APPENDIX A. SEARCH STRATEGIES

	Search Terms (MEDLINE and Embase)
1	exp Adenocarcinoma/ or adenocarcinoma.mp.
2	neoplasm.mp. or exp Neoplasms/
3	(hematologic or haematologic or lymphoma or leukemia).ti,ab.
4	1 or 2
5	4 not 3
6	Radiation Dose Hypofractionation/ or (radiotherapy minibeam$1 or radiation hypofractionated dose or radiation dose hypofractionation or hypofractionated radiation therapy or short?course radiation therapy).ti,ab.
7	dose fractionation/ or dose response relationship, radiation/ or radiotherapy dosage/
8	((radiotherapy* or radiat*) adj2 (dose or dosage or regimen* or schedule*)).tw.
9	hypofractionat*.mp.
10	hypo-fraction*.mp.
11	multi-fraction*.tw.
12	(hypo adj3 fraction*).tw.
13	Stereotactic body radiation therapy/ or SBRT.mp.
14	Stereotactic ablative body radiation therapy/ or SABR.mp.
15	(Stereotactic body radiation therapy or SBRT).tw.
16	(Stereotactic ablative body radiation therapy or SABR).tw.
17	or/6-16
18	5 and 17
19	Randomized controlled trial.pt. or randomized.mp. or placebo.mp.
‘21	('clinical ’trial‘ or 'randomized controlled ’study‘ or 'randomized controlled ’rial‘ or 'double blind clinical ’study‘ or 'single blind clinical ’tudy‘ or 'random alloc’tion').ti,ab.
22	(meta-analy$ or metaanaly$ or meta analy$).tw. or exp Meta-Analysis/ or (systematic adj (review$ or overview$)).tw. or (systematic review or literature review or rapid review or umbrella review or meta synthesis or metasynthesis or meta-analysis or meta-synthesis or integrative review or data synthesis or comparative effectiveness review).mp
23	or/19-22
24	(Animals/ or Models, Animal/ or Disease Models, Animal/) not Humans/
25	((animal or animals or canine* or cat or cats or dog or dogs or feline or goat or hamster* or horse or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep98urrent98ryrinar*) not (human* or patient*)).ti,kf,jw.
26	24 or 25
27	23 not 26
28	18 and 27
29	limit 28 to (case reports or comment or editorial or letter or news or newspaper article or personal narrative or conference abstract) [Limit not valid in Embase; records were retained]
30	28 not 29
31	limit 398urrentglish language
32	(child or children or pediat* or neonat*).ti,ab.

33	31 not 32
	Removed duplicates in EndNote
	Removed “childhood” cancer articles in EndNote
	Removed “commentary” articles in EndNote
	Removed “abstract” in EndNote
	Removed “annual meeting” in EndNote
	Removed “conference”, “proceedings”, and “symposium” in EndNote
	Removed duplicates in Distiller

APPENDIX B. EXCLUDED STUDIES

1. Concurrent boost with adjuvant breast hypofractionated radiotherapy and toxicity assessment. *Middle East Journal of Cancer*. 2015;6(1):21-27. *Ineligible study design*
2. Aboziada MA, Shehata S. Acute and late adverse effects of breast cancer radiation: Two hypo-fractionation protocols. *Journal of Solid Tumors*. 2017;7(2):1-6. *Ineligible outcome*
3. Adebahr S, Kirste S, Sprave T, et al. Psma-pet/mri-based focal dose escalation in patients with primary prostate cancer treated with stereotactic body radiation therapy (Hypofocal-sbrt): Study protocol of a randomized, multicentric phase iii trial. *Cancers*. 2021;13(22):5795. *Ineligible study design*
4. Alayed Y, Cheung P, Chu W, et al. Two StereoTactic ablative radiotherapy treatments for localized prostate cancer (2STAR): Results from a prospective clinical trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2019;135:86-90. *Ineligible intervention/comparison*
5. Awwad H, El-Baki HA, El-Bolkainy N, et al. Pre-operative irradiation of T3-carcinoma in bilharzial bladder: a comparison between hyperfractionation and conventional fractionation. *International journal of radiation oncology, biology, physics*. 1979;5(6):787-94. *Ineligible intervention/comparison*
6. Bartelink H, Horiot J-C, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007;25(22):3259-65. *Ineligible intervention/comparison*
7. Bartelink H, Van den Bogaert W, Horiot JC, Jager J, van Glabbeke M. Concomitant cisplatin and radiotherapy in a conventional and modified fractionation schedule in locally advanced head and neck cancer: a randomised phase II EORTC trial. *European journal of cancer (Oxford, England : 1990)*. 2002;38(5):667-73. *Ineligible intervention/comparison*
8. Bates TD. A prospective clinical trial of postoperative radiotherapy delivered in three fractions per week versus two fractions per week in breast carcinoma. *Clinical Radiology*. 1975;26(3):297-304. *Ineligible intervention/comparison*
9. Bauman G, Chen J, Rodrigues G, Davidson M, Warner A, Loblaw A. Extreme hypofractionation for high-risk prostate cancer: Dosimetric correlations with rectal bleeding. *Practical radiation oncology*. 2017;7(6):e457-e462. *Ineligible intervention/comparison*
10. Beaudry MM, Carignan D, Foster W, et al. Ultra-Hypofractionated (UHF) Compared to Moderate-Hypofractionated (MHF) Prostate IGRT With HDR Brachytherapy Boost (BB): Four-Year Toxicities and Local Control. *International journal of radiation oncology, biology, physics*. 2021;111(3):e265. *Ineligible study design*
11. Beckendorf V, Guerif S, Le Prise E, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *International journal of radiation oncology, biology, physics*. 2011;80(4):1056-63. *Ineligible intervention/comparison*
12. Beckendorf V, Guerif S, Le Prise E, et al. The GETUG 70 Gy vs. 80 Gy randomized trial for localized prostate cancer: feasibility and acute toxicity. *International journal of radiation oncology, biology, physics*. 2004;60(4):1056-65. *Ineligible intervention/comparison*

13. Beitler JJ, Zhang Q, Harris J, et al. Final results of local-regional control and late toxicity of rtog 9003: A randomized trial of altered fractionation radiation for locally advanced head and neck cancer. *International Journal of Radiation Oncology Biology Physics*. 2014;89(1):13-20. *Ineligible intervention/comparison*
14. Benson R, Prashanth G, Mallick S. Moderate hypofractionation for early laryngeal cancer improves local control: a systematic review and meta-analysis. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngo–ogy - Head and Neck Surgery*. 2020;277(11):3149-3154. *Ineligible study design*
15. Bentzen SM, Haviland JS, Bliss JM, Yarnold JR. Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: An analysis of the UK START (Standardisation of Breast Radiotherapy) trials of radiotherapy fractionation. *Radiotherapy and Oncology*. 2016;121(3):420-423. *Ineligible study design*
16. Bhangoo RS, Vargas CE, DeWees TA, et al. Updated Toxicity and Quality-of-Life Outcomes From a Randomized Phase III Trial of Extreme Hypofractionated vs. Standard Fractionated Proton Therapy for Low-Risk Prostate Cancer. *International journal of radiation oncology, biology, physics*. 2021;111(3):e266. *Ineligible intervention/comparison*
17. Bolner A, Signor M, Gava A, et al. Long-term results of conventional radiotherapy versus accelerated hyperfractionated radiotherapy versus concomitant radiotherapy and chemotherapy in locoregionally advanced carcinoma of the oropharynx. *Tumori*. 2006;92(1):41-54. *Ineligible intervention/comparison*
18. Bonner JA, McGinnis WL, Stella PJ, et al. The possible advantage of hyperfractionated thoracic radiotherapy in the treatment of locally advanced nonsmall cell lung carcinoma: results of a North Central Cancer Treatment Group Phase III Study. *Cancer*. 1998;82(6):1037-48. *Ineligible intervention/comparison*
19. Bourgier C, Acevedo-Henao C, Dunant A, et al. Higher toxicity with 42 Gy in 10 fractions as a total dose for 3D-conformal accelerated partial breast irradiation: results from a dose escalation phase II trial. *Radiation oncology (London, England)*. 2012;7:141. *Ineligible study design*
20. Brunt AM, Haviland JS, Bliss JM, et al. Five-fraction Radiotherapy for Breast Cancer: FAST-Forward to Implementation. *Clinical Oncology*. 2021;33(7):430-439. *Ineligible study design*
21. Buchholz TA, Strom EA, Oswald MJ, et al. Fifteen-year results of a randomized prospective trial of hyperfractionated chest wall irradiation versus once-daily chest wall irradiation after chemotherapy and mastectomy for patients with locally advanced noninflammatory breast cancer. *International journal of radiation oncology, biology, physics*. 2006;65(4):1155-60. *Ineligible intervention/comparison*
22. Bujko K, Rutkowski A, Pietrzak L, et al. Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders: A prospective multicentre study. *Radiotherapy and Oncology*. 2013;106(2):198-205. *Ineligible intervention/comparison*
23. Buyyounouski MK, Pugh S, Rodgers J, et al. Primary Endpoint Analysis of a Randomized Phase III Trial of Hypofractionated vs. Conventional Post-Prostatectomy Radiotherapy: NRG Oncology GU003. *International journal of radiation oncology, biology, physics*. 2021;111(3):S2-S3. *Ineligible study design*
24. Chatterjee S, Chakraborty S. Hypofractionated radiation therapy comparing a standard radiotherapy schedule (over 3 weeks) with a novel 1-week schedule in adjuvant breast

cancer: an open-label randomized controlled study (HYPORT-Adjuvant)-study protocol for a multicentre, randomized phase III trial. *Trials*. 2020;21(1):819. *Ineligible study design*

25. Choi KH, Ahn SJ, Jeong JU, et al. Postoperative radiotherapy with intensity-modulated radiation therapy versus 3-dimensional conformal radiotherapy in early breast cancer: A randomized clinical trial of KROG 15-03. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2021;154:179-186. *Ineligible intervention/comparison*
26. Cooke S, van Diessen J, Sikorska K, et al. Sites of First Progression in the Randomized PET-Boost Trial for Patients With Locally Advanced NSCLC. *International journal of radiation oncology, biology, physics*. 2021;111(3):S91. *Ineligible intervention/comparison*
27. Corkum M, Loblaw A, Hasan Y, et al. Prostate high dose-rate brachytherapy as monotherapy for prostate cancer: Late toxicity and patient reported outcomes from a randomized phase II clinical trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2021;156:160-165. *Ineligible intervention/comparison*
28. Cox JD, Pajak TF, Marcial VA, et al. ASTRO plenary: interfraction interval is a major determinant of late effects, with hyperfractionated radiation therapy of carcinomas of upper respiratory and digestive tracts: results from Radiation Therapy Oncology Group protocol 8313. *International journal of radiation oncology, biology, physics*. 1991;20(6):1191-5. *Ineligible intervention/comparison*
29. Coy P, Hodson I, Payne DG, et al. The effect of dose of thoracic irradiation on recurrence in patients with limited stage small cell lung cancer. Initial results of a Canadian Multicenter Randomized Trial. *International journal of radiation oncology, biology, physics*. 1988;14(2):219-26. *Ineligible intervention/comparison*
30. Cummings B, Warde P, Waldron J, et al. Five year results of a randomized trial comparing hyperfractionated to conventional radiotherapy over four weeks in locally advanced head and neck cancer. *Radiotherapy and Oncology*. 2007;85(1):7-16. *Ineligible intervention/comparison*
31. De Felice F, Musio D, Abate G, Moscarelli E, Bulzonetti N, Tombolini V. Impact of clinical complete response on treatment outcomes in patients with locally advanced HPV-negative oropharyngeal squamous cell carcinoma. *Journal of Cancer Research and Clinical Oncology*. 2020;146(2):477-483. *Ineligible study design*
32. Dearnaley D, Huddart R, Graham J, et al. A randomised trial of accelerated radiotherapy for localised invasive bladder cancer. *Radiotherapy and Oncology*. 2005;75(1):34-43. *Ineligible intervention/comparison*
33. Dearnaley DP, Sydes MR, Langley RE, et al. The early toxicity of escalated versus standard dose conformal radiotherapy with neo-adjuvant androgen suppression for patients with localised prostate cancer: results from the MRC RT01 trial (ISRCTN47772397). *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2007;83(1):31-41. *Ineligible intervention/comparison*
34. Deore SM, Shrivastava SK, Supe SJ, Viswanathan PS, Dinshaw KA. Alpha/beta value and importance of dose per fraction for the late rectal and recto-sigmoid complications. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]*. 1993;169(9):521-6. *Ineligible population*

35. Erlandsson J, Ahlberg M, Holm T, et al. Tumour regression after radiotherapy for rectal ca–cer - Results from the randomised Stockholm III trial. *Radiotherapy and Oncology*. 2019;135:178-186. *Ineligible outcome*
36. Fadavi P, Jafarnejadi B, Nafissi N, Mahdavi SR, Javadinia SA. Outcome of hypofractionated breast irradiation and intraoperative electron boost in early breast cancer: A randomized non-inferiority clinical trial. *Cancer Reports*. 2021;4(5):e1376. *Ineligible study design*
37. Fernandez K, Brand DH, Gao A, et al. Estimates of Alpha/Beta (alpha/beta) Ratios for Individual Late Rectal Toxicity Endpoints: An Analysis of the CHHiP Trial. *International Journal of Radiation Oncology Biology Physics*. 2021;110(2):596-608. *Ineligible intervention/comparison*
38. Fersino S, Fiorentino A, Giaj Levra N, et al. Impact of Ialuril Soft Gels in reducing urinary toxicity during radical hypofractionated radiotherapy in prostate cancer: a preliminary experience. *Minerva urologica e nefrologica = The Italian journal of urology and nephrology*. 2016;68(1):9-13. *Ineligible intervention/comparison*
39. Finney R. The treatment of carcinoma of the bladder by external irradiation. A clinical trial. Part II. *Clinical Radiology*. 1971;22(2):225-229. *Ineligible study design*
40. Forster T, Jakel C, Akbaba S, et al. Fatigue following radiotherapy of low-risk early breast ca–cer - a randomized controlled trial of intraoperative electron radiotherapy versus standard hypofractionated whole-breast radiotherapy: the COSMOPOLITAN trial (NCT03838419). *Radiation oncology (London, England)*. 2020;15(1):134. *Ineligible study design*
41. Fragkandrea I, Kouloulias V, Mavridis P, et al. Radiation induced pneumonitis following whole breast radiotherapy treatment in early breast cancer patients treated with breast conserving surgery: A single institution study. *Hippokratia*. 2013;17(3):233-238. *Ineligible outcome*
42. Fu KK, Clery M, Ang KK, Byhardt RW, Maor MH, Beitler JJ. Randomized phase I/II trial of two variants of accelerated fractionated radiotherapy regimens for advanced head and neck cancer: results of RTOG 88-09. *International journal of radiation oncology, biology, physics*. 1995;32(3):589-97. *Ineligible intervention/comparison*
43. Fu KK, Pajak TF, Marcial VA, et al. Late effects of hyperfractionated radiotherapy for advanced head and neck cancer: long-term follow-up results of RTOG 83-13. *International journal of radiation oncology, biology, physics*. 1995;32(3):577-88. *Ineligible intervention/comparison*
44. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *International journal of radiation oncology, biology, physics*. 2000;48(1):7-16. *Ineligible intervention/comparison*
45. Fu X-L, Wang L-J, Qian H, et al. Hyperfractionated accelerated radiation therapy for nonsmall cell lung cancer: Clinical phase I/II trial. *International Journal of Radiation Oncology Biology Physics*. 1997;39(3):545-552. *Ineligible intervention/comparison*
46. Gerard J-P, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(36):4558-65. *Ineligible intervention/comparison*
47. Ghadjar P, Hayoz S, Bernhard J, et al. Acute Toxicity and Quality of Life After Dose-Intensified Salvage Radiation Therapy for Biochemically Recurrent Prostate Cancer

After Prostatectomy: First Results of the Randomized Trial SAKK 09/10. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(35):4158-66. *Ineligible intervention/comparison*

48. Ghoshal S, Goda JS, Mallick I, Kehwar TS, Sharma SC. Concomitant boost radiotherapy compared with conventional radiotherapy in squamous cell carcinoma of the head and–eck--a phase III trial from a single institution in India. *Clinical oncology (Royal College of Radiologists (Great Britain))*. 2008;20(3):212-20. *Ineligible intervention/comparison*
49. Goel A, Kaushal V, Hooda HS, Das BP. Comparison of two radiation dose schedules in post mastectomy carcinoma of the breast. *Indian journal of medical sciences*. 2000;54(7):278-83. *Ineligible intervention/comparison*
50. Gronberg BH, Killingberg KT, Flotten O, et al. High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial. *The Lancet Oncology*. 2021;22(3):321-331. *Ineligible intervention/comparison*
51. Gupta M, Mahajan R, Kaushal V, Seem RK, Gupta M, Bhattacharyya T. Prospective randomized trial to compare accelerated (six fractions a week) radiotherapy against concurrent chemoradiotherapy (using conventional fractionation) in locally advanced head and neck cancers. *Journal of cancer research and therapeutics*. 2015;11(4):723-9. *Ineligible intervention/comparison*
52. Ha B, Cho KH, Lee KH, et al. Long-term results of a phase II study of hypofractionated proton therapy for prostate cancer: moderate versus extreme hypofractionation. *Radiation oncology (London, England)*. 2019;14(1):4. *Ineligible intervention/comparison*
53. Hafeez S, Patel E, Webster A, et al. Protocol for hypofractionated adaptive radiotherapy to the bladder within a multicentre phase II randomised trial: radiotherapy planning and delivery guidance. *BMJ open*. 2020;10(5):e037134. *Ineligible intervention/comparison*
54. Hall WA, Deshmukh S, Pugh SL, et al. Quality of Life Implications of Dose-Escalated External Beam Radiation for Localized Prostate Cancer: Results of a Prospective Randomized Phase 3 Clinical Trial, NRG/RTOG 0126. *International Journal of Radiation Oncology Biology Physics*. 2022;112(1):83-92. *Ineligible intervention/comparison*
55. Halvorsen TO, Valan CD, Slaaen M, Gronberg BH. Associations between muscle measures, survival, and toxicity in patients with limited stage small cell lung cancer. *Journal of cachexia, sarcopenia and muscle*. 2020;11(5):1283-1290. *Ineligible outcome*
56. Hannan R, Tumati V, Xie X-J, et al. Stereotactic body radiation therapy for low and intermediate risk prostate cancer-Results from a multi-institutional clinical trial. *European journal of cancer (Oxford, England : 1990)*. 2016;59:142-151. *Ineligible intervention/comparison*
57. Hatton MQF, Lawless CA, Faivre-Finn C, et al. Accelerated, Dose escalated, Sequential Chemoradiotherapy in Non-small-cell lung cancer (ADSCaN): a protocol for a randomised phase II study. *BMJ open*. 2019;9(1):e019903. *Ineligible outcome*
58. Haviland JS, Mannino M, Griffin C, et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2018;126(1):155-162. *Ineligible outcome*
59. Heemsbergen WD, Incrocci L, Sinzabakira F, Pos FJ. Patient-Reported Outcomes in the Acute Phase of the Randomized Hypofractionated Irradiation for Prostate Cancer

(HYPRO) Trial. *International Journal of Radiation Oncology Biology Physics*. 2021. *Ineligible outcome*

60. Henk JM, Adams GE, Ash D. A study of the effect of misonidazole in conjunction with radiotherapy for the treatment of head and neck cancer. *British Journal of Radiology*. 1984;57(679):585-595. *Ineligible intervention/comparison*
61. Hopwood P, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *The Lancet Oncology*. 2010;11(3):231-40. *Ineligible outcome*
62. Horiot JC, Le Fur'R, N'Guyen T, et al. Hyperfractionated compared with conventional radiotherapy in oropharyngeal carcinoma: an EORTC randomized trial. *European journal of cancer (Oxford, England : 1990)*. 1990;26(7):779-80. *Ineligible intervention/comparison*
63. Horiot JC, Le Fur'R, N'Guyen T, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 1992;25(4):231-41. *Ineligible intervention/comparison*
64. Jain S, Poon I, Soliman H, et al. Lung stereotactic body radiation therapy (SBRT) delivered over 4 or 11 days: a comparison of acute toxicity and quality of life. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2013;108(2):320-5. *Ineligible intervention/comparison*
65. Jeremic B, Shibamoto Y, Igrutinovic I. Absence of cervical radiation myelitis after hyperfractionated radiation therapy with and without concurrent chemotherapy for locally advanced, unresectable, nonmetastatic squamous cell carcinoma of the head and neck. *Journal of cancer research and clinical oncology*. 2001;127(11):687-91. *Ineligible intervention/comparison*
66. Johnson RJ, Walton RJ, Lim ML, Zylak CJ, Painchaud LA. A randomized study on survival of bronchogenic carcinoma treated with conventional or short fractionation radiation. *Clinical radiology*. 1973;24(4):494-7. *Ineligible intervention/comparison*
67. Kacprowska A, Jassem J. Hypofractionated radiotherapy for early breast cancer: Review of phase III studies. *Reports of Practical Oncology and Radiotherapy*. 2012;17(2):66-70. *Ineligible study design*
68. Kang B-H, Yu T, Kim JH, et al. Early Closure of a Phase 1 Clinical Trial for SABR in Early-Stage Glottic Cancer. *International journal of radiation oncology, biology, physics*. 2019;105(1):104-109. *Ineligible study design*
69. Katori H, Tsukuda M, Watai K. Comparison of hyperfractionation and conventional fractionation radiotherapy with concurrent docetaxel, cisplatin and 5-fluorouracil (TPF) chemotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). *Cancer Chemotherapy and Pharmacology*. 2007;60(3):399-406. *Ineligible intervention/comparison*
70. Kawahara D, Ozawa S, Kimura T, et al. Marginal prescription equivalent to the isocenter prescription in lung stereotactic body radiotherapy: preliminary study for Japan Clinical Oncology Group trial (JCOG1408). *Journal of radiation research*. 2017;58(1):149-154. *Ineligible study design*

71. Kim KN, Dyer MA, Qureshi MM, et al. Hypofractionated radiotherapy and surgery compared to standard radiotherapy in early glottic cancer. *American journal of otolaryngology*. 2020;41(5):102544. *Ineligible study design*
72. Kim Y-J, Cho KH, Pyo HR, et al. A phase II study of hypofractionated proton therapy for prostate cancer. *Acta oncologica (Stockholm, Sweden)*. 2013;52(3):477-85. *Ineligible intervention/comparison*
73. Kinhikar R, Ghadi Y, Sahoo P, et al. Dosimetric comparison of three-dimensional conformal radiotherapy, intensity modulated radiotherapy, and helical tomotherapy for lung stereotactic body radiotherapy. *Journal of Medical Physics*. 2015;40(4):190-197. *Ineligible study design*
74. Kirova YM, Campana F, Savignoni A, et al. Breast-conserving treatment in the elderly: long-term results of adjuvant hypofractionated and normofractionated radiotherapy. *International journal of radiation oncology, biology, physics*. 2009;75(1):76-81. *Ineligible study design*
75. Koerber SA, Katayama S, Sander A, et al. Prostate bed irradiation with alternative radio-oncological approaches (PA–OS) - a prospective, multicenter and randomized phase III trial. *Radiation oncology (London, England)*. 2019;14(1):122. *Ineligible study design*
76. Konski AA, Winter K, Cole BF, Ang K-K, Fu KK. Quality-adjusted survival analysis of Radiation Therapy Oncology Group (RTOG) 90-03: phase III randomized study comparing altered fractionation to standard fractionation radiotherapy for locally advanced head and neck squamous cell carcinoma. *Head & neck*. 2009;31(2):207-12. *Ineligible intervention/comparison*
77. Kougioumtzopoulou A, Platoni K, Kelekis N, et al. Moderate Hypofractionated Radiotherapy for Localized Prostate Cancer: The Triumph of Radiobiology. *Reviews on recent clinical trials*. 2021. *Ineligible study design*
78. Koukourakis G, Zacharias G, Petridis A. Evidence based whole breast hypo-fractionated radiation therapy in patients with early breast cancer. *Journal of BUON : official journal of the Balkan Union of Oncology*. 2015;20(2):473-8. *Ineligible study design*
79. Kron T, Chesson B, Hardcastle N, et al. Credentialing of radiotherapy centres in Australasia for TROG 09.02 (Chisel), a Phase III clinical trial on stereotactic ablative body radiotherapy of early stage lung cancer. *The British journal of radiology*. 2018;91(1085):20170737. *Ineligible study design*
80. Krug D, Baumann R, Combs SE, et al. Moderate hypofractionation remains the standard of care for whole-breast radiotherapy in breast cancer: Considerations regarding FAST and FAST-Forward. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]*. 2021;197(4):269-280. *Ineligible study design*
81. Krug D, Dellas K, Dunst J, et al. Impact of guideline changes on adoption of hypofractionation and breast cancer patient characteristics in the randomized controlled HYPOSIB trial. *Strahlentherapie und Onkologie*. 2021;197(9):802-811. *Ineligible intervention/comparison*
82. Lawton C, Scott C, Sause WT, et al. Response, toxicity, failure patterns, and survival in five radiation therapy oncology group (RTOG) trials of sequential and/or concurrent chemotherapy and radiotherapy for locally advanced non-small-cell carcinoma of the lung. *International Journal of Radiation Oncology Biology Physics*. 1998;42(3):469-478. *Ineligible intervention/comparison*
83. Liu L, Yang Y, Guo Q, et al. Comparing hypofractionated to conventional fractionated radiotherapy in postmastectomy breast cancer: a meta-analysis and systematic review. *Radiation oncology (London, England)*. 2020;15(1):17. *Ineligible study design*

84. Lukka HR, Pugh SL, Bruner DW, et al. Patient Reported Outcomes in NRG Oncology RTOG 0938, Evaluating Two Ultrahypofractionated Regimens for Prostate Cancer. *International journal of radiation oncology, biology, physics*. 2018;102(2):287-295. *Ineligible intervention/comparison*
85. Marcial VA, Hanley JA, Chang C, Davis LW, Moscol JA. Split-course radiation therapy of carcinoma of the nasopharynx: results of a national collaborative clinical trial of the Radiation Therapy Oncology Group. *International journal of radiation oncology, biology, physics*. 1980;6(4):409-14. *Ineligible intervention/comparison*
86. Mark RJ, Gorman V, Wolski M, McCullough S. Five Day Accelerated Partial Breast Irradiation (APBI) Using Stereotactic Body Radiation Therapy (SBRT) in Stage 0-II Breast Cancer: A Report of 218 Cases With Up to 39 Month Follow-Up. *International journal of radiation oncology, biology, physics*. 2021;111(3):e208. *Ineligible study design*
87. Marzi S, Saracino B, Petrongari MG, et al. Modeling of alpha/beta for late rectal toxicity from a randomized phase II study: conventional versus hypofractionated scheme for localized prostate cancer. *Journal of experimental & clinical cancer research : CR*. 2009;28:117. *Ineligible outcome*
88. Mendez LC, Arifin AJ, Bauman GS, et al. Is hypofractionated whole pelvis radiotherapy (WPRT) as well tolerated as conventionally fractionated WPRT in prostate cancer patients? The HOPE trial. *BMC cancer*. 2020;20(1):978. *Ineligible study design*
89. Michalski JM, Perez CA, Purdy JA, et al. Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. *International Journal of Radiation Oncology Biology Physics*. 2000;46(2):391-402. *Ineligible intervention/comparison*
90. Min C, Connolly E, Chen T, Jozsef G, Formenti SC. Hypofractionated radiation therapy for early stage breast cancer: outcomes, toxicities, and cost analysis. *The breast journal*. 2014;20(3):267-73. *Ineligible study design*
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APPENDIX C. PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	Thank you.
2	2	Yes	Thank you.
3	3	Yes	Thank you.
4	4	Yes	Thank you.
5	5	Yes	Thank you.
6	6	Yes	Thank you.
7	7	Yes	Thank you.
8	9	Yes	Thank you.
9	10	Yes	Thank you.
10	11	Yes	Thank you.
11	12	Yes	Thank you.
Is there any indication of bias in our synthesis of the evidence?			
12	1	No	Thank you.
13	2	No	Thank you.
14	3	No	Thank you.
15	4	No	Thank you.
16	5	No	Thank you.
17	6	No	Thank you.
18	7	No	Thank you.
19	9	No	Thank you.
20	10	No	Thank you.
21	11	No	Thank you.
22	12	No	Thank you.
Are there any published or unpublished studies that we may have overlooked?			
23	1	No	Thank you.
24	2	No	Thank you.

Comment #	Reviewer #	Comment	Author Response
25	3	No	Thank you.
26	4	No	Thank you.
27	5	No	Thank you.
28	6	Yes	Reviewer did not provide which studies they thought were missed, so we were unable to directly address this comment.
29	7	No	Thank you.
30	9	No	Thank you.
31	10	Yes - This report appears to be incomplete and the results are not analyzed properly. i would refer the authors to the appendix of this article which is an extremely complete bibliography of all hypofractionated schedules: https://www.redjournal.org/article/S0360-3016(20)31341-9/fulltext	The cited article is a review of all radiation fractionation treatments that were published during the COVID-19 pandemic (and indexed by MEDLINE). As such, this review included many articles with study designs, treatments, and patient populations that would not be eligible for this ESP report. However, we have examined the bibliography for this review and found no additional articles that met our eligibility criteria.
32	11	No	Thank you.
33	12	No	Thank you.
Additional suggestions or comments can be provided below.			
34	1	Page 1, bullet 3 this statement implies a negative connotation since it sees no difference in survival or disease progression which is in fact the positive point that with no difference in acute or late harms altered fractionation regimens offer the same survival and disease free progression	We used standard language recommended by GRADE to describe the summary results. The GRADE ratings were based on the effect findings and the thresholds for minimally important differences that were discussed and agreed upon with our partners and TEP members. The current wording does not provide an intrinsic “negative” or “positive” connotation. The alternate wording “offer the same survival and disease-free progression” is not fully accurate and is not consistent with GRADE recommendations.
35	1	Page 6, Line 22 this does not makes sense. Lung SBRT is small volume and we don't usually see esophagitis. if this is looking at large volume palliative lung hypofractionation then the two should be separated	We checked these results, and they are consistent with reviewer statement that these outcomes are rare (see pg. 58 in the final report). Because the study sizes were very small (total N=101 for each of 2 trials, Ball et al. and Nyman et al.), there were no events observed in either arm in Ball et al. and only 1 event (in the control arm) in Nyman et al. Thus, we have very low certainty in the evidence for differences (or lack thereof) in this harm outcome. We excluded studies

Comment #	Reviewer #	Comment	Author Response
			evaluating palliative therapy as our report was focused on radiation treatment for curative intent.
36	2	Overall, this report is comprehensive and attempts to synthesize the published data for the purposes of informing national policy on hypofractionated radiotherapy for the definitive treatment of several common cancer subtypes. The draft report is 214 pages long and the body of the report before the references is 69 pages long. There are several forest plots that are not labeled (is the left side of the plot always hypofractionated or conventional?) so the reader is left to scrutinize the data to deduce which arm is favored for which study and for the overall measure of the combined study data. Overall, the document should be combed over by a technical editor for grammar, as there are several instances where commas are either placed in error or omitted in error and this makes reading the manuscript and following along much more challenging. My suggestions for changes are as follows:	The length of this report reflects the large scope of the key questions addressing benefits and harms of hypofractionation for multiple types of cancer. Moreover, this sized scope (and thus length of report) is not unusual for ESP projects. We have also included a much shorter "Executive Summary" with Key Findings that summarize the results and certainty of evidence for cancer types and outcomes of interest. The forest plots and pooled estimates all reflect the relative rate of the event of interest (eg, survival; toxicity) in the hypofractionation group divided by the rate of the event in the control group. Thus, a RR > 1.0 always indicates that the rate of an event is greater in the hypofractionation group. We have added labeling to all the forest plots to indicate which direction favors hypofractionation vs. conventional or standard of care.
37	2	p 1; line 13, needs a comma between "cancer" and "evidence"	This has been addressed.
38	2	p 1; line 18, need the word "of" inserted between "or" and "very"	This has been addressed.
39	2	p 1; line 44 or 45, this entire sentence is awkward and does not reflect or adequately inform the reader on the definition of hypofractionation. I would suggest the following wording: "Hypofractionation is a treatment schedule in which the total dose of radiation is divided into large doses per fraction and the treatment is given once a day or less often over a smaller total number of fractions and a shorter overall period of time compared to conventional fractionation."	Thank you for the suggested wording; we have revised this sentence.
40	2	p 1; line 52, "has" should be "have"	This has been addressed.

