	Low: 8 (21%) Intermediate: 16 (15%) High: 8 (16%)	NR	QoL
Makishima 2017[42]	Risk Groups	Progression-free Survival	99%, 95% CI [93.2, 99.9]	NR	NR

N=93	*Biochemical relapse-free rate*		
	5 years		
	Other Adverse Events	1 (1.5%)	NR
	GR3 non-infectious cystitis		
	55 months		
	Other Adverse Events	4 (4.3%)	NR
	GR2 urinary frequency		
	55 months		
	Other Adverse Events	1 (1.5%)	NR
	Hematuria		
	55 months		
	Other Adverse Events	4 (4.3%)	NR
	GR2 rectal bleeding		
	55 months		
	Other Adverse Events	5.8%	NR
	Cumulative incidence of GR ≥ 2 GU morbidities		
	5 years		
	Other Adverse Events	4.3%	NR

		Cumulative incidence of GR ≥ 2 GI morbidities *5 years*			
Mendenhall 2014[43] *N=211*	Low Risk Intermediate Risk High Risk	Late GU Toxicity *GR3+ GU toxicity* *5 years*	Low: 4 (4.49%) Intermediate: 4 (4.88%) High: 2 (5%)	NR	EPIC sexual in patients with ADT therapy (only 2 patients in subgroup)
		Late GI toxicity *GR3+ GI toxicity* *5 years*	Low: 0 (0%) Intermediate: 1 (1.22%) High: 0 (0%)	NR	
		Quality of Life *IPSS QoL score* *4+ years*	Change Scores Low: -1, *p* = 0.7 Intermediate: -1, *p* = 0.74 High: -2, *p* = 0.12	Change in median scores from baseline at 4+ years	
		Quality of Life *EPIC bowel* *4+ years*	Change Scores Low: -4, *p* = 0.002 Intermediate: 0, *p* = 0.31 High: -1, *p* = 0.22	Change in median scores from baseline at 4+ years	
		Quality of Life *EPIC urinary irritative/ obstructive* *4+ years*	Low: 6, *p* = 0.2 Intermediate: 0, *p* = 0.98 High: 0, *p* = 0.21	Change in median scores from baseline at 4+ years	
		Quality of Life	Low: 0, *p* = 0.21 Intermediate: 0, *p* = 0.71	NR	

		EPIC urinary incontinence 4+ years	High: 0, p = 0.16		
	(Without ADT) Low Risk Intermediate Risk High Risk	Quality of Life *EPIC sexual* *4+ years*	Change Scores Low: -29, p = 0.006 Intermediate: -24, p < 0.0001 High: -76	NR	
	Low Risk Intermediate Risk High Risk	Overall Survival *Details NR* *5 years*	Low: 93% Intermediate: 88% High: 86%	NR	
		Disease Progression *Details NR* *5 years*	Low: 10 Intermediate: 1 High: 8	NR	
Mishra 2019[44] *N=1343*	Pencil Beam Passive Scattering	Early GI Toxicity *GR2+ GI toxicity* *3 months*	7 (3%) vs 24 (2%) RR = 1.32, 95% CI [0.79, 2.19], p = 0.29	Adjusted multivariate analysis pencil beam vs passive scatter	NR
		Early GU Toxicity *GR2+ GU toxicity* *3 months*	52 (22%) vs 167 (15%) RR = 1.57, 95% CI [1.28, 1.94], p < 0.001	Adjusted multivariate analysis pencil beam vs passive scatter	
		Late GI Toxicity *GR2+ GI toxicity*	11 (5%) vs 71 (6%) RR = 0.94, 95% CI [0.47, 1.90], p = 0.87	Adjusted multivariate analysis pencil beam vs passive scatter	

		3 months			
		Late GU Toxicity *GR2+ GU toxicity* *3 years*	15 (6%) vs 129 (12%) RR = 0.78, 95% CI [0.44, 1.39], *p* = 0.47	Adjusted multivariate analysis pencil beam vs passive scatter	
Mishra 2020[45] *N=304*	Pencil Beam Passive Scattering	Quality of Life *EPIC urinary* *1 year*	Mean Change (SD): -3 (17.2) vs -1.9 (11.6), *p* = 0.61 OR = 0.66, 95% CI [0.36, 1.23], *p* = 0.19	Adjusted analysis of 1 minimally important decline in scores (passive scatter vs pencil beam)	NR
		Quality of Life *EPIC bowel* *1 year*	Mean Change (SD): -9.2 (17.2) vs -6.6 (4.9), *p* = 0.25 OR = 0.76, 95% CI [0.44, 1.33], *p* = 0.33	Adjusted analysis of 1 minimally important decline in scores (passive scatter vs pencil beam)	
		Quality of Life EPIC sexual 1 year	Mean Change (SD): -8.9 (22.9) vs 9.7 (18.5), *p* = 0.81 OR = 0.88, 95% CI [0.47, 1.66], *p* = 0.70	Adjusted analysis of 1 minimally important decline in scores (passive scatter vs pencil beam)	
Murakami 2020[46] *N=1075*	Intermediate Risk with ADT Intermediate Risk without ADT	Progression-free Survival *Biochemical relapse-free survival* *Timing NR*	HR = 0.49, 95% CI [0.26, 0.93], *p* = 0.029	Benefit of ADT on BRF survival within intermediate risk patients	NR
	High Risk with ADT High Risk without ADT	Progression-free Survival	HR = 0.75, 95% CI [0.36, 1.55], *p* = 0.433	No benefit of ADT on BRF survival within high risk patients	

