Hypofractionation Radiation Therapy for Definitive Treatment of Selected Cancers

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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.

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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:

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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.

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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

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

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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):

- o Overall adverse events
- o 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
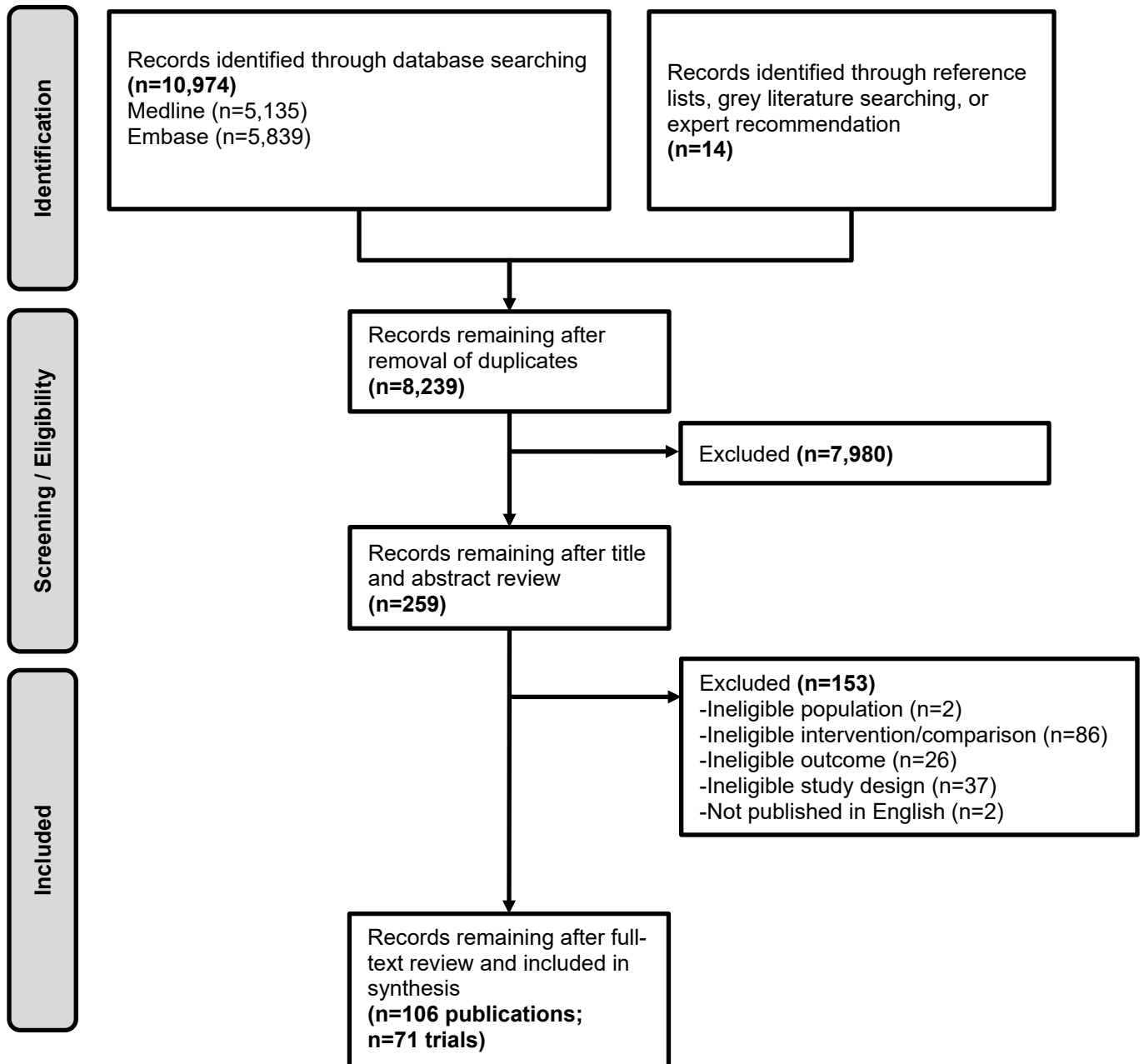
LITERATURE OVERVIEW

