Evidence Synthesis Program

Hypofractionation Radiation Therapy for Definitive Treatment of Selected Cancers

May 2023

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

Recommended citation: Landsteiner A, Sowerby C, Ullman K, et al. Hypofractionation Radiation Therapy for Definitive Treatment of Selected Cancers: A Systematic Review. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project 09-009; 2023.

AUTHORS

Author roles, affiliations, and contributions to the present report (using the CRediT taxonomy) are summarized in the table below.

Author	Role and Affiliation	Report Contribution
Adrienne Landsteiner, PhD, MPH*	Senior Scientist, Minneapolis Evidence Synthesis Program (ESP) Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Supervision, Project administration
Catherine Sowerby, BA*	Research Associate, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Project administration
Kristen Ullman, MPH*	Program Manager, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing
Maylen Anthony, MPH	Research Associate, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Visualization, Writing – original draft, Writing – review & editing
Caleb Kalinowski, MS	Research Associate, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Visualization, Writing – original draft, Writing – review & editing
Elizabeth Ester, MD	Staff Physician, Minneapolis VA Health Care System Adjunct Assistant Professor, Department of Radiation Oncology, University of Minnesota Minneapolis, MN	Conceptualization, Methodology, Writing – review & editing
Philipp Dahm, MD, MHSc	Staff Physician, Minneapolis VA Health Care System Professor, Department of Urology, University of Minnesota Minneapolis, MN	Conceptualization, Methodology, Writing – review & editing
Kassahun Lemu, MPH	Research Volunteer, Minneapolis ESP Center Minneapolis, MN	Investigation
Wei Duan-Porter, MD, PhD	Co-Director, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Visualization, Writing – original draft, Writing – review & editing, Supervision
Timothy J. Wilt, MD, MPH	Co-Director, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision

**These are all lead authors who contributed equally to this report.*

This report was prepared by the Evidence Synthesis Program Center located at the **Minneapolis VA Health Care System,** directed by Timothy J. Wilt, MD, MPH and Wei Duan-Porter, MD, PhD and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development.

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the National VA Radiation Oncology Quality Task Force. The scope was further developed with input from Operational Partners (below), the ESP Coordinating Center, the review team, and the technical expert panel (TEP). The ESP consulted several technical and content experts in designing the research questions and review methodology. In seeking broad expertise and perspectives, divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Ultimately, however, research questions, design, methodologic approaches, and/or conclusions of the review may not necessarily represent the views of individual technical and content experts.

ACKNOWLEDGMENTS

The authors are grateful to the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

Lindsay Puckett, MD
National VA Radiation Oncology Quality Task Force

Maria Kelly, MD
Executive Director
National Radiation Oncology Program

Eva Katsoulakis, MD
National VA Radiation Oncology Quality Task Force

John Park, MD
National VA Radiation Oncology Quality Task Force

Abhishek Solanki, MD
National VA Radiation Oncology Quality Task Force

Technical Expert Panel

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

Sue Yom, MD, PhD, FASTRO
Chief of the Radiation Oncology Head & Neck, Cutaneous, and Thoracic Services
University of California San Francisco

Howard M. Sandler, MD, MS
Chair of the Department of Radiation Oncology
Cedars-Sinai Medical Center

Jennifer Wo, MD
Radiation Oncologist
Massachusetts General Hospital

Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix C for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

TABLE OF CONTENTS

FIGURES AND TABLES

ABBREVIATIONS TABLE

Abbreviation	
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
APBI	Accelerated partial breast irradiation
ARD	Absolute risk difference
ASTRO	American Society for Radiation Oncology
BCQ	Breast cancer questionnaire
CC	Coordinating Center
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COE	Certainty of evidence
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
EBRT	External Beam Radiation Therapy
EORTC QLQ-C30	European Organization for Research and Treatment core quality of life questionnaire
ESP	Evidence Synthesis Program
FACT-B	Functional assessment of cancer therapy for breast cancer
FACT-G	Functional assessment of cancer therapy – general
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GU	Genitourinary
HR	Hazard ratio
IMRT	Intensity-modulated radiation therapy
KQ	Key Question
LR	Local recurrence
LRR	Local-regional recurrence
MeSH	Medical Subject Heading
NCI	National Cancer Institute
NSCLC	Non-small cell lung carcinoma
NPC	Nasopharyngeal carcinoma
NR	Not repored
OS	Overall survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
QOL	Quality of life
RCT	Randomized controlled trial
RoB	Risk of bias
RR	Risk ratio
RTOG	Radiation Therapy Oncology Group

Abbreviation	
SABR	Stereotactic ablative body radiation therapy
SBRT	Stereotactic body radiation therapy
SCLC	Small cell lung cancer
SR	Systematic review
TEP	Technical expert panel
UK	United Kingdom
US	United States
VA	Department of Veterans Affairs
WBI	Whole breast irradiation

EXECUTIVE SUMMARY

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.
    - Most studies were not designed to evaluate the comparative effectiveness on overall or cancer-specific survival. Few studies were sufficiently similar enough to permit pooling or assess consistency, replicability and/or broader applicability.
- For breast cancer, moderate hypofractionation results in little to no difference in overall survival, disease-free survival, and local-regional recurrence; there were also generally no differences in treatment harms (with variable certainty for different harms).
- For individuals with prostate and rectal cancer, hypofractionation therapy probably results in little to no difference in overall survival and may result in little to no difference in disease-free or progression-free survival versus conventionally fractionated radiotherapy.
    - Hypofractionation may result in little to no difference in treatment harms.
- For individuals with small cell lung cancer, hypofractionation may result in little to no difference in overall and progression-free survival over 15–36 months follow-up.
    - Evidence is generally very uncertain regarding comparative treatment harms.
- For non-small cell lung cancer, evidence from 1 small RCT suggests that SBRT may result in little to no difference in overall survival versus conventionally fractionated radiotherapy through 36 months.
    - Evidence is generally very uncertain regarding comparative treatment harms.
- For early stage glottic cancer, hypofractionation may result in little to no difference in overall and disease-free survival, and most harms; the evidence is mostly very uncertain for locally advanced or recurrent head and neck cancers.
- For breast cancer, evidence indicated no differences in comparative effects of moderate hypofractionation versus conventional radiotherapy across a variety of patient, tumor, and adjuvant treatment characteristics; few studies addressed these questions for other cancers.
- No RCTs evaluated bladder, pancreatic, or skin cancers.
- We found no data on cost, resource use, or access. Radiation treatment cost, duration, and access as well as patient burden are likely relevant factors influencing practice and policy decisions. While mean treatment duration and number of treatment days varied widely across cancers and treatment regimens, they typically ranged 2–3 weeks and 10–15 treatment days less with hypofractionation versus conventional radiation.
    - Based on limited data, ultra-hypofractionation in selected cancers resulted in even greater reductions in treatment duration and dose numbers at roughly similar total doses versus conventional radiotherapy.

INTRODUCTION

The VA cares for an estimated 175,000 Veterans annually in their cancer treatment program. Radiation treatment for curative or definitive cancer therapy is an important and frequently used option. The Evidence Synthesis Program (ESP) is responding to a request from the Department of Veterans Affairs (VA) National Radiation Oncology Quality Task Force for an evidence review on the comparative effectiveness of hypofractionation versus conventional radiation therapy for adults with breast, prostate, lung, rectal, head and neck, bladder, pancreas, melanoma, or non-melanoma skin cancers.

Hypofractionation is a treatment regimen in which the total dose of radiation is divided into larger doses per fraction (given once a day or less often), resulting in fewer fractions and shorter overall treatment durations compared to conventional fractionation. While hypofractionation has been recommended for certain cancers by the American Society for Radiation Oncology (ASTRO), it has not been universally adopted. The ASTRO guideline cited the following rationale for its recommendation: "Hypofractionated radiation has the advantage of shortening treatment duration, is respectful of resource utilization, and appears cost-effective." To date, the comparative effectiveness and harms of hypofractionation versus conventional radiation for definitive therapy have not been summarized for many cancer types; only breast and prostate cancers have been summarized by recent systematic reviews.

Effectiveness, harms, and patient quality of life are important outcomes to assess and understand when developing guidelines for clinicians who treat Veterans with cancer. Although the VA has implemented hypofractionation for common cancer types, such as prostate and breast, variation remains across facilities. The National VA Radiation Oncology Quality Task Force has been tasked with developing and establishing guidelines for the VA and community clinicians who treat Veterans with cancer.

We summarize the available randomized trial evidence on the comparative efficacy and harms of hypofractionation versus conventional or long-course radiation as definitive therapy among adults with breast, prostate, lung, rectal, head and neck, bladder, pancreas, melanoma, and non-melanoma skin cancers. The cancers captured in this review were prioritized by the Operational Partners and where radiotherapy was likely to be used as definitive treatment.

METHODS

Data Sources and Searches

We searched MEDLINE and Embase from inception to January 5, 2022. We supplemented this search with a review of systematic reviews identified through a search of Cochrane and AHRQ databases. The search was limited to randomized controlled trials and the English language.

Study Selection

After duplicates were removed, citations were uploaded into DistillerSR. Using prespecified inclusion and exclusion criteria, titles and abstracts were screened by 2 reviewers for potential relevance to the key questions. Articles included by either reviewer underwent full-text screening. At the full-text screening stage, 2 independent reviewers agreed on the final inclusion or exclusion decision. Articles that met eligibility criteria were included for risk of bias (RoB) assessment and data abstraction.

Data Abstraction and Assessment

Data from published articles were abstracted by 1 reviewer and verified by a second reviewer. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion when consensus could not be reached. Two reviewers independently assessed the RoB for each trial using the Cochrane risk of bias for randomized trials (RoB 2) tool.

Synthesis

Eligible articles were summarized by cancer type and outcomes (*eg,* survival, recurrence, and toxicity). Studies assessed to be of high RoB had study characteristics extracted but no outcomes data. High RoB studies were not included in pooled analyses. Meta-analysis was conducted for each cancer type when sufficient evidence was available ($k > 4$). Assumptions regarding clinical and statistical heterogeneity were also assessed prior to any analysis.

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology to rate overall certainty of evidence for critical outcomes as high, moderate, low, or very low using GRADEpro GDT. Specific thresholds indicating clinically meaningful effects for decision making of hypofractionated versus conventionally fractionated radiation therapy for each of our critical outcomes were derived through consensus input by our internal content experts, Operational Partners, and technical expert panel. We used these thresholds, rather than measures of statistical significance, to determine if hypofractionation resulted in differences (*ie,* clinically meaningful effects) in outcomes versus the comparator.

RESULTS

Results of Literature Search

A total of 106 publications were included, comprising 71 trials across the 5 cancers of interest. Of the identified 71 trials, 46 were assessed as low or some concerns RoB. The remaining trials were assessed as high RoB and were not included in detailed results or synthesis of findings.

Of the 46 trials rated low or some concerns for RoB, most compared moderate hypofractionation to conventional radiotherapy ($k = 35$). The majority of the trials evaluated breast ($k = 17$) or prostate ($k = 18$) cancers; while fewer trials looked at lung ($k = 5$), head and neck ($k = 4$) or rectal ($k = 2$) cancers. No randomized controlled trials were identified for pancreatic, melanoma, or non-melanoma skin cancers. A third of the studies enrolled less than 500 participants. The included trials evaluating lung, head and neck, and rectal cancers all had sample sizes less than 500. All trials enrolled populations with a median or mean age of ≥45. Studies varied in tumor and treatment regimen charatcteristics. The majority of trials conducted in the breast or prostate populations tended to have longer follow-up times (> 5 years), whereas the lung, head and neck, and rectal cancer trials tended to have shorter durations (< 5 years). Few were designed to adequately assess overall or disease specific survival.

Summary of Results for Key Questions

A summary of the GRADE certainty of evidence findings is provided below. A full description of the accompanying meta-analysis findings, tables, and figures are in the full report.

ES Table. Certainty of Evidence for All Important Outcomes by Cancer Type

Cancer Type	Follow-up	Total N (# Trials)	Certainty	Summary Statement
Overall Survival				
Breast	5-10 years	9436 (7)	⊕⊕⊕⊕ High	Hypofractionation results in little or no difference in overall survival
Prostate	3-10 years	4988 (8)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in overall survival
NSCLC: hypofractionation vs conventional	1 year	132 (2)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in overall survival
NSCLC: SBRT vs conventional	3 years	102 (1)	⊕⊕◯◯ Low	SBRT may result in little to no difference in overall survival
NSCLC: SABR vs conventional	2 years	101 (1)	⊕⊕⊕◯ Moderate	SABR probably results in little to no difference in overall survival
SCLC	15-24 months	218 (2)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in overall survival
Early stage glottic cancer	3 years	516 (2)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in overall survival
Recurrent or locally advanced head & neck cancer	5 years	117 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in overall survival
Rectal	3 years	771 (2)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in overall survival
Disease-free or Progression-free Survival				
Breast	5-10 years	7574 (6)	⊕⊕⊕⊕ High	Hypofractionation results in little or no difference in disease-free survival
Prostate	2-10 years	1378 (6)	⊕⊕◯◯ Low	Hypofractionation may result in little or no difference in biochemical recurrence-free survival
Prostate	2-10 years	1521 (7)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in prostate cancer-specific survival
NSCLC: hypofractionation vs conventional	9-15 months	132 (2)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in progression-free survival

Cancer Type	Follow-up	Total N (# Trials)	Certainty	Summary Statement
NSCLC: SBRT vs conventional	3 years	102 (1)	⊕⊕⊕◯ Moderate	SBRT probably results in little to no difference in progression-free survival
SCLC	3 years	177 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in progression-free survival
Early stage glottic Cancer	3 years	516 (2)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in progression-free survival
Recurrent or locally advanced head & neck cancer	5 years	117 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in progression-free survival
Rectal	3 years	515 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little or difference in disease-free survival
Local-regional Recurrence				
Breast	5-10 years	7948 (6)	⊕⊕⊕⊕ High	Hypofractionation results in little or no difference in local-regional recurrence
Any Toxicity				
Breast	≤3 months	287 (1)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in less overall acute toxicity
Breast	6 months	271 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in overall late toxicity
Skin Toxicity				
Breast	6 months (acute)	1370 (5)	⊕⊕◯◯ Low	Hypofractionation may result in little or no difference in acute skin toxicity
Breast	5-10 years (late)	2054 (2)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in late skin toxicity
Pneumonitis				
Breast	6 months (acute)	1549 (2)	⊕⊕⊕⊕ High	Hypofractionation results in little or no difference in acute pneumonitis
NSCLC: hypofractionation vs conventional	1 year (acute and late)	96 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference on acute and late pneumonitis

Cancer Type	Follow-up	Total N (# Trials)	Certainty	Summary Statement
	15-24 months (acute)	36 (1)	⊕⊕◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on acute pneumonitis
NSCLC: SABR/SBRT vs conventional	2 years (acute and late)	101 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of SABR on acute and late pneumonitis
	1 year (acute and late)	102 (1)	⊕⊕◯◯ Low	SBRT may result in little to no difference in acute and late pneumonitis
SCLC	3 months (acute)	177 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on acute pneumonitis
	2 years (late)		⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on late pneumonitis
Gastrointestinal Toxicity				
Prostate	3-5 months (acute)	6702 (10)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in acute GI toxicity
Prostate	2-9 years (late)	4109 (9)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in late GI toxicity
Genitourinary Toxicity				
Prostate	3-5 months (acute)	6703 (10)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in acute GU toxicity
Prostate	2-9 years (late)	5069 (9)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little to no difference in late GU toxicity
Cough				
NSCLC: hypofractionation vs conventional	1 year (acute and late)	96 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little or no difference in *acute and late cough*
NSCLC: SABR/SBRT vs conventional	2 year (acute and late)	101 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of SABR on acute and late cough
	1 year (acute and late)	102 (1)	⊕⊕◯◯ Low	SBRT may result in little to no difference in acute and late cough

Cancer Type	Follow-up	Total N (# Trials)	Certainty	Summary Statement
SCLC: hypofractionation vs hyperfractionation	3 months (acute)	177 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on acute cough
	2 years (late)		⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on late cough
Esophagitis				
NSCLC: hypofractionation vs conventional	1 year (acute)	36 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on acute pharyngitis/esophagitis
	1 year (acute and late)	96 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference on acute and late esophagitis
NSCLC: SABR/SBRT vs conventional	2 year (acute and late)	101 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of SABR on acute and late esophagitis
	1 year (acute and late)	102 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of SBRT on acute and late esophagitis
SCLC: hypofractionation vs hyperfractionation	2 years (acute)	177 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effects of hypofractionation on acute esophagitis
Acute Mucositis				
Early stage glottic cancer (grade 3-4)	3 months	516 (2)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in acute mucositis
Recurrent or locally advanced head & neck cancer (grade 3)	3 months	117 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in acute mucositis
Acute Dysphagia				
Early stage glottic cancer (grade 1-2)	3 months	360 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in acute dysphagia
Late Mucositis				
Early stage glottic cancer	5 years	156 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in late mucositis

Cancer Type	Follow-up	Total N (# Trials)	Certainty	Summary Statement
Recurrent or locally advanced head & neck cancer (grade 3)	11 months	132 (1)	⊕⊕◯◯ Low	Hypofractionation may result in an increase in late mucositis
Late Soft Tissue Necrosis				
Early stage glottic cancer	4.8 years	360 (1)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little to no difference in soft tissue necrosis
Late Xerostomia				
Recurrent or locally advanced head & neck cancer	11-25 months	249 (2)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in late xerostomia
Temporal Lobe Necrosis				
Recurrent or locally advanced head & neck cancer	25 months	117 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on temporal lobe necrosis
Acute Diarrhea				
Rectal	<30 days	515 (1)	⊕⊕◯◯ Low	Hypofractionation may result in a reduction in acute diarrhea
Late Anal Incontinence				
Rectal	>30 days	256 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little or no difference in late anal incontinence
Late Bowel Obstruction				
Rectal	>30 days	256 (1)	⊕⊕◯◯ Low	Hypofractionation may result in a reduction in late bowel obstruction

Abbreviations. NSCLC=non-small cell lung cancer; SABR/SBRT=stereotactic ablative radiotherapy/stereotactic body radiation therapy; SCLC=small cell lung cancer.

DISCUSSION

Radiotherapy requires balancing tumor cell destruction with limiting normal tissue damage. Additionally, radiotherapy, as with all treatment options, should consider patient preferences and values, treatment burden, and costs. Our systematic review of randomized trials found that hypofractionation results in similar overall and disease-free or progression-free survival as well as most treatment-related harms versus conventional radiotherapy in patients with breast or prostate cancer. The evidence was more sparse and less consistent for adults with small cell and non-small cell lung cancer though generally indicate similar effects on overall and disease-free or progression-free survival and harms. Data are limited for head and neck and rectal cancer and we found no studies in adults with pancreatic, bladder, melanoma, or non-melanoma skin cancers.

Hypofractionation has seen a marked increase in use over the last 20 years, in part due to advances in treatment technology. Hypofractionation may provide similar efficacy and harms while reducing the therapeutic and economic burden to the patient by delivering an effective dose in a shorter period of time and with fewer treatment sessions. Additionally, the technological advancements that allow for more controlled dose delivery and more sophisticated planning of radiotherapy have potentially increased the ability to deliver the individual higher hypofractionation doses in a safe manner. In an effort to assess the highest quality evidence, we focused our review on data from randomized controlled trials. A number of the included studies used a non-inferiority approach to investigate whether hypofractionation was not substantially worse than conventional radiotherapy for survival and harms outcomes. Researchers and policy makers justify this study approach because of beliefs that hypofractionation offers other advantages in patient and health system feasibility, convenience, and access to care and thus would be preferred if there were not clinically meaningful differences in effectiveness or harms.

Of the 8 cancers initially prioritized for this review, we found no RCTs enrolling individuals with bladder, pancreatic, melanoma, and non-melanoma cancers. Only 1 or 2 RCTs rated as low risk of bias or as having some bias concerns were available for rectal and head and neck. Breast and prostate cancers both had a number of RCTs identified, as well as several prior systematic reviews related to hypofractionation. Previously published reviews in the other cancer types were primarily comprised of retrospective non-RCTs which have important limitations in outcome assessment.

Similar to other reviews among individuals with breast cancer, our findings suggest overall survival, local regional recurrence, and harms outcomes may not differ between hypofractionation and conventional radiotherapy. While there was greater variation in the harms outcomes, none of the analyses suggested a clinically meaningful difference in toxicity, based on *a priori* consensus derived thresholds, between hypofractionation and conventional radiotherapy. However, evidence certainty for acute and late harms was very low or low, in part due to a limited number of trials capturing the harm of interest as well as down rating for imprecision.

In men with prostate cancer, previous reviews found that overall survival and harms were similar between hypofractionation regimens compared to conventional radiotherapy. Our findings also support those results. Several review authors cited the need for longer follow-up periods and additional trials to provide clearer evidence regarding harms. While evidence certainty was low to moderate, many of the outcomes demonstrated little to no difference between

hypofractionation and conventional radiotherapy. Such findings for survival are not unexpected given the indolent course of most localized prostate cancers even if treated expectantly.

For individuals with non-small cell lung cancer, evidence certainty for hypofractionation versus conventional therapy and SABR/SBRT versus conventional radiotherapy was either low or very low for all outcomes, making assessment challenging. Similarly, for individuals with small cell lung cancer, the evidence certainty for hypofractionation versus hyperfractionation was either low or very low for all outcomes. The included studies captured populations with variation in stage and location of disease. This variation in population coupled with smaller trial population sizes and short follow up periods were some of the noted concerns that led to a reduction in the certainty of evidence.

We found very limited evidence on whether comparative effectiveness and harms varied by patient and tumor characteristics. What evidence was available suggests that use of the selected hypofractionation regimen may result in similar outcomes versus the comparator conventional radiotherapy approach regardless of stage.

Limitations

This review focused on specific cancers with the use of radiation therapy for curative intent with or without surgery and/or chemotherapy. Studies evaluating palliative therapies were excluded, and as such, extension of the report findings should not be made to these populations. The search was limited to publications in English; there may be relevant studies to the research questions that were missed due to this limitation.

Other limitations are mainly due to the existing data. For pancreatic, bladder, melanoma, and non-melanoma skin cancers, we found no eligible studies. Except for breast and prostate cancer, most other cancers had few trials and these were generally small and short term. The use of non-inferiority comparisons as the primary goal in multiple trials indicates a belief that hypofractionation regimens result in similar outcomes as conventional radiation therapy; in this case, the preference for hypofractionation treatment would be due to greater convenience and less resource use. However, smaller, potentially clinically meaningful effects on survival and disease progression outcomes cannot be confidently ruled out. Additionally, costs and access were not evaluated by eligible studies We also found little to no evidence to address our second key question, whether comparative effectiveness and harms varied by patient and tumor characteristics. These factors increase challenges for clinicians, researchers, and policy makers in applying our findings, especially to patients, cancers, and treatment regimens not directly studied.

Future Research

Randomized controlled trials of hypofractionation (moderate and ultrahypofractionation) compared with conventional radiation therapy are needed for most of the cancers addressed in this review, with the possible exception of breast and prostate cancers. However, even in breast and prostate cancer, evidence certainty was often low or based on relatively short follow-up. Furthermore, harms outcomes data were sparse and more varied in definition. Consistency and standardization regarding outcomes measurement and reporting will aid in summarizing and assessing the certainty of evidence.

Effectively assessing differences in overall or disease-specific survival likely requires large and longer-term studies. These requirements are practically relevant if trying to assess whether treatment effects vary by patient and tumor characteristics. However, such RCTs are expensive and the studied treatments may be outdated due to advances in diagnostic and treatment approaches. Therefore, it may be reasonable to first focus on important intermediate outcomes of effectiveness and treatment harms. This is particularly so in breast and prostate cancer, where survival outcomes are generally excellent with either regimen through 5–10 years; thus harms and patient care burden are likely more important treatment decision factors. For many patients and cancers, radiation treatment cost, duration, sessions, access, and patient burden are likely relevant factors influencing practice and policy decisions. More research focused on these outcomes will be needed.

Conclusions

For individuals with breast, prostate, or rectal cancer, hypofractionation therapy probably results in little to no difference in overall survival, and may result in little to no difference in disease-free or progression-free survival versus conventional radiotherapy. Evidence is more limited for harms. Hypofractionation results in fewer treatment days and thus may improve treatment access and reduce patient and caregiver burden. RCTs are needed in all cancers but particularly among patients with pancreatic, melanoma, non-melanoma, head and neck, rectal, bladder, and lung cancer. There is little to no evidence to address whether comparative effectiveness and harms vary by tumor or patient characteristics.

EVIDENCE REPORT

INTRODUCTION

PURPOSE

The Evidence Synthesis Program (ESP) is responding to a request from the Department of Veterans Affairs (VA) National Radiation Oncology Quality Task Force for an evidence review on the comparative effectiveness of hypofractionation versus conventional or long-course radiation among adults with breast, prostate, lung, rectal, head and neck, bladder, pancreas, melanoma, or non-melanoma skin cancer. Findings from this review will be used to establish treatment guidelines for the VA and community clinicians who treat Veterans with cancer. An understanding of the evidence on hypofractionation compared to conventional radiation treatment will inform use of hypofractionation in the VA and community settings.

BACKGROUND

In 2018, 1.7 million new cancer cases were reported to the Centers for Disease Control and Prevention (CDC) and the National Cancer Institute (NCI) in the United States (US). Of those 1.7 million newly diagnosed cancer cases, the most common diagnoses were breast, lung, and colorectal cancer among females and prostate, lung, and colorectal cancer among males.[1] An estimated 40,000 cancer cases are reported annually to the VA Central Cancer Registry.[2] Similar to the general US male population,[2] the most frequently diagnosed and treated cancers within the VA are prostate, lung, and colorectal. Treatment regimens for each cancer type are complex and vary widely by patient and cancer characteristics. Treatments have also evolved dramatically over the past 3 decades.[3] Radiotherapy for curative or definitive cancer therapy is an important and frequently used treatment option.

Hypofractionation is a treatment regimen in which the total dose of radiation is divided into larger doses per fraction (given once a day or less often), resulting in fewer fractions and shorter overall treatment durations compared to conventional fractionation. The reduction in number of fractions (thus treatment sessions) for hypofractionation regimens can improve patient convenience, increase treatment scheduling access, and potentially be cost effective. These factors are cited as potential reasons to prioritize hypofractionation over conventional radiotherapy.[3] While hypofractionation has been recommended by the American Society for Radiation Oncology (ASTRO) for certain cancers, it has not been universally adopted.[4,5] The ASTRO guideline cited the following rationale: “Hypofractionated radiation has the advantage of shortening treatment duration, is respectful of resource utilization, and appears cost-effective. While health economic endpoints were not considered, it is recognized that the very nature of hypofractionation is such that there are potential advantages in terms of cost and convenience for patients.”[5] To date, the comparative effectiveness and harms of hypofractionation versus conventional radiation for definitive therapy has not been summarized for many cancer types; only breast and prostate cancers have had comprehensive assessments in previous systematic reviews.

The VA cares for an estimated 175,000 Veterans annually in their cancer treatment programs; many undergo “definitive treatment” with an intent to cure cancer, including through the use of radiation therapies.[2] Effectiveness, harms, and patient quality of life are important factors to

assess and understand when developing guidelines for clinicians who treat Veterans with cancer. Although the VA has implemented hypofractionation for common cancer types, such as prostate and breast, variation remains across facilities. Also, many Veterans receive their cancer care in community settings, with variation in treatments between community and academic clinicians. The National VA Radiation Oncology Quality Task Force has been tasked with developing and establishing treatment guidelines for the VA and community clinicians who treat Veterans with cancer. This systematic review was nominated to assist and guide their decision-making.