		Biochemical relapse-free survival *Timing NR*			
Nakajima 2018[47] *N=526*	Conventional Fractionation Hypofractionation	Early GU toxicity *GR2+ GU toxicity* *Timing NR*	38 (15%) vs 16 (5.9%), $p < 0.001$ Univariate OR = 0.4, 95% CI [0.2, 0.7]	Difference between conventional and hypofractionated	Toxicity by risk group within fractionation
		Early GI Toxicity *GR1+ GU toxicity* *Timing NR*	2 (0.8%) vs 2 (0.7%), $p = 1$	Difference between conventional and hypofractionated	
Negoro 2020[48] *N=168*	Time of Day: Morning Noon Night	Quality of Life IPSS QoL score	Mean Change (SD) Morning: 0.52 (0.15) Noon: 1.19 (0.16) Night: 1.24 (0.24) $p = 0.004$	Difference between radiation timing (Kruskal-Wallis/Fisher's exact test)	NR
Takagi 2017[49] *N=1375*	Low Risk Intermediate Risk High Risk Very High Risk	Progression-free Survival *Freedom from biochemical relapse* *5 years*	Low: 99%, 95% CI [96, 100] Intermediate: 91%, 95% CI [88, 93] High: 86%, 95% CI [82, 89] Very High: 66%, 95% CI [53, 76] Low vs Very High: $p < 0.001$ Intermediate vs Very High: $p < 0.001$ High vs Very High: $p < 0.001$	NR	GI/GU toxicity
		Progression-free Survival	Low: 95%, 95% CI [88, 98] Intermediate: 87%, 95% CI [83, 90] High: 71%, 95% CI [64, 77]	NR	

Freedom from biochemical relapse *8 years*	Very High: 55%, 95% CI [41, 67] Low vs Very High: $p < 0.001$ Intermediate vs Very High: $p < 0.001$ High vs Very High: $p < 0.001$	
Prostate-cancer-specific Survival *Cancer-specific survival* *5 years*	Low: 100% Intermediate: 100% High: 99%, 95% CI [97, 100] Very High: 95%, 95% CI [94, 98] Low vs Very High: $p < 0.001$ Intermediate vs Very High: $p < 0.001$ High vs Very High: $p = 0.014$	NR
Prostate-cancer-specific Survival *Cancer-specific survival* *8 years*	Low: 100% Intermediate: 99%, 95% CI [97, 100] High: 98%, 95% CI [95, 99] Very High: 92%, 95% CI [81, 97] Low vs Very High: $p < 0.001$ Intermediate vs Very High: $p < 0.001$ High vs Very High: $p = 0.014$	NR
Overall Survival *Details NR* *5 years*	Low: 98%, 95% CI [93, 99] Intermediate: 96%, 95% CI [94, 98] High: 96%, 95% CI [93, 97] Very High: 90%, 95% CI [80, 96]	NR

			Low vs Very High: p = 0.003 Intermediate vs Very High: p = 0.01 High vs Very High: p = 0.047		
		Overall Survival *Details NR* *8 years*	Low: 94%, 95% CI [88, 97] Intermediate: 90%, 95% CI [87, 93] High: 89%, 95% CI [84, 93] Very High: 86%, 95% CI [73, 93] Low vs Very High: p = 0.003 Intermediate vs Very High: p = 0.01 High vs Very High: p = 0.047	NR	
Takagi 2020[50] *N=2021*	Very Low Risk Low Risk Intermediate Favorable Risk Intermediate Unfavorable Risk High Risk Very High Risk	Progression-free Survival *Freedom from biochemical relapse* *5 years*	Very Low: 100% Low: 98.5%, 95% CI [96, 99.4] Intermediate Favorable: 93%, 95% CI [89.4, 95.4] Intermediate Unfavorable: 89.7%, 95% CI [86.6, 92.1] High: 88.2%, 95% CI [85, 90.7] Very High: 75.5, 95% CI [69.1, 80.7]	NR	NR
		Progression-free Survival *Freedom from biochemical relapse* *10 years*	Very Low: 100% Low: 88.3%, 95% CI [80.8, 83] Intermediate Favorable: 85.5%, 95% CI [79.9, 89.6] Intermediate Unfavorable: 79.2%, 95% CI [74.3, 83.4] High: 68.4%, 95% CI [61.6, 74.3]	NR	

			Very High: 62.8%, 95% CI [53.5, 70.6]		
		Overall Survival *Details NR* *5 years*	Very Low: 100% Low: 98.5%, 95% CI [96.1, 99.4] Intermediate Favorable: 96%, 95% CI [93.2, 97.6] Intermediate Unfavorable: 97.1%, 95% CI [95.2, 98.2] High: 95.9%, 95% CI [93.8, 97.3] Very High: 91.8, 95% CI [87.2, 94.9]		
Vargas 2018[51] *N=82*	Hypofractionation Conventional Fractionation	Any GI Toxicity *GR2+ GI toxicity* *5 years*	17 (37%) vs 11 (40.7%), *p* = 0.48	Difference between dosage arms	NR
		Any GU Toxicity *GR2+ GU toxicity* *5 years*	6 (13%) vs 3 (27%), *p* = 0.99	Difference between dosage arms	
		Quality of Life *EPIC urinary* *24 months*	Mean (SD): 90.92 (7.3) vs 91.31 (13.11), *p* = 0.92	Difference between dosage arms	
		Quality of Life *EPIC urinary* *4 years*			