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
$\geq$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
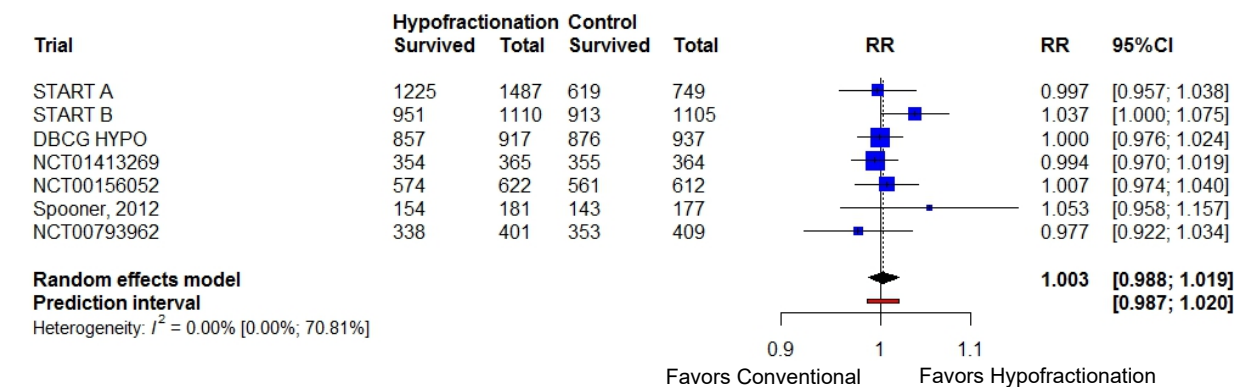
Trial	Hypofractionation		Control		RR	RR	95%CI
	Survived	Total	Survived	Total			
START A	1225	1487	619	749		0.997	[0.957; 1.038]
START B	951	1110	913	1105		1.037	[1.000; 1.075]
DBCG HYPO	857	917	876	937		1.000	[0.976; 1.024]
NCT01413269	354	365	355	364		0.994	[0.970; 1.019]
NCT00156052	574	622	561	612		1.007	[0.974; 1.040]
Spooner, 2012	154	181	143	177		1.053	[0.958; 1.157]
NCT00793962	338	401	353	409		0.977	[0.922; 1.034]
Random effects model						**1.003**	**[0.988; 1.019]**
Prediction interval							[0.987; 1.020]
Heterogeneity: I^2 = 0.00% [0.00%; 70.81%]							

0.9   1   1.1

Favors Conventional   Favors Hypofractionation

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

Trial	Hypofractionation		Control		RR	RR	95%CI
	Survived	Total	Survived	Total			
START A	1175	1487	595	749		0.995	[0.951; 1.040]
START B	928	1110	883	1105		1.046	[1.006; 1.088]
NCT01413269	333	365	338	364		0.983	[0.941; 1.025]
NCT00156052	531	622	533	612		0.980	[0.937; 1.025]
Spooner, 2012	114	181	104	177		1.072	[0.908; 1.266]
NCT00793962	305	401	292	401		1.045	[0.963; 1.133]
Random effects model						**1.007**	**[0.973; 1.042]**
Prediction interval							[0.948; 1.070]
Heterogeneity: I^2 = 36.72% [0.00%; 74.77%]							

0.8   1   1.25

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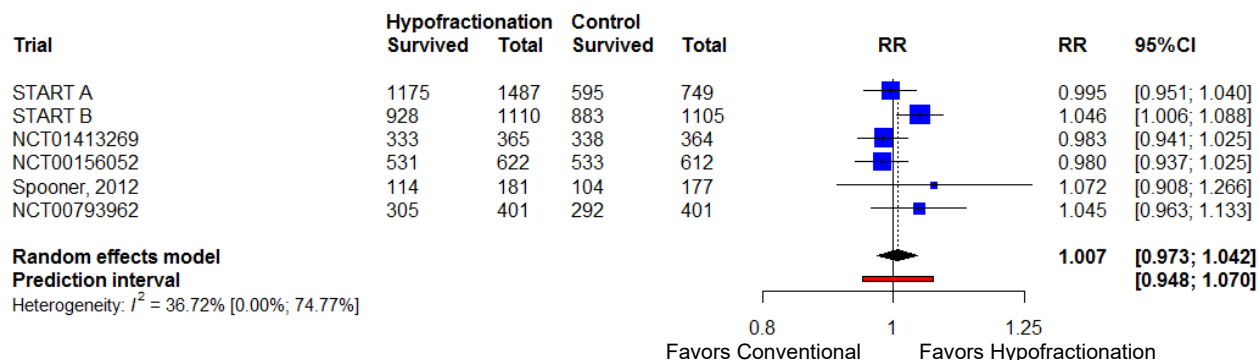
Moderate hypofractionation results in little to no difference in disease-free survival compared to conventional radiotherapy (high COE; Figure 3). Six[11,12,20,25-28,32,33] of the 7 trials reporting