In this review, we summarize the available randomized trial evidence on the comparative efficacy (including health-related quality of life) and harms of hypofractionation versus conventional or long-course radiation as definitive therapy among adults with breast, prostate, lung, rectal, head and neck, bladder, pancreas, melanoma, or non-melanoma skin cancer. We also assessed whether comparative efficacy and harms varied by patient and tumor characteristics. The cancers captured in this review were prioritized by the Operational Partners and where radiotherapy treatment was deemed definitive.

METHODS

TOPIC DEVELOPMENT

In response to a request from the National VA Radiation Oncology Quality Task Force, this evidence review topic was developed to aid the Task Force in guideline development for radiation treatment in select cancers within VA. In collaboration with our Operational Partners and technical expert panel (TEP), we developed the analytic framework, scope, protocol, and key questions for this review.

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number [CRD42021287645]).

DATA SOURCES AND SEARCHES

We searched MEDLINE and Embase from inception to January 5, 2022. We supplemented this search with a review of systematic reviews identified by keyword search through Cochrane and AHRQ databases. We limited the search to randomized controlled trials and the English language. See Appendix A for complete search strategies.

STUDY SELECTION

After duplicates were removed, citations were uploaded into DistillerSR.[6] Using prespecified inclusion and exclusion criteria, titles and abstracts were screened by 2 reviewers for potential relevance to the key questions. Articles included by either reviewer underwent full-text screening. At the full-text screening stage, 2 independent reviewers agreed on the final inclusion or exclusion decision. Articles that met eligibility criteria (below) were included for data abstraction.

	Eligibility Criteria
Population	Adults, 18 years or older, diagnosed with 1 of the following cancers: breast, prostate, lung, rectal, head and neck, bladder, pancreas, melanoma, and non-melanoma skin cancer receiving radiation with definitive treatment intent (*ie*, non-palliative)
Intervention	Hypofractionation (>220 cGy (2.2 Gy) per fraction) • Moderate hypofractionation • Ultrahypofractionation/extreme hypofractionation • Stereotactic body radiation therapy (SBRT)/Stereotactic ablative body radiation therapy (SABR)
Comparator	Standard or conventional or long-course radiation [180 to 220 cGy (1.8 – 2.2 Gy) per fraction] (unless SCLC in which hyperfractionation is the standard of care)
Outcomes	Survival: Overall, Disease-specific Recurrence (evidence of progression)/Control (no evidence of progression): Biochemical (prostate), Local, Regional, Systemic/distant metastatic Toxicity: All adverse events of grade 2-5, Specific adverse events grade 2-5 relevant to each cancer Quality of Life: Overall and cancer-specific

	Cost/resource use
Timing	Effectiveness outcomes timing: short-term (≤2 years) vs long-term (>2 years) Toxicity timing: Any [(acute = during and within 90 days post treatment) (late = greater than 90 days post treatment)]
Setting	Any non-hospice setting
Study Design	RCT or SR with RCT inclusion

DATA ABSTRACTION AND ASSESSMENT

Data from published articles were abstracted by 1 reviewer and verified by a second reviewer. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion when consensus could not be reached. The following elements were abstracted for included articles: study characteristics (country, funding source, inclusion and exclusion criteria), population characteristics (age, sex, cancer stage, risk stage), tumor characteristics, intervention and comparator characteristics (dose, fractions and duration of treatment), and outcomes (overall and disease-specific survival, recurrence, toxicity, overall quality of life, and cost/resource use).

Two reviewers independently assessed the articles risk of bias (RoB) using the Cochrane risk of bias tool for randomized trials (RoB 2).[7]

KEY QUESTIONS

The following key questions (KQs) were the focus of this review:

KQ1: What are the comparative efficacy and harms of hypofractionation (see Table 1) versus conventional radiation therapy in the definitive treatment of adults with breast, prostate, lung, rectal, head and neck, bladder, pancreas, melanoma, or non-melanoma skin cancer?

KQ2: In the treatment of adults with the above types of cancer, do the efficacy and harms of hypofractionation strategies vary by cancer stage, prostate cancer NCCN risk stratification, or other patient characteristics?

Table 1. Hypofractionation Definitions by Dose

Term	Dose (EBRT Fraction Size)
Conventional fractionation	180 to 220 cGy (1.8–2.2 Gy)
Moderate hypofractionation	> 220 to 499 cGy (> 2.2–4.99 Gy)
Ultrahypofractionation/extreme hypofractionation/stereotactic body radiation therapy (SBRT)/stereotactic ablative body radiation therapy (SABR)	≥ 500 cGy (≥ 5.00 Gy)

SYNTHESIS

The eligible articles were summarized by cancer type (including cell type for lung cancer) and outcomes (*eg*, survival, recurrence, and toxicity). Studies that were assessed to be high RoB had study characteristics but not outcome data extracted. These studies were not included in any pooled analyses. Meta-analysis was conducted using R version 4.2.1 for each cancer type when 5 or more sufficiently comparable studies were available.

Prior to the pooling of data, we examined clinical and methodological variation to determine appropriateness of quantitative synthesis. If applicable, we pooled outcomes from clinically homogeneous studies. We pooled studies with cancers of similar disease site and cell type and stage (*eg,* lung but stratified by NSCLC vs SCLC), hypofractionation category (hypofractionation vs ultra-hypofractionation), and radiotherapy approach (*eg,* partial breast vs whole breast). We calculated absolute risk differences (ARD) and risk ratios (RR) with corresponding 95% confidence intervals (CI) for categorical outcomes.

We did not pool effect measures for outcomes with 4 or fewer contributing RCTs. We used the Hartung–Knapp–Sidik–Jonkman random-effects model to estimate pooled effects and corresponding 95% CIs. Anticipated absolute event rates and corresponding risk differences were also generated in R**.**

Heterogeneity was assessed using the I^2 statistic, prediction interval, and visual inspection of forest plots. We anticipated conducting subgroup analyses to explore potential causes of heterogeneity (and address KQ2) by cancer stage, prostate cancer risk status, and radiotherapy categorization. When quantitative synthesis was not appropriate, findings were summarized narratively.

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to rate overall certainty of evidence (COE) for critical outcomes as high, moderate, low, or insufficient using GRADEpro GDT.[8,9] Briefly, for each prioritized outcome, we evaluated characteristics of the evidence across 5 domains: study limitations (risk of bias), imprecision (number of events, sample size, and precision of effect estimates reported by included studies), inconsistency (whether the direction and magnitude of effects are similar [or different] across the included studies), indirectness (how applicable the results were to our key questions), and publication bias (preferential reporting of positive results). The overall certainty of evidence takes into consideration individual ratings in each of these 5 domains, but domains may not be weighted equally in determining the overall rating.

Specific thresholds indicating clinically meaningful effects for decision-making of hypofractionation versus conventional radiation therapy for each of our critical outcomes were derived *a priori* through consensus input by our internal content experts, Operational Partners, and TEP members. These thresholds (Table 2) were used to define clinically meaningful differences and assess certainty of evidence when comparing the intervention to comparator for each outcome. When appraising the threshold, a difference of that size would be enough to impact clinical management. Consistent with GRADE methodology, when more than 1 trial provided outcome estimates, we calculated ARD for those outcomes by applying the pooled RR to the control event rate and specified follow-up time periods from exemplar studies. After discussion with our content experts and Operational Partners, the following outcomes were prioritized for certainty of evidence assessment. GRADE was not performed for subgroups such as radiotherapy approach, disease location, or disease severity.

- Survival outcomes:
    - Overall survival
    - Disease-free survival
    - Local-regional survival/recurrence
- Harms outcomes (acute or late):

- Overall adverse events
- Specific adverse events by cancer:
  - Prostate: genitourinary (GU) and gastrointestinal (GI)
  - Breast: Skin, lymphedema, and pneumonitis
  - Head and Neck: Mucositis, dysphagia, radionecrosis, and xerostomia
  - Lung: Pneumonitis and esophagitis
  - Bladder: GU and GI
  - Rectal: GU and GI

Table 2. Clinically Meaningful Thresholds

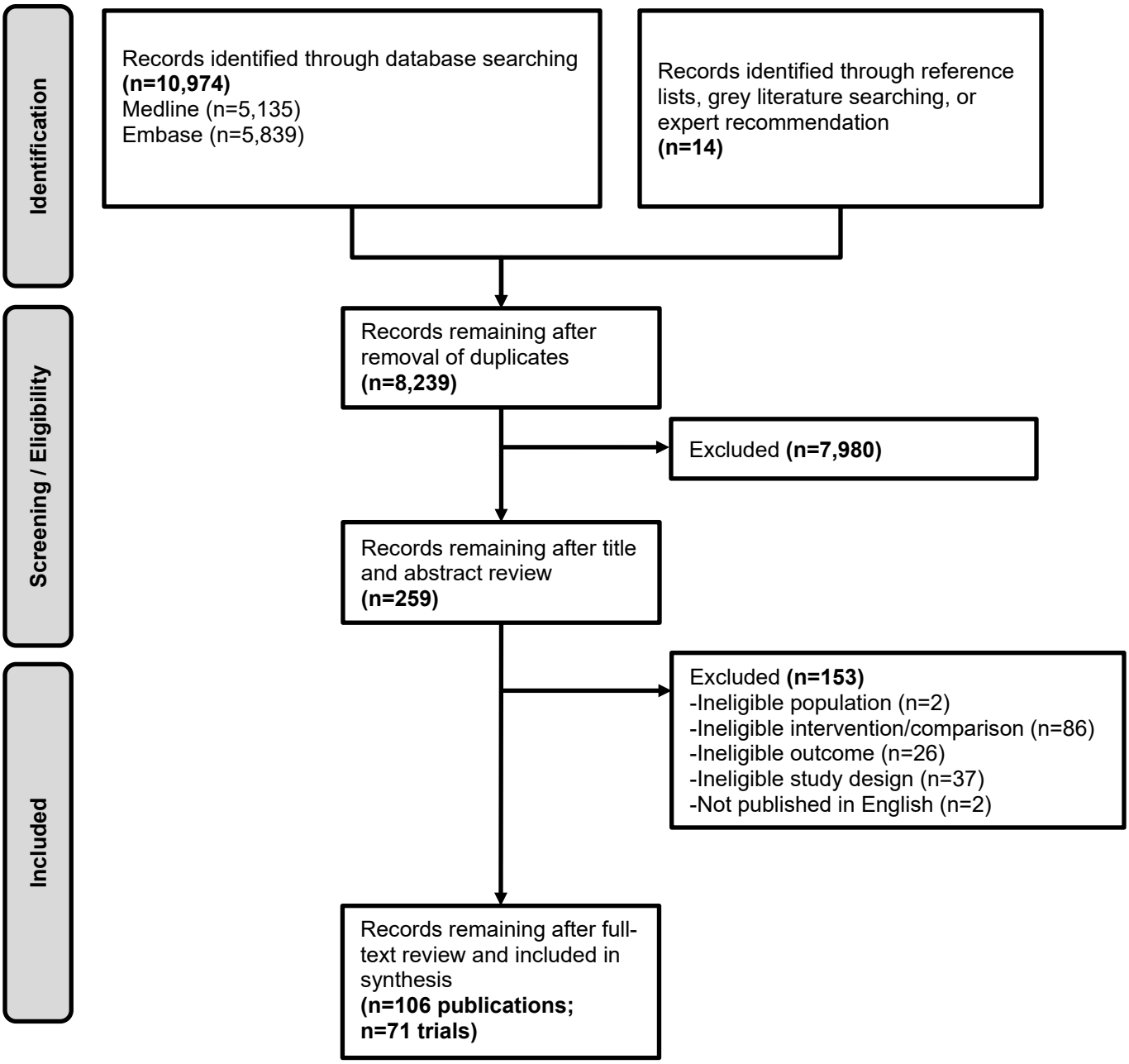
Outcome	Threshold Level	Notes
Overall survival	5% absolute difference over any length of follow-up	Context: follow-up length of the study and the number of events will be a limiter to consider (*ie,* the study design limits the measurement)
Disease-specific survival	5% absolute difference over any length of follow-up	Context: follow-up length of the study will be a limiter to consider (*ie,* the study design limits the measurement)
Local-regional survival	10% absolute difference over any length of follow-up	Context: follow-up length of the study will be a limiter to consider (*ie,* the study design limits the measurement)
Harms ≥ grade 2	10% difference	
Harms ≥ grade 3	5% difference	Grade 3 or greater will be used as a measure of harm when grade 2 or greater not presented by the author

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 1) summarizes the results of the study selection process (full list of excluded studies available in Appendix B).

Figure 1. Literature Flowchart



LITERATURE OVERVIEW

A total of 106 publications were included, comprising 71 trials across the 5 cancers of interest. Of the identified 71 trials, 46 were rated low or some concerns for RoB; characteristics for these trials are summarized in Table 3. No eligible trials were identified for bladder, pancreatic cancer, melanoma, or non-melanoma skin cancer.

The majority of trials rated low or some concerns for RoB compared hypofractionation to conventional radiotherapy, except for a small number of trials in breast, prostate, and lung cancer populations where ultra-hypofractionation was evaluated (Table 3). There was substantial variability in the hypofractionation and comparator treatment regimens and cancer characteristics for each cancer type. The majority of these trials evaluated breast or prostate cancer, 5 addressed lung cancer, 4 for head and neck, and only 2 for rectal cancer. A third of trials enrolled ≤ 500 participants or less. All enrolled populations with a median or mean age ≥ 45 years. All but 1 prostate cancer RCT enrolled men age ≥ 65 years. Trials conducted for breast and prostate cancer tended to have longer follow-up times of ≥ 5 years (range 5–10 years, $k = 13$ [76%] for breast and $k = 10$ [56%] for prostate). All lung and rectal cancer trials had ≤ 3 years of follow-up. While many studies reported overall or disease-specific survival, few were designed with these as their primary outcomes.

The remaining trials were assessed as high RoB; detailed results were not abstracted from these studies or included in the synthesis of findings. Study characteristics for trials rated high RoB are provided in Appendices D–H (by cancer type).

Table 3. Summary Characteristics of Included Studies Assessed as Low or Some Concerns for Risk of Bias

	Breast Cancer (Total=17)	Prostate Cancer (Total=18)	Lung Cancer (Total=5)	Other Cancers (Total=6)
Intervention vs comparator				
Hypofractionation vs. conventional	12	14	3	6
Ultra-hypofractionation vs. conventional	2	2	2*	—
Ultra-hypofractionation vs. hypofractionation	3	2	1*	—
Median length of follow-up				
<5 years	4	8	5	4
≥5 years	13	10	—	2
Outcomes				
Survival	13	12	5	6
Harms	11	17	3	5
Acute (≤90 days)	11	15	3	5
Late (>90 days)	6	12	3	5
Quality of life	4	5	2	—
Country				
US/Canada	2	4	1	—
UK/Europe	12	7	1	2

	Breast Cancer (Total=17)	Prostate Cancer (Total=18)	Lung Cancer (Total=5)	Other Cancers (Total=6)
China	2	2	1	1
Other	—	2	2	3
Multi	1	3	—	—
Sample sizes (total N)				
<100	—	4	2	1
100-500	5	7	3	4
501-1000	4	3	—	1
1,001-2,500	7	3	—	—
>2,500	1	1	—	—
Age (mean or median, years)				
45-64	8	1	2	3
≥65	—	14	2	2
Age categories only	8	—	—	—
NR	1	3	1	1

Abbreviations. NR=not reported; UK=United Kingdom; US=United States.
Notes. *One lung cancer trial compared ultra-hypofractionation (stereotactic ablation radiotherapy [SABR]) with either conventional or moderate hypofractionation.[10]

BREAST CANCER

Overview

We identified 32 eligible trials (45 publications) that evaluated hypofractionation for breast cancer. For detailed results on efficacy and harms, we focus here on 17 eligible trials (27 publications) with RoB ratings that were low or some concerns. Table 4 summarizes the characteristics of these trials, all of which enrolled middle-aged and older women (*eg*, mean or median age range 57–63 years) with breast cancer without distant metastases (*ie*, not stage IV). Most trials were conducted in Europe (k = 10),[11-22] 1 trial was conducted in the US,[23,24] 1 in Canada,[25,26] 2 others in China,[27,28] and 3 were in multiple countries.[29-31] Detailed study characteristics, outcomes, and RoB ratings for all included trials are presented in Appendix D.

Most trials (k = 12) compared moderate hypofractionation with standard conventional whole breast radiation. The remaining 5 trials compared a variety of other radiation therapy schedules and techniques, including ultra-hypofractionation versus conventional or moderate hypofractionation and use of accelerated partial breast irradiation (APBI) in some of the hypofractionation arms.

Below, we first describe results for trials comparing moderate hypofractionation with conventional whole breast radiation. We performed quantitative meta-analyses for each prioritized outcome (when there were sufficient number of trials) and qualtitative synthesis otherwise; we also assessed COE. Following these results, we provide a qualitative synthesis of findings for trials involving other radiation treatments; we did not conduct meta-analyses due to the degree of variation in radiation schedules and techniques across these remaining studies.

Table 4. Summary Characteristics of Included Breast Cancer Trials with Low or Some Concerns for Risk of Bias

Study Characteristics	Number of Studies (Total=17[a])
Radiation strategies compared	
Hypofractionation vs conventional	12
Ultra-hypofractionation vs conventional	1
Ultra-hypofractionation vs hypofractionation	2
Accelerated partial breast vs whole breast[b]	2
Median length of follow-up	
<1 year	2
1-5 years	2
≥5 years	13
Cancer stage(s) of participants	
I-II	9[c]
I-III	6
III	1
DCIS only	1[d]
Survival outcomes	
Overall survival	11
Disease-free survival	6
Local recurrence	9
Locoregional recurrence	8
Harms outcomes	
Overall toxicity (grade ≥2)	3
Acute skin toxicity	9
Acute pneumonitis	3
Late skin toxicity	3
Late pneumonitis	1
Late lymphedema	3
Quality of life outcome	4

Abbreviations. DCIS=ductal carcinoma in situ; RCT=randomized controlled trial.
[a] 17 eligible trials, reported in 26 publications.
[b] The main comparison for 2 trials was between accelerated partial breast irradiation (APBI) and whole breast irradiation (WBI). One trial used conventional dosing for the WBI treatment,[14] while the other used moderate hypofractionation dosing.[31]
[c] Three trials also included participants with DCIS.[23,24,29,31]
[d] One trial included participants with DCIS and meeting criteria for "increased risk of recurrence" (see Appendix D for detailed information).[30]

Moderate Hypofractionation versus Conventional Whole Breast Radiation

Twelve trials evaluated moderate hypofractionation, consisting of 3–5 weeks of 13–16 daily treatments (total dose range 40.0–43.5 Gy, dose per fraction 2.65–2.9 Gy), compared with conventional radiotherapy of 5 weeks of 25 daily treatments (total dose 50.0 Gy, dose per fraction 2.0 Gy). Thus hypofractionation regimens typically resulted in approximately 10 fewer

treatment days versus conventional radiotherapy. Other cancer therapies were commonly used in addition to radiation therapy: these included chemotherapy, hormone therapy, and trastuzumab. Most trials included participants with stage I–III ($k = 5$)[11-13,25-27,32,33] or stage I–II ($k = 5$) [19-24,29,34] breast cancer. Two of the latter trials also included participants with ductal carcinoma in situ (DCIS).[23,24,29,34] Additionally, 1 trial focused solely on those with DCIS with a range of high-risk factors,[30] and 1 trial on stage III only.[28] Total sample sizes ranged from 121 to 2,327, with the largest being Standardisation of Breast Radiotherapy (START) trials A[11,33] and B[12,33] ($N = 2,327$ and 2,236, respectively). Median follow-up times ranged from less than 1 year to 16.9 years, with most having 5–0 years of follow-up ($k = 8$;[11-13,20,23-27,29,32-34] START A and B with median of 9.3 and 9.9 years, respectively). Most of these trials had local or local-regional recurrence as the primary outcome ($k = 7$),[11,12,20,25-28,30,32,33] while the remaining trials were primarily examining differences in cosmetic ($k = 3$)[13,23,24,29,34] or toxicity outcomes ($k = 2$).[19,21,22]

Key Question 1

Table 5 provides the key findings and certainty of evidence for efficacy and harms in comparing moderate hypofractionation and conventional radiation therapy in the treatment of breast cancer. Of note, overall and disease-free survival were 80% or greater and local-regional recurrence less than 5% for both hypofractionation and conventional radiation therapy at 10 years follow-up. Any acute (but not any late) toxicity, grade ≥ 2, were less with hypofractionation.

Table 5. Certainty of Evidence for Moderate Hypofractionation versus Conventional Radiation Therapy for Breast Cancer Outcomes

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Overall survival (OS) Absolute effect size estimates based on control event rate at 6 and 9.9 years* **MCID: 5% difference**	5-9.9 years *N* = 9436 (7 RCTs)[11,12,20,25-29,33]	**RR = 1.003** (0.99, 1.02)	**87.8%** (86.5, 89.2)	87.5%	*6 years:* **0.3% more** (1.1 fewer to 1.7 more)	⊕⊕⊕⊕ High	Hypofractionation results in little to no difference in overall survival.
			82.9% (81.6, 84.2)	82.6%	*9.9 years:* **0.2% more** (1 fewer to 1.6 more)		
Disease-free survival (DFS) Absolute effect size estimates based on control event rate at 6 and 9.9 years* **MCID: 5% difference**	5-9.9 years *N* = 7574 (6 RCTs)[11,12,20,26-28,33]	**RR = 1.007** (0.97, 1.04)	**85.8%** (82.9, 88.7)	85.2%	*6 years:* **0.6% more** (2.3 fewer to 3.6 more)	⊕⊕⊕⊕ High	Hypofractionation results in little to no difference in disease-free survival.
			80.5% (77.8, 83.3)	79.9%	*9.9 years:* **0.6 more** (2.2 fewer to 3.4 more)		

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Local-regional recurrence (LRR) Absolute effect size estimates based on control event rate at 6 and 9.9 years* **MCID: 10% difference**	5-10 years *N* = 7948 (6 RCTs)[11,12,20,27-29,33]	**RR = 0.98** (0.81, 1.17)	**3.2%** (2.6, 3.8)	3.3%	*6 years:* **0.1% fewer** (0.6 fewer to 0.6 more)	⊕⊕⊕⊕ High	Hypofractionation results in little to no difference in local-regional recurrence.
			4.7% (3.9, 5.6)	4.8%	*9.9 years:* **0.1% fewer** (0.9 fewer to 0.8 more)		
Any acute toxicity (grade ≥2) Absolute effect size estimates based on control event rate ≤3 months† **MCID: 10% difference**	3 months *N* = 287 (1 RCT)[23]	**RR = 0.61** (0.50, 0.74)	**47.1%** (35.0, 59.2)	78%	**30.8% fewer** (39.2 fewer to 20.6 fewer)	⊕⊕⊕◯ Moderate[a]	Hypofractionation probably results in less overall acute toxicity.
Any late toxicity (grade ≥2) Absolute effect size estimates based on control event rate at 6 months† **MCID: 10% difference**	6 months *N* = 271 (1 RCT)[23]	**RR = 0.96** (0.67, 1.36)	**31.0%** (16.7, 45.3)	32%	**1.4% fewer** (12.5 fewer to 9.7 more)	⊕⊕◯◯ Low[a,b]	Hypofractionation may result in little to no difference in overall late toxicity.

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Acute skin toxicity (grade ≥2) Absolute effect size estimates based on control event rate at 3 months‡ **MCID: 10% difference**	3 months *N* = 1370 (5 RCTs)[19,22,23,27,32]	**RR = 0.56** (0.31, 0.999)	**4.1%** (2.3, 7.4)	7.4%	**3.3% fewer** (5.1 fewer to 0 fewer)	⊕⊕◯◯ Low[a,c]	Hypofractionation may result in little to no difference in acute skin toxicity.
Late skin toxicity (grade ≥2) Risk ratios and absolute effect size estimates based on control event rate at 5 and 10 years§ **MCID: 10% difference**	5-10 years *N* = 2054 (2 RCTs)[25,28]	**RR = 0.94** (0.46, 1.96)	**3.1%** (1.5, 6.5)	3.3%	*5 years:* **0.2% fewer** (1.8 fewer to 3.2 more)	⊕⊕◯◯ Low[a,d]	Hypofractionation may result in little to no difference in late skin toxicity.
		RR = 1.16 (0.63, 2.13)	**8.9%** (4.8, 16.5)	7.7%	*10 years:* **1.2% fewer** (2.9 fewer to 8.8 more)		
Acute pneumonitis (grade ≥2) Risk ratio and absolute effect size estimates based on control event rate at 3 months‡ **MCID: 10% difference**	6 months *N* = 1549 (2 RCTs)[27,28]	**RR = 0.63** (0.25, 1.61)	**1.9%** (0.8, 4.9)	3.0%	**1.1% fewer** (2.3 fewer to 1.9 more)	⊕⊕⊕⊕ High	Hypofractionation results in little to no difference in acute pneumonitis.

Notes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
* Estimated using data from the START B trial[12]
† Estimated using data from the NCT01266642 trial[23,24,34]
‡ Estimated using data from the NCT01413269 trial[27]
§ Estimated using data from the NCT00156052 trial[25,26,32]

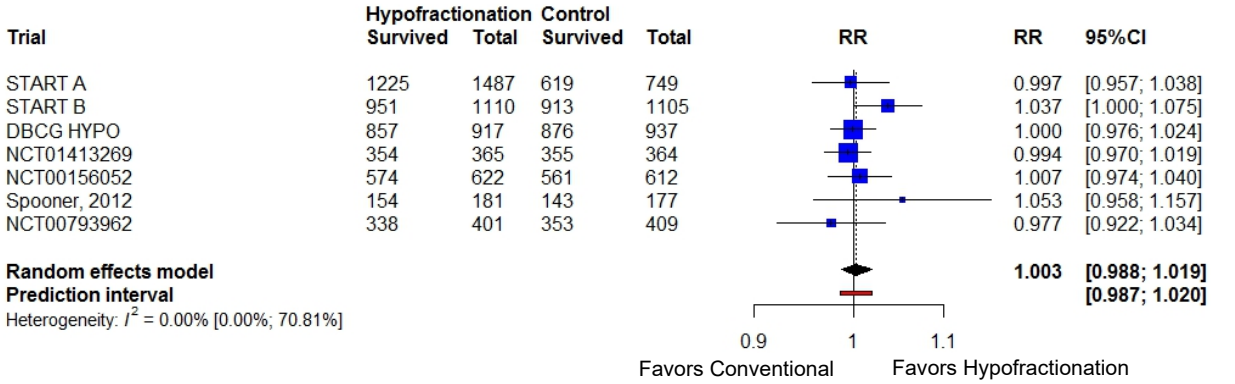
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded one level for study limitations (studies with some concerns for risk of bias)
b. Downgraded one level for imprecision (CI crossing MCID in one direction)
c. Downgraded one level for inconsistency (variance of point estimates across studies)
d. Downgraded one level for indirectness (1 of 2 studies did not report only grade 2+)

Abbreviations. CI=confidence interval; DFS=disease-free survival; LRR=local-regional recurrence; MCID=minimal clinically important difference; NR=not reported; OS=overall survival; RCT=randomized controlled trial; RR=risk ratio.