		Quality of Life *EPIC bowel* *24 months*	Mean (SD): 89.24 (13.67) vs 93.28 (6.67), *p* = 0.29	Difference between dosage arms	
		Quality of Life *EPIC erectile function* *24 months*	Mean (SD) 46.44 (25.62) vs 60.35 (22.04), *p* = 0.12	Difference between dosage arms	
Vargas 2018[52] *N=75*	Hypofractionation Conventional Fractionation	Quality of Life *EPIC urinary* *4 years*	Mean (SD): 85.4 (12.47) vs 90.2 (9.91), *p* = 0.32	Difference between dosage arms	NR
		Quality of Life *EPIC bowel* *4 years*	Mean (SD): 92.1 (13.9) vs 95.2 (4.28), *p* = 0.47	Difference between dosage arms	
		Quality of Life *EPIC sexual* *4 years*	Mean (SD): 47.3 (21.67) vs 61.3 (19.53), *p* = 0.14	Difference between dosage arms	
		Any GI Toxicity *GR2+ GI toxicity* *4 years*	9 (19.6%) vs 5 (17.2%), *p* > 0.99	Difference between dosage arms	
		Any GU Toxicity *GR2+ GU toxicity*	14 (30.4%) vs 10 (34.5%), *p* = 0.8	Difference between dosage arms	

	4 years

Abbreviations. AA=African American patients; ADT=androgen deprivation therapy; ANOVA=analysis of variance; ASTRO=American Society for Therapeutic Radiology and Oncology; AUA=area under the curve; BRF=biochemical relapse-free survival; CGE=cobalt gray equivalent; CI=confidence interval; EPIC=Expanded Prostate Cancer Index Composite; FFBP=freedom from biochemical progression; GEE=generalized estimating equation; GI=gastrointestinal; GR1/2/3=Grade 1/2/3; GU=genitourinary; Gy=the gray (symbol: Gy) is a derived unit of ionizing radiation dose in the International System of Units (SI); HR=hazards ratio; IPSS=International Prostate Symptom Score; NSD=no significant difference; OR=odds ratio; PBT=proton beam therapy; PSA=prostate-specific antigen; QoL=quality of life; RR=risk ratio; SD=standard deviation; TURP= transurethral resection of the prostate; W=white patients.

QUALITY ASSESSMENT OF INCLUDED PRIMARY STUDIES

Observational Studies (Rated with ROBINS-I for Observational Studies)

Author Year	Selection Bias[a]	Bias in Classification of Interventions[a]	Bias Due to Departures from Intended Interventions[a]	Bias Due to Measurement of Outcomes[a]	Bias Due to Confounding[a]	Bias Due to Missing Data[a]	Bias in the Selection of Reported Results[a]	Overall Bias
Bai 2020[1]	Unclear Excluded patients from study who did not complete EPIC at baseline. Unclear number and characteristics of those excluded.	Low Interventions clearly defined and tracked in database.	Unclear Appears that patients received intervention as intended. ADT use not balanced across groups as co-intervention.	Unclear Standard EPIC questionnaire used. Self-reported responses may have been influence by knowledge of intervention received.	High Most baseline characteristics balanced, but PBT group received higher dose-fractionations. No attempt to control for confounding.	High Excluded ~50% of patients who did not complete 3-month EPIC questionnaire.	Low All analyses appear to be reported.	High
Barsky 2021[2] & Santos 2019[12]	Unclear Patients without prospectively collected toxicity data excluded. Unclear number and characteristics of those excluded.	Low Interventions clearly defined and tracked in health record.	Low Appears that patients received intervention as intended. ADT use balanced across groups as co-intervention.	Low Failure and survival well-defined and tracked in health record.	Low Matched cohort, but age remained different between groups.	Unclear Unclear level and handling of missing data.	Low All analyses appear to be reported.	Low

Author Year	Selection Bias[a]	Bias in Classification of Interventions[a]	Bias Due to Departures from Intended Interventions[a]	Bias Due to Measurement of Outcomes[a]	Bias Due to Confounding[a]	Bias Due to Missing Data[a]	Bias in the Selection of Reported Results[a]	Overall Bias
Coen 2012[3]	Unclear Patients selected from 2 different overlapping timeframes. PBT group was subset of RCT comparing PBT dosages, Brachytherapy group was retrospective cohort.	Low Interventions clearly defined and tracked in health record.	Low Appears that patients received intervention as intended. No patients received ADT.	Low Failure and survival well defined and tracked in health record.	Low Matched cohort, but baseline patient and intervention characteristics not presented; unclear if differences in unmatched variables.	Unclear Unclear level and handling of missing data.	Low All analyses appear to be reported.	Low
Dutz 2019[4]	Low States patients were consecutive. PBT and IMRT patients were selected from 2 different overlapping timeframes.	Low Interventions clearly defined and tracked.	Low Appears that patients received intervention as intended. ADT use and anticoagulants balanced across groups as co-intervention.	Unclear GI/GU toxicity classified by CTCAE. Self-reported QoL may have been influenced by knowledge of intervention received.	Low Matched cohort, but difference in age and dose between groups at baseline.	Low Excluded cases with missing data. All data available for early toxicity, 75% of participants included for late toxicity. Unclear missing data for QoL.	Low All analyses appear to be reported.	Low

Author Year	Selection Bias[a]	Bias in Classification of Interventions[a]	Bias Due to Departures from Intended Interventions[a]	Bias Due to Measurement of Outcomes[a]	Bias Due to Confounding[a]	Bias Due to Missing Data[a]	Bias in the Selection of Reported Results[a]	Overall Bias
Fang 2014[5]	Low PBT and IMRT patients selected from 2 different overlapping timeframes.	Low Interventions clearly defined and tracked.	Unclear Appears that patients received intervention as intended. Use of ADT differed between groups.	Low GI/GU toxicity classified by CTCAE.	Low Matched cohort had residual confounding in several variables. Used multivariate analysis for residual confounding.	Unclear Unclear level of missing data for late toxicities.	Low All analyses appear to be reported.	Low
Gray 2013[6]	Unclear Patients came from 3 different prospective cohort studies during different time periods and at different centers.	Low Interventions clearly defined and tracked.	Unclear Appears that patients received intervention as intended. No patients received ADT; unclear other co-interventions.	Unclear Self-reported QoL responses may have been influence by knowledge of intervention received.	High Baseline differences between groups in patient and clinical characteristics. No adjustment for confounding.	Unclear Unclear level and handling of missing data.	Low All analyses appear to be reported.	High