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

Trial	Hypofractionation Events	Total	Control Events	Total	RR	RR	95%CI
START A	94	1487	45	749		1.052	[0.746; 1.485]
START B	42	1110	53	1105		0.789	[0.531; 1.172]
DBCG HYPO	14	794	19	814		0.755	[0.381; 1.496]
NCT01413269	14	365	12	364		1.163	[0.546; 2.481]
Spooner, 2012	25	181	21	177		1.164	[0.677; 2.002]
NCT00793962	31	401	29	401		1.069	[0.657; 1.740]
Random effects model						**0.977**	**[0.813; 1.174]**
Prediction interval							**[0.741; 1.287]**

Heterogeneity: I^2 = 0.00% [0.00%; 74.62%]

0.5   1   2

Favors Hypofractionation   Favors Conventional

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

Trial	Hypofractionation Events	Total	Control Events	Total	RR	RR	95%CI
NCT01413269	11	365	27	363		0.405	[0.204; 0.804]
NCT00156052	9	73	28	73		0.321	[0.163; 0.633]
TomoBreast	13	37	9	32		1.249	[0.617; 2.531]
NCT01266642	50	138	103	149		0.524	[0.410; 0.670]
DRKS00017763	19	70	30	70		0.633	[0.396; 1.013]
Random effects model						0.555	[0.308; 0.999]
Prediction interval							[0.139; 2.221]
Heterogeneity: $I^2 = 54.77\%$ [0.00%; 83.31%]							

0.2   0.5   1   2   5
Favors Hypofractionation   Favors Conventional
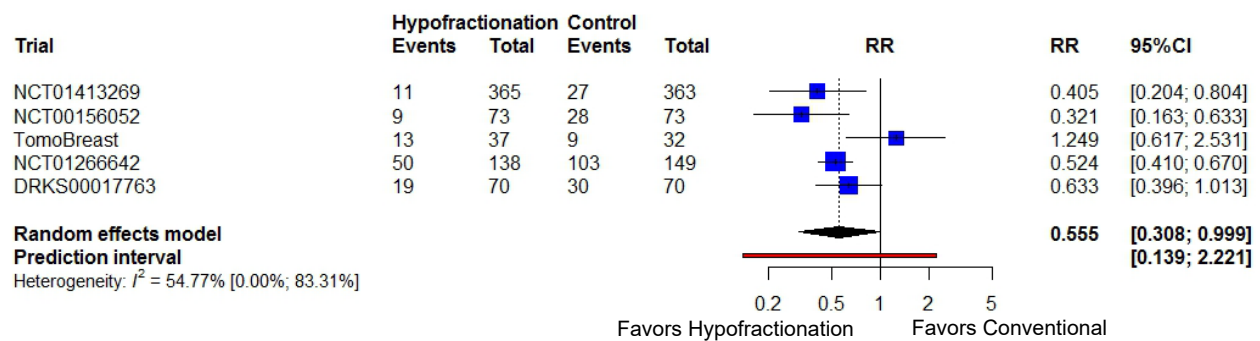
Hypofractionation may result in little to no difference in acute skin toxicity (low COE; Figure 5). Five trials (total n=1,370) assessed acute skin toxicity over a median follow-up of 4–8 weeks.[19,22,23,27,32] Acute skin toxicity was evaluated by CTCAE or the Radiation Therapy Oncology Group (RTOG)/European 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.
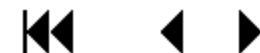
Overall Survival