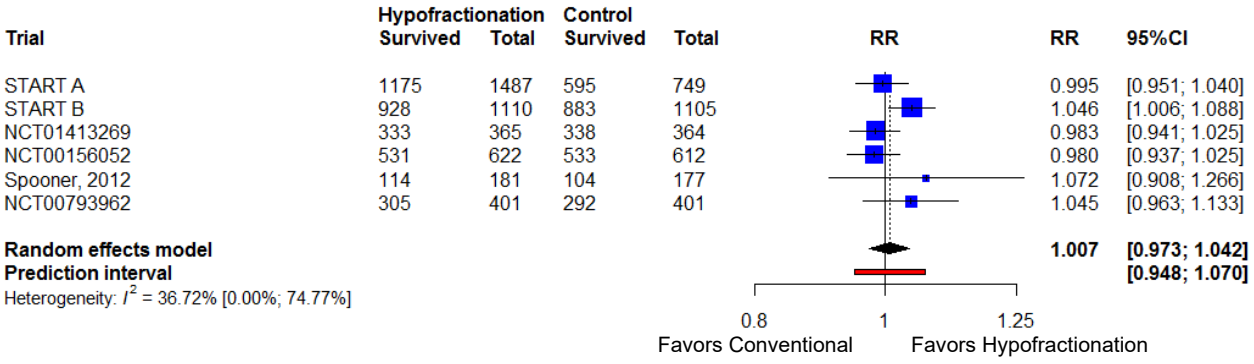
Survival & Recurrence Outcomes

Figure 2. Breast Cancer Overall Survival: Moderate Hypofractionation versus Conventional Radiation Therapy



Hypofractionation results in little to no difference in overall survival compared to conventional radiotherapy (high COE; Figure 2). Overall survival was reported by 7 trials (total N = 9,436);[11,12,20,25-29,32,33] pooled estimate for RR was 1.003 (95% CI [0.99, 1.02]). All but 1 of these trials included breast cancer stages I–II, with 4 trials also including stage III.[11,12,26,27] One trial focused on stage III cancer only (Spooner et al).[20,29] The largest trials were START A and B, both including stages I–III cancer and conducted in the United Kingdom (UK).[11,12,33] A third trial was also conducted in the UK,[20] 2 trials in China,[27,28] 1 in Canada,[26] and 1 in multiple countries.[29] Using the reported absolute survival rates from the START B trial,[12,33] we estimated that the ARD comparing hypofractionation versus conventional radiation is 0.3% (95% CI [-1.1, 1.7]) at 6 years and 0.2% at 9.9 years (95% CI [-1, 1.6]). Although none of the trials evaluated overall survival as the primary outcome, there appeared to be sufficient follow-up (5–15 years median follow-up) and for a relatively large number of participants.

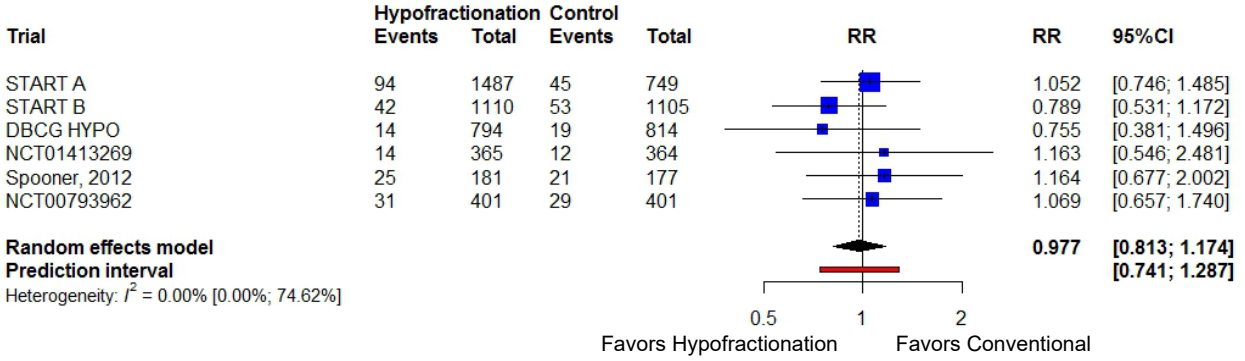
Figure 3. Breast Cancer Disease-free Survival: Moderate Hypofractionation versus Conventional Radiation Therapy



Moderate hypofractionation results in little to no difference in disease-free survival compared to conventional radiotherapy (high COE; Figure 3). Six[11,12,20,25-28,32,33] of the 7 trials reporting

overall survival also presented results on disease-free survival; data on 7,574 participants from these trials were pooled, giving an RR of 1.02 (95% CI [0.98, 1.07])). As above, we used the reported disease-free survival rates from START B to estimate the ARD as 2.0 (95% CI [-1.6, 5.8]) at 6 years and 1.9 (95% CI [-1.5, 5.4]) at 9.9 years. The main concern regarding these findings is the lack of precision in the pooled estimate, with the 95% CI crossing the MCID of 5% in 1 direction (although this was in favor of moderate hypofractionation).

Figure 4. Breast Cancer Local-regional Recurrence: Moderate Hypofractionation versus Conventional Radiation Therapy



There was also little to no difference in local-regional survival between conventional and hypofractionation (high COE; Figure 4). Six[11,12,20,27-29,33] of the 7 trials reporting overall survival also reported rates of loco-regional recurrence. We pooled data from 7,948 women included in these 6 trials, finding an RR of 0.98 (95% CI [0.81, 1.17]). Once again, we used results from START B to estimate the ARD of -0.1% (95% CI [-0.6, 0.6]) at 6 years, and -0.1% (95% CI [-0.9, 0.8]) at 9.9 years.

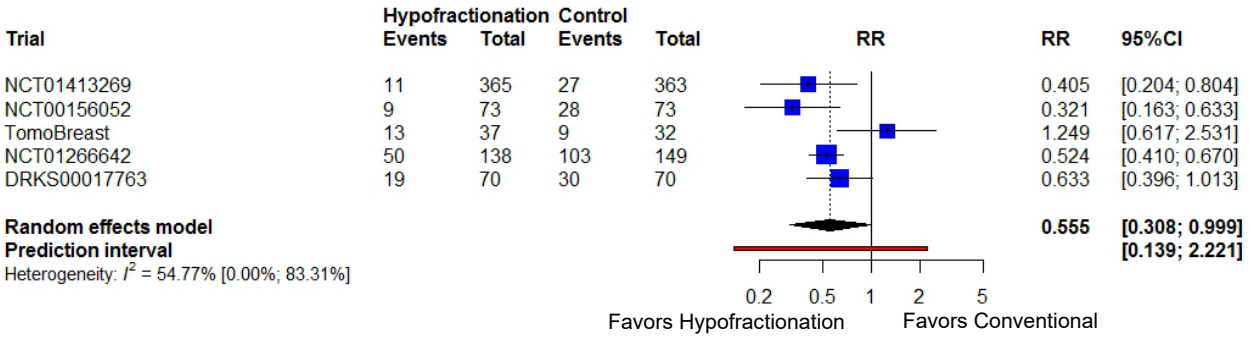
Five trials (total $N = 7,824$) also reported results on local recurrence rates over a median follow-up range 5–10 years. All of these included breast cancer stages I–III.[11-13,25-27] Four[11,12,25-27,33] of the 7 trials that reported overall survival (described above) had local recurrence as the primary outcome. Once again, the largest of these were START A and B conducted in the UK.[11-13] The fifth trial was the START Pilot, which was primarily examining cosmetic outcomes but also reported local recurrence.[13] A sixth trial stated that the primary outcome will be local recurrence but has thus far only reported results on quality of life.[30] No trial found a difference in local recurrence rates between moderate hypofractionation and conventional radiation therapy; absolute recurrence rates were 1–9% in the moderate hypofractionation arms.

Toxicity & Harms

Hypofractionation probably results in less overall acute toxicity, but no difference in late toxicity at 6 months, compared to conventional radiotherapy (moderate and low COE, respectively). Only 1 trial reported on overall acute and late toxicity, assessed with the Common Terminology Criteria for Adverse Events (CTCAE).[23] This trial was conducted at MD Anderson in Texas and enrolled 287 women with DCIS or stage 1–II invasive breast cancer. The primary goal was to evaluate cosmetic outcomes at 3 years post-radiation. Rates of any acute toxicity grade ≥2 (during radiation or within 42 days post-radiation) were 47% (65/138) in the hypofractionation

group and 78% (116/149) in the conventional radiation arm ($p < 0.001$). Late toxicity grade ≥2 (assessed at 6 months) were 31% (40/129) for the hypofractionation arm and 32% (46/142) for conventional radiation ($p = 0.81$). The main methodological limitations were unclear allocation concealment (not reported in paper), which was particularly concerning as there were imbalances in number of participants per arm and also in potentially important participant characteristics (*eg*, 74% vs 83 invasive cancer for conventional vs hypofractionation arms, respectively). These imbalances could have also occurred by chance, which is more likely to occur with the smaller sample size in this study.

Figure 5. Breast Cancer Acute Skin Toxicity: Moderate Hypofractionation versus Conventional Radiation Therapy



Hypofractionation may result in little to no difference in acute skin toxicity (low COE; Figure 5). Five trials (total n=1,370) assessed acute skin toxicity over a median follow-up of 4–8 weeks.[19,22,23,27,32] Acute skin toxicity was evaluated by CTCAE or the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) criteria. Three trials included breast cancer stages I–II[19,22,23] and 2 trials included stages I–III.[27,32] Two trials were conducted in Europe,[19,22] 1 was conducted in the US,[23] 1 was in China,[27] and 1 was in Canada.[32] Pooled analyses using data from these 5 trials gave an RR of 0.56 (95% CI [0.31, 0.999]). Using the reported absolute acute toxicity rates from the NCT01413269 trial (Wang et al),[27] we estimated that the ARD is -3.3% (95% CI [-5.1, 0]) at 3 months, indicating fewer events in the hypofractionation arm. However, the CI crosses 0 and doesn't exceed the pre-specified MCID of 10%. Additionally, there was inconsistency in estimates across studies and methodological concerns for some of the studies. These included issues with randomization and/or missing data from loss to follow-up.

Hypofractionation may result in little to no difference in late skin toxicity compared to conventional radiotherapy (low COE). Two trials ($N = 1,683$) evaluated late skin toxicity, both using RTOG/EORTC criteria; median follow-up was 5–10 years.[25,28] One trial was conducted in Canada and included breast cancer stages I–III,[25] while the other occurred in China and focused on stage III breast cancer.[28] The Canadian trial found no differences in rates of grade 2–3 skin toxicity at 5 or 10 years (3% [14/449] and 9% [21/235] in the hypofractionation arm, 3% [14/424] and 8% [17/220] for conventional radiation; p-values not reported).[25] The Chinese trial also reported no differences in toxicity at a median follow-up of 58 months; rates of grade 1–2 toxicity were 21% (86/401) in the hypofractionation arm and 22% (90/409) for conventional radiation ($p = 0.67$).[28] There was also 1 participant with grade 3 toxicity in the hypofractionation arm and none in the conventional radiation group.[28] Main concerns impacting the COE include

missing data in 1 trial due to loss to follow-up (1,234 participants randomized at baseline, but only 873 at 5 years and 455 at 10 years with data on toxicity),[25] and the difficulty of applying results reported as combined grade 1–2 toxicity in the other trial (when the outcome of interest is grade ≥ 2 toxicity).[28]

Hypofractionation results in little to no difference in acute pneumonitis compared to conventional radiotherapy (high COE). Two trials (total $N = 1,549$) evaluated acute pneumonitis, both using CTCAE.[27,28] One trial included breast cancer stages I–III,[27] while the other included stage III only.[28] Both trials were conducted in China and reported no differences in acute pneumonitis between treatment arms. Rates of grade 2 acute pneumonitis were low, ranging 2–3% in the moderate hypofractionation arm. No grade 3 events were observed in either trial.

Only 1 trial reported results on late pneumonitis, finding no events of any grade in either arm.[23]

Several other adverse events were reported by trials comparing moderate hypofractionation with conventional radiation therapy. These included skin ulceration, lymphedema, and lung fibrosis. Detailed outcomes on toxicity and harms for these events (along with those described above) are found in Appendix Table 4.

Quality of Life

Three trials reported quality of life over follow-up periods of 2–3 years.[21,23,24,30] One trial assessed quality of life using EORTC Quality of Life Questionnaire (QLQ-C30) and the Functional Assessment of Cancer Therapy General (FACT-G) and for Breast Cancer (FACT-B),[30] while another trial used only EORTC QLQ-C30,[22] and the third only FACT-G and FACT-B.[23,24] None of these trials found differences in overall quality of life or global health status during follow-up. One trial also reported results for domains of functioning (*eg*, physical and emotional functioning), also finding no differences for domain-level scores.[22] Detailed results for these trials are provided in Appendix Table 5.

Key Question 2

Six trials comparing moderate hypofractionation with conventional radiation performed subgroup analyses to assess moderation in effect by a variety of patient and disease characteristics.[11-13,25,27,29,33] Most did not find any effect variation by these characteristics, although these trials may not have been sufficiently powered to detect subgroup effects across all these factors. The largest study involved post-hoc subgroup analyses of combined data from the 3 START trials (A, B, and pilot; $N = 5,861$).[33] This showed that the treatment effects of moderate hypofractionation versus conventional radiation were similar irrespective of age, type of primary surgery, axillary node status, tumor grade, adjuvant chemotherapy use, or use of tumor bed boost.

Two of the other trials enrolled women with stages I–III cancer, and both determined that treatment effect on local recurrence was similar across variation in use of adjuvant chemotherapy and a variety of patient prognostic factors (age, cancer stage, tumor size, *etc*).[25,27] However, 1 of these trials reported that hypofractionation compared to conventional may be less effective for those with high-grade tumors (hazard ratio [HR] = 3.08, 95% CI [1.22, 7.76]), compared to those with low or medium grades (HR = 0.70, 95% CI [0.31, 1.58], and HR = 0.57, 95% CI [0.29, 1.12], respectively; test for interaction $p = 0.01$).[25] In the high-grade tumor group,

hypofractionation treatment had a substantially higher local recurrence rate at 10 years (ARD 10.9%, 95% CI [-19, -3]).

The sixth trial included women with DCIS or invasive stage I–II breast cancer, and reported analyses examining treatment effects on local-regional recurrence separately for those with DCIS and invasive cancer.[29] There were no differences in local-regional recurrence by treatment arm for the whole sample (HR = 0.90, 95% CI [0.51, 1.59]; risk difference [RD] = -0.3%, 95% CI [-2.3, 1.7]), or separately for those with invasive cancer (HR = 0.75, 95% CI [0.37, 1.49]; RD = -0.7%, 95% CI [-2.7, 1.3]), or DCIS only (HR = 1.40, 95% CI [0.49, 4.06]; RD = 1.6%, 95% CI [-5.6, 8.8]).

Other Radiation Therapy Comparisons

Three trials compared ultra-hypofractionation (total doses 26–30 Gy, dose per fraction 5.2–6.0 Gy) with either moderate hypofractionation (total dose 40.0 Gy, dose per fraction 2.67 Gy) [16-18] or conventional radiation.[15,35] Two of these were conducted in the UK,[15-17,35] and the other one was conducted in Belgium.[18] Two other trials compared accelerated partial breast irradiation (APBI) to whole breast radiation, either moderate hypofractionation or conventional dosing. One of these was conducted in Italy, with the APBI arm receiving twice daily doses of 3.85 Gy per dose over 5–8 days, for a total dose of 38.5 Gy, while the whole breast radiation group received either moderate hypofractionation (daily dose of 2.65 Gy, total 42.5 Gy) or conventional radiation (daily dose 2.0 Gy, total 50 Gy).[31,36] The other trial occurred in Canada and used intensity-modulated radiotherapy (IMRT) in the APBI arm (6 Gy per fraction non-consecutively over 2 weeks, total dose 30 Gy), compared with conventional whole breast radiation (2.0 Gy per dose, total 50 Gy).[14,37,38] Four trials[14,15,18,31,35-38] included women with stage I–II cancer (one of these also included DCIS),[31,36] and the fifth enrolled stage I–III.[16,17] The primary outcomes being evaluated were either local recurrence (k = 3)[16,17,31,36-38] or cosmetic results (k = 2).[15,18,35] Follow-up ranged from 6–10 years for 4 of these trials,[14-17,31,35-38] whereas 1 trial reported only acute outcomes at 2–4 weeks post-radiation.[18]

Key Question 1

Survival & Recurrence Outcomes

Four of these trials reported overall survival and local recurrence rates, all finding no differences between treatment arms.[15,16,31,38] Sample sizes were 520–4,096, and absolute overall survival rates were high (92–98%). Local recurrence rates were generally low across all studies (1.0–3.5%). Two trials evaluated ultra-hypofractionation versus moderate hypofractionation[16,17] or conventional whole breast radiation.[15,35] The other 2 compared APBI with either moderate hypofractionation or conventional whole breast radiation,[14,31,36-38] as described above. Two of these trials also reported local-regional recurrence, also finding no difference between treatment arms; one compared ultra-fractionation with moderate hypofractionation to the whole breast (2.3% vs 3.2% at 5 years),[16] and the other compared APBI with conventional whole breast radiation (3.5% vs 2.7% at 10 years).[38] No trial reported disease-free survival. Detailed results on survival and recurrence outcomes are provided in Appendix Table 3.

Toxicity & Harms

All trials reported acute skin toxicity, which varied substantially across the different treatment arms. The trial comparing ultra-hypofractionation with conventional whole breast radiation

reported lower rates in the ultra-hypofractionation arm (12% [27/217] versus conventional 46% [51/110]).[15] The 2 trials comparing ultra-hypofractionation with moderate hypofractionation reported a wide range of results (ultra-hypofractionation 16–41% vs 12–55% moderate hypofractionation).[17,18] In contrast, both trials examining APBI found lower rates of acute skin toxicity in the APBI arms (2–9%), compared with whole breast radiation (31–38%).[31,38]

The 2 trials evaluating ABPI both assessed acute and late overall toxicity.[14,38,31] One of these used RTOG/EORTC criteria and defined acute as any event ≤ 6 months (and late after 6 months).[38] The other trial used CTCAE and reported as acute any event ≤ 3 months.[31] Both trials reported higher rates of acute toxicity in the whole breast radiation group (38–46%), compared with the ABPI arm (2–28%, $p < 0.001$, both studies). For late toxicity, 1 trial reported more toxicity in the whole breast radiation group (3% vs 0% in APBI, $p = 0.02$),[38] while the other found more toxicity in the ABPI group (13% whole breast vs 33% APBI, $p < 0.001$).[31] One of the APBI trials also reported late skin toxicity, finding no differences (0 APBI vs 0.4% whole breast).[38] The other APBI trial evaluated acute pneumonitis, also finding no differences (0.2% APBI vs 0.8% whole breast).[31] Detailed results on toxicity and harms are provided in Appendix Table 4.

Quality of Life

One trial that compared ultra-hypofractionation with moderate hypofractionation evaluated quality of life.[18] This trial measured global health status using the EORTC QLQ-C30 and reported results favored hypofractionation ($p = 0.005$, results otherwise not reported).

Key Question 2

Both trials evaluating APBI reported analyses on subgroup effects related to local recurrence at 8–10 years, finding no differences for a variety of patient and disease characteristics.[14,31] The factors included patient age, adjuvant therapy, invasive cancer versus DCIS, and tumor size and other characteristics. Although 1 of these was a relatively large trial ($N = 2,135$),[31] it lacked sufficient power to examine subgroup effects for all of these characteristics.

PROSTATE CANCER

Overview

We identified 20 eligible trials (40 publications) that evaluated hypofractionation for prostate cancer. Of these, 18 trials (38 publications) were judged to have RoB ratings that were low or of some concerns and had outcomes data extracted. Table 6 provides an overview of trial characteristics. Sample sizes varied widely (range 40 to 3,216); 4 trials had a sample size > 1000.[39-43] All trials included older males with histologically confirmed prostate cancer (reported mean and median ages ranged from 63–75). All but one trial enrolled men age ≥ 65 years. The majority of trials described their populations as clinically localized prostate cancer ($k = 12$). Risk levels of enrolled participants varied, with 6 trials including men with low or intermediate risk prostate cancer, 6 trials including intermediate to high risk prostate cancer, 2 trials only describing their populations as early-stage localized, and 4 only describing their populations as localized, and including low to high risk prostate cancer. The majority of trials ($k = 13$) compared hypofractionation (total dose range 52.2–72 Gy, dose per fraction 2.4–3.4 Gy, treatment duration: 3.5–6.5 weeks) to conventional fractionation (total dose range 64–80 Gy, dose per fraction 1.8–2.0 Gy, treatment duration: 6.5–8.4 weeks), (approximately 21 versus 38

treatments for hypofractionation versus conventional radiation therapy, respectively) while few compared hypofractionation (total dose 56 Gy, dose per fraction 3.5 Gy, treatment duration: 4 weeks) to hypofractionation (total dose range 67-70.2 Gy, dose per fraction 2.7 Gy, treatment duration: 5 weeks) ($k = 2$)[44,45] or ultra-hypofractionation (total dose range 36.25–42.7 Gy, dose per fraction 6.1–7.25 Gy, treatment duration: 2–2.5 weeks) to conventional fractionation (total dose range 76–78 Gy, dose per fraction 2 Gy, treatment duration: 5–8 weeks) ($k = 2$).[39,46] One trial compared ultra-hypofractionation (total dose 36.25 Gy, dose per fraction 7.25 Gy, treatment duration: 1–2 weeks) to a combined arm of conventional and hypofractionation (total dose range 62–78, dose per fraction 2–3.1 Gy, treatment duration: 4 weeks).[47] The countries in which the trials were conducted varied greatly, with most trials having sites in Europe ($k = 9$)[39,40,43,44,47-51] and North America ($k = 7$),[41,43,47,52-55] and few with sites in China ($k = 2$),[46,56] Iran ($k = 1$),[45] Australia ($k = 2$)[43,57] and New Zealand ($k = 1$).[40] Only 4 trials were held in multiple countries.[40,43,47,58] Ten RCTs reported follow-up of ≥ 5 years.

Detailed study characteristics, outcomes, and RoB ratings for all included trials are presented in Appendix E.

Table 6. Summary Characteristics of Included Prostate Cancer Trials Assessed as Low or Some Concerns Risk of Bias

	Number of Studies (Total=18)
Intervention vs. comparator	
Hypofractionation vs conventional	13
Hypofractionation vs hypofractionation	1
Ultra-hypofractionation vs conventional	2
Ultra-hypofractionation vs hypofractionation	2
Median length of follow-up	
<1 year	4
1-5 years	4
≥5 years	10
Survival outcomes	
Overall survival	10
Prostate-specific survival	8
Metastasis-free survival	3
Biochemical recurrence-free	6
Local recurrence	3
Harms outcomes	
Acute gastrointestinal	14
Acute genitourinary	15
Late gastrointestinal	12
Late genitourinary	12
Quality of life outcome	5
Population classified as	
Early-stage localized	2
Localized (low to high risk)	4
Low risk	1
Low to intermediate risk	4
Intermediate risk	4
Intermediate to high risk	3
High risk	3

Key Question 1

Table 7 provides the key findings and certainty of evidence for efficacy and harms in comparing hypofractionation and conventional radiation therapy in the treatment of prostate cancer.

Below, we provide more detailed information about each outcome and results for comparisons of other radiation strategies. Overall and disease-specific survival exceeded 90% at 5 years for both hypofractionation and conventional radiation therapy regimens with little to no differences in GI or GU toxicity.

Table 7. Certainty of Evidence for Moderate Hypofractionation versus Conventional Radiation Therapy for Prostate Cancer Outcomes

Outcome and Minimal Clinically Important Difference (MCID)	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Overall survival (OS) Absolute effect size estimates based on control event rate at 5 years* **MCID: 5% difference**	3-10 years *N* = 4988 (8 RCTs)[40,41,48,53-55,57,59-62]	**RR = 1.01** (0.98, 1.05)	**92.3%** (89.5, 95.9)	91.4%	**0.9% more** (1.8 fewer to 4.6 more)	⊕⊕⊕◯ Moderate[a]	Hypofractionation probably results in little to no difference in overall survival.
Prostate cancer-specific Survival Absolute effect size estimates based on control event rate at 5 years† **MCID: 5% difference**	2-10 years *N* = 1521 (7 RCTs)[48,53-55,57,59-63]	**RR = 1.00** (0.99, 1.01)	**96.2%** (95.2, 97.1)	96.2%	**0.0%** (1 fewer to 1 more)	⊕⊕⊕◯ Moderate[a]	Hypofractionation probably results in little to no difference in prostate cancer-specific survival.
Biochemical recurrence-free survival Absolute effect size estimates based on control event rate at 5 years† **MCID: 5% difference**	2-10 years *N* = 1378 (6 RCTs)[49,54-57,60,61,63]	**RR = 0.93** (0.85, 1.02)	**53.6%** (49, 58.8)	57.7%	**4.0% fewer** (8.6 fewer to 1.2 more)	⊕⊕◯◯ Low[a,b]	Hypofractionation may result in little to no difference in biochemical recurrence-free survival.
Acute GI toxicity (grade ≥ 2) **MCID: 10% difference**	3-5 months *N* = 6702 (10 RCTs)[40,41,43,50,51,54-56,64,65]	**RR = 1.23** (1.03, 1.58)	**16.6%** (13.9, 21.3)	13.5%	**3.1% more** (0.4 more to 7.8 more)	⊕⊕⊕◯ Moderate[a]	Hypofractionation probably results in little to difference in acute GI toxicity.
Acute GU toxicity (grade ≥ 2) **MCID: 10% difference**	3-5 months *N* = 6703 (10 RCTs)[40,41,43,50,51,54-56,64,65]	**RR = 1.01** (0.77, 1.32)	**28.4%** (21.6, 37.1)	28.1%	**0.3% more** (6.5 fewer to 9 more)	⊕⊕⊕◯ Moderate[a]	Hypofractionation probably results in little to no difference in acute GU toxicity.

Outcome and Minimal Clinically Important Difference (MCID)	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Late GI toxicity (grade ≥ 2) Absolute effect size estimates based on control event rate at 5 years* **MCID: 10% difference**	2-9 years *N* = 4109 (9 RCTs)[40,41,43,52-56,60,64-66]	**RR = 1.11** (0.45, 2.57)	**4.2%** (1.7, 9.8)	3.8%	**0.4% more** (2.1 fewer to 6 more)	⊕⊕⊕◯ Moderate[a]	Hypofractionation probably results in little to no difference in late GI toxicity.
Late GU toxicity (grade ≥ 2) Absolute effect size estimates based on control event rate at 5 years* **MCID: 10% difference**	2-9 years *N* = 5069 (9 RCTs)[40,41,43,52-56,60,64-66]	**RR = 1.12** (0.98, 1.28)	**1.6%** (1.4, 1.8)	1.4%	**0.2% more** (0 fewer to 0.4 more)	⊕⊕⊕◯ Moderate[a]	Hypofractionation probably results in little to no difference in late GU toxicity.

Notes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
* The comparison group is estimated based on the 5-year median data from the CHHiP trial.[40]
† The comparison group is estimated based on the 5-year median data from the Lukka trial.[54]

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

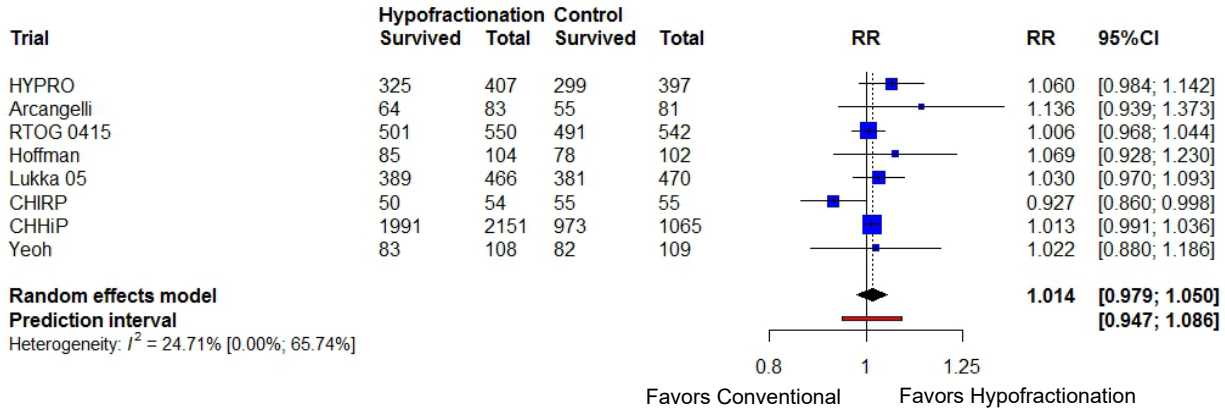
Explanations
a. Downgraded one level for study limitations
b. Downgraded one level for imprecision (CI crossing MCID in one direction)
c. Downgraded two levels for imprecision (CI crossing MCID in both directions)

Abbreviations. CI=confidence interval; GI= gastrointestinal; GU=genitourinary; MCID=minimal clinically important difference; RCT=randomized controlled trial; RR=risk ratio.