Comment #	Reviewer #	Comment	Author Response
41	2	p 1; line 60; The word "Quality" should be inserted between "Oncology" and "Task"	This has been addressed.
42	2	p 2; line 6 or 7, there should be a comma after the word "review"	This has been addressed.
43	2	p 3; line 13, there should be a comma after the word "trials" and before the number "47"	This has been addressed.
44	2	p 3, line 13, the comma after bias should either be a period followed by a new sentence or a semicolon	This has been addressed.
45	2	p 3, line 32 or 33, there should be a "<" sign before the number 5	This has been addressed.
46	2	p 5, line 40, the text is missing the word "no" between "or" and "difference"	This has been addressed.
47	2	p 7, line 17, delete the comma after the word "intent"	This has been addressed.
48	2	p 7, line 29, sentence is missing the word "cancers" between the word "bladder" and the period	This has been addressed.
49	2	p 7, line 36, replace the semicolon with a colon	This has been addressed.
50	2	p 7, line 37 or 38, Replace the word "There" with "While there"	This has been addressed.
51	2	p 7, line 38 or 39, remove the word "however" and add the words "in toxicity" after the word "difference"	This has been addressed.
52	2	p 7, line 39 or 40, replace "vs." with "and" and place a comma between the words "reviews" and "our"	This has been addressed.
53	2	p 7, line 47, remove the word "Additionally", remove the comma, and capitalize the letter I in the word "in"	This has been addressed.
54	2	p 7, line 50 or 51, replace the words "more clear" with the word "clearer"	This has been addressed.
55	2	p 7, line 52, the text is missing the word "was" between "certainty" and "low"	This has been addressed.

Comment #	Reviewer #	Comment	Author Response
56	2	p 9, line 25, add the text "in the United States" after the word "(NCI)"	This has been addressed.
57	2	p 9, lines 37 and 38, this entire sentence is awkward and does not reflect or adequately inform the reader on the definition of hypofractionation. I would suggest the following wording: "Hypofractionation is a treatment schedule in which the total dose of radiation is divided into large doses per fraction and the treatment is given once a day or less often over a smaller total number of fractions and a shorter overall period of time compared to conventional fractionation."	As noted above, this has been revised.
58	2	p 11, line 11 or 12, the word "prostate," needs to be inserted in between "breast," and "lung"	This has been addressed.
59	2	p 11, line 31, replace "is" with "are"	This has been addressed.
60	2	p 11, line 32 or 33, add the word "the" between the words "in" and "definitive"	This has been addressed.
61	2	p 11, line 35 or 36, add the word "the" between the words "do" and "efficacy"	This has been addressed.
62	2	p 11, line 37, remove the words "prostate cancer NCCN"	“Prostate cancer NCCN risk stratification” was specifically requested and approved by partners and TEP members for Key Question 2. Both Key Questions and the review protocol were developed and approved a priori. They cannot be changed at this time and changing the Key Question at this time would not accurately represent how we conducted the review.
63	2	p 11, line 38, replace the word "and" with the word "or"	This has been addressed.
64	2	p 11, lines 40 to 43, this entire sentence is awkward and does not reflect or adequately inform the reader on the definition of hypofractionation. I would suggest the following wording: "Hypofractionation is a treatment schedule in which the total dose of radiation is divided into large doses per fraction and the treatment is given once a day or less often over a smaller total	Thank you for the suggested wording; we have revised this sentence.

Comment #	Reviewer #	Comment	Author Response
		number of fractions and a shorter overall period of time compared to conventional fractionation."	
65	2	p 11, line 56 or 57, remove the word "Cyberknife" (that is a specific model or brand of linear accelerator sold and marketed by a particular vendor and not a type of radiation therapy)	This has been addressed.
66	2	p 14, line 37 or 38, add the words "per fraction" after the words "Hypofractionation: [>220 cGy (2.2 Gy)]"	This has been addressed.
67	2	p 14, line 42 or 43, add the words "per fraction" after the words "…long course radiation [180 to 220 cGy (1.8 to 2.2 Gy)]"	This has been addressed.
68	2	p 15, line 5, add the symbol "</=" before the first use of the phrase "2 years" on this line	This has been addressed.
69	2	p 19, line 46 or 47, remove the parentheses and remove the word "see", add a comma after the word "trials" and before the number "47"	This has been addressed.
70	2	p 20, line 5 or 6, add the word "of" between "populations" and "less"	This has been addressed.
71	2	p 20, lines 9 or 10, add the word "follow-up" between the words "shorter" and "durations"	This has been addressed.
72	2	p 42, line 7 or 8, the total dose range states "66-50 Gy", is this correct?	This has been corrected to read "66-80 Gy".
73	2	p 42, line 16 or 17, the total dose range states "66-50 Gy", is this correct?	This has been corrected to read "66-80 Gy".
74	2	P 45, line 18 or 19, add the words "in small cell lung cancer" after the word "harms"	This has been addressed.
75	2	P 51, line 15, all of the patients in the study reference #74 Choudhury et al. had recurrent nasopharyngeal carcinoma, so this sentence needs to be corrected	In response to other reviewer comments, we have reorganized this section such that the results for early stage glottic cancer are separately described from those on recurrent nasopharyngeal (Tian et al.) or locally advanced head and neck cancer (Choudhry et al.).
76	2	P 51, line 23 or 24 to 24 or 25, 3.125 Gy per fraction is referred to as "ultra-hypofractionation".	As noted above, this section has been reorganized. We have double-checked that treatments are correctly described as moderate hypofractionation.

Comment #	Reviewer #	Comment	Author Response
		This is internally inconsistent with the authors' definitions in Table 1 of this manuscript.	
77	2	P 51, line 48 or 49, replace the words "squamous cell carcinoma" with the word "larynx" and change the number "3" to the number "2" then add one more row in this same category of "Sub-cancer type" called Not specified" and list that sub-cancer type as k=1	As noted above, this section has been reorganized. We no longer have a summary table in this section. We have double-checked that descriptions of the included cancer diagnoses are correct.
78	2	P 60, line 29 or 30, insert the word "survival" between the words "free" and "at"	This has been addressed.
79	2	p 63; line 13, needs a comma between "cancer" and "evidence"	This has been addressed.
80	2	p 63; line 17 or 18, need the word "of" inserted between "or" and "very"	This has been addressed.
81	2	p 63, line 21, replace the word "requires" with the word "require"	This has been addressed.
82	2	p 65, line 37 or 38, the text is missing the word "no" between "or" and "difference"	This has been addressed.
83	2	p 67, line 13 and 14 states, "…in an effort to capture the evidence with the likelihood of highest quality." What does that mean? Can it be rephrased for clarity?	We have rephrased this sentence to indicate that this refers to the restriction of eligibility to RCTs. Furthermore, we did not abstract detailed outcomes from RCTs rated as high risk of bias.
84	2	P 67, line 25, add the word "cancers" between the word "bladder" and the period	This has been addressed.
85	2	P 67, line 40 or 41 to line 43, remove the entire sentence "Our review found greater variation in the harms related outcomes, however none of the analyses suggested a clinically meaningful difference between hypofractionation vs. conventional radiotherapy." This is redundant as it was just stated in the preceding paragraph verbatim.	This has been addressed.
86	2	P 67, lines 50 to 52 or 53, remove the phrase "previous systematic reviews and meta-analyses reported similar findings to our report; little or no difference in overall survival between the	This has been addressed.

Comment #	Reviewer #	Comment	Author Response
		hypofractionation and conventional radiotherapy." This is redundant as it was just stated two paragraphs earlier verbatim.	
87	3	Overall, the authors have done an admirable job of synthesizing a large volume of research across multiple disease sites and condensed it into a reasonable format that covers the salient issues of treatment outcome and toxicity in a relatively short period of time. The authors should be commended for their efforts.	Thank you.
88	4	in the executive summary key findings, the first bullet point has a typo: Key Findings • Despite many randomized trials enrolling individuals with different cancers evidence was limited regarding the comparative effectiveness and harms of hypofractionation versus radiotherapy for definitive (non-palliative) therapy. should read: Key Findings • Despite many randomized trials enrolling individuals with different cancers evidence was limited regarding the comparative effectiveness and harms of hypofractionation versus CONVENTIONALLY FRACTIONATED radiotherapy for definitive (non-palliative) therapy.	The key findings have been substantially revised, and we have clarified the intervention comparisons.
89	5	Page 1, Line 9 Hypofractionated vs. conventional radiotherapy. This phrase is a little confusing as is, consider rewording.	This has been revised to "hypofractionation versus conventionally fractionated radiotherapy"
90	5	Page1, Line 13 Use 'or' instead of and. Also, consider specifying what type of evidence as the group was specific in that regard. Same with bullet 3.	This has been addressed.
91	5	Page 1, Line 21	This has been addressed.

Comment #	Reviewer #	Comment	Author Response
		Hypofractionated radiation or radiotherapy is the preferred language. This bullet does not read well, consider rewording	
92	5	Page1 Line 41 This should be reworded, too vague	This has been addressed.
93		Page 2, Line 9 consider listing only those that were ultimately performed and mention in methods that others were considered and ulimately not pursued due to lack of data	This has been reworded to clarify which cancers were included in the review and which among these did not have any eligible trials. We believe it is also important to highlight existing evidence gaps for clinicians, policy makers and researchers. In this case, the lack of RCTs for several cancer types suggest areas for future research.
94	5	ES-Table 1 please offer more explanation or N and # trials. Consider adding a qualifier in the first column such as (early) or (late) where applicable	We have revised the column heading to read “Total N” for total number of participants across all eligible trials for that outcome. We have also added early and/or late as descriptors for the toxicity outcomes.
95	5	Page 8, After Conclusions Due to the enormity of the scope of this project, I would highly recommend disease site expert review per section. Within the first several pages there are numerous English language errors/ typos and others have noted errors in findings such as a study being marked as SCC instead of SCLC.	We have undertaken an additional round of reviews (of a revised draft) and assured that those with the relevant expertise had the opportunity to review the report. We have corrected the designation of the specified trial to NSCLC (.
96	5	Page 21, Line 7 First sentence is awkward, please revise. Many are not familiar with ROB	We have revised this sentence for greater clarity. We also describe ROB ratings in the Methods.
97	5	Page 44, Line 15 This needs to be broken out to hypofractionated and ultrahypofractionated. Unfair to pool them as they represent different populations (early vs locally advanced lung cancer)	The lung cancer section has been reorganized to separate the ultrahypofractionated comparison trials from the hypofractionated trials. The lung cancer trials were not pooled due to clinical heterogeneity and the decision a priori to not pool if fewer than 5 trials were identified.
98	5	Table 1 – Cancer type has an asterisk which is not explained. Initially, I was unclear how these are organized within subsections. Based on the first two findings, I thought perhaps certainty of evidence and was looking for a pattern. Consider making it alphabetical to reduce any confusion on	We have removed the asterisk. The Summary of Key Findings is organized by outcome, and then the respective cancers. This reflects the organization of the results sections in the main report.

Comment #	Reviewer #	Comment	Author Response
		organization. Overall though , looks very good. *(comments on a revised draft report)*	
98	5	Page 46 line 30 please write out the number three *(comments on a revised draft report)*	We have revised this sentence to clarify the number of treatments and the dose per fraction.
99	5	Table 16 in OS, SCLC and Glottic Caner have a typo that I believe should read “may” *(comments on a revised draft report)*	This has been addressed.
100	6	I have concerns about entire manuscript after reading briefly through the lung.. they discuss 5 trials but then only mention 3 in their key question and summary for lung NSCLC.	The overview of lung cancer section correctly states that there were 5 trials that were rated low or some concerns for risk of bias (4 trials for NSCLC, and 1 for SCLC). The NSCLC trials involving SABR/SBRT have now been further regrouped. The summaries of findings for each individual cancer type, as well as in the Discussion, are by outcome. The total # of trials listed for each outcome is often less than the total # of eligible trials for that cancer, since not all trials report all outcomes of interest.
101	6	They say that the ROY study is a small cell study see below but it is a squamous cell study. They misclassify this study…	As noted above, we have corrected this misclassification.
102	6	Someone has to go through each disease site… I also noted mistakes they put hyperfraction for an SBRT dosing in the appendix somewhere for lung …..	As noted above, we undertook an additional round of reviews of an interim revised draft, in order to assure that relevant experts had the opportunity to review. We have also reorganized the lung cancer section and separately pulled out the SABR/SBRT trials.
103	6	[Regarding lung cancer results for Key Question 1]: Roy is small cell and even so their conclusions do not make sense Ball et al Superior survival in hypofrac statistically significant Roy et al SBRT superior OS statistically significant and study listed in appendix but not listed in their key question section Nyman not statistically significant btwn conventional and hypofrac Qui the p values not reported, median survival not	As noted above, we have corrected the classification of the Roy et al. trial. We have also reorganized the lung cancer section to separately discuss results for SABR/SBRT in NSCLC. With this reorganization and separate evaluation of the certainty of evidence for overall survival (SABR vs. conventional) and progression-free survival (SBRT vs. conventional), these were changed from low to moderate certainty for these 2 comparisons. As we described in the Methods section, we evaluated 5 domains in determining the certainty of evidence according to GRADE recommendations. This process does not rely on the p-value of each individual trial effect estimate. Within the Results section for lung cancer, we have also now provided more

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		statistically different small cell Iyengar not statistically different	information about the factors that impacted the certainty of evidence assessment for each outcome.
104	7	sCLC and nSCLC is typically noted SCLC and NSCLC in the literature. The lower case "s" is very atypical.	This has been changed throughout the report.
105	7	For SCLC, the Qui trial's dose 65 Gy (there is a typo in Appendix table 11 with "GY" and not "Gy") in 26 daily fractions has a higher biologically effective dose (BED) as compared to conventional fractionation or 42 Gy in 15 fractions as in the Gronberg trial. The BED in the Qui trial is a major confounder.	This typo has been addressed. We provide detailed description of the intervention and comparator treatments in the Qui et al. trial and we downgraded the certainty of evidence for outcomes in SCLC due to substantial methodological limitations of this study.
106	7	Finally, the biggest issue is the unclear separation between SBRT for the lung and Hypofractionation for the lung. These are much different modalities and cannot be lumped together for analysis. The Iyengar trial had stage III patients, which is completely different than the SBRT trials which had stage I patients. The manuscript does not make clear this distinction and there should be a clear SBRT for NSCLC section and separate hypofractionation for NSCLC section. Regimens also for different stages (I/II vs III) should be made as well.	As noted above, we have reorganized the lung cancer results section, such that results from SABR/SBRT trials are separated from the other NSCLC trials. We agree that this is more informative for interpreting these results, given the differences in both treatment characteristics and patient populations.
107	7	The conclusion that "Hypofractionation may result in a reduction in overall survival" in table 1 for NSCLC is highly problematic! It appears SBRT is lumped into that conclusion. Again, this must be changed.	As noted above, results from.SABR/SBRT trials are now separately considered. The detailed results, summary findings, and conclusions have been updated to reflect this.
108	7	Table ES-1 spelling error “Hypofractionation ay result…” for SCLC and early glottic - Should be "may" *(comments on a revised draft report)*	This had been addressed.
109	9	Breast Cancer. The authors are commended for compiling the many randomized trials comparing various hypofractionation regimens in breast cancer.	Thank you.

Comment #	Reviewer #	Comment	Author Response
110	9	Prostate Cancer. The authors are commended for compiling the many randomized trials comparing various hypofractionation regimens in prostate cancer. The authors can consider breaking down the data in terms of risk groups, but probably not necessary and I think the results would largely be the same: little difference between hypofractionation, ultrahypofractionation (SBRT), and conventional (standard) radiation.	Thank you. We are limited in stratification of results by risk groups to what is reported in the published articles. When stratified results are provided, we have included those in our report.
111	9	Rectal Cancer. The authors are commended for this evaluation of hypofractionation in rectal cancer.	Thank you.
112	9	Head and Neck Cancer The authors are commended for compiling the data comparing various hypofractionation regimens in Head and Neck Cancers. However, there are some concerns. I disagree with the assessment to key question 2. Given available data, I think results do indeed vary by tumor characteristics. The majority of data here is for early stage glottic cancer, and it is worthwhile to separate out the data for glottic cancer from other head and neck cancers. I think sufficient data exist to support moderate hypofractionation for treatment of early stage glottic cancer on the basis of Yamazaki 2006, Moon 2014, and Kodaira 2018. Moderate hypofractionation for T1 glottic cancer is the preferred regimen per NCCN guidelines. Somewhat beyond the scope of this report, but worth noting for awareness, is the literature on accelerated and hyperfractionation in head and neck cancers.	We appreciate reviewer's suggestion to separately group studies of early stage glottic cancer from trial for more advanced (or recurrent) disease. We have now reorganized those results and separately assessed certainty of evidence for early glottic cancer, and advanced or recurrent disease.
113	9	Lung Cancer. The authors are commended for compiling the trials comparing various RT fractionations for lung cancer. However, there are some important points to consider that I think are lost in the manuscript as	Thank you. As noted above, we have substantially reorganized the results to report findings separately for NSCLC and SCLC (and for SABR/SBRT within NSCLC). We have noted that none of the eligible trials directly addressed Key Question 2 by providing stratified results by patient or disease characteristics. Thus, we did not identify results to

Comment #	Reviewer #	Comment	Author Response
		it currently reads and should be addressed in some detail, which would strengthen the report. First, I disagree with the answer to KQ2. Results do vary by tumor characteristics: histology matters (NSCLC vs SCLC), stage matters (early stage versus locally advanced), and location of tumor matters (peripheral, central, ultracentral). Specifically, data is supportive of ultrahypofractionation (SBRT) for early-stage NSCLC. I agree completely with considering SCLC separately from NSCLC.	answer this question. As we have separated out the studies of NSCLC and the one trial of SCLC, we cannot compare the results across these subtypes of lung cancer.
114	9	SBRT was compared against conventional radiation therapy in two trials, SPACE, and CHISEL, that are reported in this manuscript, as well as numerous non-randomized series. The CHISEL trial compared SBRT versus conventional or moderately fractionated RT in biopsy proven, FDG PET/CT staged patients with NSCLC. The SPACE trial compared SBRT to conventional and did not require biopsy proven NSCLC and did not require FDG PET/CT, thus CHISEL is more applicable to current practice. The results of CHISEL are not subtle and favor SBRT in early-stage NSCLC. Freedom from local failure (HR 0.32) strongly favored SBRT as did Lung cancer specific survival (HR 0.49). The Freedom from Local Failure was not described in the report as currently written and I think should be added. While the authors of this report describe the trial as small in total N, the trial was adequately powered. In fact, I do not think there would be equipoise for a trial to now compare SBRT versus conventional RT for most early-stage NSCLC. Rather, the comparison being made now in randomized trials (including within VA) is between SBRT and surgery for operable patients. Other unanswered questions are evaluating various fractionation regimens for ultracentral lung tumors. These important points are lost in the current version of the report which	As noted above, we have reorganized this section and separately considered results from SABR/SBRT trials in NSCLC. Regarding the inclusion of freedom from local failure, the selected outcomes of interest that would be assessed for certainty of evidence were prioritized by the operational partners and TEP for this report; however, all outcomes of interest for each trial are reported in the appendix tables. We appreciate the context of currently ongoing trials, as well as questions to be addressed by future research in this area.

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		as currently written broadly concludes that evidence is uncertain on the effects of hypofractionation in NSCLC. Given the variance with stage, I strongly recommend separating the key questions of overall survival, progression-free survival, and lung cancer specific survival, between the categories of early stage and locally advanced NSCLC. Early Stage NSCLC trials should be evaluated separately from those that include locally advanced disease. The Iyengar trial compared, for example, moderately hypofractionated versus conventional RT in patients who were ineligible for chemotherapy and were mostly Stage III. This is a very different situation than early stage NSCLC (for example CHISEL), with very different treatment volumes.	
115	9	The descriptions in the table describing radiation regimens have some errors. For example, Slawson et al, page 174, table describes 2Gy/30 Total 60 Gy (6 weeks) as hyperfractionation which is incorrect: it is conventional (or Standard). Similarly, Singh et al, page 175, table describes 20 Gy, 3 fractions, Total dose 60 Gy as hyperfractionation which is incorrect: it is ultrahypofractionation (ie SBRT).	This has been corrected.
116	9	Bladder Cancer. The authors are commended for their evaluation of hypofractionation in bladder cancer. However, there are some concerns with the report as written. The description of the BC2001 Trial (Huddart et al 2013) and its results are not reported correctly and are misinterpreted in the report as it currently reads. This should be addressed in the tables as well as the text, and will strengthen the manuscript. BC2001 did not randomize patients between hypofractionated RT and conventional RT. Rather, it randomized patients (in a 2 x 2 factorial design) to reduced high dose volume RT (RHDVRT) versus standard whole bladder RT (stRT), and also	We agree with the reviewer that this trial is not eligible. We have now removed it from the results.

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		to RT alone versus RT with chemotherapy. RHDVRT in this trial does not mean hypofractionated and stRT does not mean conventional fractionated. In RHDVRT, the full bladder was treated to a reduced dose with the gross tumor partial bladder volume receiving the full dose. In stRT, the full bladder received the full dose. In either RHDVRT or stRT, two radiation regimens were allowed: either 55 Gy in 20 fractions or 64 Gy in 32 fractions, but this was not randomized. The choice between the two was up to each participating center. Both of these regimens were considered standard RT regimens in the UK where the trial took place.	
117	9	A separate randomized Trial, Bladder Carbogen Nicotinamide (BCON), randomized patients to RT with or without carbogen. In this trial, similarly, these two radiation regimens were allowed, and again these regimens were up to the treating centers. A meta-analysis of these trials (Chaudhury et al, Lancet Oncology, 2021) aimed to compare 55 Gy in 20 fractions to 64 Gy in 32 fractions using individual patient data from the two trials. This meta-analysis concluded that the hypofractionated regimen of 55 Gy in 20 fractions was non-inferior to 64 Gy in 32 fractions for invasive locoregional control and toxicity, and is superior in regard to invasive locoregional control. Chaudhury et al Lancet Oncol . 2021 Feb;22(2):246-255. doi: 10.1016/S1470-2045(20)30607-0. PMID: 33539743. 33539743.	We appreciated this additional information about another trial involving hypofractionation in bladder cancer. Due to the choice of the radiation regimen and the key intervention studied being carbogen, the BCON trial also does not meet our eligibility criteria. As a hypofractionated radiation regimen was not randomized in either BCON or the Huddart et al. trial, meta-analysis using these data (as was done by Chaudhury et al.) would not provide high certainty results regarding the efficacy of hypofractionation.
118	10	Glottic T1 cancers have been shown in 2 randomized trials to have better local control with hypofractionation. Survival is not an issue for these cancers as they are salvaged with surgery so patients do not die from this disease. Moderate hypofractionation 55 Gy in 20 fractions has been tested in phase 2 trials and is currently being	As noted above, we have now separated out the results from trials for early stage glottic cancer, where there may not be expected differences in survival, from those for locally advanced or recurrent head and neck cancer. Although no included studies directly addressed resource utilization or cost, we do provide the length of treatment and number of sessions, as an indicator of the relative burden (on patients

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		explored in the IAEA-HYPNO trial. Again, the benefit is not survival but decreased use of resources in under-resourced settings or strained public health sectors. I unfortunately do not feel that the conclusions are written in such a way as to demonstrate a strong understanding of this literature.	and health systems) of different radiation therapies. In Discussion, we have added the importance of considering resource use (especially when comparing treatments with similar survival and toxicity outcomes).
119	11	Comments re: VAESP-D-22-00053 Hypofractionation Radiation Therapy… I focused on the Prostate section since that is my area of expertise. 1. I didn't see the Catton "PROFIT" trial. Why did that trial not make the selection of studies in Figs 8 and 9? Catton CN JCO 35:1884, 2017 is reference 39. 2. Overall I have no suggestions or edits to make.	The Catton “PROFIT” trial was not included in Figure 7 (prostate-cancer specific survival) or Figure 8 (prostate-cancer biochemical recurrence) because neither of these outcomes were reported in the publication. This study reported “biochemical clinical failure” which was a composite outcome of 4 different outcomes; it would not be appropriate to combine this outcome with biochemical recurrence, which was separately reported in other studies.

APPENDIX D. BREAST CANCER

Appendix Table 1. Risk of Bias Ratings for All Eligible Breast Cancer Trials

Trial	Outcome	Domain 1: Risk of Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk of Bias in Measurement of Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
APBI-IMRT-Florence[14,37,38]	Harms	Low	Low	Some concerns	Low	Low	Low	Some concerns
	Mortality	Low	Low	Some concerns	Low	Low	Low	Some concerns
	Survival	Low	Low	Some concerns	Low	Low	Low	Some concerns
Baillet[103]	Harms	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns	High
Das[104]	Harms	Some concerns	Some concerns	High	High	Low	Some concerns	High
	Survival	Some concerns	Some concerns	High	High	Low	Some concerns	High
FAST[15,35]	Harms[15]	Low	Low	Low	Low	Low	Low	Low
	Mortality[15]	Low	Low	Low	Low	Low	Low	Low
	Survival[15,35]	Low	Low	Low	Low	Low	Low	Low
FAST-Forward[16,17]	Harms[17]	Low	Low	Low	Some concerns	Low	Low	Some concerns
	Mortality[16]	Low	Low	Low	Low	Low	Low	Low
	Survival[16]	Low	Lowf	Low	Low	Low	Low	Low
Hosseini[105]	Harms	Some concerns	Low	Low	Some concerns	Low	Some concerns	High
Hou[106]	Mortality	Some concerns	Low	Low	Low	Low	Low	High
	Survival	Some concerns	Low	Low	Low	Low	Low	High
Kalita[107]	Harms	Some concerns	Some concerns	High	Low	Low	Some concerns	High
King[30]	QoL	Low	Low	Low	Low	Some concerns	Low	Some concerns
Kumbhaj[108]	Harms	Some concerns	Some concerns	High	High	High	Some concerns	High
	Survival	Some concerns	Some concerns	High	High	Low	Some concerns	High
Maiti[109]	Harms	High	High	High	Some concerns	Low	Low	High
	Mortality	High	High	High	Low	Low	Low	High
	Survival	High	High	High	Some concerns	Low	Low	High
Offersen[29]	Mortality	Low	Low	Low	Low	Low	Low	Low
	Survival	Low	Low	Low	Low	Low	Low	Low
Owen[13]	Survival	Low	Some concerns	Some concerns	Low	Low	Low	Some concerns
RAPID[31,36]	Harms[31,36]	Low	Low	Low	Some concerns	Low	Low	Some concerns
	Mortality[31]	Low	Low	Low	Low	Low	Low	Low
	Survival[31]	Low	Low	Low	Low	Low	Low	Low
Purohit[110]	Harms	Some concerns	Some concerns	High	High	Some concerns	Some concerns	High
Rastogi[111]	Harms	Some concerns	Low	Some concerns	High	Some concerns	Some concerns	High
	Survival	Some concerns	Low	Some concerns	High	Some concerns	Some concerns	High

Trial	Outcome	Domain 1: Risk of Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk of Bias in Measurement of Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
Rodriguez-Li[112,113]	Harms[112,113]	Some concerns	Some concerns	High	Some concerns	Low	Low	High
	Mortality[112]	Some concerns	Some concerns	High	Low	Low	Low	High
	Survival[112,113]	Some concerns	Some concerns	High	Low	Low	Low	High
Schmeel[19]	Harms	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
Shahid[114]	Harms	Some concerns	Some concerns	High	Some concerns	Low	Low	High
	Mortality	Some concerns	Some concerns	High	Some concerns	Low	Low	High
	Survival	Some concerns	Some concerns	High	Some concerns	Low	Low	High
NCT01266642[23,24,34]	Harms[23,24]	Some concerns	Low	Low	Low	Low	Low	Some concerns
	Survival[24]	Some concerns	Low	Low	Some concerns	Low	Some concerns	High
	QoL[23,24,34]	Some concerns	Low	Low	Some concerns	Low	Low	Some concerns
Spooner[20]	Mortality	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
	Survival	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
START[11,12,33]	Mortality	Low	Low	Low	Low	Low	Low	Low
	Survival	Low	Low	Low	Low	Low	Low	Low
Swanick[115]	QoL	Some concerns	Low	Low	Some concerns	Some concerns	Low	High
Taher[116]	Harms	High	Low	High	Low	Some concerns	Some concerns	High
TomoBreast[21,22]	Harms[22]	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
	QoL[21]	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
Van Hulle[18]	Harms	Some concerns	Some concerns	Some concerns	Low	Low	Low	Some concerns
	QoL	Some concerns	Some concerns	Some concerns	Low	Low	Low	Some concerns
Wang 2019[28]	Harms	Low	Low	Low	Low	Low	Low	Low
	Mortality	Low	Low	Low	Low	Low	Low	Low
	Survival	Low	Low	Low	Low	Low	Low	Low
Wang 2020[27]	Harms	Low	Low	Low	Low	Low	Low	Low
	Mortality	Low	Low	Low	Low	Low	Low	Low
	Survival	Low	Low	Low	Low	Low	Low	Low
NCT00156052[25,26,32]	Harms[25,32]	Low	Low	Low	Some concerns	Low	Low	Some concerns
	Mortality[25,26]	Low	Low	Low	Low	Low	Low	Low
	Survival[25,26]	Low	Low	Low	Low	Low	Low	Low
	QoL[32]	Low	Low	Some concerns	High	High	Low	High
Yadav[117]	Harms	High	Some concerns	High	Low	Low	Low	High
Zhao 2016[118]	Harms	Some concerns	Some concerns	Some concerns	Some concerns	Low	Low	High
	Mortality	Some concerns	Some concerns	Some concerns	Some concerns	Low	Low	High
	Survival	Some concerns	Some concerns	Some concerns	Some concerns	Low	Low	High

Trial	Outcome	Domain 1: Risk of Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk of Bias in Measurement of Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
Zhao 2017[119]	Harms	Some concerns	Some concerns	High	Low	Low	Low	High
	Mortality	Some concerns	Some concerns	High	Low	Low	Low	High
	Survival	Some concerns	Some concerns	High	Low	Low	Low	High