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
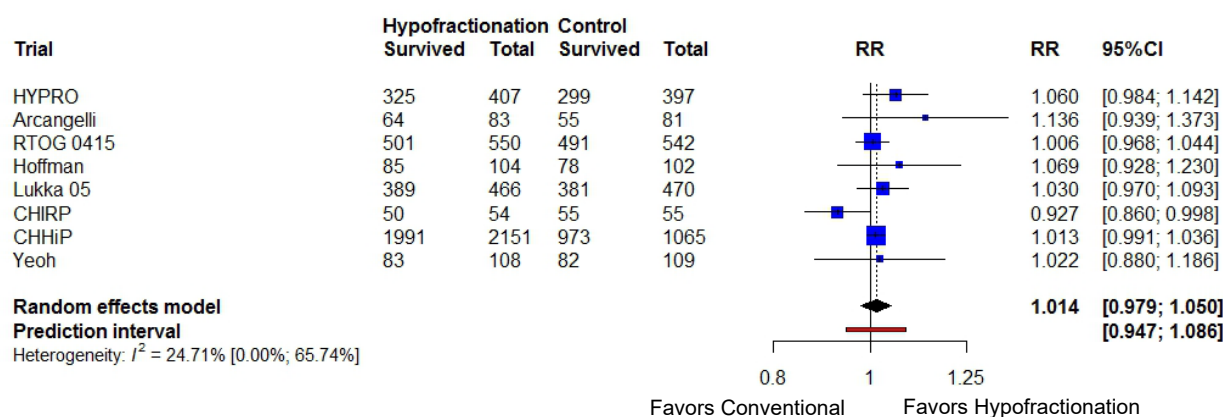
Trial	Hypofractionation Survived	Total	Control Survived	Total	RR	RR	95%CI
HYPRO	325	407	299	397		1.060	[0.984; 1.142]
Arcangelli	64	83	55	81		1.136	[0.939; 1.373]
RTOG 0415	501	550	491	542		1.006	[0.968; 1.044]
Hoffman	85	104	78	102		1.069	[0.928; 1.230]
Lukka 05	389	466	381	470		1.030	[0.970; 1.093]
CHIRP	50	54	55	55		0.927	[0.860; 0.998]
CHHiP	1991	2151	973	1065		1.013	[0.991; 1.036]
Yeoh	83	108	82	109		1.022	[0.880; 1.186]
Random effects model						**1.014**	**[0.979; 1.050]**
Prediction interval							**[0.947; 1.086]**
Heterogeneity: I^2 = 24.71% [0.00%; 65.74%]							

0.8   1   1.25

Favors Conventional   Favors Hypofractionation

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

TrialID	Hypofractionation Survived	Total	Control Survived	Total	RR	RR	95%CI
HYPRO	64	82	79	98		0.968	[0.833; 1.125]
Arcangelli	82	85	74	83		1.082	[0.994; 1.178]
Pollack	145	152	143	151		1.007	[0.957; 1.060]
Hoffman	104	104	102	102		1.000	[0.981; 1.019]
Lukka 05	453	466	452	470		1.011	[0.987; 1.035]
CHIRP	54	54	55	55		1.000	[0.965; 1.036]
Yeoh	106	108	105	109		1.019	[0.974; 1.066]
Random effects model						**1.006**	**[0.994; 1.019]**
Prediction interval							**[0.990; 1.023]**
Heterogeneity: I^2 = 0.00% [0.00%; 70.81%]					0.9 1 1.1		

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

Trial	Hypofractionation Events	Total	Control Events	Total	RR	RR	95%CI
Arcangelli	18	83	25	85		0.737	[0.436; 1.246]
Pollack	28	151	25	152		1.127	[0.691; 1.840]
Lukka 05	249	466	271	470		0.927	[0.826; 1.039]
CHIRP	4	54	7	55		0.582	[0.181; 1.875]
Yeoh	37	108	39	109		0.958	[0.666; 1.376]
Zhong	3	46	2	46		1.500	[0.263; 8.562]
Random effects model						**0.927**	**[0.846; 1.017]**
Prediction interval							**[0.800; 1.075]**
Heterogeneity: I^2 = 0.00% [0.00%; 74.62%]					0.2 0.5 1 2 5		
					Favors Hypofractionation Favors 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