Author Year	Selection Bias[a]	Bias in Classification of Interventions[a]	Bias Due to Departures from Intended Interventions[a]	Bias Due to Measurement of Outcomes[a]	Bias Due to Confounding[a]	Bias Due to Missing Data[a]	Bias in the Selection of Reported Results[a]	Overall Bias
Halpern 2016[7]	Low Patients selected from SEER database. Inclusion/exclusion appears to be same across all groups.	Low Interventions clearly defined and tracked.	Unclear Appears that patients received intervention as intended. Difference in receipt of ADT between groups.	Low Complications recorded from health records.	High High level of baseline differences between groups. No adjustment for confounding.	Unclear Unclear level and handling of missing data.	Low All analyses appear to be reported.	Moderate
Hoppe 2014[8]	Unclear Patients came from 2 different cohorts during different time periods and at different centers.	Low Interventions clearly defined and tracked.	Unclear Appears that patients received intervention as intended. Difference in receipt of ADT between groups.	Unclear Self-reported QoL responses may have been influence by knowledge of intervention received.	Moderate High level of baseline differences between groups. Adjusted with generalized estimating equation for specific QoL outcomes, but not minimally important differences analysis. Did not use matching or propensity-based adjustment.	Unclear Unclear level and handling of missing data.	Low All analyses appear to be reported.	Moderate

Author Year	Selection Bias[a]	Bias in Classification of Interventions[a]	Bias Due to Departures from Intended Interventions[a]	Bias Due to Measurement of Outcomes[a]	Bias Due to Confounding[a]	Bias Due to Missing Data[a]	Bias in the Selection of Reported Results[a]	Overall Bias
Kim 2011[9]	Low Patients selected from SEER database. Inclusion/exclusion appears to be same across all groups.	Low Interventions clearly defined and tracked.	Unclear Appears that patients received intervention as intended. Unclear if differences in co-interventions.	Low GI/GU toxicity classified by procedure codes.	High Baseline characteristics not reported for individual radiation therapy types. Hazard ratio includes adjustment for some covariates. Did not use matching or propensity-based adjustment.	Unclear Unclear level and handling of missing data.	Low All analyses appear to be reported.	Moderate
Liu 2021[10]	Low Patients selected from national cancer database. Inclusion/exclusion appears to be same across all groups.	Low Interventions clearly defined and tracked.	Low Appears that patients received intervention as intended. ADT use balanced across groups as co-intervention.	Low Survival well defined.	Low Baseline characteristics varied between groups but utilized matching and multivariate analysis to balance groups.	Unclear Unclear level and handling of missing data.	Low All analyses appear to be reported.	Low

Author Year	Selection Bias[a]	Bias in Classification of Interventions[a]	Bias Due to Departures from Intended Interventions[a]	Bias Due to Measurement of Outcomes[a]	Bias Due to Confounding[a]	Bias Due to Missing Data[a]	Bias in the Selection of Reported Results[a]	Overall Bias
Pan 2018[11]	Low Patients selected from MarketScan Commercial claims database.	Low Interventions clearly defined and tracked.	Low Appears that patients received intervention as intended.	Low GI/GU toxicity classified by procedure codes.	Low Baseline characteristics varied between groups but utilized matching and multivariate analysis to balance groups.	Unclear Missing cost data accounted for by general representation theorem. Unclear how missing toxicity data were handled.	Low All analyses appear to be reported.	Low
Sheets 2012[13]	Low Patients selected from SEER database. Inclusion/exclusion appears to be same across all groups.	Low Interventions clearly defined and tracked.	Unclear Appears that patients received intervention as intended. ADT use not balanced across groups as co-intervention.	Low GI/GU toxicity classified by procedure codes.	Low Baseline characteristics varied between groups but utilized matching to balance groups.	Unclear Unclear level and handling of missing data.	Low All analyses appear to be reported.	Low

Author Year	Selection Bias[a]	Bias in Classification of Interventions[a]	Bias Due to Departures from Intended Interventions[a]	Bias Due to Measurement of Outcomes[a]	Bias Due to Confounding[a]	Bias Due to Missing Data[a]	Bias in the Selection of Reported Results[a]	Overall Bias
Vapiwala 2021[14]	Low All patients in prospective database with prostate cancer treated with PBT or IMRT.	Low Interventions clearly defined and tracked.	Unclear Appears that patients received intervention as intended. ADT use not balanced across groups as co-intervention.	Low GI/GU toxicity classified by CTCAE.	Low Large number of differences between groups but used inverse probability weighting to balance the groups.	Low Analysis done with and without complete data and used multiple imputation.	Low All analyses appear to be reported.	Low
Xiang 2020[15]	Low National cancer database. Inclusion/exclusion criteria appears to be the same across groups.	Low Interventions tracked in database with quality checks.	Low Database covers major departures from interventions.	Low Secondary cancer tracked in national cancer database.	Low Unclear if prostate cancer group differed on characteristics, but used multivariate analysis and matching to control for confounding.	Unclear Appears that missing characteristics variables included as "unknown" category. Unclear level and handling of other missing data.	Low All analyses appear to be reported.	Low

Author Year	Selection Bias[a]	Bias in Classification of Interventions[a]	Bias Due to Departures from Intended Interventions[a]	Bias Due to Measurement of Outcomes[a]	Bias Due to Confounding[a]	Bias Due to Missing Data[a]	Bias in the Selection of Reported Results[a]	Overall Bias
Yu 2013[16]	Low Patients selected from database. Inclusion/exclusion appears to be same across all groups.	Low Interventions clearly defined and tracked.	Unclear Appears that patients received intervention as intended. ADT use not balanced across groups in overall sample.	Low GI/GU toxicity classified by procedure codes.	Low Baseline characteristics varied between groups, but utilized matching and multivariate analysis to balance groups.	Unclear Unclear level and handling of missing data.	Low All analyses appear to be reported.	Low