Appendix Table 2. Study Characteristics for All Eligible Breast Cancer Trials

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
Hypofractionation vs Conventional Radiation						
BIG3-07/TROG 07.01 NCT00470236 (King, 2020)[30] SOME CONCERNS 11 countries (118 sites) National Health and Medical Research Council, Susan G. Komen for the Cure, Breast Cancer Now, OncoSuisse Federation Against Cancer, Dutch Cancer Society 2 years	**Inclusion:** Women ≥ 18 years old with completely excised DCIS and increased risk of local recurrence (age <50 years, or in those ≥ 50 years old, symptomatic presentation, palpable tumour, tumour ≥ 15 mm, multifocal disease, intermediate or high nuclear grade, central necrosis, comedo histology, and/or radial surgical margin < 10 mm **Exclusion:** NR Other treatments: • Radiation boost • Hormone therapy	N = 532 ≥ 50 years old: 445 (84) Race: NR Tumor grade: NR	42.5 Gy/16 fractions over 3.5 weeks	N = 615 ≥ 50 years old: 495 (80) Race: NR Tumor grade: NR	50 Gy/25 fractions over 5 weeks	**Primary endpoint:** Local recurrence (NR) **QoL**
DBCG HYPO NCT00909818 (Offersen, 2020)[29] LOW	**Inclusion:** Women > 40 years old, had breast-conserving surgery without	N = 917 Median age (IQR): 59 (41,82) Race: NR	40 Gy/15 fractions over 3 weeks	N = 937 Median age (range): 59 (42-83) Race: NR	50 Gy/25 fractions over 5 weeks	**Primary endpoint:** Cosmetic (breast induration at 3 years) **Survival**

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics N Baseline Characteristics (n, %) Dose/Fraction Total Dose Time	Conventional Characteristics N Baseline Characteristics (n, %) Dose/Fraction Total Dose Time	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
Denmark, Germany, and Norway (8 centers) Danish Cancer Society, Centre for Interventional Research in Radiation Oncology, and Danish Comprehensive Cancer Center Radiotherapy Group 9 years	immediate reconstruction, early stage (pT1/2, pN0/1, M0) or DCIS requiring radiotherapy to the residual breast only **Exclusion:** Need for regional lymph node radiation, previous breast cancer or bilateral, past radiation of thorax or breast, breast implants, comorbidity which may increase sensitivity to radiation (*eg*, dermatomyositis, or symptomatic heart/lung disease), or any difficulty completing protocol Other treatments: • Radiation boost • Chemotherapy • Hormone therapy • Trastuzumab	DCIS: 123 (13) Tumor stage: T1a: 64 (8) T1b: 191 (24) T1c: 403 (51) T2: 136 (17) Node status: N0: 683 (86) N1: 76 (10) Isolated tumor cells: 35 (4)	DCIS: 123 (13) Tumor stage: T1a: 48 (6) T1b: 196 (24) T1c: 414 (51) T2: 156 (19) Node status: N0: 661 (81) N1: 107 (13) Isolated tumor cells: 46 (6)	• Locoregional recurrence • OS

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
DRKS00017763 (Schmeel, 2020)[19] SOME CONCERNS Germany (University Hospital, Bonn) Funding NR 6 weeks	**Inclusion:** Women > 18 years old, had breast-conserving surgery **Exclusion:** Metastatic disease, chemotherapy, need for regional nodal irradiation, previous radiation to ipsilateral breast, breast-reconstruction or any previous surgery in radiation area, active smoking, active skin condition, use of topical or oral corticosteroids, tattoos in the irradiation area Other treatments: NR	N = 71 Mean age (SD): 59.9 (±10.7) Race N (%): Caucasian: 70 (99) Cancer staging: T1: 48 (68) T2: 16 (23)	40.05 Gy/15 fractions	N = 72 Mean age (SD): 59.0 (11.7) Caucasian: 70 (97) Cancer staging: T1: 43 (60) T2: 16 (23)	50 Gy/25 fractions	**Primary endpoint:** Dermatitis, grade ≥ 2
NCT00156052 (Whelan, 2010[25]; Whelan, 2002[26]; Arsenault, 2020[32]) LOW Canada (8 centers)	**Inclusion:** Women with invasive breast cancer, had lumpectomy and negative axillary lymph nodes **Exclusion:** Cancer involving margins of excision, tumor >	N = 622 ≥ 60 years old: 277 (45) Race: NR Tumor grade:	42.5/16 fractions over 22 days	N = 612 ≥ 60 years old: 309 (51) Race: NR Tumor grade:	50 Gy/25 fractions over 35 days	**Primary endpoint**: Local recurrence **Survival:** • OS • Disease-free **Harms:**

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
Canadian Breast Cancer Research alliance, Canadian Cancer Society 10 years	5 cm, breast width >25 cm Other treatments • Chemotherapy • Hormone therapy	I: 215 (35) II: 244 (39) III: 117 (19) Unknown: 46 (7)		I: 209 (34) II: 236 (39) III: 116 (19) Unknown: 51 (8)		Toxicity (acute): • Skin (some concerns) Toxicity (late): • Skin (some concerns) **QoL** (high)
NCT00793962 (Wang, 2019)[28] LOW China (1 site) National Key Projects of Research and Development of China, Chinese Academy of Medical Science Innovation Fund for Medical Sciences, and Beijing Marathon of Hope, Cancer Foundation of China 5 years (median follow-up 59.5 months)	**Inclusion:** Women 18–75 years old, had mastectomy and axillary dissection with negative margions and ≥ 4 positive axillary lymph nodes or primary T3/4 disease; Karnofsky score ≥ 60% **Exclusion:** Bilateral breast cancer, positive supraclavicular or internal mammary node, distant metastasis, had breast reconstruction or previous radiation, had past or current other cancer, or other serious	N = 406 ≥ 50 years old: 194 (48) Race: NR Cancer stage: Stage 3: 377 (94) Tumor grade: 3: 121 (30)	43.5 Gy/15 fractions over 3 weeks	N = 414 ≥ 50 years old: 202 (49) Race: NR Cancer stage: Stage 3: 384 (94) Tumor grade: 3: 111 (27)	50 Gy/25 fractions over 5 weeks	**Primary endpoint:** Locoregional recurrence **Survival** • OS • Disease-free **Harms:** Toxicity (acute) • Skin • Pneumonitis Toxicity (late): • Skin • Lymphoedema

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
	comorbidity (drug use, mental illness, collagen vascular disease, *etc*) Other treatments: • Chemotherapy • Hormone therapy • Trastuzumab					
NCT01266642 (Shaitelman, 2015[23]; Shaitelman, 2018[120]; Weng, 2021[121]) SOME CONCERNS US (1 site) American Society of Clinical Oncology, Breast Cancer Research Foundation, Cancer Prevention and Research Institute of Texas, University of Texas MD Anderson Cancer Center, gift from	**Inclusion**: Women ≥ 40 years, DCIS or stage I-II breast cancer (Tis-T2, N0-N1a, M0), breast-conserving surgery with negative margins (defined as "no tumor on ink") and no need for third field to cover regional lymph nodes **Exclusion**: Ongoing treatment for another cancer, past breast cancer, bilateral breast cancer, prior overlapping irradiation, or lack of fluency in English or Spanish.	N = 138 ≥ 50 years old: 119 (86) Race: White: 99 (72) Hispanic: 20 (15) Black: 17 (12) Asian: 2 (1) DCIS: 24 (17) Node status: pN0: 95 (69) pN1mic: 6 (4) pN1a: 7 (5) Tumor grade: 1: 34 (25) 2: 73 (53)	2.66 Gy/fraction 42.56 Gy duration NR	N = 149 ≥ 50 years old: 136 (92) Race: White: 116 (78) Hispanic: 16 (11) Black: 15 (10) Asian: 2 (1) DCIS: 39 (26) Node status: pN0: 101 (68) pN1mic: 14 (9) pN1a: 1 (1) Tumor grade: 1: 40 (27) 2: 70 (47)	2.0 Gy/fraction 50 Gy duration NR	**Primary endpoint:** cosmetic (3 years) **Survival** (high): • OS • Local recurrence **Harms:** Toxicity (acute) • Overall • Skin Toxicity (late) • Overall • Skin • Pneumonitis • Lymphedema **QoL**

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
Ann and Clarence Cazalot, and NCI 5 years	Other treatments: • Boost radiation • Chemotherapy	3: 30 (22)		3: 39 (26)		
NCT01413269 (Wang, 2020)[27] LOW China (4 centers) Chinese Academy of Science 5 years (median follow-up 73.5 months)	**Inclusion:** Women 18-70 years old with invasive breast cancer, T1/2 disease, had undergone lumpectomy and axillary dissection (or sentinel node biopsy if sentinel nodes were negative) with negative margins (microscopically tumor-free ≥1 mm) **Exclusion:** Supraclavicular/ internal mammary node or distant metastasis, received neoadjuvant chemotherapy, bilateral breast cancer, or had undergone	N = 365 ≥ 45 years old: 216 Race: NR Staging: I: 247 (68) II: 106 (29) III: 12 (3) Tumor grade: 1-2: 228 (63) 3: 101 (28) Unknown: 36	2.9 Gy/fraction 43.5 Gy 3 weeks (+ boost 8.7 Gy in 3 fractions over 3 days)	N = 364 ≥ 45 years old: 223 Race: NR Staging: I: 248 (68) II: 104 (29) III: 12 (3) Tumor grade: 1-2: 248 (72) 3: 82 (23) Unknown: 34	2 Gy/fraction 50 Gy 5 weeks (+ boost 10 Gy in 5 fractions over 1 week)	**Primary endpoint**: Local recurrence **Survival:** • Locoregional recurrence • Disease-free • OS **Harms:** Toxicity (acute) • Skin • Pneumonitis Toxicity (late) • Lymphedema • Lung fibrosis

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
	previous irradiation or malignancies Other treatments: • Chemotherapy					
START A ISRCTN59368779 (START Trialists, 2008[11]; Haviland, 2013[33]) LOW UK (17 sites) Cancer Research UK, UK Medical Research Council, Department of Health Median follow-up 9.3 years	**Inclusion:** Women ≥ 18 years, invasive breast cancer (pT1-3a pN0-1M0) requiring radiotherapy after BCS or mastectomy with clear tumor margins ≥1 mm and no immediate reconstruction **Exclusion:** NR Other treatments: • Chemotherapy • Hormone therapy	**Arm A:** N = 750 Mean age (SD): 57.0 (±10.7) Race: NR Cancer stage: *Tumor size in cm* <1: 26 (4) 1-: 347 (46) 2-: 203 (27) 3-: 169 (23) Not known: 5 (1%) *Node status* N0: 536 (72) N1: 197 (26) Not known: 17 (2) Tumor grade: 1: 150 (20) 2: 379 (51)	**Arm A:** 3.2 Gy/fraction 41.6 Gy 5 weeks	N = 749 Mean age (SD): 57.6 (±10.5) Race: NR Cancer stage: *Tumor size in cm* <1: 24 (3) 1-: 362 (48) 2-: 202 (27) 3-: 156 (21) Not known: 5 (1) *Node status* N0: 514 (69) N1: 222 (30) Not known: 13 (2) Tumor grade: 1: 157 (21) 2: 369 (49)	2.0 Gy/fraction 50 Gy 5 weeks	**Primary endpoint:** Locoregional recurrence **Survival:** • OS • Local recurrence • Distant metastasis • Disease-free

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics N Baseline Characteristics (n, %)	Hypofractionation Characteristics Dose/Fraction Total Dose Time	Conventional Characteristics N Baseline Characteristics (n, %)	Conventional Characteristics Dose/Fraction Total Dose Time	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		3: 207 (28)		3: 212 (28)		
		Arm B: N = 737 Mean age (SD): 57.1 (±10.5) Race: NR Cancer stage: *Tumor size in cm* <1: 24 (3) 1-: 355 (48) 2-: 198 (27) 3-: 157 (21) Not known: 3 (0.3) *Node status* N0: 497 (67) N1: 224 (30) Not known: 16 (2) Tumor grade: 1: 149 (20) 2: 368 (50) 3: 210 (29)	**Ar** 3.3 3.0 Gy/fraction 39 Gy 5 weeks			

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
START B ISRCTN59368779 (START Trialists, 2008[12]; Haviland, 2013[33]) LOW UK (23 sites) Cancer Research UK, UK Medical Research Council, Department of Health Median follow-up 9.9 years	**Inclusion:** Women ≥ 18 years, invasive breast cancer (pT1-3a pN0-1M0) requiring radiotherapy after BCS or mastectomy with clear tumor margins ≥1 mm and no immediate reconstruction **Exclusion:** NR Other treatments: • Chemotherapy • Hormone therapy	N=1110 Mean age (SD): 57.8 (±9.5) Race: NR Cancer stage: *Tumor size in cm* <1: 167 (15) 1-: 542 (49) 2-: 288 (26) 3-: 107 (10) Not known: 6 (0.5) *Node status* N0: 804 (72) N1: 266 (24) Not known: 40 (4) Tumor grade: 1: 311 (28) 2: 532 (48) 3: 248 (22)	2.67 Gy/fraction 40.05 Gy 3 weeks	N=1105 Mean age (SD): 57.0 (±10.4) Race: NR Cancer stage: *Tumor size in cm* <1: 151 (14) 1-: 552 (50) 2-: 287 (26) 3-: 113 (10) Not known: 2 (0.2) *Node status* N0: 831 (75) N1: 238 (22) Not known: 36 (3) Tumor grade: 1: 306 (28) 2: 518 (47) 3: 261 (24)	2.0 Gy/fraction 50 Gy 5 weeks	**Primary endpoint:** Locoregional recurrence **Survival:** • OS • Local recurrence • Distant metastasis • Disease-free
START Pilot Trial # NR (Owen, 2006)[13] SOME CONCERNS UK (2 sites)	**Inclusion:** < 75 years old, operable invasive breast cancer (T1-3, N0/1, M0), had breast-preserving surgery and complete macroscopic resection	Arm 1 (42.9 Gy): N = 466 Arm 2 (39 Gy): N= 474	Arm 1: 3.3 Gy/fraction 42.9 Gy 5 weeks Arm 2: 3 Gy/fraction	N = 470 Demographics and cancer stage by arm NR	2 Gy/fraction 50 Gy 5 weeks	**Primary endpoint:** Cosmetic (late change in breast appearance) **Survival:** • Local recurrence

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
Marks and Spencer PLC, Cancer Research UK 10 years	**Exclusion**: NR Other treatments: • Radiation boost (2 Gy/fraction x 7) • Chemotherapy • Hormone therapy	Demographics and cancer stage by arm NR	39 Gy 5 weeks			
Trial Name/# NR (Spooner, 2012)[20] SOME CONCERNS UK (3 sites) Cancer Research UK 15 years (median follow-up 16.9 years)	**Inclusion:** Women with stage I/II breast cancer, had complete surgical resection, tumor <5 cm, no clinically palpable axillary nodes, no systemic disease **Exclusion:** Past cancer, or history of radiation or chemotherapy Other treatments: • Chemotherapy • Tamoxifen (all)	N = 181 Median age (IQR): 59 (48-66) for whole group, NR by arm Race: NR Tumor grade: NR (by arm)	2.66 Gy/fraction 40 Gy 3 weeks	N = 177 Median age (IQR): 59 (48-66) for whole group, NR by arm Race: NR Tumor grade: NR (by arm)	2 Gy/fraction 50 Gy 5 weeks	**Primary endpoint:** locoregional recurrence (5 years) **Survival:** • OS • Disease-free
TomoBreast NCT00459628 (Nan Parijs, 2012[22]; Versmessen, 2012[21])	**Inclusion:** Women ≥ 18 years old, stage I-II (T1-3N0M0 or T1-2N1M0), had BCS or mastectomy with clear margins and	N = 59 ≥ 50 years old: 22 (59) Race: NR	2.8 Gy/fraction 42 Gy 3 weeks	N = 62 ≥ 50 years old: 22 (69) Race: NR	2 Gy/fraction 50 Gy 5 weeks	**Primary endpoint:** Lung and cardiac function changes (3 years) **Harms:** Toxicity (acute)

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
SOME CONCERNS Belgium (1 site) Foundation against Cancer 3 years (median follow-up 28 months)	axillary node dissection or sentinel node biopsy, had pre-operative imaging (CT, MRI, and/or PET) **Exclusion:** Past breast or thoracic radiation, psychiatric or addictive disorder Other treatments • Boost radiation • Chemotherapy • Hormone therapy	Tumor size: T1: 39 (66) T2: 20 (34) Node status: N0: N1: Tumor grade: 1: 11 (30) 2: 18 (49) 3: 8 (22) Unknown: 0		Tumor size: T1: 38 (61) T2: 24 (39) Node status: N0: N1: Tumor grade: 1: 11 (34) 2: 8 (25) 3: 10 (31) Unknown: 3		• Skin **QoL**

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
Ultra-hypofractionation vs Conventional Radiation						
FAST NCT00107497 (Brunt, 2020[35]; FAST Trialists, 2011[15]) LOW UK (18 sites) National Health Service, Cancer Research UK/Institute of Cancer 10 years	**Inclusion**: Women ≥ 50 years old, had breast conserving surgery, tumor < 3.0 cm, complete microscopic resection of tumor, and negative axillary node status **Exclusion**: Mastectomy, lymphatic radiotherapy, tumor bed boost dose and neoadjuvant or adjuvant chemotherapy Other treatments: • Hormone therapy	**Arm A:** N = 308 Mean age (SD): 62.9 (±7.5) Race: NR Tumor size: <1 cm: 84 (30) 1-2 cm: 165 (54) ≥2 cm: 59 (19) Tumor grade: 1: 113 (37) 2: 159 (52) 3: 35 (11) Unknown: 1 (0.3)	**Arm A:** 30 Gy/5 fractions over 5 weeks	N = 302 Mean age (SD): 63.1 (±7.2) Race: NR Tumor size: <1 cm: 90 (30) 1-2 cm: 166 (55) ≥2 cm: 46 (15) Tumor grade: 1: 94 (31) 2: 176 (58) 3: 29 (10) Unknown: 3 (1)	50 gy/25 fractions over 5 weeks	**Primary endpoint:** Cosmetic (change in breast appearance at 2 years) **Survival:** • OS • Local recurrence • Regional metastasis • Distant metastasis • Breast cancer-specific deaths **Harms:** Toxicity (acute) • Skin
		Arm B: N = 305 Mean age (SD): 62.7 (±6.8) Race: NR Tumor size: <1 cm: 87 (29) 1-2 cm: 160 (53) ≥2 cm: 58 (19) Tumor grade: 1: 102 (33)	**Arm B:** 28.5 Gy/5 fractions over 5 weeks			

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics N Baseline Characteristics (n, %)	Hypofractionation Characteristics Dose/Fraction Total Dose Time	Conventional Characteristics N Baseline Characteristics (n, %)	Conventional Characteristics Dose/Fraction Total Dose Time	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		2: 168 (55) 3: 34 (11) Unknown: 1 (0.3)				
Ultra-hypofractionation vs Moderate Hypofractionation						
FAST-Forward ISRCTN19906132 (Brunt, 2020[16]; Brunt, 2016[17]) LOW UK (97 sites) National Institute for Health Research, Cancer Research UK 5 years (median follow-up 71.5 months)	**Inclusion**: ≥ 18 years old with stage pT1-3 pN0-1 M0 breast cancer, had breast conservation surgery or mastectomy, axillary staging and/or dissection, and complete microscopic excision of primary tumor **Exclusion**: Contralateral breast cancer, or past cancer (except if non-breast malignancy was treated with curative intent and ≥5 years disease free),breast reconstruction using implants, concurrent chemotherapy, or radiation to any regional lymph node areas (except	**Arm A:** N = 1367 Median age (IQR): 61 (53, 67) Race: NR Cancer stage: *Tumor* T1mi: 5 (0.4) T1a: 68 (5.0) T1b: 270 (19.8) T1c: 601 (44.0) T2: 389 (28.5) T3: 30 (2.2) Unknown: 4 (0.3) *Node* N0: 1124 (82.2) N1: 243 (17.8) Unknown: 0	**Arm A:** 27 Gy/5 fractions over 1 week	N = 1361 Median age (IQR): 60 (53, 66) Race: NR Cancer stage: *Tumor* T1mi: 4 (0.3) T1a: 69 (5.1) T1b: 258 (19.0) T1c: 612 (45.0) T2: 394 (28.9) T3: 31 (1.5) Unknown: 3 (0.2) *Node:* N0: 1103 (81.0) N1: 257 (18.9) Unknown: 1 (0.1)	40 Gy/15 fractions over 3 weeks	**Primary endpoint:** Local recurrence **Survival:** • OS • Locoregional recurrence • Distant metastases **Harms** (some concerns): Toxicity (acute) • Skin
		Arm B: N = 1368 Median age (IQR): 61 (52, 66) Race: NR	**Arm B:** 26 Gy/5 fractions over 1 week			

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics N Baseline Characteristics (n, %) Dose/Fraction Total Dose Time		Conventional Characteristics N Baseline Characteristics (n, %) Dose/Fraction Total Dose Time		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
	lower axilla included in tangential fields to breast/chest wall) Other treatments: • Chemotherapy • Hormone therapy • Trastuzumab	Tumor information: *Tumor stage:* T1mi: 6 (0.4) T1a: 51 (3.7) T1b: 256 (18.7) T1c: 602 (44.0) T2: 424 (31.0) T3: 25 (1.8) Unknown: 4 (0.3) *Node status:* N0: 1110 (81.1) N1: 256 (18.7) Unknown: 2 (0.1)				
YO-HAI5 NCT03677427 (Van Hulle, 2021)[18] SOME CONCERNS Belgium (single center) University Hospital, Ghent 2-4 weeks	**Inclusion**: Women ≥ 18 years old, treated with BCS and adjuvant whole breast radiation (± boost) **Exclusion**: Lymph node metastases or distant metastases; bilateral breast irradiation or history of radiation to the same region; life expectancy < 2 years; planned reconstructive surgery; conditions	N = 106 Median age (range): 59 (37-83) Race: NR Staging (pTNM): T1N0M0: 86 (81) T1N1(mi)M0: 4 (4) T2N0M0: 11 (10) TisN0M0: 5 (5)	5.7 Gy/fraction 28.5 Gy 10-12 days	N = 94 Median age (range): 62 (26-84) Race: NR Staging (pTNM): T1N0M0: 77 (82) T1N1(mi)M0: 2 (2) T2N0M0: 7 (7) TisN0M0: 8 (9)	2.67 Gy/fraction 40.05 Gy 10-12 days	**Primary endpoint**: Cosmetic (breast retraction at 2 years) **Harms:** Toxicity (acute) • Skin **QoL**

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
	making toxicity evaluation difficult (*eg*, skin disorders); inability to follow protocol **Other treatments:** • Chemotherapy • Hormone therapy • Trastuzumab					
APBI vs WBI						
APBI-IMRT Florence NCT02104895 (Meattini, 2015[37]; Livi, 2015[14]; Meattini, 2020[38]) SOME CONCERNS Italy (1 site) Funding: none Median follow-up 10.7 years	**Inclusion**: Women > 40 years old with early cancer (tumor ≤ 2.5 cm) "suitable for BCS" **Exclusion**: Past cancer solid Tumor); history cardiovascular disease (*eg*, heart failure, angina); FEV_1 <1 L/m; extensive intraductal carcinoma; multiple foci cancer; final surgical margins <5 mm; or absence of surgical clips in tumor bed.	N = 260 ≥ 60 years: 168 (61) Cancer stage: *Tumor:* pTis: 23 (9) pT1a: 28 (11) pT1b: 98 (38) pT1c: (97 (37) pT2: 14 (5) *Node status:* N0: 241 (89) N1: 19 (7) Unknown: 9 (4) Tumor grade: 1: 124 (48)	APBI-IMRT: 30 Gy/5 fractions over 2 weeks	N = 260 ≥ 60 years: 139 (53) Cancer stage: *Tumor:* pTis: 32 (12) pT1a: 18 (7) pT1b: 88 (34) pT1c: 107 (41) pT2:15 (6) *Node status:* N0: 229 (82) N1: 31 (13) Unknown: 14 (5) Tumor grade: 1: 103 (40)	50 Gy/25 fractions (+ boost 2 Gy/fraction x 5 fractions)	**Primary endpoint:** LC **Survival:** • OS • Locoregional recurrence • Distant metastasis • Breast cancer-specific survival **Harms** Toxicity (acute) • Overall • Skin Toxicity (late) • Overall • Skin

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
	Other treatments: • Chemotherapy • Hormone therapy	2: 110 (38) 3: 26 (10)		2: 124 (48) 3: 33 (13)		
RAPID NCT00282035 (Whelan, 2019[31]; Olivotto, 2013[122]) SOME CONCERNS 3 countries (33 sites) Canadian Institutes for Health Research, Canadian Breast Cancer Research Alliance Median follow-up 8.6 years	**Inclusion:** Women ≥ 40 years old with DCIS or invasive ductal carcinoma who had BCS with microscopically clear margins, and negative axillary nodes (by sentinel node biopsy or axillary dissection for invasive cancer, or clinical exam for DCIS) **Exclusion:** Tumor > 3 cm, lobular carcinoma, >1 primary breast tumor Other treatments: • Chemotherapy • Hormone therapy	N = 1070 ≥ 50 years old: 939 (88) Race: NR DCIS: 191 (18) Invasive cancer: 879 (82) Staging (invasive cancer): Tumor size: <1.5cm: 613 (70) ≥1.5cm: 266 (30) Node status: pN0: 874 (99) pNi+,pNMi: 5 (<1) Tumor grade: 1: 387 (44) 2: 353 (40) 3: 133 (15) Unknown: 6 (1)	APBI: 3.85 Gy/fraction 38.5 Gy 5-8 days (87% 3DCRT, 10% IMRT)	N = 1065 ≥ 50 years old: 939 (88) Race: NR DCIS: 190 (18) Invasive cancer: 875 (82) Staging (invasive cancer): Tumor size: <1.5cm: 587 (67) ≥1.5cm: 288 (33) Node status: pN0: 865 (99) pNi+,pNMi: 10 (1) Tumor grade: 1: 362 (41) 2: 361 (41) 3: 143 (16) Unknown: 9 (1)	WBI: 82% received: 2.65 Gy/fraction 42.5 Gy 18% received: 2 Gy/fraction 50Gy 4-5 weeks (+boost in 21%, 10 Gy in 4-5 fractions)	**Primary endpoint:** local recurrence **Survival:** • OS • Disease-free **Harms:** Toxicity (acute) • Overall • Skin • Pneumonitis Toxicity (late) • Overall

Notes. *Unable to extract.

Abbreviations. 3DCRT=three-dimensional conformal radiation therapy; APBI=accelerated partial breast irradiation; BCS=breast-conserving surgery; CT=computed tomography; DCIS=ductal carcinoma in situ; IMRT=intensity-modulated radiation therapy; MRI=magnetic resonance imaging; NR=not reported; OS=overall survival; PET=positron emission tomography; QoL=quality of life; SD=standard deviation; TNM=TNM Classification of Malignant Tumors; UK=United Kingdom; US=United States; WBI=whole-breast irradiation.

Appendix Table 3. Detailed Results for Survival Outcomes for Breast Cancer Trials Rated "Low" or "Some Concerns" Risk of Bias

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
Breast-cancer-specific deaths	*Ultra-hypofractionation vs Conventional Radiation*				
	FAST **NCT00107497** (FAST Trialists, 2011)[15] Low	10 years	Arm A (30 Gy): 2/305 (1) Arm B (28.5 Gy): 6/302 (2)	2/301 (1)	Comparison NR
	APBI vs WBI				
	APBI-IMRT Florence **NCT02104895** (Meattini, 2020)[38] Some concerns	10 years	5 years: 2/260 (1) 7 years: 3/260 (1) 10 years: 5/260 (2)	5 years: 3/260 (1) 7 years: 6/260 (2) 10 years: 8/260 (3)	HR (95% CI): 0.65 (0.21, 1.99), P = 0.45
Overall survival	*Hypofractionation vs Conventional Radiation*				
	DBCG HYPO NCT00909818 (Offersen, 2020)[29] LOW	9-year survival	93% (deaths: 60/917)	93% (deaths: 61/937)	HR (95% CI): 0.98 (0.65, 1.47) RD (95% CI): 0.0% (−2.9%, 2.8%) P = 0.93
	NCT00156052 (Whelan, 2002[26], 2010[25]) LOW	10 years	84.6% (deaths: 122/622)	84.4% (deaths: 126/612)	RD (95% CI): -0.2% (-4.3%, 4.0%), P = 0.79
		5 years (median follow-up 69 months)	92.3% (deaths: 48/622)	91.7% (deaths: 51/612)	P = 0.78
	NCT00793962 (Wang, 2019)[28] LOW	Deaths all-cause, median follow-up 59.5 months	84% (deaths: 63/401)	86% (deaths: 56/409)	HR (95% CI): 1.13 (0.78, 1.62) Log-rank P = 0.53

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
	NCT01413269 (Wang, 2020)[27] LOW	Death from any cause at 5 years (median follow-up 73.5 months)	97.5% (deaths: 11/365)	98% (deaths: 9/364)	HR (95% CI): 1.20 (90.50, 2.80) Log-rank P = 0.680
	START A (START Trialists, 2008[11]; Haviland, 2013[33]) LOW	Median follow-up 5.1 and 9.3 years	Arm A (41.6 Gy): 5 years: 88% (deaths: 89/750) 9 years: 83% (deaths: 128/750) Arm B (39 Gy): 5 years: 89% (deaths: 83/737) 9 years: 82% (deaths: 134/737)	5 years: 89% (deaths: 84/749) 9 years: 83% (deaths: 130/749)	HR (95% CI): Arm A (41.6 Gy): 1.04 (0.77, 1.40), P = 0.81 Arm B (39 Gy): 1.00 (0.74, 1.36), P = 0.99
	START B ISRCTN59368779 (START Trialists, 2008[12]; Haviland, 2013[33]) LOW	Median follow-up 6 and 9.9 years	6 years: 90% (deaths: 107/1110) 10 years: 86% (deaths: 159/1110)	6 years: 88% (deaths: 138/1105) 10 years: 83% (deaths: 192/1105)	HR (95% CI): 0.80 (0.65, 0.99), P = 0.04
	Trial Name/# NR (Spooner, 2012)[20] SOME CONCERNS	Deaths at 2, 5, 10, 15 years	2 years: 94% (deaths: 11/181) 5 years: 85% (deaths: 27/181) 10 years: 70% (deaths: 54/181)	2 years: 92% (deaths: 7/177) 5 years: 81% (deaths: 34/177) 10 years: 67% (deaths: 58/177)	HR (95% CI): 1.02 (0.76, 1.35)

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
			15 years: 53% (deaths: 85/181)	15 years: 52% (deaths: 85/177)	
	Ultra-hypofractionation vs Conventional Radiation				
	FAST NCT00107497 (FAST Trialists, 2011)[15] LOW	Median follow-up at 3.1 years	Arm A (30 Gy): 98% (deaths 5/305) Arm B (28.5 Gy): 96% (deaths 12/302)	98% (deaths: 6/301)	Comparison NR
	Ultra-hypofractionation vs Moderate Hypofractionation				
	FAST-Forward ISRCTN19906132 (Brunt, 2020)[16] LOW	Deaths any cause, 5 years (median follow-up 71.5 months)	Arm A (27 Gy): 92% (deaths: 105/1367) Arm B (26 Gy): 93% (deaths: 90/1368)	93% (deaths: 92/1361)	HR (95% CI): Arm A (27 Gy): 1.12 (0.85, 1.48), P = 0.42 Arm B (26 Gy): 0.96 (0.72, 1.28), P = 0.78
	APBI vs WBI				
	APBI-IMRT Florence NCT02104895 (Meattini, 2020)[38] SOME CONCERNS	All cause deaths, 10 years	5 years: 98% (deaths: 5/260) 7 years: 97% (deaths: 9/260) 10 years: 92% (deaths: 18/260)	5 years: 97% (deaths: 8/260) 7 years: 94% (deaths: 15/260) 10 years: 92% (deaths: 20/260	HR (95% CI): 0.95 (0.50, 1.79), P = 0.86
	RAPID NCT00282035 (Whelan, 2019)[31] SOME CONCERNS	Median follow-up 8.6 years	93% (deaths: 76/1070)	94% (deaths: 64/1065)	HR (95% CI): 1.18 (0.84, 1.64)

