Evidence Synthesis Program

Hypofractionation Radiation Therapy for Definitive Treatment of Selected Cancers

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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.

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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.

ABBREVIATIONS TABLE

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

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

EXECUTIVE SUMMARY

Key Findings

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

INTRODUCTION

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

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

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

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

METHODS

Data Sources and Searches

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

Study Selection

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

Data Abstraction and Assessment

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

Synthesis

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

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

RESULTS

Results of Literature Search

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

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

Summary of Results for Key Questions

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

Limitations

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

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

Future Research

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

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

Conclusions

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