Overall Survival

There was probably little to no difference in overall survival between hypofractionation or conventional radiotherapy (RR = 1.01, 95% CI [0.98, 1.05]; Figure 6) (ARD = 0.9%, 95% CI [-1.8, 4.6] at a median follow-up of 5 years based on events in the conventional radiotherapy group of the CHHiP trial[40]; moderate COE). Hypofractionation was provided as total dose range of 52.5–72 Gy, dose per fraction 2.4–3.4 Gy, 21 treatment sessions, and conventional radiation therapy as total dose range 64–80 Gy, dose per fraction 1.8–2.0 Gy, 38 treatment sessions. Eight trials included overall survival as an outcome of interest in understanding the comparative effectiveness of hypofractionation versus conventional radiotherapy in the treatment of prostate cancer (Table 7).

Figure 6. Prostate Cancer Overall Survival: Hypofractionation versus Conventional

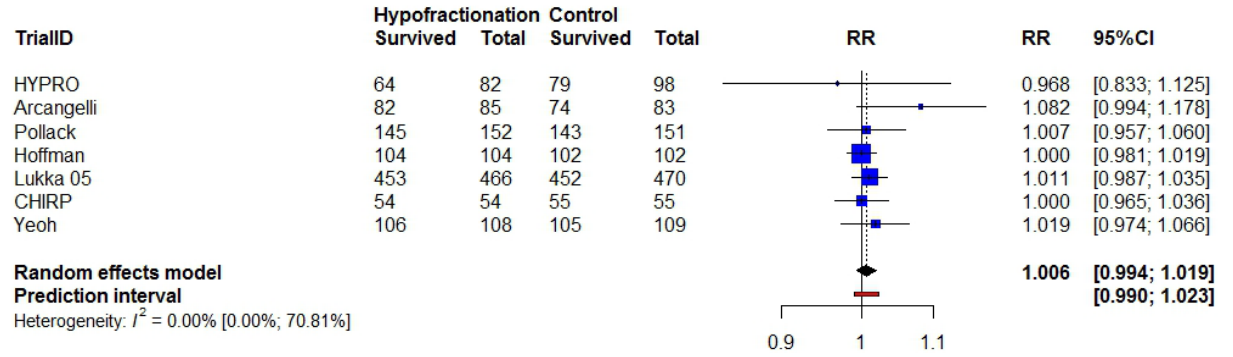


Two additional trials reported overall survival as an outcome of interest. Both compared ultra-hypofractionation (total dose range 36.25–42.7 Gy, dose per fraction 6.1–7.25 Gy) to conventional fractionation (total dose range 76–78 Gy, dose per fraction 2 Gy) (k = 2).[39,46] Both trials reported there was no difference in overall survival at 1 year[46] or at 5 years.[39]

Prostate-cancer-specific Survival

There was probably little to no difference in prostate-cancer-specific survival between hypofractionation and conventional radiotherapy (RR = 1.01, 95% CI [0.99, 1.02]; Figure 7; moderate COE). The estimated ARD is 0% (95% CI [-1.0, 1.0]) at a median follow-up of 5 years, using the reported event rates in the conventional radiotherapy group from the Lukka trial.[54] Hypofractionation was provided at a total dose range of 52.5–72 Gy and dose per fraction of 2.4–3.4 Gy and conventional radiation therapy at a total dose range of 64–80 Gy, dose per fraction of 1.8–2.0 Gy. Seven trials included prostate-cancer-specific survival as an outcome of interest (Table 7).

Figure 7. Prostate-cancer-specific Survival: Hypofractionation versus Conventional

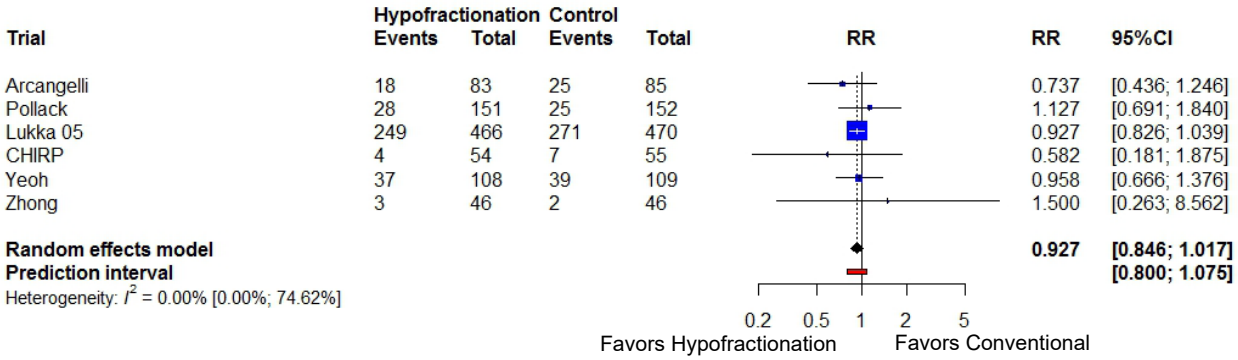


One additional trial reported 5-year prostate-cancer-specific survival as an outcome of interest. This trial compared ultra-hypofractionation (total dose 42.7 Gy, dose per fraction 6.1 Gy) to conventional fractionation (total dose 78 Gy, dose per fraction 2 Gy) and reported no difference.[39]

Biochemical Recurrence

There may be little to no difference in freedom from biochemical recurrence between hypofractionation (total dose range 52.5–70.2 Gy, dose per fraction 2.5–3.1 Gy) or conventional (total dose range 64–80 Gy, dose per fraction 2.0 Gy) radiotherapy (RR = 0.927, 95% CI [0.85, 1.02]; Figure 8) (ARD = -4.0%, 95% CI [-8.6, 1.2]; at a median follow-up of 5 years based on events in the conventional radiotherapy group of the Lukka trial[54]; low COE). Six trials included prostate cancer biochemical recurrence as an outcome of interest (Table 7).

Figure 8. Prostate Cancer Biochemical Recurrence: Hypofractionation versus Conventional

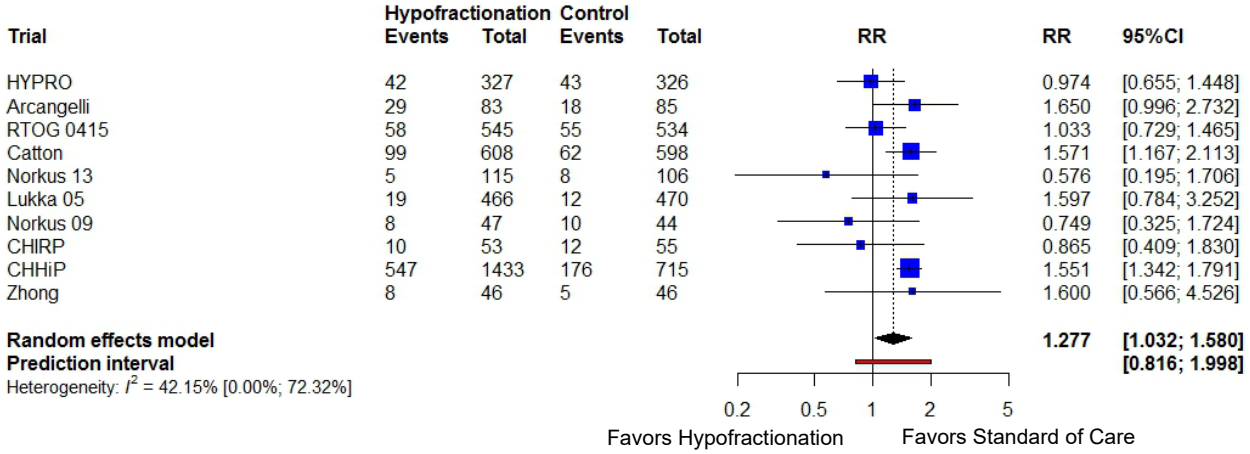


Acute GI

There was probably little to no difference in grade ≥ 2 acute GI toxicity between hypofractionation (total dose range 52.5–70 Gy, dose per fraction 2.5–3.4 Gy) or conventional (total dose range 66–80 Gy, dose per fraction 1.8–2.0 Gy) radiotherapy (RR = 1.28, 95% CI [1.03, 1.58]; Figure 9) (ARD = 3.1%, 95% CI [0.4, 7.8]; moderate COE). Ten trials captured

acute GI outcomes when investigating hypofractionation versus standard of care in prostate cancer treatment (Table 7).

Figure 9. Prostate Cancer Acute GI: Hypofractionation versus Standard of Care



Four additional trials reported on acute GI toxicity as an outcome of interest.

One compared ultra-hypofractionation (total dose 36.25 Gy, dose per fraction 7.25 Gy) to conventional fractionation (total dose 76 Gy, dose per fraction 2 Gy) and found no difference between groups in regard to acute GI toxicities.[46]

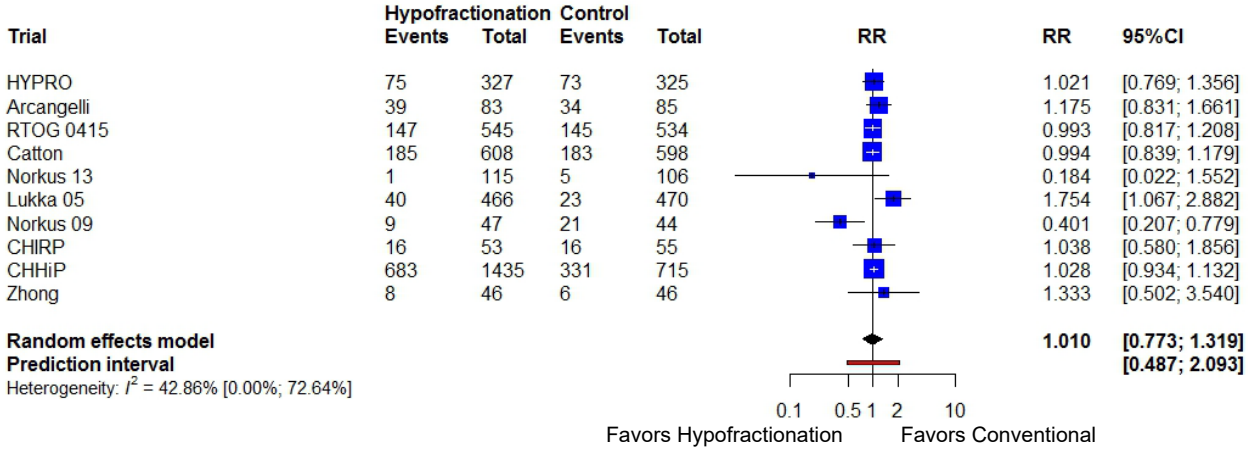
Two trials compared hypofractionation (total dose 56 Gy, dose per fraction 3.5 Gy) to hypofractionation (total dose range 67–70.2 Gy, dose per fraction 2.7 Gy).[44,45] Neither trial found a difference in acute GI toxicity between hypofractionation compared to a different dose of hypofractionation.

One trial compared ultra-hypofractionation (total dose 36.25 Gy, dose per fraction 7.25 Gy) to a combined arm of conventional and hypofractionation (total dose range 62–78, dose per fraction 2–3.1 Gy) and did not report any difference in acute GI toxicities.[47]

Acute GU

There was probably little to no difference in grade ≥ 2 acute GU toxicity between hypofractionation (total dose range 52.5–70 Gy, dose per fraction 2.5–3.4 Gy) or conventional (total dose range 66–80 Gy, dose per fraction 1.8–2.0 Gy) radiotherapy (RR = 1.010, 95% CI [0.773, 1.319]; Figure 10) (ARD = 0.3%, 95% CI [-6.5, 7.8]; moderate COE). Ten trials captured acute GU outcomes when investigating hypofractionation versus conventional radiotherapy in prostate cancer treatment (Table 7).

Figure 10. Prostate Cancer Acute GU: Hypofractionation versus Conventional



Five additional trials reported on acute GU toxicity as an outcome of interest.

Two compared ultra-hypofractionation (total dose range 36.25–42.7 Gy, dose per fraction 6.1–7.25 Gy) to conventional fractionation (total dose range 76–78 Gy, dose per fraction 2 Gy).[39,46] One of these trials reported no difference in GU toxicities in ultra-hypofractionation compared to conventional fractionation,[39] while one reported a statistically significant difference (3% vs 24%, $p = 0.04$), suggesting that ultra-hypofractionation may reduce acute GU toxicities[46]; however, this finding was not supported by other publications.

Two trials compared hypofractionation (total dose 56 Gy, dose per fraction 3.5 Gy) to hypofractionation (total dose range 67–70.2 Gy, dose per fraction 2.7 Gy).[44,45] Neither trial found a difference in acute GU toxicity between hypofractionation compared to a different dose of hypofractionation.

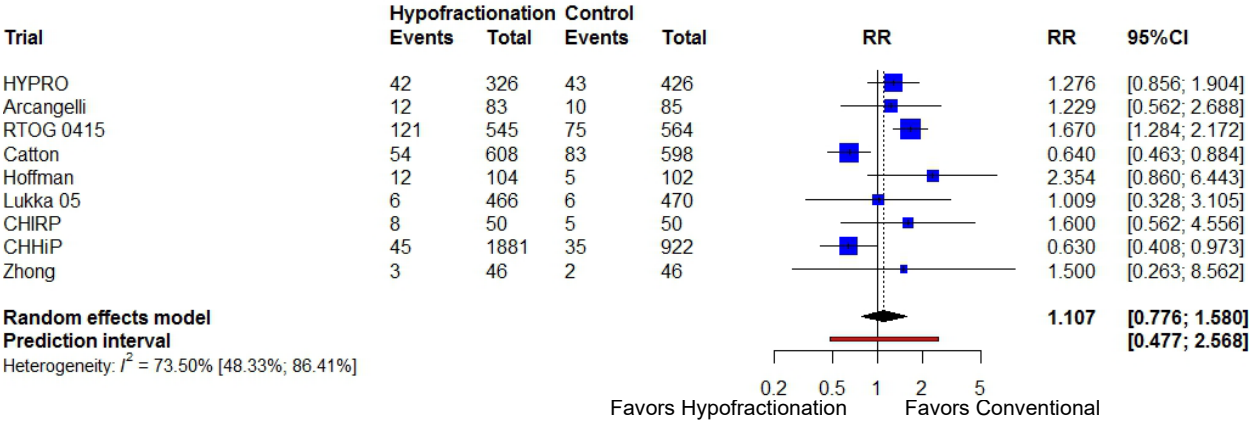
One trial compared ultra-hypofractionation (total dose 36.25 Gy, dose per fraction 7.25 Gy) to a combined arm of conventional and hypofractionation (total dose range 62–78, dose per fraction 2–3.1 Gy) and did not report any difference in acute GU toxicities.[47]

Late GI

There was probably little to no difference in grade ≥ 2 late GI toxicity between hypofractionation (total dose range 52.5–70 Gy, dose per fraction 2.4–3.4 Gy) or conventional (total dose range 66–80 Gy, dose per fraction 1.8–2.0 Gy) radiotherapy (RR = 1.11, 95% CI [0.78, 1.58]; Figure 11) (ARD = 0.4%, 95% CI [-2.1, 6.0] at 5 years; moderate COE). Nine trials captured late GI outcomes when investigating hypofractionation versus standard of care in prostate cancer treatment (Table 7).

One additional trial reported late GI toxicity, but was excluded from this analysis (and subsequent certainty of evidence rating) due to authors only reporting cumulative risk as a percent and not providing number of events.[52]

Figure 11. Prostate Cancer Late GI: Hypofractionation versus Conventional



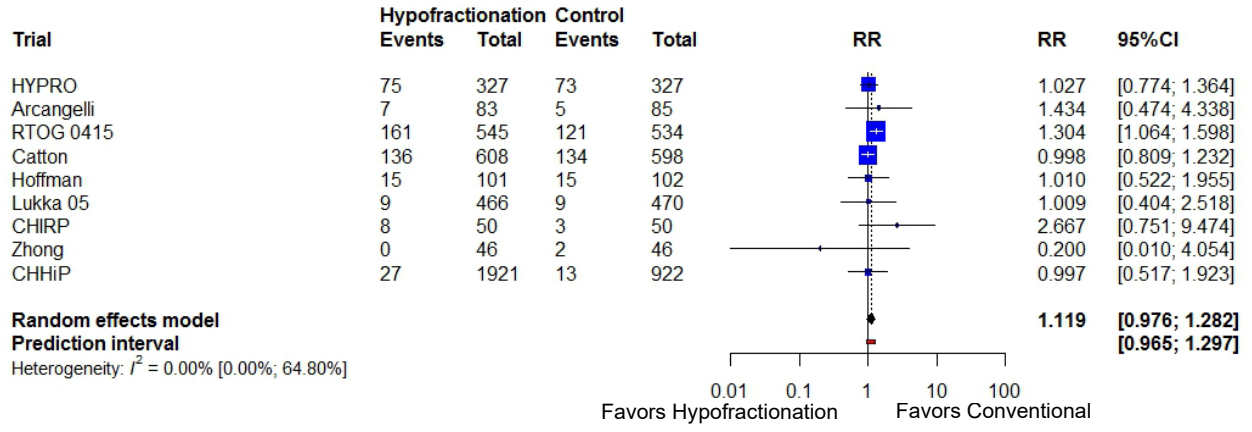
Two additional trials reported late GI toxicity as an outcome of interest. Both compared ultra-hypofractionation (total dose range 36.25–42.7 Gy, dose per fraction 6.1–7.25 Gy) to conventional fractionation (total dose range 76–78 Gy, dose per fraction 2 Gy) (k = 2).[39,46] Both trials reported no difference in late GI toxicity at 1 year[46] or at 5 years.[39]

Late GU

There was probably little to no difference in grade ≥ 2 late GU toxicity between hypofractionation (total dose range 52.5–70 Gy, dose per fraction 2.4–3.4 Gy) or conventional (total dose range 66–80 Gy, dose per fraction 1.8–2.0 Gy) radiotherapy (RR = 1.12, 95% CI [0.98, 1.28]; Figure 12) (ARD = 0.2, 95% CI [0, 0.4] at 5 years; moderate COE). Nine trials captured late GU outcomes when investigating hypofractionation versus standard of care in prostate cancer treatment (Table 7).

One additional trial reported late GU toxicity, but was excluded from this analysis (and subsequent certainty of evidence rating) due to authors only reporting cumulative risk as a percent and not providing number of events.[52]

Figure 12. Prostate Cancer Late GU: Hypofractionation versus Conventional



Two additional trials reported late GU toxicity as an outcome of interest. Both compared ultra-hypofractionation (total dose range 36.25–42.7 Gy, dose per fraction 6.1–7.25 Gy) to conventional fractionation (total dose range 76–78 Gy, dose per fraction 2 Gy).[39,46] One trial reported a statistically significant difference between the ultra-hypofractionation group and the conventional group in late GU toxicity at 1 year follow-up (6.1% vs 2.4%, respectively; p = 0.004); however, at 5 years follow-up, no difference was found (4.5% vs 4.8%; p = 1.00).[39] The second trial reported no difference at 1 year post-treatment.[46]

Local Recurrence

Three trials reported on local recurrence as an outcome of interest.[49,54,61,63] All 3 compared hypofractionation (total dose range 52.5–70.2 Gy, dose per fraction 2.6–3.1 Gy) to conventionally fractionated radiotherapy (total dose range 66–80 Gy, dose per fraction 2 Gy). All 3 trials reported no difference between groups in regard to local recurrence at 3 years,[49] 5 years,[54] 5.8 years,[61] or 10 years post-treatment.[63]

Metastases

Three trials reported on metastases as an outcome of interest.[49,54,61,63] All 3 compared hypofractionation (total dose range 52.5–70.2 Gy, dose per fraction 2.6–3.1 Gy) to conventionally fractionated radiotherapy (total dose range 66–80 Gy, dose per fraction 2 Gy). All 3 trials reported no difference between groups in regard to metastases at 3 years,[49] 5 years,[54,61,63] or 10 years post-treatment.[63]

Quality of Life

Five trials reported on an overall, or global, quality of life (QoL) measure using a validated instrument.[47,58,67-69] There was variability in the measures used to assess QoL across trials, and measures used included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30), Extended Prostate Cancer Index (EPIC), International Prostate Symptom Score (IPSS), EuroQoL5, Functional Assessment of Cancer Therapy-Prostate (FACT-P), Short Form Survey (SF)-12, and and SF-36. Three trials were comparisons of hypofractionation (total dose range 60–70 Gy, dose per fraction 2.5–3 Gy) to conventional fractionation (total dose range 73.8–76 Gy, dose per fraction 1.8–2 Gy).[67-69] One trial compared ultra-hypofractionation (total dose 42.7, dose per fraction 6.1) to conventional radiotherapy (total dose 78 Gy, dose per fraction 2 Gy),[58] and the remaining trial compared ultra-hypofractionation (total dose 36.25 Gy, dose per fraction 7.25 Gy) to a combined arm of conventional and hypofractionation (total dose range 62–78, dose per fraction 2–3.1 Gy). None of the 5 trials identified any differences in quality-of-life scores between groups on any of the measures used, at any time point during the trial (follow-up ranged from 6 months to 6 years).

Key Question 2

Of the included trials, 1 provided stratified analyses of harms (acute GI and acute GU) by age subgroups.[40,70] In a secondary analysis of the data from the Conventional of Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) trial,[40] authors reported no difference in acute GI or acute GU in patients treated with hypofractionation (total dose 60 Gy, dose per fraction 3 Gy) compared to conventional fractionation (total dose 74 Gy, dose per fraction 2 Gy) when stratified by participants greater or less than 75 years old.[70]

Three trials limited enrollment to men with high-risk disease. Comparative effects and harms appeared similar. Two trials compared ultra-hypofractionation to conventional radiotherapy. Comparative results appeared similar.

LUNG CANCER

Overview

Of 8 eligible trials, 5 were assessed as low and some concerns for RoB.[10,71-74] Table 8 provides summary characteristics of the included lung cancer studies. A more expansive summary characteristics table can be found in Appendix Table 12. Four of these trials[10,72-74] evaluated non-small cell lung cancer (NSCLC), while the remaining trial[71] enrolled individuals with small cell lung cancer (SCLC). Trials were conducted in the United States,[74] Scandinavia,[72] India,[73] China,[71] and Australia and New Zealand.[10] Variation in lung cancer populations, stage of cancer, and radiotherapy comparisons precluded meta-analyses; we provide a narrative summary.

Of the 4 trials evaluating NSCLC, 2 compared hypofractionation versus conventional radiotherapy.[73,74] In Roy et al ($N = 36$; stage IIIA–IIIB), 1 group received conventional radiotherapy to a total dose of 60 Gy in 30 fractions over 6 weeks compared to another group that received 48 Gy in 20 fractions over 4 weeks. In the second trial, Iyengar et al ($N = 96$, stage II–III) compared an experimental hypofractionated image-guided radiotherapy (IGRT) of 60 Gy in 15 fractions over 3 weeks versus conventionally fractionated radiotherapy (CFRT) of 60 Gy in 30 fractions over 6 weeks. Roy et al had a median follow up period of 15 months, and Iyengar et al had a median follow up of 8.7 months.

The other 2 trials compared SBRT/SABR to moderate hypofractionation or conventional radiotherapy for NSCLC.[10,72] Ball et al[10] enrolled adults ($N = 101$) with T1-T2a disease and compared SABR (48–54 Gy total dose, consisting of either 4 treatments of 12 Gy each or 3 sessions of 18 Gy) with a standard radiotherapy of 66 Gy in 33 daily fractions or 50 Gy in 20 daily fractions, depending on institutional preference. Nyman et al[72] enrolled adults ($N = 102$) with stage I disease and compared total dose 66 Gy (22 Gy per fraction, 3 fractions over 1 week) versus conventional radiotherapy with total dose 70 Gy (2.0 Gy per fraction for 5 days a week for 7 weeks). Ball et al had a median follow-up period of 2.6 years for SABR and 2.1 years for the comparator arm, and Nyman et al had a median follow up of 3.1 years.

Trials of radiotherapy for NSCLC had a variety of primary endpoints, though all were small in size and relatively short in follow-up duration. Ball et al and Roy et al both specified local treatment failure or a local-regional response rate as the primary outcomes, while Nyman et al indicated progression-free survival and Iyengar et al specified overall survival (at 1 year).[10,72-74]

The single SCLC trial[71] compared 2 different chemotherapy and concurrent thoracic radiation therapy regimens (CCTRT): once-daily CCTRT at 65 Gy in 26 daily fractions for 5 days a week over 36 days versus twice daily CCTRT at 45 Gy in 30 twice-daily fractions, with an interfractional interval of at least 6 hours, for 5 days a week over 19 days. The trial analyzed data from 182 patients (170, 93%; stage IIIA-B) with a median follow up of 24.3 months. The primary outcome was progression-free survival.[71]

Detailed study characteristics, outcomes, and RoB ratings for all included trials are presented in Appendix F.

Table 8. Summary Characteristics of Lung Cancer Studies Assessed as Low or Some Concerns Risk of Bias

	Number of Studies (Total=5)
Intervention vs comparator	
Hypofractionation vs conventional	2
SBRT/SABR vs conventional	2
hypofractionation vs hyperfractionation	1
Sub-cancer type	
Small cell lung cancer (SCLC)	1
Non-small cell lung cancer (NSCLC)	4
Median follow-up:	
<1 year	1
1-2 years	3
≥3 years	1
Survival outcomes	
Overall survival	5
Lung cancer-specific survival	1
Progression-free survival	2
Harms outcomes	
Acute cough	4
Acute esophagitis	5
Acute pneumonitis	5
Late cough	4
Late esophagitis	3
Late pneumonitis	4
Quality of life outcome	2
Cancer stage	
I	2
I-III	1
II-III	1
III	1

Key Question 1

Tables 10 through 12 provide the key findings and certainty of evidence for efficacy and harms in comparing hypofractionation or SABR/SBRT to conventional radiation therapy or hyperfractionation in the treatment of non-small cell or small cell lung cancer. As there were fewer than 4 trials in each of these groups, we did not pool outcomes using meta-analyses. Additionally, authors reported outcomes at different time points and levels of severity, further limiting the degree to which they could be grouped in the certainty of evidence assessments. We describe these results in greater detail below. In general, given the very low certainty of evidence, we are uncertain about the comparative effectiveness and harms of hypofractionation versus conventional radiation therapy for individuals with non-small cell or small cell lung cancer.

Table 9. Certainty of Evidence for Hypofractionation versus Conventional Radiation Therapy for NSCLC Lung Cancer Outcomes

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Overall survival (OS) **MCID: 5% difference**	1 year *N* = 132 (2 RCTs)[73,74]	Unable to assess*	**75%**	52%	**23% more**	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of hypofractionation on overall survival.
			37.7% (24.2, 51.0%)	44.6%	**6.9% fewer**		
Overall survival (OS) **MCID: 5% difference**	Median length of time *N* = 132 (2 RCTs)[73,74]	Unable to assess*	**24.73 months**	12.33 months	**12.4 months more**	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of hypofractionation on overall survival.
			8.2 months (5.4, 12.4)	10.6 months	**2.4 months fewer**		
Progression-free survival (PFS) **MCID: 5% difference**	Median length of time *N* = 132 (2 RCTs)[73,74]	Unable to assess*	**17 months**	5.36 months	**11.64 months more**	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of hypofractionation on progression-free survival.
			6.4 months (4.1, 7.8)	7.3 months	**0.9 months fewer**		

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Acute and Late Cough (grade ≥ 2) Risk ratio and absolute effect size estimates based on control event rate from 1 trial[†] **MCID: 10% difference**	1 year *N* = 96 (1 RCT)[74]	**RR = 0.33** (0.04 to 3.03)	**2.1%** (0.2, 19.8)	6.5%	**4.4% fewer** (6.3 fewer to 13.3 more)	⨁⨁◯◯ Low[c,d]	Hypofractionation may result in little to no difference on acute and late cough.
Acute Pharyngitis/esophagitis (grade ≥ 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial[‡] **MCID: 5% difference**	1 year *N* = 36 (1 RCT)[73]	**RR = 0.33** (0.04 to 2.91)	**5.6%** (0.6, 48.5)	16.7%	**11.1% fewer** (16 fewer to 31.8 more)	⨁◯◯◯ Very low[b,c]	The evidence is very uncertain about the effect of hypofractionation on acute pharyngitis/esophagitis.