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
Disease-free survival	*Hypofractionation vs Conventional Radiation*				
	NCT00156052 (Whelan, 2002)[26] LOW	Free from events (local, regional, and distant recurrence; deaths) within 5 years (median follow-up 69 months)	85.4% (events: 91/622)	87.1% (events: 79/612)	P = 0.37
	NCT00793962 (Wang, 2019)[28] LOW	Free from locoregional recurrence, distant metastasis, or death, median follow-up 59.5 months	76% (events: 96/401)	73% (events: 109/401)	HR (95% CI): 0.88 (0.67, 1.16) Log-rank P = 0.43
	NCT01413269 (Wang, 2020)[27] LOW	5-year survival from events (local or locoregional recurrence, distant metastasis, or death due to any cause)	93% (events: 32/365)	94% (events: 26/364)	HR (95% CI): 1.24 (0.74, 2.07) Log-rank P = 0.421
	START A ISRCTN59368779 (START Trialists, 2008[11]; Haviland, 2013[33]) LOW	Survival from any breast cancer-related event including local, regional, or distant relapse, breast cancer death, or contralateral breast cancer, median follow-up 5.1 and 9.3 years	Arm A (41.6 Gy): 5 years: 88% (events: 91/750) 9 years: 80% (events: 149/750) Arm B (39 Gy): 5 years: 84% (events: 115/737) 9 years: 78% (events: 163/737)	5 years: 86% (events: 102/749) 9 years: 79% (events: 154/749) 102/749 (13.6%)	HR (95% CI): Arm A (41.6 Gy): 0.94 (0.75, 1.17), P = 0.57 Arm B (39 Gy): 1.08 (0.87, 1.35), P = 0.48
	START B ISRCTN59368779	Survival from any breast cancer-related event including local, regional, or distant	6 years: 89% (events: 127/1110)	6 years: 85% (events: 164/1105)	HR (95% CI): 0.79 (0.65, 0.97), P = 0.02

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
	(START Trialists, 2008[12]; Haviland, 2013[33]) LOW	relapse, breast cancer death, or contralateral breast cancer, median follow-up 6.0 and 9.9 years	10 years: 84% (events: 182/1110)	10 years: 80% (events: 222/1105)	
	Trial Name/# NR (Spooner, 2012)[20] SOME CONCERNS	Any recurrence or death at 2, 5, 10, 15 years	2 years: 89% (events: 20/181) 5 years: 81% (events: 34/181) 10 years: 61% (events: 67/181) 15 years: 46% (events: 98/181)	2 years: 86% (events: 25/177) 5 years: 73% (events: 48/177) 10 years: 59% (events: 73/177) 15 years: 44% (events: 99/177)	HR (95% CI): 0.98 (0.75, 1.29)
Local recurrence	*Hypofractionation vs Conventional Radiation*				
	NCT00156052 (Whelan, 2002[26];Whelan, 2010[25]) LOW	Recurrent tumor within the treated breast within 5 years (median follow-up 69 months)	21/622 (2.8)	23/612 (3.2)	RD (95% CI): 0.4% (-1.5%, 2.4%) P-value NR
		Recurrent tumor within the treated breast within 10 years	41/622 (6.2)	42/612 (6.7)	RD (95% CI): 0.5% (-2.5%, 3.5%) Noninferiority test P < 0.001
	NCT01413269 (Wang, 2020)[27] LOW	5-year relapse in breast or chest wall	1% (events: 5/365)	2% (events: 8/364)	HR (90% CI): 1.63 (0.64, 4.15) Noninferiority test P = 0.017

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
	START A ISRCTN59368779 (START Trialists, 2008[11]; Haviland, 2013[33]) LOW	Recurrence in breast or chest wall, median follow-up 5.1 and 9.3 years	Arm A (41.6 Gy): 5 years: 28/750 (4) 9 years: 37/750 (5) Arm B (39 Gy): 5 years: 31/737 (4) 9 years: 47/737 (6)	5 years: 25/749 (3) 9 years: 40/749 (5)	HR (95% CI): Arm A (41.6 Gy): 0.90 (0.57, 1.40), P = 0.63 Arm B (39 Gy): 1.20 (0.79, 1.83), P = 0.39
	START B ISRCTN59368779 (START Trialists, 2008[12]; Haviland, 2013[33]) LOW	Recurrence in breast or chest wall, median follow-up 6.0 and 9.9 years	6 years: 25/1110 (2) 10 years: 36/1110 (3)	6 years: 34/1105 (3) 10 years: 50/1105 (5)	HR (95% CI): 0.70 (0.46, 1.07), P = 0.10
	START Pilot Trial # NR (Owen, 2006)[13] SOME CONCERNS	10-year recurrence (ipsilateral breast or overlying skin)	42.9 Gy: 42/466 (9) 39 Gy: 66/474 (14)	50/470 (11)	HR (95% CI): 42.9 Gy: 0.86 (0.57, 1.30) 39 Gy: 1.33 (0.91, 1.92)
	Ultra-hypofractionation vs Conventional Radiation				
	FAST NCT00107497 (Brunt, 2020[35]; FAST Trialists, 2011[15]) LOW	Recurrence in ipsilateral breast and/or overlying skin, median follow-up at 3.1 and 9.9 years	Arm A (30 Gy): 3.1 years: 0/305 (0) 9.9 years: 4/305 (1) Arm B (28.5 Gy): 3.1 years: 0/302 (0) 9.9 years: 4/302 (1)	3.1 years: 2/301 (1) 9.9 years: 3/301 (1)	HR (95% CI): Arm A (30 Gy): 1.36 (0.30, 6.06) Arm B (28.5 Gy): 1.35 (0.30, 6.05)
	Ultra-hypofractionation vs Moderate Hypofractionation				
	FAST-Forward ISRCTN19906132 (Brunt, 2020)[16]	Recurrence in ipsilateral breast, chest wall or skin, 5	Arm A (27 Gy): 27/1367 (2) Arm B (26 Gy):	31/1361 (2)	HR (95% CI): Arm A (27 Gy): 0.86 (0.51, 1.44), P = 0.56

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
	LOW	years (median follow-up 71.5 months)	21/1368 (1)		Arm B (26 Gy): 0.67 (0.38, 1.16), P = 0.15
	APBI vs WBI				
	APBI-IMRT Florence NCT02104895 (Meattini, 2020)[38] SOME CONCERNS	Recurrence in ipsilateral breast, 10 years	5 years: 6/260 (2) 7 years: 7/260 (3) 10 years: 9/260 (4)	5 years: 3/260 (1) 7 years: 5/260 (2) 10 years: 6/260 (2)	HR (95% CI): 1.56 (0.55, 4.37), P = 0.40
	RAPID NCT00282035 (Whelan, 2019)[31] SOME CONCERNS	Recurrence in ipsilateral breast, median follow-up 8.6 years	37/1070 (4)	28/1065 (3)	HR (90% CI): 1.27 (0.84, 1.91)
Locoregional recurrence	*Hypofractionation vs Conventional Radiation*				
	DBCG HYPO NCT00909818 (Offersen, 2020)[29] LOW	9-year recurrence (ipsilateral recurrence in the breast tissue and overlying skin, in ipsilateral axilla, fossa supraclavicularis, or in the internal mammary chain lymph nodes)	14/794 (2)	19/814 (2)	HR (95% CI): 0.90 (0.51, 1.59) RD (95% CI): −0.3% (−2.3%, 1.7%) P-value NR
	NCT00793962 (Wang, 2019)[28] LOW	Recurrence in ipsilateral chest wall or regional lymph nodes, median follow-up 59.5 months	31/401 (8)	29/401 (9)	HR (90% CI): 1.10 (0.72, 1.69) Non-inferiority P < 0.0001
	NCT01413269 (Wang, 2020)[27]	5-year disease recurrence in the ipsilateral	3% (events: 14/365)	4% (events: 12/364)	HR (95% CI): 0.87 (0.46, 1.66)

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
	LOW	breast and/or regional lymph nodes			Log-rank P = 0.758
	START A ISRCTN59368779 (START Trialists, 2008[11]; Haviland, 2013[33]) LOW	Local or ipsilateral axilla, or supraclavicular fossa, median follow-up 5.1 and 9.3 years	Arm A (41.6 Gy): 5 years: 30/750 (4) 9 years: 42/750 (6) Arm B (39 Gy): 5 years: 35/737 (5) 9 years: 52/737 (7)	5 years: 28/749 (4) 9 years: 45/749 (6)	HR (95% CI): Arm A (41.6 Gy): 0.91 (0.59, 1.38), P = 0.65 Arm B (39 Gy): 1.18 (0.79, 1.76), P = 0.41
	START B ISRCTN59368779 (START Trialists, 2008[12]; Haviland, 2013[33]) LOW	Local or ipsilateral axilla, or supraclavicular fossa, median follow-up 6.0 and 9.9 years	6 years: 29/1110 (3) 10 years: 42/1110 (4)	6 years: 36/1105 (3) 10 years: 53/1105 (5)	HR (95% CI): 0.77 (0.51, 1.16), P = 0.21
	Trial Name/# NR (Spooner, 2012)[20] SOME CONCERNS	5-year recurrence	25/181 (43)	21/177 (40)	HR NR ("no significant differences")
	Ultra-hypofractionation vs Moderate Hypofractionation				
	FAST-Forward ISRCTN19906132 (Brunt, 2020)[16] LOW	Local or regional (axilla, supraclavicular fossa, and internal mammary chain), 5 years (median follow-up 71.5 months)	Arm A (27 Gy): 35/1367 (3) Arm B (26 Gy): 29/1368 (2)	43/1361 (3)	HR (95% CI): Arm A (27 Gy): 0.80 (0.51, 1.25), P = 0.33 Arm B (26 Gy): 0.66 (0.41, 1.06), P = 0.08
	APBI vs WBI				
	APBI-IMRT Florence NCT02104895 (Meattini, 2020)[38] SOME CONCERNS	Includes recurrence in ipsilateral axillary, supraclavicular or	5 years: 6/260 (2) 7 years: 7/260 (3) 10 years: 9/260 (4)	5 years: 4/260 (2) 7 years: 6/260 (2) 10 years: 7/260 (3)	HR (95% CI): 1.33 (0.49, 3.56), P = 0.58

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
		internal mammary nodes, 10 years			
Regional metastasis	*Ultra-hypofractionation vs Conventional Radiation*				
	FAST NCT00107497 (FAST Trialists, 2011)[15] LOW	Spread to axilla, supraclavicular fossa, and/or internal mammary chain, median follow-up at 3.1 years	Arm A (30 Gy): 0/305 (0) Arm B (28.5 Gy): 2/302 (1)	1/301 (0.3)	Comparison NR
Distant metastasis	*Hypofractionation vs Conventional Radiation*				
	START A ISRCTN59368779 (START Trialists, 2008[11]; Haviland, 2013[33]) LOW	Relapse in non-irradiated organs, median follow-up 5.1 and 9.3 years	Arm A (41.6 Gy): 5 years: 69/750 (9) 9 years: 110/750 (15) Arm B (39 Gy): 5 years: 93/737 (13) 9 years: 121/737 (16)	5 years: 73/749 (10) 9 years: 100/749 (13)	HR (95% CI): Arm A (41.6 Gy): 1.08 (0.82, 1.41), P = 0.58 Arm B (39 Gy): 1.24 (0.95, 1.61), P = 0.11
	START B ISRCTN59368779 (START Trialists, 2008[12]; Haviland, 2013[33]) LOW	Relapse in non-irradiated organs, median follow-up 6.0 and 9.9 years	6 years: 87/1110 (8) 10 years: 121/1110 (11)	6 years: 122/1105 (11) 10 years: 158/1105 (20)	HR (95% CI): 0.74 (0.59, 0.94), P = 0.01
	Ultra-hypofractionation vs Conventional Radiation				
	FAST NCT00107497 (FAST Trialists, 2011)[15] LOW		Arm A (30 Gy): 2/305 (1) Arm B (28.5 Gy): 10/302 (3)	5/301 (2)	Comparison NR

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
	Ultra-hypofractionation vs Moderate Hypofractionation				
	FAST-Forward ISRCTN19906132 (Brunt, 2020)[16] LOW	5 years (median follow-up 71.5 months)	Arm A (27 Gy): 69/1367 (5) Arm B (26 Gy): 76/1368 (6)	59/1361 (4)	HR (95% CI): Arm A (27 Gy): 1.16 (0.82, 1.64), P = 0.41 Arm B (26 Gy): 1.27 (0.90, 1.79), P = 0.17
	APBI vs WBI				
	APBI-IMRT Florence NCT02104895 (Meattini, 2020)[38] SOME CONCERNS	Includes recurrence to distant organs (visceral and bone sites), 10 years	5 years: 4/260 (2) 7 years: 6/260 (2) 10 years: 7/260 (3)	5 years: 8/260 (3) 7 years: 15/260 (6) 10 years: 20/260 (8)	HR (95% CI): 0.89 (0.32, 2.47), P = 0.83

Appendix Table 4. Detailed Results for Toxicity Outcomes for Breast Cancer Trials Rated "Low" or "Some Concerns" Risk of Bias

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
Harms					
Acute toxicity, overall	*Hypofractionation vs Conventional Radiation*				
	NCT01266642 (Shaitelman, 2015)[23] SOME CONCERNS	CTCAE v4.0, grade ≥ 2 < 3 months	65/138 (47)	116/149 (78)	P < 0.001
	APBI vs WBI				
	APBI-IMRT Florence NCT02104895 (Meattini, 2020)[38] SOME CONCERNS	RTOG, grade ≥ 2 ≤ 6 months	5/246 (2.0)	98/260 (38)	P = 0.0001
	RAPID NCT00282035 (Whelan, 2019)[31] SOME CONCERNS	CTCAE v3, grade 2-3 ≤ 3 months	Grade 2: 281/1070 (26) Grade 3: 19/1070 (2)	Grade 2: 466/1065 (44) Grade 3: 18/1065 (2)	Grade ≥ 2: P < 0.0001
Acute pneumonitis	*Hypofractionation vs Conventional Radiation*				
	NCT00793962 (Wang, 2019)[28] LOW	CTCAE 3.0, grade 1-3	Grade 1: 61/401 (15) Grade 2:14/401 (3) Grade 3: 0/401 (0)	Grade 1: 62/409 (15) Grade 2: 7/409 (2) Grade 3: 0/409 (0)	P = 0.28
	NCT01413269 (Wang, 2020)[27] LOW	CTCAE 3.0, grade 2 < 3 months	7/365 (2)	11/363 (3)	P = 0.22
	APBI vs WBI				
	RAPID NCT00282035 (Whelan, 2019)[31] SOME CONCERNS	CTCAE v3, grade 2-3 ≤ 3 months	Grade 2: 2/1070 (< 0.1) Grade 3: 0/1070 (0)	Grade 2: 7/1065 (0.7) Grade 3: 1/1065 (< 0.1)	Comparison NR

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
Acute skin toxicity	*Hypofractionation vs Conventional Radiation*				
	DRKS00017763 (Schmeel, 2020)[19] SOME CONCERNS	CTCAE v4.03, grade ≥ 2	19/70 (27)	30/70 (43%)	OR (95% CI): 2.01 (0.99, 4.09) P = 0.05
	NCT01266642 (Shaitelman, 2015)[23] SOME CONCERNS	CTCAE v4.0, grade ≥ 2 < 3 months	50/138 (36)	103/149 (69)	P < 0.001
	NCT00156052 (Arsenault, 2020)[32] SOME CONCERNS	ECOG, grade 2-3 At 4-6 weeks	9/73 (12)	28/73 (38)	P-value NR
	NCT01413269 (Wang, 2020)[27] LOW	CTCAE v3.0, grade 2-3 < 3 months	11/365 (3)	27/363 (0.7)	P = 0.02
	TomoBreast NCT00459628 (Nan Parijs, 2012)[22] SOME CONCERNS	RTOG, grade 2-3 Within 4 weeks	Grade 2: 10/37 (27) Grade 3: 3/37 (8)	Grade 2: 7/32 (22) Grade 3: 2/32 (6)	Comparison NR
	Ultra-hypofractionation vs Conventional Radiation				
	FAST NCT00107497 (FAST Trialists, 2011)[15] LOW	RTOG, grade 2-4	Arm A (30 Gy): 2: 13/111 (12) 3: 3/111 (3) 4: 0/111 (0) Arm B (28.5 Gy): 2: 9/106 (9) 3: 2/106 (2) 4: 0/106 (0)	2: 39/110 (36) 3: 12/110 (11) 4: 0/110 (0)	Comparison NR

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
	Ultra-hypofractionation vs Moderate Hypofractionation				
	FAST-Forward ISRCTN19906132 (Brunt, 2016)[17] LOW	RTOG, grade 2-3 (substudy 1) Within 4 weeks	Arm A (27 Gy): Grade 2: 20/51 (39) Grade 3: 5/51 (10) Arm B (26 Gy): Grade 2: 14/52 (27) Grade 3: 3/52 (6)	Grade 2: 24/55 (55) Grade 3: 6/55 (14)	P-value NR
		CTCAE v4.03, grade 2-3 (substudy 2) Within 4 weeks	Arm A (27 Gy): Grade 2: 11/41 (27) Grade 3: 1/41 (2) Arm B (26 Gy): Grade 2: 19/53 (36) Grade 3: 0/53 (0)	Grade 2: 22/43 (51) Grade 3: 0/43 (0)	P-value NR
	YO-HAI5 NCT03677427 (Van Hulle, 2021)[18] SOME CONCERNS	CTCAE v4.03, grade 2 16.7 days ± 6.0 days post	17/105 (16)	11/94 (20)	P-value NR
	APBI vs WBI				
	APBI-IMRT Florence NCT02104895 (Livi, 2015)[14] SOME CONCERNS	RTOG, grade ≥ 2 ≤ 6 months	5/246 (2)	98/260 (38)	P = 0.0001
	RAPID NCT00282035 (Whelan, 2019)[31] SOME CONCERNS	CTCAE v3, grade 2-3 ≤ 3 months	Grade 2: 101/1070 (9) Grade 3: 1/1070 (<0.1)	Grade 2: 322/1065 (30) Grade 3: 6/1065 (0.6)	Comparison NR

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
Acute skin toxicity (undefined)	*Hypofractionation vs Conventional Radiation*				
	NCT00793962 (Wang, 2019)[28] LOW	CTCAE 3.0, grade 1-3	Grade 1-2: 351/401 (89) Grade 3: 14/401 (3)	Grade 1-2: 357/401 (87) Grade 3: 32/401 (8)	P < 0.0001
Acute skin ulceration	*Hypofractionation vs Conventional Radiation*				
	NCT01266642 (Shaitelman, 2015)[23] SOME CONCERNS	CTCAE v4.0, grade ≥ 2 < 3 months	1/138 (1)	2/149 (1)	P = 0.19
Late toxicity, overall	*Hypofractionation vs Conventional Radiation*				
	NCT01266642 (Shaitelman, 2015)[23] SOME CONCERNS	CTCAE v4.0, grade ≥ 2 6 months	40/129 (31)	46/142 (32)	P = 0.81
	APBI vs WBI				
	APBI-IMRT Florence NCT02104895 (Meattini, 2020)[38] SOME CONCERNS	RTOG, grade ≥ 2 > 6 months to 10 years	0/246 (0%)	7/260 (3)	P = 0.02
	RAPID NCT00282035 (Whelan, 2019[31]; Olivotto, 2013[122]) SOME CONCERNS	CTCAE v3, grade 2-3 > 3 months through 3 and 8.6 years	3 years: Grade 2: 2/1070 (< 0.1) Grade 3: 0/1070 (0) 8.6 years: Grade 2: 298/1070 (28) Grade 3: 48/1070 (5)	3 years: Grade 2: 2/1070 (< 0.1) Grade 3: 0/1070 (0) 8.6 years: Grade 2: 131/1065 (12) Grade 3: 11/1065 (1)	Grade ≥ 2: 8.6 years: P < 0.0001

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
Late dermatitis	*Hypofractionation vs Conventional Radiation*				
	NCT01266642 (Shaitelman, 2015)[23] SOME CONCERNS	CTCAE v4.0, grade ≥ 2 6 months	0/138	1/142 (1)	P = 0.73
Late lymphedema	*Hypofractionation vs Conventional Radiation*				
	NCT00793962 (Wang, 2019)[28] LOW	RTOG, grade 1-3	Grade 1-2: 78/401 (19) Grade 3: 3/401 (1)	Grade 1-2: 81/409 (20) Grade 3: 3/409 (1)	P = 0.96
	NCT01266642 (Shaitelman, 2015)[23] SOME CONCERNS	CTCAE v4.0, grade ≥ 2 6 months	2/129 (2)	7/142 (5)	P = 0.78
	NCT01413269 (Wang, 2020)[27] LOW	RTOG, grade 2 >6 months	2/365 (0.5)	2/363 (0.6)	P = 0.74
Late lung fibrosis	*Hypofractionation vs Conventional Radiation*				
	NCT01413269 (Wang, 2020)[27] LOW	RTOG, grade 2 > 6 months	0/365 (0)	1/363 (0.3)	P = 0.51
Late pneumonitis	*Hypofractionation vs Conventional Radiation*				
	NCT01266642 (Shaitelman, 2015)[23] SOME CONCERNS	CTCAE v4.0, grade ≥ 2 6 months	0/129 (0)	0/142 (0)	NA
Late skin toxicity	*Hypofractionation vs Conventional Radiation*				
	NCT00156052 (Whelan, 2010)[25] SOME CONCERNS	RTOG, grade 2 and 3 Over 5 years	14/449 (3)	14/424 (3)	P-value NR
		RTOG, grade 2 and 3 Over 10 years	21/235 (9)	17/220 (8)	P-value NR
	NCT00793962 (Wang, 2019)[28]	RTOG, grade 1-3	Grade 1-2: 86/401 (21)	Grade 1-2: 90/409 (22)	P = 0.67

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
	LOW	Median follow-up 58 months	Grade 3: 1/401 (<1)	Grade 3: 0/409 (0)	
	APBI vs WBI				
	APBI-IMRT Florence NCT02104895 (Livi, 2015)[14] SOME CONCERNS	RTOG, grade ≥ 2 > 6 months to 5 years	0/246 (0)	2/260 (1)	P = 0.26
Late skin ulceration	*Hypofractionation vs Conventional Radiation*				
	NCT01266642 (Shaitelman, 2015)[23] SOME CONCERNS	CTCAE v4.0, grade ≥2 6 months	0/129 (0)	0/142 (0)	NA

Appendix Table 5. Detailed Results for Quality of Life Outcomes for Breast Cancer Trials Rated "Low" or "Some Concerns" Risk of Bias

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
Overall QoL	*Hypofractionation vs Conventional Radiation*				
	BIG3-07/TROG 07.01 NCT00470236 (King, 2020)[30] SOME CONCERNS	EORTC QLQ-C30, overall score at 6 months, 1 year, and 2 years	Mean (SD): 6 months: 77.8 (18.2) 1 year: 79.2 (18.2) 2 years:78.9 (19.1)	Mean (SD): 6 months: 78.1 (18.2) 1 year: 78.0 (18.0) 2 years: 78.7 (18.9)	Comparison NR
	NCT01266642 (Shaitelman, 2015[23]; Shaitelman, 2018[120]) SOME CONCERNS	FACT-G and FACT-B v4, total mean scores at baseline, 6 months FACT-B TOI v4, mean scores at baseline, 3 years	FACT-G: Baseline: 92.8 6 months: 91.6 FACT-B: Baseline: 120.1 6 months: 124.5 FACT-B TOI: Baseline: 74.5 3 years: 77.9	FACT-G: Baseline: 91.6 6 months: 93.6 FACT-B: Baseline: 118.8 6 months: 122.3 FACT-B TOI: Baseline: 74.0 3 years: 77.6	FACT-G: Baseline: P = 0.35 6 months: P = 0.12 FACT-B: Baseline: P = 0.46 6 months: P = 0.20 FACT-B TOI: Baseline: P = 0.72 3 years: P = 0.20
Global health status (QL)	*Hypofractionation vs Conventional Radiation*				
	TomoBreast NCT00459628 (Versmessen, 2012)[21] SOME CONCERNS	EORTC QLQ-C30, mean (SD) at baseline, end of radiation, 3 months, annually years 1-3	Baseline: 67.2 (17.5) End of therapy: 59.0 (2.9) 3 months: 65.8 (3.1) 1 year: 72.6 (3.1) 2 years: 76.2 (3.8) 3 years: 78.5 (5.3)	Baseline: 69.0 (21.7) End of therapy: 67.0 (2.2) 3 months: 68.5 (2.2) 1 year: 72.3 (2.5) 2 years: 72.3 (3.2) 3 years: 74.4 (4.1)	Significant difference only at end of radiation (P = 0.029), otherwise NS (P-value NR)

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
	Ultra-hypofractionation vs Moderate Hypofractionation				
	YO-HAI5 NCT03677427 (Van Hulle, 2021)[18] SOME CONCERNS	EORTC QLQ-C30/BR23, ≥ 10 pts decrease (from baseline) 16.7 days ±6.0 days post	Global score: 16/105 (15) Physical functioning: 7/105 (7) Social functioning: 12/105 (11)	Global score: 30/94 (32) Physical functioning: 23/94 (24) Social functioning 29/94 (31)	P = 0.005 P = 0.0005 P =0.0007
Physical functioning	*Hypofractionation vs Conventional Radiation*				
	TomoBreast NCT00459628 (Versmessen, 2012)[21] SOME CONCERNS	EORTC-QLQ C30, mean (SD) at baseline, end of radiation, 3 months, annually years 1-3	Baseline: 83.2 (16.0) End of therapy: 79.4 (2.0) 3 months: 82.0 (2.2) 1 year: 83.6 (2.0) 2 years: 88.7 (1.9) 3 years: 89.9 (3.2)	Baseline: 84.1 (18.7) End of therapy: 80.1 (1.6) 3 months: 80.7 (1.7) 1 year: 85.4 (2.0) 2 years: 84.1 (3.5) 3 years: 84.9 (3.3)	Differences NS (P-value NR)
Role functioning			Baseline: 66.4 (29.3) End of therapy: 65.0 (4.2) 3 months: 75.8 (4.3) 1 year: 84.7 (4.5) 2 years: 94.1 (5.4) 3 years: 97.5 (8.7)	Baseline: 70.2 (27.4) End of therapy: 66.9 (3.5) 3 months: 81.9 (4.6) 1 year: 79.9 (3.6) 2 years: 81.1 (4.3) 3 years: 80.3 (3.2)	Differences NS (P-value NR)
Emotional functioning			Baseline: 74.4 (20.0) End of therapy: 75.4 (2.6) 3 months: 78.5 (2.7) 1 year: 77.3 (2.8) 2 years: 80.7 (4.1) 3 years: 81.3 (4.5)	Baseline: 78.8 (18.1) End of therapy: 76.0 (2.5) 3 months: 75.6 (2.6) 1 year: 76.7 (3.5) 2 years: 76.7 (4.4) 3 years: 77.7 (6.2)	Differences NS (P-value NR)

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation Arm N Events/Total N (%)	Comparison Arm N Events/Total N (%)	Results
Social functioning			Baseline: 82.2 (19.8) End of therapy: 71.7 (3.1) 3 months: 82.6 (2.9) 1 year: 84.7 (3.7) 2 years: 90.5 (4.5) 3 years: 89.7 (7.0)	Baseline: 80.6 (22.6) End of therapy: 78.6 (2.1) 3 months: 83.9 (2.6) 1 year: 89.4 (3.3) 2 years: 92.5 (6.2) 3 years:92.9 (7.4)	Differences NS (P-value NR)

APPENDIX E. PROSTATE CANCER TABLES

Appendix Table 6. Risk of Bias Ratings for All Eligible Prostate Cancer Trials

Trial	Outcome	Domain 1: Risk of Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk of Bias in Measurement of the Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
Alexidis[123,124]	Harms	Low	Low	High	Low	Low	Some concerns[123] Low[124]	High
	QoL	Low	Low	High	Low	Some concerns[123] Low[124]	Some concerns	High
Arcangelli	Harms[49,60,65]	Low	Low	Some concerns	Low	Low	Low	Some concerns
	Survival[49,60,61]	Low	Low	Some concerns	Low	Low	Low	Some concerns
Catton[43]	Harms	Low	Low	Low	Low	Low	Low	Low
CHHiP	Harms[40,70,125]	Low	Low	Some concerns	Low	Low	Low	Some concerns
	Survival[40]	Low	Low	Some concerns	Low	Low	Low	Some concerns
	QoL[69]	Low	Low	Some concerns	Low	Low	Low	Some concerns
CHIRP[55]	Harms	Low	Low	Some concerns	Low	Low	Low	Some concerns
	Survival	Low	Low	Some concerns	Low	Some concerns	Low	Some concerns
Fonteyne[44]	Harms	Low	Low	Some concerns	Low	Low	Low	Some concerns
Hoffman	Harms[53,66]	Low	Low	Low	Low	Low	Low	Low
	Survival[53]	Low	Low	Low	Low	Low	Low	Low

Trial	Outcome	Domain 1: Risk of Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk of Bias in Measurement of the Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
Houshyari[45]	Harms	Low	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
HYPO-RT-PC	Harms[39]	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns
	Survival[39]	Some concerns	Some concerns	Low	Some concerns	Low	Low	Some concerns
	QoL[58]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
HYPRO	Harms[64]	Low	Low	Low	Low	Low	Low	Low
	Survival[48,59]	Low	Low	Low	Low	Low	Low	Low
	QoL[126]	Low	Low	Low	High	Low	Low	High
Lukka 05[54]	Harms	Low	Low	Low	Low	Low	Low	Low
	Survival	Low	Low	Low	Low	Low	Low	Low
Marzi[127]	Harms	Low	High	High	Some concerns	Low	Low	High
Norkus 09	Harms[51]	Low	Some concerns	Low	Low	Low	Low	Some concerns
Norkus 13[50,128]	Harms	Low	Low	Low	Low	Low	Low	Low
PACE-B[47]	Harms	Low	Low	Some concerns	Low	Low	Low	Some concerns
	QoL	Low	Low	Some concerns	Low	Low	Low	Some concerns
Pollack	Harms[52]	Low	Low	Low	Low	Low	Low	Low
	Survival[63]	Low	Low	Low	Low	Low	Low	Low
	QoL[68]	Low	Low	Low	Low	Low	Low	Low
Poon[46]	Harms	Low	Some concerns	Low	Low	Low	Some concerns	Some concerns
	Survival	Low	Some concerns	Low	Low	Low	Some concerns	Some concerns

Trial	Outcome	Domain 1: Risk of Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk of Bias in Measurement of the Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
RTOG 0415	Survival[41]	Low	Low	Low	Low	Low	Low	Low
	QoL[67]	Low	Low	Low	Low	Low	Low	Low
Yeoh[57,62,129]	Survival	Low	Some concerns	Low	Low	Low	Low	Some concerns
Zhong[56]	Harms	Some concerns	Some concerns	Low	Low	Some concerns	Low	Some concerns
	Survival	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns

Appendix Table 7. Study Characteristics for All Eligible Prostate Cancer Trials

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
Alexidis, 2019[123,124] Trial # NR High Greece Funding NR Follow-up 19 weeks	Patients between 40 and 85 years old with histologically proven localized prostate cancer (cT1c-cT3bN0M0), PSA ≤ 40 ng/mL and WHO performance status of 0-2. Patients were excluded if they had received past pelvic irradiation, any type of prostatectomy (suprapubic or transurethral), suffered from inflammatory bowel disease, a history of bladder cancer or transurethral resection of bladder tumor or impaired urinary function; a calculated risk of lymph node involvement ≥ 5%, T3 disease and GS ≥ 8, T3 disease and PSA > 10 ng/ml, GS 8-9 and stage T3 or T4 or PSA > 10 ng/ml. Other treatments: ADT was given 2 months prior	2.25 Gy/fraction 72 Gy 32 fractions Weeks NR N=72 Mn age (range): 69.8 (NR) Race: NR PSA ng/mL: < 10=45 (62.5) ≥ 10=36 (37.5) Gleason score: < 6: 31 (43.1) 7: 30 (41.7) 8-9: 11 (15.3) Tumor stage: T1: 32 (44.4) T2: 34 (47.2) T3: 6 (8.3)	2 Gy/fraction 74 Gy 37 fractions Weeks NR N=67 Md age (range): 70.9 (NR) Race: NR PSA ng/mL: < 10=39 (58.2) ≥ 10=28 (41.8) Gleason score: < 6: 29 (43.3) 7: 31 (46.3) 8-9: 7 (10.4) Tumor stage: T1: 28 (41.8) T2: 36 (53.7) T3: 3 (4.5)	Harms* • GU/GI toxicity Quality of life

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
		Risk Category: NR	Risk Category: NR	
Aluwini, 2015[48,59,64,126,130] **HYPRO** ISRCTN85138529 Low 7 centers in the Netherlands The Dutch Cancer Society Median follow-up 89 months	Intermediate-risk and high-risk patients with prostate cancer between 44-85 years with histologically confirmed stage T1b–T4 NX–0 MX–0, prostate-specific antigen of ≤ 60 ng/mL and a WHO performance status of 0–2. We Patients were excluded if previous pelvis irradiation, radical prostatectomy, evidence of pelvic nodal disease (determined by CT of pelvis), presence of distant metastases (determined by bone scintigraphy), and low-risk patients (stage T1b–T2a, Gleason score ≤ 6, prostate-specific antigen ≤ 10 ng/mL). Other treatments: 67% of patients received concomitant ADT for median 32 months	5.6 Gy/fraction 3.4 Gy 19 fractions 6.5 weeks N=403 Mn age (range): 70 (66-74) Race: NR PSA ng/mL: ≤ 10: 124 (31) 10-20: 159 (39) > 20: 120 (30) Gleason score: ≤ 6:122 (30) 7: 181 (45) 8: 60 (15) 9: 7 (9) 10: 3 (1)	2.0 Gy/fraction 78 Gy 39 fractions 8 weeks N=391 Mn age (range): 71 (67-75) Race: NR PSA ng/mL: ≤ 10: 103 (26) 10-20: 157 (40) > 20: 131 (34) Gleason score: ≤ 6:119 (31) 7: 178 (46) 8: 57 (15) 9: 33 (8) 10: 4 (1)	Harms • Acute GU/GI toxicity • Late GU/GI toxicity* Survival* • Overall • Prostate-specific Quality of life (high)

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
		Tumor stage: T1a: 0 T1b: 3 (1) T1c: 55 (14) T2a: 50 (12) T2b: 35 (9) T2c: 49 (12) T3a: 157 (39) T3b: 47 (12) T4: 7 (2) Risk category NR	Tumor stage: T1a: 1 (0) T1b: 3 (1) T1c: 55 (14) T2a: 45 (12) T2b: 38 (10) T2c: 48 (12) T3a: 160 (41) T3b: 38 (10) T4: 3 (1) Risk category NR	
Arcangelli, 2010[49,60,61,65] Trial # NR Some concerns Italy Funding NR Median follow-up 9 years	Inclusion criteria: (1) histological proof of prostate adenocarcinoma of not more than 6 months; (2) high-risk features; (3) total PSA level ≤ 100 ng/mL; (4) no evidence of distant metastases; (5) no contraindications for 9-month total androgen deprivation; (6) no previous pelvic radiotherapy; (7) no previous hormonal therapy; (8) no previous major pelvic surgery; (9) no previous prostate surgery other than transurethral resection of the prostate; (10) no evidence of ulcerative colitis; (11) WHO	3.1 Gy/fraction 62 Gy 20 fractions 5 weeks N=83 Md age (range): 75 (61-82) Race NR PSA ng/mL: ≤ 20: 35 (42)	2.0 Gy/fraction 80 Gy 40 fractions 8 weeks N=85 Md age (range): 75 (54-83) Race NR PSA ng/mL: ≤ 20: 27 (32)	Harms • Acute GU/GI toxicity • Late GU/GI toxicity* Survival • Biochemical recurrence-free • Local recurrence • Metastases • Overall • Prostate-specific

Trial Name, Year **Trial #** **Risk of Bias** **Country** **Funding** **Follow-up**	**Inclusion/Exclusion Criteria** **Other Treatments**	**Intervention (Hypofractionation) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Comparator (Conventional) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Outcomes Reported** (Risk of Bias If Different by Outcome) ***Primary**
	performance status #2; (12) no pelvic node > 1 cm at the CT or MR evaluation; (13) no previous malignant tumors, with the exception of adequately treated cutaneous carcinomas; (14) no evidence of infectious or psychotic disease Other treatments: All participants received 9-month ADT	> 20: 48 (58) Gleason score: ≤ 7: 22 (27) > 7: 61 (73) Tumor stage: < T2c: 54 (65) ≥ T2c: 29 (35) Risk category NR	> 20: 58 (68) Gleason score: ≤ 7: 20 (24) > 7: 65 (76) Tumor stage: < T2c: 48 (56) ≥ T2c: 37 (44) Risk category NR	
Brand, 2019[47] **PACE-B** NCT01584258 Some concerns 37 centers in the United Kingdom, Ireland and Canada Accuray and National Institute of Health Research	Only patients suitable for radical radiotherapy, but not willing to have or not suitable for radical prostatectomy were recruited. Eligible patients were men aged at least 18 years, with WHO performance status of 0–2, life expectancy of at least 5 years, and histologically confirmed prostate adenocarcinoma. All patients had NCCN low-risk or intermediate-risk disease. Other treatments: ADT not permitted	3.1 Gy/fraction 62 Gy 20 fractions 4 weeks Or Conventionally fractionated RT 2.0 Gy/fraction 78 Gy 39 fractions 7-8 weeks	2.0 Gy/fraction 36.25 Gy 5 fractions 1-2 weeks N=433	Harms • Acute GU/GI toxicity • Late GU/GI toxicity Quality of life

Trial Name, Year **Trial #** **Risk of Bias** **Country** **Funding** **Follow-up**	**Inclusion/Exclusion Criteria** **Other Treatments**	**Intervention (Hypofractionation) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Comparator (Conventional) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Outcomes Reported** (Risk of Bias If Different by Outcome) ***Primary**
Median follow-up 12 weeks		N=441 Mean age (range): 70 (66-74) Ethnicity: Black 25 (6) East Asian 3 (1) Mixed heritage 2 (<1) South Asian 9 (2) White 386 (89) Other 7 (2) PSA ng/mL: < 10: 299 (69) 10-20: 133 (31) Gleason score: 3+3: 84 (19) 3+4: 348 (81) Tumor stage: T1c: 78 (18) T2a: 130 (30) T2b: 57 (13) T2c: 167 (39)	Mean age (range): 70 (65-74) Ethnicity: Black 25 (6) East Asian 3 (1) Mixed heritage 2 (<1) South Asian 9 (2) White 386 (89) Other 7 (2) PSA ng/mL: < 10: 283 (68) 10-20: 132 (32) Gleason score: 3+3: 61 (15) 3+4: 354 (85) Tumor stage: T1c: 76 (18) T2a: 105 (25) T2b: 81 (20) T2c: 153 (37)	

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
		Risk category (NCCN) Low: 38 (9) Intermediate: 394 (91)	Risk category (NCCN) Low: 30 (7) Intermediate: 385 (93)	
Catton, 2017[43] NCT00304759 Low 27 Centers: Canada (14), Australia (12), France (1) Canadian Institutes for Health Research Median follow-up 6 years	Eligible patients had a histologic diagnosis of intermediate risk carcinoma of the prostate (T1-2a, Gleason score ≤ 6, and PSA=10.1-20 ng/mL; T2b-2c, Gleason ≤ 6, and PSA ≤ 20 ng/mL; or T1-2, Gleason = 7, and PSA ≤ 20 ng/mL) without evidence of disease spread to the lymph nodes or bone. Exclusion criteria were prostate cancer diagnosis > 6 months before study entry, previous therapy for prostate cancer other than biopsy or transurethral resection, > 12 weeks of hormone therapy for treatment of prostate cancer, any malignancy diagnosed within 5 years of entry except for nonmelanoma skin cancer, radiation treatment plan that did not meet dose constraints for the hypofractionation arm of the trial, and previous pelvic RT or inflammatory bowel disease.	3 Gy/fraction 60 Gy 20 fractions 4 weeks N=608 Md age (range): 72 (68-75) Race: NR PSA ng/mL: < 10=405 (67) ≥ 10=203 (33) Gleason score: 3+3: 57 (9) 3+4: 382 (63) 4+3: 169 (28) Tumor stage: T1a, T1b: 4 (<1) T1c: 328 (54)	2 Gy/fraction 78 Gy 39 fractions 8 weeks N=598 Md age (range): 71 (67-75) Race: NR PSA ng/mL: < 10=419 (49) ≥ 10=179 (30) Gleason score: 3+3: 56 (9) 3+4: 380 (64) 4+3: 162 (27) Tumor stage: T1a, T1b: 3 (<1) T1c: 308 (52)	Harms • GU/GI toxicity

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)		Comparator (Conventional) Characteristics Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		T2a: 163 (27) T2b: 73 (12) T2c: 40 (7) Other treatments: Androgen deprivation therapy was not permitted. Risk category: NR		T2a: 159 (27) T2b: 91 (15) T2c: 37 (6) Other treatments: Androgen deprivation therapy was not permitted. Risk category: NR	
Dearnaley, 2012[40,69,70,125] **CHHiP** SRCTN97182923 Some concerns 71 centers in the UK, Ireland, Switzerland and New Zealand Cancer Research UK, Department of	Men older than 16 years who had histologically confirmed T1b–T3aN0M0 prostate cancer and a WHO performance status of 0 or 1, were eligible. A PSA concentration less than 30 ng/mL and a risk of seminal vesicle involvement less than 30% were needed. Patients were ineligible if they had both T3 tumors and a Gleason score of 8 or higher, or a life expectancy of less than 10 years. Other exclusion criteria included previous pelvic radiotherapy or radical prostatectomy, previous androgen suppression, another active malignancy in the past 5 years (other than cutaneous basal-cell carcinoma), comorbid conditions	3 Gy/fraction 60 Gy 20 fractions 4 weeks N=1074 Mean age (range): 69 (48-84) Race NR PSA ng/mL: < 10: 518 (48)	3 Gy/fraction 57 Gy 19 fract 3.8 weeks N=1077 Mean age (range): 69 (44-83) Race NR PSA ng/mL: < 10: 539 (50) ≥ 10: 528 (50)	2 Gy/fraction 74 Gy 37 fractions 7.4 weeks N=1065 Mean age (range): 69 (48-85) Race NR PSA ng/mL: < 10: 510 (48) ≥ 10: 544 (52)	Harms • Acute GU/GI toxicity • Late GU/GI toxicity Survival • Overall

Trial Name, Year **Trial #** **Risk of Bias** **Country** **Funding** **Follow-up**	**Inclusion/Exclusion Criteria** **Other Treatments**	**Intervention (Hypofractionation) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Comparator (Conventional) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Outcomes Reported** (Risk of Bias If Different by Outcome) ***Primary**
Health, National Institute for Health Research Cancer Research Network, and NHS funding to the National Institute of Health Research Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London. Median follow-up 62.4 months	precluding radical radiotherapy, hip prosthesis, and full anticoagulation treatment. Other treatments: Men with NCCN intermediate-risk or high-risk disease received short-course androgen suppression for 3–6 months before and during RT; this was optional for patients with low-risk disease.	≥ 10: 551 (52) Gleason score: ≤ 6: 387 (36) 7: 658 (61) 8: 29 (3) Tumor stage: T1a-b-c-x: 422 (39) T2a-b-c-x: 561 (52) T3a-T3x: 90 (8) Unknown: 1 (<1) Risk category (NCCN) Low: 164 (15) Intermediate: 784 (73) High: 126 (12)	Gleason score: ≤ 6: 364 (34) 7: 681 (63) 8: 32 (3) Tumor stage: T1a-b-c-x: 392 (36) T2a-b-c-x: 582 (54) T3a-T3x: 102 (9) Unknown: 1 (<1) Risk category (NCCN) Low: 163 (15) Intermediate: 784 (73) High: 130 (12)	Gleason score: ≤ 6: 371 (35) 7: 656 (62) 8: 38 (4) Tumor stage: T1a-b-c-x: 356 (33) T2a-b-c-x: 623 (58) T3a-x: 85 (8) Unknown: 1 (<1) Risk category (NCCN) Low: 157 (15) Intermediate: 779 (73) High: 129 (12)	

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
Fonteyne, 2018[44] Trial #NCT01921803 Some concerns Belgium Stichting tegen kanker (non-profit) Follow-up 3 months	Patients with histologically confirmed stage T1-T4N0M0 prostate cancer and WHO performance status of 0 t	3.5 Gy/fraction 56 Gy 16 fractions Weeks NR N=77 Baseline characteristics NR	2.68 Gy/fraction 67 Gy 25 fractions Weeks NR N=80 Baseline characteristics NR	Harms* • GU/GI toxicity
Hoffman, 2014[53,66] NCT00667888 Low United States Funding NR Median follow-up 8.5 years	Eligible patients had biopsy-proven prostate adenocarcinoma, good performance status (Zubrod <2), clinical sIe (c) T1b-T3b disease (1992 AJCC staging system), PSA ≤ 20 ng/mL, Gleason score < 10, and no clinical, radiographic, or pathologic evidence of nodal or bone metastasis. Other treatments: ADT similar across groups	2.4 Gy/fraction 72 Gy 30 fractions 6 weeks N=101 Median age (range): 69 (41-83) Race: NR	1.8 Gy/fraction 75.6 Gy 42 fractions 8.4 weeks N=102 Median age (range): 67 (48-84) Race: NR	Harms • Late GU/GI toxicity* Survival • Overall • Prostate-specific

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
		PSA ng/mL: < 10: 93 (91) ≥ 10: 9 (9) Gleason score: 6: 33 (32) 7: 68 (67) 8: 1 (1) Tumor stage: T1: 70 (69) T2: 32 (31) Risk category (NCCN) Low: 28 (27) Intermediate: 73 (72) High: 1 (1)	PSA ng/mL: < 10: 88 (87) ≥ 10: 13 (13) Gleason score: 6: 37 (37) 7: 63 (62) 8: 1 (1) Tumor stage: T1: 76 (75) T2: 25 (25) Risk category (NCCN) Low: 29 (29) Intermediate: 71 (70) High: 1 (1)	
Houshyari, 2021[45] Trial # NR Some concerns Iran	Eligible patients had histologically confirmed stage T1-T3aN0M0 PCa (according to the 7th edition of AJCC), PSA ≤ 40 and ECOG performance status of 0–2. Exclusion criteria included lymph node involvement, distant metastasis, co-existing malignancy (except for basal	3.5 Gy/fraction 56 Gy 16 fractions 4 weeks N=20 Median age (SD): 72 (6.0)	2.7 Gy/fraction 70.2 Gy 26 fractions 5 weeks N=20 Median age (SD): 68.5 (8.9)	Harms* • Acute GU/GI toxicity

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
Funding NR Follow-up 3 months	cell skin cancer), and previous RT to the pelvis. Other treatments: Patients with intermediate and high-risk disease received ADT for 3 months before and during RT, and continued up to 6 and 36 months, respectivetly.	Range 56-80 Race: NR PSA ng/mL: < 10: 11 (55) ≥ 10: 9 (45) Gleason score: ≤ 6: 4 (20) 7: 10 (50) ≥ 8: 6 (30) Tumor stage: T1-T2a: 7 (35) T2b-T2c: 8 (40) T3: 5 (25) Risk category (D'Amico): Low: 2 (10) Int. 13 (65) High: 5 (25)	Range 55-86 Race: NR PSA ng/mL: < 10: 5 (25) ≥ 10: 15 (75) Gleason score: ≤ 6: 5 (25) 7: 7 (35) ≥ 8: 8 (40) Tumor stage: T1-T2a: 4 (20) T2b-T2c: 7 (35) T3: 9 (45) Risk category (D'Amico): Low: 1 (5) Int. 11 (55) High: 8 (40)	
Lee, 2016[41,67] **RTOG-0415** Trial# NR	Men age ≥ 18 years with prostate adenocarcinoma were eligible if they met the following criteria: a clinical classification of T1b to T2c (according to AJCC staging system, 6th edition),	2.5 Gy/fraction 70 Gy 28 fractions 5.6 weeks	1.8 Gy/fraction 73.8 Gy 41 fractions 8.2 weeks	Harms • Acute GU/GI toxicity

Trial Name, Year **Trial #** **Risk of Bias** **Country** **Funding** **Follow-up**	**Inclusion/Exclusion Criteria** **Other Treatments**	**Intervention (Hypofractionation) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Comparator (Conventional) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Outcomes Reported** (Risk of Bias If Different by Outcome) ***Primary**
Low United States National Cancer Institute Median follow-up 5.8 years	a Gleason score of 2 to 6, and PSA < 10. Additional criteria were no nodal or distant metastatic disease, Zubrod performance status < 2, and no prior bilateral orchiectomy, chemotherapy, RT, cryosurgery, or definitive surgery for prostate cancer. Patients with another invasive cancer, other than localized basal or squamous cell skin carcinoma, were not eligible unless continually free of that cancer for a minimum of 5 years. Other treatments: NR	N=550 Age: ≤ 59: 95 (17.3) 60-69: 251 (45.6) ≥ 70: 204 (37.1) Race: American Indian/AK Native: 1 (0.2) Asian: 8 (1.5) Black: 99 (18) Native Hawaiian or other Pacific Islander: 1 (0.2) White: 436 (79.3) NR: 5 (0.9) PSA ng/mL: < 4: 112 (20.4) 4 to < 10: 43.8 (79.6) Gleason score: 2-4: 0 5-6: 550 (100)	N=542 Age: ≤ 59: 87 (16.1) 60-69: 239 (44.1) ≥ 70: 216 (39.9) Race: American Indian/AK Native: 5 (0.9) Asian: 7 (1.3) Black: 91 (16.8) Native Hawaiian or other Pacific Islander: 1 (0.2) White: 430 (79.3) NR: 8 (1.5) PSA ng/mL: < 4: 106 (93.5) 4 to <10: 436 (80.4) Gleason score: 2-4: 2 (0.4) 5-6: 540 (99.6)	• Late GU/GI toxicity Survival • Overall Quality of life

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
		Tumor stage: T1: 442 (80.4) T2: 408 (19.6) Risk category NR	Tumor stage: T1: 411 (75.8) T2: 131 (24.2) Risk category NR	
Lukka, 2005[54] Trial # NR Low Canada Funding NR Median follow-up 5.7 years	Men with early-stage adenocarcinoma of the prostate (T1-2 according to International Union Against Cancer TNM classification) were eligible for the trial. Patient exclusion criteria were as follows: PSA > 40 ng/L; previous therapy for PCa (other than biopsy or transurethral resection of the prostate); previous hormone therapy; prior or active malignancy other than nonmelanoma skin cancer, colon cancer, or thyroid cancer treated a minimum of 5 years before the trial and presumed cured; a simulated volume exceeding 1,000 mL; previous pelvic radiotherapy; presence of inflammatory bowel disease; diagnosis of serious nonmalignant disease that would preclude radiotherapy or surgical biopsy; geographically inaccessible for follow-up; a psychiatric or	2.63 Gy/fraction 52.5 Gy 20 fractions 28 days N=466 Mean age (range): 70 (53-84) Race: NR PSA ng/mL: Mean (range): 10.6 (0.3-39) Gleason score: 2-4: 35 (8) 5: 67 (14) 6: 181 (39) 7: 134 (29) 8-9: 49 (11)	2.0 Gy/fraction 66 Gy 33 fractions 45 days N=470 Mean age (range): 70.3 (53-84) Race: NR PSA ng/mL: Mean (range): 10.4 (0.4-40) Gleason score: 2-4: 35 (8) 5: 67 (14) 6: 181 (39) 7: 134 (29) 8-9: 49 (11)	Harms • Acute GU/GI toxicity • Late GU/GI toxicity* Survival • Biochemical recurrence-free • Local recurrence • Metastases • Overall • Prostate-specific

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
	addictive disorder that would preclude obtaining informed consent or adherence to protocol; inability to commence radiotherapy within 26 weeks of the date of last prostatic biopsy. Other treatments: NR	Tumor stage: T1a: 0 T1b: 9 (2) T1c: 114 (25) T2a: 135 (29) T2b: 130 (28) T2c: 78 (17) Risk category NR	Tumor stage: T1a: 3 (1) T1b: 13 (3) T1c: 116 (25) T2a: 122 (26) T2b: 123 (26) T2c: 93 (20) Risk category NR	
Marzi, 2009[127] Trial # NR High Italy Funding NR Median follow-up 30 months	Eligible participants were < 85 with at least two of the following risk factors present: T2c-T4, PSA > 10 ng/ml, Gleason score 7-10. Other eligibility criteria were no nodes involvement present at CT or MRI, no other previous RT or prostatectomy, no other malignant disease except for Basal cell carcinoma or other tumors in the past 5 years.	3.1 Gy/fraction 62 Gy 20 fractions 5 weeks N=57 Age: ≤ 75: 31 > 75: 26 Race: NR PSA ng/mL: ≤ 10:18 (32) > 10:39 (68) Gleason score:	2 Gy/fraction 80 Gy 40 fractions 8 weeks N=57 Age: ≤ 75: 29 > 75: 28 Race: NR PSA ng/mL: ≤ 10: 14 (25) > 10: 43 (75) Gleason score:	Harms* • Late rectal toxicity

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
		≤ 6: 9 (16) > 6: 48 (84) Tumor stage: < T2c: 27 (47) ≥ T2c: 30 (53) Other treatments: Hormonal treatment was given 2 months prior Risk category: NR	≤ 6: 5 (9) > 6: 52 (91) Tumor stage: < T2c: 26 (46) ≥ T2c: 31 (54) Other treatments: Hormonal treatment was given 2 months prior Risk category: NR	
Norkus, 2009[51,131] Trial # NR Some concerns Lithuania Funding NR Follow-up 12 months	Inclusion criteria were as follows: prostate adenocarcinoma of low- and intermediate-risk group, with risk of seminal vesicle and/or pelvic lymph node involvement of < 15% regarding Partin's nomograms and Roach formula, no hormonal therapy or surgical castration before radiotherapy Other treatments: NR	57 Gy 17 frons 3.5 weeks Given as 13 fractions of 3 Gy plus 4 fractions of 4.5 Gy N=47 Median age (range): 63 (53-75) Race: NR	2 Gy/fraction 74 Gy 37 fractions 7.5 weeks N=44 Median age (range): 65 (50-78) Race: NR	Harms • Acute GU/GI toxicity • Late GU/GI toxicity*

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
		PSA ng/mL: ≥ 10: 47 > 10: 0 Gleason score: ≤ 6: 42 7: 2 ≥ 8: 0 Tumor stage: T1: 20 T2: 26 T3: 1 Risk category NR	PSA ng/mL: ≥ 10: 44 > 10: 0 Gleason score: ≤ 6: 44 7: 0 ≥ 8: 0 Tumor stage: T1: 16 T2: 26 T3: 2 Risk category NR	
Norkus, 2013[50,128] Trial # NR Low Lithuania Funding NR	The inclusion criteria were as follows: histologically proven prostate adenocarcinoma; PSA ≤ 100 ng/ml; ECOG performance status < 2; no evidence of distant metastases; no other malignancy except basal cell skin cancer; no contraindications for ADT; no previous prostate surgery including transurethral resection; and most importantly, high risk features according to NCCN criteria: stage	3.15 Gy/fraction 63 Gy 20 fractions 4-5 weeks (4 fractions/week) N=115 Mean age (SD): 65 (6)	2.0 Gy/fraction 76 Gy 38 fractions Weeks NR (5 fractions/week) N=106 Mean age (SD): 65 (7)	Harms* • Acute GU/GI toxicity

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
Follow-up 12 weeks	T3a-T3b, biopsy Gleason score of 8–10; pretreatment PSA level > 20 ng/mL, or the presence of at least 2 of the following clinical characteristics: pretreatment PSA of 11–20 ng/ mL, T ≥ 2c, GS = 7. Exclusion criteria included lymph node involvement and previous RT to the pelvis. Other treatments: All patients received ADT ~3-4 month prior to RT and continued for a total duration of ≥ 6 months.	Race: NR PSA ng/mL: ≤ 20: 92 (80) > 20: 23 (20) Gleason score: ≤ 7: 107 (93) > 7: 8 (7) Tumor stage: ≤ T2c: 17 (15) > T2c: 98 (85) Risk category NR	Race: NR PSA ng/mL: ≤ 20: 76 (72) > 20: 30 (28) Gleason score: ≤ 7: 90 (85) > 7: 16 (15) Tumor stage: ≤ T2c: 20 (19) > T2c: 86 (81) Risk category NR	
Pollack, 2006[52,63,68,132] NCT00062309 Low United States National Cancer Institute &	Men with stage T1-3 adenocarcinoma of the prostate and Gleason score ≥ 5 were eligible if they had intermediate to high-risk features. Intermediate risk was defined as Gleason score 7, pretreatment initial PSA > 10–20 ng/mL, or ≥ 3 biopsy cores of Gleason score ≥ 5, as long as no high-risk features were present. High risk was defined as Gleason score 8–10, Gleason score 7 in ≥ 4 cores, cT3 disease, or an initial PSA > 20 ng/mL	2.7 Gy/fraction 70.2 Gy 26 fractions Weeks NR N=151 Mean age (SD): 66.7 (7.6) Race: NR	2.0 Gy/fraction 76 Gy 38 fractions Weeks NR N=152 Mean age (SD): 66.9 (8.4) Race: NR	Harms • Acute GU/GI toxicity • Late GU/GI toxicity Survival • Biochemical recurrence-free • Local recurrence

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
Florida Biomed Bankhead Coley Median follow-up 122.9 months	Other treatments: Long-term ADT planned for 24 months in those with high risk; for those with less than high risk, ADT planned for up to 4 months	PSA ng/mL: < 10: 95 (62.9) ≤ 10-20: 41 (27.2) > 20: 15 (9.9) Gleason score: 6: 53 (35.1) 7: 70 (46.4) 8-10: 28 (18.5) Tumor stage: T1: 61 (40.4) T2: 71 (47.0) T3: 19 (12.6) Risk category NR	PSA ng/mL: < 10: 99 (65.1) ≤ 10-20: 40 (26.3) > 20: 13 (8.6) Gleason score: 6: 51 (38.8) 7: 72 (47.4) 8-10: 29 (19.1) Tumor stage: T1: 59 (383.8) T2: 77 (50.7) T3: 16 (10.5) Risk category NR	• Metastases • Prostate-specific
Poon, 2022[46] NCT02339701 Some concerns China	Men aged ≥ 18 years with a histologic diagnosis of prostate adenocarcinoma and NCCN low- or intermediate-risk (T1-2, Gleason score ≤ 7 and PSA < 20 ng/mL) localized disease were eligible. Additional criteria were Zubrod performance status < 2, no nodal or distant metastasis, and no prior	SBRT 7.25 Gy/fraction 36.25 Gy 5 fractions 2 weeks N=31 Median age (range):	CFRT 2.0 Gy/fraction 76 Gy 38 fractions 7.5 weeks N=33 Median age (range):	Harms • Acute GU/GI toxicity • Late GU/GI toxicity Survival • Overall

Trial Name, Year **Trial #** **Risk of Bias** **Country** **Funding** **Follow-up**	**Inclusion/Exclusion Criteria** **Other Treatments**	**Intervention (Hypofractionation) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Comparator (Conventional) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Outcomes Reported** (Risk of Bias If Different by Outcome) ***Primary**
"This study did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors." Median follow-up 2.3 years	bilateral orchiectomy, chemotherapy, RT, cryosurgery, or definitive surgery for PCa. Patients with another invasive cancer, other than localized basal or squamous cell skin carcinoma, were ineligible. Other treatments: Neoadjuvant ADT was given in 10 patients (SBRT: 4; CFRT: 6). Total of 6 months of ADT prescribed 3 months prior to RT.	68 (53-78) Race NR PSA ng/mL: Mean (SD): 9.2 (5.0) Gleason score: 5: 3 (9) 6: 16 (51) 7: 12 (38) Tumor stage: T1a: 1 (3) T1c: 16 (51) T2a: 7 (22) T2b: 5 (16) T2c: 2 (6) Risk category (NCCN) Low: 16 (51) Intermediate: 15 (48)	70 (55-81) Race NR PSA ng/mL: Mean (SD): 8.6 (5.4) Gleason score: 5: 0 6: 22 (66) 7: 11 (33) Tumor stage: T1a: 0 T1c: 15 (45) T2a: 10 (30) T2b: 3 (9) T2c: 5 (15) Risk category (NCCN) Low: 16 (48) Intermediate: 17 (51)	
Wang, 2021[55] **CHIRP** NCT01488968	Patients were eligible if they had newly diagnosed, histologically proven PCa, classified as high-risk	2.72 Gy/fraction 68 Gy 25 fractions	2.0 Gy/fraction 78 Gy 39 fractions	Harms • Acute GU/GI toxicity

Trial Name, Year **Trial #** **Risk of Bias** **Country** **Funding** **Follow-up**	**Inclusion/Exclusion Criteria** **Other Treatments**	**Intervention (Hypofractionation) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Comparator (Conventional) Characteristics** **Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Outcomes Reported** (Risk of Bias If Different by Outcome) ***Primary**
Some concerns Canada Alberta Cancer Foundations, Alberta Innovates-Health Solutions Median follow-up 38 months	disease (1 or more of: clinical stage ≥ T3, Gleason ≥ 8, or PSA ≥ 20 ng/mL). Patients were excluded if they had any of the following: clinical or radiologic evidence of distant metastasis, previous prostatectomy or more than 1 transurethral resection of prostate, previous pelvic radiation therapy (RT), history of inflammatory bowel disease, anal stenosis, colorectal surgery, repeated endoscopic examinations, interventions related to anorectal diseases, hip prostheses, or ≥ 4 month history of AST. Other treatments: AST was offered for 18 months	Weeks NR N=55 Md age (range): 67 (49-79) Race: NR PSA ng/mL: < 10: 12 (22) ≥ 10: 42 (78) Gleason score: 6: 2 (4) 7: 26 (48) 8: 15 (28) 9: 11 (20) Tumor stage: Tx: 0 T1: 5 (9) T2: 24 (44) T3: 23 (43) T4: 2 (4) Risk category (IPSS):	Weeks NR N=56 Md age (range): 70 (49-80) Race: NR PSA ng/mL: < 10: 13 (24) ≥ 10: 42 (76) Gleason score: 6: 2 (4) 7: 15 (27) 8: 19 (35) 9: 19 (35) Tumor stage: Tx: 1 (2) T1: 6 (11) T2: 29 (53) T3: 19 (35) T4: 0 Risk category (IPSS):	• Late GU/GI toxicity* Survival • Biochemical recurrence-free • Overall • Prostate-specific