Notes. a. Low concern - study is overall good quality across all domains; Some concerns - Study raises some concerns in at least one domain, but not judged to be high risk of bias; High - Multiple and/or serious risk of bias that severely weaken confidence in results (ROBINS-I tool for evaluating observational studies)
b. The SEER Program provides information on cancer statistics in an effort to reduce the cancer burden among the US population. SEER is supported by the Surveillance Research Program (SRP) in NCI's Division of Cancer Control and Population Sciences (DCCPS).
Abbreviations. 3DCRT=three dimensional conformal radiation therapy; ADT=androgen deprivation therapy; CTCAE=Common Terminology Criteria for Adverse Events; EBRT=external beam radiation therapy; ED=erectile dysfunction; EPIC=Expanded Prostate Cancer Index Composite; GI=gastrointestinal; GU=genitourinary; IMRT=intensity modulated radiation therapy; PBT=proton beam therapy; PSA=prostate specific antigen; QoL=quality of life; RCT=randomized controlled trial; SBRT=stereotactic body radiation therapy; SEER=The Surveillance, Epidemiology, and End Results; TURP=transurethral resection of the prostate.

STRENGTH OF EVIDENCE

Conclusions Derived from Comparative Studies Having Low Risk of Bias

Outcome	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence
PBT vs IMRT for Initial Therapy of Prostate Cancer							
Early GI Toxicity	3 cohort studies[4,5,14]	Low risk of bias	Direct	Inconsistent	Imprecise	Not detected	Low SOE: RR_{Mean} = 0.76, 95% CI [0.39, 1.50]
Early GU Toxicity	3 cohort studies[4,5,14]	Low risk of bias	Direct	Consistent	Precise	Not detected	Low SOE: RR_{Mean} = 0.65, 95% CI [0.28, 1.34]
Secondary Malignancy	1 cohort study[15]	Low risk of bias	Direct	Unknown	Precise	Not detected	Insufficient SOE: It is unclear whether PBT and IMRT differ in risk of secondary malignancy after treatment.
Quality of Life	1 cohort study[4]	Low risk of bias	Direct	Unknown	Imprecise	Not detected	Insufficient SOE: It is unclear whether PBT and IMRT differ in quality-of-life scores following treatment.
Overall Survival	1 cohort study[10]	Low risk of bias	Indirect	Unknown	Imprecise	Not detected	Insufficient SOE: It is unclear whether PBT and IMRT differ in survival following treatment.
PBT vs Brachytherapy for Initial Therapy of Prostate Cancer							
Rates of Toxicity	0 studies						Insufficient SOE: No data on toxicities were reported in the available comparative studies.
Overall Survival	2 cohort studies[3,10]	Low risk of bias	Direct	Consistent	Imprecise	Not detected	Low SOE: PBT and brachytherapy confer similar impacts on overall survival.

Outcome	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence
Heterogeneity of Treatment Effects for PBT							
Differences in Treatment Toxicity by Race	2 cohort studies[19,20]	Moderate risk of bias for one study	Direct	Consistent	Precise	Not detected	Low SOE: Black and white patients had similar GU and GI toxicity rates after PBT.
Effect of Anticoagulant Use on Rates of Rectal Bleeding	3 cohort studies[22,25,41]	Moderate risk of bias	Direct	Consistent	Precise	Not detected	Low SOE: Patients who use anticoagulant medications have a higher rate of rectal bleeding following PBT.
Effect of Prior Prostate Surgery on Rates of GU Toxicity	2 cohort studies[27,50]	Moderate risk of bias	Direct	Consistent	Precise	Not detected	Low SOE: Patients who have had prior prostate surgery have a higher rate of GU toxicity following PBT.
Influence of Baseline Cancer Risk Score on Rate of Cancer Relapse	13 cohort studies[18-20,25,29-31,34,35,38,39,42,43,49,50]	Moderate risk of bias	Direct	Inconsistent	Precise	Not detected	Low SOE: Patients with worse baseline risk assessment experience higher rates of cancer relapse over time.
Impact of Technical Characteristics of PBT Delivery on Patient Outcomes							
Effect of Hypofractionation Dosing Schedules on GU and GI Toxicity Rates	2 RCTs and 2 cohort studies[26,33,47,51,52]	Moderate risk of bias for the cohort studies	Direct	Consistent	Precise	Not detected	Low SOE: Patients who received hypofractionated dosing schedules had similar rates of GU and GI toxicity as patients who received conventional dosing schedules.
Effect of Hypofractionation Dosing Schedules on Cancer Relapse Rates	1 RCT[26]	Low risk of bias	Indirect	Consistent	Precise	Not detected	Insufficient SOE: It is unclear whether patients who receive hypofractionated dosing schedules have different rates of cancer control than patients who receive conventional dosing schedules.

Outcome	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence
Effect of Pencil Beam Scanning on Patient Outcomes	1 cohort study[44,45]	Moderate risk of bias	Direct	Consistent	Precise	Not detected	Insufficient SOE: It is unclear whether pencil beam scanning confers benefits in any patient outcomes when compared to passive scatter scanning techniques.
Effect of Total Radiation Dose on GU and GI Toxicity rates	2 cohort studies[17,21]	Moderate risk of bias	Direct	Consistent	Precise	Not detected	Insufficient SOE: It is unclear whether higher total radiation doses cause higher rates of GU or GI toxicity.
PBT vs IMRT for Therapy of Relapsed Prostate Cancer							
Disease Progression Following Treatment	1 cohort study[2]	Low risk of bias	Indirect	Consistent	Precise	Not detected	Insufficient SOE: It is unclear whether PBT has advantages over IMRT for the treatment of relapsed prostate cancer following original initial therapy with radical prostatectomy.