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Acute and late esophagitis (grade ≥ 2)							
Risk ratio and absolute effect size estimates based on control event rate from 1 trial[†]	1 year *N* = 96 (1 RCT)[74]	**RR = 2.21** (0.84, 5.79)	**24.0%** (9.2, 62.9)	10.9%	**13.1% more** (1.7 fewer to 52 more)	⊕⊕◯◯ Low[b,c]	Hypofractionation may result in little to no difference on acute and late esophagitis.
MCID: 10% difference							
Acute pneumonitis (grade ≥ 3)							
Risk ratio and absolute effect size estimates based on control event rate from 1 trial[‡]	15-24 months *N* = 36 (1 RCT)[73]	**RR = 0.53** (0.02, 14.79)	**2.9%** (0.1, 82.2)	5.6%	**2.6% fewer** (5.5 fewer to 76.6 more)	⊕◯◯◯ Very low[b,c]	The evidence is very uncertain about the effect of hypofractionation on acute pneumonitis.
MCID: 5% difference							

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Acute and Late Pneumonitis (grade ≥ 2)							
Risk ratio and absolute effect size estimates based on control event rate from 1 trial†	1 year *N* = 96 (1 RCT)[74]	**RR = 1.23** (0.29, 5.19)	**8.0%** (1.9, 33.8)	6.5%	**1.5% more** (4.6 fewer to 27.3 more)	⨁⨁◯◯ Low[b,c]	Hypofractionation may result in little to no difference on acute and late pneumonitis.
MCID: 10% difference							

Notes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
* Study authors did not provide count level data to allow for calculation of a relative effect.
† Estimated using data from Iyengar et al.[74]
‡ Estimated using data from Roy et al.[73]

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded one level for inconsistency (variance of point estimate across studies)
b. Downgraded one level for imprecision (CI crossing MCID in one direction)
c. Downgraded one level for indirectness (acute and late harms grouped together or study did not include grade 2 harms)
d. Downgraded one level for study limitations (small n, short follow up, or no events)

Abbreviations. CI=confidence interval; PFS=progression-free survival; MCID=minimal clinically important difference; NR=not reported; OS=overall survival; RCT=randomized controlled trial; RR=risk ratio.

Table 10. Certainty of Evidence for SBRT/SABR versus Conventional Radiation Therapy for NSCLC Lung Cancer Outcomes

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			SBRT/SABR	**Conventional**	**Difference**		
Overall survival (OS) **MCID: 5% difference**	2 years *N* = 101 (1 RCT)[10]	Unable to assess*	**77%** (67, 88)	59%	**18% more***	⊕⊕⊕◯ Moderate[b]	SABR probably results in a better overall survival.
Overall survival (OS) **MCID: 5% difference**	3 years *N* = 102 (1 RCT)[72]	Unable to assess*	54%*	59%*	5% fewer*	⊕⊕◯◯ Low[a, b]	SBRT may result in little to no difference in overall survival.
Progression-free survival (PFS) **MCID: 5% difference**	3 years *N* = 102 (1 RCT)[72]	Unable to assess*	42%*	42%*	0%*	⊕⊕⊕◯ Moderate[b]	SBRT probably results in little to no difference in progression-free survival.
Lung cancer-specific survival **MCID: 5% difference**	2.1 years *N* = 101 (1 RCT)[10]	HR = 0.49 (0.21, 1.14)	-*	-*	-*	⊕⊕◯◯ Low[a,b]	SABR may result in little to no difference in lung cancer specific survival.

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			SBRT/SABR	**Conventional**	**Difference**		
Acute and late cough (grade ≥ 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial[†] **MCID: 5% difference**	2 years *N* = 101 (1 RCT)[10]	**RR = 2.12** (0.10, 45.78)	**3.0%** (0, 26.8)	0.0%	**3% more** (1 fewer to 7 more)	⊕◯◯◯ Very low[b,c,d]	The evidence is very uncertain about the effect of SABR on acute and late cough.
Acute and late cough (grade 2 and 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial[‡] **MCID: 10% difference**	1 year *N* = 102 (1 RCT)[72]	**RR = 2.21** (0.58, 8.35)	**12.5%** (3.3, 47.3)	5.7%	**6.8% more** (2.4 fewer to 41.6 more)	⊕⊕◯◯ Low[b,c]	SBRT may result in little to no difference in acute and late cough.

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			SBRT/SABR	**Conventional**	**Difference**		
Acute and late pneumonitis (grade ≥ 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial† **MCID: 5% difference**	2 years *N* = 101 (1 RCT)[10]	**RR = 0.53** (0.01, 26.16)	**0.0%**	0.0%	**0.0% fewer**	⨁◯◯◯ Very low[b,c,d]	The evidence is very uncertain about the effect of SABR on acute and late pneumonitis.
Acute and late pneumonitis (grade 2 and 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial‡ **MCID: 10% difference**	1 year *N* = 102 (1 RCT)[72]	**RR = 0.44** (0.09, 2.17)	**4.2%** (0.8, 20.5)	9.4%	**5.3% fewer** (8.6 fewer to 11.1 more)	⨁⨁◯◯ Low[b,c]	SBRT may result in little to no difference in acute to late pneumonitis.

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			SBRT/SABR	**Conventional**	**Difference**		
Acute and late esophagitis (grade ≥ 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial† **MCID: 5% difference**	2 years *N* = 101 (1 RCT)[10]	**RR = 0.53** (0.01, 26.16)	**0.0%**	0.0%	**0.0% fewer**	⨁◯◯◯ Very low[b,c,d]	The evidence is very uncertain about the effect of SABR on acute and late esophagitis.
Acute and late esophagitis (grade 2 and 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial† **MCID: 10% difference**	1 year *N* = 102 (1 RCT)[72]	**RR = 0.55** (0.02, 16.09)	**0.0%**	1.9%	**1.9% fewer**	⨁◯◯◯ Very low[b,c,d]	The evidence is very uncertain about the effect of SBRT on acute and late esophagitis.

Notes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
* Study authors did not report these results or provide count level data to allow for calculation of these measures and/or CI.
† Estimated using data from Nyman et al.[72]
‡ Estimated using data from Ball et al.[10]

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded one level for imprecision (CI crossing MCID in one direction)
b. Downgraded one level for study limitations (small n, short follow up, or no events)
c. Downgraded one level for indirectness (acute and late harms grouped together)
d. Downgraded one level for other considerations (0 events observed in 1 or more arms)

Abbreviations. CI=confidence interval; PFS=progression-free survival; MCID=minimal clinically important difference; NR=not reported; OS=overall survival; RCT=randomized controlled trial; RR=risk ratio.

Table 11. Certainty of Evidence for Hypofractionation versus Hyperfractionation for SCLC Lung Cancer Outcomes

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Hyperfractionation**	**Difference**		
Overall survival (OS) **MCID: 5% difference**	3 years *N* = 177 (1 RCT)[71]	Unable to assess*	**56.2%** (43.2, 69.1)	41.5%	**14.7% more**	⨁⨁◯◯ Low[a,b]	Hypofractionation may result in little to no difference in overall survival.
Progression-free survival (PFS) **MCID: 5% difference**	3 years *N* = 177 (1 RCT)[71]	Unable to assess*	**37.2%** (26.0, 48.3)	19.9%	**17.3% more**	⨁⨁◯◯ Low[a,b]	Hypofractionation may result in little to no difference in progression-free survival.
Acute cough (grade ≥ 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial† **MCID: 5% difference**	3 months *N* = 177 (1 RCT)[71]	**RR = 1.08** (0.02, 53.95)	**0.0%** (0, 0)	0.0%	**0.0% fewer** (0 fewer to 0 fewer)	⨁◯◯◯ Very low[a,c,d]	The evidence is very uncertain about the effect of hypofractionation on acute cough.

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Hyperfractionation**	**Difference**		
Late cough (grade ≥ 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial[†] **MCID: 5% difference**	2 years *N* = 177 (1 RCT)[71]	**RR = 1.08** (0.02, 53.95)	**0.0%** (0, 0)	0.0%	**0.0% fewer** (0 fewer to 0 fewer)	⨁◯◯◯ Very low[a,c,d]	The evidence is very uncertain about the effect of hypofractionation on late cough.
Acute pneumonitis (grade ≥ 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial[†] **MCID: 5% difference**	3 months *N* = 177 (1 RCT)[71]	**RR = 0.72** (0.12, 4.21)	**2.4%** (0.4, 13.7)	3.3%	**0.9% fewer** (2.9 fewer to 10.5 more)	⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of hypofractionation on acute pneumonitis.

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Hyperfractionation**	**Difference**		
Late pneumonitis (grade ≥ 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial† **MCID: 5% difference**	2 years *N* = 177 (1 RCT)[71]	**RR = 1.08** (0.02, 53.95)	**0.0%** (0, 0)	0.0%	**0.0% fewer** (0 fewer to 0 fewer)	⊕◯◯◯ Very low[a,c,d]	The evidence is very uncertain about the effect of hypofractionation on late pneumonitis.
Acute esophagitis (grade ≥ 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial† **MCID: 5% difference**	2 years *N* = 177 (1 RCT)[71]	**RR = 0.88** (0.45, 1.72)	**15.3%** (7.8, 29.9)	17.4%	**2.1% fewer** (9.6 fewer to 12.5 more)	⊕◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of hypofractionation on acute esophagitis.

Notes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
* Study authors did not provide count level data to allow for calculation of a relative effect.
† Estimated using data from Qiu et al.[71]

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded one level for study limitations (small n, short follow up, *etc*)
b. Downgraded one level for imprecision (CI crossing MCID in one direction)
c. Downgraded one level for indirectness (acute and late harms grouped together or study did not include grade 2 harms)
d. Downgraded one level for other considerations (0 events observed in 1 or more arms)

Abbreviations. CI=confidence interval; PFS=progression-free survival; MCID=minimal clinically important difference; NR=not reported; OS=overall survival; RCT=randomized controlled trial; RR=risk ratio.

Overall Survival

NSCLC

Four trials included non-small cell lung cancer (NSCLC) populations. Two of the included trials compared hypofractionation to conventional radiotherapy.[73,74] The evidence is very uncertain regarding the impact of hypofractionation on overall survival in comparison to conventional radiotherapy in NSCLC populations (very low COE). Roy et al[73] included locally advanced squamous cell lung cancer patients, while Iyengar et al[74] included patients with stage II or III NSCLC. Roy et al reported a median overall survival of 24.7 months for those in the hypofractionation arm in comparison to 12.3 months for those in the conventional radiotherapy arm. Roy et al reported an overall survival at 1 year of 75% for the hypofractionated arm and 52% for those treated with conventional radiation.[73] In contrast, Iyengar et al reported a median overall survival of 8.2 months (95% CI [5.4, 12.4]) for the hypofractionation arm compared to 10.6 months (95% CI [8.4, 15.3]) for those in the conventional radiotherapy arm. A 1 year overall survival of 37.7% (95% CI [24.2, 51.0%]) was reported for the hypofractionated arm and 44.6% (95% CI [29.9, 58.3%]) for those in the conventional radiotherapy arm.[74]A key difference between these 2 trials centers around the allowance for concurrent chemotherapy during radiotherapy. Roy et al allowed for the administration of chemotherapy prior to radiotherapy and during the radiotherapy schedule. Iyengar et al included only patients that were ineligible for concurrent chemoradiotherapy, but allowed patients to have sequential consolidative chemotherapy after radiotherapy at the discretion of the treating physician.

The evidence suggests that SABR probably results in better overall survival in NSCLC populations (moderate COE). The evidence suggests that SBRT may result in little to no difference in overall survival in NSCLC populations (low COE). Two trials compared SABR/SBRT with either conventional or moderate hypofractionation[10] or conventional radiotherapy.[72] Both included stage 1 NSCLC, though the latter required patients be medically inoperable. Ball et al reported a 2 year overall survival of 77% (95% CI [67, 88%]) for those who had received SABR and 59% (95% CI [44, 78%]) for those that received conventional radiotherapy.[10] Nyman et al reported a hazard ratio of 0.75 (95% CI [0.43, 1.30]) for overall survival, with a 2 year overall survival of 72% for those receiving SBRT and 68% for those receiving conventional radiotherapy.[72]

SCLC

The single small cell lung cancer trial by Qiu et al[71] compared hypofractionation to hyperfractionation. The evidence suggests that hypofractionation may result in little to no difference in overall survival compared to hyperfractionation in SCLC populations (low COE).The authors reported no difference in overall survival between the 2 groups. Patients were enrolled if their lung cancer was determined to be limited stage. Qiu reported a 2 year overall survival of 69.9% (95% CI [59.9, 79.9]) among those in the hyperfractionation group compared to 74.2% (95% CI [64.0, 84.3%]) for those in the hypofractionation group.[71]

Progression-free Survival

NSCLC

The 2 trials for NSCLC comparing hypofractionation to conventional radiotherapy report disparate findings for PFS. The evidence is very uncertain regarding the impact of

hypofractionation on PFS in comparison to conventional radiotherapy in NSCLC populations (very low COE). Roy et al reported a PFS of 17 months for those in the hypofractionation arm and 5.36 months in the conventional radiotherapy arm. In contrast, Iyengar et al reported a PFS of 6.4 (95% CI [4.1, 7.8]) months for those in the hypofractionation arm compared to 7.3 (95% CI [5.0, 10.6]) months for those that received conventional radiotherapy ($p = 0.77$).

Of the 2 trials reporting on SABR/SBRT compared to conventional radiotherapy, only the Nyman et al trial reported findings for PFS. The evidence suggests that SBRT probably results in little to no difference in PFS in NSCLC populations (moderate COE). Nyman et al reported a hazard ratio of 0.85 (95% CI [0.52, 1.36]) for PFS, with a 2 year PFS of 53% for those receiving SBRT and 54% for those receiving conventional radiotherapy.[72]

SCLC

Hypofractionation may result in little to no difference in PFS at 2 years when compared to hyperfractionation in SCLC populations (low COE). Qiu et al reported a 2 year PFS of 28.4% (95% CI [18.2, 38.6%]) for those in the hyperfractionation trial arm compared to 42.3% (95% CI [31.1, 53.5%]) for those in the hypofractionation trial arm.[71]

Lung-cancer-specific Survival

The evidence suggests that SABR may result in little to no difference in lung-cancer-specific survival in NSCLC populations (low COE). Only Ball et al reported lung-cancer-specific survival with a HR of 0.49 (95% CI [0.21, 1.15]; $p = 0.09$) when comparing individuals receiving SABR to individuals receiving conventional radiotherapy.[10]

A consistent concern with the included lung cancer trials stems from the sample sizes. Qiu et al was the only trial to meet the established enrollment goal, whereas none of the studies in NSCLC did so. Iyengar et al designed the trial to demonstrate that hypofractionation would improve local control, and by extension this would improve overall survival. However, both this study and Roy et al closed enrollment early and then analyzed results for only half the number of participants as the enrollment goals. Similarly, Nyman et al also scaled the trial down due to slow enrollment accrual. The reduction in trial sample size leads to reduced power to detect meaningful differences. In combination with the relatively short follow-up periods (and thus less opportunity to detect events), this contributed to lower levels of confidence in these survival outcomes.

Harms

NSCLC

The evidence provides very low or low certainty of evidence for the effect of hypofractionation on harms outcomes when compared to conventional radiotherapy. Both trials used CTCAE v. 3.0 to classify harms; however, Roy et al reported harms grade ≥ 3, while Iyengar et al reported ≥ 2.0. Roy et al reported counts of acute pharyngitis/oesophagitis and acute pneumonitis, while Iyengar et al reported counts of acute and late cough, esophagitis, and pneumonitis. Roy et al reported counts of acute pharyngitis/oesophagitis as 3/18 (16.7%) among those in the conventional radiotherapy arm compared to 1/8 (5.5%) among those in the hypofractionation arm ($p = 0.05$).[73] Iyengar et al reported counts of acute and late esophagitis as 12/50 (24.0%) among those in the hypofractionation arm compared to 5/46 (10.9%) among those in the conventional radiotherapy arm.[74] Iyengar et al reported pneumonitis counts of 4/50 (8%) among

those in the hypofractionation arm compared to 3/46 (6.5%) among those in the conventional radiotherapy arm.[74] Only Iyengar et al included cough as an outcome of interest, with 1/50 (2%) among those in the hypofractionation arm compared to 3/46 (5.6%) among those in the conventional radiotherapy arm.[74]

The evidence provides very low or low certainty of evidence for the effect of SBRT/SABR on harms outcomes when compared to conventional radiotherapy. The Ball et al trial makes use of the CTCAE v. 4.0 and reports grade 3 and 4 to classify harms, while the Nyman et al trial makes use of the CTCAE v. 3.0 and reports grade 2 and 3. Ball et al report counts of acute and late cough as 2/66 (3%) among those in the SABR arm versus 0/35 (0%) among those in the conventional radiotherapy arm.[72] Nyman et al reported acute and late cough counts of 6/48 (12.5%) among the SBRT arm compared to 3/53 (5.7%) among the conventional radiotherapy arm.[72] Ball and Nyman both report counts of acute and late esophagitis. Ball et al report 0/66 (0%) for those in the SABR compared to (0%) among those in the conventional radiotherapy arm.[10] Nyman et al reported 0/48 (0%) among those in the SBRT arm compared to 1/53 (1.9%) among those in the conventional radiotherapy arm.[72] Both trials also reported a count of acute and late pneumonitis, with Ball et al reporting 0/66 (0%) among those in the SABR arm compared to 0/35 (0%), and Nyman et al reporting 2/48 (4.2%) among those in the SBRT arm compared to 5/53 (9.4%) among those in the conventional radiotherapy arm.

SCLC

The evidence is very uncertain regarding the impact of hypofractionation on PFS in comparison to hyperfractionation in SCLC populations (very low COE). Qiu et al used CTCAE v. 4.0 to report acute and late harms ≥ 3 for the SCLC trial population. Qiu et al reported 0 cases of acute or late cough and late pneumonitis for both the hypofractionation and hyperfractionation trial arms. Acute esophagitis counts were 13/85 (15.3%) for the hypofractionation arm compared to 16/92 (17.4%) for the hyperfractionation arm. Acute pneumonitis counts were 2/85 (2.4%) for the hypofractionation arm compared to 3/92 (3.3%) for the hyperfractionation trial arm.[71]

As the trials were primarily powered to assess differences in survival and harms and toxicities were listed as secondary outcomes of interest, the reduction in trial enrollment numbers and final trial population sizes are concerning. Secondly, as harms and toxicities can be rare events, the short trial duration and reduced trial population sizes contributed to the imprecision (wide confidence intervals) captured in the effect measures.

Quality of Life

Two studies reported quality of life outcomes, both in NSCLC populations.[10,73] Ball et al and Roy et al both reported a quality of life measure using the EORTC QLQ-C30. Ball et al assessed quality of life at 1 month before treatment, 3 months post-treatment, then every 3 months for 2 years and every 6 months for 2–5 years. Authors used these data to estimate the area under the curve (AUC) for quality of life over 3.5 years, and used linear mixed effects models to calculate differences in AUC overall and at 3 and 6 months for the global score and subdomains; no significant differences between treatment arms were found for any of these comparisons.[10] Roy et al reported quality of life pre and post-treatment: there were no differences in pre-treatment scores between the hypofractionation arm (median 50, range 8.3–66.7) and the conventional radiotherapy arm (median 41.7, range 0-58.3; $p = 0.24$), or at post-treatment (hypofractionation arm median 66.7, range 41.7–100; conventional arm median 58.3, range 8.3–100; $p = 0.44$).[73]

A final concern of note is the variation in disease location and cancer stage of the included participants in each trial. These differences across trials are a challenge for reviewers as it can preclude grouping of trials, thereby preventing a strong assessment of the evidence. These nuances in disease site and progression are important and trials that provide a replicated approach and design are a necessity to understand the comparative effectiveness of hypofractionation/SBRT/SABR to conventional radiotherapy.

Key Question 2

Trials did not stratify outcomes by the subgroups of interest; as such, there was no information to address KQ2 regarding whether results of a specific treatment regimen varied by patient or tumor characteristics in either lung cancer type. However, 1 study specifically enrolled individuals with stage I disease while 2 other trials enrolled individuals with stage II–III disease.[10,72,74] We did not observe any large differences in comparative outcomes in studies enrolling individuals with different stage disease, though other factors may account for findings.

HEAD AND NECK CANCER

Overview

Of 8 eligible studies addressing head and neck cancer, we focus here on results from the 4 trials rated as low or some concerns for RoB. Two trials examined the effects of moderate hypofractionation compared with conventional radiotherapy for stage I–II glottic squamous cell carcinoma.[75,76] The third trial evaluated salvage IMRT, hypofractionation versus conventional dosing, for locally recurrent nasopharyngeal carcinoma.[77] The fourth trial compared moderate hypofractionation with conventional radiation therapy for locally advanced (stage III–IVB) squamous cell carcinoma of the head and neck.[78] All 4 trials were conducted in Asia (Korea,[75] Japan,[76] China,[77] and India[78]). Detailed study characteristics, results, and RoB ratings for all eligible trials are found in Appendix G. Because of the low number of studies, we were unable to perform quantitative meta-analyses. Below, we first describe the main results from the 2 trials addressing early stage glottic cancer. Then, we present findings from the other trials which evaluated recurrent nasopharyngeal carcinoma and locally advanced head and neck cancer.

Hypofractionation versus Conventional Radiation Therapy for Early Stage Glottic Cancer

Moon et al[75] evaluated the efficacy and harms of moderate hypofractionation (total dose range 63–67.5 Gy, dose per fraction 2.25 Gy) with conventional radiation (total dose range 66–70 Gy, dose per fraction 2.0 Gy) (approximately 29 vs 34 treatments, respectively) for 156 participants with T1 (N = 139) or T2 (N = 16) glottic squamous cell cancer; none had nodal involvement or distant metastasis. Most participants were male (N = 151, 97%) and smokers (N = 122, 78%). Half were 65 years or older (N = 81, 52%). Both radiation therapies were given once per day, lasting a median of 42 days in the hypofractionation arm and 50 days in the conventional arm. The primary goal was to demonstrate non-inferiority in local control rates, with a margin of 10%. The estimated sample size needed was 282 patients, but the trial was stopped early (at 55% of total sample size) due to poor enrollment. Median follow-up was 67 months.

Kodaira et al[76] examined the effects of moderate hypofractionation (total dose range 60–64.8 Gy, dose per fraction 2.4 Gy) with conventional radiation (total dose range 66–70 Gy, dose per fraction 2.0 Gy) for 370 participants with T1 (N = 278) or T2 (N = 92) glottic squamous cell

cancer (approximately 26 versus 34 treatments, respectively). Although participants were required to be T1-2N0M0 at enrollment, subsequent staging after randomization demonstrated that 1 person was N2M1 in the hypofractionation arm and one was actually T3 in the conventional arm; 2 participants in each arm also had other active cancers. Most participants were male ($N = 256$, 96%), and the median ages were 67-68; smoking status was not reported. Both radiation therapies were given once per day for 5 days a week. The primary goal was to demonstrate non-inferiority in progression-free survival at 3 years, with a margin of 5%. Median follow-up was 4.8 years. Twelve participants did not complete the radiation therapy (3 in hypofractionation arm, 9 in conventional arm); all participants were included in the intention-to-treat analyses for effectiveness. Two participants in each group did not receive any of the prescribed radiation therapy, and these were excluded from analyses focused on harms of treatment.

Key Question 1

Table 12 summarizes the key findings and certainty of evidence for efficacy (survival and local recurrence) and harms of hypofractionation compared with conventional radiation therapy. Overall survival exceeded 90% at 3 years in both hypofractionation and conventional radiation therapy, and there was little to no difference in toxicity outcomes. Below, we describe these results in greater detail. Neither trial examined quality of life.

Hypofractionation (total dose range 50–67.5 Gy, dose per fraction 2.22–3.125 Gy) may result in little to no difference on overall survival or progression-free survival, compared with conventional radiotherapy (low COE). For 5-year overall survival, Moon et al[75] reported 86.6% in the hypofractionation arm and 82.5% for conventional radiation (HR not reported [NR], $p = 0.36$), while Kodaira et al[76] found at 3 years 93.5% and 98.4% survival for hypofractionation versus conventional radiation, respectively (comparison p-value NR). Moon et al[75] reported 5-year progression-free survival of 88.5% for hypofractionation and 77.8% for conventional (HR = 1.55, $p = 0.21$). Local recurrence occurred in 9 participants (12%) in the hypofractionation arm and 16 (20%) for conventional radiation.[75] Kodaira et al[76] reported 3-year progression-free survival of 81.7% for hypofractionation and 79.9% for conventional radiation, giving a difference of 1.8% (95% CI [-5.1%, 8.8%]) slightly in favor of hypofractionation. However, the CI exceeded the pre-specified non-inferiority margin of -5%, indicating that non-inferiority was not confirmed. Local recurrence was found in 20 participants (11%) in the hypofractionation arm and 34 (18%) in the conventional arm. The main methodological limitations were the small sample size and relatively low event rates, particularly in the Moon et al trial,[75] which reduced the ability to detect meaningful differences.

Regarding toxicity and harms from radiation therapy, hypofractionation may also result in little to no difference on acute mucositis, acute dysphagia, or late mucositis (low COE). Hypofractionation also probably results in little to no difference in late soft tissue (neck) necrosis (moderate COE). Moon et al[75] used RTOG/EORTC criteria to assess toxicity, finding no differences in rates of acute or late mucositis or laryngeal harms between hypofractionation and conventional radiation therapy. However, rates of these events were very low, with no grade ≥ 2 mucositis or laryngeal harms in the acute period, and only 1 participant with grade 2 mucositis and 2 participants with grade 2 laryngeal harms in the late stage (all in the conventional arm). Kodaira et al[76] used CTCAE v. 3 to evaluate toxicity and grouped grades 1-2 together in reporting the results. For acute toxicity, they found no grade 3 or 4 dysphagia, but there were

some participants with grade 3 mucositis (*eg*, 11 participants [6%] with mucositis at any site in the hypofractionation arm, and 9 participants [5%] for conventional radiation). One participant in Kodaira et al[76] had late grade 4 soft tissue necrosis in the conventional radiation arm (none in the hypofractionation arm). In addition to the methodological limitations related to low sample sizes and event rates, there were challenges with applying these findings related to grade 1-2 events being reported together in Kodaira et al.[76]

Key Question 2

Moon et al[75] evaluated for differences in effects of hypofractionation versus conventional radiation therapy for progression-free survival by T stage, finding that these were similar (no difference in survival) for T1 and T2 participants. Kodaira et al[76] did not report any findings on potential differences in comparative effectiveness by cancer stage or other participant characteristics.