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
		Mild (0-7): 16 (30) Moderate (8-19): 24 (44) Severe (20-35):12 (22) Not done: 2 (4)	Mild (0-7): 21 (38) Moderate (8-19): 20 (36) Severe (20-35):9 (16) Not done: 5 (9)	
Widmark, 2019[39,58] **HYPO-RT-PC** ISRCTN45905321 Some concerns 12 centers in Sweden and Denmark The Nordic Cancer Union, Swedish Cancer Society and the Swedish Research Council Median follow-up 5 years	Participants were men up to 75 years of age with histologically verified intermediate-to-high-risk prostate cancer and WHO performance status between 0 and 2. Intermediate-to-high-risk prostate cancer was categorized according to the TNM classification system as T1c−T3a with no evidence of lymph node involvement or distant metastases with one or two of the following risk factors: stage T3a, Gleason score of at least 7, or PSA of at least 10 ng/mL. The maximum PSA allowed was 20 ng/mL and no ADT was permitted.	6.1 Gy/fraction 42.7 Gy 7 fractions 2.5 weeks N=589 (598 randomized) Mean age (range): 68 (64-72) Race: NR PSA ng/mL: ≤ 10: 357 (61) > 10: 232 (39) Gleason score: 5: 5 (1) 6: 99 (17) 7: 447 (76) 8: 33 (6) 9: 5 (1)	2.0 Gy/fraction 78 Gy 39 fractions 8 weeks N=591 (602 randomized) Mean age (range): 69 (65-72) Race: NR PSA ng/mL: ≤ 10: 356 (60) > 10: 235 (40) Gleason score: 5: 2 (< 1) 6: 106 (18) 7: 444 (75) 8: 37 (6) 9: 2 (< 1)	Harms • Acute GU/GI toxicity • Late GU/GI toxicity Survival • Overall • Prostate-specific

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
		Tumor stage: T1c: 313 (53) T2: 252 (43) T3a: 24 (4) Risk category NR	Tumor stage: T1c: 289 (49) T2: 275 (47) T3a: 27 (5) Risk category NR	
Yeoh, 2006[57,62,129] Trial # NR Some concerns Australia Funding NR Median follow-up 90 months	Inclusion criteria NR Other treatments: Androgen deprivation therapy, which was not standard practice for T2b disease at the time, was one of the exclusion criteria for the study	2.75 Gy/fraction 55 Gy 20 fractions 4 weeks N=108 Median age (range) for entire study: 69 (44-82) Race: NR PSA ng/mL: NR Gleason score: NR	2 Gy/fraction 64 Gy 32 fractions 6.5 weeks N=109 Median age (range) for entire study: 69 (44-82) Race: NR PSA ng/mL: NR Gleason score: NR	Survival • Biochemical recurrence free • Overall • Prostate-specific

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/Exclusion Criteria Other Treatments	Intervention (Hypofractionation) Characteristics	Comparator (Conventional) Characteristics	Outcomes Reported (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time N Baseline Characteristics (n, %)	
		Tumor stage: NR Risk category NR	Tumor stage: NR Risk category NR	
Zhong, 2021[56] NCT02934685 Some concerns China National Natural Science Foundation of China & VARIAN Research Foundation Median follow-up 26 months	Male patients were eligible if 1) they were aged ≥ 50 years, 2) had histologically confirmed prostate adenocarcinoma, 3) had good performance status (ECOG score 0-1), and 4) had clinical stage T1-3 disease by the 2009 AJCC criteria. Exclusion criteria were 1) clinical stage T4, 2) evidence of nodal or distant metastases, 3) previous pelvic radiation therapy, or 4) previous malignancies. Other treatments: Per NCCN guidelines, intermediate-risk and high-risk patients received, respectively, 4-6 months and 24 months of neoadjuvant/concurrent androgen deprivation therapy.	2.5 Gy/fraction 70 Gy 28 fractions 5.6 weeks N=46 Age (range): (54-84) ≤ 70: 4 (8.7) > 70: 42 (91.3) Race: NR PSA ng/mL: < 10: 12 (26.1) ≥ 10: 34 (73.9) Gleason score: ≤ 6: 17 (37.0) 7: 19 (41.3) ≥ 8: 10 (21.7)	2 Gy/fraction 80 Gy 40 fractions 8 weeks N=46 Age (range): (61-86) ≤ 70: 9 (19.6) > 70: 37 (80.4) Race: NR PSA ng/mL: < 10: 14 (30.4) ≥ 10: 32 (69.6) Gleason score: ≤ 6: 16 (34.8) 7: 16 (34.8) ≥ 8: 14 (30.4)	Harms • Acute GU/GI toxicity • Late GU/GI toxicity* Survival • Biochemical recurrence free

Trial Name, Year **Trial #** **Risk of Bias** **Country** **Funding** **Follow-up**	**Inclusion/Exclusion Criteria** **Other Treatments**	**Intervention (Hypofractionation) Characteristics**	**Comparator (Conventional) Characteristics**	**Outcomes Reported** (Risk of Bias If Different by Outcome) *Primary
		Dose/Fraction **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	**Dose/Fraction** **Total Dose** **Time** **N** **Baseline Characteristics (n, %)**	
		Tumor stage: T1: 7 (15.2) T2: 25 (54.3) T3: 14 (30.4) Risk category (NCCN): Low: 16 (34.8) Int. 19 (41.3) High: 11 (23.9)	Tumor stage: T1: 8 (17.4) T2: 26 (56.5) T3: 12 (26.1) Risk category (NCCN): Low: 15 (32.6) Int. 17 (37.0) High: 14 (30.4)	

Abbreviations. ADT=androgen deprivation therapy; AJCC=American Joint Committee on Cancer; AST=androgen suppression treatment; CFRT=conventional fractionated radiotherapy; CHHiP=Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer trial; CHRIP=Conventional versus Hypofractionated Radiation in High Risk Prostate Patients trial; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; GI=gastrointestinal; GS=Gleason score; GU=genitourinary; Gy=gray; HYPO-RT-PC=Hypofractionated Radiotherapy for Prostate Cancer trial; HYPRO=Hypofractionated versus Conventionally Fractionated Radiotherapy for Patients with Prostate Cancer trial; IPSS=International Prostate Symptom Score; Md=median; Mn=mean; MR=magnetic resonance; MRI=magnetic resonance imaging; NCCN=National Comprehensive Cancer Network; NHS=National Health Service (UK); ng/mL=nanograms per millimeter; NR=not reported; PACE-B=Prostate Advances in Comparative Evidence trial; PCa=prostate cancer; PSA=prostate-specific antigen; PTV=planning target volume; RT=radiotherapy; SBRT=stereotactic body radiotherapy; SD=standard deviation; UK=United Kingdom; WHO=World Health Organization.

Appendix Table 8. Detailed Results for Survival Outcomes for Prostate Cancer Trials Rated "Low" or "Some Concerns" Risk of Bias

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/total N; %	Comparison N Events/Total N; %	Results
Biochemical recurrence-free	**Arcangelli, 2010**[49] **Arcangelli, 2012**[61] **Arcangelli, 2017**[60] Some concerns	3-year Time from first day of radiotherapy to biochemical relapse according to the most recent Phoenix definition of nadir PSA +2 ng/mL	87%	79%	P = 0.04
		4-year	82%	60%	P = 0.004
		5-year	85%	79%	P = 0.65
		10-year	72%	65%	HR = 1.62 (0.88-2.97) P = 0.15
	Avkshtol, 2020[63] NCT00062309 Low	10-year Phoenix definition	74.6%* (66.1 to 83.7)	78.9%* (71.3 to 87.3)	P = 0.49
	Lukka, 2005[54] Low	5-year Houston definition	249/466 (53.4%)*	271/470 (57.7%)*	NR
	Wang, 2021[55] **CHIRP** NCT01488968 Some concerns	3-year Phoenix criteria	97.3% (92% to 102.6%)	91% (81.0% to 100.8%)	P = 0.61
	Yeoh, 2011[57] Some concerns	7.5-year Phoenix and ASTRO criteria	ASTRO 44% Phoenix 53%	ASTRO 44% Phoenix 34%	P = NS HR = 0.65 (0.42-0.99) P < 0.05
	Zhong, 2021[56] NCT02934685 Some concerns	2-year	94.6%	95%	P = 0.70

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/total N; %	Comparison N Events/Total N; %	Results
Local recurrence	**Arcangelli, 2010**[49] **Arcangelli, 2012**[61] Some concerns	3-year	3/83 (3.6%)	1/85 (1.2%)	P = 0.06
		5.8 years	7/83 (8.4%)	10/85 (11.8%)	NR
	Avkshtol, 2020[63] NCT00062309 Low	10-year	4.7%	4%	P = 0.82
	Lukka, 2005[54] NCT01488968 Low	5-year Based on the prostate clinical evaluation at time of digital rectal examination. Signs or symptoms of local recurrence were confirmed through prostate biopsy.	2/466 (0.4%)	1/470 (0.2%)	NR
Metastases	**Arcangelli, 2010**[49] **Arcangelli, 2012**[61] Some concerns	3-year	6/83 7.2%	10/85 11.8%	P = 0.46
		5-year	90%	86%	NS
	Avkshtol, 2020[63] NCT00062309 Low	5-year	7.5% (3.4 to 12.0)	4.0% (1.3 to 7.3)	ARD = 3.5% (-1.8 to 8.8)
		10-year	14.3% (8.5 to 20.5)	6.4% (2.8 to 10.08)	ARD = 7.8% (0.7 to 15.1) HR = 1.93 (0.93 to 4.0) P = 0.08
	Lukka, 2005[54] Low	5-year Distant disease recurrence of metastases outside the prostate included recurrent tumor found in regional pelvic lymph nodes, bone (abnormal bone x-rays or bone scan), liver (abnormal liver scan, ultrasound, or CT scan), and	10/466 2%	4/470 1%	NR

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/total N; %	Comparison N Events/Total N; %	Results
		lung (abnormal chest x-ray consistent with metastases).			
Overall survival	**Arcangelli, 2012**[61] **Arcangelli, 2017**[60] Some concerns	5-year	92%	82%	NS
		10-year	75%	64%	HR = 1.45 (0.80 to 2.59) P = 0.22
	Dearnaley, 2012[40] **CHHiP** SRCTN97182923 Some concerns	5-year Time from randomization to death from any cause.	60 Gy 93%	57 Gy 92%	74 Gy 91%
	de Vries, 2020[59] **Incrocci, 2016**[48] **HYPRO** ISRCTN85138529 Low	7-year	80.8% (76.5 to 84.4)	77.6% (73.0 to 81.5)	HR = 0.82 (0.61 to 1.09) P = 0.17
		5-year	86.2% (82.3 to 89.4)	85.9% (81.8 to 89.2)	HR = 1.02 (0.71 to 1.46) P = 0.92
	Lee, 2016[41] **RTOG-0415** Low	5-year	92.5% (89.9 to 94.5)	93.2% (90.7 to 95.1)	HR = 0.95 (0.64 to 1.41)
	Hoffman, 2018[53] Low NCT00667888	8-year	90% (82.2 to 94.5)	85.2% (76.2 to 91.0)	NS
		10-year	82.8% (72.0 to 89.8)	76.1% (64.3 to 84.4)	NS
	Lukka, 2005[54] Low	5-year Time from randomization to death from any cause or date of last visit for patients still alive	87.6%	85.2%	HR = 0.85 (0.63 to 1.15)
	Poon, 2022[46] NCT02339701 Some concerns	1 year	100%	97%	P = 0.08

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/total N; %	Comparison N Events/Total N; %	Results
	Wang, 2021[55] **CHIRP** NCT01488968 Some concerns	3-year	94.8% (87.5 to 102.1)	100%	P = 0.12
	Widmark, 2019[39] **HYPO-RT-PC** ISRCTN45905321 Some concerns	5-year	94% (92 to 96)	96% (95 to 98)	HR = 1.11 (0.73 to 1.69)
	Yeoh, 2006[62] **Yeoh, 2011**[57] Some concerns	5-year	86.4%	84.1%	P = NS
		7-year	71%	69%	P = NS
Prostate-specific survival	**Arcangelli, 2012**[61] **Arcangelli, 2017**[60] Some concerns	5-year	98%	92%	NS
		10-year	95%	88%	HR = 2.40 (0.77 to 6.84) P = 0.07
	Avkshtol, 2020[63] NCT00062309 Low	10-year	95.6% (92.6 to 99.5)*	95.6% (92.7 to 99.5)*	NR
	Incrocci, 2016[48] **de Vries, 2020**[59] **HYPRO** ISRCTN85138529 Low	5-year	45/61 (73.7%)*	44/59 (74.6%)*	NR
		7-year	64/82 (78.0%)*	79/98 (80.1%)*	NR
	Hoffman, 2018[53] Low	10-year	100%	100%	--
	Lukka, 2005[54] Low	5-year Time from randomization to death from any cause or date of last visit for patients still alive	453/466 (97.2%)*	452/470 (96.2%)*	NR

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/total N; %	Comparison N Events/Total N; %	Results
	Wang, 2021[55] **CHIRP** NCT01488968 Some concerns	3-year	54/54 (100%)	55/55 (100%)	--
	Widmark, 2019[39] **HYPO-RT-PC** ISRCTN45905321 Some concerns	5-year Cumulative incidence of prostate cancer death analyzed with non-prostate cancer death as competing risk	98% (97 to 100)*	> 99% (99 to 100)*	P = 0.46
	Yeoh, 2006[62] **Yeoh, 2011**[57] Some concerns	5-year	107/108 (99.1%)*	106/109 (97.2%)*	NR
		7-year	106/108 (98.2%)*	105/109 (96.3%)*	NR

Notes. *Calculated by review authors.
Abbreviations. ARD=absolute rate difference; ASTRO=American Society for Radiation Oncology; CHHiP=Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer trial; CHRIP=Conventional versus Hypofractionated Radiation in High-Risk Prostate Patients trial; CT=computed tomography; HR=hazard ratio; HYPO-RT-PC=Hypofractionated Radiotherapy for Prostate Cancer trial; HYPRO=Hypofractionated versus Conventionally Fractionated Radiotherapy for Patients with Prostate Cancer trial; NR=not reported; NS=non-significant.

Appendix Table 9. Detailed Results for Toxicity Outcomes for Prostate Cancer Trials Rated "Low" or "Some Concerns" Risk of Bias

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, %		Comparison N Events/Total N, %	Results
Acute genitourinary (GU) toxicity	**Aluwini, 2015**[130] **HYPRO** ISRCTN85138529 Low	4-week grade ≥ 2; RTOG	191/401 47.6%		171/385 44.4%	P = 0.37
		3-month grade ≥ 2; RTOG	75/327 22.9%		73/325 22.4%	P = 0.89
	Arcangelli, 2011[65] Some concerns	Acute (1 month after the end of treatment) grade ≥ 2; RTOG/EORTC	39/83 47.0%		34/85 40.0%	P = 0.45
	Brand, 2019[47] **PACE-B** NCT01584258 Some concerns	Any point < 12 weeks after radiotherapy; grade ≥ 2; RTOG	118/432 27.3%		96/415 23.1%	Grade 2 only (92% of events) ARD = −4.2 (−10.0 to 1.7) P = 0.16
	Catton, 2017[43] NCT00304759 Low	During first 14 weeks; - grade ≥ 2; RTOG	185/608 30.4%		183/598 30.6%	NR
	Dearnaley, 2012[125] **Wilson, 2018**[70] **CHHiP** SRCTN97182923 Some concerns	< 18 weeks; grade ≥ 2; RTOG	60 Gy 356/720 49.4%	57 Gy 327/715 45.8%	74 Gy 331/715	60 Gy vs 74 Gy: P = 0.34 57 Gy vs 74 Gy: P < = 0.90
		< 18 weeks; grade ≥ 3; RTOG	NR		NR	60 Gy vs 74 Gy: <75 years P = 0.97 74 Gy vs 60 Gy: ≥ 75 years P = 0.004 57 Gy vs 74 Gy < 75 years P = 0.57 ≥ 75 years P = 0.08

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, %	Comparison N Events/Total N, %	Results
	Fonteyne, 2018[44] NCT01921803 Some concerns	Grade ≥ 2 occurring within 2 months after HFRT; CTCAE v4.0 or RTOG	47/77 61.0%	47/80 58.8%	NR
	Houshyari, 2021[45] Trial # NR Some concerns	Grade ≥ 2 occurring ≤ 5 months after randomization; RTOG	1/20 5.0%	1/20 5.0%	NS
	Lee, 2016[41] **RTOG-0415** Low	Grade ≥ 2 within 90 days of RT completion; CTCAE	147/545 27.0%	145/534 27.2%	NS
	Lukka, 2005[54] Low	≤ 5 months; grade 3 & 4, standardized National Cancer Institute of Canada toxicity scale	40/466 8.6%	23/470 7.4%	ARD -3.7 (-7.0 to -0.5)
	Norkus, 2009[51] Some concerns	12 weeks; grade 2; RTOG/EORTC (no grade ≥ 3 observed)	9/47 19.1%	21/44 14.6%	P = 0.003
	Norkus, 2013[50] Low	12 weeks; grade 2; RTOG/EORTC (no grade ≥ 3 observed)	1/115 0.9%	5/106 4.7%	P = 0.18
	Poon, 2022[46] NCT02339701 Some concerns	First occurrence of worst severity of adverse event from beginning of RT until ≤ 30 days after RT completion); CTCAE (no grade ≥ 3 observed)	1/31 3.2%	8/33 24%	P = 0.04
	Wang, 2021[55] **CHIRP** NCT01488968 Some concerns	Grade ≥ 2; CTCAE v4.0 (deemed related to treatment during or within 12 weeks after completion of RT)	16/53 30.2% (17.8 to 42.5)	16/55 30.9% (18.7 to 43.1)	P = 1.0
	Widmark, 2019[39] **HYPO-RT-PC**	Grade ≥ 2 at treatment end; RTOG	158/569 27.8%	132/578 22.8%	P = 0.06

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, %		Comparison N Events/Total N, %	Results
	ISRCTN45905321 Some concerns					
	Zhong, 2021[56] NCT02934685 Some concerns	Grade ≥ 2; CTCAE v3.0 (no Grade ≥3 observed)	8/46 17.4%		6/46 13.0%	P = 0.13
Acute gastrointestinal (GI) toxicity	**Aluwini, 2015**[130] **HYPRO** ISRCTN85138529 Low	4-week grade ≥ 2; RTOG	108/400 27.0%		70/385 18.2%	P = 0.003
		3-month grade ≥ 2; RTOG	42/327 12.8%		43/326 13.2%	P = 0.90
	Arcangelli, 2011[65] Some concerns	Acute (1 month after the end of treatment) grade ≥ 2; RTOG/EORTC	29/83 35%		18/85 21%	P = 0.07
	Brand, 2019[47] **PACE-B** NCT01584258 Some concerns	Any point < 12 weeks after radiotherapy; grade ≥ 2; RTOG	53/432 12.3%		43/415 10.4%	Grade 2 only (95% of events) RD −1.9 (−6.2 to 2.4; P = 0.38)
	Catton, 2017[43] NCT00304759 Low	During first 14 weeks; - grade ≥ 2 RTOG	99/608 16.3%		62/598 10.4%	P = .003
	Dearnaley, 2012[125] **Wilson, 2018**[70] **CHHiP** SRCTN97182923 Some concerns	<18 weeks; grade ≥2; RTOG	60 Gy 277/720 38.5%	57 Gy 270/713 37.9%	74 Gy 176/715 24.6%	60 Gy vs 74 Gy: P < 0.0001 57 Gy vs 74 Gy: P < 0.0001 “By 18 weeks, both bowel and bladder toxicity by RTOG assessment were similar between treatment groups”

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, %	Comparison N Events/Total N, %	Results
	Wilson, 2018[70] **CHHiP** SRCTN97182923 Some concerns	< 18 weeks grade ≥ 3; RTOG	NR	NR	60 Gy vs 74 Gy: < 75 years P < 0.0001 ≥ 75 years P = 0.10 57 Gy vs 74 Gy < 75 years P < 0.0001 ≥ 75 years P = 0.05
	Fonteyne, 2018[44] Trial #NCT01921803 Some concerns	Grade ≥ 2 occurring within 2 months after HFRT; CTCAE v4.0 or RTOG	21/77 27.3%	16/80 20.0%	NR
	Houshyari, 2021[45] Trial # NR Some concerns	Grade ≥ 2 occurring ≤ 5 months after randomization; RTOG	10/20 50.0%	12/20 60.0%	NR
	Lee, 2016[41] **RTOG-0415** Low	Grade ≥ 2 within 90 days of RT completion: CTCAE	58/545 10.6%	55/534 10.3%	NS
	Lukka, 2005[54] Low	≤ 5 months; grade 3 & 4, standardized National Cancer Institute of Canada toxicity scale	19/466 4.1%	12/470 2.6%	ARD -1.5 (-4.0 to 0.8)
	Norkus, 2009[51] Some concerns	Grade 2; RTOG/EORTC	8/47 17.0%	10/44 22.7%	NS
	Norkus, 2013[50] Low	12 weeks; grade 2; RTOG/EORTC (no grade ≥ 3 observed)	5/115 4.3%	8/106 7.5%	P = 0.37
	Poon, 2022[46] NCT02339701 Some concerns	First occurrence of worst severity of adverse event from beginning of RT until ≤ 30 days after RT completion); CTCAE (no grade ≥ 3 observed)	2/31 6.4%	7/33 21.2%	NR

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, %	Comparison N Events/Total N, %	Results
	Wang, 2021[55] **CHIRP** NCT01488968 Some concerns	Grade ≥ 2; CTCAE v4.0 (deemed related to treatment during or within 12 weeks after completion of RT)	10/53 18.9% (8.3 to 29.4)	12/55 21.8% (10.9 to 32.7)	P = 0.81
	Zhong, 2021[56] NCT02934685 Some concerns	Grade ≥ 2; CTCAE v3.0 (no grade ≥ 3 observed)	8/46 17.4%	5/46 10.9%	P = 0.19
Late genitourinary (GU) toxicity	**Aluwini, 2016**[64] **HYPRO** ISRCTN85138529 Low	3-year cumulative incidences of grade ≥ 2; RTOG/EORTC	21.9% (18.1 to 26.4)	17.7% (14.1 to 21.9)	HR 1.19 (0.88 to 1.59) P = 0.26
	Arcangelli, 2011[60,65] Some concerns	3-year grade ≥2; modified ("clinical") LENT-SOMA scale; occurring or persisting for ≥ 6 months after end of RT	7/83	5/85	P = 0.92
		9-year grade ≥ 2; modified ("clinical") LENT-SOMA scale; occurring or persisting for ≥ 6 months after end of RT	NR (reported as freedom from late toxicity, 86%)	NR (reported as freedom from late toxicity, 79%)	P = 0.68
	Catton, 2017[43] NCT00304759 Low	6 months onward; grade ≥ 2 RTOG	136/608 22.4%	134/598 22.4%	NR
	Dearnaley, 2012[125] **Wilson, 2018**[70] **CHHiP** SRCTN97182923 Some concerns	2-year; grade ≥ 2; RTOG	60 Gy 16/959 1.7%	57 Gy 11/962 1.1%	60 Gy vs 74 Gy: P = 0.71 74 Gy vs 57 Gy: P = 0.68

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, %	Comparison N Events/Total N, %	Results
		5-year; grade ≥ 2; RTOG	60 Gy 88/NR	57 Gy 57/NR	60 Gy vs 74 Gy: HR = 1.34 (0.98 to 1.85) P = 0.07 57 Gy vs 74 Gy: HR = 0.85 (0.60 to 1.12) P = 0.37
		5-year grade ≥ 2; RTOG/RMH/LENT-SOM	NR	NR	60 Gy vs 74 Gy: < 75 years P = 0.012 ≥ 75 years P = NS 57 Gy vs 74 Gy < 75 years P = NS ≥ 75 years P = NS
	Hoffman, 2014[53,66] Low NCT00667888	5-year (> 90 days after RT completion); grade ≥ 2 RTOG	15/101 15.8% (9.8 to 24.9)	15/102 16.5% (10.2 to 26.1)	P = 0.97
		5-year (> 90 days after RT completion); grade ≥ 2 RTOG	Intermediate/high vs low NCCN 0.63 (0.22 to 1.77) P = .38	Intermediate/high vs low NCCN 0.90 (0.31 to 2.64) P = .85	--
		8-year (> 90 days after RT completion) grade ≥ 2; RTOG	15/104 15.1% (9.4 to 23.8)	16/102 16.4% (10.4 to 25.4)	P = 0.84
	Lee, 2016[41] **RTOG-0415** Low	> 90 days after RT completion; grade ≥ 2; CTCAE	161/545 29.5%	121/534 22.6%	Grade 2: RR = 1.31 (1.07 to 1.61) P = 0.009 Grade 3:

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, %	Comparison N Events/Total N, %	Results
					RR = 1.56 (0.76 to 3.18) P = 0.22
	Lukka, 2005[54] NCT01488968 Low	> 5 months; grade 3 & 4, standardized National Cancer Institute of Canada toxicity scale	9/466 1.9%	9/470 1.9%	ARD = 0.0 (-1.9 to 1.9)
	Pollack, 2013[52] NCT00062309 Low	5-year cumulative risk; modified LENT/RTOG criteria	21.5% (14.4% to 29.6%)	13.4% (8.0% to 20.1%)	P = 0.16
	Poon, 2022[46] NCT02339701 Some concerns	1-year grade ≥ 2; CTCAE	6/31 19.4%	8/33 24.2%	NR
	Wang, 2021[55] **CHIRP** NCT01488968 Some concerns	Cumulative grade ≥ 2; CTCAE v4.0 (related to treatment that occurred > 3 months after RT completion)	8/50 16.0% (5.8 to 26.2)	3/50 6.0% (0 to 12.6)	P = 0.20
	Widmark, 2019[39] **HYPO-RT-PC** ISRCTN45905321 Some concerns	1-year grade ≥ 2; RTOG	32/528 6.1%	13/529 2.4%	P = 0.004
		5-year grade ≥ 2; RTOG	11/243 4.5%	12/249 4.8%	P = 1.00
	Zhong, 2021[56] NCT02934685 Some concerns	2-year grade ≥ 2; RTOG/ EORTC	0/46 0%	2/46 4.4%	P = 0.50

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, %		Comparison N Events/Total N, %	Results
Late gastrointestinal (GI) toxicity	**Aluwini, 2016**[64] **HYPRO** ISRCTN85138529 Low	3-year cumulative incidences; grade ≥ 2; RTOG/EORTC	41.3% (36.6 to 46.4)		39.0% (34.2 to 44.1)	HR = 1.16 (0.94–1.43) P = 0.16
	Arcangelli, 2011[60,65] Some concerns	3-year grade ≥ 2; modified ("clinical") LENT-SOMA scale; occurring or persisting for ≥ 6 months after end of RT	12/83 14.4%		10/85 11.8%	P = 0.55
		9-year grade ≥ 2; modified ("clinical") LENT-SOMA scale; occurring or persisting for ≥ 6 months after end of RT	NR (reported as freedom from late toxicity, 86.5%)		NR (reported as freedom from late toxicity, 84.6%)	P = 0.57
	Catton, 2017[43] NCT00304759 Low	6 months onward; grade ≥ 2 RTOG	54/608 8.9%		83/598 13.9%	P = .006
	Dearnaley, 2012[40] **Wilson, 2018**[70] **CHHiP** SRCTN97182923 Some concerns	2-year; grade ≥ 2; RTOG	60 Gy 28/959 2.9%	57 Gy 17/962 2.8%	74 Gy 35/922 3.8%	60 Gy vs 74 Gy: P = 0.31 74 Gy vs 57 Gy: P = 0.0075
		5-year grade ≥ 2; RTOG	60 Gy 105/NR	57 Gy 95/NR	74 Gy 111/NR	60 Gy vs 74 Gy: HR = 0.94 (0.72 to 1.23) P = 0.65 57 Gy vs 74 Gy: HR = 0.84 (0.64 to 1.11) P = 0.22

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, %	Comparison N Events/Total N, %	Results
		5-year grade ≥ 2; RTOG/RMH/LENT-SOM	NR	NR	60 Gy vs 74 Gy: < 75 years P = NS ≥ 75 years P = NS 57 Gy vs 74 Gy < 75 years P = NS ≥ 75 years P = NS
	Hoffman, 2014[53,66] Low NCT00667888	5-year (> 90 days after completion of RT); grade ≥ 2 RTOG	11/101 10.0% (5.5 to 17.8)	5/102 5.1 (2.1 to 11.7)	P = 0.11
		5-year (> 90 days after RT completion); grade ≥ 2 RTOG	Intermediate/high vs low NCCN HR = 0.22 (0.06 to 0.74) P = .02	Intermediate/high vs low NCCN HR = 0.61 (0.10 to 3.65) P =. 59	--
		8-year (> 90 days after completion of RT) grade ≥ 2 RTOG	12/104 12.6% (7.3 to 21.2)	5/102 5.0% (2.1 to 11.6)	P = .08
	Lee, 2016[41] **RTOG-0415** Low	> 90 days after RT completion; grade ≥ 2; CTCAE	121/545 22.2%	75/534 14.0%	Grade 2: RR = 1.59 (1.22 to 2.06) P = 0.005 Grade 3: RR = 1.55 (0.80 to 2.99) P = 0.19
	Lukka, 2005[54] Low	>5 months; grade 3 & 4, standardized National Cancer Institute of Canada toxicity scale	6/466 1.3%	6/470 1.3%	ARD = 0.0 (-1.7 to 1.6)
	Pollack, 2013[52] NCT00062309 Low	Overall crude incidence at 5 years (≥ 3 months after	18.1%	22.5%	P = 0.39

Outcome	Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, %	Comparison N Events/Total N, %	Results
		the end of RT); LENT/RTOG criteria			
	Poon, 2022[46] NCT02339701 Some concerns	1-year grade ≥ 2; CTCAE	4/31 12.9%	6/33 18.2%	NR
	Wang, 2021[55] **CHIRP** NCT01488968 Some concerns	Cumulative grade ≥ 2; CTCAE v4.0 (related to treatment that occurred > 3 months after RT completion)	8/50 16.0% (5.8 to 26.2)	5/50 10.0% (1.7 to 18.3)	P = 0.55
	Widmark, 2019[39] **HYPO-RT-PC** ISRCTN45905321 Some concerns	5-year grade ≥ 2; RTOG	3/244 1.2%	9/249 3.6%	P = 0.14
	Zhong, 2021[56] NCT02934685 Some concerns	2-year grade ≥ 2; RTOG/ EORTC	3/46 6.5%	2/46 4.3%	P = 0.92

Abbreviations. ARD=absolute rate difference; CHHiP=Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer trial; CHRIP=Conventional versus Hypofractionated Radiation in High Risk Prostate Patients trial; CTCAE=Common Terminology Criteria for Adverse Events; EORTC=European Organization for Research and Treatment of Cancer; GI=gastrointestinal; GU=genitourinary; Gy=gray; HFRT=hypofractionated radiotherapy; HR=hazard ratio; HYPRO=Hypofractionated versus Conventionally Fractionated Radiotherapy for Patients with Prostate Cancer trial; LENT-SOM=Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scale; NCCN=National Comprehensive Cancer Network; NR=not reported; NS=non-significant; PACE-B=Prostate Advances in Comparative Evidence trial; RMH=Royal Marsden Hospital scoring system; RR=risk ratio; RT=radiation therapy; RTOG=Radiation Therapy Oncology Group.