Abbreviations. GI=gastrointestinal; GU=genitourinary; IMRT=intensity modulated radiation therapy; PBT=proton beam therapy; RCT=randomized control trial; SOE=strength of evidence.

APPENDIX E: PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	Thank you for your feedback.
2	2	Yes	Thank you for your feedback.
4	4	Yes	Thank you for your feedback.
5	5	Yes	Thank you for your feedback.
Is there any indication of bias in our synthesis of the evidence?			
6	1	No	Thank you for your feedback.
7	2	Yes – Assumption was made that external beam techniques have improved over time, but that proton techniques have not. Thus older data from protons is acceptable, but not older data from photons (although not consistently applied throughout the whole process).	The issue of evolution of proton therapeutic techniques is addressed in the section on technological issues on page 23.
8	2	Yes - Key question one ask for differences in benefits and HARMS between treatments. Second malignancies were mentioned as one of the "potential harms" for comparison, but then were not evaluated in the literature review.	We added a section to the Results section regarding evidence about second malignancies.
9	4	No	Thank you for your feedback.
10	5	No	Thank you for your feedback.
Are you aware of any published or unpublished studies that we may have overlooked?			
11	1	No	
12	2	Yes - Xiang M, Chang DT, Pollom EL. Second cancer risk after primary cancer treatment with three-dimennsional conformal, intensity-modulated, or proton beam radiation therapy. Cancer 2020, 126:3560-3568. NCDB evaluation of second malignancies for different modalities; prostate cancer showed the greatest difference between protons and IMRT/3-D of any of the 9 tumor types, statistically very significant.	Thank you for this identifying this citation; we have reviewed it and added it to our report.

Comment #	Reviewer #	Comment	Author Response
13	4	No	Thank you for your feedback
14	5	No	Thank you for your feedback
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
15	1	Table ES, page 3. Suggest adding "…with PBT" after "Patients with worse baseline risk assessments experienced higher rates of cancer recurrence over time".	Thank you. This change was made.
16	2	Overall, this is an excellent review of the current literature on PBT vs IMRT/3-D. There are a few gaps which could be filled in to make this a make complete assessment. As was stated in the report, there will be significantly more high quality data in the next few years with completion and publication of the prospective comparative trials.	Thank you for your feedback; we have addressed your individual comments as noted below.
17	2	Executive summary No mention of second malignancy rates (although mentioned on page 8) Primary differences would be expected in decreased side effects, not in tumor control (this is the ALARA principle – we reduce the total body exposure for imaging because of risks, not taken into consideration here for differences in treatment)	A section on second malignancies for the PBT vs IMRT comparison has been added to the Strength of Evidence table.
18	2	Page 9 Studies comparing PBT to older techniques were excluded – were studies comparing older techniques of PBT excluded? There has been a change in PBT technology and techniques as well.	The included studies all were published after 2010 and generally included only patients who were initially diagnosed with prostate cancer after 2000. This clarification was added to the first paragraph of the Literature Overview section on page 14.
19	2	P14-15 Most of these studies did not control for dose, which is very highly correlated with GI and GU toxicity (eg, Sheets and Yu). Coen study – most of "proton" patients only received 36% of dose with protons, the majority with photons	Dosage ranges are included in the summary of the comparative studies in Table 1. The problem of proton dosage in the Coen study is also now addressed in the section on brachytherapy on p. 22.
20	2	Page 19	Thank you for catching this typographical error regarding survival rates. The sentence was corrected.

Comment #	Reviewer #	Comment	Author Response
		10-year survival was superior in the PBT group (80.1%) than in IMRT/3-D group (71.3%), but was called “significantly lower” for the PBT group. Evidence is called inconclusive because the number of IMRT vs 3-D patients in the external beam group is not defined. This treats PBT as though there has been no change in planning or treatment processes during this time period. This is using “historical treatment bias” in one group but not the other…	The identified study (Liu et al. Clin Genitourin Cancer 2021;19:255-66) included patients treated between 2004 and 2015. It grouped the patients receiving IMRT or 3-dimension conformal radiotherapy (3DCRT) into a single group and provided no data comparing the IMRT and 3DCRT sub-groups. Thus, it is not possible to determine whether there were differences in the dates of treatment between the IMRT and 3DCRT sub-groups. A new sentence was added to this paragraph to clarify these issues.
21	2	Page 19 Next paragraph compares protons to brachytherapy, showing no difference in survival. Please evaluate evidence for second malignancies for these two comparisons – PBT and brachytherapy have lower risks of 2nd malignancies compared to IMRT/3-D, at least should be considered as one of the differences between the treatments	We identified no studies comparing PBT to brachytherapy for any toxicity, including second cancer incidence. This lack of evidence is now called out in the summary.
22	2	Xiang M, Chang DT, Pollom EL. Second cancer risk after primary cancer treatment with three-dimennsional conformal, intensity-modulated, or proton beam radiation therapy. Cancer 2020, 126:3560-3568.	Thank you for this citation, we have reviewed it and added it to our report.
23	4	Excellent manuscript - well written with comprehensive references.	Thank you for your comment.
24	5	Page/line: 4/9: "individualized decision" - probably should be changed. Within the VA, there are limitations to resources and referrals, and the decision may not be individualized pending local/VA policy. It could be substituted to a "complex" or "nuanced".	Thank you. This change was made.
25	5	Page/line: 5/39: "anatomical structures including nerves, the urethra, and the rectum". With regard to notable anatomic structures, the bladder is a critical one with significant effects on GU toxicity.	Thank you. This change was made.