Table 12. Certainty of Evidence for Moderate Hypofractionation versus Conventional Radiation Therapy for Early Stage Glottic Cancer Outcomes

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Overall survival (OS) Risk ratio and absolute effect size estimates based on control event rate within 3 years* **MCID: 5% difference**	3 years *N* = 516 (2 RCTs)[75,76]	**RR = 0.95** (0.91, 0.99)	**93.5%** (89.7, 97.6)	98.4%	**4.8% fewer** (-8.7, -0.8)	⊕⊕◯◯ Low[a,b]	Hypofractionation may result in little to no difference in overall survival.
Progression-free survival (PFS) Risk ratio and absolute effect size estimates based on control event rate within 3 years* **MCID: 10% difference**	3 years *N* = 516 (2 RCTs)[75,76]	**RR = 1.02** (0.93, 1.13)	**81.7%** (74.0, 90.3)	79.9%	**1.8% more** (-5.9, 10.4)	⊕⊕◯◯ Low[a,b]	Hypofractionation may result in little to no difference in progression-free survival.
Acute mucositis (grade 3-4) Risk ratio and absolute effect size estimates based on control event rate from 1 trial* **MCID: 5% difference**	3 months *N* = 516 (2 RCTs)[75,76]	**RR = 1.18** (0.50, 2.78)	**6.0%** (2.6, 14.2)	5.1%	**0.9% more** (-2.5, 9.1)	⊕⊕◯◯ Low[b,c]	Hypofractionation may result in little to no difference in acute mucositis.

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Acute dysphagia (grade 1-2) Risk ratio and absolute effect size estimates based on control event rate from 1 trial* **MCID: 10% difference**	3 months *N* = 360 (1 RCT)[76]	**RR = 1.07** (0.96, 1.20)	**80.3%** (71.8, 89.9)	74.6%	5.7 more (-2.8, 15.3)	⊕⊕◯◯ Low[b,c]	Hypofractionation may result in little to no difference in acute dysphagia.
Late mucositis (grade ≥ 2) Absolute effect size estimates based on control event at 5 years† **MCID: 10% difference**	5 years *N* = 156 (1 RCT)[75]	Not estimable	**0%**	1.2%	1.2% fewer (-3.6, 1.2)	⊕⊕◯◯ Low[a,d]	Hypofractionation may result in little to no difference in late mucositis.
Late soft tissue necrosis (neck, grade 3-4) Absolute effect size estimates based on control event rate from 1 trial* **MCID: 5% difference**	4.8 years *N* = 360 (1 RCT)[76]	Not estimable	**0%**	0.6%	0.1% fewer (-1.5, 1.5)	⊕⊕⊕◯ Moderate[d]	Hypofractionation probably results in little to no difference in late soft tissue necrosis.

Notes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
* Estimated using data from from Kodaira et al.[76]
† Estimated using data from Moon et al.[75]

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded one level for study limitations
b. Downgraded one level for imprecision (CI crossing MCID in one direction)
c. Downgraded one level for indirectness (used data for grade 1-2)
d. Downgraded for other concerns (rare events with few detected in control group and none in hypofractionation arm)

Abbreviations. CI=confidence interval; MCID=minimal clinically important difference; NA=not applicable; OS=overall survival; PFS=progression-free survival; RCT=randomized controlled trial; RR=risk ratio.

Hypofractionation versus Conventional Radiation Therapy for Recurrent Nasopharyngeal Cancer and Locally Advanced Head and Neck Cancer

Tian et al[77] evaluated the efficacy and harms of IMRT moderate hypofractionation (total dose 60 Gy, dose per fraction 2.22 Gy; 27 treatments) compared with conventional dose (total dose 68 Gy, dose per fraction 2 Gy; 34 treatments) for 117 participants with T1-2 ($N = 25$), T3 ($N = 46$), and T4 ($N = 26$) nasopharyngeal carcinoma. Most participants had no nodal involvement but 15 were N1-2. Most participants were male ($N = 94$, 80%), and the median age was 47.5 in the hypofractionation arm and 46.0 years in the conventional group. Smoking status was not reported. Both radiation therapies were given once per day for 5 days a week. The primary goal was to demonstrate non-inferiority in overall survival at 5 years, with a margin of 5%. Median follow-up was 25 months. Two participants did not complete the assigned radiation treatment (1 in each arm). All participants were included in the intention-to-treat analysis for efficacy and harms.

Choudhury et al[78] compared moderate hypofractionation (total dose 50 Gy, dose per fraction 3.125 Gy; 16 treatments) with conventional radiation therapy (total dose 66 Gy, dose per fraction 2 Gy; 33 treatments). Hypofractionation treatment lasted 3 weeks, while the conventional radiation occurred over either 5.5 weeks (6 daily fractions per week) or 6.5 weeks (5 daily fractions per week). Participants had stage III ($N = 48$), IVA ($N = 55$), or IVB ($N = 31$) squamous cell carcinoma. Additionally, they had to be older than 50 years and have significant comorbidities (*eg*, diabetes, chronic kidney disease, and cardiac condition) and/or poor performance status (Eastern Cooperative Oncology Group [ECOG] 3-4). Smoking status was not reported. The primary outcome was overall response rates, and the median follow-up was 11 months. Sixteen participants did not complete the assigned treatment (6 in the hypofractionation arm and 18 in the conventional arms), and baseline data were not reported for these individuals. Per-protocol analyses were conducted for efficacy and harms.

Key Question 1

Table 13 summarizes the key findings and certainty of evidence for efficacy and harms of moderate hypofractionation compared with conventional radiation therapy for recurrent and locally advanced head and neck cancer. The evidence is very uncertain about the effect of hypofractionation on overall survival and progression-free survival (very low COE) as well as most treatment toxicities.

Tian et al[77] reported 57% overall survival in the hypofractionation arm and 38% in the conventional arm at 3 years, and 44% in the hypofractionation arm and 30% in the conventional arm for 5 years ($p = 0.06$). For 5-year progression-free survival, there were also no differences (57% for hypofractionation and 55% in the conventional arm, $p = 0.58$).[77] Local recurrence occurred in 12 participants (20%) in the hypofractionation arm and in 11 participants (19%) in the conventional arm.[77] Main concerns for these findings were due to limitations in the study design (unclear allocation concealment), imprecision of the estimates (related to small sample sizes), and limited applicability of these results (as the study only enrolled patients with recurrent cancer). Survival outcomes from Choudhury et al[78] were rated high ROB due to substantial deviations from the protocol (12–17% of participants did not receive the allocated treatment) and missing outcomes assessment (median follow-up was far shorter than the goal of 4 years for overall survival).

Regarding toxicity and harms from radiation therapy, the evidence is also very uncertain on the effects of hypofractionation compared with conventional radiation therapy for acute mucositis, temporal lobe necrosis, and late xerostomia (very low COE). However, hypofractionation may result in an increase in late mucositis (low COE). Both trials used RTOG criteria to assess toxicity. Tian et al[77] found no difference in rates of grade 3 acute mucositis (8.4% hypofractionation vs 13.7% conventional, $p = 0.39$), while Choudhury et al[78] reported unclear results for grade 2-3 acute mucositis (64% hypofractionation vs 37–69% conventional arms, $p = 0.01$ for comparison across all 3 arms). Regarding late grade 3 xerostomia, Tian et al[77] once again found no difference (13.5% hypofractionation vs 10.3% conventional, $p = 0.42$), but Choudhury et al[78] showed more grade 2-3 events in the hypofractionation arm (52% hypofractionation vs 13–36% conventional arms, $p = 0.005$ for comparison across all 3 arms). Choudhury et al[78] also found greater rates of grade 2-3 late mucositis for hypofractionation (45% vs 11–36% conventional arms, $p = 0.001$). Tian et al[78] reported no difference in temporal lobe necrosis (20.3% hypofractionation vs 22.4% conventional, $p = 0.59$). There were similar concerns as noted above for survival outcomes.

Key Question 2

Neither trial evaluated whether outcomes for hypofractionation versus conventional radiation therapy were different for various patient, disease, or treatment characteristics.

Table 13. Certainty of Evidence for Moderate Hypofractionation versus Conventional Radiation Therapy for Recurrent Nasopharyngeal Cancer and Locally Advanced Head and Neck Cancer

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	Conventional	Difference		
Overall survival (OS) Risk ratio and absolute effect size estimates based on control event rate at 5 years* **MCID: 5% difference**	5 years *N* = 117 (1 RCT)[77]	**RR = 1.45** (0.89, 2.37)	**44.1%** (27.0, 71.9)	30.4%	**19.0 more** (2.6, 35.4)	⊕◯◯◯ Very Low[a,b,c]	Hypofractionation may result in better overall survival.
Progression-free survival (PFS) Risk ratio and absolute effect size estimates based on control event rate at 5 years* **MCID: 10% difference**	5 years *N* = 117 (1 RCT)[77]	**RR = 1.02** (0.78, 1.32	**67.9%** (53.0, 82.7)	66.7%	**1.2 more** (-16.4, 18.7)	⊕◯◯◯ Very Low[a,d]	The evidence is very uncertain about the effect of hypofractionation on progression-free survival.
Acute mucositis (grade 3) Risk ratio and absolute effect size estimates based on control event rate at 3 months* **MCID: 5% difference**	3 months *N* = 117 (1 RCT)[77,78]	**RR = 0.61** (0.21, 1.77)	**8.5%** (3.0, 24.4)	13.8%	**5.3 fewer** (-10.8, 10.6)	⊕◯◯◯ Very Low[a,d]	The evidence is very uncertain about the effect of hypofractionation on acute mucositis.

Outcome and MCID	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Late xerostomia (grade 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial* **MCID: 5% difference**	11-25 months *N* = 249 (2 RCTs)[77,78]	**RR =1.31** (0.48, 3.54)	**13.6%** (5.0, t 36.7)	10.3%	**3.2 more** (-5.3, 26.3)	⊕◯◯◯ Very Low[a,d,e]	The evidence is very uncertain about the effect of hypofractionation on late xerostomia.
Late mucositis (grade 3) Risk ratio and absolute effect size estimates based on control event rate from 1 trial† **MCID: 5% difference**	11 months *N* = 132 (1 RCT)[78]	**RR = 4.00** (1.05, 15.24)	**13.6%** (3.6, 52.0)	3.4%	**10.2 more** (0.2, 48.6)	⊕⊕◯◯ Low[b,c]	Hypofractionation may result in an increase in late mucositis.
Temporal lobe necrosis (grade NR) Risk ratio and absolute effect size estimates based on control event rate from 1 trial* **MCID**: **10% difference**	25 months *N* = 117 (1 RCT)[77]	**RR = 0.907** (0.45, 1.82)	**20.3%** (10.1,40.8)	22.4%	**2.1 fewer** (-12.3, 18.4)	⊕◯◯◯ Very low[a,c,d]	The evidence is very uncertain about the effect of hypofractionation on temporal lobe necrosis.

Notes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
* Estimated using data from Tian et al.[77]
† Estimated using data from Choudhury et al.[78]

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded one level for study limitations
b. Downgraded one level for imprecision (CI crossing MCID in one direction)
c. Downgraded one level for indirectness
d. Downgraded two levels for imprecision (CI crossing MCID in both directions)
e. Downgraded one level for inconsistency

Abbreviations. CI=confidence interval; MCID=minimal clinically important difference; NR not reporte; OS=overall survival; PFS=progression-free survival; RCT=randomized controlled trial; RR=risk ratio.

RECTAL CANCER

Overview

Two trials investigating the comparative effectiveness of hypofractionation versus conventional radiotherapy were identified and included in the review. Bujko et al[80] was assessed as low RoB for the survival outcomes and some concerns for the harms outcomes. The Stockholm III[81] trial was assessed as low RoB for all outcomes. Both trials[80,81] included a patient population diagnosed with adenocarcinoma of the rectum. Bujko et al[80] was conducted in Poland and reported a median follow-up of 35 months. There were 515 participants in the trial, which compared ultra-hypofractionation (5 Gy/fraction; 5 treatments) to conventional radiotherapy (1.8 Gy/fraction; 28 treatments). Stockholm III[81] was conducted in Sweden, had 385 participants, and reported a median follow-up of 5.2 years. Additionally, Stockholm III[81] reported outcomes for 3 different arms: ultra-hypofractionation (5 Gy/fraction; 5 treatments) with surgery within 1 week, ultra-hypofractionation (5 Gy/fraction; 5 treatments) with surgery within 4–8 weeks, and conventional radiotherapy (2 Gy/fraction; 25 treatments) with surgery within 4–8 weeks. The 2 arms that are relevant to our review compared hypofractionation and conventional radiotherapy with surgery within 4–8 weeks.

Detailed summary characteristics, outcomes, and RoB ratings for all included trials are presented in Appendix H.

Key Question 1

Table 14 provides the key findings and certainty of evidence for efficacy and harms in comparing moderate hypofractionation and conventional radiation therapy in the treatment of rectal cancer. Overall survival was approximately 70% and disease-free survival approximately 50% at 3 years regardless of treratment groups.

Survival

Hypofractionation probably results in little to no difference in overall survival compared to conventional radiotherapy (moderate COE). Bujko et al[80] reported a 3-year overall survival rate (hypofractionation: 73%, conventional: 65%; HR = 0.73, 95% CI [0.53, 1.01]). Detailed results for this trial are provided in Appendix Table 22.

Disease-free Survival

Hypofractionation may result in little to no difference in disease-free survival (low COE). Stockholm III[81] reported a hazard ratio and 95% CI for overall survival at the end of follow-up (0.81, 95% CI [0.53, 1.24]; overall p = 0.62). Bujko et al[80] reported a 3-year disease-free survival rate (hypofractionation: 53%, conventional: 52%; HR = 0.96, 95% CI [0.75, 1.24]; *p* = 0.85).

Stockholm III[81] also reported distant metastases (hypofractionation: 38/128 [29.7%], conventional: 35/128 [27.3%]; HR = 1.25, 95% CI [0.76, 2.04]) and local recurrence (hypofractionation: 1/128 [0.7%], conventional: 4/128 [3.1%]; HR = 1.22, 95% CI [0.33, 3.45]). Detailed results for these trials are provided in Appendix Table 22.

Harms

Bujko et al[80] reported any acute toxicity (hypofractionation: 119/256 [46.5%], conventional: 155/259 [59.8%], effect measure NR), while Stockholm III[81] reported overall late toxicity (hypofractionation: 51/128 [39.8%], conventional: 60/128 [46.9%]; $p = 0.53$). Hypofractionation may result in a decrease in acute diarrhea and late bowel obstruction but may result in little to no difference in late anal incontinence compared to conventional radiotherapy (low COEs). Bujko et al[80] reported acute diarrhea (hypofractionation: 36/256 [14%], conventional: 70/259 [27.0%], effect measure NR). Stockholm III[81] reported 2 late outcomes: anal incontinence (hypofractionation: 5/128 [3.9%], conventional: 8/128 [6.3%]; $p = 0.32$) and bowel obstruction (hypofractionation: 11/128 [8.5%], conventional: 19/128 [14.8%]; $p = 0.25$). Due to clinical variability in disease type and a sparsity of outcome data, we did not conduct pooled analyses. Detailed results for these trials are provided in Appendix Table 23.

Quality of Life

We found no studies that measured quality of life in rectal cancer.

Key Question 2

Trials did not stratify outcomes by the subgroups of interest. As such, there was no information to address KQ2 regarding whether results varied by patient or tumor characteristics.

Table 14. Certainty of Evidence for Moderate Hypofractionation versus Conventional Radiation Therapy for Rectal Cancer Outcomes

Outcome Minimal Clinically Important Difference (MCID)	Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	What Happens
			Hypofractionation	**Conventional**	**Difference**		
Overall survival (OS) **MCID: 5% difference**	3 years *N* = 771 (2 RCTs)[80,81]	**RR = 1.07** (0.94, 1.22)	**69.7%** (61.3, 79.5)	65.2%	**4.6% more** (3.9 fewer to 14.3 more)	⊕⊕⊕◯ Moderate[a]	Hypofractionation probably results in little to no difference in overall survival.
Disease-free survival (DFS) **MCID: 5% difference**	3 years *N* = 515 (1 RCT)[80]	**RR = 1.04** (0.79, 1.38)	**29.5%** (22.4, 39.1)	28.3%	**1.1% more** (6 fewer to 10.8 more)	⊕⊕◯◯ Low[a,b]	Hypofractionation may result in little to difference in disease-free survival.
Acute diarrhea (grade ≥ 2) **MCID: 10% difference**	< 30 days *N* = 515 (1 RCT)[80]	**RR = 0.58** (0.40, 0.84)	**15.7%** (10.8, 22.7)	27%	**11.4% fewer** (16.2 fewer to 4.3 fewer)	⊕⊕◯◯ Low[a,b]	Hypofractionation may result in a reduction in acute diarrhea.
Late anal incontinence (grade ≥ 3) **MCID: 5% difference**	After 30 days *N* = 256 (1 RCT)[81]	**RR = 0.64** (0.21, 1.90)	**4.0%** (1.3, 11.9)	6.3%	**2.3% fewer** (4.9 fewer to 5.6 more)	⊕⊕◯◯ Low[a,b]	Hypofractionation may result in little to no difference in late anal incontinence.
Late bowel obstruction (grade ≥ 3) **MCID: 5% difference**	After 30 days *N* = 256 (1 RCT)[81]	**RR = 0.61** (0.30, 1.20)	**9.1%** (4.5, 17.8)	14.8%	**5.8% fewer** (10.4 fewer to 3.0 more)	⊕⊕◯◯ Low[a,b]	Hypofractionation may result in a reduction in late bowel obstruction.

Notes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded one level for imprecision (wide CI)
b. Downgraded one level for study limitations

Abbreviations. CI=confidence interval; DFS=disease-free survival; OS=overall survival; RCT=randomized controlled trial; RR=risk ratio.

DISCUSSION

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.
    - Most studies were not designed to evaluate the comparative effectiveness on overall or cancer specific survival. Few studies were sufficiently similar enough to permit pooling or assess consistency, replicability, and/or broader applicability.
- For breast cancer, moderate hypofractionation results in little to no difference in overall survival, disease-free survival, and local-regional recurrence; there were also generally no differences in treatment harms (with variable certainty for different harms).
- For individuals with prostate and rectal cancer, hypofractionation therapy probably results in little to no difference in overall survival, and may result in little to no difference in disease-free or progression-free survival versus conventionally fractionated radiotherapy.
    - Hypofractionation may result in little to no difference in treatment harms.
- For individuals with small cell lung cancer, hypofractionation may result in little to no difference in overall and progression-free survival over 15–36 months follow-up.
    - Evidence is generally very uncertain regarding comparative treatment harms.
- For non-small cell lung cancer, evidence from 1 small RCT suggests that SBRT may result in little to no difference in overall survival versus conventionally fractionated radiotherapy through 36 months.
    - Evidence is generally very uncertain regarding comparative treatment harms.
- For early stage glottic cancer, hypofractionation may result in little to no difference in overall and disease-free survival, and most harms; the evidence is mostly very uncertain for locally advanced or recurrent head and neck cancers.
- For breast cancer, evidence indicated no differences in comparative effects of moderate hypofractionation versus conventional radiotherapy across a variety of patient, tumor, and adjuvant treatment characteristics; few studies addressed these questions for other cancers.
- No RCTs evaluated bladder, pancreatic, melanoma, or non-melanoma skin cancers.
- Decisions to widely implement hypofractionated radiotherapy, especially in patients with cancers where there is little to no evidence, would require extrapolation of findings from this report to, or conduct of RCTs in, populations, tumors, and radiation therapy regimens not currently evaluated in RCTs.

- We found no data on cost, resource use, or access. Radiation treatment cost, duration, and access as well as patient burden are likely relevant factors influencing practice and policy decisions. While mean treatment duration and number of treatment days varied widely across cancers and treatment regimens, they typically ranged 2–3 weeks and 10–15 treatment days less with hypofractionation versus conventional radiation. Based on limited data, ultra-hypofractionation in selected cancers resulted in greater reductions in treatment duration and sessions versus conventional radiotherapy.

Table 15. Summary of Key Findings and Certainty of Evidence

Cancer Type	Follow-up	N (# Trials)	Certainty	Summary Statement
Overall Survival				
Breast	5-10 years	9436 (7)	⊕⊕⊕⊕ High	Hypofractionation results in little or no difference in overall survival.
Prostate	3-10 years	4988 (8)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in overall survival.
NSCLC: hypofractionation vs conventional	1 year	132 (2)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in overall survival.
NSCLC: SBRT vs conventional	3 years	102 (1)	⊕⊕◯◯ Low	SBRT may result in little to no difference in overall survival.
NSCLC: SABR vs conventional	2 years	101 (1)	⊕⊕⊕◯ Moderate	SABR probably results in little to no difference in overall survival.
SCLC	15-24 months	218 (2)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in overall survival.
Early stage glottic Cancer	3 years	516 (2)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in overall survival.
Recurrent or locally advanced head & neck cancer	5 years	117 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in overall survival.
Rectal	3 years	771 (2)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in overall survival.
Disease-free or Progression-free Survival				
Breast	5-10 years	7574 (6)	⊕⊕⊕⊕ High	Hypofractionation results in little or no difference in disease-free survival.
Prostate	2-10 years	1378 (6)	⊕⊕◯◯ Low	Hypofractionation may result in little or no difference in biochemical recurrence-free survival.
Prostate	2-10 years	1521 (7)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in prostate cancer-specific survival.
NSCLC: hypofractionation vs conventional	9-15 months	132 (2)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in progression-free survival.

Cancer Type	Follow-up	N (# Trials)	Certainty	Summary Statement
NSCLC: SBRT vs conventional	3 years	102 (1)	⊕⊕⊕◯ Moderate	SBRT probably result in little to no difference in progression-free survival.
SCLC	3 years	177 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in progression-free survival.
Early stage glottic Cancer	3 years	516 (2)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in progression-free survival.
Recurrent or locally advanced head & neck cancer	5 years	117 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in progression-free survival.
Rectal	3 years	515 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little or difference in disease-free survival.
Local-regional Recurrence				
Breast	5-10 years	7948 (6)	⊕⊕⊕⊕ High	Hypofractionation results in little or no difference in local-regional recurrence.
Any Toxicity				
Breast	≤3 months	287 (1)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in less overall acute toxicity.
Breast	6 months	271 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in overall late toxicity.
Skin Toxicity				
Breast	6 months (acute)	1370 (5)	⊕⊕◯◯ Low	Hypofractionation may result in little or no difference in acute skin toxicity.
Breast	5-10 years (late)	2054 (2)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in late skin toxicity.
Pneumonitis				
Breast	6 months (acute)	1549 (2)	⊕⊕⊕⊕ High	Hypofractionation results in little or no difference in acute pneumonitis.
NSCLC: hypofractionation vs conventional	1 year (acute and late)	96 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference on acute and late pneumonitis.
	15-24 months (acute)	36 (1)	⊕⊕◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on acute pneumonitis.

Cancer Type	Follow-up	N (# Trials)	Certainty	Summary Statement
NSCLC: SABR/SBRT vs conventional	2 years (acute and late)	101 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of SABR on acute and late pneumonitis.
	1 year (acute and late)	102 (1)	⊕⊕◯◯ Low	SBRT may result in little to no difference in acute and late pneumonitis.
SCLC	3 months (acute)	177 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on acute pneumonitis.
	2 years (late)		⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on late pneumonitis.
Gastrointestinal Toxicity				
Prostate	3-5 months (acute)	6702 (10)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in acute GI toxicity.
Prostate	2-9 years (late)	4109 (9)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in late GI toxicity.
Genitourinary Toxicity				
Prostate	3-5 months (acute)	6703 (10)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little or no difference in acute GU toxicity.
Prostate	2-9 years (late)	5069 (9)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little to no difference in late GU toxicity.
Cough				
NSCLC: hypofractionation vs conventional	1 year (acute and late)	96 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little or no difference in acute and late cough.
NSCLC: SABR/SBRT vs conventional	2 year (acute and late)	101 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of SABR on acute and late cough.
	1 year (acute and late)	102 (1)	⊕⊕◯◯ Low	SBRT may result in little to no difference in acute and late cough.
SCLC: hypofractionation vs hyperfractionation	3 months (acute)	177 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on acute cough .
	2 years (late)		⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on late cough.

Cancer Type	Follow-up	N (# Trials)	Certainty	Summary Statement
Esophagitis				
NSCLC: hypofractionation vs conventional	1 year (acute)	36 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on acute pharyngitis/esophagitis.
	1 year (acute and late)	96 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference on acute and late esophagitis.
NSCLC: SABR/SBRT vs conventional	2 year (acute and late)	101 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of SABR on acute and late esophagitis.
	1 year (acute and late)	102 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of SBRT on acute and late esophagitis.
SCLC: hypofractionation vs hyperfractionation	2 years (acute)	177 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effects of hypofractionation on acute esophagitis.
Acute Mucositis				
Early stage glottic cancer (grade 3-4)	3 months	516 (2)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in acute mucositis.
Recurrent or locally advanced head & neck cancer (grade 3)	3 months	117 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in acute mucositis.
Acute Dysphagia				
Early stage glottic cancer (grade 1-2)	3 months	360 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in acute dysphagia.
Late Mucositis				
Early stage glottic cancer	5 years	156 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little to no difference in late mucositis.
Recurrent or locally advanced head & neck cancer (grade 3)	11 months	132 (1)	⊕⊕◯◯ Low	Hypofractionation may result in an increase in late mucositis.
Late Soft Tissue Necrosis				
Early stage glottic cancer	4.8 years	360 (1)	⊕⊕⊕◯ Moderate	Hypofractionation probably results in little to no difference in soft tissue necrosis.

Cancer Type	Follow-up	N (# Trials)	Certainty	Summary Statement
Late Xerostomia				
Recurrent or locally advanced head & neck cancer	11-25 months	249 (2)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation in late xerostomia.
Temporal Lobe Necrosis				
Recurrent or locally advanced head & neck cancer	25 months	117 (1)	⊕◯◯◯ Very Low	The evidence is very uncertain about the effect of hypofractionation on temporal lobe necrosis.
Acute Diarrhea				
Rectal	<30 days	515 (1)	⊕⊕◯◯ Low	Hypofractionation may result in a reduction in acute diarrhea.
Late Anal Incontinence				
Rectal	>30 days	256 (1)	⊕⊕◯◯ Low	Hypofractionation may result in little or no difference in late anal incontinence.
Late Bowel Obstruction				
Rectal	>30 days	256 (1)	⊕⊕◯◯ Low	Hypofractionation may result in a reduction in late bowel obstruction.

Abbreviations. NSCLC=non-small cell lung cancer; SABR/SBRT=stereotactic ablative radiotherapy/stereotactic body radiation therapy; SCLC=small cell lung cancer.

Radiotherapy requires balancing tumor cell destruction with limiting normal tissue damage. Additionally, radiotherapy, as with all treatment options, should consider patient preferences and values, treatment burden, and costs. Hypofractionation regimens have seen a marked increase in use in large part due to advances in treatment technology over the last 20 years.[82] Technological advancements on controlling dose delivery and planning of radiotherapy have increased the ability to deliver hypofractionation (*ie*, higher doses per fraction) in a safe manner.[83]

Our findings suggest that hypofractionation may result in little to no difference in efficacy and most harms, while reducing treatment duration and number of sessions when used as definitive therapy for individuals with breast and prostate. The evidence was more sparse and less consistent for adults with small cell and non-small cell lung cancer though generally indicate similar effects on overall and disease-free or progression-free survival and harms. Data are limited for head and neck and rectal cancer and we found no studies in adults with pancreatic, bladder, melanoma or non-melanoma skin cancers.

We found very limited evidence on whether comparative effectiveness and harms varied by patient and tumor characteristics. What evidence was available suggests that for use of the selected hypofractionation regimen may result in similar outcomes versus the comparator conventional radiotherapy approach regardless of stage. For breast and prostate cancer, the comparative effectiveness of a specific treatment regimen did not vary by tumor stage or patient characteristics. No studies directly addressed this for the other cancers; however, there were no clear patterns in differences in comparative effectiveness of hypofractionation when looking at trials focused on higher vs. lower stage cancer. Because many regimens were intentionally different and studies designed to address different regimens based on tumor type, stage or risk a higher level question could be: “does a hypofractionation regimen specifically designed based on tumor characteristic provide similar or superior outcomes to a comparably designed radiation therapy regimen given in a conventional manner?” While data are limited they suggest that studied hypofractionation regimens resulted in little to no difference in outcomes versus the selected conventional radiation therapy comparator regardless of stage or tumor risk.