Hypofractionation Radiation Therapy   *Evidence Synthesis Program*

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

Trial	Hypofractionation Events	Total	Control Events	Total	RR	RR	95%CI
HYPRO	42	327	43	326		0.974	[0.655; 1.448]
Arcangelli	29	83	18	85		1.650	[0.996; 2.732]
RTOG 0415	58	545	55	534		1.033	[0.729; 1.465]
Catton	99	608	62	598		1.571	[1.167; 2.113]
Norkus 13	5	115	8	106		0.576	[0.195; 1.706]
Lukka 05	19	466	12	470		1.597	[0.784; 3.252]
Norkus 09	8	47	10	44		0.749	[0.325; 1.724]
CHIRP	10	53	12	55		0.865	[0.409; 1.830]
CHHiP	547	1433	176	715		1.551	[1.342; 1.791]
Zhong	8	46	5	46		1.600	[0.566; 4.526]
Random effects model						1.277	[1.032; 1.580]
Prediction interval							[0.816; 1.998]

Heterogeneity: I^2 = 42.15% [0.00%; 72.32%]

0.2   0.5   1   2   5
Favors Hypofractionation   Favors 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).

39

Figure 10. Prostate Cancer Acute GU: Hypofractionation versus Conventional

Trial	Hypofractionation Events	Total	Control Events	Total	RR	RR	95%CI
HYPRO	75	327	73	325		1.021	[0.769; 1.356]
Arcangelli	39	83	34	85		1.175	[0.831; 1.661]
RTOG 0415	147	545	145	534		0.993	[0.817; 1.208]
Catton	185	608	183	598		0.994	[0.839; 1.179]
Norkus 13	1	115	5	106		0.184	[0.022; 1.552]
Lukka 05	40	466	23	470		1.754	[1.067; 2.882]
Norkus 09	9	47	21	44		0.401	[0.207; 0.779]
CHIRP	16	53	16	55		1.038	[0.580; 1.856]
CHHiP	683	1435	331	715		1.028	[0.934; 1.132]
Zhong	8	46	6	46		1.333	[0.502; 3.540]
Random effects model						1.010	[0.773; 1.319]
Prediction interval							[0.487; 2.093]

Heterogeneity: I^2 = 42.86% [0.00%; 72.64%]