Appendix Table 10. Detailed Results for Global Quality of Life for Prostate Cancer Studies Rated "Low" or "Some Concerns" Risk of Bias

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N	Comparison N Events/Total N	Results
Fransson, 2021[58] **HYPO-RT-PC** ISRCTN45905321 Some concerns	Mean difference in clinically relevant deterioration of global health/quality of life (EORTC QLQ-30) at 6 years after treatment	46/125 (37%)	56/134 (42%)	MD 5.0% (95% CI [-5.0,15.0]) P = 0.41
Brand, 2019[47] **PACE-B** NCT01584258 Some concerns	EPIC 26	NR	NR	"We observed no significant difference between the study groups in the proportion of patients with a clinically significant reduction from baseline for any EPIC-26 subdomain score area, neither assessed at any time nor at week-12 only."
Bruner, 2019[67] **RTOG-0415** NCT00331773	EuroQol-5 EPIC	NR	NR	"There were no differences between arms at any time point for the EuroQol-5 questionnaire." "There were no differences in change score between arms with respect to any of the EPIC domain scores at 6, 24, or 60 months."
Shaikh, 2017[68] NCT00062309 Low	IPSS overall (minimum clinically important difference [0.5 SD change from baseline]) at 5 years	NR	NR	HR = 1.11 (95% CI [0.56, 2.18])
	IPSS QoL (minimum clinically important difference [0.5 SD change from baseline]) at 5 years	NR	NR	HR = 0.68 (95% CI [0.29, 1.62])
Wilkins, 2015[69] **CHHiP** SRCTN97182923 Some concerns	2-year FACT-P, SF-12 and SF-36	NR	NR	"We identified no significant differences in health-related quality of life domain scores measured by FACT-P, SF-12 and SF-36 between treatment groups at 24 months."

Abbreviations. CHHiP=Conventional of Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer trial; CI=confidence interval; EORTC QLQ-30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EPIC-26=Extended Prostate Cancer Index, 26 item; FACT-P=Functional Assessment of Cancer Therapy-Prostate; HR=hazard ratio; HYPO-RT-PC=Hypofractionated Radiotherapy for Prostate Cancer trial;

IPSS=International Prostate Symptom Score; MD=mean difference; NR=not reported; PACE-B=Prostate Advances in Comparative Evidence trial; QoL=quality of life; SF-12=Short Form Survey 12 item; SF-36=Short Form Survey 36 item; SD=standard deviation.

APPENDIX F. LUNG CANCER TABLES

Appendix Table 11. Risk of Bias Ratings for All Eligible Lung Cancer Trials

Trial	Outcome	Domain 1: Risk of Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk of Bias in Measurement of the Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
Ball[10]	Harms	Low	Low	Low	Low	Low	Low	Low
	Survival	Low	Low	Low	Low	Low	Low	Low
	QoL	Low	Low	Low	Low	Low	Low	Low
Gronberg[133]	Harms	Some concerns	High	High	Low	Low	Some concerns	High
	Survival	Some concerns	High	High	Low	Low	Some concerns	High
	QoL	Some concerns	High	High	Low	Low	Some concerns	High
Iyengar[74]	Harms	Low	Low	Low	Low	Low	Low	Low
	Survival	Low	Low	Low	Low	Low	Low	Low
Roy[73]	Harms	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
	Survival	Low	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
	QoL	Low	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Singh[134]	Harms	High	Low	Low	Some concerns	Low	Low	High
	Survival	High	Low	Low	Some concerns	Low	Low	High
	QoL	High	Low	Low	Some concerns	Low	Low	High
Slawson[135]	Survival	Some concerns	High	High	Low	Low	Some concerns	High
Nyman[72]	Harms	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
	Survival	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
	QoL	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
Qiu[71]	Harms	Low	Low	Low	Low	Low	Low	Low

Trial	Outcome	Domain 1: Risk of Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk of Bias in Measurement of the Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
	Survival	Low	Low	Low	Low	Low	Low	Low

Appendix Table 12. Study Characteristics for All Eligible Lung Cancer Trials

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Standard of Care Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
Qui, 2021[71] NCT02337712 LOW Multicenter NR NR Median follow-up of 24.3 months	Eligibility criteria included being 18 to 75 years old and having pathologically confirmed SCLC with LS as defined by the Veterans Administration Lung Cancer Study Group; measurable lesions based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria; and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to	N = 88 Age, median(range): 58 (35-75) Female: 14 (15.9%) ECOG PS 0 40(45.5%) 1 48(54.5%) Unknown 0 Nonsmoker 16(18.2%) Smoker 72(81.8%) Unknown 0	65 Gy in 26 daily fractions for 5 days a week over 36 days, once daily	N = 94 Age, median(range): 58 (19-75) Female: 11(11.7%) ECOG PS 0 49(52.1%) 1 43(45.7%) Unknown 2(2.1%) Nonsmoker 11 (11.7%) Smoker 82(87.2%) Unknown 1(1.1%) UICC/AJCC stage	45 GY in 30 twice-daily fractions, with an interfractional interval of at least 6 hours, for 5 days a week for 19 days	Survival: • PFS • OS • LPFS • DMFS Harms: Acute • Cough • Dyspnea** • Pneumonitis • Pleural effusion** • Atelectasis** • Esophagitis • Nausea** • Vomiting** • Anemia**

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Standard of Care Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
	1; an acceptable radiation therapy target volume as judged by the radiation oncologists; adequate bone marrow and hepatic renal functions; forced expiratory volume in 1 second greater than 1 L; no prior chemotherapy, radiation therapy, surgery, or other anticancer therapy; weight loss ≤ 10% within the past 3 months; and the ability to provide informed consent. Patients with mixed small and non-small cell carcinoma were excluded.	UICC/AJCC stage IA-B 1(1.2%) IIA-B 3(3.5%) IIIA-B 84(95.3%)		IA-B 2(2.2%) IIA-B 6(6.5%) IIIA-B 86(91.3%)		• Leukopenia** • Lymphopenia** • Neutropenia** • Thrombocytopenia ** • Fatigue** • Fever** • Weight loss** Late: • Cough • Hemoptysis** • Dyspnea** • Pneumonitis • Pleural effusion** • Pulmonary fibrosis** • Anemia** • Leukopenia** Primary Endpoint: PFS Secondary Endpoint: OS, locoregional progression-free survival (LPFS), distant metastasis free survival (DMFS), and toxicities
Ball, 2021 (CHISEL)[10] NCT01014130 LOW	Eligible patients had cytologically or histologically proven stage	N = 66	18 Gy/fraction 54 Gy total 3 fractions	N = 35	66 Gy in 33 daily 2 Gy fractions over 6. 5 weeks or, 50 Gy	Survival: • LTF • OS

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Standard of Care Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
Multicenter: 11 hospitals in Australia and 3 hospitals in New Zealand Funding: The Radiation and Optometry Section of the Australian Government Department of Health with the assistance of Cancer Australia, and the Cancer Society of New Zealand and the Cancer Research Trust New Zealand (formerly Genesis Oncology Trust). Median follow-up per group for local treatment failure was 2.1 years (IQR 1. 2-3. 6) for patients randomly assigned to standard radiotherapy and 2. 6 years	T1N0M0 or T2aN0M0 NSCLC according to the seventh edition of the Union for International Cancer Control TNM staging manual. Eligible cancer types: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, bronchioloalveolar cell carcinoma, large cell neuroendocrine carcinoma, and non-small-cell carcinoma not otherwise specified. Patients were aged 18 years or older and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The tumour had to be noncentral, defined as at least 1 cm from the	Age, median(IQR): 73.2 (68.9-78.6) Female: 30(45%) ECOG PS 0 18(28%) 1 47(72%) Missing 1(1%) Current smoker No 45 (69%) Yes 20 (31%) Missing 2 (1%) Current or previous smoker No 2 (3%) Yes 63 (97%) Missing 1 (1%) T stage 1 47 (71%) 2a 19 (29%)	For tumours < 2 cm from chest wall: 12 Gy/fraction 48 Gy total 4 fractions	Age, median(IQR): 77 (69.6-81.2) Female: 15(43%) ECOG PS 0 10 (29%) 1 25 (71%) Unknown 0 Current Smoker No 21 (60%) Yes 14 (40%) Missing 0 Current or previous smoker No 0 Yes 35 (100%) Missing 0 T stage 1 24 (69%) 2a 11 (31%)	in 20 daily 2. 5 Gy fractions over 4 weeks according to institutional preference	• LCSS Harms: • Dyspnea** • Cough • Fatigue ** • Chest wall pain ** • Lung infection ** • Pain ** • Cataract ** • Hypoxia ** • Weight loss ** • Pulmonary fibrosis** • Dermatitis radiation ** • Nausea ** • Atelectasis ** • Pneumonitis • Pleural effusion** • Fracture ** • Anorexia ** • Dysphagia ** • Bronchopulmonary haemorrhage ** • Dizziness ** • Dry mouth** • Infections and infestations ** • Superficial soft tissue fibrosis **

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Standard of Care Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
(IQR 1. 6-3. 6) for patients assigned to SABR	mediastinum and 2 cm from the bifurcation of the lobar bronchi. To be eligible, the patient's tumour had to be assessed as medically inoperable by a multidisciplinary team including thoracic surgeons and respiratory physicians, or the patient had to have refused surgery. Patients were ineligible if they had had previous chemotherapy or radiotherapy for the index cancer, or had multiple synchronous primary tumours requiring radiotherapy. To be eligible, patients needed to have a life expectancy of 2 years or more.					• Back pain** • Diarrhoea ** • Non-cardiac chest pain** • Pericardial effusion** • Respiratory, thoracic, and mediastinal disorders** • Skin and subcutaneous tissue disorders ** • Vomiting** • Abdominal distension** • Abdominal pain** • Anxiety ** • Constipation ** • Dehydration ** • Dry skin ** • Dysgeusia ** • Erythema multiforme ** • Esophagitis • Gastro-oesophageal reflux disease ** • Laryngeal inflammation ** • Mucosal infection **

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Standard of Care Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
						• Musculoskeletal and connective tissue disorder** • Myalgia** • Oral haemorrhage** • Toothache** • Upper respiratory infection** • Urinary tract infection** Primary endpoint: Local treatment failure Secondary endpoint: Overall survival, lung cancer-specific survival, treatment-related toxicity, and quality of life
Iyengar, 2021[74] NCT01459497 LOW Multicenter: 9 cancer centers in Texas, USA This study was supported by a	Eligibility criteria: Histologically proven stage II/III or recurrent NSCLC. A Zubrod (ECOG) performance status of 2 or greater (0 indicates asymptomatic; 5, death); had greater than 10% weight loss in the previous 6 months, and/or were ineligible for	N = 50 Age N (%) 50-59: 6 (12.0) 60-69:13 (26.0) 70-79: 18 (36.0) 80-90: 13 (26.0) Female: 20 (40)	60 Gy 15 fractions	N = 46 Age N (%) 50-59 9 (19.6) 60-69 12 (26.1) 70-79) 17 (37.0) 80-90) 8 (17.4) Female: 13 (28.3)	60 Gy 30 fractions	Survival: • OS • MOS • PFS • LC Harms: Cardiovascular: • Pericardial effusion** • SVC syndrome**

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Standard of Care Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
grant from the Cancer Prevention and Research Institute of Texas (principal investigator, Dr Timmerman). Median follow-up of 8.7 (3.6-19.9) months	concurrent chemoradiotherapy after consultation with radiation and medical oncologists. Patients were ineligible if they had a total gross tumor volume greater than 500 mL, had undergone prior regional radiotherapy, received chemotherapy within 1 week of study registration, or were pregnant or lactating.	Baseline performance status 0 1 (2.0) 1 16 (32.0) 2 28 (56.0) 3 5 (10.0) T category T0 1 (2.0) T1 12 (24.0) T2 19 (38.0) T3 10 (20.0) T4 8 (16) N category N0 8 (16.0) N1 12 (24.0) N2 26 (52.0) N3 4 (8.0) Stage IB 1 (2.0) 0 II 12 (24.0) III 36 (72.0) Recurrent IV 1 (2.0)		Baseline performance status 0 1 (2.2) 1 13 (28.3) 2 29 (63.0) 3 3 (6.5) T category T0 1 (2.2) T1 5 (10.9) T2 15 (32.6) T3 15 (32.6) T4 10 (21.7) N category N0 15 (32.6) N1 3 (6.5) N2 17 (37.0) N3 11 (23.9) Stage IB 1 0 II 10 (21.7) III 35 (76.1) Recurrent IV 1 (2.2)		Death NOS Fatigue** Gastrointestinal tract: • Anorexia** • Dysphagia** • Esophagitis • Nausea** Musculoskeletal: • Back pain** • Chest wall pain** Respiratory: • ARDS** • Atelectasis** • Bronchitis** • Cough • DLCO decline** • Dyspnea ** • FEV1 decline** • Hemoptysis** • Pleural effusion** • Pneumonia** • Pneumonitis • Pulmonary fibrosis** • Wheezing ** Skin: • Dermatitis ** • Dryness ** • Hyperpigmentation ** • Pruritus**

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Standard of Care Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
						Primary endpoint: OS Secondary endpoint: MOS, PFS, Toxicity
Nyman, 2016 **SPACE trial[72]** NCT01920789 LOW Multicenter: 9 Scandinavian Centers This study was supported by grants from the Nordic Cancer Union (NCU), and King Gustav V Jubilee Clinic Cancer Foundation in Gothenburg Median follow-up of 37 months	The inclusion criteria were patients in WHO performance status 0 to 2 with stage I ($T_{1-2}N0M0$, AJCC 6th edition) non-small cell lung cancer who were medically inoperable or refused surgery. The tumors should be morphologically verified. If that was impossible due to peripheral lesion and poor lung function (intolerance for pneumothorax), there had to be an increasing tumor size in repeated CT-scans and a positive PET-	N = 49 Age mean (range) 73 (57-86) Female: 27 (55%) Baseline performance status 0 11 (22.5%) 1 27 (55%) 2 10 (20.5%) Missing 1 (2%) Tumor stage T1 26(53%) T2 23(47%)	66 Gy 3 fractions (1 week)	N = 53 Age mean (range) 75 (62-85) Female: 34 (64%) Baseline performance status 0 5 (9.5%) 1 33 (62%) 2 14 (26.5%) Missing 1 (2%) Tumor stage T1 40(75%) T2 13(25%)	70 Gy 35 fractions (7 weeks)	Survival: • PFS • OS • LC Quality of life Harms: • Toxicity (acute, late) Esophagitis Pneumonitis Dyspnea ** Fibrosis** Cough Skin reactions** Rib fractures** Primary endpoint: PFS

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Standard of Care Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
	scan. The main exclusion criteria were central tumor growth adjacent to trachea, main bronchus or esophagus, maximal tumor diameter >6 cm, patients with prior malignancy in the last five years and if previous radiotherapy had been delivered to the thorax.					Secondary endpoint: OS, LC, Toxicity, QoL
Roy, 2016[73] Clinical Registry of India number CTRI/2013/11/004143 LOW Single Center: All India Institute of Medical Sciences, New Delhi, India NR Median follow-up 15 months	Eligibility criteria included newly diagnosed patients (previously untreated) of biopsy-proven SCC of the lung with a performance status score of Eastern Co-operative Oncology Group 0–1, stages IIIA and IIIB, without significant haematological or other systemic (renal, hepatic or pulmonary)	Hypofractionation N = 18 Age Median (range): 60 (42-70) Mean±SD: 58±8.48 Female: 1 Smoker:17 Non-smoker:1 Stage IIIA:7	48 Gy 20 fractions (4 weeks)	Standard RT N = 18 Age Median (range): 55 (42-70) Mean±SD: 56±8.08 Female: 1 Smoker:17 Non-smoker:1 Stage IIIA:8	60 Gy 30 fractions (6 weeks)	Survival: • ORR • PFS • OS Quality of life** Harms: Toxicity (acute) Haemotological: • Anaemia** • Neutropaenia** • Thrombocytopaenia** Non-haemotological: • Skin reaction**

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Standard of Care Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
	impairments. Patients with hypersensitivity to platinum agents or comorbidities that can adversely affect treatment and outcome or those who had prior or synchronous malignancies were excluded from the study.	IIIB:11		IIIB:10		• Anorexia** • Mucositis** • Laryngitis** • Pharyngitis/oesophagitis • Pneumonitis • Peripheral neuropathy** • Hyponatraemia** Toxicity (late) • Lung fibrosis** • Oesophageal morbidity** • Skin morbidity** • Neurological toxicity** Primary endpoint: ORR Secondary endpoint: OS, PFS, Toxicity, QoL
Gronberg, 2015[133] Registration NR High NR	Eligible patients were ≥ 18 years old (no upper limit); had SCLC ineligible for surgery and confined	Hypofractionation N = 84 Age Median(range): 63(40-85) Female:39 (46%)	42 Gy 15 fractions (once daily)	Twice daily thoracic RT N = 73 Age Median(range):63(44-79)	45 Gy 30 fractions (twice daily, hyper-fractionation)	Survival: • PFS • OS HRQoL Harms:

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics N Baseline Characteristics (n, %) Dose/Fraction Total Dose Time	Standard of Care Characteristics N Baseline Characteristics (n, %) Dose/Fraction Total Dose Time	Outcomes Reported (Risk of Bias If Different by Outcome)
Study supported by the Central Norway Regional Health Authority (RHA), the Norwegian University of Science and Technology (NTNU) and the Norwegian Cancer Society. Median follow-up for PFS was 59 months (range 29‑97); Median follow-up for OS was 81 months (range 52‑119)	to 1 hemithorax and the mediastinum, contralateral hilus and supraclavicular regions; measurable disease according to RECIST v1.0; no other active cancer; no prior chest-radiotherapy; WHO performance status (PS) 0‑2; leukocytes ≥3.0 x 10^9/l, platelets ≥100 x10^9/l, bilirubin <1.5 x ULN and creatinine <125 µmol/l. One negative cytology was required if pleural effusion was present.	Baseline WHO performance status 0 31 (37%) 1 42 (50%) 2 11 (13%) Stage I 7 8% II 7 8% IIIA 34 40% IIIB 30 36% Unknown 6 7%	Female:37 (51%) Baseline WHO performance status 0 20 (27%) 1 39 (53%) 2 14 (19%) Stage Stage I 6 8% II 9 12% IIIA 21 29% IIIB 28 38% Unknown 9 12%	Toxicity • Esophagitis • Pneumonitis • Anemia** • Leukopenia** • Thrombocytopenia ** • Neutropenia** • Neutropenic infection** • Infection without neutropenia** • Dysphagia** • Dyspnea** Primary endpoint: PFS Secondary endpoint: OS, Toxicity, HRQoL
Slawson, 1988[135] Registration NR High Single Center. Department of Radiation Oncology, University of Maryland Medical	Eligible patients had locally advanced, non-metastatic, measurable lung cancer. Patients were required to have a pathologically-proved, previously unirradiated lung cancer. Patients	Hypofractionation N = 73 Baseline ECOG performance status: 0-1 62 2-3 38 Stage III 96	5 Gy/fraction Total 60 Gy 12 fractions (12 weeks)	Hyperfractionation N = 77 Baseline ECOG performance status: 0-1 64 2-3 36 Stage III 97	2 Gy/fraction Total 60 Gy 30 fractions (6 weeks)	Survival • Median survival • Local failure • Local and distant failure • Distant failure Harms (acute) • Weight loss

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Standard of Care Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
Supported from Developmental Account, Department of Radiation Oncology, University of Maryland Medical Systems Median follow-up NR	had to have measurable disease and no evidence of distant metastases to sites other than the ipsilateral supraclavicular region and/or brain.	IV 4		IV 3		• Nausea and vomiting Toxicity • Esophagitis • Skin reaction Harms (late) • Skin fibrosis
Singh, 2019[136] Registration NR High Multi-center, three centers in the US. Supported by Roswell Park Alliance Foundation grant. Median follow-up 53.8 months	Eligibility criteria included the following: patients aged 18 years or older with a Zubrod (ECOG) performance status score of 0 to 2, deemed medically inoperable or refused surgery, and with early-stage, histologically proven NSCLC defined as American Joint Committee on Cancer sixth edition T1 to T2 (≤5 cm) N0M0 after staging by computed tomography (CT) and positron	SBRT Arm 1 N = 49 Age, mean (SD) 77(8) Female 27 (55%) T stage T1a 20 (41%) T1b 21 (43%) T2a 8 (16%) Overall Stage 1A 39 (80%) 1B 10 (20%)	30 Gy/fraction Total 30 Gy 1 fraction	SBRT Arm 2 N = 49 Age, mean (SD) 75 (8) Female 23 (47%) T stage T1a 27 (55%) T1b 16 (33%) T2a 6 (12%) Overall stage 1A 42 (86%) 1B 7 (14%)	20 Gy/fraction Total 60 Gy 3 fractions	Survival • LC • PFS • OS QoL Harms Any AE Toxicity (acute) • Pneumonia • COPD • Cough • Dyspnea • Dyspnea, exertional • Wheezing Primary endpoint: Toxicity

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Standard of Care Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (n, %)	Dose/Fraction Total Dose Time	
	emission tomography (PET) studies. Tumors had to be characterized as peripheral per Radiation Therapy Oncology Group (RTOG) 0236.					Secondary endpoint: LC, OS, PFS, QoL

Notes. *Risk of bias differed by outcome; **Did not extract.
Abbreviations. SCLC=small cell lung cancer; LS=limited stage4; ECOG PS=Eastern Cooperative Oncology Group performance status; AJCC=American Joint Committee on Cancer; UICC=Union for International Cancer Control; NOS=not otherwise specified; PFS=progression-free survival; OS=overall survival; LPFS=locoregional progression-free survival; DMFS=distant metastasis free survival; LC=local control; MOS=Median Overall Survival; ORR=overall response to treatment; HRQoL=health-related quality of life.

Appendix Table 13. Detailed Results for Survival Outcomes for Lung Cancer Trials Rated "Low" or "Some Concerns" Risk of Bias

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
Overall Survival				
Qui, 2021[71] NCT02337712 LOW	Median OS months	39.3 (31.1, 47.2)	33.6 (30.2, 37.0)	P = 0.14
	2-year OS	74.2% (64.0, 84.3)	69.9% (59.9, 79.9)	NR
	3-year OS	56.2% (43.2, 69.1)	41.5% (29.0, 54.0)	NR
	5-year OS	56/88*	48/94*	NR

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
	Median OS (95% CI)	SABR: 5 years (3.4 to not estimable)	Standard RT: 3 years (1.9 to not estimable)	HR = 0.53 (95% CI [0.30, 0.94]) (P = 0.027)
	Kaplan Meier 2-year overall survival % (95% CI)/time (years) from randomization until death from any cause	SABR: 77% (67, 88)	Standard RT: 59% (44, 78)	NR
Iyengar, 2021[74] NCT01459497 LOW	1 year overall survival median rate (95% CI)/time from randomization until death from any cause	37.7% (95% CI [24.2%, 51.0%])	44.6% (95% CI [29.9%, 58.3%])	P = 0.29
	Median overall survival rate (95% CI)]/ time from randomization until death from any cause	8.2 months (95% CI [5.4,12.4])	10.6 months (95% CI [8.4, 15.3])	P = 0.17
Nyman, 2016[72] NCT01920789 LOW	Kaplan Meier [median rate (95% CI)]/date of randomization to death 1 year	81%	89%	HR = 0.75 (95% CI [0.43,1.30])
	2 years	68%	72%	
	3 years	54%	59%	
Roy, 2016[73] CTRI/2013/11/004143 LOW	Kaplan Meier (log-rank test)/period from date of diagnosis to death or last follow-up	75% Median OS: 24.7 months	52% Median OS: 12.3 months	P = 0.007 (log-rank test)
Progression-free Survival				
Qui, 2021[71] NCT02337712 LOW	Median PFS months	17.2 (11.8, 22.6)	13.4 (10.8, 16.0)	P = 0.03
	2-year PFS	42.3% (31.1, 53.5)	28.4% (18.2, 38.6)	NR

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
	3-year PFS	37.2% (26.0, 48.3)	19.9% (9.7, 30.1)	NR
Iyengar, 2021[74] NCT01459497 LOW	Rate (95% CI)/time from randomization until progression of disease	6.4 months (95% CI [4.1, 7.8])	7.3 months (95% CI [5.0, 10.6])	P = 0.77
Nyman, 2016[72] NCT01920789 LOW	Kaplan Meier [median rate (95% CI)]/ date of randomization to progression 1 year	76%	87%	HR = 0.85 (95% CI) [0.52, 1.36])
	2 years	53%	54%	
	3 years	42%	42%	
Roy, 2016[73] CTRI/2013/11/004143 LOW	Kaplan Meier (log-rank test)/period from date of diagnosis to the date of locoregional failure, distant metastasis, or last follow-up	Median PFS: 17 months	Median PFS: 5.4months	P = 0.053
Local Progression-free Survival				
Qui, 2021[71] NCT02337712 LOW	Kaplan Meier [median rate (95% CI)]/time from randomization until first confirmation of loco-regional progression	22/88	37/94	NR
	Median LPFS months	NA	23.9 (17.3, 29.1)	P = 0.017
	2-year LPFS months	68.5 (56.3, 80.7)	49.8 (37.1, 62.5)	NR
	3-year LPFS months	60.8 (47.2, 74.3)	39.7 (24.6, 54.8)	NR
Distant Metastasis-free Survival				
Qui, 2021[71] NCT02337712 LOW	Kaplan Meier [median rate (95% CI)]/time from randomization until first confirmation of distant metastasis	35/88	44/94	NR
	Median DMFS months	31.2 (NA)	19.5 (14.9, 24.2)	P = 0.124

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
	2-year DMFS months	57.2 (45.4, 69.0)	43.5 (31.0, 56.0)	NR
	3-year DMFS months	47.9 (35.0, 60.8)	35.8 (22.9, 48.7)	NR
Lung-cancer-specific Survival				
Ball, 2019[10] NCT01014130 LOW	Kaplan Meier [median rate (95% CI)]/time (years) randomization until death from lung cancer	7/66	10/35	HR = 0.49 (95% CI [0.21, 1.14]), P = 0.092
Mortality				
Qui, 2021[71] NCT02337712 LOW	Total deaths	32/88 (36.4)	46/94 (48.9)	NR
	Treatment-related deaths	1/85 (1.2)	2/92 (2.2)	NR
Ball, 2019[10] NCT01014130 LOW	Total deaths	26/66 (33)	22/35 (63)	NR
	Death from cancer	7/66 (10.6)	10/35 (28.5)	NR
	Death from lung cancer and other causes	4/66 (6)	0/35 (0)	NR
	Death from other causes	13/66 (19.7)	11/35 (31)	NR
	Death from other malignancy	2/66 (3)	1/35 (3)	NR
	Death from unknown cause	1/66 (1.5)	0/35 (0)	NR
Iyengar, 2021[74] NCT01459497 LOW	Median follow-up was 8.7 (3.6- 19.9) months. Total treatment period deaths	5/50 (10)	NR	NR
	24-month exploratory analysis NSCLC deaths	11/38 (28.9)	19/39 (48.7)	P = .10
Nyman, 2016[72] NCT01920789 LOW	Total deaths during follow-up	18/49 (37)	21/53 (39.6)	NR
	Death from lung cancer	5/49 (10)	8/53 (15)	NR

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
Roy, 2016[73] CTRI/2013/11/004143 LOW	Median follow-up 15 months Death due to toxicity	1/18 (5.5)	1/18 (5.5)	NR

Appendix Table 14. Detailed Results for Toxicity Outcomes for Lung Cancer Trials Rated "Low" or "Some Concerns" Risk of Bias

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
Acute Cough				
Qui, 2021[71] NCT02337712 LOW	≥ Grade 3 (first 90 days post treatment)/CTCAE	0/85 (0)	0/92 (0)	NR
Late Cough				
Qui, 2021[71] NCT02337712 LOW	≥ Grade 3 (greater than 90 days post treatment)/CTCAE	0/85 (0)	0/92 (0)	NR
Acute and Late Cough				
Ball, 2019[10] NCT01014130 LOW	≥ Grade 3 (worst toxicity per patient per toxicity type)/CTCAE	2/66 (3.0)	0/35 (0)	NR
Iyengar, 2021[74] NCT01459497 LOW	≥ Grade 2/CTCAE	1/50 (2.0)	3/46 (6.5)	NR
Nyman, 2016[72] NCT01920789 LOW	≥ Grade 2 (maximal toxicity)/ CTCAE 3.0	6/48 (12.5)	3/53 (5.7)	P = 0.22

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
Acute Pneumonitis				
Qui, 2021[71] NCT02337712 LOW	≥ Grade 3 (first 90 days post treatment)/CTCAE	2/85 (2.4)	3/92 (3.3)	NR
Roy, 2016[73] CTRI/2013/11/004143 LOW	≥ Grade 3)/CTCAE	0/18 (0)	1/18 (5.5)	P = 0.99
Late Pneumonitis				
Qui, 2021[71] NCT02337712 LOW	≥ Grade 3 (greater than 90 days post treatment)/CTCAE	0/85 (0)	0/92 (0)	NR
Acute and Late Pneumonitis				
Ball, 2019[10] NCT01014130 LOW	≥ Grade 3) (worst toxicity/patient/toxicity type)/ CTCAE	0/66 (0)	0/35 (0)	NR
Iyengar, 2021[74] NCT01459497 LOW	≥ Grade 2/CTCAE	4/50 (8.0)	3/46 (6.5)	NR
Nyman, 2016[72] NCT01920789 LOW	CTCAE 3.0 (maximal toxicity)	2/48 (4.2)	5/53 (9.4)	P = 0.085
Acute Esophagitis				
Qui, 2021[71] NCT02337712 LOW	≥ Grade 3 (first 90 days post treatment)/ CTCAE	13/85 (15.3)	16/92 (17.4)	NR
Acute Pharyngitis/Esophagitis				
Roy, 2016[73] CTRI/2013/11/004143 LOW	≥ Grade 3/ CTCAE	1/18 (5.5)	3/18 (16.7)	P = 0.05

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
Acute and Late Esophagitis				
Iyengar, 2021[74] NCT01459497 LOW	≥ Grade 2/ CTCAE	12/50 (24.0)	5/46 (10.9)	NR
Nyman, 2016[72] NCT01920789 LOW	CTCAE 3.0 (maximal toxicity)	0/48 (0)	1/53 (1.9)	P = 0.006
Ball, 2019[10] NCT01014130 LOW	≥ Grade 3 (worst toxicity/patient/toxicity type)/ CTCAE	0/66 (0)	0/35 (0)	NR
All Adverse Events				
Iyengar, 2021[74] NCT01459497 LOW	Rate/CTCAE (≥ grade 2)	65/50 (130.0)	36/46 (78.3)	NR

Abbreviations. CTCAE=Common Terminology Criteria for Adverse Events (version 4.0); EORTC=European Organization for Research and Treatment for Cancer; CFRT=Conventionally Fractionated Radiotherapy.

Appendix Table 15. Detailed Results for Global Quality of Life for Lung Cancer Studies Rated "Low" or "Some Concerns" Risk of Bias

Trial Name, Year Trial # Risk of Bias	Effect Measure/ Definition	Hypofractionation N events/Total N	Standard Care N Events/Total N	Results
Ball, 2019[10] NCT01014130 LOW	EORTC QLQ-C30 Mean AUC (95% CI) for the difference in quality of life between arms/Global Health Status	NR	NR	AUC for the difference in quality of life between arms Overall AUC (95% CI): 5.19 (-3.9, 14) 3 months AUC (95% CI): -1.0 (-12.9, 10.2) 6 months AUC (95% CI): 5.0 (-6.37, 16.8)
Roy, 2016[73] CTRI/2013/11/004143 LOW	Global Health Status *median (range*): European Organisation for Research and Treatment of Cancer QOL questionnaire C30 and LC13/ 2-sample Wilcoxon rank-sum test was used to compare the QOL parameters among the 2 arms	Pre 50 (8.3, 66.7)	Pre 41.7 (0-58.3)	P = 0.24
		Post 66.7 (41.7, 100)	Post 58.3 (8.3, 100)	P = 0.44

Abbreviations. QLQ=Quality of Life Questionnaire; HRQL=health related quality of life.