As noted above, hypofractionation resulted in fewer treatment days and shorter treatment duration than conventional treatments despite fairly similar overall treatment doses. Differences varied by cancers and treatment regimens but ranged from about 10-15 treatment days less for hypofractionation compared to conventional radiation therapy. This reduce patient and care giver burden related to travel and attendance for therapy and increase patient access and health system capacity for radiation therapy appointments. Our results provide important information for clinicians, patients, health system decision makers, and clinical guideline groups. They also provide a basis for future research given the limitations of existing studies, the gaps in evidence, and the need to consider specific cancer and patient characteristics when developing individualized treatment recommendations.

In an effort to focus on evidence of the highest quality and lowest risk of bias, we restricted eligible studies to RCTs of hypofractionation for specific cancers. A number of the included studies were designed to evaluate non-inferiority for survival or recurrence outcomes; thus their goal was to investigate whether hypofractionation was not substantially worse than conventional radiotherapy. If there are no meaningful differences in effectiveness or harms between hypofractionation and conventional radiation therapy, hypofractionation may be preferred because it offers greater convenience for patients, and less resource use for health systems.

However, no eligible trials reported data on treatment costs or access; this information may be particularly useful to policymakers and operations leadership. Hypofractionation regimens were generally shorter and involved fewer number of treatment sessions, compared with conventional radiation therapy. This may indicate greater availability of treatment slots, although preparations and planning sessions may also be more extensive for hypofractionation techniques. Additionally, the ability to provide hypofractionation regimens may require that health systems make substantial upfront investment in new equipment and software, and staff training.

The majority of evidence in breast cancer compared moderate hypofractionation with conventional radiation therapy. This showed no differences in survival and recurrence, but that hypofractionation probably results in less overall acute toxicity. For prostate cancer, hypofractionation vs. conventional radiation therapy also had similar effects on survival and recurrence, as well as toxicity and harms Prior systematic reviews have examined hypofractionation for breast and prostate cancers. For breast cancer, these include Andrade, 2019,[84] Hickey, 2016,[85] Liu, 2020,[86] Sayan, 2021,[87] and Valle, 2017.[88] They found similar results to our review in that overall survival outcome was not different between hypofractionation and conventional radiation therapy. Previous reviews on prostate cancer include Arcangelli, 2018,[89] Botrel, 2013,[90] Cao, 2017,[91] Carvalho, 2018,[92] Datta, 2017,[93] Ferella, 2019,[94] Guo, 2019,[95] Hickey, 2019,[96] Koontz, 2015,[97] Lehrer, 2020,[98] Morgan, 2018,[99] Royce, 2019,[100] Sanchez-Gomez, 2019,[101] and Siepe, 2018.[102] These previous reviews also found that overall survival and harms were similar for hypofractionation and conventional radiotherapy, once again in agreement with our findings. Several review authors[86,87,94,95,98,101] also noted the need for longer follow-up periods and more evidence evaluating harms in future trials.

Studies were typically small in sample size and short in treatment duration and often not designed or intended to address survival or progression outcomes. For several cancers, including lung, head and neck, and rectal cancers there were few studies and reported outcomes. There were only 2 RCTs of rectal cancer and these were small in sample size, and participants differed in clinical characteristics that could influence the findings. While there were more RCTs capturing lung and head and neck cancer patient populations, we were unable to pool these results due to substantial differences in patient and disease characteristics, as well as treatment comparisons. For prostate cancer it is not surprising that there were no differences in survival between regimens given the indolent nature of most early stage prostate cancer and excellent outcomes and fewer harms with no definitive treatment (i.e. observation or active monitoring).

While some cancers had many eligible studies few were designed to adequately address outcomes of interest and provide at least moderate or high certainty of evidence regarding comparative effectiveness and harms of a specific radiation therapy regimen. Such evidence certainty is typically required for clinical guideline development, policy recommendations and practice implementation in most clinical situations. Despite this researchers rarely attempted to replicate prior findings. Published studies were infrequently clinically similar enough to permit pooling and often varied in the populations enrolled, interventions evaluated and outcomes reported. Thus, many of our findings and summary of evidence conclusions are necessarily limited based on few studies, small sample size and short follow-up duration for specific treatment regimens and cancer types/stages. For example, in lung cancer, certainty of evidence was either low or very low for all comparisons and all outcomes. Three of the 5 trials ended study enrollment early when they had only accrued ~50% of the anticipated enrollment goal. The small sample sizes and short trial durations lead to smaller event rates and thus, inadequate

power to detect meaningful differences. This was a major concern that led to a reduction in the certainty of evidence. Larger trials of longer duration will be needed to better evaluate the comparative effectiveness of these radiation treatments for lung cancer.

Finally, the applicability of our findings beyond populations, cancers, and treatment regimens studied is not known. Such clinical variation makes policy decisions regarding system wide recommendations for broad implementation of hypofractionation radiotherapy as a preferred approach across and even within cancers challenging.

LIMITATIONS

This review focused on specific cancers with the use of radiation therapy for curative intent with or without surgery and/or chemotherapy. Studies evaluating palliative therapies were excluded, and as such, extension of the report findings should not be made to these populations. The search was limited to publications in English; there may be relevant studies to the research questions that were missed due to this limitation.

Other limitations are mainly due to the existing data. For pancreatic, bladder and melanoma and nonmelanoma skin cancers we found no eligible studies. Except for breast and prostate cancer, most other cancers had few trials and these were generally small and short-term. The use of non-inferiority comparisons as the primary goal in multiple trials indicates a belief that hypofractionation regimens result in similar outcomes as conventional radiation therapy; in this case, the preference for hypofractionation treatment would be due to greater convenience and less resource use. However, smaller, potentially clinically meaningful, effects on survival and disease progression outcomes cannot be confidentally ruled out. Additionally, costs and access were not evaluated by eligible studies We also found little to no evidence to address our second key question whether comparative effectiveness and harms varied by patient and tumor characteristics. These factors increase challenges for clinicians, researchers and policy makers in applying our findings especially to patients, cancers and treatment regimens not directly studied.

FUTURE RESEARCH

Randomized controlled trials of hypofractionation (moderate and ultrahypofractionation) compared with conventional radiation therapy are needed for most of the cancers addressed in this review, with the possible exception of breast and prostate cancers. However, even in breast and prostate cancer evidence certainty was often low or based on relatively short follow-up. Furthermore, harms outcomes data was sparse and more varied in definition. Consistency and standardization regarding outcomes measurement and reporting will aid in summarizing and assessing the certainty of evidence.

Effectively assessing differences in overall or disease specific survival likely requires large and longer-term studies. These requirements are practically relevant if trying to assess whether treatment effects vary by patient and tumor characteristics. However, such RCTs are expensive and the studied treatments may be outdated due to advances in diagnostic and treatment approaches. Therefore, it may be reasonable to first focus on important intermediate outcomes of effectiveness and treatment- harms. This is particularly so in breast and prostate cancer were survival outcomes are generally excellent with either regimen through 5-10 years; thus harms and patient care burden are likely more important treatment decision factors. For many patients and cancers, radiation treatment cost, duration, sessions, access, and patient burden are likely

relevant factors influencing practice and policy decisions. More research focused on these outcomes will be needed.

CONCLUSIONS

For individuals with breast, prostate, or rectal cancer, hypofractionation therapy probably results in little to no difference in overall survival; and may result in little to no difference in disease-free or progression-free survival versus conventional radiotherapy. Evidence is more limited for harms. Hypofractionation results in fewer treatment days and thus likely reduces patient and caregive burden and improves treatment access. RCTs are needed in all cancers but particularly among patients with pancreatic, melanoma, non-melanoma, head and neck, rectal, bladder, and lung cancer. There is little to no evidence to address whether comparative effectiveness and harms vary by tumor or patient characteristics.

REFERENCES

1. USCS Brief United States Cancer Statistics: Highlights from 2018 Incidence. (Centers for Disease Control and Prevention, US Department of Health and Human Services) (2021).
2. Zullig LL, Sims KJ, McNeil R, et al. Cancer Incidence Among Patients of the U.S. Veterans Affairs Health Care System: 2010 Update. *Military Medicine*. 2017;182:e1883.
3. Lievens Y. Hypofractionated Breast Radiotherapy: Financial and Economic Consequences. *The breast journal*. 2010;19:192-197.
4. Smith BD, Bellon JR, Blitzblau R, et al. Radiation Therapy for the Whole Breast: Executive Summary of an American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline. *Practical Radiation oncology*. 2018;8:145-152.
5. Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline. *Journal of Clinical Oncology*. 2018;36(34).
6. DistillerSR. Accessed Jan-Nov 2022. https://www.evidencepartners.com/
7. Methods C. Risk of Bias 2 (RoB 2) tool. https://methods.cochrane.org/risk-bias-2
8. Inc. MUaEP. GRADEpro GDT: GRADEpro Guideline Development Tool. https://acp.gradepro.org/app/
9. Schunemann H, Brozek J, Guyatt G, al e. *GRADE Handbook*. 2019.
10. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. *The Lancet Oncology*. 2019;20(4):494-503.
11. Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *The Lancet Oncology*. 2008;9(4):331-41.
12. Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet (London, England)*. 2008;371(9618):1098-107.
13. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *The Lancet Oncology*. 2006;7(6):467-71.
14. Livi L, Meattini I, Simontacchi G, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *European Journal of Cancer*. 2015;51(4):451-463.
15. Group FT, Agrawal RK, Alhasso A, et al. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2011;100(1):93-100.
16. Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet (London, England)*. 2020;395(10237):1613-1626.
17. Brunt AM, Wheatley D, Yarnold J, et al. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2016;120(1):114-8.

18. Van Hulle H, Vakaet V, Monten C, et al. Acute toxicity and health-related quality of life after accelerated whole breast irradiation in 5 fractions with simultaneous integrated boost. *Breast (Edinburgh, Scotland)*. 2021;55:105-111.
19. Schmeel LC, Koch D, Schmeel FC, et al. Acute radiation-induced skin toxicity in hypofractionated vs. conventional whole-breast irradiation: An objective, randomized multicenter assessment using spectrophotometry. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2020;146:172-179.
20. Spooner D, Stocken DD, Jordan S, et al. A randomised controlled trial to evaluate both the role and the optimal fractionation of radiotherapy in the conservative management of early breast cancer. *Clinical oncology (Royal College of Radiologists (Great Britain))*. 2012;24(10):697-706.
21. Versmessen H, Vinh-Hung V, Van Parijs H, et al. Health-related quality of life in survivors of stage I-II breast cancer: randomized trial of post-operative conventional radiotherapy and hypofractionated tomotherapy. *BMC Cancer*. 2012;12:495.
22. Van Parijs H, Miedema G, Vinh-Hung V, et al. Short course radiotherapy with simultaneous integrated boost for stage I-II breast cancer, early toxicities of a randomized clinical trial. *Radiation oncology (London, England)*. 2012;7:80.
23. Shaitelman SF, Schlembach PJ, Arzu I, et al. Acute and Short-term Toxic Effects of Conventionally Fractionated vs Hypofractionated Whole-Breast Irradiation: A Randomized Clinical Trial. *JAMA oncology*. 2015;1(7):931-41.
24. Shaitelman SF, Lei X, Thompson A, et al. Three-year outcomes with hypofractionated versus conventionally fractionated whole-breast irradiation: Results of a randomized, noninferiority clinical trial. *Journal of Clinical Oncology*. 2018;36(35):3495-3503.
25. Whelan TJ, Pignol J-P, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *The New England journal of medicine*. 2010;362(6):513-20.
26. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *Journal of the National Cancer Institute*. 2002;94(15):1143-50.
27. Wang S-L, Fang H, Hu C, et al. Hypofractionated Versus Conventional Fractionated Radiotherapy After Breast-Conserving Surgery in the Modern Treatment Era: A Multicenter, Randomized Controlled Trial From China. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2020;38(31):3604-3614.
28. Wang S-L, Fang H, Song Y-W, et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. *The Lancet Oncology*. 2019;20(3):352-360.
29. Offersen BV, Alsner J, Nielsen HM, et al. Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2020;38(31):3615-3625.
30. King MT, Link EK, Whelan TJ, et al. Quality of life after breast-conserving therapy and adjuvant radiotherapy for non-low-risk ductal carcinoma in situ (BIG 3-07/TROG 07.01): 2-year results of a randomised, controlled, phase 3 trial. *The Lancet Oncology*. 2020;21(5):685-698.
31. Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. *Lancet*. 2019;394(10215):2165-2172.

32. Arsenault J, Parpia S, Goldberg M, et al. Acute Toxicity and Quality of Life of Hypofractionated Radiation Therapy for Breast Cancer. *International journal of radiation oncology, biology, physics*. 2020;107(5):943-948.
33. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *The Lancet Oncology*. 2013;14(11):1086-1094.
34. Weng JK, Lei X, Schlembach P, et al. Five-Year Longitudinal Analysis of Patient-Reported Outcomes and Cosmesis in a Randomized Trial of Conventionally Fractionated Versus Hypofractionated Whole-Breast Irradiation. *International journal of radiation oncology, biology, physics*. 2021;111(2):360-370.
35. Brunt AM, Haviland JS, Sydenham M, et al. Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2020;38(28):3261-3272.
36. Olivotto IA, Berrang T, Truong PT, et al. Interim cosmetic and toxicity results from RAPID: A randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *Journal of Clinical Oncology*. 2013;31(32):4038-4045.
37. Meattini I, Di Brina L, Mangoni M, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy technique compared to whole breast irradiation for patients aged 70 years or older: subgroup analysis from a randomized phase 3 trial. *Breast Cancer Research and Treatment*. 2015;153(3):539-547.
38. Meattini I, Lucidi S, Marrazzo L, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-florence trial. *Journal of Clinical Oncology*. 2020;38(35):4175-4183.
39. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet (London, England)*. 2019;394(10196):385-395.
40. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *The Lancet Oncology*. 2016;17(8):1047-1060.
41. Lee WR, Dignam JJ, Amin MB, et al. Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2016;34(20):2325-32.
42. Appelt AL, Vogelius IR, Farr KP, Khalil AA, Bentzen SM. Towards individualized dose constraints: Adjusting the QUANTEC radiation pneumonitis model for clinical risk factors. *Acta oncologica (Stockholm, Sweden)*. 2014;53(5):605-12.
43. Catton CN, Lukka H, Gu C-S, et al. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35(17):1884-1890.
44. Fonteyne V, Sarrazyn C, Swimberghe M, et al. 4 Weeks Versus 5 Weeks of Hypofractionated High-dose Radiation Therapy as Primary Therapy for Prostate Cancer:

Interim Safety Analysis of a Randomized Phase 3 Trial. *International journal of radiation oncology, biology, physics*. 2018;100(4):866-870.
45. Houshyari M, Mofid B, Alavi Tabatabaee M, Taghizadeh-Hesary F, Bakhshandeh M. Acute toxicity of 4-week versus 5-week hypofractionated radiotherapy in localised prostate cancer. *Journal of Radiotherapy in Practice*. 2021.
46. Lam D, Wong K, Cheung M, et al. Prospective randomized phase II study of stereotactic body radiotherapy (SBRT) vs. conventional fractionated radiotherapy (CFRT) for Chinese patients with early-stage localized prostate cancer. *Current Oncology*. 2022;29(1):27-37.
47. Naismith O, Ostler P, van der Voet H, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *The Lancet Oncology*. 2019;20(11):1531-1543.
48. Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *The Lancet Oncology*. 2016;17(8):1061-1069.
49. Arcangeli G, Saracino B, Gomellini S, et al. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. *International journal of radiation oncology, biology, physics*. 2010;78(1):11-8.
50. Karklelyte A, Valuckas KP, Griskevicius R, Janulionis E, Aleknavicius E. Acute toxicity and quality of life in high risk prostate cancer patients: Updated results of randomized hypofractionation trial. *Reports of Practical Oncology and Radiotherapy*. 2018;23(4):284-289.
51. Norkus D, Miller A, Kurtinaitis J, et al. A randomized trial comparing hypofractionated and conventionally fractionated three-dimensional external-beam radiotherapy for localized prostate adenocarcinoma : a report on acute toxicity. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]*. 2009;185(11):715-21.
52. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013;31(31):3860-8.
53. Hoffman KE, Voong KR, Levy LB, et al. Randomized Trial of Hypofractionated, Dose-Escalated, Intensity-Modulated Radiation Therapy (IMRT) Versus Conventionally Fractionated IMRT for Localized Prostate Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2018;36(29):2943-2949.
54. Lukka H, Hayter C, Julian JA, et al. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005;23(25):6132-8.
55. Wang MH, Vos LJ, Yee D, et al. Clinical Outcomes of the CHIRP Trial: A Phase II Prospective Randomized Trial of Conventionally Fractionated Versus Moderately Hypofractionated Prostate and Pelvic Nodal Radiation Therapy in Patients With High-Risk Prostate Cancer. *Practical radiation oncology*. 2021;11(5):384-393.
56. Zhong Q-Z, Xia X, Gao H, et al. Hypofractionated versus conventionally fractionated image-guided volumetric-modulated arc radiotherapy for localized prostate cancer: a phase II randomized trial from China. *Aging*. 2021;13(5):6936-6944.
57. Yeoh EE, Botten RJ, Butters J, Di Matteo AC, Holloway RH, Fowler J. Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: final results of

phase III randomized trial. *International journal of radiation oncology, biology, physics*. 2011;81(5):1271-8.
58. Fransson P, Nilsson P, Gunnlaugsson A, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial. *The Lancet Oncology*. 2021;22(2):235-245.
59. de Vries KC, Wortel RC, Oomen-de Hoop E, Heemsbergen WD, Pos FJ, Incrocci L. Hyprofractionated Versus Conventionally Fractionated Radiation Therapy for Patients with Intermediate- or High-Risk, Localized, Prostate Cancer: 7-Year Outcomes From the Randomized, Multicenter, Open-Label, Phase 3 HYPRO Trial. *International journal of radiation oncology, biology, physics*. 2020;106(1):108-115.
60. Arcangeli G, Saracino B, Arcangeli S, et al. Moderate Hypofractionation in High-Risk, Organ-Confined Prostate Cancer: Final Results of a Phase III Randomized Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35(17):1891-1897.
61. Arcangeli S, Strigari L, Gomellini S, et al. Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancer. *International journal of radiation oncology, biology, physics*. 2012;84(5):1172-8.
62. Yeoh EE, Holloway RH, Fraser RJ, et al. Hypofractionated versus conventionally fractionated radiation therapy for prostate carcinoma: updated results of a phase III randomized trial. *International journal of radiation oncology, biology, physics*. 2006;66(4):1072-83.
63. Avkshtol V, Ruth KJ, Ross EA, et al. Ten-Year Update of a Randomized, Prospective Trial of Conventional Fractionated Versus Moderate Hypofractionated Radiation Therapy for Localized Prostate Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2020;38(15):1676-1684.
64. Aluwini S, Pos F, Schimmel E, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial. *The Lancet Oncology*. 2016;17(4):464-474.
65. Arcangeli G, Fowler J, Gomellini S, et al. Acute and late toxicity in a randomized trial of conventional versus hypofractionated three-dimensional conformal radiotherapy for prostate cancer. *International journal of radiation oncology, biology, physics*. 2011;79(4):1013-21.
66. Hoffman KE, Voong KR, Pugh TJ, et al. Risk of late toxicity in men receiving dose-escalated hypofractionated intensity modulated prostate radiation therapy: results from a randomized trial. *International journal of radiation oncology, biology, physics*. 2014;88(5):1074-84.
67. Bruner DW, Pugh SL, Lee WR, et al. Quality of Life in Patients With Low-Risk Prostate Cancer Treated With Hypofractionated vs Conventional Radiotherapy: A Phase 3 Randomized Clinical Trial. *JAMA oncology*. 2019;5(5):664-670.
68. Shaikh T, Li T, Handorf EA, et al. Long-Term Patient-Reported Outcomes From a Phase 3 Randomized Prospective Trial of Conventional Versus Hypofractionated Radiation Therapy for Localized Prostate Cancer. *International journal of radiation oncology, biology, physics*. 2017;97(4):722-731.
69. Wilkins A, Mossop H, Syndikus I, et al. Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *The Lancet Oncology*. 2015;16(16):1605-16.

70. Wilson JM, Dearnaley DP, Syndikus I, et al. The Efficacy and Safety of Conventional and Hypofractionated High-Dose Radiation Therapy for Prostate Cancer in an Elderly Population: A Subgroup Analysis of the CHHiP Trial. *International journal of radiation oncology, biology, physics*. 2018;100(5):1179-1189.
71. Qiu B, Li Q, Liu J, et al. Moderately Hypofractionated Once-Daily Compared With Twice-Daily Thoracic Radiation Therapy Concurrently With Etoposide and Cisplatin in Limited-Stage Small Cell Lung Cancer: A Multicenter, Phase II, Randomized Trial. *International journal of radiation oncology, biology, physics*. 2021;111(2):424-435.
72. Nyman J, Hallqvist A, Lund J-A, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2016;121(1):1-8.
73. Roy S, Pathy S, Mohanti BK, et al. Accelerated hypofractionated radiotherapy with concomitant chemotherapy in locally advanced squamous cell carcinoma of lung: evaluation of response, survival, toxicity and quality of life from a Phase II randomized study. *The British journal of radiology*. 2016;89(1062):20150966.
74. Iyengar P, Zhang-Velten E, Westover K, et al. Accelerated Hypofractionated Image-Guided vs Conventional Radiotherapy for Patients with Stage II/III Non-Small Cell Lung Cancer and Poor Performance Status: A Randomized Clinical Trial. *JAMA Oncology*. 2021.
75. Moon SH, Cho KH, Chung EJ, et al. A prospective randomized trial comparing hypofractionation with conventional fractionation radiotherapy for T1-2 glottic squamous cell carcinomas: results of a Korean Radiation Oncology Group (KROG-0201) study. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2014;110(1):98-103.
76. Kodaira T, Kagami Y, Shibata T, et al. Results of a multi-institutional, randomized, non-inferiority, phase III trial of accelerated fractionation versus standard fractionation in radiation therapy for T1-2N0M0 glottic cancer: Japan Clinical Oncology Group Study (JCOG0701). *Annals of Oncology*. 2018;29(4):992-997.
77. Tian Y-M, Zhao C, Guo Y, et al. Effect of total dose and fraction size on survival of patients with locally recurrent nasopharyngeal carcinoma treated with intensity-modulated radiotherapy: a phase 2, single-center, randomized controlled trial. *Cancer*. 2014;120(22):3502-9.
78. Choudhury K, Sharma S, Maiti S, Roy C, Mallick C. A comparison of outcomes with 'Christie Regimen' and pure accelerated radiotherapy versus conventional radiation in locally advanced squamous cell carcinoma of head and neck: A randomized controlled study. *Clinical Cancer Investigation Journal*. 2012;1(3):118-126.
79. Bujko K, Pietrzak L, Kepka L, et al. Neoadjuvant treatment for unresectable rectal cancer: An interim analysis of a multicentre randomized study. *Radiotherapy and Oncology*. 2013;107(2):171-177.
80. Bujko K, Wyrwicz L, Rutkowski A, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2016;27(5):834-42.
81. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. *The Lancet Oncology*. 2017;18(3):336-346.

82. Zeman EM. *The History and Radiobiology of Hypofractionation. In: Kaidar-Person, O., Chen, R. (eds) Hypofractionated and Stereotactic Radiation Therapy.* 2018.
83. Nahum AE. The Radiobiology of Hypofractionation. *Clinical Oncology*. 2015;27:260-269.
84. Andrade TRM, Fonseca MCM, Segreto HRC, Segreto RA, Martella E, Nazario ACP. Meta-analysis of long-term efficacy and safety of hypofractionated radiotherapy in the treatment of early breast cancer. *The breast journal*. 2019;48:24-31.
85. Hickey B, James M, Lehman M, et al. Hypofractionated radiation therapy for early breast cancer. *Cochrane Database of Systematic Reviews*. 2016(7).
86. 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*. 2020;15.
87. Sayan M, Yehia ZA, Ohri N, Haffty BG. Hypofractionated Postmastectomy Radiation Therapy. *Advances in radiation oncology*. 2021;6.
88. Valle LF, Agarwal S, Bickel KE, Herchek HA, Nalepinski DC, Kapadia NS. Hypofractionated whole breast radiotherapy in breast conservation for early-stage breast cancer: a systematic review and meta-analysis of randomized trials. *Breast Cancer Res Treat*. 2017;162:409-417.
89. Arcangeli G, Arcangeli S, Pinzi V, Benassi M, Benassi M, Strigari L. Optimal Scheduling of hypofractionated radiotherapy for localized prostate cancer: systematic review and metanalysis of randomized clinical trials. *Cancer treatment reviews*. 2018;70:22-29.
90. Botrel TEA, Clark O, Pompeo ACL, et al. Hypofractionated external-beam radiation thearpy (HEBRT) versus conventional external-beam radiation (CEBRT) in patients with localized prostate cancer: a systematic review and meta-analysis. *Core Evidence*. 2013;8:1-13.
91. Cao L, Yang Y-J, Li Z-W, et al. Moderate hypofractionated radiotherapy is more effective and safe for localized prostate cancer patients: a meta-analysis. *Oncotarget*. 2017;8(2):2647-2658.
92. Carvalho IT, Baccaglini W, Claros OR, et al. Genitourinary and gastrointestinal toxicity among patients with localized prostate cancer treated with conventaional versus moderately hypofractionated radiation therapy: systematic review and meta-analysis. *Acta Oncologica*. 2018;57:1003-1010.
93. Datta NR, Stutz E, Rogers S, Bodis S. Conventional Versus Hypofractionated Radiation Therapy for Localized or Locally Advanced Prostate Cancer: A Systematic Review and Meta-analysis along with Therapeutic Implications. *International Journal of Radiation Oncology*. 2017;99:573-589.
94. Ferella L, Limoncin E, Vittorini F, et al. Are we ready for a paradigm shift from high-dose conventional to moderate hypofractionated radiotherapy in intermediate-high risk prostate cancer? A systematic review of randmozed controlled trials with tiral sequential analysis. *Critical reviews in oncology/hematology*. 2019;139:75-82.
95. Guo W, Sun Y-C, Bi J-Q, He X-Y, Xiao L. Hypofractionated radiotherapy versus conventional radiotherapy in patients with intermediate-to high-risk localized prostate cancer: a meta-analysis of randomized controlled trials. *BMC Cancer*. 2019;19.
96. Hickey B, James M, Daly T, Soh F, Jeffery M. Hypofractionation for clinically localized prostate cancer. *Cochrane Database of Systematic Reviews*. 2019(9).