0.1   0.5 1 2   10

Favors Hypofractionation   Favors 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]
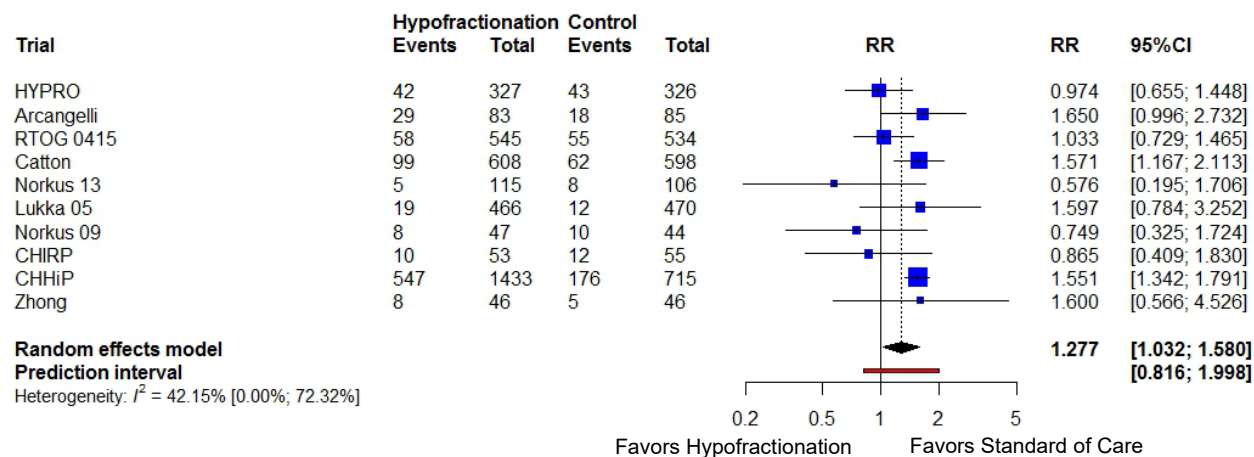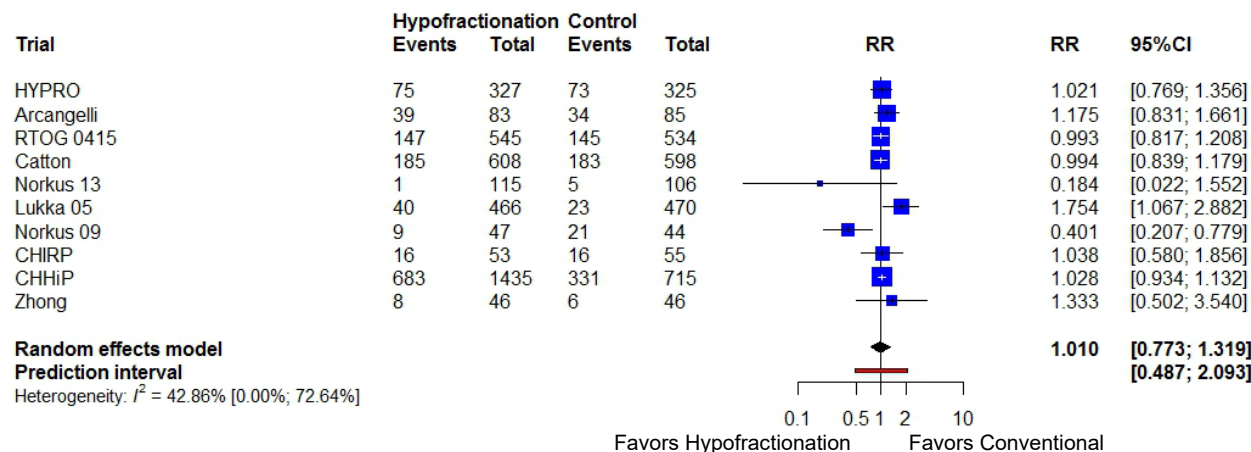
Late GI

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

Trial	Hypofractionation Events	Total	Control Events	Total	RR	RR	95%CI
HYPRO	42	326	43	426		1.276	[0.856; 1.904]
Arcangelli	12	83	10	85		1.229	[0.562; 2.688]
RTOG 0415	121	545	75	564		1.670	[1.284; 2.172]
Catton	54	608	83	598		0.640	[0.463; 0.884]
Hoffman	12	104	5	102		2.354	[0.860; 6.443]
Lukka 05	6	466	6	470		1.009	[0.328; 3.105]
CHIRP	8	50	5	50		1.600	[0.562; 4.556]
CHHiP	45	1881	35	922		0.630	[0.408; 0.973]
Zhong	3	46	2	46		1.500	[0.263; 8.562]
Random effects model						**1.107**	**[0.776; 1.580]**
Prediction interval							**[0.477; 2.568]**

Heterogeneity: I^2 = 73.50% [48.33%; 86.41%]

0.2   0.5   1   2   5
Favors Hypofractionation   Favors 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]