APPENDIX G. HEAD AND NECK CANCER TRIALS

Appendix Table 16. Risk of Bias Ratings for All Eligible Head and Neck Cancer Trials

Trial	Outcome	Domain 1: Risk of Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk of Bias in Measurement of the Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
Bjordal[137]	QoL	Some concerns	High	Some concerns	High	Low	Low	High
Choudhury[78]	Harms	Low	Low	Low	Low	Low	Low	Low
	Survival	Low	Low	Some concerns	High	Low	Low	High
Kachhwaha[138]	Harms	Some concerns	High	High	Low	Low	Some concerns	High
	Survival	Some concerns	High	High	Low	Low	Some concerns	High
Kodaira[76]	Harms	Low	Low	Low	Low	Low	Low	Low
	Survival	Low	Low	Low	Low	Low	Low	Low
Moon[75]	Harms	Low	Low	Some concerns	Low	Low	Some concerns	Some concerns
	Survival	Low	Low	Some concerns	Low	Low	Low	Some concerns
Tian[77]	Harms	Some concerns	Low	Low	Low	Low	Low	Some concerns
	Survival	Some concerns	Low	Low	Low	Low	Low	Some concerns
Tolia[139]	QoL	High	Some concerns	Some concerns	Low	Low	Some concerns	High

Trial	Outcome	Domain 1: Risk of Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk of Bias in Measurement of the Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
Yamazaki[140]	Harms	Some concerns	High	High	Low	Low	Some concerns	High
	Survival	Some concerns	High	High	Low	Low	Low	High

Appendix Table 17. Study Characteristics for Eligible Head and Neck Cancer Trials

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	Conventional Characteristics N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	Outcomes Reported (Risk of Bias If Different by Outcome)
Bjordal, 1994[137] HIGH Norway Norwegian Cancer Society Follow-up survey 7-11 years after original RCT	NR The study was based on a larger randomized study that was carried out at the Norwegian Radium Hospital (NRH) between 1979 and 1984.	N = 101 Mean age (range) 68 (34, 92) Female N = 23 (22.8) Stage I: 58 (57.4) II: 18 (17.8) III: 13 (12.9) IV: 12 (11.9) No stage: 0 (0)	65.8 Gy/28 fractions 4 days a week for 7 weeks	N = 103 Mean age (range) 67 (32, 91) Female N = 26 (25.2) Stage I: 39 (37.9) II: 21 (20.4) III: 18 (17.5) IV: 22 (21.4) No stage: 3 (2.9)	70 Gy/35 fractions 5 days a week for 7 weeks	**Primary endpoint:** Quality of life
Choudhury, 2012[78] SOME CONCERNS Country NR (Single-center) Funding NR Median follow-up of 11 months	**Inclusion**: Patients with chemotherapy, surgery (other than biopsy from primary and or neck nodes for histology confirmation), and radiation naïve non-metastatic, inoperable, locally advanced squamous cell carcinoma of head and neck, AJCC stages III to IVB with tumor characteristics of T3 and T4 with or without N2-3, M0, with reduced	N = 44 (18 for disease-free survival outcome) Mean age (range) 61.3 (50, 72) Female N = 5 (11.4) Stage III: 16 (36.4) IV A: 18 (40.9) IV B: 10 (22.7)	50 Gy/16 fractions over 3 weeks	**Arm B (Conventional)** N = 42 (22 for disease-free survival outcome) Mean age (range) 61.1 (50, 71) Female N = 7 (16.7) Stage III: 16 (38.1) IV A: 17 (40.5)	66 Gy/33 fractions 6 fractions per week over 5.5 weeks	**Primary endpoint:** Toxicities **Survival** • OS • Disease-free survival **Harms**: Acute toxicity • Mucositis Late toxicity • Xerostomia (parotid)

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	Conventional Characteristics N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	Outcomes Reported (Risk of Bias If Different by Outcome)
	creatinine clearance (<60 ml/min), age more than 50 years, significant co-morbidities like uncontrolled diabetes, cardiac disease, poor performance status (ECOG 3 and 4).	ECOG performance status 3: 30 (68.2) 4: 14 (31.8)		IV B: 9 (21.4) ECOG performance status 3: 33 (78.6) 4: 9 (21.4) **Arm C (Conventional)** N = 46 (18 for disease-free survival outcome) Mean age (range) 61.0 (50, 73) Female N = 5 (10.9) Stage III: 14 (30.4) IV A: 20 (43.5) IV B: 12 (26.1) ECOG 3: 35 (76.1) 4: 11 (23.9)	66 Gy/33 fractions over 6.5 weeks	
Kachhwaha, 2021[138] HIGH	**Inclusion**: Age < 70 years; ECOG 0–2; no previous history of	N = 25 Age	55 Gy/20 fractions	N = 25 Age	66 Gy/33 fractions	**Primary endpoints**: Overall survival, disease-free survival

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	
India Funding NR Follow-up NR	malignancy-oriented treatment; adequate baseline organ functions (hematological, renal function test, liver function test, and others); and CT or MRI of head and neck was done to exclude node involvement and for tumor extension. **Exclusion**: Distant metastasis; other concurrent malignancies; history of previous surgery, radiotherapy, and/or chemotherapy; and pregnant and lactating women.	≤ 55: 16 (64) 56-70: 9 (36) Female N = 1 (4) T stage 1: 13 (52) 2: 12 (48) ECOG 0: 9 (36) 1: 16 (64) 2: 0 (0) Tobacco use Smoker: 21 (84) Chewer: 6 (24) Alcoholic: 6(24)	5 days a week for 4 weeks	≤ 55: 13 (52) 56-70: 12 (48) Female n=2 (8) T stage 1: 11 (44) 2: 14 (56) ECOG 0: 7 (28) 1: 16 (64) 2: 2 (8) Tobacco use Smoker: 19 (76) Chewer: 5 (20) Alcoholic: 5 (20)	5 days a week for 6.5 weeks	**Survival:** • OS • DFS **Harms**: Toxicity (late) • Dysphagia
Kodaira, 2018[76] LOW Japan (Multicenter)	**Inclusion**: Patients with histologically confirmed squamous cell carcinoma of the glottis, diagnosed with T1 or T2 (no impaired cord morbidity) N0M0	N = 186 Median age (IQR) 67 (62, 72)	**T1 Patients (N = 140)**	N = 184 Median age (IQR) 68 (63, 73)	**T1 Patients (N = 137)**	**Primary endpoint**: Progression-free survival at 3 years **Survival** • PFS

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	
Health Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan (20S-5, 20S-6, 17-17, 16-12, 17S-5 H21-018, H24-007 to all authors), and the National Cancer Center Research and Development Funds (23-A-16, 23-A-21, 26-A-4 and 29-A-3 to all authors). Median follow-up of 4.8 years (IQR, 3.4, 6.2 years)	disease. Radiation therapy was expected to be completed within the recommended duration without interruption due to national holidays. Age 20–80 years, ECOG 0–1, no previous surgery or RT, and no previous cancer or additional current cancers. Patients were required to have sufficient organ function.	Female N = 6 (3.2) Stage: T T1a: 100 (53.8) T1b: 40 (21.5) T2: 46 (24.7) T3: 0 (0) Stage: N N0: 185 (99.5) N2: 1 (0.5) M0: 185 (99.5) M1: 1 (0.5)	2.4 Gy x 25 fractions 60 Gy **≥ T2 Patients (N = 46)** 2.4 Gy x 27 fractions 64.8 Gy	Female N = 8 (4.3) Stage: T T1a: 104 (56.5) T1b: 33 (17.9) T2: 46 (25) T3: 1 (0.5) Stage: N N0: 184 (100) N2: 0 (0) M0: 184 (100) M1: 0 (0)	66 Gy/33 fractions **≥ T2 Patients (N = 47)** 70 Gy/25 fractions	• OS **Harms**: Toxicity (acute) • Mucositis (larynx) • Any mucositis • Dysphagia Toxicity (late): • Soft-tissue necrosis
Moon, 2014[75] SOME CONCERNS Korea (Multicenter) NCC Grant No.	**Inclusion**: histologically confirmed glottic squamous cell carcinoma, 18 years of age or older, Karnofsky Performance Score of 60 or higher, 1997 AJCC stage I or II (T1–2N0M0), no prior RT or chemotherapy for	N = 74 Age < 65: 33 (45) ≥ 65: 41 (55) Female N = 2 (3)	**T1 Patients (N = 65)** 63 Gy/28 fractions Once daily	N = 82 Age < 65: 42 (51) ≥ 65: 40 (49) Female N = 3 (4)	**T1 Patients (n = 74)** 66 Gy/33 fractions Once daily	**Primary endpoint**: Progression-free survival at 5 years **Survival:** • OS • PFS

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	
1310070 from the National Cancer Center Median follow-up of 67 months (range, 2, 122 months)	laryngeal cancer, and no history of malignancies for 5 years except non-melanoma skin cancer. Patients with gross residual disease despite stripping or laser excision of a glottic carcinoma were allowed to enroll.	Stage: T T1a: 45 (61) T1b: 20 (27) T2a: 7 (9) T2b: 2 (3) Smoker Yes: 58 (78) No: 16 (21)	**T2 Patients (N = 8)** 67.5 Gy/30 fractions Once daily	Stage: T T1a: 48 (59) T1b: 26 (32) T2a: 7 (8) T2b: 1 (1) Smoker Yes: 64 (78) No: 18 (22)	**T2 Patients (N = 8)** 70 Gy/35 fractions Once daily	**Harms**: Toxicity (acute and late) • Mucositis • Larynx
Tian, 2014[77] NR SOME CONCERNS China (Single-Center) Funding NR Median follow-up of 25.0 months (range, 6,118 months)	**Inclusion**: 1) histologically confirmed locally recurrent NPC or NPC diagnosed by clinical symptoms and radiological findings in those patients with disease located in the skull base or intracranial cavity that was inaccessible for biopsy; 2) no evidence of distant metastases at diagnosis; 3) > 6 months between the end of primary radiation therapy (RT) and disease recurrence; and 4) a Karnofsky performance status score of at least 70	N = 59 Median age (range) 47.5 (25,61) Female N = 10 (16.9) Stage: T T1: 6 (10.2) T2: 7 (11.9) T3: 24 (40.7) T4: 22 (37.3) Stage: N N0: 50 (84.7) N1-2: 9 (15.3)	60 Gy/27 fractions 5 days per week	N = 58 Median age (range) 46.0 (28,65) Female N = 13 (22.4) Stage: T T1: 4 (6.9) T2: 8 (13.8) T3: 22 (37.9) T4: 24 (41.4) Stage: N N0: 52 (89.7) N1-2: 6 (10.3)	68 Gy/34 fractions 5 days per week	**Primary endpoint:** Overall survival **Survival:** • OS • Progression-free survival • Local recurrence **Harms:** Toxicity (acute) • Mucositis Toxicity (late) • Xerostemia • Mucosal necrosis • Temporal lobe necrosis

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	
	Exclusion: Previous chemotherapy, RT, or definitive surgery after the diagnosis of locally recurrent NPC. Patients with another active cancer or unstable cardiac or renal disease that required treatment.					
Tolia, 2013[139] HIGH Greece Funding NR Follow-up NR	**Inclusion**: a) 18 years or older; b) Inoperable disease (the constitutional state of all patients precluded an operation for medical reasons and/or severe comorbidities); c) Newly diagnosed moderately advanced head and neck carcinoma; d) Pathologically proven squamous cell tumor. e) Receiving RT and regular follow-up at the radiation oncology Unit of Attikon University Hospital; f) Prospectively randomized selected patients; & g) Completion of the self-reported questionnaire.	N = 13 Median Age (Range) 61 (46,76) Female N = 3 (23.1) Stage IVa: 10 (76.9) IVb: 3 (23.1)	64.4 Gy/28 fractions 5 day per weeks	N = 9 Median age (range) 67 (54,78) Female N = 2 (22.2) Stage IVa: 6 (66.7) IVb: 3 (33.3)	70 Gy/35 fractions 5 days per week	**Primary endpoint**: overall survival **Survival:** • OS **Quality of Life:** (EORTC QLQ-H&N35) **Harms:** Overall toxicity (acute and late)

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	
Yamazaki, 2006[140] HIGH Japan Supported by a grant from the Ministry of Health and Welfare of Japan Median follow-up of 64 months (Range, 24,122 months)	**Inclusion**: Patients with invasive, previously untreated, T1 squamous cell carcinoma of the true vocal cords were enrolled in this trial with curative intent at the Department of Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases.	N = 88 Mean Age (SD) 64 (9) Female N = 3 (3) Stage: T T1a: 71 (81) T1b: 17 (19) Smoker Yes: 82 (93) No: 6 (7)	**Arm A-1 (N = 71)** 60 Gy/30 fractions over 6 weeks **Arm A-2 (N = 17)** 66 Gy/33 fractions over 6.6 weeks	N = 92 Mean age (SD) 65 (10) Female N = 7 (8) Stage: T T1a: 73 (79) T1b: 19 (21) Smoker Yes: 83 (90) No: 9 (10)	**Arm B-1** (N = 73) 56.25 Gy/25 fractions over 5 weeks **Arm B-2 (N = 19)** 63 Gy/28 fractions over 5.6 weeks	**Primary endpoint**: progression-free survival **Survival:** • PFS • OS **Harms**: Toxicity (acute) • Dermatitis • Mucositis

Notes. *Risk of bias differed by outcome.
Abbreviations. AJCC=American Joint Committee on Cancer; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; DFS=Disease-Free Survival; ECOG=Eastern Cooperative Oncology Group performance assessment; EORTC QLQ-H&N 35=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck module; MRI=magnetic resonance imaging; NPC=nasopharyngeal cancer; OS=Overall Survival; PFS=progression-free survival.

Appendix Table 18. Detailed Results for Survival Outcomes for Head and Neck Cancer Trials Rated "Low" or "Some Concerns" Risk of Bias

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
Overall Survival				
Tian, 2014[77] NR SOME CONCERNS	3-year overall survival	57.4% (deaths: 25/59)	38.0% (deaths: 36/58)	P = 0.06
	5-year overall survival	44.2% (deaths: 33/59)	30.3% (deaths: 39/56)	
Kodaira, 2018[76] NR LOW	3-year overall survival	174/186 (93.5%) 95% CI: (88.9%, 96.3%)	181/184 (98.4%) 95% CI: (95%, 99.5%)	NR
Moon, 2014[75] NR SOME CONCERNS	2-year overall survival	100%	96.2%	P = 0.359
	5-year overall survival	86.6%	82.5%	
Progression-free Survival				
Kodaira, 2018[76] NR LOW	3-year	152/186 (81.7%) 95% CI: (75.4%,87.0%)	147/184 (79.9%) 95% CI: (73.4%, 85.4%)	P = 0.047
Moon, 2014[75] SOME CONCERNS	5-year	88.5%	77.8%	HR: 1.55 P = 0.213
Tian, 2014[77] NR SOME CONCERNS	5-year	56.8%	55.2%	P = 0.58
Local Recurrence				
Kodaira, 2018[76] NR LOW	3-year	8/186 (4.3%)	5/184 (2.7%)	NR

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
Moon, 2014[75] NR SOME CONCERNS	5-year	9/74 (12.2%)	16/82 (19.5%)	NR
Tian, 2014[77] NR SOME CONCERNS	5-year	12/35 (34.2%)	11/44 (25%)	NR
Mortality				
Tian, 2014[77] NR SOME CONCERNS	Median follow-up 25.0 months Total deaths	35/59	44/58	NR
	Death due to disease progression	18/35 (51.4%)	18/44 (40.9%)	P value = 0.95
	Death due to late complications	14/35 (40.0%)	24/58 (54.5%)	P value = 0.02
	Death due to other causes	3/35 (8.5%)	2/44 (4.5%)	NR
Kodaira, 2018[76] NR LOW	Death due to glottic cancer	8 (4.3)	5 (2.7)	NR
	Death due to other diseases	11 (5.9)	10 (5.4)	NR

Abbreviations. CTCAE=Common Terminology Criteria for Adverse Events; EORTC QLQ-H&N 35=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck module.

Appendix Table 19. Detailed Results for Toxicity Outcomes for Head and Neck Cancer Trials Rated "Low" or "Some Concerns" Risk of Bias

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
Acute Dysphagia				
Kodaira, 2018[76] NR LOW	Acute grade 3-4 (no specified time period)/CTCAE v. 3.0	0/177 (0)	0/183 (0)	NR
Acute Mucositis				
Kodaira, 2018[76] NR LOW	Acute CTCAE v.3.0 (time period NR)	Mucositis (laryngeal) Grade 1-2: 164/183 (89.6) Grade 3-4: 10/183 (5.5) Any mucositis Grade 1-2: 172/183 (94) Grade 3-4: 11/183 (6)	Mucositis (laryngeal) Grade 1-2: 159/177 (89.8) Grade 3-4: 7/177 (4) Any mucositis Grade 1-2: 165/177 (93.2) Grade 3-4: 9 (5.1)	NR
Moon, 2014[75] NR SOME CONCERNS	Acute grade ≥ 2 RTOG/EORTC	0/74	0/82	P = 1.0
Tian, 2014[77] NR SOME CONCERNS	Acute grade 3 RTOG/EORTC	5/59 (8.5)	8/58 (13.8)	P = 0.39
Late Mucositis				
Moon, 2014[75] NR SOME CONCERNS	Late RTOG/EORTC (median follow-up 67 months)	Grade 2: 0 Grade 3-4: 0	Grade 2: 1 Grade 3-4: 0	P = 0.78
Choudhury, 2012[78] NR LOW	Late RTOG/EORTC mucositis 2 and 3	Grade 2: 14/44 Grade 3: 6/44	Grade 2: 30/88 Grade 3: 3/88	P = 0.001

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
Late Laryngeal				
Moon, 2014[75] NR SOME CONCERNS	Late RTOG/EORTC (median follow-up 67 months)	Grade 2: 0 Grade 3-4: 0	Grade 2: 2 Grade 3-4: 0	P = 0.84
Late Xerostomia				
Choudhury, 2012[78] NR LOW	Late RTOG/EORTC grade 2 and 3 (parotid only)	Grade 2: 14/44 Grade 3: 6/44	Grade 2: 30/88 Grade 3: 3/88	P = 0.005
Tian, 2014[77] NR SOME CONCERNS	Late grade 3 RTOG/EORTC	8/59 (13.6)	6/58 (10.3)	P = 0.42
Late Tissue Necrosis				
Kodaira, 2018[76] NR LOW	Late soft tissue (cervix) CTCAE v.3.0 (time period NR)	Grade 1-2: 1/184 (0.5) Grade 3: 0/184 (0) Grade 4: 0/184 (0)	Grade 1-2: 0/182 (0) Grade 3: 0/182 (0) Grade 4: 1/182 (0.6)	NR
Tian, 2014[77] NR SOME CONCERNS	Temporal lobe necrosis	12/59 (20.3)	13/58 (22.4)	P = 0.59

Abbreviations. CTCAE=Common Terminology Criteria for Adverse Events; EORTC QLQ-H&N 35=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck module; RTOG=Radiation Therapy Oncology Group.

APPENDIX H. RECTAL CANCER TRIALS

Appendix Table 20. Risk of Bias Ratings for All Eligible Rectal Cancer Trials

Trial	Outcome	Domain 1: Risk oif Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk tf Bias in Measurement of the Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
Bujko	Harms[79,80]	Low	Low	Low	Low	Low	Low[80] Some[79] concerns	Low[80] Some[79] concerns
	Survival[80]	Low	Low	Low	Low	Low	Low	Low
Stockholm III	Harms[81]	Low	Low	Low	Low	Low	Low	Low
	Mortality[81,141]	Low	Low	Low	Low	Low	Low	Low
	Survival[81,141]	Low	Low	Low	Low	Low	Low	Low
TROG	Harms[142]	Some concerns	High	High	Low	Low	Low	High

Appendix Table 21. Study Characteristics for All Eligible Rectal Cancer Trials

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	
Stockholm III, 2017[81] NCT00904813 LOW Sweden (multicenter) Swedish Research Council, Swedish Cancer Society, Stockholm Cancer Society, Stockholm County Council, Karolinska Institute Median follow-up was 5·2 years (IQR 3·7–6·1; range 2·0–14·6).	**Inclusion**: Patients scheduled for an open abdominal procedure with a biopsy-proven primary adenocarcinoma of the rectum, defined as an adenocarcinoma within 15 cm of the anal verge, without signs of non-resectability or distant metastases, and without previous radiotherapy to the abdominal or pelvic regions, signs of severe ischemic disease, or symptoms of severe arteriosclerosis, with no age restriction, were eligible.	**Arm A: hypo with surgery within 1 week** N = 129 Median age (IQR) 67 (62,74) Female N = 48 (37) ypStage I: 38 (29) II: 43 (33) III: 48 (37) IV: 0 (0) Unknown: 0 (0)	25 Gy/5 fractions with surgery within 1 week	N = 128 Median age (IQR) 66 (61,73) Female N = 55 (43) ypStage I*: 37(29) II: 46(37) III: 37(30) IV: 5(4) Stage x: 1(1)	50 Gy/25 fractions with surgery after 4-8 weeks	**Primary endpoint**: Time to local recurrence **Survival:** • Local recurrence • Distant metastases • OS • Recurrence-free survival **Harms**: Toxicity • Overall • Bowel obstruction (late) • Anal incontinence (late)
		Arm B: hypo with surgery within 4-8 weeks N = 128 Median age (IQR) 67 (62,75) Female n=49 (38)	25 Gy/5 fractions with surgery after 4-8 weeks			

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	
		ypStage I: 55 (43) II: 31 (24) III: 31 (24) IV: 7 (6) Unknown: 3 (2)				
Bujko, 2016[80] NCT00833131 LOW/SOME CONCERNS* Poland (multicenter) Grant No. N N403 580538 Polish Ministry of Science and Higher Education Median follow-up was 35 months	**Inclusion**: Primary or locally recurrent rectal cancer involving or abutting adjacent organs or structures (cT4) or a palpably fixed cT3 lesion, pathologically proven adencarcinoma, ≤ 75 years of age, WHO performance status ≤ 2 in patients fit for major surgery and chemotherapy along with informed written consent signed by patients. The involvement of mesorectal fascia as diagnosed by MRI was not used as the entry criterion, because of the long waiting time for pelvic MRI in Poland.	N = 261 Median Age (IQR) 60 (54,66) Female N = 78 (30) T Stage 0: 37 (17) 1: 3 (1) 2: 47 (22) 3: 110 (51) 4a: 4 (2) 4b: 15 (7) Residual cancer after resection: 4 N/A: 41 N stage 0: 150 (69) 1: 43 (20) 2: 26 (12)	25 Gy/ 5 fractions over 5 days, once daily (consolidation chemotherapy of 3 cycles of FOLFAX)	N = 254 Median age (IQR) 60 (56,65) Female N = 85 (33) T stage 0: 24 (12) 1: 5 (3) 2: 53 (26) 3: 92 (46) 4a: 9 (5) 4b: 19 (9) Residual cancer after resection: 3 N/A: 49 N stage 0: 136 (68)	50.4 Gy/ 28 fractions over 5.5 weeks, once daily (concomitantly with oxliplatin and boluses of 5-fluorouracil and leucovorin)	**Primary endpoint**: R0 resection rate (correlated with DFS)** **Survival** (low): • OS • DFS **Harms** (some concerns): Toxicity (acute) • Overall • Diarrhea

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics		Conventional Characteristics		Outcomes Reported (Risk of Bias If Different by Outcome)
		N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	N Baseline Characteristics (N, %)	Dose/Fraction Total Dose Time	
	Exclusion: Distant metastases, active coronary artery disease, cardiac arrhythmia, congestive heart failure, history of peripheral neuropathy and a history of cerebral stroke.	No data: 1 N/A: 41		1: 37 (19) 2: 26 (14) No data: 5 N/A: 49		
Trans-Tasman Radiation Oncology Group (TROG), 2017[142] HIGH Australia & New Zealand (27 centers) The National Health and Medical Research Council (NHMRC, No 209123), Cancer Council Victoria, and The Royal Australian and New Zealand College of Radiologists (RANZCR). Dr Nabila Ansari was supported by the	**Inclusion**: Patients were those with clinically resectable adenocarcinoma of the rectum, ultrasound or magnetic resonance imaging staged as T3, with the lower border of the tumor within 12 cm of the anal verge and with no evidence of any distant metastases. **Exclusion**: Recurrent rectal cancer, other cancers in the prior 5 years, unstable cardiac disease, active infection, and prior radio therapy. All patients had an Eastern	N = 161 Median age (range) 63 (26,80) Female N = 46 (29) ECOG performance status 0: 101 (63) 1: 59 (37) 2: 1 (1) T3 stage: 161 (100) N stage 0: 90 (56)	25 Gy/5 fractions over 5 days, followed by resection 3-7 days later Six monthly cycles of 5FU 425 mg/m^2 and folinic acid 20 mg/m^2 given daily for 5 days commenced 4-6 weeks after surgery	N = 161 Median age (range) 64 (29,82) Female N = 41 (25) ECOG performance status 0: 87 (54) 1: 71 (44) 2: 3 (2) T3 stage: 161 (100) N stage 0: 90 (56)	50.4 Gy/ 28 fractions over 5 weeks & 3 days Concurrent chemotherapy with continuous infusion of 5FU (225 mg/m^2/d) was administered daily for the duration of radiation. Surgery was performed 4 to 6 weeks after chemotherapy	**Primary endpoint**: 3-year local recurrence **Harms**: Toxicity (acute) Preop. radiation AEs (Grade 1–4) • Radiation dermatitis** • Diarrhea** • Proctitis** • Pain due to radiation** • Dysuria** • Urinary frequency/urgency** • Hematuria** • Neuropathic pain**

Trial Name, Year Trial # Risk of Bias Country Funding Follow-up	Inclusion/ Exclusion Criteria	Hypofractionation Characteristics N Baseline Characteristics (N, %) Dose/Fraction Total Dose Time	Conventional Characteristics N Baseline Characteristics (N, %) Dose/Fraction Total Dose Time	Outcomes Reported (Risk of Bias If Different by Outcome)
NOTARAS Scholarship of the University of Sydney and the Post Fellowship Training Board in Colorectal Surgery of the Colorectal Surgical Society of Australia and New Zealand (CSSANZ) and the Royal Australasian College of Surgeons (RACS). Follow-up NR	Cooperative Oncology Group performance status of 0 to 2.	1: 59 (37) 2: 1 (1) X: 11 (7) M0 stage: 161 (100)	1: 59 (37) 2: 2 (1) X: 10 (6) M0 stage: 161 (100)	• Perineal pain**

Notes. *Risk of bias differed by outcome.
**Unable to extract.
Abbreviations. OS=Overall Survival; DFS=Disease-Free Survival; CTCAE=Common Terminology Criteria for Adverse Events (version 4.0), ypStage=pathological stage after neoadjuvant treatment.

Appendix Table 22. Detailed Results for Survival Outcomes for Rectal Cancer Trials Rated "Low" or "Some Concerns" for Risk of Bias

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results	
Overall Survival					
Bujko, 2016[79,80] NCT00833131 LOW	3-year overall survival rate	73%	65%	HR (95% CI): 0.73 (0.53, 1.01), P = 0.046	
Stockholm III, 2017[81] NCT00904813 LOW	Hazard ratio/overall survival at the end of follow-up	NR	NR	Surgery within 1 week HR (95% CI): 0.94 (0.63, 1.4) Surgery within 4-8 weeks HR (95% CI): 0.81 (0.53, 1.24)	Overall P value = 0.62 (ref group Arm A)
Disease-free Survival					
Bujko, 2016[79,80] NCT00833131 LOW	3 year DFS rate	53%	52%	HR (95% CI): 0.96 (0.75, 1.24), P = 0.85	
Distant Metastases					
Stockholm III, 2017[81] NCT00904813 LOW	HR for time to first metastases event	Arm A (surgery within 1 week): 29/129 (22.4) Arm B (surgery within 4-8 weeks): 38/128 (29.7)	35/128 (27.3) (surgery within 4-8 weeks)	HR (95% CI): 1.45 (0.89, 2.37) HR (95% CI): 1.25 (0.76, 2.04)	Overall P = 0.33 (ref group Arm A)
Local Recurrence (Recurrence-free Survival)					
Stockholm III, 2017[81] NCT00904813 LOW	HR for time to first recurrence event	Arm A (surgery within 1 week): 3/129 (2.4) Arm B (surgery within 4-8 weeks): 1/128 (.7)	4/128 (3.1) (surgery within 4–8 weeks)	HR (95% CI): 0.38 (0.06, 2.56) HR (95% CI): 1.22 (0.33, 3.45)	Overall P = 0.52 (ref group Arm A)

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results	
Mortality					
Bujko, 2016[79,80] NCT00833131 LOW	Median follow-up of 35 months Total deaths	64/261 (24.5)	84/254 (33.1)	NR	
	Deaths in patients with cancer	52/64 (81.3)	67/84 (79.8)	NR	
	Deaths from treatment complications	6/64 (9.4)	13/84 (15.4)	NR	
	Deaths from intercurrent disease	4/64 (6.3)	2/84 (2.4)	NR	
	Death from unknown causes	2/64 (3)	2/84 (2.4)	NR	
Stockholm III, 2017[81] NCT00904813 LOW	Total deaths	Arm A (surgery within 1 week): 51/129 (39.5) Arm B (surgery within 4-8 weeks): 43/128 (33.6)	49/128 (38.2) (surgery within 4-8 weeks)	NR	
	Intercurrent deaths	Arm A (surgery within 1 week): 29/51 (56.9) Arm B (surgery within 4-8 weeks): 15/43 (34.9)	19/49 (38.8)	HR (95% CI) (surgery within 1 week): 0.46 (0.24, 0.90) HR (95% CI) (surgery within 4-8 weeks): 0.70 (0.38, 1.26)	Overall P = 0.06 (ref group = Arm A)

Appendix Table 23. Detailed Results for Toxicity Outcomes for Rectal Cancer Trials Rated "Low" or "Some Concerns" for Risk Of Bias

Trial Name, Year Trial # Risk of Bias	Effect Measure/Definition	Hypofractionation N Events/Total N, (%)	Comparison N Events/Total N, (%)	Results
Any Toxicity (Acute)				
Bujko, 2016[79,80] NCT00833131 SOME CONCERNS	Early toxicity occurring during radio(chemo)therapy or within the interval to surgery/CTCAE grade ≥ 2	119/256 (46.5)	155/259 (59.8)	NR
Acute Diarrhea				
Bujko, 2016[79,80] NCT00833131 SOME CONCERNS	Early toxicity occurring during radio(chemo)therapy or within the interval to surgery/CTCAE grade ≥ 2	36/256 (14.0)	70/259 (27.0)	NR
Late Anal Incontinence				
Stockholm III, 2017[81] NCT00904813 LOW	Late toxicity after 30 days from surgery/RTOG grade 3-4	Arm A (surgery within 1 week): 11/129 (8.5) Arm B (surgery within 4-8 weeks): 5/128 (3.9)	8/128 (6.3) (surgery within 4-8 weeks)	P = 0.32
Late Bowel Obstruction				
Stockholm III, 2017[81] NCT00904813 LOW	Late toxicity after 30 days from surgery/RTOG grade 3-4	Arm A (surgery within 1 week): 12/129 (9.3) Arm B (surgery within 4-8 weeks): 11/128 (8.5)	19/128 (14.8) (surgery within 4-8 weeks)	P = 0.25
Overall Late Toxicity				
Stockholm III, 2017[81] NCT00904813 LOW	Late toxicity after 30 days from surgery/RTOG grade 3-4	Arm A (surgery within 1 week): 56/129 (43.4) Arm B (surgery within 4-8 weeks): 51/128 (39.8)	60/128 (46.9) (surgery within 4-8 weeks)	P = 0.53

Abbreviations. CTCAE=Common Terminology Criteria for Adverse Events (version 4.0); RTOG=Radiation Therapy Oncology Group.