Comment #	Reviewer #	Comment	Author Response
		Perhaps "nerves, the bladder, the urethra and the rectum"	
26	5	Page/line: 5/48: "high-intensity photons". Please change to "high-energy"; the intensity is not the basis of the radiation therapy. For example, dermatologists utilize UV and light therapy which is also "intense photons" but not "high-energy" like megavoltage photons.	Thank you. This change was made.
27	5	Page/line: 6/7: "and stereotactic radiosurgery (SRS)" - should be changed to "stereotactic ablative body radiation (SABR)". SRS is a technique specifically for the brain (as termed within radiation oncology). SABR is another name for SBRT	Thank you. These wording changes were made.
28	5	Page/line: 6/11: "with several dozen treatment sessions" - should be changed to "few dozen". The longest treatment duration for prostate cancer (within the modern standard of care) is 44-45 fractions of daily radiation, and few dozen (meaning up to 4 dozen) should suffice. Several dozen implies many months of radiation therapy.	Thank you. This change was made.
29	5	Page/line: 8/45: "Potential Harms". Would it be worthwhile to include "financial cost" (or something like "socioeconomic factors")? Proton beam therapy is typically considerably more expensive than photon radiation, and patients may experience excessive costs/financial toxicity with regards to it. As there are less proton centers in the US as well, the costs of transportation are often sizeable.	Thank you. These issues were added to the Analytic Framework.
30	5	Page/line: 16/14: "Rates of early GU toxicity ranged from 0 to 45%...". This statement/data are generated from the studies, but they do differ from traditional estimates of the IMRT toxicity, and may subsequently decrease the comparative benefit. Since the proton-photon benefit, while consistently cited, is small - would it be worthwhile to explore the consistency of these reported IMRT GU toxicity rates with at least one meta-analysis from IMRT	We agree with this concern and have extensively revised the meta-analyses to address it. The analysis now better stratifies by endpoint and improves comparability of estimates. The description of these analyses is now more extensive and addresses important issues regarding methodological variability in the primary studies (particularly in outcome definitions). As a result of these new analyses, the

Comment #	Reviewer #	Comment	Author Response
		GU toxicity in general? The Vapiwala 2021 early GU toxicity study seems to have an outsized risk ratio of 0.06 (an ORDER OF MAGNITUDE different (the other two are 0.62 and 0.74 versus Vapiwala's 0.06) versus the other two studies on page 17). Similarly, the late GU toxicity in that study was defined by >3mo, which is in stark comparison to the others.	final Strength of Evidence assessment for GU toxicity was revised from Moderate to Low.
31	5	Page/line: 19/8: "10-year survival rates were significantly lower in the PBT group (80.1%) than in the external beam photon group (71.3%)" - this is a typo and needs to be changed to "significantly HIGHER".	Thank you. This change was made.
32	5	Page/line: 20/52: "conventional forms of beam scanning" - this should be changed to "conventional proton beam therapy" (or similar). Conventional proton therapy (passive scattering) typically does not involve "beam scanning". Proton PBS involves a thin "raster laser-like painting" of the target (in a scanning fashion, hence pencil beam scanning), while passive scattering creates a complex portal field, usually with physical compensators.	Thank you. This change was made.
33	5	Page/line: 22/29: "Harms of any type of radiation therapy" - this should be changed to "any type of prostate-directed radiation therapy". Patients who receive radiation therapy to the breast or brain (for example) will not experience appreciable or directly related GI/GU/sexual toxicity, as those organs are essentially untouched by the radiation.	Thank you. This change was made.
34	5	Page/line: 22/34: "a series of adequately controlled". This seems superficial (perhaps even specious). As there are no RCTs included in the analysis, this should be "adequately case-controlled" or "adequately compared". The studies cited do not seem to include or utilize true controlling methodology, which would involve randomization or blinding	Thank you. This sentence has been re-written to clarify the methods used in the observational studies.

Comment #	Reviewer #	Comment	Author Response
35	5	Page/line: 24/28: "EarlyToxicity" - should be "Early Toxicity". This is a typo of the reference	The title for this reference was corrected.

APPENDIX F: RESEARCH IN PROGRESS

Status	Study Title	Study Design	Information Resources
Studies with Comparator (eg, PBT vs Other Treatment)			
Recruiting	Radiation Therapy (Hypofractionated Proton Beam Therapy or IMRT) for the Treatment of Recurrent, Oligometastatic Prostate Cancer Following Primary Localized Treatment	RCT	ClinicalTrials.gov ID: NCT04190446
Recruiting	Prostate bed irradiation with alternative radio-oncological approaches	RCT	German Clinical Trials Register ID: DRKS00015231
Recruiting	Prostate Advanced Radiation Technologies Investigating Quality of Life (PARTIQoL): A Phase III Randomized Clinical Trial of Proton Therapy vs IMRT for Low or Intermediate Risk Prostate Cancer	RCT	ClinicalTrials.gov ID: NCT01617161
Recruiting	Phase III Study of Image Guided Radiation Therapy with or Without Androgen Suppression for Intermediate Risk Adenocarcinoma of the Prostate	RCT	ClinicalTrials.gov ID: NCT01492972
Recruiting	A Prospective Comparative Study of Outcomes with Proton and Photon Radiation in Prostate Cancer	Prospective Cohort	ClinicalTrials.gov ID: NCT03561220
Recruiting	Prostate Cancer Patients Treated with Alternative Radiation Oncology Strategies	RCT	ClinicalTrials.gov ID: NCT04083937