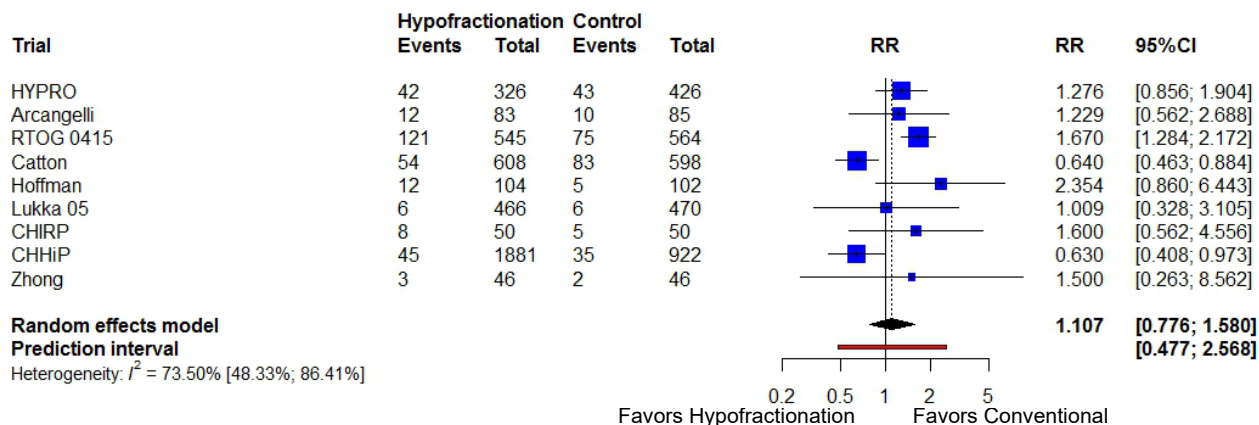### Late GU

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

Trial	Hypofractionation Events	Total	Control Events	Total	RR	RR	95%CI
HYPRO	75	327	73	327		1.027	[0.774; 1.364]
Arcangelli	7	83	5	85		1.434	[0.474; 4.338]
RTOG 0415	161	545	121	534		1.304	[1.064; 1.598]
Catton	136	608	134	598		0.998	[0.809; 1.232]
Hoffman	15	101	15	102		1.010	[0.522; 1.955]
Lukka 05	9	466	9	470		1.009	[0.404; 2.518]
CHIRP	8	50	3	50		2.667	[0.751; 9.474]
Zhong	0	46	2	46		0.200	[0.010; 4.054]
CHHiP	27	1921	13	922		0.997	[0.517; 1.923]
Random effects model						**1.119**	**[0.976; 1.282]**
Prediction interval							**[0.965; 1.297]**

Heterogeneity: I^2 = 0.00% [0.00%; 64.80%]

0.01   0.1   1   10   100
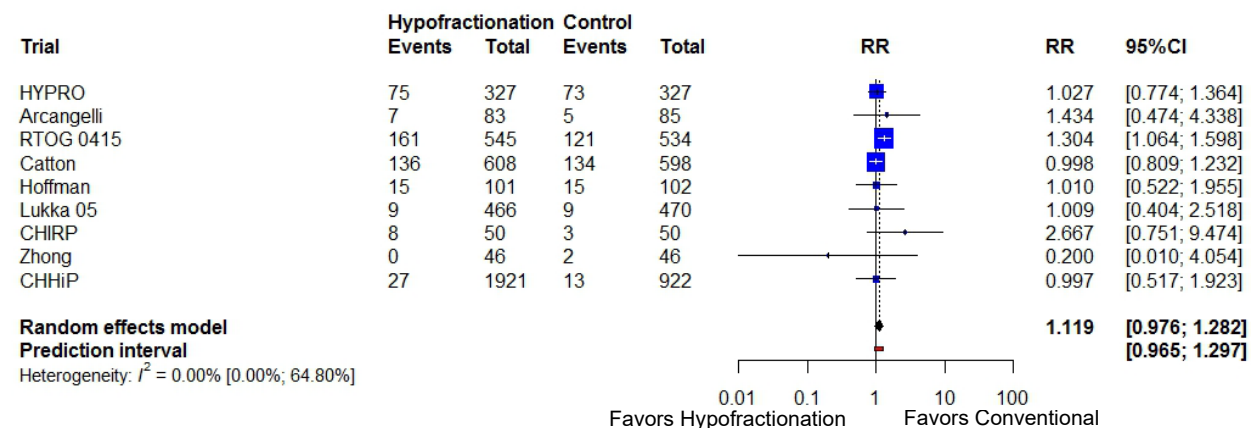Favors Hypofractionation   Favors Conventional

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/esoph agitis (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[†] **MCID: 10% difference**	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.
Acute pneumonitis (grade ≥ 3)							
Risk ratio and absolute effect size estimates based on control event rate from 1 trial[‡] **MCID: 5% difference**	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.

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[†] **MCID: 10% difference**	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.

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).
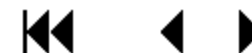* Study authors did not report these results or provide count level data to allow for calculation of these measures and/or CI.
† Estimated using data from Nyman et al.[72]
‡ Estimated using data from Ball et al.[10]

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.

    o 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.

    o 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.

    o 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.

    o 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.

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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 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 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.

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