97. Koontz BF, Bossi A, Cozzarini C, Wiegel T, D'Amico A. A Systematic Review of Hypofractionation for Primary Management of Prostate Cancer. *European Urology* 2015;68:683-691.
98. Lehrer EJ, Kishan AU, Yu JB, et al. Ultrahypofractionated versus hypofractionated and conventionally fractionated radiation therapy for localized prostate cancer: A systematic review and meta-analysis of phase III randomized trials. *Radiotherapy and Oncology*. 2020;148:235-242.
99. Morgan SC, Hoffman K, Loblaw A, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline. *Journal of clinical oncology*. 2018;36.
100. Royce TJ, Lee DH, Keum N, et al. Conventional Versus Hypofractionated Radiation Therapy for Localized Prostate Cancer: A Meta-analysis of Randomized Noninferiority Trials. *European urology focus*. 2019;5:577-584.
101. Sanchez-Gomez LM, Polo-deSantos M, Rodriguez-Melcon JI, Angulo JC, Luengo-Matos S. Hypofractionated radiation therapy versus conventional radiation therapy in prostate cancer: A systematic review of its safety and efficacy. *Actas urologicas espanolas*. 2015;39:367-374.
102. Siepe G, Buwenge M, Nguyen NP, et al. Postoperative Hypofractionated Radiation Therapy in Prostate Carcinoma: A Systematic Review. *Anticancer research*. 2018;38:1221-1230.
103. Baillet F, Housset M, Maylin C, et al. The use of a specific hypofractionated radiation therapy regimen versus classical fractionation in the treatment of breast cancer: a randomized study of 230 patients. *International journal of radiation oncology, biology, physics*. 1990;19(5):1131-3.
104. Das P, Das T, Jana A, Gupta P, Gupta P, Das S. Comparison of result and outcome of conventional and hypofractionated radiotherapy in post-operative breast cancer patients. *International Journal of Medical Science and Public Health*. 2018;7(6):452-456.
105. Hosseini S, Shahabadi M, Salek R, et al. Accelerated hypofractionated whole breast radiotherapy for early breast cancer; arandomized phase iii clinical trial. *Acta Medica Iranica*. 2019;57(11):645-652.
106. Hou H-L, Song Y-C, Li R-Y, et al. Similar Outcomes of Standard Radiotherapy and Hypofractionated Radiotherapy Following Breast-Conserving Surgery. *Medical science monitor : international medical journal of experimental and clinical research*. 2015;21:2251-6.
107. Kalita AK, Bhattacharyya M, Jagtap VK, et al. Radiotherapy in Post Mastectomy High Risk Breast Cancer: Early results of a Prospective Study comparing Conventional versus Hypofractionated Radiotherapy. *Journal of Medical Science and Clinical Research*. 2018;6(7):743-751.
108. Kumbhaj P, Sharma R, Saini P, Patel P. Study of two different dose fractionation schedules of post mastectomy chest wall irradiation in carcinoma breast patients. *International Journal of Medical Science and Public Health*. 2013;2(4):1001-1005.
109. Maiti S, Meyur S, Mandal BC, Shenoi LR, Biswas S, Basu S. Comparison of conventional and hypofractionated radiation after mastectomy in locally advanced breast cancer: A prospective randomised study on dosimetric evaluation and treatment outcome. *Journal of Radiotherapy in Practice*. 2021;20(1):30-38.
110. Purohit R, Sharma N, Kumar R, Jakhar SL. Comparison of Acute Toxicities in Conventional and Hypofractionated Radiotherapy in Post-Mastectomy Breast Cancer. *Journal of Medical Science and Clinical Research*. 2016;4(6):10721-10724.

111. Rastogi K, Jain S, Bhatnagar AR, Bhaskar S, Gupta S, Sharma N. A Comparative Study of Hypofractionated and Conventional Radiotherapy in Postmastectomy Breast Cancer Patients. *Asia-Pacific Journal of Oncology Nursing*. 2017;5(1):107-113.
112. Li X, Sanz J, Foro P, et al. Long-term results of a randomized partial irradiation trial compared to whole breast irradiation in the early stage and low-risk breast cancer patients after conservative surgery. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*. 2021;23(10):2127-2132.
113. Rodriguez N, Sanz X, Dengra J, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *International journal of radiation oncology, biology, physics*. 2013;87(5):1051-7.
114. Shahid A, Athar MA, Asghar S, Zubairi T, Murad S, Yunas N. Post mastectomy adjuvant radiotherapy in breast cancer: a comparision of three hypofractionated protocols. *JPMA The Journal of the Pakistan Medical Association*. 2009;59(5):282-7.
115. Swanick CW, Lei X, Shaitelman SF, et al. Longitudinal analysis of patient-reported outcomes and cosmesis in a randomized trial of conventionally fractionated versus hypofractionated whole-breast irradiation. *Cancer*. 2016;122(18):2886-94.
116. Taher AN, El-Baradie MM, Essa H, Zaki OE, Ezzat S. Hypofractionation versus Conventional Fractionation Radiotherapy after Conservative Treatment of Breast Cancer: Early Skin Reactions and Cosmetic Results. *Journal of the Egyptian National Cancer Institute*. 2004;16(3):178-187.
117. Yadav BS, Loganathan S, Sharma SC, Singh R, Dahiya D. Comparison of Toxicity and Cosmetic Outcomes After Accelerated Partial Breast Irradiation or Whole Breast Irradiation Using 3-Dimensional Conformal External Beam Radiation Therapy. *Advances in Radiation Oncology*. 2020;5(2):171-179.
118. Zhao XB, Ren GS. Analysis of radiotherapy optimization regimens after modified radical mastectomy. *European review for medical and pharmacological sciences*. 2016;20(22):4705-4709.
119. Zhao S, Huang F, Chen X, Cao X, Yu J, Liu Y. The long-term outcome of adjuvant hypofractionated radiotherapy and conventional fractionated radiotherapy after breastconserving surgery for early breast cancer: A prospective analysis of 107 cases. *Journal of Thoracic Disease*. 2017;9(10):3840-3850.
120. Akakura K, Suzuki H, Ichikawa T, et al. A randomized trial comparing radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy for locally advanced prostate cancer: results at median follow-up of 102 months. *Japanese journal of clinical oncology*. 2006;36(12):789-93.
121. Phase 1 clinical trial of stereotactic body radiation therapy concomitant with neoadjuvant chemotherapy for breast cancer. *International Journal of Radiation Oncology Biology Physics*. 2013;85(5):1193-1199.
122. Aissa AB, Espeli V, Squiban D, et al. Phase i study of sorafenib combined with radiation therapy and temozolomide as first-line treatment of high-grade glioma. *British Journal of Cancer*. 2014;110(11):2655-2661.
123. Alexidis P, Karatzoglou S, Dragoumis D, et al. Late results of a randomized trial on the role of mild hypofractionated radiotherapy for the treatment of localized prostate cancer. *Journal of Cancer*. 2020;11(5):1008-1016.

124. Alexidis P, Tzitzikas I, Hatzimouratidis K, et al. The role of hypofractionated radiotherapy for the definitive treatment of localized prostate cancer: Early results of a randomized trial. *Journal of Cancer*. 2019;10(25):6217-6224.
125. Dearnaley D, Syndikus I, Sumo G, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. *The Lancet Oncology*. 2012;13(1):43-54.
126. Wortel RC, Oomen-de Hoop E, Heemsbergen WD, Pos FJ, Incrocci L. Moderate Hypofractionation in Intermediate- and High-Risk, Localized Prostate Cancer: Health-Related Quality of Life From the Randomized, Phase 3 HYPRO Trial. *International journal of radiation oncology, biology, physics*. 2019;103(4):823-833.
127. Marzi S, Benassi M, Landoni V, et al. Modeling of alphabeta for late rectal toxicity from a randomized phase II study: Conventional versus hypofractionated scheme for localized prostate cancer. *Journal of Experimental and Clinical Cancer Research*. 2009;28(1):117.
128. Norkus D, Karklelyte A, Engels B, et al. A randomized hypofractionation dose escalation trial for high risk prostate cancer patients: interim analysis of acute toxicity and quality of life in 124 patients. *Radiation oncology (London, England)*. 2013;8:206.
129. Yeoh EEK, Fraser RJ, McGowan RE, et al. Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: early results of a Phase III randomized trial. *International journal of radiation oncology, biology, physics*. 2003;55(4):943-55.
130. Aluwini S, Pos F, Schimmel E, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. *The Lancet Oncology*. 2015;16(3):274-83.
131. Norkus D, Miller A, Plieskiene A, Janulionis E, Valuckas KP. A randomized trial comparing hypofractionated and conventionally fractionated three-dimensional conformal external-beam radiotherapy for localized prostate adenocarcinoma: a report on the first-year biochemical response. *Medicina (Kaunas, Lithuania)*. 2009;45(6):469-75.
132. Pollack A, Hanlon AL, Horwitz EM, et al. Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. *International journal of radiation oncology, biology, physics*. 2006;64(2):518-26.
133. Gronberg BH, Halvorsen TO, Flotten O, et al. Randomized phase II trial comparing twice daily hyperfractionated with once daily hypofractionated thoracic radiotherapy in limited disease small cell lung cancer. *Acta oncologica (Stockholm, Sweden)*. 2016;55(5):591-7.
134. Singh AK, Gomez-Suescun JA, Stephans KL, et al. One Versus Three Fractions of Stereotactic Body Radiation Therapy for Peripheral Stage I to II Non-Small Cell Lung Cancer: A Randomized, Multi-Institution, Phase 2 Trial. *International journal of radiation oncology, biology, physics*. 2019;105(4):752-759.
135. Slawson RG, Salazar OM, Poussin-Rosillo H, Amin PP, Strohl R, Sewchand W. Once-a-week vs conventional daily radiation treatment for lung cancer: final report. *International journal of radiation oncology, biology, physics*. 1988;15(1):61-8.
136. Singh AK, Gomez-Suescun JA, Hermann GM, et al. One Versus Three Fractions of Stereotactic Body Radiation Therapy for Peripheral Stage I to II Non-Small Cell Lung Cancer: A Randomized, Multi-Institution, Phase 2 Trial. *International Journal of Radiation Oncology Biology Physics*. 2019;105(4):752-759.
137. Bjordal K, Kaasa S, Mastekaasa A. Quality of life in patients treated for head and neck cancer: a follow-up study 7 to 11 years after radiotherapy. *International journal of radiation oncology, biology, physics*. 1994;28(4):847-56.

138. Kachhwaha A, Jakhar S, Syiem T, Sharma N, Kumar H, Sharma A. Hypofractionated radiotherapy versus conventional radiotherapy in early glottic cancer T1-2N0M0: A randomized study. *Journal of Cancer Research and Therapeutics*. 2021;17(6):1499-1502.
139. Tolia M, Kelekis N, Kouloulias V, et al. Radiobiological and quality of life study of conventional and accelerated fractionated radiotherapy in patients with head and neck squamous cell carcinoma: Correlation of efficacy with cell cycle analysis parameters. *Head and Neck Oncology*. 2013;5(4):36.
140. Yamazaki H, Nishiyama K, Tanaka E, Koizumi M, Chatani M. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *International journal of radiation oncology, biology, physics*. 2006;64(1):77-82.
141. Erlandsson J, Ahlberg M, Holm T, et al. Tumour regression after radiotherapy for rectal cancer - Results from the randomised Stockholm III trial. *Radiotherapy and Oncology*. 2019;135:178-186.
142. Ansari N, Solomon MJ, Fisher RJ, et al. Acute Adverse Events and Postoperative Complications in a Randomized Trial of Preoperative Short-course Radiotherapy Versus Long-course Chemoradiotherapy for T3 Adenocarcinoma of the Rectum: Trans-Tasman Radiation Oncology Group Trial (TROG 01.04). *Annals of surgery*. 2017;265(5):882-888.

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*
91. Murray J, Griffin C, Gulliford S, et al. A randomised assessment of image guided radiotherapy within a phase 3 trial of conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2020;142:62-71. *Ineligible outcome*
92. Murthy V, Mallick I, Gavarraju A, et al. Study protocol of a randomised controlled trial of prostate radiotherapy in high-risk and node-positive disease comparing moderate and extreme hypofractionation (PRIME TRIAL). *BMJ open*. 2020;10(2):e034623. *Ineligible intervention/comparison*
93. Niibe Y, Karasawa K, Mitsuhashi T, Tanaka Y. Hyperfractionated radiation therapy for hypopharyngeal carcinoma compared with conventional radiation therapy: local control, laryngeal preservation and overall survival. *Japanese journal of clinical oncology*. 2003;33(9):450-5. *Ineligible intervention/comparison*
94. Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M, Bujko K. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *British Journal of Surgery*. 2006;93(10):1215-1223. *Ineligible intervention/comparison*
95. Olivotto IA, Weir LM, Kim-Sing C, et al. Late cosmetic results of short fractionation for breast conservation. *Radiotherapy and Oncology*. 1996;41(1):7-13. *Ineligible study design*

96. Ottosson S, Zackrisson B, Kjellen E, Nilsson P, Laurell G. Weight loss in patients with head and neck cancer during and after conventional and accelerated radiotherapy. *Acta oncologica (Stockholm, Sweden)*. 2013;52(4):711-8. *Ineligible intervention/comparison*
97. Parajon SB, Payo MPP, Aguera AI, et al. Extreme weekly hypofractionation in breast cancer in elderly. *Translational Cancer Research*. 2020;9(Supplement1):S139-S145. *Ineligible study design*
98. Park G, Kim YJ, Kim YS, Ahn H, Park W, Lee Js. Salvage hypofractionated accelerated versus standard radiotherapy for the treatment of biochemical recurrence after radical prostatectomy (SHARE): the protocol of a prospective, randomized, open-label, superiority, multi-institutional trial. *Trials*. 2021;22(1):728. *Ineligible study design*
99. Perez CA, Stanley K, Rubin P, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. *Cancer*. 1980;45(11):2744-53. *Ineligible intervention/comparison*
100. Pietrzak L, Bujko K, Kepka L, et al. Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: Report of a randomised trial. *Radiotherapy and Oncology*. 2007;84(3):217-225. *Ineligible intervention/comparison*
101. Pinto LH, Canary PC, Araujo CM, Bacelar SC, Souhami L. Prospective randomized trial comparing hyperfractionated versus conventional radiotherapy in stages III and IV oropharyngeal carcinoma. *International journal of radiation oncology, biology, physics*. 1991;21(3):557-62. *Ineligible intervention/comparison*
102. Pollack A, Kwon D, Walker G, et al. Prospective Validation of Diagnostic Tumor Biomarkers in Men Treated With Radiotherapy for Prostate Cancer. *Journal of the National Cancer Institute*. 2017;109(2):1-8. *Ineligible outcome*
103. Poortmans PM, Collette L, Horiot J-C, et al. Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2009;90(1):80-5. *Ineligible intervention/comparison*
104. Poulsen M, Denham J, Spry N, et al. Acute toxicity and cost analysis of a phase III randomized trial of accelerated and conventional radiotherapy for squamous carcinoma of the head and neck: a Trans-Tasman Radiation Oncology Group study. *Australasian radiology*. 1999;43(4):487-94. *Ineligible intervention/comparison*
105. Poulsen MG, Denham JW, Peters LJ, et al. A randomised trial of accelerated and conventional radiotherapy for stage III and IV squamous carcinoma of the head and neck: a Trans-Tasman Radiation Oncology Group Study. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2001;60(2):113-22. *Ineligible intervention/comparison*
106. Prosnitz LR, Albers ME, Huang AT, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *New England Journal of Medicine*. 1998;338(25):1798-1804. *Ineligible intervention/comparison*
107. Quilty PM, Duncan W, Kerr GR. Results of a randomised study to evaluate influence of dose on morbidity in radiotherapy for bladder cancer. *Clinical radiology*. 1985;36(6):615-8. *Ineligible intervention/comparison*
108. Rasmusson E, Gunnlaugsson A, Wieslander E, et al. Erectile Dysfunction and Absorbed Dose to Penile Base Structures in a Randomized Trial Comparing Ultrahypofractionated and Conventionally Fractionated Radiation Therapy for Prostate Cancer. *International journal of radiation oncology, biology, physics*. 2020;107(1):143-151. *Ineligible outcome*

109. Reddy JP, Lei X, Huang S-C, et al. Quantitative Assessment of Breast Cosmetic Outcome After Whole-Breast Irradiation. *International journal of radiation oncology, biology, physics*. 2017;97(5):894-902. *Ineligible outcome*
110. Rezvani M, Alcock CJ, Fowler JF, Haybittle JL, Hopewell JW, Wiernik G. A comparison of the normal-tissue reactions in patients treated with either 3F/Wk or 5F/Wk in the BIR (British Institute of Radiology) trial of radiotherapy for carcinoma of the laryngo-pharynx. *International journal of radiation biology*. 1989;56(5):717-20. *Ineligible intervention/comparison*
111. Ringash J, Waldron JN, Siu LL, et al. Quality of life and swallowing with standard chemoradiotherapy versus accelerated radiotherapy and panitumumab in locoregionally advanced carcinoma of the head and neck: A phase III randomised trial from the Canadian Cancer Trials Group (HN.6). *European Journal of Cancer*. 2017;72:192-199. *Ineligible intervention/comparison*
112. Saad E, Radwan RH, Hadi EA. Comparison between hypo-fractionated dose-escalated volumetric modulated arc therapy and conventional concurrent chemo-radiation in locally advanced head and neck cancer: A pilot study. *Journal of Radiotherapy in Practice*. 2020;19(2):132-138. *Ineligible intervention/comparison*
113. Sanguineti G, Giannarelli D, Petrongari MG, et al. Leukotoxicity after moderately Hypofractionated radiotherapy versus conventionally fractionated dose escalated radiotherapy for localized prostate Cancer: a secondary analysis from a randomized study. *Radiation oncology (London, England)*. 2019;14(1):23. *Ineligible outcome*
114. Sause WT, Cooper JS, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. *International journal of radiation oncology, biology, physics*. 1991;20(3):429-32. *Ineligible outcome*
115. Schwartz DL, Sosa A, Chun SG, et al. SBRT for early-stage glottic larynx cancer-Initial clinical outcomes from a phase I clinical trial. *PloS one*. 2017;12(3):e0172055. *Ineligible study design*
116. Scobioala S, Kittel C, Elsayad K, et al. A treatment planning study comparing IMRT techniques and cyber knife for stereotactic body radiotherapy of low-risk prostate carcinoma. *Radiation oncology (London, England)*. 2019;14(1):143. *Ineligible intervention/comparison*
117. Servagi Vernat S, Guilbert P, Bouche G, Ramiandrisoa F, Bellefqih S. Hypofractionated radiotherapy in rectal cancer for elderly patients. *Cancer/Radiotherapie*. 2018;22(6-7):644-646. *Not published in English*
118. Sethukavalan P, Cheung P, Tang CI, et al. Patient costs associated with external beam radiotherapy treatment for localized prostate cancer: the benefits of hypofractionated over conventionally fractionated radiotherapy. *The Canadian journal of urology*. 2012;19(2):6165-9. *Ineligible outcome*
119. Shah C, Badiyan S, Khwaja S, et al. Evaluating radiotherapy options in breast cancer: does intraoperative radiotherapy represent the most cost-efficacious option? *Clinical breast cancer*. 2014;14(2):141-6. *Ineligible intervention/comparison*
120. Shi Y-s, Xu S-j, Zheng X-k, Yan W-p, Chen L-h. Therapeutic effect of three-dimensional conformal radiotherapy on locally advanced pancreatic carcinoma. *Di 1 jun yi da xue xue bao = Academic journal of the first medical college of PLA*. 2004;24(2):213-219. *Not published in English*
121. Siegel R, Burock S, Wernecke K-D, et al. Preoperative short-course radiotherapy versus combined radiochemotherapy in locally advanced rectal cancer: a multi-centre

prospectively randomised study of the Berlin Cancer Society. *BMC cancer*. 2009;9:50. *Ineligible outcome*
122. Skladowski K, Maciejewski B, Golen M, et al. Continuous accelerated 7-days-a-week radiotherapy for head-and-neck cancer: long-term results of phase III clinical trial. *International journal of radiation oncology, biology, physics*. 2006;66(3):706-13. *Ineligible intervention/comparison*
123. Storey MR, Pollack A, Zagars G, Smith L, Antolak J, Rosen I. Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. *International journal of radiation oncology, biology, physics*. 2000;48(3):635-42. *Ineligible intervention/comparison*
124. Strigari L, Arcangeli G, Arcangeli S, Benassi M. Mathematical model for evaluating incidence of acute rectal toxicity during conventional or hypofractionated radiotherapy courses for prostate cancer. *International journal of radiation oncology, biology, physics*. 2009;73(5):1454-60. *Ineligible outcome*
125. Swindell R, Coote J, Stratford J, et al. Dose-escalated hypofractionated intensity-modulated radiotherapy in high-risk carcinoma of the prostate: Outcome and late toxicity. *Prostate Cancer*. 2012:450246. *Ineligible study design*
126. Syndikus I, Morgan RC, Sydes MR, Graham JD, Dearnaley DP. Late gastrointestinal toxicity after dose-escalated conformal radiotherapy for early prostate cancer: results from the UK Medical Research Council RT01 trial (ISRCTN47772397). *International journal of radiation oncology, biology, physics*. 2010;77(3):773-83. *Ineligible intervention/comparison*
127. Tallari RV, Singh OP, Yogi V, Yadav S. Five versus ten fractions per week radiotherapy in locally advanced head and neck cancer. *Journal of Cancer Research and Therapeutics*. 2017;13(2):224-229. *Ineligible intervention/comparison*
128. Thorpe CS, McGee LA, Vern-Gross TZ, et al. MC1635: Randomized Phase III Trial of Hypofractionated Radiotherapy to the Whole Breast After Breast Conserving Surgery. *International journal of radiation oncology, biology, physics*. 2021;111(3):S6-S7. *Ineligible study design*
129. Tsang Y, Haviland J, Venables K, Yarnold J. The impact of dose heterogeneity on late normal tissue complication risk after hypofractionated whole breast radiotherapy. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2012;104(2):143-7. *Ineligible outcome*
130. Vargas CE, Hartsell WF, Dunn M, et al. Hypofractionated Versus Standard Fractionated Proton-beam Therapy for Low-risk Prostate Cancer: Interim Results of a Randomized Trial PCG GU 002. *American journal of clinical oncology*. 2018;41(2):115-120. *Ineligible intervention/comparison*
131. Vargas CE, Niska JR, Keole SR, et al. Initial toxicity, quality-of-life outcomes, and dosimetric impact in a randomized phase 3 trial of hypofractionated versus standard fractionated proton therapy for low-risk prostate cancer. *Advances in Radiation Oncology*. 2018;3(3):322-330. *Ineligible intervention/comparison*
132. Verbanck S, Hanon S, Schuermans D, et al. Mild Lung Restriction in Breast Cancer Patients After Hypofractionated and Conventional Radiation Therapy: A 3-Year Follow-Up. *International journal of radiation oncology, biology, physics*. 2016;95(3):937-945. *Ineligible outcome*
133. Verbanck S, Hanon S, Schuermans D, et al. Small airways function in breast cancer patients before and after radiotherapy. *Breast cancer research and treatment*. 2012;135(3):857-65. *Ineligible outcome*

134. Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. *Lancet (London, England)*. 2019;394(10215):2155-2164. *Ineligible intervention/comparison*
135. Videtic GMM, Truong PT, Dar AR, Yu EW, Stitt LW. Shifting from hypofractionated to "conventionally" fractionated thoracic radiotherapy: a single instit'tion's 10-year experience in the management of limited-stage small-cell lung cancer using concurrent chemoradiation. *International journal of radiation oncology, biology, physics*. 2003;57(3):709-16. *Ineligible study design*
136. Voong KR, Lal LS, Kuban DA, et al. Long-term economic value of hypofractionated prostate radiation: Secondary analysis of a randomized trial. *Advances in Radiation Oncology*. 2017;2(3):249-258. *Ineligible outcome*
137. Waldron J, Warde P, Payne D, et al. Durable therapeutic gain despite competing mortality in long-term follow-up of a randomized hyperfractionated radiotherapy trial for locally advanced head and neck cancer. *Clinical and Translational Radiation Oncology*. 2020;21:69-76. *Ineligible intervention/comparison*
138. Wang G, Song M, Xu H, Fang Y. Prospective trial of combined hyperfractionated radiotherapy and bronchial arterial infusion of chemotherapy for locally advanced nonsmall cell lung cancer. *International journal of radiation oncology, biology, physics*. 1996;34(2):309-13. *Ineligible intervention/comparison*
139. Weissberg JB, Son YH, Percarpio B, Fischer JJ. Randomized trial of conventional versus high fractional dose radiation therapy in the treatment of advanced head and neck cancer. *International journal of radiation oncology, biology, physics*. 1982;8(2):179-85. *Ineligible intervention/comparison*
140. Witte M, Pos F, Incrocci L, Heemsbergen W. Association between incidental dose outside the prostate and tumor control after modern image-guided radiotherapy. *Physics and Imaging in Radiation Oncology*. 2021;17:25-31. *Ineligible outcome*
141. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial radiation therapy Oncology Group (RTOG) 0212: Impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *International Journal of Radiation Oncology Biology Physics*. 2011;81(1):77-84. *Ineligible intervention/comparison*
142. Wortel RC, Heemsbergen WD, Smeenk RJ, et al. Local Protocol Variations for Image Guided Radiation Therapy in the Multicenter Dutch Hypofractionation (HYPRO) Trial: Impact of Rectal Balloon and MRI Delineation on Anorectal Dose and Gastrointestinal Toxicity Levels. *International journal of radiation oncology, biology, physics*. 2017;99(5):1243-1252. *Ineligible intervention/comparison*
143. Wortel RC, Pos FJ, Heemsbergen WD, Incrocci L. Sexual Function After Hypofractionated Versus Conventionally Fractionated Radiotherapy for Prostate Cancer: Results From the Randomized Phase III HYPRO Trial. *The journal of sexual medicine*. 2016;13(11):1695-1703. *Ineligible outcome*
144. Yang F, Usmani NH, Danielson BL, et al. Conventional vs. Hypofractionation Radiation for High-Risk Prostate Cancer Patients (CHIRP): 24 Months Patient-Reported Quality of Life Outcomes of the Randomized Phase II CHIRP Trial. *International journal of radiation oncology, biology, physics*. 2021;111(3):S79. *Ineligible study design*

145. Yeoh EE, Botten R, Russo A, et al. Chronic effects of therapeutic irradiation for localized prostatic carcinoma on anorectal function. *International journal of radiation oncology, biology, physics*. 2000;47(4):915-24. *Ineligible intervention/comparison*
146. Yeoh EK, Holloway RH, Fraser RJ, Botten RJ, Di Matteo AC, Butters J. Pathophysiology and natural history of anorectal sequelae following radiation therapy for carcinoma of the prostate. *International journal of radiation oncology, biology, physics*. 2012;84(5):e593-9. *Ineligible outcome*
147. Yom SS, Torres-Saavedra P, Caudell JJ, et al. Reduced-Dose Radiation Therapy for HPV-Associated Oropharyngeal Carcinoma (NRG Oncology HN002). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2021;39(9):956-965. *Ineligible intervention/comparison*
148. Yuan C, Wang Q. Comparative analysis of the effect of different radiotherapy regimes on lymphocyte and its subpopulations in breast cancer patients. *Clinical and Translational Oncology*. 2018;20(9):1219-1225. *Ineligible outcome*
149. Zackrisson B, Modig H, Franzen L, et al. Two-year results from a Swedish study on conventional versus accelerated radiotherapy in head and neck squamous cell carci–oma - The ARTSCAN study. *Radiotherapy and Oncology*. 2011;100(1):41-48. *Ineligible intervention/comparison*
150. Zemplenyi AT, Kalo Z, Kovacs G, et al. Cost-effectiveness analysis of intensity-modulated radiation therapy with normal and hypofractionated schemes for the treatment of localised prostate cancer. *European journal of cancer care*. 2018;27(1). *Ineligible study design*
151. Zilli T, Jorcano S, Bral S, et al. Once-a-week or every-other-day urethra-sparing prostate cancer stereotactic body radiotherapy, a randomized phase II trial: 18 months follow-up results. *Cancer medicine*. 2020;9(9):3097-3106. *Ineligible intervention/comparison*
152. Zygogianni A, Platoni K, Patriki E, et al. A randomized study comparing two hypofractioned 3-D conformal radiotherapy for stage IIIb-IV non small cell lung cancer. *Journal of BUON : official journal of the Balkan Union of Oncology*. 2020;25(2):842-847. *Ineligible population*

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

Comment #	Reviewer #	Comment	Author Response
		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.

Comment #	Reviewer #	Comment	Author Response
		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.

Comment #	Reviewer #	Comment	Author Response
		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

Comment #	Reviewer #	Comment	Author Response
		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.