Status	Study Title	Study Design	Information Resources
Recruiting	Preference-based Comparative Study on Definitive Radiotherapy of Prostate Cancer with Protons in Standard Fractionation and Standard Dosage	Non-randomized Controlled Trial	ClinicalTrials.gov ID: NCT02766686
Active, not recruiting	A Phase II Trial of Proton Radiation Therapy or Intensity-modulated Radiation Therapy Using Mild Hypofractionation for Low- and Intermediate-risk Adenocarcinoma of the Prostate	Prospective Cohort	ClinicalTrials.gov ID: NCT01352429
Active, not recruiting	Proton-Based Stereotactic Ablative Body Radiotherapy for Prostate Cancer	Prospective Cohort	ClinicalTrials.gov ID: NCT03159676
Studies without Other Treatment Comparator (eg, Case Series or Pre-Post Design)			
Enrolling by Invitation	Assessing the Effectiveness of Photon Therapy with a Proton Therapy Boost in the Treatment of Prostate Cancer as Compared to Phone Therapy Alone	Case Series/ Uncontrolled Pre-Post Study	ClinicalTrials.gov ID: NCT03564275
Recruiting	Phase II Study of Pencil Beam Scanning Proton Stereotactic Body Radiation Therapy for Prostate Cancer	Case Series/ Uncontrolled Pre-Post Study	ClinicalTrials.gov ID: NCT04842890
Recruiting	Carbon Ion Boost Followed by Pelvic Proton Radiotherapy for Prostate Cancer with Pelvic Lymph Nodes Metastases: Prospective Phase II Study	Case Series/ Uncontrolled Pre-Post Study	ClinicalTrials.gov ID: NCT05106699
Recruiting	Extended-Field Lymph Node Proton Irradiation for High Risk Prostate Cancer	Case Series/ Uncontrolled Pre-Post Study	ClinicalTrials.gov ID: NCT04725903

Status	Study Title	Study Design	Information Resources
Recruiting	"Spot-Scanning Based Hypofractionated Proton Therapy for Low and Intermediate Risk Prostate Cancer" "Hypofraktionierte Protonentherapie Mit Spot-Scanning-Technik Bei Prostatakarzinom Mit Niedrigem Oder Mittlerem Risiko"	Case Series/ Uncontrolled Pre-Post Study	ClinicalTrial.gov ID: NCT03740191
Recruiting	A Phase II Study of Dose-escalated Proton-based Radiation Therapy Delivered with a Simultaneous Integrated Boost (SIB) to Intraprostatic Tumors (IPT) Visible on Pretreatment Magnetic Resonance Image	Non-randomized Controlled Trial	ClinicalTrials.gov ID: NCT03624660
Recruiting	A Phase II Randomized Trial of Hypofractionated Proton Therapy in Patients with a Localized Prostate Adenocarcinoma	RCT	ClinicalTrials.gov ID: NCT03285815
Recruiting	A Phase II Study of Hypofractionated Image Guided Proton Therapy for Low and Intermediate Risk Prostate Cancer	Case Series/ Uncontrolled Pre-Post Study	ClinicalTrials.gov ID: NCT02040610
Active, not recruiting	A Phase II Study of Proton-Based Radiation Therapy with Elective Pelvic Nodal Irradiation, Concomitant Docetaxel, and Adjuvant Androgen Deprivation for High-risk Prostate Adenocarcinoma	Non-randomized Controlled Trial	ClinicalTrials.gov ID: NCT01040624

Status	Study Title	Study Design	Information Resources
Active, not recruiting	Prospective Evaluation of Hypofractionation Proton Beam Therapy with Concurrent Treatment of the Prostate and Pelvic Nodes for Clinically Localized, High Risk or Unfavorable Intermediate Risk Prostate Cancer	Case Series/ Uncontrolled Pre-post Study	ClinicalTrials.gov ID: NCT02874014
Active, not recruiting	Phase II Trial of Hypofractionated Proton Beam Therapy in Men with Localized Prostate Adenocarcinoma	Case Series/ Uncontrolled Pre-post Study	ClinicalTrials.gov ID: NCT01950351
Active, not recruiting	An Expanded Phase II Study of Hypofractionated Dose Intense Image Guided Proton Radiation Therapy for Low and Intermediate Risk Adenocarcinoma of the Prostate	Non-randomized Controlled Trial	ClinicalTrials.gov ID: NCT01368055
Active, not recruiting	A Phase III Prospective Randomized Trial of Standard-fractionation vs. Hypo-fractionation With Proton Radiation Therapy for Low Risk Adenocarcinoma of the Prostate	RCT	ClinicalTrials.gov ID: NCT01230866
Active, not recruiting	A Phase II Trial of Proton Radiation Therapy of Using Standard Fractionation for Low- and Low-intermediate Risk Adenocarcinoma of the Prostate	Case Series/ Uncontrolled Pre-post Study	ClinicalTrials.gov ID: NCT01045226
Active, not recruiting	A Phase II Study of Hypofractionated Image Guided Proton Radiation Therapy for Low and Intermediate Risk Adenocarcinoma of the Prostate	Non-randomized Controlled Trial	ClinicalTrials.gov ID: NCT00693238

Status	Study Title	Study Design	Information Resources
Completed	Semen Analysis Following Definitive Treatment of Prostate Cancer with Proton Radiation Therapy Alone	Case Series/ Uncontrolled Pre-post Study	ClinicalTrials.gov ID: NCT01072513
Completed No results posted	Proton Beam Radiation Therapy for Early Stage Adenocarcinoma of the Prostate	Case Series/ Uncontrolled Pre-post Study	ClinicalTrials.gov ID: NCT00585962
Unknown	Prospective Evaluation of Quality of Life After Proton Therapy for Prostate Cancer	Prospective Cohort	ClinicalTrials.gov ID: NCT00489814

Abbreviations. IMRT=intensity modulated radiation therapy; IPT=intraprostatic tumors; RCT=randomized controlled trials; SIB=simultaneous integrated boost.

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